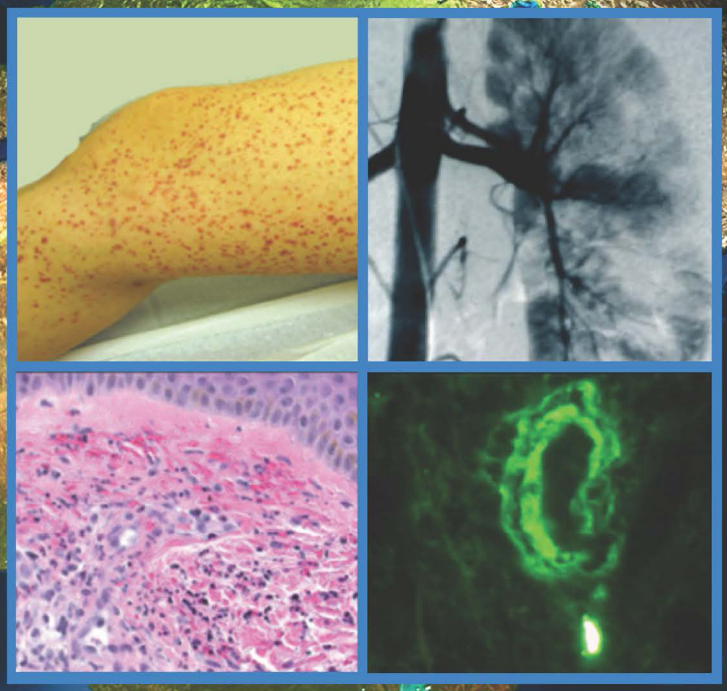
David S. Younger, MD, MPH, MS
Editor

The Vasculitides

General Considerations and Systemic Vasculitis

(Second Edition)

Volume 1



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THE VASCULITIDES

VOLUME 1

GENERAL CONSIDERATIONS AND SYSTEMIC VASCULITIS

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VOLUME 1

GENERAL CONSIDERATIONS AND SYSTEMIC VASCULITIS

(SECOND EDITION)

DAVID S. YOUNGER, MD, MPH, MS
EDITOR

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FOREWORD TO THE VASCULITIDES

Charles D. Pusey and Richard A. Watts

Clinical and basic research into the systemic vasculitides have continued to gather momentum over the last four years since publication of the first edition of this book. We have attended two more International Vasculitis and ANCA Workshops, in London in 2015 and Tokyo in 2017. Both of these excellent meetings have covered the area of vasculitis more broadly and extensively than in the past. The present edition of this book contains contributions from many of those participating in these meetings.

Classification and nomenclature in vasculitis is increasingly harmonised and agreed across different specialties. There have been a number of genetic studies in ANCA-associated vasculitis (AAV) in which the genetic associations appear to be more closely related to ANCA specificity, i.e., MPO-ANCA or PR3-ANCA, than to clinical classification. The extent of overlap between the different vasculitic conditions is also becoming more apparent, in particular the co-existence of AAV and anti-GBM disease.

In terms of pathogenesis, there is increasing evidence for the contribution of complement activation in AAV. This has been nicely demonstrated in animal models, and a phase 2 trial of a C5a receptor inhibitor has recently been reported. Another area of increasing interest is the role of neutrophil extracellular traps (NETs) which appear to play a part both in tissue inflammation and in the generation of autoimmunity.

The number of clinical trials in vasculitis continues to expand. The use of rituximab for induction therapy in AAV is now well established, and different approaches to its use in maintenance therapy have been published. There are ongoing investigations of other novel agents, such as belimumab and abatacept. The results of the PEXIVAS study, which examines the use of additional plasma exchange, and of standard or reduced corticosteroid dose, are eagerly awaited.

In the area of large vessel vasculitis, there have also been rapid developments. The genetic basis of Takayasu arteritis and giant cell arteritis is becoming clearer, with evidence of different genetic risk factors underlying the two conditions. Imaging, especially the role of PET-CT in disease assessment, is becoming better established. The treatment of giant cell arteritis has taken a large step forward with the introduction of IL-6 blockade as an established therapy. However, many questions remain, especially when to use IL-6 blockade and for how long. This

treatment should permit many patients to avoid the deleterious consequences of long term high dose steroids.

We believe that the breadth and depth of the contributions in the second edition of this book surpass the high standards set in the first edition. The publication of this new edition precedes the 19th International Vasculitis and ANCA Workshop to be held in April 2019 in Philadelphia.

PREFACE

Systemic and nervous system vasculitides are a heterogeneous group of related disorders, each characterized by vascular inflammation such that it has the potential to cause serious morbidity and mortality if unrecognized and therefore untreated. Systemic vasculitis affect all populations and every nationality and walk-of-life, from childhood to older age. The first edition of The Vasculitides published in 2014 to meet the urgent need for a clear, concise and reliable textbook regarding the epidemiology, pathogenesis, clinical presentation, laboratory evaluation and management of these disorders, assembled participants of the 16th International Vasculitis and ANCA Workshop in Paris, France. Five years later, two subsequent meetings have taken place, in London and Tokyo. The 19th International Vasculitis & ANCA Workshop in April 2019 at the University of Pennsylvania promises to be an exceptional venue to share translational scientific discoveries, data from clinical trials, and advances in the clinical assessment, pathophysiology, genetic biomarkers, and standard-of-care and novel therapies of vasculitis.

The second edition, which is an update of the original two-volume book, remaining encyclopedic in content, adds six new chapters, incorporating the participation of investigators who did not have an opportunity to contribute the first volume, including some from the previous meeting in Japan. The new chapters are Health Related Quality of Life and Measurements, Neutrophilic Cell Pathology, Complement Factors in ANCA-Associated Vasculitis, Isolated Aortitis/IgG4 Disease, Anti-GBM Disease, and the Autoimmune Encephalitides. An additional six chapters were reassigned or incorporate new contributors. Five chapters left out of the present edition, made room for new and updated content without increasing the page length. Participants attending the 19th International Vasculitis & ANCA Workshop and preparing to both share their experience and enrich their knowledge in the clinical and scientific complexities and broad scope of organ involvement, that are the hallmarks of vasculitis, will no doubt want to receive an advance copy of this book or obtain one at the meeting.

I wish to express my appreciation to my coauthors, all experts in their individual field of interest in vasculitis, for allowing me to, once again, assemble them for the task of producing a 2nd edition of *The Vasculitides*. And many thanks to Ms. Lauren Bangug, Clinical Coordinator, for assisting in the preparation of the final manuscript.

I have had the good fortune of interacting with thought-provoking medical students, neurology trainees, public health doctoral students and professors at New York University, in

the Department of Neurology, Division of Neuroepidemiology, and at City University of New York, in the Department of Health Policy and Management. Like my coauthors, we strive for the highest ethical standards in medical and public health practice and research. My wife Holly and sons Adam and Seth encourage me to take on projects that promote core values of medicine and humanity, as my patients educate me daily in empathy and humility.

David S. Younger, MD, MPH, MS
September 30, 2018
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I. General Considerations

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Chapter 1

HISTORY AND BACKGROUND OF VASCULITIS

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ABSTRACT

The descriptions of previous poorly understood and obscure diseases by early workers, and their insights and discoveries that followed have formed many of the foundations of modern medicine. The original descriptions of inflammatory vascular diseases in particular shaped the cultural context of medical science and provided the catalysts and inspirations that fueled later clinical investigation. The transition from the so-called *romantic era* to the *scientific era* of medicine in turn mirrored advances in the pathogenesis, treatment and classification of the vasculitides. The stories of the early contributions from Hippocrates to Kussmaul will forever guide clinicians in the fundamental humanity of this discipline.

Keywords: vasculitis, history

INTRODUCTION

The study of the history of vasculitis provides insights into the evolution of clinical thinking and the pathophysiologic that guided the evolution of concepts integral to the modern appreciation of this fascinating group of diseases. Forms of idiopathic vasculitis were identified as early as the nineteenth century, moreover accounts of idiopathic vasculitis in the form of what is presently termed Behçet disease can be found in the writings of Hippocrates [1] as can those related to giant cell arteritis by the oculist Ali ibn Isa in Baghdad in 1000 AD [2].

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VASCULITIS IN HISTORICAL CONTEXT

The introduction of scientific methodology in the nineteenth century brought to a close the romantic era of medicine and ushered in the scientific era, promoted by the advent of university-based systematized anatomic pathology and technical developments notably microscopic anatomy. Such advances were critical to the development of theories of the cellular basis of disease embraced by Rudolf Virchow and others between 1848 and 1858 [3, 4].

Yet even in 1554, Antoine Saporta [5] provided the classical description of non-traumatic macrovascular disease related to infectious disease due in the occurrence of syphilitic aneurysms in an affected patient. Over time, anatomic pathologists frequently noted inflamed vessels. By the early nineteenth century, infection was accepted as a cause of vasculitis [6, 7] and other forms of vascular disease were more clearly delineated including atherosclerotic disease and developmental arterial disease of the arteries [8]. The first clear description of non-infectious vascular inflammation was likely by Joseph Hodgson in 1815 [9] in his inspection of large arteries at postmortem examination and the recognition of arterial intimal inflammation suggesting that such changes could result from high intravascular pressure, trauma, and a systemic inflammatory state. Moreover, vascular inflammation previously related only to syphilitic infection, could also be associated with other diseases [9]. During the same era, John Hunter [10] described inflammation of the veins.

The advent of microscopy enabled further investigation of the nature of vascular inflammation and its origins. The anatomic pathologist Karl von Rokitansky, who viewed arteritis as having its origin in the adventitia, was unlike Virchow who employed careful microscopic studies of his anatomic specimens and postulated that inflammation instead began in the intima and media [3, 11].

Polyarteritis Nodosa

Adolf Kussmaul and Rudolf Maier described the first clearly recognizable patient with idiopathic vasculitis of the polyarteritis nodosa type (PAN) in 1865 [12] in a 27-year-old journeyman, the findings of whom influenced and systematized later observations. The patient, Carl Seufarth had improved from a prior infectious illness one month earlier when he was arrested in destitute circumstances after wandering into the city of Freiburg, in the Black Forest of Germany during the summer of 1865, and taken to the municipal jail where the officers recognized his poor medical state. He was later transferred to the University of Freiburg Internal Medicine Clinic where he was and was able to walk up the two flights of stairs to Dr. Kussmaul's office, where he examined him, and thereafter hospitalized. Over the ensuing months, Seufarth developed fever, generalized muscle aching, mononeuritis multiplex of the arms and legs, abdominal pain, and proteinuria. He died on May 30, 1865 and an English account of his case was later published [13]. Working closely together with Kussmaul, the anatomic pathologist Rudolf Maier, at the University of Freiburg performed detailed postmortem microscopic examination and described the findings under the rubric of periarteritis nodosa, and later PAN. In their words, there was a "peculiar, mostly nodular thickening of countless arteries of and below the caliber of the liver artery and the major

branches of the coronary arteries of the heart, principally in the bowel, stomach, kidneys, spleen, heart, and voluntary muscles and, to a lesser extent, also in the liver, subcutaneous cell tissue, and in the bronchial and phrenic arteries" [12]. The nodular thickened vessels revealed inflammatory changes in the media and adventitia. The kidneys had changes of "acute Bright's disease." Maier wrote, *"The change affects the intralobular arteries, which have glomeruli at their bifurcations, and extends into these branches and even into the glomeruli"* [12].

Kussmaul and Maier ascribed the pathological alterations in the arteries to "inflammation of the arteries affecting principally the perivascular sheath, in which the media also had a part, at least in its outer layers," recognizing that the inflammatory changes "often attacked neighboring tissues in the opposite direction, for example, the renal parenchyma, connective and muscle tissues." The investigators initially considered the disease to be a result of infectious causes including a worm infestation, both because of the peculiar nature of the pea-size nodules, which appeared in the tissue below the epidermis of Seufarth's abdomen, and the thickened fibrotic nature of the affected vessels. Indeed, an abstract cited their patient as an example of nematode aneurysmal disease before Maier [14] conducted a later thorough microscopic evaluation.

There may even have been earlier cases of PAN, but none was so recognized in the medical literature. Karl von Rokitansky provided a very brief clinical description of a patient seen in 1852 at the University of Vienna found to have fatal aneurysmal coronary and mesenteric arterial changes [15] believed to be an early example of PAN. However, Rokitansky did not undertake microscopic examination of the tissue, and it was not until his student Hans Eppinger later examined the specimens microscopically that it was clear that the patient had PAN [16]. Kussmaul did not consult Rokitansky about his earlier patient because of his unfavorable experience as a visiting clinician in Rokitansky's Institute of Anatomic Pathology institute at about 1840. Instead, he collaborated with Virchow who affirmed that while he might have seen a similar patient but did understand its fundamental nature [12, 17]. Attesting to the rarity of the disorder, only about 30 additional cases were described in Europe and the United States in the ensuing four decades [17-19], and into the twentieth century.

Necrotizing Vasculitis

The first cases of vasculitis were macroscopically apparent and could be assessed with the naked eye. A clear understanding of microscopic necrotizing vasculitis did not emerge until well into the twentieth century. Davson in 1948, and Wainwright in 1950, provided the first English language accounts of microscopic PAN or polyangiitis that affected small arterial capillaries and venules, particularly in the kidney and lungs, often associated with necrotizing glomerulonephritis [20, 21]. The neuropathologist Friedrich Wohlwill of Hamburg provided the first coherent description of microscopic necrotizing vasculitis, coining the term microscopic PAN in a description of two reported patients in 1923 [22]. Both patients described by Wohlwill [22] had antecedent illnesses characterized by weight loss, fevers, clinical evidence of nephritis, widespread muscle pain, and paresis consistent with mononeuritis multiplex. At postmortem examination, there was evidence of glomerulonephritis, and widespread inflammation of small vessels on microscopic examination. He also described inflammatory involvement with marked polymorphonuclear cell infiltration of arterioles, capillaries and venules [22]. Wohlwill [22] conceived of a direct relationship to the disease

described by Kussmaul and Maier, drawing upon his findings of systemic vascular inflammation and "a well characterized and uniform disease, which practically demand the assumption of a unified etiology [22].

In 1931, Heinz Klinger described a patient with necrotizing granulomatous vasculitis with glomerulonephritis that he considered a form of periarteritis nodosa [23]. He also described a second patient with similar findings and hemoptysis on presentation postulating a possible infectious etiopathogenesis [23]. Friedrich Wegener reported further patients which were interpreted as forms of periarteritis nodosa, however, it was clear that he viewed the disease course and related pathology as unique and anatomically distinctive particularly the invasive granulomatous process, which he believed to be due to an infectious agent [24, 25], and the granulomatous vasculitis as a form of rheumatoid or rheumatic disease [26].

In 1949, Churg and Strauss [27] described an eosinophilic form of granulomatous polyangiitis with the constellation of "allergic granulomatosis, allergic angiitis, and periarteritis nodosa. This combination of findings was previously reported by Ophüls [28] in 1923 in a patient who with granulomatous nodules, particularly of the pericardium and peritoneum with eosinophilic infiltration of the bronchi and pulmonary tissue, and concomitant arteritis, capillaritis, venulitis, and nephritis. Otani [29] also described a variant of periarteritis nodosa in 1924 in the description of a 35-year-old woman with asthma and eosinophilia. Churg and Strauss [30] provided more clinical information and systemization to the disease that eventually bore his name in a subsequent analysis of 13 patients, all of whom had asthma and granulomatous lesions in small arteries of parenchymal organs including the epicardium. These investigators [30] considered the disease to be essentially a "malignant expression" of allergic granulomatosis in contrast to other more benign forms of allergic granulomatosis such as Loeffler syndrome.

In the decades that followed, investigators provided additional clinical observations, anatomic correlations, and pathophysiologic connections between various forms of necrotizing vasculitis employing antineutrophil cytoplasmic antibodies (ANCA) that contrasted with other forms of necrotizing vasculitis. First detected in 1982 in the sera of patients with Ross River Arbovirus infection and idiopathic segmental necrotizing glomerulonephritis [31], ANCA have advanced concepts of the immunopathogenesis of necrotizing vasculitis. Subsequently detected in the sera of patients with GPA and MPA and to a lesser extent, in eosinophilic GPA (eGPA) (20), further elucidation of the role of these antibodies led to considerable advances in the understanding of the pathogenesis of systemic vasculitis [32].

Large Vessel Vasculitis

Patients with large vessel vasculitis or *pulseless disease* have been described for the past 3000 years [8]. Early descriptions of the condition were initially related to trauma while those in the late eighteenth and nineteenth centuries were causally associated with arterial sclerosis [4, 33, 34]. The formidable anatomic pathologist Morgnani [35] described an approximately 40-year-old woman with absent radial pulses for at least six years prior to her death in which postmortem examination showed ectasia of the proximal aorta with stenosis of the lower portion, and histologically normal radial artery vessels.

In 1839, Davy [36] described two patients with likely large vessel vasculitis including a 55-year-old male who presented with weak arm pulses and later vertigo. The physical findings

were of "a throbbing pulse at the upper part of the sternum, and a slight prominence of the bone there to some little extent". Davy [36] suspected an aortic arch aneurysm, which was indeed found one and one-half years later at postmortem examination. So stated, a large aneurysm of the aortic arch was found and "all the great vessels arising from the arch were completely closed up at their origin". Davy [36] described absent arm pulses in a 36-year-old man who like the first patient, was a soldier in the British Army. Postmortem examination in the second patient showed aortic arch dilatation and occlusion of the left subclavian and carotid arteries.

A further description from this era was given by Savory [37] in 1854 of a 22-year-old woman who was ill for five years with pulseless arteries of the arms and neck, and blindness over the ensuing year. Postmortem examination in that patient showed marked stenosis of the aortic arch and it branches, without aneurysms. Savory [37] was probably aware of the previous descriptions by Rokitansky [15], and further differentiated his patient by ascribing the observed inflammation to an origin in the intima and media, rather than the adventitia.

It has been speculated that Ali ibn Isa [2] may have described a patient with temporal arteritis at about 1000 AD when reporting, "one treats not only migraine and headache in those patients that are subject to chronic eye disease but also acute, sharp, catarrhal affections, including those showing heat in and inflammation of the temporal muscles. These disease conditions may terminate in loss of eyesight; frequently, they are attended by a considerable degree of chemosis." While it remains unclear whether this actually represents a case of giant cell arteritis, there is no doubt that in 1890, Hutchinson [38] provided the first clinical description of what is truly regarded as contemporary temporal arteritis when he reported a "peculiar form of Thrombotic Arteritis of the aged, which is sometimes productive of Gangrene," in an 80-years-old man. His patient, a servant named Rumbold, presented with headache and "red streaks on his head, which were painful and prevented him from wearing his hat." Hutchinson [38] recounted that that the patient lived for several years without "any other manifestation of arterial disease."

The clinical syndrome and histological aspects of giant cell arteritis was clearly delineated by Horton, Magath, and Brown [39] at the Mayo Clinic in 1932. Indeed, they obtained the first biopsies of the affected temporal arteries in living patients and described the typical findings including "peculiar circumscribed areas of what appear to be granulation tissue…in the adventitia of the blood vessels, which suggested granulomas," stating further that "this represented the most characteristic lesion present." Like Hutchinson [38], of whose work they apparently were not aware, these investigators [39] initially regarded the disease as benign, as "complete recovery occurred in each case," however on further follow-up, they observed that two of their first patients died within two years of what they termed "unrelated conditions." By 1938, visual loss was associated with giant cell arteritis by Jennings (40). The association of headache with occasional jaw claudication prompted the term "cranial arteritis" in 1946 by Kilbourne and Wolffe [41].

Much earlier in 1908, Takayasu [42] described a young woman with peculiar retinal artery changes and "wreath-like anastomosis surrounding the optic disc at a distance of 2 or 3 mm, and surrounding this was another circular anastomosis". Takayasu [42] described "lumps" in the surrounding vessels that were seen to "move from day-to-day." These findings were discussed at the 12th Annual Meeting of the Japanese Society of Ophthalmology whereupon other discussants noted the relation of pulseless radial arteries to the retinal artery changes in their own patients, an association that Takayasu had not appreciated [42]. By 1925, Beneke [43] reported the first comprehensive histopathologic analysis of affected large vessels in

patients with pulseless disease of Takayasu arteritis type. There was virtually complete medial necrosis, intimal sclerosis, adventitial scarring and thickening of large arteries at postmortem examination in affected patients. More importantly, Beneke [43] described giant cells which he related instead atheromatous changes and white blood cell infiltrates of greater importance to the disease pathogenesis.

Other Forms of Idiopathic Vasculitis

Henoch-Schönlein Purpura

The disease known as Henoch-Schönlein purpura (HSP) likely first appeared in a report by William Heberden [44] in 1801 in the account of a 4-year-old with purpuric lesions of the leg, buttock, and scrotum; as well as in a 5-year-old with similar lesions and abdominal pain. Ollivier [4] described a youngster with purpura and abdominal pain in 1827, but the distinct disease awaited the description of "peliosis rheumatica" by Schönlein in 1837. In 1874, Henoch [46] reported four affected children with joint pain, purpuric rash, abdominal pain, and diarrhea recognizing the potentially fatal aspect of the disease. The cause of the disease has been ascribed to infection, although a specific infectious agent has yet to be definitively identified. In 1915, Frank [47] postulated an allergic cause so termed "anaphylactoid purpura". Glanzmann [48] postulated that the combination of infection and hypersensitivity culminated in the observed findings of purpura, nephritis and abdominal pain, although a potentially causative antigen was not identified.

Behçet Disease

Oral and genital mucosal ulcers and eye inflammation of Behçet disease may have been recognized by Hippocrates but was certainly described by Blüthe (49) in 1908, Planner and Remenovsky [50] in 1922, Shigeta [51] in 1924, and Whitwell in 1934 [52]. One of latter described patients [52], a 29-year-old woman, with oral and genital ulcers, likely erythema nodosa, and venous emboli of the leg, had the cardinal features of so-called Adamantiades-Behçet. Adamantiades [53] described a 22-year-old soldier patient with oral and genital ulcerations who experienced recurrent iritis and hypopyon, and was thought to have syphilis based on a positive Wassermann reaction. Treatment for syphilis was unsuccessful. In his initial description, Behçet [54] described two patients, a 34-year-old woman and 40-year-old man with recurrent oral and genital aphthous ulcerations, uveitis and hypopyon. Behçet [54] speculated an infectious viral cause, undertaking a detailed examination for the presence of viral products whereas a vasculitic etiopathogenesis was not contemplated.

Kawasaki Disease

In 1961, childhood febrile mucocutaneous lymph node syndrome was first described by Kawasaki [55] in Tokyo. The suspected causes included allergic, infectious, and autoimmune mechanisms. In a subsequent report in 1974 based on more than 6000 patients seen in Japan, Kawasaki [56] indicated he noted "infantile periarteritis nodosa-like arteritis of the coronary artery accompanied by thrombosis and aneurysm…" Kawasaki disease is increasingly regarded as an infantile/juvenile form of PAN.

Single Organ Vasculitis

A multitude of single organ vasculitides has been recognized in the past several decades. Diaz-Perez and Winkelmann [57] at Mayo Clinic described a cutaneous form of PAN in 1974. A nonsystemic vasculitic neuropathy (NSVN) was described by Dyck and coworkers at the Mayo Clinic in 1986 [58]. Granulomatous angiitis (GANS), isolated angiitis of the central nervous system (IACNS) and primary angiitis of the CNS (PACNS) are equivalent terms for a potentially lethal adult CNS vasculitis, clinically and pathologically characterized beginning with the description by Cravatio and Fegin in 1959 [20, 59]. An equivalent disease affects children although curiously without granulomatous pathology. The occurrence of idiopathic vasculitis in isolated organs which has become increasingly recognized, and on occasional may evolve to affect other organs, was included in the 2012 Revised Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides [60]. Since the initial description by Kussmaul and Maier [14], secondary forms of vasculitis due to hypersensitivity, infection, and vasculitis occurring in the context of other autoimmune rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus have also been described. Vasculitis has also been related to the presence of systemic cancer. Indeed, in 1958, Guichard [61] introduced the term “paraneoplastic" to describe the latter occurrence.

VASCULITIS CLASSIFICATION, NOMENCLATURE, MANAGEMENT GUIDELINE DEVELOPMENT AND RECENT ADVANCES

Early attempts to categorize the vascular diseases were based upon the likeliest etiological postulates to explain a given gross anatomical feature. Indeed, Rokitansky’s [11] nineteenth century classification of aneurysms included those arising as a result of increased blood pressure and aging, non-atheromatous muscularis inflammation, trauma, pseudomembranous intimal proliferation of the intima or adventitial weakness of the intima at the site of atheroma. In 1952, Zeek [62, 6]) offered the first modern classification system of vasculitis, dividing them simplistically into hypersensitivity and angiitis, allergic granulomatous angiitis, rheumatic arteritis, periarteritis nodosa, and temporal arteritis; granulomatosis and polyangiitis and Takayasu arteritis were not included.

In 1990, the classification of vasculitis by the American College of Rheumatology (ACR) distinguished one form another based on review of nearly 1200 cases of vasculitis [64]. The 1994 [60] and 2013 Revised CHCC [65] provided better systematization and nosology, recognizing both primary idiopathic vasculitis and secondary vasculitis including those associated with hepatitis C viral infection, while foregoing the category of hypersensitivity vasculitis.

Classification criteria continue to be reexamined and revised. A major effort in this regard is the prospective enrollment of now nearly 6000 patients into the Diagnostic and Classification Criteria in Vasculitis (DCVAS) study headquartered at Oxford University and cosponsored by the American College of Rheumatology and the European League Against Rheumatism (66). DCVAS is a multinational, observational study that aims to develop diagnostic criteria and

update classification criteria in vasculitis. DCVAS investigators have recruited over 6000 patients from 133 sites in 32 countries who have vasculitis, and vasculitis mimics.

A number of more recent contributions have made recent advances in the management of vasculitis possible and certainly will be seen in their historical context. Development of investigator cooperatives including the Vasculitis Clinical Research Consortium, the European Vasculitis Study Group, and others has greatly enhanced the ability to pursue investigation into the pathogenesis and genetics of vasculitis, as well pursuit of multicenter treatment studies. These include the advent of large scale, formal randomized trials such as the Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE), tocilizumab in patients with Giant Cell Arteritis (GiACTA), CYClophosphamide or AZathioprine As a REMission therapy for vasculitis (CYCAZAREM),and many others at the national and international level has been a major reason for improvement in vasculitis care [67, 68]. An important result of the more systematic and collaborative efforts in developing outcome measures such as the Birmingham Vasculitis Activity Score and its variants among many others [68, 69]. These approaches have are improving outcomes and lowering drug toxicity rates in patients suffering from these diseases.

Pursuit of these therapeutic studies by the various work groups has resulted in insights about how long to use cyclophosphamide, how and when to use methotrexate, azathioprine and more recently mycophenolate mofetil and other drugs in various forms of vasculitis. The studies of rituximab and other biological therapies in ANCA associated vasculitis (AAV) such as mepolizumab that targeted eosinophilic granulomatosis with polyangiitis were groundbreaking, as were later trials of biological therapy for other forms of vasculitis. These included abatacept and tocilizumab for giant cell arteritis (GCA). Such efforts led to the approval of rituximab by the Food and Drug Administration (FDA) for AAV; and tocilizumab for GCA, the latter as the first non-glucocorticoid agents ever approved by the FDA for treatment of any form of vasculitis.

Just as investigator networks have advanced the knowledge and therapeutics of vasculitis, support groups, partnerships and networks have emerged worldwide over the past three decades including, the Vasculitis Foundation in the United States, Vasculitis United Kingdom (UK), and the Arbeits-Kreis Vaskulitis in Germany. History favorably record their unique contributions in brining patients' voices to the forefront of vasculitis care and research, at the same time educating patients, families, physicians and allied healthcare providers about vasculitis.

New tests such as the ANCA (anti-neutrophil cytoplasmic autoantibodies) that came into routine use in the late 1980's and early 1990's, have been supplemented by other new tests developed in the last 30 years to more precisely image involved blood vessels and organs. These include highly sensitive magnetic resonance imaging (hsMRI); MRI and computed tomographic angiography (MRA and CTA), 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with CT (^{18}F-FDG PET/CT), and vascular ultrasonography techniques.

While many of the systemic vasculitides described as "idiopathic," have been discovered, some cases of PAN are also recognized to be a result of concomitant infections with hepatitis B and C virus (HBV and HCV). Likewise, a number of genes contribute to the risk for AAV and GCA and determine in part, how the diseases will affect patients [70].

CONCLUSION

The contributions of early workers in vasculitis had a profound impact in forming our modern concepts of vasculitis. They reflect careful clinical observation, the application of emerging technologies, and advances in therapy, which form the basis for our understanding of these disease entities. They are the product of an ongoing tradition of investigation, which is alive and well today. Our current knowledge of vasculitis is the result of a both long and recent history of applied clinical observation and basic science investigation. Better recognition of vasculitis in clinical practice, development of research networks and patient involvement in vasculitis care, improved imaging modalities, outcome measure development, and application of novel therapeutics based upon better understanding of disease pathogenesis have also led to better effective treatment of vasculitis.

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Chapter 2

OVERVIEW OF PRIMARY AND SECONDARY VASCULITIDES

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ABSTRACT

The systemic vasculitides are heterogeneous clinicopathologic disorders that share the common feature of vascular inflammation. The resulting disorder can vary depending upon involvement of specific organs, caliber of blood vessels, the underlying inflammatory process, and individual host factors. The cumulative result is diminished blood flow, vascular alterations and eventual occlusion with variable ischemia, necrosis and tissue damage. An international revised nomenclature system based on the current state of knowledge provides clinicians and investigators alike with the necessary nosology and findings relevant to classify each of the vasculitides. This chapter is an introduction and overview of the clinical presentation, differential diagnosis, laboratory evaluation, and treatment of systemic and nervous system vasculitides.

INTRODUCTION

The term vasculitides refers to heterogeneous disorders characterized by vascular inflammation affecting vessels of different sizes from large arteries to capillaries or tiny venules. This leads to diminished blood flow or vessel occlusion resulting in ischemia, necrosis and subsequent tissue damage. Blood vessels themselves can also be damaged in vasculitis resulting in permanent stenosis, aneurysmal change or rupture.

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CLASSIFICATION AND NOSOLOGY

The 2012 Revised Chapel Hill Consensus Conference (CHCC) [1] serves as a guide for the categorization of diverse forms of vasculitis based upon the vessels involved (Table 1).

Large vessel vasculitis (LVV) including giant cell arteritis (GCA) and Takayasu arteritis (TAK) affects the aorta, its major branches and analogous veins. Medium vessel vasculitis (MVV) inclusive of polyarteritis nodosa (PAN) and Kawasaki disease (KD) involves main visceral arteries and veins and initial branches. Small vessel vasculitic (SVV) involvement affects intraparenchymal arteries, arterioles, capillaries, veins and venules, with a disease mechanisms related to anti-neutrophil cytoplasmic antibody (ANCA) or immune complexes.

Table 1. Classification of Vasculitides

Large Vessel Vasculitis
Giant cell arteritis
Takayasu arteritis
Medium Vessel Vasculitis
Polyarteritis nodosa
Kawasaki disease
Small Vessel Vasculitis
ANCA-Associated Vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Immune-Complex Vasculitis
Cryoglobulinemia
IgA vasculitis (Henoch-Schönlein)
Hypocomplementemic urticarial vasculitis (anti-C1q)
Variable Vessel Vasculitis
Behçet disease
Cogan syndrome
Single Organ Vasculitis
Primary Angiitis of the CNS
Nonsystemic peripheral nerve vasculitis
Idiopathic aortitis (IgG4)
Vasculitis Associated with Systemic Collagen Vascular Disease
Systemic lupus erythematosus
Rheumatoid arthritis vasculitis
Vasculitis Associated with Infection
Acute bacterial meningitis
Tuberculous meningitis
Spirochete disease
Neurosyphilis
Lyme neuroborreliosis
Varicella zoster virus
HIV/AIDS

Adapted from [1].

The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA) (Wegener granulomatosis [WG type]), eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome [CSS]), and microscopic polyangiitis (MPA) (microscopic polyarteritis), while vasculitic disorders associated with immune complexes (IC) includes IgA vasculitis (IgAV) (Henoch-Schönlein purpura [HSP]), cryoglobulinemic vasculitis (CV), and Hypocomplementemic urticarial vasculitis (HUV) associated with C1q antibodies. Vasculitis without a predominant vessel size and caliber, respectively from small to large, involving arteries, veins and capillaries, comprises the category of variable vessel vasculitis (VVV), characteristic of Behçet disease (BD) and Cogan syndrome. Vascular inflammation confirmed to a single organ system such as vasculitis restricted to the central nervous system (CNS) and peripheral nervous system (PNS), and IgG4 related aortitis ((IgG4-related disease [RD]), are collectively referred to as single organ vasculitides (SOV).

There is a separate category for vasculitis associated with systemic disease notably for connective tissue disorders such as rheumatoid arthritis vasculitis (RAV) and systemic lupus erythematosus (SLE); and another for vasculitis associated with a probable specific etiology, such as substance abuse and infection designated by the specific vasculitic disorder with a prefix to denote the causative agent.

In 2008, the Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) reported methodology and overall clinical, laboratory and radiographic characteristics for several childhood systemic vasculitides [2] followed by a final validated classification [3] based upon vessel size, similar to the CHCC nomenclature [1].

Insight into effective therapies of systemic vasculitides have been guided by collaborative evidence-based randomized clinical trials (RCT) or observational cohorts by the French Vasculitis Study Group (FVSG) database, United States-Canadian Vasculitis Clinical Research Consortium (VCRC), European Vasculitis Study Society (EUVAS), the European League Against Rheumatism (EULAR), The French Vasculitis Cohort of Patients with Primary Vasculitis of the Central Nervous System (COVAC), Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), the Pediatric Vasculitis Initiative (PedVas), the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), and the web-based network BrainWorks.

Despite disparities in vessel involvement and end-organ damage, it is usually possible to reach a presumptive diagnosis of primary and secondary vasculitides in the majority of patients based upon the combination of presenting symptoms and signs, disease-specific serological studies, and visceral and neurovascular imaging studies, while awaiting the results of tissue histopathology.

This chapter is an overview of primary and secondary vasculitides in adults and children for clinicians treating such patients. Five major challenges encountered in clinical practice will be addressed and emphasized as follows.

First, clinical, pathological, and serological differentiation and diagnosis of the primary vasculitides including, LVV (GCA, TAK), MVV (PAN, KD), SVV (AAV [MPA, GPA, EGPA] and IC-mediated types [IgAV and anti-C1q]); and VVV (BD and Cogan syndrome), all of which share demonstrable histopathological evidence of systemic vasculitis.

Second, recognition of secondary vasculitides associated with an underlying primary systemic illness, in which some but not all patients will demonstrate evidence of vasculitis including, CV, RA vasculitis (RAV), and CNS vasculitis associated with SLE, syphilis, Lyme neuroborreliosis (LNB); bacterial meningitis, tuberculosis (TB), varicella zoster virus (VZV),

and human immunodeficiency virus type 1 (HIV) and acquired immune deficiency syndrome (AIDS).

Third, the identification of the SOV, PCNSA, NSPNV, and IgG4-RD.

Fourth, a recommended laboratory approach to the diagnosis of vasculitides.

Fifth and last, evidence-based treatment options for each of the vasculitides. Interested readers are recommended to another in-depth overview [4].

DIFFERENTIATION OF PRIMARY VASCULITIDES

Large Vessel Vasculitides

The concepts of GCA and TAK have evolved over a century, with considerable advances in the past decade that have translated into more improved diagnosis and management.

Giant Cell Arteritis

First named temporal arteritis for the site of granulomatous giant cell inflammation and vessel involvement [5], those with associated blindness due to vasculitic involvement of ophthalmic and posterior ciliary vessels were subsequently classified as cranial arteritis [6], and later generalized GCA [7] when giant cell lesions were discerned along the aorta, its branches, and in other medium- and large-sized arteries at postmortem examination. There are five discriminating features of GCA including, age >50 years at onset, new localized headache, temporal artery tenderness or decreased temporal artery pulse, ESR >50 mm/hour, and biopsy of an artery showing necrotizing arteritis and a predominance of mononuclear cells or granulomatous process with multinucleated giant cells (Figure 1), that collectively serve as useful guideposts in recognizing GCA.

Unrecognized and therefore untreated or inadequately treated, there is a high likelihood of large artery complication. Nuenninghoff and coworkers [8] reported patients with large-artery complications representing 27% of 168 patients in a GCA cohort at the Mayo Clinic between 1950 and 1999 that included aortic aneurysm or dissection in 18%, large artery stenosis in 13%, cervical artery stenosis in 9%; and subclavian, axillary or brachial artery stenosis in 4%.

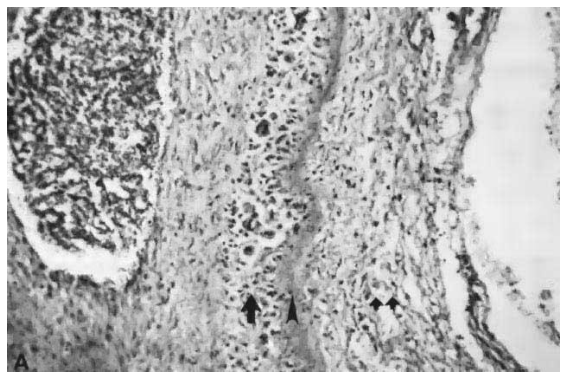
Temporal artery biopsy is the only sure way of establishing the diagnosis however false negative findings on the contemplated affected side may be due to inadvertent sampling of a vasculitic-free length of vessel. The pathological heterogeneity of GCA was further exemplified by the occasional finding of intracranial lesions in several patients who also qualified for the diagnosis of granulomatous angiitis of the nervous system (GANS) [9]; however PNS involvement in GCA remains exceedingly uncommon [10].

Takayasu Arteritis

Contemporaneously, another LVV was described in the Japanese literature as unusual changes of the central vessels of the retina in the absence of peripheral arterial pulses in women [11]. Patients with so called pulseless disease [12], occlusive thromboaortopathy [13] or TAK [14], manifested constitutional complaints of malaise, fever, stiffness of the shoulders, nausea, vomiting, night sweats, anorexia, weight loss, and irregularity of menstrual periods weeks to

months before the local signs of vasculitis were recognized in up to two-thirds of patients. TAK is the commonest large vessel vasculitis among Asian women.

The non-invasive assessment of LVV includes performance of color-Doppler sonography (CDS), contrast enhanced high-resolution magnetic resonance imaging (MRI) combined with MRA, and contrast-enhanced computed tomography (CT) combined with CTA to visualize the vessel wall and the lumen of large vessels. The signs of early inflammation that include vessel wall thickening and mural inflammation, as well as the late complications of stenosis and aneurysms, can be ascertained.



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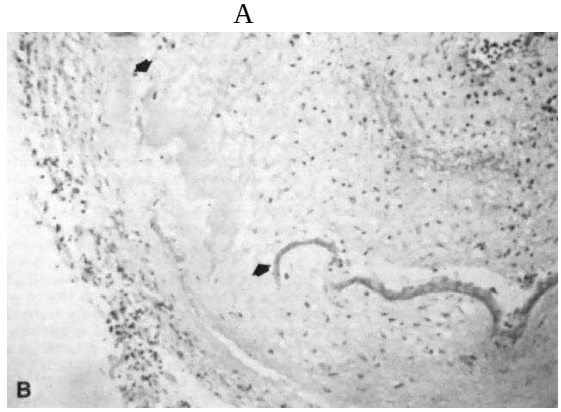

B

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Figure 1. Giant cell arteritis. A. An early lesion of a large muscular artery, necrosis, inflammation, and giant cell formation (single arrow) can be seen immediately adjacent to the internal elastic lamina (arrowhead), which is undergoing degenerative changes, and there is some intimal proliferation (double arrows) (stain, hematoxylin and eosin; original magnification, ×100). B. This more advanced lesion has complete segmental destruction of the internal elastic lamina and virtually the entire media (arrows). Marked intimal proliferation has nearly occluded the lumen, and few inflammatory cells remain (stain, hematoxylin and eosin; original magnification, ×50).

^{18}F- Fluorodeoxyglucose (FDG) positron emission tomography (PET) detects increased FDG uptake by metabolically active cells, including inflammatory cells infiltrating the vessel wall in vasculitis, while digital subtraction angiography (DSA) is a useful modality to demonstrate luminal changes. Moreover, such studies can assist the surgeon in centering on an involved segment of vessel. Performance of CDS is better suited to study superficial vessels

such as the internal and external carotid artery and its branches, while MR and CT are best suited for deep vessels. When performed together, they can be used to monitor disease extent and severity through the demonstration of early vascular changes in wall thickness and mural inflammation, to which PET can be added to ascertain active inflammation in vessels affected by GCA and TAK. Since the early reports of a salutary effect of corticosteroids on GCA in 1950 [15], corticosteroids have remained the standard of care because of their ability to reduce disease-related morbidity, mortality, and symptoms that negatively impact on quality of life. However they are not curative, do not prevent relapses, and are associated with significant toxicity. Disease-related morbidity in GCA which largely results from cranial ischemic events or LVV, leads to visual loss in up to 20% of patients.

The risk factors for GCA-related ischemic events include visual loss, prior ischemic events, marked intimal hyperplasia on temporal artery biopsy, elevated inflammatory markers, older age at diagnosis, hypertension, ischemic heart disease, and absence of systemic manifestations [16]. While there is no treatment to date that has been found to completely reverse blindness in GCA once it has occurred, there is strong evidence to suggest that once corticosteroids have been started the risk of visual loss is low [17]. For this reason, corticosteroids should be started while the diagnostic evaluation is in progress and continued for up to one year before tapering to the lowest maintenance levels.

Ohigashi and colleagues [18] ascertained an improved prognosis among 106 consecutive patients with TAK in those with onset before 1999 compared to those diagnosed after 2000 (4.2% versus 0%) that was attributed to reduction in the time from onset to diagnosis, replacement of digital subtraction angiography (79% versus 9%) with ultrasound (6% versus 34%), CTA (24% versus 77%), MRA (21% versus 57%), and ^{18}F-FDG PET (0% versus 20%); less frequent complications of moderate or severe aortic regurgitation, and not surprisingly, an increase in the use and maximal dose of corticosteroids (70% versus 97%); and the use of first and second-line immunosuppressant agents (7% versus 42%). Surgical treatment of TKA was similar between those with onset before 1999 and after 2000 (22.5% versus 22.8%).

Medium Vessel Vasculitides

Polyarteritis Nodosa and Kawasaki Disease

Kernohan and Woltman [19] summarized the clinicopathological aspects of adult PAN at postmortem examination, while Krahulik and colleagues [20] described fulminant childhood PAN (cPAN), three decades after the first description of the first American patient by Longcope in 1908 [21]. The dominant clinicopathological syndrome was peripheral neuritis that occurred in one-half of patients early in the illness with a predilection for the legs. The combination of acute and chronic lesions correlated with known exacerbations. Arteritic lesions along nutrient arteries of the peripheral nerves were characterized by invasion of the intima, media and adventitia by polymorphonuclear, plasma cells, eosinophils, and lymphocytes associated with swelling of the media, fibrinoid necrosis, and fragmentation of the internal elastic lamina (Figure 2). So impressed was Dr. Harry Lee Parker by the frequency of arteritic lesions in the PNS, that he conceptualized nerve and muscle biopsy as a useful mode for the diagnosis in life during a discussion of the paper by Kernohan and Woltman [19]. Variants of cPAN were contemporaneously recognized in infants and young children under the rubric of mucocutaneous lymph node syndrome, infantile PAN before arrival at the preferred term KD

[22-25] for the childhood syndrome affecting children of all ages and races, with worldwide occurrence.

A retrospective study of 348 adult patients registered in the French Vasculitis Study Group (FVSG) [26] who satisfied criteria for the diagnosis of PAN between 1963 and 2005 noted constitutional findings included fever, weight loss, myalgia, and arthralgia at presentation in 93% of patients. PNS involvement included peripheral neuropathy and mononeuritis multiplex in nearly equal proportion in 79%, and cutaneous involvement notably, purpura, skin nodules, and livedo reticularis were noted in 50% of patients; CNS involvement was noted in 5% of patients.

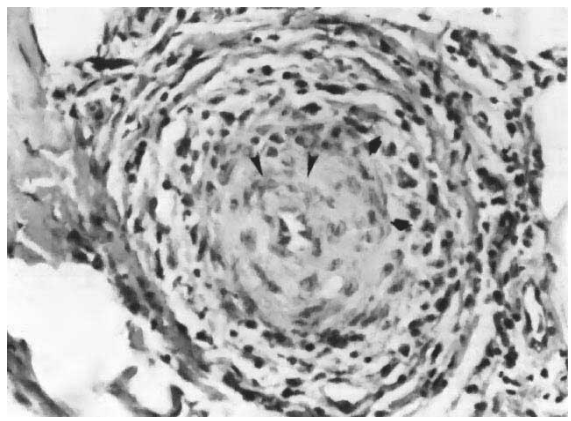

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Figure 2. This small muscular artery from muscle is from a patient with polyarteritis nodosa. In the third, or proliferative, phase illustrated here, chronic inflammatory cells replace the neutrophils of the second phase; there is evidence of necrosis of the media (arrows), early intimal proliferation (arrowheads), and fibrosis. The lumen is almost completely occluded. Ultimately, in the healing phase, this process is replaced by dense, organized connective tissue (stain, hematoxylin and eosin; original magnification, ×250).

The classification criteria for cPAN requires histological evidence of necrotizing vasculitis in medium-or small-sized arteries or angiographic abnormalities demonstrating aneurysm formation or vascular occlusions, as a mandatory criterion, plus two of five features among them myalgia, skin involvement, hypertension, neuropathy, or abnormal urinalysis or impaired renal function [6], with disease manifestations ranging from a benign cutaneous form with clinical, laboratory and molecular characteristics of Familial Mediterranean Fever [27, 28] to severe disseminated multisystem disease. Ozen and colleagues [29] studied 110 children of mean age 9 years, from twenty-one pediatric centers worldwide diagnosed with cPAN dividing them into four groups including systemic PAN (57%), cutaneous PAN (30%), and classic PAN with hepatitis B surface antigen (HBsAg) (4.6%). Children with serological and microbiologic evidence of preceding streptococcal infection have also been described [30]. The FVSG study [26] allowed for a comparison of diagnostic modalities in adult PAN.

Only 6 of 47 sera so tested manifested a positive ANCA finding by immunofluourescent testing (IFT) and enzyme linked immunosorbant assay (ELISA) techniques, rendering it helpful in support of PAN especially when negative to differentiate it from AAV and MPA. Cutaneous nerve biopsy performed in 129 patients, including 108 with peripheral neuropathy and 21

without peripheral neuropathy, showed typical vasculitic lesions respectively in 83% and 81%, compared to muscle biopsy that revealed vasculitis respectively in 68% and 60% of patients. Angiography showed renal and gastrointestinal microaneurysms or stenosis respectively in 66% and 57% of patients. Patients with HB virus (HBV)-related PAN had more frequent peripheral neuropathy, abdominal pain, cardiomyopathy, orchitis, and hypertension than those with non-HBV-related PAN, with respective five-year relapse-free survival rates of 59% and 67% in scheduled therapeutic regimens depending upon involvement in clinical trials, or according to the standard of care at the time of diagnosis, among them glucocorticoids and cyclophosphamide [31, 32]. The predictors of a poor prognosis were age >65 years, hypertension, and gastrointestinal involvement, and cutaneous manifestations or non-HBV-related PAN had higher rates of relapse.

Henegar and colleagues [33] identified three positive predictive parameters including HBV antigen and DNA in serum, arteriographic anomalies, and mononeuropathy or polyneuropathy; and five negative predictive parameters including detection of ANCA; asthma, ear, nose and throat signs; glomerulopathy; and cryoglobulinemia, that yielded a70.6% sensitivity for control vasculitides and 92.3% specificity for all controls.

Small Vessel Vasculitides

ANCA-Associated Vasculitis

Microscopic Polyangiitis

Wohlwill [34], Davson and colleagues [35] and Wainwright and Davson [36] recognized that fever, arthralgia, purpura, hemoptysis, pulmonary hemorrhage, abdominal pain, and gastrointestinal bleeding preceded the explosive phase of systemic necrotizing vasculitis in some patients with a disorder other than PAN that affected the kidney and lungs, with rapidly progressive glomerulonephritis and pulmonary capillaritis. Such patients with selective involvement of small microscopic arteries, arterioles, capillaries and venules including glomerular and pulmonary alveolar capillaries were deemed to have microscopic PAN. Among thirty-four such patients described by Savage and colleagues [37] the clinical symptoms and signs at presentation were constitutional (67%), arthralgia (65%), purpura (44%), hemoptysis in (32%), abdominal pain (32%), mouth ulcers (21%), sensory peripheral neuropathy (18%), and CNS (headache, seizures) (18%). Eighty-five additional patients studied by Guillevin and colleagues [38] with MPA so termed, had renal involvement (79%), weight loss (73%), skin involvement (purpura, livedo, nodules, urticarial) (62%), mononeuritis multiplex neuropathy (57%), fever (55%), arthralgia (50%), myalgia (48%), vascular manifestations [hypertension, cardiac failure, pericarditis] 50%, lung involvement (alveolar hemorrhage, pneumonitis, pleurisies) (24%), and CNS involvement (12%). Ahn and colleagues [39] noted pANCA or anti-MPO antibody positivity in 69% of Korean MPA patients, compared to 74.5% of positive ANCA in European patients, of whom 87% had a pANCA staining pattern. Antibodies to PR3 were present in 8% of patients compared to MPO in 61% of those as determined by ELISA. Childhood MPA (cMPA) appears to be very uncommon and the criteria for diagnosis require three of the following features to be present: abnormal urinalysis, granulomatous inflammation on tissue biopsy, nasal sinus inflammation; subglottic, tracheal, or endobronchial stenosis;

abnormal chest radiograph or chest CT scan, and PR3 ANCA or cANCA staining [3]. Those with cMPA accounted for four of the first 32 children in the United States/Canadian ARChiVe registry [40].

Eosinophilic Granulomatosis with Polyangiitis

Contemporaneous with the description of MPA, the first patient with EGPA was probably Case 1 of Lamb [41] reported in 1914 also under the heading of PAN. That patient, a 26-year-old man with two years of worsening asthma, developed fever, palpable purpura, nodular skin lesions, hemoptysis, vomiting, urinary difficulty and granular urinary casts. He died one month later and postmortem examination showed necrotizing arteritis of small arteries, with dense collections of extravascular eosinophils and tissue eosinophilia in the heart, stomach, and kidney. Decades later, Churg and Strauss [42] described the clinical and postmortem findings of thirteen patients with asthma, fever, and hypereosinophilia, accompanied by eosinophilic exudation, fibrinoid change, and granulomatous proliferation or the so called allergic granuloma. The latter was found within vessels walls and in extravascular connective tissue of major organ systems, leading to cardiac, pulmonary, gastrointestinal, skin, PNS and CNS manifestations. In 1990, the American College of Rheumatology (ACR) [43] developed criteria for the classification of EGPA that included ascertainment of four or more of the following: asthma, eosinophilia of >10%, mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates on chest radiograph, paranasal sinus abnormality, and extravascular eosinophils on tissue biopsy that included an artery, arteriole or venule. These criteria were inadequate since a patient with asthma and paranasal sinusitis could also fit the designation of EGPA. The 1994 CHCC [1] characterized EGPA as an eosinophil-rich and granulomatous inflammatory process that involved the respiratory tract, with necrotizing vasculitis that affected small to medium-sized vessels such as capillaries, venules, arterioles and arteries, with associated asthma and eosinophilia. Among 383 patients enrolled in the FVSG Cohort [44] who satisfied the ACR criteria [43] or in 1994 CHCC definition for EGPA [45], the mean age at presentation was 50 years without sex predominance. Clinical manifestations at presentation included asthma (91%), peripheral neuropathy (51%), weight loss (49%), ear, nose and throat signs (48%), non-erosive sinusitis and polyposis (41%), skin lesions (39%), purpuric rash (22%), lung infiltrates (38%), gastrointestinal involvement (23%), renal manifestations (22%), cardiomyopathy (16%), CNS (5%), and cranial nerve involvement (3%). A total of 108 (31%) patients tested positive for ANCA with significantly more frequent ear, nose and throat, peripheral nerve and renal involvement, but less frequent cardiac manifestations. Small numbers of children have been included in large studies of EGPA sufficient to allow comparisons to adults. Among 133 vasculitic patients in the ARChiVe registry, only two were reported to be of the EGPA type [46].

Granulomatosis with Polyangiitis

Godman and Churg [47] described the syndrome of GPA that included granuloma in the nasopharynx, sinuses and lower respiratory tract with focal segmental glomerulonephritis and disseminated small vessel vasculitis. In a landmark article, Godman and Churg [47] concluded that MPA, EGRA and GPA were related to one another yet distinct from PAN. This astute conclusion was based mainly on pathological features was later substantiated by their common association with ANCA, but not so for PAN [48]. Fauci and colleagues [49] and Hoffman and colleagues [50] at the National Institutes of Health (NIH), respectively reported a prospective

series of eighty-five patients with GPA, and a retrospective assessment of 180 patients followed for 6 months to 24 years. The presenting signs included pulmonary infiltrates (71%), sinusitis (67%), arthritis and arthralgia (44%), fever (34%), cough (34%), otitis (25%), and hemoptysis (22%), with an overall predominance of organ system involvement in the lung (94%), paranasal sinuses (91%), kidney (85%), joints (67%), and nasopharynx and nose (64%). Fauci and colleagues [49] established the efficacy of cyclophosphamide and prednisone in achieving complete remissions in 93% of patients, as well as, the tendency of patients to relapse and accrue additive mortality from both disease and treatment. The characteristic histopathology is a necrotizing granulomatous vasculitis which may be found in lung and renal biopsy tissue although the latter is less common. Instead, a focal, segmental glomerulonephritis is often seen. Other inflammatory or vasculitic phenomenon can be encountered such as leukocytoclastic vasculitis in skin lesions, and acute and chronic inflammation in sinus, retro-orbital, and tracheal tissues. A limited form of GPA without glomerulonephritis was described [51] that was a long-term disease stage or phenotype accounting for about 5% of all patients characterized by destructive and space-consuming lesions associated with relapse rates of 46% and local damage [52].

The 1990 ACR criteria for the classification of GPA [53] which preceded routine ANCA testing, included the presence of two or more from criteria from among four including nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge); abnormal chest radiograph (showing nodules, fixed infiltrates or cavities); urinary sediment (showing microhematuria >5 red blood cells per high power field, or red cell casts in urinary sediment); and granulomatous inflammation on biopsy tissue (within the wall of an artery or in the perivascular or extravascular area of an artery or arteriole).

A proposed classification tree substituted hemoptysis for granulomatous inflammation on a tissue biopsy if the latter was not available. Baseline serum samples for 180 participants in the WG Etanercept Trial Research Group (WGET) found that when IF, direct and capture ELISA ANCA testing were performed at baseline, 166 (92%) were seropositive, including 96% with severe disease and 83% with limited disease.

Holle and colleagues [54] who prospectively compared a highly sensitivity (hs)PR3-ANCA ELISA to the IFT noting an excellent performance of the hsPR3-ANCA ELISA in identifying GPA and other AAV disorders associated with PR3-ANCA suggesting that the former by used as screening test. Since the early observations of ANCA provided by van der Woude and colleagues in 1985 [55], and Falk and Jennette [56] and Goldschmeding and colleagues [57], and ensuing progress in the differentiation and understanding of ANCA subtypes [58], the past quarter century has witnessed a renaissance in the understanding of primary systemic vasculitis with convincing clinical evidence to support an important role for ANCA in the development of AAV. An AAV classification appears to better recognize ANCA disease and predict prognosis than other any existing clinical classification systems [59].

However as with other autoimmune disorders, the etiology and pathogenesis appears to be multifactorial, involving the interplay of initiating and predisposing environment and genetic factors [60-62]. Induction with corticosteroids and either cyclophosphamide followed by maintenance with rituximab [63-68] or azathioprine [69-71] is recommended treatment. Among 197 ANCA-positive patients with GPA or MPA in nine centers participating in the Rituximab in ANCA-Associated Vasculitis-Immune Tolerance Network (RAVE-ITN), a randomized, double-blind, double-dummy, non-inferiority trial [72] comparing rituximab 375 mg per square meter (m^2) body-surface area (BSA) per week for 4 weeks to cyclophosphamide

2 mg per kilogram of body weight per day controls for severe AAV, 67% of study patients compared to 42% of controls achieved the primary end point of remission of disease without use of prednisone at six months.

Treatment and efficacy and safety data in children with AAV continue to be largely derived from adult GPA studies, however as described in ARChiVe, pediatric patients in the United States and Canada are being offered pulse methylprednisolone for 3 to 5 days, followed by oral prednisone, and cyclophosphamide orally or with one of two intravenous regimens, followed by maintenance therapy, most frequently with methotrexate [40].

Early outcome results last year for the treatment of childhood AAV, in particular GPA, reported by Morishita and colleagues on behalf of ARCHiVe Investigators Network and the Pediatric Vasculitis (PedVas) Initiative [73] was somewhat unencouraging. Among 105 children with AAV, mainly GPA, who received corticostereoids, cyclophosphamide, methotrexate, or rituximab for remission-induction, and plasma exchange in conjunction with cyclophosphamide and/or rituximab, 42% achieved remission at 12 months (Pediatric Vasculitis Activity Score [PVAS] of 0, CS dose < 0.2 mg/kg/day), 21 (48%) of whom discontinued CS by 12 months; all but 3 remaining on maintenance treatment at 12 months receiving azathioprine, methotrexate, rituximab, mycophenolate mofetil, and cyclophosphamide. However, up to 63% had a (Pediatric Vasculitis Damage Index [PVDI) score of 1 or more by 12 months, with the presence of renal, ear, nose and throat, or pulmonary damage; moreover, 41% of children reported hospitalizations. Thus, a significant proportion of patients were not in remission at 12 months, and more than one-half of the patient cohort experienced damage early in the disease course. The 12-month remission rate of 42% in the cohort was significantly lower than Sacri and colleagues [74] who reported 73% remission at post-induction and 90% overall remission rate (including secondary remissions after a median time of 6.7 months).

Immune Complex Vasculitis

The foundations for IC-mediated or hypersensitivity vasculitis were conceptualized in the mid-twentieth century, as an immunologic response to antigenic material associated with clinically evident purpura, and small vessel inflammation affecting arterioles, capillaries, and post-capillary venules. It was likened by Zeek [75] to the anaphylactoid Arthus reaction produced by the experimental injection of horse serum into rabbits [76].

IgA Vasculitis (Henoch-Schönlein Purpura)

Children with HSP were described by Gairdner [77] with anaphylactoid purpura including one who developed rash, colic, melanotic stools, intussusception, and hematuria following by a typical exanthema and fatal convulsion. Postmortem examination showed scattered cortical hemorrhages associated with cerebral necrotizing arteriolitis. Levitt and Burbank [78] described the clinicopathological findings in two previously non-allergic patients with recurrent fatal attacks of HSP after injection of penicillin and ingestion of strawberries respectively that included glomerulonephritis alone or with systemic arteriolitis. The findings of IgA deposits in cutaneous blood vessel walls and in glomerular mesangial biopsies of patients with HSP and IgA nephropathy (IgAN) [79, 80] were circumstantially convincing enough to substitute the term IgAV for HSP. IgAV/HSP is the commonest vasculitis in children. The 1990 ACR criteria [81] for the identification of HSP included age less than or equal to 20 years at disease onset,

palpable purpura, acute abdominal pain, and tissue biopsy showing granulocytes in the walls of small arteries or venules. The presence of any two or more of these criteria distinguished 85 patients who were diagnosed as having HSP by physicians who submitted cases for the vasculitis criteria compared to 722 patients diagnosed with other forms of vasculitis, arriving at sensitivity of 87.1% and specificity of 87.7%. The addition of gastrointestinal bleeding in a classification tree format respectively increased sensitivity to 89.4% and specificity to 88.1%. The EULAR/PRINTO/PReS classification criteria [3] which recognizes the contribution of IgA deposits, differs in the mandatory finding of purpura with predominance in the legs, and the presence of one of the four following features: diffuse abdominal pain, arthralgia or arthritis; a biopsy showing predominant IgA deposits, and renal involvement including proteinuria and hematuria Derived from the analysis of 827 patients in the database, the calculated sensitivity, specificity for the clinical and laboratory findings in between the consensus panel and specific definition were respectively 100% and 87%. Peru and colleagues [82] studied 254 children with IgAV/HSP between 2003 and 2006 with a distribution of skin, joint, GI and renal manifestations respectively of 100%, 66%, 56% and 30%. The disorder commences with fever and palpable purpura, although early lesions can be urticarial. Arthralgia and abdominal pain precede, accompany or follow the rash. Melena is common as are signs of peritonitis. Proteinuria and hematuria are of variably severity and renal pathology may be of a mild glomerulitis to necrotizing or proliferative glomerulonephritis. Ozen and coworkers [3] noted palpable purpura, commonly in crops with lower limb predominance in 89% of patients, arthritis or arthralgia in 78%, diffuse abdominal pain in 60%, proteinuria and hematuria combined in 33%; and IgA deposition in 10% of children. The treatment of IgAV/HSP remains empiric and largely supportive, with conflicting conclusions in retrospective and uncontrolled case series of immune suppression in severe HSP nephritis [46]. Extrarenal manifestations can be managed by symptomatic treatment.

A meta-analysis of 15 studies based on a comprehensive review of the literature in the Medline database from 1956 to 2007, and Cochrane Controlled Trials Registry among 15 studies and over 1300 patients [46] found that early treatment conferred a protective effect on developing persistent renal disease (odds ratio [OR] .43) and the likelihood of surgical intervention for abdominal pain (OR .75), as well as a statistically significant positive effect on shortening the duration of abdominal symptoms (OR 5.42).

C1q (Hypocomplementemic Urticarial) Vasculitis

McDuffe and colleagues [83] later described several patients with recurrent attacks of erythematous, urticarial, and hemorrhagic skin lesions that lasted 24 hours at a time, associated with recurrent attacks of fever, joint swelling, abdominal distress, and depressed serum complement. When tested by immunodiffusion against purified preparations RF and human C1q, several patients reacted strongly with purified C1q. Skin biopsies showed leukocytoclasia, characteristic of necrotizing vasculitis, anaphylactoid purpura, or mild nonspecific perivascular infiltration. Immunofluorescence of skin specimens showed fixation of Ig in the patient with necrotizing vasculitis. Renal biopsy showed mild to moderate glomerulonephritis indistinguishable for those seen in other forms of chronic membranoproliferative glomerulonephritis. The differences from SLE included more urticarial and purpuric skin lesions, with relatively mild renal or absent and other visceral involvement in the patients with HUV. An etiopathogenesis related to chronic vascular inflammation resulting from deposits of immune complexes in small vessel walls seemed likely. Zeiss and colleagues [84] characterized

C1q IgG precipitins from HUV sera that precipitated C1q in agarose gel among four additional patients. Wisnieski and Naff [85] later showed C1q binding activity in IgG from HUV sera. Buck and colleagues [86] defined the HUV syndrome as the presence of UV with multi-organ involvement notably arthralgia or arthritis, angioedema, pulmonary, ocular, renal, and pericardial. However, anti-C1q antibodies are elevated and the serum low C1q levels are reduced in virtually all children so studied. Antihistamines are the drug of choice with cutaneous lesions to control itching, but they may be insufficient in controlling the formation of immune complexes when given late in the inflammatory cascade. There is yet a consensus on the most effective therapeutic regimen; however plasmapheresis and intravenous immune globulin (IVIg) are alternative immunosuppressant modalities.

Variable Vessel Vasculitis

Behçet Disease

Behçet [87] described the clinicopathological findings of a 28-year-old Turkish patient with relapsing oral, genital and oral eruptions over 4 years, accompanied by severe headache, memory loss, dizziness, lethargy, fatal seizures and coma. Postmortem examination showed perivascular inflammatory cell infiltration of the meninges, brain, and central retinal artery and optic nerve with necrotic cerebral lesions. The first well-documented American patient with nervous system involvement of BD was described by Wolf and coworkers [88], namely a 22-year-old woman with a five year history of recurrent oral and genital ulceration, and a two year course of progressive visual loss, headache, hemiparesis, ataxia, tremor, dysarthria, cranial nerve palsy, cerebellar and corticospinal tract disease, and mental deterioration, which responded to prednisone therapy. The most widely used diagnostic criteria of BD were formulated by the International Study Group (ISG) [89] that included recurrent oral ulcerations plus any two of genital ulceration, typical defined eye lesions, typical skin lesions, or a positive pathergy. Recurrent oral ulcerations were categorized as minor aphthous, major aphthous, and herpetiform ulcerations that recurred at least three times in a 12-month period. Recurrent genital ulcerations were defined as aphthous ulceration and scarring. Eye lesions were defined as anterior uveitis, posterior uveitis or cells in the vitreous on slit lamp examination; and retinal vasculitis. Compatible skin lesions included erythema nodosum, pseudofolliculitis, papulopustular lesions, and aceneiform nodules in post-adolescent patients not receiving corticosteroids. A positive pathergy test of cutaneous hypersensitivity was defined as positive when a sterile pustule developed after twenty four to forty-eight hours at the site of a needle prick to the skin [90]. Although the usual onset of BD is in the third or fourth decade of life, pediatric-onset patients have been described [91]. The neuropathological findings in BD in brain biopsies and postmortem examination have been remarkably consistent among patients over the past several decades evidencing perivascular cuffing of small meningovascular and parenchymal arteries and veins, rarely medium-sized arteries displaying fibrinoid degeneration and recanalization, and examples of venous thrombosis. Cortical venous sinus thrombosis (CVST) [92] in BD presents with subacute or chronic onset of symptoms of isolated intracranial hypertension accompanied by headache, blurred vision, and diplopia [93], and underlying necrotizing vasculitis. Venous infarcts occur in up to 63% of those with CVST of other causes, but in only 6% of patients with BD. The inflammatory cell infiltrates are generally comprised of lymphocytes, both T-, and B-cells, macrophages, rarely plasma cells and eosinophils, with

reactive astrocytosis and microscopic gliosis in neighboring cerebral, cerebellar and brainstem white matter. Matsumoto and colleagues [94] noted large vessel lesions in seven of eight patients age 31 to 56 years with BD, including saccular aneurysms of the sinus of Valsalva or aortic arch, thoracic and abdominal aorta, pulmonary, femoral, and iliac arteries, and thrombotic occlusions in the pulmonary vein and superior and inferior vena. Aortitis was noted histologically in six of the eight patients that was active in one, scarred in six, and intermixed in another. Active aortitis was characterized by intense infiltration of inflammatory cells in the media and adventitia more frequently than in the interim with occasional giant cell formation. Although anticoagulation would not be recommended for BD-related CVST, it might be considered in association with arterial occlusions, with both venous and arterial occlusive episodes warranting prompt consideration of corticosteroids alone or in association with another immunosuppressant agent.

Cogan Syndrome

The first patient with Cogan syndrome of non-syphilitic interstitial keratitis (IK) was reported by Mogan and Baumgartner [95], that of a 26-year-old man with recurrent pain, spasm and redness of the left eye with photophobia, excessive tearing, and marked conjunctival injection, followed by severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, and deafness. A diagnosis of recurrent interstitial keratitis and explosive Menière disease was made. Vestibuloauditory symptoms were later described by Cogan [96]. Haynes and colleagues [97] set forth diagnostic criteria for typical Cogan syndrome according to the definitions established in a review of 30 patients seen at the National Eye Institute of the NIH by Cogan [96, 98, 99]. Symptoms of IK developed abruptly and gradually resolved, associated with photophobia, lacrimation, and eye pain which was unilateral or bilateral. Such symptoms tended to recur periodically for years before becoming quiescent. Vestibuloauditory dysfunction was manifested by sudden onset of Menière-like attacks of nausea, vomiting, tinnitus, vertigo, and frequently progressive hearing loss that characteristically occurred before or after the onset of IK. However within one to six months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of one to three months, certainly no longer than two years. With less than 100 reported patients with this rare childhood and young adult disorder, the majority of reported patients with typical Cogan syndrome have appeared as single case reports or patient series, often without pathological confirmation or evidence of systemic vasculitis in a biopsy or at postmortem examination. Early recognition of the diagnosis of childhood Cogan syndrome is important in instituting corticosteroid therapy to preserve hearing especially when hearing loss is a later occurrence. A combination of oral and intravenous corticosteroids may be considered in children who partly but not fully improve. Most patients with Cogan syndrome (58%) treated with corticosteroids derived a favorable response in both vestibuloauditory and ophthalmologic manifestations, with the remainder demonstrating only ophthalmologic (23%) or vestibuloauditory improvement (19%) alone [100]. Other therapies include methotrexate (23%), cyclophosphamide (10%), azathioprine (5%), entanercept (3%), hydroxchloroquine (2%), and IVIg (2%). Surgical cochlear implantation can led to objective and subjective benefits with improved hearing.

RECOGNITION OF SECONDARY VASCULITIDES

Cryoglobulinemic Vasculitis

The presence in the serum of one or more immunoglobulins (Ig) that precipitate below core body temperatures and redissolve on rewarming is termed cryoglobulinemia [100, 101]. Wintrobue and Buell [102] described the first patient with cryoglobulinemia, that of a 56-year-old woman who presented with progressive frontal headache, left face and eye pain; and right shoulder, neck and lumbar discomfort after a bout of shingles. This was followed by Raynaud symptoms, recurrent nosebleeds, exertional dyspnea and palpitation, and changes in the eye ground attributed to central vein thrombosis. Postmortem examination showed infiltrating myeloma of the humerus and lumbar vertebra, and splenic enlargement. A unique plasma protein was detected that spontaneously precipitated with cold temperature and solubilized at high temperature that differed from Bence-Jones proteinuria of other myeloma patients. Brouet and coworkers [103] provided modern classifications of cryoglobulinemia among 86 patients that included type 1, composed of a single monoclonal Ig; and types II and III as mixed cryoglobulinemia (MC), composed of different Ig, with a monoclonal component in type II, and polyclonal Ig in type III. In the absence of well-defined disease the presence of MC was termed "essential". Since recognition of hepatitis C virus (HCV) infection in patients with MC [104, 105], and the recognition of the high rate of false-negative serological tests in type II MC [106], it became evident that HCV was associated in most patients with MC. Cryoglobulinemic vasculitis is characterized by the classical triad of purpura, weakness and arthralgia, frequent multiple organ involvement, and infrequent late lymphatic and hepatic malignancies. The commonest clinical manifestations of HCV- negative MC vasculitis in the CryoVas survey [107] included purpura (75%), peripheral neuropathy (52%), arthralgia or arthritis (44%), glomerulonephritis (36%), cutaneous ulcers (16%), and cutaneous necrosis (14%). A connective tissue disease was diagnosed in 30% of patients, and B-cell non-Hodgkin lymphoma (B-NHL) was noted in 22% of patients, whereas MCV was considered essential in 48% of patients. There was a greater frequency of joint involvement (53% versus 40%), peripheral neuropathy (74% versus 52%), CNS involvement (9% versus 2%) in those with HCV-MC compared to those with HCV-negative MC [108], with an equal frequency of purpura (71% versus 75%) and renal involvement (34% versus 35%). Cacoub and colleagues [109] noted five high prevalent extrahepatic manifestations in chronic HCV infection including, arthralgia (23%), paresthesia (17%), myalgia (15%), pruritus (15%), and sicca syndrome (11%), and a 40% prevalence of cryoglobulins. These findings suggest the possibility of an independent role of HCV infection in the clinicopathological manifestations of MC and MCV. Among 114 patients including 18 children and 96 adults with cryoglobulinemia between 2000 and 2012, children had more frequent prolonged fever (17% versus 3%), petechiae and purpura (27% versus 15%), arthralgia and arthritis (66% versus 16%), and cutaneous involvement (77% versus 50%, than adults [110]. Aggressive optimal therapy of HCV-related CV with PEGylated (PEG)-INF alpha to improve the pharmacologic properties, and ribavirin with a protease inhibitor in the instance of HCV genotype 1 infection, should be considered as induction therapy for CV and administered for forty-eight weeks for all HCV genotypes [108]. An induction phase of immunosuppression such as rituximab plus antivirals is recommended in patients with more severe HCV-related CV exemplified by worsening renal function, mononeuritis multiplex, extensive skin disease including ulcers and distal necrosis [111].

Terrier and colleagues [107] showed a greater therapeutic efficacy of rituximab and corticosteroids compared with corticosteroids alone and alkylating agents with corticosteroids in achieving complete clinical, renal, and immunologic responses and a prednisone dosage of < 10 mg per day at six months. However, this regimen was associated with severe infections, particularly when high doses of corticosteroids were employed.

Plasmapheresis combined with immunosuppression can be useful in fulminant HCV-related CV to engender an immediate effect but should be continued to avoid post-pheresis rebound worsening. Rituximab, fludarabine, and cyclophosphamide treatment is effective treatment for refractory CryoVas associated with lymphoma. One-year, 2-year, 5-year, 10-year survival rates of 91%, 89%, 79% and 65% respectively, have been reported in patients with CV [108] with fatalities related to serious infection and disease flares of CV.

Systemic Lupus Erythematosus

Although distinctly uncommon, two collagen-vascular disorders, SLE and RA can be associated with vasculitis of the nervous system. The early concepts of the collagen-vascular disorders introduced by Klemperer [112, 113] stemmed from the appreciation of fibrinoid necrosis using collagen staining in patients with SLE. As collagen swells and fragments, it dissolves to form a homogeneous hyaline and granular periodic acid-Schiff (PAS)-positive material. The latter fibrinoid material contains immunoglobulins, antigen–antibody complexes, complement, and fibrinogen. The organ-specific responses to this fibrinoid material, especially of the CNS, leads to recognizable clinical sequela due to vascular and parenchymal damage.

The ACR delineated criteria for the diagnosis of SLE [114]. The recognition of neuropsychiatric lupus (NPSLE) was noted in 6.4% of a cohort of 1,253 SLE patients defined by the ACR [115]. According to Tomic-Lucic and colleagues [116] those with late-onset SLE due to development of disease after age 50 year, had a frequency of NPSLE of 6.6% compared to 36.6% in early-onset disease despite less major organ involvement and more benign course. Once thought to be an important cause of CNS or cerebral lupus, true vasculitis was present in only 12% of postmortem examinations in the series of Johnson and colleagues [117], and in 26.7% of late-onset SLE patients compared to 16.6% of those with early-onset SLE. A comparison of the cumulative incidence of clinical manifestations in the two latter groups showed that seizures were more common in early-onset patients compared to later-onset patients (6.6% versus 0%), similarly for multiple cerebrovascular attacks (23.3% versus 3.3%), cranial and peripheral neuropathy (6.6% versus 3.3%). Nonetheless, there was no mention of CNS vasculitis among 150 patients with SLE described by Estes and Christian [118], despite the finding of neurological complications in 30% of patients that included focal deficits, seizures, dementia, stupor, and coma. Devinsky and colleagues [119] noted a prevalence of 3.5% of psychiatric involvement that included organic affective, delusional and hallucinatory syndromes in a cohort of 50 patients with SLE, one-half of whom had CNS lesions. Feinglass and colleagues [120] noted neuropsychiatric manifestations at onset of SLE among 3% of 140 patients compared to 37% in the course of the illness; however headache was not specifically tabulated. Cerebral dysfunction in SLE can be caused by large vessel or small vessel involvement or both. In the series by Fienglass and colleagues [120] vasculitis was noted overall in 28% of patients, as well as in 46% of those with neuropsychiatric involvement compared to 17% of patient lacking neuropsychiatric involvement. Postmortem examination of

the CNS in ten of nineteen fatalities showed two cases of multiple large and small infarcts, which in one of them, demonstrated inflammatory cells infiltrates in the walls of medium-sized vessels, and perivascular infiltrates around small arterioles. Although active CNS vasculitis was absent in the brain and spinal tissue of all fifty patients reported by Devinsky and colleagues [119], two had evidence of inactive healed CNS vasculitis so suggested by focal disruption of the elastic lamina and mild intimal proliferation of a single medium-sized artery, one of which had active systemic vasculitis of the PAN type, both of whom evidenced Libman-Sacks endocarditis and embolic brain infarcts. Focal angiitis of the CNS with cyst-like formation around affected blood vessels was noted at postmortem in the patient described by Mintz and Fraga [121] with typical SLE rash, cutaneous vasculitis, and active neuropsychiatric involvement. Trevor and colleagues [122] summarized the literature of large named cerebral vessel occlusions from 1958 to 1965 noting one patient with a middle cerebral artery (MCA) stenosis progressing to occlusion and three others with angiographic internal carotid artery (ICA) occlusions, adding three new patients and suggesting a relation of the occurrence to cerebral arteritis. Two women, one age 21 and the other age 42 years, presented with headache followed by focal neurological symptoms attributed respectively to lesions along the left MCA followed by right ICA occlusions, and a right MCA stenosis progressing to occlusion in four months. A third patient had a left ICA occlusion without mention of headache. Among the four literature patients, one had angiographic occlusion of the MCA, and three others had occlusion of the ICA.

Johnson and colleagues [117] attributed the vasculitic nature of this process histopathologically to cerebral vasculitis mediated by acute inflammation and necrosis. Younger and colleagues [123] reported large named cerebral vessel occlusion attributed to circulating anticardiolipin antibodies in a young man in whom a vasculitic mechanism was not evoked. A number of fluorescent antibody tests provide serological support of SLE. The antinuclear antibody (ANA) screen produces a homogenous pattern in the majority of patients, with antibodies to native double-stranded DNA (anti-dsDNA) and reactivity to the smith (Sm) and ribonucleoprotein (RNP) antigens, the combination of which constitutes the extractable nuclear antigen (ENA). Circulating IgG and IgM antibodies with an affinity for charged phospholipids, antiphospholipid antibodies (APA), some of which have procoagulant activity such as the lupus anticoagulant (LAC) and the generic anticardiolipin (aCL) antibody assay using cardiolipin as the antigen probe for APA are all important determinants of prothrombotic events, especially in the CNS wherein there is a propensity for occlusive microangiopathy. Circulating SLE-related antibodies can impact the CNS by affecting both vascular mechanisms and brain tissue directly. Immune complex mediated vasculitis probably affecting small vessels is thought to account for much of the damage in CNS lupus in light of spite of the paucity of cerebral vasculitis evident in the form of inflammatory infiltrates in vessel walls at postmortem examination. In those with discrete vascular infarcts, there is a known association with the presence of circulating pathogenic antibodies which predisposes some individuals to a high risk of stroke due to both small and large vessel occlusion [123, 124]. Lupus cerebritis and meningoencephalitis are two neurological disturbances that can be associated with preceding headache. So noted in up to 75% of patients with SLE depending upon criteria [125], an etiopathogenesis related to antibody-mediated neuronal dysfunction is likely given the lack of correlation of symptoms of NPSLE and CNS lesions at postmortem examination, together with the transient nature of the disturbance. Patients with SLE are also predisposed to infectious episodes including those yet treated due to impaired B-cell function and humoral immunity, in

addition to others receiving immunosuppressant medication rendered impaired in T-cell function and cell mediated immunity [125]. The treatment of CNS Lupus should be guided by the tempo of the presenting neurological features, duration of disease activity, results of serological studies, comorbid disorders, and the presence of true vasculitis, with most patients receiving corticosteroids and those with true vasculitis of the brain considered for concomitant immunosuppressant therapy. Despite less major organ involvement and decreased incidence of neurological complications overall, late-onset SLE has a poor prognosis because of the higher frequency of comorbid conditions, longer exposure to classical vascular risk factors, both the less likelihood of treatment with higher doses of corticosteroids and the concomitantly higher rate of complications to cyclophosphamide when administered [116].

Rheumatoid Arthritis Vasculitis

A joint working group from the ACR and the European League Against Rheumatism (EULAR) published the 2010 classification criteria for RA [126]. Extra-articular RA (ExRA) occurrence is associated with increased comorbidity and mortality [127]. Criteria for severe ExRA were proposed in 2004 [128]. Active RA with high disease activity is associated with increased risk of severe ExRA manifestations. Major cutaneous vasculitis and vasculitis involving other organs are two such ExRA occurrences.

The diagnosis of RAV has generally been ascertained according to the criteria of Scott and Bacon [129] according to the presence of one or more of the following: 1) mononeuritis multiplex; 2) peripheral gangrene; 3) biopsy evidence of acute necrotizing arteritis plus fever and weight loss; and 4) deep cutaneous ulcers or active ExRA disease if associated with typical digital infarcts or biopsy evidence of vasculitis. Watts and colleagues [130] reported an annual incidence of RAV of 11.6 per million inhabitants between 1988 and 1992 in the Norfolk area of the United Kingdom, and a rate of 3.6 per million between 1998 and 2002. Myasoedova and coworkers [131] reported a ten-year cumulative incidence of 50% of any ExRA, including cutaneous and other organ-specific RAV in a retrospective population-based cohort study of 463 RA patients in Olmsted County, Minnesota from 1995 to 2007. The ten-year cumulative incidence of RAV, but not other ExRA, was significantly lower in the 1995-2007 cohort (0.6%) compared to the 1985 to 1994 cohort (3.6%). The markers of RA severity including RA positivity, erosion and joint destructive changes (21% among those in the 1985 to 1994 cohort, compared to 29% in 1995 to 2007), use of methotrexate, other disease-modifying anti-rheumatic drugs, and systemic corticosteroids were significantly associated with ExRA development between 1995 and 2007. Vollerstein and colleagues [132] studied 52 patients with RAV at the Mayo Clinic from 1974 to 1981, who developed clinical vasculitis evidenced by classic ischemic skin lesions, mononeuritis multiplex, or a positive tissue biopsy in comparison to population controls. The initial manifestation of vasculitis was seen in skin (26 patients), nerve (20 patients) or both (3 patients), and mononeuritis multiplex presented in one (2 patients), two (9 patients), three (5 patients) or four nerves (4 patients). More than 90% of tissue biopsy specimens revealed vascular necrosis and inflammation. At diagnosis, 80% of patients began therapy with aspirin and other non-steroidal anti-inflammatory drugs however three-fourths continued or began corticosteroid therapy. Sixteen of the original 52 patients eventually received cytotoxic immunosuppressive therapy. Compared to the general population, those with RAV had decreased survival that was immediately evident and continued for six years.

Compared with a previously reported incidence cohort [133] and adjusted for referral bias, survival of RAV was not different from classic RA. The factors that predicted decreased survival in RAV in a univariate proportional-HR model included older age, failure to receive previous non-steroidal anti-inflammatory drugs, previous administration of cytotoxic immunosuppressive agents, a higher dose of corticosteroids at diagnosis, decision to continue or initiate corticosteroids, and abnormal urinary sediment. Ouyang and coworkers [134] estimated CNS involvement in RA to be extremely uncommon, and other authors [135, 136] found CNS vasculitis to be decidedly rare. Puéchal and colleagues [137] found vasculitic involvement of vasa nervorum of both small- and medium-sized arteries indistinguishable from PAN in 64% of patients, with a mortality ranging from 28 to 44% according to the length of follow-up. Epineurial and perineurial vasculitis was observed with the same frequency among those with primary sensory neuropathy as others with predominant motor involvement, respectively 67% versus 64%. A greater extent of the neuropathy and motor involvement tended to predict decreased survival, however mononeuritis multiplex was not associated with a poor five-year survival rate (57%) than was distal symmetrical sensory or sensorimotor neuropathy (55%). Scott and Bacon [129] reported that five patients (24%) died in the group receiving methylprednisolone and cyclophosphamide, postmortem examination in four of whom failed to demonstrate active vasculitis.

By comparison, seven patients (29%) died receiving other treatments, of which one so studied at postmortem examination showed active vasculitis. Three forms of vasculitis classically occur in RA affecting all calibers of blood vessels from dermal postcapillary venules to the aorta, usually in association with circulating IgM and IgG rheumatoid factor as measured by the latex fixation test, decreased complement levels, and a positive ANA. The first is a proliferative endarteritis of a few organs, notably the heart, skeletal muscle, and nerves characterized by inflammatory infiltration of all layers of small arteries and arterioles, with intimal proliferation, necrosis, and thrombosis. The second is fulminant vasculitis indistinguishable from PAN with less severe leukocytosis, myalgia, renal and gastrointestinal involvement, and bowel perforation. The third type takes the form of palpable purpura, arthritis, cryoglobulinemia, and low complement levels. The literature contains references to RAV with involvement of the CNS at postmortem examination in only nine patients. Detailed postmortem findings evidencing CNS vasculitis has been reported in only nine patients [134-136, 138-142] with accompanying clinical neurological findings including, delirium, confusion, seizures, hemiparesis, Gerstman-like syndrome, blindness, and peripheral neuropathy. Postmortem examination has shown widespread systemic vasculitis, single major cerebral artery involvement, generalized PAN-like changes in the CNS, isolated CNS vasculitis affecting the temporal lobes and brainstem with diffuse infiltrative thickening of the pia arachnoid, rheumatoid nodular formation, and inflammatory cell infiltration of leptomeningeal vessels in subjacent brain tissue including the midbrain, medulla, and upper cervical cord; and chronic perivasculitis and transmural chronic inflammatory cell infiltration with severe fibrinoid necrosis of the media of small leptomeningeal vessels and cortical arterioles.

Despite development of new and potent drugs for RA, there are no available evidence-based recommendations for treatment of systemic rheumatoid vasculitis [143]. Complete remission of systemic rheumatoid vasculitis occurred in nearly three-fourths treated with rituximab, with a significant decrease in daily prednisone dosage and an acceptable toxicity profile, making it a suitable therapeutic option to induce remission but maintenance therapy was necessary. Bartels and Bridges [144] recommended prednisone therapy to initially decrease

systemic inflammation with a dose dependent upon the degree of systemic inflammation and level of organ system involvement. The presence of CNS involvement mandated intravenous corticosteroid therapy and consideration of cytotoxic or biologic agents from among them methotrexate, azathioprine, cyclophosphamide, anti-TNF agents and rituximab. Bartolucci and colleagues [145] reported the successful induction of a prompt symptomatic response in ten patients with systemic vasculitis not responsive to conventional treatment, including two with RA and associated vasculitis. Puéchal and colleagues [146] demonstrated evidence of efficacy of adjunctive anti-TNF therapy and corticosteroids for treatment of active refractory systemic RAV with remission achieved in two-thirds of patients, and a significant decrease in prednisone dose, with a higher risk of infection in the most severely ill patients.

Bacterial Meningitis

The category of secondary vasculitides related to infection includes acute bacterial and mycobacterial meningitis, spirochete organisms notably neurosyphilis, LNB, and viral agents notably VZV, and HIV/AIDS.

The relationship between vascular and parenchymatous cerebral changes including vasculitis, and acute and chronic neurological symptoms and signs was studied extensively in 9 infants and 5 children by Adam and colleagues [147] with *Hemophilus (H.) influenzae* meningitis. Fever, stiff neck, and alteration of consciousness followed a respiratory infection, with subsequent enlargement of the head and separation of the fontanels, followed later by lethargy, coma and death despite sulfadiazine antibiotics and antiserum in the earliest stages of meningitis lasting one to two weeks (7 patients), moderate stages of two to four weeks (4 patients) or late in the stage of meningitis of more than four weeks (three patients). Vascular inflammation by neutrophilic cells so noted in five patients (36%) was typified by inflammation of meningeal veins (2 patients) or meningeal arteries (1 patient) among those with early stage meningitis involvement; with involvement of meningeal arteries in the moderate stage patient, and in subarachnoid arteries of the patient in late stage meningitis. Vascular inflammation was absent in nine patients (63%), four of whom manifested vascular endothelial hyperplasia of meningeal vessels, while the remaining five were reported to have no vascular alterations. Based upon the clinicopathological findings, the authors [147] proposed that from the earliest stages of meningitis, pathological changes could be found in small and medium sized subarachnoid arteries and veins comprised of neutrophilic cellular inflammation accompanied by endothelial cell swelling, multiplication and crowding of lumina, a reaction that ensued over 48 to 72 hours. This was followed by infiltration of adventitial connection by neutrophilic cells, and in the intima of arteries accompanied by lymphocytes forming a conspicuous layer. Foci of vascular necrosis occurred in some cases. Vascular inflammation of the adventitia of subarachnoid vessels was believed to be due to involvement of the arachnoid membrane which formed the adventitia of the subarachnoid vessels, thus in a sense, the vessel wall was affected from the very beginning by the inflammatory process arising within itself. Subintimal inflammation was believed to have an origin in the foci of necrosis with spread beneath the intima along the line of least resistance. Spinal and cranial nerves surrounded by purulent exudates from the beginning of the infectious process at the base of the brain, were infiltrated by inflammatory cells only after several days, and not very pronounced in comparison to meningeal and cortical vessels, with comparatively more lymphocytes. Among 34 other infants

and children reported by Smith and Landing [148] with *H. influenzae* meningitis of 2 to 42 days, six postmortem studied patients showed involvement of arterial vessels and venous lesions in 10 cases, three of whom had cortical necrosis and concomitant arteritis, and five had phlebitis. However in only one patient, a 10-week-old infant who died the evening of admission was arteritis believed to be responsible for brain damage. In this subject, postmortem examination disclosed acute inflammation of the walls of several veins and small arteries in the polymorphonuclear meningeal exudate overlying the cortical surface and extending into the superficial cortex, with narrowing of the lumina by endothelial proliferation and fibrin thrombi, associated with extensive early cortical necrosis.

Tuberculosis

Although the different forms of bacterial purulent meningitis was possible only after development of modern bacteriologic methods and the introduction of the lumbar puncture as a diagnostic measure by Quinke in 1891, TB meningitis was the first type of meningitis to be described clinically as dropsy of the brain in 1768, and subsequently shown to be inflammatory when meningeal tubercles and visceral tubercles were found to be identical in 1830. The tuberculoma, once the commonest intracranial tumor, is now exceptionally rare. The chief neurological signs and symptoms of tuberculous meningitis reflecting meningeal irritation are neck stiffness and positive Kernig sign; and raised intracranial pressure notably headache and vomiting with mental changes, seizures, and focal neurological signs. According to Smith and Daniel [149], arteritis is the rule in the vicinity of tuberculous lesions, wherein vessel walls are invaded by mononuclear cells, with the adventitia more heavily involved than the media. The subintimal and intimal regions form a layer of homogenous fibrinoid material that later involves the media, and the vessel lumen is reduced by inflammatory cell exudation beneath the fibrinoid material, the end results of which are reduction or complete obliteration of the lumen, proliferative endarteritis, and cerebral infarction. The vessels most heavily involved are those at the base of the brain and others in the Sylvian fissure.

Pathologically-proven TB-associated CNS vasculitis was described in five heterogeneous patients [149-151]. The first patient described by Smith and Daniel [149] was an 18-year-old girl with fever, confusion, right hemiplegia, back and neck pain for several days followed by incontinence, complete flaccid paraplegia, delirium dementia, generalized spasticity and death. Postmortem examination showed advanced tuberculous meningitis with dense basal adhesions, hydrocephalus, and obliteration of the spinal subarachnoid space by adhesions, hemorrhagic infarction, and widespread arteritis with acute fibrinoid necrosis, without tuberculomas. The second case was Patient 4 of Greitz [150], a 4-year-old girl with fever, left arm weakness and increasing disorientation that rapidly progressed to coma, nuchal rigidity, and spasticity of the legs. Vertebral angiography showed local widening of a branch of the left posterior cerebral artery and a posterior fossa mass. The patient died soon afterward and at postmortem examination there was tuberculous meningitis with typical tuberculous vasculitis consisting of inflammatory changes in arteries at the base of the brain, notably in small vessels with intimal swelling leading to concentric narrowing of vessel lumina. Headache was a presenting symptom in one of three patients described by Leher [151], none of whom had a prior history of tuberculosis, and all of whom had diagnostic angiographic abnormalities and histopathologic evidence of tuberculous arteritis. A third pathologically-proven case of TB-associated CNS

vasculitis was Patient 1 of Leher [151], a 33-year-old man with anorexia and insomnia. Carotid angiography showed narrowing of the supraclinoid ICA as well as narrowing of two convexity vessels in the Sylvian fissure. At postmortem examination there was marked eccentric left fronto-pareital region arterial narrowing due to fibroblastic proliferation of the intima with large numbers of inflammatory cells below the elastica. Headache was not mentioned in two other histopathologically confirmed patients with tuberculous vasculitis. The fourth case was Patient 2 of Leher [151], a 33-year-old man presented with fever and stiff neck. Cerebral angiography demonstrated irregularity of the supraclinoid ICA and reduction in the caliber of the convexity MCA vessels. He died shortly thereafter and postmortem examination disclosed tuberculous leptomeningitis and arteritis of the ICA and MCA with thickened vessel walls and narrowed lumina. The fifth case was Patient 4 of Leher [151], a 39-year-old man who presented with confusion and stupor, was found to have indentation of the lateral aspect of the ICA as it entered the subarachnoid space above the anterior clinoid on cerebral angiography. Ventriculography showed a block at the aqueduct of Sylvius. He died shortly thereafter and postmortem examination showed widely distributed systemic tuberculosis with binding of vessels at the base of the brain that showed arteritis, accompanied by infarction of the basal ganglia and brainstem.

Kopsachilis and colleagues [152] described a 39-year-old man without known tuberculosis, who developed sudden visual loss in one eye. Fluorescein angiography showed an infero-temporal branch retinal vein occlusion consisting of blockage with areas of hemorrhage, exudation, and late leakage. This was followed by optic disc swelling and headache. Biopsy of an enlarged cervical and submandibular lymph node revealed caseating epithelioid ant cells confirming tuberculosis. Treatment with antituberculous treatment leads to improved visual acuity.

Syphilis

Meningovascular syphilis comprises 39 to 61% of all symptomatic cases of neurosyphilis and tends to occur more frequently in patients with concurrently infected HIV/AIDS. It is characterized by obliterative endarteritis that affects blood vessels of the brain, spinal cord and leptomeninges precipitating substantial ischemic injury.

Often referred to as Heubner arteritis, it involves medium-sized to large arteries with lymphoplasmacytic intimal inflammation and fibrosis however there is a variant form termed Nissl-Alzheimer arteritis that characteristically affects small vessels and produces both adventitial and intimal thickening. Both types can lead to vascular thrombotic occlusions and cerebral infarction, with preferential involvement of the MCA.

The search for the cause of stroke in young adults should include meningovascular syphilis as a potential etiology. Sudden acute severe headache heralded onset of occlusion of bilateral vertebral and proximal basilar artery documented by MRA [153] in a 35-year-old African man. He responded to thrombectomy with restoration of blood flow but succumbed to fatal pontine and subarachnoid hemorrhages. Postmortem examination revealed reactive plasma reagin (RPR) and a positive Venereal Disease Research Laboratory (VDRL) test in CSF with CNS vasculitis characterized by mural thrombi along the vertebrobasilar arteries with well-defined lines of Zahn of alternating layers of fibrin, platelet and red blood cell aggregates, and inflammatory cell infiltration of the arterial walls particularly in the adventitia. Headache of

two to three weeks in duration were the presenting features of two other patients with stroke syndromes [27] one of whom had narrowing of bilateral M1 segments of the MCA, reactive CSF VDRL positive Treponema pallidum hemagglutin-assay and fluorescent treponemal antibody-absorption (FTA-Abs) staining in the CSF, similar to second patient who instead presented with a stroke in the territory of the posterior cerebral artery (PCA) without focal changes on cerebral angiography, neither of whom were studied pathologically for true vasculitis.

One patient with abrupt onset of confusion, aphasia, and hemiparesis had carotid angiography that documented normal named cerebral vessels except for smaller than average caliber, with an abnormal complement fixation test of the blood and CSF, positive colloidal gold curve test, and leptomeningeal biopsy that showed lymphocytic infiltration, focal fibrosis, and chronic perivasculitis consistent with meningovascular syphilis [154].

Neither headache nor confirmatory pathological evidence of CNS vasculitis was mentioned in a patient with basilar artery stenosis and serologically confirmed syphilis in the CSF presumed to be due to meningovascular syphilis [155] so suggested by a positive string sign of the mid-basilar artery at cerebral angiography.

Lyme Neuroborreliosis

The term Lyme neuroborreliosis was introduced by Veenendaal-Hilbers and colleagues [156] in 1988 to emphasize that CNS involvement due to *B. burgdorferi* infection, the causative agent of Lyme disease. Among 20 patients described in the literature with neurovascular clinical syndromes ascribed to CNS vasculitis in which detailed information was available including documentation of positive CSF Lyme serology, two patients [157, 158] who presented with headache were ultimately noted to have histopathologically confirmed vasculitis on brain biopsy. Patient 3 of Oksi and colleagues [157] was an 11-year-old boy with headache and hyperactivity syndrome who developed gait difficulty concomitantly with a stroke visualized on brain MRI. Subsequent craniotomy and biopsy of the area of enhancement disclosed lymphocytic vasculitis of small vessels without fibrinoid necrosis, and CSF *B. burgdorferi* serology was positive. Headache and the MRI improved with intravenous antimicrobial therapy. Patient 2 of Topakian and coworkers [158] presented with headache, fatigue, malaise, nausea and vomiting first considered migrainous then psychosomatic until subsequent MRI disclosed ischemic brain infarctions, MRA was compatible with diffuse vasculitis, and CSF showed lymphocytic pleocytosis with positive oligoclonal bands, and diagnostic CSF and serum *B. burgdorferi* serology. Brain biopsy showed vasculitis involving leptomeningeal arteries comprised of lymphoplasmacytic vessel wall infiltration with focal necrosis. Epithelioid cells were beaded in multiple granuloma-like formations in the leptomeninges. There was symptomatic improved after a course of intravenous antimicrobial therapy. A third patient reported by Miklossy and colleagues [159], a 50-year-old man with leg spasticity and CSF pleocytosis for 15 months who progressed to hemiparesis and ventilatory support, was later found to have diagnostic *B. burgdorferi* serology in serum and CSF. Postmortem examination showed perivascular lymphocytic inflammation of leptomeningeal vessels, some of which displayed infiltration of the vessel walls, duplication of the elastic lamina, narrowing of lumina, and complete obstruction of some leptomeningeal vessels by organized thrombi. Seventeen other patients with presumed CNS vasculitis due to *B.*

burgdorferi infection of the CNS were reported, so suggested by complaints of headache [27, 28, 156, 162-164], while unmentioned in the case report of eight others [165-168], none of whom had histologically-proven CNS vasculitis.

Varicella Zoster Virus Infection

VZV is the cause of childhood chickenpox and most children manifest only mild neurologic sequela. However, after it resolves, the virus becomes latent in neurons of cranial and spinal ganglia of nearly all individuals, and has the propensity to reactivate in elderly adults and immunocompromised individuals to produce shingles. An uncommon but serious complication of virus reactivation is ischemic and hemorrhagic stroke. VZV vasculopathy affects both immunocompetent and immunocompromised individuals typically presenting with headache and mental status changes with or without focal neurological deficits and a spectrum of vascular damage from vasculopathy to vasculitis with stroke [169, 170]. Both large and small vessels can be involved and MRI shows multifocal ischemic lesions, commonly at gray-white matter junctions. The diagnosis of VZV can be missed when symptoms and signs occur months after zoster, or in the absence of a typical zoster rash.

Fourteen patients with VZV-related vasculopathy with detailed clinicopathologic data have been described in the literature. One patient presented with headache, fever, mental status change, focal neurological deficits, and focal narrowing of the ICA, anterior cerebral artery (ACA) and MCA, with CSF antibodies to VZV, but without a rash [171]. VZV DNA and VZV-specific antigen were found in three of five cerebral arteries examined with histologically-confirmed CNS vasculitis involving the circle of Willis. Patient 1 of Eidelberg and colleagues [172] who presented with headache and herpes zoster ophthalmicus (HZO) rash was deemed to have CNS vasculitis based upon complete occlusion of the MCA and so treated, however postmortem examination showed no evidence of vasculitis. Headache was not mentioned in five other patients despite histologically-proven widespread small vessel granulomatous angiitis associated with lymphoma in two patients [173] and basilar branch vessel involvement of granulomatous angiitis in another [174]. One patient with contralateral hemiplegia one month after HZO was found at postmortem examination to have endarteritis of unilateral ACA, MCA and PCA [175] with VZV DNA from the involved vessels. One patient with AIDS, unilateral weakness and garbled speech due to ischemic infarction in association with lumbosacral zoster rash, was found to have CNS vasculitis of vessels of the circle of Willis with VZV DNA without herpetic inclusions at postmortem examination. Finally, neither headache nor supporting histopathology was present in seven other patients with VZV-vasculopathy including five patients with HZO and contralateral hemiparesis [176], and two patients with HZO and contralateral delayed hemiparesis [177].

Nagel and colleagues [178] analyzed virus-infected cerebral and temporal arteries from three patients with VZV vasculopathy. Several characteristic were noted in all VZV-infected arteries so studied including, disrupted internal elastic lamina, hyperplastic intima composed of cells expressing a-smooth muscle actin and smooth muscle myosin heavy chain but not endothelial cells expressing CD31, and decreased medial smooth muscle cells. The location of VZV antigen, degree of neointimal thickening and disruption of the media were related to the duration of disease. The presence of VZV primarily in adventitia early in infection and later in the media and intima supported the hypothesis that after reactivation from ganglia, VZV spread

transaxonally to the arterial adventitia followed by transmural spread of virus. Stroke in VZV vasculopathy appears to result from changes in arterial caliber and contractility produced in part by abnormal accumulation of smooth muscle cells and myofibroblasts in thickened neointimal and disruption of the media [178]. Nagel and colleagues [178] also studied the immune characteristics of virus-infected temporal artery three days after onset of ischemic optic neuropathy, and after ten months of protracted CNS disease in the MCA. In both early and later VZV vasculopathy, T-cells, activated macrophages, and rare B-cells were found in adventitia and intima, whereas neutrophils and VZV antigen were abundant along with a thickened intima associated with inflammatory cells in vasa vasorum. Viral antigen but not leukocytes were found in the media in late VZV vasculopathy [179].

HIV/AIDS

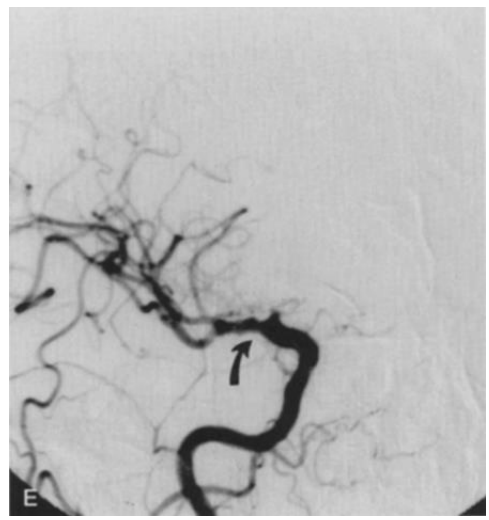
Early in the HIV/AIDS epidemic, it was clear that a significant proportion of infected persons were intravenous drug users. Their associated risk behavior exposed them to infection through sharing of contaminated needles thereby increasing the risk of spread of HIV and other blood borne infections. The two postulated periods in the neurobiology of HIV when autoimmune disease manifestations and cerebral vasculitis can occur are shortly after seroconversion and before the spread of productive infection, and after initiation of highly active antiretroviral therapy (HAART) in association with the immune reconstitution inflammatory syndrome (IRIS) [180]. The timing of early HIV invasion has been difficult to ascertain based on the presence of one or well-recognized clinicopathological HIV/AIDS syndromes including HIV encephalitis, HIV-associated dementia and AIDS-dementia complex [181-183], all of which are indicative of symptomatic infection. Headache associated with irritation and confusion was the presenting feature of a 42-year-old homosexual man without evidence of immunodeficiency who developed cerebral granulomatous angiitis in association with human-T-lymphotropic virus type II (HTLV-III). At postmortem examination there was evidence of fibrous intimal scarring and marked luminal narrowing of the ACA, MCA and PCA and their proximal branches, with mononuclear cell infiltration of the vessel walls and numerous multinucleated giant cells near the internal elastic lamina. Six presymptomatic HIV-seropositive drug abusers by Gray and colleagues [160] had non-necrotizing cerebral vasculitis at postmortem examination.

IDENTIFICATION OF SINGLE ORGAN VASCULITIDES

Primary Angiitis of the Central Nervous System

Adult and childhood isolated angiitis or vasculitis are prototypical primary vasculitic disorders restricted to the CNS. Childhood and adult isolated CNS angiitis (IACNS), primary angiitis of the CNS (PACNS), granulomatous angiitis of the brain (GAB) and GANS, and adult and childhood PACNS (cPACNS) are all equivalent terms for a prototypical primary vasculitic disorder restricted to the CNS [184-188]. The diagnosis of PACNS [184], like IACNS [185] originally relied upon classic angiographic (Figure 3) or histopathologic features of angiitis

within the CNS in the absence of systemic vasculitis or another cause for the observed findings. The typical patient with PACNS presented with headache of gradual onset often accompanied by the signs and symptoms of dementia, while only later developing focal neurological symptoms and signs. The clinical course might be rapidly progressive over days to weeks, or at times insidiously over many months with seemingly prolonged periods of stabilization. Those with GAB or GANS [186] presented with headache, mental change, and elevated CSF protein content with or without pleocytosis. Hemiparesis, quadriparesis, and lethargy were associated with a poor prognosis and mandated the need for combined meningeal and brain biopsy to establish the diagnosis with certainty. Granulomatous giant cell and epithelioid cell infiltration in the walls of arteries of various caliber, from named cerebral vessels to small arteries and veins, were noted at postmortem examination.



Reproduced from reference [4], with permission.

Figure 3. Radiographic features of cerebral vasculitis. Ectasia and beading in the M1 segment and lack of flow in the A1 segment of the right anterior cerebral artery (arrow).

A recent retrospective cohort of PCNSV from the Mayo Clinic [187] and a multicenter prospective cohort of PACNS from the French Vasculitis Study Group, French NeuroVascular Society and the French Internal Medicine Society [189] have stratified cases of based upon clinical, neuro-radiographic and histopathologic laboratory features, offering additional insights into the management of CNS vasculitis.

Between 2004 and 2011, Salvarani and collaborators [187] enrolled 105 patients, of whom (64%) met inclusion criteria for the diagnosis of probable CNS vasculitis based upon cerebral angiography manifesting areas of smooth-wall segmental narrowing or dilatation, and occlusions that affected multiple cerebral arteries without the proximal vessel changes of atherosclerosis or other causes); and 58 patients (36%) who met the definite diagnosis based upon a CNS tissue biopsy showing transmural vascular inflammation involving leptomeningeal or parenchymal vessels. The latter histopathology was granulomatous in 35 (60.3%), lymphocytic in 13 (22.4%), and necrotizing alone in 10 (17.2%). These histological patterns appeared to identify subsets of disease rather than different stages of the same process since no individual patient had histological evidence of more than one pattern. A favorable response to

therapy including corticosteroids (prednisone) alone or in association with cyclophosphamide was observed in 85% of patients. Three patients treated with biological agents including rituximab (1 patient) and a tumor necrosis factor-α inhibitor (2 patients) for treatment of refractory disease, were also improved. Relapses were observed in 27% of patients, and 25% of patients had discontinued therapy by the time of the last follow-up visit. While response to treatment was not associated with any histological pattern of the biopsy specimen, treatment with corticosteroids alone was associated with more frequent relapses (OR, 2.90), while large named vessel involvement (OR 6.14) and cerebral infarcts at the time of diagnosis (OR, 3.32) were associated with a poor response to treatment. Among the patients diagnosed exclusively by angiography alone, relapses were more frequent when there was large-vessel involvement (30%) than only small-vessel changes (9%), with an increased mortality rate due to fatal neurovascular problems caused by PCNSV. Subsets of patients with PCNSV showed equally interesting insights.

An associated poor prognosis of GANS was noted by Molloy and colleagues [190] who described granulomatous vasculitis changes in CNS tissue biopsies of 10 of 13 (77%) patients with amyloid-beta-related angiitis (ABRA). Salvarani and coworkers [191] noted granulomatous vasculitis in all 8 (100%) cerebral biopsies of patients with lymphoma and PCNSV, two of whom had concomitant cerebral amyloid angiopathy. Among 131 consecutive patients with PCNSV, 11 (8.4%) had a rapidly progressive course that was resistant to immunosuppressive therapy resulting in severe disability or death. Such patients had bilateral cortical and subcortical infarction on initial brain MRI and LVV on cerebral angiography with granulomatous and necrotizing vasculitis in brain tissue biopsies. All 11 patients failed to respond to aggressive immunosuppressive therapy, only one of whom survived with major fixed neurological deficits.

In 2018, De Boysson and colleagues [189] described the treatment and long-term outcomes of an observational cohort of 112 patients with PCNSV derived from three main networks: the French Vasculitis Study Group, French Neurovascular, Society, and the French Internal Medicine Society. The three main criteria inclusion were (1) involvement of CNS vessels evidenced by biopsy or based or imaging (on digital subtraction angiography or MRA), showing intracranial arterial stenoses, occlusions, or fusiform dilations); (2) a complete workup performed, including infectious and immunologic serologies (HIV, hepatitis B virus, hepatitis C virus, syphilis, tuberculosis, antinuclear and ANCA, echocardiography and whole body imaging, to exclude other alternative conditions affecting CNS vessels; and (3) a >6 months follow-up (unless the patient died before 6 months of a biopsy-proven PCNSV) to prevent the inclusion of other vasculopathies, such as reversible cerebral vasoconstriction syndrome (RVCS) where vascular lesions reverse within the first months [192]. The rate of prolonged remission was defined by the absence of relapse at ≥12 months after diagnosis; as was the functional status at last follow-up in accordance with three main groups of treatments administered: CS (group 1); induction treatment with CS and an immunosuppressant, but no maintenance (group 2); and combined treatment with CS and an immunosuppressant for induction followed by maintenance therapy (group 3). Good functional status was defined as a modified Rankin Scale score ≤2 at the last follow-up.

Among the 112 patients reported by De Boysson and colleagues [189], 33 (29%) patients were included with a diagnostic CNS tissue biopsy, and 68 (61%) and 11 (10%) respectively had digital subtraction angiography or MR angiography consistent with PCNSV. Remission was achieved with the initial induction treatment in 106 (95%) of the 112 patients. Prolonged

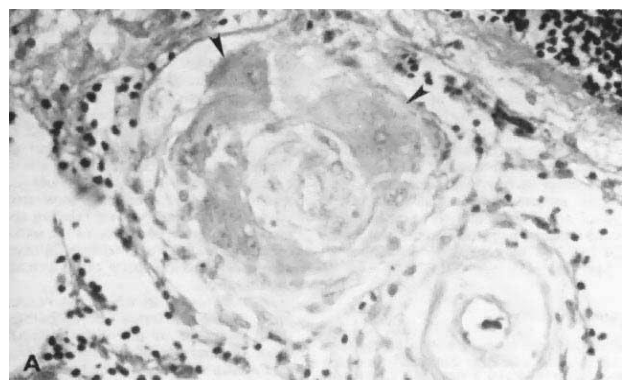
remission without relapse was observed in 70 (66%) patients after a mean of 57 months (range 12-198) of follow-up. A good functional status at last follow-up (ie, modified Rankin Scale score ≤2) was observed in 63 (56%) patients. The overall mortality was 8%. More prolonged remissions (P=0.003) and a better functional status at the last follow-up (P=0.0004) were observed in group 3. In multivariate analysis, the use of maintenance therapy was associated with prolonged remission (OR, 4.32 [1.67-12.19]; P=0.002) and better functional status (OR, 8.09 [3.24-22.38]; P<0.0001). There findings suggest that maintenance therapy with an immunosuppressant combined with corticosteroids leads to the best long-term clinical and functional outcomes in patients with PCNSV after having achieved remission with either corticosteroids alone or in combination with another immunosuppressant. In that regards, cyclophosphamide in combination with corticosteroids for induction, and azathioprine for maintenance were the two main immunosuppressants used in this registry. Whether other combinations or sequences can achieve better results remained to be ascertained.

The past decade has also revealed insights into childhood PACNS (cPACNS) [193], one of the many childhood inflammatory brain diseases that affect small and large vessels. So called angiographically-negative small-vessel cPACNS (SVcPACNS) is associated with persistent headache, cognitive decline, mood disorder, focal seizures and abnormal brain neuroimaging in children. Brain biopsy findings include inflammatory cell infiltrates in intramural arterioles, capillaries, or venules consisting predominantly of a mixture of lymphocytes and macrophages, with occasional plasma cells, polymorphonuclear cells, and eosinophils. Granulomatous inflammation and multinucleated giant cells are generally absent. Awaiting the results of The PedVas Initiative, a Canadian and United Kingdom collaborative study (ARChiVe Investigators Network within the PedVas Initiative [ARChiVe registry], BrainWorks, and DCVAS) of pediatric and adult cases of AAV (GPA) and PACNS (NIH identifier, NCT02006134), there is yet satisfactory prevalence and incidence data or evidence-based guidelines to treat cPACNS. The PedVas Initiative has been prospectively collecting clinical and biobank data in January 2013 of registered cases, within 12 months of study entry. The approach to diagnosis and management has been to first differentiate cPACNS and SVcPACNS respectively from angiography-positive, and angiography-negative, brain biopsy-positive mimickers. However, it has been difficult to reconcile the early outcome results of the PedVas Initiative employing corticosteroids, cyclophosphamide, methotrexate, or rituximab for remission-induction of childhood GPA [73] for the analogous therapy of cPACNS using similar protocols for AAV, due to the disappointing rate of remission status (42%) and visceral organ damage (63%) in its study cohort.

The aim of treatment in cPACNS has nonetheless been to rapidly control the underlying inflammatory response and stabilize the blood-brain barrier while protecting the brain from further insults. Methylprednisolone has been the first-line agent administered intravenously at a dose of 30 mg/kg/day to a maximum of 1 gram per day for 3 to 5 days followed by 1 to 2 mg/kg/day of oral CS to a maximum of 60 mg/day of prednisone. After stabilization, immunosuppressive treatment is directed at the likeliest inflammatory pathways involved in the primary vasculitic process. Induction therapy with corticosteroids and pulse cyclophosphamide followed by maintenance therapy with azathioprine or mycophenolate mofetil has been recommended in cPACNS. Children with SV-cPACNS were treated in an open-label study [194] with cyclophosphamide in doses of 500 to 750 mg/m2 monthly infusions for six months, and followed with maintenance therapy of azathioprine of 1 mg/kg/day and a target dose of 2 to 3 mg/kg/day, and mycophenolate mofetil at titrated doses of 800 to 1200

mg/m2/day followed for up to 24 months employing pediatric stroke outcome measures (PSOM). Among 19 such patients, 13 completed 24 months of follow-up, of whom 9 had a good neurological outcome by PSOM scoring, 8 experienced disease flares, and 4 achieved remission of disease; and mycophenolate mofetil was more effective than azathioprine. One retrospective analysis [188] found that cyclophosphamide conferred little benefit over azathioprine in patients with GAB so treated and in fact, increased the risk for potentially fatal side effects.

The approach to the patient with presumed PACNS begins with exclusion of disorders that can mimic primary CNS vasculitis including RVCS. The evaluation is incomplete without sampling of the CSF which often demonstrates elevation of the protein content and lymphocytic pleocytosis [188]. Cerebral angiography, high-resolution MRA and CTA, all provide complementary information however a small vessel vasculitis may escape detection, making it necessary to contemplate combined brain and meningeal biopsy for tissue confirmation (Figure 4).



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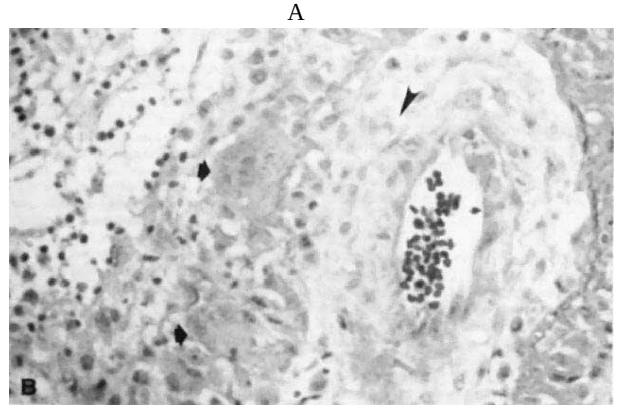

B

Reproduced from reference [4], with permission.

Figure 4. Central nervous system vasculitis. A. The media and adventitia of this small leptomeningeal artery have been almost completely replaced by multinucleated giant cells (arrowheads). There is intimal proliferation with obliteration of the vascular lumen, and a dense, perivascular, mononuclear inflammatory infiltrate can be seen (stain, hematoxylin and eosin; original magnification, ×250). B. A somewhat larger leptomeningeal vessel shows necrosis of the media and internal elastic lamina with multinucleated giant cell formation (arrows), intimal proliferation (arrowhead), and lymphocytic infiltration of the adventitia and neighboring meninges (stain, hematoxylin and eosin; original magnification, ×250).

Idiopathic Aortitis-IgG4-Related Disorders

In 1972, an unusual form of inflammatory aortic disease or aortitis came to light in the surgical literature with far-reaching implications for concepts of autoimmunity. Walker and colleagues [193] noted that 10% of 217 patients presenting with abdominal aneurysms at Manchester Royal Infirmary between 1958 and 1969 for resection showed excessive thickening of aneurysm walls and perianeurysmal adhesions at operation. Subsequent histological examination of the walls of the aneurysms showed extensive active chronic inflammatory changes including plasma-cell infiltration.

The clinical features of patients with inflammatory aneurysms differed from those with atherosclerotic disease due to generally younger age by a decade, lower incidence of rupture, lack of claudication of intermittent the limbs and presence of peripheral pulses, less likelihood of unusual presenting features, elevated ESR, and lack of calcification on preoperative abdominal Rojo-Leyva and colleagues [196] noted idiopathic aortitis in 43% of 1,204 aortic specimens gathered over a period of 20 years. In 96% of the patients with idiopathic aortitis patients and aneurysm formation, aortitis was present only in the thoracic aorta. In 2001, Hamano and colleagues [197] noted a high concentrations of IgG4 associated with sclerosing pancreatitis characterized by obstructive jaundice, infrequent attacks of abdominal pain, irregular narrowing of the pancreatic duct, sonolucent swelling of the parenchyma, lymphoplasmacytic infiltration, fibrosis, and a favorable response to corticosteroid treatment. One year later, Hamano and coworkers [198] noted the association of sclerosing pancreatitis with raised concentrations of IgG4 among those with concomitant hydronephrosis that caused ureteral masses later diagnosed as retroperitoneal fibrosis (RPF).

Histologic examination of ureteral and pancreatic tissues revealed abundant tissue infiltration by IgG4-bearing plasma cells. In the same year, 2008, three important observations were made. First, Sakata and colleagues [199] concluded that inflammatory abdominal aortic aneurysm (IAAA) was related to IgG4 sclerosing disease. Second, Kasashima and colleagues [200] concluded that IAAA was an IgG-RD together with RPF. Third, Ito and colleagues [201] described a patient with IAAA, hydronephrosis caused by RPF and high levels of IgG4, in whom treatment with corticosteroids led to clinical improvement and reduction in IgG4 levels. Histological inspection of the aortic wall specimen showed lymphocytoplasmacytic infiltration. Immunohistochemical analysis of the tissue showed IgG4 positive plasma cells. The findings suggested that IAAA had an etiopathogenesis similar to autoimmune pancreatitis and that some cases of IAAA and RPF could be aortic and periaortic lesions of an IgG4-RD. One year later in 2009, Khosroshahi and colleagues [202] described thoracic aortitis due to IgG4-RD with marked elevation of the serum IgG4 levels with progression to autoimmune pancreatitis, and Stone and coworkers [203] described IgG4-related thoracic aortitis with a media-predominant pattern of aortic wall infiltration and marked elevation of serum IgG4 levels, unequivocally linking IgG4-RD with thoracic lymphoplasmacytic aortitis.

Color-Doppler sonography, MRI combined with MRA and CTA, which adequately visualize the aortic wall and lumen, combined with FDG PET to detect increased uptake by metabolically active cells including inflammatory cells infiltrating the vessel wall, are essential in the assessment of the extent and severity of the various forms of aortitis including IgG4 types. The histopathologic analysis of biopsy specimens has been the cornerstone of the diagnosis of IgG4-RD.

A 2012 consensus statement on the pathology of IgG4-RD by Deshpande and colleagues [204] proposed a terminology scheme for the diagnosis of IgG4-RD based upon the morphological appearance and tissue IgG4+ plasma cell counts in biopsy tissue. Three histopathological features associated with IgG4-RD included a dense lymphoplasmacytic infiltrate, fibrosis arranged at least focally in a storiform pattern, and obliterative phlebitis in morphological specimens. The majority of cells were T-cell with scattered B-cells, and an essential component of plasma cells with occasional eosinophils and macrophages. The level IgG4 antibody, which represents less than 5% of the total IgG in healthy individuals is tightly regulated and has a unique structure and functional property. It undergoes half antibody exchange *in vivo* resulting in recombined antibodies composed of two different binding specificities. Their production is driven in part by Th2 cytokines that mediate allergic reactions and IgE production. It does not activate complement pathways and has reduced effector function relative to other IgG subtypes. It remains unclear as to whether IgG4 directly mediates the disease process or reflects a protective response induced by anti-inflammatory cytokines, making it simply a valuable biological marker of IgG4-RD.

A Japanese consensus management guideline [205] suggested the initiation of oral prednisolone for induction of remission at a dose of 0.6 mg per kilogram per day for 2 to 4 weeks, with tapering by 5 mg every 1 to 2 weeks based on clinical manifestations, biochemical blood tests, and repeated imaging, to a maintenance dose of 2.5 to 5 mg per day for up to 3 months. Re-administration of corticosteroids is advised for treating relapses. Treatment with azathioprine, mycophenolate mofetil and methotrexate can be used as corticosteroid sparing agents or as remission-maintenance drugs after corticosteroid-induced remissions. Patients with recurrent or refractory disease and B-cell depletion may be considered for rituximab [206].

Nonsystemic Peripheral Nerve Vasculitis

The vasculitic neuropathies are heterogeneous disorders that present in the setting of systemic vasculitis or in the absence thereof where necrotizing arteritis may remain clinically and pathologically restricted to the peripheral nerves as a SOV. The Peripheral Nerve Society [207] established guidelines for the classification, diagnosis, investigation, and treatment of NSVN. Pathologically-definite vasculitic neuropathy is defined by active or chronic peripheral nerve and muscle tissue lesions that show cellular invasion of the walls of blood vessels with accompanying acute vascular damage (fibrinoid necrosis, endothelial loss/disruption, internal lamina loss/fragmentation, smooth muscle media loss/fragmentation/separation, acute thrombosis, vascular/perivascular hemorrhage or leukocytoclasia) or chronic vascular damage (intimal hyperplasia, fibrosis of media, adventitial/periadventitial fibrosis or chronic thrombosis chronic thrombosis with recanalization), without evidence of another primary disease process that could mimic vasculitis pathologically such as lymphoma, lymphomatoid granulomatosis or amyloidosis.

Patients with NSVN lack symptoms, signs, or laboratory evidence of involvement of other organs (demonstrable by laboratory evidence of PR3-, MPO-ANA, mixed cyroglobulins, SSA, SSB, Sm, RNP, Scl-70, centromere, dsDNA, CCP serology; ESR >100 mm per hour, or tissue biopsy evidence of vasculitis in another organ other than muscle; serologic, PCR or culture evidence of a specific infection associate with vasculitis), and no predisposing factors (other than diabetes) of a connective tissue disease, sarcoidosis, inflammatory bowel disease, active

malignancy, HUV, cutaneous PAN, or exposure to drugs likely to cause vasculitis. Inflammation of microvessels less than 40 to 70 μm in diameter without vascular damage are broadly referred to as MV.

The management of NPNV has remained uncertain because of the very concept presumes that the vasculitic disease process is widespread within the nerves and not present elsewhere in the body. This assumption has been called into question by four lines of evidence.

First, the definition of NPNV allows for the finding of vasculitic lesions in muscle tissue, [207] perhaps making the syndrome more appropriately termed peripheral nervous system vasculitis or "PNSV". Moreover, the detection of vasculitis in cutaneous nerve and muscle tissue specimens has been incorporated into the FVSG database to establish the diagnosis of systemic vasculitis. Among 129 patients with PAN [208] who underwent nerve biopsy with (108 patients) or without (21 patients) peripheral neuropathy, vasculitic lesions were noted in cutaneous nerve tissue in 83% and 81% of patients respectively, compared to 68% and 60% of cases where muscle biopsytissue was examined.

Second, the lack of long-term follow-up in most cases series ranging from 6 months to 22 years [209].

Third, the report of only two proposed cases, both with foci of vasculitis outside the PNS in a visceral organ [19] or the temporal artery [210]. Patient 1 in the series of pathologically confirmed cases of PAN by Kernohan and Woltman [19] was a 54-year-old man with five years of progressive generalized painful peripheral neuropathy that was so severe before death that he was partially paralyzed, and unable to speak or swallow. Postmortem examination showed PAN limited to the nerve trunks of the arms and legs. The brain, cranial nerves, and spinal cord were normal except for early acute changes without evidence of vasculitis. Examination of all other organs failed to reveal a single vascular lesion, except one small artery in the capsule of the prostate gland. Torvik and Berntzen [210] described a 76-year-old woman with diffuse fever, pain, and central scotoma of the eye that improved with corticosteroids. A biopsy of the temporal artery and pectoralis muscle disclosed necrotizing arteries of small arteries and arterioles in small adventitial vessels of the temporal artery without frank temporal arteritis. However, postmortem examination evidence of healed vasculitis in numerous small arteries and arterioles of muscle and nerve tissue measuring 50 to 200 microns in diameter without vasculitis in visceral organ or the CNS. .

Fourth, the inclusion of patients with diabetes according to the 2010 guidelines [210] may be introducing selection bias. Over the years, there has been increasing support for the contribution of autoimmune mechanism in the pathogenesis of diabetic neuropathy. Diabetes itself appears to be caused by autoimmune mechanisms directed at insulin-producing pancreatic beta cells, and a variety of autoantibodies have been detected in patients with type-1 diabetes (T1D) or insulin dependent (IDDM), including anti-islet cell cytoplasmic antibodies, present in up to 80% of newly diagnosed patients and glutamic acid decarboxylase (GAD) antibodies, also present in patients with autoimmune stiff person syndrome. Younger and colleagues [211] reported the clinicopathologic and immunohistochemical findings of sural nerve biopsy tissues in a cohort of 20 patients with heterogeneous forms of diabetic neuropathy. That series was continued to a total of 107 patients [212], of which 3 (3%) showed MV, and 3 (3%) showed necrotizing arteritis. Although diabetes has not been considered a predisposing factor in PNV, the presence or absence of diabetes became a defining feature of patients with LSRPN [213, 214]. In the only postmortem case of LSRPN described by Younger [215], sural nerve biopsy showed mononuclear inflammatory cells surrounding a small epineurial artery with extension

into the vascular wall, with reactive luminal connective tissue suggesting recanalization of a thrombus. An adjacent nerve fascicle showed marked loss of myelinated nerve fibers. The patient was treated for painful diabetic lumbosacral plexopathy (DLSRPN) and peripheral nerve vasculitis according to prevailing standards with 2 g/kg intravenous immunoglobulin for 5 days, followed by 750 mg of intravenous cyclophosphamide and 1,000 mg of methylprednisolone intravenously for 3 additional days. Acute tubular necrosis, increasing lethargy, unresponsiveness, and aspiration pneumonia supervened and the patient expired 4 weeks after admission. General autopsy showed no evidence of systemic or peripheral nerve vasculitis. The brain showed diffuse loss of neurons in all sampled cortical areas, including the cerebellum, consistent with anoxia secondary to cardiac arrest. Sections of extradural lumbar plexus, sciatic, and femoral nerve tissue showed perivascular epineurial inflammation with infiltration of adjacent endoneurium. This case exemplifies the restricted nature of LSRPN as an example of a true NSVN.

Thereare far more studies of living cohorts with NSPNV. Kissel and colleagues [216] reported that 4.5% of 350 consecutive nerve biopsies performed at a single institution evidenced peripheral neuropathy secondary to necrotizing angiopathy. Six patients manifested a distal symmetrical sensorimotor polyneuropathy, while ten had a mononeuritis multiplex presentation, eight of whom had overlapping involvement of peripheral nerves that obscured the picture of mononeuritis. In three-quarters (12 patients), a specific underlying collagen vascular disease was not diagnosed despite extensive clinical, radiologic, and serological evaluation. Said and colleagues [217] studied 100 patients with necrotizing arteritis in muscle or nerve biopsy tissue that occurred in the context of a connective tissue disorder in fifty-five patients and in association with a disorder unrelated to connective tissue pathology in thirteen others. The commonest complaints at presentation in this cohort were specific cutaneous manifestation of vasculitis, including livedo, cutaneous necrosis, and nodules in one-third. Thirty-two patients had neuropathy only and necrotizing arteritis, the most common complaints at of which were spontaneous pain of neurogenic or muscle origin (48%).

More recently, Collins and colleagues [218] described forty-eight patients with NSPNV, 85% of whom had extensive, overlapping involvement of multiple nerves. Peroneal nerve and peroneal muscle tissue biopsy was 58% diagnostically sensitive compared to 47% for sural nerve biopsy for the diagnosis of vasculitis. Combination therapy with corticosteroids and cytotoxic agents was more effective than corticosteroids monotherapy for inducing remission and improving disability, with trends toward reduced relapses and chronic pain. Overall, ten patients died (21%) over the period of 63 months follow-up, five (10%) of whom were related to the disease or treatment, including two patients who succumbed to pulmonary emboli as a result of limited mobility of the legs or myocardial infarction in another; and two patients, one of whom had fatal sepsis and another metastatic bladder cancer as a consequence of cyclophosphamide toxicity.

There are no ongoing observational cohort studies to guide the treatment of NPNV. Recommendations for the treatment of NSPNV [210] include prednisone monotherapy unless there is rapidly progressive neuropathy at the dose of 1 mg per kilogram per day, with tapering over one year to a low dose. Combination therapy employing cytotoxic drugs including cyclophosphamide, methotrexate, and azathioprine may be employed with adjuvant plasma exchange or IVIg. However, IVIg showed efficacy in a multicenter RCT of the treatment of small-to-medium systemic vasculitis due to EGPA with persistent disease activity [219].

This suggests that IVIg may be appropriate, first-line therapeutic modality in NSPNV. Moreover, the benefit of IVIg may be achieved without the risk of potentially fatal cytotoxic side-effects. However there has not been a prospective RCT of IVIg in NSPNV. A variety of mechanisms have been thought to be responsible for the beneficial effects of IVIg in NSPNV and other systemic vasculitides including neutralization of autoantibodies, inhibition of complement pathways, alteration of Fc receptor expression, and alteration of cytokine profiles [220]. Careful monitoring should be performed to observe desired therapeutic responses and to avoid potentially serious drug side effects.

CONCLUSION

In no other disorder have there been so many triumphs as in the diagnosis and treatment of primary systemic vasculitis. Physicians in a variety of subspecialties including neurology, rheumatology, immunology/allergy, dermatology and clinical pathologist, all working side-by-side, aided by subspecialities of public health, epidemiology, genetics, and clinical trial specialists, have benefited the outlook for individual patients and population cohorts around the globe. Yet it starts with clinical acumen typically of the general practitioner. This chapter on clinical approach was written with such diverse backgrounds in mind, from generalist to subspecialist with the hope that it will bring the field up to date and to the present.

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Chapter 3

EPIDEMIOLOGY OF PRIMARY SYSTEMIC VASCULITIS

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ABSTRACT

The epidemiology of the vasculitides has been extensively studied over the past the years, yet despite this, there remain a number of areas where there is a deficit of data. The first problem is that the vasculitides are generally rare conditions and this makes conducting accurate epidemiological studies difficult. The second is the lack for some conditions, as for example, the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) of a reliable and validated classification system. Overall, the vasculitides are diseases of the age spectrum, with Kawasaki disease and IgA vasculitis being conditions of childhood, and giant cell arteritis occurring in those age 60 years or more. The AAV also occur more commonly with increased age. The occurrence of the vasculitides in different ancestries has been less well studied, primarily because there are many health care systems in which it is not possible to derive epidemiological data. Kawasaki disease is much more common in far Eastern populations than Europeans, while IgA vasculitis is more common in Asians. Giant cell arteritis occurs in those of northern European ancestry. The AAV have an overall uniform occurrence, but granulomatosis with polyangiitis is more common than microscopic polyangiitis in Europeans, whereas the reverse is true in the Far East. Improving classification systems and health care systems will hopefully mean that some of the gaps in our knowledge will be filled over the next few years.

Keywords: epidemiology, primary systemic vasculitis, vasculitides

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INTRODUCTION

The epidemiology of systemic vasculitis has been increasing well described over the past 30 years; however, there remain formidable challenges and gaps in our knowledge.

Obtaining accurate epidemiological data is important for several reasons. Knowledge of the occurrence and pattern of disease in a given population is important for planning health services; identification of patterns of occurrence such as epidemics or seasonality may provide clues to the causes of disease both infectious and environmental. Comparison of disease occurrence between populations also provides clues as causation and also possible permit exploration of genetic risk factors.

The challenges fundamentally relate to the difficulty of conducting high quality epidemiology research in rare diseases. Accurate epidemiology requires a discrete population from within a well-defined geographical boundary. Universal health care systems with registration of patients receiving inpatient or ambulatory care are ideal for this type of research, in many parts of the world such universal health care systems do not exist and it is therefore much more difficult if not impossible to obtain reliable data. To collect a sufficiently large number of patients for reliable data from a rare disease either takes a long time or requires a large population, both of which make it harder to conduct high quality epidemiology research. A further requirement is a reliable classification system. The American College of Rheumatology (ACR) (1990) system for the classification of vasculitis is widely used, but has several major deficiencies in particular the absence of microscopic polyangiitis (MPA) and the results of ANCA testing. New classification systems are being developed as part of the Diagnosis and Classification of Vasculitis (DCVAS) project and will be available within the next 2 to 3 years. With increasing interest in the occurrence of disease in different populations accurate determination of ancestry is important, populations have become multi-ethnic with genetic admixture occurring. Such studies can be conducted either in a single population of multi-ancestry or by direct comparison of population in geographically dispersed areas, for example in the United Kingdom (UK) versus Japan. When comparing populations from different ancestries, it is important to ensure that the age structure of the studied population is the same. This is especially important for vasculitis, in which several types show a marked age tropism, as with IgA vasculitis (IgAV) and Kawasaki disease (KD) and giant cell arteritis (GCA) at opposite ends of the age spectrum.

Two main approaches have been used in studying the epidemiology of the vasculitides. The first is active surveillance with development of a complete cohort from a well-defined geographical area often based around a single referral center, examples being Norwich in the UK, Skane in Sweden, and Olmsted County in the United States (US) (Watts et al. 2012; Mossberg et al. 2018; Chandran et al. 2015). The second is passive surveillance using administrative databases, for example the UK Clinical Research Practice Database (UKCPRD) (Pearce et al. 2017). The former method has the major advantage that it is often possible to examine the individual patient case records to confirm the diagnosis and formally classify the individual patient. Because of the difficulties of collecting a complete cohort, such studies tend to have relatively small denominator populations, and total numbers of patients. The use of administrative databases has the advantage of automatic data collection, large populations and hence large numbers of patients. The downside is that it is usually impossible or impracticable to confirm the diagnosis and classification of any individual. Algorithms are being developed

which have been validated to extract information from administrative databases. (Sreih et al. 2016).

More recently, large-scale genetic epidemiology data has been published for many of the vasculitides. Again, there are formidable challenges to these studies, not least being the large number of well-characterized patients required for genome-wide association studies (GWAS). High quality data is now available for the large vessel vasculitides, Kawasaki disease and the AAV. This chapter focuses on the descriptive epidemiology of the vasculitides.

LARGE VESSEL VASCULITIS

The two main types of large vessel vasculitis (LVV), Takayasu arteritis (TAK) and GCA, are clinically considered to be the ends of a spectrum (Grayson et al. 2012). Recent genetic data, however, suggests that the two conditions are distinct (Carmona et al. 2017). It is well known that GCA occurs in the older patient age > 50 years whereas Takayasu arteritis (TAK) occurs predominately in those age < 40 years. This has left patients presenting with a large vessel vasculitis in their 40s essentially unclassifiable, and it is unclear whether they have late onset TAK or early onset GCA

Takayasu Arteritis

Takayasu arteritis occurs in those age <40 years and presents with large LVV involving the aorta and its branches. For the purpose of epidemiological studies, the case definition has generally followed the ACR 1990 criteria for the classification of TAK (Arend et al. 1990).

There remains relatively little epidemiological data on TAK. The available data is summarized in Figures 1 and 2. Takayasu arteritis was first described in Japan and there has long been a view that it occurs more frequently in non-European populations. Most studies suggest there is a female predominance. In populations of European ancestry the annual incidence is 0.4 to 3.4/million, whilst it is 2.2/million in Kuwait/Arabia and 2.6/million in USA (Saritas et al. 2016; Dreyer et al.; Moriwaki et al. 1997). A recent Norwegian study observed an overall increase in the incidence over the last decade and a 3.5 to 5-fold difference in prevalence when comparing populations of north European ancestry to those of Asian and African ancestry respectively (Gudbrandsson et al. 2016). Although the incidence remains at similar levels in Japan, TAK is far more common in Japan with an estimated prevalence of 43/million with a strong female predominance (83.8%) and median age at onset at age 35 years, which was significantly lower in women (34 years) than males (43.5 years) ($P < 0.001$) (Watanabe et al. 2015).

Giant Cell Arteritis

Giant cell arteritis remains the commonest form of systemic vasculitis in those aged > 50 years. GCA is usually classified for epidemiology studies using the ACR 1990 criteria. Not all studies required a temporal artery biopsy to confirm the diagnosis, this can make it difficult to

compare studies. The incidence is highest in populations of northern European ancestry with the highest incidences and prevalence being recorded in Scandinavian populations, and in Olmsted County Minnesota, a population that is predominately of Scandinavian ancestry. The available data is presented in Figure 3. Some studies have suggested an increasing incidence but it is not always clear that this does not reflect better case identification and awareness of the disease. GCA is much less common in non-European populations especially from Asia. The prevalence in Japan appears to be 100-fold less than in Olmsted County. GCA is rarely observed in African ancestry populations (Kobayashi et al. 2003; Chandran et al. 2015). Some studies have suggested an increasing incidence over time, but it is not always clear that this does not reflect better case identification, changing rates of temporal artery biopsy and awareness of the disease. A recent Scandinavian study described a rise in reported incidence from 1972 to 1992 but no further increase up to 2012 (Brekke et al. 2017).

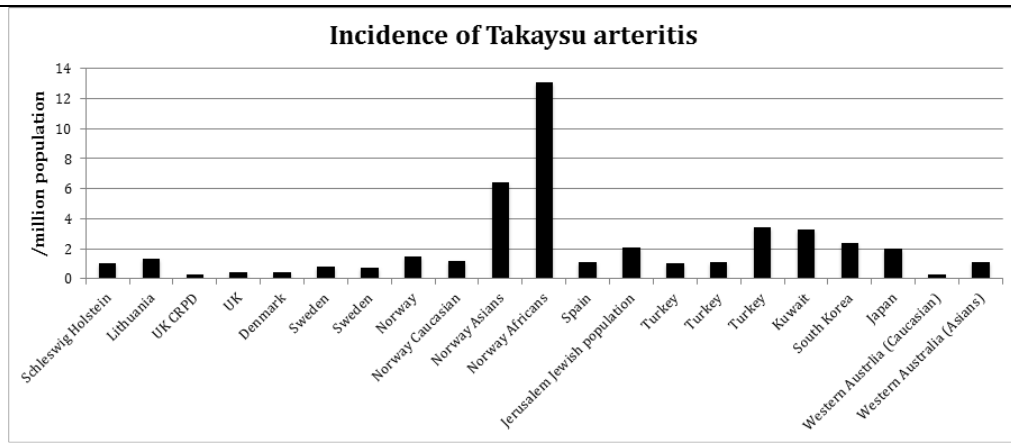

Figure 1. Global incidence of Takayasu arteritis.

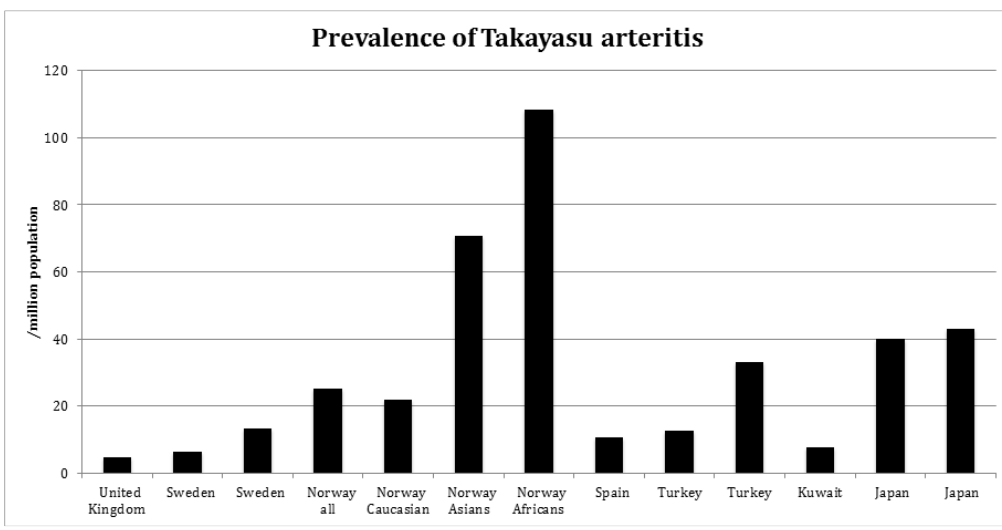

Figure 2. Global prevalence of Takayasu arteritis.

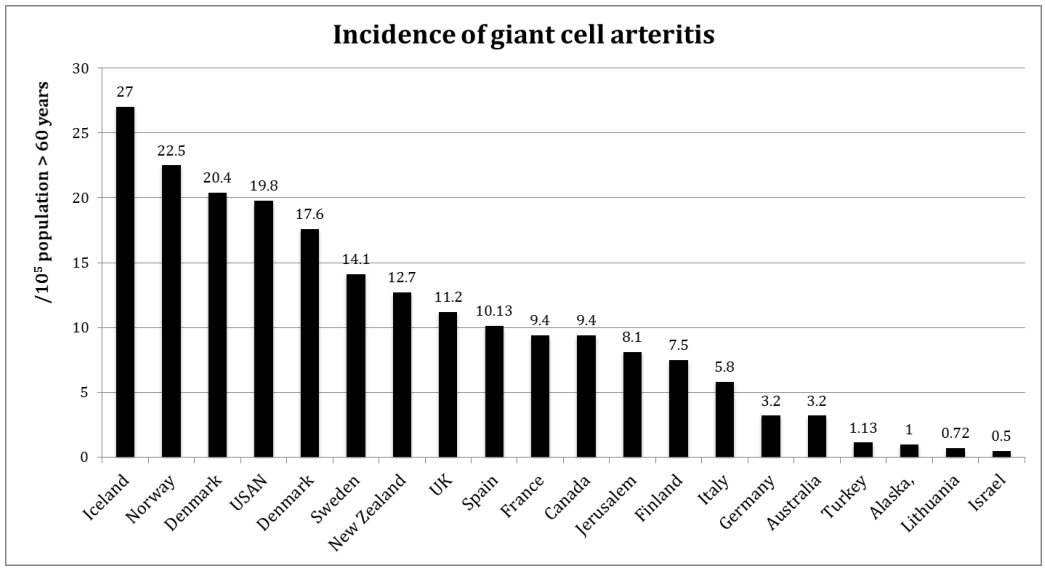

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Figure 3. Annual incidence of giant cell arteritis.

Environmental factors have long been thought to be important in the etiopathogenesis of GCA. There is an inconsistent relation with season of onset, some studies reporting a summer time preponderance but this has not been confirmed. Infection has also been suspected but no clear link has emerged.

Genetic epidemiology studies have shown that HLA-DRB1*04 is the strongest risk factor for GCA, and it has been suggested that variation in population HLA-DRB1*04 frequency may partly explain variations in GCA incidence, with the incidence being higher in populations with the greatest frequency of HLA-DRB1*04 (Mackie et al. 2015).

In conclusion there is still no good explanation for the striking age tropism shown by GCA, immune senescence combined with a strong genetic background is the most likely explanation.

MEDIUM VESSEL VASCULITIS

Kawasaki Disease

Kawasaki disease is a medium sized vasculitis which predominately affects children age < 5 years, and is the predominant cause of childhood-acquired heart disease in the developed world (Burns & Glode 2004). It was originally described by Kawasaki in Japan in the 1960 but has been recognized as occurring in most populations, there are however, marked differences in occurrence between populations. Populations of Asian ancestry have the highest incidence of KD. The incidence of KD continues to increase in Japan in 2012, where the annual incidence rates were 243.1/100,000 population aged 0 to 4 years in 2011 and 264.8 in 2012/100,000 (Makino et al. 2015a). In Japan, the cumulative incidence now means that by the age of 10 years 1.5/100 boys and 1.2/100 girls have been affected by KD (Nakamura et al. 2017). By

contrast, recent data from Italy suggests that the incidence rate was 5.7/100,000 children 0 to 14 years old, and 14.7 years among children < 5 years (Cimaz et al. 2017). The present epidemiological data is summarized in Figure 4. Most studies suggest that it is more common in boys. In Japan, there have been several epidemics of KD but none since 1986, raising the possibility of an infectious etiology, however so far no single infectious agent has been identified.

Several countries have reported distinct seasonality in KD, but there is no overall pattern even allowing for differences in latitude and longitude. Japan reports two seasonal peaks of KD incidence in January and July, with a nadir in October (Makino et al. 2015a). Korea, at approximately similar latitude, has similar peaks in June/July and December/January. (Kim et al. 2017) Taiwan has peaks in May/June and the lowest incidence is reported from November to January (Huang et al. 2009). Seasonality data from China are more variable (Uehara & Belay 2012). In Chandigarh (India), a consistent peak in October with a nadir in February is observed. KD has been reported to occur more commonly in the winter months in mainland US, Canada and Europe, and in the more temperate regions of Australia.

In Europe, the USA and Australia, the previously observed increase in incidence appears to have plateaued. Whereas, in North-East Asian countries (so as Japan and Korea) (Makino et al. 2015b; Kim et al. 2014; Huang et al. 2009) report an incidence 10 to 20 times higher than the US and Europe, and the incidence is continuing to increase. The current incidence in Japan is 265/100 000 in those < 5 years of age (Makino et al. 2015a). China and India, the two most populous countries, from where only more recent and less complete epidemiological data are available, the incidence also appears to be increasing, mirroring rapid industrialization and economic growth.

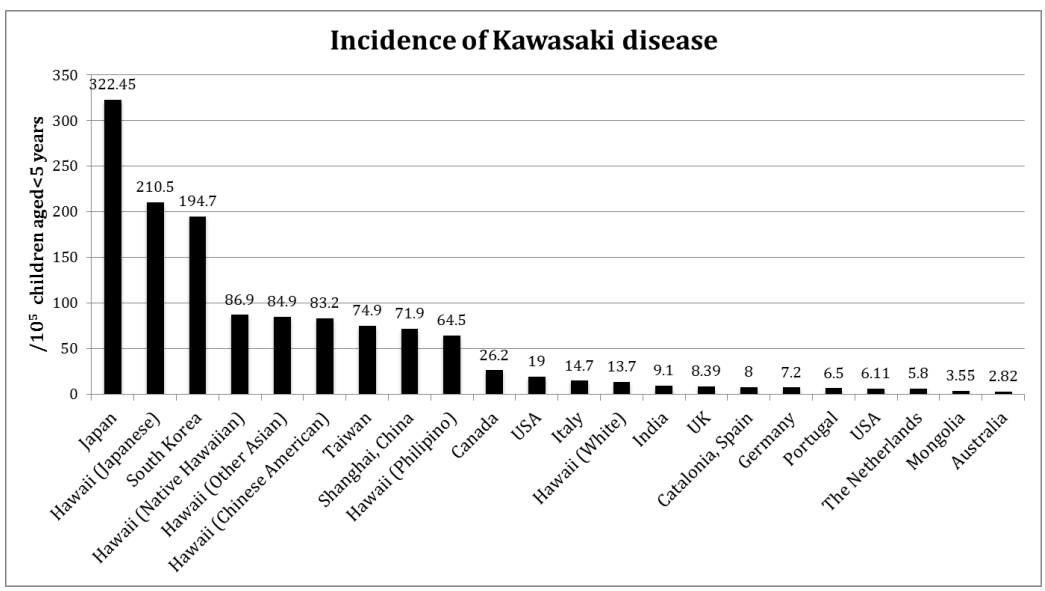

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Figure 4. Annual incidence of Kawasaki disease.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a rare vasculitis of medium vessels associated with development of aneurysms. Following the introduction of modern classification systems especially the 1994 Chapel Hill Consensus definition it has become increasing uncommon (Jennette et al. 1994). It should be remembered that up until the 1990s the term PAN was used to cover several types of vasculitis, which would now be considered to be AAV. PAN is one of the few types of vasculitis for which a clear infectious cause has been recognized, Hepatitis B (HBV) infection is well-recognized cause of PAN. However, polyarteritis nodosa associated with HBV infection has become very uncommon since the introduction of vaccination programs and effective screening of blood donations. Before vaccination against HBV was available, more than one-third of adults with PAN were infected by HBV. Currently, less than 5% of patients with PAN are HBV positive.

The annual incidence of PAN currently ranges from 0 to 1.6 cases/million inhabitants in European countries. There is not a clear ethnic variation. There is a 1.5:1 male preponderance, and it occurs rarely in children (Figure 5).

SMALL VESSEL VASCULITIS

ANCA-Associated Vasculitis

The AAV (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA], eosinophilic granulomatosis with polyangiitis [EGPA]) have all been extensively studied over the past 20 years resulting in a large amount of available epidemiologic data. However, the field has been hindered by inadequate and poorly performing classification criteria, which has meant that it can be difficult to compare studies from different populations. Although widely used, the ACR (1990) criteria do not include MPA or ANCA testing, while the Chapel Hill Consensus Definitions from 1994 and 2012 were not intended to be used as classification criteria. These issues led to overlapping classification and inconsistency in their application. Results from the forthcoming DCVAS study may help to clarify this situation.

The overall incidence rates of AAV in Europe are reported to be in the range of 13 to 20/million (Figure 6), and the incidence of GPA has increased since the 1980s. The combined annual incidence of GPA and MPA in the UK was reported to be 1.5/million in the beginnings of the 1980s, and subsequently increased to 6.1/million at the end of the 1980s (Andrews et al. 1990). Similarly, during the same time period, the incidence of GPA increased in Sweden from 3 to 8/million (Knight et al. 2006). This increase could be due to several factors including: i) increased awareness among physicians, ii) the introduction of routine ANCA testing, and, iii) a genuine increase in incidence rates. However, the incidence has been stable since the early 2000s, suggesting that the likely explanation was increasing physician awareness following the introduction of routine ANCA testing. Geographical factors may also play a role. A comparison study from three regions in Europe showed overall incidence rates of all AAV to be quite similar; about 19/million (Watts et al. 2001). There were, however, differences in the incidence of GPA and MPA between northern and southern Europe; with GPA more common in the north, and MPA more common in southern Europe (Watts et al. 2001). However, the north-

south gradient was not evident in southern Sweden which had an incidence rate of MPA more comparable to that of southern Europe (Mohammad et al. 2009). A recent Norwegian study reported higher rates of MPA than previously noted, suggesting that the north-south gradient might not be as pronounced as previously thought, or that there were changing environmental factors. Studies from New Zealand and Australia showed quite similar incidence rates for GPA comparable with those of northern Norway (Ormerod & Cook 2008; Gibson et al. 2006). By contrast, the proposed latitudinal gradient was observed in New Zealand (O'Donnell et al. 2007). Using the International Classification of Disease, patients coded as GPA were more frequent in southern New Zealand latitudes. Patients with EGPA were previously studied in the PAN group. The highest incidence rate for EGPA, 2.7/million (Watts et al. 2000) was reported from Norwich (UK); and recently 2.3/million (Ormerod & Cook 2008) from Australia.

The gender distribution of AAV is fairly similar in most studies with a slight increased ratio of men to women. The age-specific incidence for the whole group of AAV shows a clear increase with age. However, some variation has been reported between studies; the peak incidence in the age group of 55 to 64 years (Gonzalez-Gay et al. 2003), 65 to 74 years (Watts et al. 2000), and others ≥ age 75 years (Mohammad et al. 2009).

There is a need for studies in other regions and in other ancestries. There is only one study from central and Latin America as opposed to Europe and more recently Asia and Oceania. In a Peruvian population, MPA was more frequent than GPA (Sánchez Torres et al. 2005).

There are relatively few prevalence estimates compared with incidence studies of AAV. The prevalence of AAV is estimated to be 46 to 184/million (Ormerod & Cook 2008; Reinhold-Keller et al. 2000). The prevalence of AAV has generally increased over the last 20 years, reflecting improved patient survival and increased case identification, as shown by multiple retrieval sources.

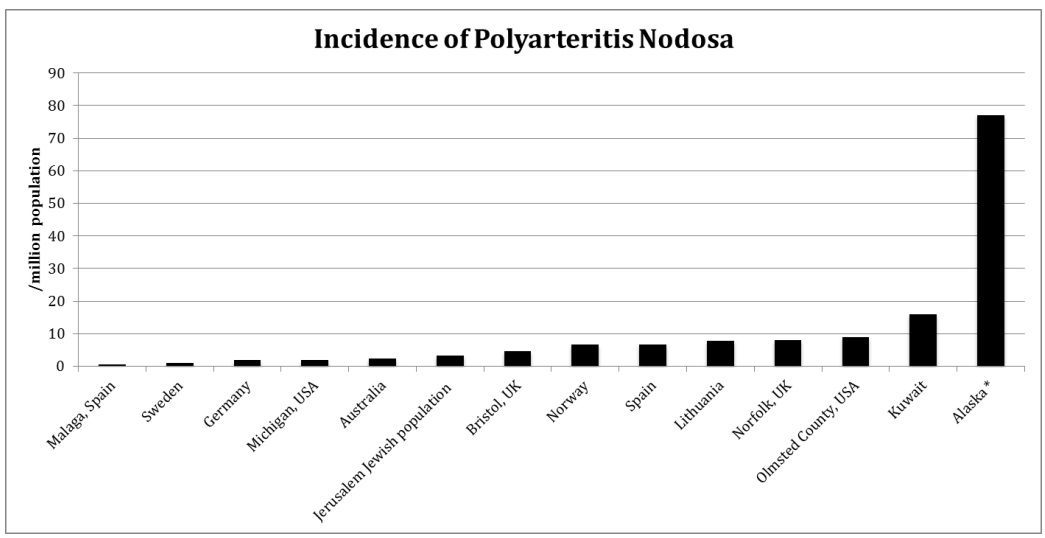

Figure 5. Incidence of polyarteritis nodosa.

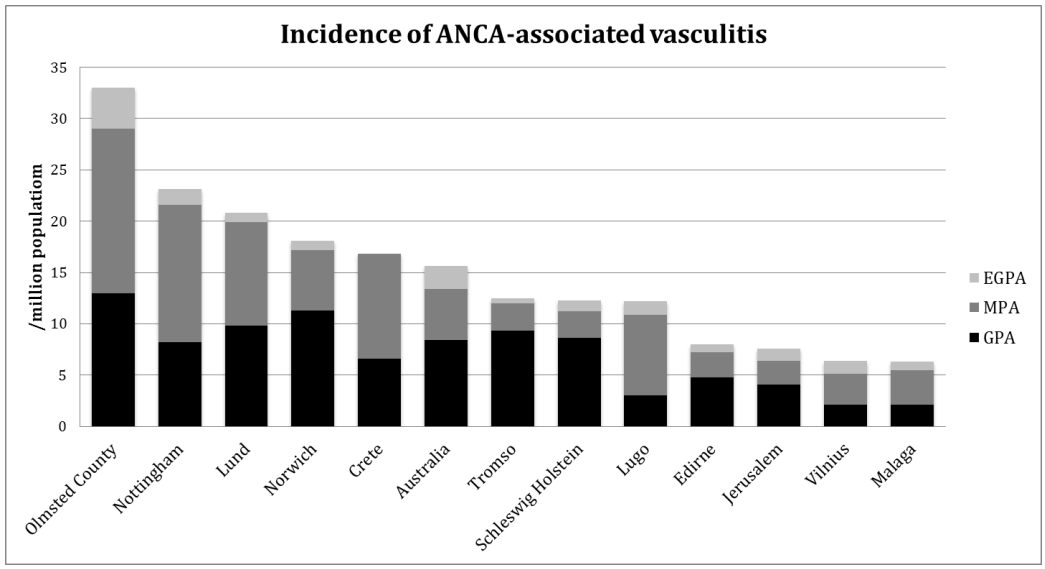

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Figure 6. Annual incidence of ANCA-associated vasculitis.

The prevalence of GPA doubled in northern Germany from 58/million in 1994, to 98/million in 2006 (Herlyn et al. 2014). A study from an urban multi-ethnic population of Paris showed a low prevalence of GPA of 23.7/million (Mahr et al. 2004). In Northern Europe, the prevalence of GPA in Norway increased from 30.4/million in 1988, to 95.1/million in 1998 (Koldingsnes & Nossent 2000), and was 160/million in Sweden in 2003 (A. J. Mohammad et al. 2007). The prevalence of GPA in the southern hemisphere was estimated at 112/million in New Zealand and 95/million in Australia (Ormerod & Cook 2008; Gibson et al. 2006).

There is a paucity of data on the prevalence of MPA which varies from 25.1/million to 94/million. (Figure 7). As expected, the prevalence of EGPA is much lower than either GPA or MPA, with the highest estimate being 45.7/million.

Genetic factors are clearly important as it has long been observed anecdotally that cases of AAV are relatively rare in non-Caucasian populations. The first study to show differences in the occurrence of AAV in different ethnic groups was reported from Paris, so suggesting that GPA was less common in people of non-European ancestry than MPA (Mahr et al. 2004). A study directly comparing two ethnically different populations, white UK Caucasian and the Japanese showed that the overall similar incidence rate for AAV, but GPA and PR3-ANCA vasculitis were much less common in Japan than in Europe (Fujimoto et al. 2011); whereas in Japan, MPA and MPO-vasculitis were the dominant form of AAV compared to Latin America (Peru) wherein MPA was more common than GPA (Sánchez Torres et al. 2005). In New Zealand, GPA was twice as common in Europeans than Maoris or Asians (O'Donnell et al. 2007). Large case series from China suggest that MPA is more common than GPA (Liu et al. 2008). A multi ethnic series from Chapel Hill, US found that GPA was relatively uncommon in African Americans (Cao et al. 2011). These differences may reflect global variation in the frequency of the allele HLA DPB1*0401, which has been associated with GPA (Watts et al. 2014). The north-south gradient in Europe may also reflect genetic differences between northern and southern Europeans (Tian et al. 2009). The clinical phenotype of systemic lupus

erythematosus (SLE) has been shown to differ between northern and southern Europeans (Chung et al. 2009) accounting for the different clinical phenotypes of AAV in northern and southern European populations commensurate with their different genetic background.

A recent study of the UKCPRD that investigated the role of preceding illness in the cause of GPA found a 5-fold (odd ratio [OR] 5.1 95% CI 2.7 - 9.4, $p < 0.0001$) increased risk of diagnosis of bronchiectasis in the 5 years preceding the diagnosis of GPA (Pearce et al. 2018). Patients with GPA were 2 to 3 times more likely than controls to have a previous diagnoses of an autoimmune disease and chronic renal impairment, and these effects also remained stable more than 5 years prior to diagnosis. People with GPA were more likely to have a diagnosis of pulmonary fibrosis (OR 5.7, 95% confidence interval [CI] 1.7 - 19.5, $p = 0.01$) and sinus infections (OR 2.7, 95% CI 1.8 - 4.2, $p < 0.0001$) recorded in the 3 years before diagnosis, but not before. A history of smoking, and a higher socio-economic status were significantly, but less strongly associated factors.

In an attempt to unravel the link between disease and latitudinal gradient, an ecological study was undertaken to examine the relationship between ambient ultra-violet radiation (UVR) and incident data from several international epidemiological studies. Ambient UVR was obtained from satellite data using the longitude and latitude of the largest urban center in any given area. The crude incidence rates of both EGPA and GPA increased with latitude, although only GPA achieved statistical significance. Using a negative binomial regression there was a modest increase in the incidence of both EGPA (3.4%) and GPA (3.5%) per higher degree of latitude. MPA showed no association in either analysis (Gatenby et al. 2009). Although UVR has local effects on the immune system in the skin (Ponsonby et al. 2005), and is of particular importance in SLE, the most plausible explanation for these findings is the effect on vitamin D synthesis, a hormone that has profound effects on the immune system, a finding observed in a wide range of inflammatory rheumatologic conditions. (Gatenby et al. 2013) There is however no population data on vitamin D from the cohorts for which we have AAV incident data and no series measuring vitamin D in patients and matched controls (Gatenby 2013).

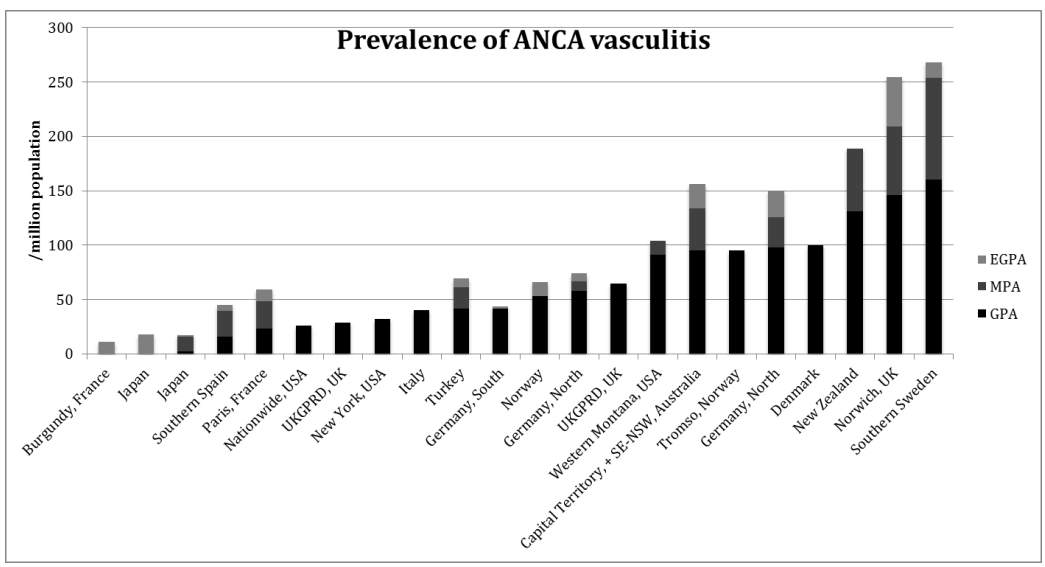

Figure 7. Prevalence of ANCA-associated vasculitis.

Silica appears to be a consistently identified risk factor among existing case-control studies for both GPA and MPA. This is not surprising given its known association with a number of other autoimmune syndromes (Steenland 2005). Commonly inhaled, the association with AAV is observed even in the absence of respiratory tract disease so suggesting an impact beyond the immediately exposed airways. Environmental dust was likely proposed as an important determinant with an association to silica (Gómez-Puerta et al. 2013). Studies in Japan after two large earthquakes suggested an increased incidence in the years immediately after earthquake (Yashiro et al. 2000; Takeuchi et al. 2017). However, an increased incidence was not seen after the Twin Towers attack in New York (Webber et al. 2015).

IMMUNE COMPLEX SMALL VESSEL VASCULITIS

IgA Vasculitis

IgA vasculitis or Henoch-Schönlein purpura, is an immune complex vasculitis that predominantly affecting small vessels (Jennette et al. 2013). This common childhood systemic vasculitis has the clinical characteristics of cutaneous palpable purpura, arthralgia/arthritis, bowel angina, and hematuria/proteinuria. The annual incidence which ranges from 3.5 to 27.6/100,000 in children, is highest between the ages of 4 and 6 years (70/100,000) (Gardner-Medwin et al. 2002). Two recent European studies reported similar incidences; a suburban area of Paris described an annual incidence of 18.6/100 000 (13.6 -24.5) children, and 17.5/100,000 (16 - 19.1) in Sweden (Piram et al. 2017; Mossberg et al. 2018). In the French study the annual distribution of diagnoses consistently showed a trough in summer months; 72% of children had infectious symptoms (mainly upper respiratory tract) a few days before the onset of IgAV; and 23% had a North African background (Piram et al. 2017). The outcome of IgAV in children is generally good with a low rate of development of renal failure.

IgA vasculitis is much less common in adults. Recent studies from Finland and Spain suggest an incidence of about 1.4 to 1.5/million adults, whereas earlier studies from the UK and Spain suggested an incidence up to 10-fold higher. It is not certain whether this represents different case capture approaches or classification. Adult onset IgAV is more common in males (63%) and has a mean age of onset of 50 years (Audemard-Verger et al. 2017).

Anti-Glomerular Basement Membrane Disease

Anti-glomerular basement membrane (GBM) disease or Goodpasture syndrome, is a vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti-basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents. This autoimmune disorder presents mainly with rapidly progressive glomerulonephritis and pulmonary hemorrhage in conjunction with increased serum levels of anti-GBM antibodies. The target “Goodpasture antigen” is the non-collagenous (NC1) region of the α3 chain of type IV collagen. Some patients also have ANCA present, leading to the suggestion of an overlap with AAV. Authorities debate whether the disorder represents a true

vasculitis or a vasculopathy. An Irish study calculated the national incidence at 1.64/million per year during the 11-year period of 2003 to 2014) (Canney et al. 2016).

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) is a rare form of immune complex vasculitis in which circulating cryoglobulins are demonstrated in serum or tissue. There is an association with myeloproliferative disorders, connective tissue diseases, in particular hepatitis C virus (HCV) infection. The incidence and prevalence of CV vasculitis is unknown. The outcome is dependent on the underlying condition. Modern antiviral therapies for HCV are highly effective in curing the infection and consequently improving the prognosis of affected individuals.

Hypocomplementemic Urticarial Vasculitis

There is very little data on the epidemiology of hypocomplementemic urticarial vasculitis (HUVS). A study from Sweden reported on 16 patients (14 women) all of whom were anti-C1Q antibody positive during the years 2000 to 2015 and derived from a well-defined population of 1,474,105. The annual incidence was 0.7/million with a point prevalence on 31 December 2015 of 9.5/million. There was no detectable age variation. The median age of onset was 51 years. The 5-year survival was 92%, with a 10-year survival of 83% (Sjöwall et al. 2018).

OTHER VASCULITIDES

Behçet Disease

The epidemiology of Behçet disease (BD) is characterized by a striking geographic variation with a greater incidence in an area spanning from China to the eastern Mediterranean Sea, leading to the descriptive term, *Silk Road disease*. The majority of studies in BD have been prevalence rather than incidence studies including many from countries where the health care system is challenged to obtain accurate incidence figures. Two main methods have been used: census surveys and sample surveys.

A recent meta-analysis of 45 population based surveys confirmed the geospatial variation in the prevalence of BD (Maldini et al. 2018). The global overall prevalence was 10.3/100,000 inhabitants. In Turkey the pooled prevalence was 119.8/100,000 inhabitants, 31.8/100,000 in the Middle East, 4.5/100,000 for Asia and 3.3/100,000 for Europe (Maldini et al. 2018). In Europe, there was a north-south increase in prevalence, suggesting that BD in those of Northern European ancestry. The case finding methodology has also strongly influenced the reported figures, with sample surveys giving generally higher estimated of the population prevalence compared census surveys; notwithstanding, the method employed to classify cases probably does not influence prevalence estimates (Maldini et al. 2017).

The geospatial distribution of BD is strongly related to expression levels of HLA-B*51, with prevalence being highest in Europe and the Middle and Far East, where HLA-B*51 is found in > 15% of individuals, and the prevalence being lowest in Africa (Wallace 2014).

SECONDARY VASCULITIS

Rheumatoid Vasculitis

Rheumatoid vasculitis (RV) first became widely recognized and reported in the 1960s. In the UK, the first estimate of the incidence was from Bath/Bristol in the 1970s and suggested an incidence of 6/million (Scott et al. 1981). In Spain, the annual incidence of biopsy proven RV during 1988–1997 was 6.4/million (González-Gay & García-Porrúa 1999). A detailed study conducted in Norfolk, UK, between 1988 and 2010, compared the incidence of RV between 1988 and 2000 with the period 2001 to 2010 (Ntatsaki et al. 2014). The annual incidence deceased from 9.1/million to 3.9/million. This decline occurred predominately during the late 1990s. The incidence in the Norfolk study was equal in both males and females. The decline in RV has been attributed to better disease control especially with the much wider use of methotrexate during the 1990s, and predates the common use of biologic drugs.

Several US studies have supported this decline in RV; a population based study of the incidence of extra-articular RA reported a reduction in the 10 year cumulative incidence of RV from 3.6% in 1985-1994 to 0.6% between 1995 and 2007 (Myasoedova et al. 2011). The reduction of the prevalence of RV was also reported in a serial cross-sectional study of both hospitalised and ambulatory patients from the US veteran population seen between 1985 and 2006, comprising a similar duration of cohort observation with our study of 22 years (Bartels et al. 2009). There has also been a decline in hospitalisation in California of SRV patients between 1980 and 2001 (Ward 2004).

CONCLUSION

The epidemiology of the vasculitides is much better understood now than was the case 20 - 30 years ago, however much of the data comes from populations of European descent. The main exceptions to this are KD and BD, which have very clear variations in geographical occurrence, for most other types of vasculitis it remains unclear how much geographical variation occurs. These variation give clues to possible genetic differences. There is still relatively little data from much of Asia especially the Indian subcontinent, Africa and Latin America. Knowledge of environmental risk factors is also sparse for most of the vasculitides.

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Chapter 4

HEALTH RELATED QUALITY OF LIFE AND ITS MEASUREMENT IN THE VASCULITIDES

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ABSTRACT

Patient reported outcomes (PRO) using mainly the generic Short-Form 36 have been studied in diverse systemic vasculitides, in particular in patients with anti neutrophil cytoplasmic antibody–associated vasculitis (AAV), who report significant impairment in their health-related quality of life (HRQOL). Patients report different priorities regarding disease assessment compared with their physicians and this should be captured in clinical studies. The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group, has gained endorsement by OMERACT for use of a disease-specific PRO, the AAV-PRO and generic Patient Reported Outcome Measurement Information System (PROMIS) instruments in clinical trials of vasculitis. Generic and disease-specific instruments are complimentary to each other and require further study to assess their utility in longitudinal settings, including their ability to distinguish between treatments of varying efficacy in randomized clinical trials (RCTs). This chapter reviews HRQOL measures in systemic vasculitis further separable by the caliber of vessels involved.

INTRODUCTION

Systemic vasculitis can be organ and life-threatening [1-3]. International randomized controlled trials with standardized outcome measurement have revolutionized their treatment

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[4-6]. Irreversible damage, ongoing disease activity and adverse effects of medications can all impact on Health-related quality of life (HRQoL) scores [7-9]. This chapter describes HRQoL and its measurement in systemic vasculitis.

CLASSIFICATION OF VASCULITIDES

The Revised 2012 International Chapel Hill Consensus Conference established distinct categories for the classification of vasculitis based upon the caliber vessels involved [10]. Large vessel vasculitis (LVV) including giant cell arteritis (GCA) and Takayasu arteritis (TAK) affects the aorta, its major branches and analogous veins. Medium vessel vasculitis (MVV) inclusive of polyarteritis nodosa (PAN) and Kawasaki disease (KD), involves main visceral arteries and veins and initial branches. Small vessel vasculitis (SVV) involvement affects intraparenchymal arteries, arterioles, capillaries, veins and venules, with disease mechanisms related to anti-neutrophil cytoplasmic antibody (ANCA) or immune complexes. The group of AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The subgroup of variable vessel vasculitis (VVV) includes Behçet disease (BD).

BACKGROUND

Measurement of HRQoL scores in systemic vasculitis has historically been based on generic patient reported outcomes (PROs), mainly the Short-Form 36 (SF-36) [11]. The benefits of the SF-36 is that it is a well- recognized and validated outcome measure [11] and allows comparison between patients with systemic vasculitis and other conditions. Limitations in the use of generic PROs can include a reduction in face and content validity, as they have not been designed to capture areas of most interest to patients with that specific disease [12]. This lack of specificity reduces the ability to detect differences in state between patients and in the same patient over time [12]. In GCA, the SF-36 does not detect differences between patients with and without visual loss or systemic involvement for example [13]. Trials in AAV fail to show difference in SF-36 scores between arms, despite use of less toxic medications such as cyclophosphamide versus rituximab [14]. Whether this is a lack of sensitivity with the SF-36 or due to glucocorticoid effects in the arms remains unanswered. The difference in HRQoL scores as measured by the SF-36 in a randomized controlled trial (RCT) of tocilizumab in GCA, which may be attributable to the reduction in glucocorticoid-related adverse effects in the tocilizumab only arm [15], requires further analysis.

The Outcome Measurement in Rheumatology (OMERACT) initiative is an international collaboration to define core sets of outcome measurements for use in RCTs [16]. Working groups include researchers, clinicians, patient partners, and methodologists; other stakeholders including the Food and Drug Administration (FDA) and representatives from pharmaceutical companies participate in the workshops [16]. The Vasculitis Working Group published a core set of domains and outcome measures for use in clinical trials in AAV in 2011 [17], and LVV in 2017 [18] and a core-set of domains for BD at OMERACT 2018. Due to the appreciation that patients and their physicians commonly rank aspects of their disease in different orders

[19], groups have recently been focused on the patient perspective in systemic vasculitis. This has included the development of a new disease-specific PRO, the AAV-PRO [20], underpinning qualitative work in TAK and BD [21, 22] and evaluation of alternative generic PROs such as the Patient Reported Outcome Measurement Information System (PROMIS) [23].

Disease-specific PROs developed with patient involvement at every stage are in line with guidance from the FDA on the development of PROs [24]. They should be based on underpinning qualitative research with patients and the specific disease to identify the full range of impacts of the disease and its treatment, ensuring good face and content validity [25]. Themes rewritten as candidate questionnaire items, including stems and response categories, and corresponding questionnaire items are then piloted and tested within cognitive interviews to check readability and understanding [26]. Large scale testing within a survey is then performed, using statistical analyses such as Exploratory Factor analysis [27] and Rasch analysis [28] to confirm the ideal structure of the PROM and validate its measurement properties [20, 29].

Generic and disease-specific PROs are complimentary [30] and can be used together, and adapted to the specific context of the study. The growing recognition of the importance of PROs in the assessment of vasculitis, and the availability of validated instruments to capture PROs in vasculitis, will likely mean patients' perspectives will also be incorporated into composite outcome measures in future trials.

SMALL VESSEL VASCULITIS

ANCA-Associated Vasculitis

Vasculitic involvement in the subgroup of AAV variably effects the kidneys, lungs, nervous system, skin, ears nose and throat, and eyes, resulting in intrusive symptoms, and irreversible damage and impact on HRQoL [2, 31].

The generic SF-36 has been used in clinical studies of patients with AAV and is a core outcome measure listed within the 2010 OMERACT core set [17]. Data from four European RCTs of newly diagnosed patients with AAV demonstrated impairment in HRQoL at entry [32]. Physical functioning scores were the most affected, particularly in those with neurological involvement and of older age [33]. A Scottish case-control study demonstrated that patients with AAV were twice as likely to have fatigue than matched controls, with levels of fatigue strongly associated with impairment in physical function [34]. Survey data suggests that AAV-related fatigue is multifactorial, with associations seen with increasing levels of pain, sleep disturbance and inflammation [35]. Fatigue was ranked by patients as being of greatest importance to their HRQoL, in contrast to physicians, who ranked being dialysis or oxygen dependent as more important [19].

The OMERACT Vasculitis Group has identified the lack of a disease-specific PRO for AAV [36]. An international collaboration of researchers and patients has overseen the development of a new PRO to fulfill this unmet need. Qualitative interviews with 50 patients with AAV from the United Kingdom (UK), United States (US) and Canada identified the following domains of interest: symptom severity, and the impact of problems and limitations

imposed by patients' ANCA-associated vasculitis and treatment on their work and domestic roles, family and social interactions, including activities and interests outside the home; and psychological state [31]. Themes used as underpinning data to develop candidate items for the new PRO and tested using cognitive interviewing and psychometric evaluation to create the final validated PRO [20].

The AAV-PRO 29-item questionnaire has six subscales/domains: "Organ-Specific Symptoms," "Systemic Symptoms," "Treatment Side Effects," "Social and Emotional Impact," "Concerns about the Future," and "Physical Function." The domains offer a comprehensive profile of the impact of AAV and its treatment on patients' everyday life [20].

AAV-PRO domain scores distinguish between patients who self-report active disease versus disease in remission, and therefore can be used as an outcome measure to define treatment success from the patient's perspective [20]. Scores for each separate domain are examined separately to provide a profile of the overall impact of the disease and its treatment on HRQoL. A greater focus is placed on pre-specified domains depending on the aims of the trial. For example, in a non-inferiority trial of a glucocorticoid-sparing agent, the treatment domain of the AAV-PRO might be key, but other investigators may instead wish to collect and analyze all domain scores to examine any differences across the symptoms and HRQoL domains. Further work is necessary to determine whether summary component scores are applicable to AAV-PRO.

Women scores are higher (i.e., worse) on all six subscales of the AAV-PRO [20] and in other conditions [37, 38]. Such trends in women were previously been reported in AAV [32]. Younger people (<65) scored higher (worse) on the Social and Emotional Impact subscale of the AAV-PRO, a trend also seen in other chronic diseases in this age group, potentially due to feeling different to peers, being unable to achieve ambitions and uncertainty at key stages of usual transition into adulthood [37, 39]. Younger age is a possible risk factor for negative illness perceptions in AAV, and increased levels of fatigue [40].

The PROMIS, which is a collection of generic item banks of self-reported health drawn originally from different diseases, in relation to fatigue and physical function, has been examined in patients with GCA, and appears feasible, with scores correlating with relevant SF-36 domain scores [23]. Further testing of different PROMIS item banks across other HRQoL domains within the systemic vasculitides is ongoing.

LARGE VESSEL VASCULITIS

Takayasu Arteritis

The symptoms of TAK are attributable to involvement of the aorta, its major branches, and the pulmonary arteries [41]. Constitutional symptoms related to systemic disease include weight loss, fever and fatigue; while those associated with vascular inflammation and occlusion lead to pain, claudication and tissue loss [41].

Health-related quality of life examined in Turkish patients via generic SF-36 showed worse scores in patients with TAK than healthy controls, in line with scores from patients with ankylosing spondylitis and rheumatoid arthritis [42]. A patient survey in the US identified an association between use of immunosuppressant medications and worse HRQoL probably due to severity of disease, while younger patients and those in remission had better HRQoL [7]. Patients with TAK have higher levels of anxiety and depression than healthy controls as well as physical limitations [43].

A review by the OMERACT Large Vessel Vasculitis Working Group identified the lack of a disease–specific PRO for TAK [44]. Qualitative research, including individual interviews and focus groups in the US and Turkey have identified domains of importance to patients with TAK [21]. Salient themes include, "Pain and Discomfort," "Fatigue and Low Energy Levels" and "Emotional Effects," that could underpin the future development of a disease-specific PRO [21].

Giant Cell Arteritis

Giant cell arteritis is associated with inflammation of cranial and neck vessels [45] and is a medical emergency due to the risk of blindness in 20% [46, 47]. Prompt treatment with high dose glucocorticoids (GC) is needed to protect vision [48, 49]. Presenting features include vice-like headache, jaw claudication, flu-like symptoms and inflammatory pain and stiffness in the shoulders and hips (polymyalgia rheumatica, present in 50%) [47]. For 60 years GC alone have been the mainstay of treatment, but patients are concerned about the risks [50-53]. Patient report the psychological impact of weighing up the necessity of treatment with GCs to prevent blindness, versus fears about adverse effects [50]. The use of novel biologic medications such as tocilizumab versus standard GC regimens, does appear to benefit patients in terms of their HRQoL at one year [15], and this should be examined further.

Qualitative research in the UK has revealed the impact of GCA on patients' lives is due to their symptoms (e.g., pain, visual disturbance and musculoskeletal symptoms), adverse effects of glucocorticoids, and the disruption to normal life [54]. Patients fear blindness and have concerns about delay in diagnosis [54]. Patients with GCA ranked "losing sight in both eyes permanently," "having intense or severe pain" and "feeling weak, tired or exhausted" as the most important domains of health-related quality of life [55].

The OMERACT Vasculitis Working Group has highlighted the development of a disease-specific PROM for GCA as one of the next steps in their research agenda [18, 56]. Generic PROs alone may not be specific enough for use in GCA. SF-36 scores in patients with GCA do not correlate with visual loss or systemic complications, so may be unable to differentiate between clinically important groups [13, 57].

Underpinning qualitative work with patients in the UK and Australia was presented, revealing themes including: "Anxieties around getting a diagnosis of GCA," "Description of symptoms related to GCA and its treatment," "Lack of bodily strength, stability and stamina; difficulties with completing daily tasks," "Difficulties with participating in social activities, work and caring roles," "Not feeling normal and impact on general perception of health," "Anxiety and fear of the future" [58]. Themes are being developed further into candidate questionnaire items for a disease specific PRO for GCA.

VARIABLE VESSEL VASCULITIS

Behçet Disease

Behçet disease is a variable vessel vasculitis affecting veins and arteries of different sizes [10]. Male and female patients present in young adulthood with a spectrum of different disease manifestations [59]. Organ involvement can include mucocutaneous (such as oral and genital ulcers, nodular and papulopustular skin lesions), ophthalmological (panuveitus), musculoskeletal (usually monoarthritis or arthralgia), neurological (from parenchymal stroke-like syndromes, to cerebral venous thrombosis [60]) and/or gastro-intestinal involvement (which can present in a similar to inflammatory bowel disease) [59].

Patients with BD have worse SF-36 scores compared with healthy controls, particularly in women and those with high disease activity [61]. Mucucutaneous (oral and genital ulcers), central nervous system, musculoskeletal and ocular involvement are all independent predictors of worse HRQoL [61]. Physical functioning is most impaired in panuveitus compared with other ocular presentations [61]. Sexual function can be impaired in men and women [62]. Patients reporting high activity in relation to their joints, oral ulcers and fatigue, scored highly on the physical domains of the Nottingham Health Profile (NHP); joint and oral ulcer activity was also correlated with high psychosocial subscale NHP scores [8].

A systematic review of outcome measures used in BD by the OMERACT Vasculitis Working Group revealed a lack of standardization and large variability in terms of outcomes used across trials [63].

There is a validated disease specific HRQoL measure, namely, the BD-QoL scale [29, 64-66] which has undergone cross-cultural adaptation and validation in Korean and Arabic [64, 67]. Item development was based on underpinning qualitative work with patients with BD in the UK, and included the following salient themes: “Relationships,” “Emotions,” “Limitations in Day to Day Activities” and “Self-Image” [29].

Generic measures to evaluate HRQOL in trials in BD have largely been the SF-36 [68] and the EQ-5D [63]. A range of different symptom-specific tools have been used, including the Oral Health and Related Quality of Life scale, which has been validated in Turkey and the UK in BD [69]. Symptoms specific tools to measure impact on Sexual Function (e.g., the Arizona Sexual Experience Scale [62] and Sleep (e.g., the Pittsburgh Sleep Quality Index [70]) have also been used, but not in a systematic way across trials [63]. Psychological impact has most commonly been measured within trials of BD using the Beck Depression Index [71] and Beck Anxiety Scale [66, 72].

The OMERACT Vasculitis Working Group continues to work towards standardized assessment of BD within clinical trials [22]. A new core set of outcome domains for BD, including HRQoL as a core domain, was ratified at OMERACT 2018. The core domain set will be published this year; next steps within the OMERACT process will be to evaluate and recommend appropriate tools with which to measure these domains, including HRQoL [73]. Use of generic, disease-specific and symptom specific tools may be appropriate depending on context, i.e., whether the trial is focused on a specific organ manifestation.

CONCLUSION

The impact of symptoms and side effects of treatment in systemic vasculitis can affect all aspects of HRQoL, depending on stage of life. Systemic vasculitis affects people of working age [74], those planning a family [75] or active retirement [54]. Patients also face the situation of having a rare autoimmune rheumatic disease [76] which can be isolating, results in delays to get a diagnosis and treatment, and difficulties in navigating health care systems between different specialists [76].

Patients have different perspectives on their disease and its impact than their clinicians and it is important to capture this within clinical studies using validated outcome measures.

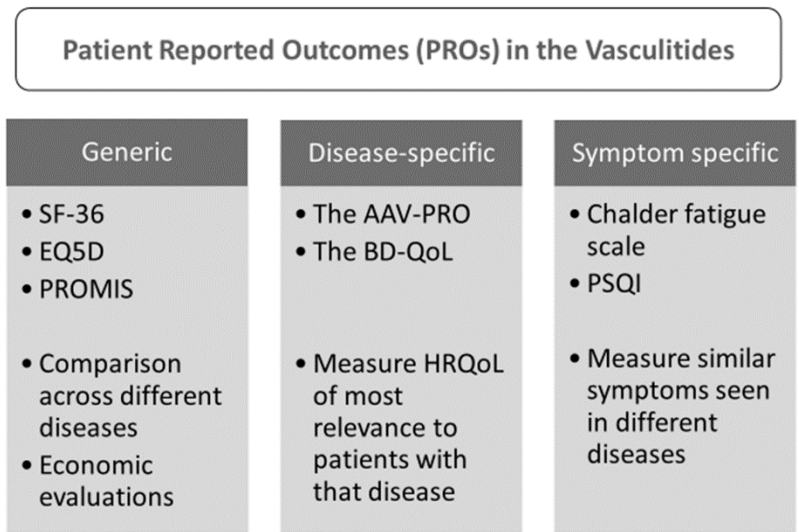

Figure 1. Patient Reported Outcomes (PROs) in the Vasculitides.
Key. SF-36: The Short Form 36; EQ5D: The EuroQOL five dimensions questionnaire; PROMIS: Patient Reported Outcome Measurement Information System; AAV-PRO: Disease specific PRO for ANCA-associated vasculitis; BD-QoL: Disease specific PRO for Behcet's Disease; PSQI: Pittsburgh Sleep Quality Index.

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Chapter 5

NEUTROPHILIC CELL PATHOBIOLOGY IN THE VASCULITIDES

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ABSTRACT

Neutrophils play a critical role in the pathogenesis of vasculitides, especially in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). ANCA cooperates with pro-inflammatory cytokines in activating neutrophils. Activated neutrophils contribute to the development of small vessel vasculitis. The ANCA-cytokine sequence is pivotal to the understanding the pathogenesis of AAV. Recent studies reveal that neutrophil extracellular traps (NETs) extruded from activated neutrophils are implicated in vascular endothelial cell (VEC) injury. NETs are also implicated in the mechanism of ANCA production. These findings suggest that the NETs-ANCA vicious cycle is involved in the pathogenesis of AAV. This chapter updates the literature relating to ANCA-cytokine sequence theory.

Keywords: ANCA-associated vasculitis, ANCA-cytokine sequence, NETs-ANCA vicious cycle, NETs-ANCA-cytokine sequence

INTRODUCTION

Neutrophils play critical roles in the pathogenesis of vasculitides, especially in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). They are primed by pro-inflammatory cytokines, such as TNF-α, and express myeloperoxidase (MPO) and proteinase 3 (PR3) on the cell surface. ANCA binds to the antigen and simultaneously bridges the antigen and bystander Fcγ receptor on the cell, which activates neutrophils. Consequently,

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the activated neutrophil releases reactive oxygen species (ROS) and lytic enzymes, in turn contributing to the development of small vessel vasculitis (SVV). This ANCA-cytokine sequence therapy is pivotal for the understanding of AAV [1]. Recent studies have revealed that neutrophil extracellular traps (NETs) extruded from the activated neutrophils are also implicated in vascular endothelial cell (VEC) injury [2, 3]. Recent reports suggest involvement of NETs in the mechanism of ANCA production [4-6], as well as in ANCA-mediated cytotoxicity.

This chapter focuses on NETosis and the neutrophilic cell metamorphosis of NET formation in AAV.

Discovery of NETs

In 2004, Brinkmann and coworkers [7] reported that phorbol myristate acetate (PMA)-stimulated neutrophils extrude decondensated DNA that form extracellular web-like structure decorated with bactericidal proteins, such as MPO and PR3. These substances, termed NETs, bind to, and kill bacteria. NET formation is regarded as an important event of innate immunity.

Patients with chronic granulomatous diseases (CGD) who fail to generate NETs are susceptible to diverse bacterial and fungal infections. However, restoration of NET formation in CGD results in resistance to such infections [8]. NETs appear to be an innate response that binds microorganisms, prevents them from spreading, and ensures a high local concentration of antimicrobial activity derived from neutrophils [9].

Process of NET Formation

PMA-stimulated neutrophils undergo cell death with NET formation [10]. Since the characteristics of cell death resembles neither typical necrosis nor apoptosis, Steinberg and colleagues [11] coin NETosis for neutrophilic cell death with NET formation. NETosis induction by PMA requires activation of the Raf-MEK-ERK pathway, with NADPH oxidase-dependent production of ROS, and RIPK1-RIPK3-MLKL signaling [12, 13]. In this pathway, peptidylarginine deiminase 4 (PAD4)-dependent citrullination of histones induces decondensation of DNA resulting in a mixture of DNA and bactericidal proteins, contained originally in intracytoplasmic granules [14]. Thereafter, these substances extrude from the ruptured plasma membranes of neutrophils.

NETs in AAV

Kessenbrock and coworkers [4] first showed that ANCA derived from AAV induces NETs from TNF-α-primed neutrophils obtained from healthy donors. They also demonstrated co-localization of extracellular DNA, neutrophilic enzymes, and histones. NET formation was evident in crescents of glomeruli affected by AAV.

Subsequent investigations noted similar findings using citrullinated histones as a specific marker of NETs [15-17].

Vascular Endothelial Cell Toxicity of NETs

Carmona-Rivera and coinvestigators [18] demonstrated that direct incubation of VEC lines with NETs promoted VEC death. The cytotoxicity of NETs is mediated by matrix metalloproteinase (MMP)-9, which is externalized from neutrophils. NET formation and activation of MMP-2 in VECs culminates in cell death. The neutralization of MMP-9 prevents MMP-2 activation in VECs leading to a decrease in NET-medicated cytotoxicity.

Thrombosis Induced by NETs

Patients with AAV are predisposed to deep vein thrombosis (DVT), especially during the active stage of the disease [19]. As ANCA induces NET from the primed neutrophils, NETs are critically associated with DVT as histones within NETs bind platelets and coagulate blood [20, 21]. Such findings are consistent with an abundance of NETs detected in DVTs of patients with AAV [15, 17]. The collective findings suggest a link between AAV, accelerated thrombosis and DVT via NETs.

Degradation of NETs

NETs play an essential role in the innate immune system with excessive formation and persistence of NETs, a consequence of which is the heightened risk of adverse events. Notwithstanding, NETs are strictly regulated *in vivo*. The most important NET degradation factor is serum DNase I [22].

Propylthiouracil Induces DNase I-Resistant NETs

Propylthiouracil (PTU) is an anti-thyroid drug used for the treatment of hyperthyroidism. Approximately 30% of patients administered with PTU produce MPO-ANCA, some of whom develop MPO-AAV. The majority of PTU is metabolized in the liver. However, MPO in neutrophils also modifies PTU [23]. We hypothesize that PTU influences the formation or regulation of NETs and induces MPO-ANCA, and subsequently MPO-AAV [5]. We examined whether the addition of PTU created an impact on the formation or regulation of NETs *in vitro*. Widely extended DNA fibers studded with MPO are observed when human neutrophils are treated with PMA alone. To the contrary, treatment with PMA with PTU leads to a rounded-shape distribution of DNA fibers. The ensuing NETs surround dead neutrophils. Although DNase completely digests PMA-induced normal NETs, abnormal NETs induced by PMA with PTU is barely digested by DNase I. These findings clearly indicate that PTU influences NET formation and degradation by DNase I.

DNase I-Resistant NETs Cause ANCA Production

Next, we examined whether the DNase I-resistant NETs induced the production of MPO-ANCA *in vivo*. For this purpose, we generated rodent models. WKY rats and BALB/c mice are given oral PTU with intra-peritoneal injection of PMA [5, 24]. Contrary to the finding that widely extended NETs are observed in the peritoneal tissues of the PMA-injected models without PTU administration (PMA-treated models), NETs in the PMA-injected models with PTU administration (PTU/PMA-treated models) do not extend outward. Those in peritoneal tissues of PTU/PMA-treated models are significantly larger than NETs of PMA-treated models. These findings correspond to *in vitro* data indicating an abnormal conformation and impairment of NETs degradation induced by PMA with PTU. As expected, MPO-ANCA is produced in the PTU/PMA-treated models [5, 24]. Moreover, the amount of NETs in the peritoneal tissues and the titer of MPO-ANC are significantly decreased when PTU/PMA-treated mice are administered the PAD inhibitor, Cl-amidine [24]. The collective findings clearly indicate that PTU induces the NETs disorder and the subsequent production of MPO-ANCA.

Implications of Disordered NETs in the Pathogenesis of AAV

Although most patients with MPO-AAV are not administered PTU, undetermined environmental factors that act like PTU, such as infectious exposures may induce the disorder of NETs and trigger the MPO-ANCA production resulting in the development of MPO-AAV [25].

NETs-ANCA Vicious Cycle in AAV

Hakkim and colleagues [22] demonstrated that a subgroup of systemic lupus erythematosus (SLE) patients hardly digested NETs because of the low activity of serum DNase I. Similar to SLE patients, serum DNase I activity in AAV is significantly lower than healthy controls [26]. These findings suggest that involvement of the NETs-ANCA vicious cycle in the pathogenesis of AAV (Figure 1).

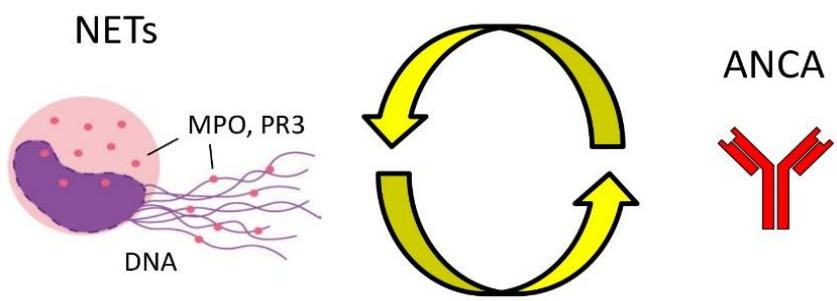

Figure 1. NETs-ANCA vicious cycle in the pathogenesis of AAV. An excessive formation and/or persistence of NETs under low degradation condition can cause ANCA production. Simultaneously, ANCA can induce further NET formation from primed neutrophils.

The Formation of the Pauci-Immune Lesion in AAV

AAV is characterized by necrotizing crescentic glomerulonephritis and SVV. Although the pathogenic role of ANCA in the formation of necrotizing lesions can be demonstrated, there is little deposition of immunoglobulins (Ig) in affected tissues. This histological feature is termed, "pauci-immune". Futamata and colleagues [27] reported the release of elastase from NET-forming neutrophils, digesting Ig, including ANCA, in pauci-immune lesions in AAV.

CONCLUSION

Neutrophils play a critical role in the pathogenesis of vasculitides, especially AAV. The ANCA-cytokine sequence is pivotal to the etiopathogenesis of AAV. There is an increasing literature supporting the role for an NETs-ANCA vicious cycle in AAV and the related contribution of NETs-ANCA-cytokine sequence theory.

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Chapter 6

COMPLEMENT FACTORS IN ANCA-ASSOCIATED VASCULITIS

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are potentially life-threatening autoimmune diseases. The histopathological hallmark is a "pauci-immune" necrotizing crescentic glomerulonephritis. It has been assumed that the complement system is not involved in the development of AAV, however, new evidence suggests that the complement system is crucial in the pathogenesis of AAV. This article reviews updated information on clinical, *in vivo* and *in vitro* evidence for the role of complement activation in the development of AAV. Activation of the alternative pathway is crucial for the development of AAV, and the complement activation product C5a plays a central role. Activation of the alternative pathway of complement, at least in part *via* activated neutrophils, results in the generation of C5a, which is a strong chemoattractant for neutrophils. C5a is also effective in neutrophil priming, a process leading to increased membrane expression of the ANCA antigens, enabling neutrophils to be further activated by ANCA. Blocking complement, especially C5, is a potentially promising approach in the treatment of AAV.

Keywords: ANCA, complement, renal, vasculitides

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INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are life-threatening systemic autoimmune diseases, comprising granulomatosis with polyangiitis [GPA, previously named Wegener's granulomatosis (WG)], microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiits (EGPA) [1]. ANCA are serological markers for the abovementioned vasculitides, predominantly IgG class autoantibodies against primary granule constituents of neutrophils and lysosomes of monocytes. By indirect immunofluorescence (IIF) on ethanol-fixed neutrophils, two fluorescence patterns of ANCA are distinguished, a cytoplasmic staining pattern (cANCA) and a perinuclear staining pattern (pANCA). Most patients with a cANCA pattern have ANCA directed against proteinase-3 (PR3) while pANCA is associated with several antigens, in particular, myeloperoxidase (MPO) [2].

Renal involvement occurs frequently in AAV and is histopathologically characterized by pauci-immune necrotizing crescentic glomerulonephritis (NCGN), characterized by little or no glomerular staining for immunoglobulins or complement. It was previously assumed that the complement system was not involved in the development of AAV, however, emerging evidence has suggests that activation of the complement system plays a significant role in the pathogenesis of AAV. This article reviews updated information on clinical, *in vivo* and *in vitro* evidence for the role of complement system in the development of AAV.

THE COMPLEMENT SYSTEM

At the turn of the nineteenth century, the complement system was already considered a major part of the innate immune system and is one of the main effector mechanisms of antibody-mediated immunity. A wide range of its biological activity is due to the cooperation of more than 30 plasma proteins [3, 4]. In humans, the complement can be activated *via* the three pathways: classical pathway, alternative pathway and lectin pathway.

The classical pathway is initialized when C1q binds to antibody attached to antigen, activating C1r and C1s, which cleave C4 and C2. The lectin pathway is activated when mannose-binding lectin (MBL) encounters conserved pathogenic carbohydrate motifs, activating the MBL-associated serine proteases (MASPs) and cleaving C4 and C2 the cleavage products of which form the classical and lectin pathway C3 convertase, including C4bC2a, which cleaves C3 into C3b and C3a. The latter is a chemo-attractant factor while sufficient C3b associates with C4bC2a to form the C5 convertase of the classical and lectin pathways, including C4bC2aC3b.

The alternative pathway is activated when C3 undergoes spontaneous hydrolysis and forms the initial alternative pathway C3 convertase, including $C3(H_2O)Bb$, in the presence of factors B and D, leading to additional C3 cleavage and eventual formation of both alternative pathway components C3 (C3bBb) and C5 convertase (C3bBbC3b). Properdin facilitates alternative pathway activation by stabilizing alternative pathway convertases.

All three pathways culminate in the formation of the convertases, which in turn generate the major effectors of the complement system that includes among others, anaphylatoxins C4a/C3a/C5a, membrane attack complex (MAC) and the opsonin C3b. Anaphylatoxins are

potent proinflammatory molecules derived from the cleavage of C4, C3, and C5. MAC is the terminal assembly of complement components C5b through C9, which directly lyse targeted surfaces. C3b induces phagocytosis of opsonized targets and also serves to amplify complement activation through the alternative pathway.

Due to the destructive potential of complement activation, especially in light of the potent feedback amplification ability of the alternative pathway, complement activities need to be confined to appropriate pathogenic surfaces. The generation of potent effectors needs to be tightly regulated to prevent collateral damage to healthy host tissues. Several steps are involved in complement activation checked by inhibitors so that the final system represents an intricate, homeostatic balance between the efficient detection and destruction of pathogens and the minimization of bystander tissue damage. Among them, complement factor H (CFH) is a key regulatory component of the alternative complement pathway. CFH impedes the formation of alternative pathway C3 convertases (C3bBb) by competing with factor B for binding to C3b, and accelerates the decay of C3bBb. CFH acts as a co-factor for the factor I-mediated proteolytic inactivation of C3b.

CD46, CD55 and CD59 are major membrane-associated regulators of complement in human cells. CD46 (membrane cofactor protein), is a ubiquitously expressed type 1 transmembrane glycoprotein that acts as a cofactor for factor I mediated cleavage of C3b and C4b, preventing formation of the classical and alternative C3 convertase. CD46 also regulates the amplification loop of the alternative pathway of activation of complement [5]. CD55 (decay accelerating factor) is a glycosylphosphatidylinositol (GPI) anchored protein, which serves to inhibit assembly of new C3 convertases and shorten the half-life of preformed convertases, thereby limiting their ability to participate in further complement activation [6]. CD59 (protectin) is a naturally occurring inhibitor of MAC found tethered to the membranes of cells *via* a GPI anchor [7].

Additional complement regulators include the above mentioned factor I, which mediates cleavage of C3b and C4b, preventing formation of active convertases; in addition to cofactor activity and surface-expressed complement receptor 1 (CR1). The latter exhibits decay accelerating activity and cofactor activity for factor I. C1 inhibitor, a serine protease that irreversibly binds to and inactivates C1r, C1s, MASP-1, and MASP-2, limits classical and lectin pathway activation, as well as C4-binding protein (C4BP) [8].

CROSS-TALK BETWEEN COMPLEMENT AND OTHER SYSTEMS

Cross-Talk between Complement and the Coagulation System

The complement and coagulation systems have a number of common characteristics and many potential implications for health and diseases. Activation of both systems lead to conversion of zymogens and assembly of proteolytic complexes that are mainly serine protease-mediated activation steps. Recent evidence indicates that some serine proteases, in particular, plasmin and thrombin from the coagulation cascade, directly activate C3 and C5, independent of the traditional C3/C5 convertase, generating biologically active C3a and C5a [9, 10].

The interaction between platelets and complement has important implications for innate immunity especially when the latter is in an activated form [11]. Platelets may express the

receptors of C3a and C5a (C3aR and C5aR) [12], while C5b-9 may induce platelets to release α-granules and microparticles [13]. Del Conde and co-workers [14] found that activated platelets activate the complement system which in turn increases C3a generation, C3b deposition, and C5b-9 formation. For detailed information of the interaction between complement and platelets, see the comprehensive review by Speth and colleagues [15].

Cross-Talk between Complement and Pattern Recognition Receptors

Pattern recognition receptors (PRRs) are essential components in the innate immunity, recognizing pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [16]. PRRs include Toll-like receptors (TLRs), leucine-rich repeat-containing receptors (NLRPs), nucleotide-binding oligomerization domain (NOD)-like receptors, RIG-I-like receptors, and C-type lectin receptors [17]. Examples of PAMPs include endotoxin or lipopolysaccharide (LPS) of gram-negative bacteria, lipoteichoic acid of gram-positive bacteria, and β-glucan of fungi [18]. The crosstalk starts when MBL binds to common carbohydrate PAMPs on gram-positive and gram-negative bacteria and yeast, as well as viruses and parasites, activating the lectin pathway through the abovementioned chain reaction [19].

Furthermore, substantial studies have revealed more intense interactions between complement and TLRs as well as NLRPs in a variety of inflammatory diseases. For example, Raby and co-workers [20] demonstrated *in vitro* activation of TLRs that mediated the down-regulation of C5a-like receptor 2 (C5L2), thus enhancing C5a-induced inflammatory responses. In a mouse model of polymicrobial sepsis, factor B, which is the unique component of the alternative pathway, acts as a downstream effector of TLR signaling [21].

Cross-Talk between Complement and Adaptive Immunity

The complement system provides a link between innate and adaptive immunity. Complement depletion can impair antibody production, as there might well be a requirement for functional C3 in the induction of thymus-dependent, but not thymus-independent antibody production [22]. The deeper mechanism might involve antigen-bound C3dg, and iC3b cleavage product binding to B-cell-expressed CR2 (CD21), which facilitates antigen presentation to B-cells, lowering the threshold for its activation [23].

There are other unexpected roles for complement as a regulator of T-cell immunity. Immune cells, including T-cells and antigen-presenting cells (APCs), produce alternative pathway complement components during cognate interactions [24]. The subsequent local complement activation yields production of the anaphylatoxins C3a and C5a, which bind to C3aR and C5aR respectively on both partners to augment effector T-cell proliferation and survival, while simultaneously inhibiting regulatory T-cell induction and function [25]. CFH, as an immunological brake, may directly affect the function of adaptive immunity by decreasing the production of key proinflammatory Th1-cytokines, including interleukin (IL)-12, interferon (IFN)-γ, IL-6 and IL-8, from dendritic cells, while promoting the production of immunomodulatory mediators (IL-10 and transforming growth factor [TGF]-β), impairing effector CD4 (+) T cell alloproliferation and conversely, inducing Foxp3 (+) regulatory T-cells

(Tregs) [26]. Figure 1 shows an overview of the complement system and the interactions with other systems.

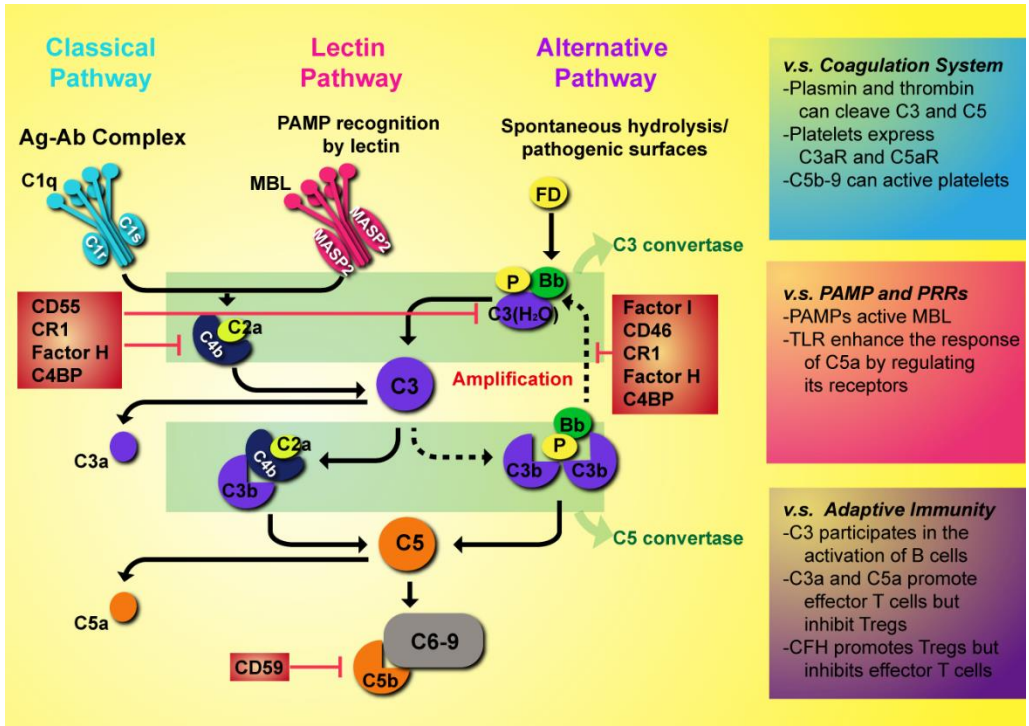

Figure 1. The three pathways of complement activation: the classical, lectin and alternative pathways. There are three pathways of complement activation: the classical, lectin and alternative complement pathways. Activation of the classical pathway begins with the binding of immune complexes to C1q leads to the activation of its C1r and C1s serine protease subunits. Then, C1s activates C4 and C2 and subsequently results in the formation of the classical pathway C3 convertase, C4bC2a. The alternative pathway is initiated by hydrolysis of C3. Factor D cleaves the C3b-bound factor B, resulting in the formation of C3bBb, the C3 convertase. The lectin pathway is activated through the binding of MBL and MASP. MASP can cleave and activate C4 and C2 to form C4bC2a. Activation of any abovementioned pathway leads to activation of C3. Activation of C3 generates C3b and C3a, a chemo-attractant factor. Sufficient activation of C3 leads to the activation of C5. C5 activation leads to the formation of C5a and C5b-9. There are also crosstalk between the complement system and coagulation system, pattern recognition receptors and adaptive immunity.

PATHOGENIC ROLE OF ANCA AND NEUTROPHILS IN AAV

The pathogenesis of AAV is complex as can be appreciated in ANCA-mediated glomerulonephritis, which is attributed to possible infectious mediation and a multistep process that includes recruitment and priming of neutrophils to glomeruli. There, recruited ANCAs initiate injury by activation of primed and adherent neutrophils directly leading to endothelial injury. ANCA-induced neutrophil activation also causes an inflammatory amplification loop leading to complement activation and generation of C5a that might in turn exert its role the development of AAV [27].

ANCA IN THE PATHOGENESIS OF AAV

The most convincing evidence for the pathogenic role of ANCA comes from animal studies. Xiao and co-workers [28] immunized MPO-/- mice with mouse MPO and obtained MPO-ANCA IgGs or MPO-reacting splenocytes. MPO-ANCA IgGs or MPO-reacting splenocytes were injected into recipient mice. All the mice that received MPO-ANCA IgGs developed pauci-immune crescentic glomerulonephritis. The mice that received high doses of MPO-reacting splenocytes developed severe NCGN with systemic necrotizing vasculitis. Schreiber and co-workers [29] reported a modified mouse model of anti-MPO induced disease, further documenting the pathogenic potential of ANCA. MPO knockout (MPO-/-) mice were immunized with mouse MPO and exposed to irradiation and transplanted bone marrow (BM) cells from either MPO-/- or MPO+/+ wild type mice. Transfer of MPO+/+ BM cells into irradiated MPO-/- mice led to disease development, while transfer of MPO-/- BM cells into irradiated MPO+/+ mice did not, demonstrating that MPO+/+ BM-derived cells were pathogenic targets for anti-MPO IgG in the cause of disease. Little and co-workers [30] immunized rats with human MPO, inducing the generation of antibodies against human MPO, cross-reacting with rat neutrophils. Almost all the recipient rats developed pauci-immune glomerulonephritis and pulmonary capillaritis, indicating a direct pathogenic role of ANCA *in vivo*.

In vitro studies have verified the pathogenic role of ANCAs. Neutrophils stimulated by pro-inflammatory factors, especially TNF-α or C5a, target antigens of ANCAs, MPO and PR3, move from the cytoplasm to the cell membrane in a process termed priming. ANCAs combined with their target antigens, and cross-linked with Fc receptors on neutrophils, are induced to undergo a respiratory burst and degranulate, playing a direct pathogenic role in the development of systemic vasculitis [31]. A randomized controlled trial by the European Vasculitis Study Group (EUVAS) [32, 33] showed superiority of plasma exchange (PEX) over intravenous methylprednisolone in restoring renal function, thus supporting a pathogenic role for circulating ANCA in renal vasculitis.

NEUTROPHILS IN THE PATHOGENESIS OF AAV

Investigators [28] reported the development of NCGN in an experimental mouse model of accompanied by glomerular accumulation of neutrophils and macrophages providing direct evidence that neutrophils played a major role in the pathogenesis of anti-MPO-induced NCGN in this animal model and implicated neutrophils in the induction of human ANCA disease. Later studies [34] showed that neutrophil depletion prevented disease development in recipient mice. While pro-inflammatory mediators could prime neutrophils by inducing translocation of more ANCA antigens from the cytoplasm to the cell surface *in vitro;* ANCAs further activate primed neutrophils to undergo respiratory burst and degranulation, suggesting the pathogenic role of neutrophils in AAV.

One other important mechanism of neutrophil effector function in the development of AAV was reported by Kessenbrock and colleagues [35] who found that ANCA-mediated neutrophil activation induced the formation of neutrophil extracellular traps (NETs), which are fibrous networks containing DNA, histones, and neutrophil granule proteins, triggering vasculitis and

promoting the autoimmune response against neutrophil components. Excessive NETs formation was further found to be related to active clinical disease in patients with AAV [36]. NETs could enhance the uptake of ANCA antigens PR3 and MPO by myeloid dendritic cells [37], and activate autoreactive B-cells and ultimately the induction of ANCAs [38].

EMERGING ROLE OF THE COMPLEMENT SYSTEM IN THE PATHOGENESIS OF AAV

ANCA-associated glomerulonephritis, characterized by pauci-immune NCGN histopathologically, showed little, if any, immunoglobulin and complement deposition in the glomeruli of AAV patients leading to the initial assumption that the complement system might not be involved in the development of AAV. However, observations in animal models and human disease, as well as increasingly sophisticated mechanism studies *in vitro* and in rodent models *in vivo*, have allowed a more nuanced understanding of complement system in the pathogenesis of AAV.

Evidence from the Animal Studies

Pre-treatment of mice with cobra venom factor to deplete complement, and C5 deficient mice fail to develop glomerulonephritis and vasculitis whereas disease development was comparable to wild type mice in C4-deficient mice, and C5- or factor B-deficient mice were completely protected from the disease [39]. This suggests that complement activation via the alternative pathway of complement system is critical to the development of AAV. The importance of inflammatory cell activation by C5a in amplifying the anti-MPO IgG-induced inflammatory response, was later appreciated. Huugen and colleagues [40] found that pretreatment with anti-C5 inhibiting monoclonal antibody prevented or strongly attenuated the development of ANCA-associated glomerulonephritis in mice. Schreiber and co-workers [41] investigated the role of the C5aR (CD88) in a model of ANCA-induced NCGN noting that C5aR-deficient mice were protected from developing NCGN. Xiao and investigators [42] further elucidated the role of C5a and its receptors in a mouse model of anti-MPO-induced NCGN, noting that CD88 deficiency ameliorated the disease, while C5L2 deficiency resulted in more severe disease. This indicated that CD88 enhances, while C5L2 suppresses, the inflammatory reactions. A recent study by Dick and co-workers [43] delineated the a role of CD88 in the generation of anti-MPO autoimmunity, and effector responses that resulted in renal injury by employing an experimental active autoimmunity to MPO by an anti-GBM globulin trigger model, however the pathological changes were prevented by CD88 inhibition.

Evidence from Human Studies

Several studies found a certain degree of immune complex and complement C3c deposition, which correlated with poorer renal function [44, 45]. Chen and colleagues [46] analysed renal biopsies in 112 patients with ANCA-associated pauci-immune

glomerulonephritis noting that C3c could be detected in glomeruli of a third of specimens. However, the intensity of C3c deposition was mild to moderate, and patients with C3c deposition had more severe lesions in the kidneys than those without C3c deposition, along with higher levels of proteinuria, poorer renal function at presentation, higher percentage of crescents and more severe tubulointerstitial lesions.

Scaglioni and co-workers [47] found that 26.4% of patients with ANCA-associated glomerulonephritis were actually not pauci-immune, and immune deposits were associated with higher proteinuria. Researchers investigated various components of complement in kidney specimens of patient. Xing and coinvestigators [48] found that C5b-9, C3d, and factor B, but not C4d, could be detected in the renal specimens; while C3d and factor B co-localized with C5b-9 in active glomerular lesions. The deposition of Bb, a marker of the alternative complement pathway activation in glomeruli of AAV patients correlated positively with the proportion of crescents, the extent of interstitial infiltrates, interstitial fibrosis and tubular atrophy; and negatively with the proportion of normal glomeruli [49]. Similar results were found in a study by Hilhorst and colleagues [50] who analyzed 187 renal biopsies of ANCA-associated pauci-immune glomerulonephritis detecting C3c, C3d, C4d and C5b-9 in the majority of tissue specimens. C3d and properdin staining were particularly associated with the proportion of cellular crescents, and presence of properdin correlated with the level of proteinuria. The staining of the two receptors of C5a, including CD88 and C5L2, were noted mainly on infiltrating neutrophils and macrophages in kidney specimens of patients with AAV. The staining of CD88 was down-regulated, while the staining of C5L2 was up-regulated, and that of CD88 was associated with initial renal function and the extent of interstitial fibrosis [51]. Given that CD88 can be rapidly internalized after the interaction with C5a [52], the down-regulation of CD88 in renal biopsies of AAV might be a result of C5a-mediated internalization and contribute to the self-protection mechanism to alleviate the C5a-mediated inflammation [51].

Besides the components of complement deposited in kidneys, Gou and co-workers [49] studied urinary levels of various components of complement in AAV patients noting that urinary levels of Bb, C3a, C5a and C5b-9 in active stage of AAV were higher than those in remission. In particular, correlation analysis showed that in patients with active AAV, urinary levels of Bb correlated with disease severity, including initial serum creatinine and the proportion of normal glomeruli in renal specimens. Circulating levels of various components of complement in AAV were also detected and similar circumstances were found in the circulation of AAV patients. Plasma levels of C3a, C5a, soluble C5b-9 and Bb were also elevated, while plasma levels of properdin were lower in active AAV compared to the remission phase. Plasma levels of C4d did not significantly differ between the active and remission stages. Disease activity was related to plasma levels of Bb, the proportion of crescents in the renal specimen, erythrocyte sedimentation rate (ESR), and the Birmingham Vasculitis Activity Score (BVAS) [53].

Other studies [54-57] examined serum C3 and C4 levels in those with hypocomplementemia at diagnosis of AAV, noting a worse prognosis when present. A study by Manenti and colleagues [58] that included 46 patients with AAV, observing that 8 out of 30 renal biopsies had evidence of a thrombotic microangiopathy (TMA), similar to a large-Chinese cohort [59]. Manenti and colleagues [58] also noted that 35% of patients had a decreased C3 level in the circulation, and a low C3 level was associated with decreased renal survival and the presence of TMA.

Using proteomic analysis by mass spectrometry, Sethi and co-workers [60] found amounts of C3 and moderate amounts of C9, implicating activation of the alternate and terminal pathway of complement in pauci-immune NCGN with negative ANCA serology, suggesting that its cause may be promoted by a genetic or acquired defect in in the alternative complement pathway.

CFH, which is a key regulator of the alternative complement pathway, inhibits amplification of the complement cascade both in the fluid phase and on host cell surfaces. Quantitative deficiency or impaired function of CFH, resulting in dysregulation of the alternative complement pathway, is involved in the pathogenesis of several autoimmune diseases, including TMA and C3 glomerulopathy [61-63]. Chen and colleagues [64] found that plasma CFH levels in active AAV patients were lower than those in remission, and related to parameters of disease activity, including BVAS, initial serum creatinine, and proportion of crescents in renal specimens. In multivariate survival analysis, plasma CFH levels were independently associated with the composite outcome of end stage renal disease (ESRD) and death. The functional activities of CFH including its interaction with, and the regulation of C3b; binding to mCRP and endothelial cells, and rendering of protection of host cells against complement attack, are all impaired in AAV patients [65].

Cheng and colleagues [66] reported that the expression levels of CD46, CD55 and CD59, the three major membrane associated regulators, were dysregulated in kidneys of patients with AAV, and associated with the severity of renal injury of AAV patients.

Evidence from *In Vitro* Studies

Among the various components of the complement system, C5a plays a central role in the pathogenesis of AAV. Schreiber and co-workers [41] found that recombinant C5a dose-dependently primed neutrophils for an ANCA-induced respiratory burst. At the cellular level, activation of p38 mitogen-activated protein kinase (p38MAPK), extracellular signal-regulated kinase (ERK), phosphoinositol 3-kinase (PI3K) and protein kinase C (PKC) pathways were all indispensable steps in the translocation of ANCA antigens and activation of neutrophils by ANCAs [67, 68].

Among the two receptors of C5a, CD88 contributes to the initiation of acute inflammatory responses, such as the respiratory burst and chemotaxis, while the function of C5L2 remains more controversial. C5L2 may function as a “default” or “scavenger” receptor, by competing with CD88 for binding of C5a [69, 70]; and a proinflammatory role for C5L2 has been suggested [71, 72]. By blocking C5L2 with neutralized antibodies, Hao and co-workers [73] found that C5a primed neutrophils could be mitigated, as well as the ANCA-induced C5a-primed neutrophils respiratory burst and degranulation, suggesting C5L2 might also play a pro-inflammatory role in C5a-primed neutrophils in ANCA-induced activation. However, that premise was inconsistent with the findings of Xiao and colleagues [42] who demonstrated that knockout of C5L2 was associated with more severe disease.

The reason for discrepancies in the function of C5L2 in AAV is not well understood but may be related to different *in vitro* and in vivo experimental environments, and differences in human and murine models of disease. Moreover, the function of C5L2 may be different in various cells, species, and disease contexts [74]. Whether C5L2 plays a pro- or anti-inflammatory role in the development of AAV will require further investigation.

Two key down-stream molecules, sphingosine-1-phosphate (S1P) and high mobility group box 1 (HMGB1), appear to play important roles in the cellular and molecular mechanisms of neutrophil activation by C5a. As a potent bioactive sphingolipid metabolite, S1P can regulate a number of cellular processes in autoimmune disorder [75-77], and participates in the regulation of the balance between expression of CD88 and C5L2 in endotoxin-induced lung inflammation [78]. According to Hao, and Sun and colleagues [79, 80] plasma levels of S1P are elevated in the active stage of AAV; and S1P is released from neutrophils in an autocrine or paracrine manner upon the C5a-priming process, which further activates neutrophils and injure glomerular endothelial. S1P may up-regulate the expression of CD88 on the surface of neutrophils, and blocking S1P receptors could attenuate activation of C5a-primed neutrophils by ANCAs and exert a protective effect in endothelial injury.

HMGB1 exists within the nucleus ubiquitously, but it becomes a pro-inflammatory mediator when released extracellularly [81]. Circulating and urinary levels of HMGB1 are associated with disease activity in AAV [82, 83], and HMGB1 could prime neutrophils by increasing translocation of the ANCA antigens PR3 and MPO. These primed neutrophils may be further activated by ANCAs, resulting in the respiratory burst and degranulation of neutrophils, and the formation of NETs [84, 85]. During the process of C5a priming, HMGB1 may be released from the neutrophil cytoplasm into the extracellular space, further enhancing the effects of C5a on neutrophil activation. Blocking HMGB1 could mitigate C5a-mediated translocation of ANCA antigens, and ANCA-induced respiratory burst and degranulation of C5a-primed neutrophils [86]. HMGB1 could exert its direct or indirect role on the endothelial injury in the presence of ANCAs [87, 88]. Hence the interactions between S1P and C5a, as well as HMGB1 and C5a, play a notable role in neutrophils for ANCA-mediated activation.

Complement activation could lead to the activation of neutrophils and further activate the complement system especially via the alternative pathway. In the study by Xiao and co-workers [39] supernatant from human neutrophils stimulated with ANCAs activated complement in normal human sera, a finding indicating that ANCA-activated neutrophils may release certain substances that subsequently activate the complement system. Camous and colleagues [89] demonstrated that activated neutrophils could further activate the alternative complement pathway via their cell membranes and microparticles.

Leffler and colleagues [90] discovered that NETs could activate the complement system via the classical pathway by the interaction with C1q. Wang and co-workers [91] noted that NETs released from ANCA-activated neutrophils could activate the complement system via the alternative pathway. Schreiber and colleagues [92] observed that NETs provided a scaffold for alternative pathway activation that in turn contributed to endothelial cells damage. They further established the *in vivo* relevance of NETs and the requirement of RIPK1/3/MLKL-dependent necroptosis for disease induction using both murine AAV models and in human kidney biopsies.

An *in vitro* study by Chen and coinvestigators [93] revealed pathophysiological mechanisms of CFH in the pathogenesis of AAV. On one hand, CFH inhibited ANCA-induced neutrophil activation by interacting with neutrophils and protected against glomerular endothelial injury, indicating a deficient function of CFH from patients with active AAV in their ability to bind neutrophils and inhibit neutrophil activation by ANCAs. On the other hand, MPO, which could be released from ANCA-stimulated neutrophils, influenced the complement regulatory activity of CFH [94]. Those would contribute to better understanding of complement system in the pathogenesis of AAV.

EVIDENCE OF CROSS-TALK BETWEEN COMPLEMENT AND OTHER SYSTEMS IN AAV

Cross-Talk between Complement and Coagulation System in AAV

The complement and coagulation systems have a number of common characteristics and have many potential implications for health and diseases.

Several studies have reported that patients with AAV are in a hypercoagulable state, with an increased risk of developing venous thromboembolic events (VTEs) [95-97], indicating the involvement of coagulation system in AAV. C5a was found to induce expression of tissue factor (TF) on neutrophils and endothelial cells, thus triggering the extrinsic coagulation system [98, 99]. Huang and colleagues [100] found that stimulation of neutrophils with C5a and ANCAs not only resulted in the respiratory burst and degranulation, but also led to release of TF bearing microparticles and NETs; and subsequently activated the coagulation system and thrombin generation.

Platelet counts are usually elevated in patients with active AAV. Willeke and co-workers [101] found that platelet counts correlated with disease activity in AAV, while Miao and colleagues [102] demonstrated that platelets were activated in AAV via thrombin-PARs pathway, and could activate the alternative pathway of complement, further enlightening the connection between the complement system and platelets.

Cross-Talk between Complement and TLRs in AAV

In an animal model of MPO-AAV mediated by passive transfer of anti-MPO antibodies, LPS can aggravate the disease via a TLR4 dependent manner [103]. Wang and colleagues [104] investigated the renal expression of TLRs in kidneys of patients with AAV by immunohistochemistry noting that expression of TLR2 and TLR4 was up-regulated in AAV, while that of glomerular TLR4 was inversely related to baseline serum creatinine and the proportion of crescents. HMGB1 is a typical ligand of TLR2 and TLR4. The interaction of HMGB1 and C5a likely plays an important role in ANCA-induced neutrophil activation [86] like that of both complement and TLRs in AAV. The role of PRRs other than TLRs have received little attention in AAV.

Cross-Talk between Complement and Adaptive Immunity in AAV

The study by Dick and colleagues [43] revealed the genetic absence or pharmacological inhibition of CD88 resulting in reduced autoimmunity to MPO, with an attenuated Th1 response, increased Tregs, and reduced generation of MPO-ANCA.

One other study using murine models of MPO-AAV by the same author [105] found that C3aR did not alter histological disease severity. However, it promoted macrophage recruitment to the inflamed glomerulus and inhibited the generation of MPO-ANCA while not influencing T cell autoimmunity. Thus, complement activation, especially via the alternative pathway, plays an important role in the pathogenesis of human AAV, indicating potent and promising

intervention targets for management of patients with AAV and ameliorating the course of ANCA-mediated disorders. Figure 2 shows the pathogenic role of complement in the pathogenesis of AAV.

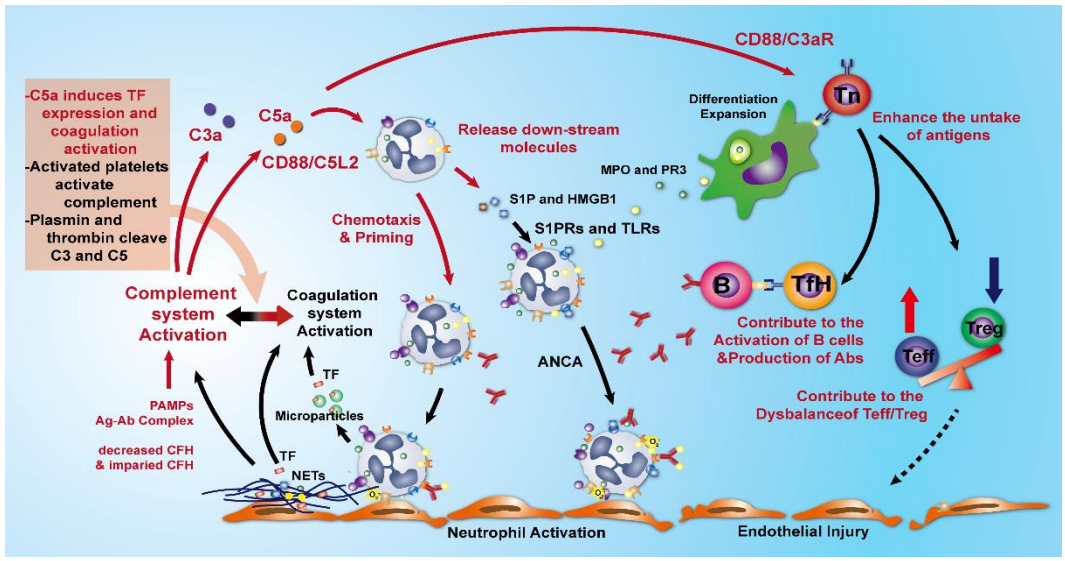

Figure 2. The roles of complement system in a pproposed working model showing the pathogenic events of ANCA-associated vasculitis.

IMPLICATIONS FOR MANAGEMENT OF PATIENTS WITH AAV

As progress is made in understanding the molecular pathogenesis of this disease, new targets will be found for potential therapeutic attack, including targeting C5, C5a/C5aR, C1 and C3. Eculizumab, the first available anti-complement treatment, is a fully humanized recombinant monoclonal antibody that binds C5 with high affinity. Eculizumab efficiently blocks C5 cleavage and prevents the formation of C5a and C5b-9 [106]. Several well-designed studies have demonstrated the therapeutic efficacy of eculizumab in paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic-uremic syndrome (aHUS) [107-109], leading to approval of eculizumab for these indications by the FDA. Subsequent small-scale studies and case reports have studied eculizumab in other renal diseases, including C3 glomerulopathy, IgA nephropathy, resistant lupus nephritis and anti-phospholipid antibody syndrome [110-113], but not in cases of AAV.

Castellano and colleagues investigated C1 inhibition in renal ischemia-reperfusion injury using a swine model [114]. The infusion of C1-inhibitor led to reduced deposition of various complement activation products in glomerular and peritubular capillaries, and reduced the number of infiltrating inflammatory cells. Several clinical trials of C1 inhibition in renal transplantation are ongoing [(NCT01147302, NCT01134510 and NCT02134314].

Paixão-Cavalcante and colleagues [115] reported a humanized monoclonal antibody binding to C3 that inhibited C3 cleavage by the nephritic factor-stabilized convertase. Zhang and co-workers [116] employed soluble CR1 therapy in C3 glomerulopathy noting that it prevented the dysregulation of the alternative pathway C3 convertase.

Blocking of C5aR has been regarded as a novel therapeutic target for the treatment of patients with AAV. A multicenter phase 2 randomized, double-blinded placebo-controlled trial led by the EUVAS evaluated the efficacy and safety of CCX168 (avacopan), a small molecule that blocks CD88 (ClinicalTrials.gov Identifier: NCT01363388) among 67 patients randomly divided into three arms: (1) prednisone 60 mg/day; standard of care control, (2) CCX168 30 mg twice a day plus prednisone 20 mg/day; and (3) CCX168 30 mg twice a day without prednisone. All patients received intravenous cyclophosphamide (15 mg/kg per 2 to 4 wks) or rituximab (375 mg/m^2 intravenous weekly for 4 weeks). The primary end point at 12 weeks was reached in 70% of patients in the control group, 86% of patients in the reduced-steroid group, and 81% of patients in the avacopan plus placebo group, demonstrating noninferiority for both avacopan groups. There were no apparent differences in the response rates with respect to disease category or ANCA type. However, assessment of the change in BVAS and urinary albumin to creatinine ratio suggested that patients in the avacopan groups had a more rapid and consistent improvement in the study parameters by 4 weeks. Quality-of-life indicators were improved with the steroid-free protocol. The incidence of total and serious adverse events was similar in the three arms suggesting that C5a receptor inhibition with avacopan was effective in replacing high-dose glucocorticoids in treating vasculitis [117]. A phase 3 randomized trial was launched (ClinicalTrials.gov Identifier: NCT02994927) to include patients with AAV and eGFR≥15 ml/min/1.73 m^2 with sustained remission as an end-point.

Other agents that target complement include TP10, which is a C3 soluble complement receptor; and two inhibitory peptides of C3: AMY-101 and compstatin; and small molecule factor D inhibitors to block complement activation. Although there are trials of the treatment of C3 glomerulopathy, TMA and IgA nephropathy, there are none so far in AAV [118].

CONCLUSION

In conclusion, activation of the complement system, especially the alternative pathway, plays a central role in the development of AAV. Among various components of the complement system, C5a plays a central role priming neutrophils to undergo the respiratory burst with degranulation and release of NETs in the presence of ANCAs, and contributing to the development of systemic vasculitic lesions. The stimulation of neutrophils with C5a in conjunction with ANCAs leads to the release of TF-bearing microparticles and NETs that subsequently activate the coagulation system and generate thrombin. Neutrophils, ANCA and complement system form a positive feedback loop and lead to the development of AAV. The inhibition of complement, especially C5a, is a promising approach for remission induction in AAV. However, whether the same mechanism can also maintain long term remission through control of neutrophil activation remains to be explored.

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Chapter 7

EXPERIMENTAL AUTOIMMUNE VASCULITIS: INSIGHTS INTO HUMAN VASCULITIS USING ANIMAL MODELS

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ABSTRACT

Over the last decade several different experimental models have been described that try to recapitulate the clinical features of ANCA associated vasculitis. Although all are limited to some extent in their ability to mirror human disease, together they have provided important and sometimes unexpected insights into disease pathogenesis, as well as new avenues for therapeutic innovation.

Rodent models of both MPO-, and more recently, PR3-ANCA associated vasculitis have replicated some of the clinical features found in affected patients with ANCA-associated vasculitis (AAV), notably with pulmonary and renal involvement. The vast majority of successful work in this field has concerned MPO-AAV, yet there remains the need for a better model for aspects of PR3-AAV, including the granulomatous lesions found in granulomatosis with polyangiitis, and the relapsing nature of the illness. By virtue of the means by which they are induced and their time course, such experimental animal models have not replicated the complex and varied human disease AAV phenotype. However, the effector pathways and the final organ damage appear very similar to those found clinically, allowing many conclusions to be drawn regarding disease etiology. This chapter reviews the salient experimental animal models that replicate the vasculitic lesions in human AAV. Further refinement of these models may yield the full spectrum of the human condition, providing insight regarding organ tropism and therapeutic targets for disease subtypes.

Keywords: vasculitis, ANCA, animal, models

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INTRODUCTION

Anti-neutrophil cytoplasm antibodies (ANCA) are associated with diseases characterized by relapsing necrotising vasculitis of small calibre blood vessels, frequently involving the kidneys and lungs respectively leading to pauci-immune glomerulonephritis and pulmonary capillaritis.

Many organs may be affected and, as a result, the conditions cause significant morbidity and mortality. The precise disease triggers are not known, but clinical associations with infection have been reported, with experimental data implicating altered responses to microorganisms as potentially important initiators of autoimmune responses.

ANCA are directed towards two autoantigen, proteinase 3 (PR3) and myeloperoxidase (MPO), found in neutrophil granules and monocyte lysosomes that are involved in innate immune responses to infection, while the clinical significance of other proposed ANCA targets, including lysosome associated membrane protein (LAMP)-2 [1] and moesin [2] remain to be completely characterised. The ANCA-associated vasculitides (AAV) are more common in older age and although they can be treated with immunosuppressive therapies, the disease relapses in up to 50% of treated patients and with re-treatment, there is the increased likelihood of treatment related adverse events.

Animal models of experimental autoimmune vasculitis (EAV) have been developed to dissect the pathological basis of disease, to understand the role of ANCA in the etiopathogenesis of AAV, and to replicate the clinical features. The use of murine models has been favoured because they allow the use of genetically altered animals so that key molecules and pathways involved in pathogenicity can be investigated.

The most novel insight gained from such an approach was the discovery the importance of the alternate complement pathway employing passive anti-MPO antibody transfer in C5 and factor B deficient animals [3], a finding that later prompted a therapeutic trial targeting complement C5a receptor as adjunctive therapy in patients with AAV and renal disease.

Development of adequate models has taken considerable time, with many attempts and refinements over the years. There remain major deficiencies in modelling granulomatous PR3-AAV, relapsing disease overlap syndromes and non-pulmonary-renal involvement such as cardiac, neurological and gastrointestinal disease.

Moreover, the impact of age and immune senescence, infectious triggers, and latent viral infections on disease susceptibility and initiation need further exploration. The inability to model PR3-AAV in mice is in part due to differences between human and rodent neutrophil PR3 expression.

These important omissions and differences should lend some caution to translating the findings from one animal model to all forms of human AAV. PR3-and MPO-AAV may have certain common features, such as the occurrence of pauci-immune glomerulonephritis and pulmonary capillaritis, but they also display many diverse characteristics that translate into important differences in disease phenotype and outcome.

These in turn influence the long-term clinical management. Moreover, genetic studies that demonstrate the differing molecular associations of PR3- and MPO highlight the necessity of considering the two entities separately.

MODELS OF MPO-AAV

There have been many historical attempts at developing models of MPO-AAV, but most have failed to mirror the clinical findings, as they were associated with significant immune complex deposition, a major deviation from the pauci-immune characteristics of clinical disease. Spontaneous models of crescentic nephritis and vasculitis characterised by the presence of circulating MPO-ANCA have been reported, for example the spontaneous crescentic glomerulonephritis/Kinjoh (SCG/Kinjoh) mice. However, they are not pauci immune and have an array of other autoantibodies besides MPO-ANCA [4]. Significant advances were made in this field through use of knockout and genetically manipulated mice strains, in particular rat strains inherently susceptible to glomerulonephritis. Those strategies included the passive transfer of pathogenic antibody, which proved useful in modelling the acute vascular injury response, and active immunization with MPO that resulted in activation of both humoral and cellular immune elements, consequently providing more insight into the adaptive autoimmune response and potential responses to novel therapies.

Murine Models

Xiao and colleagues [5] developed an acute passive transfer model using purified antibody or splenocytes taken from MPO-deficient mice immunized with purified murine MPO. This took advantage of the allo-immune response to MPO in MPO-deficient mice, generating antibodies and lymphocyte responses that were sufficiently potent to induce disease. Anti-MPO antibodies injected into wild type or RAG-deficient recipient mice led to development of necrotizing pauci-immune glomerulonephritis, and in some cases, pulmonary capillaritis over 6 to 13 days. It was further noted that splenocytes transfer recipients developed glomerular immune deposits, whereas antibody transfer recipients remained pauci-immune. Virtually all subsequent work was conducted with the model that used a passive transfer strategy even though the degree of induced disease was much milder.

The development of glomerulonephritis using cell transfer was dependent on B-cells rather than T-cells, and required the presence of neutrophils [6]. This model was replicated at other centres and further refined to produce augmented disease through the addition of lipopolysaccharide (LPS) [7], mimicking the effects of infection, and exacerbating autoimmunity via toll like receptor (TLR) activation and up-regulation of tumour necrosis factor-α. Further investigation of the model using different mouse strains, demonstrated that the genetic background of the mice had a profound effect on the severity of the model, with 129S6 mice developing worse crescentic disease than C57BL/6 mice in which the model was first generated [8], and with augmented pulmonary-renal disease in the absence of the inhibitory Fcγ-II receptors [9]. That model demonstrated a critical role for alternative, but not classical, complement components in disease induction [3], which was surprising given the lack of clinical evidence of complement consumption in AAV. Since the available small molecule inhibitors of C5a receptor were only active against the human form of the receptor, Xiao and colleagues [10] adapted the murine anti-MPO transfer model by generating mice transgenic for the human C5a receptor allowing them to test the inhibitor in the murine model and demonstrate its efficacy in reducing renal disease.

A subsequent human trial using this C5a receptor antagonist in treatment of AAV was initiated [11]. Further modifications of this model used a bone marrow transplant approach in which immunization of MPO-deficient mice with murine MPO, were subjected to lethal irradiation followed by transfer of either MPO-expressing or MPO-deficient bone marrow.

MPO expression on hematopoietic cells was necessary for disease induction [12], as only transfer of MPO-sufficient cells resulted in disease manifested as necrotizing glomerulonephritis. With various refinements, this model [5] revolutionised the understanding of the mechanisms of acute anti-MPO induced vascular injury. However, all of the model variations had limitations, as these were not autoimmune in nature, but relied instead on alloimmune responses to MPO. Comparisons of the avidity of alloimmune anti-MPO antibodies and other autoimmune ones formed by immunizing WT mice with MPO have not been reported, although it is suspected that there would be significant differences reflecting the propensity for disease induction with this model compared to previous failed attempts by direct MPO immunization. Furthermore, as with all induced models, they begin downstream of the break in clinical immune tolerance with a pre-formed anti-MPO antibody, restricting some of the potential insights into clinical disease initiation. A slightly different strategy for modelling MPO autoimmunity was adopted by Ruth and co-workers [13]. The investigators [13] immunized C57BL/6 mice with MPO in adjuvant, both human and murine, generating cellular and humoral anti-MPO responses, followed by low dose sub-nephritogenic nephrotoxic serum to induce a local renal immune response within glomeruli. In contrast to the passive MPO model, this technique depended upon T-cell and not B-cell immunity. Effector CD4+ cell depletion attenuated crescentic glomerulonephritis and effector cell influx without altering ANCA titers. However, B cell-deficient mice, with no ANCA, still developed severe crescentic glomerulonephritis with accumulation of effector cells [13]. The proposed explanation of the model was that it relied upon deposition of MPO in the glomerular circulation following neutrophil migration and de-granulation in response to deposited nephrotoxic serum. There was in turn a subsequent adaptive cellular immune response towards the deposited MPO already induced by the prior immunization of MPO in adjuvant. This model was used by Gan and colleagues [14] to illustrate the importance of the key Th17 effector cytokine IL-17A. To test whether IL-17A also drives autoimmune delayed-type hypersensitivity in the kidney, the investigators [14] injected MPO into the kidneys of MPO-sensitized mice noting that IL-17A deficiency reduced accumulation of renal macrophages and renal CCL5 mRNA expression, lending support to the clinical findings of elevated IL-17 levels in patients with acute and more severe disease in AAV [15]. This model also demonstrated the importance of innate immune pathway stimulation as a co-stimulus for disease induction as well as the pathogenic role of TLR in initiating autoimmune AAV in a series of experiments in which TLR-2 induced Th17 CD4 cells while TLR-9 directed vasculitis by enhanced Th1 autoimmunity [16]. These observations were likely due in part to the mimicking influence of infection and TLR signalling on development of ANCA autoimmunity and organ related disease leading to glomerulonephritis.

Rat Models

A model of MPO-AAV was developed by immunization of a susceptible Wistar-Kyoto (WKY) rat strain with human MPO, in Complete Freund's adjuvant (CFA).

This approach resulted in generation of MPO-ANCA and MPO-reactive T-cells [17] with development of a crescentic, pauci-immune glomerulonephritis, and pulmonary capillaritis in a proportion of treated animals (Figure 1) [18]. The induced anti-human MPO antibodies cross-reacted with rat MPO, displaying significant homology to the human molecule.

Although ANCA-IgG was not found to transfer disease in this model, it did increase leukocyte-endothelial interaction [19], and clearly showed that the composition of the adjuvant providing the innate immune stimulation and the genetic background of the rat were critical to the determination of severity and disease susceptibility. Lewis rats, which share the same MHC Rt1 locus as the WKY strain, do not develop vasculitis or glomerulonephritis despite achieving similar levels of anti-MPO antibodies, demonstrating that non-MHC genes are important in mediating the pathogenic potential of MPO-ANCA.

The significant genetic differences conferring susceptibility to other forms of glomerulonephritis including nephrotoxic nephritis and anti-glomerular basement membrane disease, in these rats has been described, largely related to differences in macrophage reactivity and Fc receptor activation [20].

The role of certain genetic loci as susceptibility factors in the MPO-AAV model and resulting disease severity was examined using congenic Lewis/WKY animals demonstrating the critical role of chromosome 13 and 16 susceptibility loci in the development of experimental autoimmune vasculitis [21].

While the murine T-cell mediated model implicates deposited MPO directing a delayed type hypersensitivity response within the kidney, it does not appear to be the main mechanism in the rat MPO autoimmune model [18] as there is no evidence of deposited MPO.

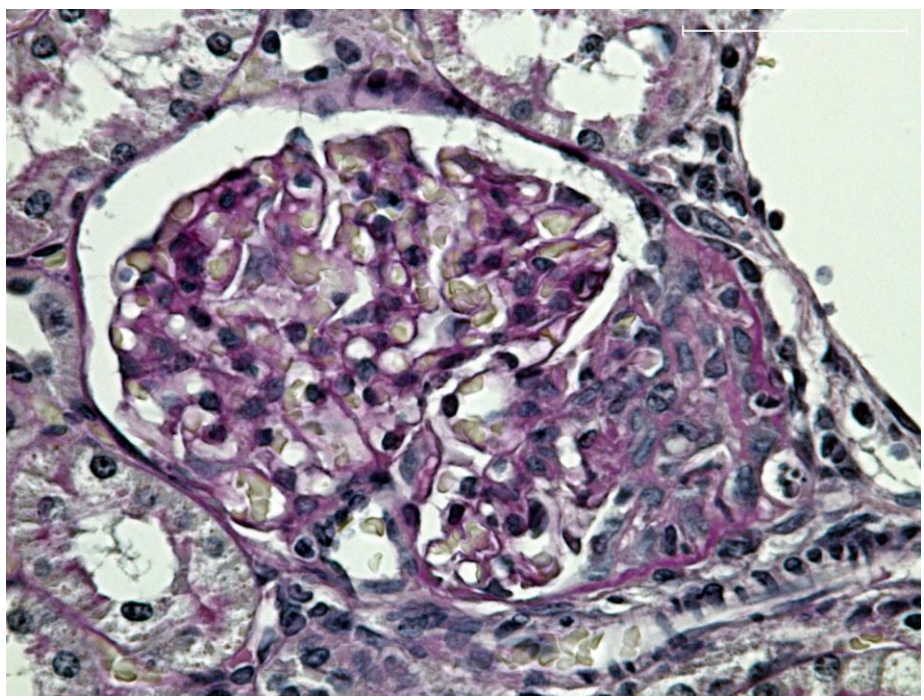

Figure 1. Photomicrograph of a single glomerulus from a rat with experimental autoimmune vasculitis demonstrating crescentic change (PAS x400).

Experimental animal models of vasculitis that may be contrived or manipulated to produce the desired phenotype do not necessarily have to be mediated through identical pathways. MPO-ANCA induced in MPO deficient animals by an alloimmune anti-MPO response may be very different from the autoimmune anti-MPO response.

Indeed, it is now appreciated that there is significant heterogeneity in anti-MPO antibodies found in patients with different epitope reactivity and with interference of immune reactive sites under certain circumstances [22]. It would therefore be of interest to investigate the differences between induced anti-MPO antibodies from different rodent models. Epitope differences may contribute to why the model cannot be transferred with anti-MPO T-cells. This may relate in part to the short duration of follow up in comparison to the immunized rat model, which takes four or more weeks to develop similar glomerular lesions.

In the combined anti-MPO/nephrotoxic nephritis model, the anti-MPO response is a recall response in a previously immunized animal.

When considered together, the rodent models demonstrate that vasculitis, as manifested by pulmonary and renal disease, may be induced when a sufficient anti-MPO immunity threshold is achieved. Patients rarely display an exclusively T- or B-cell response, or a uniquely innate or adaptive immune response.

Rather, the observed disease represents the sum of these different pathways. Reductionist models can provide critical insights into individual mechanisms or pathways of disease induction, even though they may be incapable of defining them all. In particular, none of the models currently explains why or how immune tolerance to self-antigens is broken in the first instance, with later destructive anti MPO reactivity.

RODENT MODELS OF PR3-AAV

There have been no spontaneous experimental models in rodents of glomerulonephritis or vasculitis in association with anti-PR3 antibodies, nor PR3-ANCA in association with other autoantibodies. This is likely related to differences between humans and rodents in PR3 and its cellular expression. Despite immunizing rats and mice with combinations of human or murine PR3, chimeric molecules, and demonstrating induction of PR3-ANCA, van der Geld and colleagues [23] were unable to experimentally generate vasculitis. Pfister and colleagues [24] immunized PR3- and neutrophil elastase-deficient mice with murine PR3, transferred the resultant antibodies into LPS-primed mice, and did not observe significant renal or pulmonary pathology. There was a mild increase in panniculitis following intradermal TNF injection and PR3-ANCA transfer compared to controls. Primo and colleagues [25] described the successful transfer of PR3-ANCA producing splenocytes isolated from recombinant murine PR3-immunized autoimmune-prone non-obese diabetic (NOD) mice into naïve NOD-severe combined immunodeficient (SCID) recipients lacking endogenous T-cells and B-cells.

The immunized NOD mice developed PR3-ANCA without apparent disease despite prolonged follow up while the NOD-SCID mice that received PR3-reactive splenocytes rapidly developed signs of disease with vasculitis and necrotizing crescentic glomerulonephritis. Moreover, there were no granulomata observed despite significant anti-PR3 immune reactivity; and C57BL/6-RAG mouse recipients of the same splenocytes did not develop disease.

These findings suggested that there were protective mechanisms operating in immunized NOD mice mediated by regulatory lymphocyte populations, while the genetic background and degree of immunodeficiency appeared to play an important role in disease susceptibility. In the successful anti-MPO splenocyte transfer model of Xiao et al. [5], the recipient strain was C57BL/6-RAG2-/- further underscoring the difference between MPO and PR3 immunity. The presence of glomerular immune deposits was not discussed in the report by Primo and colleagues [25]. Their results were of limited applicability to human anti-PR3 associated AAV. Relle and colleagues [26] successfully created transgenic FVB mice that expressed human PR3 into which they infused monoclonal anti-PR3 antibodies.

However, expression of PR3 was under the control of the promoter meaning that protein was expressed only in glomeruli. Not surprisingly, they [26] did not detect any pathological features of vasculitis as the current AAV paradigm for pathogenesis proposes interaction of the antibody with PR3 on neutrophils and monocytes, not glomerular cells, with resultant activation of these cells and bystander microvascular injury.

One hallmark of ANCA vasculitis is that the glomerular lesions are pauci-immune, meaning that there is little or no local glomerular immune complex formation. One wonders whether different results would have been obtained if human PR3 had been expressed on the surface of myeloid cells, although it is likely that one would need to link it to other membrane bound proteins such as CD177 to see the intracellular effect of ANCA binding.

Little and co-workers [27] recently described the use of humanized immunodeficient NOD SCID IL2-receptor knockout mice, which received human hematopoietic stem cells and developed a human-mouse chimeric immune system. These mice developed mild glomerulonephritis and lung hemorrhage without evidence of granulomata following passive transfer of PR3-ANCA containing IgG derived from patients with severe systemic vasculitis.

These exciting developments open the way for further investigation of pathogenic mechanisms and definition of immune requirements for the induction of anti-PR3 associated vasculitis.

CONCLUSION

By inducing an abnormal immune response to MPO, investigators have succeeded in generating pathological changes in mice and rats that mimic human MPO-ANCA-AVV, although most models exhibit much milder disease than that usually seen in patients. Passive transfer of pathogenic antibody has proven a useful tool for investigating the molecular mechanisms underlying acute vascular injury, and supports the concept that anti-MPO antibodies, in conjunction with neutrophils, are capable of inducing such injury.

This provides a rationale in support of therapeutic strategies that aim to remove these antibodies, such as plasma exchange and rituximab.

Active immunization of mice and rats with MPO has provided a more accurate model of an immune response that involves both cellular and humoral immunity allowing investigation of the role of T-cells, specifically those of the Th17 axis that have been implicated in autoimmune disease. Such active immunization strategies are well suited to long-term therapeutic trials of novel agents, although for this to be truly useful, the disease phenotypes of the particular models will need to be more severe.

Table 1. Models of MPO- and PR3-ANCA Associated Vasculitis and Glomerulonephritis

Model	Induction protocol	Proposed Mechanism	Organs affected	Severity	Comments/Reference
Passive anti-MPO Ab transfer	Anti-MPO-Ab induced in MPO-deficient mice and transferred into LPS primed recipients	ANCA induced neutrophil degranulation, dependent on B-cells and alternative complement activation	Lungs, kidneys	Mild crescentic GN, more severe in 129 strain	Noticeable strain effect
MPO-ANCA DTH model	MPO-immune response induced by immunization of MPO in CFA, followed by subnephritogenic dose of nephrotoxic serum in C57BL/6 mice	Delayed type hypersensitivity response to planted nephrotoxic antigen, allowing neutrophil degranulation and deposition of MPO target. T-cell, but not B-cell dependent.	Kidney only	Mild crescentic GN	Dosing and timing of nephrotoxic serum critical
Experimental autoimmune vasculitis	Immunization of WKY rats with human MPO in CFA	Induction of anti-MPO Ab and T- cells.	Lungs, Kidney	Mild crescentic GN	Dose dependent effect of MPO on disease severity
PR3-ANCA vasculitis in NOD mice	Immunization of NOD mice with recombinant PR3 in CFA and passive transfer of splenocytes into NOD-SCID mice	Development of PR3-ANCA and presumably PR-3 specific B-cells. No comment on T-cell reactivity	Lungs, kidneys	Crescentic GN	NOD-RAG recipients did not develop disease while NOD-SCID did, suggesting that significant other factors apart from PR3 reactive splenocytes play a role.
PR3-ANCA vasculitis in humanized mice	Generation of chimeric human-mouse immune system by transfer of human CD34+stem cells to NOD SCID IL2-receptor KO mice followed by passive transfer of human PR3-ANCA	Generation of myeloid and lymphoid chimerism providing human neutrophil and monocyte targets for PR3-ANCA	Lungs, kidneys	Mild proliferative GN	

Modelling of anti-PR3 associated disease in animals is significantly less advanced and, by virtue of the differences in PR3 structure and expression between mice and men, will probably rely in the future on the use of humanized and transgenic *in vivo* systems. The generation of an animal model incorporating both anti-PR3 associated vasculitis and granuloma formation, as well as, relapsing disease, cardiac, gastrointestinal and neurologic disease remains a major challenge for the next decade.

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Chapter 8

GENETIC ASPECTS OF VASCULITIS

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ABSTRACT

The generation of large-scale genotyping data is substantially increasing the understanding of human diseases with a complex genetic component. Such data analysis has been applied to the vasculitides, which are characterized by inflammatory damage of the blood vessels. They show a very complex etiology in which both environmental and genetic factors seem to contribute to the predisposition and clinical phenotype of the disease. During the last decade, a large number of genetic studies, genome-wide association studies in some cases, have been performed on vasculitides and, strikingly, most of the identified risk loci shared susceptibility factors amongst them. This reinforces the idea that some immunological pathways are key players in the major hallmarks of these diseases.

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However, since the current knowledge of the genetic basis of the vasculitides is often based on studies performed in reduced populations, further collaborative studies on larger cohorts are required to provide the last pieces of the genetic puzzle underlying vasculitides, giving us a better perspective of their etiopathogenesis and allowing novel approaches for the development of more effective therapies.

INTRODUCTION

Vasculitides present a complex etiology in which both environmental and genetic factors appear to influence the development and progression of disease. The genetic component of these disorders is supported by the identification of an increased risk among first-degree relatives of affected patients and monozygotic twins. For most vasculitides familial aggregation has been described in case reports or small series without quantification. In the absence of family studies, differing prevalence of these diseases in different ethnic groups supports the existence of important genetic components.

Two main approaches, candidate gene studies and high-throughput genotyping, including genome-wide association studies (GWAS), have been used to identify disease-associated genes in complex diseases both of which involve genotyping of genetic variations, mainly the single-nucleotide polymorphisms (SNP) in cases and controls. Until recently, all genetic studies in vasculitides were designed as candidate gene studies, examining a SNP or a set of polymorphisms within certain *loci* with a potential role in a particular phenotype or disease. In these studies, the selection of a candidate gene or genomic region was based on its biological function or its location in a region implicated by previous associations or linkage studies. In contrast to candidate gene studies, the GWAS approach, in which millions of polymorphisms are analyzed across the whole genome, is unbiased and it does not require prior hypotheses about the type of genes or polymorphisms most likely to be associated with the phenotypes of interest. The recent publication of GWAS in vasculitides has increased the understanding of potential underlying genetic mechanisms. Moreover, the two methodologies have shown that the human leukocyte antigen (HLA) region harbors the strongest genetic contribution to the pathophysiology of vasculitides. This genomic region occupies a large segment of DNA extending about 3.6 megabases on the short arm of chromosome 6, and containing hundreds of genes involved in immune function.

This chapter summarizes the genetic aspects of vasculitides giving an overview of the recent progress in the elucidation of their genetic component. Two Chapel Hill Consensus Conference (CHCC) nomenclatures, one in 1994 and a Revised version in 2012 [1, 2], provided consensus on nosology and definitions for the commonest forms of vasculitis in adults based upon the caliber of vessels involved. The Pediatric Rheumatology European Society (PRES), European League against Rheumatism (EULAR), and the Pediatric Rheumatology International Trials Organization (PRINTO) proposed specific classification criteria, as well as, clinical, laboratory and radiographic characteristics for the commonest childhood vasculitis syndromes, based upon vessel size [3, 4], similar to the 2012 Revised CHCC nomenclature [2]. These overlapping nomenclatures form the basis for the definition of most recent cohorts of vasculitides to which reference is made in this chapter.

LARGE VESSEL VASCULITIS

Giant Cell Arteritis

Increasing knowledge suggests that giant cell arteritis (GCA) has an important genetic basis [5]. Familial aggregation with sharing of HLA alleles has been reported for GCA from several decades ago [6-13].

However, until recently most studies were performed in unreplicated Spanish and Italian populations [14] usually with small sample sizes. Despite these initial limitations, GCA was always considered as one of the best examples of vasculitis in which a genetic influence has been implicated in both disease susceptibility and severity. As discussed below, the establishment of international collaborative groups and the recent large scale genetic studies performed in this type of vasculitis have represented a turning point in the elucidation of its pathogenic mechanisms [15, 16].

HLA Association

Early candidate gene studies identified HLA class II region as the most consistent susceptibility *locus* for GCA. Carriage of HLA-DRB1*04 alleles (specifically DRB1*0401 and DRB1*0404) was proposed as the main contributor of the GCA genetic component [17-29]. An increased predisposition for the development of visual manifestations as well as resistance to corticosteroid treatment in GCA patients was related to the presence of HLA-DRB1*04 allele [26, 30, 31], which gave an idea of the crucial role that this allele may have in GCA pathophysiology. On the other hand, associations between GCA and alleles of the HLA class I region, including HLA-B*15, HLA-A*31, HLA-B*8, HLA-Cw3 and HLA-Cw6, as well as the nearby gene MHC class I polypeptide-related sequence A (*MICA*), encoding a stress-inducible transmembrane molecule, were also reported [17, 32-34], although not as consistent as those of the class II region.

The publication of the first large scale genetic study of GCA in 2015 definitively represented a considerable leap in the understanding of the genetic contribution of the HLA system to the susceptibility of this form of vasculitis. In collaboration with the UKGCA Consortium, the Vasculitis Clinical Research Consortium (VCRC), and many other research groups and hospitals from Europe, our group carried out a dense fine-mapping of immune-related *loci* using the Immunochip platform, a custom high-density genotyping array designed for immunogenetics studies [35]. One of the advantages of this chip is the presence of a high SNP coverage in the HLA region, which allows imputation of two- and four-digit classical HLA alleles as well as polymorphic amino acids using reference panels [36, 37]. We performed a comprehensive interrogation of the HLA region at the amino acid level using this bioinformatics approach in a total of 1,651 GCA patients and 15,306 unaffected controls. Our results highlighted the class II molecules as the main contributors to GCA risk, specifically HLA-DRβ1 and HLA-DQα1. The class I gene *HLA-B* was also associated, but with a considerable lower statistical significance. We proposed a model of 3 amino acid positions that explained most of the HLA association with GCA, which included positions 13 and 56 of HLA-DRβ1 and HLA-DQα1, respectively, as well as 45 of HLA-B. All three positions were located at the binding pocket of the protein, suggesting a possible involvement in antigen recognition. The top signal corresponded to presence of histidine at position 13 of HLA-DRβ1, consistent

with the previous associations between GCA and HLA-DRB1*04 classical alleles, as His13 is one of the amino acids that define them [16].

Non-HLA Association

The protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) gene encodes a tyrosine phosphatase known as LYP that it is expressed mainly in lymphoid tissues and is involved in several signaling pathways associated with the immune response, including the T-cell receptor (TCR) pathway in which LYP plays a central role in its negative control, but also the humoral activity of B-cells. A functional *PTPN22* variant (rs2476601/R620W) has been associated with several autoimmune diseases, representing the clearest example of a common genetic risk factor in autoimmunity [38]. *PTPN22* R620W represented the strongest non-HLA association signal in the Immunochip of GCA [16], which confirmed previously reported observations through the candidate gene approach [39]. This association was initially identified in a large discovery cohort from Spain and subsequently replicated in three European replication cohorts from the United Kingdom (UK), Germany and Norway. It has been demonstrated that the R620W change interferes with the ability of LYP to bind its partner c-src tyrosine kinase (CSK) [40] which prevents the formation of the complex between both proteins and the suppression of the T-cell activation.

The first GWAS performed in GCA was published on 2017. The involvement of the European Vasculitis Genetics Consortium (EVGC) allowed the recruitment of three additional cohorts to the first case/control set of the Immunochip, comprising a total of 2,134 GCA patients and 9,125 controls from 11 populations of European origin (Spain, Italy, UK, USA, Canada, France, Germany, Norway, The Netherlands, Ireland and Switzerland) [15]. The analysis of a total of 1,844,133 genetic markers across the whole genome led to the identification of two genes involved in angiogenesis and vascular remodeling as the most relevant non-HLA genetic factors of GCA, i.e., plasminogen (*PLG*) and prolyl 4-hydroxylase subunit alpha 2 (*P4HA2*). The first one encodes a precursor of both plasmin and angiostatin proteins [41]. The GCA-associated *PLG* variants were predicted to affect their gene expression, which could unbalance the plasminogen/plasmin system favoring a pro-inflammatory environment [15]. On the other hand, *P4HA2* encodes the α subunit of the collagen prolyl 4-hydroxylase, a hypoxia responsive enzyme involved in collagen biosynthesis [42]. Some of the *P4HA2* alleles that conferred risk to GCA were predicted to alter *P4HA2* expression in lymphoblastoid cells and the aorta [15].

Different lines of evidence clearly suggest that Th17 cells are crucial players in GCA development. They include both presence of this cell type and increased levels of IL17 in the vascular lesions of GCA patients. Interestingly, corticosteroid therapy seems to be more effective on Th17 cells than on Th1 cells under a GCA background [43-45]. Consistent with these observations, associations between GCA and *IL17A* gene polymorphisms were described in a candidate gene study performed on 2014 [46].

The NLR family pyrin domain containing 1 (*NLRP1*) gene, another autoimmune disease-associated *locus*, was also confirmed as a GCA susceptibility gene in a study on Spanish and Italian populations [47]. This gene encodes a cytoplasmic protein involved in the assembly of the inflammasome that activates caspases 1 and 5 which results in the activation of proinflammatory cytokines. As expected, considering its inflammatory nature, different cytokines have been implicated in GCA pathogenesis. Amongst them, the interleukin 10 (*IL10*) gene represents the most consistent association [48, 49]. This gene encodes an anti-

inflammatory Th2 cytokine with pleiotropic effects in the immune system, including the negative control of Th1 cytokines such as interferon gamma (IFN-γ), the regulation of the B cell function, and the repression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity. Two independent studies in Italian [48] and Spanish [49] populations indicated that variation of the *IL10* promoter region may be involved in the pathogenic mechanisms leading to GCA.

Other genes encoding cytokine or cytokine receptors that have been suggested as possible genetic risk factors for GCA: *IL33*, encoding an IL-1 family member with strong immunomodulatory functions; *IL4*, encoding a protein that acts reciprocally with IFN-γ inducing the Th2 immune response; *IL6*, with pleiotropic effects that may exert both pro-inflammatory and anti-inflammatory functions; *IL18*, encoding a pro-inflammatory cytokine with cytotoxic T-cell functions; monocyte chemotactic protein-1 (*MCP1*), encoding a chemoattractant protein for mononuclear cells to the sites of inflammation; regulated and normal T-cell expressed and secreted (*RANTES*), encoding a potent chemotactic factor for immune cells; the *IL2/IL21* region of cytokines important in the correct function of the immune system; IL12 receptor beta 2 (*IL12RB2*), a key player in the inflammatory response; tumor necrosis factor (TNF), encoding a proinflammatory cytokine involved in the regulation of immune cells; and *IFNG*, encoding a key cytokine involved in innate and adaptive immunity against intracellular pathogens and tumor control [50-59].

The possible role of a number of important molecules for the endothelial function in GCA predisposition and severity has been also explored. Although most of the studies were low-powered and without replication, evidence of association was observed for intercellular adhesion molecule 1 (*ICAM1*), encoding a cell surface glycoprotein involved in the interactions between immune and endothelial cells during inflammation; vascular endothelial growth factor (*VEGF*), encoding an important vasculogenic mediator; cytokine-inducible and endothelial nitric oxide synthases (*NOS2A* and *NOS3*), involved in the regulation of the oxidative stress; and matrix metalloproteinase 9 (*MMP9*), encoding an enzyme with proteolytic activity on the extracellular matrix [52, 60-66].

Finally, genes of the innate immunity may also have a role in GCA pathogenesis. Significant associations have been reported for toll-like receptor 4 (*TLR4*), implicated in signal transduction events induced by lipopolysaccharide from Gram-negative bacteria; Fc gamma receptor 2A and 3A (*FCGR2A* and *FCGR3A*), encoding cell-surface proteins of the immunoglobulin superfamily; and myeloperoxidase (*MPO*), an important gene in the neutrophil function [67-69]. However, all these associations require confirmation in larger and independent cohorts.

Takayasu Arteritis

A few candidate gene studies exploring the possible role of genetic polymorphisms in Takayasu arteritis (TAK) were performed before the publication of three recent large scale analyses, i.e., a genome scanning of exonic regions in a Japanese cohort [70], an Immunochip in Turkish and North Americans [71], and an unbiased GWAS also in Turkish and North Americans [72].

HLA Association

Different genetic studies showed that *HLA-B* alleles are involved in the disease susceptibility. Specifically, HLA-B*5201 was associated with TAK in multiple cohorts of diverse ethnicities including different populations from Asia and Mexico [73-78], which was confirmed in the GWAS of Japanese [70]. However, this association was not observed in North American and Arab populations [79, 80]. In the former [79], a positive correlation of HLA-DR4/MB3 and a strongly negative association of HLA-DR1 with TAK were reported, whereas in Arab patients [80] the association with this region was narrowed down to HLA-A2, HLA-A9, HLA-Bw35 and HLA-DR7 alleles.

Studies on polymorphisms of the gene encoding the human complement factor 4 (C4), located at the class III region of the HLA, showed a significantly high frequency of C4A2 and C4BQ0 allotypes in strong association with HLA-Bw52 [81]. Furthermore, the analysis of *MICA*, situated between the class I and class III regions, revealed an association between the MICA-1.2 allele and TAK, even in the absence of HLA-B52 [82].

A subsequent study [83] in which five microsatellites, C1-2-A, MIB, C1-4-1, C1-2-5 and C1-3-1, around the *HLA-B* and *MICA* genes were analyzed in Japanese TAK patients, suggested two different disease-susceptibility *loci* for TAK, one that mapped near the C1-2-A *locus*, and another closely linked to the *HLA-B* gene. Very recently, the *MICA* and the HLA-DQB1/HLA-DRB1 regions were also described as TAK risk factors in the Immunochip study on Turkish and American cohorts [71].

Non-HLA Association

The most consistent associations with TAK outside the HLA region rely on *IL6*, the leukocyte immunoglobulin like receptor B3 (*LILRB3*) region, *IL12B* and the *FCGR2A/FCGR3A loci*. The two first loci were identified in the GWAS on 2015 [72]. *IL6* was previously suggested as a TAK *locus* by candidate gene studies [84]. This gene encodes an important cytokine with key roles in different aspects of the immune response, including the differentiation of Th17 cells and regulatory T-cells (Treg). Consistent with this association, an altered production of several cytokines, including IL-6, IL-2 and IL-12, were detected in TAK patients. Increased levels of IL-6 and IL-12 and a lower number of CD3+ T cells producing IL-2 in the active phase of the disease were described [85-87]. Polymorphisms of the genes encoding these cytokines were correlated with altered protein levels [84, 88-93]. Regarding the second non-HLA signal of the GWAS, *LILRB3* is located in an immune-regulatory gene rich region on chromosome 19q13.4, which contains genes encoding for killer immunoglobulin-like receptors (KIR), leucocyte immunoglobulin-like receptors (LILR), and leucocyte-associated immunoglobulin-like receptors (LAIR). Remarkably, the top marker within the associated region was related to reduced transcription levels of multiple genes including *LILRB3* [72]. On the other hand, *IL12B* showed a high association peak in both the exome screening study and the Immunochip, whereas *FCGR2A/FCGR3A* was identified as a susceptibility region for TAK in the Immunochip [70, 71].

Two genes encoding members of the IL-1 cytokine family, *IL1B* encoding IL-1β, and IL-1 receptor antagonist (*IL1RN*) encoding IL1-Ra, were involved in TAK predisposition [94]. IL-1 may mediate the inflammatory response occurring in the vascular wall by activating monocytes and expression of adhesion molecules on endothelial cells, inducing secretion of other inflammatory mediators. IL1-Ra inhibits the activities of IL-1α and IL-1β, and modulates a variety of IL-1 related immune and inflammatory responses.

Functional and genetic studies [95-97] have reported an implication of both genes in cardiovascular disease, a common feature in TAK patients. In addition, different polymorphisms of *IL1B* and *IL1RN* were associated with TAK in the Mexican population [94], which suggests a crucial role of IL-1 in the vasculitis lesions of TAK.

Genes encoding cardiovascular-related molecules may also play a role in TAK development [98, 99]. For instance, paraoxonase 1 (*PON1*), a high density lipoprotein (HDL)-associated enzyme involved in prevention of lipid peroxidation, was diminished in activity in TAK patients suggesting a possible role of these lipoproteins in TAK vascular dysfunction [98]. A recent study in the Mexican population [99] suggested that variation within *PON1* may be involved in TAK susceptibility by influencing development and progression of arterial damage.

MEDIUM VESSEL VASCULITIS

Kawasaki Disease

A large number of genetic studies have been conducted in order to unravel the genetic component of Kawasaki disease (KD) [100] focused mainly on candidate genes implicated in the immune response. In addition, since the most serious complication of KD is the development of coronary artery lesions (CAL), the role of cardiovascular-related *loci* has been extensively studied. However, sample sizes have often been insufficient and only a few associations have been replicated in subsequent studies [100].

In the last years, six GWAS on KD have been published [101-106]. This approach has represented an important step forwards to the understanding of the genetic basis of this vasculitis.

HLA Association

The involvement of the HLA region in KD is controversial. Association between KD and HLA class I molecules was evidenced [107-111], but the results were inconsistent. Early studies reported an association between HLA-Bw22 now called Bw54, and KD in the Japanese population [107, 108], whereas the HLA-Bw51 and HLA-B44 alleles were predominantly associated with the disease in Caucasians [109-111]. On the contrary, in a recent GWAS [105], a significant association of HLA class II region with Japanese KD patients was identified. Specifically, the strongest association signal was observed at the intergenic region between HLA-DQB2 and HLA-DOB (rs2857151). This association was replicated in a subsequent Han Chinese study [112]. A suggestive association signal was also observed in the HLA class III region (rs2516390), close to the nuclear factor of kappa light polypeptide gene enhancer in the B-cell inhibitor-like 1 (*NFKBIL1*) and lymphotoxin alpha (*LTA*) genes.

However, no significant associations of HLA alleles were documented in other published GWAS. Thus, a consistent allele or haplotype of HLA conferring KD susceptibility has not yet been identified.

Non-HLA Association

Several genes have been suggested to play a role in KD susceptibility through candidate gene studies [113-125]. Susceptibility *loci* include 1) cytokines and their receptors, such as *IL4*,

TNF, the chemokine (C-C motif) receptor 2-3-5 (*CCR2-CCR3-CCR5*) gene cluster which encodes three receptors of different chemokines that play a critical role in the selective accumulation and activation of inflammatory cells in affected tissues; 2) genes encoding cardiovascular-related molecules, including *VEGF* implicated in the predisposition to this vasculitis and CALs development in different populations, and *MMP3, 9, 13* also associated with CAL; and 3) genes involved in innate immunity, like mannose binding lectin 2 (*MBL2*) involved in complement activation and associated with an increased risk of CAL, and *NLRP1* involved in the inflammasome assembly.

Potential *loci* implicated in KD susceptibility in Japanese families include the 19q32.2 and 4q35 regions. Subsequent fine-scale studies [126] of the 19q32.2 region have led to the identification of functional polymorphisms of the inositol 1,4,5-triphosphate 3-kinase C (*ITPKC*) gene significantly associated with the susceptibility to KD, with particular risk of developing CAL in both Japanese and Caucasian patients. This gene encodes one of the three isoenzymes that phosphorylate inositol 1, 4,5-trisphosphate (IP3) acting as an important molecule in the regulation of T-cell activation.

Regarding the 4q35 linkage region, several immune genes have been mapped around the peak of linkage, including the IFN regulatory factor 2 (*IRF2*), *TLR3* and caspase 3 (*CASP3*) that play central roles in apoptosis. A subsequent positional candidate gene study [127] in Japanese and Americans of European ancestry subjects identified a functional *CASP3* variant that altered the gene expression in immune effector cells. This SNP was shown to influence KD susceptibility. Both the *ITPKC* and *CASP3* associations with KD were replicated in the Taiwanese population [128, 129].

More recently, based on previously published suggestive linkage signals at chromosome 12q24 [125], a missense SNP located within exon 2 of the calcium release-activated calcium modulator 1 (*ORAI1*) gene was described as a risk factor for KD in the Japanese population. This gene encodes a membrane calcium selective ion channel involved in T-cell activation through the Ca2+/NFAT pathway. Strikingly, the frequency of the risk allele is more than 20 times higher in Japanese compared to that in Europeans, suggesting that *ORAI1* may be related to the differential KD incidence between populations of Asian and European descent [130].

In 2009, the first GWAS performed on KD Caucasian patients [101] led to the identification of eight putative novel susceptibility *loci*. Five of these genes, calcium/calmodulin-dependent protein kinase II delta (*CAMK2D*), CUB and Sushi multiple domains 1 (*CSMD1*), ligand of numb-protein X1 (*LNX1*), N-acetylated alpha-linked acidic dipeptidase-like 2 (*NAALADL2*), and t-complex 1 (*TCP1*), formed a functionally close network of 35 genes defined in the Ingenuity database (Ingenuity Systems, Redwood City, CA, www.ingenuity.com). This gene network suggests possible mechanisms by which one or more infectious triggers may lead to deregulated inflammation and apoptosis, and cardiovascular pathology.

In 2011, another GWAS [103] was conducted in a Korean population, and two novel susceptibility signals were identified: a SNP close to the Dab reelin signal transducer homolog 1 (*DAB1*) gene associated with KD predisposition, and an intronic variant of pellino E3 ubiquitin protein ligase 1 (*PELI1*) gene which is involved in the TLR pathway associated with CAL development. The first GWAS in the Han Chinese population [106] identified several putative genetic variants associated with KD susceptibility, although none of them reached GWAS statistical significance due to a limited sample size.

The highest peaks included three SNP close to coatomer protein complex beta-2 subunit (*COPB2*) gene, one located within the intronic region of endoplasmic reticulum amino peptidase 1 (*ERAP1*), and six clustered in an area containing immunoglobulin heavy chain variable region (*IGHV*) genes.

A well-powered GWAS [102] in KD patients from different populations of European ancestry (Australia, UK, Netherlands and US) identified two *loci* that exceeded the threshold for GWAS significance. One of them was *ITPKC*, confirming this gene as a risk factor for KD, and a functional polymorphism (H131R, rs1801274) of *FCGR2A*. Finally, both Taiwanese [104] and Japanese [105] groups independently reported GWAS results in 2012 [104, 105]. In both studies, significant associations were observed in the B-lymphoid tyrosine kinase (BLK) region. The most strongly associated polymorphism in the Taiwanese study [104] was in high linkage disequilibrium (LD) with a genetic variant associated with systemic levels of BLK and increased risk of systemic lupus erythematosus (SLE). SNP around cluster domain 40 (*CD40*, a member of the *TNFR* superfamily that potentially contributes to inflammation and autoimmune disease processes through the selection of autoreactive T cells in the thymus and the activation of B- and T- cells) were also associated with KD at GWAS level in both studies. Interestingly, increased cell surface expression of CD40L, the ligand of CD40, and elevated serum levels of soluble CD40L have been detected in KD. On the other hand, the Japanese study also replicated the association of the previously identified *FCGR2A* functional SNP.

On 2016, Shimizu and colleagues [131] performed a pathway-based analysis followed by gene stability selection using the previously published GWAS data of individuals of European ancestry [102]. They identified variants associated with both susceptibility to KD and aneurysm formation within the solute carrier family 8 member A1 (*SLC8A1*) gene, which encoded protein contributes to the regulation of calcium flux and calcium-dependent cellular processes. The results were further replicated in an independent cohort of Japanese origin [131].

Finally, a recent whole genome screening of a 6-member African American family with two affected KD children identified rare compound heterozygous variants in another TLR member, *TLR6*, shared between both affected siblings [132].

Small Vessel ANCA-Associated Vasculitis

Early genetic studies in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which comprises granulomatosis with polyangiitis (GPA) [Wegener type], microscopic polyangiitis (MPA) and eosinophlic granulomatosis with polyangiitis (EGPA) (Churg-Strauss type), focused on self-evident candidate genes encoding respective ANCA target antigens, proteinase 3 (PR3) and myeloperoxidase (MPO).

Subsequent studies reported a clear familial aggregation of GPA, with a relative risk of 1.56 for first-degree relatives, which indicated the importance of the genetic component for this disease [133]. In 2012, the ‘European Vasculitis Study Group’ (EUVAS) conducted the first GWAS in AAV [134] (including a large cohort of GPA and MPA patients), reporting more consistent associations with the disease, and suggesting genetic distinctions between the clinical entities of AAV that may be associated with ANCA specificity. Subsequently, two additional GWAS were performed by the VCRC (one only in patients diagnosed with GPA and another in a cohort including GPA and MPA cases) [135, 136]. Those studies definitively helped to increase the knowledge on AAV genetics.

HLA Association

Several early low-power studies [137-139] suggested that different HLA class I and class II *loci* might be involved in the predisposition to GPA including HLA-DQw7, HLA-DR3, HLA-DR1, HLA-DR9 and HLA-B50. However, only the HLA DPB1*0401 allele was firmly associated with GPA, although other neighboring *loci* such as ring finger protein 1 (*RING1*), a transcriptional repressor, and retinoid X receptor beta (*RXRB*), involved in mediating the effects of retinoic acid, may have independent effects [140,141].

HLA-DP also showed the highest association signals in the three AAV GWAS [134-136], with HLA-DPB1*04 as main contributor of GPA risk [135]. Interestingly, the main associations in the HLA region were observed in the subgroup of patients with presence of anti-PR3 antibodies, although there were also associations in the cohort of AAV patients positive for anti-MPO [134]. Hence, it is likely that HLA-DP alleles are a key factor for autoantibody production in AAV, particularly for anti-PR3.

An increased prevalence of HLA-DR4 was also associated with AAV in general, and more specifically with GPA. One study [142] performed in a Dutch population showed that the three subtypes of AAV had a similar HLA antigen distribution, except for HLA-DR1, which was more prevalent in GPA patients, and HLA-DR8, which showed a decreased frequency in EGPA patients in comparison with the other two subtypes. Other evidences suggested that HLA-DRB4 could represent a risk factor specific for EGPA [143].

Non-HLA Association

PRTN3 and *MPO* encode the two major ANCA autoantigens PR3 and MPO respectively. PR3 is a neutrophil intracellular protease that can be also located on the plasma membrane.

It has been proposed that elevated membrane expression of PR3 is involved in progression of chronic inflammatory diseases, including AAV, and that this fact is likely to be genetically determined.

More than one decade ago, the entire coding and promoter sequences of *PRTN3* were analyzed to identify polymorphisms that could influence the pathophysiology of GPA. The genetic variations described in that study [144] included seven SNPs, one amino acid change (Val119Ile), one 84 base pair insertion/deletion (INDEL), and a microsatellite.

Among them, only one SNP affecting a putative transcription factor-binding site (rs62132295, A-564G) was associated with GPA. In the AAV GWAS [134], this *PRTN3* variant was not associated at GWAS level, although a suggestive P-value with GPA but not with MPA was yielded. However, a stronger size effect was observed when the GPA patients were stratified accordingly with the type of autoantibody production instead of the clinically defined syndromes.

Patients positive for anti-PR3 show a stronger association with *PRTN3* rs62132295 than those positive for anti-MPO, when compared with cohort controls. Additionally, the allele frequencies of this SNP also differed considerably between both subsets of patients. Similar results were observed for the serpin A1 (*SERPINA1*) gene [134], which encodes a serine protease inhibitor known as α1-antitrypsin whose targets include PR3 that protects tissues against enzymes from inflammatory cells like neutrophils. The Z (null) allele seems to be specifically associated with anti-PR3 presence rather than with the clinical subtypes, since the most significant P-value was obtained when the AAV patients showing this autoantibody were compared against controls. *SERPINA1* was the only *locus* outside the HLA region that reached GWAS significance. The association between this gene and ANCA positivity has been

confirmed in many candidate gene studies [145-150]. The autoimmune disease-associated *PTPN22* functional variant R620W was also reported to confer risk to AAV through candidate gene studies [151,152]. Specifically, it was first implicated in the susceptibility to develop GPA [152], and this association was further confirmed in a higher cohort in which both GPA and MPA patients were included [151].

The second GWAS was performed in North American GPA patients of European descent. The study reported semaphorin 6A (*SEMA6*A), on chromosome 5, as a novel susceptibility marker for GPA. Although the role of semaphorins remains unclear, they seem to control axon guidance, vasculogenesis, cardiogenesis, osteoclastogenesis, tumor metastasis, and immune regulation [135]. The same consortium conducted another GWAS in GPA and MPA patients from European origin on 2017, and confirmed *PRTN3*, *SERPINA1* and *PTPN22* as the strongest non-HLA susceptibility genes for this forms of vasculitis [136].

Another gene that has been associated with AAV predisposition is cytotoxic T-lymphocyte associated antigen 4 (*CTLA4*), which encodes a central regulatory molecule expressed on T-cells that inhibits T-cell function and peripheral tolerance. It has been reported that elevated levels of CTLA4 are expressed in GPA patients [153].

In concordance, many studies have described associations of different *CTLA4* polymorphisms with AAV [154-159], thus supporting the idea that *CTLA4* represents another common susceptibility factor in autoimmunity.

There are other genes of the immune system that showed less consistent evidence of association with AAV, and confirmation in independent cohorts is still required [160]. These include, *IL10*, *CD226*, an adhesion molecule expressed on the surface of natural killer cells, platelets, monocytes and T cells; IL2 receptor alpha (*IL2RA*), an important Treg marker; leukocyte immunoglobulin-like receptor A2 (*LILRA2*), an immunoreceptor expressed in immune cells; integrin, beta 2 complement component 3 receptor 3 and 4 subunit (*ITGB2*), which participates in cell adhesion as well as cell-surface mediated signaling; and *FCGR2A/3B* members of IgG receptor family. Except for *SERPINA1*, *PRTN3*, *CTLA4* and *CD226*, none of the above described genetic associations have been confirmed at the 95% significance level in the AAV GWAS [134].

Small Vessel Immune Complex Vasculitis

IgA Vasculitis/Henoch-Schönlein Purpura

Similar to the other vasculitides, the understanding of the genetic background of IgA vasculitis/Henoch-Schönlein purpura (IgAV/HSP) remains elusive, and further research on well-powered cohorts is still needed to unravel the genetic basis and pathogenic mechanisms leading to this vasculitis.

Until the publication of the first GWAS of IgAV/HSP in 2017, the current knowledge of the genetic component of IgAV/HSP was based exclusively on candidate gene studies including genes mainly involved in the immune and inflammatory responses, but also in endothelial function, mechanisms of complement system activation, coagulation and fibrinolysis, and antioxidation [161].

HLA Association

There is a limited number of studies on the HLA region in IgAV/HSP, all of which have been performed in Spanish, Italian and Turkish populations [161, 162]. In relation to the HLA class II region, an association of the HLA-DRB1*01, HLA-DRB1*07, and HLA-DRB1*11 alleles with IgAV/HSP was first reported in Italy [163] and subsequently confirmed in independent cohorts from Spain [164, 165] and Turkish [166]. The HLA alleles DRB1*01 and DRB1*11 increase the risk for the disease onset, whereas DRB1*07 confer a protective effect to the disease. Also, a protective effect against IgAV/HSP development was described in patients carrying the HLA-DRB1*03 haplotype [165].

The publication of the first GWAS of IgAV/HSP confirmed the HLA class II region as the major susceptibility locus for IgAV/HSP. The authors also used the imputation method described in the GCA section to narrow down the HLA association to a region between *HLA-DQA1* and *HLA-DQB1*. As observed in GCA, positions 13 and 11 of the HLA-DRβ1 carried the strongest disease risk [167].

Other HLA class II alleles have been associated with specific IgAV/HSP clinical characteristics in Turkish cohorts [166] including HLA-DRB1*14, significantly reduced in IgAV/HSP patients with joint involvement, and HLA-DRB1*13, increased in IgAV/HSP patients with nephrotic proteinuria. An association between HLA class I alleles and IgAV/HSP have been also reported, although they remain controversial.

In relation to the class I region, HLA-B35 was first described as a susceptibility factor for nephritis development in IgAV/HSP patients from Spain [168], whereas this allele was subsequently associated with increased risk of the overall disease in a Turkish cohort [169]. The study on IgAV/HSP patients from Turkey [169] also suggested that the presence of the antigens HLA-A2, HLA-A11, and the absence of HLA-A1, HLA-B49, and HLA-B50, influenced IgAV/HSP predisposition. In a recent study, López-Mejías and collaborators [170] reported an association between HLA-B*41:02 and predisposition to IgAV/HSP in Spaniards irrespective of the HLA-DRB1 status.

In addition, HLA-A3 and HLA-B44 were associated with joint involvement, and HLA-A1, HLA-B56, and HLA-B58 were associated with disease severity.

Regarding class III, there is evidence of association between the *C4 locus* (involved in the clearance of immune complexes) and IgAV/HSP [171, 172].

Non-HLA Association

In relation to genes involved in inflammatory pathways, polymorphisms of *IL1RN*, *IL8* and *IL1B* have been shown to influence renal involvement in IgAV/HSP patients of European origin [173-176]. Interestingly, a SNP of *IL1B* has been recently described as a potential marker of severe renal manifestations and renal sequelae in patients with IgAV/HSP from Spain [177]. On the other hand, a promoter polymorphism of the *TGFB1* gene and a non-synonymous variant of the Mediterranean fever gene (*MEFV*) has been also associated with susceptibility and severity of IgAV/HSP in Chinese children [178, 179]. Regarding *MEFV*, this gene encodes a protein known as pyrin that is an important modulator of innate immunity. The name of the gene is based on the fact that variations within this *locus* are related to the phenotype of the Mediterranean fever (a hereditary periodic fever syndrome). Interestingly, a connection between *MEFV* mutations and IgAV/HSP has been suggested [179-181].

Molecules involved in the endothelial function could be also important players in IgAV/HSP. Several studies [182-186] have explored the role of an INDEL polymorphism in

the angiotensin I converting enzyme (*ACE*) gene, which is involved in the control of the blood pressure, with contradictory results. Some of them [182-184] suggested that the presence of the deletion may increase the predisposition to IgAV/HSP, while others did not find evidence of association with the disease [185, 186].

Another member of the rennin–angiotensin system, the angiotensinogen (*AGT*) gene has been also suggested to be involved in HPS pathophysiology [184].

On the other hand, a CCTTT repeat polymorphism within *NOS2A*, involved in the metabolism of nitric oxide as indicated before, was associated with IgAV/HSP predisposition and nephritis presence in a cohort from northwest Spain [187]. Similarly, genetic polymorphisms of the *VEGF* gene have been suggested to have a potential implication in the development of nephritis in patients with IgAV/HSP [188, 189].

Other *loci* involved in IgAV/HSP susceptibility or nephritis development include *CTLA4* and *PON1* (which inhibits T cell function and regulates the formation of oxidized lipoproteins, respectively, as indicated before in this chapter) [166, 190].

VARIABLE VESSEL VASCULITIS

Behçet Disease

Although the pathogenesis of Behçet disease (BD) is still poorly understood, major contributors of BD genetics have been identified mainly due to the publication of three GWAS conducted in Turkish, Japanese, Korean and Italian populations [191-193], a follow-up study of one of them [194], and a Immunochip in Spaniards [195].

HLA Association

As observed in most autoimmune diseases, the HLA region harbors the highest susceptibility *loci* for BD, specifically the HLA class I region. In this sense, HLA-B51 (in particular HLA-B51*01 and HLA-51*08) represents the most robust genetic association with BD. This association has been confirmed in populations of different ancestry groups since it was first described in the early eighties [191-193, 196, 197]. Subsequently, the HLA-A26 allele was also reported to have an independent contribution to disease predisposition [198]. In the Immunochip study HLA-B51 also represented the primary-association marker for BD, but two independent susceptibility signals, HLA-B*57 and HLA-A*03, were also described. Besides, the authors proposed an amino acid model comprising the position 97 of HLA-B and the position 66 of HLA-A which accounted for most of the genetic risk of the HLA region [195].

However, a recently published analysis of imputed GWAS data from a Turkish cohort [194] evidenced that the HLA-B51 association with BD is explained by a SNP located between the *HLA-B* and *MICA loci* (rs116799036). The authors also identified three additional independent signals within the extended HLA region located at the psoriasis susceptibility 1 candidate 1 (*PSORS1C1*) gene, HLA-F antisense RNA 1 (*HLA-F-AS1*), and HLA-Cw*1602.

Non-HLA Association

The three GWAS and the Immunochip performed in BD [191-193, 195] represented a turning point in the understanding of the genetic contribution of the non-HLA *loci* to the disease.

One of the most significant associations with BD described to date is *IL10*. This gene was previously suggested as a genetic factor for BD in candidate gene studies [199, 200], and confirmed by the GWAS data on the Turkish [191] and Japanese [192] populations. However, the recent GWAS on Koreans [193] failed to reproduce this finding. As indicated previously in this chapter, this genetic association is shared with GCA and AAV, but also with other autoimmune diseases such as ulcerative colitis, type 1 diabetes or SLE [197].

Another genomic region associated with BD at GWAS level is *IL23R/IL12RB2* [191, 192, 201]. As stated before, the latter gene encodes a subunit of the IL-12 receptor whose expression is regulated by IFN-γ.

This pathway is crucial in the Th1 and Th17 cell differentiation and it is involved in the inflammatory response. On the other hand, IL-23 is another important immunoregulatory cytokine that also promote Th17 function associated with the active intraocular inflammation in BD patients. Shortly before the publication of the two first BD GWASs [191, 192], an association between *IL23R* and BD was reported in the Han Chinese population [201]. Moreover, this gene harbored the strongest non-HLA signal in the Immunochip [195]. Similarly to *IL10*, the association was confirmed using the GWAS methodology in Turkish and Japanese [191, 192], but not in Koreans [193].

In 2013, the GWAS on Koreans [193], which had a lower statistical power than those on Turkish [191] and Japanese [192] cohorts, identified the GTPase IMAP family member (*GIMAP*) cluster, whose members play an important role in T cell function as well as T cell development and selection, as a novel genetic factor for BD. The peak signal outside the HLA region was observed in *GIMAP4*.

Functional studies performed by the authors evidenced that the minor allele of the associated polymorphism led to lower protein activity than the major allele, and that BD patients showed a lower *GIMAP4* expression in CD4 T cells.

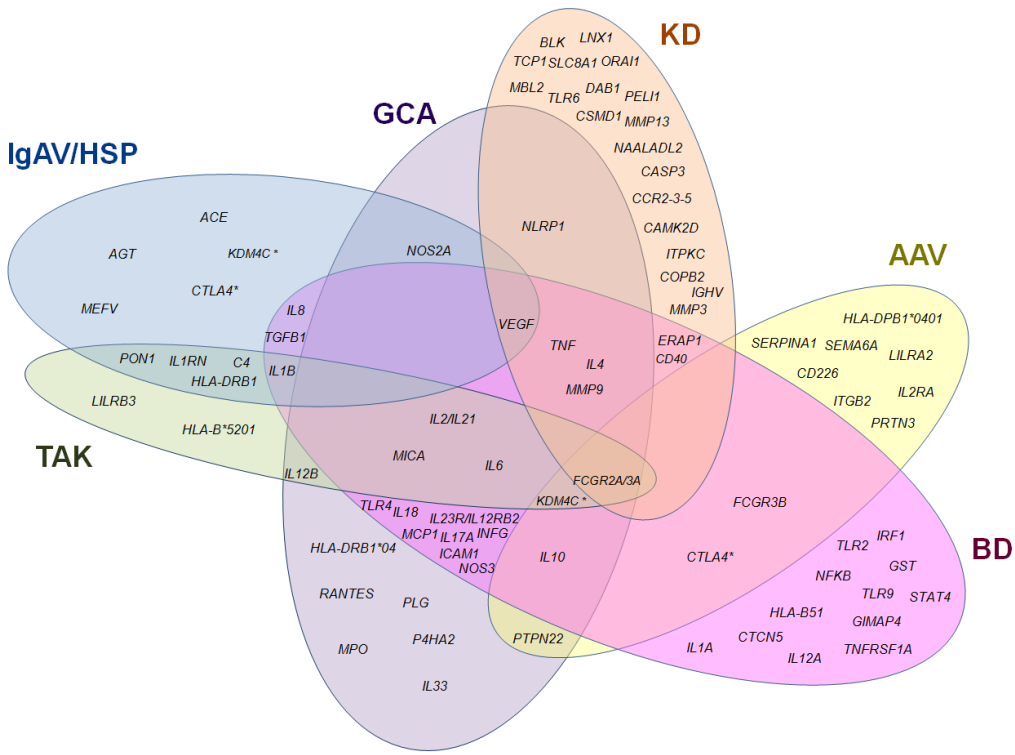
Regarding the Immunochip, besides *IL23R*, two additional non-HLA risk *loci* for BD were established at the genome-wide level of significance, *IL12A* (which encodes a subunit of the heterodimeric cytokines IL-12 and IL-35) and the jerky like (*JRKL*)/contactin 5 (*CNTN5*) region. The function of *JRKL* is unknown, and *CTCN5* encodes a member of the immunoglobulin superfamily involved in the control of cell surface interactions during the development of the nervous system [195].

A large number of additional genetic associations with BD have been suggested through candidate gene studies, although most of them do not rely on consistent results. For example, associated variants have been identified in 1) genes encoding cytokines/chemokines, such as transforming growth factor beta 1 (*TGFB1*), *TNF*, *IFNG*, *IL1A*, *IL1B*, *IL2*, *IL4*, *IL6*, *IL8*, *IL17A*, *IL18*, and *MCP1* amongst others [200, 202-217]; 2) genes involved in the endothelial function, including *VEGF*, *ICAM1*, *MMP9*, *NOS3*, and glutathione S-transferase (*GST*) [218-225]; 3) important immunomodulatory genes, like *NFKB*, *IRF1*, *CTLA4*, *STAT4*, and *CD40* [226-232]; and 4) genes encoding receptors of the innate immunity, as *TLR2*, *TLR4*, *TLR9*, TNF receptor superfamily 1A (*TNFRSF1A*), *FCGR2A*, *FCGR3A* and *FCGR3B* [233-238]. Interestingly, an epistatic interaction between the KD-associated *ERAP1* gene and *HLA-B* was proposed to

influence BD predisposition in the Spanish population [239]. Nevertheless, studies on well-powered cohorts are required to definitively confirm or discard these associations.

SHARED GENETIC COMPONENT IN VASCULITIS

A large number of the known susceptibility loci described across this chapter are shared amongst different vasculitides (Figure 1), which supports the hypothesis of common molecular pathways influencing the development of autoimmune diseases in general and vasculitides in particular [240]. In this regard, the Immunochip platform is a valuable tool that allows comparison of the genetic landscape between different immune-mediated conditions, as it contains a large panel of SNPs covering most immune genes and in all cases the markers analyzed are the same [241]. In order to obtain genetic insights into the common immunopathological pathways involved in vasculitis development, our group carried out two cross-phenotype meta-analyses of Immunochip data from different forms of vasculitis in collaboration with several consortia [242, 243].



TAK, Takayasu arteritis; IgAV/HSP, IgA vasculitis/Henoch-Schönlein purpura; KD, Kawasaki disease; GCA, giant cell arteritis; AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; BD, Behçet disease.**CTLA4* is shared between IgAV/HSP, BD and AAV; *KDM4C* is a common risk factor for GCA, TAK, AAV, IgAV/HSP and BD (both genes appear twice in the figure due to limitations in ellipse overlapping).

Figure 1. Shared genetic risk factors in vasculitides.

In the first of them, the previously published Immunochip studies of GCA and TAK [16, 71] were combined to evaluate the shared genetic component of large vessel vasculitis (LVV). As expected, no genetic pleiotropy was observed within the HLA, consistent with the fact that GCA and TAK are archetypal HLA class II and class I diseases, respectively. However, a significant genetic correlation was detected outside the HLA region, with IL12B representing the strongest shared susceptibility factor for both forms of LVV. This common association is in agreement with the key role proposed for Th1 and Th17 cells in the granuloma formation of LVV, as its encoded protein is the P40 subunit of both IL-12 and IL-23 (involved in Th1 and Th17 cell differentiation, respectively) [244]. Other genes that showed suggestive signals of common association were NOS2A, ERAP1, REL and PRKQC [242].

The second inter disease analysis was aimed at deciphering the shared genetic component of all forms of vasculitis. Hence, Immunochip data from GCA, TAK, AAV, and IgAV/HSP were combined and meta-analyzed. The pooled cohort included a total of 2,465 patients diagnosed with any of these four types of vasculitis and 4,632 unaffected controls. Interestingly, a common signal was identified within the lysine demethylase 4C (*KDM4C*) gene, which encodes a histone demethylase involved in epigenetic mechanisms. The shared association was confirmed in an additional cohort that included a subset of BD patients [243].

CONCLUSION

Despite the recent advances in the identification of the risk factors underlying vasculitides predisposition, there is still a long road ahead before completing the big picture of their genetic landscape.

In most studies, the limited statistical power and the lack of replication in independent cohorts have made difficult the identification of consistent genetic association signals. However, the establishment of big consortia has represented an important step forward that has facilitated the collection of cohorts large enough to perform adequately powered studies. These international collaborative efforts will definitively help to identify novel risk factors and to confirm previously reported genetic associations.

The use of high throughput genotyping has been also of great help, and data mining of the generated large-scale genetic data is producing valuable insights into the specific and common immunopathological pathways that lead to the development of the different forms of vasculitis.

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II. SYSTEMIC VASCULITIS

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Chapter 9

NOMENCLATURE AND PATHOLOGIC FEATURES OF VASCULITIDES

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ABSTRACT

The goal of this chapter is to establish a general framework for categorizing vasculitis, which also serves as a framework for diagnosing vasculitis. The basis for the names and definitions used in this chapter is the 2012 Chapel Hill consensus conference nomenclature system for vasculitides. The major subdivisions are large vessel vasculitis, medium vessel vasculitis, small vessel vasculitis, variable vessel vasculitis, single-organ vasculitis, vasculitis associated with systemic disease, and vasculitis associated with a probable etiology. Although the names of the first four categories imply that vessel diameter is a defining feature of many forms of vasculitis, the different functional and structural characteristic of vessels are more important than the diameter of the vessel in determining their involvement in different forms of vasculitis, as well as the nature of the pathogenic events that are inducing the inflammation. Vasculitides that will be defined in this chapter include Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, Kawasaki disease, microscopic polyangiitis, granulomatosis with polyangiitis (Wegener), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, IgA vasculitis (Henoch-Schönlein), hypocomplementemic urticarial vasculitis (anti-C1q vasculitis), Behçet disease and Cogan syndrome. Many factors must be taken into consideration to make an accurate and precise clinical diagnosis of vasculitis. These include the type of vessels affected, as for example arteries versus venules; the histopathologic features of the inflammatory process such as leukocytoclastic inflammation or granulomatous inflammation; the immunopathologic features that may include IgA-dominant deposits or a paucity of immunoglobulin in vessel walls; the serologic findings such as cryoglobulins or anti- neutrophil cytoplasmic autoantibodies; any significantly associated systemic diseases such as rheumatoid arthritis

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or systemic lupus erythematosus; and associated etiologies such as hepatitis C virus infection or propylthiouracil exposure; the organ system distribution such as lung versus brain; accompanying extravascular lesions such as necrotizing granulomatosis or aphthous ulcers; or other possible factors. In a given patient, the goal of the clinician is to make a diagnosis, namely, assign a disease name that specifies the nature of the root disease process in the patient, and correctly assigns the particular form of vascular inflammation to the observed signs and symptoms that comprise the clinical criteria of that disorder, while providing useful predictions about disease outcome and appropriate treatment.

Keywords: nomenclature, pathology, vasculitides, Chapel Hill Consensus Conference 2012, ANCA

INTRODUCTION

Vasculitis is inflammation in vessel walls. The categorization and diagnosis of vasculitis is based on the nature of the inflammatory injury in vessels, including the etiology, pathogenesis, pathologic features and associated organ system dysfunction. The diagnosis of vasculitis is based on signs and symptoms of the disease or diagnostic criteria that allow a conclusion about the nature of the inflammatory injury in vessels, including the etiology, pathogenesis and pathologic features. Criteria that lead to a diagnosis in a specific patient may or may not involve direct microscopic visualization of inflammation or its sequela, such as vascular scarring in a tissue sample. However, to make a diagnosis of vasculitis, a conclusion must be reached that vasculitis with certain characteristic pathologic changes is occurring or has occurred in the patient. Thus, the underlying basis for the diagnosis of all patients with vasculitis is the nature of the pathologic inflammatory process that caused the vasculitis, although this does not mean that the pathologic lesions must be directly visualized histologically to make an actionable diagnosis.

This chapter reviews the pathology of many forms of vasculitis and presents an approach to nomenclature, classification and diagnosis that derives from these pathologic lesions. The 2012 Chapel Hill consensus conference nomenclature system (2012 CHCC) will be emphasized [1], since it modified and extended the 1994 CHCC nomenclature [2]. Disease nomenclature is a system of names used to identify and categorize diseases; and as for all words, each name has a definition.

The primary underlying defining characteristics of vasculitis in a patient are the cause and the nature of the vascular inflammation including the type of inflammation and the vascular distribution of inflammation. A diagnosis that refers only to cause or only to clinical/pathologic phenotype is problematic since 1) One cause can produce more than one pattern of injury, for example myeloperoxidase-specific anti-neutrophil cytoplasmic autoantibodies (MPO-ANCA) causing either microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA); and 2) One type of vasculitis can be induced by multiple causes, for example MPA caused by MPO-ANCA or proteinase 3-specific ANCA (PR3-ANCA). When possible, the definition of a vasculitis should include a reference not only to the nature of the inflammatory vascular injury but also the likeliest cause if known. For example, the name IgA vasculitis (IgAV) emphasizes that the vasculitis is caused by IgA1-dominant immune deposits in the walls of small vessels. The alternative name, Henoch-Schönlein purpura (HSP) was originally based on a set of

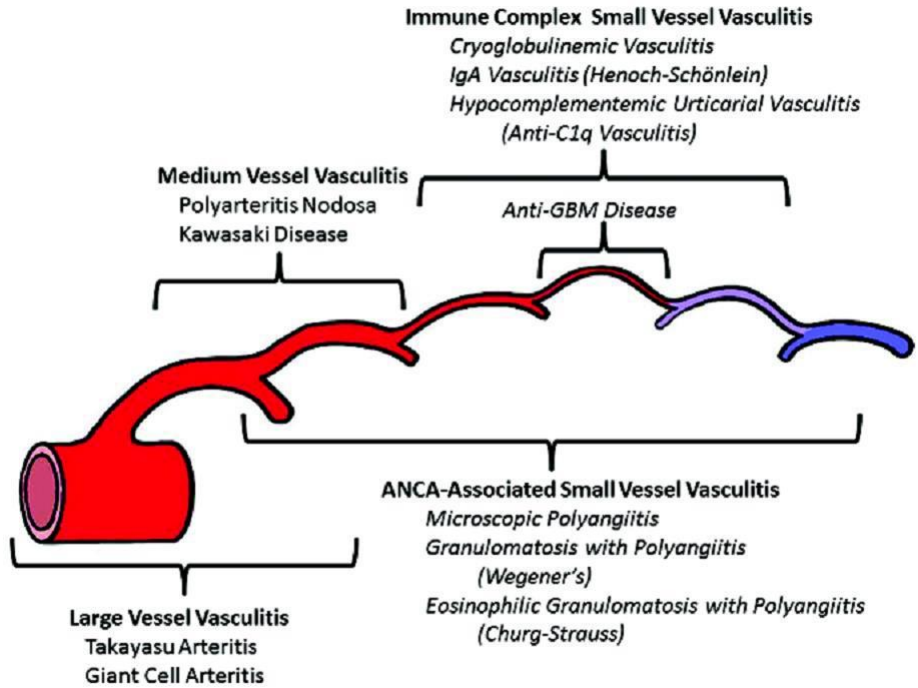
clinical manifestations that can be caused by multiple etiologies. Use of the term IgAV emphasizes the need to carefully consider the specific cause of the clinical manifestations. However, in a clinical setting, as with other pathologic features, there may be diagnostic criteria that warrant a confident diagnosis of IgA vasculitis in the absence direct observation of IgA in vessel walls by immunohistology. The conclusion that a patient has IgAV predicts clinically important clinical characteristics that guide prognosis and therapy. In patients with similar initial clinical manifestation of purpura, arthralgia and glomerulonephritis, the prognosis and appropriate treatment is very different depending on whether or not the clinical findings, including laboratory testing and pathologic observations are indicative of IgAV, cryoglobulinemic vasculitis, lupus vasculitis, MPO-ANCA MPA or PR3-ANCA GPA. However, the etiology and precise pathogenesis of some forms of vasculitis remains unknown, for example in Kawasaki disease (KD) and Takayasu arteritis (TAK). In this circumstance, the only defining features are the nature of the vasculitis and associated clinical features with no indication in the name about the cause.

The CHCC 2012 provides names and definitions for many forms of vasculitis, but does not provide specific diagnostic criteria or classification criteria [1]. Specific observations that can practicably be made in a patient for clinical management purposes comprise diagnostic criteria. Specific observations that can be made in a patient for inclusion in a cohort of patients for a clinical trial or other research project comprise classification criteria. Although definitions may remain unchanged, diagnostic criteria and classification criteria evolve over time as modalities for evaluating patients develop, for example in improved imaging methods and more sensitive and specific laboratory tests become available.

A widely used first level of categorization of vasculitides divides vasculitides into large vessel vasculitis (LVV), medium vessel vasculitis (MVV) and small vessel vasculitis (SVV) (Figure 1) (Table 1) [1, 2]. This is somewhat problematic because it implies that the size or diameter of the involved vessel alone is the major defining feature for these categories and the major basis for susceptibility to different forms of vasculitis, however this is definitely not the case. The different functional and structural characteristic of these categories of vessels are more important than the diameter of the vessel in determining their involvement in the different forms of vasculitis. The relative size of vessels is merely a convenient characteristic that facilitates reference to these biologically different types of vessels. Another source of confusion is the fact that there is overlap in the types of vessels that can be involved in different forms of vasculitis. In particular, medium and small arteries can be involved by LVV, MVV and SVV.

LARGE VESSEL VASCULITIS (LVV)

CHCC 2012 [1] defines LVV as vasculitis affecting large arteries more often than other vasculitides, and defines large arteries as the aorta and its major branches. However, the point is made that any size artery may be affected. Importantly, the definition states that LVV affects large vessels "more often than other vasculitides" rather than LVV has more large vessels affected since in a given patients with LVV, there may be, and often are numerically more involved medium and small vessels than large ones.



Reproduced from reference [1] with permission.

Figure 1. Diagram showing the predominant distribution of vessels affected by large vessel vasculitis, medium vessel vasculitis, and small vessel vasculitis. All categories of vasculitis can affect all types of arteries, but large vessel vasculitis most often affects large arteries. Medium arteries are most often affected by medium vessel vasculitis but large and small arteries may be affected. Small vessel vasculitis preferentially affects venules and capillaries, although arteries and veins may be affected. ANCA (antineutrophil cytoplasmic antibody) associated vasculitis affects a broad spectrum of vessels, whereas immune complex vasculitis usually affects capillaries or venules or both.

For example, a patient with giant cell arteritis may have involvement of the aorta, a carotid artery and several major branches of the carotid artery all of which are considered large arteries; however, many more medium and small arteries extending into the scalp, tongue, orbit and eye also may be involved. Thus, in a given patient with a LVV, there may be numerically more medium and small arteries affected. These same arteries can be affected by SVV, but SVV rarely affects the aorta and its main branches. Large vessel, including the aorta, can also be affected by variable vessel vasculitis (VVV) including Behçet disease (BD) and Cogan syndrome (CS); and by infectious vasculitis (e.g., aortitis caused by tertiary syphilis) and lymphoplasmacytic disease, for example aortitis as a component of IgG4-related disease [3]. Inflammation of large vessels with histopathologic features of Takayasu arteritis (TAK) and GCA may occur as isolated single organ vasculitides (SOV), such as isolated aortitis or isolated GCA along visceral arteries. Whether these represents limited expressions of TAK or GCA, or a distinct form of SOV has not been definitively determined.

In addition to the vascular distribution, LVV is characterized pathologically by a predominance of monocytes, macrophages, sometimes including multinucleated giant cells and lymphocytes even in the acute phase of vascular inflammation [3-5].

Table 1. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

Large vessel vasculitis (LVV)
Takayasu arteritis (TAK)
Giant cell arteritis (GCA)
Medium vessel vasculitis (MVV)
Polyarteritis nodosa (PAN)
Kawasaki disease (KD)
Small vessel vasculitis (SVV)
Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis (Wegener's) (GPA)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
Immune complex SVV
Anti-glomerular basement membrane (anti-GBM) disease
Cryoglobulinemic vasculitis (CV)
IgA vasculitis (Henoch-Schönlein) (IgAV)
Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
Variable vessel vasculitis (VVV)
Behçet disease (BD)
Cogan's syndrome (CS)
Single-Organ vasculitis (SOV)
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis Isolated aortitis
Others
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis C virus–associated cryoglobulinemic vasculitis
Hepatitis B virus–associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated (paraneoplastic) vasculitis
Others

In addition, overt fibrinoid necrosis of the vessel wall is absent or a minor feature of LVV lesions, whereas in the acute phase of MVV and SVV there often is a predominance of neutrophils and conspicuous fibrinoid necrosis. LVV may have focal areas of medial coagulative necrosis, possible caused by occlusion of vasa vasorum. It is important to realize that within a week or two of the inception of a focus of acute inflammation in MVV and SVV, the inflammation at that site evolves into chronic inflammation with replacement of neutrophils

and necrosis by mononuclear leukocytes and scarring that can be indistinguishable pathologically from chronic LVV. However, many forms of MVV and especially SVV have multiple sites of inflammation arising at different times so that there may be at least some diagnostic acute lesion in a tissue specimen even if there are many less specific chronic lesions.

The two major categories of LVV are TAK and GCA. Although on average there are some pathological and clinical features that differ between these two categories of disease, the most objective difference is that the onset of TAK is primarily before 50 years old while that of GCA is typically after age 50 years. Thus, CHCC 2012 defines Takayasu arteritis (TAK) as arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches with an onset usually in patients younger than 50 [1]. GCA is defined as arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries, often involves the temporal artery, and with onset usually in patients older than 50 and often associated with polymyalgia rheumatica (PMR) [1].

In the past, the term temporal arteritis was used as synonymous with GCA but this is not an acceptable approach because not all GCA involves the temporal arteritis and not all vasculitis affecting the temporal arteries is GCA. For example, the temporal arteries can be affected by polyarteritis nodosa (PAN), MPA, and GPA [6-8].

Active aortitis and arteritis of TAK and GCA is characterized by transmural inflammation with influx of monocytes, macrophages and lymphocytes (predominantly T lymphocytes) [3-5]. Multinucleated giant cells, formed by the fusion of monocytes into syncytial cells, often are identifiable but are not required for a pathologic diagnosis (Figure 2). Weakening and dilation of vessel walls results in aneurysm formation, and scarring and fibrotic intimal thickening result in narrowing of lumens and ischemia in downstream tissues. In arteries with an elastic media, such as the aorta and its initial branches, special stains for elastic fibers demonstrate a mouth eaten appearance with irregular zones of lysis of the multi-laminated elastic media. In non-elastic arteries, there is focal fragmentation of the internal elastic lamina at the junction between the media and the intima. Fibrinoid necrosis is uncommon and when present is usually a minor feature of the overall injury. The presence of extensive fibrinoid necrosis should raise the possibility of some form of MVV or SVV [6-8].

MEDIUM VESSEL VASCULITIS (MVV)

CHCC 2012 [1] defines MVV as vasculitis predominantly affecting medium arteries defined as the main visceral arteries and their branches. Any size artery may be affected and inflammatory aneurysms and stenoses are common. In the acute phase, the inflammation typically is accompanied necrosis, which may result of spillage of plasma constituents into the vessel wall and perivascular tissues where the constituent coagulation cascade contacts thrombogenic stimuli, including tissue factor, resulting in the formation of fibrin. This irregular accumulation of fibrin in areas of necrosis is called fibrinoid necrosis and is deeply eosinophilic in hematoxylin and eosin (H&E) stained sections (Figure 3), and red (fuchsinophilic) in Masson trichrome stained sections (Figure 4A).

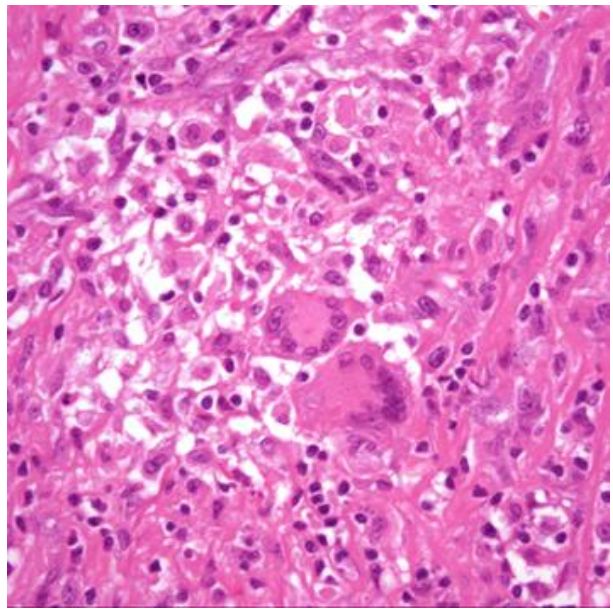
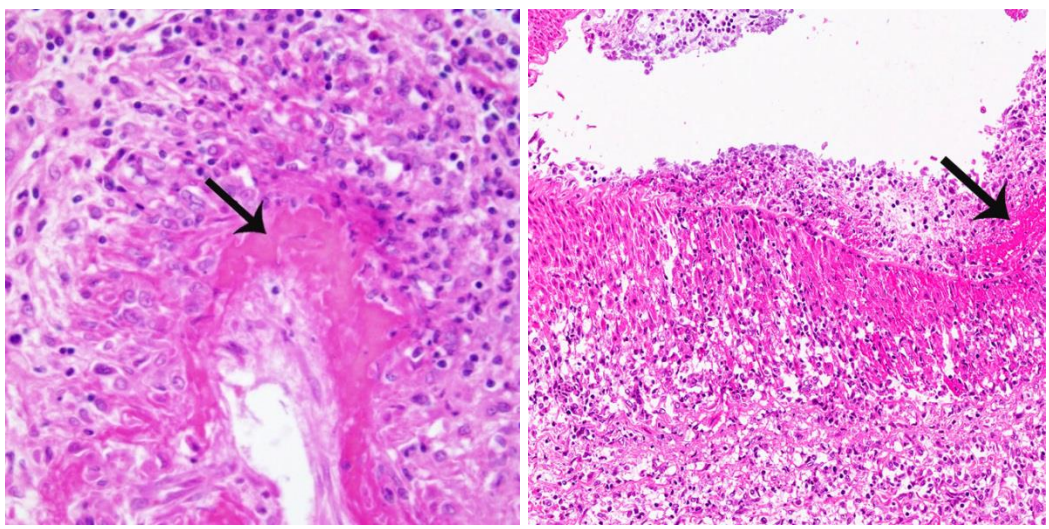


Figure 2. Multinucleated giant cells in the inflamed media of the aorta (aortitis) in a patient with giant cell arteritis (H&E stain).



a b

Figure 3. A (left): Irregular accumulation of eosinophilic fibrin in areas of fibrinoid necrosis with adjacent neutrophil-rich leukocyte infiltration in a medium artery in a patient with polyarteritis nodosa. B (right): Renal interlobar artery in a patient with Kawasaki disease with transmural inflammation including intimal arteritis, medial inflammation with dehiscence of medial cells, adventitial inflammation and a small focus of intimal fibrinoid necrosis (arrow).

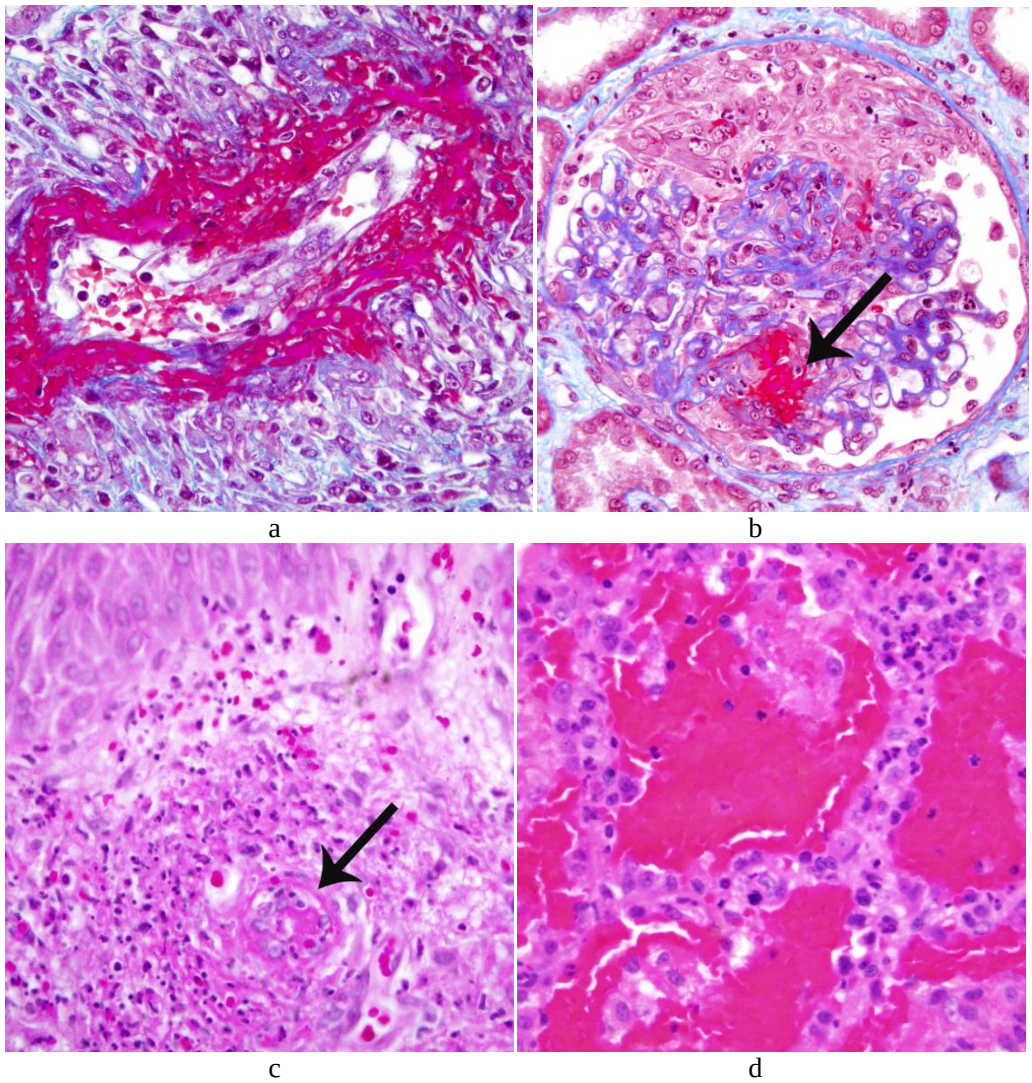


Figure 4. ANCA associated vasculitis with A: necrotizing arteritis with extensive fibrinoid necrosis that stains red with a Masson trichrome stain, B: glomerulonephritis with segmental fibrinoid necrosis (arrow) that is red with the Masson trichrome staining and a cellular crescent overlying the top of the tuft, C: dermal leukocytoclastic angiitis affecting a venule (arrow) with adjacent hemorrhage and leukocyte infiltration with numerous neutrophils and leukocyte nuclear fragmentation (leukocytoclasia), D: hemorrhagic alveolar capillaritis with neutrophils in the alveolar septa and hemorrhage in the alveolar air spaces.

Within a week or two, foci of fibrinoid necrosis are replaced by collagenous matrix as the site of acute necrosis transforms into chronic scar. The initial infiltrating inflammatory cells are neutrophils, especially in polyarteritis nodosa; and monocytes, especially in Kawasaki disease. As the acute phase of inflammation transforms into the chronic phase of inflammation and sclerosis, macrophages and T lymphocytes become the predominant inflammatory cells.

The two major categories of MVV are PAN and KD. CHCC 2012 [1] defines PAN as necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules; and not associated with ANCA or mucocutaneous lymph node syndrome. The absence of ANCA helps distinguish the necrotizing arteritis of PAN from the histopathologically indistinguishable necrotizing arteritis of ANCA-associated vasculitis (AAV) [9, 10]. The absence of mucocutaneous lymph node syndrome distinguishes PAN from the necrotizing arteritis of KD [1]. Further, necrotizing arteritis that is indistinguishable from PAN also can secondarily occur in systemic lupus erythematous (SLE), rheumatoid arthritis (RA) and other systemic autoimmune and autoinflammatory conditions; secondary to infection notably with the hepatitis B virus (HBV); and as a component of variable vessel vasculitis (VVV) in BD and CD; or as a SOV such as cutaneous arteritis.

Thus, a diagnosis of PAN is a diagnosis of exclusion, that is, all other forms of vasculitis that can cause necrotizing arteritis must be excluded before a diagnosis of PAN is appropriate. In a clinical setting, this can be difficult and may require that a patient initially have a generic diagnosis of necrotizing arteries until a more specific diagnosis is warranted.

KD is defined as arteritis associated with the mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries [1]. Coronary arteries are often involved although the aorta and other large arteries may be involved. KD usually occurs in infants and young children, with onset after 5 years old very uncommon. The acute necrotizing arteritis of KD can resemble the acute lesion of PAN, which is why this disease was once called infantile PAN by some investigators. However, in general, compared to PAN the acute arteritis of KD has more monocytes, less neutrophils, and more vessel wall edema (medial cell dehiscence) and less fibrinoid necrosis (Figure 3B). Coronary arteritis can occur anywhere along the course of coronary arteries in the epicardium and myocardium, but occurs most often in the origin of the coronary arteries adjacent to the aorta. Inflammatory aneurysms form at the sites of inflammation and necrosis, and may induce thrombosis resulting in myocardial infarction, which is the major cause for mortality in KD.

SMALL VESSEL VASCULITIS (SVV)

CHCC 2012 [1] defines SVV as vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries and venules. Medium arteries and veins may be affected. As noted already, LVV and MVV also can affect arteries, and MVV can cause acute necrotizing inflammatory lesions in arteries that are indistinguishable from the lesions of SVV necrotizing arteritis. Both MVV and LVV cause necrotizing arteritis with conspicuous fibrinoid necrosis (Figure 3A and 4A). Thus, identifying arteritis does not distinguish between MVV and SVV. Whether or not arterioles are involved also is not an effective means of distinguishing between MVV and SVV because identifying arterioles versus small arteries is problematic. The most workable definition of arterioles is “the smallest branches of arteries.” Definitions of arterioles based on structural features such as layers of muscle cells in the media and absence on internal elastica; do not consistently identify a distinct vessel type.

Thus using arteriolar involvement is not a reliable approach to distinguishing between MVV and SVV. The best approach for identifying a SVV is to identify involvement of venules

and capillaries, for example dermal venulitis (Figure 4C), glomerular capillaritis (glomerulonephritis) (Figure 4B) or pulmonary alveolar capillaritis (Figure 4D).

According to CHCC 2012 [1], SVV is further subcategorized on the basis of immunopathologic findings into AAV or immune complex SVV (Table 1) (Figure 1). AAV has few or no deposits of immunoglobulin or complement in affected vessel walls, whereas immune complex SVV has moderate to marked vessel wall deposits of immunoglobulin and/or complement components (Figure 5).

This paucity of immunostaining for immunoglobulins in involved vessels in patients with AAV is the basis for the pathologic term "pauci-immune" to distinguish AAV and glomerulonephritis from immune complex vasculitis and glomerulonephritis.

This subcategorization is warranted in part because there is compelling evidence that the ANCA and the vessel wall immune deposits are not only useful biomarkers for diagnosis but also are prime movers in the pathogenesis of the vascular inflammation [13].

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS

CHCC 2012 [1] defines AAV as necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels including capillaries, venules, arterioles and small arteries, and association with MPO-ANCA or PR3-ANCA. However, not all patients have ANCA. A prefix should be added to the name indicating the ANCA reactivity, for example PR3-ANCA, MPO-ANCA, or ANCA-negative [1, 15].

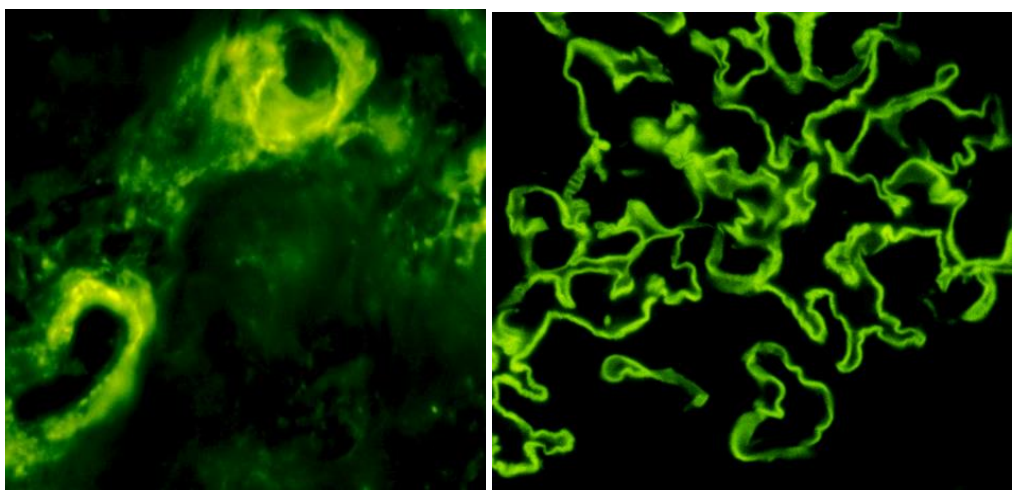


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Figure 5. A. Dermal venules with granular vessel wall staining for IgA in a patient with IgA vasculitis (Henoch-Schönlein purpura) (Fluoresceinated anti-IgA stain). B. Glomerular capillary basement membranes with linear staining for IgG in a patient with anti-GBM disease (Fluoresceinated anti-IgG stain).

AAV are further categorized as MPA, GPA and EGPA [1]. Thus, when adequate information is available, an optimum AAV diagnosis based on CHCC 2012 includes both the ANCA serotype and the clinicopathologic phenotype, such as MPO-ANCA MPA, PR3-ANCA MPA, MPO-ANCA GPA, PR3-ANCA GPA, ANCA-negative GPA, and MPO-ANCA-EGPA. In a clinical setting, the serotype alone predicts some disease characteristics (Figure 6) and outcomes as for example the frequency of recurrence after induction of remission; while the clinicopathologic variant alone also predicts some disease characteristics and outcomes. However, the two together give a more complete picture about the patient and expected treatment [14, 15]. Thus, from a practical perspective, the available information may require that a more generic diagnosis be made initially, as for example MPO-ANCA AAV, and then refined after more thorough evaluation or as clinical manifestations evolve such as the emergence of compelling evidence for GPA rather than MPA.

MPA is defined as necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels such as capillaries, venules, and arterioles [1].

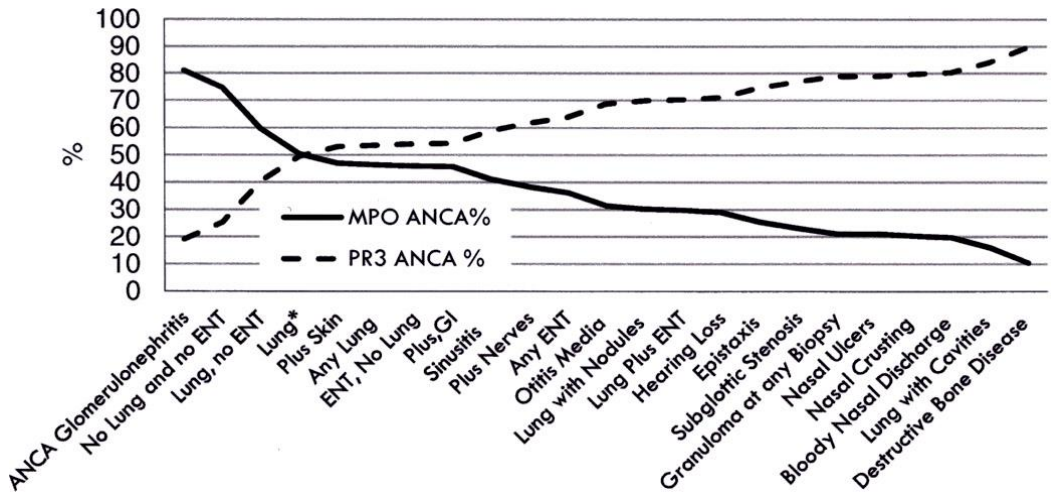

Figure 6. Frequency of PR3- and MPO-ANCA specificity correlated with clinical manifestations of AAV disease. Organ groupings are not mutually exclusive.
Abbreviations: No Lung and No ENT (ear, nose and throat involvement): Vasculitis in any organ except the lungs and the ENT system; Lung no ENT: Vasculitis localized in the lungs but not in the ENT system; Lung: Vasculitis localized in the lungs without indicative markers such as nodules or cavities, or histological proof such as granulomas indicative of granulomatous inflammation; Plus Gastrointestinal (GI involvement): Vasculitis localized at any organ plus involvement of the gastrointestinal tract; Plus Skin: Vasculitis localized at any organ plus dermal involvement; Plus Nerves: Vasculitis localized at any organ plus involvement of the nerves; Any Lung: Any type of pulmonary vasculitis such as pulmonary hemorrhage, infiltrates, nodules, cavities, granulomas, or respiratory arrest; ENT, no Lung: Vasculitis localized to the ENT system but not in the lungs; Any ENT: Any type of vasculitic manifestation of the ENT system; Lung with nodules: Vasculitis localized at the lungs with radiographic proof of nodules; Lung plus ENT: Any type of pulmonary vasculitis plus any type of vasculitic manifestation of the ENT system. Reproduced from [14] with permission.

Necrotizing arteritis involving small and medium arteries may be present (Figure 4A). Necrotizing glomerulonephritis is very common (Figure 4B). Pulmonary capillaritis often occurs (Figure 4D). Granulomatous inflammation is absent.

All of the lesions observed in MPA can occur in patients with GPA and EGPA. Thus, among patients with AAV, a diagnosis of MPA is a diagnosis of exclusion, once GPA and EGPA are ruled out. Of course, in a clinical setting this is never unequivocal, because a patient thought to have MPA may in fact have an occult focus of necrotizing granulomatosis. This may not be a major problem because the presentation at that time may be primarily as MPA, and if the GPA features become overt, the working diagnosis would change to GPA.

The histopathologic lesions of immune complex SVV can be indistinguishable from those of AAV. For example, leukocytoclastic angiitis or vasculitis (LCV) (Figure 4C) in the skin can be caused by any of the systemic variants of AAV including MPA, GPA, and EGPA, as well as, most if not all forms of immune complex SVV, including but not limited to IgAV, cryoglobulinemic vasculitis (CV) and serum sickness.

Light microscopy alone is not sufficient to identify the cause of LCV. Additional data are required, such as serologic findings and tissue immunostaining.

GPA is defined as necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels such as capillaries, venules, arterioles, arteries and veins [1]. Necrotizing glomerulonephritis is common. The defining granulomatosis of GPA is a very destructive lesion that in the acute phase resembles an abscess (Figure 7A) more than a typical granuloma. In the acute phase, neutrophils predominate at the sites of granulomatosis, and a few scattered multinucleated giant cells are the only histologic features justifying a designation of granulomatosis.

However, as the lesions evolve, the neutrophils in the central zone of necrosis lyse and are replaced by amorphous necrotic debris, and epithelioid macrophages form palisades that wall of the zone of necrosis in a typical granulomatous pattern (Figure 7B).

EGPA is defined as eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present. The asthma that precedes EGPA typically is late onset, and affected patients often have a prodromal phase of eosinophil rich inflammatory disease for example eosinophilic pneumonia or eosinophilic gastroenteritis, prior to the onset of definitive manifestations for vasculitis or glomerulonephritis [15]. Eosinophils are conspicuous at sites of tissue inflammation, including sites of vasculitis (Figure 8).

However, similar prominence of eosinophils can be observed in lesion of MPA and GPA, thus this is not diagnostic in the absence of the asthma and blood eosinophilia.

With sensitive clinical assays, 90% or more of patients with active untreated MPA and GPA are ANCA positive, with PR3-ANCA more frequent in GPA and MPA in Europe and North America [16].

However, <50% of patients with EGPA are positive for ANCA, almost always MPO-ANCA [16]. Interestingly, more than 75% of EGPA patients with renal disease are ANCA-positive compared to approximately 25% of EGPA patients with no clinical evidence for kidney disease [17].

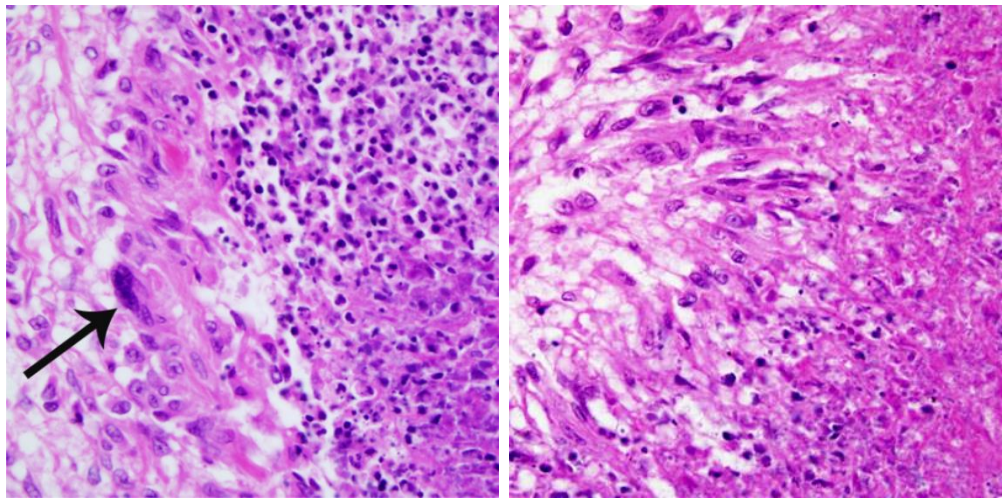

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Figure 7. Lung tissue from a patient with granulomatosis with polyangiitis (Wegener's) showing A: an early lesion with an intense infiltrate of neutrophils on the right and an adjacent accumulation of macrophages including a multinucleated giant cell (arrow), B: more advanced granulomatosis with an amorphous zone of necrosis on the right and an adjacent zone of palisading epithelioid macrophages (Hematoxylin and eosin [H&E] stain).

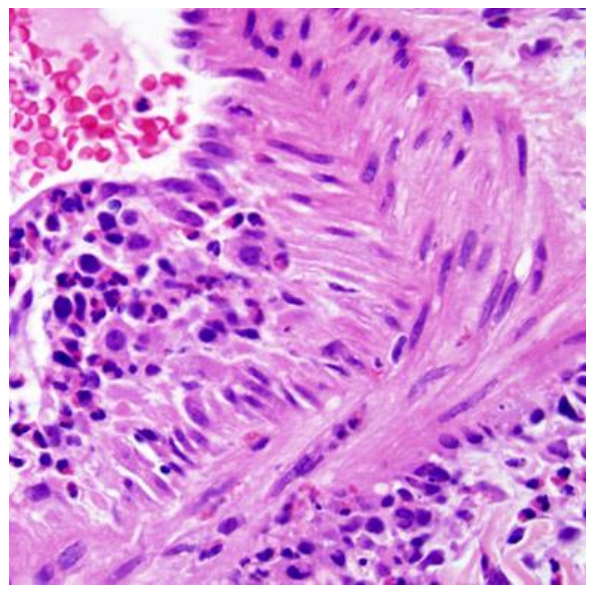

Figure 8. Arteritis in a patient with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) showing intimal arteritis with numerous eosinophils in an expanded intima (left), scattered eosinophils in the media, and numerous eosinophils in the adventitia (right) (H&E stain).

Organ limited expressions of AAV occur, for example isolated cutaneous vasculitis, lung capillaritis, upper respiratory tract granulomatosis, or pauci-immune necrotizing and crescentic glomerulonephritis also called renal-limited vasculitis. In some but not all patients, multisystem involvement is identified later. Isolated granulomatosis often is considered a limited form of

GPA and isolated vasculitis as a limited form of MPA if the lesions otherwise are identical to those observed in systemic AAV.

IMMUNE COMPLEX SMALL VESSEL VASCULITIS

CHCC 2012 [1] defines immune complex SVV as vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels such as capillaries, venules, arterioles and small arteries; glomerulonephritis is frequent.

Immune complex SVV differs immunopathologically from AAV with respect to the extent of immunoglobulin deposited in vessel walls. This most likely is a reflection of the different etiologies and pathogenic mechanisms. Immune complex vasculitis appears to result from initial extensive localization of immune complexes in vessel walls followed by complement activation and mediation of inflammation. The immunoglobulin is diffusely distributed in the walls of affected small vessels. In contrast, AAV appears to be mediated by more direct interaction of ANCA with neutrophils and monocytes resulting in activation that in turn releases factors that activate the alternative complement pathway, which amplifies the inflammation to cause the severe necrotizing lesions of AAV [13].

There are many forms of immune complex SVV caused by immune complexes of different compositions. The antigens in pathogenic immune complexes can be derived from heterologous sources such as infectious pathogens or drugs, or from endogenous sources such as autoantigens. CHCC 2012 only defines several of these many variants: anti-glomerular basement membrane (anti-GBM) disease, CV, IgAV, and hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis).

Anti-GBM disease is defined as vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti-basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.

From an immunopathologic perspective, anti-GBM disease is somewhat distinct from many other forms of immune complex vasculitis and glomerulonephritis because immunostaining of involved capillaries shows linear staining rather than granular staining (Figure 5B). This is because the target autoantigen is a diffusely distributed constituent component of the glomerular and alveolar capillary basement membranes, type IV collagen. Thus, immune complexes containing anti-GBM antibodies and type IV collagen form in situ diffusely along these basement membranes resulting in the linear staining. By contrast, other types of immune complexes gather stochastically and irregularly within vessels walls producing the granular pattern of immunostaining. The inflammatory vascular injury of anti-GBM disease affects glomerular capillaries, pulmonary capillaries, or both, with focal rupture of capillary walls and hemorrhage into the urinary space or alveolar air spaces.

By routine light microscopy, neutrophils often are not conspicuous at sites of necrosis, probably because they are destroyed in the process of activation and necrosis. However, in some lung specimens, more overt pulmonary capillaritis with influx of neutrophils is observed [18]. Approximately a third of patients with anti-GBM disease also have ANCA, usually MPO-ANCA [19]. They have an initial renal outcome more like anti-GBM disease than AAV with a

higher rate of progression to end stage [19]. Renal biopsy specimens from patients with concurrent anti-GBM and ANCA may reveal necrotizing arteritis as well as glomerulonephritis.

Cryoglobulinemic vasculitis (CV) is defined as vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum [1]. Skin, glomeruli and peripheral nerves are often involved. Localization of cryoglobulins in vessel walls incites inflammation (vasculitis) by complement activation [20, 21]. Monoclonal cryoglobulins (type I) are not as effective at activating inflammatory mediator systems as are mixed cryoglobulins (types II and III), which are immune complexes composed of anti-antibodies or rheumatoid factors (RF) bound to target antibodies. An important cause for cryoglobulinemia is hepatitis C virus (HCV) infection [21]. Acute CV affecting venules, arterioles and small arteries typically has neutrophilic infiltration with leukocytoclasia (Figure 9). The inflammation may be accompanied by luminal or vessel wall deposits of PAS-positive hyaline material composed of coagula of cryoglobulins (Figure 9). Cryoglobulinemic glomerulonephritis occurs as a renal limited process and as a component of systemic CV. Cryoglobulinemic glomerulonephritis usually has a membranoproliferative pattern but may have other patterns of proliferative glomerulonephritis. A frequent finding is hyaline material in glomerular capillary lumens ("hyaline thrombi") that are coagula of cryoglobulins.

Although glomerulonephritis is a frequent component of many forms of immune complex SVV, the glomerular lesions, including immunopathologic features, are very helpful in distinguishing among them, for example, CV with membranoproliferative lesions and IgG/IgM deposits, IgAV with IgA-dominant deposits, anti-GBM disease with necrosis and linear IgG, and AAV vasculitis with necrosis and a paucity of immunoglobulin deposits.

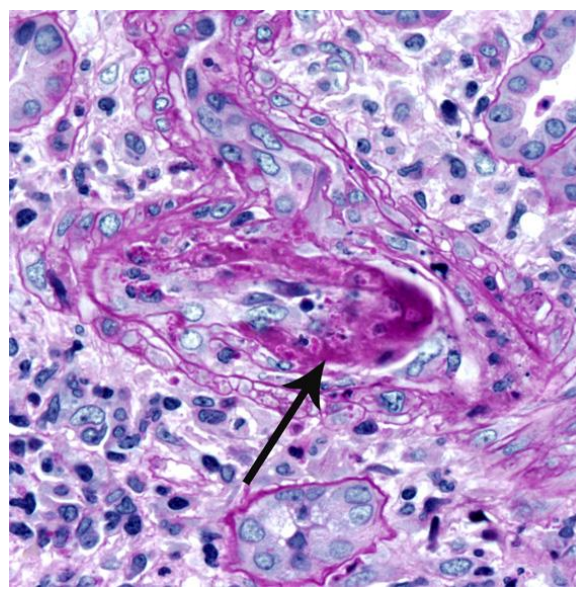

Figure 9. Inflammation of a small interlobular renal artery in a patient with cryoglobulinemic vasculitis. The arrow points to some hyaline material in the lumen that may be aggregated cry globulins. Some of the vessel wall leukocytes are undergoing leukocytoclasia (PAS stain).

IgAV is defined as vasculitis, with IgA1-dominant immune deposits, predominantly affecting small vessels such as capillaries, venules, and arterioles (Figure 5A) [1]. IgAV often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur. The shift in terminology to IgA vasculitis is prompted in part by mounting evidence that abnormally reduced glycosylation of the O-linked glycans in the hinge region of IgA1 molecules play a pivotal pathogenic role in IgA vasculitis and IgA nephropathy [22, 23].

In patients with these diseases, serum IgA1 has reduced terminal galactosylation and sialylation, resulting in increased exposure of N-acetylgalactosamine at the ends of the hinge region glycans. There also is evidence that patients have autoantibodies that recognize these abnormally glycosylated IgA1 hinge regions, which could result in immune complex formation. In addition to forming pathogenic immune complexes, abnormal glycosylation of the glycans in the hinge region of IgA1 molecules could play a pathogenic role through a variety of other mechanisms, such as reduced clearance from the circulation because of lack of receptor engagement by the abnormal IgA, increased aggregation of IgA in the circulation resulting in mesangial trapping, and increased affinity of the abnormal IgA for mesangial matrix.

Purpura hematuria and proteinuria are frequent clinical manifestations of IgA vasculitis that also are shared by other forms of SVV, including AAV and cryoglobulinemic vasculitis [24]. Demographic, clinical, laboratory and pathology observations all help resolve the differential diagnosis. For example, IgAV is most frequent in children, especially children under 10 years old, whereas AAV and CV are more common in older patients. However, all can occur at any age. Useful disease markers include immunohistologic findings such as IgA1 deposits, cryoglobulin deposits, and a paucity of deposits; and serologic tests under glycosylated IgA1, RF and ANCA.

The glomerular lesions in the kidney are indistinguishable from those of IgA nephropathy although necrosis, crescents and capillary wall deposits are somewhat more frequent in IgA vasculitis patients who undergo renal biopsy. In addition to the glomeruli, IgA1-dominant immune deposits occur in renal arterioles and peritubular capillaries in <20% of patients. IgA1-dominant immune deposits also can be identified in small vessels of the skin and gut; however, this is not of value in differentiating IgA vasculitis from IgA nephropathy because many IgA nephropathy patients also have IgA in dermal venules.

HUV is accompanied by urticaria and hypocomplementemia affects small vessels such as capillaries, venules, and arterioles, and is associated with anti-C1q antibodies [1]; glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common.

HUV is characterized by recurrent episodes of urticaria with underlying leukocytoclastic vasculitis that causes hemorrhage into the lesions [24]. Skin manifestations include painful, tender, burning or pruritic lesions that persist for greater than 24 hours, often with central or diffuse areas of hemorrhage. HUV can be isolated or associated with autoimmune diseases (including lupus), infections, drug reactions, or neoplasms. Proteinuria and hematuria occur in 20-30% of patients and the underlying glomerular lesion usually has a membranoproliferative pattern, but other proliferative and focal necrotizing lesions may occur. Glomeruli and dermal vessels have granular deposits of IgG, IgA, IgM, C3 and C1q, which resembles the “full house” immunostaining seen in SLE.

IgG autoantibodies to the collagen-like region of C1q (anti-C1q) are usually present and may play a role in pathogenesis [25]. The hypocomplementemia appears to be secondary to

classical pathway activation with reduced C1, C2, C4, and C3. The marked localized edema (urticarial) may be a manifestation of enhanced complement mediated vascular permeability resulting from an effect of anti-C1q antibodies on complement activation.

VARIABLE VESSEL VASCULITIS

VVV is a category of vasculitis that was not included in the CHCC 1994 nomenclature system [2]. The CHCC 2012 defines VVV as vasculitis with can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries). Two protean vasculitides are included, Behçet disease (BD) and Cogan's syndrome (CS) [1]. Although these disease are rare and vasculitis caused by them is even rarer, they were included for completeness and so that they will be considered in the differential diagnosis of patients with vasculitis.

BD is clinically characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and central nervous system (CNS) inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis and arterial aneurysms may occur. The associated vasculitis can involves both arteries and veins of all sizes for example the aorta and large arteries to small mucosal and cutaneous veins, venules, arterioles and arteries (Figure 10) [24, 27-29]. The aorta and other large arteries such as the pulmonary arteries may demonstrate transmural neutrophil-rich inflammation resulting in aneurysm formation, and small vessels have leukocytoclastic angiitis. Aortitis and arteritis can result in aneurysm formation, vascular stenoses and occlusions. Arterial complications are less common than venous lesions, which include phlebitis and thrombosis. A variant called 'vasculo-Behçet disease' has prominent vascular complications including vasculitis, thrombosis, stenoses, occlusions, and aneurysms.

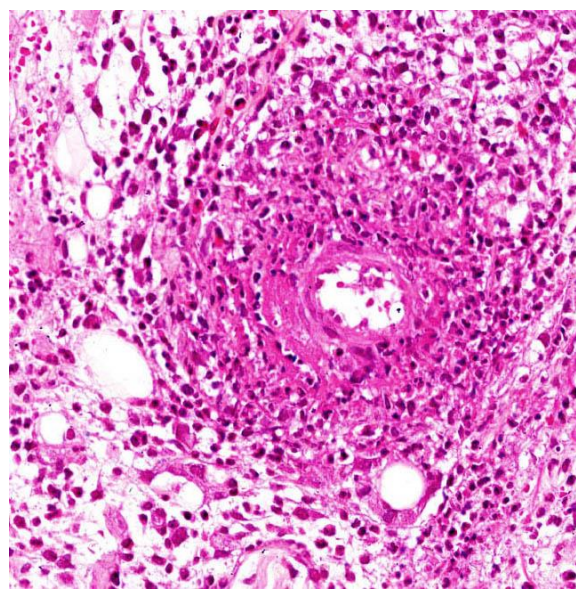

Figure 10. Leukocytoclastic angiitis affecting a small subcutaneous artery in a patient with Becher's disease (H&E stain).

CS is clinically characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction [30-32]. The associated vasculitis which occurs in approximately 15% of affected patients, includes arteritis of small, medium or large arteries; aortitis, aortic aneurysms, and aortic and mitral valvulitis [1]. Involved vessels can have transmural infiltration of neutrophils in the acute phase.

The differential diagnosis of a patient with CS includes GPA, EGPA, RV, and relapsing polychondritis, all of which may be complicated by inflammatory eye disease and, less commonly, sensorineural hearing loss [30].

SINGLE-ORGAN VASCULITIS

CHCC 2012 defines SOV as vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis [1]. The involved organ and vessel type should be included in the name, for example cutaneous small vessel vasculitis, testicular arteritis, and CNS vasculitis. Vasculitis distribution may be unifocal, multifocal or diffuse within an organ. Some patients originally diagnosed with SOV will develop additional disease manifestations that warrant redefining the case as one of the systemic vasculitides, as for example cutaneous arteritis later developing into systemic polyarteritis nodosa. A diagnosis of SOV always requires careful exclusion of systemic vasculitis.

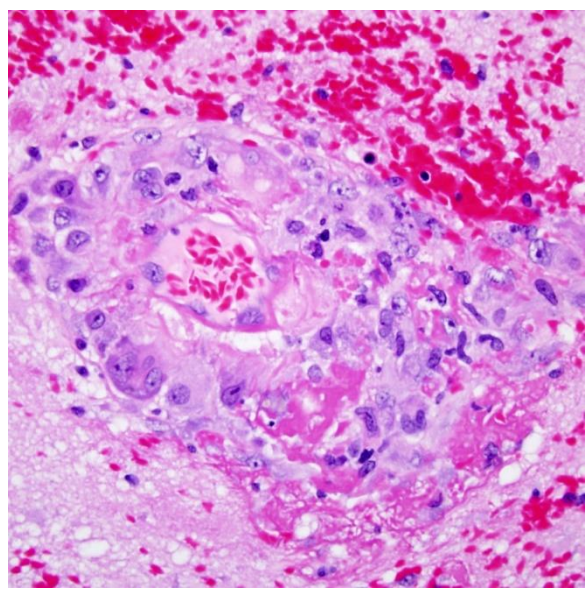

Figure 11. Primary central nervous system vasculitis (CNS single organ vasculitis) affecting a small intracerebral artery with granulomatous inflammation resulting in perivascular hemorrhage (H and E stain).

Many forms of SOV have been reported, for example cutaneous LCV [24], cutaneous arteritis or cutaneous polyarteritis [24, 33, 34], primary angiitis of the CNS (PACNS) [35] or the equivalent term primary CNS vasculitis (PCNSV) [36]; isolated aortitis, and others [37]. The histopathologic pattern of injury can resemble any of the recognized forms of systemic vasculitis, although necrotizing arteries and granulomatous arteritis are most frequent.

An extended period of surveillance is recommended to substantiate the accuracy of the diagnosis of SOV and that excision of the affected site provides a cure [37]. Moreover, CHCC 2012 recommends that the term SOV not be used for organ-limited expressions of vasculitides that usually have multisystem involvement, for example GPA confined to the lungs also known as lung-limited GPA; or ANCA-positive pauci-immune necrotizing glomerulonephritis without systemic vasculitis also known as renal-limited-AAV.

VASCULITIS ASSOCIATED WITH SYSTEMIC DISEASE

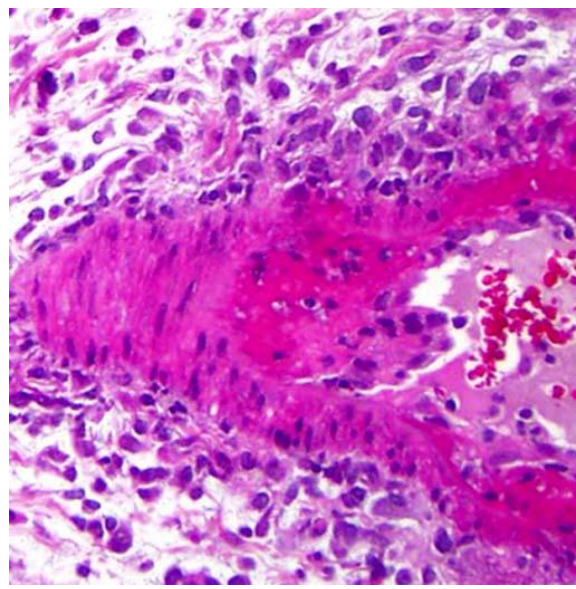

Figure 12. Necrotizing arteritis in the perirenal adipose tissue of a patient with systemic lupus erythematosus showing focal fibrinoid necrosis and leukocyte infiltration (H and E stain).

CHCC 2012 acknowledges that vasculitis can be associated with different systemic diseases, which may be causing the vasculitis [1]. Therefore the name or diagnosis should include a prefix term specifying the systemic disease such as rheumatoid vasculitis, lupus vasculitis and sarcoid vasculitis (Figure 12). There is a subjective distinction between vasculitis secondary to a systemic inflammatory disease and vasculitis that is characteristic of a systemic inflammatory disease. In some instances, it may be a relatively infrequent feature of a systemic disease as for example vasculitis in rheumatoid arthritis, or a frequent feature and therefore characteristic component of the systemic disease, such as in GPA; however in CS, vasculitis falls into a gray zone. The important concept is that whenever a vasculitis is identified, the possibility of vasculitis secondary to a systemic disease should be considered.

VASCULITIS ASSOCIATED WITH PROBABLE ETIOLOGY

CHCC 2012 acknowledges that vasculitis may be associated with a probable specific etiology [1]. In this case, the name or diagnosis should have a prefix term specifying the association, for example hydralazine-associated microscopic polyangiitis, HBV-associated vasculitis and HCV-associated CV, minocycline-associated vasculitis, and paraneoplastic vasculitis.

The likelihood that an association with a probable etiology is because of a causal relationship depends on the credibility of the supporting data. Some etiologic relationships are reflected in the names of major categories and others designate categorical subsets. For example, propylthiouracil-associated MPO-ANCA and HCV-associated CV are designations that each refer to two different etiologies that act in sequence to cause vasculitis, highlighting the importance of using diagnostic terms that provide information about likely or definite causes of vasculitis in a given patient.

Emerging data from genomic, proteomic and metabolomic studies are demonstrating previously unrecognized probable etiologies and pathogenic mechanisms [38]. Monogenic mutations have been discovered associated with various patterns of vasculitis. For example, Deficiency of Adenosine deaminase 2 (DADA2) resulting from mutations in the CECR1 gene can cause a necrotizing vasculopathy that resembles PAN pathologically and clinically. However, DADA differs clinically from typical PAN because the onset usually is in childhood [39].

CONCLUSION

Many factors must be taken into consideration in rendering an accurate and precise clinical diagnosis of vasculitis in a given patient, such as the clinical signs and symptoms, results of laboratory tests, and the observed histopathology of involved organ tissue. Important parameters include the types of vessels affected, as for example arteries or venules; the pathologic features of the inflammatory process such as leukocytoclastic inflammation versus granulomatous inflammation; immunopathologic features such as IgA-dominant deposits or paucity of immunoglobulin in vessel walls; serologic findings such as cryoglobulins or ANCA; associated systemic disease such as RA or SLE; proximate etiologies such as HCV and propylthiouracil; the distribution of lesions to affected organ systems such as the lungs versus the gut; and any accompanying extravascular lesions such as necrotizing granulomatosis or aphthous ulcers, and other factors.

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Chapter 10

CLASSIFICATION OF PEDIATRIC VASCULITIDES

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ABSTRACT

The primary systemic vasculitides in childhood are quite uncommon with the exception of Ig A vasculitis (Henoch-Schönlein purpura) and Kawasaki disease. Although children and adults share many characteristics in vasculitis, they also differ in certain aspects of different vasculitic diseases. The criteria of the 2012 Chapel Hill Consensus nomenclature and the validated Ankara 2008 classification for childhood vasculitides can be applied to pediatric practice. Advances in the understanding and diagnosis of childhood primary systemic vasculitis will continue to shape classification criteria in the future.

Keywords: pediatric, vasculitis, classification

INTRODUCTION

Vasculitis is characterized by the inflammation of the blood vessels leading to vascular stenosis, occlusion, aneurysm, or rupture [1]. The vasculitides have specific vessel involvements, specific organ system choices and sometimes age selections. In fact, the types of vasculitis and their course differ in childhood. With an overall estimated incidence of childhood vasculitis of about 50 cases per 100,000 children per year [2], the most frequent vasculitic disorders are IgA Vasculitis (Henoch Schonlein purpura) (IgAV (HSP)) and Kawasaki disease (KD) [2]. The prevalence of childhood HSP and KD range from 13.5/100,000 for IgAV (HSP) [3, 4], and 135 to 200/100,000 IgAV/for KD in Japan to 9 to 17/100,000 in Caucasians [5]. This compares with the lower prevalence of adult vasculitides wherein the estimated annual incidence for IgAV (HSP) is 0.8 to 1.8/100000 [6], and around 10/million

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total population for both granulomatosis with polyangiitis (GPA) (Wegener granulomatosis) and microscopic polyangiitis (MPA) [7, 8].

The 2012 revised definitions of the Chapel Hill consensus conference vastly improved the understanding of the vaculitides [9]. The new nomenclature is reviewed elsewhere in this volume, however neither are they intended to be classification or diagnostic criteria.

Many vasculitides affect both children and adults. However, some, like KD, occur exclusively in childhood, while others such as temporal arteritis rarely if ever occur in childhood. Children and adults also differ in the etiology, relative frequency of some clinical manifestations, and prognostic characteristics of different vasculitides [9, 10]. This may be due to immune system differences between adults and children. With aging, certain changes occur in the immune system. With aging, there is progressive thymic involution that decreases the number of naïve and regulatory T-cells. There is continuous reshaping of the immune repertoire by persistent antigenic challenges as well as, reduced production of naïve B cells and dysregulation of toll-like receptors that have major roles in innate immunity [11]. These changes may have direct linkages with different autoimmune disease susceptibility.

Disease classification systems are based on arbitrary combinations of different disease characteristics with the purpose of differentiation of closely related syndromes [12]. The primary objective of classification criteria is to define homogenous patient populations mainly for research purposes and epidemiological data; not to diagnose disease in individuals [13]. A diagnosis is made by considering all clinical features of the patient, not only the classification criteria [14]. However, classification criteria are used for diagnosis in practice, albeit with a low sensitivity [14]. In 1990, the American College of Rheumatology (ACR) proposed classification criteria for adult patients with vasculitides [16-20]. However, it had a number of shortcomings. For example, ACR criteria excluded MPA as a disease category, and there was no reference to antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) or KD [16-20]. In as much as the ACR criteria were not validated in children, they were not suitable for childhood vasculitis. With this background, in 2005, the vasculitis-working group of the Pediatric Rheumatology European Society (PRES) proposed preliminary classification criteria for some of the commonest childhood vasculitides: HSP/IgAV, childhood polyarteritis nodosa (PAN), GPA, childhood Takayasu arteritis (TA) and KD [21]. These criteria were validated and took the final form at the 2008 Ankara Consensus Conference with support from the European League Against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) [22, 23]. In a recent study [24], the Ankara 2008 criteria performed better in a large cohort of North American GPA patients.

IgA Vasculitis / Henoch-Schönlein Purpura

HSP/IgAV is the most common form of childhood vasculitis with an incidence of at least 135 per 1 million children [3, 4]. About 90% of IgAV/HSP patients are younger than 10 years of age [25]. The disease is less severe in children than in adults [26]. To fulfill ACR classification criteria for HSP/IgAV, two of the following are required: age < 20 years, palpable purpura, abdominal pain, and vessel wall granulocytes on biopsy [17].

During the revision process for children, the major change was to make palpable purpura a mandatory criterion [23]. The biopsy criterion was also revised as presence of IgA deposition

in any biopsy to increase the specificity of the criteria in children. In addition, it is important to define IgA deposits as "predominant" to differentiate HSP/IgAV from other diseases with IgA deposits [22-24].

It was agreed to use the United Nations/UNICEF definition of a "child" as 18 years or less [27]. Thus, the age criterion in IgAV/HSP was deleted [21]. As the joint involvement is more common in children, it was added to the group of criteria [23]. Renal involvement is the main because of late morbidity and mortality in pediatric IgAV/HSP patients and approximately 40% of children with IgAV/HSP develop nephritis within six weeks of presentation [28]. Renal involvement was also considered as a new criterion to underline its importance in long-term prognosis [23].

In its final form, for IgAV/HSP classification, the Ankara 2008 criteria required the presence of palpable purpura with lower limb predominance plus one of the following four features: diffuse abdominal pain, any biopsy showing predominant IgA deposition, arthritis or arthralgia, and renal involvement (any hematuria and/or proteinuria). If purpura has an atypical distribution, the demonstration of IgA deposits in a biopsy is required [23]. The sensitivity and specificity of these criteria were found as 100% and 87% respectively in children [23].

KAWASAKI DISEASE

KD is an acute, self-limited systemic vasculitis of medium- and small-sized vessels predominantly occurring in children aged 6 months to 5 years [29]. It is the second most common childhood vasculitis and the leading cause of acquired heart disease in children in developed countries [30]. The distribution is worldwide. However, among children younger than 5 years of age, the incidence in Japan (135 to 200 per 100,000) is 10 to 15 times greater than the Caucasian incidence (9 to 17 per 100,000) [5].

KD classification was based on either Japanese or American classification criteria [31, 32]. The Japanese classification criteria for KD requires the presence of five of the following six features: characteristic fever, bilateral conjunctivitis, changes in lips and oral cavity, polymorphous exanthema, changes of peripheral extremities, and cervical lymphadenopathy [32]. The American classification required fever plus four of the remaining five criteria [31].

The major complication of KD is damage to coronary arteries; and while 25% of untreated KD patients suffer from coronary artery aneurysm, this decreases to 4% with proper treatment [33]. In the aforementioned 2006 criteria, it was agreed that a child with typical echocardiographic changes could be classified as KD without fulfilling four of the remaining criteria [21]. The second modification was the addition of perianal desquamation to the criterion describing the changes in extremities [21]. After these modifications, the classification criteria for KD included fever persisting for at least five days (mandatory criterion) plus four of five additional features: changes in the peripheral extremities or perianal area, polymorphous exanthema, bilateral conjunctival injection, changes of lips and oral cavity and/or injection of oral and pharyngeal mucosa, and cervical lymphadenopathy. In the case of fever and coronary artery disease detected by echocardiography, fever than four of the remaining five criteria are enough to classify a patient as having KD [21]. The American Heart Association recently published suggestions for the diagnosis and management of KD [33].

POLYARTERITIS NODOSA

PAN is a necrotizing vasculitis characterized by aneurysmal nodules along the walls of predominantly medium-sized arteries and multi-organ involvement that affects individuals of all ages [30]. The estimated annual incidence is 2 to 9/million in adults in Europe and the United States [34]. The epidemiologic data are scarce in childhood. However, it is the third most common vasculitis after HSP and KD in children [10, 35].

The ACR requires at least three of the following 10 criteria for the diagnosis of PAN: granulocytic or mixed leukocytic infiltrates in a biopsy of an arterial wall, arteriographic abnormalities, livedo reticularis, myalgia, diastolic blood pressure >90 mmHg, mono or polyneuropathy, elevated blood urea nitrogen or creatinine, testicular pain/tenderness, hepatitis B reactants, and weight loss >4 kg [19].

Modified forms of ACR criteria were being used for PAN classification in childhood [36, 37], however, they were found insufficient, and so, all criteria were revised again.

As hepatitis B serology positivity is unusual in childhood PAN probably due to the vaccination protocols [10], this criterion was removed. Furthermore, according to the 2012 Chapel Hill nomenclature, if the vasculitis is related to hepatitis B infection, it should be classified under “vasculitis associated with probable etiology” [9]. Monogenic diseases may mimic common vasculitic disorders such that deficiency of adenosine deaminase2 mimics PAN with similar histopathological features [38].

The childhood PAN criteria designates the typical histopathology or angiographic abnormalities as a mandatory criterion [23]. In the final validation, the criteria for the signs and symptoms of vasculitis in specific organ systems and testicular pain and tenderness were removed [23]. With all these modifications, the criteria had a sensitivity of 89.6% and a specificity of 99.6% [23].

The Ankara 2008 classification for childhood PAN requires histologic evidence of necrotizing vasculitis in medium- or small-sized arteries or angiographic abnormalities (conventional angiography if magnetic resonance angiography is negative) as a mandatory criterion, plus one of the following five: skin involvement, myalgia or muscle tenderness, hypertension, peripheral neuropathy, and renal involvement [23]. Renal involvement is specified as involvement of medium to small size arteries excluding glomeruli.

CUTANEOUS PAN

CPAN is a form of PAN affecting small- and medium-sized vessels limited to the skin [39]. It constitutes a large group in pediatric practice. In an international survey of childhood vasculitis, approximately one-third of the children with PAN were categorized as CPAN [10]. Although there are no formal classification criteria for CPAN, in 2005, it was defined as cutaneous polyarteritis characterized by the presence of subcutaneous nodular, painful, non-purpuric lesions with or without livedo reticularis, and with no systemic involvement (except for myalgia, arthralgia, and non-erosive arthritis) [22]. The other defined characteristic features were skin biopsy demonstrating necrotizing non-granulomatous vasculitis, negative tests for ANCA and association with evidence of streptococcal infection [22].

MICROSCOPIC POLYANGIITIS

MPA is a pauci-immune necrotizing small vessel vasculitis. Necrotizing glomerulonephritis occurs in most of the patients with MPA [40]. There are no specific classification criteria for MPA. However, it is described in the 2012 Chapel Hill Consensus Conference (CHCC) [9].

GRANULOMATOSIS WITH POLYANGIITIS (GPA) (WEGENER GRANULOMATOSIS)

GPA is a necrotizing ANCA-associated vasculitis affecting small- to medium-sized vessels [40]. AAV are rare in childhood with an incidence of 0.24/100,000 children annually with GPA as the most frequently diagnosed form [41].

For classification of GPA, the ACR criteria require two of the following four features: nasal-oral inflammation, abnormal chest X ray, abnormal urinalysis, and granulomatous inflammation on biopsy [20].

Approximately 90% of GPA patients are ANCA (mostly classical ANCA) positive [42]. So, any ANCA positivity was added as a new criterion. Most features of GPA are similar in children and adults. However, subglottic stenosis has been reported to be more common in pediatric patients [43, 44]. Based on these data, the presence of subglottic, tracheal, or endobronchial stenosis was added to the group of criteria [23]. Another minor modification was the addition of chest computed tomography (CT) scan results to the definitions based on radiological imaging [23].

According to the final classification, childhood GPA requires at least three of the following six criteria: granulomatous inflammation on biopsy, upper airway involvement, laryngo-trachea-bronchial stenosis, pulmonary involvement (chest radiograph or CT), any ANCA positivity, and renal involvement [23]. It had a sensitivity and specificity of 93.3% and 89.2% respectively, in the validation cohort [23]. In a study on 100 children with GPA, the Ankara 2008 criteria was significantly more sensitive than the ACR 1990 criteria in classifying these patients [24]

TAKAYASU ARTERITIS

TA is a granulomatous large vessel vasculitis involving the aorta and its main branches leading to stenosis and aneurysms [40]. The mean prevalence of TA was 4.7/million in adults [45]; however, pediatric incidence data for TA are not available. It is predominantly the disease of the third decade, but it can occur in children, as well [46]. In fact, 20% of all TA patients are younger than 19 years of age at disease onset [47] and it has been suggested that age at onset younger than 15 years was associated with a probability of delay in diagnosis [48]. Thus, it is important for pediatricians to suspect and classify children with TA.

The ACR criteria for TA requires the presence of three of the following six criteria: age < 40 years, claudication of the extremities, decreased brachial pulse, and blood pressure

difference >10 mmHg between arms, bruit over subclavian arteries or aorta, and arteriographic abnormalities [18].

During the process of revising these criteria for children, the age criterion was deleted and the "angiographic abnormalities" was made a mandatory criterion and modified with imaging modalities such as CT and magnetic resonance imaging (MRI) [23]. Hypertension may be the only symptom in children with TA at presentation, so it was included as a new criterion [21]. The increased acute phase reactants were also included in the criteria as this was an important finding before the onset of complications and could help with the differential diagnosis. With all these modifications, the criteria had a sensitivity of 100% and a specificity of 99% in children [23].

The final classification criteria for childhood TA are angiographic abnormalities of the aorta and its main branches and pulmonary arteries showing aneurysm/dilatation (mandatory criterion) plus one of the five as follows: pulse deficit or claudication, four-limb blood pressure discrepancy, bruits, hypertension, and elevation of acute phase reactants [23].

Finally yet importantly, a group of pediatricians has suggested new classification criteria for childhood Behçet diseases based on a large cohort of cases [49].

CONCLUSION

Primary systemic vasculitides are relatively uncommon in children as compared to adults. However, certain vasculitides such as KD do occur almost exclusively in childhood. Although children and adults may share many common characteristics in vasculitis, they differ in certain aspects such as the etiology, the frequency of some clinical manifestations, and prognosis. As most of the pediatric vasculitides are rare diseases, collaborative multicenter studies are needed to improve these criteria contemporaneously with advances in the diagnostic approach and improved etiopathogenic understanding of these disorders. The pediatric community is also awaiting the classification task led by the adult rheumatologists, which will surely affect our practice as well.

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Chapter 11

DETECTION TECHNIQUES AND CLINICAL RELEVANCE OF ANCA TESTING

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ABSTRACT

Antineutrophil cytoplasmic antibodies (ANCA) testing is an established diagnostic tool in the necrotizing small vessel vasculitis and their presence define ANCA-associated vasculitides (AAV) including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA). These autoantibodies are also detected in a wide range of inflammatory and infectious diseases leading to a critical reappraisal in the diagnostic significance. The diagnostic utility of ANCA depends on the type of assay performed and the clinical setting. Methods of ANCA detection have been standardized in large multicenter studies. Classically, laboratories screen for ANCA by indirect immunofluorescence (IIF) on ethanol-fixed neutrophils, and positive IIF samples are further analyzed for antibodies to proteinase 3 (PR3) or myeloperoxidase (MPO) by immunoassay. Such diagnostic algorithm is based on an international consensus statement on testing and reporting of ANCA published in 1999. Novel methods for PR3- and MPO-ANCA detection have been developed to improve the performance of traditional ANCA-specific assays and new high quality immunoassays have been shown to have superior diagnostic performance compared to IFT. The 2017 revised consensus recommendations on ANCA testing state that high quality antigen-specific immunoassays are the preferred screening methodology for the diagnosis of ANCA-associated vasculitis. ANCA subtype (PR3-ANCA and MPO-ANCA) are associated with different epidemiological, genetic and clinical features. The remaining challenges in routine clinical practice include the methodological aspects of test performance by antigen-specific immunoassays, the application of testing in clinical settings with low pretest probability of vasculitis, and the value of serial testing in the prediction of disease relapse.

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Keywords: ANCA, proteinase 3, myeloperoxidase, ANCA-associated vasculitides

INTRODUCTION

In 1982, Davies and colleagues [2] discovered the association of the antineutrophil antibody in segmental necrotizing glomerulonephritis, and three years later, Van der Woude and coworkers [3] characterized their presence as a diagnostic tool and marker of disease in Wegener's granulomatosis. The spectrum of diseases associated with antineutrophil cytoplasmic antibodies (ANCA) has since increased. Two ANCA are highly associated markers for ANCA-associated vasculitides (AAV), the latter of which includes granulomatosis with polyangiitis (GPA, [Wegener`s]), microscopic polyangiitis (MPA), eosinophil granulomatosis with polyangiitis (EGPA), and primary pauci-immune crescentic glomerulonephritis, namely C-ANCA synonymous with cytoplasmic fluorescence and specificity for proteinase 3 (PR3-ANCA) and P-ANCA with perinuclear fluorescence and specificity for myeloperoxidase (MPO-ANCA).

However, ANCA can be demonstrated in patients with inflammatory disease due to irritable bowel disease (IBD), autoimmune liver disease, rheumatoid arthritis (RA), drug-induced vasculitides and infections, often with multiple antigen specificities and unclear clinical significance. Accurate identification of all patients with AAV and the avoidance of misdiagnosis can be achieved by use a "gating policy" based on clinical information given to the laboratory at the time of request. This policy limits requests for ANCA testing exclusively to clinical scenarios that may suggest a diagnosis of necrotizing vasculitis.

The clinical utility of serial ANCA measurements for predicting and assessing clinical relapses is under discussion, but may be informative in subsets of patients, such as patients with renal involvement or alveolar hemorrhage and in patients treated with rituximab.

The new testing strategy for ANCA in vasculitis directly identifies the ANCA target antigen (PR3- and MPO-ANCA) and has a particular value for the AAV sub classification. Indeed, new studies have shown that AAV can be classified based on ANCA serotype, since PR3- and MPO-ANCA- diseases are strongly associated with distinguishable genetic alleles, different clinical and histological features. ANCA presence and the antigen specificity also may have important value as a prognostic factor and may serve as a guide for immunosuppressive therapy. This chapter considers current data on ANCA testing, the application of particular ANCA assays, and how such testing can be used in the management of patients with small-vessel vasculitis.

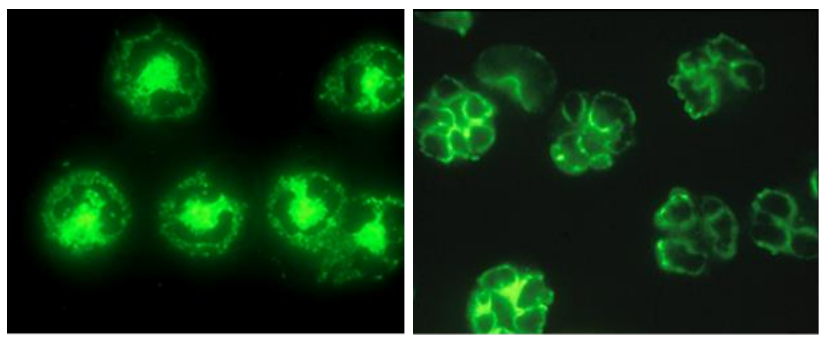
ANCA TESTING IN SMALL-VESSEL VASCULITIS

According to the international consensus statement of 1999 [5], ANCA testing by IFT for screening followed by mandatory antigen-specific ELISA for positive IFT tests [5, 6] has become the standard in many laboratories. The three major patterns demonstrated with IFT (Figure 1). The first is granular cytoplasmic neutrophil fluorescence with central interlobular accentuation ("C-ANCA") so noted overall in 90% of patients, in particular in active generalized GPA. The second is perinuclear neutrophil staining often with nuclear extension

("P-ANCA") so noted in those with MPA and EGPA. So-called "atypical" patterns are infrequent, comprising a mix of cytoplasmic and perinuclear fluorescence, with multiple antigen specificities such as in association with drug exposure, IBD and RA, most often in the absence of vasculitis [4]. However, the interpretation of IFT patterns can be tricky even for experienced laboratories, and studies have shown that misinterpretation can happen frequently. IFT is also a time consuming method, followed by ELISA as a two-step process even more so.

The alternative to conventional IFT is *image analysis*, which quantifies fluorescence in a single dilution of a patient sample in comparison with the intensity of standardized calibrators. Evaluation of the image analysis for the potential to detect ANCA in a cohort a consecutive PR3-ANCA positive GPA patients [10] revealed detectable ANCA levels in 75% of patients at the time of renal relapse, indicating a lower diagnostic sensitivity as compared with IFT and capture ELISA (100%). Quantitative image analysis predicted disease relapse somewhat better than IFT, but was comparable to direct ELISA [9].

Due to significant differences in sensitivity, specificity and predictive value among commercially available ANCA ELISA kits the combined method of IFT and ELISA have been shown to provide the highest diagnostic performance in a meta-analysis [22]. In recent years, many new developments for ANCA testing have become available. New solid phase methods like chemiluminescent immunoassays (CLIA), addressable laser bead immunoassays, fluorescent-enzyme immunoassays (FEIA) and line or dot immunoassays as well as IFT assays have become commercially available.



(a) C-ANCA (b) P-ANCA

(c) A-ANCA

Figure 1. ANCA immunofluorescence patterns on ethanol-fixed neutrophils. (a) C-ANCA; (b) P-ANCA; and (c) A-ANCA.

A *multiplex* technology offers the unique opportunity to detect the presence of multiple autoantibodies at the same time and in the same sample. This new automated immunoassay builds on a synthesis of bead-based multiplex assays and flow cytometry. Trevisin and colleagues [11] compared the performance of a flow cytometric immunoassay for PR3 and MPO-ANCA with IFT and ELISAs in active and treated vasculitis and inflammatory bowel disease and found a specificity of 88% compared with 96% and 94% respectively for IFT and both ELISA. The PR3- and MPO-ANCA immunoassay was almost as sensitive as IFT, and more sensitive than, but just as specific as most ELISA in detecting ANCA in active and treated vasculitis [11]. A major advantage of this assay is the ability to screen simultaneously for a panel of autoantibodies relevant to vasculitis, however, prospective studies are needed this automated method in the initial screening of patients with suspected vasculitis.

With the emergence of new detection technologies, a comparative study to challenge current recommendations seemed required. In 2016 a multicenter study [21] led by the European Vasculitis Society (EUVAS) compared sensitivity and specificity of various antigen specific immunoassays and IFT. The results showed no significant difference for several classical ELISA, automated FEIA, chemiluminescence assay, multiplexed flow immunoassay and multiplexed microbead IFT assay. Furthermore, the study showed a significant difference and high variability in the performance of IFT at two expert laboratories. Differences between automated multiparameter IFT devices were also observed. Thus, the diagnostic value of immunoassays is at least as high as, if not better than IFT [21].

In 2017, a revised international consensus on ANCA detection has been published [1]. Screening for ANCA by high-quality immunoassays is recommended as the preferred method. IFT adds little value to ANCA screening, especially if the pre-test probability for AAV is high. If test results for both PR3-ANCA and MPO-ANCA are negative, yet the clinical likelihood of small-vessel vasculitis is high, then using another immunoassay or IFT, or referral to an experienced laboratory is recommended.

DIAGNOSTIC SIGNIFICANCE OF ANCA

Whereas PR3- and MPO-ANCA have been shown to be highly specific for AAV, the diagnostic value of such testing in other non-vasculitic conditions is very limited. An overestimation of the diagnostic relevance of a positive ANCA test may erroneously misdirect clinicians and delay adequate treatment. ANCA-positivity has been noted in diverse autoimmune disorders. Among them the connective tissue diseases systemic lupus erythematous, RA, and Felty syndrome; the gastrointestinal disorders including ulcerative colitis, Crohn disease, and autoimmune hepatitis; infectious disorders including tuberculosis, leprosy, and subacute bacterial endocarditis; malignancy, and in association with the drugs propylthiouracil, hydralazine, and illicit cocaine use. Since the diagnostic accuracy of ANCA testing in vasculitis should be improved by an increased pretest probability, it makes sense that such testing should be guided by the likelihood of AAV. According to the consensus statement [1], adherence to clinical ordering guidelines for ANCA, testing can reduce the number of false-positive tests by 27% without missing a single patient with AAV [12]. A symptom related gating policy for ANCA testing could reduce the total number of ANCA tests performed by more than 20% with appreciably increased efficiency and cost saving. Arnold and colleagues

[13] investigated the impact of a gating policy at a single regional center in the year prior to and following the consensus guidelines [5] to ensure appropriate usage by auditing clinical outcomes in patients in whom ANCA testing was declined and documenting the absence of either GPA or MPA in all so studied. Their findings demonstrated that adherence to gating policy for ANCA testing coupled with close liaison between clinician and laboratory does not result in either a missed or delayed diagnosis of a small-vessel vasculitis belonging to the GPA-MPA spectrum.

ANCA LEVELS AND DISEASE ACTIVITY

The clinical usefulness of measuring ANCA levels in relation to disease activity and in guiding therapy is still controversial. Although ANCA titers are typically high at presentation and predictably relate to disease activity [14], there are potential confounders of the relationship between ANCA levels and disease activity including, publication bias against negative results, definition of relapse, intensity of clinical screening for disease activity, intervals of follow-up visit, and variable methods and intervals employed in sequential ANCA detection. A rise in serial ANCA measurements in patients with AAV presumably in remission status can be a clue to the prediction of disease relapse. However ANCA levels should not be used alone to guide treatment. Notwithstanding, a significant increase in ANCA levels or the reappearance of ANCA in the proper clinical and histopathological context, may suggest the need for more attentive management.

PR3- AND MPO-ANCA-SUBTYPES

Of all the possible known ANCA target antigens, only two, PR3 and MPO are closely associated with small-vessel vasculitis. Extra renal manifestations, granuloma formation and relapse were more frequent in patients with PR3-ANCA than in those with MPO-ANCA [15, 16]. Among 173 patients screened at the time of diagnosis with renal biopsy tissue, both active and chronic renal lesions were more common in MPO-ANCA-positive than PR3-ANCA-positive [17]. Despite substantial overlap, there were clinical and pathologic differences between patients with PR3-ANCA and MPO-ANCA that may reflect different pathogenic interactions between ANCA, their target antigens, and organ involvement at the molecular level. A genome-wide association study [18] confirmed a genetic component in the pathogenesis of AAV revealing distinctions between GPA and MPA that were associated with ANCA specificity, suggesting that the response against PR3-ANCA was a central pathogenic feature of PR3-ANCA associated vasculitis. Moreover, the strongest genetic associations were with antigenic specificity of ANCA, not the clinical syndrome. *HLA-DP* and the genes encoding a_1-antitrypsin (*SERPINA1*), proteinase 3 (*PRTN3*) were associated with PR3-ANCA specificity, whereas MPO-ANCA was associated with *HLA-DQ*.

About 10% of patients with GPA do not have demonstrable ANCA by IFT or antigen specific assays and are likely to have localized disease. Moreover, ANCA-negative patients and generalized GPA tend to be younger in age, more likely to be of female gender, with less

lung and kidney involvement, lower rate of relapse, and improved outcome compared to those ANCA-positive patients.

Since ANCA specificity seems to affect the phenotype of small vessel vasculitis, the initial response to remission-inducing drug therapy, long-term prognosis and relapse risk more than the clinical diagnosis, it has been suggested that classification of AAV by ANCA specificity could provide more useful information than clinical diagnosis [19].

CONCLUSION

ANCA serology and the associated clinical manifestation of AAV continue to attract the attention of clinicians and investigators alike. In addition, to be providing a useful diagnostic tool for small vessel vasculitis, ANCA testing may be useful in predicting relapses and in guiding therapy. Worldwide, most laboratories currently perform IFT to screen for ANCA positivity patients with small-vessel vasculitis, with later confirmation employing PR3- and MPO-ANCA immunoassays. However, in recent studies new high-quality antigen-specific immuno-assays have been shown to have equal or better diagnostic performance than IFT. Therefore, the new international consensus of 2016 recommends screening for ANCA with immunoassays primarily since there is no apparent benefit of combining it with IFT. Notwithstanding, any testing strategy applicable to vasculitis should be able to identify relevant ANCA target antigens since these correlate best with the clinicopathological aspects, disease activity, and propensity for relapse. The solution to problems regarding ANCA-diagnosis lies in focusing upon the implementation of high-quality immunoassay testing according to the revised international consensus, and restriction of such tests to those with the highest pretest probability of AAV.

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Chapter 12

CLASSIFICATION AND PATHOGENICITY OF ANCA-ASSOCIATED VASCULITIS

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ABSTRACT

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) include several distinct multi-systemic disorders, the diagnoses of which rely on recognition of a compatible clinical syndrome supported by radiological, immunological and histological laboratory findings. If unrecognized, there may be significant delays in treatment culminating in multi-organ morbidity. The pathogenesis of AAV is complex, involving both innate and adaptive immune systems, with loss of tolerance to autoantigens leading to the production of antibodies that activate cytokine-primed neutrophils. The factors leading to production of ANCA are incompletely understood, but may involve cross-reactivity to bacterial antigens and the expression of complementary peptides. T-cells appear to play a role in both loss of self-tolerance and in the cause of tissue injury. Moreover, peripheral blood T-cells show evidence of persistent activation driven partly by cytomegalovirus infection. Activation of the alternative complement pathway has recently emerged as a significant pathogenic mechanism in the development of glomerulonephritis in AAV.

Keywords: ANCA, vasculitides, classification, pathogenesis, pathogenicity

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INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of rare life-threatening autoimmune disorders that includes microscopic polyangiitis (MPA) and its renal limited variant (RLV), granulomatosis with polyangiitis (GPA, previously known as Wegner's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg-Strauss syndrome (CSS)). Although these diseases can manifest in many different ways, there is significant overlap between GPA, MPA and RLV in clinical features, presentation, pathogenesis and treatment. This article reviews the current understanding of classification and pathogenesis of MPA, RLV and GPA.

EPIDEMIOLOGY

AAV are rare diseases with an annual incidence of <10 per million population [1, 2] and peak age of onset in the seventh and eight decades [3]. They form a highly heterogeneous group, both in terms of severity and organ involvement, and thus manifest in a wide variety of clinical presentations.

NOMENCLATURE AND CLASSIFICATION

Although there are no diagnostic criteria, the Chapel Hill Consensus Conference (CHCC) (Table 1) [4] provided useful nomenclature and definitions for the classification of the vasculitides, classifying AAV as small-vessel vasculitides (SVV) according to the caliber of the vessels involved and associated clinicopathological features. Subsequently, the European Medicines Agency (EMEA) algorithm was developed to accurately classify patients with AAV for epidemiological studies [5, 6]. This algorithm employs clinical, serological, histological and radiological criteria to minimize the problem of patients being unclassified or assigned to overlapping categories. Table 2 shows an extent and severity categorization of AAV utilized by the European Vasculitis Study Group [7]. Revised classification criteria and validated diagnostic criteria are currently under development.

Table 1. Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis: definitions [4]*

Granulomatosis with polyangiitis (Wegener's) (GPA)	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Renal limited vasculitis (RLV)	Pauci-immune necrotizing glomerulonephritis with no apparent extra-renal features at presentations.

*Adapted from reference 4.

Table 2. European Vasculitis Study Group disease extent and severity categorization for antineutrophil cytoplasmic antibody-associated vasculitides [7]*

Category	Definition
Localized	Upper and/or respiratory tract disease with systemic involvement or constitutional symptoms
Early systemic	Any, but without any imminent organ-threatening or life-threatening disease
Generalized	Renal or other organ-threatening disease with serum creatinine <500μmol/L (5.6mg/dL)
Severe	Renal or other vital organ failure with serum creatinine >500μmol/L (5.6mg/dL)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

*Adapted from reference 5.

CLINICAL PRESENTATION

The clinical presentation can be divided into systemic symptoms and organ-specific symptoms, the former commonly including fever, night sweats, malaise, weight loss, arthralgia and myalgia which may occur multiply and wax and wane over several months [8]. About 96% of patients with GPA and 88% of those with MPA have systemic symptoms at presentation [9]. Due to the highly variable presentation and lack of diagnostic criteria there may be significant delay in establishing the diagnosis in GPA and MPA, with respective median times from symptom onset to diagnosis of 4.5 and 6 months [9]. The single most notable difference between GPA and MPA or RLV is the presence of granulomata in GPA which are not seen in MPA or RLV.

Ophthalmic

AAV may cause inflammation of various structures of the eye including the lids and nasolacrimal system. Lane and colleagues [9] described ophthalmic involvement in 40% of patients with GPA at the time of presentation compared to 4% of those with MPA; and in 48% of patients with GPA at some point during the disease. Such involvement ranges from mild inflammation to severe sight-threatening inflammation with episcleritis, conjunctivitis, scleritis, keratitis, uveitis, and retinal vasculitis [10]. Eye redness may be painless or severely painful, and proptosis, diplopia and visual loss may occur secondary to retrobulbar orbital pseudotumor [11]. Intra-ocular granulomata may also develop and need to be differentiated from tumors. Nasolacrimal duct obstruction occurs in approximately 10% of patients with GPA and results in chronic epiphora and places patients at increased risk of chronic infection [10]. Fibro-vascularization of the palpebral surface of the eyelids may result in entropion and trichiasis [12, 13]. Optic nerve ischemia may also occur [8].

Ear, Nose and Throat (ENT)

Up to 77% of patients with GPA will have upper respiratory tract symptoms at presentation compared to 29% of those with MPA [9]. Nasal disease is more common than deafness and

middle ear involvement in both GPA and MPA. More than 90% of patients with GPA develop ear and upper airway disease [14, 15]. Typical nasal symptoms of GPA include rhinitis, nasal stuffiness and pain, epistaxis, and brown or bloody crusting. The characteristic "saddle-nose deformity" is secondary to septal erosion due to chronic nasal inflammation. Patients with GPA are at increased risk of nasal and sinus infections due to chronic damage which increases the difficulty in differentiating secondary infection from disease activity.

Middle ear involvement in GPA presents as conductive hearing loss with the commonest cause being Eustachian tube dysfunction secondary to nasopharyngeal disease [16, 17]. Sensorineural hearing loss is due to inner ear disease which may also be associated with vestibular dysfunction with some patients presenting with vertigo and balance disturbance [17, 18]. The mechanism of inner ear involvement in GPA is poorly understood when compared to middle ear involvement [19].

Involvement of the trachea may present with pain, cough, hoarseness, wheezing or stridor, however it is often asymptomatic at onset. The development of subglottic or bronchial stenosis can lead to severe dyspnea requiring tracheostomy or reconstruction [11].

Pulmonary

Pulmonary involvement occurred at presentation in 63% of patients with GPA compared to 29% of those with MPA [9]. Pulmonary manifestations range from new-onset asthma and 'antibiotic-resistant' pneumonia to life-threatening alveolar hemorrhage. In those with GPA the symptoms may be due to single or multiple lung nodules and granulomata, and may be misdiagnosed as cavitating infectious or neoplastic lesions; mediastinal and hilar lymphadenopathy may also occur [20]. Pulmonary capillaritis is responsible for lung hemorrhage and rapidly changing alveolar infiltrates and should be suspected in patients with falling hemoglobin levels in conjunction with hemoptysis and dyspnea. Those with MPA may also develop pulmonary interstitial fibrosis [21]. Other indicators of pulmonary involvement include wheezing, productive or non-productive cough, and exertional dyspnea. [8].

Renal

This is often a severe manifestation of AAV [3] that affects an estimated 77% of patients with GPA and 92% of those with MPA at presentation [9]. Renal vasculitis presents with proteinuria, hematuria, and red cell casts due to focal necrotizing glomerulonephritis [22]. It can lead to rapid deterioration of renal function with eventual dialysis dependency. Hematuria may be visible or non-visible, while proteinuria is usually insufficient to cause nephrotic syndrome [8]. Renal biopsy is the most appropriate method of identifying and prognosticating glomerulonephritis in AAV [23, 24].

Nervous System

AAV can affect the peripheral (PNS) and central nervous system (CNS), as observed in 19% of patients with GPA and 17% of those with MPA at presentation [9]. Involvement of the

PNS usually manifests as motor or sensory deficits in a mononeuritis multiplex or distal sensory polyneuropathy distribution. While typically painless in the acute stage, pain syndromes commonly develop as a result of neuro-regeneration. Involvement of the CNS occurs in 8% of patients with AAV at presentation [15], presenting with weakness, dysphagia, blindness or other CNS disturbances [25]. Three distinct patterns of CNS involvement have been identified: during the generalized phase the small and medium sized vessels of the CNS can become inflamed; secondly, localized granulomatous masses from the upper respiratory tract may invade the CNS; thirdly, granulomata may develop within CNS structures [26].

Cutaneous

Cutaneous involvement occurs in 42% of GPA and 25% of MPA patients at diagnosis [9]. A wide range of signs are seen that include purpura, papules, urticaria, infiltrative erythema, infarction and splinter hemorrhage, ulcerated nodules, livedo reticularis, and digital gangrene [27]. The type of lesion is determined by the size of the blood vessel affected. The most common manifestation is a palpable purpuric rash beginning along the lower extremities that may become ulcerated or vesicular. The urticarial rash seen in vasculitis can be differentiated from allergic non-vasculitic urticaria by the fact that it will usually last for more than one day and may progress to purpuric lesions [28].

Cardiac

Direct cardiac involvement is uncommon in either GPA or MPA however the former may be associated with coronary arteritis, pericarditis and valvular disease. Endocarditis can occur as a result of aortic valvular lesions [29]. MPA may be associated with pericarditis, heart failure and hypertension however the incidence is very low [30].

Gastrointestinal

Gastrointestinal involvement occurs at presentation in up to 30% of patients with AAV [14, 31-33]. Gastrointestinal involvement may present with ischemic or vasculitic colitis, bloody diarrhea, pain and progression to ulceration, perforation and infarction [11, 34]. 30-56% of patients with MPA have been found to have GI involvement [35, 36], the commonest presenting symptom of which was pain, noted in 97% of patients, followed by nausea, vomiting, diarrhea, melena, and hematemesis [37]. Rarely, other intra-abdominal organs can be involved such as the gallbladder and pancreas [34].

ETIOPATHOGENESIS

There is evidence for a pathogenic role of ANCA in the etiopathogenesis of inflammation and organ damage mediated by immune mechanisms. With regards to the innate immune

system, neutrophils play a pivotal role in the effector phase causing organ and tissue damage. Complement activation, particularly the alternative pathway, seems to be important in glomerulonephritis. The adaptive immune system is important in the development of autoimmunity with the production of autoantibodies against proteinase 3 or myeloperoxidase by B-cells and there is increasing evidence for a pathogenic role for T-cells. Genetic susceptibility factors are encoded by certain human leukocyte antigen (HLA) haplotypes [38], notably *HLA-DPB1*0401* alleles are associated with an increased risk for development of GPA [39], while *HLA-DRB1*0901* is associated with MPA [40]. In addition, the DRB1*15 haplotype was associated with anti-PR3 AAV in African American patients [41]. Polymorphisms of genes involved in the control of the immune system and associated with increased risk of vasculitis include CD226, PTPN22 protein, CTLA-4, IL-10, and TLR9 [42-47], although none are specific for AAV. A recent genome-wide association study correlated single-nucleotide polymorphisms in *HLA-DPB1* and *PRTN3* with frequency of autoreactive T-cells and neutrophil expression of PR3 [48], thus providing a functional link between genetic risk factors and the immunopathology of AAV.

Copy number variation of FcγR3b and human ß-defensin (DEFB4) may represent further important mechanisms in AAV susceptibility [42, 49]. Genes expressed by memory T-cells as well as a CD8+ T-cell transcription signature have been described in both systemic lupus erythematosus and AAV with associated poorer outcome. This signature is thought to comprise enriching genes involved in the IL-7 receptor and T-cell receptor signaling pathway [50].

Recent work by Yang and colleagues [51] has addressed the contribution of epigenetic mechanisms to AAV pathogenesis. Chromatin immunoprecipitation (ChIP) performed on peripheral blood neutrophils demonstrated an association between specific histone modifications at the MPO and PRTN3 *loci* and active AAV. However, it is unclear whether these histone modifications in themselves play a pathogenic role.

Carriage of the dysfunctional z allele of the α-1-antitrypsin (A1AT) gene is associated with an increased risk of developing AAV and predicts more severe outcomes [52-57]. Patients carrying the z allele not only have an increased risk of AAV but also have increased concentrations of circulating A1AT polymers capable of priming circulating neutrophils for ANCA-induced activation [58].

Environmental factors may also have a role in disease development. Provocation of an immune response and inflammation is thought to occur after exposure to silica dust with 22-46% of patients with AAV having documented exposure to silica prior to disease development. It is proposed that exposure results in accelerated apoptosis of macrophages and polymorphonuclear leukocytes, thereby triggering disease development [59, 60].

Infectious triggers have also been implicated in the etiopathogenesis of AAV. A contributory role of low-grade *Staphylococcus aureus* infection in the etiopathogenesis of AVV has been suggested based on the observation that 63% of patients with GPA had chronic nasal carriage when compared with 20% of control individuals [61]. Moreover, nasal carriage has been associated with disease relapse [61, 62], and patients who received maintenance co-trimoxazole treatment were observed to have fewer relapses [63]. A study of bronchioalveolar lavage fluid (BALF) in GPA patients identified increased levels of infection compared to controls and demonstrated that BALF was permissive for bacterial growth [64].

Molecular mimicry may also underlie the development of necrotizing and crescentic glomerulonephritis (NCGN) through infection with fimbriated bacteria, such as *Escherichia coli* and *Klebsiella pneumonia* [65]. The bacterial adhesion protein FimH was found to be

homologous to a major epitope of LAMP-2 which is in turn recognized by anti-LAMP-2 antibodies in pauci-immune NCGN [66, 67] although these results have not been replicated by other researchers [68].

The development of AAV has been linked to several drug exposures, most commonly propylthiouracil with a prevalence of ANCA expression ranging from 4% to 46% [69, 70]. D-penicillamine, hydralazine and minocycline have also been associated with disease. Sulphasalazine, and other similar drugs, may increase autoantibody production as they induce apoptosis which in turn increases expression of ANCA antigen targets on the surface of apoptotic neutrophils [71, 72].

ANCA PATHOGENICITY

Since the discovery of ANCA there has been considerable debate as to whether or not it has a direct pathogenic role with most authors now accepting that anti-myeloperoxidase (MPO) antibodies are pathogenic based on the results of clinical, laboratory and animal studies. Proteinase 3 (PR3) was found to be the target antigen of the cytoplasmic-ANCA indirect immunofluorescence pattern while MPO is the target antigen of the perinuclear-ANCA pattern, with the specificity of PR3-ANCA and MPO-ANCA for AAV as high as 98% [73, 74].

Clinical Evidence for ANCA Pathogenicity

The most striking clinical evidence for the pathogenicity of ANCA was the report of a neonate developing pulmonary hemorrhage and glomerulonephritis caused by transplacental transfer of ANCA IgG from the mother who had anti-MPO antibody positive MPA [75]. There has, however, been a lack of clear consistent evidence of a relationship between the serum ANCA titer and disease activity [76-79]. A meta-analysis of studies investigating the association between ANCA and disease activity found a rise in the serum ANCA titer and persistent presence of ANCA was only modestly predictive of future disease relapse, suggesting that serial ANCA measurements had a limited utility in guiding treatment decisions in individual patients [80]. It is possible that there are subtle changes in ANCA such as glycosylation state or change in the predominant subclass that are related to disease activity and undetected by routine assays [81-84].

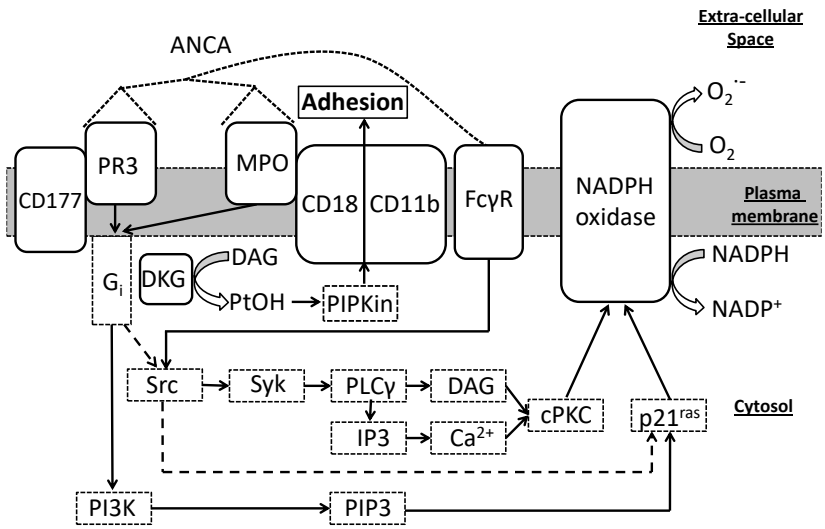
Animal Models of AAV

Several murine and rat models of anti-MPO AAV have been created; unfortunately to date there has not been a suitable animal model for anti-PR3 [85-87]. Xiao and colleagues [88] immunized MPO-/- mice with purified MPO to generate high avidity anti-MPO antibodies. Granulomatous inflammation, necrotizing and crescentic glomerulonephritis, and systemic necrotizing vasculitis developed when mouse splenocytes were transferred to Rag2-/- mice or when anti-MPO containing IgG was transferred to wild-type mice. Levels of tumor necrosis alpha (TNF-α) were increased and renal injury enhanced when lipopolysaccharide (LPS) was

added. The importance of cytokines in the pathogenic process was emphasized by the finding that these effects could be ameliorated by addition of anti-TNF-α antibodies [88]. Prominent macrophage and neutrophil invasion was found at sites of glomerular injury which, along with the observation that crescentic glomerulonephritis did not develop in neutrophil-depleted mice, supports the important role of neutrophils in the pathogenesis of AAV [89].

Leukocyte adhesion and transmigration were shown by intravital microscopy to be enhanced by anti-MPO IgG in wild-type mice pre-treated with cytokines. β2-integrins (CD18) and Fcγ receptors were shown to be necessary as recruitment was not seen following the co-administration of anti-CD18 antibodies or in Fc receptor γ chain-/- mice [90]. Kuligowki and colleagues [91] found that high-dose anti-MPO induced β-integrin dependent adhesion in the absence of LPS, while LPS was necessary to induce adhesion at low doses of anti-MPO.

In Vitro Activation of Neutrophils by ANCA



Abbreviations: Cbl, Casitas b-lymphoma protein; cPKC, protein kinase C; DAG, diacylglycerol; DGK, diacylglycerol kinase; G_i, G protein; IP3, inositol 1, 4, 5-triphosphate; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol 3, 4, 5-triphosphate; PIPKin, phosphatidylinositol-4-phosphate-5-kinase; PLCγ, phospholipase C γ; PtOH, phosphatidic acid; Src, tyrosine kinase; Syk, spleen tyrosine kinase.

Figure 1. Summary of the neutrophil intracellular signaling pathways activated by ANCA cross ligation of MPO or PR3 and Fcγ receptors. This activation results in superoxide production, degranulation and adhesion to the endothelium. Separate pathways are activated by either interaction with the ANCA antigens or Fcγ receptors. Signaling must be induced via both pathways for full neutrophil activation, which is highlighted by the protection to development of vasculitis demonstrated in mice lacking phosphatidylinositol-3 kinase γ.

In vitro work on the effect of patient-derived IgG containing ANCA demonstrated ANCA-activation of cytokine primed neutrophils. During the priming process, MPO and PR3 were translocated to the plasma membrane of neutrophils where they can interact with ANCA [92-94]. In addition to increasing surface expression of ANCA, interleukin (IL)-18, TNFα and granulocyte macrophage colony stimulating factor lead to mobilization of nicotinamide adenine

dinucleotide phosphate (NADPH) oxidase complex components necessary for superoxide generation [94-97]. Subsequent crosslinking between ANCA and Fcγ receptors and ANCA antigens results in degranulation, production of pro-inflammatory cytokines, adhesion to endothelium and generation of superoxide with multiple signaling pathways implicated [98-103] (Figure 1). Neutrophil gene expression is also induced by binding of both intact ANCA and $F(ab')_2$ portions [104].

Effect of ANCA on Neutrophil-Endothelium Adhesion

Endothelial necrosis is a histological feature of small vessel disease in AAV, with exposure of the basement membrane leading to platelet aggregation, thrombosis and occlusion [105]. Swelling, necrosis and dehiscence of endothelial cells is an early histological feature and thought to be the mediated by ANCA activation of cytokine-primed circulating neutrophils. This results in neutrophil adhesion to and transmigration through endothelium, associated with neutrophil degranulation and production of superoxide. Adhesion and transmigration of leukocytes is promoted by the release of chemoattractant proteins by endothelial cells and upregulation of adhesion molecules. The serum concentrations of soluble factors associated with this process include vascular endothelial growth factor (VEGF), inter-cellular adhesion molecule (ICAM)-3, P-selectin, thrombomodulin, angiopoietin-2, matrix metalloproteases 1, 3, and 9; endothelial microparticles and stem cells [106-112].

In vitro studies showed that ANCA stabilized adhesion and promoted transmigration of neutrophils flowing over endothelial cells [113]. In shear stress models employing human endothelial cells and healthy donor neutrophils, this interaction depended on the interaction between neutrophil-expressed CXCR1 and CXCR2, and CD18/CD11b and their ligands on endothelial cells, [113-115]. An MPO-/- animal model demonstrated stimulation of neutrophil-endothelial adhesion dependent on the action of CD18 [90].

In activated neutrophils, intracellular F-actin polymerizes making the neutrophil more rigid and less deformable. This may lead to retention of neutrophils in small diameter capillaries and increased contact with endothelium, promoting damage leading to cell detachment and lysis [116, 117]. One study demonstrated reduced CXCR1 and CXCR2 expression on neutrophils from AAV patients, even those in remission where expression showed an inverse relationship with serum IL-8 concentrations. Reduced chemokine receptor expression impaired endothelial transmigration but not adhesion, which may increase contact with endothelium and promote intra-vascular retention of activated neutrophils [118]. The actions of endothelial cells inhibit the neutrophil production of superoxide, implying that granule content release may be a more important pathogenic mechanism in AAV [89-91].

ANCA and Neutrophil Cell Death

Neutrophil apoptosis does not normally result in the release of the intracellular contents, thus preventing inflammation. ANCA-activated neutrophils were shown to undergo dysregulated and accelerated apoptosis which may lead to increased inflammation associated with the release of granule contents, increased surface expression of MPO and PR3, and macrophage-mediated uptake of ANCA opsonized neutrophils [71, 119, 120].

More recently, there has been increasing focus on the relationship between ANCA and neutrophil extracellular trap (NET) formation. NETs are reticular structures released by activated neutrophils, composed of decondensed chromatin and associated antimicrobial proteins [121]. Since the first description of their structure in 2004, NETs have been implicated in the pathogenesis of a range of inflammatory and autoimmune disorders [122].

Kessenbrock and colleagues first demonstrated the presence of NETs in glomeruli from AAV patients [123], suggesting a potential role in mediating tissue damage. Since then, NETs were shown to be more prevalent in nerve tissue from patients with MPA neuropathy than other types of neuropathy [124], and circulating levels of NET remnants were found to be increased in AAV patients compared to healthy controls [125]. Individual case reports identified NETs in cutaneous lesions [126] and thrombus [127] from AAV patients. Taken together, these findings suggest that NETs could play a role in mediating autoimmune damage in multiple organ systems. Notably, ANCA-induced NETs associate with alternative complement pathway components C3b and C5b-9 in human serum, with subsequent activation of the alternative complement pathway *in vitro* [128]. This provides a possible link between NETosis and mechanisms of complement-mediated damage in AAV.

Kessenbrock and colleagues also showed that ANCA could stimulate neutrophils to release NETs [123]. Interestingly, independent work found that neutrophils from AAV patients exhibited increased NET production compared to neutrophils from healthy controls when stimulated with ANCA [129]. MPO-ANCA affinity but not titer correlated with increased levels of NETs in AAV patients [40], and the pro-inflammatory mediator high-mobility group box 1 (HMGB1) was identified as an additional factor that potentiates ANCA-induced NET release *in vitro* [130]. In addition, there is evidence that NET degradation is impaired in serum from MPA patients [131], which could contribute to both NET-induced tissue damage and immunogenicity.

Since NETs represent a source of autoantigens PR3 and MPO, it is possible that disordered NETosis plays a role in the induction of autoimmunity. Sangaletti and colleagues loaded myeloid dendritic cells (mDCs) with NET components and transferred them into naïve mice [132]. This induced circulating PR3- and MPO-ANCA and resulted in pulmonary-renal vasculitis. In contrast, injection of mDCs co-cultured with apoptotic neutrophils resulted in autoantibody production in the absence of this disease phenotype. This study demonstrated that NET components are able to induce ANCA-like disease in a murine model, implying that NETs represent a potential source of autoantigens in AAV. Therefore, NETosis may contribute to a positive feedback loop in which ANCA induce both NET-mediated tissue damage and the exposure of NET-derived autoantigens. However, this model does not explain how tolerance to these autoantigens is broken, and thus far there is limited evidence that this process plays a pathogenic role in humans.

Cell-Mediated Immunity

Both B- and T-cells have important roles in the pathogenesis of AAV and are important in the induction of autoimmunity and the development of tissue inflammation. The production of autoantibodies, implying a loss of self-tolerance to PR3, MPO and possibly LAMP-2, could occur via several possible mechanisms. The presence of low levels of specific autoantibodies (SAA) to MPO and PR3 in the healthy population has led to the theory that ANCA form part

of the natural repertoire [133]. One explanation for the non-pathogenic nature of SAA is that compared to MPO-ANCA derived from patients with AAV, significantly lower titers of SAA MPO are found with lower avidity suggesting that high affinity autoantibodies underlying the autoimmune pathology of AAV may result from dysregulation of SAA-producing B-cells. However, the precise mechanism remains unknown and larger cohort studies are required [133]. One intriguing suggestion has been the role of complementary peptides in the production of anti-PR3 ANCA. These peptides are produced by the transcription and translation of the DNA complementary to the PR3 gene. The peptides so produced generate an anti-complementary PR3 (cPR3) response which leads to an anti-idiotype response producing anti-PR3 antibodies [134]. It has also been suggested that cPR3 shows homology with proteins from staphylococcal bacteria. T-cells specific for cPR3 have also been identified in AAV patients [135].

T-cells are required to allow IgG subclass switching, a process which has been shown to be essential in the pathogenesis of AAV [136]. The importance of T-cells in the disease process is further supported by the presence of high levels of soluble IL-2 receptors and activated CD4+ cells in patient blood and sera, as well as soluble CD4 and CD8 [137]. MPO and PR3 have been shown to promote the proliferation of autoreactive T-cells [138-140].

Regulatory CD4+ T-cells (Treg) important in the maintenance of self-tolerance have functional defects in patients with GPA in remission [141, 142]. The percentage of Treg cells was found to be inversely related to the disease relapse rate in patients with GPA and was associated with both functional and numerical defects in PR3-specific Treg cells [143].

There has been increasing interest in the role of IL-17 producing helper T-cells (Th17) in autoimmune disease in which higher proportions of Th17 cells were found in the peripheral blood of AAV patients compare to controls [144]. Furthermore, in patients with GPA there was expansion of the effector Th17 population and increased IL-17A production by T-cells stimulated with aCD3/aCD28 *in vitro* [145]. MPO-specific Th17 cells were identified in AAV patients with MPO-ANCA, suggesting a pathogenic role [146]. Mice deficient in IL-17A were almost completely protected from developing GN in an anti-MPO model of vasculitis [147].

T-cells are prominent at sites of inflammation in AAV particularly in the kidney where they are the predominant infiltrating cell type [148]. Four major subtypes, Th1, Th2, Th17 and Treg, were identified in inflamed AAV tissue [149-152]. The presence of interstitial Foxp3-positive Treg predicted renal survival in patients with MPO ANCA-associated glomerulonephritis, suggesting a beneficial role in suppression of inflammation [153].

Large populations of T-cells and macrophages have been found in the granulomatous and vasculitic lesions in AAV and studies have demonstrated the involvement of CD4+ T cells in AAV disease manifestation, particularly effector memory T cells (T_{EM}) [154]. The theory that CD4+ cells migrate to sites of inflammation in AAV was supported by the observation of decreased levels of peripheral blood CD4 T_{EM} in patients with GPA with active disease compared to those in remission [154]. Moreover, the observation that T-cell depletion is effective in controlling disease in therapy-resistant patients supports their role in inflammation [155]. GPA patients in remission were found to have a significantly increased circulating proportion of Th17 effector memory cells and decreased proportion of Th1 effector memory cells compared to healthy controls [156]. The degree of this aberrant distribution of T_{EM} subsets was associated with tendency to relapse and multi-organ disease involvement, providing further evidence for the pathogenic importance of the Th17 response in AAV.

One particularly interesting population of Th cells in AAV is the frequently reported expanded population of CD4+CD28- cells which has been associated with increased disease severity [154, 157-161]. CD4+CD28- cells have potent effector functions and are a major source of Th-1 type cytokine secretion, predominantly IFNγ and TNFα and express perforin and granzyme B [162]. The expansion of this cell population is driven by cytomegalovirus infection in AAV, and was no difference between AAV patients and controls matched for CMV-specific IgG seropositivity. Recent evidence showed that prior infection with both Epstein-Barr virus (EBV) and CMV was associated with increased percentage of peripheral CD4+CD28- cells compared to either infection alone in the context of GPA [163]. The expansion of this population in AAV patients was associated with a reduced number of naïve helper T-cells and an increased risk of infection and mortality [164].

B-cells are responsible for the production of ANCA and are thus vital in the pathogenesis of AAV. Tissues affected by GPA, such as nasal lesions, contain B-cells [148, 165] and the proportion of activated B cells is increased in active GPA [158]. That treatment with the B-cell depleting anti-CD20 monoclonal antibody rituximab has been shown to induce disease remission and reduce ANCA titers in AAV supports a role for B-cells in the pathogenesis of the disease [166, 167]. Such B-cells appear to be able to evade the regulatory processes that ensure tolerance to self-proteins. For example, autoreactive B-cells may persist due to low surface expression of CD19, resulting in decreased signaling strength and thus allowing them to evade normal tolerance mechanisms [168].

Further work has examined the role of regulatory B-cells (Breg) in AAV [169], although this is made challenging by the absence of a definitive Breg phenotype [170]. The CD19+CD24(hi)CD38(hi) B-cell is one subset that has been demonstrated to possess regulatory potential [171]. AAV patients with active disease were observed to have significantly lower proportions of CD19+CD24(hi)CD38(hi) B-cells than healthy controls, and B-cells from such patients produced less IL-10 when stimulated *in vitro* [169]. Both the CD19+CD24(hi)CD38(hi) and IL-10+ B-cell populations increased as patients transitioned from active disease to remission [169]. Taken together, these findings suggest that active AAV is associated with deficits in regulatory B-cells.

The selection and maturation of B cells that produce anti-PR3 ANCA may occur in sites of early granulomatous inflammation as histological examination of granulomata in GPA show B-cell clusters closely associated with numerous PR3-positive cells [165]. The proteasome inhibitor bortezomib was studied in a murine model of AAV, noting that bortezomib treatment was associated with MPO-specific plasma cell depletion, reduced anti-MPO titers, and prevention of crescentic GN [172]. One case of refractory MPA successfully treated with bortezomib was recently reported [173]. However, further investigation into timing of treatment and adverse effect profile is needed before bortezomib can be recommended as a routine treatment for refractory AAV.

Complement-Mediated Mechanisms

The presence of immune complex deposits in skin tissue of patients with cutaneous vasculitic lesions, and in renal biopsy tissue in those with ANCA-associated crescentic glomerulonephritis, suggests a role for complement-mediated immune mechanisms in development of inflammation and glomerular damage in AAV [174]. Chen and colleagues

[175] demonstrated that approximately 33% of renal biopsy samples from patients with ANCA-associated NCGN demonstrated C3c expression. Membrane attack complex (MAC), along with C3d and factors B and P were found in glomeruli and microvasculature of human renal biopsy tissue [176]. Xiao and colleagues [177] employed renal biopsy samples from patients with MPO-ANCA-associated pauci-immune NCGN to study the various complement components. All biopsy samples showed MAC, factor B and C3d. Diseased glomeruli were found to express C3d and factor B that co-localized with expression of MAC. This, coupled with the observation that C4d was not detected in either frozen renal sections or paraffin-fixed sections, strongly suggested that the renal damage associated with AAV was secondary to the alternative pathway of the complement system [176]. In addition, complement deposition has been associated with more severe renal disease [175].

Multiple retrospective studies have demonstrated an association between hypocomplementemia at AAV onset, likely reflecting systemic activation of the complement cascade, and poor outcomes [178-180]. In the largest of these studies, low serum C3 at disease onset was an independent predictor of end-stage renal disease and death [179].

In vitro studies indicate that C5a, acting via the neutrophil C5a receptor (C5aR), plays a role in priming neutrophils for ANCA activation via the alternative pathway [181]. This suggests that an amplification loop, comprising C5a and neutrophil C5aR, might mediate ANCA-induced neutrophil activation [181, 182].

Additionally, there is evidence that regulation of the alternative pathway is impaired in AAV. Complement factor H, a negative regulator of the alternative pathway, was detected at significantly lower levels in patients with active MPO-AAV compared to patients in remission and healthy controls [183]. Furthermore, patients with active AAV exhibited deficient factor H function, shown by reduced regulation of C3b and impaired protection of erythrocytes against plasma-mediated lysis [184]. These data reinforce the role of the alternative pathway in AAV, and suggest that impaired negative regulation of this pathway could play a role in its pathogenesis. It is not yet understood what mechanisms underlie this dysregulation.

Perhaps the most convincing evidence of the role of the complement comes from animal models where the development of vasculitis is completely blocked by complement depletion [185]. Xiao and co-workers [182] studied the role of specific complement activation pathways in the development of NCGN and vasculitis using wild type and knockout mice for the common pathway component C5, the classic and lectin binding pathway component C4, and the alternative pathway component Factor B. They showed that $C5^{-/-}$ and Factor $B^{-/-}$ mice, but not $C4^{-/-}$ mice, were protected from disease development after injection of anti-MPO IgG. Their findings suggested that stimulation of neutrophils by ANCA caused release of factors that activate complement via the alternative pathway, initiating an inflammatory amplification loop that mediated severe necrotizing inflammation. Inhibition of complement factor C5 protected against anti-MPO IgG-mediated NCGN, with an 80% reduction in glomerular crescent formation when anti-C5 monoclonal antibodies were administered one day after disease induction [185].

The use of C5 inhibition to treat AAV has also been tested in patients. In a recent randomized controlled trial, C5a receptor inhibitor avacopan was non-inferior to high-dose prednisolone in achieving clinical response in active vasculitis treated with cyclophosphamide or rituximab [186]. In addition to providing a possible means of reducing glucocorticoid exposure, this trial provides further evidence for the role of complement in AAV.

CONCLUSION

The AAV comprising GPA, MPA and RLV are life-threatening diseases affecting small to medium sized vessels with significant overlap in their non-organ specific and organ specific features. Current diagnosis of AAV relies on recognition of a clinical picture and supporting evidence from radiological, immunological and histological investigations. Their highly variable clinical presentation and absence of diagnostic criteria often leads to a delay in diagnosis and initiation of effective therapy. The pathogenesis of AAV is complex, involving both the innate and adaptive immune systems. Significant advances have been made in understanding the AAV over the past few decades, notably with development of animal models. Future development of effective treatment approaches and preventative strategies will be targeted based on improving understanding of pathogenic mechanisms in AAV.

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Chapter 13

CRYOGLOBULINEMIC VASCULITIS

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ABSTRACT

Cryoglobulinemic vasculitis, also termed mixed cryoglobulinemia syndrome, is a rare systemic small vessel vasculitis due to the vessel deposition of immune-complexes, mainly mixed IgG-IgM cryoglobulins. In the majority of cases, it is associated with the hepatitis C virus infection, immunological, and neoplastic diseases. Cryoglobulinemic vasculitis is characterized by the classical triad of purpura, weakness, and arthralgia, frequent multiple organ involvement, and with infrequent late lymphatic and hepatic malignancies. The etiopathogenesis of cryoglobulinemic vasculitis is not completely understood. However, hepatitis C viral infection and associated lymphotropism, genetic, and environmental factors play important roles in B-lymphocyte expansion and cryoglobulin and immune-complex production. The diagnosis is suggested by clinical evidence of purpura, circulating mixed cryoglobulinemia and low C4 levels, and pathologically evident leukocytoclastic vasculitis in skin biopsy lesions. The prognosis is poor in patients with renal disease, liver failure, malignancy, and/or widespread vasculitis with multiple organ involvement. Treatment is directed toward eradicating hepatitis C infection employing the new direct-acting antivirals, immunomodulatory, and immunosuppressant medications as warranted by the level of clinical severity.

INTRODUCTION

Cryoglobulinemic vasculitis (CV) is a small vessel vasculitis (SVV) due to the vascular deposition of cryoprecipitable and/or non-cryoprecipitable immune-complexes (IC) and

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complement [1]. Cryoglobulinemia and cryoimmunoglobulinemia are interchangeable terms that refer to the presence in the serum of one (monoclonal cryoglobulinemia) or more immunoglobulins (Ig) or mixed cryoglobulinemia (MC), which precipitate at temperatures below 37°C and re-dissolve on rewarming [1].

NOSOLOGY AND CLASSIFICATION

Cryoglobulinemia is classified into three categories according to the Ig composition [1]. Type I cryoglobulinemia consists of singular isotypes or subclass of Ig, whereas types II and III MC contain ICs composed respectively of polyclonal IgG autoantigens and monoclonal or polyclonal IgM autoantibodies, the latter of which contain rheumatoid factor (RF) activity. Type II MC shows a microheterogeneous composition with immunoblotting and two-dimensional polyacrylamide gel electrophoresis of oligoclonal IgM or a mixture of polyclonal and monoclonal IgM [1-4]. This serological subset represents an intermediate evolutionary state between type III and type II MC, so termed type II–III MC. These findings are in agreement with molecular studies that show the presence of oligoclonal B-lymphocyte proliferation in liver and bone marrow tissue from patients with MC [1-6]. Whereas cryoglobulinemia type I is often asymptomatic and usually associated with well-known hematological disorders [1-6], MC occurs in diverse infectious and systemic disorders and frequently presents as an isolated laboratory finding without clinical significance. Mixed cryoglobulinemia syndrome (MCs) and CV are interchangeable terms for the resultant distinctive SVV related to cryoglobulinemia [1-6].

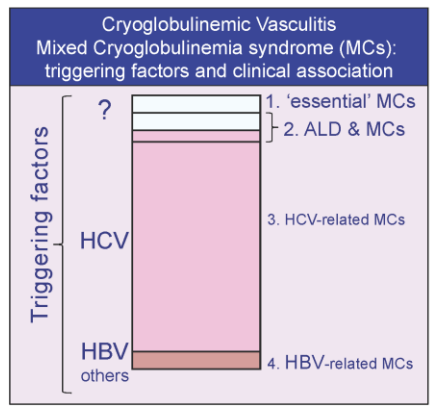
EPIDEMIOLOGY

Cryoglobulinemic vasculitis is a rare disorder of yet certain prevalence with marked heterogeneity in its geographical distribution, and increased prevalence in Southern more than Northern Europe or Northern America. The male to female ratio is 3:1, with the most common age at onset of disease in the fourth to fifth decades and in older age [1-5]. Because of the clinical polymorphisms of CV the prevalence of single manifestation such as skin vasculitis, nephritis, chronic hepatitis, and peripheral neuropathy vary largely among cohorts. The relationship between hepatitis C virus (HCV) with cryoglobulinemia and CV has been examined in numerous cohorts [1, 4, 5]. Low levels of circulating MC are detectable in more than 50% of patients while overt CV develops in approximately 5% of HCV-infected individuals [1, 8]. Considering the high prevalence of HCV infection worldwide, an increasing number of patients with HCV-related CV and extrahepatic manifestations are expected to occur particularly in underdeveloped countries where HCV prevalence is increased relative to the general population [1, 4]. Essential MCs (EMCs) and CV, so defined as the absence of a recognized triggering factor that underlie a systemic infectious or specific neoplastic disorder, occur less frequently in individuals of Southern European descent and in selected geographic areas where there is a higher prevalence of HCV infection and CV [1, 4].

ETIOPATHOGENESIS

The triggering factors and etiopathogenesis of CV and MCs are depicted in Figures 1 and 2. Vascular deposition of circulating IC, cryoglobulins and complement mediated by humoral and local factors, affects small vessels, predominantly arterioles, capillaries, and venules similar to Henoch-Schonlein purpura, another IC type of SVV, with variable systemic organ involvement [1-5]. Mild to moderate chronic hepatitis is related in up to two-thirds of affected patients with CV suggesting a pathogenic role for hepatotropic viruses [1-4, 9].

Hepatitis B virus (HBV) is a possible causative factor in <5% of patients, while HCV is considered the main pathogenic agent in CV [1, 4, 5]. First proposed by two independent groups who recognized the increased prevalence of serum anti-HCV antibodies in CV patients relative to the general population [10, 11], the causative link between HCV and CV was later established when the presence of HCV RNA was detected by polymerase chain reaction (PCR) in 86% of patients with CV [7]. The causative role of HCV in CV is apparent in up to 95% of patients among cohorts of diverse geographical derivation [1, 4-6, 9]. In consideration of the striking association of HCV with CV, EMC occurs in a minority of patients [1, 4].

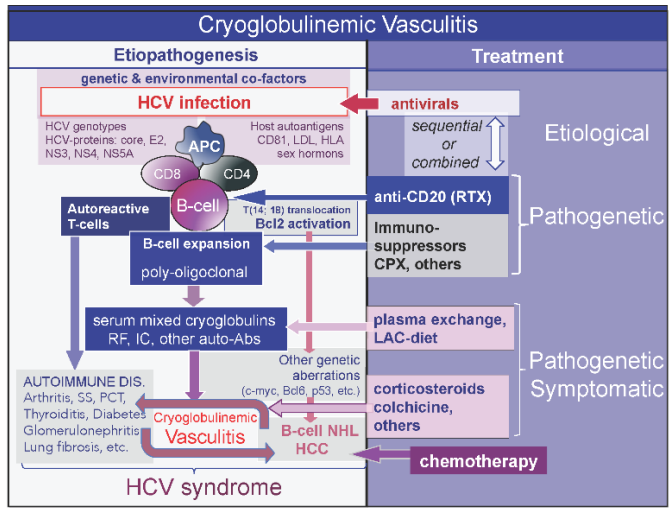


Abbreviations: MC, mixed cryoglobulinemia; MCs, mixed cryoglobulinemia syndrome; ALD, autoimmune-lymphoproliferative disorders, HCV, hepatitis C virus; HBV, hepatitis B virus.

Figure 1. The different clinical and virological subsets of MCs can be schematically summarized as follows: (1) Essential MC; (2) Essential MC and HCV-related MC as an overlapping syndrome (lymphoproliferative disorders, Sjögren syndrome, rheumatoid arthritis, autoimmune hepatitis, and B-cell lymphomas); (3) Subsets of HCV-associated MC; and (4) MC associated with other infectious agents notably hepatitis-B virus.

The clinical features and prognosis of CV are linked to the natural history of chronic HCV infection with different CV phenotypes believed to be the result of contributory genetic and environmental cofactors which hitherto remain unknown [1, 4, 12]. The role of HCV in autoimmunity has been ascribed to viral lymphotropism [1, 4, 5, 12] wherein the HCV, which lacks the ability to integrate into the host genome due to absence of reverse transcriptase activity, chronically stimulates the immune system leading to autoimmune phenomena. The proposed etiopathogenesis (Figure 2) is connected to HCV-related epitopes, autoantigens, and molecular mimicry-related mechanisms such as the association with the anti-GOR autoantibody, as well as the binding of HCV to host low-density lipoprotein (LDL), specific

antiviral IgG and IgM, RF and cryoglobulins, and monoclonal RF bearing B-cells that express the WA cross-idiotype. Collectively, these immunological phenomena are the cause and the consequence of chronic stimulation of B-lymphocytes with expansion of B-cell subpopulations. HCV-related lymphomagenesis represents an important model of virus-driven malignancy, similarly to that observed for mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach related to gastrointestinal Helicobacter (H.) pylori infection [1, 4, 12], two malignancies characterized by an analogous multistep and multifactorial etiopathogenesis.



Abbreviations: HCV, hepatitis C virus; RF, rheumatoid factor; IC, immune-complex; pSS, primary Sjögren syndrome; SS, sicca syndrome; PCT, porphyria cutanea tarda; HCC, hepatocellular carcinoma; B-NHL, B-cell non-Hodgkin lymphoma; CPX, cyclophosphamide; RTX, rituximab; LAC, low antigen-content.

Figure 2. Left: CV is the most frequent extrahepatic manifestation of the so-called HCV syndrome. CV represents a crossing road between benign and malignant HCV-related complications. Given its biological characteristics, HCV may be involved in a wide number of autoimmune and lymphoproliferative disorders. This figure summarizes the main causative factors including, infection, toxics, genetic and environmental causes potentially involved in the pathogenesis of the complex HCV syndrome, in particular of CV. These factors, alone or in combination, may trigger two nonexclusive multistep pathogenic processes, notably the production of benign poly-oligoclonal B-cell proliferation responsible for organ- and non-organ-specific autoimmune disorders including IC-mediated CV; and another characterized by different oncogenic alterations, which ultimately leads to malignant complications. Right: Therapeutic strategies in patients with HCV-related CV and other autoimmune lymphoproliferative disorders. Following the multistep pathological process leading from HCV infection to overt CV, etiologic, pathogenic and symptomatic treatments are instituted at different levels.

The interaction between the HCV E2 envelope protein and CD81 molecule, a ubiquitous tetraspannin present on the surface of B cells, likely represents an important pathogenic step in the development of HCV-related autoimmune and lymphoproliferative disorders that results in potent sustained polyclonal stimulation of the B-lymphocytes [1, 4, 12]. The occurrence of HCV-related autoimmune-lymphoproliferative disorders may also be related to t(14;18) translocations found in B-cells of HCV-infected patients leading to increased expression of the Bcl-2 protein, with inhibition of apoptosis and abnormally prolonged B-cell survival [1, 4, 12,

13]. Apart from cryoglobulin production with or without overt CV, HCV-driven lymphoproliferation could explain the pathogenic role of HCV infection in idiopathic B cell lymphoma [1, 4]. Since the first description in 1994 [14], epidemiological and laboratory studies have confirmed this association in geographical areas where both HCV-associated CV and lymphoproliferative disorders occur [1, 4, 12].

The etiopathogenesis of HCV-negative CV [15] remains a challenge to explain apart from concurrent infectious processes including HBV and concomitant autoimmune rheumatologic and lymphoproliferative disorders (Figure 1). Patients with human immunodeficiency virus (HIV) type I infection may also have HCV co-infection. HIV may exert continuous antigenic stimulation of B-cells leading to MC type III production early in its course, followed by monoclonal type II MC, and the typical manifestations of CV [1-4, 12].

CLINICAL MANIFESTATIONS

The demographic, clinical-serologic and virologic findings of 270 patients with CV at our institution are shown in Table 1. The triad of purpura, weakness and arthralgia, the clinical hallmark of CV and MCs, were frequent seen in addition to chronic hepatitis, type 1 membranoproliferative glomerulonephritis (MPGN), peripheral neuropathy, skin ulcers, diffuse vasculitis, and in some instances, malignant B-cell non-Hodgkin lymphoma (B-NHL) and hepatocellular carcinoma [1-5, 9, 12]. Although the prevalence of singular clinical-serological features of CV in our cohort was comparable among those with type II and III MC, the reported clinical variability may relate to bias of ascertainment from renal or rheumatology clinics, and cohorts of geographically diverse origin [1-5, 8].

There are different presenting clinical-serological patterns that vary from mild arthralgia and sporadic purpura in those with MC alone, to more severe cutaneous and systemic involvement of classical MCs [1-4]. In all such patients, the disease combines MC with RF activity, low C4 levels, and the clinical-pathological features of orthostatic purpura due to leukocytoclastic vasculitis (LCV) with variable multi-organ involvement. Patients chronically infected with HCV demonstrate asymptomatic serum MC that may precede the clinical onset of disease by years to decades [1, 4]. Conversely, some patients show typical cryoglobulinemic manifestations without serum cryoglobulins. The absence of this serological hallmark is not surprising since cryoglobulins represent only a portion of IC that cryoprecipitate, which may be transient and vary both among patients and during follow-up in individual patients [1, 4]. Most experts agree that repeated cryoglobulin determinations are necessary for a definite diagnosis in such patients.

Cutaneous manifestations are the most common clinical feature of CV, with orthostatic purpura, the pathognomonic feature, varying largely in dimension and diffusion to sporadic isolated petechiae and severe vasculitic lesions, and complicated by torpid ulcers of the legs and malleoli [16]. Repeated episodes of purpura lead to stable, sock-like ochraceous discoloration of the legs [1, 4]. Humoral cofactors and vascular disturbances stemming from increased cryocrit levels, chronic venous insufficiency and physical stress all contribute to vasculitic alterations. More intense purpuric manifestations may occur in the afternoon with prolonged standing and when cryocrit levels are highest, especially in muggy weather conditions. Arthralgia, non-erosive oligoarthritis, and less frequently frank arthritis may also

be noted. When CV occurs in association with the sicca syndrome, there was mild xerostomia and xerophthalmia in up to one-half of patients [1, 4].

Table 1. Cryoglobulinemic vasculitis: Demographic, Clinicoserological, and Virological Findings at a Single Institution*

Total Number of Patients	270
Mean age at disease-onset (± SD), years (range)	55 (±14) (29-74)
Female/Male ratio	3:1
Disease duration, mean ± SD years (range)	14 (±11) (2-42)
Purpura	98%
Weakness	98%
Arthralgia	93%
Non-erosive arthritis	9%
Raynauds phenomenon	32%
Sicca syndrome	51%
Peripheral neuropathy	81%
Renal involvement	32%
Liver involvement	73%
B-cell non-Hodgkin lymphoma	12%
Hepatocellular carcinoma	3%
Mean cryocrit% (±SD)	4.1 (±14)
Type II/type III mixed cryoglobulins	2/1
Mean C3 (±SD) in mg/dl (normal 60-130)	91 (±35)
Mean C4 (±SD) in mg/dl (normal 20-55)	10 (±14)
Antinuclear antibodies	31%
Antimitochondrial antibodies	9%
Anti-smooth muscle antibodies	15%
Anti-extractable nuclear antigen antibodies	9%
Anti-HCV RNA	92%
Anti-HBV antibodies	30%
HBsAg	1%

*Evaluated at the end of the patient follow-up period.

Peripheral nervous system involvement that includes small fiber neuropathy of the legs with painful, burning paresthesia that worsens at night is often resistant to treatment. A minority of patients develop large fiber sensorimotor involvement, but when present, most often occurs with abrupt asymmetric onset of mononeuritis. Peripheral neuropathy may also be triggered or exacerbated during the first several weeks of treatment with interferon-alpha (IFN-α) in patients so disposed [1, 4]. Central nervous system vasculitis, albeit rare, presents with focal deficits such as dysarthria and hemiplegia, which may be difficult to distinguish from more common atherosclerotic vascular sequela.

Systemic liver involvement is rarely observed in other systemic vasculitides, but is present in CV, and generally preceded by mild to moderate chronic hepatitis that is apparent at presentation or develops in two-thirds of patients particularly those with HCV-related CV [1, 4]. Clinically overt liver cirrhosis occurs in one-quarter of patients, while life-threatening hepatorenal syndrome occurs in association with progressive CV [9]. The overall outcome of CV-associated chronic hepatitis seems to be more favorable than HCV-related hepatitis without

MCs, whereas hepatocellular carcinoma is less frequently observed in HCV-related CV compared to the overall population of HCV-infected individuals. Such differences are difficult to fully explain, however, the relatively low prevalence of the 1b HCV genotype in those that develop CV, along with a lower median consumption of alcohol might predict a more benign clinical course of liver involvement [1, 4]. Immune complex-mediated glomerulonephritis, most often seen in type 1 MPGN, affects the prognosis and survival of patients with CV due to hypothesized immune mechanisms [1, 4]. Intestinal vasculitis presents with severe life-threatening acute abdominal pain necessitating prompt diagnosis and aggressive treatment [1, 4].

Interstitial lung disease characterized by subclinical alveolitis has been described in those with CV and in association with isolated HCV infection [1, 4]. When present, interstitial lung disease can be a predisposing condition to pulmonary infections, and in rare instances, to clinically manifest interstitial lung fibrosis. Capillaritis complicated by severe cough and hemoptysis, are other rare manifestations of CV-related lung involvement, as well as overt hyperviscosity syndrome are due to high levels of serum cryoglobulins [1, 4].

A low or undetectable C4 level with a normal C3 fraction occurs in patients with CV regardless of disease activity. *In vitro* consumption of hemolytic complement is due to the anti-complement activity of cryo-Ig [1, 4]. A sudden increase in C4 from low to abnormally high levels can precede the development of B-NHL [1]. The absence of a clear-cut correlation between the severity/activity of CV clinical manifestations and the observed cryocrit levels may be related to the large variability of cryo- and non-cryoprecipitable IC ratio and/or the intrinsic ability of IC to activate complement, as well as the possible in situ formation of IC [1].

Endocrine disorders occur more frequently in CV than in the general population including thyroid disturbances, type II diabetes mellitus, and gonadal dysfunction [1, 12, 17]. The former include autoimmune thyroiditis, subclinical hypothyroidism, and rarely thyroid cancer. Reversible hyperthyroidism occurs as a complication of IFN-α treatment [1].

B-NHL, the most common malignancy in association with CV, is often seen late in the course of MCs [1, 4, 12]. The development of B-NHL may be a consequence of peripheral B-cell expansion of lymphoid infiltrates in the liver and bone marrow. Such lymphoid infiltrates, which are considered to be early indolent lymphomas, are indistinguishable from more advanced B-cell cancers that include chronic lymphocytic leukemia, small lymphocytic lymphoma, and immunocytoma [1, 4, 12]. While the majority of affected patients remain stable for years, overt B-NHL is observed in approximately 10% of affected patients most often late in the course of CV [1, 4-6, 12]. Other neoplastic manifestations, including hepatocellular carcinoma and papillary thyroid cancer occur in the natural progression of CV [1, 4, 12]. Accordingly, MC may be considered, in part, a pre-neoplastic disorder in which careful clinical monitoring is recommended even when the severity of MCs is mild.

DIAGNOSIS

There are no standardized methodologies for the measurement of cryoglobulin levels [1, 4] nor have the diagnostic criteria for CV been prospectively validated. In 1966, Meltzer and Franklin [2] described EMCs in patients with the triad of purpura, weakness, and arthralgia,

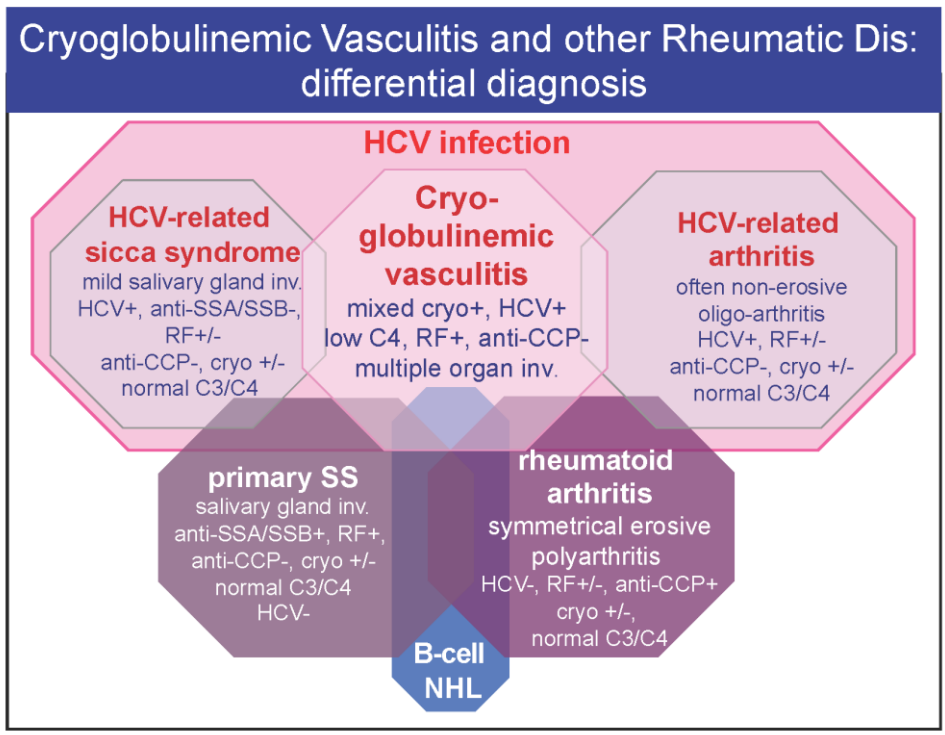
circulating MC, low C4 levels, LCV of arterioles, capillaries and venules, and multiorgan involvement without discernible infectious, autoimmune, or systemic involvement [1-6]. Recent classification criteria for CV were developed by a cooperative multicenter study using a standardized methodology [18]. Successively validated in MC patients referred to experts from a larger number of countries, these criteria may be usefully employed in epidemiological and clinical-pathogenic studies, and prospective therapeutic trials [19]. Evidence of MC in the serum of patients with suspected CV is necessary for a definite classification of the disease [18, 19], taking into account the above-mentioned variability of IC cryoprecipitation needing repeated cryoglobulin determinations [1].

DIFFERENTIAL DIAGNOSIS

Figure 3 describes aspects of the differential diagnosis of CV which shares a number of etiopathogenic events with both HCV-related and idiopathic disorders, namely sicca syndrome, primary Sjögren syndrome (pSS), polyarthritis, classical rheumatoid arthritis, autoimmune hepatitis, and B-NHL [1, 4, 12]. Therefore, a differential diagnosis with regard to the presence or absence of HCV infection should be carefully made in all patients with cryoglobulinemia and/or some autoimmune/neoplastic manifestations; a correct disease classification may decisively affect the overall clinical therapeutic approach and outcome. The presence of HCV in the large majority of individuals with CV may nonetheless lead to difficulty in the differentiation of CV from HCV-infected patients with other extrahepatic manifestations that characterize the HCV syndrome [12, 20]. Such patients develop slow progression from mild HCV-associated hepatitis to various extrahepatic manifestations including arthralgia, RF-positive arthritis, sicca syndrome, Raynaud's phenomenon, and others to clinically overt cryoglobulinemic syndrome (Figure 2). Of note, a minority of patients with long-lasting CV develop a clinically relevant malignancy [1, 20].

Patients with mild CV complain of arthralgia often without synovitis [1, 4, 21, 27] while those with HCV-associated CV and symmetrical erosive polyarthritis are more likely to have the syndrome of overlapping CV-rheumatoid arthritis further definable by serum anti-cyclic citrullinated peptide (anti-CCP) IgG antibodies and RF serology (Figure 3). Sicca syndrome occurs in up to one-half of patients with CV; however, formal criteria are satisfied in only a minority of patients [1, 4, 12, 21]. Patients with pSS shares various symptoms with CV including purpura, xerostomia, xerophthalmia, arthralgia, and laboratory evidence of RF seropositivity, cryoglobulinemia, and the associated complication of B-cell lymphoma [21]. Histopathological alteration of the salivary glands and the specific autoantibody pattern (anti-Ro/SSA-La/SSB) of pSS are rarely found in patients with MCs. Moreover, pSS is rarely complicated by chronic hepatitis, glomerulonephritis, or concomitant HCV infection. In this regard, HCV infection should be considered an exclusionary criterion for pSS [21]. In rare cases, and often in subjects without HCV infection, the differential diagnosis may be challenging. In those instances, it may be more appropriate to classify such patients as CV-pSS overlap syndrome [1, 4, 12, 21]. This clinical condition shows a rather severe clinical progression, less frequent Ro/SSA and La/SSB seropositivity, high levels of serum MC, hypocomplementemia, with frequent autoimmune-vasculitic manifestations, and a higher risk of lymphoma [4, 21, 27].

Autoimmune hepatitis may be associated with HCV infection in the same geographic areas that HCV-associated CV occur. The differential diagnosis between CV and autoimmune hepatitis may be difficult due to the presence of hepatic and extrahepatic autoimmune phenomena in both entities [1, 4, 12]. The presence of the typical features of CV including LCV, hypocomplementemia, glomerulonephritis, but generally mild hepatitis may collectively be a clue in differentiating CV from classical autoimmune hepatitis [1, 4, 12].



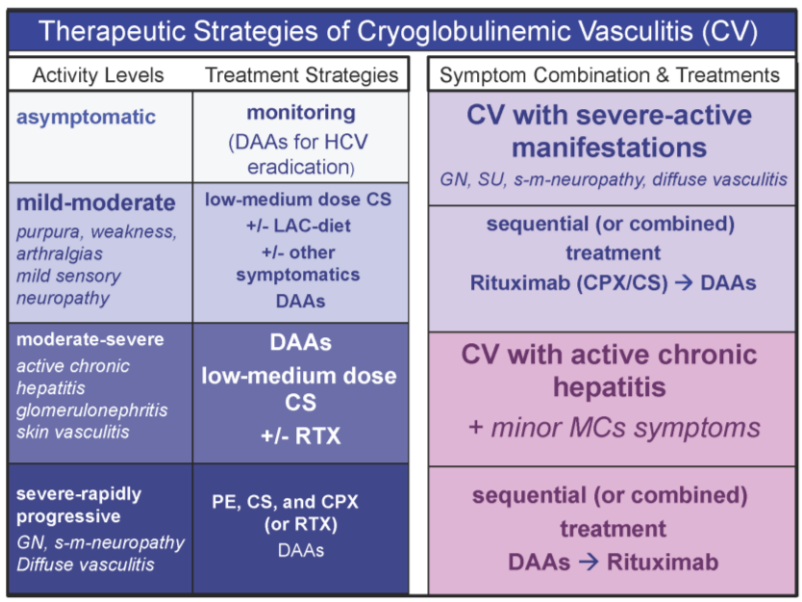
Abbreviations: CV, cryoglobulinemic vasculitis; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; pSS, primary Sjogren syndrome; LCV, leukocytoclastic vasculitis; B-NHL, B-cell non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

Figure 3. Differential diagnosis of CV and other rheumatic diseases. In clinical practice, it is possible to observe some clinical overlap syndromes involving CV and other autoimmune lymphoproliferative disorders. In particular, pSS and RA may share some clinico-pathological features with CV, including a possible association with HCV infection. However, a correct differential diagnosis may be done based on some considerations: pSS shows a typical histopathological pattern of salivary gland involvement and specific autoantibodies anti-Ro (SSA) and La (SSB), which are rarely found in patients with CV. Conversely, cutaneous LCV, visceral organ involvement including glomerulonephritis, hepatitis, low C4 and HCV infection, are typically found in CV. On the other hand, erosive symmetrical polyarthritis and serum anti-CCP characterize classic RA. Moreover, B-NHL may complicate CV, pSS, and RA. B-NHL may be suspected after careful clinical-serological monitoring. Finally, incomplete variants of both pSS and RA, namely isolated sicca syndrome and arthritis, can be associated to CV in the setting of chronic HCV infection, but they do not generally present typical clinical-serological and pathological features of pSS or RA.

PROGNOSIS

The overall 10-year survival of CV is estimated to be about 50% [9]. The clinical course and prognosis of CV relates mainly to disease manifestations, response to treatments and comorbid disorders, as well as, complications accrued to CV and its treatment [9]. Those with renal disease, liver failure, lymphoproliferative and other malignancies demonstrate the least favorable outcome [1, 4, 9, 12]. Careful monitoring of patients to avoid life-threatening complications of CV, including nephropathy, widespread systemic vasculitis, hepatitis, and malignancy, favor a better prognosis.

TREATMENT



Abbreviations: HCV, hepatitis C virus; CS, corticosteroids; LAC, low-antigen-content; DAAs: direct-acting antivirals; CPX, cyclophosphamide; RTX, rituximab; MCs, mixed cryoglobulinemic syndrome; GN: glomerulonephritis; s-m-neuropathy: sensory-motor neuropathy; SU: skin ulcers

Figure 4. Therapeutic strategy of cryoglobulinemic vasculitis according to the activity and severity of the disease or symptom combination. Asymptomatic generally require careful monitoring. Those with mild manifestations such as transient purpuric lesions of the legs may be monitored and offered therapy to eradicate HCV infection. Individuals with moderate to severe manifestations, mainly active chronic hepatitis are treated with new direct-acting antiviral therapies. Patients with severe, rapidly progressive disease complications or a partial response to traditional therapy receive aggressive treatment regimens similar to other systemic vasculitides; employing, sequential or combined treatment schedules.

Figure 4 summarizes the therapeutic approach to CV. Taking into account three important aspects of disease pathogenesis, the treatment can be aimed at chronic immune stimulation by eradicating HCV infection, attenuating the resultant T- and B-cell activation, and attenuating the production of cryoglobulins and IC, as well as, the identification and treatment of B-cell

lymphoproliferation to avert the development of B-NHL. This multistep, multifactorial etiopathogenesis-oriented approach to therapy targets HCV infection, B-cell proliferation, and the resultant CV inflammatory involvement. The recent introduction of direct acting antivirals (DAAs) led to sustained clearance of HCV in the large majority of patients so treated [4, 22-27], without the frequent side-effects previously observed with IFN-α treatment, such as peripheral neuropathy, thyroiditis, and rheumatoid-like polyarthritis [1, 4, 12]. Preliminary studies suggest a role for DAAs in the treatment and eradication of HCV, whereby elevated its tolerability and efficacy, offers new hope in the management of severe complications [22-27]. However, the variable and unpredictable CV response to the antiviral therapy observed in some patients, including the paradoxical response with disease exacerbation or new symptom appearance, indicates that DAAs effect on CV needs to be further evaluated. The immune system of a single patient may be decisive in the clinical outcome following antiviral treatment. There is a point of no return in a viral-driven lymphoproliferative disorder that may affect the overall clinical response after HCV eradication. Like H. pylori-associated gastric lymphomas [1, 4], HCV-associated CV is more responsive to biologically based treatment of the underlying infection, early in the he early phase of the illness.

Physicians must choose from among available therapies for CV including low-antigen-content (LAC) diets, plasma exchange (PE), and immunosuppressant regimens employing corticosteroids, rituximab, and cyclophosphamide alone or in combination depending upon the severity and activity of the illness and clinical manifestations [1, 4, 17]. A LAC-diet improves the clearance of circulating IC by restoring the activity of the reticuloendothelial system, which becomes overloaded, by circulating cryoglobulins [1, 4, 21]. It reduces the input of alimentary macromolecules crossing the mucosal barrier of the gut as some foods such as dairy products and eggs present a potential antigenic activity and might otherwise be pathogenic. Reduction of the alimentary input of macromolecules directed to mononuclear phagocytic system improves its function in conditions characterized by abnormal endogenous hyperproduction of IC responsible for organ damage such as MCs. Combined LAC-diet and 2 to 4 mg per day of 6-methyl-prednisolone may be sufficient to ameliorate mild manifestations of CV such as sporadic purpura and arthralgia. The limitations of an LAC-diet treatment include poor patient compliance, which can be improved by tailoring the treatment duration, for example 7 to 14 days of restricted diet followed by 14 to 28 days of free diet. Those with mild-moderate symptoms including palpable purpura may be particularly sensitive to the small variations in daily steroid dosage of 1 to 2 mg, and derive benefit from dietary therapy.

Cyclophosphamide and in particular, rituximab are each first-line therapies for EMCs [1, 4, 21, 22]. Rituximab is first-choice treatment based on the results of observational and controlled studies in seronegative and seropositive HCV patients with CV [1, 4, 21, 22, 27-31]. Traditional and double-filtration PE can reduce the levels of circulating IC and cryoglobulins [1, 4, 21]. Oral cyclophosphamide at the dose of 50 to 100 mg per day for 2 to 6 weeks during the tapering of PE sessions, as well as rituximab, reinforces the beneficial effects of PE. Moreover, the latter can also potentiate the effect of cyclophosphamide [9], and is beneficial in the treatment of fulminant manifestations of CV such as widespread vasculitis and/or rapidly progressive MPGN [9].

The treatment of CV should be tailored to individual patients according to the severity of clinical symptoms, with the most severe vasculitic manifestations treated promptly with combination corticosteroids, PE, and cyclophosphamide or rituximab [1, 4, 9, 21]. Pilot studies suggest that sequential or combined antiviral and immunosuppressive treatment is a useful

strategy [4, 27, 30, 31] especially in those with major clinical manifestations and partial or transitory remission after antiviral therapy (Figure 4). Clinically asymptomatic patients may be monitored without treatment even in the presence of elevated cryocrit levels; in these patients, an attempt to HCV eradication should be always considered. Careful clinical monitoring of the disease is mandatory in all cases with particular attention to neoplastic transformation [1, 4].

CONCLUSION

Cryoglobulinemic vasculitis is an important model for the study of autoimmune and lymphoproliferative diseases mediated by viral infections. Recent advancements in the understanding of the underlying multifactorial and multistep processes in the etiopathogenesis of CV have translated into more effective etiological treatment modalities including antivirals treatments directed at eradication of HCV infection as both a triggering factor and contributor to the self-perpetuating mechanism of autoimmune disease. In addition, pathogenetic therapies may be employed to target the variably severe consequences of LCV, systemic SVV, multiorgan involvement, and malignancies. Future challenges in CV include improvements in the differential diagnosis with some overlapping disorders, as well as the improvement in therapeutic strategies tailored to different CV clinical variants in selected patients.

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Chapter 14

AORTITIS AND PERIAORTITIS

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ABSTRACT

Aortitis and periaortitis are inflammatory diseases of the aorta and its branches. They differ in the extension of inflammation, which is confined to the aortic wall in aortitis and extends in the periaortic space in periaortitis. Although aortitis occurs as either an infectious or a non-infectious process, the latter suggests an etiology related to large-vessel vasculitis. Periaortitis and aortitis are recognizable fibro-inflammatory systemic disorders, categorized under the rubric of IgG4-related diseases. This chapter reviews the nosology, pathogenesis, histopathology and clinical phenotype of the different forms of aortitis and periaortitis, and discusses their diagnosis and management.

Keywords: aortitis, periaortitis, IgG4-related disease, fibrosis, vasculitis, giant cell arteritis, Takayasu arteritis

ABBREVIATIONS

ANCA	anti-neutrophil cytoplasm antibody;
AAV	ANCA associated vasculitis;
CRP	C-reactive protein;
CT	computed tomography;
CTL	cytotoxic T lymphocyte;
ECD	Erdheim Chester disease;
ESR	erythrocyte sedimentation rate;
^{18}F-FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography;

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GCA	giant cell arteritis;
HLA	human leucocyte antigen;
IAAA	inflammatory abdominal aortic aneurysm;
IgG4-RD:	IgG4-related disease;
IL	interleukin;
LVV	large vessel vasculitis;
MRI	magnetic resonance imaging;
NK	Natural killer;
PDGF	platelet-derived growth factor;
RPF	retroperitoneal fibrosis;
SLE	systemic lupus erythematosus;
SUV	standardized uptake value;
TA	Takayasu arteritis;
TLR:	toll-like receptor;
US	ultrasonography.

INTRODUCTION

Aortitis and periaortitis are in the spectrum of systemic inflammatory disorders characterized by chronic inflammation that may be limited to the aortic wall or to the adjacent periaortic space. Both conditions may arise in the context of a recently recognized clinical-pathological entity known as an IgG4-related disease (IgG4-RD), characterized by marked fibrosis and T-lymphocyte and IgG4-positive plasma cell infiltration of various organs.

In 2015, a standardized classification for inflammatory diseases of the aorta was proposed as a part of a consensus statement issued by the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology [1]. The committee identified three general categories of inflammatory aortic disease: (a) atherosclerosis, (b) atherosclerosis with excessive inflammation and (c) aortitis/periaortitis.

Atherosclerosis is a degenerative inflammatory process that starts from the intimal layer of arteries. It is classified as mild, moderate, or severe based on the medial destruction and the presence of extracellular lipid deposition with fibrosis. In some cases, the inflammatory reaction is unusually intense but always due to atherosclerosis. Two major examples of this phenomenon are atherosclerosis with excessive neutrophilic inflammation and inflammatory abdominal aortic aneurysms (IAAA).

The terms aortitis and periaortitis are reserved for inflammatory aortic conditions unattributed to atherosclerosis alone. Aortitis is a pathological term that describes an extensive inflammatory process that involves the media and/or the intima of the aortic wall.[2] The inflammatory response affects the aorta at any level and extends to its major branches and other large vessels. Aortitis can be the presenting feature of large vessel vasculitides (LLV), but may also occur in the absence of clinical symptoms or signs of systemic vasculitis making it an incidental diagnosis on imaging studies or in histologically studied specimens of surgically resected aortic tissue [1]. Aortitis rarely develops in association with concomitant rheumatologic disorders or in the presence of an infectious illness.

It is recommended to apply the term periaortitis to an inflammatory process that arises from the adventitia of the aortic wall and extends into the surrounding periaortic space. The ensuing pathological lesion consists of a fibrous component and a chronic inflammatory infiltrate. Periaortitis typically involves mainly the lower abdominal aorta and the common iliac arteries and can arise around either a dilated or non-dilated aorta. The tissue infiltrating the retroperitoneum frequently encases adjacent structures such as the ureters and the inferior vena cava [3]. Originally, periaortitis was thought to be confined to the abdominal aorta, although histopathologic studies provided evidence of simultaneous involvement of other vascular districts [4]. Computed tomography (CT), magnetic resonance imaging (MRI) and especially ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) imaging identify vascular inflammation in virtually all large arteries. The thoracic aorta and the epiaortic arteries are involved in about a third of patients suffering from abdominal periaortitis wherein the condition is typically asymptomatic [5]. The coronary, renal, mesenteric and coeliac arteries may rarely be involved. While diverse causes of periaortitis and aortitis may be clearly distinguishable, the differential diagnosis is often challenging when an affected patient presents with nonspecific systemic symptoms or fever of unknown origin, and the inflammatory process diffusely involves the aorta.

In 2001, Hamano and colleagues [6] first described IgG4-RD noting an association between sclerosing pancreatitis and high serum levels of IgG4+. The recognition of other involved sites led to the concept of a fibro-inflammatory systemic disease. Large vessels involved by IgG4-RD [7] present clinically as aortitis or periaortitis. Notwithstanding, the corresponding lesions are similar throughout the different affected sites.[8]

CLASSIFICATION AND NOSOLOGY

Aortitis is classified into two main groups, according to the presence or absence of an infectious source. While infectious aortitis is now rare in developing countries as a result of the introduction of antibiotics, it nevertheless remains important to differentiate the infectious and non-infectious entities since the therapeutic strategies significantly differ [2].

Infectious aortitis develops in the course of septicemia or embolization of a septic embolus as a complication of infective endocarditis [1]. Pre-existing aortic wall damage in the form of arteriosclerotic lesions or vascular dilatation facilitates infection. Elderly men and immune compromised patients are populations at the greatest risk for the most common associated organisms, namely, gram-positive bacteria including *Staphylococcus spp*, *Enterococcus spp* and *Streptococcus pneumoniae* that typically involve the thoracic aorta; and gram-negative bacteria, notably *Salmonella spp,* that affect the abdominal aorta. Syphilitic aortitis develops in the setting of tertiary syphilis, typically involving the ascending aorta. *Treponema pallidum* preselects the *vasa vasorum* of the aortic wall leading to ischemic injury of the medial layer, with secondary aneurysmal dilatation. Tuberculous aortitis should be suspected in those with pulmonary and extrapulmonary tuberculosis in the course of miliary spread or direct extension of the infectious process from adjacent tissues, such as infected lymph nodes or lung lesions [2]. In those cases, the thoracic and abdominal aorta are affected with comparable frequency [1]. Fungal infection-related aortitis occurs in immune-compromised patients or in others chronically exposed to broad-spectrum antibiotics [1].

Table 1. Aortitis and periaortitis: Classification and Etiologic Basis

Infectious aortitis	Non-infectious aortitis	Idiopathic/IgG4 related periaortitis	Other diseases with periaortic infiltration
Bacterial (Staphylococcus spp, Streptococcus pneumoniae, Salmonella spp, Escherichia spp, Treponema pallidum, etc.)	Large-vessel vasculitides (Giant cell arteritis, Takayasu arteritis)	Idiopathic retroperitoneal fibrosis	Infections (Actinomycosis, Tuberculosis, Histoplasmosis)
Mycobacterium tuberculosis	ANCA associated vasculitides	Inflammatory abdominal aortic aneurysm	
Fungi (Candida, Aspergillus, Cryptococcus, Paracoccidioidomycosis)	Other vasculitides (Behçet Disease's, Cogan syndrome)	Perianeurysmal retroperitoneal fibrosis	Drugs (Ergot-alkaloid derived drugs, Methyldopa, Beta-adrenergic blockers, Phenacetin, Paracetamol, Aspirin, Hydralazine, Carboplatin, Methotrexate, Etanercept, Infliximab)
	Idiopathic/IgG4 related Isolated Aortitis	Thoracic periaortitis without aneurysm	
	Connective tissue diseases (Systemic lupus erythematosus, Relapsing polychondritis, Sarcoidosis)	Thoracic aorta aneurysm without periaortitis	Malignancies (Metastases of carcinomas: breast, lung, pancreas, stomach, colon, rectum, kidney, bladder, prostate, ovary and cervix; Carcinoid tumors, Hodgkin and non-Hodgkin lymphomas)
		Periaortitis with thoracic aorta aneurysm	
	Inflammatory arthritides (Rheumatoid arthritis, Ankylosing spondylitis)	Diffuse thoraco-abdominal periaortitis	Others (radiation therapy, abdominal trauma and surgery, Erdheim–Chester disease)

Non-infectious aortitis associated with LVV, including giant cell arteritis (GCA) and Takayasu arteritis (TA) represents two large groups of cases [2]. Aortic involvement occurs in systemic rheumatic disorders. Rheumatoid arthritis vasculitis (RAV), in which aortitis is an uncommon extra-articular manifestation, may be associated with vascular involvement of vessels of any size and may appear in any phase of the illness, although typically in the later stages [9]. The aortic root, the ascending aorta [10] and the branches of the aortic arch [11] can be involved in ankylosing spondylitis. Aortitis is also described in cases of systemic lupus erythematosus (SLE), most often manifesting as an aortic aneurysm or dissection [12, 13]; and in rare cases of relapsing polychondritis [14].

Large vessel involvement occurs in several small vessel vasculitides (SVV). In anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV), aortitis may present with stenosing arteritis, aneurysmal disease and aortic dissection [15]. Vasculitis involvement of the *vasa vasorum* affecting the aortic root is associated with valvular dysfunction in some cases of Behçet disease [16] Aortitis also occurs in a minority of patients with Cogan syndrome [17] with severe incipient complications thereof [18]. Aortitis is unusual in sarcoidosis [19]. Cryptic isolated aortitis involving the ascending aorta may be detected in clinically asymptomatic patients, without evidence of a coexisting rheumatic disease [1].

Periaortitis has to be distinguished from aortitis not only for classification purposes, but also for its clinical and therapeutic implications. Periaortitis usually affects the infra-renal portion of the abdominal aorta and the iliac arteries. The aorta is undilated in idiopathic retroperitoneal fibrosis (RPF) while IAAA and perianeurysmal retroperitoneal fibrosis are the perianeurysmal forms [3]. Abdominal periaortitis must be differentiated from other diseases leading to periaortic retroperitoneal infiltration, particularly malignancies, granulomatous infections, drug-related and radiotherapy-induced conditions, and Erdheim-Chester disease [20]. In some patients, an idiopathic form of periaortitis involves the thoracic aorta with three possible patterns: thoracic periaortitis without aneurysm, thoracic aorta aneurysm without periaortitis, and periaortitis surrounding a thoracic aorta aneurysm.

Both aortitis and periaortitis can arise in the context of IgG4-RD signaling involvement as a multifocal disease; and in other cases, isolated to the thoracic tract. IgG4-related aortitis accounts for 75% of thoracic aortitis with a lymphoplasmacytic pattern [21]. Periaortitis is a common manifestation of IgG4-RD, responsible for up to 50% of periaortitis cases [22]. Table 1 summarizes the main etiologies of aortitis and periaortitis.

MAIN HISTOLOGIC PATTERNS

Aortitis may exhibit four different histological patterns of inflammation, namely granulomatosus/giant cell, lymphoplasmacytic, mixed inflammatory and suppurative, each related to different etiologies [1].

The *granulomatosus/giant cell pattern* is the most common pattern of inflammation in aortitis. It is characterized by the presence of large activated epithelioid macrophages with or without giant cells and compact granulomas. An accompanying lymphoplasmacytic infiltrate is often present. This pattern occurs in GCA- and TA-related aortitis, isolated aortitis, and aortitis associated with rheumatoid arthritis, ANCA associated vasculitides (AAVs), sarcoidosis, mycobacterial and fungal infections.

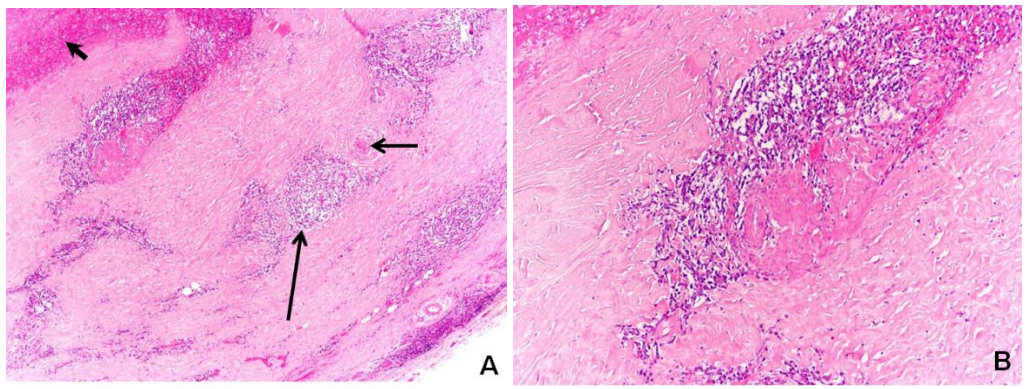

Figure 1. Histopathological findings in a case of IgG4-related aortitis. Figure A (Hematoxylin and eosin, original magnification x4) shows inflammation and fibrosis involving the aortic adventitia and the periaortic soft tissue. Nodular lymphoplasmacytic infiltrates (long arrow) are seen in the context of abundant adventitial and periadventitial fibrosis. Fibrosis has an irregular pattern and is often organized around small adventitial and periadventitial vessels (short arrow). The arrowhead indicates the aortic media. Figure B (Hematoxylin and eosin, original magnification x10) shows a detail of the image shown in Figure A, where a cluster of inflammatory mononuclear cells can be observed in the context of irregular fibrosis. Immunohistochemistry performed in this case (not shown) demonstrated an $IgG4^+/IgG^+$ plasma cell ratio of 50%.

The *lymphoplasmacytic pattern* consists of lymphocytes and plasma cells without a granulomatous/giant cell component. It is seen in IgG4-RD, SLE and syphilitic aortitis (Figure 1).

The *mixed inflammatory pattern* is relatively uncommon. The inflammatory infiltrate is composed of almost all inflammatory cell types: macrophages, lymphocytes, plasma cells, eosinophils, mast cells and neutrophils without a granulomatous component. It is associated with aortitis in Cogan's syndrome, Behçet disease and relapsing polychondritis.

The *suppurative pattern* is characterized by a marked neutrophilic infiltrate and extensive necrosis. This pattern occurs in some forms of infectious aortitis such as infections with Gram-positive cocci, *Salmonella*, *Pseudomonas* and fungi.

Idiopathic periaortitis (either IgG4-related or unrelated) histologically shows two components: a fibrous tissue and a chronic inflammatory infiltrate. The fibrous component includes an extracellular matrix of type I collagen fibers and a population of fibroblasts and myofibroblasts. The inflammatory infiltrate displays a *lymphoplasmacytic pattern.* It consists of B and T lymphocytes, macrophages, plasma cells and rare eosinophils [20].

The histopathological appearance of IgG4-related forms of aortitis and periaortitis is comparable to that of their IgG4-unrelated counterparts; however, the IgG4-related forms more frequently show a storiform pattern of fibrosis, lymphoid aggregates with germinal centers, tissue eosinophilia, and obliterative phlebitis, and by definition, a higher proportion of $IgG4^+$ plasma cells. The diagnosis of IgG4-related forms requires a ratio of $IgG4^+$/total IgG^+ plasma cells > 40% [23].

CLINICAL PHENOTYPES

Herein, we describe the clinical phenotype of the most common aortitis and periaortitis syndromes, with particular emphasis on non-infectious forms, and we highlight the characteristics of these two conditions in the course of IgG4-RD.

Giant Cell Arteritis

This medium- and large-vessel vasculitis usually affects the aorta and its major branches with a predilection for the branches of the carotid and vertebral arteries [24]. Defined in the past as "temporal arteritis," the term is inadequate to describe GCA because not all patients have temporal artery involvement and other categories of vasculitis can affect the temporal arteries. GCA is the most common type of non-infectious arteritis in North America and Western Europe. It occurs primarily in elderly individuals older than 50 years. Women are affected two to three times more commonly than men [25].

The typical histological pattern of GCA is a granulomatous inflammatory infiltrate composed of lymphocytes, macrophages and in 50% of the cases, multinucleated giant cells.[25] Inflammation has a focal nature, with "skip" lesions, wherein non-affected arterial segments intermingle with inflamed tracts. It is located mainly in the intima-media junction of the vessel wall but it can be present throughout the artery. At the beginning of the disease process, the intimal layer appears thickened by the inflammatory infiltrate and edema, at later stages by myofibroblast migration. The media remains well preserved, although focal smooth muscle necrosis may occur. The adventitia is inflamed in a moderate proportion of cases [26].

The pathogenesis of GCA has not been fully explained but dysregulated interactions between the vessel wall and the immune system are key to disease development [27]. The allelic variant of human leucocyte antigen (HLA)-DRB1*04 is the most common genetic association with GCA. The involvement of class II HLA molecules implies antigen-presentation to $CD4^+$ T cells which then triggers the vasculitic lesion [28]. The involved antigens are still unknown, both infectious agents and autoantigens have been suspected.

Vascular dendritic cells located at the adventitia-media border of the artery have a critical role in the initiation of disease. Dendritic cells become activated once their toll-like receptors (TLRs) are engaged by microbial products and turn into non-tolerogenic cells able to present potential auto-antigens to T cells; their ability to produce chemokines is thus enhanced, thus leading to recruitment of T cells and macrophages into the vascular wall through the *vasa vasorum* [28]. The activated dendritic cells express CD86, a co-receptor required to trigger T-cell activation, and produce cytokines, such as interleukin (IL)-6 and IL-12 that guide the differentiation of T cells into selected functional lineages [27].

IL-6 is a pleiotropic cytokine released also by endothelial cells, vascular smooth muscle cells, lymphocytes and macrophages and implicated in the production of acute-phase proteins. IL-6 shifts T-cell differentiation towards the Th17 lineage and blocks the anti-inflammatory T regulatory cell expansion. Th17 cells produce a plethora of cytokines (IL-17, IL-21, and IL-22) that recruit macrophages and neutrophils and activate vascular smooth muscle cells, fibroblasts and endothelial cells.

The IL-6/IL-17 cytokine cluster seems to play an important role in early GCA, while the IL-12/IFN-γ cytokine cluster appears to drive the tissue remodeling during chronic disease [27]. IL-12 promotes the differentiation of the Th1 lineage, which releases IFN-γ into the microenvironment. IFN-γ amplifies T-cell responses and stimulates macrophage activation. Macrophages have the potential to induce arterial wall injury through multiple pathways. They release reactive oxygen intermediates and metalloproteinases that lead to the fragmentation of the internal elastic lamina. Macrophages produce also platelet-derived growth factor (PDGF) and vascular endothelial growth factor that are critically involved in intimal layer proliferation. Myofibroblasts, stimulated by IFN-γ and PDGF migrate in the intima where they replicate and secrete extracellular matrix leading to concentric intima hyperplasia [28]. Outgrowth of the intima is consistently associated with marked neoangiogenesis. The end result is a vascular occlusion caused by the vessel wall thickening or the formation of arterial aneurysm (particularly thoracic aorta aneurysm) caused by destruction of the arterial wall [28].

Medium-sized arteries, such as the branches of external and internal carotid arteries and the vertebral arteries respond with occlusion of the lumen and, consequently, ischemic organ damage. Clinical symptoms reflect end organ ischemia.

The classic manifestations are headache, scalp tenderness, jaw claudication, blindness, stroke, transient ischemic attacks and vertigo. Similarly, involvement of the subclavian, axillary, and proximal brachial arteries leads to arm claudication and absent or asymmetric pulses [28]. Compared to patients with cranial symptoms, those with aortic arch syndrome tend to be younger at diagnosis and have a longer duration of symptoms prior to diagnosis [29].

Instead of forming stenotic lesions, the aorta responds with wall destruction. Aortitis most often occurs in the thoracic aorta while involvement of the branches of the abdominal aorta and lower extremity arteries is less common. It may produce chest or back pain but it is more frequently asymptomatic until complications arise. These complications are aneurysm formation and rupture, dissection and aortic valve insufficiency (Figure 2). In early studies, the prevalence of aortic involvement in patients with GCA was based on the rate of aneurysm diagnosed fortuitously or after acute events and autopsy data, remaining under-estimated. Recently, the large use of imaging techniques (essentially CT, MRI or PET) in the diagnosis and follow-up of LVVs showed that aortic involvement may be more prevalent than previously reported, with a frequency ranging from 33%[30] to 50% [31-33]. The risk of aortic structural damage significantly increases in the first 5 years from diagnosis and progresses slowly afterwards, suggesting that chronic inflammation of the vascular wall is the major determinant of aortic damage [34].

In almost all patients with GCA, a syndrome of systemic inflammation accompanies vascular manifestations and presents with nonspecific symptoms including malaise, anorexia, weight loss, fever and depression. Around 40% of patients with GCA also have polymyalgia rheumatica, characterized by aching and morning stiffness involving the neck, shoulder and pelvic girls [25].

Takayasu Arteritis

This disease predominantly affects the aorta and its major branches, along with pulmonary arteries. In accordance with the Chapel Hill consensus conference nomenclature, TA is a

granulomatous vasculitis that usually occurs before the age of 50 years [24]. It is a rare disease with few reports regarding prevalence and incidence. Nonetheless, the highest prevalence has been described in Japan with 40 cases/million [35], but incidence rates seem to be similar in different countries worldwide [36]. It affects predominantly young women, with a peak incidence around the second and third decade [36].

The inflammatory process is a panarteritis affecting all the three layers of the vessels, with a focal distribution, which results in narrowing of the lumen due to the fibrosis with stenosis and occlusion, or aneurysmal formation in cases where the process is more rapid [26, 37].

In the acute phase, *vasa vasorum* of the adventitia appear inflamed with granulomatous inflammatory infiltrates involving the media, too. The most abundant cells are T and B cells, along with granulocytes and eosinophils. Giant cells are present as in GCA and this feature may account for the difficulties in differentiating the two vasculitides. Neovascularization and proliferation of the smooth cells and fibroblasts lead to derangement of the intima. In chronic stages of the disease fibrosis and dense scarring lead to a thickening of the adventitia and the intima appears as a "tree bark," a characteristic common to other aortitides. The disruption of the elastic fibers may lead to aneurysm formation (Figure 2) [1, 37].

The pathogenesis of TA is not well understood. Various antigens have been explored but the exact triggers and involved immunologic pathways remain obscure. Current evidences suggest an autoimmune mechanism with a prominent cell-mediated immunity, along with genetic predisposition mediated by HLA alleles. In particular a strong association was reported between class I HLA alleles and TA [38].

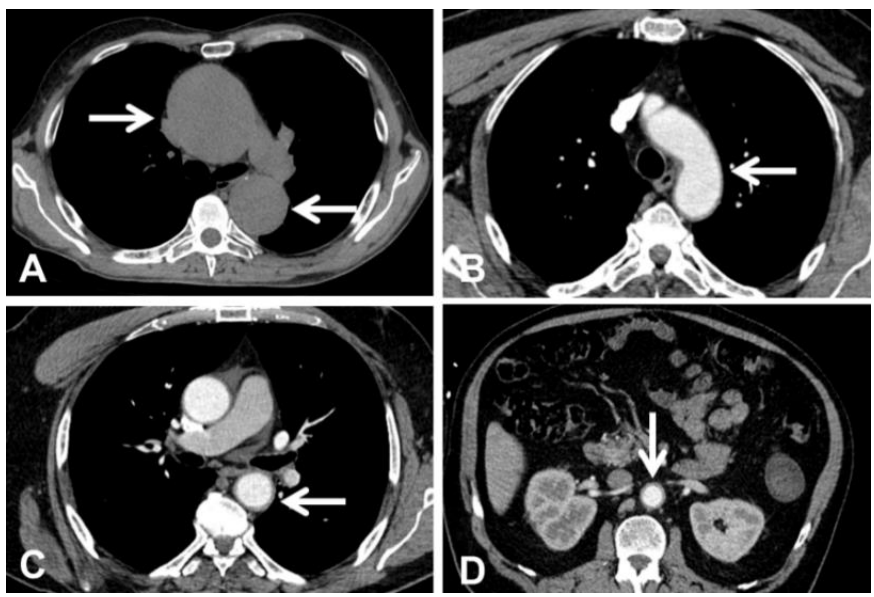

Figure 2. Computed tomographic (CT) findings in aortitis. The images A-C show the CT appearance of thoracic aortitis: (A) aneurysms of ascending (upper arrow) and descending aorta (lower arrow); (B, C): wall thickening of the aortic arch (B, arrow) and of the descending aorta (C, arrow). CT appearance of abdominal aortitis (D, arrow).

Natural killer (NK) cells and γδ T lymphocytes appear to have a role in inducing apoptosis of the vascular cells by releasing perforin. These cells are activated by 65-kDa heat shock protein (HSP) which is overexpressed in aortic samples of patients affected by TA [39]. Similar to GCA, $CD4^+$ T cells have a leading role particularly in the formation of granulomas. Both Th1 and Th17 pathways are expanded and correlate with disease activity [40].

The clinical manifestations are variable during the early stages of the disease with anorexia, fever and malaise. In fibrotic stages (also known as pulseless stages) symptoms are related to vascular stenosis and aneurysms [41]. Most typical clinical features include: diminished or absent pulses with limb claudication and discrepancies in blood pressure, multiple vascular bruits, renovascular hypertension and retinopathy [37]. Complications are related to organ ischemia and congestive heart failure due to hypertension and valve regurgitation when thoracic aneurysms are present.

Isolated Aortitis

Isolated aortits is a single-organ vasculitis found primarily in the ascending part of the thoracic aorta [24]. This condition is not a component of a systemic vasculitis like GCA and TA, or associated with a systemic disease such as SLE or sarcoidosis. The disorder emerged with the advent of aortic surgery and histopathologic examination of the aortic surgical specimens. The introduction of new imaging techniques facilitated recognition of the disease before development of structural aortic abnormalities requiring surgery.

The epidemiology of isolated aortitis has not been clearly established, but its prevalence is probably underestimated, as the disease may remain undiagnosed for a long time. The incidence of isolated aortitis in the population of patients undergoing thoracic aortic surgery is between 3.8% and 4.4% [42-44]. Some studies show a higher incidence in women [42, 43] others in men [44, 45]. The mean age of patients at diagnosis ranges from 63 to 72 years [42-44]. Unlike those with TA and GCA, patients with isolated aortitis do not have symptoms related to systemic illness or extra-aortic arteritis [43].

Most cases of isolated aortitis show a granulomatous/giant cell pattern of inflammation localized in the medial layer. The inflammatory infiltrate comprises macrophages, giant cells, lymphocytes, plasma cells and well-formed granulomas replacing irregular areas of medial destruction. Adventitial inflammation contains minimal mononuclear cell infiltration without granuloma formation.

Isolated aortitis is identified incidentally during radiological exams or in the repair of the complications of aortic surgery [46]. Isolated aortitis can lead to thoracic aortic aneurysms, aortic dissection and aortic valve regurgitation. The aortic aneurysm is certainly the most frequent complication, so noted in 95% of patients with isolated aortitis and is usually localized in the ascending tract [42, 43].

Recent studies have evaluated the rate of new aortic events in patients with the diagnosis of isolated aortitis [47, 48]. Follow-up data indicate that patients with isolated aortitis are at increased risk for subsequent aortic events, such as new aneurysms and dissections also involving the descending thoracic aorta or the abdominal aorta. Even in the absence of signs of systemic vasculitis, aortitis identified in the ascending aorta is associated with an increased frequency of distal aortic events during long-term follow-up. Patients with isolated aortitis should be monitored with periodic aortic imaging.

Though the studies are limited, there is an increasing evidence that patients with aortitis isolated to aortic ascending segment have actually a smoldering systemic vasculitis that is subclinical in other districts at the time of presentation and fully manifests at a later time [46].

IgG4-Related Aortitis

Since the first description of IgG4-RD, diverse clinical entities without clear nosology have been categorized in the spectrum of this systemic fibro-inflammatory disease, including cases of aortitis, once considered isolated or idiopathic.

IgG4-related aortitis preferentially affects the thoracic aorta and particularly the aortic arch [21, 49]. It presents with a lymphoplasmacytic pattern and accounts for a significant proportion of non-infectious thoracic aortitis cases, and about 75% of cases of lymphoplasmacytic thoracic aortitis [21, 50]. The vasculitic process can also involve the abdominal aorta, along with medium-sized vessels originating from the aorta, such as the carotid and coronary arteries [7, 51]. Small vessel involvement has also been described, thus supporting the idea that IgG4-RD may be included in the category of vasculitis of vessels of variable size [52].

IgG4-related aortitis occurs among elderly men aged 60 years or older, in keeping with the epidemiology of the systemic and other organ-limited forms of IgG4-RD [50].

The inflammatory infiltrate affects predominantly the adventitia with a lesser involvement of the media (Figure 1), in contrast with other LVV.[1] Histological findings are typical and are the same throughout different lesions, regardless of the involved site. The main features are storiform fibrosis, obliterative phlebitis, moderate eosinophilia and dense lymphoplasmacytic infiltrates, with a predominance of T and B cells that occasionally organize into germinal centers [23]. IgG4-immune staining of the affected tissue is mandatory to have a “definite” diagnosis of IgG4-related aortitis. However, in cases not undergoing surgery or when the pathological specimen is unavailable, evidence of aortitis on imaging studies, along with increased serum IgG4 levels, supports a “possible” diagnosis of this condition [49].

The pathogenesis of IgG4-RD, and consequently of IgG4-related aortitis, remains unclear although significant advances have been made: IgG4 antibodies does not seem to have a central role, and their anti-inflammatory characteristics lead to consider them as an attempt to dampen a primary inflammatory process [53]. The immune mechanisms are probably cell-mediated. A subpopulation of $CD4^+$ T cells with a cytotoxic phenotype (CTLs) has been found in IgG4-RD lesions and clonally expanded in the circulation, which appears to orchestrate the pathogenic mechanisms activated by antigen-presenting B cells [54]. The latter have a pivotal role in initiating and maintaining the disease, as shown by the efficacy of B cell-depleting therapies, such as rituximab. The antigens that trigger the immune response are unknown.

IgG4-related aortitis occurs sub-acutely and is often asymptomatic. It may be diagnosed after an incidental finding on CT (Figure 2) or after pathological examination of surgical specimens. It can also present with symptoms related to the presence of aneurysms, whereas end organ ischemia is far less common and appear when medium-size vessels such as the main aortic branches are also involved [7]. Acute pain may indicate dissection, which has also been described as a complication of IgG4-related aortitis [55]. Involvement of other organs may be absent at onset and appear only during follow-up with a metachrounous pattern [56], leading to difficulties in promptly recognizing IgG4-RD. The most frequent clinical pictures of IgG4-RD include sclerosing pancreatitis (type 1 autoimmune pancreatitis), Mikulicz disease and RPF,

but several other conditions may be found such as diffuse lymphadenopathy, sclerosing cholangitis, pseudotumor of the orbit, and tubulo-interstitial nephritis.

Periaortitis

Periaortitis is a fibroinflammatory disorder characterized by the presence of fibrosis accompanied by a variable number of chronic inflammatory cells that extend from the adventitia of the aortic wall into the surrounding periaortic space [57]. The term "chronic periaortitis," proposed by Mitchison in 1980 underlines the nature of the inflammatory infiltrate and has traditionally been applied to describe this condition.

Periaortitis includes three main entities: idiopathic RPF, inflammatory abdominal aortic aneurysms (IAAAs) and perianeurysmal RPF. In idiopathic RPF, the aorta is undilated and the retroperitoneal fibroinflammatory tissue frequently entraps neighboring structures such as the ureters and the inferior vena cava (Figure 3); in IAAAs, the mass develops around a dilated aorta without involving adjacent organs (Figure 3). Perianeurysmal RPF represents a combination of these two diseases, the aorta is dilated and the periaortic tissue causes obstruction of other structures.

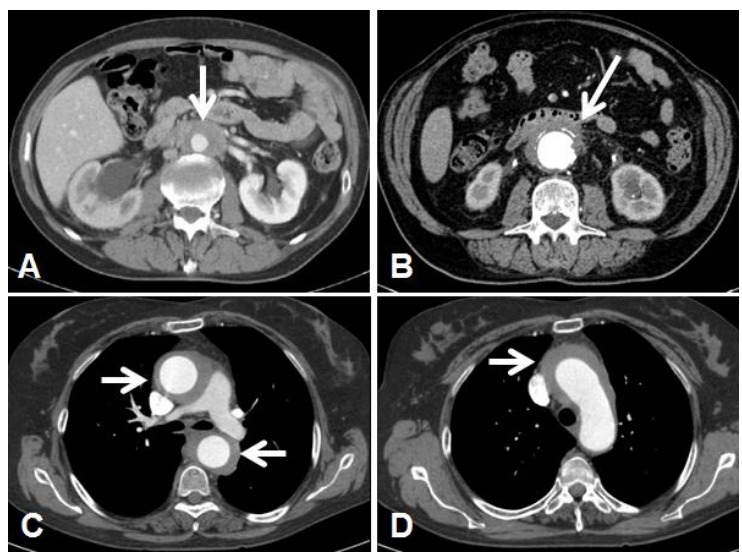

Figure 3. CT findings in periaortitis. The images show the CT appearance of periaortitis with typical localization (A), where the soft-tissue mass (arrow) surrounds the anterior and lateral sides of the abdominal aorta, spreads to the right ureter and causes hydronephrosis. CT appearance of peri-aneurysmal periaortitis (B): the fibro-inflammatory tissue encircles a dilated abdominal aorta (arrow). CT appearance of thoracic periaortitis (C, D). The perivascular tissue surrounds the ascending thoracic aorta (C, upper arrow), the aortic arch (D, arrow) and the descending thoracic aorta (C, lower arrow).

Periaortitis is a rare disease and data about its epidemiology are limited to idiopathic RPF and IAAAs. The incidence of idiopathic RPF is 0.1-1.3 per 100,000 person-years and its prevalence 1.4/100,000 inhabitants [58, 59]. IAAAs represent 4-10% of all abdominal aortic aneurysms [60]. The mean age at onset is 50-60 years [61], although rarely cases have been

reported in pediatric patients [62]. Men are affected two to three times more often than women and this ratio is higher in the aneurysmal forms [58].

Pathologic changes in periaortitis involve both the aortic wall and the surrounding soft tissues. The typical macroscopic appearance of periaortitis is that of a greyish mass infiltrating the retroperitoneal tissue surrounding the abdominal aorta, the iliac arteries and, in most cases, the inferior vena cava and the ureters [63]. The mass usually develops between the origin of the renal arteries and the pelvic brim. In some instances, periaortitis shows atypical localizations, which might be peri-duodenal, peri-pancreatic, pelvic, presacral, peri-ureteral or peri-renal and not characterized by involvement of the periaortic space. These cases are thought to have a different pathogenesis.

Microscopic examination reveals the presence of two components: a fibrous tissue and an inflammatory infiltrate [20]. The fibrous component comprises fibroblasts that show signs of activation and transition into myofibroblasts (α-smooth muscle actin expression) and produce an extracellular matrix composed of type I collagen fibers organized in thick irregular bundles. The inflammatory infiltrate consists of numerous lymphocytes, plasma cells, macrophages and scattered eosinophils. The inflammatory cells are interspersed within the collagen bundles (diffuse pattern), but also organized in nodular aggregates, usually around small vessels (perivascular nodular pattern). These aggregates have a B-cell core surrounded by T cells, which are predominantly $CD4^+$. In some cases, these lymphoid follicles have the structure of germinal centers, which is a sign of ectopic lymphoneogenesis, thus proving the presence of a highly structured immune-mediated/autoimmune response.

The aortic wall shows intimal atherosclerosis, medial thinning and adventitial inflammation and fibrosis. The composition of the inflammatory infiltrate in the aortic adventitia is similar to that of the retroperitoneal one. When the pattern is arranged in nodular aggregates, these are usually centered on the adventitial *vasa vasorum* which can show signs of vasculitis [64].

The pathogenesis of periaortitis is still unclear. The theory proposed by Parums and Mitchinson suggests that it is due to a local inflammatory reaction against antigens localized in the atherosclerotic plaques of the aorta such as oxidized low-density lipoproteins or ceroid [65, 66]. These antigens would be presented by plaque macrophages to B and T lymphocytes residing in the adventitia, where they would elicit a fibro-inflammatory response inducing lymphocyte activation and immunoglobulin production. This theory, however, cannot explain the presence of constitutional symptoms and the increase in acute phase reactant levels in patients with periaortitis, and the frequent associations with autoimmune or fibro-inflammatory diseases involving other organs. Additionally, periaortitis may affect patients without atherosclerotic lesions and involve vascular territories/segments spared by atherosclerosis [67]. Recently, it has been proposed that periaortitis may actually be a systemic autoimmune disease rather than the result of a local inflammatory reaction [64]. This theory is supported by similarities to systemic LLV, such as GCA and TA: the inflammatory process starts in the adventitial layer leading to perivascular infiltrates surrounding aortic *vasa vasorum*. Thus, it cannot be excluded that periarotitis originates as a primary aortitis which subsequently induces a fibro-inflammatory reaction into the periaortic space [3].

The pathogenesis of the disease is probably multifactorial, recognizing genetic, environmental and immune-mediated determinants. The role of genetic factors is demonstrated by the association between periaortitis and the HLA class II allele HLA-DRB1*03, a marker

of autoimmune diseases such as SLE, type 1 diabetes, autoimmune thyroiditis and myasthenia gravis [68].

A more recent study also describes an increased susceptibility to the aneurysmal forms of periaortitis in patients carrying the Δ32 polymorphism of the *CCR5* gene [69]. CCR5 is expressed on many immune cells, particularly Th1 cells, and acts by binding to different chemokines, including RANTES, MIP-1a and MIP-1b. The *CCR5*Δ32 polymorphism creates a truncated, nonfunctional receptor and probably shifts the immune response toward a Th2 pattern.

Among environmental agents, cigarette smoking and asbestos exposure are significantly associated with an increased risk of developing the disease. Interestingly, smoking and asbestos had a multiplicative effect on disease risk, with an odds ratio of 12.04 (95% confidence interval, 4.32 to 38.28) in co-exposed subjects [70]. The role of other environmental or infectious agents remains elusive.

The immunopathogenic model of periaortitis is based on the hypothesis that the disease is antigen-driven, although the triggering antigens are still unknown. Based on the available experimental evidence, it can be postulated that antigen-presenting cells present such hypothetical antigens to $CD4^+$ T cells within the aortic wall, probably in the adventitia. $CD4^+$ T cells expand, secrete IL-6 [71], which enhances the production of acute-phase proteins and promotes the activation of B cells and fibroblasts. $CD4^+$ T cells also secrete Th2 cytokines such as IL-4, IL-10 and IL-13, which induce B-cell expansion and maturation into plasma cells producing, in a fraction of cases, IgG4. Lymphoid cells also release eotaxin-1 (also known as CCL11), which drives tissue infiltration by eosinophils and mast cells, whose products induce fibroblast activation [72]. Once activated, fibroblasts mature into myofibroblasts and secrete collagen, promoting fibrosis. The pathogenic importance of IL-6 and of B cells was confirmed in vivo by the efficacy of therapies targeting selectively the IL-6 receptor (tocilizumab) and the B-cell marker CD20 (rituximab) [71, 73].

The clinical presentation of periaortitis includes two types of manifestations: localized, due to the compressive effects of the retroperitoneal mass, and systemic, related to the inflammatory nature of the disease. The more frequent localized symptom, present in about 80% of the patients, is side, back or abdominal pain. It is usually described as persistent and dull, not exacerbated by movement or palpation; it transiently responds to nonsteroidal anti-inflammatory drugs and, in cases of ureteral involvement, it can be colic-like [3]. Ureteral involvement is the most frequent complication and can be unilateral or bilateral. In cases with unilateral involvement, ureteral obstruction can also be asymptomatic for a long time and, at diagnosis, these patients present with renal hypoplasia/atrophy, whose frequency is estimated to be up to 30%. However, most cases are symptomatic and bilateral involvement usually leads to acute renal failure. Other urologic manifestations are frequent: they range from testicular pain, often accompanied by hydrocele and/or varicocele due to spermatic vein encasement by periaortitis, to retrograde ejaculation and erectile dysfunction [20]. The extrinsic compression of retroperitoneal lymphatic vessels and veins can be the cause of lower extremity edema and deep vein thrombosis. Claudication and intestinal ischemia are less common. Systemic symptoms include fatigue, weight loss, anorexia, sleep disturbances and low-grade fever [3].

Periaortitis can affect not only the lower abdominal aorta and the iliac arteries but also other vascular segments. This may suggest that in such cases, periaortitis actually represents a primary, diffuse inflammatory disease of the aorta and its major branches (Figure 3) [5]. In

1970, Mitchinson described for the first time the presence of mild inflammation and fibrosis in the adventitial layer of the thoracic aorta in autopsy studies performed on patients with abdominal periaotitis [4]. Subsequent reports have also documented the involvement of coronary arteries [57], renal arteries [74], and celiac axis, superior and inferior mesenteric arteries [75].

A recent study performed in a large cohort of patients showed that, in one third of cases, periaortitis might also affect the thoracic aorta and the epiaortic arteries [5]. The perivascular tissue may develop around the ascending aorta, the aortic arch, the descending aorta and the origin of epiaortic arteries. Three main patterns can be observed: periaortitis with thoracic aorta aneurysm, thoracic periaortitis without aneurysm and thoracic aorta aneurysm without periaortitis [5]. Histology of the thoracic tissue is definitely similar to that found in abdominal periaortitis. The pathological lesions involve the adventitia and the periadventitial tissue and consist of a fibrous component and a chronic inflammatory infiltrate comprising lymphocytes, histiocytes, plasma cells, and eosinophils.

The observation that the thoracic aorta is usually spared by atherosclerosis strongly supports the hypothesis that, when periaortitis develops, it is a primary immune-mediated process [76]. The clinical presentation of thoracic involvement in periaortitis includes specific symptoms such as laryngeal nerve paralysis, dry cough, upper limb claudication and paresthesias; however, in about 85% of cases it is asymptomatic. Interestingly, the comparison of demographic and clinical characteristics of patients with and without thoracic involvement revealed that these subgroups were different. Patients with thoracic involvement had a significantly higher female prevalence, a greater age at disease onset, a higher prevalence of systemic symptoms and of back or abdominal pain [5].

The female prevalence and the advanced age in patients with thoracic aorta involvement is a feature shared by GCA, which often affects not only the epiaortic tree but also the thoracic aorta. Indeed, GCA is characterized by only mild periaortic thickening does not cause obstructive uropathy, while periaortitis, on the other hand, does not lead to typical GCA-related cranial symptoms. However, the differential diagnosis between GCA and periaortitis may become more challenging when patients present with non-specific systemic symptoms, including fever of unknown origin, and lack clinical manifestations specific for either disease.

Periaortitis may be associated with a large variety of autoimmune conditions. This observation underlines the relevance of autoimmune mechanisms in the pathogenesis of the disease. Hashimoto's thyroiditis is the most commonly associated autoimmune disorder; it may arise together with periaortitis, but it can also precede or follow periaortitis diagnosis. Overall, it has been reported that 25% of patients with periaortitis develop hypothyroidism after a median follow-up of 45 months [77]. Other associated conditions are AAV, particularly granulomatosis with polyangiitis, membranous nephropathy, SLE, rheumatoid arthritis, uveitis and psoriasis [3].

IgG4-Related Periaortitis

Periaortitis may also be a manifestation of IgG4-RD. Histological examination is mandatory to differentiate IgG4-related and –unrelated forms. However, the coexistence of other clinical conditions belonging to the spectrum of IgG4-RD may help classify periaortitis as IgG4-related [78].

Periaortitis (particularly the abdominal form) is reported among the most frequent manifestations of IgG4-RD in different studies, even if its prevalence remains quite variable, ranging from 11% to 30% [79-82]. It appears that environmental factors influence the different organ involvements, since periaortitis is more frequent in Western cohorts, whereas in Asian countries extra-vascular lesions are more common [82].

IgG4-related periaortitis may differ from IgG4-unrelated forms in terms of microscopic findings, whereas the macroscopic ones are very similar. In particular, there were no significant differences in disease localization and characteristics when CT or MRI findings were compared [83, 84]. IgG4-related IAAAs (which are considered perianeurysmal forms of periaortitis) are frequently saccular, as the IgG4-unrelated ones, but the former show a more prominent thickening of the wall due to the fibrotic tissue which is also adherent to neighboring structures, leading to an apparently lower risk of rupture [85]. IgG4-related periaortitis is distinguishable from its IgG4-unrelated counterpart especially for the organization of the fibrotic tissue, which is storiform in the former, resembling the spokes of a cartwheel. IgG4-unrelated forms usually do not show obliterative phlebitis, and the inflammatory infiltrate is less dense and not markedly enriched with $IgG4^+$ plasma cells and eosinophils [83]. However, these differences may be only slight, and it must be emphasized that the background histologic appearance of IgG4-related and -unrelated forms is often very similar, thus leading to the concept that these two entities may represent different ends of the same spectrum.

From a clinical standpoint, there are no substantial differences, except for a male predominance in IgG4-related forms [86]. The clinical manifestations of both IgG4-related and -unrelated periaortitis are comparable, with flank and abdominal pain being the most common presenting symptom. However, it must always be remembered that IgG4-related forms are more commonly associated with extra-retroperitoneal manifestations of IgG4-RD; this may help clarify the clinical picture of the disease.

DIAGNOSIS

The differential diagnosis among different forms of inflammatory aortitis and periaortitis is challenging, and histological examination is often required to have a clear definition of the disease. The particular site of inflammation makes it difficult to perform biopsies, unless aortic or retroperitoneal/ureteral surgery is required. Therefore, in most cases the diagnosis is based on laboratory tests and imaging studies, along with clinical presentation.

Aortitis in Large-Vessel Vasculitides

Both GCA and TA often manifest with typical symptoms, which render them more easily recognizable than other cases of apparently idiopathic aortitis. Cranial symptoms (e.g., jaw claudication, scalp tenderness and visual alterations) usually occur in GCA, whereas TA may manifest with signs and symptoms related to vascular stenosis (e.g., absence of pulses, bruits,

limb claudication) [87]. Acute-phase reactants, namely C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are high in most cases of GCA whereas they are frequently normal in TA, which is in line with the clinical presentation of TA, whose clinical manifestations often arise in a late, "fibrotic" stage.

Imaging studies, such as ultrasonography (US), angio-CT and angio-MRI have become crucial for the diagnosis of GCA and TA: mural thickening and enhancement are typical findings [88]. CT and MRI also show some disease-related aspects that are essential for the differential diagnosis between aortitis and periaortitis, since aortitis (also that occurring in GCA or TA) does not have the thick periaortic cuff that characterizes CP and does not lead to encasement of neighboring structures such as ureters and inferior vena cava [76]. Over the last few years, ^{18}F-FDG PET (Figure 4) has become part of the diagnostic armamentarium of LVVs, and has allowed detection of aortic involvement. The advantage of PET is that it is a whole-body imaging study, able to reveal other FDG-avid lesions, and that it provides a measurable degree of FDG uptake by means of the maximal standardized uptake value (SUVmax) that can be useful to monitor vascular inflammation. Despite its widespread use in patients with LVV, ^{18}F-FDG PET still has an uncertain role as predictor of response or as disease-monitoring tool [88].

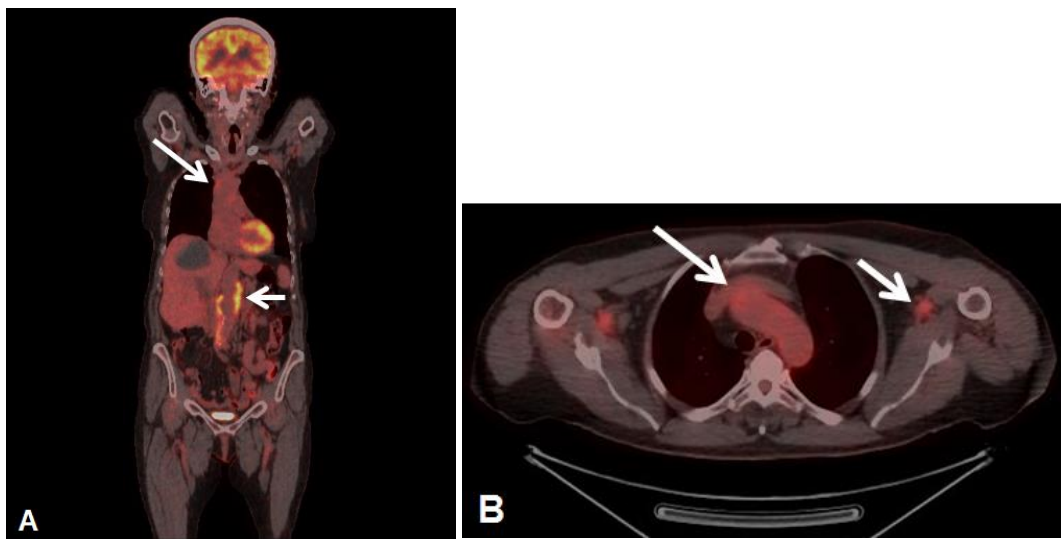

Figure 4. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) findings in patients with periaortitis and/or aortitis. (A) ^{18}F-FDG PET findings in a patient with abdominal periaortitis and thoracic aortitis. The scans show intense FDG uptake at the level of the thoracic aorta (long arrow) and of the abdominal aorta (short arrow). (B) ^{18}F-FDG PET findings in a patient with giant cell arteritis. The scans show intense FDG uptake at the level of the aortic arch (long arrow) and of the axillary arteries (short arrow).

In patients with GCA, temporal artery biopsy remains the principal diagnostic examination; however, it must be recognized that a fraction of GCA patients may lack temporal artery involvement, and this is particularly the case of those with diffuse involvement of large arteries including the aorta. In sum, the diagnosis of GCA and TA, and consequently of aortic involvement in these conditions, relies on the integration of clinical examination, laboratory tests, imaging studies and, particularly in the case of GCA, vascular (temporal artery) biopsy.

Isolated Aortitis

Isolated aortitis is by definition a vasculitis confined to the aorta, in the absence of symptoms related to other systemic diseases [24]. It tends to affect mostly the thoracic aorta in its ascending part and usually presents as a thoracic aortic aneurysm [42]. It is often an incidental finding that can be diagnosed in two distinct settings. Traditionally and most commonly, the disorder is diagnosed pathologically following surgical resection of an aortic segment for aneurysm or dissection, and the patient is clinically found to have no other signs or symptoms of vasculitis. Isolated aortitis can also be identified radiologically, most often by CT or MRI, as an isolated aneurysm or as wall thickening limited to one segment of the aorta [46]. The absence of a diffuse atherosclerotic disease or of common risk factors for atherosclerosis should heighten suspicion of isolated aortitis in patients showing the above abnormalities on CT or MRI.

Once imaging studies disclose an apparently isolated aortitis, and the patient has no associated rheumatologic diseases, it is mandatory to exclude infectious causes (Table 1); laboratory tests can be useful in this setting to rule out particularly syphilis and tuberculosis and, in patients with systemic infections or in immunocompromised subjects, fungal and bacterial etiologies. Finally, the diagnostic work-up of an isolated aortitis should also consider the exclusion of IgG4-RD, of which aortitis can also be the sole manifestation. Therefore, in the absence of a biopsy, testing serum IgG4 levels and searching for other sites potentially involved by the disease is recommended (see below).

Periaortitis

The diagnosis of periaortitis is usually based on imaging studies and requires histological confirmation only in a small proportion of patients. Indeed, the clinical signs and symptoms at disease presentation, as well as the laboratory tests are quite non-specific. Ultrasound is usually performed at onset and may detect both aneurysmal aortic dilatation and periaortitis as a hypoechoic periaortic halo. It also allows the detection of hydronephrosis; such US findings are crucial both at diagnosis and during the follow-up.

On CT, periaortitis appears as a homogeneous, plaque-like tissue, isodense to muscle, which develops around the anterolateral sides of the abdominal aorta. In the retroperitoneum, it may encase the ureters, drawing them medially, and also cause inferior vena cava compression [67]. On MRI, the inflammatory aortic/periaortic thickening and the tissue surrounding the vessels are seen as hypointense on T1-weighted images, while they are hyperintense on T2-weighted images during active disease phases, due to the presence of edema and hypercellularity. Contrast-enhancement, both on CT and MRI, is more pronounced during the early disease stages [89].

^{18}F-FDG PET is increasingly used for the diagnosis of periaortitis, although its specificity is low given that forms of periaortitis secondary to infections or neoplasms may also be FDG-avid. However, ^{18}F-FDG PET has the advantage of being able to provide whole-body imaging of metabolically active lesions, thus allowing both the detection of other vascular segments (Figure 4) involved by periaortitis and of occult neoplastic or infectious foci. In patients with multifocal fibroinflammatory conditions (e.g., periaortitis and mediastinal fibrosis), ^{18}F-FDG PET can be positive at different sites [90]. Interestingly, ^{18}F-FDG PET recently proved able to

predict response to therapy, since metabolically inactive periaortitis is less likely to respond to glucocorticoid treatment than totally inactive lesions. However, no significant differences in response to treatment were detected among patients with different degrees of FDG uptake [91].

Periaortic retroperitoneal biopsy is recommended in all cases of difficult interpretation, especially when there is suspicion of infections or malignancies, and in patients not responsive to treatment. Patients with atypical presentations usually undergo diagnostic biopsies.

Aortitis and Periaortitis in IgG4-related Disease

As reported above, aortitis and periaortitis may arise in the context of IgG4-RD. In 2008, criteria were proposed for the diagnosis of IgG4-RD [92]. They include: i) typical organ involvement (pseudotumoral lesions) with organ swelling and/or dysfunction; ii) histologically compatible features and immunohistochemical evidence of $IgG4^+/IgG^+$ plasma cells >40% together with $IgG4^+$ plasma cells >10/hpf; iii) serum IgG4 level >135 mg/dl. The diagnosis is considered to be "definite" when all three criteria are fulfilled, "probable" when i) and ii) are met, and "possible" when i) and iii) are met and histopathology is either unavailable or non-diagnostic. These criteria are widely used, even if their specificity and sensitivity still warrant validation.

It has been reported that in aortic and periaortic tissue, immune staining findings might be inconsistent with a diagnosis of IgG4-RD, even on a background where the three main characteristics (storiform fibrosis, obliterative phlebitis and lymphoplasmacytic infiltrate) are represented [93]. In these cases the diagnosis of IgG4-RD relied upon morphological findings, along with clinical and imaging data.

Laboratory abnormalities that can be found in IgG4-RD include elevation of acute- phase reactants, especially in cases with multifocal involvement, and polyclonal hypergammaglobulinemia. Peripheral eosinophilia and serum IgE increase may be encountered in about a third of cases. Positive ANCA with specificity for either myeloperoxidase or proteinase 3 may also occur, indeed overlap forms of IgG4-RD and AAV have recently been described [94].

The same imaging studies used for the diagnosis and follow-up of aortitis and periaortitis not associated with other IgG4-related lesions are employed for cases arising in the context of IgG4-RD. Thus, US, CT or MRI and ^{18}F-FDG PET may all be helpful both at diagnosis and during the follow-up to detect the major involved sites and to assess their metabolic activity, although the FDG-avidity of the different IgG4-related lesions varies widely. Typical findings are tumor-like lesions, which may be diffuse, leading to an enlargement of the involved organ, or focal. These aspects make IgG4-RD a mimicker of malignancies: in these cases biopsy is the only way to differentiate them.

Other Diseases with Periaortic Involvement

Periaortic infiltration may be observed in other disorders (Table 1) that should be excluded before arriving at the diagnosis of periaortitis, whether IgG4-related or not. Unfortunately, an increase in serum IgG4 has little value in the differential diagnosis between IgG4-related cases and secondary forms.

Malignancies may resemble periaortitis [95] and in these cases imaging studies play a fundamental role. Indeed, on CT and MRI neoplastic forms appear to be inhomogeneous and lobulated, more adherent to surrounding organs with no clear cleavage site, and often extend above the origin of the renal arteries, unlike typical periaortitis [96, 97]. In addition, periaortitis is usually located anterolateral to the aorta, whereas neoplastic masses are also anterior to the spine and tend to displace the aorta anteriorly.[96,97] Moreover, malignancies may also infiltrate muscles and erode bones [98].

One large retrospective study evaluated the utility of ^{18}F-FDG PET in differentiating neoplastic forms from idiopathic/IgG4-related ones [99]. It was reported that malignancies could have a greater FDG avidity; moreover, PET allows detection of all neoplastic sites, if the neoplasm itself is FDG-avid.

A rare cause of aortic wall and periaortic involvement is ECD, a non-Langerhans cell histiocytosis with predilection for long bones, cardiovascular system, central nervous system, and endocrine glands [100]. Interestingly, ECD can involve both the thoracic and abdominal aorta, giving rise to an aspect usually reported as "coated aorta." On imaging ECD should be suspected when the fibrous tissue surrounds the kidneys, showing the typical finding of "hairy kidneys" [101]. In these cases, a biopsy is recommended, indeed morphological and immune staining features are very different in ECD versus idiopathic periaortitis. Typical findings in ECD include tissue infiltration by $CD68^+$ $CD1a^-$ ''foamy'' histiocytes, along with diffuse lymphoplasmacytic infiltrates and abundant fibrosis [102].

The conditions (Table 1) that can result in secondary forms of periaortic disease include drugs, surgical procedures, radiotherapy and trauma [98, 103], that may be excluded by a careful review of the patient's medical history.

PRINCIPLES OF TREATMENT

A detailed review of the treatment of all causes of aortitis and periaortitis is beyond the scope of the present chapter. However, it is important to outline some aspects. The exclusion of neoplastic, infectious and other proliferative (e.g., ECD) causes of aortic disease have obvious therapeutic implications since most of the idiopathic forms of aortitis and periaortis are treated with glucocorticoid and immunosuppressive therapies. It is also important to carefully differentiate aortitis/periaortitis occurring in the setting either of LVV, systemic connective tissue or small-vessel vasculitic syndromes, or fibro-inflammatory disorders including IgG4-RD. LVVs are treated with glucocorticoids and or other conventional immunosuppressants, and only recently biologic therapies (particularly the anti-IL6 receptor antibody tocilizumab) have been introduced for the management of GCA [104]. The treatment of aortitis associated with systemic connective tissue diseases as well as systemic small-vessel vasculitis varies depending on the underlying condition; generally, the occurrence of aortitis is considered a severe complication, requiring aggressive immunosuppression. Idiopathic aortitis and periaortitis, whether isolated or in the context of IgG4-RD, are generally corticosteroid-sensitive, and therefore corticosteroids should be considered first-line treatment. In relapsing or difficult-to-treat cases, rituximab has recently proved effective [73, 105]. Aortitis and periaortitis may lead to aneurysmal dilatation of both the abdominal and thoracic aorta that

requires evaluation by vascular surgeons as prompt treatment using endovascular or surgical techniques may prevent life-threatening complications.

CONCLUSION

Inflammatory aortitis and periaortitis are inflammatory diseases of varying etiology, and recognition of them is critical for optimal management. Imaging studies such as CT, MRI, and ^{18}F-FDG-PET are widely used for their management and follow-up. Diagnostic biopsies are required in a fraction of cases, with histological patterns that may range from lympho-plasmacytic to granulomatous and suppurative presentations. The treatment will differ depending on the cause, with isolated cases and those suffering from systemic immune-mediated conditions, managed with a combinations of corticosteroids and immunosuppressive drugs. Surgical evaluation may be required in cases presenting with significant aneurysmal dilatation, or with less common complications such as dissection and rupture.

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Chapter 15

SYSTEMIC VASCULITIS AND THE LUNG

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ABSTRACT

The lungs are affected by systemic vasculitides with differing frequency, characteristics, and severity, depending on the specific vasculitis syndrome. Alveolar hemorrhage, nodules, interstitial disease and airway stenoses are the most common lung manifestations of antineutrophil cytoplasm antibody-associated vasculitides. Pulmonary vascular involvement occurs in Behçet disease and Takayasu arteritis, where it manifests as pulmonary artery aneurysm, thrombosis and stenosis. Lung involvement can occur along with other systemic features of vasculitis syndromes but can also be isolated, which leads to diagnostic and therapeutic challenges. Lung infection, pulmonary edema due to cardiac failure or renal impairment, cancer, and drug-induced lung toxicity are potential mimickers of pulmonary involvement in vasculitis. Once a diagnosis has been made, the management of lung disease in patients with vasculitis includes systemic and local therapies.

Keywords: vasculitis, lung, ANCA, AAV

INTRODUCTION

The lungs are affected by systemic vasculitides with differing frequency, characteristics and severity, which vary by type of vasculitis. There can be involvement of the airways, lung parenchyma, intra-parenchymal proximal pulmonary arteries and veins, capillary vessels or pleura. These manifestations can be clinically silent or life-threatening, as with diffuse alveolar

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hemorrhage. They can occur with other systemic manifestations of vasculitis or, less commonly, in isolation, which creates diagnostic challenges. Treatment should be tailored to the type and severity of the underlying vasculitic process and may combine systemic and local therapies. Lung infection, pulmonary edema due to cardiac failure or renal failure, cancer, and drug-induced lung toxicity can occur in patients with vasculitis.

This chapter focuses on the lung manifestations of systemic vasculitides, as defined by the Chapel Hill Consensus Conference (CHCC) [1], and prophylactic measures to limit the risk of secondary complications.

MAIN LUNG MANIFESTATIONS IN SYSTEMIC VASCULITIS

A broad spectrum of lung manifestations may occur with systemic vasculitis and include alveolar haemorrhage, lung nodules, interstitial disease, airway stenoses, fibrosis, pleural effusion and pneumothorax. These may occur in small-vessel (SVV) antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) (granulomatosis with polyangiitis [GPA], eosinophilic granulomatosis with polyangiitis [EGPA] and microscopic polyangiitis [MPA]). Lung vessel involvement manifests as pulmonary artery aneurysms, thrombosis and stenoses in the variable vessel vasculitis (VVV) Behçet disease (BD) and the large-vessel vasculitis (LVV) Takayasu arteritis (TAK). The risk of pulmonary embolism increases during disease flares in AAV.

Airway Disease

Nasal, sinus, mouth, throat and the upper airways are commonly involved in GPA leading to chronic erosive sinusitis, crusting rhinitis, nasal septum perforation and subglottic stenosis. Allergic rhinosinusitis, nasal polyposis, lower large- and small-airway disease (asthma) are manifestations associated with EGPA. Tracheo-bronchial stenosis is more characteristic of GPA but can also occur in EGPA.

Tracheo-Bronchial Stenosis

Tracheal and bronchial involvement occurs in up to 70% of patients with GPA. Stenoses of the main bronchus, seen more often the left along the first branches, are observed in less than 10% of patients [2-5]. Subglottic stenosis is the classic large airway lesion and occurs in 7% to 15% of patients with GPA [6-8]. It may cause dysphonia. Like subglottic stenosis, tracheal and bronchial stenoses cause dyspnea, with or without stridor and wheezing. Large airway obstruction occasionally requires emergency dilatation, often combined with local injections of corticosteroids, or tracheostomy. Complete bronchial occlusion can cause partial or complete collapse of the lung distally. Endobronchial lesions can cause hemoptysis if there is mucosal ulceration and erosion of an underlying vessel. Such tracheal and bronchial lesions are best studied with a combination of chest computed tomography (CT) (Figure 1) and direct visualization with fiber-optic bronchoscopy because of possible multifocal involvement with strictures, ulceration and granulomatous endobronchial lesions. These airway lesions can parallel extra-respiratory manifestations of GPA or may progress despite adequate control of the systemic vasculitis.

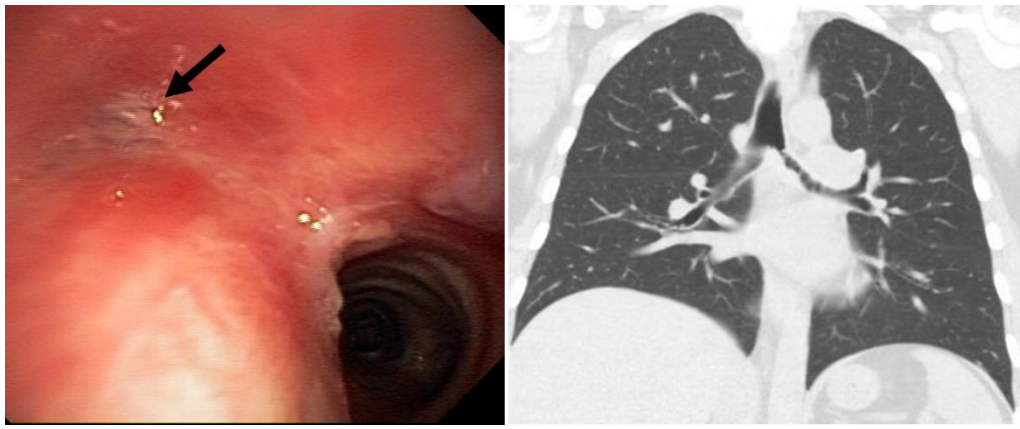

Figure 1. Left main bronchial stenosis, visible on bronchoscopy (left image), with beading appearance on axial CT scan (right image).

Asthma

Asthma is a defining feature of EGPA [9, 10] and usually develops before the onset of systemic manifestations of vasculitis. 90% of affected patients have asthma at EGPA diagnosis, but it rarely develops after the initial diagnosis. The interval between onset of asthma and EGPA diagnosis is about 9 years, on average, with a mean age at onset of asthma of 32 years, which emphasizes its relatively late-onset compared to usual asthma. Asthma typically increases in severity in the months to years before the onset of systemic manifestations of vasculitis and persists when the initial vasculitic manifestations occur, even after adequate control of the underlying vasculitis. Many patients require long-term, low-dose prednisone and inhaled corticosteroids for control of airway symptoms despite remission of the systemic vasculitis. Whether the characteristics of vasculitis-associated asthma differ from idiopathic and allergic asthma is not well understood [11]. Spirometric evaluation reveals an obstructive pattern, but no clinical findings or functional tests distinguish among these various causes of asthma. As a rule, late-onset asthma, especially if it is difficult to control and increasing blood eosinophilia should prompt consideration of EGPA.

Parenchymal Disease

Vasculitis-related parenchymal lung disease is common in GPA, MPA, EGPA, and anti-glomerular basement membrane (anti-GBM) disease but also occurs in the LVV giant cell arteritis (GCA) and the SVV immune complex (IC) disorder, Henoch-Schonlein purpura/IgA vasculitis (HSP/IgAV) [12].

Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a classical manifestation of AAV and occurs in 12% to 32% of patients with MPA and in 8% to 30% of those with GPA, 60% to 80% of those with anti-GBM disease (or Goodpasture syndrome), and in less than 10% and 2% with EGPA and IgAV, respectively. The extent and severity of pulmonary capillaritis varies from clinically silent to shortness of breath and subacute to acute fulminant hemoptysis and respiratory distress

syndrome. Hemoptysis is absent in up to one third of patients with alveolar hemorrhage, which then is diagnosed by the presence of anemia, patchy ground-glass opacities on chest CT (Figure 2), and persistently bloody returns on broncho-alveolar lavage. In addition to ground-glass opacities, chest CT may reveal alveolar consolidation and localized rather than diffuse or patchy infiltrates. CO diffusion capacity is usually increased when there is blood in the alveoli, but pulmonary function testing (PFT) is rarely indicated or performed in patients with frank alveolar hemorrhage. DAH is frequently associated with renal disease in GPA, MPA and anti-GBM disease and may be part of a pulmonary–renal syndrome. When alveolar hemorrhage occurs as an isolated event or is associated with non-specific constitutional symptoms, diagnoses other than vasculitis should be considered (Table 1) [13, 14]. Hemoptysis from lung capillaritis should be differentiated from other vasculitic causes of bleeding such as submucosal vessel rupture in patients with endobronchial GPA mucosal ulceration or rupture of larger-vessel aneurysms in patients with TAK and BD.

Table 1. Main causes of alveolar hemorrhage

Disease or disease group			Comments
Lung parenchymal disease/inflammation			
	Small vessel vasculitis	ANCA associated vasculitis	Mainly GPA and MPA (rarely EGPA)
		Anti-GBM disease	
		Immune-complex mediated vasculitides	Rarely IgA vasculitis (exceptionally, cryoglobulinemic vasculitis)
		Isolated (idiopathic) lung capillaritis	
	Other systemic diseases	Systemic lupus erythematosus	
		Antiphospholipid syndrome	
		Rheumatoid arthritis	Through lung disease and/or associated vasculitis
		Systemic scleroderma	Through lung disease and/or associated vasculitis and/or veno-occlusive disease
		Polymyositis/dermatomyositis	
		Sarcoidosis	
	Drug-related lung toxicity	Propylthiouracil, diphenylhydantoin, amiodarone, mitomycin, D-penicillamine, methotrexate, gold, haloperidol, nitrofurantoin all-trans-retinoic acid, bleomycin	Most can cause interstitial lung infiltrates rather than diffuse alveolar hemorrhage
	Toxic and irritant inhalation	Trimellitic anhydride, isocyanates, crack cocaine, pesticides, detergents	
	Miscellaneous	Lung-graft rejection	
	Infections	Human immunodeficiency virus infection, infective endocarditis, cytomegalovirus infection, herpes simplex virus infection, hantavirus infection, invasive aspergillosis, legionellosis, mycoplasmosis, leptospirosis, other bacterial pneumoniae	
Not primarily due to lung parenchymal disease/inflammation			
	Lung vessel and/or aneurysm rupture	Multiple causes: traumas, vascular malformation or fibrodysplasia, vasculitis-related aneurysms (Takayasu arteritis, Behcet's disease), lung abscess/cavity or bronchial lesions eroding nearby vessels, etc.	

Disease or disease group			Comments
	Hemostasis disorders	Thrombotic thrombocytopenic purpura and idiopathic thrombocytopenic purpura, anticoagulants, antiplatelet agents, thrombolytics; disseminated intravascular coagulation	Usually associated with another and underlying lung condition when causing diffuse alveolar hemorrhage
	Mitral stenosis and mitral regurgitation		
	Pulmonary veno-occlusive disease		
	Idiopathic pulmonary hemosiderosis		
	Pulmonary embolism		
	Malignant conditions	Lung cancer, pulmonary angiosarcoma, Kaposi sarcoma, multiple myeloma, acute promyelocytic leukemia	
	Other conditions/ miscellaneous	High-altitude pulmonary edema, barotrauma	
		Lymphangioleiomyomatosis	
		Pulmonary capillary hemangiomatosis	
		Lymphangiography	
		Tuberous sclerosis	

ANCA: antineutrophil cytoplasm antibody; EGPA: eosinophilic granulomatosis with polyangiitis; GBM: glomerular basement membrane; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

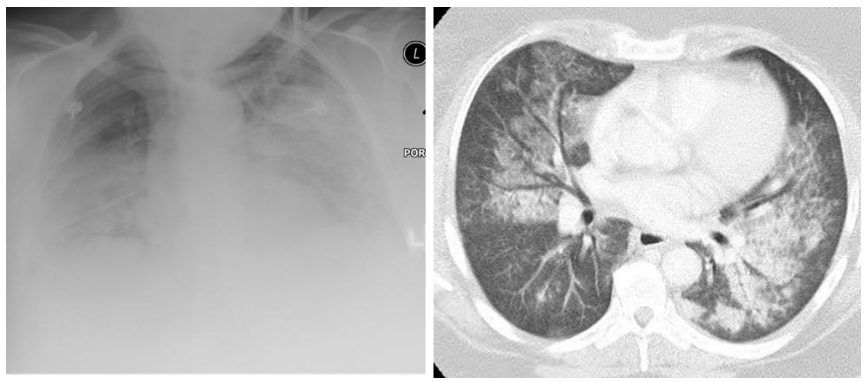

Figure 2. Diffuse alveolar hemorrhage in a patient with granulomatosis with polyangiitis (left: chest X-ray with diffuse infiltrate; right: diffuse ground-glass opacities and infiltrates on axial CT scan).

Nodules

Lung nodules are a classical feature of GPA but can also occur in EGPA [15]. They can be cavitated, single or multiple, and vary in size and location (Figures 3 and 4). No specific characteristics on chest CT differentiate them from malignancy; tuberculous, nocardial or *Burkholderia* species infections; or lymphomatoid granulomatosis and sarcoidosis (Table 2). Supra-infection of cavitating nodules, notably by *Aspergillus* species, can occur. Surgical tissue biopsy, wedge-resection and CT-guided needle aspiration of nodules in GPA may reveal non-caseating granulomatous and necrotizing inflammation [16-19]. Plain nodules can become cavitated as a result of central necrosis and evolve into nodular scars that persist beyond remission of vasculitis. They have been inconsistently associated with risks of relapse: over a follow-up of 8.8 years, the presence of cavitary nodules at diagnosis was identified as an independent predictor factor with 53% rate of relapse [20]. Non-active nodules at remission are more often plain than cavitated and smaller, measuring <15 mm in diameter [21].

Table 2. Main differential diagnoses of granulomatosis with polyangiitis with lung nodules

Other vasculitides			Comments
	Primary	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)	Lung nodules can occasionally occur
		Microscopic polyangiitis	Anecdotal cases with lung nodules
		Giant cell arteritis (temporal arteritis)	Anecdotal cases with lung nodules
		Henoch-Schonlein purpura	Anecdotal cases with lung nodules
	Secondary	Relapsing polychondritis	Few cases with lung nodules (possible overlapping diagnosis with GPA)
		Drug-induced (and/or hypersensitivity) vasculitis	Anecdotal cases with lung nodules
		Rheumatoid arthritis	Lung nodules can occasionally occur, with or without associated vasculitis
		Inflammatory bowel disease, systemic lupus erythematosus, systemic sclerosis, primary Sjogren syndrome, etc.	Rare cases with lung nodules
Granulomatous diseases			
	Lymphomatoid granulomatosis (Liebow)		Rare systemic angiodestructive lymphoproliferative disease, usually associated with chronic Epstein-Barr virus infection
	Nasal NK-cell lymphoma		
	Sarcoidosis		
	Berylliosis		
	Inflammatory bowel disease		Rare cases with lung nodules
Infections (not limiting list)			
	Tuberculosis		
	Histoplasmosis		
	Atypical mycobacterial infections		
	Blastomycosis, coccidioidomycosis, actinomycosis, cryptococcosis		
	Nocardiosis, Burkholderia cepacia infection		
	Secondary syphilis		
	Parasitic helminth infections (ascaridiasis, alveolar echinococcosis, paragonimiasis, Schistosoma mansoni, pulmonary dirofilariasis, larva migrans - toxocarosis)		Can cause lung cysts, potentially mimicking lung nodules
Cancers and hemopathies (not limiting list)			
	Lymphomas		
	Plasmacytoma		
	Carcinoid tumors		
	Lung cancer (all types)		
	Lung metastases		
Other/miscellaneous			
	Pulmonary amyloidosis Pulmonary pyoderma gangrenosum		Anecdotal cases with lung nodules
	Mineral oil (lipoid) pneumonia		
	Benign tumors	Fibroma, hamartoma, neurofibroma, blastoma, bronchial adenoma	
	Bronchogenic cysts		Can present like nodules
	Atelectasis (post-infection or -surgery)		Can present like nodules
	Anthracosilicosis		Lung nodules are usually small but can reach 1 cm in diameter and be coalescent in severe cases

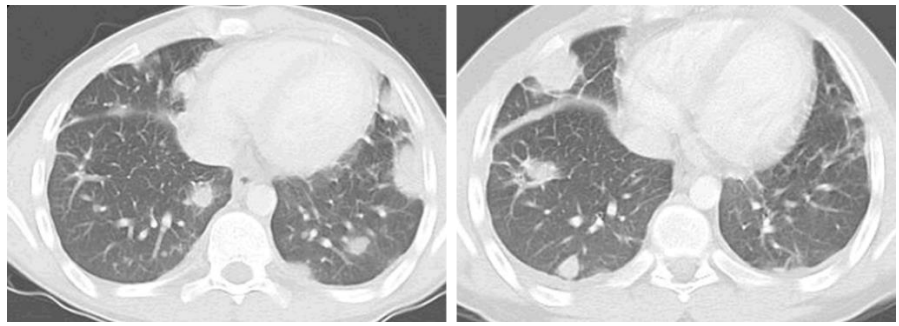

Figure 3. Multiple plain lung nodules in a patient with granulomatosis with polyangiitis (axial CT images).

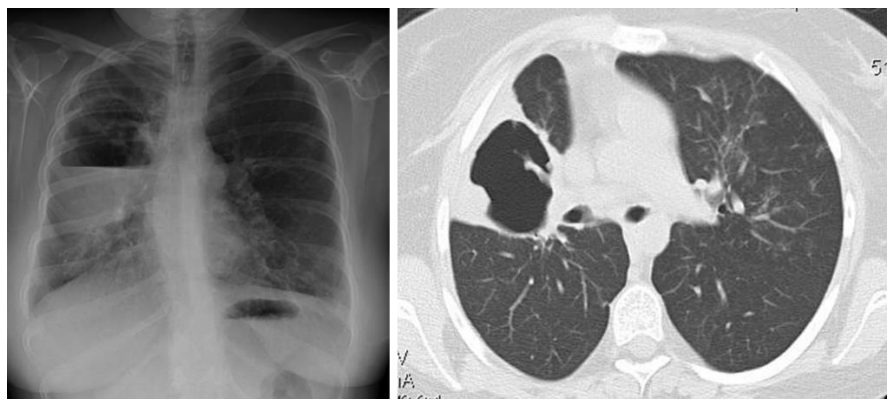

Figure 4. Large cavitation nodule in a patient with granulomatosis with polyangiitis (left: chest X-ray showing hydro-aeric cavity; right: same nodule on frontal CT scan, upper and aeric part of the nodule).

Eosinophilic Lung Infiltrates

Lung infiltrates, corresponding to eosinophilic pulmonary inflammation, occur in up to three quarters of patients with EGPA. On chest CT, they appear as patchy, multifocal, with peripheral ground-glass attenuation; uni-, or bilateral and symmetrical or asymmetrical; and sometimes as transient or migratory areas of consolidation (Figure 5). They may be associated with pleural effusions mimicking chronic eosinophilic pneumonia, although the latter presents most often with homogeneous and peripheral lung infiltrates. Broncho-alveolar lavage or thoracentesis can demonstrate the predominant eosinophilic nature of the abnormality, typical of EGPA, and exclude other diagnoses such as infection and alveolar hemorrhage [22].

Fibrosis

Fibrosis is increasingly recognized complication of AAV, mainly anti-MPO AAV. Most often the interstitial pneumonitis and fibrosis preferentially involves the lung bases (Figure 6). Interstitial lung disease (ILD) can either occur after onset or precede the onset of full vasculitis by years [23-25]. The pathogenic mechanism of ILD is not well understood but may relate to oxidative bursts of inflammatory cells triggered by ANCA, along with damage resulting from recurrent or chronic alveolar hemorrhage [26-28]. Usual interstitial pneumonia (UIP) is the most common radiologic pattern [25]. The mortality rate of pulmonary fibrosis with anti-MPO P-ANCA, mainly related to respiratory failure, is similar to that of idiopathic pulmonary

fibrosis and worse than ILD occurring with collagen vascular diseases without anti-MPO ANCA [24, 29].

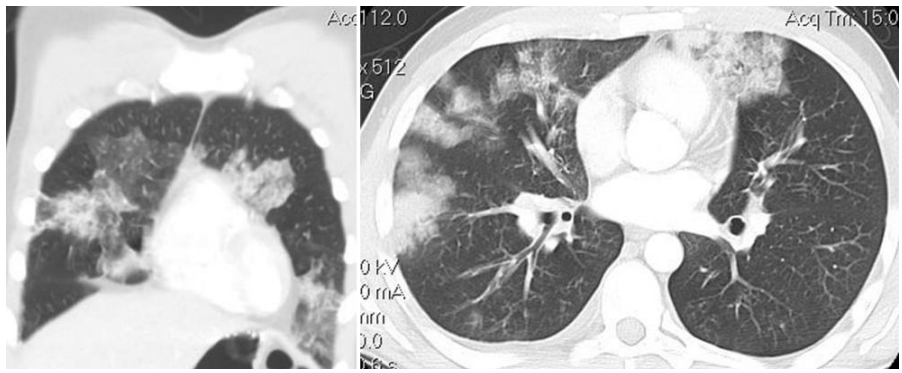

Figure 5. Patchy lung alveolar interstitial infiltrates in a patient with eosinophilic granulomatosis with polyangiitis (frontal and axial CT images).

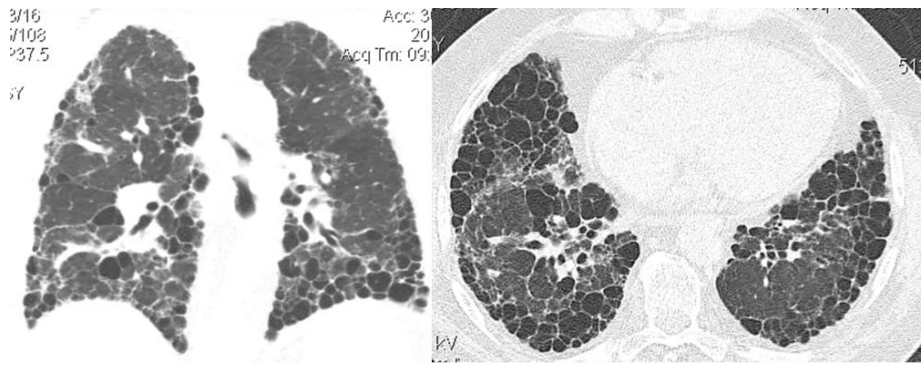

Figure 6. Massive lung fibrosis in a patient with anti-MPO-ANCA vasculitis in remission (frontal and axial CT images), with honeycombing appearance.

Non-Specific Pulmonary Consolidation

Pulmonary consolidation and infiltrates mimicking infectious pneumonia can be observed in GPA, MPA and EGPA. Diffuse interstitial lung infiltrates can be seen in GCA, TAK, IgAV, BD and cryoglobulinemic vasculitis (CV) [12, 30, 31]. ILD and alveolar hemorrhage due to pulmonary capillaritis can also occur in rheumatoid-associated vasculitis (RAV), or with systemic lupus erythematosus (SLE).

Pleural Effusion and Pneumothorax

Pleural effusions are common in EGPA and polyarteritis nodosa (PAN). They can be inflammatory or related to cardiac or renal failure. They may also be due to pulmonary embolism, which is more frequent during disease flares. Pneumo- and hydro-pneumothoraces can be caused by the outward progression of peripheral lung nodules that involve the pleura and cavitate, leading to development of bronchopleural fistula [32, 33].

Pulmonary Embolism

Patients with AAV and to a lesser extent, medium-vessel vasculitis (MVV) such as PAN, are at increased risk of venous thromboembolic events, including pulmonary embolism, during the active phase of the vasculitic disease [34, 35]. In BD, pulmonary embolism can be due to right ventricular thrombi related to increased tissue-factor expression, neutrophilic extracellular traps and neutrophil-derived micro-particles [36]. Anti-PR3-ANCA antibodies with dual reactivity to plasminogen and complementary PR3 may be pathogenic in thrombosis in GPA [37].

Pulmonary Artery Stenosis and Aneurysms

The pulmonary arteries are involved by the vasculitic process in LVV and BD and exceptionally in other vasculitides [38]. Stenoses and aneurysms of the main pulmonary arteries can occur (Figure 7). Dilations of single, multiple, unilateral and bilateral pulmonary and bronchial arteries occur in less than 5% of patients with BD referred to as Hughes-Stovin syndrome [39]. Affected patients are typically men with a history of thrombophlebitis. Pulmonary and bronchial artery aneurysms can rupture, thus leading to hemoptysis and internal haemorrhage, or demonstrate progressive occlusion with thrombosis.

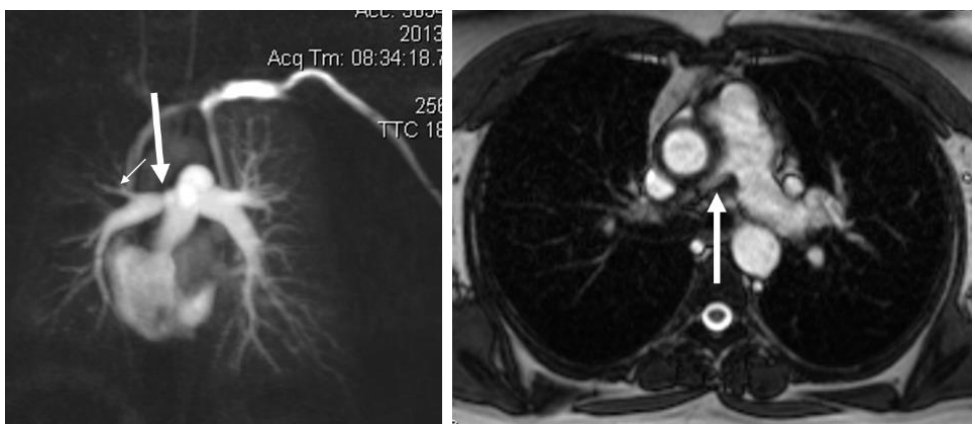

Figure 7. Main right pulmonary artery stenosis in a patient with Takayasu arteritis (CT-angiography, frontal reconstruction and axial image).

Pulmonary Hypertension

There are anecdotal reports [40, 41] of pulmonary hypertension in patients with TAK, PAN and AAV. Secondary pulmonary hypertension can result from pulmonary artery involvement, constrictive pericarditis, restrictive cardiomyopathy, or lung fibrosis [42]. Chronic thrombo-embolism can lead to pulmonary hypertension and should be actively considered as it is treatable.

Phrenic Palsy

Unilateral phrenic palsy due to mono-neuritis multiplex can occur in GPA and EGPA [43, 44]. However, it can be co-incidental, related to pre-existing conditions including trauma, or due to an unknown and unrelated cause.

LARGE-VESSEL VASCULITIDES

Parenchymal lung manifestations occur so rarely in LVV that when present, should prompt review of the diagnosis of vasculitis or consideration of a co-existing condition. However, involvement of pulmonary arteries can be an expected feature of LVV, especially in TAK.

Giant Cell Arteritis

One-quarter of patients with GCA have a dry, non-productive cough. Less common manifestations include alveolar hemorrhage, T-$CD4^+$ lymphocytic alveolitis, pleural effusion and thickening, multiple pulmonary infarctions, lung nodules and ILD [45-48].

Takayasu Arteritis

TAK can involve the pulmonary arteries, although less frequently than the aorta or other arteries with stenoses, with or without dilations (Figure 7). The involvement can be associated pulmonary hypertension, lung infarction, arterial rupture and hemorrhage, regional hypo-perfusion, and lung ventilation and perfusion mismatching suggestive of pulmonary embolism. There may be lung nodules, parenchymal consolidation, sub-pleural reticulo-linear changes, pleural effusion and thickening, pulmonary-renal syndrome, and ILD [49-56].

MEDIUM-VESSEL VASCULITIDES

Pulmonary artery and less often parenchymal involvement can occur in MVV.

Polyarteritis Nodosa

The lung parenchyma is not typically affected in PAN and the occurrence of capillaritis with alveolar hemorrhage should raise doubt about the diagnosis of PAN or question the possibility of an underlying genetic disease such as STING-associated vasculopathy [57]. Prior to the 1994 CHCC [58], patients presenting purpura, hemoptysis, and pulmonary hemorrhage that preceded the explosive phase of systemic necrotizing vasculitis affecting the kidney and lungs with rapidly progressive glomerulonephritis and pulmonary capillaritis were considered to have a microscopic form of PAN. This condition was later considered a separate category of

SVV, termed MPA [59]. Pulmonary edema and pleural effusion in PAN are usually due to renal and/or cardiac insufficiency. Patients with PAN can present with interstitial pneumonia, lung nodules and cavitary lesions. Although clinical and angiographic bronchial artery involvement is considered uncommon, seven of ten patients were found to have bronchial arteritis on post-mortem examination [60-62], so this manifestation of vasculitis may be under-recognized.

Kawasaki Disease

Children with Kawasaki disease (KD) often develop respiratory symptoms due to upper-respiratory tract inflammation. Affected children may present with pneumonia, and up to 15% show lung consolidation on chest radiography within 10 days of illness onset. Other radiographic abnormalities include peri-bronchial cuffing, pleural effusion, atelectasis and air trapping [63]. The incidence of coronary artery lesions is greater in patients with abnormal chest radiographs. Interstitial micro-nodular infiltrates and larger inflammatory pulmonary nodules can occur [64-68].

SMALL-VESSEL VASCULITIDES

Parenchymal and airway disease occur more commonly in SVV than MVV and LVV. Alveolar hemorrhage is the hallmark of GPA, MPA and EGPA; lung nodules and bronchial stenosis are more characteristic of GPA, and asthma is most consistent with EGPA [69].

Granulomatosis with Polyangiitis

Overall, 70% to 100% of patients with GPA show lung involvement, with clinical manifestations ranging from mild cough, dyspnea, chest pain, and intermittent hemoptysis to acute respiratory distress syndrome and massive alveolar hemorrhage. In 6% of patients, lung involvement remains asymptomatic, especially with lung nodules. Tracheobronchial involvement, including subglottic stenosis, ulcerating tracheo-bronchitis and sometimes endobronchial stenoses, can be seen in 17% of patients [70]. Subglottic involvement seems to be more common in the pediatric-onset GPA compared with the adult population, occurring in up to 41% of cases [71]. Although not specific, lung nodules are among the most characteristic involvement, and are present in 40% to 66% of patients with GPA, occurring as ≤ 10 in number, unilateral, bilateral, and single or multiple lesions [20]. Half of them may cavitate, especially when larger than 2 cm [72]. The differential diagnosis of lung nodules remains wide, and should include primary and metastatic tumors, sarcoidosis, tuberculosis and fungal infections (Table 2). Alveolar hemorrhage, the most feared manifestation, is usually secondary to capillaritis and is noted in 18% to 30% of patients with GPA. It can occur at disease onset or later in the course signaling relapse of the disease [20, 73]. It may appear as ground-glass opacities surrounding pulmonary nodules. In all, 30% to 50% of patients show other pulmonary infiltrates or lung consolidations, and 9% to 28% show pleural effusion. Spontaneous pneumothorax and empyema can occur, sometimes related to nodule cavitation and rupture. Pulmonary embolism

may indicate active GPA and systemic inflammation. All patients with acute presentation of GPA should undergo chest CT/HRCT, because small nodules, alveolar hemorrhage and other lesions may be missed on chest radiography. Even when the diagnosis of GPA is clinically apparent, broncho-alveolar lavage should be considered to exclude concurrent infection and clinically silent alveolar hemorrhage. Surgical lung biopsies, targeting nodules and consolidated lesions, have a diagnostic yield of 76% to 91% [3, 74]. Transbronchial biopsies are seldom positive, unless performed on a macroscopically abnormal lesion. Transbronchial cryobiopsy and video-assisted thoracoscopic biopsy are other possible diagnostic options [75].

Microscopic Polyangiitis

Alveolar hemorrhage and pulmonary–renal syndrome can be observed in MPA [59, 76, 77]. Arteritis with intimal thickening and focal destruction of the internal elastic lamina and sub-intimal fibrous scarring of the media are typical histological features in diagnostic tissue biopsy specimens. Diffuse alveolar damage and pulmonary fibrosis (Figure 6) can complicate MPA, mainly in patients with anti-MPO P-ANCA MPA. In patients with established idiopathic pulmonary fibrosis, MPO-ANCA positivity may be present in up to 5%. Seroconversion from negative to positive anti-MPO during follow up can be found in up to 15% of patients [78, 79]. The risk of developing systemic vasculitis over time is greater in MPO-ANCA positive patients than those with negative ANCA, and can be as high as 22% [78]. Additionally, pulmonary fibrosis and vasculitis may have independent outcomes, with progression of the fibrosis despite treatment and sustained good control of the vasculitis [24-26, 29]. There is little data on the role of immune suppressing therapies and anti-fibrotic therapies such as pirfenidone and nintedanib in MPO-positive IPF and MPA with pulmonary fibrosis.

Eosinophilic Granulomatosis with Polyangiitis

This rare pulmonary and systemic SVV with an annual incidence of 0.5 to 6.8 per million and a prevalence of 10.7 to 14 per million, develops through three prototypical successive phases. The prodromal phase begins with asthma and allergic manifestations, followed by tissue eosinophilia affecting visceral organs such as the lung and myocardium, and later development of vasculitic features primarily affecting the skin and peripheral nerves. The preponderance of Th2 lymphocytes and eosinophils suggests their participation in the pathogenesis of EGPA. However, ANCA production is noted in up to 40% of patients, which suggests a role in amplifying or facilitating the development of vasculitic lesions. Asthma is a predominant feature in EGPA, present in up to 91% of cases at diagnosis [9]. Lung infiltrates were reported in 39% of patients in the largest series (and up to 72% in a smaller previous series) [9, 80], presenting as multifocal peripheral consolidation in two-thirds of patients, with unilateral or bilateral, and symmetrical or asymmetrical appearance [81]. A centri-lobular perivascular dense pattern with scattered centri-lobular nodules measuring 5 mm within ground-glass opacities is often found. Multiple large nodules may occur, with occasional cavitation; however, alveolar haemorrhage is rare in EGPA, occurring in less than 5%. Non-compressive mediastinal or hilar adenopathy may also be detected on chest CT. Pleural

effusions are present in 9% to 30% of patients and are typically exudative and rich in eosinophils [9].

Anti–Glomerular Basement Membrane Disease

Anti-GBM disease, which was included in the revised 2012 CHCC [1] under the SVV category of IC diseases, typically affects young people, aged 15 to 35 years. Isolated glomerulonephritis occurs in 20% to 40% of patients and is combined with alveolar hemorrhage in 60% to 70% of patients. Isolated alveolar hemorrhage is a rare but described presenting feature of anti-GBM. Alveolar hemorrhage is strongly associated with smoking [82, 83]. Up to one third of patients with anti-GBM disease become ANCA positive at some time during their illness. Such patients have intermediate prognosis with worse renal prognosis than those with isolated AAV.

Other Small-Vessel Vasculitides

Alveolar hemorrhage occurs in less than 5% of patients with IgAV [30] and mixed CV. Other lung manifestations may be due to co-incident human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection, or a lymphoproliferative disorder.

VARIABLE VESSEL VASCULITIDES

Behçet Disease

Lung manifestations occur in less than 10% of patients with BD [84-89]. Pulmonary artery involvement is most common after aortic involvement in young men with aneurysms and thrombosis, with or without associated aneurysm or vascular stenosis [90, 91]. Clinically, it can remain silent, or present with hemoptysis. Other symptoms of pulmonary artery involvement are cough, fever, pleuritic chest pain and dyspnea [86]. Patients should be systematically screened for aneurysms, which can be seen on chest radiographs, but are best visualized by chest CT and magnetic resonance imaging (MRI). They can be multiple, unilateral or bilateral, with varying diameter, usually 1 to 7 cm. Pulmonary artery involvement is associated with poor prognosis, with mortality exceeding 25% after 7 years of follow-up. Aneurysms can rupture, causing catastrophic hemorrhage or lead to thrombosis with later pulmonary hypertension and lung infarction. Most patients have concomitant extra-pulmonary venous thrombi and thrombophlebitis (Hughes-Stovin Syndrome). A pulmonary aneurysm justifies treating with cyclophosphamide and high-dose corticosteroids. Consensus is lacking on the role of anticoagulant and antiplatelet therapies as they may be associated with massive hemorrhage and mortality risk. Surgery, embolization, and endovascular procedures should be considered in combination with systemic therapy because of the complications associated with active vasculitis. Atelectasis, nodular, or reticular opacities and cavities can occur, corresponding to foci of pulmonary hemorrhage, infarction, and diffuse alveolar hemorrhage due to SVV.

Secondary organizing pneumonia, pleural nodules or effusions resulting from vasculitis of the pleura or thrombosis of the superior vena cava, ulcerative lesions of the trachea and/or proximal bronchia as well as mediastinal lymphadenopathy can also occur. Pulmonary embolism in BD is rare and most often due to local pulmonary artery thrombosis rather than embolic peripheral venous thrombosis.

Other Vasculitides

Lung manifestations occur in patients with lupus vasculitis, RAV, sarcoidosis, systemic scleroderma, HCV infection, and illicit use of substances such as cocaine [92-96]. Alveolar hemorrhage due to capillaritis in SLE is similar to what is observed in MPA. Different pathogenic mechanisms may be involved in the development of ILD and lung nodules in RAV. Cocaine and levamisole-tainted cocaine induce lung complications including a GPA-like syndrome with skin, nasal sinus involvement and lung-nodules rather than alveolar hemorrhage. ANCA-seropositivity can be present as well as ELISA findings of specificity to PR3 and various patterns on indirect immunofluorescence [97, 98].

TREATMENT AND PROGNOSIS

Before initiating therapy for pulmonary manifestations, the treating physician should be certain that other conditions, especially infections, cancers, and drug toxicity, are not mimicking pulmonary vasculitis. These conditions may co-exist with active vasculitis, such as supra- or opportunistic infection of a lung cavity with *Mycobacteria* and *Aspergillus* species or cancer leading to paraneoplastic syndrome [99, 100]. Treatment should be individualized to the vasculitis identified, its severity and the type of organ involvement. Although lung manifestations in AAV do not necessarily confer poorer prognosis, alveolar hemorrhage and tracheo-bronchial stenoses warrant aggressive management to avert excess morbidity and mortality. It has been demonstrated that rituximab was as effective for induction therapy as cyclophosphamide in diffuse alveolar hemorrhage in the rituximab in ANCA-Associated Vasculitis (*RAVE) trial*, although patients requiring mechanical ventilation were excluded from this trial [101]. Conversely, the preliminary results of the large, controlled PEXIVAS study [102] suggested that plasma exchange did not improve survival in patients with severe diffuse alveolar hemorrhage, as opposed to reports from a few small case series or case-control studies [103]. Systemic treatment is often disappointing in subglottic and bronchial stenoses. Endoscopic dilations with bougies, balloons and repeated local injection of corticosteroids with or without mitomycin application may be effective. Tracheal stents and surgery should be considered only in refractory disease. Patients with GPA and lung nodules, without any other threatening systemic manifestations or major organ involvement, can be managed with less toxic drugs such as methotrexate. The optimal treatment strategy for lung fibrosis and ILD remains to be determined.

Consensus is lacking on the optimal clinical and laboratory monitoring of patients with vasculitis and lung manifestations, but repeated chest radiographs and PFTs at 3 to 6-month intervals earlier in the disease seem reasonable. Repeat CT, because of radiation concerns,

should be reserved to resolve uncertainties or to evaluate response to treatment, complications or new manifestations of disease. The intensity of follow-up would vary, depending on the severity of the lung lesions and the impairment of function as well as the presence of subglottic and bronchial stenotic lesions which require direct visualization at bronchoscopy.

CONCLUSION

Lung manifestations are common in several vasculitides and can present various features, some of them potentially life-threatening. After exclusion of conditions mimicking vasculitis, treatment with systemic and local therapies can be initiated with the expectation of improvement. In the longer term, complications of treatment can be as troublesome as complications of the disease. Identification of effective, less toxic and optimal combinations of therapies for the most severely affected patients, and those with chronic lung complications such as anti-MPO-ANCA–associated pulmonary fibrosis, and others with AAV will be clarified by emerging evidence from clinical trials.

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Chapter 16

SYSTEMIC VASCULITIS AND THE KIDNEY: ANCA-ASSOCIATED VASCULITIS AND GLOMERULONEPHRITIS

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ABSTRACT

Systemic vasculitides affecting small- and medium-sized vessels are particularly likely to involve the kidneys. These vasculitides include microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis, IgA vasculitis, polyarteritis nodosa, and cryoglobulinemic vasculitis. The most common culprits of kidney injury in adults are microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis, which predominantly affect small vessels and are typically associated with the presence of anti-neutrophil cytoplasmic autoantibodies. For this reason, we focus here on anti-neutrophil cytoplasmic autoantibody-associated vasculitides. Over the past three decades, tremendous progress has been made through investigative efforts to understand etiologic, pathogenetic and clinical underpinnings of these disorders. We highlight notable findings that represent key breakthroughs in the field and proceed to the clinical presentation, diagnosis, and an up-to-date discussion of studies related to clinical management for inducing and maintaining remission. Finally, we review key prognostic indicators of renal outcomes and predictors of treatment resistance and relapse. Although these diseases have been transformed from ones that were usually fatal to ones that are now chronic with potential for long-term and symptom-free remission, many challenges remain to decrease diagnostic delays, increase our understanding of molecular mechanisms of genetic and environmental risk factors for

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disease, and further refine and personalize treatment strategies that maintain remission and minimize treatment-related morbidity.

Keywords: ANCA, vasculitis, kidney

INTRODUCTION

Many forms of systemic vasculitis directly affect the kidneys, and resultant injury can lead to chronic kidney disease and even end-stage kidney disease. Vasculitides affecting small- and medium-sized vessels are particularly likely to involve the kidneys. They include polyarteritis nodosa (PAN), IgA vasculitis (IgAV, formerly Henoch-Schönlein purpura), microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), and cryoglobulinemic vasculitis. The most common causes of kidney injury among this group are IgAV in children; and MPA, GPA, and EGPA in adults. MPA, GPA, and EGPA affect predominantly small vessels, and are often, although not always, associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCA). Given their predilection for kidney involvement, further discussion in this chapter will focus primarily on these ANCA-associated vasculitides (AAV).

EPIDEMIOLOGY

Most data on the incidence and prevalence of AAV derive from studies in Caucasian populations of European descent, although there are also emerging data from Asia and parts of the Middle East. Disproportionate reporting in Caucasians may reflect case ascertainment bias, availability of diagnostic resources, or high prevalence of competing diagnoses, for example, tuberculosis in the case of granulomatous disease, rather than true difference. However, data from multi-ethnic populations suggest that there are true differences in disease incidence based on geographical location, ethnicity, or race, or a combination thereof. As an example, a study of a multi-ethnic population in a Paris suburb, 28% of who were of non-European ancestry, found that the overall prevalence of AAV, as well as PAN, in Europeans was twice that observed in non-Europeans [1]. Similar ethnic differences are seen in New Zealand, where Europeans appear to have a much higher annual incidence of AAV of 60.2 cases per million individuals than the indigenous Māori population with 34.2 cases per million individuals [2]. The annual incidence in Pacific Peoples in New Zealand of 17.26 cases per million individuals was also lower than that of Europeans.

The average incidence of AAV in Japan appears to be similar to that in the United Kingdom (UK), with 22.6 and 21.8 cases per million individuals annually, respectively, [3] however, with notable differences. In Japan, the vast majority (83%) of patients has MPA and is MPO-ANCA positive. Conversely, 66% of patients in the UK have GPA, and a similar number are proteinase 3 (PR3)-ANCA positive. Interestingly, kidney involvement was noted to be less common in patients with GPA in Japan than in the UK. AAV is also recognized in China [4] and India [5], as well as regions of the Middle East [6], but there are no data regarding incidence

and prevalence in these areas. In a study on distribution of ANCA types, MPO-ANCA was more common than PR3-ANCA in the Chinese patients (OR 6.8, CI 2.6-17.8) [7]. Though AAV is uncommon in Africans, there are rare case reports of AAV from Africa [8]. African Americans are more often MPO-ANCA positive (71% vs. 54%, p = 0.01) and younger at diagnosis (52 versus 57 years), when compared to Caucasians [9]. However, treatment response, ESRD, renal relapse, and death were similar between the two groups [9]. It is important to note that while PAN, a medium-vessel vasculitis, is not classified as an AAV; it has historically been included in most of these data. Collectively, there is believed to be an overall incidence of approximately 10 to 20 cases per million individuals annually in Caucasian patients of European descent [10]. The prevalence of AAV is approximately 46 to 184 cases per million individuals [11].

Strikingly, multiple examples exist of differences in incidence of AAV that appear to be dependent upon geographic milieu. For example, in northern Saskatchewan, Canada, a 2.69 odds ratio (OR) of developing AAV was reported in a rural versus urban setting [12]. A study from the Australian Capital Territory of New South Wales found the annual incidence of MPA to be significantly higher in rural versus urban areas (13.9 vs 1.6 cases per million individuals), with a similar trend seen in the incidence of GPA [13].

There are also multiple reports that demonstrate differences in incidence relative to latitude. A north-to-south positive gradient was observed in the Southern Hemisphere, and a south-to-north positive gradient is seen in the Northern Hemisphere. In other words, incidence of AAV appears to correlate with latitudinal equatorial proximity. This association was apparent in one study from New Zealand [2], located in the Southern Hemisphere, where an increase in incidence of GPA was noted moving from north to south. A second study comparing incidence of AAV in two regions of Europe, including Norwich, UK, latitude 52°N; and Lugo, Spain, 43°N, both in the Northern Hemisphere, found a higher incidence of GPA in Norwich, the more northerly latitude, than in Lugo, even though the overall incidence of AAV was nearly identical [14]. Interestingly, no such difference has been noted in MPA or EGPA. Similar observations regarding incidence relative to latitude have been reported elsewhere [15]. The incidence of AAV is similar in males and females, and the average age of disease-onset varies somewhat within populations, but occurs predominantly in the sixth and seventh decades of life. The relationship of disease to this demographic may be somewhat skewed since, when evaluated retrospectively, a number of patients arguably hade evidence of disease years prior to diagnosis. Diagnostic delays are well-substantiated in the literature [16, 17]. Furthermore, most studies of disease do not include pediatric patients, and it is important to remain cognizant that AAV can occur at any age [18-20].

PATHOGENESIS

Since the initial discovery of AAV and glomerulonephritis [21], incredible strides have been made in understanding the etiology and pathogenesis of these diseases. From a fundamental point of view, for autoimmunity to occur, there needs to be a break in self-tolerance to autoantigens. The three major phases of autoimmunity in a susceptible individual include initiation, propagation and resolution [22]. Genetic susceptibility and environmental factors including many infections are common initial triggers. Molecular mimicry and

autoantigen complementary to a bacterial peptide are some of the mechanisms responsible for origination of ANCA production. HLA can bind peptides, from self- or non-self-antigens and present it to T cells for initiation of immune activation. Among other genetics associations, a strong link has been found between HLA genetic regions and AAV [24].

Along with continuous antigen exposure, a defect in regulatory machinery of immune response, T regulatory cells (Tregs) and B regulatory cells results in propagation of the disease process. Although the mechanism still needs to be defined, multiple studies have shown involvement of persistently activated T cell effector arm of the adaptive immune system [23]. A balance between Tregs/effector cells is essential to prevent autoimmunity. FOXP3 is a major transcriptional factor for CD4+ Tregs; in active AAV, these Tregs, due to use of a splice variant of FOXP3, are unable to suppress effector CD4+ T cells, thus playing an important role in the propagation of autoimmunity [25]. Also, B cells with regulatory function (with high CD5 expression) are decreased in active AAV and increased during remission [26].

Various *in vitro* observations have established that ANCA can bind to cytokine-primed neutrophils, resulting in its degranulation, respiratory burst and efflux of the proteinases. In addition, upon activation, neutrophils can release proinflammatory cytokines, resulting in augmentation of inflammatory cascade. Both MPO and PR3 are cytoplasmic antigens, priming with cytokine results in its expression on cell surfaces. ANCA bind to FcγR expressed on neutrophil and F(ab′)2 segment binds to MPO/PR3 antigen on the cell surface leading to neutrophil activation [27-29].

The pathogenicity of IgG ANCA comes from different observations, clinical, *in vitro* and from animal models. The majority of patients with pauciimmune necrotizing crescentic glomerulonephritis have positive ANCA serology, but its titer does not always correlate with disease severity, remission or relapse. The first true clinical record depicting the pathogenicity comes from a case of transplacental passive transfer of anti-MPO IgG from a mother with MPA to her neonate, resulting in pulmonary hemorrhage and renal dysfunction [30]. Both clinical hints and *in vitro* results are only suggestive, but to prove the pathogenicity of IgG ANCA, one strives to fulfill Koch's postulates as established by our group in an animal model: (1) immunization of MPO knockout mice $MPO^{-/-}$ with purified mouse MPO in complete Freund's adjuvant resulting in development of anti-MPO antibody; (2) anti-MPO splenocytes containing B and T lymphocytes; (3) injection anti-MPO IgG causes pauci-immune crescentic glomerulonephritis in immune deficient $Rag2^{-/-}$ mice and also wild type mice; and (4) adoptive transfer of anti-MPO splenocytes into $Rag2^{-/-}$ resulted in a severe phenotype of vasculitis in a dose-dependent manner [31]. This demonstrates that anti-MPO antibody itself is sufficient to cause disease, but the severe phenotype seen in the adoptive transfer model is possibly due to synergistic effects of anti-MPO T lymphocytes. Studies on bone marrow transplantation approach showed that bone marrow-derived cells, neutrophils and monocytes were necessary and sufficient for induction of disease by anti-MPO antibody [32]. Systemic administration of bacterial LPS in an animal model caused enhanced circulating TNF-alpha resulting in severe phenotype of crescentic glomerulonephritis induced by IgG MPO [33]. In addition, due to unknown factors, there is evidence of activation of alternate complement pathway, priming of neutrophils by C5a by binding to C5aR results in augmentation of inflammatory pathways [34]. The observations from *in vivo* and *in vitro* studies stems the therapeutic tree in AAV, from use of cyclophosphamide, which suppresses both B cell and T cell effector function, to more specific B cell therapy with anti-CD20 monoclonal antibody.

Silica

Noted geographical differences in incidence may imply that environmental and other geo-locational triggers play a role in disease development. Silica has been implicated as one such trigger. The first account of a possible association of silica with autoimmune disease was a 1914 report of systemic sclerosis occurring in Scottish stonemasons [35]. There have since been a number of studies correlating silica exposure with the development of other autoimmune diseases, particularly rheumatoid arthritis (RA) [36], but also systemic lupus erythematosus (SLE) [37-39]. Data regarding the latter are conflicting [40], but differences in results may reflect dissimilarities in study methodology and patient characteristics. Data on the contribution of silica to the development of AAV have been inconsistent. A study of 2,288 patients from Sweden found no statistically significant association between an occupation and development of GPA, although borderline associations were seen in miners, paper workers, bakers, and animal keepers [41]. However, a meta-analysis of six case-control studies examining silica exposure and risk of AAV found an overall significant summary effect of silica exposure (summary OR 2.56; 95% confidence interval [CI] 1.51-4.36) with development of AAV [42]. This summary OR was similar to the OR seen in studies looking exclusively at either MPA (OR 3.95, 95% CI 1.89-8.24) or GPA (OR 3.56, 95% CI 1.85-8.82).

Difficulties in comparing studies like these have been due largely to study heterogeneity, with studies using different methods for ascertaining silica exposure. Negative studies have been quite large numbering up to 2,288 patients, whereas positive studies have generally been small, ranging from 16 to 129 patients, with variable inclusion criteria. For example, one study included only men [43], while others differed in the age range of patients included. All but one study [44] included only patients with glomerulonephritis, with or without other organ system involvement. Determination of ANCA seropositivity by immunofluorescence (IF) enzyme-linked immunosorbant assay (ELISA) or a combination thereof varies in the literature with one study including 3 patients who were ANCA seronegative [45]. The duration of exposure to potential silica-containing compounds, as well as the time from exposure to clinically-evident disease has varied. However, the degree of silica exposure, which included both duration and intensity of exposure, was found to be significant in a case control study of biopsy proven glomerulonephritis caused by AAV [46]. High lifetime silica exposure was associated with development of AAV when compared to none (OR 1.9, 95% CI 1.0-3.5, P = 0.05). No study of silica exposure included patients with pulmonary- or otolaryngologic-limited disease, even though exposure is likely through inhalation of crystalline particulates. However, in terms of exposure risk, the study by Hogan and coworkers [40] did not find significant differences in patients with and without pulmonary involvement. The geographical region of either study could have contributed to the variable results.

Despite data inconsistencies, silica is generally accepted as having a potential role in the development and perpetuation of AAV. Mechanisms by which silica may promote autoimmunity have not yet been fully elucidated. One study of silica-exposed workers in Brazil [47] found increased levels of soluble interleukin-2 receptor (sIL-2R), thought to reflect increased immune activation in these individuals. However, investigators did not specifically consider the role of silica in autoimmunity. Another study of slate miners demonstrated increased and chronic T-cell activation in patients with silicosis either with or without autoimmune disease, including one with pauci-immune glomerulonephritis [48], and found proliferation of peripheral blood mononuclear cells (PBMC) to be 45% higher in cell cultures

of silica-exposed patients than in healthy controls. Patients had elevated levels of both pro-inflammatory (interleukin [IL]-1β, IL-6, tumor necrosis factor [TNF]-α, interferon [IFN]-γ) and anti-inflammatory (IL-10, tumor growth factor [TGF]-γ) cytokines. Chronic T-cell activation was observed in cultured PBMC of silicosis patients in Japan [49]. In particular, activation of T responder cells (Tresp) resulted in later entry into the peripheral CD4+25+ population, whereas activation of FoxP3+ regulatory T-cells (Treg) led to more rapid and higher levels of apoptosis. The net effect was reduced inhibitory function. Silica may also contribute to immune dysregulation by increasing oxidative stress, as suggested by a study of denim sandblasting workers with silicosis in Turkey [50]. Patients had a 1.4-fold higher level of superoxide dismutase (SOD), a possible marker for increased reactive oxygen species generation in these patients [50]. Another study showed decreased L-selectin expression in workers with >16 years of occupational silica exposure, and associations with inflammatory and oxidative stress biomarkers [51]. More recently, neutrophil extracellular traps (NETs) have been implicated in the pathogenesis of AAV [52, 53]. These NETs are involved in trapping silica and have been postulated to trigger autoantibody production by exposing neoantigens [54].

Taken together, these data suggest a somewhat generalized disruption in immune homeostasis in silica-exposed individuals. However, studies to date have not specifically addressed the mechanisms by which silica may cause or promote disease in AAV. By extrapolation, silica is more likely to have an adjuvant effect in patients with predisposition to AAV rather than to be a primary trigger.

Infection

Wegener considered infection as a potential factor in the cause of GPA in the first half of the 20th century [55]. Since then *Staphylococcus (S.) aureus* has received particular attention. The first study comparing the rates of GPA relapse with carriage of *S. aureus* found that 36 of 57 (63%) patients were chronic carriers of *S. aureus*, and analysis demonstrated an adjusted relative risk (RR) for relapse of 7.16 (95% CI 1.63-31.50) independent of other factors [56]. A 2008 study of Polish patients with limited disease [57] found that 17 of 28 (60%) patients were chronic nasal carriers of *S. aureus*, independently conferring a relative hazard risk (HR) for relapse of 4.56 (CI 2.45-7.65). A third study compared nasal carriage of *S. aureus* in patients with GPA to those with rheumatoid arthritis (RA) and chronic rhinosinusitis with nasal polyps (CRS), as well as to hospital staff and subjects without regular exposure to a hospital environment, noting that 72% of patients with GPA had *S. aureus* nasal colonization, versus 28% of those with CRS, and 25% of patients without regular hospital exposure [58]. Patients with RA and hospital workers had *S. aureus* carriage rates of 46% and 58% respectively, but the differences were statistically insignificant. Colonized GPA patients had significantly higher rates of endoscopically-proven endonasal activity, with more frequent upper respiratory tract involvement at first presentation, and with significantly higher relapse rates compared to uncolonized patients. The use of prophylactic antibiotics, such as prophylactic trimethoprim/sulfamethoxazole, to reduce the relapse risk by decreasing carrier rates is controversial [59-61]. In a 2017 study of AAV [59], the relapse rates for GPA were higher for chronic nasal carriers of S. aureus, and prophylactic trimethoprim/ sulfamethoxazole reduced the number of carriers (OR 0.19, 95% CI 0.04-0.91, P = 0.04).

However, in this study, prophylactic trimethoprim/sulfamethoxazole itself did not reduce the relapse risk (OR 0.71, 95% CI 0.36-1.41, P = 0.33).

The mechanism(s) by which infection may incite disease has not been fully elucidated, but early investigations have yielded intriguing possibilities. Molecular mimicry, which leads to cross-reactivity of antibodies to both pathogen-derived and self-antigens with substantial structural homology, has been implicated as one of the etiopathogenic factors in AAV. Such cross-reactivity has been observed in several other diseases; streptococcal M proteins and cardiac myosin, as well as other proteins, cross-react in rheumatic fever [62, 63]; *Campylobacter jejuni* epitopes and peripheral gangliosides cross-react in Guillain-Barré syndrome [64]; and Epstein Barr virus epitopes and *Mycobacterium avium paratuberculosis* cross-react with myelin basic protein in multiple sclerosis [65]. A peptide or protein homologous to complementary PR3 (cPR3), transcribed and translated from the antisense strand of *PRTN3* DNA, is thought to be an inciting antigen in a subset of patients with PR3-ANCA disease. In those who are predisposed, antibodies are generated to cPR3. Anti-idiotypic antibodies, or antibodies to anti-cPR3 antibodies, are then produced that are reactive to PR3 [66, 67]. Complementary PR3 shows homology with proteins of multiple microorganisms, including two proteins found in *S. aureus*, thus suggesting a role for molecular mimicry in the pathogenesis of AAV. While PR3-ANCA and MPO-ANCA patients may have the same type of *S. aureus* as the general population, they do have different distributions of clonal complexes [68]. Given recent reports of *S. aureus* proteins binding MPO and/or PR3 antigens, it is postulated [61, 69] that this bacterial protein-autoantigen complex is then internalized and processed by B-cells and then presented to T-cells. This could account for antibody production by B-cells and role of T-cells in ANCA.

Although it remains highly controversial, lysosome-associated membrane protein 2 (LAMP-2) has been identified as a possible antigenic target in patients with AAV [70]. The $P_{41\text{-}49}$ epitope of LAMP-2 reportedly has significant homology with an epitope of FimH, having in common 8 of 9 amino acids [71], but these findings were not subsequently confirmed [72].

Illicit and Prescription Drugs

Both illicit and prescription drugs have been implicated in the cause of AAV, but the etiopathogenic mechanisms area not well understood. The ant-helminthic agent levamisole, sometimes found in cocaine, is the most recognized drug cause of vasculitis. Affected patients [73, 74] are typically MPO-ANCA positive, but may have dual positivity with MPO- and PR3-ANCA [73, 74], and typically present with cutaneous disease. While cutaneous disease in idiopathic AAV typically manifests as recurring crops of purpuric lower extremity lesions, the lesions associated with levamisole are more widespread and variable in character, with necrotic lesions involving the ears, and bullous purpura in any location. Full-thickness, large necrotic lesions are suggestive of levamisole exposure. Affected patients can have arthralgia, particularly of the large joints, and constitutional symptoms. Severe disease with isolated glomerulonephritis and pulmonary-renal syndrome occurs. Patients with signs and symptoms of AAV should be questioned regarding illicit drug use, particularly when dual MPO-ANCA and PR3-ANCA serology is present, and urine toxicology screen for the presence of cocaine and levamisole should be obtained.

The commonest prescription drug offenders include hydralazine and propylthiouracil (PTU), although penicillamine, minocycline, sulfasalazine, allopurinol, carbimazole, methimazole, and gold have all been implicated [75, 76]. Unlike levamisole-induced disease, the presentation of other drug-induced forms of disease mirrors idiopathic disease, with rapidly progressive glomerulonephritis being especially common. Serologically, patients generally have MPO antibodies at high titers, and dual positivity to MPO and PR3 is rare. Affected patients tend to be positive for other autoantibodies, including antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-histone, anti-lactoferrin antibodies, and other forms of ANCA, specifically anti-human neutrophil elastase (HNE). Propylthiouracil typically causes a pauci-immune necrotizing and crescentic glomerulo-nephritis, but other organ systems may be involved. While patients with PTU-induced disease tend to have high titers of MPO-ANCA, the ANA is not usually positive. In both illicit and prescription drug-induced AAV, cessation of the causative agent is imperative, and management is similar to that of the idiopathic forms of disease, employing immunosuppressive medication, as well as plasmapheresis and hemodialysis as indicated by disease severity.

Genetic Associations

The ability to sequence DNA from humans is becoming more and more facile, and investigators have taken full advantage of this to understand the genetic underpinnings of AAV, uncovering disease associations with both MHC and non-MHC genes [24]. Genome-wide association studies (GWAS) of patients and healthy controls of European descent revealed an association of PR3-ANCA positive AAV with *HLA-DP*, *SERPINA1* (encoding α-1 antitrypsin), and *PRTN3* (encoding PR3), whereas MPO-ANCA positive disease was associated with *HLA-DQ* [77, 78]. The largest risk was seen with single-nucleotide polymorphism (SNP) variants rs141530233 and rs1042169 at the *HLA–DPB1* locus [78]. Among non-MHC genes, an association were demonstrated with *CTLA4*, which encodes a T-cell surface molecule (CTLA-4) that down-regulates T-cell activation [77]. Two *CTLA4* single nucleotide polymorphisms (SNP), +49 G [51-53] and CT60 [77, 79, 80], have been implicated in several studies. All of the studies identifying disease association with the *CTLA4* SNP were performed in European cohorts comprising only Caucasian patients. No such association with *CTLA4* was found in Japanese patients with AAV [81]. The SNP rs3087243 of the *CTLA4* gene [80], which encodes an inhibitory regulator of T-cell activation, and rs2476601 of the *PTPN22* gene [80, 82, 83], which encodes a regulator of cytoplasmic tyrosine kinase and T-cell function, are both associated with AAV in Caucasian European cohorts [80, 81, 83]. Mutations in these genes have been implicated in other autoimmune diseases, suggesting a predisposition to general immune dysregulation [80, 82].

Racial and geographic variability may reflect differences in genetic predisposition. AAV has been rarely described in Africa [8], and it is notably rare in African Americans. An association of the *HLA-DRB1*15* alleles with PR3-ANCA positive disease has been found, conferring a 73.3-fold higher risk in African American patients than in community-based controls [84]. These alleles were also associated with PR3-ANCA positive disease in Caucasians, but with an odds ratio of only 2.2. The *DRB1*1501* allelic variant, which is of

Caucasian descent, was found in 50% of African American patients, whereas the *DRB1*1503*, of African descent, was under-represented in this group. Only the *DRB1*1501* allele was found in Caucasian patients. A significant association was found with *DRB1*16* in African American patients with MPO-ANCA positive disease. No allele has been so significantly associated with MPO-positive disease in Caucasians. In Chinese patients, the allelic variants *DRB1*1101* and *DRB1*1202* were observed significantly more often in patients with MPO-ANCA and PR3-ANCA-associated disease, respectively, than in healthy controls [85]. The finding in PR3-ANCA positive disease is difficult to interpret given the overall high prevalence of this allele in the Han population. This may reflect a particular AAV-associated haplotype. In Chinese Han population, variant rs3117242 of HLA-DPB1 was found to be associated with GPA [86]. In a Japanese cohort, *HLA-DRB1*0901* was significantly associated with MPO-ANCA positive disease [81]. Collectively, these findings lend credence to the concept that MPO- and PR3-AAV are genetically distinct diseases with phenotypic overlap. This genetic difference between PR3- and MPO-AAV was also noted in a meta-analysis demonstrating stronger association by ANCA serotype than clinical phenotype [87].

CLINICAL PRESENTATION

The most commonly recognized presentation of AAV is pulmonary-renal syndrome, with alveolar hemorrhage and kidney injury that typically manifests as a rapidly progressive glomerulonephritis. However, presentation can be influenced to some extent by the type of disease be it GPA or MPA, as well as, duration of disease prior to presentation. In terms of kidney involvement, both GPA and MPA can present with severe kidney failure, at times requiring dialysis. EGPA less commonly involves the kidneys, and when it does, kidney disease tends to be less severe than in GPA or MPA. Dysmorphic hematuria with or without red blood cell casts, proteinuria, and an elevated creatinine are all clues to the diagnosis. Proteinuria is typically within the nephritic range (<3g/day), but nephrotic-range proteinuria does not exclude the diagnosis. Kidney disease can occur absent other clinical manifestations.

LABORATORY DIAGNOSIS

Any testing for AAV begins with clinical suspicion of disease. This typically prompts non-specific studies, such as blood tests and urine microscopy, to look for elevated creatinine and dysmorphic hematuria with or without red blood cell casts, respectively, as evidence of kidney involvement. Similarly, chest radiograph or computed tomography (CT) may be used to screen for pathological changes if present. In those with otolaryngologic symptoms, endoscopic examination with biopsy is preferred, followed by more specific avenues of investigation if necessary. Tissue biopsy is the gold standard for diagnosis of AAV. In the acute setting, the lesion common to all affected tissues is segmental inflammation with fibrinoid necrosis (Figure 1), often with accompanying neutrophil infiltration initially, followed in quick succession by mononuclear leukocyte infiltration [88, 89]. As disease progresses, the lesions become

sclerotic. The finding of pauci-immune necrotizing crescentic glomerulonephritis strongly supports a diagnosis of AAV. However, lesions can be detected at various stages of development, so mild segmental fibrinoid necrosis with or without an adjacent crescent is common (Figure 1). If the acute lesion is severe, the glomerular tuft may have global necrosis with a circumferential crescent. In patients with granulomatous disease, GPA and EGPA, granulomatous inflammation most often affects the respiratory tract, including the lungs, rather than the kidneys, and is present concomitantly with small-vessel vasculitis. Lesions appear histologically as necrotic zones with surrounding mixed cellular infiltrate of neutrophils, lymphocytes, monocytes, macrophages, and often multinucleated giant cells. Eosinophils may also be present, but are more obvious, although not pathognomonic, in EGPA.

Anti-neutrophil cytoplasmic autoantibodies, first described by Davies and colleagues [90], have become routine in the diagnostic armamentarium of AAV. Treatment should not be delayed while awaiting results. A serologically-negative form of AAV is recognized in which current clinical assays do not detect MPO-ANCA or PR3-ANCA. By using highly sensitive epitope excision with mass spectrometry, Roth and coworkers identified a single small linear MPO epitope with high pathogenicity that was undetectable by usual assays due to obfuscation in serum by ceruloplasmin, the endogenous inhibitor of myeloperoxidase activity [91].

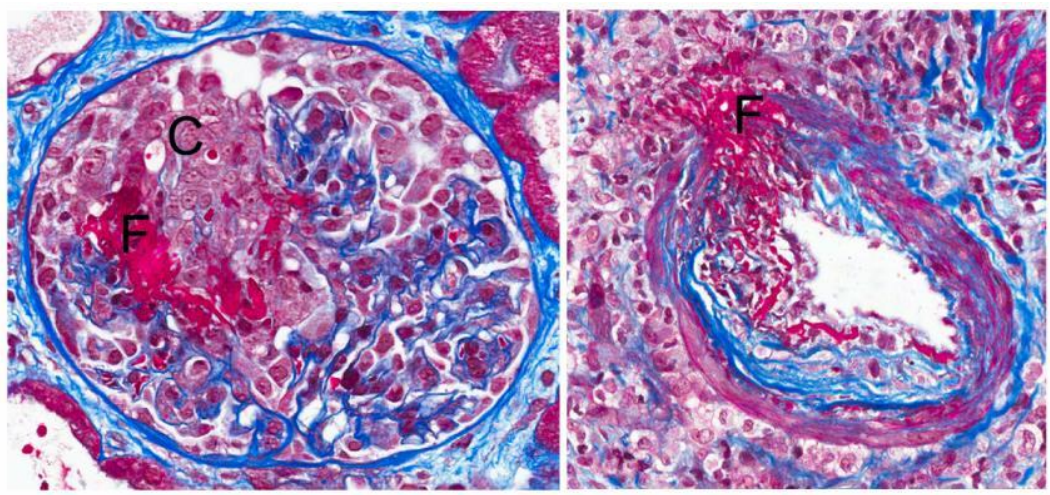

Figure 1. Photomicrographs of a kidney biopsy specimen from a patient with MPA showing a glomerulus (left panel) with segmental fibrinoid necrosis (F) and a cellular crescent (C), and an interlobular artery (right panel) with segmental fibrinoid necrosis (F). (Masson trichrome stain, X400).

Patients presenting with clinical signs and symptoms consistent with disease, but who are serologically negative, may have this or another as yet unidentified epitope that is not readily detected by currently available means. There are ANCA that occur in healthy individuals in very low titer that are not detected by routine serologic assays [92]. These are considered natural autoantibodies. Thus, while ANCA can be used to rule in disease in the appropriate clinical setting, neither their presence nor absence alone can be used to determine if disease is present. Additionally, some patients have persistently elevated autoantibody titers even in the absence of any clinical evidence of disease, thereby limiting their utility in diagnosing disease flares [93].

MANAGEMENT

Treatment of AAV can be considered in three phases: remission induction, remission maintenance, and treatment of relapse. Over the past decade, there has been an explosion of investigation into identifying ideal induction and maintenance strategies for patients with AAV.

Cyclophosphamide with corticosteroids has been used historically as induction therapy for AAV. Cyclophosphamide, an oxazaphosphorine that is chemically related to the nitrogen mustard family of alkylating agents [94], is the mainstay of AAV treatment. Multiple animal models have demonstrated its immunosuppressant activity apart from its antimitotic or cytotoxic characteristic [95, 96].

Although there is no randomized trial studying the optimum dose with glucocorticoids, the question of oral versus pulse intravenous (IV) cyclophosphamide to reduce the cumulative exposure to cyclophosphamide has been looked at. The CYCLOPS trial compared pulse iv versus daily oral cyclophosphamide in 149 patients with AAV and found no difference in time to remission, but a lower rate of leukopenia in the pulse group (HR 0.41, CI 0.23-0.71) [97]. Though the relapse rate was higher in the IV group in a long term follow up study, the mortality and renal function was similar [98]. The cumulative dose of cyclophosphamide should be kept in mind when choosing a regimen.

More recently, great strides have been made using rituximab-induced B-cell depletion for induction of remission. Rituximab, a chimeric murine/human monoclonal antibody that depletes B-cells by binding CD20 and inducing antibody-dependent cellular cytotoxicity (ADCC), was reported to be non-inferior to cyclophosphamide for induction therapy in GPA and MPA in short- [99, 100] and long-term [101] follow-up. Rituximab is approved by the Food and Drug Administration and European Medicines Agency for induction therapy in patients with GPA and MPA.

Plasmapheresis has been used in AAV patients with diffuse alveolar hemorrhage and severe renal disease [102, 103]. The MEPEX trial randomized 137 patients with AAV and serum creatinine > 5.8 mg/dL to receive plasma exchange or intravenous prednisolone, in addition to cyclophosphamide and oral prednisolone. Plasma exchange reduced risk of end stage kidney disease at 3 and 12 months [103]. A randomized controlled trial (PEXIVAS) of plasma exchange and glucocorticoid dosing was conducted in 704 AAV by Walsh and colleagues, the preliminary unpublished results of which were presented at the 2018 meeting of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) suggesting that plasma exchange was not beneficial in preventing death or progression to ESRD.

B-cell depletion to durably maintain remission is a logical next step, and there are numerous case reports, case series, and retrospective studies that suggest efficacy of this strategy [104-106]. The Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis trial (MAINRITSAN), compared low dose rituximab with azathioprine for remission maintenance in 115 AAV patients. Although rituximab was superior to azathioprine in preventing relapse, azathioprine was tapered and stopped earlier, which limits the results of the study [107]. Currently, the RITAZAREM trial (NCT01697267) in the United States is underway to also address this question of remission maintenance.

Complete depletion of peripheral B-cells cannot continue indefinitely if toxicities associated with immunosuppression are to be avoided. Targeted depletion of only B-cells with

the future capacity to produce pathogenic ANCA would be ideal. To this end, there are data suggesting that patients with active disease have a lower percentage of CD5+ B-cells compared to patients in remission, and that rituximab-exposed patients who have a robust reconstitution of CD5+ B-cells after therapy require less immunosuppression [108].

Novel treatment strategies aimed at other components of the inflammatory process, such as alternative complement pathway activation, are also needed. Alternative complement activation pathway products in kidney tissue (Bb) and urine (Bb, C3a, C5a, and soluble C5b-9) of patients with active disease correlate with severity of kidney injury [109]. In the mouse model of MPO-ANCA glomerulonephritis, blockade of the C5a receptor (C5aR) using an oral antagonist ameliorates disease in mice expressing human C5aR [110]. At present, a randomized phase 3 clinical trial (ADVOCATE) is underway to evaluate the safety and efficacy of C5aR blockade to induce remission in patients with ANCA vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine (NCT02994927).

Mepolizumab is an anti-interleukin-5 monoclonal antibody that reduces eosinophilic inflammation, and has been successfully used to prevent exacerbations of eosinophilic asthma [111]. In a study of 136 relapsing or refractory EGPA, patients were treated with mepolizumab versus placebo [112]. Mepolizumab treatment was associated with a higher rate of remission (OR 16.74, CI 3.61-77.56) at 36 and 48 weeks. The Food and Drug Administration recently approved Mepolizumab for the treatment of EGPA in 2017.

There are several alternative drug options for maintenance immunosuppression, including azathioprine, mycophenolate mofetil, methotrexate, and leflunomide. Controlled trials of these various options are limited. A meta-analysis looking at the comparative efficacy of azathioprine, mycophenolate mofetil, methotrexate, and leflunomide found a 55% probability that leflunomide is superior to the other three agents for remission maintenance [113]. However, true head-to-head comparisons are lacking. Therefore, provider preference, patient tolerance, cost, and risk of drug-specific adverse effects all play a role in which medication is selected.

OUTCOMES

Although AAV is associated with high mortality, the introduction of immunosuppressive medications has improved the survival over time [114]. The objective now is to prevent relapse and preserve organ function.

The presence of kidney disease and its severity at presentation have long been recognized as important prognostic indicators of renal outcomes in patients with ANCA-associated vasculitis [115, 116]. A recent study investigating predictors of patient and renal survival in a Dutch cohort of 273 consecutive patients with ANCA vasculitis followed for almost twenty years [117] found that overall survival was better in patients without kidney involvement (hazard ratio [HR] 0.55, CI 0.33-0.92, P = 0.02). Renal survival was worse in MPO-ANCA positive patients (HR 2.1, CI 1.11-3.8, P = 0.01).

A study of 350 patients with AAV evaluated predictors of treatment resistance and relapse [118]. Altogether, 88% of those enrolled had kidney involvement at or near the time of diagnosis and followed longitudinally for a median of 49 months. Female or black patients and those with severe kidney disease appeared to be more resistant to initial therapy. Increased

relapse risk was associated with the presence of lung (HR 1.71, CI 1.04-2.81) or upper airway disease (HR 1.73, CI 1.04-2.88) and PR3-ANCA positivity (HR 1.87, CI 1.11-3.14). Most importantly, however, severity of histopathologic findings at diagnosis does not predict patients for whom treatment would be futile [119]. While the presence of kidney disease is associated with poor renal outcomes [115, 116], lack of renal involvement is associated with increased risk of relapse [114]. More recently, a high neutrophil to lymphocyte ratio (NLR>5.9) has been shown to predict more frequent relapse in AAV during follow-up [120].

Another controversy is routine monitoring of serum autoantibodies to predict relapses. Presence of PR3-ANCA at the time of remission maintenance has been associated with high rates of relapse [121]. In a recent study of 181 MPO-ANCA positive Japanese patients, the reappearance of MPO-ANCA, after negative conversion, was associated with relapse (OR 26.2, CI 8.2-101) [122]. However, 12-29% patients do not relapse despite reappearance of MPO-ANCA [93, 122, 123]. Thus, serial monitoring of ANCA may predict relapse, but given the high proportion of patients that do not relapse, it should not be used to guide therapy.

CONCLUSION

Upon hearing the first case reports of patients with GPA [55], Ludwig Aschoff, a renowned German pathologist, described the disease as "a new and very special disease" [124]. Over the past three decades, tremendous progress, more than could have been imagined as recently as the late 20th century, has been made through investigative efforts to understand the etiologies, pathogenesis and clinical management of AAV and glomerulonephritis. They have been transformed from diseases that were usually fatal to diseases that are chronic and manageable, with the potential for long-term, symptom-free remission. Nevertheless, many challenges remain. Ideally, investigations will focus on increasing the understanding of molecular mechanisms of genetic and environmental risk factors for disease, decreasing diagnostic delays to lessen the impact of disease on patient's health, and further defining and personalizing treatment strategies that will induce and maintain remission while minimizing occurrence of relapse. Future pursuits, built upon the foundation of discoveries to date, may well lead to a cure.

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Chapter 17

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease is a rare small vessel vasculitis that typically presents with rapidly progressive glomerulonephritis, often in combination with diffuse alveolar haemorrhage. It is characterised by the presence of directly pathogenic autoantibodies directed against antigens expressed in type IV collagen in glomerular and alveolar basement membranes. Treatment aims to rapidly remove these antibodies, and to suppress ongoing antibody production, with a combination of plasmapheresis, cyclophosphamide and prednisolone. When started promptly, the majority of patients respond successfully to treatment, though recovery from severe renal dysfunction presenting with a requirement for dialysis is uncommon. In contrast to other forms of glomerulonephritis and vasculitis, relapse in anti-GBM disease is exceedingly rare, as is recurrent disease after renal transplantation. Despite its rarity, anti-GBM has been extensively studied and now serves as model autoimmune disorder, with recent studies describing novel mechanisms of HLA-associated immune susceptibility, epidemiologic clustering of disease suggesting the importance of environmental exposures, and a potential role for injurious T cell responses in inciting disease

Keywords: ANCA-associated vasculitis, basement membrane, antibodies

INTRODUCTION

Anti-glomerular basement membrane (GBM) disease is a rare small vessel vasculitis that usually presents with rapidly progressive glomerulonephritis, diffuse alveolar hemorrhage, or

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both. It is typified by the presence of autoantibodies directed against antigens intrinsic to the glomerular and alveolar basement membranes, which can be detected in serum or deposited in tissue, and it is therefore classified an immune-complex small vessel vasculitis in the Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [1]. The Consensus acknowledges the relative misnomer of anti-*glomerular* basement membrane disease, given the frequent involvement of alveolar basement membranes, though recognizes the widely accepted use of anti-GBM disease to describe this condition regardless of lung involvement. The Consensus also recognizes the phasing out of eponymous terminology in the classification of vasculitides, though the term 'Goodpasture Disease' is still often used to describe this condition, a reference dating back to a case of necrotizing glomerulonephritis and lung hemorrhage in 1919, that was at the time attributed to atypical influenza infection [2]. It was not until the 1970s, however, and the explosion in immunological laboratory methods, that the disease was fully described [3], following the demonstration of deposited anti-GBM antibodies in renal tissue [4], their detection in circulation [5], and ultimately their pathogenic potential upon passive transfer to non-human primates [6]. Treatment with plasmapheresis and immunosuppression, to rapidly remove these pathogenic autoantibodies and to prevent their ongoing production, was introduced a few years later [7], and remains the mainstay of current treatment approaches, though novel agents are under investigation. Despite its rarity, anti-GBM disease has served as a model for the study of autoimmunity, and it is often regarded as a prototypic antibody-mediated disease. However, the recent recognition of a role for cellular immune effectors in experimental models, studies of the molecular basis of genetic susceptibility to disease, and the description of atypical clinical presentations, highlight that the immuno-pathogenic mechanisms underlying anti-GBM are not yet fully understood, and require further investigation to improve treatment strategies and clinical outcomes.

EPIDEMIOLOGY

Anti-GBM disease is rare, with an estimated incidence of 1-2 per million population (pmp)/year (yr) in European populations, based on single-center biopsy- or serology-based series. A recent study from Ireland was the first to define a nationwide disease incidence, by identifying all cases over a decade via reference immunology laboratories and a national pathology database, reporting a rate of 1.64 pmp/yr [8]. The disease is well recognized in Asian populations [9-12], though is thought to be rarer in African populations [13].

Single-center series suggest that 15-20% of pulmonary-renal syndromes are caused by anti-GBM disease [14-16], and large renal biopsy series show that it accounts for 10-15% of all cases of crescentic glomerulonephritis [17], though it appears to be a rare cause of end-stage renal disease (ESRD) in both adults and children [18, 19]. Anti-GBM disease has a bimodal age distribution, with a peak incidences in the 3rd decade, where a slight male preponderance and presentation with both kidney and lung disease are observed, and in the 6-7th decades, where presentation with isolated kidney disease is more common [20-22].

GENETIC ASSOCIATIONS

The precise etiology of anti-GBM disease remains obscure, though it is likely that environmental triggers act in genetically susceptible individuals to induce disease onset. Anti-GBM disease has strong HLA-gene associations, with approximately 80% of patients inheriting an HLA-DR2 haplotype [23]. A hierarchy of associations with particular *DRB1* alleles has been identified, some positively associated with disease, such as *DRB1*1501*, an observation that has been replicated in both Caucasian and Asian populations [23-25], and some conferring a dominant-negative protective effect (e.g., *DRB1*01*). It has previously been suggested that the dominant-negative effect might be attributed to the higher affinity of the latter allele for binding peptides from the target autoantigen (thus preventing their favorable presentation on MHC molecules) [23], though a recent series of studies using mice transgenic for human HLA molecules (and lacking murine MHC Class II) suggest novel mechanisms of HLA-disease association. These experiments confirmed epidemiologic observations in humans: *HLA-DR15* transgenic mice are susceptible to the induction of experimental anti-GBM disease, whereas mice expressing either *HLA-DR1* or both *HLA-DR15* and *-DR1* are resistant [26, 27]. These studies suggest that presentation of the immunodominant T-cell epitope in the distinct binding registries of *HLA-DR15* and *–DR1* can differentially induce conventional and tolerogenic T cell responses, respectively, thus accounting for the dominant protective effect of *HLA-DR1* via induction of antigen-specific regulatory T cells, even when co-inherited with the *HLA-DR15* susceptibility allele.

In contrast to other antibody, associated glomerular diseases, such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and membranous nephropathy, where genome-wide association studies have identified polymorphisms in the target autoantigen associated with disease susceptibility, a small study did not identify any polymorphisms in *COL4A3*, the gene encoding the anti-GBM disease autoantigen, related to disease predisposition [28]. This observation may require validation in a larger cohort of patients, however, before polymorphisms in *COL4A3*, or other collagen genes, can be definitively excluded from playing a role in disease pathogenesis.

ENVIRONMENTAL ASSOCIATIONS

Goodpasture's original description of pulmonary-renal syndrome occurred during an influenza outbreak in 1919, and other small series of anti-GBM disease have likewise been described in association with influenza infection [29, 30]. Other reports have described seasonal variation and 'outbreaks' of anti-GBM disease [20, 21], and a recent Chinese study identified a high proportion of patients with prodromal respiratory tract infection at the time of anti-GBM disease diagnosis [31]. These observations suggest that those environmental triggers such as infection may contribute to disease onset, a hypothesis that is further supported by the formal identification of both spatial and temporal clustering of cases in the recent Irish study [8]. A number of mechanisms may account for this association with infection – studies in experimental animal models, for example, suggest auto-reactivity to basement membrane antigens may arise through a process of 'molecular mimicry' or idiotype anti-idiotype interactions following a primary response to microbial or other foreign peptides [32, 33]. Of

note, excess reactivity to microbial peptides has been described in patients with anti-GBM disease [34]. It is also possible that usually quiescent autoreactive lymphocytes undergo 'bystander activation' because of systemic inflammatory responses, or that pulmonary inflammation at times of infection may release usually sequestered alveolar basement membrane antigens to immune detection.

The release of sequestered antigens may also account for the association of pulmonary irritant exposure and the development of lung hemorrhage in anti-GBM disease, which occurs in nearly all patients who smoke but less frequently in non-smokers [35]. Hydrocarbon exposure has likewise been implicated in disease onset [36, 37], and there are case reports of anti-GBM disease after use of inhaled recreational drugs including cocaine and amphetamine [38-40]. It has been suggested that pulmonary irritants may increase capillary permeability, thus predisposing to alveolar bleeding, or that they may modify or expose sequestered basement membrane antigens to immune detection, resulting in disease enhancement.

IMMUNOPATHOGENESIS

The Autoantigen

The collagen IV family consists of six genetically distinct α-chains (α1-6) that trimerize with each other to make specific triple-helical protomers: α1α1α2, α3α4α5, and α5α5α6. The expression of the α3α4α5 protomer is almost exclusively restricted to the glomerular and alveolar basement membranes (with the α1α1α2 protomer being most abundantly expressed elsewhere), and the clinical pattern of renal-pulmonary disease thus reflects the restricted expression of this antigen to these locations. In the GBM, these α3α4α5 protomers polymerize end-to-end via their C-terminal non-collagenous domains (NC1) to form hexameric NC1 structures. Specialized sulfilimine bonds cross-linking opposing trimeric NC1 domains reinforce the quaternary structure of this hexamer. It has recently been shown that the generation of these crosslinks, between methionine and lysine residues in the non-collagenous domains, is dependent on the activity of peroxidasin, a peroxidase enzyme that generates hydrobromous acid, a critical intermediate for crosslink formation [41, 42]. The α3α4α5 protomers likewise associate via their N-terminal 7S domains to complete a lattice-like network that is essential for glomerular structure and function. The primary target of the autoimmune response in anti-GBM disease was first identified as a 27kDa protein in collagenase-solubilized GBM preparations, and subsequently shown to be the non-collagenase domain of the α3 chain: α3(IV)NC1 [43, 44]. Immunization with either collagenase-solubilized or recombinant forms of this protein from various species induces disease in a number of animal models, confirming the universal antigenicity of this protein.

HUMORAL IMMUNITY

Anti-GBM disease is regarded as a prototypic antibody-mediated condition, following the seminal observation of disease induction following passive transfer of autoantibody from humans to Squirrel monkeys [6]. All patients with typical anti-GBM disease have antibodies

reactive to α3(IV)NC1, and a proportion also demonstrate reactivity to α4 or α5 chains, identified either in serum or upon elution from kidney tissue, which may arise secondarily due to a process of 'epitope-spreading' within the collagen IV network [45]. Studies in animal models suggest that anti-α5 antibodies also have direct pathogenic potential, and their detection is associated with worse prognosis, though reports of human disease in the native kidney caused by anti-α5(IV)NC1 antibodies (without concurrent anti-α3(IV)NC1 antibodies) are exceptionally rare [46].

Two key B-cell epitopes within α3(IV)NC1 are recognized, designated E_A (incorporating residues 17–31 toward the amino terminus) and E_B (residues 127–141 toward the carboxy terminus) [47]. In disease, antibodies tend to be of the IgG1 and IgG3 subclass, and their titer and avidity have been associated with disease severity [48-51]. Once bound in the kidney, these antibodies can initiate a local inflammatory response *via* both complement- and FcR-dependent mechanisms. It is notable, however, that low-level natural autoantibodies that recognize the same epitopes can be identified in healthy individuals, though they tend to be of different subclass (Ig2 and IgG4 dominant) [52]. In addition, the presence of circulating anti-GBM antibodies can predate the onset of clinical disease by several months [53]. These observations suggest that additional factors contribute to disease pathogenesis.

CELLULAR IMMUNITY

The strong HLA association, the detection of high-affinity, class-switched autoantibody, and the phenomenon of 'epitope spreading,' indicates a requirement for T cell help in the generation of anti-GBM antibodies. Indeed, peripheral CD4+ cells from patients have been shown to proliferate in response to α3(IV)NC1 (as do cells from healthy individuals, but at much lower frequency), and the frequency of autoreactive CD4+ T cells has been shown to correlate with disease activity [54, 55].

Studies in experimental models of anti-GBM disease also suggest that directly nephrogenic T-cell responses may contribute to disease pathogenesis. In early avian models, mononuclear cells could transfer disease to bursectomised birds [56], and B cell deficient mice develop glomerular injury following immunization with α3 (IV) NC1 [57]. Disease has also been transferred by CD4+ T-cells from nephritic rats, expanded *in vitro* by stimulation with α3(IV)NC1, without detectable antibody responses, suggesting directly injurious responses by cellular effectors [58]. In a series of experiments using HLA transgenic mice, Ooi et al. identified an immunodominant T-cell epitope within α3(IV)NC1 that can induce both autoantibody production and glomerulonephritis in mice expressing the human *DRB1*1501* susceptibility allele (but not in mice expressing the protective *DRB1*01* allele) [26]. In addition, CD4+ T-cell clones generated from *DRB1*1501* transgenic mice and specific for the immunodominant T-cell epitope transferred disease to naïve animals. In a rat model, immunization with an immunodominant T-cell epitope resulted in glomerular injury, followed by the expansion of B cell responses to distinct α3(IV)NC1 epitopes in renal draining lymph nodes [59]. It has thus been suggested that T-cell mediated glomerular injury may be the inciting event in anti-GBM disease, that then triggers *de novo* 'internal' immunization to B-cell epitopes released from damaged GBM, and subsequent autoantibody production required for full expression of disease. Direct evidence of this phenomenon in humans is lacking, though historical case reports of patients who developed glomerulonephritis prior to the deposition of

anti-GBM antibodies, and the detection of an early T-cell infiltrate in pathology studies [60, 61], suggests that cell-mediated injury may occur in at least a subset of patients.

TOLERANCE AND AUTOIMMUNITY

α3 (IV) NC1 is expressed in human thymus [55, 62], though the finding of natural autoantibodies and autoreactive T cells in healthy individuals suggests central tolerance to the antigen is incomplete. However, additional immune 'check-points' must be broken for disease to develop. Of note, the B cell epitopes within native α3(IV)NC1 are cryptic, being sequestered within the quaternary structure of the hexameric NC1 structure stabilized by sulfilamine cross-links, such that they remain protected from immune surveillance in normal circumstances [63]. It has been shown that patient-derived anti-GBM antibodies do not bind cross-linked α3α4α5 hexamers until they are dissociated, and it is proposed that the resistance of some mouse strains to experimental anti-GBM disease is due to extensive cross-linking in murine GBM [64]. Thus a process of 'conformational transformation' of the cross-linked α3α4α5 hexamer is thought to be critical to disease pathogenesis, by exposing hidden epitopes to immune detection, and allowing the binding of pathogenic autoantibodies [45]. This may explain the association of anti-GBM disease with other pathologies that physically disrupt or modify the structure of the glomerular (e.g., ANCA vasculitis, lithotripsy) or alveolar (e.g., smoking) basement membranes, and of the induction of humoral responses following T cell mediated glomerular injury.

Relapses are rare in anti-GBM disease, suggesting that immune tolerance can be re-instated as disease resolves. This is supported by the finding of an expanding population of CD25+ antigen-specific T cells in patients after their acute presentation, that may suppress responses to α3(IV)NC1 [65].

CLINICAL PRESENTATION AND DIAGNOSIS

The majority of patients present with rapidly progressive glomerulonephritis (RPGN). As such, a short prodrome of non-specific constitutional symptoms is typical, culminating with overt features of oliguria, fluid overload and uremia. Approximately half of patients require hemodialysis at the point of initial presentation [22]. Loin pain, attributable to distension of the renal capsule, and visible hematuria are recognized. Urine microscopy may identify dysmorphic erythrocytes or red blood cells casts. Proteinuria is usually in the sub-nephrotic range (<3g/day), perhaps reflecting a severe reduction in glomerular blood flow that limits the rate at which protein filtration can occur.

Approximately 40-60% of patients have concurrent alveolar hemorrhage, which is more common in young male patients, and in current smokers [35]. It may present with cough, dyspnea, and hemoptysis, or be apparent radiographically. A disproportionately severe iron-deficient anemia should also alert to the possibility of covert underlying alveolar bleeding. A small proportion of patients (<10%) may present with isolated pulmonary disease in the absence of renal involvement. In one small series, it was found that 11% of patients with lung hemorrhage required artificial ventilation during their treatment for anti-GBM disease [66].

The presence of extra-renal/pulmonary manifestations is uncommon in anti-GBM disease, and may suggest an alternative cause of pulmonary-renal syndrome, or that the patient has co-existing ANCA positivity.

Central to the diagnosis of anti-GBM disease either is the identification of anti-GBM antibodies, in serum or deposited in tissue, along with pathological features of crescentic glomerulonephritis, with or without evidence of alveolar hemorrhage.

SEROLOGIC TESTING

Circulating anti-GBM antibodies were first described using indirect immunofluorescence techniques on normal human or primate kidney [5]. In current practice, a variety of commercial immunoassays is available, which are accepted to have high sensitivity and specificity [67]. These may use native human or animal GBM isolates, or more commonly recombinant α3(IV)NC1 preparations. It is recognized that between 5-10% of patients with demonstrable anti-GBM antibody on renal biopsy are negative by conventional serum assays. As summarized in a recent commentary by Glassock [68], this may be due to:

- Intrinsic sensitivity of the chosen assay
- Isotope or subclass of antibody not being detectable (e.g., for example, rare cases of IgA or IgG4 mediated anti-GBM disease are described)
- Antibody disappearance prior to clinical resolution
- The 'immunological sink' – high affinity antibodies rapidly bind tissue and are removed from circulation, with only low affinity antibodies remaining,
- Absence of relevant epitopes in antigens used in the detection assay
- T-lymphocyte, complement or other mediators causing tissue damage rather than a predominantly antibody mediated process

A proportion of patients who have demonstrable deposition of IgG on the GBM by immunofluorescence, but who are negative for circulating antibodies by these conventional techniques, may be positive when tested by highly sensitive biosensor assay [69]. These cases demonstrate that serological tests, though useful for rapid diagnoses, should not be the sole means of excluding a diagnosis of anti-GBM disease, and reinforces the importance of performing a renal biopsy when possible.

DEPOSITED ANTIBODY

Direct immunofluorescence for immunoglobulin on frozen kidney tissue has high sensitivity for detecting deposited antibodies, and is the gold standard for diagnosis of anti-GBM disease, typically showing a strong linear ribbon-like appearance (Figure 1A). Other causes of linear fluorescence should be excluded (including diabetes, monoclonal paraproteinemia, lupus nephritis, and rarely fibrillary glomerulonephritis). In addition, it should be noted that fluorescence might be negative or unclear in cases with severe glomerular inflammation, where the underlying architecture is so disrupted that the linear pattern may not

be recognized. In typical anti-GBM disease, these deposits are polyclonal and do not show light-chain restriction. Immunoperoxidase techniques using paraffin-embedded tissue may also be used, but may be less sensitive. In our experience, immunofluorescence on lung tissue is rarely informative.

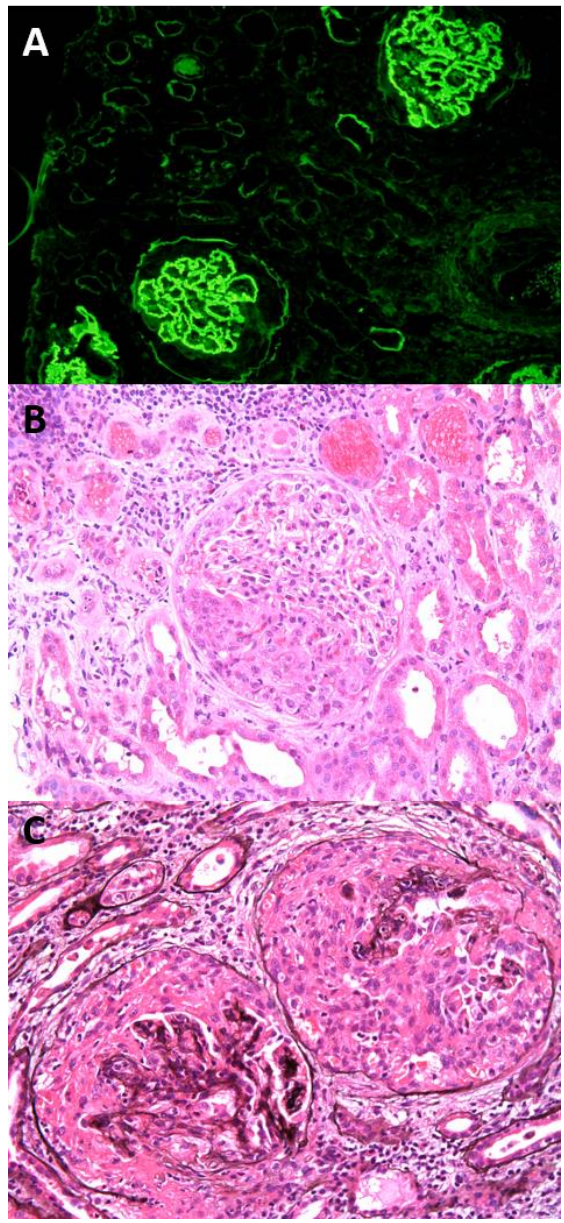

Figure 1. Renal biopsy findings in anti-GBM disease. A: Immunofluorescence for IgG in anti-GBM disease, showing bright linear deposits along glomerular (and to a lesser extent, tubular) basement membranes. B: Hematoxylin and eosin staining in anti-GBM disease, showing a circumscribed glomerular crescent with compression of the underlying tuft. Red blood cells casts are present in tubular lumens. C: Jones methenamine staining in anti-GBM disease, clearing delineating glomerular basement membranes, large circumferential and synchronous crescent formation in adjacent glomeruli, with associated rupture of Bowman's capsule.

Conventional direct immunofluorescence techniques will identify all IgG subclasses, though will not differentiate the antigenic target of the kidney-bound antibody, and so may detect anti-α3 (IV) NCI, anti-α5(IV)NC1, or other antibodies recognizing GBM components. Antibodies to non-collagen chain antigens, such as nidogen (entactin), have been identified in historical case series [70, 71], though their significance is not well characterized. In addition to detecting deposited anti-GBM antibody, immunofluorescence may demonstrate the presence of complement components, in particular C3 and C1q, along the GBM [21]. A proportion of patients may also demonstrate immunoglobulin or complement deposition along tubular basement membranes.

RENAL BIOPSY FINDINGS

Almost all patients with anti-GBM disease will have evidence of crescent formation on kidney biopsy (Figure 1B), and in 80% of patients more than 50% of glomeruli will be affected. The average proportion of affected glomeruli is approximately 75% [17, 72]. The proportion of crescents observed in the biopsy correlates strongly with the degree of renal impairment at presentation [21, 22]. These crescents will typically be of uniform age (Figure 1C), in contrast to other causes of RPGN, where a mixture of cellular, fibrocellular and fibrous crescents may be seen. Asynchronous crescent formation, or the presence of necrotizing vasculitis in larger blood vessels on renal biopsy, should thus alert to the possibility of a concomitant ANCA-mediated process. Given the acuity of disease onset, interstitial fibrosis and tubular atrophy are uncommon in anti-GBM disease (unless there is pre-existing kidney pathology) though interstitial inflammation may be observed. Electron-dense deposits are not seen in isolated anti-GBM disease, though electron microscopy is necessary to exclude concomitant glomerular pathologies, such as membranous glomerulonephritis, and may identify other diseases that may cause linear fluorescence (such as fibrillary GN and diabetic GBM thickening).

DIAGNOSIS OF ALVEOLAR HEMORRHAGE

There are no uniform diagnostic criteria for the diagnosis of diffuse alveolar hemorrhage, and diagnosis is often made on a combination of clinical, radiological and laboratory findings. This may account for the variable frequency of lung hemorrhage described in clinical series of anti-GBM disease.

Plain chest radiography may demonstrate non-specific diffuse opacification patterns with occasional predilection for the midzones and apical and costophrenic sparing [73]. High-resolution computed tomography may show ground-glass opacifications due to alveolar filling with blood, which may progress to frank consolidation, again with peripheral sparing. As hemorrhage is resorbed in the pulmonary interstitium, later imaging may show reticular or nodular appearances [74].

Acute alveolar hemorrhage may be indicated by the finding of hemorrhagic broncho-alveolar lavage fluid, classically with increasing blood content on successive washes. After 2-3 days, alveolar macrophages convert hemoglobin to hemosiderin, and these hemosiderin-laden cells may persist in the lung for several weeks, being evident on Perls staining of broncho-

alveolar samples [75]. Threshold proportions of 20-30% hemosiderin-laden cells of the total macrophage count have been suggested to be strongly indicative of diffuse alveolar hemorrhage.

An increase in diffusing capacity of the lung for carbon monoxide (KCO) has been reported in alveolar hemorrhage in anti-GBM disease, being attributed to increased CO uptake by intra-alveolar erythrocytes [76]. However, this finding may not be present in all cases [66], perhaps due to ventilation-perfusion mismatch in a proportion, such that measurement of KCO may have useful positive, but not negative, predictive value.

Lung biopsy is rarely performed in cases of alveolar hemorrhage in anti-GBM disease. When undertaken, it is likely to show alveolar lumens filled with erythrocytes and hemosiderin-laden cells. Pulmonary capillaritis may be present, with features of fibrinoid necrosis of capillary walls and inflammation and edema of the alveolar interstitium [77].

TREATMENT

The combination of immunosuppression and plasmapheresis to treat anti-GBM disease was first described in 1976 [7], and it remains the core recommendation of the latest KDIGO guideline for treating anti-GBM GN [78]. We have reproduced a recommended treatment schedule (Table 1).

Plasmapheresis aims to rapidly remove directly pathogenic anti-GBM antibodies from the circulation, and its use is supported by observational studies that suggest improved renal and patient survival compared to historical or contemporaneous cohorts treated with immunosuppression alone [22, 79, 80], and one small randomized trial [81]. The American Society for Apheresis (ASFA) includes anti-GBM disease in its recommendations for therapeutic plasmapheresis (Grade 1B, 1C) [82]. Immunoadsorption is an alternative form of extra-corporeal therapy that may be more efficient than plasma exchange for the removal of pathogenic autoantibody (though conversely it may not remove pro-inflammatory or pro-coagulant factors). In small series, it appears to have comparable outcomes to plasma exchange therapy [83, 84].

In addition to plasma exchange therapy, immunosuppression and corticosteroid treatment are required to prevent ongoing autoantibody production to reduce renal and pulmonary inflammation. Daily oral cyclophosphamide and oral prednisolone are the most commonly used agents, forming the basis of nearly all published experience in anti-GBM disease. An uncontrolled retrospective analysis suggests that daily oral cyclophosphamide may be superior to pulsed intravenous treatment [85], in contrast to AAV. The use of other immunosuppressive therapies is less well described [86-88]. Rituximab is an effective treatment for a number of other autoantibody associated glomerular diseases, though published experience in anti-GBM disease is limited to approximately 20 cases [89-98], where it has most commonly been used as adjunctive or second-line therapy in resistant disease. It appears to be associated with immunological response, though clinical outcomes are variable. At present, there is insufficient evidence to recommend its use first-line in the treatment of anti-GBM disease; however, it may be considered where there are compelling contra-indications to cyclophosphamide therapy or as adjunctive treatment in severe disease. Rituximab may also be considered for expediting antibody clearance in patients awaiting renal transplantation who remain seropositive.

Table 1. Initial treatment of Anti-GBM disease (adapted from references [13, 140])

Agent	Details and Duration	Cautions
Plasma exchange	Daily 4 L exchange for 5% human albumin solution. Add fresh human plasma (300-600 mL) within 3 days of invasive procedure (e.g., kidney biopsy) or in patients with alveolar hemorrhage. Continue for 14 days or until antibody levels are fully suppressed. Monitor antibody levels regularly after cessation of treatment as plasma exchange may require reinstatement if antibody levels rebound.	Monitor and correct as required: platelet count; aim $>70 \times 10^9$/L; fibrinogen; aim >1 g/L (may require cryoprecipitate supplementation to support PEX); hemoglobin, aim for >90 g/L; corrected calcium, aim to keep in normal range
Cyclophosphamide	2 mg/kg/day given orally for 2–3 months. Reduce dose to 2 mg/kg in patients >55 years.	Stop if leukocyte count falls to $<4 \times 10^9$/L and restart at reduced dose when recovered. Insufficient evidence to recommend use of IV cyclophosphamide.
Corticosteroids	Prednisolone 1 mg/kg/day (maximum 60 mg) given orally. Reduce dose weekly to 20mg by 6 weeks, then gradually taper until complete discontinuation at 6–9 mo.	There is no evidence to support the use of methylprednisolone, and it may increase the risk of infection
Prophylactic treatments	Prophylaxis against oropharyngeal fungal infection (e.g., nystatin, amphotericin, or fluconazole) while on high-dose steroids. Peptic ulcer prophylaxis (e.g., with PPI) while on high-dose steroid treatment. Prophylaxis against PCP (e.g., cotrimoxazole) while receiving high-dose corticosteroids and cyclophosphamide. Consider acyclovir for CMV prophylaxis. Consider prophylaxis against HBV reactivation (e.g., lamivudine) in patients who have evidence of previous infection (HBV cAb positive).	H_2 receptor antagonists in those who are intolerant of PPI. Cotrimoxazole may contribute to leukopenia; monitor leukocyte count. Alternatives include nebulized pentamidine.

Abbreviations: cAB = core antibody; CMV = cytomegalovirus; GBM = glomerular basement membrane; HBV = hepatitis B virus; IV = intravenous; PCP = *Pneumocystis jiroveci* pneumonia; PEX = plasma exchange; PPI = proton pump inhibitor. Table adapted from reference [13].

Novel therapies undergoing evaluation in anti-GBM disease include IdeS (IgG-degrading enzyme of *S. pyogenes*), a streptococcoal enzyme that is able to cleave both circulating and membrane-bound immunoglobulin [99]. IdeS was safe and tolerable in early phase human studies, and was shown to be effective for the removal of anti-HLA antibodies in patients undergoing renal transplantation [100]. A clinical study in severe anti-GBM disease, where it may promote rapid clearance of pathogenic autoantibody, is ongoing (EudraCT number: 2016-004082-39). We have recently shown that treatment with fostamatinib, a spleen tyrosine kinase (SYK) inhibitor, effectively reverses crescent formation in rodent models of anti-GBM disease [101, 102] (and that intra-glomerular SYK can be detected in patient kidney biopsies [103]) so it would be of interest to explore the use of this agent in advanced clinical disease.

OUTCOME AND PROGNOSIS

Diffuse alveolar hemorrhage secondary to anti-GBM disease appears to be highly responsive to treatment, with 90-100% of cases responding to immunosuppression and plasmapheresis [22, 66]. Data on long-term respiratory outcomes, however, are scarce. One small study suggested that patients who had lung hemorrhage have significantly reduced KCO compared to controls without lung involvement [104]. However, a subsequent larger series suggested that long-term respiratory sequela after lung hemorrhage in anti-GBM disease are not common [66]. This is in contrast to AAV, where interstitial lung disease is increasingly recognized as an important long-term complication, especially in patients positive for MPO-ANCA, suggesting that distinct mechanisms of pulmonary injury in these diseases [105, 106].

Renal outcomes in anti-GBM disease may be more variable. Long-term follow up of the largest cohort of patients (n = 71) all treated with the combination of plasma exchange, cyclophosphamide and corticosteroids, suggests that this approach is effective in preserving independent kidney function in the majority of patients, including those who present with severe kidney dysfunction, provided they do not require dialysis at presentation [22]. In patients presenting with creatinine values <500umol/L, renal survival was 95% and 94% at 1- and 5-years respectively. In patients presenting with creatinine >500umol/L, but not requiring immediate dialysis, renal survival was 82% and 50% at the same respective time-points. In patients presenting with an initial requirement for dialysis, however, renal recovery occurred in only 8% at 1 year. Other reports have described similarly low levels of renal recovery in patients presenting with dialysis-dependent kidney failure, with the highest rate of approximately 20% recovery in one series [107].

Predictors of poor renal outcome include severe renal dysfunction at diagnosis, the proportion of glomeruli affected by crescents, and oliguria at presentation [21, 22, 108]. A recent worldwide, multi-center study recruited 123 cases of renal biopsy-proven anti-GBM glomerulonephritis, making it the largest histopathological study in anti-GBM disease to date [109]. It confirmed previous observations of more favorable outcomes in patients presenting with creatinine of <500μmol/L. Independent predictors of ESRD were dialysis-requirement at presentation, reduced proportion of normal glomeruli, and increased interstitial infiltrate on kidney biopsy. Of note, no patient with 100% crescents or >50% sclerotic glomeruli recovered renal function, and so withholding treatment may be considered in these cases if lung hemorrhage is not present. Rare cases of renal recovery despite adverse pathologic findings [110, 111], however, highlights the need to consider all cases for treatment, with specific attention to other features that might predict renal recovery on biopsy (such as concomitant acute tubular injury). A short trial of early treatment may be considered, and rapidly tapered if there is no evidence of renal recovery within 2-4 weeks. In addition, the potential benefit of a period of immunosuppression to expedite autoantibody clearance, thus allowing earlier kidney transplantation, should be considered in suitable patients.

Relapse is rare in anti-GBM disease, occurring in fewer than 3% of patients [22]. It is usually associated with ongoing exposure to pulmonary irritants such as cigarette smoke or hydrocarbons [112, 113], and avoidance of these precipitants is an essential part of long-term management of these cases. We recommend repeat kidney biopsy in cases of relapse with kidney involvement, in order to secure an accurate diagnosis and to exclude concomitant

pathologies such as AAV and membranous nephropathy. In confirmed cases, standard re-treatment with cytotoxic medications and corticosteroids is usually indicated.

The long-term outcome of patients who progress to ESRD due to anti-GBM GN appears to comparable to patients with ESRD of other causes, whether they remain on dialysis or undergo kidney transplantation [18, 114]. It should be noted, however, that kidney transplantation performed in the presence of anti-GBM antibodies results in a high likelihood of disease recurrence in the allograft, at frequencies of up to 50% in historical series [115], and that a period of at least six months sustained seronegativity is advised prior to undertaking transplantation in patients who have reached ESRD due to anti-GBM disease [78]. Under these circumstances, and with current immunosuppressive regimens, recurrent disease is rare [18].

VARIANT PRESENTATIONS OF ANTI-GBM DISEASE

Double-Positive Anti-GBM and ANCA-Associated GN

In some series, almost half of patients with anti-GBM disease have detectable ANCA (usually recognizing myeloperoxidase, MPO), and up to 10% of patients with ANCA have circulating anti-GBM antibodies [116-118]. This phenomenon was first reported within a few years of the first description of ANCA [116, 119], and while it is clear that the autoantibodies are antigenically distinct [120], the mechanism of this association is not understood. It has been shown that ANCA may be detected before the onset of anti-GBM disease, suggesting that ANCA-induced glomerular inflammation may be a trigger for the development of an anti-GBM response, perhaps by modifying or exposing usually sequestered disease epitopes in GBM [53].

These ‘double-positive’ patients appear to have a hybrid clinical phenotype, experiencing the early morbidity and mortality of anti-GBM disease, with severe kidney and lung disease at presentation, requiring aggressive immunosuppressive therapy and plasma exchange [121]. There is a suggestion they more be more responsive to treatment, with increased rates of recovery from dialysis. During long-term follow-up, however, they relapse at a frequency comparable to patients with AAV, suggesting they warrant more careful long-term follow up and maintenance immunosuppression, unlike patients with single-positive anti-GBM disease.

Anti-GBM Disease Associated with Membranous Nephropathy

There are several reports of anti-GBM disease associated with membranous nephropathy, occurring as a preceding, simultaneous, or succeeding diagnosis [122, 123]. As with the ANCA-association, it is postulated that disruption of glomerular architecture by one disease reveals hidden epitopes that allow the second process to occur. A rapid decline in kidney function in a patient with known membranous nephropathy should raise suspicion of the development of superimposed crescentic nephritis or anti-GBM disease, and re-biopsy is recommended. We suggest that such cases are treated initially as for anti-GBM disease, though how they should be managed in the long-term is not clear. The authors of a recent case report suggest that rituximab may be a useful agent to treat both pathologies simultaneously [92].

Post-Transplant Anti-GBM Disease in Alport Syndrome

After kidney transplantation for Alport syndrome, recipients may develop anti-GBM antibodies as an alloimmune response to the neo-antigens contained in 'normal' α3, α4 or α5 chains expressed in the kidney allograft. In classical X-linked Alport syndrome (caused by mutations in the *COL4A5* gene encoding the α5 collagen chain) these antibodies do not recognize the individual E_A and E_B epitopes of the α3 chain recognized by sera from typical Goodpasture patients, but rather a distinct, composite epitope on the α5 chain, that is not sequestered within the native hexamer of the Goodpasture antigen [45]. It should be noted that commercially available anti-GBM assays, which are optimized to detect reactivity to the α3(IV)NC1 antigen, might fail to detect circulating antibodies in this setting. Anti-GBM antibodies may be detected in 5-10% of Alport patients following transplantation, though the development of overt glomerulonephritis in the allograft is less frequent (perhaps owing to the effects of maintenance immunosuppression). When glomerulonephritis develops, however, it usually occurs early and carries a high risk of graft loss [124, 125]. Repeated transplantation in this setting almost invariably leads to more aggressive disease recurrence and rapid graft loss, and is undertaken at very high risk [126]. Individuals with large *COL4A*5 gene deletions are at increased risk of post-transplant anti-GBM disease, and recent guidelines encourage the use of genetic testing to inform discussions regarding the risk of *de novo* anti-GBM disease after transplantation [127].

'ATYPICAL' ANTI-GBM DISEASE

'Atypical Anti-GBM disease' is a term that has been used variably to describe cases with classical linear IgG staining on renal biopsy, but uncharacteristic clinicopathologic features. A large series (n = 20) of 'atypical' cases was recently reported by Nasr and colleagues – all had bright linear GBM staining for immunoglobulin on kidney biopsy, though none had detectable α3(IV)NC1 antibodies by commercial ELISA, and none had lung hemorrhage [128]. Most had had only mild renal insufficiency, though all had proliferative glomerular changes on renal biopsy, but without diffuse crescent formation. Treatment was with heterogeneous immunosuppression (and generally did not include plasma exchange), and both patient and renal survival at one year were favorable, at 93% and 85%, respectively. Of note, GBM staining was IgM dominant in two cases, and IgA dominant in another. In addition, half of the patients had restriction for either kappa or lambda lights on immunofluorescence testing, though none had glomerular capillary wall deposits on electron microscopy (that would be expected in proliferative GN with monoclonal immunoglobulin deposits; PGNMID), nor did they have identified features of an underlying plasma cell dyscrasia. A number of other case reports and small series have similarly described 'atypical' cases, with similarly indolent renal disease and seronegativity by conventional assay. One recent report describes a case of florid anti-GBM disease with kappa-light chain restriction on GBM staining in association with a circulating paraprotein [129], thus suggesting that anti-GBM disease may occur within the spectrum of 'monoclonal gammopathy of renal significance.' A number of mechanisms for the unusual pattern of renal injury in these cases have been proposed, including differences in antibody

isotype or subclasses, varied antigenic targets, and differential pathogenicity in antibodies related to their ability to fix complement or recruit inflammatory cells [130].

ANTI-GBM DISEASE AFTER ALEMTUZUMAB THERAPY

Secondary autoimmune phenomena after alemtuzumab, an anti-CD52 lymphocyte depleting treatment for relapsing-remitting multiple sclerosis (MS), are common [131]. Autoimmune thyroid disease occurred in up to 30% of patients in controlled trials, and there are case reports of both membranous nephropathy and anti-GBM disease following treatment [132, 133]. It has been proposed that T-cell reconstitution after alemtuzumab is driven largely by homeostatic expansion of cells that have escaped deletion (rather than by thymopoesis), resulting in a T-cell pool that is enriched for autoreactive cells [134]. Anti-GBM disease has not been reported when alemtuzumab is used for other indications other than MS (e.g., renal transplantation), perhaps due to the use of maintenance immunosuppression, or due to the shared HLA susceptibilities in MS and anti-GBM disease. Careful monitoring of patients for renal pathology after treatment with alemtuzumab is needed in order to facilitate early detection and treatment [135]. We suggest conventional treatment for anti-GBM disease occurring in this setting.

ISOLATED PULMONARY INVOLVEMENT IN ANTI-GBM DISEASE

Presentation with isolated or predominant pulmonary involvement in anti-GBM disease is recognized, though uncommon, being estimated to occur in <10% of patients in larger series. Such cases are not extensively characterized, perhaps reflecting publication bias from renal centers, though there are small case series [136, 137]. Some patients may have mild urinary abnormalities and minor proliferative changes on renal biopsy, but with preserved excretory renal function, while others may have no clinical or histological evidence of renal of renal inflammation. Renal biopsy, however, may still reveal linear deposits of immunoglobulin, including in those patients who are negative by serological assay. A small series from Sweden recently described four young female patients who presented with severe alveolar hemorrhage and favorable renal outcome, who were seronegative for circulating anti-GBM antibodies by conventional assay [138]. They were, however, found to have circulating IgG4 anti-GBM antibodies by dedicated ELISA, and this was confirmed on kidney biopsy. Together, these findings suggest that clinical presentation in anti-GBM disease may be influenced by differences in antibody subclass or antigen target, and highlight the need to consider variant anti-GBM disease in cases of ‘idiopathic’ pulmonary hemorrhage.

CONCLUSION

Despite its rarity, anti-GBM disease has been extensively studied, and it now serves as a model autoimmune disorder: it has a well-characterized autoantigen with defined epitopes; it demonstrates the directly pathogenic potential of specific autoantibodies; T-cell responses

contribute to disease pathogenesis, both as orchestrators of the immune response and as effectors of tissue injury; and recent work sheds light on the molecular mechanisms via which HLA inheritance may confer autoimmune susceptibility. However, variant and atypical presentations demonstrate that anti-GBM disease cannot be regarded as a 'one-dimensional' entity [139], and that the mechanisms which induce the aberrant adaptive immune response directed to self-antigen are not fully understood and may not be common to all patients. Further insights into these inciting events and, given the extreme rarity of relapses, the mechanisms via which immune tolerance is reinstated as disease resolves, may have important therapeutic implications not just in anti-GBM disease, but also for a spectrum of autoimmune disorders in future. The abrupt clinical presentation of life-threatening lung hemorrhage and rapidly progressively glomerulonephritis, however, renders the disease of equal import to physicians as to immunologists, as early recognition and prompt initiation of immunosuppression and plasmapheresis is necessary to preserve kidney function and prevent mortality. Current treatment strategies, when introduced early enough, appear to be effective, though improved prognostic and therapeutic approaches are required for those presenting with advanced renal failure.

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Chapter 18

SYSTEMIC VASCULITIS OF THE GASTROINTESTINAL TRACT

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ABSTRACT

Systemic vasculitides are a cause of vascular inflammation throughout the body including the gastrointestinal tract. The nature of gastrointestinal (GI) involvement depends on the size and location of the affected vessels. Involvement of large vessels typically leads to downstream ischemia and tissue infarction. Medium vessel involvement can cause hemorrhage from ruptured aneurysms, downstream ischemia and tissue infarction. Small vessel involvement typically leads to ulceration, patchy infarction and bleeding. Severe GI involvement in systemic vasculitis confers a worse prognosis. Management of the underlying vasculitic process includes some form of immunosuppression however surgical intervention to manage intra-abdominal pathology caused by the vasculitic process may also be necessary. Revascularization procedures may be needed to manage aneurysm formation and to rescue ischemic tissue. This chapter reviews GI involvement in primary and secondary vasculitic diseases and outlines their management. Consideration will be given to GI tract complications due to immunosuppressive therapy for systemic vasculitis.

Keywords: systemic, vasculitis, gastrointestinal, autoimmunity

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INTRODUCTION

The hallmark of vasculitis is inflammation in the blood vessels seen histologically as fibrinoid necrosis or in some cases granulomatous inflammation. Inflammation and occlusion of the vessel lumen of muscular arteries leads to downstream tissue ischemia and necrosis while focal involvement of the vessel wall can result in aneurysm formation and vessel rupture with catastrophic bleeding [1]. Vasculitis affects any part of the body depending on the blood vessel or vascular bed involved. In some vasculitides, gastrointestinal tract (GIT) involvement is common. In considering how different vasculitides can affect the GIT it is important to revisit the classification of vasculitis.

Vasculitis can be classified as primary or secondary in nature, and localized or systemic in its distribution and organ involvement. The 2012 Chapel Hill Consensus Conference (CHCC) [2] provides a useful nosology and definitions of the vasculitides based upon the caliber of the vessel involved and the associated clinicopathological features (Table 1). Primary systemic vasculitides occur as a primary process, whereas secondary vasculitides are secondarily associated with another underlying condition such as connective tissue disease, hypersensitivity reactions to drugs or infection. Localized or single organ vasculitides manifest symptoms confined to a single organ or to the skin whereas systemic vasculitides are characterized by constitutional symptoms and multiorgan involvement.

Overall, the extent and distribution of GIT involvement by the underlying vasculitic process, whether primary or secondary, depends mainly upon the size and location of affected vessels. A vasculitic cause for a given GIT disturbance should be suspected when unusual sites such as the stomach, duodenum, and rectum are involved by mesenteric ischemia along with systemic features or multi-organ involvement, particularly in young patients [3]. In a recent series reporting endoscopically confirmed upper GI involvement amongst 148 patients with vasculitis, IgA vasculitis was the most prevalent underlying vasculitic process (57%) followed by Takayasu arteritis (TA) (14%), microscopic polyangitis (MPA) (10%) and polyarteritis nodosa (PAN) (7%) [4]. Notably, patients with Bechet disease (BD) were excluded from this study.

Table 1. Classification of Vasculitis*

	Primary	Secondary
Large vessel	Giant cell arteritis	
	Takayasu arteritis	
Medium vessel	Polyarteritis nodosa	
	Kawasaki disease	
Small vessel	Henoch-Schonlein purpura	Systemic lupus erythematosus
	Granulomatosis with polyangiitis	Rheumatoid vasculitis
	Microscopic polyangiitis	Cryoglobulinemia
	Eosinophilic granulomatosis with polyangiitis	Other (drugs, infections, malignancy)

*Adapted from reference 13.

Acute mesenteric ischemia and tissue infarction secondary to vasculitis are well recognized [5-10]. Although relatively rare, vasculitic GIT involvement leading to acute abdominal pathology is potentially catastrophic and it is therefore important to promptly diagnose it in the appropriate clinical setting. Mesenteric vasculitis accounts for less than 5% of all patients with

chronic mesenteric ischemia [11], while other GIT manifestations of vasculitis include ulceration, submucosal oedema, hemorrhage, paralytic ileus, bowel obstruction and perforation [12].

This chapter will consider both primary and secondary vasculitides first giving a brief outline of the diseases followed by specific GIT involvement with consideration of the investigations, management and prognostic implications of GIT involvement. Treatment-related GIT morbidity will also be considered.

PRIMARY SYSTEMIC VASCULITIS

Large Vessel Vasculitides

Vasculitic involvement of large vessels leads to symptoms similar to mesenteric ischemia and may be difficult to differentiate from atherosclerotic disease when systemic features are absent or not apparent.

Takayasu Arteritis

Epidemiology

Takayasu arteritis involves large arteries and is pathologically characterized by granulomatous inflammation of the aorta and its major branches [13]. The disease, which has a female preponderance with a predominant age at onset of 10 to 40 years [14, 15], is rare but has an increased incidence in Asian, Mexican and Japanese populations [16].

Classification and Diagnostic Criteria

Table 2. The American College of Rheumatology 1990 Criteria for the Classification of Takayasu Arteritis*

Criteria	Definition
Age at disease onset <40 years	Development of symptoms or findings related to Takayasu arteritis at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both of brachial arteries
BP difference >10mmHg	Difference of >10mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia or similar causes; changes usually focal or segmental

For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.

*Adapted from reference 15.

In 1990 the American College of Rheumatology (ACR) published criteria for the classification of TA [15], while other useful classification and diagnostic criteria were published in 1988 by Ishikawa [17], and later modified by Sharma and colleagues [18], both of which are shown in Tables 2 and 3.

Table 3. Ishikawa Criteria for Diagnosis of Takayasu Arteritis*

Criteria	Definition
Three Major Criteria	
1. Left mid subclavian artery lesion	The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography
2. Right mid subclavian artery lesion	The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice to the point 3 cm distal to the orifice determined by angiography
3. Characteristic signs and symptoms of at least 1 month duration	These include limb claudication, pulselessness or pulse differences in the limbs, an unobtainable or significant blood pressure difference (> 10 mmHg systolic blood pressure difference in limb), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea or palpitations
Ten Minor Criteria	
1. High ESR	Unexplained persistent high ESR >20 mm/hour (Westergren) at diagnosis or presence of the evidence in patient's history
2. Carotid artery tenderness	Unilateral or bilateral tenderness of common carotid arteries on palpation. Neck muscle tenderness is unacceptable
3. Hypertension	Persistent blood pressure >140/90 mmHg brachial or >160/90 mmHg popliteal
4. Aortic regurgitation or annuloaortic ectasia	By auscultation, angiography or Doppler echocardiography. By angiography or two-dimensional echocardiography
5. Pulmonary artery lesion	Lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or in bilateral pulmonary arteries determined by angiography
6. Left mid common carotid lesion	Presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography
7. Distal brachiocephalic trunk lesion	Presence of the most severe stenosis or occlusion in the distal third determined by angiography
8. Descending thoracic aorta lesion	Narrowing, dilatation or aneurysm, luminal irregularity or any combination determined by angiography. Tortuosity alone is not acceptable
9. Abdominal aorta lesion	Narrowing, dilatation or aneurysm, luminal irregularity or aneurysm combination
10. Coronary artery lesion	Documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus

The presence of two major, one major and three minor, or four minor criteria suggests a high probability of TA.
*Adapted from reference 18.

Clinical Features

Constitutional symptoms including fatigue, weight loss, arthralgia and fever are common in TA particularly in the early stages of the disease. Specific symptoms such as claudication of extremities, headaches, presyncope, syncope, and angina depend on the affected vessels involved [19] (Tables 2 and 3).

Imaging

Conventional angiography is the gold standard for vascular assessment in TA with common sites of involvement located along the middle and proximal parts of the left subclavian

and carotid arteries [19]. A study of 60 patients with TA found the abdominal aorta to be involved in 47% of patients employing conventional angiography, with the vast majority of abnormalities due to stenotic rather than aneurysmal vascular changes [19]. Involvement of the abdominal aorta occurs in the descending aortic syndrome that can lead to mesenteric vasculitis in TA. Mesenteric vessel involvement is seen in up to 18% of patients with TA studied by conventional angiography [3, 16, 19]. Although mesenteric vascular involvement of TA is relatively common on radiological assessment, symptomatic GIT involvement on presentation is rare with one study looking at TA in children reporting only 9% presenting with abdominal symptoms [20].

Due to the invasive nature of conventional angiography, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and positron emission tomography (PET) have been employed in the evaluation of TA, particularly when therapeutic intervention is not anticipated. CTA averts the risk of arterial puncture, accurately depicts luminal changes, and provides useful information on mural changes such as arterial wall thickening and mural thrombi that might otherwise not be appreciated on conventional angiography [20]. MRA avoids the risks of radiation and the need for intravenous injection of iodinated contrast, while providing a generalized arterial survey similar to that of CTA. PET may have a role in differentiating between active lesions and scar formation along areas of vascular wall thickening [21]. A recent meta-analysis found PET to have a sensitivity of 87% and specificity of 73% for assessing TA disease activity [22].

Gastrointestinal Involvement

GI involvement is manifested by mesenteric artery ischemia presenting mainly as postprandial mesenteric angina that may require revascularization. Diarrhea and GI haemorrhage commonly occur due to mesenteric vessel involvement. Rarely this may culminate in acute intestinal infarction which is catastrophic when it occurs [16, 19]. There is a single case report of TA initially presenting as intestinal gangrene secondary to intestinal infarction [23]. Aneurysmal dilatation is a recognized complication of TA particularly along the descending thoracic and abdominal aorta [18]. There is a single report of a patient with TA manifesting as primary aortic-esophageal fistula formation associated with a saccular aneurysm of the proximal descending aorta [24].

Treatment

Treatment in TA can be divided into pharmacological therapy aimed at suppressing inflammation, and revascularization. Corticosteroids are the mainstay of pharmacotherapy although methotrexate, azathioprine, anti-tumor necrosis factor (TNF) therapy, and cyclophosphamide have all been used in patients with TA refractory to corticosteroids [25-27].

Revascularization treatment in TA is delivered by open conventional bypass grafting or endovascular means including, percutaneous transluminal angioplasty with or without stent insertion [28]. Advances in interventional radiology have led to more widespread use of endovascular techniques in the management of high-risk patients. There are several patient reports and case series of TA in the literature describing the successful outcome of endovascular repair of challenging stenotic and aneurysmal lesions [29-33]. Comparisons of the surgical versus endovascular management of lesions of the abdominal aorta in TA shows that the risk of complication, especially restenosis, is higher with endovascular than surgical intervention

[34, 35]. A multicenter retrospective study found that over a median follow up of 6.5 years the risk of complications following endovascular repair was 50% compared to 37.5% after surgical repair [35]. Multivariable analysis revealed that patients with TA and evidence of systemic inflammation at the time of revascularisation, as defined by an erythrocyte sedimentation rate (ESR) > 30 mm/hour and C-reactive protein (CRP) level > 6 mg/L, were 7-fold more likely to develop post-procedural complications including restenosis.

Giant Cell Arteritis

Epidemiology and Classification

Giant cell arteritis (GCA) is characterized by granulomatous inflammation that predominantly affects the thoracic aorta and its branches. The age of onset is greater than 50 years with an increased incidence in those 70 to 80 years of age, and a higher incidence in Northern Europeans and North Americans of Scandinavian descent compared to other ethnic groups [36]. The 1990 ACR criteria are shown in Table 4. It should be noted that these criteria were intended for the classification not the diagnosis of GCA [37].

Table 4. The American College of Rheumatology 1990 Criteria for the Classification of Giant Cell Arteritis*

Criteria	Definition
Age at disease onset >50 years	Development of symptoms beginning at age 50 years or older
New headache	New onset of or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness on palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated ESR	ESR > 50mm in the 1st hour by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

For the purposes of classification at least 3 criteria must be fulfilled; sensitivity 93.5%, specificity 91.2%.
*Adapted from reference 37.

Clinical Features

The commonest manifestation of GCA is headache followed by scalp tenderness, jaw claudication and visual disturbances; constitutional symptoms such as fever, fatigue and weight loss are also prominent [5, 36]. Approximately 20% of patients with GCA develop clinical manifestations reflecting large vessel involvement including aneurysmal and stenotic lesions of the abdominal aorta which in turn can lead to GI sequelae [36].

Gastrointestinal Involvement

GCA can affect both the liver and the bowel. Asymptomatic involvement of the liver, as manifested by elevated serum alkaline phosphatase and transaminase levels, is reported in up to 50% of patients with GCA [38]. The mechanism leading to liver enzyme derangement is not fully understood however when liver biopsy has been conducted in cases of symptomatic liver involvement, this has demonstrated granulomatous inflammation of medium-sized arterioles within the portal tracts [39]. Whilst clinically evident mesenteric involvement is uncommon,

occult radiographic manifestations are noted on arteriography in 18% of patients with GCA [5, 40, 41].

In total there have been 11 reported cases of GCA with bowel involvement, mainly in the form of mesenteric ischemia. Of 11 patients with bowel involvement in GCA, nine were biopsy-proven [5, 8, 42-49], of whom four presented with abdominal symptoms in the absence of symptoms of temporal arteritis. Temporal artery biopsy was positive in only two of the four patients suggesting a negative temporal artery biopsy may not be able to reliably exclude GCA involving the mesenteric vasculature [5].

Treatment

The mainstay of treatment in GCA is high dose corticosteroids to induce remission. Methotrexate is recommended as an adjunctive therapy, while TNF-α and interleukin (IL)-6 inhibitors may have a role in the treatment of relapsing or refractory disease [36, 50-52]. The IL-6 inhibitor tocilizumab has shown particular promise with a recent phase three randomized controlled trial demonstrating significant improvement in sustained remission rates and steroid sparing effects in both newly diagnosed and relapsing GCA [52]. For occlusive disease surgical revascularization is indicated. Comparison of the outcomes of 15 patients undergoing open revascularization for occlusive mesenteric vasculitis secondary to TA, PAN, GCA and indeterminate vasculitis compared to 163 patients undergoing open operations for atherosclerotic disease [11] showed that both groups had similar freedom from mesenteric symptoms and primary graft patency. In this study 8 of the 15 patients with vasculitic disease had active inflammation at the time of intervention and by the end of follow up (mean follow-up 41 months) 14 of 15 patients remained asymptomatic suggesting that surgical revascularization even during active disease is an effective treatment for occlusive mesenteric vasculitis.

MEDIUM VESSEL VASCULITIDES

Ischemia and infarction in dependent organs associated with bleeding in the GIT and within the abdominal cavity, and aneurysm formation occurs in the context of vasculitic involvement affecting medium size vessels typified by polyarteritis nodosa (PAN) and Kawasaki disease (KD).

Polyarteritis Nodosa

Epidemiology

This systemic necrotizing vasculitis is characterized by fibrinoid necrosis that typically involves medium sized arteries [53]. It typically affects middle-age and older individuals with a peak onset in the 6th decade of life. Hepatitis B virus (HBV) infection is associated in up to one third of patients with PAN and is an important consideration with regards to treatment and prognosis [54].

Classification and Diagnosis

Diagnosis of PAN entails the integration of clinical, angiographic and biopsy findings (table 5). Angiographic evaluation is very helpful in the diagnosis and management of PAN. The gold standard is conventional arteriography, with increasing utilization of both CTA and MRA. The typical findings are multiple aneurysms less than 1 cm in diameter that are most often found in the distribution of the renal and mesenteric arteries, the superior mesenteric artery being the commonest vessel involved in some series [16, 55]. The lesions classically affect branch points and the bifurcation of arteries due to segmental erosion and inflammation that weakens the arterial wall [3]. These aneurysms are not pathognomonic for the condition as they can be found in granulomatosis with polyangiitis (GPA) as well as in systemic lupus erythematosus (SLE) [56].

Table 5. The American College of Rheumatology 1990 Criteria for the Classification of Polyarteritis Nodosa*

Otherwise unexplained weight loss of > 4 kg
Presence of livedo reticularis
Testicular pain or tenderness
Myalgia (excluding that of the shoulder hip and girdle) or weakness
Mononeuropathy or polyneuropathy
New onset rise in diastolic blood pressure >90 mmHg
Elevated levels of serum blood urea nitrogen (>40 mg/dL or >14.3 mmol/L) or creatinine (>1.5 mg/dL or >132 µmol/L)
Evidence of hepatitis B virus infection via serum antibody or antigen serology
Characteristic arteriographic abnormalities not resulting from non-inflammatory disease processes
A biopsy of medium or small sized artery containing polymorphonuclear cells

For the purposes of classification at least 3 criteria must be fulfilled; sensitivity 82%, specificity 87%.
*Adapted from reference 53.

Clinical Features

Table 6. Clinical Features of Polyarteritis Nodosa*

Manifestation	Specific Problems	Frequency (%)
Systemic symptoms	Fever, malaise, weight loss	80
Neuropathy	Mononeuritis multiplex, polyneuropathy	75
Arthralgia and/or myalgia	Articular and/or diffuse extremity pain	60
Cutaneous	Livedo reticularis, purpura, ulcers	50
Renal disease	Elevated creatinine, hematuria, glomerulonephritis	50
Gastrointestinal symptoms	Abdominal pain, rectal bleeding	40
Hypertension	New onset	35
Respiratory manifestations	Infiltrates, nodules, cavities	25
Central nervous system disease	Stroke, confusion	20
Orchitis	Testicular pain, swelling	20
Cardiac involvement	Cardiomyopathy, pericarditis	10
Peripheral vascular disease	Claudication, ischemia, necrosis	10

*Adapted from reference 57.

Clinical features of PAN include constitutional symptoms such as malaise, weight loss and fever as well as specific symptoms and signs reflecting the extent of multi-system involvement [57] (Table 6).

Gastrointestinal Involvement

GI involvement occurs in 14 to 65% of patients with PAN affecting both the bowel and hepatobiliary system [55]. Abdominal pain is the most commonly reported GI symptom in PAN. Bowel manifestations of PAN include ulceration, obstruction, infarction, and perforation and hemorrhage that can affect the stomach, small and large bowel and the appendix with the small bowel being most commonly affected [56-58]. Bowel involvement can arise from stenotic lesions that lead to bowel wall ischemia and aneurysm formation that results in hemorrhage. Necrosis of the bowel wall with the potential for subsequent perforation can develop if systemic inflammation gives rise to transmural ischemia and confers a poor prognosis [55]. Liver involvement occurs in 16 to 56% of patients and can manifest as fibrinoid necrosis of the liver, hepatic artery aneurysms, liver infarction or hepatolithiasis [55, 59, 60]. Small vessel vasculitis of the arteries that supply the bile ducts and gall bladder can lead to intrahepatic sclerosing cholangitis, bile duct stricture, cholecystitis, and hemobilia. Pancreatic involvement can also occur in the form of pancreatitis, pseudocysts and pancreatic insufficiency [55]. Hepatobiliary involvement is potentially life threatening with death due to rupture of the hepatic artery reported [61].

A retrospective analysis of 54 patients with PAN reported GI involvement in 24 (44%) with two-thirds noting abdominal pain at presentation, while all others had abdominal pain at some point in their illness. Of the 24 patients with GIT involvement at presentation 13 (54%) developed an acute abdomen secondary to bowel infarction, perforation, acute cholecystitis, gall bladder infarction, aneurysmal rupture of hepatic, splenic or renal arteries, or bleeding from perforated gastric ulcers [62]. Multiple aneurysm formation is a defining feature of PAN and is noted in 50 to 70% of those with involvement of the GIT with the hepatic artery affected in 50 to 60%; splenic artery in 45%; and pancreatic artery in 25 to 35% [62-64]. Massive internal hemorrhage due to rupture of an aneurysm within the intestine is rare but nonetheless carries a high mortality of up to 75% [64-67].

Treatment

The mainstay of treatment for mild PAN is corticosteroids. However GI involvement constitutes severe disease, which has been shown to have a better outcome when treated with a combination of cyclophosphamide and corticosteroids [68]. PAN secondary to HBV infection is treated with two weeks of corticosteroids followed by antiviral treatment combined with plasma exchange. Those so treated with antiviral therapy do not experience HBV relapses once viral replication has stopped and seroconversion has been achieved [54].

Occlusive mesenteric disease can be managed successfully with open revascularization [11]. Percutaneous endovascular trans-catheter embolization is increasing used to deal with ruptured visceral artery aneurysms associated with PAN [69]. If tissue necrosis or gangrene occurs due to infarction then definitive surgical management in the form of resection is indicated [70].

Kawasaki Disease

Epidemiology and Clinical Features

Kawasaki disease (KD) is one of the commonest childhood vasculitides with a particularly high incidence and prevalence in East Asia. Most patients have disease onset before 5 years of age with a peak incidence at 30 months [71]. The diagnosis is confirmed by the presence of fever for more than five days, and the presence of four of the following five diagnostic criteria: bilateral conjunctival injection; changes of the mucous membranes of the upper respiratory tract including injected pharynx, fissured lips or strawberry tongue; polymorphous rash; limb changes including peripheral edema, erythema, or periungual desquamation; and cervical adenopathy. Untreated KD is a self-limiting disease that lasts for 10 to 12 days; however, coronary artery aneurysms develop in 20% to 25% of patients with significant associated morbidity and mortality [71].

Gastrointestinal Involvement

GI involvement is relatively uncommon but tends to involve the gallbladder and the liver leading to acute non-calculous distension of the gallbladder (gallbladder hydrops), hepatic dysfunction with elevated serum transaminase concentrations and febrile cholestatic jaundice [73-72]. Presentation with an acute abdomen was reported in 4.6% of children with KD [73] due to vasculitic appendicitis, paralytic ileus, or hemorrhagic duodenitis. KD may be an important cause of febrile cholestatic jaundice with up to 21% of febrile cholestatic cases overall being attributed to KD in a recent series [74]. A high index of suspicion for KD should therefore be maintained for children presenting with febrile cholestatic jaundice.

Treatment

Treatment of KD with aspirin and intravenous immunoglobulin (IVIg) reduces the incidence of coronary artery complications compared with aspirin alone [75]. There are no studies that have investigated the GI outcomes or GI response to treatment in KD. Interestingly, elevated bilirubin and gamma-glutamyl transpeptidase (γGT) have been associated with non-responsiveness, defined by persistent fever, to IVIg treatment [76].

SMALL VESSEL VASCULITIDES

Involvement of small vessels by vasculitis can lead to ulceration, erosions, strictures and occasionally perforation.

IgA Vasculitis/Henoch-Schönlein Purpura

Epidemiology and Clinical Features

IgA vasculitis/Henoch-Schönlein purpura (IgAV/HSP) is a small vessel vasculitis characterized by a leukocytoclastic vasculitis and deposition of IgA-containing immune complexes. It is the commonest form of systemic vasculitis in children with a peak incidence at four to six years of age, although adult patients have been described [77]. It is usually self-

limiting and characterized by the tetrad of palpable purpura in the absence of thrombocytopenia or coagulopathy; arthritis or arthralgia; abdominal pain; and renal involvement. The disease follows a more severe course when it presents in adults with a higher incidence of renal impairment and end-stage renal disease [78].

Diagnosis

Although childhood IgAV/HSP is typically clinically diagnosed, adults generally undergo skin or renal biopsy for tissue confirmation. Imaging can be helpful in assessing the GI manifestations of IgAV/HSP especially ultrasonography for the detection of increased bowel wall thickness, hematomas, and intussusception [79].

Gastrointestinal Involvement

GI involvement occurs in 50% of children with IgAV/HSP and can affect the hepatobiliary system or the bowel in a number of ways [16]. Bowel manifestations include; intussusception [80, 81], intestinal ischemia and infarction, intestinal perforation, gastrointestinal hemorrhage and purpura [82-88] esophageal necrosis [89], ileitis and ileal stricture [90], fistulae formation and acute appendicitis [91]. Hepatobiliary features include; pancreatitis [92] and hydrops of the gallbladder [93]. Functional GIT disorders such as irritable bowel syndrome are reported to have a higher prevalence in children with IgAV/HSP despite resolution of acute flares and are associated with increased steroid use [94]. GI symptoms tend to occur within eight days of the appearance of the rash although they may precede the rash. Abdominal pain in seen in 60-70% of children with IgAV/HSP and is thought to be caused by submucosal bleeding and oedema [95]. A 2001 Spanish study [96] noted that 16.7% of affected children presented with abdominal pain as the solitary symptom; 7.6% presented with abdominal pain and a rash, and 2.6% with abdominal pain, rash and joint pains. Altogether, 70.5% of patients progressed to mesenteric ischemia, and 30.8% had evidence of GI bleeding. The commonest GI manifestation in childhood IgAV/HSP was intussusception. Although the prognosis of IgAV/HSP in children is good, adult onset IgAV/HSP often has a less favorable outcome [78]. In adults severe GI involvement, manifested by abdominal pain and bleeding [97-99], can be associated with a fatal outcome [100-102].

Predictive Markers in Gastrointestinal IgAV/HSP

Due to the high frequency of GI complications in IgAV/HSP and its potentially serious complications predictive markers have been sought. Serum amyloid A and faecal calprotectin have both been demonstrated to be significantly increased in GIT IgAV/HSP compared to non GIT IgAV/HSP [103, 104]. In a study of 70 patients with IgAV/HSP compared to controls serum amyloid A levels were significantly increased in cases of IgAV/HSP with GIT involvement but were not increased in renal or joint involvement [103]. Faecal calprotectin is a heterodimer of calcium binding proteins and elevated stool levels are associated with GI inflammation [105]. Faecal calprotectin is a useful screening tool in the diagnostic workup of

inflammatory bowel disease [106]. In a study of 66 children with IgAV/HSP faecal calprotectin levels were found to be significantly different between groups with and without GIT involvement as well as being significantly different between groups with and without renal involvement [104].

Hematological ratios such as neutrophil-lymphocyte ratio and platelet-lymphocyte ratio have been associated with GIT IgAV/HSP and have been suggested as screening tools for GI involvement [107, 108].

Personalised medicine and genomics may be another approach to risk stratification of GIT IgAV/HSP. A Chinese study has reported an association between platelet-activating factor acetyl-hydrolase gene polymorphisms and GI bleeding [109]. None of these predictive markers are in routine use and further prospective studies with larger numbers are needed to confirm these findings before they could be used in routine clinical practice.

Treatment

Management of IgAV/HSP is largely supportive with administration of non-steroidal anti-inflammatory drugs and corticosteroids for severe abdominal pain and joint involvement. There is no convincing evidence to suggest that early use of corticosteroids reduces the risk of renal involvement or acute GI complications [110]. Plasma exchange, IVIg, mycophenolate mofetil (MMF) and single dose cyclophosphamide have all been reported in the management of GIT IgAV/HSP [111-114]. In one case series of eight children with severe GIT IgAV/HSP involvement six responded to IVIg with two having a further relapse both of which responded to a second dose of IVIg [113]. Plasma exchange has also been reported to improve disease control in a case series [111]. The management of intussusception in children with IgAV/HSP often requires surgical correction [115].

ANCA-Associated Vasculitis

Epidemiology and Classification

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of autoimmune inflammatory conditions comprising GPA, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) that predominantly affect small- to medium-sized blood vessels.

The individual annual incidence of the AAV is 10 to 20 per million population with a peak age of onset in the seventh and eighth decades [118]. Table 7 lists classification criteria for the AAV [13].

Clinical Features

The clinical features of AAV include constitutional symptoms including malaise, joint pains and weight loss, and other symptoms and signs depending on the extent of systemic involvement. The upper and lower airways, skin, peripheral and central nervous system, as well as the kidneys, are typically involved organ systems [119].

Table 7. Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis: Definitions

Granulomatosis with polyangiitis (Wegener's) (GPA)	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA)	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia

*Adapted from reference 13.

Gastrointestinal Involvement

Abdominal pain and diarrhea in EGPA results from eosinophilic gastroenteritis and mesenteric vasculitis leading to bowel ulceration, ischemia, and perforation [12]. Up to one third of patients with EGPA manifest GI involvement with severe involvement associated with increased mortality [120]. The potential for GI involvement is varied and can include upper or lower GI bleeding, perforation of the esophagus, stomach, small and large intestine, bowel ischemia, bowel obstruction secondary to stenosis, colitis and cholecystitis; the commonest manifestation is abdominal pain [16, 116].

GI involvement in GPA is reported in 0-26% of patients [117-122]. Seventy-one percent of GPA patients who ever have GIT involvement will have it at presentation [123]. Abdominal pain, diarrhea and blood loss are the commonest findings. More severe GI involvement can lead to ulceration, massive hemorrhage, ischemia of the small and large intestine or bowel perforation [3, 117, 124-128]. Isolated granulomatous pancreatic lesions, presenting with painless jaundice, pancreatitis and abdominal pain, have been reported in GPA, often being misdiagnosed radiologically as adenocarcinoma [129-131].

GI involvement is uncommon in MPA but can include hemorrhage, ulceration, and intestinal ischemia, in some cases as the presenting feature of disease [132-135]. Life-threatening gallbladder bleeding secondary to vasculitic involvement of the gallbladder has been reported [136].

The French Vasculitis Study Group (FVSG) developed a Five Factor Score (FFS; Table 8) to predict outcomes in patients with PAN and EGPA. The presence of one or more factors predicted a higher mortality [137]. In a retrospective analysis of 1108 consecutive patients with PAN, MPA, EGPA and GPA registered in the FVSG database; age >65 years, cardiac symptoms, gastrointestinal involvement and renal insufficiency, which were all independently associated with a higher five year mortality [138]. More recently, GIT involvement in EGPA was associated with more frequent relapses of disease but had no association with overall survival [139].

Treatment

Management of AAV entails induction of disease remission followed by maintenance treatment and therapy directed at disease relapses. Different immunosuppressive agents can be used depending on disease severity ranging from methotrexate for localized and early systemic

disease, to a combination of high dose corticosteroids, plasma exchange and cyclophosphamide or rituximab in severe life-threatening disease [140]. Where GI involvement has been complicated by large GI hemorrhage definitive intervention in the form of transarterial embolization or surgical intervention has been successful [128, 141].

Table 8. The Five Factor Score*

	Factor	Definition
1	Renal involvement	Proteinuria >1g/24 hours
2	Renal impairment	Serum creatinine >1.582 mg/dl
3	Gastrointestinal involvement	Presence of any of the following: bleeding, perforation, infarction pancreatitis
4	Central nervous system involvement	
5	Cardiac involvement	Presence of cardiomyopathy

*Adapted from reference 138.

SECONDARY VASCULITIDES

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune condition that can affect any part of the body and GIT. SLE can cause lupus mesenteric vasculitis which can affect any part of the GIT but shows a predilection for the superior mesenteric artery [3]. Mesenteric vasculitis is reported in 0.2-9.7% of patients with SLE and affects around 60% of SLE patients presenting with abdominal pain [142]. The underlying pathogenesis arises from complement activation, immune complex deposition and thrombotic processes [142]. Ultimately this leads to ulceration, bleeding, stricture formation, and perforation resulting from tissue ischemia and infarction [143-146]. Rarely mesenteric vasculitis can be the presenting feature of SLE [145, 146]. GI involvement in SLE is generally associated with increased mortality, in some case series being as high as 50% [147]. Mesenteric vasculitis is generally treated initially with high dose intravenous methylprednisolone then with a tapering regime of oral corticosteroid [148]. Cyclophosphamide has also been reported to be effective [149].

VARIABLE VESSEL VASCULITIS

Behçet Disease

Behçet disease is a non-specific necrotizing vasculitis that affects multiple organs and blood vessels of all sizes. It is classically characterized by oro-genital ulceration, ocular disease, skin lesions and a positive pathergy test. BD has a prevalence of between 3.8-420 per 100000 population, and is most prevalent in countries along the old Silk Road such as Turkey [150]. GI involvement occurs in 2.8 to 60% of patients [150]. GIT involvement frequently mimics inflammatory bowel disease with features such as diarrhea, abdominal pain, rectal bleeding and endoscopic findings including mucosal ulceration with a preference for the ileocecal region and

esophagus [12]. The GIT features of BD arise from large vessel vasculitis resulting in ischemia and infarction or from neutrophilic phlebitis leading to mucosal ulceration [151, 152]. Ulceration is often deep and can penetrate through the bowel wall leading to perforation, hemorrhage and fistula formation [153-155]. The most common hepatic manifestation of BD is Budd-Chiari syndrome, seen in 1.3-3.2% of patients, which can result in portal hypertension, ascites, varices and liver failure [150]. It is associated with significant mortality, one study reporting a mean survival of 10.4 months [156]. Other rare GIT complications of BD include carotid-esophageal fistula, aortic pseudoaneurysm rupture into the colon and pancreatitis [157-159].

Disease Monitoring

Intestinal BD can be monitored clinically with the Disease Activity Index for Intestinal BD (DAIBD), categorizing activity as quiescent, mild, moderate and severe [160]. Fecal Calprotectin has been shown to be raised in intestinal BD and correlate with disease severity; this could potentially become a predictive marker for intestinal BD [161].

Treatment

There is no universally accepted treatment regime, however 5-ASA and sulfasalazine have been the mainstay of treatment for mild to moderate disease and corticosteroids for severe disease or to induce remission [162, 163]. Azathioprine, anti-TNF therapy, thalidomide and methotrexate have also been used successfully in intestinal BD [164-166]. For Budd-Chiari Syndrome the mainstay of management is cyclophosphamide and corticosteroids whilst anticoagulation remains controversial [167]. Surgical intervention is generally used for uncontrolled GI bleeding and perforation [168]. Endoscopic intervention has been used for ulcer related GI bleeding [169]. Large vessel involvement can be treated via open surgical techniques or via the endovascular approach [170].

Other Secondary Vasculitides

GI complications occur in other autoimmune conditions such as rheumatoid arthritis (RA) and mixed connective tissue disease (MCTD) due to secondary vasculitis. In patients with RA vasculitis, up to 38% of cases have involvement of the mesenteric vessels leading rarely to ischemic ulceration and bowel perforation [171]. Secondary vasculitis leading to GI involvement in MCTD is rare and occurs in the form of small and large bowel ulceration and perforation [172, 173] as well as fatal hemorrhage [174]. Vasculitic GI manifestations occur in patients with Hepatitis C virus infection, as well as non-infectious mixed cryoglobulinemic vasculitis, ranging from abdominal pain to GI bleeding, infarction, duodenitis, hepatic and mesenteric vasculitis and perforation. GI perforation is associated with increased mortality [175-177]. In addition, GI involvement has been described in vasculitis secondary to the drugs propylthiouracil [178], hydroxyurea [179] and cocaine [180], or infection associated with cytomegalovirus (CMV) [181].

Urticarial vasculitis (UV) is a rare small vessel vasculitis thought to be secondary to immune complex deposition into the blood vessel wall. Clinical features include urticarial rash, angioedema and tissue ischemia. The etiology of UV is usually idiopathic however; it can also

be secondary to autoimmune disease, paraneoplastic disease, drug reactions and infections [182]. UV secondary to infection has been reported to present as circumferential duodenitis and ulceration secondary to duodenal ischemia [183].

Treatment-Related GI Side Effects

As the treatment of vasculitis often involves immunosuppression with drugs such as corticosteroids, cyclophosphamide, azathioprine, methotrexate and biological therapies such as rituximab, treatment-related morbidity of the GI tract must be considered. Reactivation of CMV can lead to GI inflammation in the context of immunosuppression. Symptoms of abdominal pain, diarrhea and bleeding, as well as endoscopic signs of erythema, nodules and ulceration, are non-specific but similar to those of vasculitis [12]. It is very important to secure the diagnosis with biopsy specimens and peripheral blood CMV viral load. CMV disease usually responds to anti-viral therapy. Candida involvement of the oral cavity and the esophagus is a recognized complication of high-dose corticosteroid treatment. British Society of Rheumatology Guidelines for the management of ANCA-associated vasculitis recommend that anti-fungal prophylaxis should be considered in patients receiving immunosuppressive therapy [140, 179]. However, according to a recent meta-analysis there is no clear evidence that the use of topical anti-fungal preparations such as nystatin is effective in preventing fungal colonization and infection in immunosuppressed patients [184]. Finally, corticosteroids and NSAID can lead to gastroduodenal ulceration as well as small and large intestine enteropathy [12].

CONCLUSION

GI involvement in vasculitis largely reflects the size of the blood vessel involved. Large vessel involvement may lead to stenotic lesions manifesting as ischemia or infarction of large, but often unusual segments of the GI tract. Medium vessel involvement is typified by aneurysmal as well as stenotic disease that can produce ischemia or infarction and bleeding whilst small vessel disease can present with abdominal pain, patchy ulceration, infarction and bleeding as well as intestinal perforation. Hepatobiliary and pancreatic involvement can occur and represent common GIT manifestations in some vasculitides. Treatment is aimed at controlling the underlying vasculitic process with immunosuppression although open surgical or endovascular therapy is important in the management of mesenteric vasculitis. Severe gastrointestinal involvement in vasculitis is associated with a higher mortality.

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Chapter 19

RHEUMATOID ARTHRITIS VASCULITIS

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ABSTRACT

Rheumatoid arthritis is a systemic autoimmune disease characterized by inflammatory synovitis. The presence ok fever, weight loss, digital infarcts, deep cutaneous ulcers, mononeuritis multiplex, peripheral gangrene, and other extra-articular complications suggest rheumatoid vasculitis. It is confirmed by the presence of necrotizing arteritis in a biopsy of involved skin, nerve or muscle tissue. Accurately recognized and properly treated with immunosuppressant and biological therapies, the morbidity and damage related to rheumatoid vasculitis can be mitigated. Thus, it is important to consider the diagnosis in any patient with RA in whom features emerge that could suggest the presence of arteritis. This chapter considers the epidemiology, clinical and laboratory manifestations, histopathology, and management of rheumatoid vasculitis.

Keywords: rheumatoid, vasculitis, classification, clinical, pathology, treatment

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory synovitis. An estimated 1,293,000 adults ≥18 year of age in the United States have RA representing about 0.6% of the adult population. Rheumatoid vasculitis (RV) is suggested by the presence fever, weight loss, digital infarcts, deep cutaneous ulcers, mononeuritis multiplex, peripheral gangrene, and other extra-articular complications extra-articular (ExRA) complications, including necrotizing vasculitis, the initial histopathologic manifestations of which are generally found in a biopsy of skin, nerve and muscle tissue in the majority of affected patients. While not strikingly different from classical or definite RA, those

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with RV have a reduced survival compared to the general population that is immediately evident and continues for up to six years [1, 2]. Vasculitis is a particularly significant ExRA manifestation, as it typically requires an escalation of immunosuppressive therapy at a time when patients may have already accrued significant disease-related tissue damage and therapy-related complications. It is important to consider RV because unrecognized and therefore untreated, the morbidity of this RA feature is substantial. This chapter discusses the epidemiology, clinical manifestations, histopathology, and treatment of RV.

HISTORICAL ASPECTS

The earliest reported patients with RA were children described in 1951 by Pirani and Bennett [3] with particularly severe RA progressing from childhood. The first patient was ill for four decades with numerous exacerbations and rare remissions with progressive limitation of the joints and a diagnosis of Still's disease that emerged into chronic disseminated RA before he died. Postmortem examination was notable for severe deforming RA and ankylosis, with left cerebellar hemorrhage, atrophy of bone, skin and muscle; healed glomerulonephritis and marked inflammatory spinal arachnoiditis with splenic follicular necrosis. The second patient presented at age 22 years after many years of disability unable to walk bedridden when he died. Postmortem examination was notable for severe deforming RA and ankylosis with widespread polyarteritis nodosa (PAN). A third patient developed progressive joint deformities from age 17 months before fatal pneumonia. Postmortem examination was notable for RA involving all joints and chronic aortitis. In the same year, Sokoloff and colleagues [4] reported arteritis in small muscular arteries of muscle biopsy tissue in 5 of 57 (10%) adults with RA, the histopathology of which included, mononuclear and polymorphonuclear cell adventitial infiltration, slight necrosis, endothelial cell injury, and secondary elastic involvement without vascular thrombosis or aneurysm formation, and frequent cardiac complication manifesting as pericarditis. The incidence of arteritis is estimated to occur overall in about 8.8% of patients with RA. These observations were followed by 10 additional patient descriptions in 1957 by Sokoloff and Bunim [5] of arteritis in patients with RA. The age range was 30 to 65 years (mean 47 years), at presentation, with a duration of arthritis of 6 months to 30 years (mean 9 years). The diagnosis of RV was established at postmortem examination in five patients and by biopsy of muscle, subcutaneous nodules, and synovial tissue antemortem in five patients. Postmortem examination showed widespread arteritis in three patients, with isolated involvement of the testis in one patient, and the sciatic nerve and coronary artery in another patient. Among the five patients who were diagnosed antemortem, arteritis was detected in muscle biopsy tissue in two patients, in early subcutaneous nodules in two others, and in synovial tissue of another patient. In contrast to the earlier study conducted by the same author of vasculitic muscle biopsy lesions in RA [4], the pathological features of the subsequent 10 patients [5] resembled PAN. Two additional patients with RV were mentioned after publication of the latter study by the same authors [5], both with necrotizing arteritis, in which one was associated with arteritis of the pancreas, and another with isolated peripheral nerve vasculitis (PNV).

TERMINOLOGY AND NOSOLOGY

In 2010, the American College of Rheumatology (ACR), and the European League Against Rheumatism Collaborative Initiative jointly published RA classification criteria [6] that replaced the 1987 Revised ACR criteria for RA [7], defining definite RA by the presence of synovitis in at least one joint, the absence of a better alternative diagnosis, and achievement of a threshold score from the individual scores in four domains in involved joints, in addition to a compatible symptom duration, serological abnormalities, and increased acute-phase responses. This represented a focus upon features associated with earlier disease that was associated with persistent and erosive disease rather than late-stage features thereof. The Revised 2012 Chapel Hill Consensus Conference (CHCC) [8] provides a useful nosology for the vasculitides, categorizing RV as a vasculitis associated with systemic disease. Scott and Bacon [9] described the response to early treatment with intravenous cyclophosphamide and methylprednisolone compared to conventional drug regimens, defining eligible patients as those meeting one or more criteria of the following criteria including, MNM, peripheral gangrene, biopsy evidence of acute necrotizing arteritis plus systemic disease manifested by fever and weight loss; and deep cutaneous ulcers or active ExRA disease if associated with typical digital infarcts or biopsy tissue evidence of vasculitis (Table 1). Overall, the combination of intravenous cyclophosphamide and methylprednisolone resulted in more frequent healing of vasculitic lesions including leg ulcers and neuropathy, and a lower mortality than did other conventional treatments.

Table 1. Scott and Bacon Criteria for RV[1]

Mononeuritis multiplex or peripheral neuropathy
Peripheral gangrene
Biopsy evidence of acute necrotizing arteritis plus systemic illness such as fever or weight loss
Deep cutaneous ulcers or active extra-articular disease (pleurisy, pericarditis, scleritis) if associated with typical digital infarcts or biopsy evidence of vasculitis

[1][9].

EPIDEMIOLOGY

In a population-based study of patients living within the Norwich Health Authority in the United Kingdom from 1988 to 1994, the overall annual incidence rate of RV was 12.5 per million (95% CI 8.5 to 17.7) [10]. In a retrospective cohort study of hospitalized RA patients in Malmo, Sweden, from 1990 to 1994, the annual incidence rate of RV was calculated to be 7.1 per million (95% CI 2.7 to 16.1) [11]. This annual incidence rate may underestimate the true incidence rate, as not all patients with RV are hospitalized. There are conflicting data as to whether the incidence of RV has changed or remained stable over recent decades. However, the preponderance of data does suggest that the incidence of RV may in fact be decreasing, perhaps due to improvements in therapy for RA. In an incident RA cohort in Olmsted County, Minnesota, from 1955 to 1994 [12], the 10-year cumulative incidence rate of severe RV,

defined as major cutaneous vasculitis and neuropathy due to vasculitis, remained stable by decade of RA diagnosis (2.1% for 1955-1964, 3.5% for 1965-1974, 2.5% for 1975-1984, 4.3% for 1985-1994, p-value = 0.72). However, looking at more recent data from Olmsted County, Minnesota [13], the 10-year cumulative incidence of RV decreased from 3.6% in the 1985-1994 RA cohort to 0.6% in the 1995-2007 RA cohort on ($p = 0.011$). In a retrospective study of the prevalence of RV among US veterans [14], the prevalence of RV decreased significantly between 2000 and 2001 for both inpatient and outpatient US veterans. The prevalence decreased by 31% (41/1000 RA cases to 28/1000 RA cases, $p < 0.003$) among ambulatory US veterans and by 53% (32/1000 RA cases to 15/1000 RA cases, $p < 0.001$) among hospitalized US veterans. Moreover, an extension of the Norwich Health Authority studies from 1988 to 1994 [10] to 2002 showed a decline in the annual incidence rate of RV over the period 1988 to 2002 [15]. The annual incidence rate of RV in 1988-1992 was 11.6 per million (95% confidence interval [CI] 7.4 to 17.0); in 1993-1997 it was 8.9 per million (95% CI 5.3 to 13.6); and in 1998-2002 it was 3.6 per million (95% CI 1.6 to 7.1) [15]. The overall annual incidence rate of RV during the time period 1988 to 2002 in the former Norwich Health Authority in the UK was 7.9 per million (95% CI 5.9 to 10.4) [15]. Data from a population-based database of hospitalizations in California compiled by the California Office of Statewide Health Planning and Development indicated that the risk of hospitalization for RV was 33% lower in the period 1998 to 2001 than 1983 to 1987 (adjusted rate ratio 0.67, 95% CI 0.61–0.74; p = value < 0.0001). Adjusting for age, sex, and ethnicity, the rate decreased from 170 per 100,000 persons with RA in 1983 to 99 per 100,000 persons with RA in 2001 [16]. A plausible explanation for the declining incidence of RV include more aggressive early therapy and improved therapeutic armamentarium including the use of biologics for treating RA in general,. Conversely, there have been rare case reports of vasculitis occurring in the context of therapy with TNF inhibitors, although the magnitude of that complication of anti- TNF therapy in patients with RA is very low [17–21].

Patients who develop RV typically have longer-standing RA lasting 10 years or more [22, 23]. In a retrospective study of 50 patients with RV, the mean duration or RA prior to the onset of RV was 13.6 years [24]. Although RA more frequently affects women than men [22], men are more likely to develop RV than women with RA [10, 23]. In a population-based study of patients living within the Norwich Health Authority in the United Kingdom from 1988 to 1994, the annual incidence rate of RV in men was 15.8 per million (95% CI 9.5 to 24.7) compared to 9.4 per million (95% CI 4.8 to 16.4) in women [10]. Patients with erosive, seropositive disease are also more likely to develop RV than those without destructive disease who are seronegative [23, 25]. Moreover, the presence of certain other extra-articular manifestations of RA, such as rheumatoid nodules and Felty syndrome, has been associated with the development of RV [23, 25, 26]. Smoking is a major risk factor for later development of both RA in general and RV in particular [27–29]. In a case-control study of 45 RA patients with RV and 211 RA patients without RV, a significantly greater percentage of RV patients were current smokers (p-value < 0.02) [28]. In a case-control study of patients with severe RA with and without ExRA from the Mayo Clinic in Rochester, Minnesota, and 3 RA cohorts in Sweden, smoking was an independent predictor of RV in a multivariate mode [29].

An intriguing observation from a large case-controlled study of RV reported from the Mayo clinic suggested that hydroxychloroquine and low dose aspirin use in patients with RA might be protective against the development of RV, perhaps related to the benefits of those interventions with regard to vasculopathy and atherosclerosis [30].

Genetic factors likely also contribute to the development of RV. In a meta-analysis of individual patient data from 1,568 patients with RA, 129 of whom had RV, those with RV were significantly more likely than others without RV to have a "double dose" of the shared epitope: HLA-DRB1*0401/*0401 (OR 6.2, 95% CI 1.01–37.9), *0401/*0404 (odds ratio [OR] 4.1, 95% CI 1.1–16.2), and *0101/*0401 (OR 4.0, 95% CI 1.4–11.6) [31]. In a case-control study of 46 patients with RV and 178 RA without ExRA from the Mayo Clinic and Sweden, the HLA-C3 allele was positively associated with RV (allele frequency 0.411 in RV patients versus 0.199 in RA controls without ExRA (p-value < 0.001) [29].

CLINICAL PRESENTATION

As mentioned, RV often presents relatively late in the course of the disease and can occur at a time when articular disease activity is not high. Rheumatoid vasculitis can manifest in a variety of ways including, deep cutaneous ulcers [32], digital gangrene [33], nail fold infarcts [34], MNM [35], and scleritis [36, 37]. Systemic vasculitis commonly extends beyond the peripheral nervous system (PNS) and skin, to internal organs including, the stomach, heart, intestine, pancreas, kidney, and gallbladder [22, 38–40]. A postmortem series of 81 Japanese patients with RA showed histologically evident necrotizing arteritis in 25 (30.8%) patients; however, there was no mention of frequency of clinically significant antemortem vasculitic disease. Therefore, the true prevalence of clinically significant arteritis in this cohort might have been significantly less than the 30.8% stated.

Scott and colleagues [24] reported the clinical features of 50 patients with RV based clinically on the development of deep cutaneous ulceration, acute peripheral neuropathy, mononeuritis or MNM; peripheral gangrene or severe systemic disease in the presence of typical digital or nail fold infarcts. So defined, the clinical manifestations of RV in the 50 patients included cutaneous features of digit infarcts, ulcerations, purpura, and gangrene noted in 44 (88%) patients; rheumatoid nodules in 43 (86%); systemic features of weight loss, hepatomegaly and splenomegaly in 41 (82%); sensory or motor neuropathy in 21 (42%); and cardiac involvement. This included pericarditis, arrhythmia, aortic incompetence, and myocardial infarction in 17 (34%); pulmonary involvement including fibrosing alveolitis, pleurisy, effusions and lung nodules in 17 (34%); renal involvement due to amyloid, chronic renal failure, proteinuria and hematuria in 12 (24%); ophthalmic manifestations of scleritis in seven (14%); and gastrointestinal features in five (10%). An open study by Scott and Bacon[9] of 45 RV patients analyzed treatment with intravenous cyclophosphamide plus methyl-prednisolone given (21 patients) versus conventional drug regimens including oral azathioprine, prednisolone, D-penicillamine, chlorambucil, oral cyclophosphamide, prostaglandin infusion, and intramuscular methotrexate, in whom the diagnosis of vasculitis was noted in 57% of the former group versus 46% of the latter. In this cohort of severe RV receiving intermittent bolus intravenous cyclophosphamide plus methylprednisolone versus other modalities, rheumatoid nodules were seen respectively in 90% and 71% of patients, nail infarcts in 78% and 70% of cases, neuropathy in 52% and 25%, leg ulcers in 43% and 33%, cardiac involvement in 34% and 18%, peripheral gangrene in 14% and 8%, and ophthalmic manifestations in 14% and 12%. There was more severe initial disease, a higher incidence of

neuropathy, and frequent evidence of necrotizing arteritis on biopsy in the former group compared to the latter.

Puéchal and colleagues [41] studied RV among 32 patients defined by the RA and histologically proven necrotizing vasculitis in cutaneous nerve or muscle biopsy tissue specimens respectively in 4 (14%) and 10 (36%) of patients, and together in 14 (50%). The clinical presentation of their patients included 5 (14%) patients with mononeuritis, 18 (51%) patients with MNM, and 12 (34%) patients with distal symmetrical sensory or sensorimotor neuropathy. Cutaneous lesions were seen in 12 (38%) patients including, purpura in nine, ulcers in six, nail-edge infarcts in four, livedo in four, gangrene in two, and one patient each with maculopapular rash or bullous rash. Cardiac involvement was evidenced in four (12.5%) patients including, pericarditis, and fatal rupture of a small mitral valve, congestive heart failure, and myocardial infarction. Eye involvement was noted in two (6%) patients including scleritis and scleromalacia. Life threatening gastrointestinal involvement was noted in 2 (6%) patients due to small bowel perforation and necrosis by endarteritis, accompanied by acute abdomen with sepsis and gangrenous toes and cutaneous ulcers, despite treatment with high-dose corticosteroids and cyclophosphamide therapy,. Altogether, among the 32 patients, all had evidence of PNV that was accompanied by cutaneous vasculitic involvement in 12 patients, 4 of whom had cardiac involvement, and 2 with concomitant vasculitic involvements of nerve, skin, and eye. Four patients had PNV and kidney involvement, and two others had lung involvement.

Vollerstein and colleagues [1] studied 52 patients with RV at the Mayo Clinic from 1974 to 1981 who developed clinical vasculitis evidenced by classic ischemic skin lesions, MNM, or a positive tissue biopsy in comparison to population controls. The initial manifestation of vasculitis was seen in skin in 26 (50%) patients; nerve in 20 (38%) patients, or both in 3 (6%) patients. Serositis, pulmonary or renal manifestations were present each in six patients (12%); and three patients (6%) had eye findings. Mononeuritis presented in 2 (4%) patients; while mononeuritis multiplex involved two nerves in 9 (12%) patients; three nerves in 5 (10%) patients, and four nerves altogether in four (13%) patients. More than 90% of tissue biopsy specimens revealed vascular necrosis and inflammation.

Despite advances in therapy of RA in general, the morbidity and even mortality of RV remains high. A study from the UK reported a mortality rate as high as 60% at 5 years in patients diagnosed with RV despite aggressive therapy usually with cyclophosphamide and high dose corticosteroids. Organ damage and infection were the leading causes of death in this cohort [42].

SEROLOGICAL STUDIES

Among 50 patients with RV described by Scott and colleagues [24], IgM rheumatoid factor (RF) was positive in 94% of patients, the C1q assay was abnormal in 65% of patients, serum antinuclear antibody (ANA) titers were raised in 59% of patients; immune complex assay was positive in 50% of patients overall; with abnormally reduced serum C3 and C4 complement levels respectively in only 0.73% and 0.2% of patients. Serological findings were not mentioned in a report by Scott and Bacon [9] of 45 patients with RV treated with cyclophosphamide and methylprednisolone or other regimens.

In the series of 32 patients with RV described by Puéchal and colleagues [41], in whom vasculitis was obtained in cutaneous nerve or muscle biopsy tissue specimens, articular erosions were noted in all patients, RF seropositivity was demonstrated in 97% of patients, ANA antibody elevation was noted in 27%, decreased C4 complement titers in 62%, circulating immune complexes in 66%, and cryoglobulins in 13% of patients so studied. At onset of the disease, the erythrocyte sedimentation rate (ESR) was a mean of 80 mm/hour. Hepatitis B surface antigen was not detected in any of the 25 sera so studied, however one patient tested positive for hepatitis B surface antibody; there was no data available for hepatitis C seropositivity.

In the series of 52 patients with RV summarized by Vollerstein and colleagues [1], the ESR was elevated in 44 of 51 (86%) patients; low titers of ANA were noted in 15 of 43 (35%) patients; cyroglobulins in 1 of 28 (4%) patients; immune complexes in 3 of 8 (38%) patients; and C3 and C4 complement was abnormally reduced in 1 of 31 (3%) and 7 of 29 (24%) patients so studied. There is no data on the serological evaluation of the subjects reported by Scott and Bacon [9].

Anti-cyclic citrullinated peptide autoantibodies (anti-CCP) are commonly found at high titers in those with RV, but their absence does not preclude the diagnosis [43]. Anti-neutrophil cytoplasmic antibodies (ANCA) are detectable in greater than a third of patients, generally in a perinuclear (pANCA) pattern. More specific enzyme immunoassays however typically do not reveal the presence of anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) antibodies [30, 44].

HISTOPATHOLOGY

RV primarily affects small- and medium-sized vessels [23, 45]. Small-vessel disease may histologically resemble a hypersensitivity vasculitis, whereas medium-vessel disease typically resembles PAN [46]. A given patient with RV may have demonstrable vasculitic involvement of both small- and medium-vessels, with histopathological features of vascular necrosis, occlusion, and tissue ischemia. In a series of 50 patients described by Scott and colleagues [24], vasculitis was noted in 28 patients including leukocytoclastic vasculitis (LCV) of dermal and sub-dermal capillaries was seen in 16 of 19 skin biopsies performed for cutaneous rashes; and necrotizing vasculitis involving small arteries was noted from rectal biopsy tissue in 8 patients, renal biopsy tissue in 2 patients, ovarian and appendix specimens in one patient, and in the coronary artery at postmortem examination in another patient.

Among fifteen patients who died with RV, postmortem examination in seven patients showed active vasculitis in five, three of which showed systemic vasculitis; and one each with vasculitis limited to the coronary arteries, peripheral nerves and muscle, or skin; and inactive vasculitis in another patient. One remaining patient failed to show vasculitis at postmortem examination. In the later series by Scott and Bacon [9], the clinical diagnosis of RV was confirmed histologically in 57% of the patients treated with cyclophosphamide and methylprednisolone compared to 46% of those treated with other conventional therapies. Biopsy tissue specimens of 10 skin rashes showed LCV capillaritis among four patient receiving cyclophosphamide and methylprednisolone, as did six patients receiving other treatments. Deep rectal biopsy showed necrotizing arteritis in nine of 18 (50%), patients who

received cyclophosphamide and methylprednisolone compared to four of 17 (24%) patients in the group receiving other treatments.

In the series of 32 patients with RV and PNS, vasculitis described by Puéchal [41], vasculitis was found in nerve biopsy tissue with the same frequency among those with sensory or predominantly sensory neuropathy as among others with predominantly motor findings (67% versus 64%). However, vasculitic nerve lesions were no more frequent in the patients with MNM than those with distal symmetrical sensory or sensorimotor neuropathy (59% versus 78%). Among 44 nerve fascicles from 28 nerve specimens, Wallerian degeneration was noted in three-quarters of fibers compared to segmental demyelination in 1% of fascicles. There was a close correlation between the severity of the clinical neuropathy and degree of axonal loss or fiber degeneration.

Vollerstein and colleagues [1] summarized a series of 52 patients with RV defined by classical ischemic skin lesions including ulceration, gangrene, purpura or petechiae, in the absence of significant atherosclerosis; MNM, or a positive biopsy tissue specimen. Altogether, 26 patients underwent biopsies of skin, nerve or other tissues that showed vascular necrosis and inflammation I more than 90% of specimens. Vasculitis was noted in 17 of 25 (68%) skin biopsy tissues, and in 5 of 25 (25%) nerve biopsy tissues specimens, in addition to one patient each with histologic evidence of vasculitis of the kidney, gastrointestinal tract, and muscle tissues; rectal biopsy tissue specimens were not sampled for vasculitis.

PROGNOSIS

Using actuarial methods and then current ARA criteria for RA [47], Vollerstein and colleagues[1] noted decreased survival of patients with RV when compared to age- and sex-matched Upper Middle Western general population. The clinical factors that predict decreased survival in RV using an univariate proportional-hazards model in older patients includes failure to receive previous non-steroidal anti-inflammatory drug (NSAID) therapy, previous administration of cytotoxic immunosuppressive agents, a higher dosage of corticosteroids at diagnosis, the decision to continue or initiate corticosteroids, and an abnormal urinary sediment ($p < 0.05$). Increasing referral distance, concomitant comorbid disease, hypogammaglobinemia, and hypoalbuminemia also confer a trend toward decreased survival. The authors did not demonstrate a statistically significant association between decreased survival and sex, type of skin lesion, MNM or number of extremities involved, a positive biopsy, initial manifestation of vasculitis, duration of RA, activity of RA, ExRA manifestations or subcutaneous nodules, previous treatment, presence of concentration of RF, C3 and C4 levels, anemia, thrombocytosis, ESR, and abnormal chest radiograph.

Voskuyl and colleagues [48] studied the mortality of 61 RV patients in comparison to 244 RA controls. The unadjusted risk of death (HR) in RV patients compared with RA controls was 1.65 (95% CI 1.05-2.58). After adjustment for prognostic factors, the HR was reduced to 1.26 (95% CI 0.79-2.01), mainly due to removal of the effects of age and sex. There was no excess mortality seen in RV patients with severe organ involvement when compared with RV patients without severe organ involvement, although the former patients were treated more often with

cytostatic and immunosuppressive drugs. Infection was the main cause of death in RV patients and cardiovascular disease in the RA controls. Vasculitis was reported as the cause of death in only one RV patient. After allowance for general risk factors such as age and sex, there remained only a slight excess mortality in RV patients compared with RA controls.

TREATMENT

Isolated nail fold lesions tend to be benign and typically do not require an escalation of immunosuppressive therapy [34].

Cyclophosphamide

Cyclophosphamide in combination with high dose corticosteroids is the mainstay of therapy for RV [49]. An open label study compared intravenous cyclophosphamide plus intravenous methylprednisolone in 21 patients, with a variety of other treating modalities including azathioprine, prednisolone, D-penicillamine, chlorambucil, oral cyclophosphamide, prostaglandin infusion and intramuscular methotrexate in 24 patients, noting that those receiving intravenous cyclophosphamide plus intravenous methylprednisolone were more likely to experience healing or significant improvement in nail infarcts, leg ulcers, sensory neuropathy, and mononeuritis [9]. Patients receiving intravenous cyclophosphamide plus intravenous methylprednisolone were also less likely to have relapses of their RV or to suffer serious complications such as limb amputation or death. Patients receiving intravenous cyclophosphamide plus intravenous methylprednisolone did better than those receiving the other medications despite more serious disease at baseline. In a case series of 16 RA patients with necrotizing scleritis or peripheral ulcerative keratitis refractory to aggressive therapy with topical and systemic steroids and NSAID, 8 (50%) patients ultimately responded to cyclophosphamide, 6 (38%) eventually responded to methotrexate, and 1 (6%) patient eventually responded to cyclosporine A [37]. In addition to medical therapy, 9 (56%) patients with peripheral ulcerative keratitis also required surgical therapy, including ulcer debridement, conjunctival resection, application of cyanoacrylate tissue adhesive, and tarsorrhaphy. Abel and colleagues [50] reported a series of 5 patients with RV who clinically improved following treatment with oral cyclophosphamide. There are patients in whom cyclophosphamide was ineffective and those with contraindications to this particular therapy. In such instances, treatment with other medications, such as tumor necrosis factor (TNF) inhibitors [45, 51] and rituximab [52, 53], has been attempted. However, evidence to date is limited to case reports and case series.

Rituximab

Given its proven efficacy of rituximab in the treatment RA and diverse small vessel vasculitides (SVV) including ANCA associated vasculitis and cryoglobulimemic vasculitis, rituximab is an appealing candidate biologic for the treatment of RV. A retrospective study of

17 patients with RV from the Autoimmunity and Rituximab Registry reported that 12 (71%) patients who achieved a complete response, while 4 (23%) patients showed a partial response after six months of treatment with rituximab [54]. Twelve months after therapy, 14 (82%) patients achieved sustained complete responses. Hellmann and colleagues [52] report two patients with RV-associated cutaneous ulcers refractory to corticosteroids and disease modifying anti-rheumatic drug therapy but successfully treated with rituximab. Maher and Wilson [53] reported a patient with RV-associated foot drop and sural nerve necrotizing vasculitis in who foot drop improved following multiple courses of rituximab therapy.

Tumor Necrosis Factor Inhibitors

Unger and colleagues [51] reported three patients with RV who developed treatment-limiting adverse effects or a poor clinical response to cyclophosphamide and a later beneficial response to infliximab. Puéchal and colleagues [45] performed a retrospective study of nine patients with RV treated with etanercept or infliximab after failing to respond to treatment with a mean cumulative dose of 8.4 g (range 4 to 15 g) of cyclophosphamide over a mean of 6.2 months (range 3 to 10 months) and high dose corticosteroids. Of the nine patients, 5 developed a complete remission and experienced partial remission after a mean of 28.6 weeks of therapy. Two patients withdrew due to adverse effects and one patient never achieved remission. Two of the patients who responded to TNF inhibitory therapy developed four cutaneous relapses. In 2 patients with RV studied in an open-label pilot study of infliximab [55], both of whom were previously refractory to cyclophosphamide, one demonstrated complete responsiveness to infliximab and another showed a partial response. Garcia-Porrua and Gonzalez-Gay [56] reported a patient with refractory RV-associated MNM and sural nerve biopsy tissue specimen that revealed necrotizing vasculitis with fibrinoid necrosis in whom foot drop improved after treatment with methotrexate and infliximab. Van der Bijl and colleagues [57] described a patient with RV characterized by fibular mononeuropathy in who foot drop improved following the addition of infliximab to the regimen of methotrexate.

Azathioprine

Azathioprine was evaluated in RV in a small randomized, double blind, placebo-controlled study of 15 patients. No differences between the azathioprine-treated and the placebo-treated groups at a mean duration of 27 weeks of therapy [58] were recognized. In a randomized non-blinded trial in 19 patients with RV limited to cutaneous involvement eight patients were treated with azathioprine and prednisone versus continuation of the existing therapeutic regimen in 11 patients, all taking non-steroidal anti-inflammatory drugs including hydroxychloroquine (one patient), aurothioglucose or gold thioglucose, (two patients) and one each of penicillamine, and one sulfasalazine. Although patients treated with azathioprine and prednisone show greater improvement at 3 months, there appeared to be no significant difference in clinical or laboratory parameters between the two groups at 18 months, [50, 59].

Other Biologics

There are case reports suggesting that tocilizumab, an anti-interleukin (IL)-6 strategy proven effective in giant cell arteritis (GCA), a large vessel vasculitis may be of value in patients with refractory RV [60–62]. Successful treatment of RV with abatacept, a co-stimulatory molecule blocker has been described, and abatacept has been of interest in the treatment of granulomatosis with polyangiitis (GPA), another SVV. Not surprisingly however, given the rarity of the condition and the more common use of cyclophosphamide and now rituximab in patients with severe disease, our understanding of the role of some of these newer biologics in the treatment of RV remains limited.

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Chapter 20

DERMATOLOGIC ASPECTS OF SYSTEMIC VASCULITIS

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ABSTRACT

Systemic and localized vasculitis affects the skin and subcutis due to their large vascular bed, as well as, hemodynamic factors such as stasis in lower extremities, and environmental influences as occurs in cold exposure. The initial cutaneous manifestations of vasculitides include diverse and dynamic patterns of discoloration, swelling, hemorrhage, and necrosis. One-half of affected patients present with localized, self-limited disease to the skin without any known trigger or associated systemic disease, known as idiopathic cutaneous leukocytoclastic vasculitis. Cutaneous vasculitis manifests as urticaria, erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, livedo racemosa, deep punched-out ulcers and digital gangrene. Skin biopsy and dermatopathology contribute relevant information however; they require correlation with the clinical history, physical exam and laboratory findings in order to reach an accurate diagnosis in a given affected patient.

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INTRODUCTION

Systemic and localized vasculitis affects the skin and subcutis due to their large vascular bed, as well as hemodynamic factors such as stasis in lower extremities, and environmental influences as occurs in cold exposure. The initial cutaneous manifestations of vasculitides include diverse and dynamic patterns of discoloration, swelling, hemorrhage, and necrosis. One-half of affected patients present with localized, self-limited disease to the skin without any trigger or associated systemic disease, known as idiopathic cutaneous leukocytoclastic vasculitis (LCV) [1] Cutaneous vasculitis manifests as urticaria, erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, livedo racemosa, deep punched-out ulcers and digital gangrene [2]. Skin biopsy and dermatopathology contribute relevant information however; they require correlation with the clinical history, physical exam and laboratory findings in order to reach an accurate diagnosis in a given affected patient. The vasculitides that present primarily and within their course with cutaneous manifestations are summarized in Table 1. This chapter is a comprehensive overview of the clinical dermatologic aspects of primary and secondary vasculitides.

GENERAL CONCEPTS AND NOSOLOGY

The skin receives its blood supply from penetrating vessels from within the underlying subcutaneous fat, which contains medium sized vessels [3]. Branches of medium-sized vessels give rise to two vascular plexuses that intercommunicate, the deep vascular plexus lying at the interface between the dermis and subcutaneous fat, and the superficial plexus located in the superficial aspects of the reticular dermis. Further, distally, they supply the papillary dermis by forming capillary loops. These loops are composed of terminal arteriole, capillaries (arterial and venous), and post-capillary venules (Figure 1). The type of cutaneous lesions closely correlates with the size of vessel affected by vasculitis. For example, in cutaneous LCV, immune complexes (IC) deposition and inflammation mainly target post-capillary venules giving rise to small palpable purpura (Figure 2). Inflammation that targets arterioles and arteries results in large purpuric lesions with irregular borders (Figure 3) since these vessels supply multiple dermal papillae. Ulcers, nodules, pitted scars, and livedo reticularis are associated with arterial muscular vessel involvement, which is localized to the dermal-subcutis interface or within the subcutis [4]. Table 2 reviews the size of vessel affected with corresponding clinical presentation. The 2012 Revised Chapel Hill Consensus Conference (CHCC) [5] and most recent dermatological addendum for the 2012 CHCC [6] serves as a guide for the nosology and categorization of diverse forms of vasculitis based upon the vessels involved. The Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) proposed nosology and classification for several of the primary pediatric vasculitides based upon vessel size [7, 8] similar to the CHCC nomenclature [5]. The clinicopathological aspects of primary and secondary vasculitides are extensively reviewed in Chapter 2 of this text.

Table 1. Percentage of patients with systemic vasculitis presenting primarily and within their course of disease with cutaneous manifestations

Type of Vasculitis	Cutaneous manifestation as first clinical presentation	Cutaneous manifestations during their course of disease	Most common cutaneous manifestation
Microscopic polyangiitis	4 - 14%	44 - 62.4%	Purpura
Granulomatosis with polyangiitis	< 1-21%	10 - 40%	Purpura
Eosinophilic granulomatosis with polyangiitis	14%	40 - 81%	Purpura
Polyarteritis nodosa	11%	25 - 60%	Purpura
Connective tissue diseases	-	12%	Purpura*
Giant cell arteritis	< 1%	-	Scalp tenderness/blanching
Levamisole-induced vasculitis	-	60%	Purpura involving the ears
Henoch-Schönlein Purpura	-	100%	Purpura
Cryoglobulinemic vasculitis	-	100%	Purpura

* Except for Lupus Vasculitis which most commonly presents as erythematous punctate lesions of the fingertips.

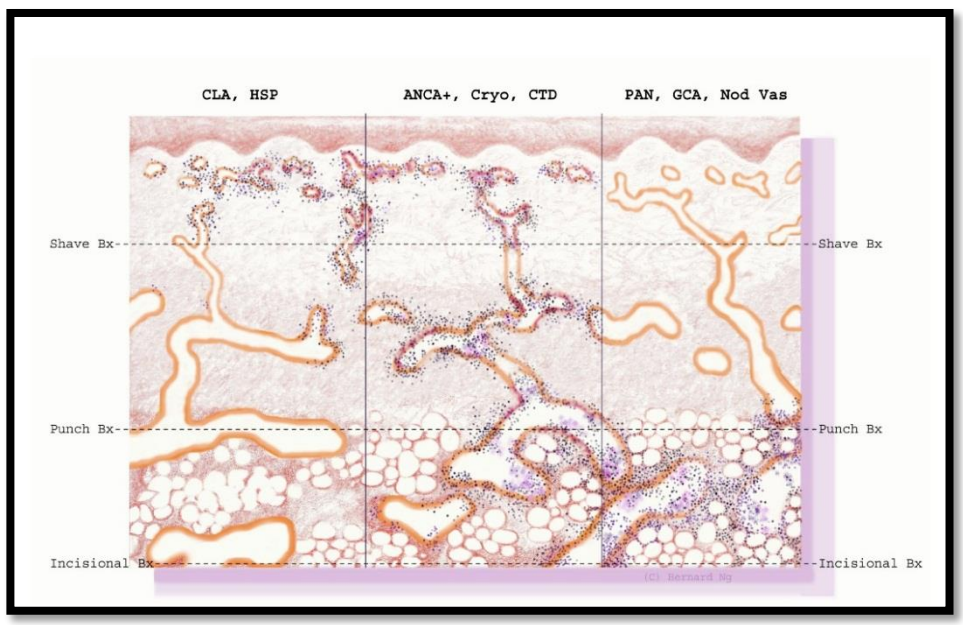


Figure 1. The size of vessel involvement is one histologic feature coupled with the predominant inflammatory cell that allow for classification of most common forms of cutaneous vasculitis. In general, HSP/IgAV cutaneous leukocytoclastic vasculitis affects superficial skin vessels whereas polyarteritis nodosa, nodular vasculitis and giant cell arteritis affect deep muscular vessels found at the dermal-subcutis interface and within the subcutis. Most other forms of vasculitis such as cryoglobulinemic vasculitis and ANCA-associated vasculitis that affect multiple visceral organs more diffusely affect the vascular tree. The depth and type of skin biopsy greatly influences the diagnostic yield.

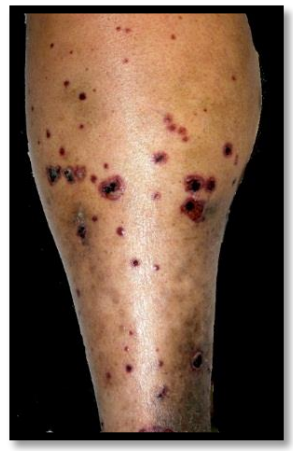


Figure 2. Typical palpable purpura, some with central necrosis in a patient with idiopathic cutaneous vasculitis of the legs.

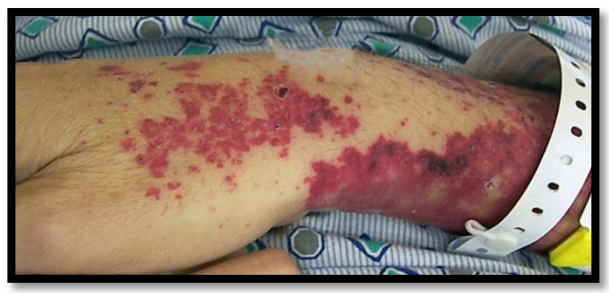


Figure 3. Large purpuric lesions with irregular borders affecting the left wrist of a patient with idiopathic systemic vasculitis.

Table 2. Clinical manifestations of vasculitis based on vessel size affected

Large vessel	Medium vessel	Small vessel
Limb claudication	Subcutaneous nodules Nodular erythema	Purpura, infiltrated/elevated erythema
Asymmetric blood pressure	Ulcers	Urticaria
Absence of pulses	Livedo reticularis	Vesiculobullous lesions
Aortic dilation	Pitted palmar/digital scars	Splinter Hemorrhages
Bruits	Digital Gangrene	Scleritis, episcleritis, uveitis
	Mononeuritis	Palisaded neutrophilic granulomatous dermatitis*
	Aneurysms	Glomerulonephritis
	Infarct	Gastric colic
	Hypertension (renal artery)	Pulmonary hemorrhage

Constitutional symptoms: fever, weight loss, malaise, arthralgias and arthritis are common to vasculitic syndromes of all vessel sizes.

* Extravascular necrotizing granuloma. Small vessel neutrophilic vasculitis is frequently seen in the vicinity of granulomas and necrosis.

Table adapted from Carlson et al. [15].

EPIDEMIOLOGY

The incidence of cutaneous vasculitis ranges from 15.4 to 29.7 cases per million per year, affecting adults more than children of all ages, with slight female predominance, and up to 90% of children diagnosed with Henoch–Schönlein purpura (HSP/ (IgA vasculitis [IgAV) [1]. The mean age at presentation of adult vasculitis is 47 years, while amongst children the mean age at onset is 7 years [1, 4]. The onset of vasculitis after exposure to a trigger such as a drug or infection is 7 to 10 days. A mean interval of 6 months occurs between the onset of symptoms and signs of systemic disease and the onset of secondary cutaneous vasculitis. Almost one-half of patients presenting with cutaneous vasculitis have disease localized to the skin without an attributable cause, trigger or associated systemic disease, referred to as idiopathic LCV [1]. The remainder of localized cutaneous vasculitis cases are attributed to recent infection and drug ingestion. LCV that results from drugs or infection is termed hypersensitivity or allergic vasculitis. The antinuclear cytoplasmic antibody (ANCA)-associated vasculitides (AAV) vasculitis syndromes include eosinophilic granulomatosis with polyangiitis (EGPA) (previously known as Churg-Strauss Syndrome [CSS]), microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) (previously known as Wegner granulomatosis [WG]) may first present with cutaneous vasculitis [9]. The onset of cutaneous vasculitis may be an indication of secondary vasculitis in association with connective tissue disease (CTD) such as systemic lupus erythematosus (SLE) vasculitis (LV) [10], and rheumatoid arthritis (RA) related vasculitis (RAV) [11].

The evolution of cutaneous vasculitis occurs in three phases, (a) single acute, self-limited episode that resolve in ≤ 6 months in association with drug exposure or an infectious trigger so noted in 60% of patients; (b) relapsing disease with symptom-free periods usually found in patients with HSP/IgAV and cryoglobulinemic vasculitis (CV) so noted in 20% of patients; and (c) a chronic, unremitting disease most often associated with primary systemic vasculitides and secondary vasculitides in association with CTD, CV, or malignancy altogether in about 20% of patients [1]. The duration of vasculitis ranges from 1 week to 318 months, with mean and median durations of 28 months and 3.7 months, respectively. Less than 20% of cutaneous vasculitis cases have extracutaneous or visceral vasculitis. Fatal disease occurs in less than 7% of patients [1, 12].

ETIOPATHOGENESIS

A variety of injurious processes can lead to identical responses in the vessel wall resulting in the activation of neutrophils, abnormal neutrophil diapedesis and fibrinoid necrosis, the hallmarks of the vasculitides [1, 13]. Other morphological patterns of vasculitis include lymphocytic endarteritis and endarteritis obliterans of transplant vascular rejection, which are not generally associated with abundant fibrin deposits and destruction of the vessel wall with loss of the elastic lamina [14, 15]. Adding to the difficulties in the histological evaluation of vasculitides are that the characteristics of the initial insult may be lost during the process of repair leading to the transformation from active, acute inflammatory lesions into older, often sclerotic lesions wherein T-cells and macrophages predominate and neovascularization transpire to compensate for the ischemic insult. Nonetheless, the type of inflammatory cell

mediating vessel damage and vessel size affected roughly correlates with pathogenic mechanisms. Ascertaining the optimal time for obtaining the skin biopsy offers relevant preserved data of the skin lesion. An estimated time of a lesion within 24 to 48 hours of its onset is ideal for the biopsy, and for immunofluorescence between 8 to 24 hours [16].

CLINICAL PRESENTATION

Systemic symptoms of fever, malaise, weight loss, arthritis, and arthralgia accompany most cutaneous vasculitides. Vasculitic lesions may affect dependent sites of the legs especially under tight fitting clothes, less so along the arms, trunk, head and neck signifying more severe disease or coexisting systemic vasculitis [17]. Cutaneous vasculitis commonly manifests as palpable purpura and infiltrated erythema indicating dermal small vessel vasculitis (SVV), less frequently as nodular erythema, livedo racemosa, punched-out ulcers, or digital gangrene due to muscular-vessel vasculitis. The type of cutaneous lesions closely correlates with the size of vessel affected by vasculitis. Sparse superficial perivascular neutrophilic infiltrates associated with nuclear debris and extravasated red blood cells result in urticarial papules and plaques, which last > 24 h, burn rather than itch, and resolve with residual pigmentation (Figure 4). A predominant small vessel vasculitis (SVV) results in purpuric macules and infiltrated erythema, whereas deeper dermal SVV correlate with palpable purpura and vesiculobullous lesions. Ulcers, nodules, pitted scars, or livedo reticularis are associated with arterial muscular vessel involvement, which will be located at the dermal–subcutis interface or within the subcutis [4].

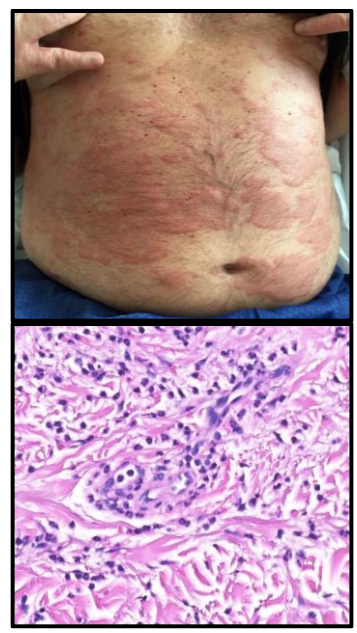


Figure 4. Urticarial vasculitis (UV): patient with hypocomplementemia presenting with an urticarial rash that lasts for more than 24 hours in fixed locations which subsequently slowly resolves spontaneously. They can possibly resolve leaving ecchymosis and hyperpigmentation. Histologically, the features (as in most cases of UV) show perivascular neutrophilic infiltrate with red blood cell extravasation but no fibrin deposition.

LABORATORY EVALUATION

Histopathologic Studies

Table 3 shows the histologic criteria for the diagnosis of cutaneous vasculitis. The diagnosis of cutaneous vasculitis of small- and medium-sized muscular vessels is established by biopsy and examination of hematoxylin and eosin (H& E)-stained sections followed by direct immunofluourescent (DIF) studies. Fibrinoid necrosis is comprised of fibrin deposition within and around the vessel wall and is a feature of nearly all early vasculitic lesions. It results from the accumulation of plasma proteins, including coagulation factors that are converted to fibrin along sites of vessel wall destruction. Inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition (Figure 5) may be accompanied by endothelial damage in the form of endothelial swelling and shrinkage due to apoptosis and sloughing (Figure 6). The finding of inflammatory cells infiltrating the adventitia and media and disrupting the endothelium or endothelialitis, is a *de facto* sign of vasculitis (Figure 7). Secondary changes that infer underling vasculitis include extravasation of red blood cells causing purpura, necrosis leading to infarction, and ulceration secondary to the ischemia and vessel obstruction. The type of inflammatory cells mediating vessel damage and the caliber of the vessels affected roughly correlate with pathogenic mechanisms listed in Table 4. Circumstantial evidence of vessel wall damage includes lamination of the adventitia, media and/or intima of vessels or so-called onion skinning (Figure 8); perivascular nuclear dust or leukocytoclasia (Figure 9) without fibrin deposits such as in early evolving LCV; sharply defined loss of the elastic lamina associated with acellular scar tissue in the healed stage of muscular vessel vasculitis; and sub endothelial, intramuscular, and adventitial inflammatory cells. Neovascularization of the adventitia (Figure 10) and the formation of small capillaries are prominent features of mature and older lesions in chronic localized SVV such as erythema elevatum dinutum, medium vessel vasculitides (MVV) such as polyarteritis nodosa (PAN), and large vessel vasculitides (LVV) such as giant cell arteritis (GCA), Luminal obliteration or endarteritis obliterans, the ischemic consequence of lymphocytic and granulomatous vasculitides, affects small- to medium-sized arteries. Endarteritis obliterans occur in several stages. First, lymphocytic endothelialitis or endarteritis is followed by formation of a sponge-like plug composed of mononuclear cells, fibrin, and red blood cells resulting in partial to complete obstruction. Perivascular lymphohistiocytic, non-neutrophilic, inflammatory infiltrates develop around affected arteries, followed by formation of dilated capillaries in the adventitia of obstructed vessels. Smooth muscle cells immigrate and proliferate in the subendothelial zone, organizing the occluding plug during the intermediate stage. The final stage is fibrosis, shrinkage, and atrophy of the occluded artery (Figure 11). Healed lesions may be associated with luminal stenosis and aneurysm formation. Persistence of vessel wall inflammation, either medial or intimal, can eventually lead to luminal obliteration or aneurysm rupture.

Immunofluorescence analysis of a tissue biopsy of involved skin lesions is indispensable. The commonest immunoreaction found in vessels by DIF is C3, followed by IgM, IgA and IgG, and fibrin deposits [1, 4]. The type of Ig and pattern of deposits in DIF will be of additional diagnostic value. For example, predominance of IgA in HSP/IgAV (Figure 12) will direct attention to renal involvement. Basement membrane zone or keratinocyte nuclear or *in vivo* ANA and IgG immunoreactions are found in vasculitides associated with CTD such as LV.

The finding of basement membrane zone immunoreactions occurs in those with HUV/C1q and CTD. In addition, IgM deposition in blood vessels, circulating RF and monoclonal production of IgM are readily seen in patients with CV and RAV.

Table 3. Histologic Diagnostic Criteria for Cutaneous Vasculitis and Associated Histology[1]

Histologic signs of acute (active) vasculitis
Dermal small vessels (venules and arterioles) (2 of 3* criteria needed)
*Angiocentric(†) and/or angio-invasive inflammatory infiltrates
*Disruption and/or destruction of vessel wall by inflammatory infiltrate
*Intramural and/or intraluminal fibrin deposition ("fibrinoid necrosis")
Dermal-Subcutaneous muscular vessels (small arteries and veins)
*Infiltration of muscular vessel wall by inflammatory cells
*Intramural and/or intraluminal fibrin deposition ("fibrinoid necrosis")§
†***Secondary changes of active vasculitis (suggestive of, but not diagnostic of vasculitis)***
RBC extravasation (petechiae, purpura, hematoma)
Nuclear dust, perivascular (leukocytoclasia)
Endothelial swelling, sloughing or necrosis
Eccrine gland necrosis (or regeneration with basal cell hyperplasia)
Ulceration
Necrosis/infarction
Histologic sequelae of vasculitis (chronic signs and healed lesions of vasculitis)
†Lamination (onion-skinning) of vessel wall constituents
†Luminal obliteration (endarteritis obliterans)
*Segmental or complete loss of elastic lamina in medium and large vessels associated with acellular scar tissue
†Reactive angioendotheliomatosis
Neo-vascularization of adventitia

*: Required for diagnosis of vasculitis.

§: Intraluminal fibrin deposition can be found in non-vasculitic arterial lesions such as malignant hypertension and anti-phospholipid antibody syndrome.

†: Other types of vessel injury (pseudovasculitis [91]) can cause same pattern.

[1] Adapted from Carlson et al. [1].

Table 4. Pathogenic Mechanisms of Vasculitis and Their Clinical Diagnostic and Histologic Correlates[1]

Pathogenic Mechanism	Vasculitic Syndrome	Vasculitis Pattern
Type I (Anphylactic)	Eosinophilic vasculitis	Eosinophilic small-vessel vasculitis
Type II (Cytotoxic-cytolytic antibody)	EGPA GPA MPA	Eosinophilic small- and medium vessel vasculitis Neutrophilic mostly small- and medium vessel vasculitis Neutrophilic mostly small- and medium vessel vasculitis
Type III (Immune complex)	HSP CLA CV PAN	Neutrophilic small-vessel vasculitis Neutrophilic small-vessel vasculitis Neutrophilic mostly small- and medium vessel vasculitis Neutrophilic medium-vessel vasculitis
Type IV (Delayed hypersensitivity)	GCA Chronic GVHD	Granulomatous medium-vessel vasculitis Lymphocytic small-vessel vasculitis

CLA = Cutaneous leukocytoclastic angiitis; CV = Cryoglobulinemic vasculitis; EGPA = Eosinophilic granulomatosis with polyangiitis; GCA = Giant cell arteritis; GPA = Granulomatosis with polyangiitis; GVHD = Graft-versus-host disease; HSP = Henoch-Schönlein purpura; MPA=Microscopic polyangiitis, PAN = Polyarteritis nodosa

[1] Adapted from Carlson et al. [1].

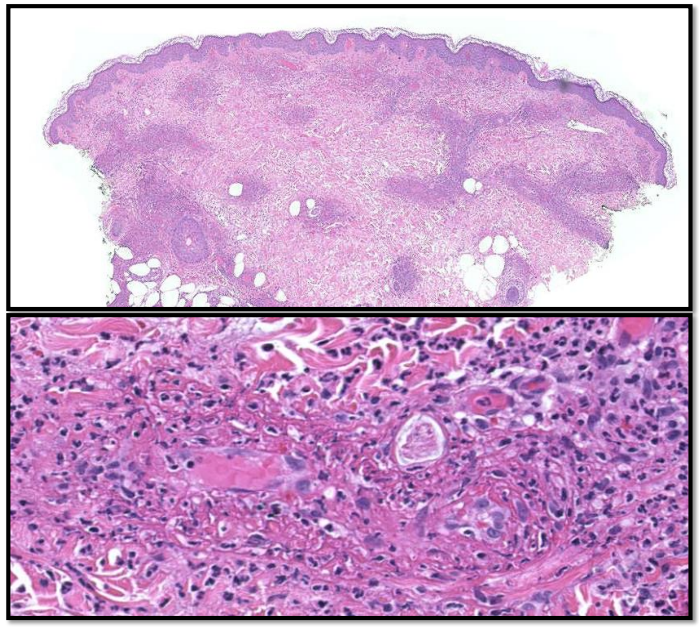


Figure 5. Inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition indicative of vasculitis.

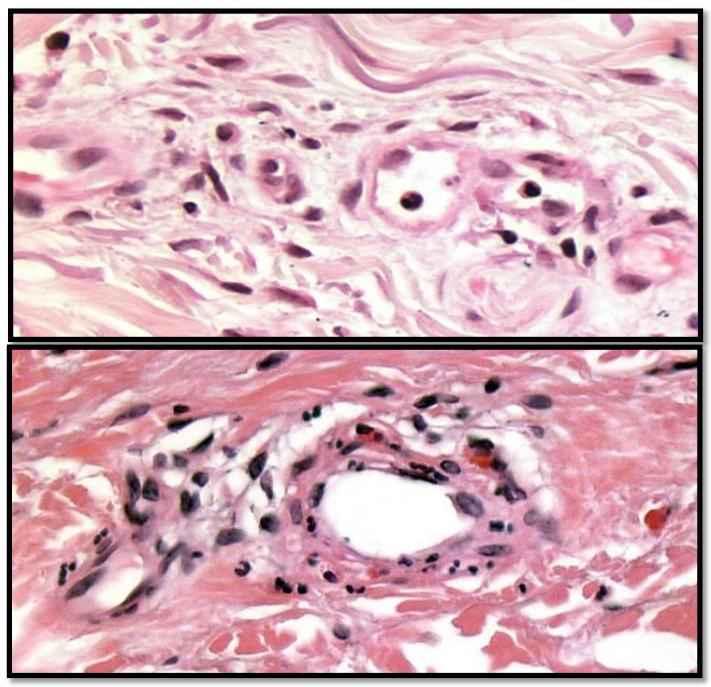


Figure 6. Endothelial swelling, shrinkage, apoptosis, and sloughing seen in early and mature lesions of urticarial vasculitis occurring in association with hepatitis C virus infection.

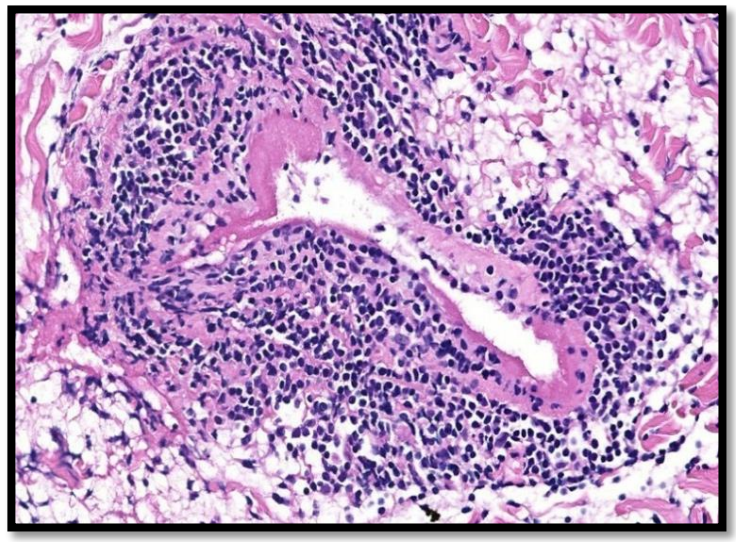


Figure 7. Lymphocytes infiltrate the adventitia and media of a small vein and the intima shows extensive fibrin deposits.

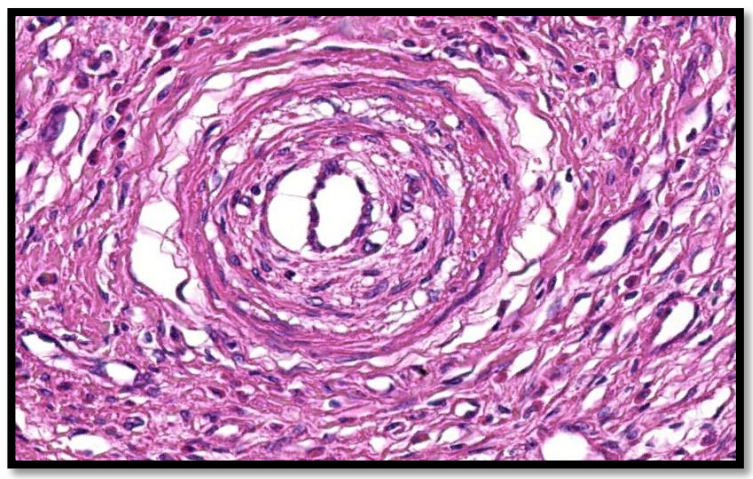


Figure 8. Erythema elevatum diutinum- chronic localized fibrosing leukocytoclastic vasculitis. Concentric rings of collagen surround this small vessel due to recurrent leukocytoclastic vasculitis. There is a cycle of vasculitis → vessel damage → and granulation tissue formation.

Further laboratory evaluation of patients with cutaneous vasculitis should be guided by the history and physical examination as to the possibility of preexisting or concomitant systemic illness, including relevant drug and infectious exposures [1, 18]. Clues to the presence of underlying systemic illness include night sweats, weight loss, dry eyes ad mucous membranes, photosensitivity, facial cutaneous eruption, oral lesions, muscle weakness, mononeuritis multiplex, arthralgia, myalgia, fever, hemoptysis, shortness of breath, cough, wheezing, eye or ear symptoms, sinusitis, hoarseness, numbness or paresthesia, abdominal or testicular pain, melena, and hematuria [1, 18]. Patients with suspected of a primary vasculitides should undergo baseline complete blood cell count (CBC) with differential, blood urea nitrogen (BUN),

creatinine, liver function panel, urinalysis, stool guaiac, hepatitis B (HBV) and C virus (HCV) serology, antinuclear antibody (ANA), cryoglobulins, and ANCA testing. Other studies include blood cultures and echocardiography when fever or heart murmurs are present, anti-streptolysin O titers in children and adults with a history of cardiac septal defect; cytokines IL-6, TNFα, C-reactive protein (CRP), activated coagulation marker complex thrombin–antithrombin III, functional endothelial markers endothelial microparticles and thrombomodulin; and ANCA serology when SVV (MPA, EGPA, GPA) is suspected. Perinuclear pattern of ANCA (pANCA) with myeloperoxidase (MPO) antibodies as well as lactoferrin and cathepsin, which occurs most often in MPA and EGPA. Cytoplasmic (cANCA) with proteinase-3 (PR3) is strongly associated with GPA.

The presence of ANCA is not diagnostic of systemic vasculitis since up to 60% of patients with cutaneous LCV can be ANCA-positive with disease limited to the skin. Positive ANCA serology so noted in diverse systemic inflammatory and pulmonary disorders that mimic vasculitis [19] usually demonstrates atypical indirect immunofluorescent patterns with negative antibodies to PR-3 and MPO by antigen specific enzyme-linked immunosorbent assays (ELISA). The absence of IC and the presence of minimal IgG and C3, so-called pauci-immune vasculitis, are expected findings in GPA, EGPA and MPA. These three vasculitides can present with negative serology and exploring other antigen targets for such situations may be of diagnostic utility. Kain and colleagues found the serum anti-human lysosomal-associated membrane protein-2 (hLAMP-2) to be positive in different assays in > 80% of untreated 122 AVV patients. Levels dropped to almost becoming undetectable once the immunosuppression therapy started, raising the possibility to be used as a biomarker and contrasting with MPO and PR3 antibodies, which do no correlate well with the disease activity due to different kinetics. Moreover, in the same study, positive anti-hLAMP-2 antibodies were found in 7 out of 8 ANCA, PR3 and MPO negative patients [20]. Inadequacies of current assay techniques limit hLAMP-2 antibody kits to be commercially available; even they have shown to have a high sensitivity and clinical correlation, but poor specificity for cutaneous AAV, as they were also detected in HSP and cutaneous polyarteritis nodosa [21].

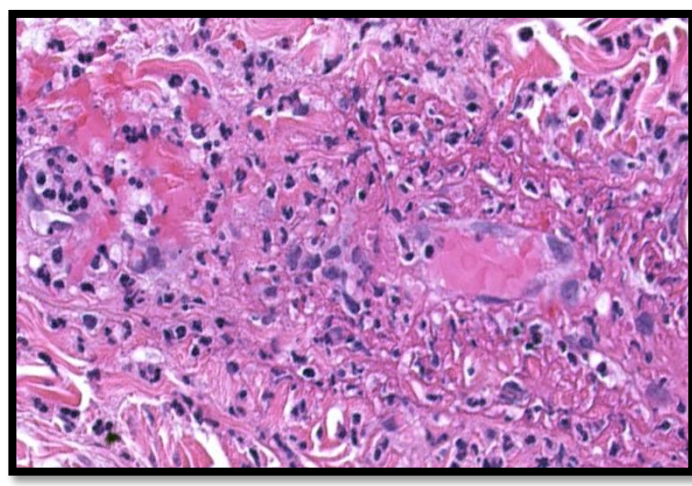


Figure 9. Deposition of neutrophilic nuclear debris or leukocytoclasia. Note the disruption of the small thin wall vessel by fibrin and numerous degenerated adventitial apoptotic neutrophilic nuclei.

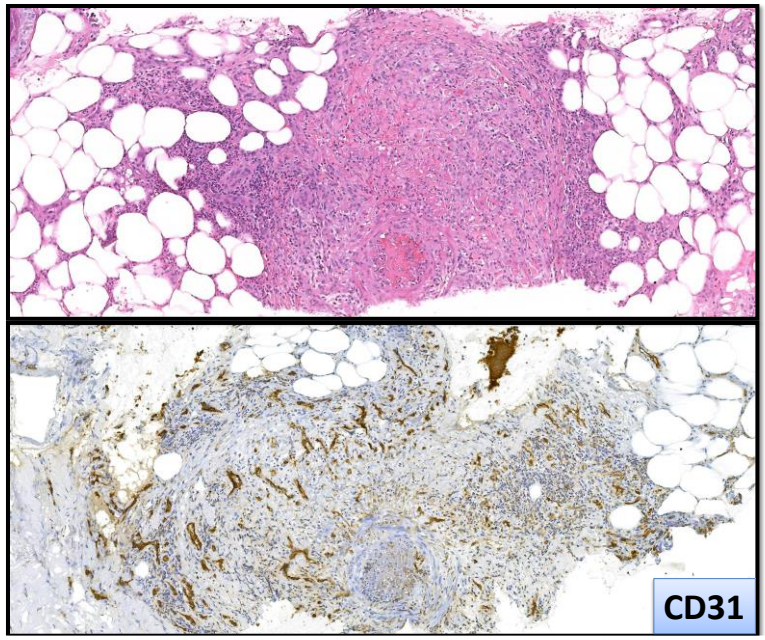


Figure 10. Neovascularization in cutaneous polyarteritis nodosa. CD31 staining marks the vasculature and as demonstrated in this image, reveals multiple newly formed vessels surrounding the affected vessel.

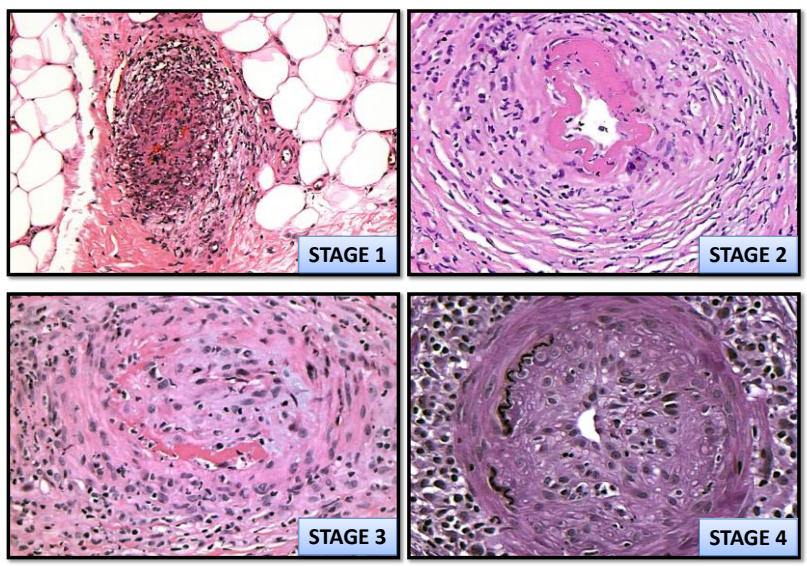


Figure 11. The four morphologic stages of cutaneous polyarteritis nodosa with end-stage healed arteritis or endarteritis nodosa. The acute stage is characterized by endothelial loss and fibrin thrombi with neutrophil infiltration without obvious internal elastic lamina disruption and medial fibrinoid necrosis. The subacute stage shows mixed cellular infiltration and unique intimal target-like fibrinoid necrosis and leakage extending through the disrupted internal elastic lamina sites to the media. The reparative stage shows intimal fibroblastic proliferation and perivascular neovascularization with predominant histiocyte and lymphocyte infiltration. The healed stage reveals minimal cellular inflammation and occlusive intimal thickening.

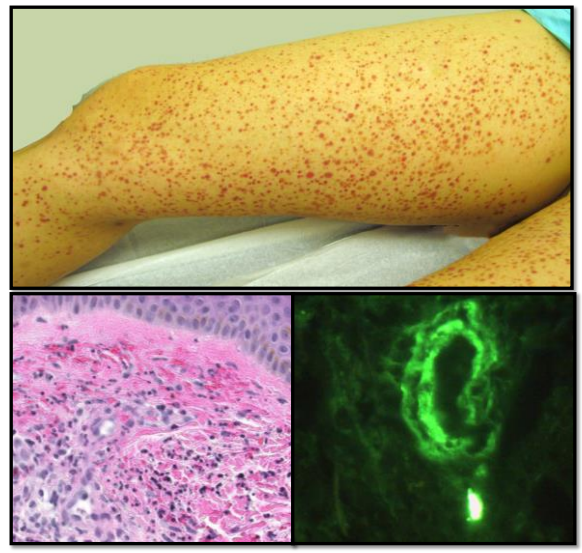


Figure 12. Petechial leg eruption in HSP/IgAV. Skin biopsy shows neutrophilic small vessel vasculitis restricted to the superficial dermis. Direct immunofluorescence demonstrates IgA vascular deposits.

Patients with suspected secondary vasculitis and biopsy-proven cutaneous vasculitis in association with a serologically specific CTD, so suggested by dry eyes and mouth, arthritis, sclerosis, or photosensitivity, should be further screened for antinuclear antibody (ANA), rheumatoid factor (RF), anti-phospholipid (aPL), Ro (SSA), La (SSB), ribonucleoprotein (RNP) and Sm (Smith) antibodies [1, 22, 23]. The secondary vasculitides in association with CTD typically involve multiple organs and vessels of variable caliber. Extravascular histologic findings can provide a clue to diagnosis of associated CTD. Examples include interface dermatitis with dermal mucin deposition so noted in SLE and dermatomyositis; dermal or subcutaneous sclerosis in scleroderma; as well as, palisading neutrophilic and granulomatosis dermatitis in RA and SLE, and tissue neutrophilia, rather than a neutrophilic dermatosis, in SLE and Sjögren syndrome [2].

PRIMARY SMALL VESSEL VASCULITIDES

ANCA-Associated Vasculitides

Microscopic Polyangiitis

This neutrophilic necrotizing SVV characteristically involves arterioles, capillaries, and venules, and occasionally small and medium arteries of the kidney and lung resulting in pulmonary capillaritis and necrotizing glomerulonephritis. It typically affects patients > 50 years of age, with a male: female ratio of 1:1.5, and a greater prevalence in Asians [24]. The largest cohorts ascertained in departments of medicine or nephrology render a bias toward certain spectrums of the disease [25] and may underestimate the true incidence of cutaneous manifestations [26]. Agard and coworkers [27] found skin lesions, primarily purpura, at presentation in 14% of 36 patients, compared to 4% by Cupps and Fauci [28]. Kluger and colleagues [29] ascertained skin manifestation in 44% of 162 patients comprised of palpable

purpura of the legs in 26%, livedo racemosa in 12%, nodular lesions in 10%, ulcer/necrosis in 6%, urticaria in 1.2%, oral and genital ulcers each in 0.6%; arthralgia, mononeuritis multiplex and ocular symptoms occurred more often as well. Guillevin and coworkers [30] observed cutaneous involvement, primarily purpura, in 62.4% of 85 patients.

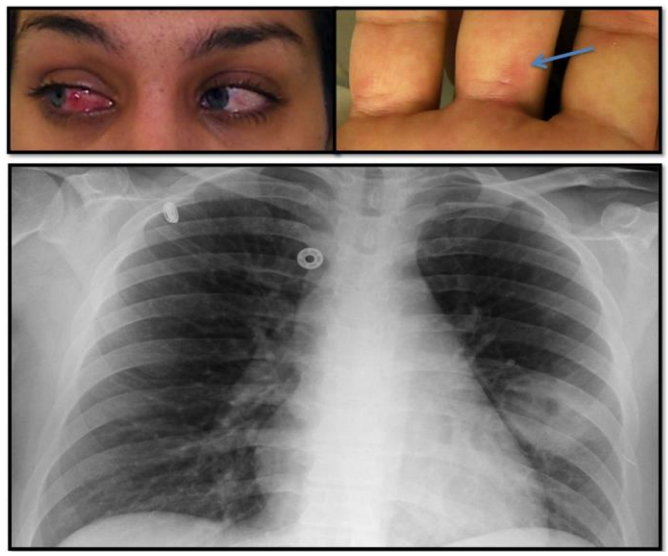


Figure 13. Granulomatosis with polyangiitis. This young 22-year old female presented with progressive ocular (episcleritis), ear, and lung symptoms and history of tuberculosis. Chest radiograph showed left lung nodule cavitation. Cutaneous exam revealed painful papules some of which were vesicular over the volar aspects of the proximal phalanges. Punch biopsy was diagnostic of granulomatosis with polyangiitis.

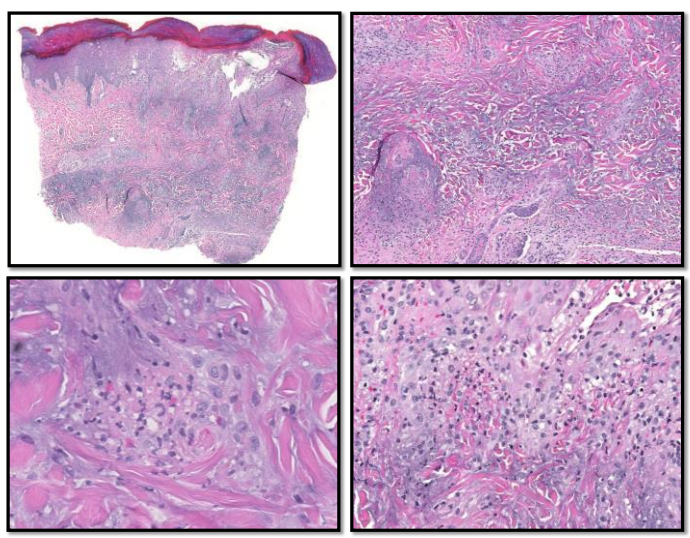


Figure 14. Punch biopsy of the patient in Figure 13 that shows regional epidermal necrosis overlying a pandermal infiltrate characterized by neutrophilic small vessel vasculitis (bottom left panel), and surrounding, palisading granulomatous inflammation associated with basophilic debris or blue collagen lytic granuloma.

The French Vasculitis Study Group (FVSG) [31], a multicenter nationwide study, that retrospectively analyzed 1553 AAV patients, noted cutaneous manifestations (CM) overall in 51.9%, typically at a younger age (57.5 years) with features of segmentary edema (19.5%) and livedo reticularis (12.4%), as compared to those with GPA and EGPA. In addition, myalgia, arthralgia, gastrointestinal hemorrhage and peripheral neuropathy were all significantly more frequently in association with CM, with less frequently impaired renal function [31].

Granulomatosis with Polyangiitis

The clinicopathological features of GPA include granulomatous inflammation of the upper and lower respiratory tracts (Figures 13, 14) and necrotizing granulomatous inflammation of the kidneys leading to glomerulonephritis [23]. The disease is not evenly distributed among geographic areas, time intervals or ethnic populations [32]. The diagnosis rests upon a positive biopsy demonstrating surrogate markers of granulomatous inflammation of the respiratory tract and kidney and the presence of systemic necrotizing vasculitis of small-to medium-sized vessels, and positive c-ANCA specifically targeting intra-granular, anti-proteinase-3 (PR3), but without blood or biopsy tissue eosinophilia. About 10% to 50% of patients with GPA develop cutaneous disease during the course of disease [33-36] that takes one of many forms including, palpable and non-palpable purpura due to small vessel neutrophilic vasculitis; subcutaneous nodules, ulcers and digital infarcts with gangrene due to medium vessel vasculitis (Figure 15). Polymorphic lesions consist of necrotic rheumatoid papules and nodules along extensor surfaces particularly the elbows; and pyoderma gangrenosum-like ulcers and gingival hyperplasia with strawberry gingivitis.

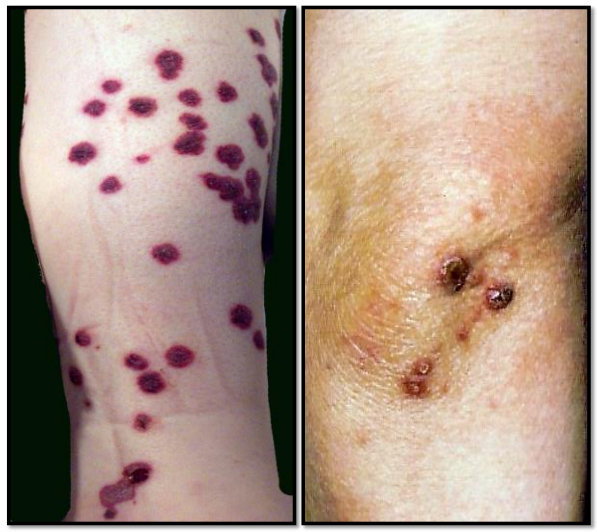
Figure 15. Digital gangrene in a patient with muscular-vessel vasculitis and radial artery thrombosis, status post thrombectomy. The patient was diagnosed subsequently as granulomatosis with polyangiitis.

Among 40 patients with the diagnosis of GPA described by Patten and colleagues [33], 16 (40%) had cutaneous and oral mucosal disease, 12 of whom had a skin alone, most commonly palpable purpura; and 2 each had oral mucosal disease or both skin and mucosal disease leading to oral ulcers, with a single example of gingival hyperplasia. Among 766 ANCA-positive patients with GPA, Comfere and colleagues [34] noted skin manifestations in about 10% of patients, several of whom underwent skin biopsy evidencing concomitant cutaneous and systemic involvement, isolated cutaneous disease several weeks to 8 years after diagnosis of systemic GPA, and others in whom the cutaneous eruptions preceded systemic involvement by one to seven years. Among 66 patients with GPA Zycinska and coworkers [35] discerned skin involvement in 21 (32%) patients, 14 (21%) of whom had skin involvement as an initial clinical presentation. The histologic identification of isolated LCV, cutaneous GPA, and positive c-ANCA/PR3-ANCA serologic test results should raise clinical suspicion for later systemic involvement.

In the AAV cohort of the FVSG, CM noted in 36.7% of cases, manifested frequent oral ulceration (4.6%) and two distinctive lesions: pyoderma gangrenosum (1.1%) and gingival hyperplasia (0.9%). There was frequent alveolar hemorrhage, arthralgia, peripheral neuropathy, renal, cardiovascular and gastrointestinal involvement. Patient with GPA and CM had more frequent vasculitis than the granulomatous phenotype and poorer relapse-free and overall survival. Patients with GPA and predominant granulomatous features manifesting lung nodules and pachymeningitis had infrequent CM [31]. The histopathology of GPA is a LCV with fibrinoid necrosis mostly affecting small vessels and preferentially the dermis. Fewer cases show deeper tissue inflammation. Other presentations include purpura, nodules, papules, urticaria and granulomatous vasculitis. Neutrophils prevailed in almost all the specimens. Among 52 pediatric GPA cases [37], CM noted in 36.5% of cases, was a presenting feature in 7.7%. Nineteen patients had specific findings related to the disease presenting as palpable purpura, folliculitis, pyoderma gangrenosum-like and nodules, with histopathologic findings of leukocytoclastic vasculitis, granulomatous inflammation, granulomatous vasculitis and palisading granulomas. Acneiform papules and pustules with perifollicular inflammation are unique to this age group [37].

Eosinophilic-Granulomatosis with Polyangiitis

Patients with EGPA present clinically with adult-onset of asthma and allergic rhinitis, and pathologically with necrotizing granulomatous inflammation, peripheral blood and tissue eosinophilia, and systemic vasculitis [23] in adults age 30 to 60 years without gender differences [38]. There is frequent renal disease and more frequent peripheral nerve, cutaneous, and cardiac involvement compared to GPA. ANCA-positive patients are more likely to have cutaneous vasculitis, alveolar hemorrhage, mononeuritis multiplex and renal disease [39]. In contrast to GPA and MPA, 40% of EGPA cases are ANCA-positive, with most manifesting p-ANCA and MPO specificity (in 30% - 40%) [40], and fewer cases presenting with c-ANCA and PR3 seropositivity. Following a prodromic initial phase of asthma and allergic rhinosinusitis, a second phase ensues with peripheral blood and tissue eosinophilia demonstrable in the lungs, heart and other organs; followed by a third phase of frank vasculitis. Cutaneous manifestations were the presenting feature of EGPA patients in about 14% of cases [41], so noted in 40% to 80% of cases [42].



Reproduced with permission from [4].

Figure 16. Dermal and subcutaneous papules around the elbows and hemorrhagic bullous purpuric macules and papules over the lower extremities in a patient with eosinophilic granulomatosis with polyangiitis.

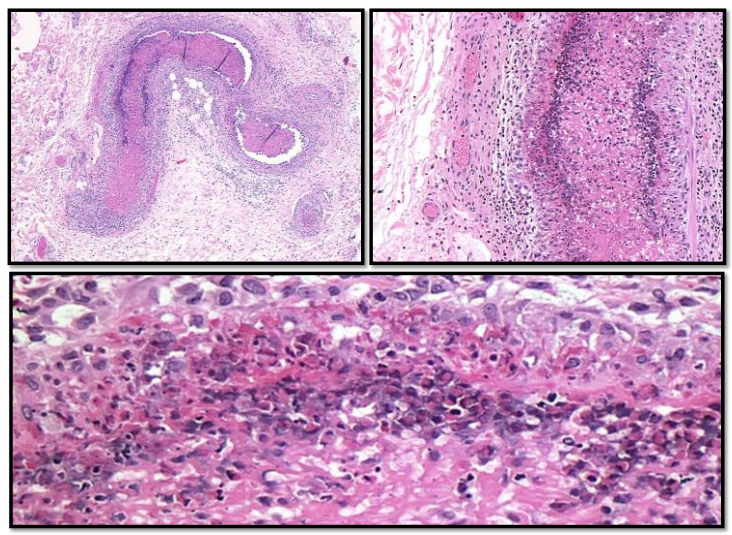


Figure 17. Eosinophilic arteritis with thrombophlebitis in a patient with eosinophilic granulomatosis with polyangiitis.

The lesions of EGPA were first described in 1951 as erythematous maculopapular lesions resembling erythema multiforme; also include petechiae, palpable purpura, urticarial papules; and cutaneous and subcutaneous nodules [43]. In a recent cohort, the skin manifestations of EGPA at initial onset included palpable purpura, petechiae, ecchymosis and hemorrhagic bullae in ≤ 50% of patients; dermal and subcutaneous papules and nodules on the scalp or symmetrically distributed over the extremities (Figure 16) in about 30%; and urticaria and erythematous macules in ≤ 25% of patients, with others manifesting livedo reticularis. In the

FVSG cohort, among 436 EGPA cases, 53% presented with CM along with more frequent fever (50.9%), arthralgia (44.1%), ocular involvement (12.5%), alveolar hemorrhage (7.8%) and gastrointestinal involvement (29.5%), without cardiovascular, neurological or renal involvement [31].

Cutaneous biopsy reveals three histopathologic changes, alone or together, including 1) eosinophil-rich neutrophilic SVV affecting dermal venules and arterioles, less commonly an eosinophil-rich muscular arteritis (Figure 17) or granulomatous histiocyte-rich arteritis of the dermal subcutaneous junction or subcutis; dermal eosinophilia; 2) palisading neutrophilic and granulomatous dermatitis with neutrophilic debris among basophilic degenerated collagen bundles, so called blue granuloma (Figure 14) or abundant eosinophils and eosinophilic granules and debris that coat degenerated collagen bundles or red granulomas (Figure 18) [23, 44, 45]; and less often, 3) granulomatous arteritis [45].

Immune Complex Vasculitides

Henoch Schönlein Purpura/IgAV

Comprising about 10% of all cases of cutaneous vasculitis and about 90% cases of primary childhood vasculitis [1, 23], HSP/IgAV is characterized by retiform or patterned purpura preceded by an upper respiratory tract infection in about one-half of children and a recent drug exposure in a minority. Isolated or predominate IgA vascular deposits, and two or more of the following support the diagnosis: age $\leq$ 20 years, colicky gastrointestinal pain or hematochezia, an upper respiratory tract infection prodrome, hematuria, and renal biopsy showing mesangioproliferative glomerulonephritis with or without IgA deposits. Renal disease is found in HSP patients with a history of recent infection, fever, lesions above the waist or spread of purpura to the trunk, and papillary dermal edema and perivascular C3 on DIF histopathology [46, 47]. Long term follow-up is necessary in children with abnormal baseline urinalysis [48] since up to 20% develop chronic renal failure compared to those with a normal baseline urinalysis in which no person developed later renal impairment [48, 49]. Patients with fever, purpura above the waist, and elevated erythrocyte sedimentation (ESR) rate are more likely to develop IgA glomerulonephritis. In addition, in the pediatric population, serum pentraxin3 levels predicts future renal disease [50]. Furthermore, the lesions above the waist and edema on the exam are associated with gastrointestinal involvement [47]. Skin biopsy in patients with HSP/IgAV demonstrates neutrophilic SVV restricted to the superficial dermis (Figure 12), although the whole dermis may eventually become involved [51]. Patients older than age 40 years with HSP/IgAV with absent eosinophils on histologic examination of skin tissue had a three-fold increased risk of renal involvement compared to those younger than age 40 with tissue eosinophilia [52]. The IgA and IgM deposits in the skin by DIF also predicts renal disease [50].

The link of HSP and familial Mediterranean fever (FMF) has been well known since recognition that the classical features of the former, including purpura, gastrointestinal tract bleeding hematuria, localized edema, arthritis and positive skin biopsies; overlapped with periodic fever and abdominal pain lasting for 1 to 3 days, of the latter [53]. Pathophysiological inflammatory mechanism include complement consumption and circulating immune complexes [54]. Features unique to HSP include the absence of classical cutaneous IgA deposits on DIF, and recurrent, dispersed purpuric lesions of atypical areas along the face and

trunk [54]. Serum anti-LAMP-2 antibodies were significantly higher in 36 HSP patients versus 51 healthy controls [55].

Cryoglobulinemic Vasculitis

Cryoglobulins are cold-precipitating immunoglobulins that persist in the serum and solubilize when rewarmed. There are three types, type I, monoclonal cryoglobulins that comprise 10% to 15% of all cases and produce non-inflammatory small vessel hyaline thrombi; type II or mixed monoclonal IgM with RF activity and polyclonal IgG cryoglobulins which comprise 50% to 60% of cases; and type III or mixed polyclonal IgM with RF activity and IgG cryoglobulins comprising 30% to 40% of cases. The oligoclonal type consists in the composite of oligoclonal IgM (several monoclonal) against polyclonal IgGs with RF activity and is described as a transitional form type or IIa, [56]. Type II and III mixed cryoglobulinemia are associated with CTD, hematologic malignancies and HCV infection. Greater than 50% of HCV-seropositive patients have mixed cryoglobulins, and a lesser frequency of vasculitis. Persistence of CV immunological features was reported in 52% of effectively treated patients with HCV after 12 weeks of anti-viral therapy who potentially may remain clinically active [57].

Cryoglobulinemic vasculitis is characterized by Meltzer's clinical triad of purpura triggered by cold exposure or prolonged standing, arthralgia, and weakness in association with mixed cryoglobulinemia. Other cutaneous manifestations include PAN-like lesions, ulcers, splinter hemorrhages, palmar erythema and even digital gangrene if digital vessels become obliterated, this later, especially whenever the cryocrit is elevated. Systemic disease in CV includes glomerulonephritis, neuropathy, and pulmonary involvement with high titers of RF and low levels of C4. Most patients demonstrate neutrophilic SVV that equally affects vessels of the superficial dermis and subcutis on skin biopsy with vascular IgM and complement deposits on DIF; a minority of patients displays PAN-like histopathology [23].

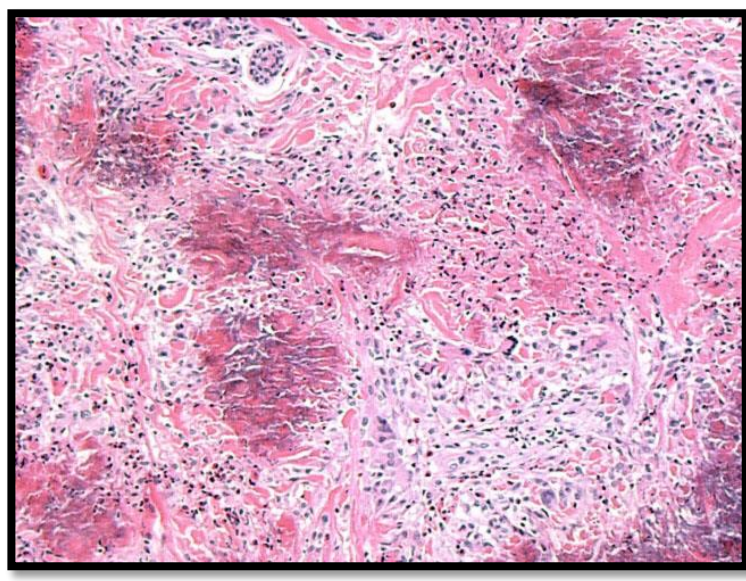
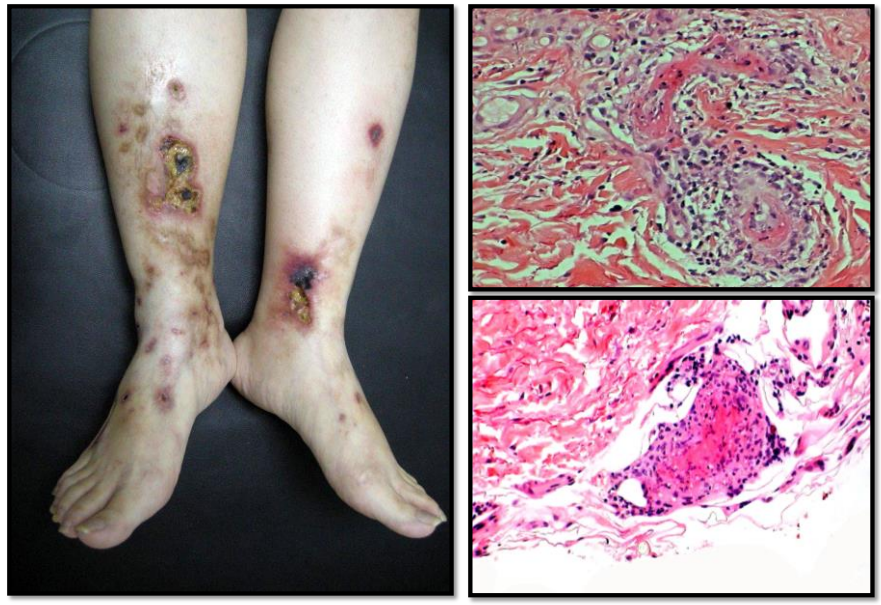


Figure 18. Multiple red collagen lytic granulomas in a patient with eosinophilic granulomatosis with polyangiitis.



Reproduced courtesy of Henry Foong, MD, Ipoh, Malaysia).

Figure 19. Severe cutaneous polyarteritis nodosa with secondary livedoid vasculopathy.

PRIMARY MEDIUM VESSEL VASCULITIS

Polyarteritis Nodosa

This less frequently seen MVV affects men and women age 40 to 60 years without sexual preference; a childhood form of PAN (cPAN) is well recognized [58] and in some familial clusters associated with recessive loss-of-function mutations in the gene encoding adenosine deaminase 2 [59]. Most of PAN cases have no known etiology and are labeled as idiopathic PAN. Secondary PAN associates with HBV, HCV infection, human immunodeficiency virus (HIV), cytomegalovirus, parvovirus B19, and human T-lymphotropic virus (HTLV). The frequency of PAN-associated with HBV has dropped in cases from 36% to less than 5% in developed countries due to effected vaccination programs [60], whereas HIV-associated PAN prevails in developed countries [61]. Other than the PAN-associated HBV subgroup, cutaneous PAN and single-organ PAN constitute other acknowledged subgroups (62).

Constitutional symptoms, fever and weight loss and myalgia are almost universal (> 90%), followed by neurologic (75%) and cutaneous manifestations (60%) (Figure 19). It affects almost any other system/organ, like the gastrointestinal (40 - 50%), renal (50%) with renovascular hypertension in < 80%, testicular (20%), musculoskeletal (arthritis in < 75%), ophthalmologic (8%), vascular (claudication, ischemia, necrosis) in 6%, cardiac (cardiomyopathy, pericarditis in 5% and heart failure in ≤ 30%, central nervous system (stroke, confusion) in 5% and respiratory (lung infiltrates and pleural effusions) in 3% [58, 63-65] implying multi-organ involvement.

Tissue biopsy of muscle, sural nerve, kidney, liver, testis, and rectum shows segmental neutrophilic muscular vessel vasculitis affecting medium- and small-sized arteries. Even the pathogenic role of immune complexes is considered to play a central role, for unknown reasons

PAN does not affect arterioles, capillaries or venules sparing vital organs (absence of capillaritis in lungs and no glomerulonephritis) which together with the negative serology for ANCA differentiates PAN from any other AAV [62]. Active vasculitic lesions are frequently associated with chronic reparative changes that show endarteritis obliterans. Skin lesions are observed in 25 to 60% of patients [66] the commonest of which palpable purpura and erythema of the legs [67]. Subcutaneous leg nodules ranging from 0.5 to 2 cm occur in proximity to blood vessels in 20% of patients. 49.7% of the cases, more often in non-HBV-related PAN (57.8 vs. 35%). Purpura was the most common type of lesion in patients with PAN with or without an associated HBV infection. Cutaneous vasculitis was found overall in about one-half of their 348-patient cohort of Pagnoux and coworkers with PAN [65], including 57.8% of 225 HBV-seronegative and in 35% of those HBV-seropositive. Interestingly, they also found on multivariate analysis that the presence of cutaneous manifestations at diagnosis, especially nodules, was associated with a higher risk of relapse. Agard and colleagues [27] reported cutaneous involvement as the initial finding in 11% of 36 patients with MPA and PAN.

Cutaneous PAN (CPAN), an indolent form of PAN confined to the skin, is suggested by tender nodules, livedo vasculopathy, livedo racemosa, ulcers, acral gangrene and neuropathy [1, 4, 68]. Deep punch and incisional biopsy demonstrates neutrophilic muscular vessel vasculitis at arterial branch points located at the dermal-subcutis junction or within the subcutis. Macular arteritis [69-72] and lymphocytic thrombophilic arteritis [73] are related variants of CPAN that represent latent or late evolutionary stages of the disease and manifest lymphocytic vasculitis [69, 74]. Nodular vasculitis or erythema induratum of Bazin, a lobular panniculitis and vasculitis of venules and septal veins [75] can be mistaken for CPAN [1, 4, 68]. Their differentiation is possible by considering the relative silhouette and patterns of elastic tissue distribution [76, 77] such that in contrast to the rounded contour of arteries, venous vessels have oval silhouettes with few or no elastic fibers.

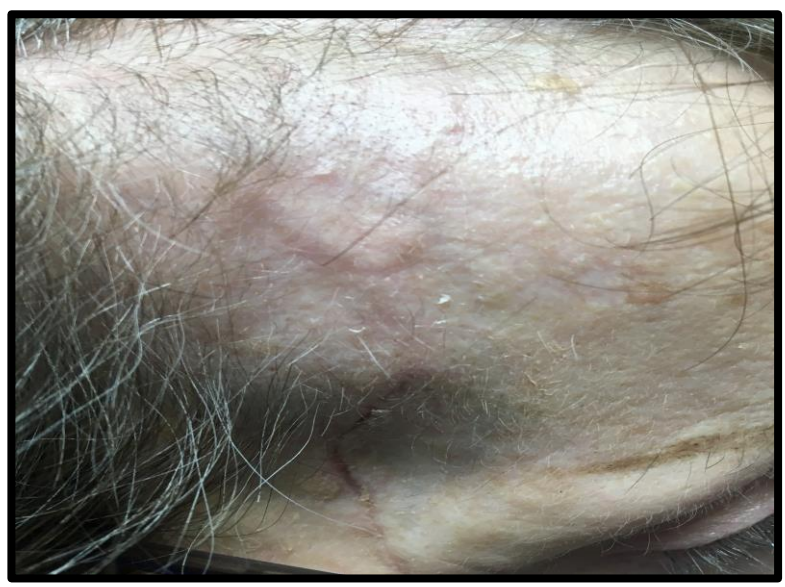


Figure 20. Giant Cell Arteritis in a patient who underwent the temporal artery biopsy (seen at the lower arterial tract) and atrophy of surrounding soft tissue. Note the irregularity of the arterial surface.

LARGE VESSEL VASCULITIS

Giant Cell Arteritis

This disorder occurs in fair-skinned Caucasian individuals of older age females presents with headache, jaw claudication, visual and neurological disturbances resulting from ischemic endarteritis obliterans, and systemic features of malaise, weight loss, and fever due to release of inflammatory cytokines. The cutaneous signs consist of scalp tenderness; blanching, decreased or loss of temporal artery pulses, and cord-like temporal artery thickening (Figure 20) and occasionally distal cutaneous ulceration in the scalp secondary to obliterative endarteritis. Accurate and timely diagnosis is important because serious morbidity especially loss of vision if the correct treatment with corticosteroids are delayed. Skin biopsies that include muscular vessels of the subcutis and temporal artery biopsies are diagnostic key elements but not necessary for treatment onset if GCA is a highly suspected cases. Areas of normal pathology between lesions, or "skip lesions" may drive to conclude false-negative tissue readings for which the artery biopsy should be at least of 20 mm and analysis should contemplate serial cross-sectioning with an additional 1 - 5% diagnostic yield improvement if a bilateral biopsy is performed [78]. Histopathologically, lesions show granulomatous vasculitis with giant-cell-containing inflammatory infiltrates, while the essential diagnostic features of temporal artery biopsy include segmental inflammation with disruption of media and intima, and fragmentation of the internal elastic lamina.

VARIABLE VESSEL VASCULITIS

Behçet Syndrome

Behçet syndrome is a systemic vasculitis sharing with Cogan syndrome the category of variable vessel vasculitis. It is a chronic relapsing inflammatory disease with high prevalence in the Silk Road countries and of unknown etiology. The clinical features are the recurrent painful oral (aphthous) and genital ulcerations, variable types of ocular inflammation with predominant choroido-retinitis and a plethora of cutaneous manifestations ranging from acneiform lesions, papulopustulosis, pseudofolliculitis, erythema nodosum-like, erythema elevatum diutinum, pyoderma gangrenosum-type lesions, Sweet's syndrome-like lesions and hyperreactivity to small injuries [79]. This later phenomenon known as the pathergy test is used routinely in the clinical practice as is one of the diagnostic criteria for Behçet syndrome. The pustule-like lesion or papule follows a skin prick by a 20-gauge needle 48 hours later and may be evident during vascular procedures. Behçet syndrome may affect any organ, including the CNS, gastrointestinal system and lungs among others. The histopathology shows variable features like classic leukocytoclastic vasculitis, perivascular inflammation and interstitial infiltrates. In the acne lesions of Behçet LCV and lymphocytic vasculitis was found in 48% of patients compared to acne of patients without Behçet and controls [80]. Other findings may show superficial thrombophlebitis and in the erythema nodosum-like lesions, septal panniculitis with medium vessel vasculitis in up to half of these lesions [81].

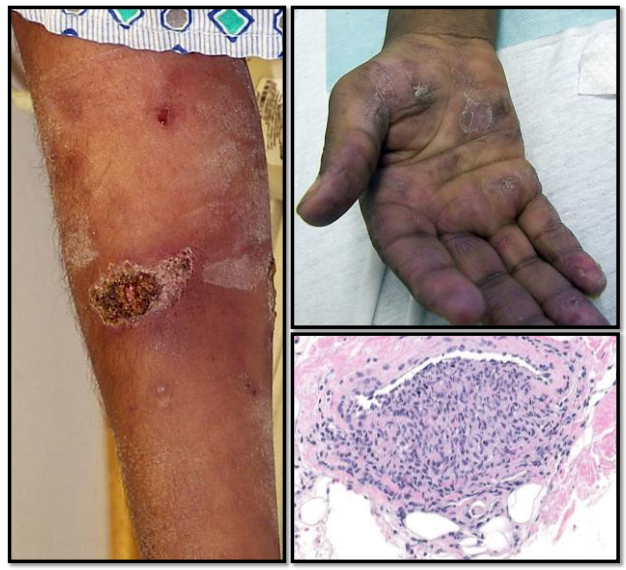


Figure 21. Cutaneous Lupus vasculitis. A young woman with longstanding systemic lupus erythematosus and multiorgan involvement with nodules, pyodermatous ulcers, painful erythematous palmar macules and punctate scars.

SECONDARY VASULITIDES

Connective Tissue Diseases

Lupus Vasculitis

Ramos-Casals and colleagues [10] noted cutaneous vasculitis in 76% of 670 patients with SLE. The commonest cutaneous lesions were erythematous punctate lesions of the fingertips and palms, followed by purpura. Female SLE patients, anti-Ro seropositive, had a 1.63 greater risk of develop cutaneous vasculitis [82]. Compared with SLE controls, those with cutaneous LV had a higher likelihood of Raynaud phenomenon and ribosomal P protein antibodies, but not greater frequency of kidney or nervous system involvement [83]. Patients with LV typically present with livedo reticularis, anemia, high ESR, and anti-La/SS-B antibodies than SLE patients without vasculitis. Additionally, they are younger, tend to have a higher SLEDAI/SLICC/ACR DI scores with musculoskeletal symptoms and hypocomplementemia, this later with a high sensitivity to detect LV. Lupus nephritis, cardiovascular features and comorbid Sjogren syndrome are significantly linked with the development of LV [84]. Arterioles and post-capillary venules are the most commonly affected by vasculitis, manifested as purpura, vesiculobullous lesions, urticaria, and splinter hemorrhages. Cutaneous ulcers, nodules, digital gangrene, necrotizing livedo reticularis, punctate acral scars, and pyoderma gangrenosum (PG)-like lesions (Figure 21), suggest arterial vessel involvement and multiorgan involvement. There may be p-ANCA and less often c-ANCA-seropositivity. Skin biopsy shows neutrophilic vasculitis with lesions that can resemble either typical LCV or PAN, or coexistence of both small and muscular vessel vasculitis in the same biopsy specimen.

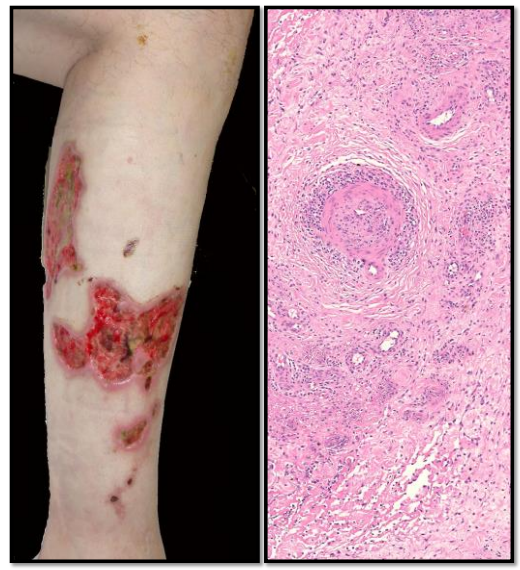


Figure 22. Arteritis and small vessel vasculitis leading to geographic ulceration in rheumatoid arthritis vasculitis.

Rheumatoid Vasculitis

The extra-articular (ExRA) manifestation of clinically evident RAV were noted in 2% of patients [22] compared to 15% to 31% in postmortem studied cases of RA [85]. The onset occurs in longstanding RA, averaging 10 - 14 years after the outset [86]. Cutaneous RAV is the most common vasculitic type within RA, typically affecting small- and medium size blood vessels. . It should be thought that patients with 'burned-out' arthritis with no or very few articular symptoms of disease activity may manifest with RAV in the context of other extra-articular features, like the lungs (pulmonary fibrosis), sclerittis, Felty syndrome or co-morbid peripheral vascular disease [87]. Moreover, the odds for developing RAV are the coexistent peripheral vascular disease, cerebrovascular disease, severe RA (with presence of severe deformities requiring surgery, radiographic evidence of erosions, nodulosis) and use of biologic therapy. Despite the advanced knowledge in the pathogenesis and the introduction of effective biologic therapies, RAV is still associated with increased premature mortality after 5 years of the diagnosis, with mortality of 25% in the 2000's that dropped from a 40% in the 90's. The significant morbidity, in about 36% of patients with RAV, relates to the systemic vessel involvement, in which the devastating inflammatory process, if untreated, leads to the recurrence or further progression in other target organs, while the excessive cytotoxic immune suppression may bring a burden of equal or more morbidity or predispose worse lethal consequences [88]. and is associated with increased premature mortality with mortality in 40% of patients by 5 years as well as significant morbidity due to both organ damage from vasculitis and consequences of the cytotoxic treatment [89]. Two drugs have proven to decrease the odds for the development of RAV, hydroxychloroquine and aspirin. The former drug, hydroxychloroquine, relies its protective properties as it has protean immune-modulatory action by several mechanisms of action, like the Toll-like receptor inhibition, anti-thrombotic and antilipemic action [90], and the by contributory anticoagulation effects of aspirin. Cutaneous manifestations of RAV are graded mild, moderate, and severe. Mild cutaneous RAV

presents with nail fold and palmar telangiectasia, thrombosis, minute digital ulceration, petechiae, and livedo reticularis. A well-known presentation are Bywater lesions consisting in periungual infarctions in long-term RA carrying without systemic implications requiring no escalade in the immune suppression [91]. Moderate cases manifest palpable purpura. Severely affected patients present with digital gangrene, nail-fold infarcts, and large cutaneous ulcers (Figure 22). The histopathology of RAV mimics that of polyarteritis nodosa without forming microaneurysms [92]. To define the vasculitic process, three layers of vessel need to be involved, distinguishing this from perivascular infiltrates without invasive features commonly seen in RA. Neutrophilic proliferation as well as, lymphocytic, and plasmacytic cells infiltrate all layers of the small arteries [93]. Patients with RA and cutaneous LCV alone without RAV, have a better prognosis than those with other ExRA involvement [22]. High acute phase reactants in a RA patient with established disease are the only proving biomarkers contrasting with the rheumatoid factor and anti-citrullinated cyclic peptide antibodies which titers are minimally or not clinically meaningful in RAV. Conversely, the absence of RF and anti-CCP antibodies have an excellent negative predictive value for RAV [94]. Some patients may express a positive anti-nuclear antibody or an anti-perinuclear antibody (atypical), other than then PR3 or MPO antigens suggestive of the underlying vasculitic process targeting other antigens in neutrophil granules. Anti-lactoferrin antibodies have been reported in the latter circumstance [95]. Minocycline-induced cutaneous PAN was reported and associated with the chronic treatment for acne treatment improving after discontinuation of the drug [96].

Drug-Induced Cutaneous Vasculitis

Hypersensitivity vasculitis due to adverse drug reactions manifests as superficial dermal neutrophilic or lymphocytic SVV on skin biopsy, and represents about 20% of cases of cutaneous vasculitis [1, 4, 68, 97]. Tissue eosinophilia is an indicator of drug-induced cutaneous SVV [98].

Tumor Necrosis Factor-α

Tumor necrosis factor-α (TNF-α) inhibitors employed in the treatment of autoimmune and rheumatic diseases [99] were the reported cause of cutaneous vasculitis in 8 patients so treated for 2 to 72 months [100], including four patients with RA, three patients with ulcerative colitis, and one patient with Crohn disease. The commonest presenting manifestation of the patients was palpable purpura, followed by ulcerated lesions, erythematous macules and blisters. After discontinuation of anti-TNF-α, none had recurrent vasculitis. Appearance of ANCA titers in patients under anti-TNF-α therapy should prompt excluding AAV overlap, for which anti-TNF-α is not efficacious, and that requires switching to disease specific therapy [101].

Levamisole

Levamisole was originally introduced as an anthelmintic agent and later employed in Behçet disease and rheumatoid arthritis for immunosuppression. It has been employed in colon cancer enhancing the immunity by potentiating the T-cell mediated immune response. More recently, Levamisole was added to cocaine to potentiate the stimulant effects as it has dopamine agonistic effects provoking a synergistic effect with cocaine [102]. Affected patients have

constitutional symptoms, arthralgia, leukopenia, agranulocytosis and cutaneous vasculitis [103, 104] with purpuric lesions of the ears, nose, cheeks, and extremities. The lesions have bright-red borders with central necrosis (Figure 23). Despite the severe and dramatic clinical appearance of these lesions, they usually resolve spontaneously within a few weeks of drug discontinuation but can recur with subsequent contaminated cocaine abuse. Subsequently, clinicians need to differentiate this presentation from other forms of vasculitis, particularly with GPA, as the degree of immune suppression will differ between both. The degree of skin necrosis has been as severe and large as to require skin grafting, and by removing the offender combined with a short course of corticosteroids will suffice to control the disease, contrasting with the management for GPA, which requires more aggressive immune suppression [105]. One-half of affected patients each demonstrated positive anti-MPO or positive anti-PR3 antibodies [103]. In addition, cocaine contaminated with levamisole by unclear mechanisms, is the mediator of ANCA-mediated vasculitis. The target, differing from AAV, was found to be the neutrophil elastase within the granules eliciting an atypical ANCA positive antibody response. Furthermore, elastase a constituent of neutrophil extracellular traps (NETs) is a target of patients exposed to cocaine/levamisole. It has been suggested that the programmed-cell death of neutrophils by NETs release, which is the extrusion of nuclear (chromosomal material) and mitochondrial DNA containing pro-inflammatory and thrombogenic peptides, is potentiated by cocaine/levamisole. This combination of drugs induces the release of highly immunogenic NETs containing high concentrations of elastase [106]. Other targets have also been reported, like the antiphospholipid antibodies found in 63% of patients [104], and anti-C1q antibodies [107].

AUTOINFLAMMATORY DISEASES

Autoinflammatory diseases (AD) comprise a heterogeneous group of diseases in which inflammation is triggered spontaneously and periodically with activation of the innate immune system. Most of them follow a well-defined Mendelian pattern of inheritance while others do not. The common onset of AD starts at early ages and in others, the onset is not seen until early or full adulthood. Although in most of the AD, the prevailing cutaneous expression reveals the group of neutrophilic dermatoses or urticarial presentation, few cases and series report true vasculitic processes, revealing the heterogeneity of disease phenotype and perhaps expressing a process outside the main pathogenesis.

Most notably of this group, Hyper-IgD syndrome has revealed true vasculitis. Hyper-IgD syndrome is characterized by periodic fever flares of 3 - 7 days, in infants and accompanied by arthralgia, abdominal pain, splenomegaly, cervical lymphadenopathy aphthous ulcers and maculopapular rash, annular erythema, palpable purpura and urticarial lesions [108]. The histopathology revealed perivascular infiltrates of variable numbers of lymphocytes and polymorphonuclear neutrophils fibrin deposits and red blood cell extravasation in a case report and analog findings in 7 out of 17 cases [109].

In cryopyrin-associated periodic syndromes (CAPS), which is a continuum of three disorders with the mutations in the NLRP3/CIAS1 gene, familial cold autoinflammatory syndrome (FCAS), Muckle Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular syndrome

(NOMID\CINCA), neutrophils urticarial dermatoses is the classical feature. Predominant perivascular and peri-eccrine and interstitial neutrophil infiltration is seen and very few lymphocytes/eosinophils. The deep dermis has also engorged vessels also filled with neutrophils [110]. Cases of cutaneous vasculitis were reported in MWS and CINCA/NOMID syndrome in which other organs are also compromised [111].

TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disorder consisting of periodic fever episodes lasting from 3 to 21 days, and in which manifestations show pleuritic chest pain, abdominal pain, conjunctivitis, periorbital edema, monoarthritis, testicular pain, myalgia, papulomacular and urticarial rash. A report revealed small vessel vasculitis and panniculitis in a 66-year old patient diagnosed with TRAPS with migratory macular erythematous rash and with positive ANCA against elastase, successfully treated with etanercept [112].

IgG4 Related Disease

The analogy in the histopathology of two small vessel vasculitides granuloma faciale (GF) and erythema elevatum diutinum (EED) with IgG4-related disease suggests that they might belong to the same spectrum. The two vasculitides, considered as a single disease with different presentations, share two distinctive features: small vasculitic lesions and concentric fibrotic processing. Granuloma faciale affects preferentially the face with one or multiple erythematous purplish plaques, and with lesions showing dense inflammatory infiltrate with neutrophils, eosinophils, lymphocytes and plasma cells and formation of perivascular concentric fibrosis.

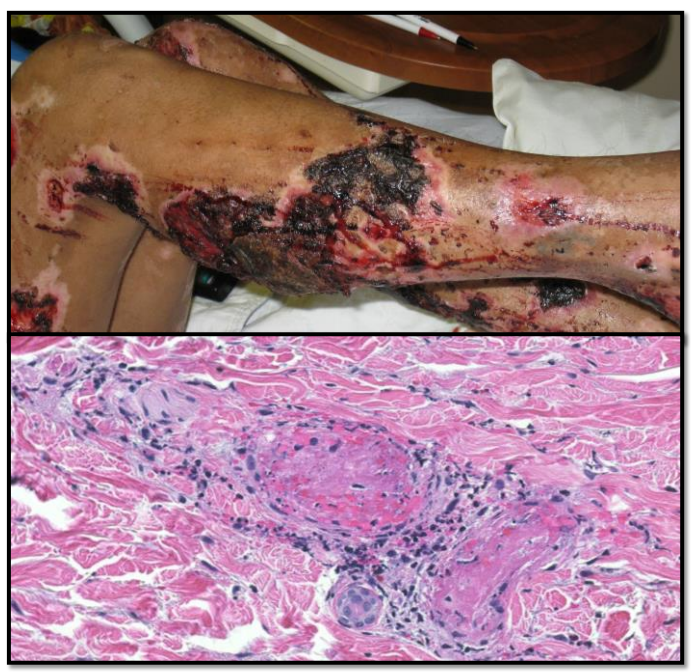
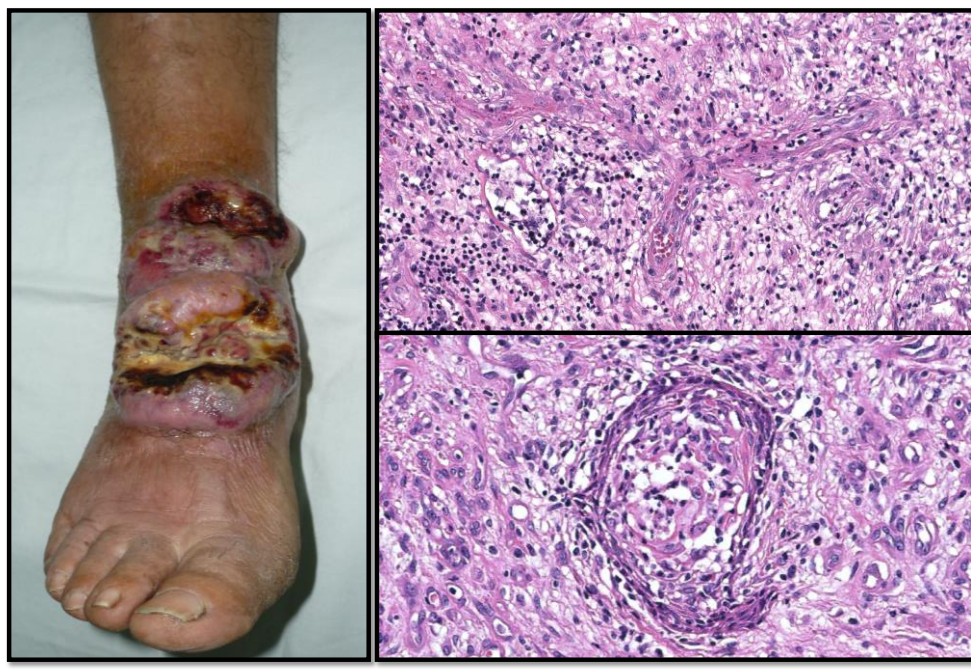


Figure 23. Levamisole-induced vasculitis shows histologic signs of a vaso-occlusive disorder and vasculitis.

Similarly, erythema elevatum diutinum presents with plaques nodular lesions preferring the trunk and lower extremities and with predominant neutrophils in the infiltrate. GF has been linked with eosinophilic angiocentric fibrosis, an eosinophil-rich infiltrate with perivascular fibrosis characteristically present in the upper respiratory tract. This latter has also been proposed being an expression of IgG4-related disease and the hypothetical link between both surmounts to the functional role of IgG4 with allergic responses and the production of IL-5 attracting eosinophils with subsequent fibrosing process formation. IgG4-related disease is a systemic illness causing mass lesions in different organs, like the pancreas, exocrine glands, lymph nodes peribiliary infiltrates, interstitial nephritis and other tissues, and associated with a predominant lymphoplasmacytic cell infiltrate producing excessive IgG4, eosinophils, storiform fibrosis and obliterative thrombophlebitis. The quantity of lymphoplasmacytic infiltrates, serum IgG4 levels, the IgG4/IgG ratio are diagnostic criteria [113] and to test whether EED and GF fulfilled these, tissues of 32 patients (GF, n = 25; EED, n = 7) were analyzed with Immunohistochemistry. However, results failed to provide confirmatory evidence in the two vasculitides attributable to the stringent diagnostic criteria and to the retrospective nature of the study [114]. In another report, however, the results in tissues of GF and EED, 7 (22.6%) out of 31 patients fulfilled criteria for IgG-related disease (IgG4/IgG ratio > 40% and > 50 cells with IgG4 IHC per high power field), but none in the EED patients. Curiously all patients were males and with recurrent multiple lesions without other organ involvement suggestive of a localized form of IgG4-related disease might be expressed as GF in some subpopulations [115]. Further prospective and larger multicentric studies are required supporting this concept.



Courtesy of Juan Carlos Graces, MD, Guayaquil, Ecuador).

Figure 24. Myelodysplastic syndrome presenting as erythema elevatum diuntinum. A large ulcerative tumor shows localized fibrosing leukocytoclastic vasculitis.

Table 5. Clinical, Pathologic, and Laboratory findings Indicating a High Probability of Systemic Disease[1]

Clinical signs or symptoms	**Suspected Systemic Vasculitis Syndrome**
High fever	Infection, systemic inflammatory disorders
Paresthesias, foot drop	EGPA, PAN
Abdominal pain	HSP, EGPA, MPA, PAN, RV, LV, BD
Frank arthritis	RV, infection, PAN, systemic inflammatory disorder
Hypertension	PAN
Purpura above waist, upper extremities	HSP, MPA, GPA, EGPA
> 1 type of vasculitic lesion*	HSP, MPA, GPA, EGPA, RV, LV, BD
Punctate palmar lesions	LV
Laboratory evaluation	**Suspected Systemic Vasculitis Syndrome**
ESR > 40mm/hr	Infection, hematologic malignancies, systemic inflammatory disorders
Elevated RF, cryoglobulins and low complement	CV
Chest x-ray: infiltrates or cavities	GPA (fixed infiltrates), EGPA (non-fixed infiltrates), MPA, malignancy
Hematuria and/or proteinuria and/or abnormal creatinine	Dermal-renal vasculitis syndrome: GPA, MPA, HSP, SLE
Hypocomplementemia	UV associated with SLE, RV, CV, infective endocarditis
Abnormal blood count	Infection, hematologic malignancy, systemic inflammatory disorders
cANCA (PR3)	GPA
pANCA (MPO)	MPA, EGPA
Eosinophilia, elevated IgE, elevated RF	EGPA
Histologic Examination	**Suspected Systemic Vasculitis Syndrome**
Deep dermal and/or subcutaneous small and/or muscular vessel vasculitis	Systemic vasculitis syndrome (GPA, EGPA, MPA, CV, BD, RV, LV, septic vasculitis), malignancy associated
Palisaded neutrophilic (extravascular) granulomatous dermatitis	GPA, EGPA, LV, RV
Tissue neutrophilia	SLE, infection
Tissue eosinophilia	EGPA and drug induced vasculitis
Direct immunofluorescence	**Suspected Systemic Vasculitis Syndrome**
Isolated or predominate IgA vascular deposits	HSP
Lupus band (IgG, IgM, and/or C3 at the BMZ)	LV, UV associated with SLE

BD = Behcet disease; BMZ = basement membrane zone; c-ANCA = cytoplasmic anti-neutrophil cytoplasmic antibody; CV = cryoglobulinemic vasculitis; EGPA = Eosinophilic granulomatosis with polyangiitis; ESR = erythrocyte sedimentation rate; GPA = Granulomatosis with polyangiitis; HSP = Henoch-Schonlein purpura; LV = lupus vasculitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PAN = polyarteritis nodosa; p-ANCA = perinuclear pattern of anti-neutrophil cytoplasmic antibody; PR-3 = antiproteinase-3; RF = rheumatoid factor; RV = rheumatoid vasculitis; SLE = systemic lupus erythematosus; UV = urticarial vasculitis

Adapted from Chen and Carlson et al. [4].

SYSTEMIC MALIGNANCY

Lymphoproliferative, myeloproliferative, and carcinomatous tumors comprise < 5% of paraneoplastic cutaneous vasculitis (Figure 24), a diagnosis that may be considered in patients with recurrent purpura, hematologic abnormalities including cytopenia, monoclonal gammopathy, immature blood cells; hematuria, abnormal tissue or nodal masses on imaging studies, and refractory responses to immune therapies. There are three such categories of

patients including, those with true paraneoplastic vasculitic syndromes wherein the vasculitis improves with extirpation or treatment of the tumor; vasculitis masquerading as malignancy such as lung masses in GPA; and malignancy masquerading as vasculitides as in emboli from an atrial myxoma and superficial migratory thrombophlebitis with pancreatic cancer. Most paraneoplastic cutaneous vasculitic syndromes are the result of a paraproteinemia secondary to lymphoproliferative disorders, including cryoglobulinemia in association with lymphocytic lymphoma and Waldenström macroglobulinemia.

PROGNOSIS

There are clinical and histologic predictors for the prognosis of cutaneous vasculitis that suggest the likelihood of concomitant or later systemic vasculitis [1, 18, 116] as shown in Table 5. The distinction between localized cutaneous and systemic vasculitis is important since the former carries a relatively favorable outcome, while the latter conveys the likelihood of permanent organ damage, increased morbidity and mortality. About 20% to 40% of patient with cutaneous vasculitis have concomitant limited systemic vasculitis notably kidney such as so called renal-dermal vasculitis while the likelihood of chronicity and systemic progression is enhanced when there is coexisting CTD, cryoglobulinemia, frank ulceration [117], arthralgia [19], more than one form of cutaneous vasculitic lesion such as ulceration and palpable purpura, putative muscular and SVV, normal serum IgA levels [17], paresthesia, fever, painless lesions [19] and cutaneous necrosis [118]. Histologically, the severity of vessel injury in cutaneous vasculitis correlates with the clinical severity and course [117, 119]. Others have noted histopathological changes of LCV were not predictive of extracutaneous involvement [120]. Lesional IgA deposits by DIF predict proteinuria and subsequent renal involvement [121]. Up to 60% of patients presenting with cutaneous vasculitis on skin biopsy have SVV restricted to the dermis while the remainder have deep dermal and pannicular SVV and muscular vessel involvement [122].

THERAPY

Therapy depends upon the nature and severity of the vasculitis. Mild hypersensitivity due to drug reactions should be treated with discontinuation of the offending agents, antihistamines for urticaria-associated pruritus, and a short course of corticosteroids in more severe cases. Simple observation may be adequate for mild cases and transient lesions of HSP/IgAV-related purpura. Non-steroidal anti-inflammatory agents, colchicine, antihistamines, and dapsone may be employed in chronic cutaneous vasculitis without recognizable cause and in selected patients prior to administration of corticosteroids and cytotoxic drugs. Rituximab has equivalent remission-induction efficacy as cyclophosphamide in AAV each in conjunction with corticosteroids [123]. Morphologic alternations of the vessel wall lumina and perivascular areas may be useful in treatment strategy. Healed arteritis with intimal thickening due to luminal occlusion should suggest the need for anticoagulation and vascular dilating agents, whereas pathologically confirmed acute and subacute arteritis

generally warrants combination immunosuppressive therapy to suppress ongoing vascular inflammation and tissue damage.

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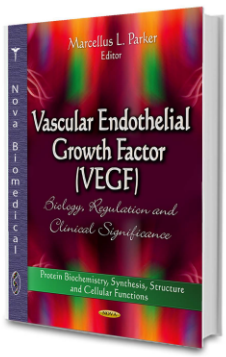

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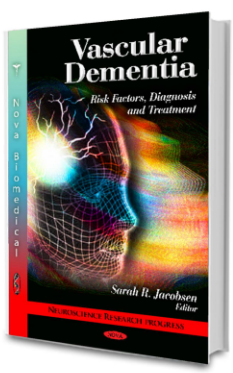

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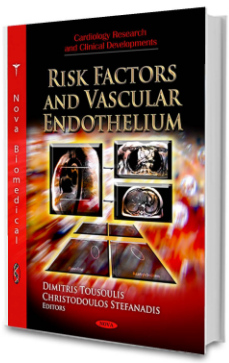

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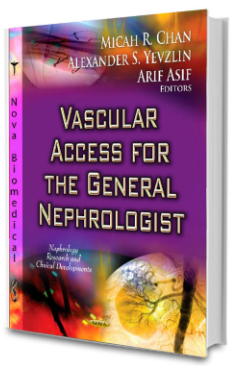

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