Overview of the Vasculitides

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KEYWORDS

• Primary • Secondary • Vasculitis • Autoimmune • Nervous system

KEY POINTS

- The systemic vasculitides are heterogeneous clinicopathologic disorders that share the common feature of vascular inflammation.
- The 2012 Revised Chapel Hill Consensus Conference serves as a guide for the categorization of diverse forms of vasculitis based on the caliber of the vessels involved.
- The underlying pathophysiology reflects diminished blood flow, vascular alterations, and eventual occlusion with variable ischemia, necrosis, and tissue damage.
- The resulting clinical disorder can vary depending on involvement of specific organs, caliber of blood vessels, the underlying inflammatory process, and individual host factors.
- This article 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. Vasculitis 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.

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 on the caliber of the vessels involved (**Boxes 1** and **2**). 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

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Box 1
Classification of vasculitides

Large vessel vasculitis
- Giant cell arteritis
- Takayasu arteritis

Medium vessel vasculitis
- Polyarteritis nodosa
- Kawasaki disease

Small vessel vasculitis
- Antineutrophil cytoplasmic antibody-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 central nervous system
- 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
- Mycobacterial tuberculous
- Spirochete disease
  - Neurosyphilis
  - Lyme neuroborreliosis
- Varicella zoster virus
- Human immunodeficiency virus type-1/AIDS

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 antineutrophil cytoplasmic antibody (ANCA) or immune complexes (IC).

The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA) (Wegener granulomatosis [WG type]), eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome), and microscopic polyangiitis (MPA) (microscopic polyarteritis), whereas vasculitic disorders associated with IC include immunoglobulin A (IgA) vasculitis (IgAV) (Henoch-Schönlein purpura [HSP]), cryoglobulinemic vasculitis (CV), and hypocomplementemia 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 (CS). Vascular inflammation confined to a single

Box 2
Laboratory evaluation of systemic and nervous system vasculitides

Studies in Blood, Urine, and Body Fluids

CBC, chemistry panel, ANA, ANCA by IIF; ANCA ELISA serology specific for PR3 and MPO (in those with IIF ANCA seropositivity, other cytoplasmic fluorescence, and ANA that results in homogeneous or peripheral nuclear fluorescence); ESR, CK, T- and B-cell subset panel, circulating IC, acute and convalescent viral, retroviral, bacterial, fungal, TB, syphilis, and Lyme serology; quantitative immunoglobulins, IFE, C1q, complement proteins, RF, cryoglobulins, anticardiolipin, and aPL, LAC, double-stranded DNA antibodies, and appropriate HLA haplotypes; urinalysis for spot and 24-hour collection for chemical and cellular microscopic analysis; bronchoscopy (in those with lung lesions) for lavage; lumbar cerebrospinal fluid analysis for protein, glucose, cell count, IgG level, oligoclonal bands, cytology, VDRL, bacterial Gram stain and culture; India ink, cryptococcal antigen and fungal culture; acid-fast and TB culture; viral encephalitis panel for real-time analysis of DNA and RNA viruses by real-time PCR; *Borrelia* burgdorferi DNA by PCR, Lyme, and HIV1 serology.

Radiological Studies

Screening color Doppler ultrasonography of the temporal arteries and great vessels, 3-T MRI, and high-field MRA or CTA and DSA (as may be appropriate) of vascular beds and major vessels; ^{18}FDG body PET-CT, nuclear medicine cerebral perfusion with SPECT.

Histopathologic Studies

Punch skin biopsy of for ENF density and histology using PLP 9.5, with IF of vessel walls and microscopic analysis for leukocytoclasia; bronchoscopy or needle tissue biopsy of lung lesion and endoscopic biopsy of kidney tissue; USG-guided temporal artery biopsy; open sural nerve and soleus muscle or superficial fibular nerve and peroneus muscle tissue biopsies for epineurial and epimysial vasculitic foci; meningeal and/or cortical brain biopsy for vasculitic foci in arteries and veins.

Abbreviations: aPL, antiphospholipid; CBC, complete blood count; CK, creatine kinase; ENF, epidermal nerve fiber; IFE, immunofixation electrophoresis; IIF, indirect immunofluorescence; LAC, lupus anticoagulant; PCR, polymerase chain reaction; PLP 9.5, protein gene product 9.5; RBC, red blood cells; SPECT, single-photon emission CT; T and B, thymus and bone marrow–derived cells; USG, ultrasonography; VDRL, venereal disease research laboratory; WBC, white blood cells.

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 cause, such as substance abuse and infection designated by the specific vasculitic disorder with a prefix to denote the causative agent. The category of SOV involves arteries or veins of any size in a single organ without features to indicate that it is a limited expression of a systemic vasculitis that includes granulomatous angiitis of the brain (GAB) and the interchangeable terms primary angiitis of the central nervous system angiitis (PACNS) and primary central nervous system vasculitis (PCNSV); isolated or nonsystemic peripheral nerve vasculitis (NSPNV), and isolated aortitis (IgG4-RD).

In 2008, the Pediatric Rheumatology European Society 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 followed by a final validated classification[2,3] based on vessel size, similar to the CHCC nomenclature.[1]

Insight into effective therapies of systemic vasculitides has 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, European Vasculitis Study Society, the EULAR, The French Vasculitis Cohort of Patients with Primary Vasculitis of the Central Nervous System, Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), the Pediatric Vasculitis Initiative (PedVas), , and the Web-based network BrainWorks.

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

This article is an overview of primary and secondary vasculitides in adults and children for clinicians treating such patients. Five major challenges encountered in clinical practice are addressed and emphasized. First, clinical, pathologic, and serologic 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 CS), all of which share demonstrable histopathologic evidence of systemic vasculitis. Second, recognition of secondary vasculitides associated with underlying primary systemic illness, in which some but not all patients will demonstrate evidence of vasculitis, including CV, RAV, and CNS vasculitis associated with SLE, syphilis, Lyme neuroborreliosis; bacterial meningitis, tuberculosis (TB), varicella zoster virus, human immunodeficiency virus type 1 (HIV1), and AIDS. Third, the identification of the SOV, PCNSA, NSPNV, and IgG4-RD. Fourth, a recommended laboratory approach to the diagnosis of vasculitides. Last, evidence-based treatment options for each of the vasculitides.

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, those with associated blindness due to vasculitic involvement of ophthalmic and posterior ciliary vessels were subsequently classified as cranial arteritis, and later generalized GCA[4,5] when giant cell lesions were discerned along the aorta, its branches, and in other medium- and large-sized arteries at postmortem examination. There are 5 discriminatory features of GCA, including age greater than 50 years at onset, new localized headache, temporal artery tenderness or decreased temporal artery pulse, erythrocyte sedimentation rate (ESR) greater than 50 mm/h, and biopsy of an artery showing necrotizing arteritis and a predominance of mononuclear cells or granulomatous process with multinucleated giant cells (**Fig. 1**), which collectively serve as useful guideposts in recognizing GCA. If unrecognized and therefore untreated or inadequately treated, there is a high likelihood of large artery

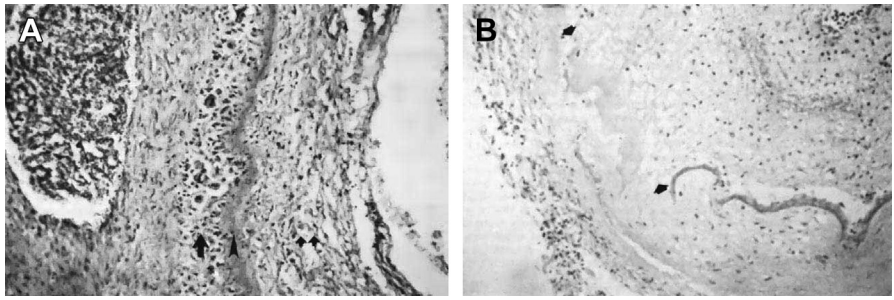

Fig. 1. GCA. (*A*) An early lesion of a large muscular artery, necrosis, inflammation, and giant cell formation (*single arrow*) can be seen immediately adjacent to the internal elastic lamina (*arrowhead*), which is undergoing degenerative changes, and there is some intimal proliferation (*double arrows*) (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). (*From* Younger DS. Vasculitis of the Nervous System. In: Younger DS, editor. Motor Disorders. Third edition. Brookfield, CT: Rothstein Publishing; 2015. p. 235–80; with permission.)

complication. Nuenninghoff and coworkers[6] 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 pathologic heterogeneity of GCA was further exemplified by the occasional finding of intracranial lesions in several patients who also qualified for that diagnosis[7]; however, PNS involvement in GCA remains exceedingly uncommon.[8]

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. Patients with so-called pulseless disease, occlusive thromboaortopathy, or TAK,[9] manifest 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 LVV among Asian women.

The noninvasive assessment of LVV includes performance of color-Doppler sonography (CDS), contrast-enhanced high-resolution MRI combined with MR angiography (MRA), and contrast-enhanced computed tomography (CT) combined with computed tomography angiography (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. PET with ^{18}F-fluorodeoxyglucose (FDG) detects increased FDG uptake by metabolically active cells, including inflammatory cells infiltrating the vessel wall in vasculitis, whereas 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.

Since the early reports of a salutary effect of corticosteroids on GCA in 1950,[10] 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. Although 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.[11] For this reason, corticosteroids should be started while the diagnostic evaluation is in progress and continued for up to 1 year before tapering to the lowest maintenance levels.

Ohigashi and colleagues[12] ascertained an improved prognosis among 106 consecutive patients with TAK in those with onset before 1999 compared with those diagnosed after 2000 (4.2% vs 0%) that was attributed to reduction in the time from onset to diagnosis, replacement of DSA (79% vs 9%) with ultrasound (6% vs 34%), CTA (24% vs 77%), MRA (21% vs 57%), and ^{18}F-FDG PET (0% vs 20%); less frequent complications of moderate or severe aortic regurgitation, and not surprisingly, an increase in the use and maximal dose of corticosteroids (70% vs 97%); and the use of first and second-line immunosuppressant agents (7% vs 42%). Surgical treatment of TKA was similar between those with onset before 1999 and after 2000 (22.5% vs 22.8%).

Medium Vessel Vasculitides

Polyarteritis nodosa and Kawasaki disease

Longcope[13] described the first American patient with periarteritis nodosa in 1908. Kernohan and Woltman[14] summarized the clinicopathologic aspects of adult PAN at postmortem examination, whereas Krahulik and colleagues[15] described fulminant childhood polyarteritis nodosa (cPAN). The dominant clinicopathologic 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 (**Fig. 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.[14] 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 for the childhood syndrome affecting children of all ages and races, with worldwide occurrence.

A retrospective study of 348 adult patients registered in the FVSG[16] 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 included peripheral neuropathy and mononeuritis multiplex in nearly equal proportion in 79%, and cutaneous involvement, notably, purpura, skin nodules, and livedo reticularis in 50% of patients. CNS involvement was noted in only about 5%

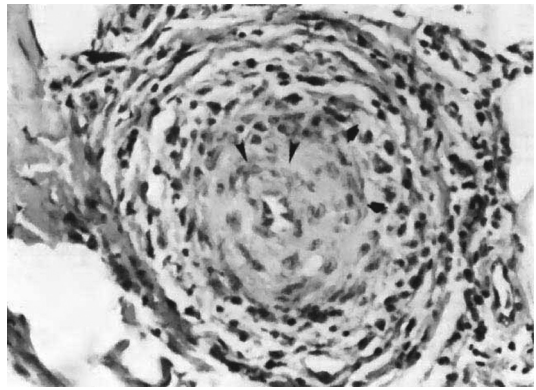

Fig. 2. This small muscular artery from muscle is from a patient with PAN. In the third, or proliferative, phase illustrated here, chronic inflammatory cells replace the neutrophils of the second phase; there is evidence of necrosis of the media (*arrows*), early intimal proliferation (*arrowheads*), 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). (*From* Younger DS. Vasculitis of the Nervous System. In: Younger DS, editor. Motor Disorders. Third edition. Brookfield, CT: Rothstein Publishing; 2015. p. 235–280; with permission.)

of patients. The classification criteria for cPAN require histologic evidence of necrotizing vasculitis in medium- or small-sized arteries or angiographic abnormalities demonstrating aneurysm formation or vascular occlusions, as a mandatory criterion, plus 2 of 5 features, among them myalgia, skin involvement, hypertension, neuropathy, or abnormal urinalysis or impaired renal function, with disease manifestations ranging from a benign cutaneous form with clinical, laboratory, and molecular characteristics of familial Mediterranean fever to severe disseminated multisystemic disease. Ozen and colleagues[17] studied 110 children with a mean age of 9 years, from 21 pediatric centers worldwide diagnosed with cPAN, dividing them into 4 groups, including systemic PAN (57%), cutaneous PAN (30%), and classic PAN with hepatitis B surface antigen (4.6%).

The FVSG study[16] allowed for a comparison of diagnostic modalities in adult PAN. Only 6 of 47 so tested manifested a positive ANCA finding by immunofluorescent (IF) and enzyme-linked immunosorbent assay (ELISA) techniques, rendering it helpful in support of PAN when negative to differentiate it from AAV, especially MPA. Cutaneous nerve biopsy performed in 129 patients, including 108 with peripheral neuropathy and 21 without peripheral neuropathy, showed typical vasculitic lesions in 83% and 81%, respectively, compared with muscle biopsy that revealed vasculitis in 68% and 60%, respectively. Angiography showed renal and gastrointestinal microaneurysms or stenosis in 66% and 57% of patients, respectively. Patients with hepatitis B virus (HBV)-related PAN had more frequent peripheral neuropathy, abdominal pain, cardiomyopathy, orchitis, and hypertension than those with non-HBV–related PAN, with respective 5-year relapse-free survival rates of 59% and 67% in scheduled therapeutic regimens depending on involvement in clinical trials, or according to the standard of care at the time of diagnosis, among them glucocorticoids and cyclophosphamide.[18,19] The predictors of a poor prognosis were age greater than 65 years, hypertension, and gastrointestinal involvement, and cutaneous manifestations or non-HBV–related PAN had higher rates of relapse. Three positive predictive

parameters include HBV antigen and DNA in serum, arteriographic anomalies, and mononeuropathy or polyneuropathy, and 5 negative predictive parameters, including detection of ANCA; asthma, ear, nose and throat signs; glomerulopathy; and cryoglobulinemia, which yielded 70.6% sensitivity for control vasculitides and 92.3% specificity for all controls.

Small Vessel Vasculitides

Antineutrophil cytoplasmic antibody-associated vasculitis

Microscopic polyangiitis Wohlwill,[20] Davson and colleagues,[21] and Wainwright and Davson[22] 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 34 such patients described by Savage and colleagues,[23] 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[24] 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[25] noted perinuclear (p)ANCA or antimyeloperoxidase (MPO) antibody positivity in 69% of Korean MPA patients, compared with 74.5% of positive ANCA in European patients, of whom 87% had a pANCA staining pattern; antibodies to proteinase 3 (PR3) were present in 8% of patients compared with MPO in 61% of those so studied as determined by ELISA. Childhood MPA (cMPA) appears to be very uncommon, and the criteria for diagnosis include 3 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 CT scan, and PR3 ANCA or cytoplasmic (c)ANCA staining.[3] Those with cMPA accounted for 4 of the first 32 children in the United States/Canadian ARChiVe registry.[26]

Eosinophilic granulomatosis with polyangiitis EGPA is contemporaneous with the description of MPA, and the first patient with EGPA was probably case 1 of Lamb[27] reported in 1914 also under the heading of PAN. That patient, a 26-year-old man with 2 years of worsening asthma, developed fever, palpable purpura, nodular skin lesions, hemoptysis, vomiting, urinary difficulty, and granular urinary casts. He died 1 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[28] described the clinical and postmortem findings of 13 patients with asthma, fever, and hypereosinophilia, accompanied by eosinophilic exudation, fibrinoid change, and granulomatous proliferation that constituted the so-called allergic granuloma that was found within vessel 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)[29] developed criteria for the classification of EGPA that included ascertainment of 4 or more of the following: asthma,

eosinophilia of greater than 10%, mononeuropathy or polyneuropathy, nonfixed 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 because a patient with asthma and paranasal sinusitis could fit the designation of EGPA. Among 383 patients enrolled in the FVSG Cohort[30] who satisfied the ACR criteria[29] or the 1994 CHCC definition for EGPA,[31] 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%), nonerosive sinusitis and polyposis (41%), skin lesions (39%), purpuric rash (22%), lung infiltrates (38%), gastrointestinal involvement (23%), renal manifestations (22%), cardiomyopathy (16%), CNS involvement (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 2 were reported to be of the EGPA type.[32]

Granulomatosis with polyangiitis Godman and Churg[33] 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[33] concluded that MPA, EGRA, and GPA were related to one another yet distinct from PAN. This astute conclusion was based mainly on pathologic features that were later substantiated by their common association with ANCA, but not so for PAN.[34] Fauci and colleagues[35] and Hoffman and colleagues[36] at the National Institutes of Health (NIH) reported a prospective series of 85 patients with GPA and a retrospective assessment of 180 patients followed for 6 months to 24 years, respectively. 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[35] 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[37] that is 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. The 1990 ACR criteria for the classification of GPA,[38] which preceded routine ANCA testing, included the presence of 2 or more from criteria from among 4, 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 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,[39] who prospectively compared hsPR3-ANCA ELISA with the IFT, noted an excellent performance of hsPR3-ANCA ELISA in identifying GPA and other AAV disorders associated with PR3-ANCA, suggesting that the former be used as screening test.

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.[40] However, as with other autoimmune disorders, the cause and pathogenesis appear to be multifactorial, involving the interplay of initiating and predisposing environment and genetic factors. Induction with corticosteroids and either cyclophosphamide followed by maintenance with rituximab, or azathioprine is recommended treatment. Among 197 ANCA-positive patients with GPA or MPA in 9 centers participating in the Rituximab in ANCA-Associated Vasculitis-Immune Tolerance Network Research Group multicenter, randomized, double-blind, double-dummy, noninferiority trial[41] of the comparison of rituximab 375 mg per square meter body surface area per week for 4 weeks and cyclophosphamide 2 mg per kilogram of body weight per day controls for severe AAV, was associated with achievement of the primary end point of remission of disease without use of prednisone at 6 months in 67% of study patients compared with 42% of controls. 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 1 of 2 intravenous regimens, followed by maintenance therapy, most frequently with methotrexate.

Early outcome results last year for the treatment of childhood AAV, in particular GPA, reported by Morishita and colleagues[42] on behalf of ARCHiVe Investigators Network and the Pediatric Vasculitis (PedVas) Initiative were somewhat discouraging. Among 105 children with AAV, mainly GPA, who received corticosteroids, 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 of 0, CS dose <0.2 mg/kg/d), 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 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,[43] who reported 73% remission at postinduction 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 by Zeek[44,45] between 1948 and 1952, as an immunologic response to antigenic material associated with clinically evident purpura, and small vessel inflammation affecting arterioles, capillaries, and postcapillary venules. It was likened by Zeek[46] to the

anaphylactoid Arthus reaction produced by the experimental injection of horse serum into rabbits.[47]

Immunoglobulin A vasculitis (Henoch-Schönlein purpura)

Children with HSP were described by Gairdner[48] with anaphylactoid purpura, including one who developed rash, colic, melanotic stools, intussusception, and hematuria, followed by a typical exanthema and fatal convulsion. Postmortem examination showed scattered cortical hemorrhages associated with cerebral necrotizing arteriolitis. The findings of IgA deposits in cutaneous blood vessel walls and in glomerular mesangial biopsies of patients with HSP and IgA nephropathy[49,50] were circumstantially convincing enough to substitute the term IgAV for HSP. IgAV/HSP is the commonest vasculitis in children. The 1990 ACR criteria[51] 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 2 or more of these criteria distinguished 85 patients who were diagnosed as having HSP by physicians who submitted cases for the vasculitis criteria compared with 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 increased sensitivity to 89.4% and specificity to 88.1%, respectively.

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 1 of the 4 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 100% and 87%, respectively. Peru and colleagues[52] studied 254 children with IgAV/HSP between 2003 and 2006 with a distribution of skin, joint, gastrointestinal, and renal manifestations of 100%, 66%, 56% and 30%, respectively. 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 pathologic condition 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. 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 more than 1300 patients[32] found that early treatment conferred a protective effect on developing persistent renal disease (odds ratio [OR] 0.43) and the likelihood of surgical intervention for abdominal pain (OR 0.75), as well as a statistically significant positive effect on shortening the duration of abdominal symptoms (OR 5.42).

C1q (hypocomplementemic urticarial) vasculitis

McDuffie and colleagues[53] 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 rheumatoid factor (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. IF of skin specimens showed fixation of immunoglobulin in the patient with necrotizing vasculitis. Renal biopsy showed mild to moderate glomerulonephritis indistinguishable from 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 IC in small vessel walls seemed likely. Zeiss and colleagues[54] characterized C1q IgG precipitins from HUV sera that precipitated C1q in agarose gel among 4 additional patients. Wisnieski and Naff[55] later showed C1q binding activity in IgG from HUV sera. Buck and colleagues[56] recognized the HUV syndrome as the presence of UV with multiorgan involvement, notably arthralgia or arthritis, angioedema, pulmonary, ocular, renal, and pericardial, although 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 IC when given late in the inflammatory cascade. There is yet a consensus on the most effective therapeutic regimen; however, plasmapheresis and intravenous immunoglobulin (IVIG) are alternative immunosuppressant modalities.

Variable Vessel Vasculitis

Behçet disease

Behçet and Matteson[57] described the clinicopathologic 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,[58] namely a 22-year-old woman with a 5-year history of recurrent oral and genital ulceration, and a 2-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[59] that included recurrent oral ulcerations plus any 2 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 3 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 acneiform nodules in postadolescent patients not receiving corticosteroids. A positive pathergy test of cutaneous hypersensitivity was defined as positive when a sterile pustule developed after 24 to 48 hours at the site of a needle prick to the skin.

Although the usual onset of BD is in the third or fourth decade of life, pediatric-onset patients have been described.[60] The neuropathologic findings of 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) in BD presents with subacute or chronic onset of symptoms of isolated intracranial hypertension accompanied by headache, blurred vision, and diplopia, 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 composed 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[61] noted large vessel lesions in 7 of 8 patients aged 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 6 of the 8 patients and was active in one, scarred in 6, 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 CS of nonsyphilitic interstitial keratitis (IK) was reported by Mogan and Baumgartner,[62] 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 a severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, and deafness. A diagnosis of recurrent IK and explosive Menière disease was made. Vestibuloauditory symptoms were later described by Cogan.[63] Haynes and colleagues[64] set forth diagnostic criteria for typical CS according to the definitions established in a review of 30 patients seen at the National Eye Institute of the NIH by Cogan. Symptoms of IK develop abruptly and gradually resolve, associated with photophobia, lacrimation, and eye pain, which may be unilateral or bilateral. Such symptoms tend 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 1 to 6 months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of 1 to 3 months, certainly no longer than 2 years. With less than 100 reported patients with this rare childhood and young adult disorder, most reported patients with typical CS have appeared as single case reports or patient series, often without pathologic confirmation or evidence of systemic vasculitis in a biopsy or at postmortem examination. Early recognition of the diagnosis of childhood CS 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 CS (58%) so 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%), etanercept (3%), hydroxychloroquine (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 that precipitate below core body temperatures and redissolve on rewarming is termed cryoglobulinemia. Wintrobe and Buell[65] 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. These symptoms were 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[66] provided modern classifications of cryoglobulinemia among 86 patients that included type 1, composed of a single monoclonal immunoglobulin, and types II and III as mixed cryoglobulinemia (MC), composed of different immunoglobulins, with a monoclonal component in type II, and polyclonal immunoglobulin 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 and the high rate of false-negative serologic tests in type II MC, it became evident that HCV was associated in most patients with MC. CV 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[67] 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 was noted in 22% of patients, whereas MCV was considered essential in 48% of patients. There was a greater frequency of joint involvement (53% vs 40%), peripheral neuropathy (74% vs 52%), CNS involvement (9% vs 2%) in those with HCV-MC compared with those with HCV-negative MC, with an equal frequency of purpura (71% vs 75%) and renal involvement (34% vs 35%). Cacoub and colleagues[68] noted 5 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 clinicopathologic 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% vs 3%), petechiae and purpura (27% vs 15%), arthralgia and arthritis (66% vs 16%), and cutaneous involvement (77% vs 50%), than adults.[69] Aggressive optimal therapy for HCV-related CV with PEGylated-interferon-α to improve the pharmacologic properties, and ribavirin with a protease inhibitor in the instance of HCV genotype 1 infection, should be considered induction therapy for CV and administered for 48 weeks for all HCV genotypes.[70] 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. Terrier and colleagues[67] 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 less than 10 mg per day at 6 months. However, this regimen was associated with severe infections, particularly when high doses of corticosteroids were used. Plasmapheresis combined with immunosuppression can be useful in fulminant HCV-related CV to engender an immediate effect but should be continued to avoid postpheresis rebound worsening. Rituximab, fludarabine, and cyclophosphamide treatment is effective treatment of 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 with fatalities related to serious infection and disease flares of CV.

Systemic Lupus Erythematosus

Although distinctly uncommon, 2 collagen-vascular disorders, SLE and rheumatoid arthritis (RA), can be associated with vasculitis of the nervous system. The early concepts of the collagen-vascular disorders introduced by Klemperer[71,72] 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-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, lead to recognizable clinical sequela due to vascular and parenchymal damage. The ACR delineated criteria for the diagnosis of SLE.[73] The recognition of neuropsychiatric lupus (NPSLE) was noted in 6.4% of a cohort of 1253 SLE patients defined by the ACR; those with late-onset SLE due to development of disease after age 50 years, had a frequency of NPSLE of 6.6% compared with 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 Richardswon,[74] and in 26.7% of late-onset SLE patients compared with 16.6% of those with early-onset SLE. A comparison of the cumulative incidence of clinical manifestations in the 2 latter groups showed that seizures were more common in early-onset patients compared with later-onset patients (6.6% vs 0%), similarly for multiple cerebrovascular attacks (23.3% vs 3.3%), cranial and peripheral neuropathy (6.6% vs 3.3%). Devinsky and colleagues[75] 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[76] noted neuropsychiatric manifestations at onset of SLE among 3% of 140 patients compared with 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 Feinglass and colleagues,[76] vasculitis was noted overall in 28% of patients as well as in 46% of those with neuropsychiatric involvement compared with 17% of patients lacking neuropsychiatric involvement. Postmortem examination of the CNS in 10 of 19 fatalities showed 2 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 50 patients reported by Devinsky and colleagues,[75] 2 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 which evidenced Libman-Sacks endocarditis and embolic brain

infarcts. Focal angiitis of the CNS with cystlike formation around affected blood vessels was noted at postmortem in the patient described by Mintz and Fraga[77] with typical SLE rash, cutaneous vasculitis, and active neuropsychiatric involvement. Trevor and colleagues[78] summarized the literature of large named cerebral vessel occlusions from 1958 to 1965 noting 1 patient with a middle cerebral artery (MCA) stenosis progressing to occlusion and 3 others with angiographic internal carotid artery (ICA) occlusions, adding 3 new patients and suggesting a relation of the occurrence to cerebral arteritis. Two women, one aged 21 and the other aged 42 years, presented with headache followed by focal neurologic symptoms attributed to lesions along the left MCA followed by right ICA occlusions, and a right MCA stenosis progressing to occlusion in 4 months, respectively. A third patient had a left ICA occlusion without mention of headache. Among the 4 literature patients, one had angiographic occlusion of the MCA and 3 others had occlusion of the ICA. Johnson and Richardswon[74] attributed the vasculitic nature of this process histopathologically to cerebral vasculitis mediated by acute inflammation and necrosis. Younger and colleagues[79] reported large named cerebral vessel occlusion attributed to circulating anticardiolipin antibodies in a young man in whom a vasculitic mechanism was not evoked. IC-mediated vasculitis probably affecting small vessels is thought to account for much of the damage in CNS lupus in light 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.

Rheumatoid Arthritis Vasculitis

A joint working group from the ACR and the EULAR published the 2010 classification criteria for RA.[80] Extra-articular RA (ExRA) occurrence is associated with increased comorbidity and mortality.[81] Criteria for severe ExRA were proposed in 2004.[82] Active RA with high disease activity is associated with increased risk of severe ExRA manifestations. Major cutaneous vasculitis and vasculitis involving other organs are 2 such ExRA occurrences. The diagnosis of RAV has generally been ascertained according to the criteria of Scott and Bacon[82] 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.

The markers of RA severity, including RA positivity, erosion and joint destructive changes (21% among those in the 1985–1994 cohort, compared with 29% in 1995–2007), use of methotrexate, other disease-modifying antirheumatic drugs, and systemic corticosteroids, were significantly associated with ExRA development between 1995 and 2007. Vollerstein and colleagues[83] 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), 2 (9 patients), 3 (5 patients) or 4 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 nonsteroidal anti-inflammatory drugs; however, three-fourths continued or began corticosteroid therapy. Sixteen of the original 52 patients eventually received cytotoxic immunosuppressive therapy. Compared with the general population, those with RAV had

decreased survival that was immediately evident and continued for 6 years. The survival of RAV was not different from classic RA.

The factors that predicted decreased survival in RAV include older age, failure to receive previous nonsteroidal 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. Puéchal and colleagues[84] 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, 67% versus 64%, respectively. A greater extent of the neuropathy and motor involvement tended to predict decreased survival; however, mononeuritis multiplex was not associated with a poor 5-year survival rate (57%) than was distal symmetric sensory or sensorimotor neuropathy (55%). Scott and Bacon[82] reported that 5 patients (24%) died in the group receiving methylprednisolone and cyclophosphamide; postmortem examination in 4 failed to demonstrate active vasculitis. By comparison, 7 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 antinuclear antibody (ANA). The first form of vasculitis 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 9 patients. Detailed postmortem findings evidencing CNS vasculitis have been reported in only 9 patients[84–91] with accompanying clinical neurologic 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. Complete remission of systemic rheumatoid vasculitis occurs 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. Prednisone therapy initially decreases systemic inflammation with a dose dependent on the degree of systemic inflammation and level of organ system involvement. The presence of CNS involvement mandates intravenous corticosteroid therapy and consideration of cytotoxic or biologic agents, including methotrexate, azathioprine, cyclophosphamide, anti–tumor necrosis factor

(TNF) agents and rituximab. Bartolucci and colleagues[92] reported the successful induction of a prompt symptomatic response in 10 patients with systemic vasculitis not responsive to conventional treatment, including 2 with RA and associated vasculitis. Puéchal and colleagues[93] 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.

IDENTIFICATION OF SINGLE-ORGAN VASCULITIDES

Primary Angiitis of the Central Nervous System

Adult- and childhood-isolated angiitis and vasculitis are prototypical primary vasculitic disorders restricted to the CNS. The diagnosis of PACNS[94] like IACNS[95] originally relied on classic angiographic (**Fig. 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 neurologic 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 the subset of GAB[96] presented with headache, mental change, and elevated cerebrospinal fluid 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, was noted at postmortem examination (**Fig. 4**).

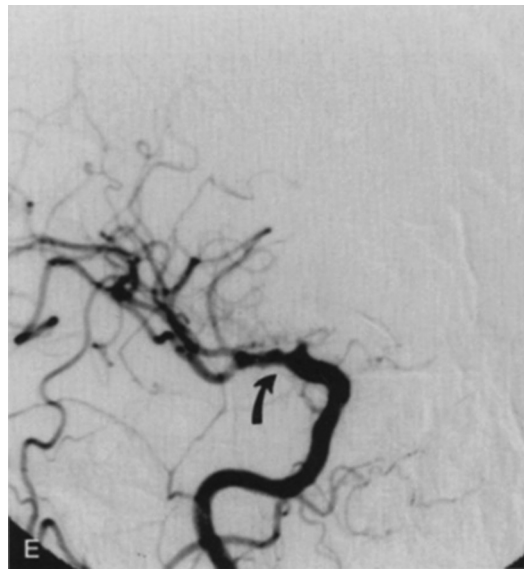

Fig. 3. Radiographic features of cerebral vasculitis. Ectasia and beading in the M1 segment and lack of flow in the A1 segment of the right anterior cerebral artery (*arrow*). (*From* Younger DS. Vasculitis of the Nervous System. In: Younger DS, editor. Motor Disorders. Third edition. Brookfield, CT: Rothstein Publishing; 2015. p. 235–80; with permission.)

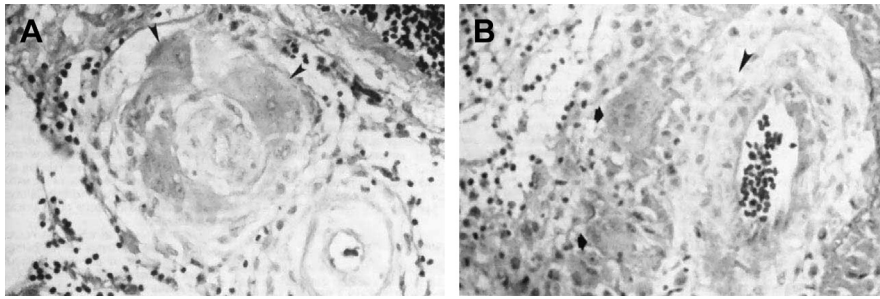

Fig. 4. CNS vasculitis. (*A*) The media and adventitia of this small leptomeningeal artery have been almost completely replaced by multinucleated giant cells (*arrowheads*). There is intimal proliferation with obliteration of the vascular lumen, and a dense, perivascular, mononuclear inflammatory infiltrate 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). (*From* Younger DS. Vasculitis of the Nervous System. In: Younger DS, editor. Motor Disorders. Third edition. Brookfield, CT: Rothstein Publishing; 2015. p. 235–80; with permission.)

The experience of adult PCNSV and GAB was summarized in a single large historical cohort by Younger and colleagues,[97] and 2 observational cohorts, one retrospective from the Mayo Clinic[98] and a multicenter prospective cohort of PACNS from the FVSG, French NeuroVascular Society, and the French Internal Medicine Society[99] have stratified cases of based on clinical, neuroradiographic, and histopathologic laboratory features, offering additional insights into the management of CNS vasculitis.

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 childhood (c)PACNS. 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. The approach to adult PACNS and cPACNS has been problematic for several reasons.

First, unlike antemortem pediatric cases of cerebral vasculitis that show angiographic evidence of large named vessel involvement, children with small-vessel (SV)-cPACNS can only be diagnosed conclusively by CNS biopsy tissues that show transmural inflammation of small meningeal and penetrating cortical vessels. Affected patients present with focal symptoms suggesting an association with stroke, but are more likely to develop subacute, nonlocalizing neurologic complaints, such as headache, behavioral changes, seizures, school failure, or cognitive decline. Moreover, childhood strokes may be highly variable in character and distribution.

Second, neuroimaging is far less specific in cPACNS. Noninvasive arterial imaging using CTA and MRA shows typically normal findings even when parenchymal MRI ranges from normal to diffusely abnormal across a wide array of lesion characteristics.

Third, childhood arterial ischemic stroke due to SV-cPACNS may show normal results on conventional angiography. Such cases, referred to as "angiography-negative SV-cPACNS,"[101] are typically unsubstantiated by histopathology even though the categorical term (SV-cPACNS) suggests a corresponding caliber of vessel involvement.

Fourth, despite the similarities to adult forms of PACNS, cPACNS series[100] fails to mention prototypical granulomatouspathologic condition, suggesting a bias of selection, making clinicopathologic comparisons to the adult form and the overall spectrum of CNS vasculitis problematic.

Fifth, awaiting the results of The PedVas Initiative, the approach of cPACNS has largely been to lump such cases into the broader category of IBrainD[102] by systematically excluding "angiography-positive" mimics of cPCANS and "angiography-negative brain biopsy-positive" mimics from true SVcPACNS. Sixth, as the approach to management of SV-cPACNS is patterned after other SVV such as AAV, it becomes difficult to reconcile the disappointing results of the PedVas Initiative[42] that showed a remission status of 42%, and visceral organ damage in 63% of cases following treatment with corticosteroids, cyclophosphamide, methotrexate, or rituximab for remission-induction, and plasma exchange in conjunction with cyclophosphamide and/or rituximab; and azathioprine, methotrexate, rituximab, mycophenolate mofetil, and cyclophosphamide for up to 12 months for remission maintenance.

Idiopathic Aortitis–Immunoglobulin G4-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[103] 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 histologic 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 aortic imaging. Rojo-Leyva and colleagues[104] noted idiopathic aortitis in 43% of 1204 aortic specimens gathered over a period of 20 years. In 96% of the patients with idiopathic aortitis and aneurysm formation, aortitis was present only in the thoracic aorta. In 2001, Hamamo and colleagues[105] 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[106] 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[107] concluded that inflammatory abdominal aortic aneurysm (IAAA) was related to IgG4 sclerosing disease. Second, Kasashima and colleagues[108] concluded that IAAA was an IgG-RD together with RPF. Third, Ito and colleagues[109] 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. Histologic 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 may be aortic and periaortic lesions of an IgG4-RD. One year later in 2009,

Khosroshahi and colleagues[110] described thoracic aortitis due to IgG4-RD with marked elevation of the serum IgG4 levels with progression to autoimmune pancreatitis, and Stone and coworkers[111] 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. CDS, MR 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 pathologic condition of IgG4-RD by Deshpande and colleagues[112] proposed a terminology scheme for the diagnosis of IgG4-RD based on the morphologic appearance and tissue $IgG4^+$ plasma cell counts in biopsy tissue. Three histopathologc features associated with IgG4-RD included a dense lymphoplasmacytic infiltrate, fibrosis arranged at least focally in a storiform pattern, and obliterative phlebitis in morphologic specimens. Most 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 2 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[113] suggested the initiation of oral prednisolone for induction of remission at a dose of 0.6 mg/kg 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. Readministration 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.[114]

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[115,116] established respective guidelines for the classification, diagnosis, investigation, and treatment of non-systemic vasculitic neuropathy (NSVN) and vasculitic peripheral neuropathy. Pathologically defined 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 clinical and laboratory evidence of involvement of other organs (demonstrable by laboratory evidence of PR3-, MPO-ANA, mixed cryoglobulins, anti-Sjögren's antibodies syndrome-related antigen A and B (SSA, SSB), Smith (Sm), ribonuclear protein (RNP), SCL-70, centromere, double-stranded DNA, citrullinated protein (CCP); ESR >100 mm per hour, or tissue biopsy evidence of vasculitis in another organ other than muscle; serologic, polymerase chain reaction 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 is broadly referred to as microscopic vasculitis or microvasculitis (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 4 lines of evidence.

First, the definition of NPNV allows for the finding of vasculitic lesions in muscle tissue, perhaps making the syndrome more appropriately termed PNS vasculitis. 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[16] 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 with 68% and 60% of cases where muscle biopsy tissue was examined.

Second, the lack of long-term follow-up in most cases series ranged from 6 months to 22 years.[117]

Third, the report was of only 2 proposed cases, both with foci of vasculitis outside the PNS in a visceral organ[14] or the temporal artery.[118] Patient 1 in the series of pathologically confirmed cases of PAN by Kernohan and Woltman[116] was a 54-year-old man with 5 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[118] 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 showed evidence of healed vasculitis in numerous small arteries and arterioles of muscle and nerve tissue measuring 50 to 200 μm in diameter without vasculitis in visceral organ or the CNS.

Fourth, the inclusion of patients with diabetes according to the 2010 guidelines[115] 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 or insulin-dependent diabetes, including anti-islet cell cytoplasmic antibodies, present in up to 80% of newly

diagnosed patients,[119] and glutamic acid decarboxylase antibodies, also present in patients with autoimmune stiff person syndrome.[120] Younger and colleagues[121] 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 107 patients,[122] 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 lumbosacral radiculoplexus neuropathy (LSRPN).[123,124] In the only postmortem case of LSRPN described by Younger,[125] 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 LSRPN 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 1000 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.

There have been far more studies of living cohorts with NSPNV. Kissel and colleagues[126] 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 symmetric sensorimotor polyneuropathy, while 10 had a mononeuritis multiplex presentation, 8 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 serologic evaluation. Said and colleagues[127] studied 100 patients with necrotizing arteritis in muscle or nerve biopsy tissue that occurred in the context of a connective tissue disorder in 55 patients and in association with a disorder unrelated to connective tissue pathologic condition in 13 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 of which were spontaneous pain of neurogenic or muscle origin (48%).

Collins and colleagues[128] described 48 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 with 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, 10 patients died (21%) over the period of 63 months' follow-up, 5 (10%) of whom were related to the disease or treatment, including 2 patients who succumbed to pulmonary emboli as a result of limited mobility of the legs or myocardial infarction in another, and 2 patients, one of whom had fatal sepsis and another had 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[115] include prednisone monotherapy unless there is rapidly progressive neuropathy at the dose of 1 mg/kg per day, with tapering over 1 year to a low dose. Combination therapy using cytotoxic drugs, including cyclophosphamide, methotrexate, and azathioprine, may be used with adjuvant plasma exchange or IVIG. The latter appears to 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. Careful monitoring should be performed to observe desired therapeutic responses and to avoid potentially serious drug side effects.

SUMMARY

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 pathology, all working side by side, aided by subspecialities of public health, epidemiology, genetics, and clinical trial specialists, have benefited from the outlook for individual patients and population cohorts around the globe. Nevertheless, it starts with clinical acumen typically of the general practitioner. This article 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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