Vasculitis

George F. Duna, MD, FACP
Leonard H. Calabrese, DO

Contents

1. The Vasculitides

The vasculitides encompass a heterogeneous group of disorders all sharing the pathologic features of vascular inflammation and vascular necrosis. These disorders pose a formidable challenge to the rheumatologist from both the diagnostic and therapeutic perspectives. Diagnostically, the signs and symptoms of vasculitis are highly variable and often nonspecific. The rheumatologic consultant must be knowledgeable regarding the laboratory, histopathologic and radiographic findings in each of these disorders in order to properly sequence their ordering and interpret them. Awareness of those varied disorders capable of mimicking vasculitis is also important. Once the diagnosis is made most forms of systemic vasculitis then pose a formidable therapeutic challenge often requiring prolonged and intense immunosuppressive therapy. Familiarity with the use of these therapies, especially their appropriate monitoring, is vital to minimize attendant toxicity. This chapter will review the key clinical elements of all the major vasculitic syndromes emphasizing those points essential for quality patient care and in particular those areas of recent clinical importance.

2. Classification

There is no universally agreed-upon classification system for the vasculitides. Varying attempts have been made in recent years, including the American Collage of Rheumatology (ACR) criteria set [1] and the Chapel Hill International consensus conference.[2] While each of these has merit, they are both limited by a variety of factors including the fact that the ACR criteria were largely developed in the pre-ANCA era and the Chapel Hill criteria give limited recognition to the varying forms of leukocytoclastic vasculitis. A working knowledge of these recent classifications is not essential for patient care, but they do provide a framework to discuss the major forms of vasculitis. We will use the classification displayed in Table 1 which represents an admixture of these systems, grouping diseases into sets that are unified on clinical grounds from the perspective of either diagnosis or treatment.

Table 1

Working Classification of Major Forms of Vasculitis

Classical Polyarteritis Nodosa
Predominantly medium sized necrotizing vasculitis, without glomerulonephritis; sparing the arterioles, capillaries, and venules
ANCA-associated Vasculitides
Wegener's granulomatosis Microscopic polyangiitis Churg-Strauss vasculitis
Necrotizing vasculitides each involving small to medium sized vessels (capillaries, venules, and arterioles). Medium sized vessel involvement variable. ANCA frequently but not invariably present. Varying degrees of granulomatous inflammation. Glomerulonephritis and pulmonary involvement common
Hypersensitivity Vasculitis Group
True hypersensitivity vasculitis Henoch-Schoenlein purpura Cryoglobulinemia (hepatitis C-associated, essential, other) Malignancy associated Connective tissue disease associated Hypocomplementemic vasculitis Associated with systemic disease
Each predominantly, but not exclusively, involving the skin. Vascular inflammation predominantly involving the small vessels (capillaries, venules, arterioles). Leukocytoclasia is a common morphologic feature
Giant Cell Group
Giant cell arteritis Takayasu arteritis
Both demonstrate granulomatous arteritis with a predilection for large vessels including the extracranial branches of the carotid artery (giant cell arteritis) and the aorta and its branches (Takayasu arteritis)

3. Classical Polyarteritis Nodosa

Epidemiology

Polyarteritis nodosa (PAN) is a rare disease. Estimates of its incidence and prevalence vary depending on the population studied, but it has been estimated to range from as low as 0.7 per 100,000 per year when limited to biopsy-proven forms in the general population to as high as 77 per 100,000 in a hepatitis B (HBV) hyperendemic Alaskan Eskimo population.[3] The sex distribution is nearly equal and is seen in all ages, but appears to peak between 40 and 60 years of age.

Pathogenesis

The pathogenesis of classical PAN is incompletely understood. Data derived from experimental forms of vasculitis (ie, serum sickness) have mostly implicated immune complex formation and deposition, but evidence for such is largely lacking in human studies. The best insights into pathogenesis of PAN stem from study of those forms associated with viral infections, especially HBV. In this variant there is strong evidence for the role of immune complexes as evidenced by immune complex detection in both blood and involved tissues. In non-HBV associated forms such findings are generally absent. Classical PAN is not associated with ANCA. There is abundant evidence for a role of adhesion molecule expression and cytokine release, though how these factors and others interact is largely unknown.[4]

Clinical Features

The clinical features of PAN often reflect its multisystemic nature.[3,5] The illness may range from mild and limited to a single organ system to fulminating and multisystemic. Virtually any organ system may be involved as part of the illness, but there is a strong tendency to spare the lungs and the renal glomerulus. Constitutional symptoms are common and the diagnosis of PAN should always be considered in the differential diagnosis of such clinical problems as fever of unknown origin, unexplained multisystem organ dysfunction, unexplained peripheral neuropathy, unexplained inflammatory arthritis or myositis and unexplained ischemic events in the gastrointestinal tract.

End-Organ Involvement

Certain end organs are more commonly involved than others. Peripheral nerves may be involved in as many as 70% of patients. The clinical presentation varies, but all are characterized by axon loss neuropathy. Mononeuritis multiplex is considered the most classical finding, but other forms of neuropathy such as symmetric polyneuropathy and even pure sensory neuropathy are occasionally seen.[3] Muscle involvement is also common and present with myalgia and/or weakness. Muscle enzymes may be elevated and electromyography may reveal findings compatible with a necrotizing myopathy.

Gastrointestinal involvement may be present in nearly 50% of patients and results from ischemia to stomach, bowel, liver and gallbladder. Clinically, symptoms may range from crampy pain to those associated with visceral perforation. Isolated involvement of organs such as gallbladder and appendix has been rarely reported and these may or may not be a part of more widespread disease. One notable abdominal complication more specific for PAN than other forms of systemic vasculitis is rupture of a microaneurysm. While extremely rare, awareness of this complication is important because of catastrophic consequences if unrecognized. Acute abdominal presentation in patients with PAN, even when treated, needs prompt surgical evaluation for possible perforation and aneurysm rupture.[6]

Renal involvement in PAN is on the basis of extraglomerular vascular involvement and may result in malignant hypertension and multiple renal infarctions. The presence of RBC casts in the urine, suggesting glomerular involvement, is much more characteristic of the ANCA-associated disorders and should prompt reevaluation of the diagnosis. This point is not always widely appreciated, for in the pre-ANCA era, classical PAN and microscopic polyangiitis were often considered as variants of the same disease.[5]

Cardiac manifestations are generally the sequelae of involvement of the coronary arteries or of malignant hypertension. Skin involvement is present in 40%-50% of patients and may range from digital necrosis to livedo reticularis, which is the most common cutaneous manifestation. Subcutaneous nodules are

often considered a classic finding in PAN, but are quite rare. They arise from involvement of muscular arteries in the subcutaneous tissues and can be biopsied when present to demonstrate characteristic histopathologic changes. A full thickness biopsy, as opposed to a punch biopsy, is the preferred technique in this situation. Orchitis is also often considered a classic finding in PAN, but it is relatively rare in patients not infected with HBV.

Limited Forms

A PAN-like disease may frequently be limited to a single end organ. In these situations, the classification of these disorders as separate entities or merely mild forms of PAN is unclear, but they do warrant special therapeutic considerations. Two syndromes deserve special mention. Isolated peripheral nerve arteritis is a not an uncommon clinical problem.[7] In these patients, peripheral nerve involvement dominates the clinical picture frequently in the presence of mild or absent constitutional symptoms. The biopsy picture of peripheral nerve is identical to classical PAN with necrotizing arteritis of medium-sized vessels of the vasonervosum. Careful study of such patients has revealed silent muscle involvement in over 50%, suggesting that this may be a mild form of a systemic disease. A second limited form of nosologic distinction is isolated cutaneous PAN. Patients with this disorder often present with isolated inflammatory subcutaneous nodules, which upon biopsy reveal necrotizing arteritis in muscular arteries of the deep dermis and subcutaneous tissues. Constitutional symptoms may be mild or absent and visceral target organ involvement is absent or limited to asymptomatic muscle involvement. Therapy for both of these variants is controversial, but generally is accomplished without the use of alkylating agents unless the condition is progressive and steroid refractory.

Virally-associated PAN

A small subset of patients with PAN have active infections with three viral blood-borne pathogens, namely HBV, hepatitis C (HCV) and human immunodeficiency virus Type 1 (HIV).[8] Infection with HCV is classically associated with the syndrome of cryoglobulinemia (discussed below), which is primarily a small vessel vasculitis readily differentiated from PAN, but may rarely present with a PAN-like picture. HIV has been reported in less than 1% of patients with PAN and is indistinguishable from patients without HIV infection. Digital ischemia leading to necrosis and prominent muscle and nerve involvement are characteristic, but not specific for this infection. Finally, HBV is the most well recognized viral infection associated with PAN. The frequency of this infection in PAN appears to be diminishing in recent years, being reported in only about 7% of cases in France.[3] In PAN associated with HBV, there appears to be a higher frequency of malignant hypertension, renal infarction and orchitis.[3] In each of these syndromes (ie, HCV, HIV, HBV) there is evidence of active viremia. It is essential to screen all suspected cases of PAN for all of these blood-borne pathogens regardless of risk factors, since history of such is not always revealing. Therapy of these disorders differs from classic PAN by virtue of the need to control both the inflammatory disease and the need to subsequently control the viral infection. The treatment of these disorders has recently been reviewed.[8]

Diagnosis

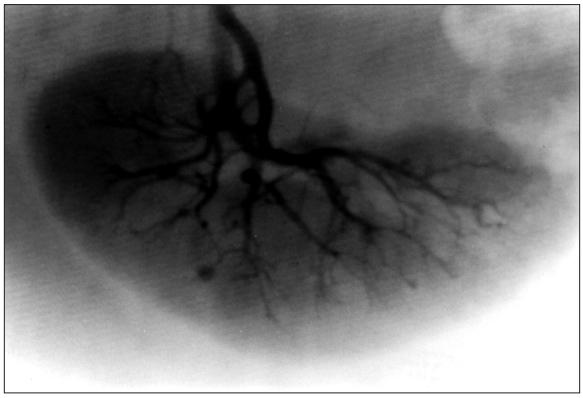
The diagnosis of PAN begins with a high degree of clinical suspicion. As noted above, the diagnosis should at least be considered in all patients with unexplained fever, weight loss, multi-system organ dysfunction, unexplained peripheral neuropathy, and unexplained visceral ischemia. There are no laboratory tests of sufficient positive predictive value to secure the diagnosis. Elevated acute phase reactants and/or elevated white blood cell count or anemia is present in excess of 95% of patients, thus tending to rule out PAN when all of these are normal. Tests for various autoantibodies such as rheumatoid factor, ANA and others have little role in securing the diagnosis though they may be frequently present. Tests for immune complexes and complement also have limited sensitivity and specificity. ANCA is generally nondetectable.

Whenever possible, diagnosis should be secured by tissue confirmation. While characteristic histopathology may be found in virtually any given end organ, the diagnostic sensitivity and specificity varies greatly depending on the clinical situation. The characteristic histopathology of PAN is a focal segmental necro-

sis of medium- and small-sized arteries. Capillaries, arterioles and venules are spared. The lesions tend to be patchy in their distribution and reflect varying stages of the inflammatory process.[5] The vessel wall may be involved asymmetrically leading to a ballooning out creating microaneurysms. These microaneurysms may be detected by angiography and when characteristic may help to secure the diagnosis. A dilemma posed by the diagnostic process for PAN is how to efficiently choose among biopsy sites (ie, muscle, nerve, testicle, other) and angiography. Albert and colleagues[9] have developed a decision analysis approach that has been highly useful in clinical practice. In this model, symptomatic muscles and/or nerves are biopsied first. If the biopsy is negative, angiography follows. If all these tests are negative, no further studies are generally warranted. Angiography is performed first only if there is no accessible symptomatic site such a muscle or nerve. If this is nondiagnostic, it is then followed by blind muscle or testicular biopsy. While only a computer model, it does offer a starting point in decision analysis for approaching such patients. It does not take into account tests such as EMG, which may help in detecting subclinical muscle/nerve involvement. We also would not agree with blind biopsy of clinically uninvolved testicular tissue, for this has very low sensitivity and is highly invasive.

Figure 1

Microaneurysms in a patient with PAN



Subtraction renal angiogram clearly demonstrating numerous microaneurysms in a patient with PAN.

Photo courtesy of Dr Joseph LiPuma, University Hospitals, Cleveland, Ohio.

4. Antineutrophil Cytoplasmic Antibody-associated Vasculitis

The discovery of antineutrophil cytoplasmic antibody (ANCA) and its development as a diagnostic tool as well as its role in nosology of the vasculitides has been of major clinical importance to the field. Three diseases—Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS)—may now be considered together, since they share a number of pathologic, clinical, and laboratory features. These include small vessel involvement (ie, venules, capillaries, and arterioles); a similar glomerular lesion (ie, focal necrosis, crescents, and absence or paucity of immunoglobulin deposition); a propensity to present as pulmonary/renal syndromes, and a varying prevalence of ANCA positivity. The epidemiology of these disorders reveals a collective incidence approaching 2 per 100,000 people in the United States and approximately 1 in 100,000 people in Sweden.[10] While each disease, in its characteristic form, may be distinguished from the others on clinical and histologic grounds, the distinctions are quite often blurred and thus, their consideration as a group is reasonable.

ANCA Methodology

ANCA was originally defined by indirect immunofluorescence assay (IFA) performed on ethanol-fixed neutrophils as substrate and broadly categorized as c-ANCA (cytoplasmic pattern) or p-ANCA (perinuclear pattern). In patients with vasculitis such as WG, MPA, and CSS, specific immunochemical assays have demonstrated two major antigenic specificities responsible for these immunofluorescent patterns. In the case of c-ANCA reactivity, proteinase-3 (PR3) is responsible for over 90% of such reactions, though other antigens may occasionally be targeted, including bactericidal/permeability-inducing protein (BPI) and rarely myeloperoxidase (MPO).[10,11] The p-ANCA pattern is more loosely associated with MPO antibodies.[11] Several other antigens capable of producing p-ANCA reactivity include elastase, azurocidin, cathepsin G, lysozyme, lactoferrin, and others.[11] Antinuclear antibodies may also yield a p-ANCA pattern, further compromising IFA as the diagnostic technique of choice.

To circumvent the lack of correlation between immunofluorescent patterns and the antigens of interest, PR3 and MPO, as well as the inherent interobserver variability of IFA, antigen-specific assays

have been developed and are readily available. Clinicians ordering ANCA need to ensure that ANCA by IFA testing is confirmed by antigen-specific testing for both PR3 and MPO. When criteria for a positive ANCA include both positive IFA and an antigen-specific test (c-ANCA and confirmatory antigen test for PR3 or p-ANCA and confirmatory antigen test for MPO), the test is highly specific for the vasculitic syndromes under discussion.

ANCA Disease Associations: Vasculitis

A large number of investigations have attempted to establish the sensitivity of PR3-ANCA and MPO-ANCA in systemic vasculitis and these have recently been reviewed.[11] In general, PR3-ANCA and MPO-ANCA are detected in a limited number of disorders, including the three small vessel vasculitic syndromes and idiopathic necrotizing crescentic glomerulonephritis. The sensitivity of ANCA varies in these disorders from 50% to over 90%. It should be noted that a significant number of patients with idiopathic small vessel vasculitis are ANCA negative and thus, a negative test in no way eliminates the diagnosis in a patient with a high pretest probability of disease. In WG, the disorder most highly associated with PR3-ANCA, the test is most likely to be positive in active untreated generalized disease (ie, with renal involvement). Correlation of ANCA with end organ damage and disease activity is less clear in the other vasculitic syndromes.

The specificities of ANCA testing appear dependent on both technical factors and the nature of the control populations tested. If IFA results are combined with antigen-specific assays, the specificity of both PR3-ANCA and MPO-ANCA are exceedingly high. Studies examining disease controls, including glomerulonephritides, granulomatous disease, and connective tissue diseases, documented that ANCA (IFA confirmed by antigen-specific assay) specificity for small vessel vasculitides exceeds 90%.[11] These studies also demonstrated the unreliability and poor specificity of IFA testing alone. Collectively, clinicians utilizing ANCA to diagnose vasculitis must demand substantial experience from their laboratories and require that IFA testing be supplemented by antigen-specific determinations. Even when these technical criteria are met, it must still be appreciated that ANCA, like any laboratory test, provides its optimal diagnostic value only when applied in clinical context.

ANCA and Disease Manifestations

In general the specificity of ANCA influences the clinical patterns of vasculitic disease, at least by association. In addition to the predilection of PR3 patients to have Wegener's and those with MPO to have MPA, a direct comparison of patient populations reveals that PR3 positive patients have more extra renal manifestations, granuloma formation and relapses. Even among patients with MPA, those with PR3 specificity are more likely to have a severe outcome or death. Thus, despite substantial overlap, there appear to be distinct clinical and pathologic differences among patients with PR3 ANCA and those with MPO-ANCA, suggesting possible differences in pathologic mechanisms.[12]

ANCA in Other Diseases

ANCA has been reported in a wide variety of other conditions and these have recently been reviewed.[11] ANCA is often encountered in patients with connective tissue diseases (rheumatoid arthritis, Felty's syndrome, systemic lupus erythematosus, myositis, and others), infections (HIV, endocarditis, cystic fibrosis, and others), and inflammatory gastrointestinal diseases (ulcerative colitis, Crohn's disease, sclerosing cholangitis, and autoimmune hepatitis). In most nonvasculitic conditions, the antibodies are largely non-PR3 and non-MPO ANCA, further stressing the importance of confirming IFA by antigen-specific testing. Drugs such as hydralazine, propyl-thiouracil, D-penicillamine, and minocycline have also been associated with high titer MPO-ANCA reactivity with or without an associated vasculitic syndrome.

ANCA and the Pathophysiology of Small Vessel Vasculitis

The role of ANCA in the pathogenesis of vasculitis has not been clearly established. Considerable and mounting evidence suggests that ANCA may either induce or augment vascular inflammation. A variety of in vitro and certain in vivo observations favor a pathophysiologic role for ANCA in certain vasculitides. [11]

In neutrophils, both MPO and PR3 are transported from primary granules to the cell membrane during activation and are part of the physiologic response of these cells to inflammatory mediators (ie, TNF alpha, IL-8). Evidence for surface expression of PR3 on circulating neutrophils and MPO release within renal lesions have both been reported in WG. The binding of PR3-ANCA, MPO-ANCA, and other ANCA to their cognate targets on neutrophils augment a variety of activation-related neutrophilic functions including degranulation, respiratory burst, nitric oxide production, chemotaxis, adhesion molecule expression, and binding to cultured endothelial cells. Collectively, these events may contribute to vascular damage. PR3 does appear capable of passive binding to the endothelial cell surface, thus serving as a target for PR3-ANCA. Binding of PR3-ANCA to endothelial cells may lead to upregulation of adhesion molecule expression and IL-8 production, both of which could contribute to vessel inflammation and injury. ANCA are capable of positively or negatively affecting the proteolytic activity of PR3 or MPO depending on epitope restriction.[4,11] Thus, if these enzymes play a homeostatic role in the inflammatory response, ANCA may have a modulatory effect.

In terms of animal models of disease a model recently reported by Xiao and colleagues has greatly strengthened the argument for causation of vasculitis by ANCA.[13] These investigators have demonstrated that anti-MPO antibodies alone are capable of inducing glomerulonephritis with crescent formation and systemic vasculitis in mice lacking functional T- or β-cells as well as in an immunocompetent wild-type strain C57BL/6J, thus offering strong support for a direct pathogenic role.

5. Wegener's Granulomatosis

Epidemiology

Rigorous epidemiologic studies of Wegener's granulomatosis (WG) have not been published. The United States experience suggests that WG affects both sexes equally, occurs in patients of all ages, and is more commonly seen in white patients.[14,15] Based on the National Hospital Discharge Survey (NHDS), the prevalence of WG in the 1986-1990 period was estimated to approximate 3/100,000 persons.[15] In northern Norway, the prevalence of WG has tripled in the last 15 years, reaching 9.5/100,000 persons.[16]

Pathogenesis

The etiology of WG is unknown. Studies have failed to identify any unique genetic markers. Several attempts to link infectious diseases to the development of WG have been unconvincing. There is no predominant season of onset.[14-16] Analysis of bronchoalveolar lavage fluid and open lung biopsy specimens in patients with recent-onset disease did not reveal bacteria, fungi, mycoplasma, respiratory viruses, or viral-like inclusions.[17] A possible relationship to silica (Si) exposure has been suggested.[18] The role of PR3-ANCA in disease pathogenesis has already been discussed.

Clinical Features

WG is characterized by its predilection to affect the upper and lower respiratory tracts and, in most cases, the kidneys (Table 2). Relatively mild forms of WG without renal involvement have been described. The course of illness may be indolent or rapidly progressive. Mild and indolent disease may go unrecognized for months to years, leading to delays in diagnosis and institution of appropriate therapy. Neither clinical nor laboratory markers are able to distinguish which patients will continue to have limited, non-renal forms of disease, and which patients will experience progression in the future.

Upper airway disease is the most common presenting feature of WG.

Nasal disease is a prominent presenting feature of WG in about one-third of cases, but eventually develops in 64%-80% of patients.[14,19] Symptoms

Table 2

Differential Diagnostic Features of the ANCA-associated Vasculitides and Polyarteritis Nodosa

	Wegener's Granulomatosis (WG)	Microscopic Polyangiitis (MPA)	Polyarteritis Nodosa (PAN)	Churg-Strauss Syndrome (CSS)	Comments
Pulmonary	+++	++	–	+++	Asthma and eosinophilia in CSS
Alveolar hemorrhage	++	++	–	+	
Glomerulonephritis	+++	+++	–	++	Progressive renal failure: uncommon in CSS
Upper airway disease	+++	+	+	++	ENT disease usually favors WG
Skin/purpura	+	+++	–	++	
Peripheral nervous system	++	+	++	+++	Often a prominent feature of CSS
Central nervous system	+	+	+	++	

and signs of nasal involvement in WG include mucosal swelling with nasal obstruction, crusted nasal ulcers and septal perforations, serosanguinous discharge, or epistaxis, and external saddle nose deformity.

Sinusitis is present at initial presentation in about one-half to two-thirds of patients with WG, and is seen in 85% of cases during the entire course of disease.[14,19] A simple CT scan of the sinuses is often anatomically more informative than plain radiographs, especially in the setting of destructive/erosive bony changes. Most patients with sinus or nasal disease will eventually develop a secondary infection of these tissues, *Staphylococcus aureus* being the predominant organism identified from cultures.

While laryngotracheal disease in WG may be asymptomatic, clinical presentations may range from subtle hoarseness to stridor and life-threatening upper airway obstruction. The most characteristic lesion is that of subglottic stenosis (SGS), occurring in up to 16% of patients.[14,19,20] The frequency of SGS is dramatically increased in pediatric and adolescent patients with WG reaching an alarming 48% figure.[20,21]

Pulmonary involvement is one of the cardinal features of WG. Pulmonary manifestations occur in 45% of cases at presentation and 87% during the course of disease.[14] Cough, hemoptysis, and pleuritis are the most common pulmonary symptoms. However, it is important to realize that up to one-third of cases with radiographically demonstrable

pulmonary lesions may not have lower airway symptoms. The most common radiologic findings include pulmonary infiltrates and nodules. The pulmonary infiltrates in WG may be quite fleeting, appearing and resolving in some cases even before the institution of therapy.[22] Persistent diffuse interstitial infiltrates are rare (<1%) and should suggest other diagnoses. Pulmonary nodules in WG are usually multiple, bilateral, and often cavitate (50%).[14,19,22] Computerized tomography of the chest often reveals infiltrates and nodules that were undetected by conventional radiographs.

Less common pulmonary manifestations of WG include pleural effusions, diffuse pulmonary hemorrhage, and mediastinal and/or hilar lymph node enlargement or mass. Diffuse pulmonary hemorrhage has been reported in up to 8% of cases, and carries a high fatality rate (50%).[22,23] In patients presenting with pulmonary symptoms, it is imperative to make every effort to exclude the presence of infection in a timely fashion since pneumonia in an immunocompromised host carries up to 50% mortality. Bronchoscopy is often needed to satisfactorily exclude infection or alternatively to establish a microbiological diagnosis by performing the appropriate stains and cultures. Pneumonia may account for up to 40% of serious infections in patients with WG, and may be the cause of death in a significant proportion of cases.[14]

The presence or absence of renal disease defines the subsets of generalized and limited WG, respectively. When renal disease is defined by pathologic findings on kidney biopsy and/or the presence of an active urinary sediment and functional abnormalities, it is then estimated to occur in 11%-18% of patients at presentation, and 77%-85% during the entire course of disease.[14,19] Extrarenal manifestations often precede renal disease. The course of renal disease varies from rapidly progressive glomerulonephritis resulting in end-stage renal disease within days or weeks to a more indolent remitting and relapsing course ultimately leading to substantial glomerulosclerosis within years.[22,24] If untreated, mean survival time for generalized WG is about 5 months.[25] Even when appropriate therapy is instituted, initial and recurrent renal damage may lead to chronic renal insufficiency in up to 42% of patients, often requiring dialysis (11%) and renal transplantation (5%).[14] The role of microscopic urinalysis in the evaluation of patients with suspected or proven WG cannot be overemphasized. In the absence of RBC casts, the presence of hematuria should lead to consideration of lower urinary tract involvement by the vasculitic process, which is uncommon, or the presence of cyclophosphamide-induced cystitis.

WG can virtually involve any other organ (Table 2).[19] Ocular inflammation can affect any segment of the eye. Proptosis is a useful diagnostic and prognostic sign. Visual loss occurs in up to 8% of cases.[14] Skin lesions (purpura, ulcers, nodules, papules, and vesicles) tend to parallel systemic disease activity. While arthralgias are more common than arthritis, the latter can mimic rheumatoid arthritis in distribution and serology with 60% of cases carrying a RF.[14,19] Nonetheless, the arthritis of WG is generally nonerosive and nondeforming. WG can involve the peripheral nervous system (PNS) (eg, distal symmetric neuropathy, mononeuritis multiplex) or the central nervous system (CNS) (eg, cranial neuropathy, CNS vasculitis). PNS involvement occurs early in the disease course, often as a presenting manifestation of severe WG.[26] Pericarditis is the most common cardiac manifestation. The gastrointestinal and genitourinary tracts are rarely involved. For each presentation, it is important to consider infections (eg, pneumonia, meningitis), drug-related complications (eg, cyclophosphamide-associated hemorrhagic cystitis), as well as disease manifestations in the differential diagnosis.

Laboratory Diagnosis

General laboratory abnormalities in untreated patients may include leukocytosis, normocytic normochromic anemia, thrombocytosis, and elevated erythrocyte sedimentation rate. These are imperfect surrogate markers of disease activity and should always be interpreted in relation to organ-specific clinical and laboratory evidence of active disease. The role of ANCA testing in the evaluation of WG and other systemic vasculitides has already been discussed. The sensitivity of PR3-ANCA is about 90% in active WG and 40% when disease is in remission. The specificity of PR3-ANCA in the diagnosis of WG is about 90%.[11] Serial measurements of ANCA titers are not consistently reliable in predicting relapses.[27,28]

Pathology

Inflammatory lesions in WG typically include necrosis, granulomatous changes, and vasculitis. The diagnostic yield of a biopsy varies with the size of the pathologic specimen and how completely it is sectioned and studied. The small amount of tissue available in head and neck biopsies (mostly from nasal and paranasal sinuses) may make it difficult to identify all of the pathologic features of WG. The diagnostic yield of lung biopsies similarly reflects the sample size of pulmonary tissue obtained. Transbronchial biopsies are rarely diagnostic (<7%), while open lung biopsies reveal various combinations of vasculitis, granulomas, and necrosis in about 90% of cases.[14,29] Nonetheless, bronchoscopy and transbronchial biopsy remain valuable in the diagnosis or exclusion of bacterial, mycobacterial, or fungal infections that can mimic or complicate WG. Capillaritis has been described in 35%-45% of WG cases in surgical biopsy and autopsy series.[30,31] However, the finding of capillaritis is not diagnostically specific. Capillaritis has been described in systemic lupus erythematosus, immune complex-associated vasculitides, dermatomyositis, rheumatoid arthritis, Henoch-Schönlein purpura, and even bronchopneumonias.[23]

Pathologically, renal disease in WG is characterized by the presence of focal and segmental glomerulonephritis (GN).[14,29] Fibrinoid necrosis and proliferative changes are seen in varying degrees. In patients with irreversible renal impairment, epithelial crescents and sclerotic lesions are commonly encountered.[14] True vasculitis of medium-sized renal arteries is only occasionally noted, and granulomatous changes are rare.[14,22] Immune complex deposition, as demonstrated by immunofluorescence or electron microscopy, is distinctly unusual.[14,19]

6. Microscopic Polyangiitis

Microscopic polyangiitis (MPA) was first recognized as a distinct entity by Davson and colleagues in 1948.[32] They described it as a subgroup of polyarteritis nodosa distinguished by the presence of segmental necrotizing glomerulonephritis. MPA was not included in the ACR classification scheme,[1] and it is assumed that most patients were labeled polyarteritis, or less frequently, WG. The Chapel Hill International Consensus Criteria 2 defined MPA as a necrotizing small-vessel vasculitis (ie, capillaries, venules, or arterioles) characterized by the absence or paucity of immune deposits. They also noted that MPA frequently is associated with necrotizing glomerulonephritis and pulmonary capillaritis. In fact, it is the most common vasculitic cause for the pulmonary-renal syndrome.[33]

Epidemiology

The prevalence of MPA is unclear. The disease tends to affect males more frequently than females.[8,34,35] The age of onset is generally in the fourth or fifth decade, but can range from early childhood to old age.[36]

Clinical Features

The general clinical features of MPA are summarized in Table 2, and reflect the propensity for widespread target organ involvement. The onset may be acute with rapidly progressive glomerulonephritis and pulmonary hemorrhage (pulmonary/renal syndrome), or at times may be extremely insidious with several years of intermittent constitutional symptoms, purpura, mild renal disease, and even periodic bouts of hemoptysis. The universal presence of renal disease in most large series reflects both the common involvement of the kidney as well as the ascertainment bias of reporting by nephrology groups.[34-38] Clearly MPA can be seen in the absence of renal disease though it is less common. The course of the renal disease is also variable. Dialysis has been required in from 25%-45% of patients in several large series.[35,36]

Lung involvement is common in MPA, present in over half of reported cases in most series. Diffuse alveolar hemorrhage (DAH) is the most serious form of lung involvement and has been reported in 12%-29% of cases.[34-38] The clinical manifestations may range from mild dyspnea and anemia without

any hemoptysis to massive hemorrhage and bleeding with profound hypoxia. The radiographic features of DAH are nonspecific, demonstrating alveolar infiltration ranging from patchy to diffuse. The characteristic finding of alveolar infiltrates in the absence of congestive heart failure or infection is helpful, but the clinical differentiation of these disorders in the acutely ill patient may at times be difficult. Hemoptysis is absent in up to one-third of patients with DAH.[39] In a recent series, the acute mortality rate was 31% while the 5-year survival rate was 68%.[40] Most survivors (68%) recovered complete respiratory function.[40] An alternative presentation of lung involvement in MPA is that of interstitial fibrosis based on recurrent episodes of DAH over several years.[39]

Other clinical features of MPA are compared to those of PAN, WG, and CSS in Table 2. Important differences are discussed below under differential diagnosis.

Pathology

The renal lesion of MPA is that of necrotizing glomerulonephritis. The characteristic features of this lesion are segmental necrosis, crescent formation (extracapillary proliferation), slight or no endocapillary proliferation, slight or no immune deposits by immunohistology, and slight or no electron-dense deposits by electron microscopy.[41] This lesion is clearly distinct from immune complex-mediated glomerulonephritis and antiglomerular basement membrane antibody-mediated disease, but is not distinguishable from the glomerular lesion of WG or idiopathic rapidly progressive crescentic glomerulonephritis.

The characteristic pulmonary histopathology is that of pulmonary capillaritis. In this lesion there is disruption of the alveolar interstitium leading to loss of integrity of the constituent capillary network resulting in red blood cell leakage into the alveolar spaces. The alveolar wall expands and becomes edematous and ultimately undergoes fibrinoid necrosis. Characteristically there is prominent neutrophilia of the alveolar septum often accompanied by leukocytoclasia. Immunohistology rarely demonstrates immune deposits.

Diagnosis

While the diagnosis of MPA may at times be based on clinical and laboratory findings, it is preferable to secure the diagnosis with histology. The most accessible and rewarding tissues are skin, kidney, and lung. It must be emphasized that in none of the organs is there a specific histopathologic picture of MPA. However, the presence of pulmonary capillaritis, necrotizing pauci-immune glomerulonephritis, or leukocytoclastic vasculitis in skin can secure the diagnosis in the patient with the appropriate degree of pretest probability and the necessary exclusions. MPO-ANCA is present in 60%-85% of patients, but occasionally patients may be PR3-ANCA positive.[11] Diagnosis of MPA based solely on the basis of a positive MPO-ANCA, in a patient with low-test probability, is fraught with risk considering the gravity of the therapy.

Differential Diagnosis

Differentiating MPA from classical polyarteritis is often based on the pattern of renal disease, which differs dramatically. In classical polyarteritis the glomerulus is largely spared and extraglomerular vascular disease (vascular nephropathy) is common. Pulmonary involvement is uncommon in classical disease and hemorrhage is virtually never encountered. Hypertension and peripheral neuropathy are much more common in classical polyarteritis as well. From the laboratory perspective, classical polyarteritis is rarely PR3- or MPO-ANCA positive and MPA is rarely associated with HBV. Angiographically classical polyarteritis nodosa is far more frequently associated with microaneurysms, which are rare in MPA.[42]

Differentiation from WG may at times be difficult because of the random nature of the granulomas in this condition. Prominent involvement of the upper respiratory tract or the presence of PR3-ANCA should seriously raise the possibility of WG since the occurrence of these findings are unusual, though not unheard of in MPA. MPA is prominent in the differential pulmonary renal syndromes along with WG, systemic lupus erythematosus, and anti-GBM disease.

7. Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS), defined by Churg and Strauss in 1951, has undergone several redefinitions, but still is ultimately characterized by three histopathologic features: necrotizing vasculitis, infiltration by eosinophils, and extravascular granulomas.[43] The use of only pathologic features to define the disease resulted in making the disorder a diagnostic rarity. In 1984, based on the limitations of defining the disease on strictly pathologic grounds, Lanham et al suggested that the diagnosis be based on clinical and pathologic grounds requiring three criteria: asthma, peak eosinophil count of greater than 1500 cells/microliter, and systemic vasculitis involving two or more organs.[44] In 1994, the International Consensus Conference held in Chapel Hill[2] defined the disease as an eosinophil-rich, granulomatous inflammation involving the respiratory tract and necrotizing vasculitis involving the medium-sized vessels associated with asthma and eosinophilia.

Epidemiology

Churg-Strauss syndrome is the rarest of the systemic vasculitides, though its exact prevalence is unknown. The male to female ratio varies from 1.1 to 3.[44,45] The age of onset ranges from 7-74 years with a mean of around 40 years.[44,45]

Pathogenesis

The etiology of CSS is unknown, but its association with allergy and atopic disorders is a dominant factor. Nearly 70% of patients have a history of allergic rhinitis, often associated with nasal polyposis. The association with asthma, usually of adult onset, is part of most case definitions. Both peripheral blood and tissue eosinophilia are prominent and the majority of patients tested have had elevated IgE levels.[44] A recent NIH workshop summarized the evidence suggesting a possible relationship between asthma therapy (cysteinyl leukotriene receptor antagonists, 5-lipoxygenase inhibitors, inhaled steroids) and the development of CSS.[46] CSS shares many of the clinical features of other ANCA-associated vasculitic syndromes, suggesting ANCA may play a possible pathogenic role in CSS. The association of ANCA with CSS is, however, less robust than with WG or MPA.

Clinical Features

The disease is generally characterized by 3 distinct phases. A prodrome dominated by allergic features is common in patients ultimately diagnosed with CSS. Allergic rhinitis and asthma may often precede diagnosis of vasculitis by 3-7 years.[44,47] The asthma can abruptly abate as the patient moves into the vasculitic phase of the illness.

Tissue infiltration by eosinophils, in the form of eosinophilic pneumonia (Loffler's syndrome) and eosinophilic gastroenteritis, may also occur in the prodrome. Since these patients may have marked constitutional symptoms and high blood eosinophilia, this stage may be difficult to distinguish from the onset of frank vasculitis on other than histologic grounds. Then the vasculitic stage advances and the clinical picture is dependent on the distribution of target organs. Finally the vasculitic stage abates and allergic disease then dominates the clinical picture. Clearly, not all patients express a sequential staging of their illness or a complete clinical syndrome. Pulmonary infiltrates may occur in both the prodromal and vasculitic phases. The radiographic appearance is generally nonspecific and variable. Lobar, interstitial, and nodular patterns have all been described with most abnormalities being fleeting in nature. Pleural effusions have been reported in up to 27% of cases and are typically rich in eosinophils.[44] Pulmonary hemorrhage is a serious complication and may occur with or without renal involvement.

Peripheral neurologic involvement often dominates the clinical picture and has been reported in the majority of patients.[42,44,47] The pattern of involvement may be that of mononeuritis multiplex, and symmetrical or asymmetrical polyneuropathy. Cranial neuropathy is less common.[47] Central nervous system involvement occurs infrequently and tends to dominate in the later stages of the illness.[48] Collectively, involvement of the peripheral nervous system is so common that CSS should be considered in any patient with asthma who develops neurologic symptoms.

Kidney involvement is less common in CSS than in MPA or WG and, when present, is rarely the cause of death. CSS shares the same renal lesion with the other ANCA-associated diseases such as necrotizing crescentic pauci-immune glomerulonephritis. A

noteworthy feature of CSS is its propensity to involve the lower urinary tract, including the prostate gland.[49] We have observed extremely high levels of prostate specific antigen, in the setting of active CSS, normalize during successful treatment. Such lower tract involvement may at times lead to obstruction.

CSS may involve a wide variety of other target organs including the skin, heart, skeletal muscle, joints, eye, and gastrointestinal tract (Table 2).[44,45] Gastrointestinal involvement may precede the vasculitic phase or coincide with it. Diarrhea, pain, or bleeding is not uncommon. Similar to PAN, abdominal complications may at times dominate.[50] Cardiac disease is common in postmortem series and may contribute heavily to morbidity and mortality.[43,44] The cardiac pathology most frequently demonstrates granulomatous nodules in the epicardium which may lead to ventricular dysfunction and congestive heart failure.[43] Coronary arteritis may also occur. Lastly a variety of ocular complications have been described including conjunctivitis, episcleritis, panuveitis, and marginal corneal ulcerations.[51]

Pathology

As noted above, the three pathologic features of CSS are necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas. Unfortunately, depending on the timing and tissue sampling, not all of these features may be present. Necrotizing vasculitis of small vessels accompanied by tissue infiltration with eosinophils is not specific for CSS and may be seen in WG and PAN.[48] The extravascular Churg-Strauss granuloma, in its fully developed form, is highly specific for the condition. Its distinctive features include an eosinophilic core, which differentiates it from the basophilic granuloma seen in numerous other disorders, but is unfortunately also referred to as a Churg-Strauss granuloma.[48]

Laboratory Tests

Peripheral eosinophilia at levels in excess of 1500 cells/microliter often occurs in the prodromal stages associated with rhinitis and asthma. Occasional patients have been described without significant blood eosinophilia, but with prominent tissue eosinophilia.[44] There is no definite correlation between eosinophilia and disease activity since eosinophils often rapidly decrease with initiation of glucocorticoid therapy. ANCA has been reported in as many as 80% of patients with CSS. The majority of these ANCAs are MPO-ANCA.[11] A negative ANCA should not dissuade clinicians from the diagnosis of CSS if there is a high pretest probability.

Diagnosis

The diagnosis of CSS should be based on the documentation of necrotizing vasculitis with eosinophils occurring in a patient with adult onset asthma/allergic rhinitis. The documentation of the presence of extravascular granulomas is of added specificity though not essential. High-yield sites for biopsy include nerve and muscle in patients with clinical evidence of their involvement.

Differential Diagnosis

Differentiation from WG, MPA, and classical PAN is generally straightforward (Table 2). Significant peripheral eosinophilia is uncommon in both of the latter conditions, though this point is often poorly appreciated. This misconception stems from early reports of such patients derived from series reportedly describing WG, but contaminated with yet unrecognized CSS patients.

Microaneurysms can be seen in both PAN and CSS and thus do little to differentiate the conditions. Asthma is uncommon in PAN as is glomerulonephritis. CSS may at times be difficult to differentiate from eosinophilic infiltrative diseases. Acute (Loeffler's syndrome) and chronic eosinophilic pneumonia are not associated with extrapulmonary disease. Hyper-eosinophilic syndrome may, however, be associated with eosinophilic infiltration of numerous target organs and at times be difficult to differentiate from CSS. In this disorder there is no true vasculitis and eosinophil counts are often much higher, at times in excess of 100,000 cells/microliter.

8. Therapy for Systemic Vasculitis

The treatment of systemic necrotizing vasculitis has been problematic for many reasons. Lack of diagnostic homogeneity, marked individual variation and disease severity, lack of uniformly acceptable diagnostic criteria, difficulty in agreeing on disease activity markers, small numbers of patients, and lack of large randomized trials have all contributed. Progress, however, has been evident in recent years as a result of advancement in many of these areas and the early results from multicenter randomized controlled trials in the field.

The goals of treatment in vasculitis are several fold. These include patient survival, remission of active major organ disease, avoidance of relapse and minimization of toxicity. Assessment of various treatment regimens must take each of these variables into account.

The treatment of classical PAN, MPA, Wegener's granulomatosis and Churg-Strauss syndrome will be considered collectively since their natural history has literally been transformed by the use of corticosteroids and immunosuppressive drugs, especially cyclophosphamide. Precisely defining the natural history of these disorders is problematic, especially for PAN since only recently has MPA been considered a separate disease entity and the results of older clinical trials are confounded by such contamination. Despite these nosologic issues, it is quite clear that each of these syndromes is capable of producing a highly fatal illness if left untreated. As discussed below, however, recent work has suggested more limited forms of each of these diseases with seemingly better prognoses and requiring less therapy.

Standard Therapy

Evidence for a gold standard of therapy for progressive life-threatening systemic necrotizing vasculitis has been generated by the pioneering studies performed at the National Institutes of Health over the past three decades. These investigations, while nonrandomized and largely observational, still represent a powerful prospective and carefully followed group of a large number of patients over a prolonged period of time. The principles of this therapeutic regimen have been applied to each of the major forms of systemic necrotizing vasculitis. The details of this treatment protocol have recently been reemphasized.[52] The essentials of this treatment regimen are outlined in Table 3.

Utilizing these treatment guidelines, prolonged survival has been reported in numerous forms of systemic necrotizing vasculitis, especially Wegener's granulomatosis. The summary report on 154 patients with the disease revealed that 91% had marked improvement and 75% achieved complete remission.[14] This is in stark contrast to the early reported experience with this disease, where the untreated survival was approximately 5 months and 82% mortality by 1 year.

Table 3

Standard Therapy for Systemic Necrotizing Vasculitis

Initial Therapy	
Glucocorticoids	Prednisone 1 mg/kg/day
Cyclophosphamide	2 mg/kg/day
Treatment Following Partial or Complete Remission	
Glucocorticoids	Taper to an every other day schedule after 1 month
Cyclophosphamide	Taper after 1 year of remission
Monitoring	
• CBC with differential every 2 weeks if stable • Urinalysis monthly after stable • Monitor every 3-6 months indefinitely after treatment is stopped	
For Critically Ill Patients	
Glucocorticoids	1 gram methylprednisolone daily for 3 days
Cyclophosphamide	3-5 mg/kg/day i.v. for 2-3 days, then 2 mg/day

Unfortunately, dramatic improvements in mortality observed with such therapy have also come at a high cost in terms of treatment-related morbidity. In the experience of the National Institutes of Health with Wegener's granulomatosis, over 50% of the treated patients experienced significant treatment-related toxicities.[14] Prominent among these have been serious or life-threatening infections including opportunistic pathogens such as *Pneumocystis carinii*. The use of high dose and prolonged glucocorticoid therapy is well known to be associated with a variety of adverse effects including immunosuppressive effects, endocrine metabolic effects, musculoskeletal effects (especially osteoporosis and osteonecrosis), cardiovascular and renal effects, neuropsychiatric problems and others.[53] Cyclosphosphamide, the mainstay of combination therapy regimens, is also associated with a variety of significant toxicities. Prominent among these is transitional cell carcinoma of the bladder. Recent epidemiologic studies have suggested that the incidence of this malignancy after the first exposure to daily oral cyclophosphamide is approximately 2% at 5 years, 5% at 10 years and 16% at 15 years.[54] Long-term studies with this therapeutic agent have also revealed an increased incidence of other forms of malignancy including cancers of the skin and myelo- and lymphoproliferative disorders.[53]

Based upon these data, multiple strategies have been evolving to limit these toxicities. The evidence for the effectiveness of such strategies varies, but certain principles of prevention have now become standard. To minimize infectious complications, meticulous monitoring of white blood cell count to avoid significant leukopenia is essential. The use of prophylaxis for PCP is now standard therapy particularly during the early phase of immunosuppression when the glucocorticoid dose is over 20 mg per day in combination with a cytotoxic drug. Trimethoprim (160 mg) and sulfamethoxazole (800 mg) 3 times weekly to all nonsulfa-allergic vasculitis patients is standard.[53]

Meticulous attention to bone health with adequate supplementation with calcium and vitamin D, and adherence to recent guidelines for the prevention and treatment of steroid-induced osteoporosis, which include the aggressive use of antiresorptive therapy, is also essential. Early detection of aseptic necrosis of bone, particularly the femoral head, may offer the prospect of early surgical intervention though the efficacy of such procedures is controversial.[53,55]

For patients on cyclophosphamide, monitoring for nonglomerular hematuria is crucial. Such monitoring must not only be performed during therapy with cyclophosphamide, but should be performed every 3-6 months after therapy has been terminated to avoid this late and potentially lethal complication. Cystoscopy should be performed at the first sign of nonglomerular hematuria. Monitoring cystoscopy every 1-2 years should be considered in patients with a history of cyclophosphamide-induced bladder injury.[53]

Strategies to Improve Outcomes in Therapy of Systemic Vasculitis

Despite these remarkable treatment advances, it is readily appreciated that daily GC and CYC, while effective, are toxic and are associated with incomplete disease suppression and an unacceptable rate of disease relapse. Over the past decade, a series of studies of the ANCA-associated vasculitidies (many of them randomized and controlled in design, performed mostly in patients), have provided evidence for new ways to maximize efficacy while reducing toxicity.

These strategies include:

1. Therapy tailored to prognostic factors;

2. Step-down therapies;

3. Alternative routes of cyclophosphamide administration;

4. Induction with other nonbiologic drugs;

5. Biologic agents; and

6. Plasmapheresis.

Therapy Tailored to Prognostic Factors

It is clear in Wegener's granulomatosis, MPA and Churg-Strauss that not all patients do equally well. In Wegener's granulomatosis, absence of renal disease and the absence of pulmonary hemorrhage have often been equated with a more benign subset. In PAN and Churg-Strauss, Guillevin and colleagues[56] have reported a series of epidemiologic investigations identifying predictors of mortality. They have identified a "five-factor score", which highlights the significance of azotemia, proteinuria, cardiomyopathy, gastrointestinal tract and central nervous system involvement as predictors of poor outcome. In patients who have only a single factor or none, therapy with glucocorticoids alone may suffice whereas those with life-threatening visceral target organ involvement with higher scores require combination therapy as outlined in Table 3. In patients with Wegener's granulomatosis with only upper respiratory tract involvement, some investigators have recently suggested elimination of cyclophosphamide in favor of other drugs such as methotrexate.[57]

Given the formidable toxicity of the standard regimen, such alternative regimens deserve careful consideration but must be applied with meticulous monitoring and switching to the standard regimen in case of disease progression.

Step-Down Therapies

Major advances in the treatment of systemic vasculitis stem from the recognition that long-term use of CYC is associated with increasing toxicity over time. In particular, the incidence of complications, such as serious infections, myelodysplasia, development of lymphoid and nonlymphoid neoplasms, such as transitional cell carcinoma of the bladder and non-Hodgkin's lymphoma, all appear to increase commensurate with exposure to this agent. From a series of studies by several groups it has been demonstrated that once remission has been achieved CYC can be discontinued; maintenance of remission can then be achieved with the use of better-tolerated drugs of the antimetabolite class. The most robust evidence for this strategy comes from the randomized placebo controlled trial of azathioprine performed by the European Vasculitis Study Group (EUVAS).[62] In this study, 155 patients were treated with daily oral GC and CYC. Once remission was achieved, patients were randomized to continue on CYC or be switched to a regimen based on azathioprine (2 mg/kg per day). Both therapies were continued and follow-up performed through 18 months. In this study the relapse rates for both the CYC and azathioprine groups were similar (15.5% and 13.7%, respectively). In addition, during the remission phase both groups had a similar number of severe adverse events. Thus, while this study did not demonstrate a clear-cut advantage in reduced toxicity over the relatively short duration of observation, it did demonstrate that azathioprine could be successfully utilized to maintain remission and thus reduce the duration of exposure to CYC. Several other reports from nonrandomized trials have demonstrated a similar role for methotrexate in initial doses of approximately 15 mg a week escalating to 25 mg a week over time.[57,119] In these studies, high-grade remissions were observed for follow-up periods for up to 2 years; the rates of toxicity and relapse were acceptable compared to historical controls. At this juncture, most authorities recommend a strategy in which the induction of remission is first accomplished with daily CYC. Once complete remission is achieved, patients switch or "step down" to either azathioprine or methotrexate. More recently, Langford and colleagues demonstrated that remission maintenance could also be achieved with the use of mycophenolate.[120] In this study, 14 patients were switched from daily GC and CYC to mycophenolate at a starting dose of 2000 mg a day. Mycophenolate was well tolerated, but during follow-up relapse occurred in 43% of the patients at a median of 10 months. Given a more recent trend to use mycophenolate in doses up to 3000 mg a day, one questions whether 2000 mg may be the optimal dose.

Alternative Routes of Cyclophosphamide Administration

Another strategy to reduce the overall exposure to CYC is to either induce remission or maintain remission with pulse therapy. To date there have been numerous uncontrolled nonrandomized studies and three randomized controlled studies; these were recently summarized in a meta-analysis by deGroot.[58,59,121] The major problem with interpretation of these nonrandomized trials is therapeutic

heterogeneity. In these studies, the dose and interval of CYC administration were not standardized. CYC pulses ranged from 375 mg to 1000 mg per square meter administered anywhere from weekly to monthly with different concomitant doses of GC and with variable adjunctive therapies. Overall, however, a high rate of remission was achieved in these studies and the incidence of serious toxicities, such as leukopenia serious infections, hemorrhagic cystitis and deaths, was rare. In the three randomized controlled studies there were lower risks of serious toxicity in the pulse vs. oral regimens, and while relapses occurred slightly more often in the pulse group they were not significantly different. From these studies we can conclude that for a significant portion of patients, pulse therapy in some form can be effective at inducing remission. However, this author feels strongly that pulse therapy is not the preferred route for induction remission in patients with life-threatening forms of vasculitis. We have found one of the most common causes of ongoing disease activity in patients being referred for "refractory vasculitis" has been inadequate CYC therapy from pulse administrations. We feel that patients are not CYC failures unless they have failed daily oral therapy. Furthermore, now that the current standard of care is to limit CYC therapy on a daily oral basis to essentially 3 to 6 months, followed by a step down to a better tolerated and safer antimetabolite, this obviates the need to limit CYC exposure via the pulse route. Despite this model of treatment, many centers prefer pulse CYC particularly for patients with mild and nonfulminate presentations.

The Use of Other Nonbiologic Drugs

As mentioned above, additional drugs have been advocated to control various forms of systemic necrotizing vasculitis, including azathioprine, methotrexate and others.[60,61] Several recent studies have demonstrated the efficacy of methotrexate and mild forms of ANCA-associated disease.[57] Caution must be exerted in patients with any degree of renal insufficiency or changing renal function with the use of this drug. Antimicrobial prophylaxis (ie, PCP, etc.) should also be employed when these drugs are combined with high-dose glucocorticoids, but there is little evidence for the efficacy of such measures at present.

The use of certain antimicrobial agents such as trimethoprim/sulfamethoxazole has garnered great interest in the treatment of Wegener's granulomatosis. A recent randomized controlled clinical trial has demonstrated the efficacy of this antimicrobial in helping maintain remission in patients with ANCA-associated vasculitis.[62] The use of this drug reduced the number of nasal and airway relapses in patients but not more serious life-threatening complications. There is no compelling evidence that trimethoprim/sulfamethoxazole is an adequate drug to induce remission in patients with ANCA-associated vasculitis. Some clinicians advocate a trial of this drug in patients with extremely limited and indolent forms of vasculitis (limited to the upper respiratory tract), though the evidence supporting such use is equivocal.

Biologic Therapy for Systemic Vasculitis

Probably the most exciting area, yet unfulfilled, is that of the potential for biologic therapies for vasculitis. Biologic therapies can be divided into 3 areas. First, the inhibitors of tumor necrosis factor, or TNF inhibitors, which have so remarkably changed the therapeutic approach to such conditions as rheumatoid arthritis, psoriatic arthritis, and spondyloarthopathy. Second, β-cell directed therapies and third, miscellaneous agents such as intravenous immunoglobulin (IVIG).[122]

As with all new therapies, there has been a flurry of observational reports of success with virtually all of the currently approved TNF inhibitors. While these types of investigations have been promising, the long-awaited WGET study yielded discouragingly negative results.[123] In this study, 174 patients with Wegener's granulomatosis were randomized to standard of care therapy with CYC plus GC, or methotrexate plus GC, based on severity of presentation. Within each of these groups, patients were then randomized to etanercept 25 mg twice weekly or placebo in a blinded fashion. After a mean follow-up of 27 months there were no significant differences between the etanercept and control groups in terms of the rates of remission, time required to achieve remission, the rates of disease flares, or any other marker of efficacy. In addition, solid cancers developed in 6 patients of the etanercept group as compared with none in the control group. Based

upon these data, it is now established that etanercept has no role in the treatment of Wegener's granulomatosis. It is possible that etanercept, a receptor construct, has a different mechanism of action and may not be ideally suited for patients with granulomatosis angiitis.[124] It is also possible that the dose of etanercept was not optimal. At this juncture, it is difficult to be enthusiastic regarding the use of TNF inhibitors in the treatment of any systemic form of life-threatening vasculitis.

Perhaps more promising at present is β-cell directed therapy with the anti-CD20 chimeric monoclonal antibody rituximab for induction of remission in patients with ANCA-associated vasculitis.[125] A recent uncontrolled study was performed in 11 patients, all with active vasculitis despite receiving maximal tolerated doses of CYC. These patients were treated with rituximab; the drug was well tolerated with adverse events being rare. Following infusion with rituximab, circulating β-cells became undetectable, ANCA titers decreased, and remissions were achieved in all patients and maintained while β-lymphocytes were absent. However, the study included patients with subacute or smoldering disease rather than fulminant or life threatening vasculitis. Based on this promising preliminary study, a large international randomized controlled trial is now underway.

Finally, a variety of miscellaneous biologic agents have been utilized for the treatment of systemic vasculitis. An interesting, small, randomized clinical trial of intravenous immunoglobulin therapy (IVIG) was reported in a group of 34 patients with active ANCA-associated vasculitis who were treatment refractory despite treatment with standard of care.[126] This therapy was moderately effective at reducing disease activity as well as reducing levels of CRP. The results were relatively transient and elevations of creatinine did occur in a quarter of the patients. The authors concluded that IVIG was capable of reducing disease activity but the effect was modest and nonenduring. We believe that IVIG may be an option for patients who cannot tolerate further immunosuppressive therapy despite the presence of persistently active disease. The situation is not uncommonly encountered in patients with active infections, bowel perforations, and other catastrophic settings.

Plasmapheresis

Plasmapheresis has been applied empirically in the treatment of many forms of systemic vasculitis; however, there have been no randomized controlled trials providing definitive evidence for its efficacy. While there is good evidence for the utility of plasmapheresis in the pulmonary renal syndrome associated antiglomerial basement membrane antibodies for its efficacy, there is no such evidence at present to support its widespread use in vasculitis. A recent uncontrolled study by Klemmer has described the use of adjunctive plasmapheresis in 20 patients with ANCA-associated small vessel vasculitis complicated by diffuse alveolar hemorrhage.[127] In this study, 20 out of 20 patients resolved their pulmonary hemorrhage with an average of 6.4 treatments. There were no complications from therapy. In addition, half of the patients who presented with azotemia were discharged with improved renal function. These authors clearly admit that this is retrospective case analysis limited by all the usual pitfalls, but it is still an interesting report. At the present time we would reserve plasmapheresis as an adjunct only for those patients with severe and uncontrolled pulmonary and/or renal manifestations resistant to traditional GC and CYC therapies.

Conclusion

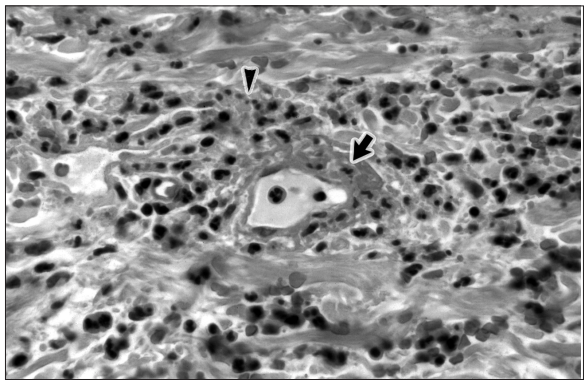
The treatment of life-threatening forms of systemic vasculitis has improved significantly over the past 30 years; however, the gold standard of therapy continues to be based on an induction regimen with daily GC and CYC therapies. Standard of care now holds that as soon as remission has been achieved the patient should be switched off of CYC and onto a step-down regimen with an antimetabolite. Preventive measures such as antimicrobial prophylaxis for pneumocystis pneumonia and preventive measures for bone health are now also standards of care. Meticulous monitoring and follow-up allow the greatest chance of therapeutic efficacy with minimal toxicity. While biologic therapies appear promising, there are no randomized controlled clinical trials demonstrating the efficacy of any agent at the present time. The treatment of vasculitis is a fast-moving field and clinicians caring for such patients need to be aware of recent advances.

9. Hypersensitivity Vasculitis Group

The nosology of this group of vasculitic disorders is not without controversy. The working definition outlined in Table 1 is based on both clinical and pathologic features and not on etiology. The diseases included are clearly heterogeneous but are bound together by their dermatologic and histopathologic features. Pathologically all of the diverse disorders in this subgroup may appear similar by light microscopy and they are often referred to collectively as the leukocytoclastic vasculititides (Figure 2). The classification scheme of the American College of Rheumatology[1] only recognizes hypersensitivity vasculitis and Henoch-Schönlein. Other conditions listed in our Table 1 would be considered secondary forms and are excluded. In the more recent Chapel Hill criteria[2] only Henoch-Schönlein and isolated cutaneous vasculitis (a disease defined solely on anatomic features) are included. Both of these schemes seem far too restrictive to accommodate the diversity of disorders that must be clinically differentiated in the patient with cutaneous small vessel vasculitis. Lastly it should be readily appreciated that several forms of systemic vasculitis which affect the small vessels can also present with cutaneous involvement, in particular the ANCA associated disease discussed above. These deserve separate classification based on the shared laboratory, clinical and pathologic features already discussed.

Figure 2

Leukocytoclasia



Skin biopsy demonstrating nuclear debris or leukocytoclasia (arrowhead) and transmural polymorphonuclear leukocyte in an area of fibrinoid necrosis (arrow) (hematoxylin and eosin x 400).

Photomicrograph courtesy of Dr Ralph Tuthill, Cleveland Clinic Foundation.

Hypersensitivity Vasculitis

This is a syndrome characterized by a small vessel vasculitis generally, but not uniformly, limited to skin in response to a foreign antigen.[63] The most common precipitating agent would be a drug, but toxins, chemicals, immunizations, microbes and foreign proteins may also be causal. Drugs that have been implicated have been numerous. The most common offending agents include penicillin, sulfonamides, allopurinol, and hydantoins.[64] The mechanism is presumed to be based on immune complex formation and deposition. Varying degrees of constitutional symptoms including fever, malaise and weight loss may also be observed. The skin is the most common target organ and the most common rash is palpable purpura. Other lesions may be observed, including a maculopapular rash, ulcers, bullae and even urticaria. Serious cases may be accompanied by varying degrees of visceral target organ involvement. The clinical course is generally monophasic occurring 7-14 days after exposure but it may at times become chronic or even relapsing in the absence of re-exposure. The treatment of true hypersensitivity vasculitis is removal of the offending agent. Above this no treatment is often required for patients with mild and self-limiting disease. For patients with progressive and/or life threatening disease, adjunctive measures, including glucocorticoids and even cytotoxic drugs, have been advocated though the evidence for their use is essentially anecdotal.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a syndrome characterized by the presence of palpable purpura, gastrointestinal tract ischemia and glomerulonephritis and is the most common form of vasculitis in children.[65] Pathologically it is characterized by vascular deposition of IgA dominant immune complexes and primarily involves the capillaries, venules and arterioles.[66]

Clinically, the peak incidence is 5 years of age and is uncommon in people over the age of 20. A respiratory prodrome is frequent and is often associated with varying degrees of fever and constitutional symptoms. Purpura, arthralgias and abdominal pains are the most frequent manifestations. Renal involvement is not uncommon with approximately 50% of patients demonstrating hematuria and pro-

teinuria but only 10%-20% with renal insufficiency.[67] Rapidly progressive glomerulonephritis and pulmonary hemorrhage are rare but reported.

The syndrome can be difficult to distinguish from true hypersensitivity vasculitis when there is no clear exposure to a drug or exogenous antigen. The frequent empiric use of antimicrobials at the onset of the respiratory prodrome of Henoch-Schönlein purpura often further confounds the distinction. Michel et al[68] have proposed that hypersensitivity vasculitis rather than Henoch-Schönlein is present with 74% accuracy if no more than two of the following are present: palpable purpura, bowel angina, gastrointestinal bleeding, hematuria and age of onset less than 20 years. The demonstration of IgA deposition in the skin or kidney is the best evidence for the diagnosis of Henoch-Schönlein, but this is not necessary in all cases.

Therapy of Henoch-Schönlein is generally supportive. Glucocorticoids may benefit the gut disease but there is little evidence that conventional dose glucocorticoids or cyclophosphamide benefit patients with progressive renal disease. The prognosis is generally excellent but in those with significant nephritis, there is a high incidence of residual renal impairment and hypertension with a 2%-5% overall progression to end stage renal disease. There is evidence from both randomized controlled trials and prospective open trials that prompt therapy with pulse methylprednisolone followed by high dose glucocorticoid therapy may be beneficial in preserving renal function.[69] Other therapies have been proposed, including intravenous gammaglobulin, but the evidence for efficacy is based on small uncontrolled observations.

Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate at temperatures <37ºC. Cryoglobulins have been classified based upon their immunochemical composition as proposed by Brouet et al.[70] In this scheme, simple cryoglobulins or those composed of a monoclonal immunoglobulin represent Type-I cryoglobulins. Type-II cryoglobulins are mixed and contain a monoclonal anti-immunoglobulin component. Type-III cryoglobulins are polyclonal, containing polyclonal anti-immunoglobulins and their cognate antigens. The diseases in which cryoglobulins can be detected are diverse as displayed in Table 4. These conditions range from β-cell neoplasms to chronic infections such as hepatitis C virus and the gamut of diseases in which immune complexes have been associated.

Table 4

Cryoglobulin Disease Associations

Type I
Multiple myeloma
Waldenström's macroglobulinemia
Other lymphoproliferative diseases with M components
Type II
Chronic hepatitis C virus infection
Sjögren's syndrome
Waldenström's macroglobulinemia
Chronic lymphocytic leukemia
Non-Hodgkin's lymphoma
Autoimmune diseases
Cold agglutinin disease
Type III
Chronic infections
Viral
Bacterial, SBE, leprosy, spirochetal
Fungal, parasitic
Autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Inflammatory bowel diseases
Biliary cirrhosis

The clinical manifestations of cryoglobulinemia depend on both the underlying disease state as well as the type of cryoglobulin present.[71] In patients with Type-I cryoglobulinemia, the levels are generally exceedingly high and they are often due to an underlying lymphoproliferative disorder. In this situation, marked cold-induced symptoms and large vessel occlusive disease can be observed. Most cases, however, are represented by Type-II cryoglobulins. This condition has formally been called "essential" mixed

cryoglobulinemia and as discussed below is associated with chronic hepatitis C viral infection in the vast majority of patients. Patients with this syndrome have long been recognized to have a syndrome characterized by varying degrees of small vessel cutaneous vasculitis manifest as palpable purpura, arthralgias, fatigue, peripheral neuropathy, glomerulonephritis and hepatosplenomegaly. Quantitative levels of cryoglobulins are also quite high in Type-II cryoglobulinemia.

Low levels of cryoglobulins (ie, <1%-2% cryocrit or <500 mg%) are characteristic of patients with Type-III cryoglobulins. The vast majority of patients with Type-III cryoglobulins have a variety of rheumatologic disorders or chronic infectious diseases associated with immune complex formation and the signs and symptoms are mostly consistent with immune complex disease.

Hepatitis C Virus (HCV)-associated Cryoglobulinemia

A major breakthrough in our understanding of the syndrome previously described as "essential" mixed cryoglobulinemia came in 1989 with identification of the viral agent responsible for non-A/non-B hepatitis. Soon after this discovery, it was found that over 90% of patients with "essential" mixed cryoglobulinemia were chronically infected with HCV.[72] Over the past decade, great advances have been made in our understanding of HCV, which represents the most common blood-borne viral infection in the United States.

Epidemiologically, approximately 1.8% of the United States and 3% of the world population is infected with HCV. While autoantibodies such as rheumatoid factor and circulating cryoglobulins are common in this disorder, frank cryoglobulinemic vasculitis is uncommon and estimated to be present in less than 1% of chronically infected patients.[72]

In patients who develop HCV-associated cryoglobulinemic vasculitis, the signs and symptoms may range from leukocytoclastic vasculitis involving only the skin to severe multisystemic vasculitis with widespread visceral target organ involvement. Skin involvement is most common taking the form of palpable purpura or a maculopapular rash and is usually intermittent, located predominantly in the lower extremities. Other skin findings include leg ulcers, livedo reticularis, urticaria, and even nodular skin lesions.

Renal involvement occurs in approximately one-third of patients with HCV-associated mixed cryoglobulinemia. The majority of these patients have Type-II cryoglobulins. Histologically, the most frequently observed lesion is that of membranoproliferative glomerulonephritis with subendothelial deposits. Clinically, patients present with hypertension, renal failure, proteinuria, acute nephritis or nephrosis. The disease usually follows an indolent course.[73,74]

Other clinical findings in patients with HCV-associated mixed cryoglobulinemia include a distal symmetric sensory motor polyneuropathy, and rarely, mononeuritis multiplex. Polyarthralgias commonly involving the hands and feet are common. Since all patients are infected with HCV, liver disease is frequent, but the extent of liver involvement in these patients is comparable to patients with chronic hepatitis C without cryoglobulinemia. This latter point is controversial since the degree of liver inflammation and presence of cirrhosis vary significantly between different studies.

The laboratory hallmarks of this syndrome are the presence of Type-II or Type-III cryoglobulins in the circulation. The majority of reports document the presence of Type-II cryoglobulins (approximately two-thirds) while approximately one-third have Type-III. There is some suggestion that there is progression from Type-III cryoglobulins to Type-II cryoglobulins over time, though this is yet unproven. Other common laboratory findings in such patients include anemia (70%), rheumatoid factor activity (80%) and depressed compliment levels, especially C4 (50%-60%).[72]

The pathogenesis of this syndrome is presumed to be one of immune complex formation and deposition. Evidence for a key role for HCV includes concentration of both HCV antigens and specific antibody within the cryoglobulins, and the identification of HCV and immunoglobulin within the vasculitic skin lesions.[73,74]

Therapy of Cryoglobulinemia

The therapy of patients with cryoglobulinemic vasculitis should be aimed at the underlying condition. In patients with lymphoproliferative disorders, successful treatment of the underlying problem is key to alleviating the signs and symptoms of vasculitis. In patients with chronic immune complex diseases such as connective tissue disease or infections, treatment of these disorders with traditional therapies is essential.

The greatest challenge today in treating cryoglobulinemic vasculitis is in those chronically infected with hepatitis HCV infection. Before HCV infection became known to be the major cause of this syndrome, patients with HCV-associated vasculitis were treated like other vasculitides with cytotoxic and immunosuppressive agents, but this largely appeared to be palliative in nature. In severe cases, plasmapheresis was added in order to reduce cryoglobulinemia more rapidly, but levels were always observed to rapidly rebound without associated immunosuppressive therapy. The concept that most patients with "essential" cryoglobulinemic vasculitis were chronically infected with HCV suggested the possibility that control of the underlying viral infection may also help alleviate the manifestations of vasculitis.

Unfortunately, the successful treatment of HCV infection in general remains elusive. The use of antiviral agents, such as interferon or more recently interferon and ribavirin, leads to enduring virologic response in less than 50% of patients. In general, patients with HCV-associated cryoglobulinemic vasculitis who are suffering acute exacerbations or rapidly progressive illness require immunosuppressive therapy with glucocorticoids and possibly cytotoxic agents to initially control the vasculitic process, and antiviral therapy alone is both inadequate and potentially dangerous. Following control of the vasculitic process, antiviral therapy is generally warranted. It has been documented in several well-controlled randomized trials to be transiently effective at controlling levels of cryoglobulin and attendant complications such as cutaneous vasculitis, but tends to relapse in those patients failing to achieve an enduring response to antiviral therapy.[75-77] For patients with Type-II mixed cryoglobulinemia who are not infected with HCV, traditional therapy with glucocorticoids, cytotoxic drugs and plasmapheresis still remains the standard of care though the evidence for this efficacy is limited to small observational studies.[8]

10. Other Forms of Cutaneous Vasculitis

Vasculitis

For the patient presenting with cutaneous leukocytoclastic vasculitis who does not appear to have hypersensitivity vasculitis due to an exogenous source, Henoch-Schönlein purpura, or cryoglobulinemia vasculitis, there are numerous other conditions that still must be considered within the differential diagnosis. Cutaneous vasculitis may at times be the initial manifestation of an underlying malignancy, generally a lympho- or myelo-proliferative disorder. Occasional patients with occult connective tissue disease may present with cutaneous vasculitis. While in most patients the underlying disorder is well-declared, occult Sjögren's syndrome should always be considered. In patients presenting with leukocytoclastic vasculitis manifest as an urticarial rash, the syndrome of hypocomplementemic or urticarial vasculitis should be considered.[78] In addition to these disorders, a variety of systemic diseases such as Behçet's syndrome and others should be kept in mind. Lastly, and of utmost importance, is the fact that some patients with systemic necrotizing vasculitis, particularly those with small vessel involvement such as the ANCA-associated diseases, may occasionally present with cutaneous vasculitis. In these cases, a diligent search for associated visceral target organ involvement such as glomerulonephritis, pulmonary involvement and the presence of ANCA can be extremely helpful.

11. Large Vessel Vasculitides

Giant cell arteritis (GCA) and Takayasu's arteritis (TA) are distinct large and medium vessel vasculitides that, nonetheless, share a number of clinical and pathologic features. Both diseases have a propensity to cause ischemic manifestations in the brain, eyes, and extremities, as well as constitutional symptoms. Pathologically, both GCA and TA are characterized by large and medium vessel infiltration with lymphocytes and macrophages, and the frequent occurrence of granulomatous/giant cell reactions. Despite the clinical and pathologic similarities, various differences exist between GCA and TA (Table 5).

Giant Cell Arteritis

Epidemiology

Giant cell arteritis (GCA) is among the most common systemic vasculitides in adults, with an annual incidence of 19-27 cases per 100,000 population above the age of 50 years.[79] It is clearly predominant in whites, particularly those of northern European descent. GCA has been associated with HLA-DR4 Class-II HLA molecules and, in particular, the allelic variants HLA DRB1*0401.[80]

Pathogenesis

In GCA, an immune insult to the vascular wall initiates a reaction that ultimately leads to arterial structural changes, intimal hyperplasia and luminal occlusion. The triggering mechanisms are unknown but GCA appears to be an antigen-driven disease. The process is dependent on T-cells found in the vicinity of the vasa vasorum in the adventitia. The major effector cells are macrophages and giant cells. The cytokines produced within the vasculitic lesions are of the Th-1 type (T-helper Type 1), with interferon gamma (IFN-γ) playing a critical role in the development of the granulomatous reaction. Increased expression of adhesion molecules stimulates leukocyte-endothelial cell interactions. The response of the artery is maladaptive and includes mobilization

Table 5

Differences Between Giant Cell Arteritis and Takayasu's Arteritis

	Giant Cell Arteritis	Takayasu's Arteritis
Age	Usually >50 years	Usually <50 years
Ethnicity	Whites	Southern Asians, Hispanics
Most Frequently Involved Vessels	Aorta and extracranial carotid arteries	Aorta and its major contributories including pulmonary, renal, and femoral arteries
Pattern of Aortic Disease	Aneurysms	Stenoses
Clinical Manifestations	PMR, headache, temporal artery tenderness, scalp tenderness, visual loss, jaw claudication, CNS ischemia due to extracranial carotid involvement	Asymmetric blood pressures or pulses, vascular bruits, limb claudication, renovascular hypertension, CNS ischemia
Response to Therapy	Usually satisfactory response to steroids	Variable and often unpredictable

and proliferation of smooth muscle cells along with matrix production and neoangiogenesis. Combined, these biologic changes ultimately lead to vessel occlusion. This, in turn, results in the ischemic manifestations associated with GCA.[81,82]

Systemically, GCA is associated with a decreased number of circulating CD8 T-lymphocytes and elevated levels of interleukin-6 (IL-6), soluble interleukin-2 receptors (sIL2-r), and soluble adhesion molecules.[79] The relationship between the systemic inflammatory response and vessel occlusion is unknown. Interestingly enough, ischemic events may occur more frequently in patients with little evidence of systemic inflammation and vice versa.[83,84]

Clinical Features

The clinical features of GCA have been well-described and include constitutional symptoms, polymyalgia rheumatica (PMR), and manifestations mostly due to inflammation of the extracranial branches of the carotid arteries (eg, headache, visual loss, jaw claudication, scalp tenderness, and ischemic CNS events.)[85] Limb claudication occurs less frequently than with TA, while renovascular hypertension is distinctly uncommon. Aortic involvement may lead to aneurysmal dilatation of the thoracic or abdominal aorta, years after the onset of GCA, often in the absence of other disease manifestations, such as during periods of presumed remission.[86] Rare manifestations include intracranial vessel involvement that often mimics CNS vasculitis and intractable cough.[85,87,88] The relationship of PMR to GCA is intriguing. The two conditions frequently coexist and, in addition, share the same epidemiologic and immunogenetic background described above.[80]

Pathology

GCA preferentially affects medium to large size muscular arteries which possess well-developed internal and external elastic laminae. Inflammatory cells penetrate through all the layers of the arterial wall. As previously indicated, CD4 T-lymphocytes and macrophages are the dominant cell population in the infiltrates. Multinucleated giant cells are formed in 50% of patients, often in close proximity to the fragmented internal elastic lamina.[89,90] In the absence of active inflammation, structural changes in the vessel wall do not allow reliable differentiation between "healed or quiescent temporal arteritis" and arteriosclerosis.[91]

Diagnosis

Biopsy of the temporal artery remains the gold standard for the diagnosis of GCA. Given the patchy distribution of histologic changes, the sensitivity of the biopsy depends on the length of segment obtained and how carefully it is sectioned and evaluated. A "negative" biopsy should prompt reexamination of the specimen. Two studies have now questioned the value of initial bilateral biopsies or sequential contralateral biopsies since the additional yield appears to be less than 5%.[92,93] Prior treatment with steroids should not dissuade clinicians from seeking pathologic confirmation of disease if the patient continues to have active symptoms or signs suggestive of GCA.[94] The presence of the hypoechoic "halo sign" on color Doppler ultrasonography of the temporal artery has been described as a noninvasive diagnostic test for GCA.[95] The hypoechoic signal is due to edema of the vessel wall, reflecting acute inflammation. In the chronic stages of disease, the signal turns hyperechoic due to fibrosis. Similar changes have been described in brachial, axillary, subclavian and carotid arteries.[96] In elderly patients presenting with constitutional symptoms and/or PMR rather than ischemic symptoms, neoplasms and infections should not be missed. In those situations, elevated acute phase reactants are rarely helpful in the differential diagnosis.

Treatment

Once GCA is suspected, treatment should be initiated promptly. In other words, diagnostic testing should not delay therapeutic intervention. Treatment is generally initiated with oral prednisone at a dose of 1 mg/kg/d (60 mg daily for most patients). In the face of ocular or CNS ischemic complications, an alternative approach is to initiate therapy with high-dose intravenous methylprednisolone. Although anecdotally successful in reversing ischemic sequelae, such an approach has not been compared directly to oral prednisone. Furthermore, the optimal dose and frequency of methylprednisolone administration is unknown. For patients presenting with constitutional symptoms and/or

PMR in the absence of ischemic symptoms, the argument has been made in small studies for initial treatment with lower doses (20-40 mg/daily) of prednisone.[97,98] Such studies, however, may not have been powered to detect small differences in the frequency of subsequent rare ischemic events.

Once GCA is brought under control, usually within 4-6 weeks, a steroid-tapering regimen is implemented. Relapses are common (up to 63%), even with the most cautious tapering regimen.[99] Although acute phase reactants are useful measures of disease activity, they are not perfect markers. The disease may remain active even after symptoms abate and acute phase reactants normalize. This has been shown in patients believed to be in remission, but found to have aortic aneurysms years after the onset of GCA.[78] This poses a difficult challenge since current clinical and laboratory parameters cannot accurately predict "true" remission, yet steroid therapy cannot be indefinitely maintained beyond the point of "presumed" remission. Long-term survival is generally better in patients without initial visual symptoms and those who were on less than 10 mg/d of prednisone equivalent at 6 months.[99] Whether cytotoxic drugs, particularly methotrexate, would allow faster steroid tapering and discontinuation, while maintaining disease control and preventing relapse, remains controversial. In a recent study, methotrexate had a steroid-sparing effect and reduced the rate of relapse from 84% to 45%.[100] However, the rate and severity of adverse events was similar in both groups.

Takayasu's Arteritis

Epidemiology

Takayasu's arteritis (TA) is a rare disease. Although the majority of reported cases are from the Far East, TA occurs worldwide. The reported incidence in the United States is 2.6 per million per year.[101] Although more common in Asian and Hispanic countries, the exact incidence rates there are unknown. TA predominantly affects women of reproductive age, but has been recognized with increasing frequency in males.[102] In addition, there has been increased recognition of TA in older patients with aortoarteritis who lack the typical features of GCA.[103] Race, sex, and age considerations should not preclude or delay the diagnosis of TA under appropriate clinical circumstances.[104] Unlike GCA, the association of TA with Class-II HLA molecules is rather weak and variable. A more consistent association exists between TA and Class-I antigens. Examples include HLA-B5 in India, its variant HLA-B52 in Japan and Korea, and HLA-B39.2 in Japan.[105,106]

Pathogenesis

Pathological samples from involved tissues are rarely available in TA, thus hindering our ability to understand disease pathogenesis. Examination of vascular lesions reveals granulomatous inflammation and cytotoxic T-lymphocytes. γ/δ T-lymphocytes recognizing heat-shock proteins significantly contribute to vessel damage in TA.[107] In contrast, such cells are rarely found in GCA. In most cases of TA, the vascular inflammation and resultant stenoses continue to progress slowly throughout the course of disease.

Clinical Features

The clinical manifestations of TA are summarized in Table 5. It has been stated that TA typically exhibits a "triphasic" pattern of disease progression through an early systemic illness with prominent constitutional symptoms, followed by a vascular inflammatory phase, and terminating in a "burned-out" or fibrotic stage. This clearly represents an oversimplification of the clinical course of TA and several caveats apply.[104]

- Constitutional symptoms may be absent in over 50% of patients.
- When present, systemic symptoms may occur early or late in the course of illness.
- Since TA may be chronic and recurrent, inflammatory and fibrotic lesions may be present simultaneously.
- Up to 20% of patients will have persistently active disease and never evolve into a burned-out stage.

Disease expression varies among different geographic areas. For example, the aortic arch and its branches are predominantly involved in Japanese series whereas the abdominal aorta and renal arter-

ies are more commonly affected in India and Thailand.[102] As a result, upper limb pulselessness, CNS ischemia, and aortic insufficiency are common presenting manifestations in Japan while renovascular hypertension prevails in Southeast Asia.

Pathology

Short of autopsy and vascular bypass procedures, tissue specimens are not available for histologic examination. TA causes a focal panarteritis with a mixed cellular infiltrate, granuloma formation, and giant cells.[90] Degeneration of the internal elastic lamina, adventitial fibrosis, and neovascularization follow. These changes are indistinct from those seen in GCA. The localized, focal lesions of TA are in contrast to the diffuse panarteritis of syphilitic aortitis, which is confined to the thoracic aorta.

Diagnosis

Angiography remains the standard procedure of choice in TA. It is useful in detecting arterial lesions and determining the extent and distribution of blood vessel involvement. When performed with pressure transducers, it also allows measurement of pressures in the aortic arch and pressure gradients across stenotic lesions. This permits recognition of hypertension in patients with bilateral subclavian stenoses. A complete aortogram with run-offs is recommended in the initial evaluation of TA. Sequential angiograms may then document new, or progressive stenoses, emerging aneurysms, or regression of vascular lesions with therapy. While angiography provides accurate information regarding luminal patency, it does not allow assessment of disease activity within the blood vessel wall. The role of non-invasive vascular imaging techniques in the diagnosis and serial follow-up of TA remains to be defined. Ultrasonography is useful in the evaluation of stenotic lesions without any radiation exposure, but can only be applied to limited sites such as the carotid arteries. Magnetic resonance angiography is useful in assessing thickness and edema of the blood vessel walls (eg, aorta or pulmonary arteries). It can also detect mural thrombi, evaluate patency of vascular shunts, and allow serial evaluation of specific lesions such as aneurysms. It is nonetheless of limited value in assessing the proximal aortic arch and distal aortic branches.[108]

Although acute phase reactants (APRs) are useful in the diagnosis and follow-up of TA, active disease may occur with normal APRs and in the absence of constitutional symptoms. Even in patients with known TA, sequential angiograms may demonstrate new lesions in up to 60% of patients believed to be in remission by clinical and laboratory criteria.[104] Similar to GCA, pathologic examination of vascular specimens obtained during bypass procedures reveal active inflammation in about 40% of patients presumed to be in clinical remission.[109]

Differential Diagnosis

The differential diagnosis of TA includes infections (tuberculosis, mycoses, syphilis), congenital collagen disorders (Ehlers-Danlos, Marfan's syndrome), fibrous dysplasias (FD), and acquired idiopathic inflammatory diseases (other vasculitides, sarcoidosis, and spondyloarthropathies).[110] In TA, stenoses are more common than aneurysms (ratios of 4:1 up to 9:1). In contrast, infectious diseases and congenital collagen disorders most often produce aneurysms, not stenoses. Acquired idiopathic inflammatory diseases may produce aneurysms and/or stenoses. Their distinction from TA is usually based on the presence of associated unique clinical features.

Making the distinction between TA and fibrous dysplasias (FD) may be a difficult task. As in TA, females are affected more commonly than males in FD. Stenoses are also more common than aneurysms. Renal arteries are the most commonly involved vessels in FD, but other sites can be affected (eg, carotid, mesenteric, iliac arteries). Although constitutional symptoms or elevated acute phase reactants favor a diagnosis of TA, 50% of patients with TA may lack such clinical or serologic evidence of inflammation. Biopsy of involved blood vessels would allow the histologic distinction of FD (bland proliferative lesion) from TA, but is impractical to obtain unless a bypass procedure is indicated.

Treatment

Takayasu's arteritis has a variable clinical course. About 20% of patients will have a monophasic self-limited illness. Another 20% will experience progressive disease despite therapy. The others, about 60% of cases, respond to immunosuppressive ther-

apy.[110,111] Corticosteroid regimens are similar to those used in GCA. Methotrexate is useful in resistant or relapsing TA.[111] Clinical and laboratory parameters are imperfect markers of disease activity. As already stated, about 40% of patients believed to be in clinical remission will have pathologically active disease at the time of bypass procedures.[109] Indications for angioplasty or revascularization include renovascular hypertension, limb claudication limiting the activities of daily living, cerebral ischemia and/or critical stenoses in 3 out of 4 cerebral vessels (carotid and vertebral arteries), moderate aortic regurgitation, and coronary artery stenosis leading to myocardial ischemia.[110] Restenoses due to recurrent inflammatory disease or fibrosis remain a problem.

12. Behçet's Syndrome

Behçet's syndrome is a systemic vasculitis of small and large vessels involving both the arterial and venous sides of the circulation. It is characterized by its association with mucocutaneous lesions, uveitis and central nervous system involvement.

Epidemiology

Behçet's syndrome is most commonly reported in the eastern Mediterranean, the Middle East, and the eastern Asian rim. Prevalence rates per 100,000 are 100-300 in Turkey; 13-17 in eastern Asia; 6.6 in Olmsted County, Minnesota; and 0.5-3 in Europe. The syndrome is most commonly reported in young adults of both sexes with a mean age of onset between 25 and 30 years. In high prevalence areas, it is associated with the HLA-B*5101 allele of HLA-B51.[112]

Pathogenesis

The pathogenesis of Behçet's syndrome remains unclear. Neutrophilic vascular lesions are characteristic in established disease while perivascular mononuclear cells are predominant in early lesions.[112] An elevated number of γδ T-cells are found in the mucosal lesions and can be stimulated by various heat shock proteins.[112,113] Cytokine analysis reveals elevated levels of IL-8, a chemokine responsible for neutrophilic activation, and other proinflammatory cytokines such as IL-1, IL-6, TNF-α, INF-γ, and sIL-2r suggesting a Th-1 response by lymphocytes.[112] Although a variety of autoantibodies have been described in Behçet's syndrome (anti-endothelial cell antibodies, ANCA, anticardiolipin antibodies, antibodies to *Saccharomyces cerevisiae* and α-tropomyosin), their exact role in disease pathogenesis remains to be elucidated. The role of infections in triggering disease exacerbation remains controversial.

Clinical Features

The International Study Group criteria for the diagnosis of Behçet's syndrome include recurrent oral ulceration plus 2 of the following 4 criteria: recurrent genital ulceration, eye lesions (anterior or posterior uveitis, retinal vasculitis), skin lesions (erythema nodosum, pseudofolliculitis, acneiform nodules), and positive pathergy test.[114]

Other manifestations include central nervous system disease (aseptic meningitis, cerebral venous thrombosis), gastrointestinal lesions (ulcerations in distal ileum and cecum), arthritis (peripheral oligoarthritis or spondyloarthropathy) and, less frequently, renal disease (glomerulonephritis, renal artery aneurysms, stensosis or renal vein thrombosis).

Vascular complications of Behçet's syndrome are heterogeneous and can involve blood vessels of any caliber on the arterial or venous sides of the systemic or pulmonary circulation. Arterial involvement results in stenoses and/or aneurysms. Venous involvement usually leads to thrombotic events. Arterial syndromes include aortitis, pulmonary hypertension or aneurysmal dilatation of the pulmonary artery (PA) with a bronchial fistula. Venous syndromes include thrombosis of superficial and deep veins, vena cava, right atrium, right ventricle, and cerebral venous sinuses. In addition, Behçet's syndrome should be considered in the differential diagnosis of patients presenting with Budd-Chiari syndrome, portal vein or renal vein thrombosis.[112]

Diagnosis

The diagnosis of Behçet's syndrome is based on the clinical presentation. There are no diagnostic laboratory tests. Angiography is useful when medium to large vessel involvement is suspected. Pathergy, an excessive skin response to trauma, reflects neutrophil hyperactivity and may support the diagnosis. Pathergy testing is performed by inserting a sterile 20-gauge needle perpendicularly into the subcutaneous tissues of the volar forearm. An erythematous papule or pustule greater than 2 mm in diameter at 48 hours represents a positive test. If the clinical presentation is consistent with Behçet's syndrome, a negative pathergy test does not exclude the diagnosis, particularly in patients from North America.

Differential Diagnosis

Patients with isolated recurrent aphthous stomatitis should not be diagnosed with "incomplete" or "pseudo" Behçet's syndrome. The differential diagnosis of the mucocutaneous lesions in Behçet's syndrome includes herpes simplex infection, Reiter's syndrome, inflammatory bowel disease, sprue, and chronic myelogenous leukemia (associated with pathergy). In Reiter's syndrome, mucocutaneous lesions are nonulcerative and painless, conjunctivitis is more common than uveitis, and the latter is limited to the anterior chamber. Crohn's disease and Behçet's syndrome have many common manifestations including: gastrointestinal manifestations; oral ulcers, uveitis, arthritis, thrombophlebitis; and erythema nodosum. However, granulomas are infrequent in Behçet's syndrome while genital ulceration, posterior uveitis, retinitis and central nervous system involvement are rare in Crohn's disease. The erythema nodosum lesions seen in Behçet's syndrome are indistinguishable from those associated with sarcoidosis, infections, pancreatic disorders and drugs. At times, it may be difficult to differentiate sarcoidosis from Behçet's syndrome on clinical grounds alone since both conditions involve the same organs and are associated with vasculitis. The pathologic documentation of non-necrotizing granulomas would, of course, help establish the diagnosis of sarcoidosis.

Treatment

Potentially effective therapies for mucocutaneous disease in Behçet's syndrome include colchicines, penicillin, dapsone, methotrexate and α-interferon. Because of its teratogenicity, thalidomide has been reserved for males with severe refractory disease. Patients with uveitis and central nervous system complications require more aggressive therapy with agents such as cyclophosphamide, chlorambucil, azathioprine, and cyclosporine. Interferon-α has also been effective in patients with resistant uveitis.[115] TNF-blocking agents are being used with increased frequency in the treatment of uveitis and vasculitis with variable but generally favorable results.[116] Finally, anticoagulation is appropriate for patients with thrombotic manifestations.

13. Vasculitis of the Central Nervous System

Vasculitis of the central nervous system (CNS vasculitis) can be primary or secondary to systemic vasculitides (eg, polyarteritis nodosa, Wegener's granulomatosis); other inflammatory diseases (eg, connective tissue diseases, sarcoidosis); infections (eg, varicella zoster virus, human immunodeficiency virus); neoplasms (eg, lymphoma); or drugs of abuse (eg, amphetamines, cocaine). There are no clinical presentations that are sufficiently specific for the diagnosis of CNS vasculitis. Symptoms may include headaches, cognitive changes, seizures and focal neurologic deficits. A prolonged syndrome of focal and nonfocal neurologic signs over 3-6 months is consistent with, but not diagnostic of, granulomatous CNS vasculitis.[117]

Cerebrospinal fluid (CSF) evaluation is an essential diagnostic test. Although it lacks specificity, it is more than 90% sensitive, revealing pleocytosis and elevated protein levels. It is also critical for the detection of CNS infections. Magnetic resonance imaging (MRI) is similarly sensitive but not specific. Common findings include leptomeningeal enhancement, multiple infracts or diffuse white matter changes. The combination of normal CSF and MRI reduces the likelihood of CNS vasculitis.[117]

Angiography is not as sensitive as clinicians expect it to be. Only 40% of cerebral angiograms demonstrate the characteristic stenoses and ectasia in multiple cerebral blood vessels. Furthermore, even a suggestive angiogram is not specific enough to secure the diagnosis, particularly since similar angiographic findings have been demonstrated in various vasospastic or vasculopathic disorders including sympathomimetic drugs, postpartum angiopathy, eclampsia, pheochromocytoma, subarachnoid hemorrhage, or migraines.[117] In most such instances, the presentation is acute with headaches and/or focal neurologic events, the CSF is unremarkable and the brain biopsies, when performed, generally do not demonstrate vasculitis. Such cases are best described as angiopathy of the CNS or reversible vasospastic CNS disorders.[117]

Brain biopsy remains the gold standard for the diagnosis of CNS vasculitis. It is also capable of detecting mimicking conditions such as lymphoproliferative diseases, sarcoidosis and infections. The sensitivity of brain biopsy in the diagnosis of CNS vasculitis is 75%. The yield can be optimized by sampling both cortex and leptomeninges.[117]

There are no controlled therapeutic trials. Patients are generally treated with high-dose corticosteroids. Patients with granulomatous angiitis of the CNS and those with biopsy-proven CNS vasculitis who progress despite corticosteroids are candidates for cyclophosphamide. Resistance to therapy should lead to a more vigorous search for secondary causes of CNS vasculitis, including infections and lymphoproliferative diseases.[117]

14. Vasculitis-mimicking Disorders

The diagnosis of systemic vasculitis is based on a high degree of clinical suspicion, but there are relatively few pathognomonic signs that allow topical diagnosis. Ischemia may be the result of vessel occlusion of any origin including thrombus, emboli, spasm, or trauma. The astute clinician must always keep in mind a number of disorders capable of mimicking vasculitis as outlined in Table 6.[118]

Table 6

Conditions Which May Mimic Vasculitis

Emboli Related
Cholesterol emboli
Septic emboli
Atrial myxoma
Thrombotic Angiopathies
Hypercoagulability states including antiphospholipid antibody syndrome
Hemoglobinopathies
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
Spasm Related
Drugs: ergots, methysergide, sympathomimetics
Vascular Malformations or Abnormal Vessel Morphology
Fibromuscular disease
Neurofibromatosis
Moya Moya

15. References

1. Hunder GG, Arend WB, Bloch DA, et al. The American College of Rheumatology criteria for the classification of vasculitis. *Arth Rheum*. 1990;33:1065-1067.

2. Jeannette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitis: proposal of an international consensus conference. *Arth Rheum*. 1994;37:187-192.

3. Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome: clinical aspects and treatment. *Rheum Dis Clin of North Amer*. 1995;21: 911-948.

4. Cid M. New developments in the pathogenesis of vasculitis. *Curr Opin Rheum*. 1996;8:1-11.

5. Rosen R, Falk RJ, Jennette JC. Polyarteritis nodosa, including microscopic form and renal vasculitis. In: *Systemic Vasculitides*. Igaku-Shoin, New York: 1991;57-78.

6. Hoffman GS, Kerr GS. Recognition of systemic vasculitis in the acutely ill patient. In: BF Mandell, ed. *Acute Rheumatic and Immunologic Diseases*. New York: Marcel Dekker, 1994:279-309.

7. Kissel JT. Vasculitis of the peripheral nervous system. *N Engl J Med*. 1994;14:361-369.

8. Vassilopoulos D, Calabrese LH. Virus associated vasculitis: clinical aspects. In: Hoffman GS, Weyand CM, eds. *Inflammatory Diseases of the Blood Vessels*. New York: Marcel Dekker; 2001:565-598.

9. Albert D, Remron D, Silverstein M. The diagnosis of polyarteritis nodosa: a literature based decision analysis approach. *Arthritis Rheum*. 1988;31:1117-1127.

10. Jennette JC, Falk RJ. Small vessel vasculitis. *N Engl J Med*. 1997;337:1512-1523.

11. Hoffman GS, Specks U. Antineutrophil cytoplasmic antibodies (ANCA). *Arthritis Rheum*. 1998;41:1521-1537.

12. Specks U. ANCA subsets: influence on disease specificity. *Cleveland Clinic Journal of Medicine*. 2002;69(Supplement ii): p. 56-59.

13. Xiao H, Heeringer P, Hu P, et al. Antineutrophile cytoplasmic antibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest*. 2002; 110(7):955-963.

14. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med*. 1992;116:488-498.

15. Cotch MF, Hoffman GS, Yerg DE, et al. The epidemiology of Wegener's granulomatosis: estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. *Arthritis Rheum*. 1996;39:87-92.

16. Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. *Arthritis Rheum*. 2000;43:2481-2487.

17. Hoffman GS, Sechler JMG, Gallin JI, et al. Bronchoalveolar lavage analysis in Wegener's granulomatosis: a method to study disease pathogenesis. *Am Rev Respir Dis*. 1991;143:401-407.

18. Stratta P, Messuerotti A, Canavese C, et al. The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. *Sci Total Environ*. 2001;270:179-190.

19. Duna GF, Galperin C, Hoffman GS. Wegener's granulomatosis. *Rheum Dis Clin North Am*. 1995;21:949-986.

20. Lebovics RS, Hoffman GS, Leavitt RY, et al. The management of subglottic stenosis in patients with Wegener's granulomatosis. *Laryngoscope*. 1992;102:1341-1345.

21. Rottem M, Fauci AS, Hallahan CW, et al. Wegener's granulomatosis in children and adolescents: clinical presentation and outcome. *J Pediatr*. 1993;122:26-31.

22. Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. *Medicine*. 1973;52:535-561.

23. Travis WD, Carpenter HA, Lie JT. Diffuse pulmonary hemorrhage. An uncommon manifestation of Wegener's granulomatosis. *Am J Surg Pathol*. 1987;11:702-708.

24. Falk RJ, Nachman PH, Hogan SL, et al. ANCA glomerulonephritis and vasculitis: a Chapel Hill perspective. *Semin Nephrol*. 2000;20:233-243.

25. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J*. 1958;2:265-270.

26. de Groot K, Schmidt DK, Arlt AC, et al. Standardized neurologic evaluations of 128 patients with Wegener's granulomatosis. *Arch Neurol*. 2001;58:1215-1221.

27. Girard T, Mahr A, Noel LH, et al. Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. *Rheumatology*. 2001;40:147-151.

28. Nowack R, Grab I, Flores-Suarez LF, et al. ANCA titers, even of IgG subclasses, and soluble CD14 fail to predict relapses in patients with ANCA-associated vasculitis. *Nephrol Dial Transplant*. 2001;16:1631-1637.

29. Travis WD, Hoffman GS, Leavitt RY, et al. Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. *Am J Surg Pathol*. 1991;15:315-333.

30. Myers JL, Katzenstein ALA. Wegener's granulomatosis presenting with massive pulmonary hemorrhage and capillaritis. *Am J Surg Pathol*. 1987;11:895-898.

31. Yoshikawa Y, Watanabe T. Pulmonary lesions in Wegener's granulomatosis. A clinicopathologic study of 22 autopsy cases. *Hum Pathol*. 1986;17:401-410.

32. Davson J, Ball J, Platt R. The kidney in periarteritis nodosa. *Q J Med*. 1948;17:175-202.

33. Jennette JC, Thomas DB, Falk RJ. Microscopic polyangiitis. *Semin Diagn Pathol*. 2001;18:3-13.

34. D'Agati V, Chander P, Nash M, et al. Idiopathic microscopic polyarteritis nodosa: ultrastructural observations on the renal vascular and glomerular lesions. *Am J Kidney Dis*. 1986;7:95-110.

35. Savage COS, Winearls CG, Evans DJ, et al. Microscopic polyarteritis: presentation, pathology and prognosis. *Q J Med*. 1985;56:467-483.

36. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum*. 1999;42:421-430.

37. Adu D, Howie AJ, Scott DGI, et al. Polyarteritis and the kidney. *Q J Med*. 1987;62:221-237.

38. Serra A, Cameron JS, Turner M, et al. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. *Q J Med*. 1984;53:181-207.

39. Schwarz MI. The nongranulomatous vasculitides of the lung. *Semin Resp Crit Care Med*. 1998;19:47.

40. Lauque D, Cardranel J, Lazor R, et al. Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. *Medicine*. 2000;79:222-233.

41. Rosen S, Falk RJ, Jennette JC. Polyarteritis nodosa including microscopic form and renal vasculitis. In: Churg A, Churg J, eds. *Systemic Vasculitides*. New York: Igaku-Shoin; 1991:57-78.

42. Guillevin L, Lhote F, Amouroux J, et al. Antineutrophil cytoplasm antibodies, abnormal angiograms and pathological findings in polyarteritis nodosa and Churg-Strauss syndrome: indications for the classification of vasculitides of the polyarteritis nodosa group. *Br J Rheumatol*. 1996;35:958-964.

43. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *Am J Pathol*. 1951;27:277-294.

44. Lanham JG, Elkon KB, Pusey CD, et al. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine*. 1984;63:65-81.

45. Lhote J, Guillevin L. Polyarteritis nodosa microscopic polyangiitis and Churg-Strauss syndrome: clinical aspects and treatment. *Rheum Dis Clin North Am*. 1995;21:911-943.

46. Lauque D, Cardranel J, Lazor R, et al. Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. *Medicine*. 2000;79:222-233.

47. Sehgal M, Swanson JW, DeRemee RA, et al. Neurologic manifestations of Churg-Strauss syndrome. *Mayo Clin Proc*. 1995;70:337-341.

48. Lanham JG, Churg J. Churg-Strauss syndrome. In: Churg A, Churg J, eds. *Systemic Vasculitides*. New York: Igaku-Shoin, 1991:101-120.

49. Chumbley LC, Harrison EG, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). *Mayo Clin Proc*. 1977;52:477-484.

50. Modigliani R, Muschart JM, Galian A, et al. Allergic granulomatous vasculitis (Churg-Strauss syndrome). Report of a case with widespread digestive involvement. *Dig Dis Sci*. 1981;26:264-270.

51. Shields CL, Shields JA, Rozanski TI. Conjunctival involvement in Churg-Strauss syndrome. *Am J Ophthalmol*. 1986;102:601-605.

52. Hoffman G. Treatment of Wegener's granulomatosis: time to change the gold standard? *Arth Rheum*. 1997;40:2099-2004.

53. Langford CA. Chronic immunosuppressive therapy for systemic vasculitis. *Curr Opin Rheum*. 1997;9:41-48.

54. Talar-Williams C, Jijazi TM, Walther MM, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener's granulomatosis. *Ann Int Med*. 1996;124: 447-484.

55. American College of Rheumatology ad hoc committee on glucocorticoid-induced osteoporosis 2001. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis 2001 update. *Arth Rheum*. 2001;44: 1495-1503.

56. Guillevin L, Lahote F, Gayraud M, Cohen P, Jarrousse B. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: a prospective study in 342 patients. *Medicine*. 1996;75:17-27.

57. Stone G, Tun W, Hellman D. Treatment of non-life-threatening Wegener's granulomatosis with methotrexate and daily prednisone as daily therapy. *J Rheum*. 1999;26:1134-1139.

58. Guillevin L, Lahote F, Cohen P, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis: a prospective, randomized trial in 62 patients. *Arthritis Rheum*. 1995;38:1638-1645.

59. Haubitz M, Schellong S, Schurek HJ, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with ANCA-associated vasculitis. *Arth Rheum*. 1998;41:1835-1840.

60. Langford CA. Wegener's granulomatosis: current and upcoming therapies. *Arthritis Res and Ther.* 5:180-191,2003.

61. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: Induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. *Arth Rheum*. 1999;42:2666-2673.

62. Jayne D, Rasmussen N, Andrasessy K, et al. A randomized trial of maintenance therapy for vasculitis associated with ANCA. *N Engl J Med*. 2003; 349:36-44.

63. Calabrese LH, Duna GF. Drug-induced vasculitis. *Curr Opin Rheum*. 1996;8:34-40.

64. Rojeau JC, Stern RS. Serious adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331:1272-1284.

65. Demarco PJ, Szer IS. Henoch-Schönlein purpura. In: Hoffman GS, Weyand CM, eds. I*nflammatory Diseases of the Blood Vessels*. New York: Marcel Dekker; 2001:321-338.

66. Kauffmann RH, Herrmann WA, Meyer CJ, et al. Circulating IgA immune complexes in Henoch-Schönlein purpura. A longitudinal study of their relationship to disease activity and vascular dysfunction of IgA. *Am J Med*. 1980;69:859-870.

67. Goldstein AR, White RH, Akuse R, Chantler C. Long-term follow-up of childhood Henoch-Schönlein nephritis. *Lancet*. 1992;339: 280-285.

68. Michel BA, Hunder GG, Bloch DA, Calabrese LH. Hypersensitivity vasculitis and Henoch-Schönlein purpura: a comparison between the two disorders. *J Rheum*. 1992;19:721-728.

69. Niaudet P, Habib R. Methylprednisolone pulse therapy in the treatment of severe forms Henoch-Schönlein nephritis. *Pediatr Nephrol*. 1998;12:238-248.

70. Clauvel JP, Danon F, Klein M, Brouet JC, Seligman M. Biologic and clinical significance of cryoglobulins. *Am J Med*. 1974;57:775-788.

71. Kallemuchikkal V, Gorevic P. Evaluation of cryoglobulins. *Arch Pathol Lab Med*. 1999;123:119-125.

72. Agnello V, Romain PC. Mixed cryoglobulinemia secondary to hepatitis C virus infection. *Rheum Dis Clin North Amer*. 1996;22:1-22.

73. Agnello V. The etiology and pathophysiology of mixed cryoglobulinemia secondary to hepatitis C virus infection. *Springer Sem Immunopathol*. 1997;19:111-129.

74. Agnello V, Abel G. Localization of hepatitis C virus on cutaneous vasculitic lesions in patients with type II cryoglobulinemia. *Arth Rheum*. 1997;40:2007-2015.

75. Ferri C, Marzo E, Longombardo G, et al. Interferon-alpha in mixed cryoglobulinemia patients: a randomized, crossover-controlled trial. *Blood*. 1993;81:1132-1136.

76. Dammacco F, Snasonno D, Han JH, et al. Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: a long-term, randomized, controlled study. *Blood*. 1994;84:3336-3343.

77. Misiani R, Bellavita P, Fenili D, et al. Interferon alpha-2a therapy in cryoglobulinemia associated with hepatitis C virus. *N Engl J Med*. 1994;330:751-756.

78. Wisneski JJ, Baer AN, Chrishanson J. Hypocomplementemic urticarial vasculitis syndrome. *Medicine* (Baltimore). 1995;74:24-41.

79. Cid MC, Font C, Coll-Vinent B, et al. Large vessel vasculitides. *Curr Opin Rheumatol*. 1998;10:18-28.

80. Weyand CM, Hunder NNH, Hicok KC, et al. HLA-DRB1 alleles in polymyalgia rheumatica, giant cell arteritis, and rheumatoid arthritis. *Arthritis Rheum*. 1994;37:514-520.

81. Weyand CM, Goronzy JJ. Pathogenic principles in giant cell arteritis. *Int J Cardiol*. 2000;75 Supl:S9-S15.

82. Cid MC, Cebrian M, Font C, et al. Ceel adhesion molecules in the development of inflammatory infiltrates in giant cell arteritis: inflammation-induced angiogenesis as the preferential site of leukocyte-endothelial cell interactions. *Arthritis Rheum*. 2000;43:184-194.

83. Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine*. 2000;79:283-292.

84. Cid MC, Font C, Oristrell J, et al. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. *Arthritis Rheum*. 1998;41:26-32.

85. Hunder GG. Giant cell arteritis and polymyalgia rheumatica. *Med Clin North Am*. 1997;81:195-219.

86. Evans JM, O'Falloon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant-cell (temporal) arteritis. *Ann Intern Med*. 1995;122:502-507.

87. Caselli RJ, Hunder GG. Neurologic aspects of giant cell (temporal) arteritis. *Rheum Dis Clin North Am*. 1993;119:941-953.

88. Olopade CO, Sekosan M, Schraufnagel DE. Giant cell arteritis manifesting as chronic cough and fever of unknown origin. *Mayo Clin Proc*. 1997;72:1048-1050.

89. Lie JT. Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathological documentation. *Semin Arthritis Rheum*. 1995;24:422-431.

90. Lie JT. Histopathologic specificity of systemic vasculitis. *Rheum Dis Clin North Am*. 1995;21:883-909.

91. Cox M, Gilks B. Healed or quiescent temporal arteritis versus senescent changes in temporal artery biopsy specimens. *Pathology*. 2001;33:163-166.

92. Danesh-Meyer HV, Savino PJ, Eagle RC Jr, et al. Low diagnostic yield with second biopsies in suspected giant cell arteritis. *J Neuroophthalmol*. 2000;20:213-215.

93. Pless M, Rizzo JF 3rd, Lamkin JC, et al. Concordance of bilateral temporal artery biopsy in giant cell arteritis. *J Neuroophthalmol*. 2000;20:216-218.

94. Achkar AA, Lie JT, Hunder GG, et al. How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? *Ann Intern Med*. 1994;120:987-992.

95. Schmidt WA, Kraft HE, Vorpahl K, et al. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med*. 1997;337:1336-1342.

96. Schmidt WA. Doppler ultrasonography in the diagnosis of giant cell arteritis. *Clin Exp Rheumatol*. 2000;18(4Suppl20):S40-42.

97. Behn AR, Perera T, Myles AB. Polymyalgia rheumatica and corticosteroids: How much for how long? *Ann Rheum Dis*. 1983;42:374-378.

98. Myles AB, Perera T, Ridley MG. Prevention of blindness in giant cell arteritis by corticosteroid treatment. *Br J Rheumatol*. 1992;31:103-105.

99. Hachulla E, Boivin V, Pasturel-Michon U, et al. Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. *Clin Exp Rheumatol*. 2001;19:171-176.

100. Jover JA, Hernandez-Garcia C, Morado IC, et al. Combined treatment of giant cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial. *Ann Int Med*. 2001;134:106-114.

101. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu's arteritis. *Arthritis Rheum*. 1990;33:1129-1134.

102. Numano F. Differences in clinical presentation and outcome in different countries for Takayasu's arteritis. *Curr Opin Rheumatol*. 1997;9:12-15.

103. Waern AU, Andersson P, Hemmingsson A. Takayasu's arteritis: a hospital region based study on occurrence, treatment and prognosis. *Angiology*. 1983;34:311-326.

104. Hoffman GS. Takayasu's arteritis: lessons from the American National Institutes of Health experience. *Int J Cardiol*. 1996;54(Suppl.):S99-S102.

105. Mehra NK, Rajalingam R, Sagar S, et al. Direct role of HLA-B5 in influencing susceptibility to Takayasu aortoarteritis. *Int J Cardiol*. 1996;54(Suppl.):S71-S79.

106. Kimura A, Kitamura H, Date Y, et al. Comprehensive analysis of HLA genes in Takayasu's arteritis in Japan. *Int J Cardiol*. 1996;54(Suppl.):S61-S69.

107. Schaufelberger C, Stemme S, Andersson R, et al. T lymphocytes in giant cell arteritic lesions are polyclonal cells expressing a/b type receptors and VLA-1 integrin receptors. *Clin Exp Immunol*. 1993;91:421-428.

108. Kerr G. Takayasu's arteritis. *Rheum Dis Clin North Am*. 1995;21:1041-1058.

109. Lagneau P, Michel JB, Vuong PN. Surgical treatment of Takayasu's disease. *Ann Surg*. 1987;205:157-166.

110. Hoffman GS. Treatment of resistant Takayasu's arteritis. *Rheum Dis Clin North Am*. 1995;21: 73-80.

111. Hoffman GS, Leavitt RY, Kerr GS, et al. Treatment of glucocorticoid-resistant or relapsing Takayasu's arteritis with methotrexate. *Arthritis Rheum*. 1994;37:578-582.

112. Calamia KT, O'Duffy JD: Behçet's disease. In: Hoffman GS, Weyand CM, eds. *Inflammatory Diseases of Blood Vessels*. New York: Marcel Dekker; 2002:473-489.

113. Yurdakul S, Hmauryudan V, Yazici H. Behçet's syndrome. *Current Opin Rheumatol*. 2004;16:38-42.

114. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet*. 1190; 335:1078-1080.

115. Kotter I, Zierhut M, Eckstein AK, et al. Human recombinant interferon alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis. *Br J Ophthalmol*. 2003; 87:423-431.

116. Sfikakis PP. Behçet's disease: a new target for anti-tumor necrosis factor treatment. *Ann Rheum Dis*. 2002; 61(Suppl. 2):ii51-ii53.

117. Calabrese LH, Duna GF. Vasculitis of the central nervous system. In: Hoffman GS, Weyand CM, eds. *Inflammatory Diseases of Blood Vessels*. New York: Marcel Dekker; 2002:511-528.

118. Churg A. Miscellaneous diseases associated with vasculitis and conditions mimicking vasculitis. In: Churg A, Churg J, eds. *Systemic Vasculitides*. New York: Igaku-Shoin; 1991:377-380.

119. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. *Am J Medicine*. 2003;114(6):463-469.

120. Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. *Arthritis & Rheumatism*. 2004;51(2):278-283.

121. de Groot K, Adu D, Savage CO, EUVAS. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrology Dialysis Transplantation*. 2001;16(10):2018-2027.

122. Langford CA, Sneller MC. Biologic therapies in the vasculitides. *Current Opinion in Rheumatology*. 2003;15(1):3-10.

123. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety [see comment]. *Arthritis & Rheumatism*. 2001;44(5):1149-1154.

124. Calabrese LH. Molecular differences in anti-cytokine therapies. *Clinical & Experimental Rheumatology*. 2003;21(2):241-248.

125. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis [see comment]. *Arthritis & Rheumatism*. 2005;52(1):262-268.

126. Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM*. 2000;93(7):433-439.

127. Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. *American Journal of Kidney Diseases*. 2003;42(6):1149-1153.