CHAPTER

48 Vasculitic Diseases of the Kidney

Julieanne G. McGregor • Patrick H. Nachman • J. Charles Jennette • Ronald J. Falk

The field of vasculitis has been one of continuous advancements in knowledge for the past quarter of a century. Evolving understanding of the pathogenesis of these disorders, including the role of antineutrophil cytoplasmic antibodies (ANCA) and exogenous and host factors that prime an individual for onset of disease or relapse, have led to improved treatment strategies. This chapter reflects our current understanding of large-, medium-, and small-vessel vasculitis.

EPIDEMIOLOGY OF VASCULITIS

The incidence of vasculitis has been difficult to determine, largely because of an inconsistent classification strategy. The advent of the Chapel Hill Nomenclature System allowed for a more precise estimation of incidence and prevalence. The incidence of giant cell arteritis varies from 15 to 30 per million in individuals older than 50 years. There is an increased incidence with age and a female-to-male ratio of 2:1.[1] Giant cell arteritis is more common in Caucasians and is uncommon in African Americans. Takayasu arteritis has been described worldwide, but the disease is much more prevalent in Japan, where there are approximately 150 new cases per year. In Olmstead County, Minnesota, the incidence is 2.6 cases per mission per year.

The incidence of vasculitis associated with ANCA appears to be on the order of 10 to 20 cases per million.[1] In contrast, polyarteritis nodosa has become a rare disease. It is possible that the perceived increase in the incidence of microscopic polyangiitis (MPA) is a consequence of the development and widespread use of ANCA testing. Nonetheless, the incidence of MPA appears to have been more common in the 1990s than in the 1980s (19.8 versus 7 cases per million). Two interesting studies reported a much higher incidence of ANCA vasculitis. One study reported a much higher incidence in Alaskan Indians in which all cases were associated with hepatitis B.[2] The other report from Kuwait after the Gulf War found an increased incidence of 16 cases per million of polyarteritis nodosa and 24 cases per million of MPA.[3] The incidence of GPA was 0.7 per million per year from 1980 to 1986, increasing to 2.8 per million per year from 1987 to 1989. There was an increase in the annual prevalence from 28.8 per million in 1990 to 64.8 per million in 2005 in a primary care population.[4] In the 1990s the prevalence of granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis, was closer to 10.6 cases per million in the United Kingdom. The annual incidence of eosinophilic granulomatosis (EGPA) ranges between 0.5 and 6.8 cases per million.[5] The prevalence of polyarteritis nodosa (PAN), MPA, GPA, and EGPA in a large multiethnic suburb of Paris based on a three-source capture-recapture method during the calendar year 2000 was estimated per 1,000,000 adults to be 30 for PAN, 25 for MPA, 24 for GPA, and 11 for EGPA. The overall prevalence was 2.0 times higher for subjects of European ancestry than for non-Europeans ($P = .01$).[6]

DIAGNOSTIC CLASSIFICATION AND PATHOLOGY OF VASCULITIDES

ANCA vasculitis can affect any vessel in the body and thus can cause various clinical signs and symptoms. Most of these manifestations are indicative of vessel involvement in a particular organ rather than a specific pathologic category of disease. Therefore, ANCA vasculitis cannot be accurately diagnosed on the basis of clinical features alone. Serologic and other laboratory data can be very helpful in narrowing the differential diagnosis or providing additional support to a presumptive diagnosis, but data are rarely definitive. As with all tissues, vessels have a limited number of nonspecific patterns of response to injury. For example, many different inflammatory stimuli cause histologically indistinguishable acute and chronic inflammation with and without necrotizing or granulomatous features. To further complicate pathologic evaluation, vasculitic lesions evolve through various stages of active (Fig. 48.1) and sclerosing injury (Fig. 48.2). Specific categories of vasculitis have a particular predilection for involvement of certain types of vessels, although there is so much overlap that type of vessel involvement alone does not provide adequate categorization (Table 48.1, Fig. 48.3). Therefore, vasculitis cannot be diagnosed accurately on

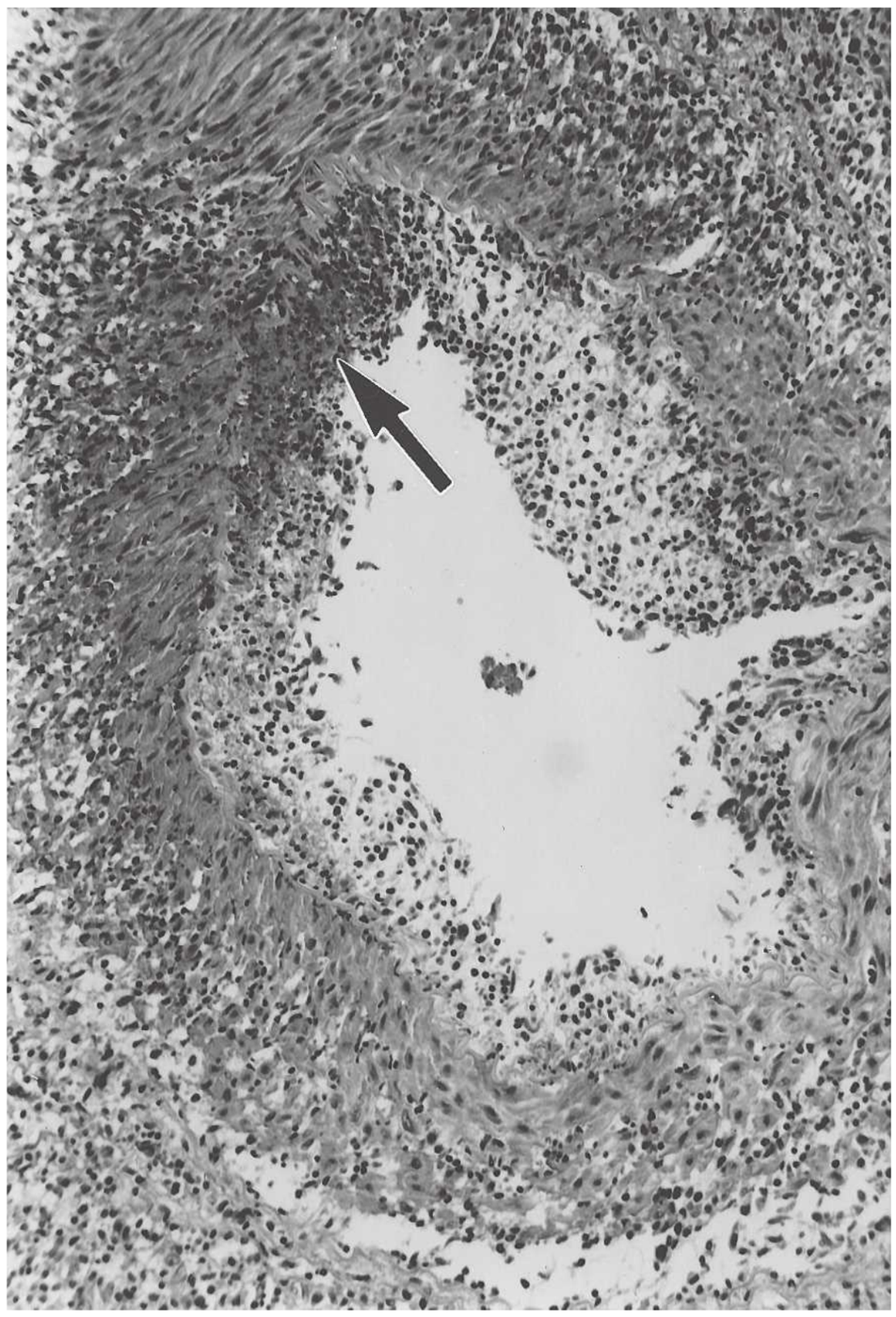

FIGURE 48.1 Acute necrotizing arteritis affecting a renal interlobar artery in a patient with Kawasaki disease. There is (*arrow*) transmural inflammation and necrosis. (Hematoxylin and eosin stain, magnification ×125.)

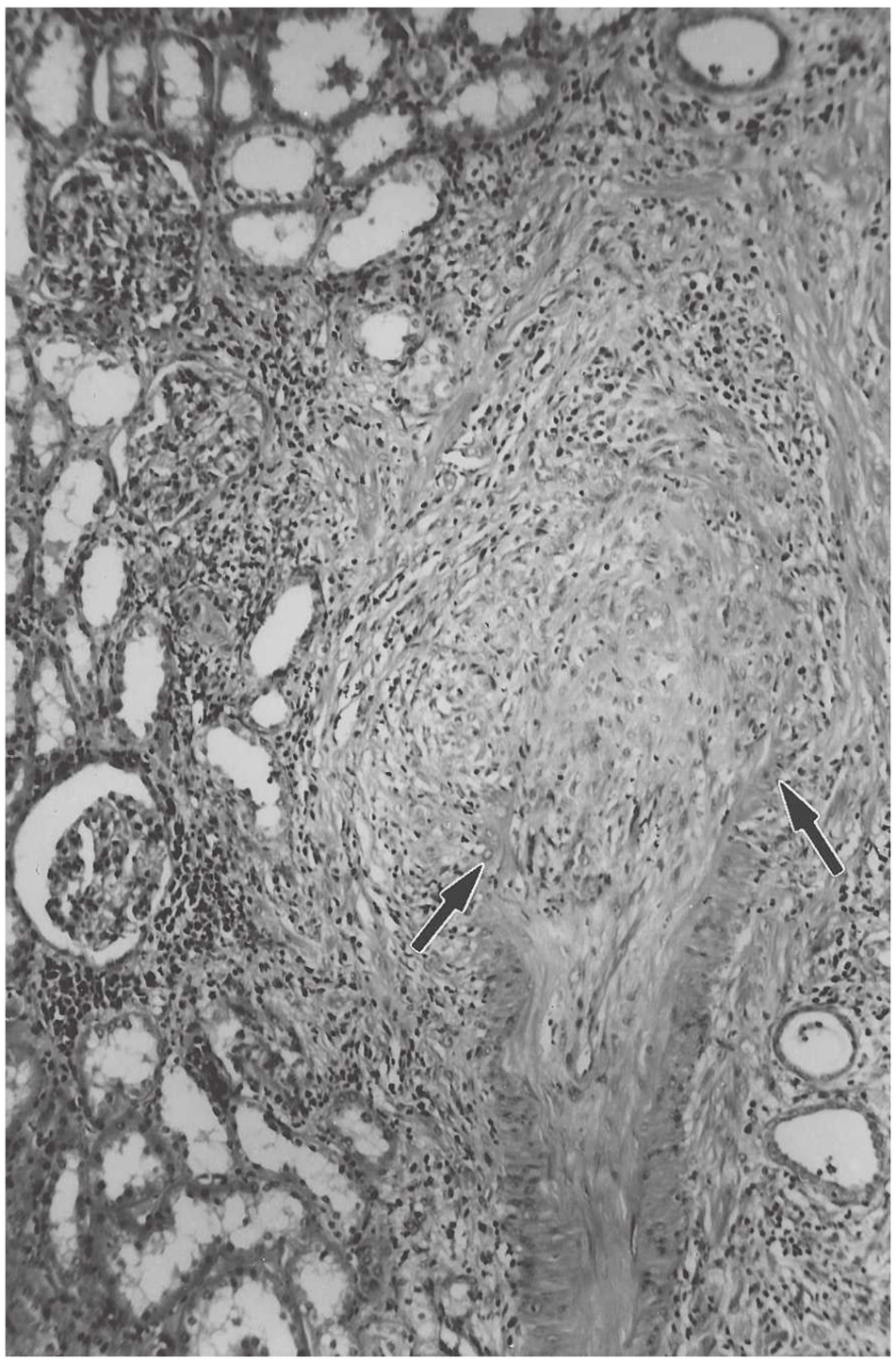

FIGURE 48.2 Chronic scarring in an arcuate artery from a patient with polyarteritis nodosa. The muscularis is completely destroyed (*arrows*), indicating that the sclerosis is secondary to a necrotizing arteritis rather than severe arteriosclerosis. (Hematoxylin and eosin stain, magnification ×75.)

the basis of pathologic features alone, especially if these are evaluated only by routine light microscopy. Recently, a pathologic classification system for ANCA vasculitis has been validated for prognostication of renal outcomes based on renal biopsy,[7] but the best approach to a specific diagnosis continues to be a combination of clinical, laboratory, and histologic data to identify distinctive clinicopathologic categories of vasculitis. Vasculitis categorization schemes will continue to be improved in the future; however, current systems provide valuable guidance for prognostication and for determining the most effective management strategy.

There are a number of approaches to the categorization of vasculitis. The system used in this chapter is a proposed modification of the Chapel Hill Nomenclature System, a system agreed upon by an international group of clinicians and pathologists with a special interest in vasculitis (Table 48.2).[8] There is a new nomenclature pending publication that recognizes a more specific categorization of vasculitides and abolishes eponyms.

Knowledge of the historical evolution of vasculitis categorization is helpful to understand the current diagnostic criteria for the classification of vasculitides. The following discussion of diagnostic classification includes a brief review of the historical events in the recognition of each category. The discussion is divided into sections discussing large-vessel vasculitis, medium-sized vessel vasculitis, and small-vessel vasculitis (Tables 48.1, Figs. 48.2 and 48.3). Large-vessel vasculitides were first recognized because of the reduced pulses and ischemic manifestations caused by chronic narrowing of major arteries. Medium-sized vessel vasculitides were first recognized because of the pseudoaneurysms caused by necrotizing lesions of medium-sized arteries, and small-vessel vasculitides were first recognized because of the glomerulonephritis and purpura caused by involvement of glomerular capillaries and dermal venules, respectively. Much of the discussion focuses on small-vessel vasculitides because these cause a higher frequency of renal disease.

TAKAYASU ARTERITIS AND GIANT CELL (TEMPORAL) ARTERITIS

Large-vessel vasculitis affects the aorta and its major branches, such as the arteries to the extremities and to the head and neck.[8] During the acute phase of disease, large-vessel vasculitis is characterized pathologically by inflammation that often

48.1 Major Diagnostic Categories of Vasculitis

Large-vessel vasculitis (chronic granulomatous arteritis)
Giant cell arteritis
Takayasu arteritis
Medium-sized vessel vasculitis (necrotizing arteritis)
Polyarteritis nodosa
Kawasaki disease
Small-vessel vasculitis (necrotizing polyangiitis)
Pauci-immune small-vessel vasculitis (usually antineutrophil cytoplasmic antibody [ANCA] positive)
Microscopic polyangiitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis
Drug-induced ANCA vasculitis
Immune complex small-vessel vasculitis
Henoch-Schönlein purpura
Cryoglobulinemic vasculitis
Lupus vasculitis
Rheumatoid vasculitis
Goodpasture syndrome
Serum sickness vasculitis
Hypocomplementemic urticarial vasculitis
Drug-induced immune complex vasculitis
Infection-induced immune complex vasculitis
Behçet disease
Paraneoplastic small-vessel vasculitis
Lymphoproliferative neoplasm-induced vasculitis
Carcinoma-induced vasculitis
Myeloproliferative neoplasm-induced vasculitis
Inflammatory bowel disease vasculitis

contains giant cells in the inflammatory infiltrates during the active phase of disease. The chronic phase is characterized by extensive vascular sclerosis with little or no active inflammation. Inflammatory and sclerotic thickening of the aorta and the arteries causes narrowing of lumina, which in turn causes ischemia and the resultant clinical manifestations. Involvement of the renal artery may cause renovascular hypertension. The two major categories of large-vessel vasculitis are Takayasu arteritis and giant cell arteritis.

In 1856, William Savory described patients with diminished peripheral pulses who probably had Takayasu arteritis involving the major arteries to the extremities.[9] However, this category of vasculitis is named for Mikito Takayasu, a Japanese ophthalmologist who reported the ocular ischemic effects of this chronic granulomatous arteritis in 1908.[10] Takayasu arteritis, which also includes "aortic arch syndrome" and "pulseless disease," most often involves the aorta and its major branches, although the pulmonary arteries may be affected.[11] Takayasu arteritis is most common in Asia, although it occurs worldwide. It rarely occurs in patients older than 40 years and is usually diagnosed during the second decade of life. Clinically, it often presents with reduced pulses, vascular bruits, claudication, and renovascular hypertension.

Giant cell arteritis rarely occurs in patients younger than 50 years and is most common in patients of northern European ethnicity.[12] Like Takayasu arteritis, giant cell arteritis affects the aorta and its major branches; however, it has a much greater predilection for the extracranial branches of the carotid artery. Frequent clinical manifestations include headache, jaw claudication, blindness, deafness, tongue dysfunction, extremity claudication, and reduced peripheral pulses. Pathologic involvement of the renal artery is common in giant cell arteritis, but symptomatic renovascular hypertension is rare. This is in contradistinction to Takayasu arteritis, which often causes renovascular hypertension.

Giant cell arteritis has also been called "temporal arteritis," partly because one of the earliest descriptions of this type of vasculitis in 1890 by Hutchinson emphasized temporal artery involvement.[13] However, the term "giant cell arteritis" is more appropriate than "temporal arteritis" because (1) not all patients with giant cell arteritis have temporal artery involvement and (2) vasculitides other than giant cell arteritis can cause temporal artery inflammation, such as polyarteritis nodosa, granulomatosis with polyangiitis, and microscopic polyangiitis.[8] If a patient with clinical manifestations of temporal artery inflammation is found by temporal artery biopsy to have a necrotizing rather than a granulomatous arteritis, the differential diagnosis should include polyarteritis nodosa, MPA, GPA, and other forms of necrotizing vasculitis. The frequent association of polymyalgia rheumatica with giant cell arteritis is a useful diagnostic aid, although not all patients with giant cell arteritis have polymyalgia rheumatica and not all patients with polymyalgia rheumatica have giant cell arteritis.

Takayasu arteritis and giant cell arteritis cannot be accurately distinguished on the basis of pathologic evaluation of involved arteries. Polymyalgia rheumatica and involvement of branches of the carotid artery are more in favor of giant cell arteritis, and preferential involvement of the aorta and arteries to the extremities is slightly in favor of Takayasu arteritis. However, the best diagnostic discriminator is age. If a patient with clinical or pathologic features of chronic granulomatous arteritis is older than 50 years, a diagnosis of giant cell arteritis is warranted, whereas a diagnosis of Takayasu arteritis is warranted if the patient is younger than 50 years.[8] The presence of renovascular hypertension in a child or a young adult is suggestive of Takayasu arteritis. In a patient older than 50 years, renal artery involvement by a chronic sclerosing process is more likely secondary to atherosclerosis than to giant cell arteritis, and Takayasu arteritis is essentially ruled out by the age of the patient.

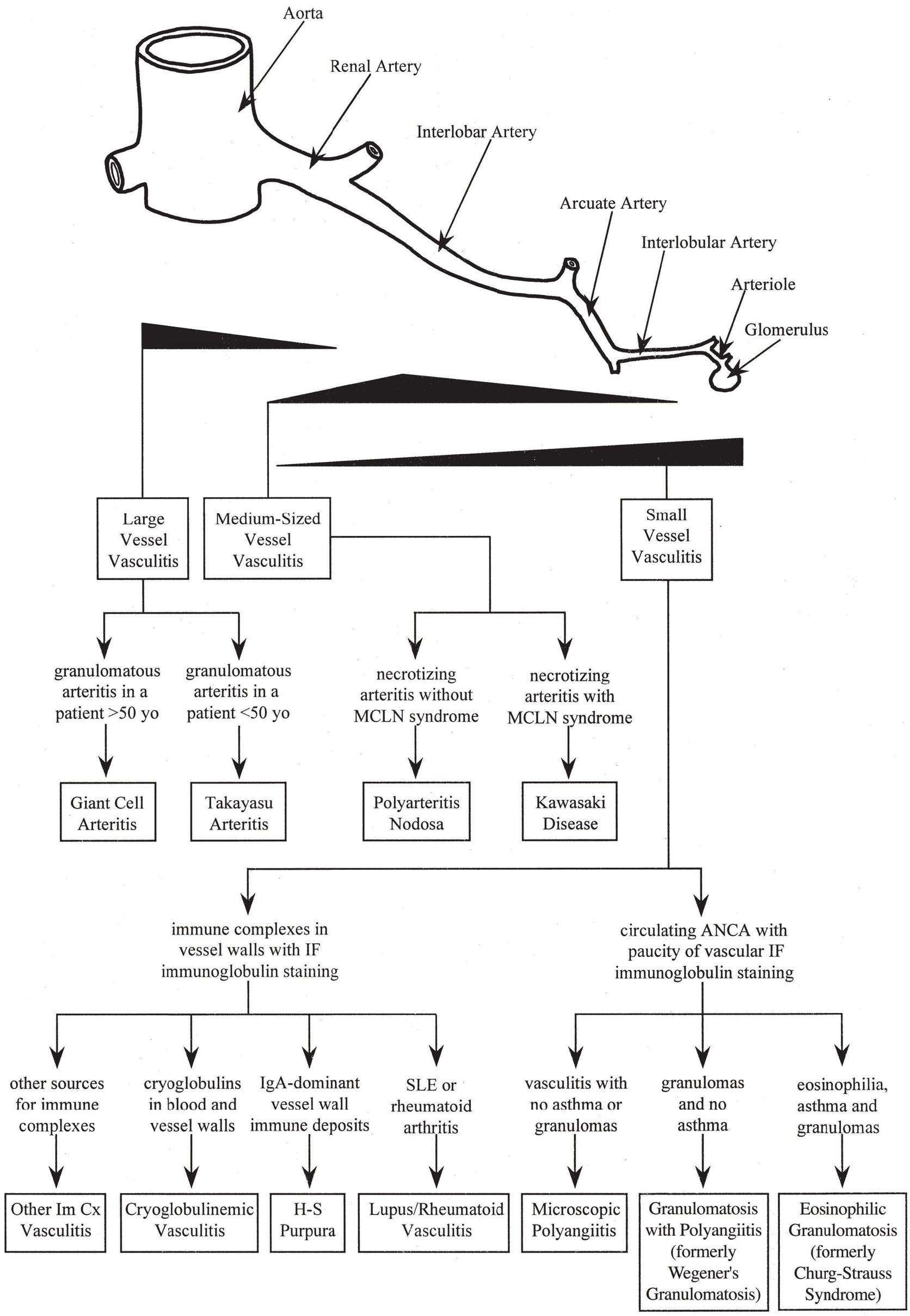

FIGURE 48.3 Predominant vascular involvement by large-vessel vasculitides, medium-sized vessel vasculitides, and small-vessel vasculitides as indicated by the positions and heights of the solid triangles. The algorithm suggests clinical and pathologic features that discriminate among different diagnostic categories of vasculitis. *yo*, years old; *MCLN*, mucocutaneous lymph node syndrome; *IF*, immunofluorescence microscopy; *ANCA*, antineutrophil cytoplasmic autoantibodies; *Im Cx*, immune complex; *SLE*, systemic lupus erythematosus; *H-S*, Henoch-Schönlein. (From Jennette JC, Falk RJ. Renal involvement in systemic vasculitis. In: Greenberg A, Cheung AK, Coffman TM, et al., eds. *National Kidney Foundation Nephrology Primer,* 2nd ed. San Diego, CA: Academic Press; 1998:200, with permission.)

48.2 Names and Definitions of Vasculitis Adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

Large-vessel Vasculitis[a]	
Giant cell arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 years and often is associated with polymyalgia rheumatica.
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50 years.
Medium-sized Vessel Vasculitis[a]	
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.
Small-vessel Vasculitis[a]	
Granulomatosis with polyangiitis[b] **(formerly Wegener granulomatosis**[c]**)**	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small-to medium-sized vessels, for example, capillaries, venules, arterioles, and arteries. Necrotizing glomerulonephritis is common.
Eosinophilic granulomatosis[c]	Eosinophil-rich and granulomatous inflammation involving respiratory tract and necrotizing vasculitis affecting small-to medium-sized vessels, and associated with asthma and blood eosinophilia.
Microscopic polyangiitis[c]	Necrotizing vasculitis with few or no immune deposits affecting small vessels, for example, capillaries, venules, or arterioles. Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillarities often occur.
Henoch-Schönlein purpura	Vasculitis with IgA-dominant immune deposits affecting small vessels, for example, capillaries, venules, or arterioles. Typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis.
Cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels, for example, capillaries, venules, or arterioles, and associated with cryoglobulins in serum. Skin and glomeruli are often involved.
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

[a]"Large artery" refers to the aorta and the largest branches directed toward major body regions (e.g., to the extremities and the head and neck); "medium-sized artery" refers to the main visceral arteries (e.g., renal, hepatic, coronary, and mesenteric arteries); and "small artery" refers to the distal arterial radicals that connect with arterioles. Note large and medium-sized vessel vasculitides do not involve vessels other than arteries.
[b]Modified nomenclature (Falk, Jennette JASN 2010).
[c]Strongly associated with ANCA.
From Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37:187, with permission.

Aortitis is a common feature of Takayasu and giant cell arteritis but is also associated with other vasculitides such as syphilis, tuberculosis, mycosis, Behçet disease, and Kawasaki disease. The most commonly involved vessels are the subclavian arteries in more than 90% of patients. Diagnostic differentiation between Takayasu and giant cell arteritis is largely based on age, with patients younger than 40 years having Takayasu arteritis and those older than 50 having giant cell arteritis. Aortic aneurysm rupture represents a morbid complication of giant cell arteritis. Aortitis may result in ischemic symptoms or infarction of the area supplied by the involved vessel. Asymptomatic aortitis may be a more common phenomenon than previously thought.[14]

Clinical Presentation

According to the Giant Cell Arteritis Guideline Development Group[15] giant cell arteritis often presents with abrupt onset headache, which is classically temporal and unilateral but can be diffuse. Presenting complaints can also include scalp pain, jaw or tongue claudication, blurring of vision, diplopia or amaurosis fugax, fever, weight loss, fatigue, polymyalgic symptoms, or limb claudication. On physical exam, tender, thickened, or beaded temporal artery with diminished or absent pulse may be noted. Visual field defect, visual loss, or afferent papillary defect can be noted. Funduscopic exam classically reflects anterior ischemic optic neuritis with pale, swollen optic disc with hemorrhages. Central retinal artery occlusion, upper cranial nerve palsies, asymmetry of pulses and blood pressure, and bruits are also features of this disease.

Early presentation of Takayasu arteritis includes low-grade fever, malaise, night sweats, weight loss, arthralgia, and fatigue. Although clinical presentations vary significantly between patients, and Takayasu arteritis seems to be a relapsing and remitting syndrome, many patients have diminished or absent pulses, Reynaud phenomenon, vascular bruits, hypertension, mesenteric angina, retinopathy, aortic regurgitation, dizziness, seizures, or amaurosis fugax. Takayasu arteritis has been reported to accompany other autoimmune diseases including rheumatoid arthritis, ulcerative colitis, systemic lupus, Crohn disease, sarcoidosis, and amyloidosis.[16,17]

Laboratory Findings

Laboratory findings in large-vessel vasculitis include a mild anemia, elevated levels of C-reactive protein, elevated erythrocyte sedimentation rate, and a generalized elevation in γ-globulin levels. Takayasu arteritis patients may be p- or c-ANCA positive. Other serologic results, including tests for lupus and infections, are typically negative. Patients typically present with only mild hematuria and proteinuria, except in patients with concomitant amyloidosis. The most common presentation is associated with hypertension and renal insufficiency, whereas renal failure is uncommon.

Pathogenesis

The pathogenesis of giant cell and Takayasu arteritis is unknown. Current consensus is that large vessel vasculitis is likely autoimmune in origin. Chauhan et al. report that serum of patients with Takayasu arteritis contains antiaortic endothelial cell antibodies directed against 60 to 65 kDa heat-shock proteins.[18] Serum-containing antiaortic endothelial cell antibodies induced apoptosis of aortic endothelial cells. There is scant evidence for a direct link between antiaortic endothelial cell antibodies and the development of Takayasu arteritis, however.

There are several tantalizing clues that infectious agents may play a role in these diseases. In animals, there is evidence that gamma herpes virus 68 causes arteritis in mice lacking the interferon-γ receptor. In humans, an association exists between giant cell arteritis and parvovirus B19 infection.[19] However, a study using polymerase chain reaction (PCR) and immunohistochemistry techniques on 147 temporal artery biopsies found no evidence of parvovirus B19 DNA in the arteries of patients with giant cell arteritis.[20] A cyclic occurrence of disease, with a peak incidence occurring every 5 to 7 years, suggests an infectious cycle. Certain genetic factors are associated with the development of giant cell arteritis. This form of vasculitis is more common in individuals of Northern European descent living in Europe or the United States,[21] and there is clustering of cases among families.[22] The development of giant cell arteritis also correlates with the expression of HLA-DR4, which is also found in high frequency among patients with polymyalgia rheumatica.[23]

Giant cell arteritis may be a consequence of either or both the humeral and cellular immune responses. The clinical and experimental findings suggest that a cell-mediated process is most likely.[24] Most inflammatory cells that invade the vessel walls are CD4-positive T cells. Elevated levels of IL-6 correlate with the severity of the disease and decrease quite rapidly when glucocorticoids are administered.[25] Levels of several other cytokines and chemokines are similarly elevated. It is hypothesized that activated monocytes infiltrate the adventitia of large vessel walls via the vasa vasorum and become macrophages that then produce interferon-γ and recruit additional leukocytes, including macrophages. Unfortunately, the antigen responsible for these interactions has yet to be elucidated.

Renal Involvement

Renal involvement in Takayasu arteritis and giant cell arteritis is usually a consequence of inflammation and scarring of the aorta adjacent to the orifice of the renal artery, leading to stenosis of the renal artery and ischemic renal failure. One of the most common clinical presentations of this phenomenon is renovascular hypertension affecting more than 50% of patients with Takayasu arteritis. In Japan, Takayasu arteritis is an important cause of hypertension in adolescents.

Glomerular lesions and necrosis occurs in patients with large-vessel vasculitis, but this may be an overlap of a small-vessel vasculitis. Several cases of glomerulonephritis in the setting of Takayasu arteritis have been reported in the literature. The renal pathology in these cases varies from case to case, including focal segmental sclerosis, mesangial proliferation, membranoproliferative lesions, and crescentic lesions.

Treatment

The cornerstone of treatment of giant cell arteritis is based on the use of high-dose corticosteroids. Typically, prednisone is started at 1 to 1.5 mg/kg/day until the erythrocyte sedimentation rate is normal and the patient is asymptomatic. Initial treatment on an alternate-day basis is ineffective in the treatment of giant cell arteritis. When compared with patients receiving daily corticosteroids, only 30% (versus 85%) of patients treated with alternate-day dosing enter an early remission, and 75% (versus 15%) experience a flare of disease activity.[26] Intravenous pulses of methylprednisolone (1 g per day for 3 to 5 days) are recommended for patients with severe visual loss because this treatment seems to prevent additional visual loss or fellow-eye involvement after initiation of corticosteroids.[27] The initiation of corticosteroids within 2 weeks before a temporal artery biopsy does not change the characteristic pathologic findings.[28] A delay in treatment to obtain a temporal artery biopsy is therefore not warranted.

Once a clinical remission is attained, a slow taper of corticosteroids is undertaken by decreasing the dose by 10% every 2 weeks to a dose of 10 mg per day, then by 1 mg per day. Other similar tapering protocols have been suggested, but no critical assessment of these recommendations is available. Switching to an alternate-day regimen may be similarly efficacious and perhaps less toxic. Symptoms usually resolve within 2 to 3 days, and the erythrocyte sedimentation rate usually normalizes within 4 to 6 weeks. Most patients with giant cell arteritis require 2 years of corticosteroids, and a few remain on a low-dose regimen indefinitely. Patients who continue to require "maintenance" dosages of more than 15 mg per day may be considered "steroid resistant."

The high rate of complications attributable to the prolonged duration of corticosteroid therapy and the age distribution of patients with giant cell arteritis has led to an interest in identifying steroid-sparing alternative drugs. Dapsone, azathioprine, cyclosporine, antimalarials, cyclophosphamide, or gold have not been found to reduce corticosteroid toxicity and still maintain therapeutic effectiveness.[29] The reported beneficial effect on the rate of relapse of adding methotrexate to corticosteroids was not confirmed by a multicenter, placebo-controlled trial.[30] A retrospective study suggests that the concomitant use of low-dose aspirin decreases the rate of visual loss and cerebrovascular events in patients with giant cell arteritis.[31] Information on the use of tumor necrosis factor (TNF)-alpha-blocking agents in the treatment of giant cell arteritis is currently limited to very small case series.

The treatment of Takayasu arteritis is similarly based on high-dose corticosteroids. In a U.S. National Institutes of Health study, treatment was initiated at 1 mg per kg (up to 60 mg per day) for 1 to 3 months, followed by a slow taper to an alternate-day regimen over the following 4 to 8 weeks, and a subsequent slow taper over the following 6 to 12 months. This regimen is associated with a remission rate of 60% and an estimated median time to remission of 22 months.[32]

Unfortunately, relapses occur in as much as 45% of patients, leading to multiple or prolonged courses of corticosteroids. Up to 40% of patients require the addition of cytotoxic drugs such as cyclophosphamide or methotrexate. In an open-label study of 18 patients with persistent or refractory Takayasu arteritis despite treatment with corticosteroids alone, the use of methotrexate was associated with an 81% remission rate.[33] Fifty percent of patients achieved a corticosteroid-free remission on methotrexate, and half of these patients remained in remission after methotrexate was withdrawn. About 20% of patients did not attain remission despite corticosteroids and methotrexate. The successful use of infliximab has been reported in several case reports of patients with active Takayasu arteritis despite conventional therapy with corticosteroids and cyclophosphamide[34] or methotrexate.[35] The use of anti-TNF therapy was assessed in a pilot, open-label trial involving a total of 15 patients with active, relapsing Takayasu arteritis. Seven patients were initially treated with etanercept and eight with infliximab. The use of anti-TNF agents led to remission in 10 of the 15 patients that was sustained for 1 to 3.3 years without glucocorticoid therapy. Four patients achieved partial remission, with a >50% reduction in the glucocorticoid requirement. Two relapses occurred during periods when etanercept was interrupted, but remission was reestablished upon reinstitution of therapy.[36]

The optimal treatment of patients with Takayasu arteritis is further complicated by the results of biopsies of affected vessels obtained at the time of bypass surgery. These data revealed evidence of persistent vascular inflammation even in the absence of clinical signs or symptoms of active disease and in the setting of a normal erythrocyte sedimentation rate.[32,37] Surgical intervention is the definitive treatment of occlusive disease in patients with progressive Takayasu arteritis, especially in the absence of response to conventional therapy.

The diagnosis and treatment of hypertension represents a very important aspect of the care of patients with Takayasu arteritis because congestive heart failure, ischemic or hemorrhagic stroke, and renal failure account for most of the deaths from this disease.[38] The diagnosis of hypertension may be missed if it is based on measurement of blood pressure in the upper extremities alone, because of the high incidence of subclavian artery stenoses, which may be bilateral. In some cases, lesions in the thoracic or abdominal aorta or the iliac or femoral arteries may give misleading normal blood pressures in the lower extremities as well. It is thus

recommended that arteriographic studies be performed with pressure transducers so that aortic pressures can be compared with extremity pressures, and to identify the extremity where blood pressure monitoring is most reliable and reflective of true blood pressure.[38]

MEDIUM-SIZED VESSEL VASCULITIS: POLYARTERITIS NODOSA AND KAWASAKI DISEASE

The medium-sized vessel vasculitides are necrotizing arteritides that have a predilection for arteries that lead to major viscera and their initial branches. In the kidneys, the major targets are the interlobar and arcuate arteries, with less frequent involvement of the main renal artery and interlobular arteries (Fig. 48.3). The two major categories of medium-sized vessel vasculitis are polyarteritis nodosa and Kawasaki disease. Pathologically, both are characterized in the acute phase by necrotizing arteritis with transmural inflammation that initially includes neutrophils and foci of fibrinoid necrosis (Fig. 48.1). The acute necrotizing inflammation often erodes completely through the artery wall and into the adjacent perivascular tissue, thereby forming a pseudoaneurysm (Fig. 48.4). Secondary complications of the arteritis include thrombosis, infarction, and hemorrhage. In only a few days, the lesions evolve from an acute neutrophil-rich inflammation to a "chronic" inflammation with predominantly mononuclear leukocytes. Sites of thrombosis and necrosis develop progressive scarring (Fig. 48.2). By definition, medium-sized vessel vasculitides do not cause glomerulonephritis, although they can cause hematuria, proteinuria (usually less than 2 g per 24 hours), and renal insufficiency as a result of renal infarction. Pseudoaneurysms near the renal surface may rupture and cause severe, even fatal, retroperitoneal and intraperitoneal hemorrhage.

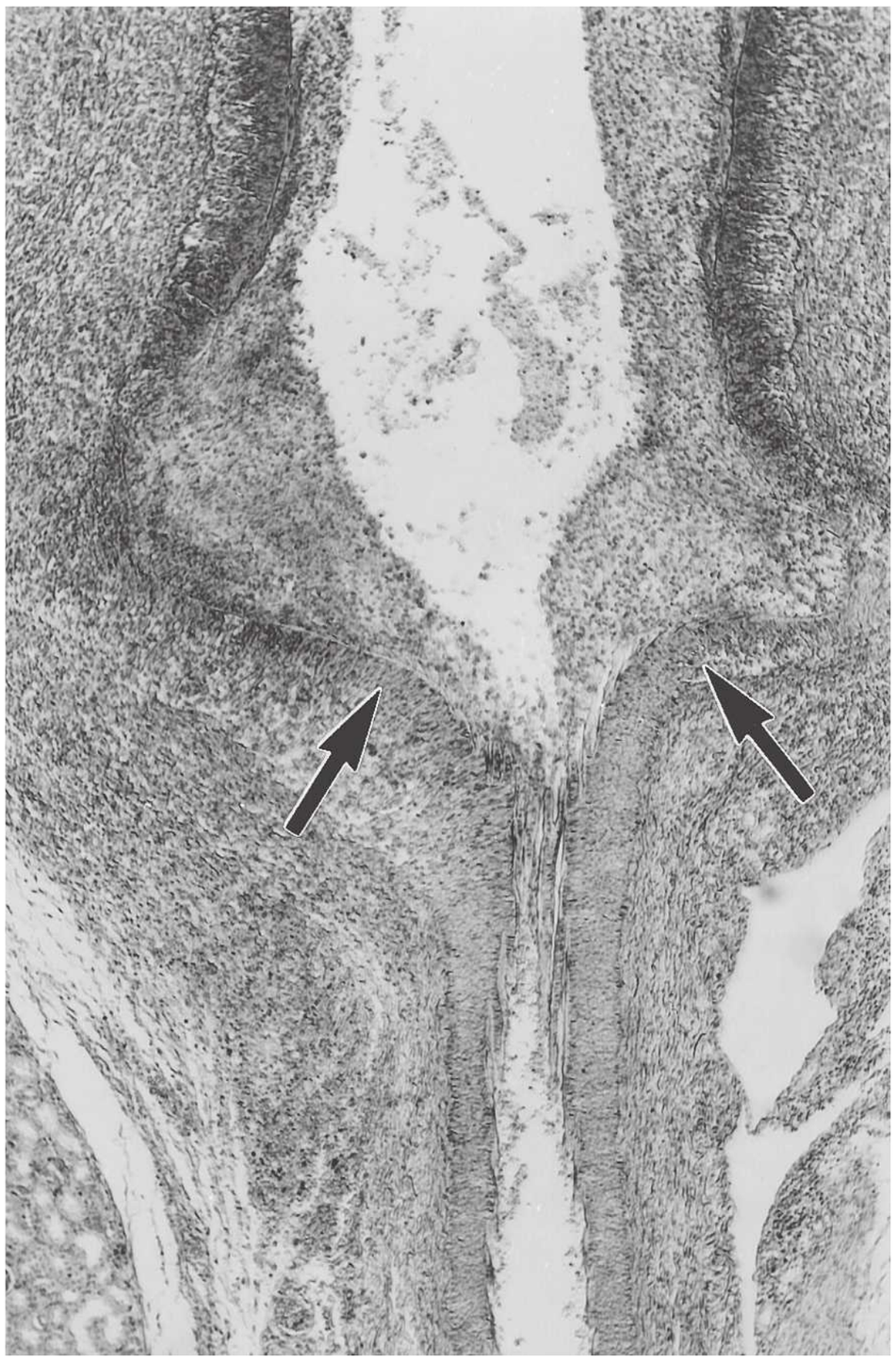

FIGURE 48.4 Acute necrotizing arteritis affecting a renal interlobar artery in a patient with Kawasaki disease. The necrotizing inflammation (*arrows*) has eroded into the perivascular tissue to produce a pseudoaneurysm. (Hematoxylin and eosin stain, magnification ×350.)

The meaning of the diagnostic term "polyarteritis nodosa" has evolved over the past century, and substantial confusion continues over how best to use it. The problem and the solution that we propose is best understood in historical context. Systemic necrotizing arteritis was first clearly described by Kussmaul and Maier in the mid-1800s.[39] They reported a patient with widespread visceral nodules caused by acute inflammation of arteries and called the process "periarteritis nodosa." Ferrari introduced the term "polyarteritis nodosa,"[40] which is more appropriate because the inflammation is transmural rather than perivascular. For approximately 50 years, essentially all patients with any pattern of necrotizing arteritis were included in the polyarteritis nodosa category. During the early to mid-1900s, astute investigators recognized that many patients with necrotizing arteritis had distinctive distributions of vascular inflammation or characteristic pathologic processes that warranted their separation from patients with arteritis alone. For example, Kawasaki disease, GPA, EGPA, and MPA were initially included in the category of polyarteritis nodosa but now are recognized as distinct entities.[8] The removal of these vasculitides from the polyarteritis nodosa category is justified not only on the basis of different patterns and distributions of vessel involvement, but also because they have different natural histories, prognoses, and treatment requirements.

The reduction of polyarteritis nodosa to a more homogeneous and clinically useful category of vasculitis began when Arnaout, among others, recognized that some patients with necrotizing arteritis had lesions that could be seen only by microscopic examination.[41] Circa 1950, Zeek et al.[42,43] and Godman and Churg[44] carried out careful evaluations of patients with arteritis and concluded that polyarteritis nodosa should be separated from the "microscopic" form of vasculitis that was characterized by involvement of not only small arteries but also venules and capillaries. As discussed later in the section on small-vessel vasculitis, Godman and Churg also concluded that polyarteritis nodosa was distinct not only from MPA but also from GPA and eosinophilic granulomatosis, and that MPA, GPA, and eosinophilic granulomatosis were related to one another.

The diagnostic approach that we advocate defines polyarteritis nodosa as necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules (Table 48.2).[8] This allows the separation of polyarteritis nodosa from other types of vasculitis, such as GPA, MPA, and eosinophilic granulomatosis, which have necrotizing arteritis as a component of a systemic polyangiitis that affects capillaries, venules, and arteries. By using this approach, the presence of glomerulonephritis rules out a diagnosis of polyarteritis nodosa and indicates the presence of some type of small-vessel vasculitis. Table 48.3 compares some of the features of polyarteritis nodosa and MPA. Note that glomerular capillaritis (glomerulonephritis) or pulmonary alveolar capillaritis with pulmonary hemorrhage rule out a diagnosis of polyarteritis nodosa and raise the possibility of MPA. Peripheral neuropathy is not a discriminator, because involvement of small epineural arteries in peripheral nerves may occur with polyarteritis nodosa or MPA. As discussed in more detail later, testing for ANCA is useful for distinguishing between polyarteritis nodosa and the ANCA-associated small-vessel vasculitides.[45–49] In a patient with necrotizing arteritis, a positive ANCA result decreases the likelihood of polyarteritis nodosa and increases the likelihood of MPA, GPA, or eosinophilic granulomatosis (i.e., increases the likelihood that the patient has or will develop necrotizing inflammation of vessels other than arteries, such as pulmonary alveolar capillaritis or glomerular capillaritis [glomerulonephritis]).

Necrotizing arteritis that is pathologically indistinguishable from the necrotizing arteritis of polyarteritis nodosa can occur in patients with Kawasaki disease (Figs. 48.1 and 48.3). Kawasaki disease is an acute self-limiting febrile illness, the second commonest vasculitis in childhood.[50] Kawasaki disease is characterized by the mucocutaneous lymph node syndrome, which includes nonsuppurative lymphadenopathy, polymorphous erythematous rash, erythema of the oropharyngeal mucosa, erythema of the palms and soles, conjunctivitis, indurative edema, and desquamation of the extremities. A major cause for morbidity and mortality in patients with Kawasaki disease is the development of a necrotizing arteritis. This arteritis has a predilection for coronary arteries but can occur anywhere, including the kidney (Figs. 48.1 and 48.3). Kawasaki disease is the most common cause of childhood-acquired heart disease.[50] Symptomatic renal involvement is rare in Kawasaki disease. Differentiation between the arteritis of Kawasaki disease and that of polyarteritis nodosa is very important because the treatment of Kawasaki disease differs from the treatment of polyarteritis nodosa (discussed in Treatment section).

The presence or absence of the mucocutaneous lymph node syndrome is an effective diagnostic discriminator between Kawasaki disease and polyarteritis nodosa.

48.3 Clinical Differences Between Polyarteritis Nodosa and Microscopic Polyangiitis

Clinical Feature	Polyarteritis Nodosa	Microscopic Polyangiitis
Rapidly progressive nephritis	No	Very common
Pulmonary hemorrhage	No	Yes
Peripheral neuropathy	Yes	Yes
Microaneurysms by angiography	Yes	Rare
Renovascular hypertension	Occasional	No
Positive hepatitis B serology	Uncommon	No
Positive antineutrophil cytoplasmic antibodies serology results	Rare	Frequent
Relapses	Rare	Frequent

From Guillevin L, Lhote F, Amouroux J, et al. Antineutrophil cytoplasmic antibodies, abnormal angiograms and pathological findings in polyarteritis nodosa and Eosinophilic granulomatosis: Indications for the classification of vasculitides of the polyarteritis nodosa group. Br J Rheumatol. 1996;35:958, with permission.

Clinical Features

Patients with polyarteritis nodosa typically have constitutional symptoms, including fever and weight loss. The presence of mononeuritis multiplex, myalgias, and arthralgias, as well as skin lesions including nodules, ulcers, livedo reticularis, and digital ischemia in half of patients, characterize the disease. There is a spectrum of disease referred to as cutaneous polyarteritis nodosa associated with streptococcal infection.[50] Cutaneous polyarteritis nodosa has periodic exacerbations but is milder than classic polyarteritis nodosa. This presentation may be along the spectrum of systemic polyarteritis nodosa. Vasculitis of the coronary arteries may lead to cardiac symptoms. The renal disease seen in polyarteritis nodosa is primarily related to vasculitis of the renal arteries resulting in renovascular hypertension and/or renal parenchymal infarction. Patients with polyarteritis nodosa do not have evidence of small-vessel

vasculitis, glomerulonephritis, or pulmonary capillaritis. In fact, the lung is rarely injured in polyarteritis nodosa, in contrast to the frequency of pulmonary disease in patients with GPA, MPA, or EGPA. Although not distinguishing features, gastrointestinal complaints and peripheral neuropathy are more common among patients with polyarteritis nodosa than patients with MPA. The skin lesions of polyarteritis nodosa closely mimic cholesterol emboli and calciphylaxis and therefore histopathologic confirmation of diagnosis is required. The prognosis of polyarteritis nodosa is really a reflection of the involvement of the kidneys, heart, central nervous system, or gastrointestinal tract.[51]

Tc-99m dimercaptosuccinic acid (DMSA) scanning of the kidneys can indirectly support the diagnosis of a medium-vessel vasculitis affecting the renal arteries by manifesting patchy areas of decreased isotope in the renal parenchyma.[52] Unquestionably, however, angiography of the renal, hepatic, and/or mesenteric vasculature via angiography is a superior approach for diagnosis of a medium vessel vasculitis. Demonstration of "aneurysms," narrowing of arteries, or pruning of the peripheral vascular tree suggest medium-vessel vasculitis. Large pseudoaneurysms, stenosis of the renal arteries or large branches, and resultant areas of ischemia or infarct within the kidney can be demonstrated by magnetic resonance angiography or computed tomography (CT) angiography.

Pathogenesis

The etiology of polyarteritis nodosa remains unclear, and most cases of polyarteritis nodosa are probably idiopathic. An association between polyarteritis nodosa and hepatitis B infection is evident by the fact that patients with hepatitis B antigenemia are at greater risk of developing polyarteritis nodosa. Hepatitis B virus has been implicated in up to one third of cases of polyarteritis nodosa.[54] A role for hepatitis B antigenemia in the pathogenesis of polyarteritis nodosa is further suggested by reports of vasculitis after hepatitis B vaccination.[55] Furthermore, treatment with antiviral agents and plasma exchange has led to resolution of the vasculitis in patients whose serology converts from being positive for the HBe or HBs antigens to the corresponding antibodies.[56,57]

Polyarteritis nodosa has been associated with a number of cancers, especially hairy cell leukemia.[58] Treatment of hairy cell leukemia with interferon-alpha (INF-α) may be associated with resolution of polyarteritis nodosa.[59] As opposed to patients with small-vessel vasculitis, patients with polyarteritis nodosa are ANCA-negative.[60]

Renal Manifestations

Both polyarteritis nodosa and Kawasaki disease are medium-sized vessel vasculitides that affect the kidney. These arteritides result in necrotizing lesions in the major renal arteries and aneurysm formation with thrombosis and renal infarction. The aneurysms are not true aneurysms but rather pseudoaneurysms. The arteritis of Kawasaki disease most commonly involves the coronary arteries, but in at least 25% of patients the lesions also involve the kidney. Tubulointerstitial nephritis is a not uncommon renal presentation in Kawasaki disease.[50] Renal manifestations of Kawasaki disease can lead to renal failure. Kawasaki disease is distinguished from polyarteritis nodosa by the pathognomonic sine qua non feature of mucocutaneous lymph node syndrome. Renal arterial involvement by polyarteritis nodosa, including interlobar and arcuate arteries, results in renal ischemia, infarction, and hemorrhage. One of the most painful and catastrophic consequences of this disease is rupture of an arterial pseudoaneurysm that causes retroperitoneal and sometimes intraperitoneal hemorrhage.

Treatment

The treatment of Kawasaki disease differs from the treatment of polyarteritis nodosa. Kawasaki disease usually is treated with aspirin and intravenous γ-globulin therapy,[53] whereas the treatment of polyarteritis nodosa classically has been based on the use of high-dose corticosteroids with the addition, in moderate to severe or organ-threatening cases, of cyclophosphamide. Unfortunately, most studies pertinent to the treatment of polyarteritis nodosa antedate the 1994 Chapel Hill consensus conference, which classified MPA among the small-vessel vasculitides separate from classic polyarteritis nodosa. Consequently, most of the older studies and reports include a substantial number of patients who would now be diagnosed with MPA and not classic polyarteritis nodosa. As a result of the consensus conference, the incidence of classic polyarteritis nodosa involving medium-sized vessels alone and without evidence for glomerulonephritis is very low and is not readily amenable to large-scale evaluation of various therapies. Fifty percent of classic polyarteritis nodosa is curable with 9 to 12 months of corticosteroid therapy alone.[61] The other 50% of polyarteritis nodosa will require cyclophosphamide therapy but once remission is obtained relapses are very uncommon.[62] The problem is compounded by the relatively recent recognition of the association of polyarteritis nodosa with hepatitis B virus (HBV) infection in a subset of patients with polyarteritis nodosa that varies from 10% to 50%, depending on the population studied.

In the absence of HBV infection, the mainstay of treatment of classic polyarteritis nodosa continues to rest on the use of high-dose corticosteroids. In patients without poor prognostic factors (no renal, cardiac, gastrointestinal, or central nervous system manifestations of disease), no survival difference was noted when treating polyarteritis nodosa with corticosteroids alone when compared to corticosteroids and cyclophosphamide.[63] Typically, prednisone is initiated at a dosage of 1 mg/kg/day for the first month. Over the course of the second month, the dosage is tapered to an alternate-day regimen so that the patient is receiving 1 mg per kg every other day by the end of the second month. It is subsequently tapered slowly by 5 mg per day weekly as tolerated. Should relapse occur after corticosteroid therapy,

the addition of cyclophosphamide or azathioprine may be beneficial.[64] The addition of an alkylating agent such as cyclophosphamide in the treatment of polyarteritis nodosa is not as well established as in the treatment of MPA or GPA, although some studies report improved patient survival when these agents were added, especially in patients with poor prognostic factors.[64] In another study, the addition of cyclophosphamide to corticosteroids and plasma exchange led to decreased relapse in the cyclophosphamide-treated group, but no improvement in the 10-year survival rate.[65] In current practice, cyclophosphamide should be reserved for patients with severe or organ-threatening disease, with disease that fails to respond to treatment with corticosteroids alone, for patients who require unacceptably high doses of corticosteroids, or for patients who are intolerant to corticosteroid side effects. No randomized study exists to critically assess the value of a daily oral regimen of cyclophosphamide compared with pulse cyclophosphamide in the outcome of patients with classic polyarteritis nodosa; however, intravenous cyclophosphamide rather than an oral regimen is recommended, not to exceed 12 pulses.[64] In patients with poor prognostic factors, six intravenous pulse treatments with cyclophosphamide not followed by maintenance therapy were noted to have greater relapse rate than 12 intravenous infusions of cyclophosphamide. Although azathioprine has been used in the treatment of classic polyarteritis nodosa, this agent is better reserved for maintenance therapy or as a steroid-sparing agent. Current recommendations for patients with polyarteritis nodosa with poor prognostic factors are to obtain remission with pulse cyclophosphamide and then continue therapy with azathioprine for 12 to 18 total months of immunosuppression.[66] Plasma exchange does not seem to improve the outcome, decrease relapse, or improve long-term survival of patients with polyarteritis nodosa not associated with HBV.[67] The successful use of infliximab in PAN resistant to "conventional therapy" has been reported in a small number of cases.[68,69]

In the setting of HBV-associated polyarteritis nodosa, treatment with immunosuppression consisting of corticosteroids with or without cyclophosphamide is thought to be deleterious because it facilitates viral replication, delays the development of protective anti-HBV antibodies, and may lead to an aggravation of hepatic involvement.[70] For this reason, it has been advocated that only a short course of corticosteroids (1 mg/kg/day) be used for 1 week, followed by a rapid taper over the following week. The prompt institution of antiviral therapy may ameliorate the vascular inflammation. Treatment with plasma exchange has been advocated to clear circulating immune complexes thought to be important in the pathogenesis of this disease,[71] although no controlled trial has critically assessed the need for plasmapheresis. The antiviral agents used have included vidarabine, INF-α-2b, or more recently combination therapy of INF-α-2b in addition to lamivudine[72] or famciclovir.[57] No large-scale trials of antiviral therapy are available to critically assess the efficacy of these combinations in patients with HBV-related polyarteritis nodosa. Current work in the treatment of chronic HBV focuses on the use of INF-α-2b, modified purine analogs such as famciclovir, or L-stereoisomers of pyrimidine derivatives such as lamivudine.[73] In an uncontrolled study, the combination of a short course of corticosteroids followed by a 6-month course of lamivudine and scheduled plasma exchange (until hepatitis B antigen or anti-HBe antibody seroconversion) resulted in a clinical remission of the vasculitis.[74] In a recent retrospective analysis of 115 patients with HBV-associated polyarteritis nodosa (according to the Chapel Hill nomenclature) followed by the French Vasculitis Study Group between 1972 and 2002, the overall remission rate was 80.9% with a subsequent overall 9.7% relapse rate.[54] The rates of relapse or death were not significantly different among patients treated with antiviral agents (vidarabine, INF-α, or lamivudine) ($n = 80$) when compared to patients treated with corticosteroids alone, or with cyclophosphamide, or plasma exchanges ($n = 35$) (5% vs. 14.3% relapse; and 30% vs. 48.6% death, respectively). However, the use of antiviral agents has led to a significantly higher rate of seroconversions from HBeAg to anti-HBeAb (49.4% vs. 14.7%; $P < .001$). Such seroconversion was associated with a clinical remission and absence of relapse.

Outcome

Most studies examining patient outcome and predictors of patient survival in polyarteritis nodosa antedate the Chapel Hill consensus conference of 1994. These studies are based on cohorts of patients that include those with MPA, EGPA, and hepatitis B–associated classic polyarteritis nodosa. Earlier studies report a 5-year survival rate of approximately 55% in patients primarily treated with corticosteroids alone.[75] The addition of cyclophosphamide or immunosuppressive therapy to glucocorticoids seems to have improved the 5-year survival rate to about 80%. Patients with bowel infarction, serious gastrointestinal bleeding, or renal insufficiency had particularly poor prognosis. In a more recent prospective study including 342 patients, of whom 119 had classic polyarteritis nodosa without HBV (89 patients with HBV, 52 patients with MPA, 82 patients with EGPA),[51] proteinuria of 10 g per day, renal insufficiency, and gastrointestinal tract involvement were the major prognostic markers for a worse outcome.

SMALL VESSEL VASCULITIS

Microscopic Polyangiitis, Granulomatosis with Polyangiitis, and Eosinophilic Granulomatosis

Small-vessel vasculitides are characterized by necrotizing inflammation of multiple types of vessels. Arteries, veins, arterioles, venules, and capillaries may be affected; however, venules and capillaries are the most frequent targets. An understanding of the small-vessel vasculitides is important for nephrologists because these diseases often involve

the kidneys and frequently cause glomerulonephritis. All of the small-vessel vasculitides listed in Table 48.1 can involve the kidneys. As mentioned in the discussion about the evolution of the definition of polyarteritis nodosa, small-vessel vasculitides with arterial involvement once were subsumed in the polyarteritis nodosa category. Zeek et al.[42,43] and Godman and Churg[44] were among the first to recognize that vasculitides that involve capillaries and venules in addition to arteries have clinical and pathologic features that are clearly distinct from those of polyarteritis nodosa.

The two major categories of small-vessel vasculitis include the "pauci-immune small vessel vasculitides" and the "immune complex–mediated small vessel vasculitides" (Table 48.1). Immune complex–mediated vasculitides, such as Henoch-Schönlein purpura (HSP), cryoglobulinemic vasculitis, lupus vasculitis, and antiglomerular basement membrane (anti-GBM) vasculitis, have extensive localization of immunoglobulin and complement in vessel walls as a consequence of deposition of circulating immune complexes or in situ immune-complex formation between circulating antibodies and planted or constitutive antigens. The pauci-immune small-vessel vasculitides have little or no vascular wall localization of immunoglobulins.[45] The pauci-immune small-vessel vasculitides often have necrotizing and crescentic glomerulonephritis as a component of the systemic necrotizing vasculitis. A pathologically identical pauci-immune necrotizing and crescentic glomerulonephritis also occurs as a renal-limited process, sometimes referred to as "idiopathic crescentic glomerulonephritis" or "renal vasculitis."[76] Pauci-immune crescentic glomerulonephritis, usually a component of systemic pauci-immune small-vessel vasculitis, is the most common type of crescentic glomerulonephritis (Table 48.4).

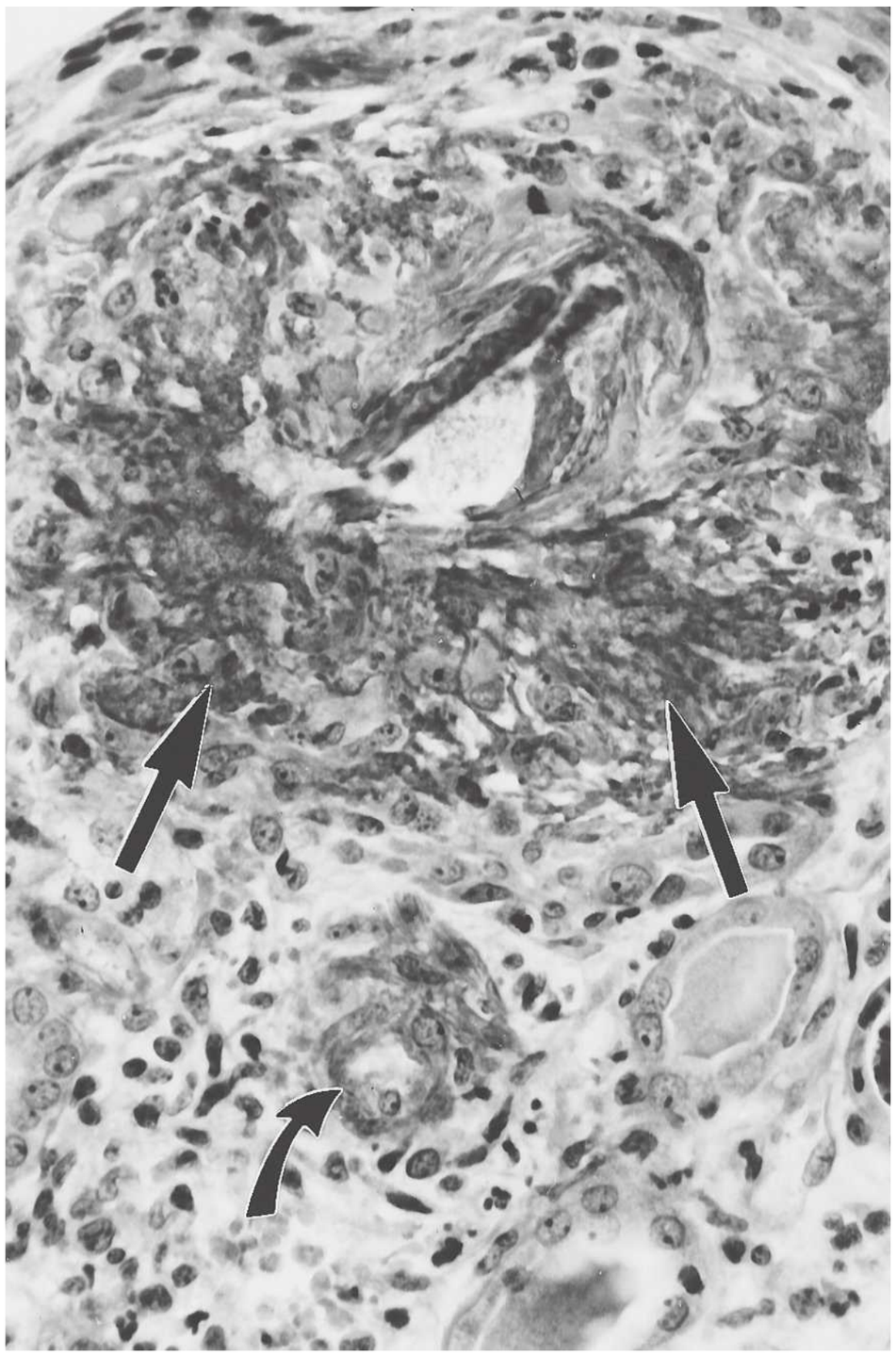

FIGURE 48.5 Necrotizing arteritis affecting an interlobular artery in a patient with microscopic polyangiitis. Note the extension of fibrinoid material into perivascular interstitium (*straight arrows*). Also note the necrotizing arteriolitis (*curved arrow*). (Masson trichrome, magnification ×350.)

TABLE **48.4** **Frequency of Immunopathologic Categories of Crescentic Glomerulonephritis in More Than 3,000 Consecutive Nontransplant Renal Biopsies Evaluated by Immunofluorescence Microscopy in the University of North Carolina Nephropathology Laboratory**

	Any Crescents (n = 540)	>50% Crescents (n = 195)	Arteritis in Biopsy (n = 37)
Immunohistology			
Pauci-immune (<2 positive immunoglobulin)	51% (277/540)	61% (118/195)[a]	84% (31/37)
Immune complex (≤2 positive immunoglobulin)	44% (238/540)	29% (56/195)	14% (5/37)[c]
Antiglomerular basement membrane	5% (25/540)[b]	11% (21/195)	3% (1/37)[d]

[a]Seventy of 77 patients tested for antineutrophilic cytoplasmic antibodies (ANCA) were positive (91%) (44 p-ANCA and 26 c-ANCA).
[b]Three of 19 patients tested for ANCA were positive (16%) (2 p-ANCA and 1 c-ANCA).
[c]Four patients had lupus and one poststreptococcal glomerulonephritis.
[d]This patient also had a p-ANCA (myeloperoxidase-ANCA).
From Jennette JC, Falk RJ. The pathology of vasculitis involving the kidney. Am J Kidney Dis. 1991;24:130, with permission.

The three major categories of systemic pauci-immune small-vessel vasculitis are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) (formerly Wegener granulomatosis), and eosinophilic granulomatosis (EGPA).[44,77] Table 48.2 and Figure 48.3 provide an approach for differentiating these three vasculitides and for distinguishing them from other types of vasculitis. These three systemic vasculitic processes along with pauci-immune necrotizing and crescentic glomerulonephritis (renal-limited disease) can be broadly referred to as ANCA disease.

It is important to note that the eponym Wegener granulomatosis has been abandoned due to the history linking Friedrich Wegener to the Nazi party and his participation in Nazi war crimes. The disease process formerly referred to as Wegener granulomatosis is now known as granulomatosis with polyangiitis or GPA.[78–80]

MPA, GPA, and EGPA share a histologically identical necrotizing vasculitis that can affect arteries (Fig. 48.5), arterioles (Fig. 48.6), venules (Fig. 48.7), and capillaries, especially glomerular capillaries (Fig. 48.8). At all of these sites, the acute lesion is characterized by segmental necrosis with mural and perivascular fibrinoid material, sometimes accompanied by thrombosis in the vascular lumen. The initial inflammatory infiltrate has conspicuous neutrophils, often undergoing leukocytoclasia (Fig. 48.7), but this usually transforms into a predominantly mononuclear leukocyte infiltrate within a few days. The glomerular lesion of pauci-immune ANCA vasculitis begins with segmental fibrinoid necrosis (Fig. 48.8) that quickly leads to crescent formation (Fig. 48.9). At the time of renal biopsy, approximately 90% of patients with pauci-immune crescentic glomerulonephritis have some degree of glomerular necrosis and crescent formation, although this may involve fewer than 50% of glomeruli. Arteritis, arteriolitis, and medullary angiitis are seen in less than 20% of renal biopsy specimens. Medullary angiitis can be severe enough to cause focal papillary necrosis.

In addition to the renal vasculitic lesions illustrated in Figures 48.5 to 48.9, patients with all three systemic pauci-immune ANCA vasculitides share histologically identical inflammatory vascular lesions in other tissues, such as pulmonary hemorrhagic alveolar capillaritis, dermal

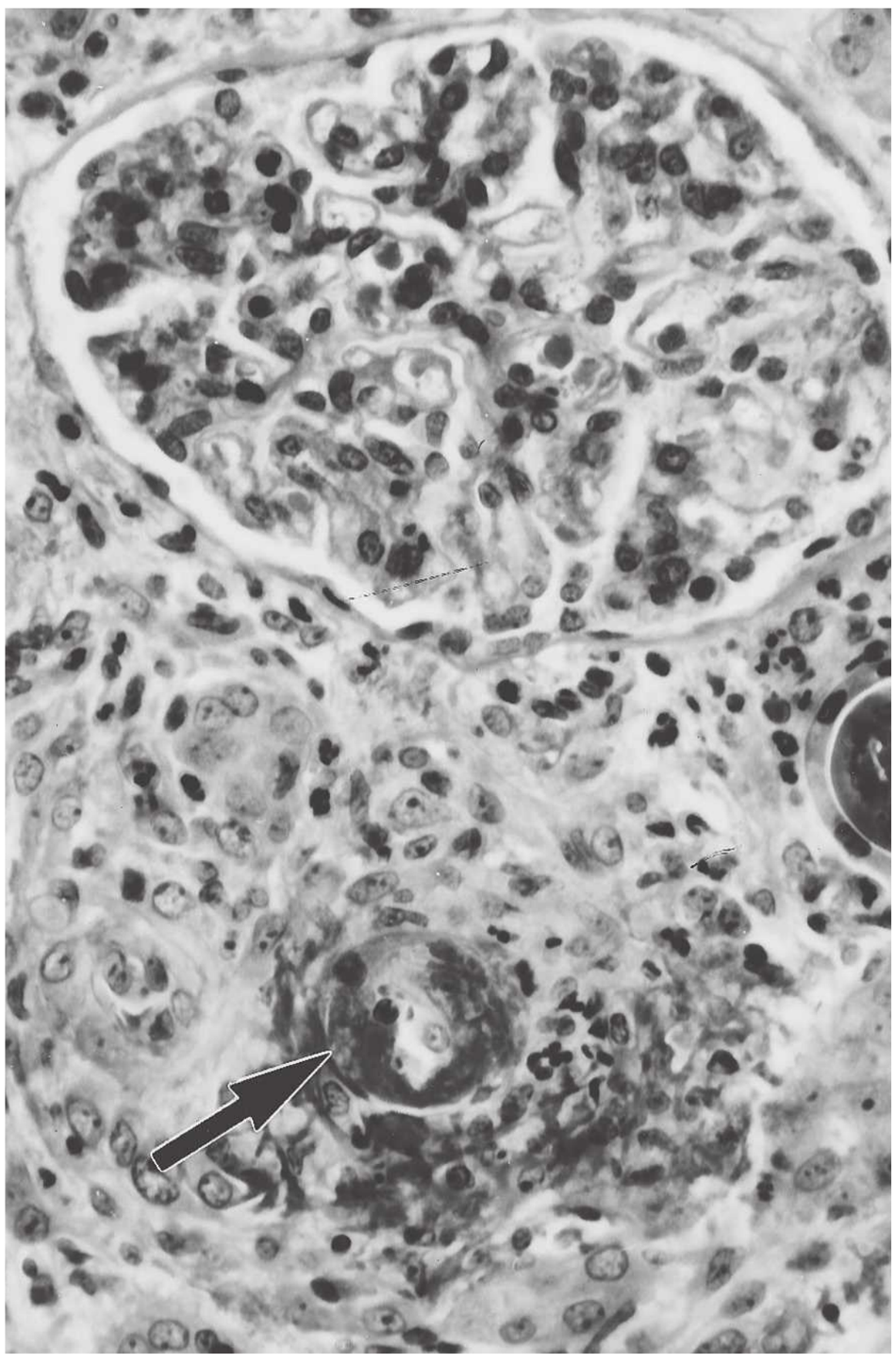

FIGURE 48.6 Necrotizing arteriolitis (*arrow*) affecting an arteriole in the renal cortex of a patient with microscopic polyangiitis. Note the fibrinoid material in the vessel wall and adjacent interstitium, and the focal perivascular leukocytoclasia. (Masson trichrome stain, magnification ×350.)

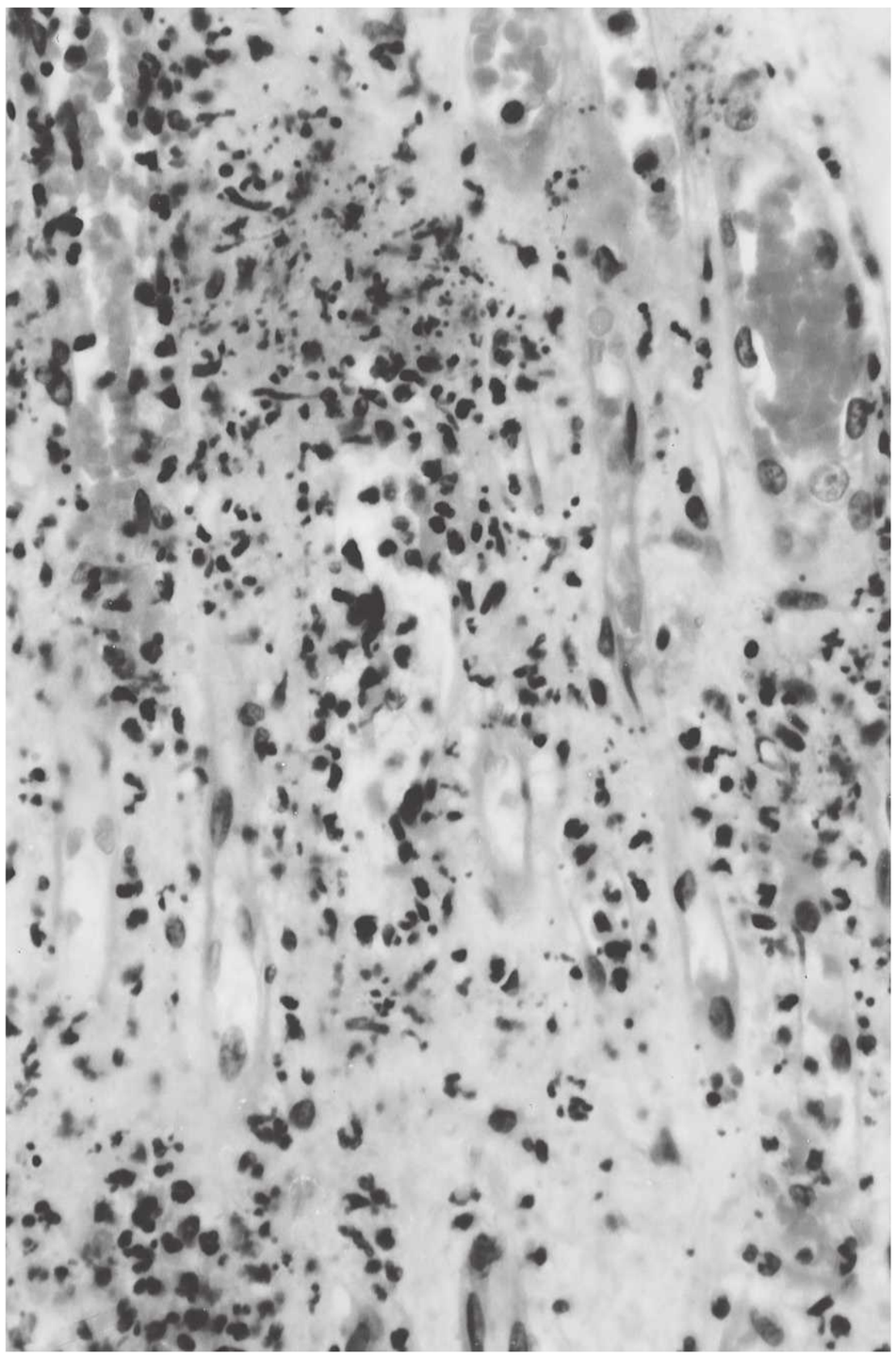

FIGURE 48.7 Leukocytoclastic medullary angiitis affecting the peritubular vasa recta in a patient with granulomatosis with polyangiitis. (Hematoxylin and eosin stain, magnification ×350.)

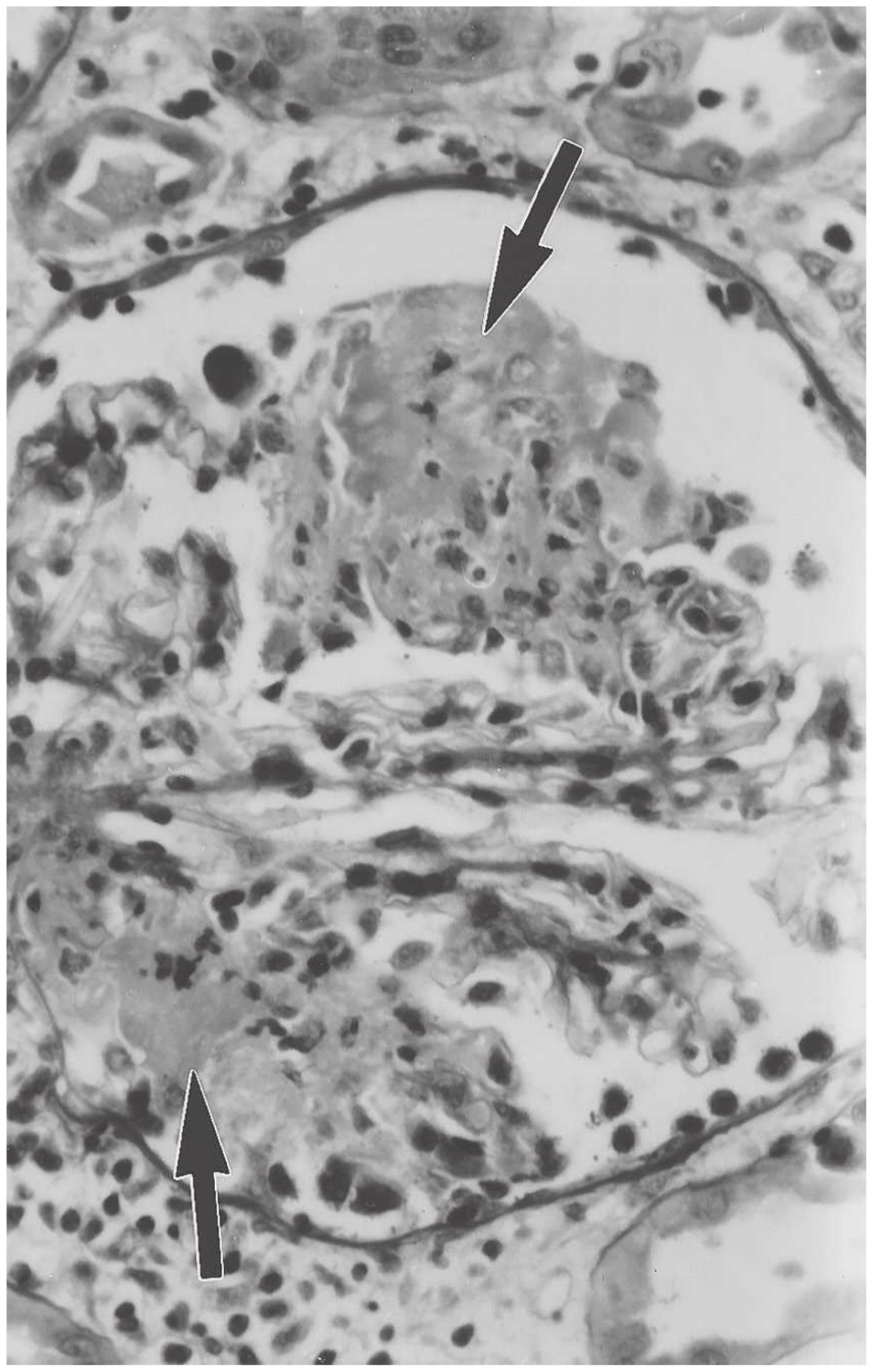

FIGURE 48.8 Segmental fibrinoid necrosis (*arrows*) in a glomerulus from a patient with microscopic polyangiitis. (Hematoxylin and eosin stain, magnification ×350.)

leukocytoclastic venulitis, and necrotizing inflammation of arteries in many tissues, including but not limited to peripheral nerves, skeletal muscle, gut, liver, pancreas, and skin. The diagnostic distinctions among the three diseases are not based on the pathologic or clinical features of vasculitis per se, but on the presence or absence of accompanying features, specifically granulomatous inflammation, asthma, and blood eosinophilia. As detailed in Table 48.2 and diagrammed in Figure 48.3, a diagnosis of MPA is warranted if a patient has systemic pauci-immune ANCA vasculitis with no evidence for necrotizing granulomatous inflammation or asthma. A diagnosis of GPA is warranted if a patient has systemic pauci-immune ANCA vasculitis with necrotizing granulomatous inflammation, usually in the upper or lower respiratory tract, and no asthma. A diagnosis of EGPA is warranted if a patient has systemic pauci-immune ANCA vasculitis with asthma and blood eosinophilia. Reaching these diagnostic conclusions does not necessarily require pathologic documentation of the lesions if reasonable clinical surrogates are identified. For example, in renal biopsy-proven pauci-immune necrotizing and crescentic glomerulonephritis, radiographic demonstration of cavitary lung nodules (in the absence of infection) or lytic bone lesions in the nasal septum are reasonable evidence for necrotizing granulomatous inflammation, warranting a diagnosis of GPA.

Serologic testing for ANCA is useful for making the diagnosis of pauci-immune ANCA vasculitis or renal-limited pauci-immune crescentic glomerulonephritis. As discussed in more detail in the "Laboratory Findings" section of this chapter, the major types of ANCA vasculitis are those that have specificity for proteinase 3 (PR3–ANCA) and for myeloperoxidase (MPO-ANCA).[46–49] In an indirect immunofluorescence microscopy assay, PR3–ANCA usually causes cytoplasmic staining of neutrophils (c-ANCA) and MPO-ANCA usually causes perinuclear staining (p-ANCA).

The clinical differential diagnosis of pauci-immune ANCA vasculitis also includes immune-complex ANCA vasculitis. Table 48.5 demonstrates significant overlap in organ system involvement among different types of pauci-immune ANCA vasculitis and immune-complex ANCA vasculitis. Upper or lower respiratory tract involvement has

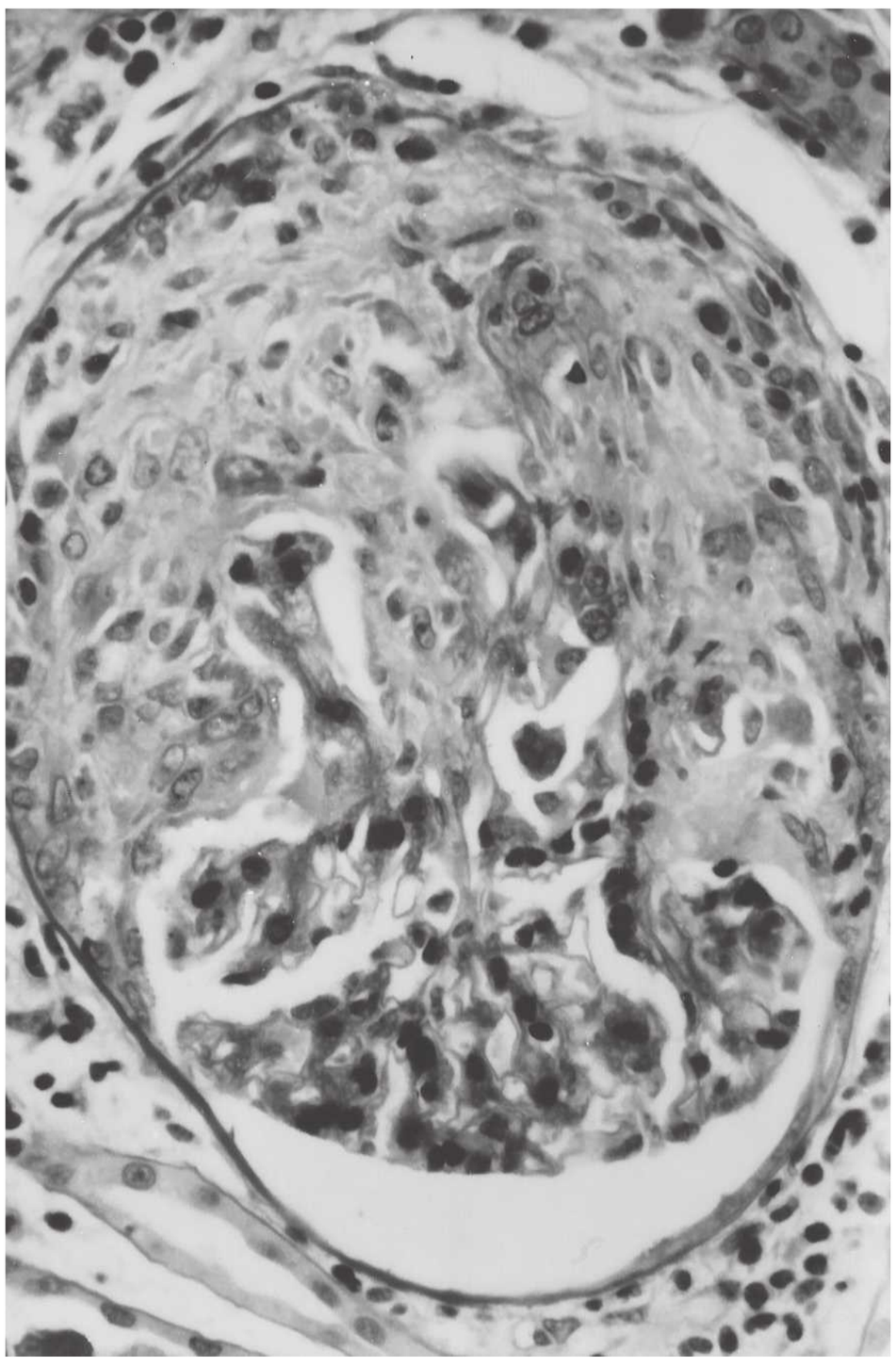

FIGURE 48.9 Cellular crescent in a glomerulus from a patient with microscopic polyangiitis. (Hematoxylin and eosin stain, magnification ×350.)

48.5 Comparison of Approximate Frequency of Manifestations of Microscopic Polyangiitis With Several Other Forms of Anca Vasculitis

	Microscopic Polyangiitis	Granulomatosis with Polyangiitis	Eosinophilic granulomatosis	Henoch-Schönlein	Cryoglobulin Vasculitis
Cutaneous	40%	40%	60%	90%	90%
Renal	90%	80%	45%	50%	55%
Pulmonary	50%	90%	70%	<5%	<5%
Ear, nose, and throat	35%	90%	50%	<5%	<5%
Musculoskeletal	60%	60%	50%	75%	70%
Neurologic	30%	50%	70%	10%	40%
Gastrointestinal	50%	50%	50%	60%	30%

From Jennette JC, Falk RJ. Small vessel vasculitis. N Engl J Med. 1997;337:1512, with permission.

the greatest discriminatory value because respiratory tract involvement is common with pauci-immune ANCA vasculitis and rare with immune-complex ANCA vasculitis. Table 48.6 and Figure 48.3 detail a number of observations that can be used to conclusively differentiate among MPA, GPA, EGPA, cryoglobulinemic vasculitis, and HSP. Direct immunofluorescence microscopy of vessels in biopsy specimens, such as glomerular capillaries or dermal venules, is useful because this demonstrates immunoglobulin A (IgA)-dominant vascular immunoglobulin deposits in HSP, IgG, and IgM deposits in cryoglobulinemic vasculitis, and little or no immunoglobulin in pauci-immune small-vessel vasculitis.

48.6 Features That Allow Differentiation of Microscopic Polyangiitis from Several Other Forms of Anca Vasculitis

	Henoch-Schönlein Purpura	Cryoglobulin Vasculitis	Microscopic Polyangiitis	Granulomatosis with Polyangiitis	Eosinophilic granulomatosis
Small-vessel vasculitis signs and symptoms[a]	+	+	+	+	+
IgA-dominant immune deposits	+	0	0	0	0
Cryoglobulins in blood and vessels	0	+	0	0	0
ANCA in blood	0	0	+	+	+
Necrotizing granulomas	0	0	0	+	+
Asthma and eosinophilia	0	0	0	0	+

[a]All of these small-vessel vasculitides can manifest any or all of the shared features of small-vessel vasculitides, such as purpura, nephritis, abdominal pain, peripheral neuropathy, myalgias, and arthralgias. Each is distinguished by the presence and just as importantly the absence of certain specific features.
From Jennette JC, Falk R. Small vessel vasculitis. N Engl J Med. 1997;337:1512, with permission.

Serologic testing also helps to focus the differential diagnosis, for example, testing for ANCA, anti-GBM, cryoglobulins, hepatitis C or B, antinuclear antibodies (ANA), and complement component levels.

In summary, the precise and accurate diagnosis of different categories of vasculitis, including ANCA vasculitis, requires the knowledgeable integration of clinical, laboratory, and pathologic data.

Demographics

ANCA vasculitis affects men and women equally. All ages are susceptible to disease, with a peak age of 74.[81] In the southeastern United States, approximately one third of all kidney biopsy patients are black. There appears to be a seasonal variation of the onset of disease, which most commonly occurs in the late fall and early spring.[82] It is possible that in northern latitudes, GPA predominates, whereas MPA is more common in southern climates.

Clinical Features

Renal Disease

The renal manifestations of ANCA vasculitis are several. Many, if not most, patients present with rapidly progressive glomerulonephritis with hematuria, proteinuria, and a rising serum creatinine over the course of days to weeks. This clinical presentation is associated with pathologic findings of glomerular necrosis and crescent formation. Invariably, interstitial inflammation results in interstitial fibrosis. At the other end of the spectrum are patients who present with much milder disease marked by isolated hematuria and low-grade proteinuria. On biopsy, these patients have focal areas of necrosis that result in areas of focal glomerulosclerosis. Persistent microscopic hematuria can be the harbinger of different renal outcomes. In some patients, persistent hematuria correlates with focal inflammation in the kidney that with additional inflammatory stimuli (e.g., infection and environmental exposure) transforms into an aggressive acute nephritis. The acute nephritic presentation is usually associated with renal insufficiency, hypertension, and biopsy findings of diffuse glomerular necrosis and crescent formation. In contrast, some patients with persistent microscopic hematuria without proteinuria have a clinically indolent disease that, in the absence of a renal biopsy, is ascribed to IgA nephropathy or thin basement membrane disease. Frequently, a renal biopsy is delayed until azotemia or significant proteinuria develops. By then, the biopsy reveals a picture of chronic glomerulonephritis with widespread glomerular sclerosis and only focal necrosis. Unfortunately in such cases, the persistent microscopic hematuria is a reflection of unrecognized, unchecked glomerular inflammation. The treatment of such patients must be evaluated on a case-by-case basis depending on the degree of scarring and renal insufficiency, as the risks of aggressive anti-inflammatory and immunosuppressive treatment may outweigh the potential benefits.

In the recently derived classification proposal for ANCA vasculitis, histopathologic renal disease was categorized based on percent of normal glomeruli, amount of cellular versus fibrous or sclerotic crescents, and degree of glomerulosclerosis.[7] Based on classifying the renal biopsy by these criteria, valuable information regarding renal outcome was validated. The information gained by this classification system may allow prediction of renal outcome based on biopsy and may eventually prove beneficial in making treatment decisions.

Proteinuria in ANCA vasculitis is usually due to glomerulosclerosis or severe necrotizing and crescentic glomerulonephritis. In most cases of acute nephritis or rapidly progressive glomerulonephritis, the amount of proteinuria is on the order of 500 to 3,000 mg per 24 hours. The mean 24-hour urine protein excretion of our patient population at presentation is only 800 mg per 24 hours. Certainly there are cases of nephrotic-range proteinuria typically associated with diffuse glomerulosclerosis.

Acute interstitial nephritis is an unusual expression of ANCA vasculitis. These patients generally present with pyuria and white blood cell casts without evidence of hematuria or proteinuria. In these cases, the glomeruli are completely spared, and inflamed vasa rectae are accountable for the clinical findings.

There are many examples of patients in whom ANCA vasculitis coexists with other forms of glomerular injury, the most common of these being anti-GBM disease. Typically patients with both ANCA and anti-GBM have vasculitis affecting vascular beds other than the kidney and the lung. Their clinical course is more consistent with an ANCA vasculitis than with anti-GBM disease. However, a retrospective analysis of patients with both ANCA vasculitis and anti-GBM suggests that these patients have more severe renal disease and a poorer prognosis than patients with ANCA alone,[83] although ANCA vasculitis patients have more frequent relapse. It is unclear whether patients with both antibodies and severe renal failure share the poor renal prognosis of dialysis-dependent patients with anti-GBM disease alone. Indeed, some patients may respond to treatment with a dialysis-free interval of months to years.

Similarly, there are patients with ANCA vasculitis and immune complex forms of glomerulonephritis (e.g., membranous glomerulopathy or IgA nephropathy). Typically, the renal biopsy reveals areas of crescent transformation or glomerular necrosis. The clinical finding of a sudden decrease in renal function and worsening of the hematuria herald this pathologic event. ANCA vasculitis may occur in patients with scleroderma, in whom the renal dysfunction is not attributable to a thrombotic microangiopathy, but to ANCA-induced necrosis and crescent formation.

As noted previously in this chapter, vessels larger than capillaries and venules are targets of inflammation. Small arteries, including the renal artery, can be injured. The most

common clinical consequence of this process is renal infarction resulting in flank pain and renal insufficiency. Persistent disease of the renal artery causes stenosis and poststenotic dilation, with the clinical presentation of renovascular hypertension. Renal arteriography is necessary to delineate the degree of renal artery disease. Angioplasty or surgical correction of the stenotic vessel is frequently curative.

Skin Disease

Because the most commonly affected vessels of ANCA vasculitis are capillaries and postcapillary venules, the typical skin lesion is palpable purpura. Lesions tend to occur in "crops," primarily on the lower extremities. With time, the lesions flatten and either disappear or leave small hyperpigmented areas. In addition to this classic dermal presentation, there are several other cutaneous lesions, including petechiae, ecchymosis, ulceration, nodules, plaque-like lesions, livido reticularis, and urticaria. Several cases of urticarial vasculitis have been observed in the absence of hypocomplementemia and immune-complex deposition. In unusual circumstances, vasculitic lesions give rise to erythema nodosum or pyoderma gangrenosum–like lesions. Biopsy of the affected area reveals a leukocytoclastic angiitis. However, in the case of nodular lesions, a simple punch biopsy may not provide sufficiently deep material to sample an involved vessel of larger caliber. A deep "excisional" biopsy is necessary.

The differential diagnosis of renal dermal vasculitic syndromes is important. In addition to the ANCA vasculitides, systemic lupus erythematosus (SLE), cryoglobulinemia, and HSP cause cutaneous vasculitides and renal disease. Each of these conditions is associated with a different natural history and treatment approach. For instance, many patients with HSP require only supportive care. If the renal dermal vasculitic syndrome is a consequence of ANCA vasculitis or lupus, immunosuppressive therapy is warranted. In addition, cutaneous vasculitis is frequently the consequence of a drug reaction. There are numerous classes of drugs that cause leukocytoclastic lesions, the most common being propylthiouracil, minocycline, phenytoin, and penicillamine.

Pulmonary Disease

The pulmonary consequences of ANCA vasculitis are numerous and involve not only the lung parenchyma, but also the respiratory tract from the subglottis to the alveolar sacs. Several clinical presentations are common. Patients with MPA typically present with pulmonary infiltrates that are frequently initially ascribed to an infectious process. Generally, these patients describe hemoptysis, although many patients have no overt evidence of pulmonary bleeding. In some cases, the infiltrates wax and wane spontaneously. Infiltrates may coalesce, resulting in dyspnea and hypoxemia. The most alarming consequence of pulmonary capillaritis is the development of massive pulmonary hemorrhage. In our series, the occurrence of pulmonary hemorrhage was the most powerful predictor of death.[84] As discussed later, the prompt institution of plasmapheresis substantially decreased the mortality rate when compared with conventional immunosuppressive treatments.

Necrotizing granulomatous inflammation is a hallmark of GPA. Focal necrotizing lesions progress to confluent areas of necrosis that when surrounded by palisading histocytes, are called "geographic necrosis."[85] Nodular lesions are of varying size, from those that can only be seen by spiral CT to those that occupy a complete lobe of the lung. In general, the larger lesions tend to cavitate. The differential diagnosis must include aspergillus or tuberculous infection, as well as other opportunistic infections. Determining whether the nodular and cavitary lesions are due to granulomatous infection or are a consequence of an opportunistic infection can present a difficult diagnostic dilemma. These two processes may coexist at times.

Similarly, recurrent alveolar hemorrhage in immunosuppressed patients may be attributable to infection. Alveolar lavage is useful in determining if alveolar hemorrhage is due to an infectious cause rather than a consequence of ANCA vasculitis alone. Bronchioalveolar lavage should be performed carefully considering the possible deterioration in oxygenation immediately after the procedure. Careful attention to the protection of airway patency is mandatory. Transbronchial biopsy of the lung in patients with these diseases often results in nondiagnostic results. Open lung biopsy may be required for diagnosing the cause of pulmonary nodules, granulomas, or cavitary lesions. In addition to the characteristic pulmonary nodules of GPA, endobronchial lesions, similar to those found in the subglottic region and trachea, can cause airway obstruction and may result in areas of collapsed lung. The lesions are usually quite sensitive to systemic glucocorticosteroid treatment.

EGPA is characterized by the presence of asthma and eosinophilia in the circulation and within tissues. The pulmonary infiltrates tend to result in diffuse alveolar involvement but nodules and cavitations also occur. Eosinophilic pneumonia of other causes can be indistinguishable from the pulmonary presentation of EGPA. Therefore, it is important to verify that a small-vessel vasculitis exists before determining that the patient has EGPA.

Patients with subglottic masses or stenosis present with stridor or a sense of breathlessness. Results of flow–volume loop study results are abnormal. These lesions necessitate emergent attention to avoid life-threatening critical airway narrowing. Direct laryngoscopy with fiberoptic instrumentation allows visualization of the lesion. Glucocorticoid treatment is usually effective, but surgical intervention may be necessary. Areas of tracheal and bronchial granulomatous lesions can occur throughout the respiratory tree and result in bronchial obstruction.

The long-term consequences of intermittent pulmonary capillaritis result in pulmonary fibrosis. In some individuals, the diagnosis of idiopathic pulmonary fibrosis prompts

consideration of ANCA vasculitis. Similarly, some patients with bronchiolitis obliterans with organizing pneumonia have had an underlying ANCA vasculitis.

Upper Respiratory Tract Disease

Vasculitis frequently affects the areas of the ear, nose, and throat. By far the most common localization occurs in the nose, especially in patients with GPA. Other areas of involvement include the nasopharynx, the paranasal sinuses, and within the larynx. With respect to the nose, persistent or repetitive episodes of rhinosinusitis are one of the first symptoms. Small ulcerations lead to a nasal discharge that becomes hemorrhagic. Once these lesions become inflamed, a thick purulent material oozes from bloody crusts covering much larger areas of ulceration and granulation tissue. Histologic evaluation of these tissues most commonly reveals nonspecific acute and chronic inflammation. With a good sample, one may find areas of fibrinoid necrosis or granulomatous inflammation. Focal areas of ischemia and infarction occur. Repetitive bouts of inflammation eventually lead to septal perforations, the loss of turbinates, and may result in a loss of support of the nasal bridge (saddle nose deformity of GPA). Even with treatment, the nasal mucosa becomes atrophic and crusty. The crusts cause epistaxis when patients sneeze or blow their nose. Staphylococcus aureus superinfections may be the root cause of these ulcerations and an important factor in their development. Topical treatment with antibacterial ointments or systemic treatment with antibiotics decreases nasal symptoms and limits the number of relapses.[86]

Sinusitis typically occurs with bloody nasal or postnasal discharge. Computed tomography may reveal bony erosions caused by granulomatous lesions typical of GPA. Necrotizing capillaritis associated with MPA or EGPA frequently causes necrotizing lesions in the sinuses as well but do not lead to bony erosions. Granulomatous inflammation that blocks the eustachian tubes leads to serous otitis media. Bacterial superinfections lead to infectious otitis media. Ventilating tubes placed in the tympanic membrane may lessen the problem. Facial nerve paralysis may occur as a result of entrapment of the nerve by granulomatous inflammation anywhere along the course of the nerve. Large granulomatous pseudotumors invade the orbit and may lead to loss of an eye.

Gastrointestinal Tract Disease

The gastrointestinal tract represents one of the least well-studied areas of involvement of ANCA vasculitis. In our experience, at least one third of patients with active necrotizing glomerulonephritis have abdominal complaints, either on presentation or at some point during the course of disease. One of the more common areas of vasculitic involvement is the gastric mucosa, causing nonhealing gastric or peptic ulcers. It is sometimes difficult to determine whether these ulcers are the consequence of vascular inflammation or glucocorticoid treatment. Endoscopic biopsy can provide a diagnosis, yet a presumptive diagnosis is made by a favorable response to glucocorticoid therapy. Similarly, pancreatitis, small bowel infarction, and ulcers throughout the gastrointestinal tract lead to abdominal pain. The most catastrophic of all abdominal vasculitic disease is transmural infarction of the bowel, leading to viscus perforation and polymicrobial sepsis. Prompt diagnosis and treatment is mandatory.

Autoimmune hepatitis and sclerosing cholangitis occur with p-ANCA that is not specific for MPO. The liver is usually not involved with necrotizing vasculitis.

Patients with ANCA vasculitis may have medium-sized artery involvement as well. Aneurysmal dilation and fibrinoid necrosis of mesenteric or renal arteries results in infarction of the affected organ. If a mesenteric artery is involved, infarctions cause substantial abdominal pain or an ischemic colitis. These patients require mesenteric arteriography to identify the areas of arterial involvement.

Neurologic Disease

Mononeuritis multiplex, or a pattern of multiple mononeuropathies, is caused by nerve impairment in anatomically separate regions. Most commonly, these areas of peripheral nerve ischemia are found in areas in the midthigh or mid upper arm, in watershed zones of poor vascular perfusion. Lesions of peripheral neuropathy occur abruptly and are very painful. The pain is described as a deep ache that is difficult to localize. Symptoms of the cutaneous distribution of the nerve occur several days after the onset of weakness and are described as a burning pain. Nerve biopsy should be performed in individuals with neuropathy as the major manifestation of vasculitis. A negative sural nerve biopsy result does not rule out the diagnosis. Repetitive biopsy of the nerve is almost useless. In a series of 200 patients with vasculitis and a neuropathy, only 27% had a vasculitis demonstrated in a muscular specimen only, 35% in a nerve only, and 27% in the nerve and the muscle.[87] Many patients develop distal peripheral sensory neuropathies. Whether these symptoms are a consequence of vasculitis, pharmaceutical treatment, or malnutrition is not clear.

The central nervous system is an uncommon locus for vasculitis disease. Vasculitis involving the central nervous system usually results in a headache,[88] without which the diagnosis is unlikely. Rarely, seizures are the presenting manifestation of central nervous system vasculitis. In GPA, meningeal disease can occur. Magnetic resonance imaging (MRI) with gadolinium infusion may reveal enhancing lesions in many separate foci. Most commonly, however, ANCA vasculitis affects vessels that are too small to produce a positive MRI scan. Cerebral angiography may reveal abnormalities in less than half of patients. If the patient has systemic hypertension, cerebrovascular disease from atherosclerosis, or renal insufficiency resulting in uremia, it may not be possible to ascertain the precise cause of central nervous system

symptoms. Treatment with antihypertensive agents and dialysis can exclude or decrease the possibility that hypertension and uremia are the cause of the symptoms. Many patients with ANCA vasculitis are older adults, and vasculitis may be impossible to differentiate from atherosclerosis in that population.

Other Organ System Diseases

Any organ system or capillary bed may be inflamed by small vessel vasculitis, resulting in numerous other clinical manifestations. Ocular manifestations of disease include iritis, uveitis, and peripheral keratitis. These lesions result in a red eye and are observed using a slit lamp by a qualified ophthalmologist.

Polychondritis may also present as a feature of disease presentation in small vessel vasculitis or as a hallmark symptom of disease relapse. There are patients who have erythema and severe tenderness of the ears that precedes signs of vasculitis in other organ systems.

Cardiac vasculitic disease results in subendocardial ischemia. The lesions can be difficult to see by using coronary arteriogram. Whether patients have coronary vascular disease as a consequence of atherosclerotic disease or of vasculitis is difficult to determine. In our population, 5% of patients had myocardial infarction at the time of their generalized disease process. Pericarditis is much less common in patients with ANCA vasculitis than in those with lupus vasculitis. A pericardial friction rub should raise the specter of a separate disease process.

In more than 90% of our patients, constitutional features are hallmarks of disease. Fatigue represents a ubiquitous finding that persists even after all of the other specific manifestations of vasculitis appear to be in remission. In addition, fever, unexplained weight loss, myalgias, and arthralgias are common. Arthralgias are frequently migratory in which joint pain occurs in one joint, only to resolve and appear in another joint at another time. Frank arthritis with synovial thickening occurs in at least 10% of patients.

Thrombosis in ANCA Disease

About 10% of patients with ANCA vasculitis have venous thromboembolic events (VTE).[89] In a retrospective analysis of a large cohort of patients with systemic vasculitis (n = 1130), the frequency of thrombotic events was 8% among patients with ANCA vasculitis compared with 2.5% among patients with polyarteritis nodosa.[90] Sixty-eight percent of VTE occurred within 3 months before or 6 months after the diagnosis of systemic vasculitis or a relapse, corresponding to a rate of 7.26 per 100 person-year during these periods compared to 1.84 per 100 person-year during follow-up (and presumably diminished disease activity). The frequency of VTE did not differ significantly among patients with GPA, MPA, or EGPA or between those with PR3- versus MPO-ANCA.

Investigation continues regarding the etiology and mechanism underlying the increased propensity for thromboembolic events in ANCA vasculitis. Results of anticardiolipin antibodies, anti-beta2-glycoprotein antibodies, factor V Leiden, prothrombin gene mutation, and methylenetetrahydrofolate reductase gene mutation measurements do not adequately explain the increased propensity for VTE in ANCA vasculitis.[91] Other factors may contribute to the increased propensity for thrombotic events among ANCA vasculitis patients. One such factor could be the presence of antiplasminogen antibodies detected in a subset of patients with PR3-ANCA.[90] In these patients, plasminogen was identified as a target of antibodies directed against complementary PR3 (cPR3), a recombinant protein translated from the antisense strand of PR3 cDNA. Functionally, antiplasminogen antibodies delayed the conversion of plasminogen to plasmin and increased the dissolution time of fibrin clots.[90] Antiplasminogen antibodies were detected in 5 of 9 patients (56%) with PR3-ANCA and a thrombotic event, compared with 5 of 57 (9%) patients with idiopathic thrombosis (P = 0.002). In an independent United Kingdom and Dutch cohort of patients with ANCA vasculitis, 24% and 26% of patients respectively had antiplasminogen antibodies compared with <1% of controls.[92] Antiplasminogen antibodies were present in both PR3 and MPO positive patients. Investigators also identified antitissue plasminogen activator antibodies in 18% of patients. These antitissue plasminogen activator antibodies were more commonly found in the population with antiplasminogen antibodies. Serum containing antiplasminogen antibodies and antitissue plasminogen activator antibodies appeared to be associated with retarded fibrinolysis in vitro. Presence of these antibodies was also correlated to fibrinoid necrosis and cellular crescents on kidney biopsy and consequently more severely reduced renal function.[92]

LABORATORY FINDINGS

Abnormal laboratory findings in patients with ANCA vasculitis include normochromic and normocytic anemia, mild to marked leukocytosis, and mild thrombocytosis. Eosinophilia is uncommon in patients with GPA and MPA but is required for the diagnosis of EGPA. Several markers of inflammation such as the C-reactive protein and the erythrocyte sedimentation rate are elevated, especially at times of disease exacerbation. Rheumatoid factor levels are positive in some individuals.

In the differential diagnosis of ANCA vasculitis, a number of other vasculitic syndromes can be excluded by serologic tests. These include tests for lupus, including ANA, anti–double-stranded DNA (dsDNA) antibodies, serum complement levels, and cryoglobulins. Rarely, a patient may have an overlap syndrome of SLE and ANCA vasculitis, with positive ANA, anti-dsDNA, and usually anti-MPO antibodies. Unlike with polyarteritis nodosa, screening for infectious diseases usually yields negative results, including assays for hepatitis B and hepatitis C. Anti-GBM antibodies should be measured at least once in the

differential diagnosis of crescentic glomerulonephritis. Tests for circulating immune complexes are not reliable.

The laboratory findings in patients with EGPA include eosinophilia in all patients. The degree of eosinophilia may reach 50% of the total leukocyte count. Elevated serum IgE levels and IgA containing immune complexes are found in some patients.[93]

ANCA Serologic Studies

Since Richard Davies reported eight patients with antibodies to neutrophils associated with necrotizing glomerulonephritis,[94] substantial advances have been made in the serologic analysis of ANCA. ANCA reacts not only to neutrophils, but also to monocytes. Effective ANCA testing must use both indirect immunofluorescent microscopy in conjunction with antigen-specific tests using highly purified MPO and PR3 antigens.[46–49] Indirect immunofluorescent microscopy has elucidated two different ANCA patterns. On ethanol-fixed human neutrophils, cytoplasmic ANCA (c-ANCA) result in diffuse immunofluorescent staining of the cytoplasm. In contrast, perinuclear ANCA (p-ANCA) stain the periphery of the nucleus using ethanol-fixed cells but have a cytoplasmic pattern when using formalin-fixed leukocytes. Most c-ANCA react with PR3, a serine proteinase found within the primary granule of neutrophils and monocytes. This serine proteinase has substantial homology with elastase and cathepsin G. Some c-ANCA (less than 10%) react with bacterial/permeability increasing protein. This pattern of reactivity is found mainly in patients with cystic fibrosis and inflammatory bowel disease.[95]

p-ANCA react with MPO in more than 90% of cases. MPO is a member of a multichain peroxidase family that also includes thyroperoxidase, eosinophil peroxidase, and lactoperoxidase. Many if not most of the p-ANCA found in diseases other than pauci-immune necrotizing glomerulonephritis and ANCA vasculitis do not react with MPO, such as in ulcerative colitis, primary sclerosing cholangitis, and Felty syndrome. The most confusing situation occurs in patients with lupus erythematosus. In these patients, p-ANCA are usually attributable to ANA, although in some rare cases, antilactoferrin and antielastase antibodies are found. Patients with lupus may have a false-positive anti-MPO test result by enzyme-linked immunosorbent assay (ELISA).[96]

The antigen specificity of circulating ANCA is not diagnostic for a particular clinicopathologic variant of ANCA vasculitis, although there are differences in the relative frequency of PR3-ANCA and MPO-ANCA in different types of pauci-immune small-vessel vasculitis (Table 48.7). For example, most patients with GPA have PR3-ANCA (c-ANCA), whereas most patients with renal-limited pauci-immune crescentic glomerulonephritis have MPO-ANCA (p-ANCA).

A positive ANCA result in a patient with strong clinical evidence for crescentic glomerulonephritis or another manifestation of ANCA vasculitis, such as purpura or pulmonary hemorrhage, has a high positive predictive value. A positive ANCA result in a patient with weak evidence for crescentic glomerulonephritis or ANCA vasculitis, such as isolated hematuria and proteinuria with normal renal function, has a much lower positive predictive value (Table 48.8). However, in a patient with weak clinical evidence for crescentic glomerulonephritis or ANCA vasculitis, a positive result increases the likelihood to a level that requires expeditious additional diagnostic evaluation, possibly including a renal biopsy, to confirm or refute the presence of a pauci-immune ANCA vasculitis or crescentic glomerulonephritis. It is important to note, however, that in serum from the Department of Defence Serum Repository on patients who developed GPA, with years of serum collected preceding disease manifestation, PR3 was noted to be significantly elevated up to 1.5 years prior to GPA diagnosis. Stable detectable PR3 is significantly associated with future incidence of GPA.[97] A negative ANCA result is more effective at ruling out pauci-immune crescentic glomerulonephritis in a patient with weak clinical evidence of ANCA vasculitis than in a patient with strong clinical evidence for small-vessel vasculitis (Table 48.8). Approximately

48.7 Approximate Frequency of Antineutrophil Cytoplasmic Antibodies (ANCAs) with Specificity for Proteinase 3 (PR3-ANCA, c-ANCA) or Myeloperoxidase (MPO-ANCA, p-ANCA) in Patients with Active Untreated Microscopic Polyangiitis, Granulomatosis with Polyangiitis, and Eosinophilic granulomatosis

	Microscopic Polyangiitis	Granulomatosis with Polyangiitis	Eosinophilic granulomatosis	Renal-limited Vasculitis[a]
PR3-ANCA c-ANCA	40%	75%	10%	20%
MPO-ANCA p-ANCA	50%	20%	60%	70%
Negative ANCA	10%	5%	30%	10%

[a]Renal-limited vasculitis refers to pauci-immune necrotizing and crescentic glomerulonephritis with no apparent extrarenal vasculitis.

48.8 Predictive Value of Combined Indirect Fluorescent Antibody and Enzyme Immunoassay Antineutrophil Cytoplasmic Antibody Testing for Pauci-immune Crescentic Glomerulonephritis[a]

Adult with	Prevalence Pretest Likelihood	Positive predictive Value Post-test Likelihood	Negative Predictive Value Post-test Unlikelihood
RPGN	47%	95%	85%
Hematuria, proteinuria (creatinine >3 mg/dL)	21%	84%	95%
Hematuria, proteinuria (creatinine 1.5–3 mg/dL)	7%	60%	99%
Hematuria, proteinuria (creatinine <1.5 mg/dL)	2%	29%	100%

[a]Data derived from an analysis of 2,315 patients, with ANCA assay sensitivity 81% and specificity 96%.
RPGN, rapidly progressing glomerulonephritis.
From Lim LC, Taylor JG III, Schmitz JL, et al. Diagnostic usefulness of antineutrophil cytoplasmic autoantibody serology. Comparative evaluation of commercial indirect fluorescent antibody (IFA) kits and enzyme immunoassay (EIA) kits. Am J Clin Pathol. 1999;111(3):363, with permission.

10% of individuals who present with pauci-immune necrotizing and crescentic vasculitis with or without systemic vasculitis will have negative serologies for ANCA. It is not clear how these individuals differ from those who present with ANCA-positive vasculitis. The clinical presentation of this group of ANCA-negative individuals is not distinct from ANCA-positive vasculitis and there is currently no difference in the approach of managing these two groups. Therefore, ANCA-negative individuals are broadly lumped into ANCA vasculitis until further study on this group mandates alterations on this course.

The ANCA result is typically negative in patients with polyarteritis nodosa, Takayasu arteritis, or giant cell arteritis. Some individuals have an overlapping disease with vasculitic involvement not only of large vessels, but also of small arteries. These patients have either PR3- or MPO-ANCA.

PATHOGENESIS

There has been an explosion of knowledge pertaining to the pathogenesis of ANCA vasculitis and pauci-immune necrotizing glomerulonephritis, but much still remains to be discovered. Although GPA, MPA, and EGPA share the hallmark of pauci-immune necrotizing ANCA vasculitis, each presents phenotypic differences. Further study into the causes of the granulomatous lesions of GPA or the stimulation of the eosinophilia and asthma in EGPA continue. Furthermore, the severity of disease varies from one patient to another. Investigations continue to evaluate the host factors that produce minimal disease in some patients and severe disease in others. Intriguing also is the observation that whereas vasculitis affects many capillary beds (e.g., kidney, skin, or lung) in some patients, it is limited to one organ in others. In many instances, the disease processes are focal. For example, only a segment of a capillary bed is affected, leaving an adjacent segment spared. This is exemplified by the observation that a segmental necrotizing lesion in a glomerulus may sit adjacent to an ostensibly normal glomerular segment.

Substantial in vitro and in vivo data suggest that ANCA play a pivotal role in the pathogenesis of pauci-immune vasculitis and glomerulonephritis.[45,89,98] ANCA are found in 85% to 90% of patients with pauci-immune glomerulonephritis and ANCA vasculitis. There is an absence of evidence for clearly delineated pathogenic mechanisms, such as immune-complex disease or direct antibody attack–mediated disease. ANCA titers tend to correlate with disease activity in some patients, although there is a paucity of evidence that ANCA titers can reliably predict disease severity or relapse. There is a clear description of transplacental transfer of MPO-ANCA from a mother with active MPA during pregnancy resulting in a pulmonary-renal vasculitic syndrome in the newborn infant.[99,100] In some human cases of a drug-induced ANCA vasculitis, cessation of the offending agent is associated with remission of small-vessel vasculitis and diminution of ANCA titers. In drug-induced ANCA vasculitis, there have been reports that the specificity is to human neutrophil elastase (HNE) ANCA. HNE belongs to the chymotrypsin family of serine proteases. HNE ANCA has been described in relation to cocaine-induced ANCA and ANCA related to antithyroid drugs.[101,102]

A number of laboratories have confirmed that ANCA induce neutrophil and monocyte activation using various methods. ANCA participate in the pathogenesis of vasculitis by interaction with MPO or PR3 that have translocated to the surface of the neutrophil or monocyte. Membrane-bound MPO/PR3 is expressed constitutively by neutrophils,[103]

and this translocation is stimulated by low concentrations of TNFα and interleukin-γ and other cytokines.[104] Patients with ANCA vasculitis aberrantly express PR3 and MPO genes through epigenetic mechanisms, and this expression correlates with disease activity.[105–107] Interestingly, although the MPO and PR3 genes are on different chromosomes, message from both of these genes is coordinately increased, suggesting a similar, but unrecognized, transcription factor that may be regulating the production of many granular constituents.[106]

ANCA binding to MPO or PR3 induce premature respiratory burst in polymorphonuclear leukocytes and degranulation of primary and secondary granules[90,108–110] at the time of their margination and diapedesis. This process leads to the release of lytic enzymes and toxic oxygen metabolites at the site of the vessel wall, causing endothelial cell damage[111] and necrotizing inflammatory injury.

Neutrophils and monocytes are activated by two coordinated and separate signal transduction pathways. Previous controversy abounded as to whether ANCA activation of neutrophils and monocytes occurred by the Fc receptor alone or whether there was F(ab′)2 stimulation.[112] Human neutrophils constitutively express receptors for IgG, including FcRIIa and FcRIIIb. The former is a widely expressed receptor, whereas the latter is a low-affinity receptor with expression that is restricted to neutrophils and eosinophils.[113] Engagement of the Fc receptor results in a number of neutrophil-activation events, including respiratory burst, degranulation, phagocytosis, cytokine production, and upregulation of adhesion molecules.[111,112] Fc receptors are likewise engaged in the activation of neutrophils and monocytes by ANCA.[111,114] Polymorphisms of the Fc receptors could play an important role in the development of ANCA vasculitis. Whereas the FcRIIa single nucleotide polymorphisms appear unimportant,[115] evidence suggests that the FcRIIIb polymorphism may influence disease severity.[116] In addition to Fc receptor–induced activation, there are substantial data that the $F(ab')_2$ portion of the antibody molecule also plays a role in leukocyte activation. ANCA $F(ab')_2$ not only induce oxygen radical production,[112] but also induce the transcription of cytokine genes in normal human neutrophils and monocytes. Some genes are upregulated by both whole ANCA immunoglobulin and ANCA $F(ab')_2$, whereas other genes are upregulated by only one or the other.[116] It is most likely that $F(ab')_2$ portions of ANCA are capable of low-level neutrophil and monocyte activation.[112] The Fc portion of the molecule almost certainly causes leukocyte activation once the $F(ab')_2$ portion of the immunoglobulin has interacted with the antigen, either on the cell surface or in the microenvironment.[111] The signal transduction pathways of F(ab′)2 and Fc receptor activation have been nicely elucidated. Both of these possible activation pathways appear to activate a specific p21ras (Kristen-ras) through separate but coordinated pathways.[117] This important observation may provide a focus for a therapeutic target.

PR3 and MPO released from neutrophils and monocytes enter endothelial cells and cause cell damage. PR3 entry into the endothelial cells induces apoptosis via production of IL-8 and chemoattractant protein-1.[118–120] Likewise, MPO has been shown to be internalized into endothelial cells by an energy-dependent process,[121] and to transcytose intact endothelium to localize within the extracellular matrix. There, in the presence of the substrates H_2O_2 and NO_2^-, MPO catalyzes nitration of tyrosine residues on extracellular matrix proteins,[122] resulting in the fragmentation of extracellular matrix protein.[122,123] Evidence now supports endothelial cell injury by ANCA-activated neutrophils being mediated by serine proteases (PR3, elastase) instead of superoxide generation.[124]

There have been a number of in vitro models of ANCA neutrophil and endothelial cell interactions using flow models and intravital microscopy. With treatment using TNF, endothelial cells capture neutrophils from the circulation. With the addition of ANCA over these rolling neutrophils, a more substantial adhesion of leukocytes to endothelial cells and transmigration of leukocytes occur. This occurs through a conformational change on CD11b that reveals an activation epitope.[125]

The Role of T Cells

There is mounting evidence implicating T cells in the pathogenesis of ANCA vasculitis. It has long been known that there are circulating T cells in patients with ANCA vasculitis that have a Th1-type cytokine profile and are in a persistent state of activation. It has been difficult to demonstrate that circulating T cells derived from affected patients are activated by the ANCA target antigens. The predominance of IgG1 and IgG4 subclasses of ANCA denotes the effects of T-cell help and IL-4 on isotype switching.[126] Furthermore, in patients with ANCA glomerulonephritis, the concentrations of soluble IL-2 receptor, which is a marker of T-cell activation, neopterin, and soluble CD30 correlate well with disease activity.[127,128]

Memory T cell populations increase and naïve T cells are decreased.[129,130] T cells are found within granulomas and active vasculitic lesions in ANCA vasculitis.[131–133] Analysis of the profile of cytokine secretion by T cells derived from tissue with granulomatous inflammation (nasal mucosa or bronchiolar lavage fluid) as well as from peripheral blood T cells revealed a T-helper 1 (T_H1) pattern of cytokines.[134] This is corroborated by the finding that T cells from patients with GPA have a decreased expression of CD28 as compared to healthy controls.[135] CD28 costimulation promotes the production of T_H2 cytokines.[136] Conversely, a recent study looking at the cytokine profile of T cells from patients with ANCA vasculitis in complete remission and receiving no immunosuppressants revealed a T_H2 cytokine profile with elevated production of IL-6 and IL-10 and low production of interferon gamma (IFN-γ).[137] These differences in the detected cytokine profiles could be due to the state of disease activity. A subset of CD134+, GITR+ (glucocorticoid-induced

TNF-receptor-related protein) effecter memory T cells have been shown to be in greatly increased numbers in patients with GPA.[138] These cells were noted in active vasculitic lesions and are powerful immune cells that initiate and sustain immune responses.[139] Interestingly, effecter memory T cells have been noted in urine suggesting T cell migration to sites of active vasculitic lesions with disease activity.[140] T cells and monocytes are the predominant cell types in inflammatory vascular and perivascular lymphoid infiltrates in ANCA vasculitis.[133] Areas of lymphoid neogenesis or tertiary lymphoid organs are described in states of chronic inflammation[141] that resemble the structure of secondary lymphoid organs consisting of B cell follicles with a surrounding mantle zone of T cells and dendritic cells. T cells are activated via antigen presentation within these areas of lymphoid neogenesis. It is postulated that tissue-specific autoantigens are presented in these tertiary lymphoid organs[139,141] and due to lack of organized lymph flow and antigen-presenting cell trafficking (which are found in secondary lymphoid organs) antigens, antigen-presenting cells, and lymphocytes bathe in a persistent milieu of activation and autoimmunity. Granulomas are thought to be a form of these areas of lymphoid neogenesis or tertiary lymphoid organs.[132,142] PR3 within granulomas leads to TH1 activation via dendritic cells.[143,144] Speculation is that production of ANCA occurs in these areas of granulomas where affinity maturation of B cells is taking place.[139,142] Although granulomas are not commonly found in the kidney biopsies of patients with ANCA vasculitis, some form of lymphoid neogenesis has been noted.[138,145,146]

IL-17, produced by Th17 effecter T cells, stimulates activation and migration of neutrophils via secretion of TNF-α and IL-1β.[147] PR3 reactive Th17 cells have been shown to be expanded in patients in remission from GPA.[148,149] IL-17 is also produced via CD45RC T helper cells in ANCA vasculitis.[150] Migration of neutrophils via these factors may be an important factor in the pathogenesis of ANCA vasculitis.

Regulatory T cells that limit immune response may be dysfunctional in ANCA vasculitis.[151] Defects noted in regulatory T cells include failure to inhibit proliferation or cytokine production of effector T cells.[152,153] Dysfunctional regulatory T cells may be linked to effector memory T cell expansion and persistent T cell activation. One study has shown an increase in FoxP3+ regulatory T cells in patients in remission from ANCA vasculitis, although this finding was not noted by other investigators.[129,154]

In vitro analyses of peripheral blood T cell proliferation in response to MPO and PR3 yielded conflicting results. Studies have shown little or no difference in T-cell reactivity to PR3 between patients with ANCA vasculitis and controls.[155,156] In the largest study looking at T cell proliferative responses in 45 patients at various stages of disease (with and without treatment), PR3 responses were seen at all stages of disease activity, and to a lesser degree in healthy controls.[157] Interestingly, T cells from only two patients with PR3-ANCA, and none of the controls, proliferated in response to MPO.

Neutrophil Extracellular Traps

Recently, neutrophil extracellular traps (NETs) were reported to be present in kidney tissue affected by ANCA vasculitis.[158] Neutrophils release NETs, which are decondensed chromatin fibers containing PR3, MPO, elsastase, LL-37, and other cytoplasmic proteins. The function of NETs is entrapment and destruction of microbes.[159] With respect to autoimmunity, it is important to note that in ANCA vasculitis, LL-37 present in NETs can modify trapped DNA leading to activated dendritic cells and B cells via toll-like receptor sensing pathways.[160] Neutrophil release of NETs in ANCA vasculitis leads to IFN-α-stimulated plasmacytoid dendritic cells in the kidney.[158] It has been postulated that IFN-α may impair regulatory T cells thus promoting further inflammation.[161] Triggering of Toll-like receptors has also been postulated to lead to local B cell maturation and autoantibody production.[162]

Role of *Staphylococcus aureus* and Superantigens

Clinical studies reveal that 60% to 70% of patients with GPA have a chronic nasal carriage of S. aureus[86] that is associated with an eightfold increased rate of relapse.[163] Importantly, in a placebo-controlled randomized trial, patients with nasal carriage of S. aureus treated with trimethoprim-sulfamethoxazole had a significantly lower rate of relapse of the nasal or upper respiratory tract disease. S. aureus superantigens are most likely implicated in disease activity. For instance, patients with superantigen-positive S. aureus strains are more likely to have a relapse of disease than carriers of superantigen-negative strains.[164] The staphylococcal acid phosphatase appears to bind to the endothelium as a consequence of its cationic nature and is recognized by the sera of patients with GPA.[164] In addition, Brown-Norway rats immunized with staphylococcal acid phosphatase and then perfused with this same protein developed severe crescentic glomerulonephritis.[165]

Environmental Factors (Including Infections)

The first report of ANCA was an association in eight patients with necrotizing glomerulonephritis and arbovirus infection with the Ross River virus.[88] Several animal models suggest an association of arteritis and infection. For instance, parvovirus B19 is associated with a vasculopathy not only in humans, but also in the Aleutian mink.[166] These animals develop a chronic parvovirus illness that results in immune complex–mediated vasculitis. There are several animal models of infection-mediated vasculitis in which there may be direct invasion of the vascular wall.

Environmental factors, particularly exposure to silica dust and other silica-containing compounds, may increase the risk of developing a number of different autoimmune diseases including scleroderma, rheumatoid arthritis, systemic sclerosis, SLE, and vasculitis.[167] Early data were derived from studies that primarily evaluated cohorts of

workers in occupations with high exposure to silica dust. This type of study is not ideal for assessing rare outcomes, such as autoimmune diseases. Case-control studies of specific autoimmune disorders have offered more insight into diseases potentially associated with silica dust exposure. Previous case-control studies have shown an association between ANCA vasculitides and exposure to silica dust or other silica-containing compounds[168,169] with odds ratios ranging from 4.4 to 14.0. More recently, a case-control study reported an association between primary systemic vasculitis and farming activities and exposure to occupational solvents, but the association with exposure to silica could not be ascertained.[170] In a study involving 129 patients with ANCA vasculitis with glomerulonephritis and 109 matched controls, only prolonged silica exposure (>23 years) was statistically significantly more common among patients than controls. There was no difference between the two groups in exposure to silica of shorter duration.[171] In contrast, exposure to silica dust was not associated with the development of lupus nephritis, in contrast to reports from occupational cohorts.[169,172,173]

Many drugs can induce vasculitis. In fact, 10% to 20% of cutaneous reactions to drug exposure are vasculitic in nature. A list of the most frequently implicated drugs includes anticonvulsants, antibiotics, penicillamine, hydralazine, nonsteroidal anti-inflammatory drugs, and propylthiouracil.[174] One of the drugs most commonly related to the development of anti-MPO–induced disease is propylthiouracil.[174] The story on cocaine is an interesting one. In 11 patients positive for MPO or PR3 ANCA with a history of cocaine use 5 patients were positive for both MPO and PR3, 8 had vasculitic rash, and 3 had renal disease involvement.[175] The hypothesis is that cocaine itself may not be the vasculitis promoting agent but in fact levamisole (an agent previously used for chemotherapy and for antihelminthic properties) that has recently been used for cutting cocaine may be associated with inducing ANCA vasculitis. This will need to be further investigated before definitive conclusions can be made.

Animal Models

There are now excellent animal models of ANCA vasculitis. The most direct evidence of the pathogenic role of anti-MPO antibodies stems from a model of transfer of either splenocytes or anti-MPO antibodies into Rag 2−/− mice.[176] In this model, MPO knockout mice (MPO−/−) were immunized with purified mouse MPO, and developed mouse anti-mouse-MPO antibodies. When splenocytes from these mice were transferred into Rag 2−/− mice, which lack functioning T and B cells, these animals developed a systemic necrotizing vasculitis and severe necrotizing and crescentic glomerulonephritis. When anti-MPO antibodies derived from immunized MPO knockout mice were transferred into Rag 2−/− mice, a pauci-immune necrotizing and crescentic glomerulonephritis was induced. This disease process occurred without antigen-driven T cells. Several follow-up studies have now been performed using this mouse model. In particular, the disease process was aggravated by the administration of lipopolysaccharide (LPS) into recipient mice by increasing the percentage of glomeruli involved with necrotizing and crescentic glomerulonephritis when anti-MPO antibodies were transferred into these mice.[177] The role of neutrophils in this response was highlighted by the abrogation of disease when the neutrophils of anti-MPO recipient mice were depleted by a selective antineutrophil monoclonal antibody (NIMP-R14).[178]

The pathogenic role of anti-MPO antibodies is also documented in a second animal model.[179] In this model, rats immunized with human MPO developed anti-rat-MPO antibodies. These animals then developed a necrotizing and crescentic glomerulonephritis, as well as pulmonary capillaritis. Microscopy of superior mesenteric vessels demonstrated that when a chemokine was applied to the vessel, the anti-MPO antibodies induced adherence and margination of leukocytes to the vessel wall. These two animal models document that anti-MPO antibodies are capable of causing a necrotizing and crescentic glomerulonephritis and a widespread systemic vasculitis, and also demonstrate that cytokines and chemokines exacerbate the injury in a manner that mimics the in vitro studies of ANCA-induced leukocyte activation.

A model of anti-PR3-induced vascular injury was developed in which a perivascular infiltrate was observed around cutaneous vessels in the setting of anti-PR3 antibodies and cytokine exposure.[89,180] Vasculitis and severe segmental and necrotizing glomerulonephritis was noted in nonobese diabetic mice with severe combined immunodeficiency given splenocytes from mice immunized with recombinant mouse PR3.[181] In summary, these animal studies document that both anti-MPO and proteinase-3 antibodies are capable of causing disease.

In immune-incompetent Rag′2 mice that developed ANCA vasculitis from the transfer of splenocytes of MPO knockout mice immunized with murine MPO, a previously unsuspected role of complement activation was demonstrated. Glomerulonephritis and vasculitis were completely blocked by complement depletion with cobra venom factor.[182] In this model, ANCA vasculitis failed to develop in mice deficient for complement factors C5 and B, whereas C4-deficient mice developed disease comparable with wild-type mice.[182] These results indicate that the alternative complement pathway (but not the classic or lectin pathways) is required for disease induction. Furthermore, the glomerulonephritis is completely abrogated or markedly ameliorated by treating the mice with a C5-inhibiting monoclonal antibody.[183] These results are corroborated by in vitro experiments that demonstrate that blockade of the C5a receptor on human neutrophils abrogated their stimulation.[184] In aggregate, results suggest an important role of complement activation in the pathogenesis of ANCA vasculitis; however, their relevance to disease in humans remains to be established.

The mannose receptor was highlighted by Chavele et al. as essential for producing crescentic glomerulonephritis

in the mouse model of nephrotoxic nephritis.[185] The mannose receptor is a pattern recognition receptor present on alternatively activated macrophages (macrophages that appear to have a reparative function rather than a proinflammatory phenotype). In normal murine kidney, the mannose receptor is present primarily on mesangial cells. The mannose receptor is a lectin scavenger receptor with a role in clearance of endogenous material. This receptor binds to myeloperoxidase, collagen IV, and glycosylated immunoglobulins and has a role in Fc-mediated responses. Mannose receptor-deficient mice who displayed normal antibody and T cell function were protected from crescentic glomerulonephritis via mesangial cell apoptosis, diminishment of Fc-mediated responses, and generation of anti-inflammatory macrophages. The implications of these findings may eventually lead to targeted therapy that preserves adaptive immune responses.

Theories of Autoimmunity: Why Do Patients Make ANCA?

For all autoimmune diseases, the critical question is whether the most proximate cause is the formation of the autoantibody or the abnormal T cell clone. There have been a number of theories that may provide a basis for the alteration of self-antigens, the most plausible of which is known as the theory of molecular mimicry.[186] This theory suggests that there is an immune response directed against a microbial antigen that mimics the amino acid sequence or structure of a self-protein. To date, it has been difficult to demonstrate this theory in human autoimmune disease. A serendipitous finding in ANCA vasculitis has spawned a theory of autoantigen complementarity. Although the details of this theory and the proof that it may pertain to ANCA vasculitis is beyond the scope of this chapter, a brief description of this observation is germane for the understanding of ANCA vasculitis (Fig. 48.10).[187,188]

It has been known for decades that proteins transcribed and translated from the sense strand of DNA bind to proteins that are transcribed and translated from the antisense strand of DNA. Some patients with PR3 ANCA harbored antibodies to an antigen complementary to the middle portion of PR3. These anticomplementary PR3 antibodies formed an anti-idiotypic pair with PR3-ANCA. Moreover, cloned complementary PR3 proteins bind to PR3 and function as a serine proteinase inhibitor. What is the source of the complementary PR3 antigen? Preliminary data suggest that these proteins are found on a variety of microbes, some of which have been associated with ANCA vasculitis and also found in the genome of some patients with both PR3- and MPO-ANCA.[188] These studies need to be confirmed and expanded to understand what the source of the complementary PR3 antigen is in any given person, and just as importantly, whether these complementary proteins are capable of inducing disease. If these observations remain true, they may provide a promising avenue for the detection of the proximate cause of the autoimmune response in any given person.

There has been an alternate theory proposed for the genesis of pauci-immune necrotizing and crescentic glomerulonephritis based on the observation that some patients

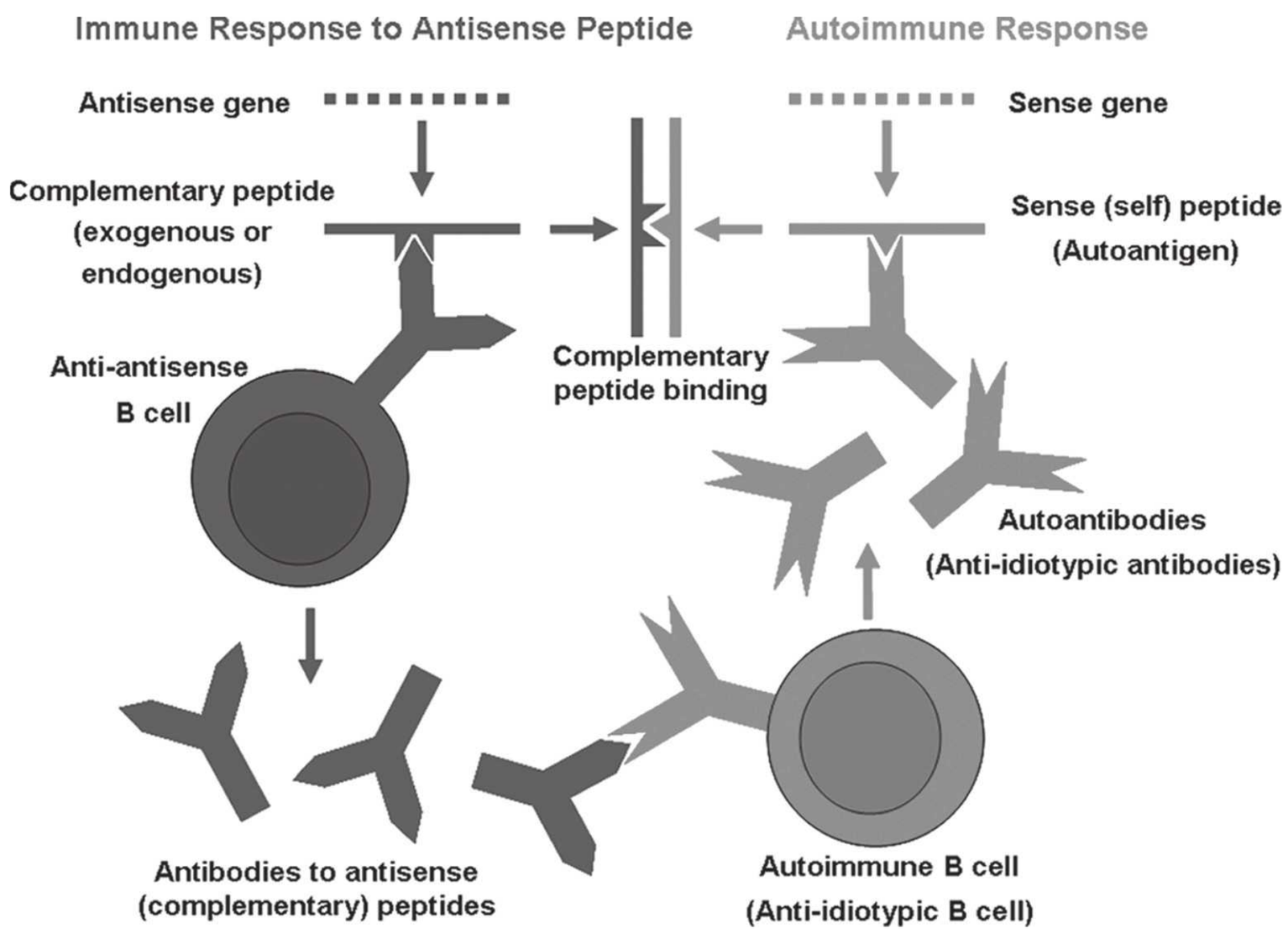

FIGURE 48.10 Schematic of a mechanism for the development of autoimmunity (theory of autoantigen complementarity) as a consequence of an immune response to a protein whose amino acid sequence is complementary to a self-protein.

with ANCA vasculitis have antibodies to another neutrophil protein, lysosome-associated membrane protein 2 (LAMP2). Kain et al. document that LAMP2 is capable of neutrophil activation and endothelial damage in vitro.[189] LAMP2 has homology to a protein expressed by fimbriated bacteria (FimH). Antibodies to either FimH peptides or LAMP2 peptides were shown to induce necrotizing and crescentic glomerulonephritis in rats. The theory proposed that anti-LAMP2 antibodies could therefore result from molecular mimicry as a result of infection with gram-negative organisms making FimH. From 680 ANCA patients between two academic centers, anti-LAMP-2 reactivity was present in 21% of ANCA sera and 16% of the control group with urinary tract infections. Titers of anti-myeloperoxidase and anti-proteinase 3 antibodies were 1,500-fold and 10,000-fold higher than anti-LAMP-2 titers, respectively. There was no correlation between anti-LAMP-2 antibodies and disease activity. Data do not support a mechanixtic relationship between anti-LAMP-2 antibodies and ANCA glomerulonephritis.[190,191]

Pathogenesis of Eosinophilic Granulomatosis

Eosinophilic granulomatosis is characterized by a necrotizing vasculitis involving primarily the small- and medium-size vessels, peripheral blood eosinophilia, allergic rhinitis, eosinophil-rich granulomatous inflammation presenting with pulmonary nodules, and upper airway and bronchial lesions leading to severe asthma. Forty percent of patients with EGPA are ANCA positive, usually directed against MPO.[192] ANCA-positive and -negative EGPA appear to differ to some extent with regard to the frequency and character of organ involvement. ANCA-positive patients are more likely to manifest signs of necrotizing glomerulonephritis, pulmonary hemorrhage, peripheral neuropathy, and purpura, whereas ANCA-negative patients are more likely to present cardiac involvement and pulmonary infiltrates.[62,192] Potential triggers of disease include desensitization treatment, inhaled antigens, free-base cocaine, and the use of leukotriene receptor antagonists (LTRA); however, only 23% of patients with EGPA report a potential triggering factor.[192] It is unclear whether the use of LTRAs stimulates a reduction in corticosteroid dose allowing for greater disease manifestation, whether they are prescribed to patients with severe asthma representing an early phase of the disease, or if LTRAs are causative of EGPA. Upon careful review of all cases of suspected drug-induced EGPA reported to the U.S. Food and Drug Administration (FDA) between 1996 and 2003 (n = 1274), the diagnosis could be confirmed in 181 cases, 90% of whom had a preceding exposure to LTRA.[193] A positive ANCA test was detected in 42% of the cases tested.

IL-5 and other Th2 cytokines seem to have a key role in the development of eosinophilia in EGPA[194] and patients with active EGPA appear to have elevated plasma levels of IL-5.[195] Peripheral blood mononuclear cell production of IL-5 may be increased in vitro in the setting of T cell activation.[194] IL5 induces terminal differentiation of committed eosinophil precursors,[196] prolongs their survival,[197] induces their degranulation and antibody-depended cytotoxicity,[198] and promotes their adhesion to endothelial cells and transmigration from the vasculature.[199]

T cells from patients with EGPA exhibit increased production of Th2 cytokines IL-4 and IL-13.[200] Migration of eosinophils to inflammatory sites appears to be mediated by Eotaxin-3.[201] Increased levels of Eotaxin-3 correlate to levels of disease activity and inflammation.[202]

Patients with EGPA have elevated production of the Th-1 cytokine IFNγ from peripheral T cell lines.[194] A recent study compared chronic eosinophilic pneumonia and asthma to EGPA and noted decreased CD4+ CD25+ T cells that produce IL-10 in active EGPA. These cells were noted to be increased in EGPA for patients in remission.[203] The relative importance of Th-1 and Th-2 responses may differ in patients with predominantly eosinophilic/allergic phenotype versus vasculitic/granulomatous manifestations of EGPA. Patients with active EGPA also exhibit decreased frequency of peripheral Treg cells,[204] and increased frequency of Th17 cells when compared to patients with asthma and chronic eosinophilic pneumonia.[203] Treg cells increase and Th17 cells decrease in EGPA remission.

TREATMENT

Induction

The treatment of ANCA vasculitis and glomerulonephritis rests primarily on the use of induction methylprednisolone, high-dose corticosteroids, cyclophosphamide, and most recently rituximab. As the serum creatinine concentration at the time of treatment is a significant determinant of long-term renal outcome, pulse methylprednisolone (7 mg/kg/day for 3 days) is used to curb the active inflammation as soon as possible. This is followed by instituting prednisone at a daily dosage of 1 mg/kg/day (not to exceed 80 mg per day for the first month of therapy). Corticosteroids are then tapered over the second month to an alternate-day dosing schedule and subsequently decreased every week by 10 to 20 mg per day until they are eventually discontinued by the end of the fourth to fifth month. In our population, patients maintained on corticosteroids beyond 6 months have no decrease in risk of relapse but do have a significantly greater risk of infections and a trend toward development of new onset diabetes mellitus. This is in contradistinction to meta-analysis data that noted a higher relapse rate in studies where corticosteroids were discontinued prior to 12 months of therapy.[205] This meta-analysis had significant heterogeneity among the studies included and duration of glucocorticoid dosing was not the primary treatment variable in any of the randomized controlled trials. Furthermore, this analysis was not based on patient-level data, and duration of glucocorticoid therapy was estimated from the described protocols. The rate of decrease in corticosteroid dosing should be tailored based on an assessment of each patient's disease activity.

The beneficial role of cyclophosphamide in the treatment of acute ANCA vasculitis is evidenced by the substantial improvement in the rate of remission (56% to 85%) and a threefold decrease in the risk of relapse associated with the use of this drug.[206] For many years cyclophosphamide

has been administered as a daily oral regimen or as monthly intravenous pulses. When the intravenous route is used, it is usually started at a dose of 0.5 g per m^2 of body surface area, which is subsequently increased to a maximal dosage of 1 g per m^2. This dose is adjusted to maintain the 2-week leukocyte nadir at more than 3,000 per mm^3. When the daily oral regimen is used, cyclophosphamide is given at a daily dosage of 1.5 to 2 mg per kg.[206] To prevent severe leukopenia, careful attention to the leukocyte count must be maintained throughout this therapy. Cyclophosphamide was traditionally continued for a total of 6 to 12 months. Investigation into intravenous cyclophosphamide therapy has led the community away from using daily oral cyclophosphamide as first-line induction therapy. The intravenous regimen allows for a two to three times smaller total dose of cyclophosphamide than the oral regimen. A regimen of daily oral cyclophosphamide may be associated with a decreased risk of relapse.[207] However, in a meta-analysis of three randomized controlled trials comparing pulse versus oral continuous cyclophosphamide, pulse cyclophosphamide attained a statistically higher rate of remission, and lower rates of leukopenia and infections. Pulse cyclophosphamide was associated with a higher rate of relapse, which was not statistically significant.[208] The final outcomes of patients (death or end-stage kidney disease [ESKD]) were no different in the two groups despite the lower rate of relapse in the oral cyclophosphamide group.[208] The question of pulse versus oral cyclophosphamide was even more definitively addressed in a large, randomized controlled trial of pulse versus daily oral cyclophosphamide for induction of remission.[74] One-hundred and forty-nine patients with newly diagnosed ANCA vasculitis with renal involvement (creatinine $<$ 500 μM per L) were randomized to receive either pulse cyclophosphamide, 15 mg per kg every 2 weeks for three infusions then an infusion every 3 weeks, or daily oral cyclophosphamide, 2 mg per kg per day. GPA, MPA, and renal-limited disease were evenly spread across the groups, as was serum positivity for PR3 versus MPO. Demographics, serum creatinine, and markers for disease severity were well matched between the groups. Primary outcome was time to remission. Change in renal function, adverse events, and cumulative dose of cyclophosphamide was also evaluated. Cyclophosphamide therapy was continued 3 months beyond the time of remission. All patients were then switched to azathioprine (2 mg/kg/day orally) until month 18, end of study follow-up. All patients received prednisolone starting at 1 mg per kg orally, tapered to 12.5 mg at the end of month 3 and to 5 mg at the end of the study (month 18). Median time to remission was 3 months for both groups. The two treatment groups did not differ in time to remission or proportion of patients who achieved remission at 9 months. No differences in renal function were noted between the two groups at any time point. Due to power constraints, the study could not detect a difference in relapse rates between the two groups. By 18 months, 13 patients in the pulse group and 6 in the daily oral group had a relapse (HR, 2.01 [CI, 0.77 to 5.30]). Absolute cumulative cyclophosphamide dose in the daily oral group was almost twice that in the pulse group with consequent statistically significant increased rate of leukopenia in the daily oral group. Serious infections did not differ between the two treatment groups. Overall, with the results of this randomized controlled trial confirming the similar rates and time to remission of the two cyclophosphamide regimens, and pulse cyclophosphamide being associated with about half of the cumulative dose of the medication and a significantly lower rate of leukopenia, the pulse regimen is considered first-line induction therapy for ANCA vasculitis. The trend toward a higher rate of relapse with pulse cyclophosphamide appears late (after 15 to 18 months) and is of unclear clinical significance on the long-term outcome of patients.

Strategy in the above study was to use cyclophosphamide three months after the documentation of remission followed by azathioprine for remission maintenance until 18 months (end of follow-up). In another report, cyclophosphamide was used for 3 months once remission was attained followed by azathioprine continued for 12 to 24 months.[209] This regimen offers the advantage of a limited use of cyclophosphamide and results in similar rates of remission and relapse as cyclophosphamide-only–based therapies.

In an uncontrolled study, 32 patients with 34 episodes of active ANCA vasculitis received induction treatment with oral MMF 1,000 mg twice daily for at least 12 months and oral prednisolone 1 mg per kg once daily for 6 weeks followed by a taper.[210] Complete remission was obtained in 78% of patients and partial remission in 19%. Relapse occurred in 52% of those who obtained complete remission and 100% after partial remission. The median relapse-free survival was 16 months and all but two patients were still on MMF at the time of relapse. Patients who had previously been treated successfully with cyclophosphamide responded better than those who had not, suggesting that MMF is unlikely to succeed in patients who are "resistant" to cyclophosphamide therapy.

In a controlled study of MMF plus corticosteroids compared to cyclophosphamide plus corticosteroids for induction therapy in ANCA vasculitis, 35 patients from Nanjing, China, were evaluated for remission at 6 months.[211] Follow-up beyond 6 months is not provided. The groups were well matched for demographic characteristics, activity score, duration and severity of kidney disease, and proteinuria. In the intention-to-treat analysis, assuming that those lost to follow-up did not respond, the remission rate at 6 months was 77.8% in the MMF group versus 47.1% in the cyclophosphamide group ($P = .09$ by Fisher's test). However, when patients lost to follow-up were excluded from the analysis, 61.5% of patients in the cyclophosphamide group had remission resulting in a difference of 16.3% between the groups ($P = .4$). The results of this study are limited by the small sample size and the very short duration of follow-up.

MMF was studied in 17 patients with MPO-positive pANCA MPA with active urine sediment or biopsy proven renal involvement and creatinine less than three with no

life- or organ-threatening disease manifestations.[212] MMF 1,000 mg orally was given twice a day for 18 months in conjunction with corticosteroids (IV methylprednisolone 1 to 3 g followed by oral prednisone at 1 mg per kg per day tapered off by 6 months). Thirteen out of 17 patients reached the primary outcome of remission at 6 months with stable renal function. Of these, 12 patients remained in remission through month 18. Adverse events reported in this study were mild and treated by MMF titration in all but one patient who was deemed MMF intolerant.

Patients suffering primarily from mild ANCA vasculitis without renal involvement may benefit from the use of methotrexate in lieu of cyclophosphamide. In an uncontrolled study, methotrexate afforded rates of remission comparable to those published for cyclophosphamide.[213] An open-label study suggests that methotrexate could be used for maintenance therapy after the induction of remission with cyclophosphamide and corticosteroids,[214] but may be associated with a relatively high rate of relapse. In a randomized controlled trial of induction therapy among patients with "early" ANCA vasculitis comparing weekly methotrexate (15 mg per week escalating to a maximum of 20 to 25 mg per week by 12 weeks) to daily oral cyclophosphamide (2 mg/kg/day to a maximum of 150 mg per day), the rate of remission at 6 months was comparable among the two treatment groups (89.8% for methotrexate vs. 93.5% for cyclophosphamide, P = .041). However, the onset of remission in methotrexate-treated patients with relatively extensive disease or pulmonary involvement was delayed. Methotrexate was associated with a significantly higher rate of relapse than cyclophosphamide (69.5% vs. 46.5%), and 45% of relapses occurred while patients were receiving methotrexate.[215] Importantly, patients enrolled in this trial did not have organ- or life-threatening manifestations, or significant renal involvement. The dose of methotrexate must be reduced in patients whose creatinine clearance is less than 80 mL per min, and its use is contraindicated when creatinine clearances are less than 10 mL per min. Most experience of methotrexate in GPA has involved patients with no renal involvement or with glomerulonephritis and near-normal renal function.

Recent investigation into cyclophosphamide-sparing induction strategies for ANCA vasculitis has led to the possibility of using alternative induction therapy protocols including rituximab. Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen, effectively depletes B lymphocytes, but not plasma cells. Two recent non-inferiority randomized control trials evaluating rituximab and prednisone compared to cyclophosphamide with prednisone have been published.[216,217] **R**ituximab for **A**NCA-associated **V**asculitis (RAVE) is a placebo-controlled study of 197 patients with new-onset and relapsing ANCA vasculitis comparing oral cyclophosphamide and prednisone (n = 99) to four infusions of 375 mg per m^2 rituximab plus prednisone (n = 98).[216] There was no difference between the arms in complete remission (55% in cyclophosphamide arm, 64% in rituximab arm) off all therapy including prednisone at 6 months (P = .21). Adverse events and relapse within the first 6 months did not differ among patients with new onset disease. In patients presenting with relapse and randomized between the two arms, the rituximab protocol was significantly better. The RITUXVAS trial evaluated 44 patients with more severe disease.[217] This trial compared 6 to 10 infusions of cyclophosphamide followed by maintenance therapy with azathioprine to four infusions of 375 mg per m^2 rituximab in combination with two infusions of cyclophosphamide without maintenance therapy. Remission rates at 12 months of 76% in the rituximab group and 82% in the cyclophosphamide alone group were noted but adverse events were 45% and 36% in the rituximab and cyclophosphamide group respectively and 1-year mortality rate was 18% in both groups. In both RAVE and RITUXVAS, rituximab is noninferior to cyclophosphamide but enthusiasm is tempered by elevated adverse event rates that may signify no improvement in safety over cyclophosphamide. Analysis of long-term outcomes of these trials including sustained remission, rate of relapse, and safety data is anticipated, as rituximab has now received approval by the FDA.

Patients presenting with pulmonary hemorrhage also benefit from the institution of plasmapheresis in a regimen similar to that used for patients with Goodpasture disease. Although no controlled data are available, early and aggressive institution of plasmapheresis has in our experience substantially diminished the mortality rate associated with massive pulmonary hemorrhage.[218] Plasmapheresis is typically performed daily until the pulmonary hemorrhage ceases and then every other day for a total of 7 to 10 treatments. Plasma is replaced with a solution of 5% albumin, but two units of fresh-frozen plasma are administered at the end of the treatment to replace clotting factors and minimize the risk of persistent or renewed bleeding. In a randomized trial of plasma exchange versus methylprednisolone as additional therapy in patients with severe ANCA vasculitis (creatinine >500 μmol per L or dialysis dependent), the use of plasma exchange was associated with a significant improvement in the recovery of renal function and dialysis-free survival.[219] Meta-analyses of five studies confirmed the benefit of adjunct plasmapheresis noting a reduction in risk of requiring dialysis 12 months after therapy initiation.[220] Plasmapheresis is recommended as adjunct in ANCA vasculitis induction therapy for patients who present with life- or organ-threatening manifestations of vasculitis. On the basis of several relatively small studies, plasmapheresis does not seem to be of added benefit over the use of corticosteroids and cyclophosphamide in patients without pulmonary hemorrhage or severe renal involvement.[221,222] Further investigation into the effects of plasmapheresis in ANCA vasculitis is currently under way in a randomized control study.[223]

Treatment of Relapse

With the use of an alkylating agent, the rate of remission is on the order of 70% to 85%. Patients who require dialysis at the time of diagnosis have a decreased probability of recov-

ering sufficient renal function to discontinue dialysis (about 50%). Patients that do recover sufficient renal function do so within the first 3 months of treatment. In a retrospective analysis of 523 patients with ANCA vasculitis followed over a median of 40 months, 136 patients reached ESKD.[224] Relapse rates of vasculitis were significantly lower on chronic dialysis (0.08 episodes per person-year) compared with the rate of the same patients before ESKD (0.20 episodes per person-year) or with patients with preserved renal function (0.16 episodes per person-year). Infections were almost twice as frequent among patients with ESKD on maintenance immunosuppressants and were an important cause of death. In the absence of active extrarenal vasculitis, immunosuppression may be stopped after 3 months if no signs of renal recovery have occurred as the risk/benefit ratio does not support the routine use of maintenance immunosuppression therapy in ANCA vasculitis patients on chronic dialysis.

Relapse in ANCA vasculitis occurs in about 45% of patients over a median of 44 months,[225] but relapse patterns are not uniform among patients. In our experience, 80% of relapses occur in the first 18 months after immunosuppressive therapy is discontinued. Others have not detected such a clustering of relapses in the early months after discontinuing therapy.[226] Recurrent disease may resemble clinically the initial presentation but is sometimes associated with new organ involvement.

The risk of relapse is not uniform among patients with ANCA vasculitis. Multivariate analysis of 258 patients with the disease who were treated and attained remission showed that presence of PR3-ANCA antibody and involvement of the lungs and upper respiratory tract were independent risk factors for relapse. Of the patients who presented none of these risk factors, 26% relapsed in a median of 62 months (median among those who relapsed was 20 months). In contrast, 47% of the patients who presented with a single risk factor experienced a risk for relapse (95% CI 1.1–3.9, P = .038). Of patients presenting with all three risk factors, 73% relapsed in a median of 17 months (median among those who relapsed was 15 months), corresponding to a 3.7-times increased risk of relapse (95% CI 1.4–9.7, P = .007) compared to those with no risk factors.[225] In a retrospective analysis of a separate large independent cohort of patients from the French Vasculitis Study Group, the presence of PR3-ANCA and lung involvement were found to be risk factors for relapse (hazard ratio 1.66 [95% CI 1.15–2.39] for PR3–ANCA and HR 1.56 [95% CI 1.11–2.20] for lung involvement).[227]

Recurrent glomerulonephritis is usually indicated by the recurrence or worsening of hematuria with an increase in serum creatinine. An increase in proteinuria alone or the gradual increase in serum creatinine without hematuria may be the result of progressive chronic scarring, rather than recurrent active inflammation. Repeated renal biopsy is sometimes indicated to best differentiate between recurrent disease and progressive scarring and to avoid unnecessary immunosuppression in the latter case.

Whether ANCA titers are predictive of a relapse is a matter of controversy. To determine the occurrence of a relapse, serial measurements of ANCA titers should be interpreted only in the context of the clinical history and physical and laboratory examination of the patient. Although ANCA titers correlate with disease activity when a group of patients are considered, the ANCA titer may not correlate in an individual patient. Some patients maintain a high titer level despite clinical remission, whereas others exhibit clinical evidence of active vasculitis in the absence of a rise in titer. ANCA titers are best used in serial measurements and interpreted in consideration with each patient's pattern.

Several studies have addressed whether ANCA could reliably predict the future occurrence of a relapse.[228] PR3-ANCA has been the focus of study in this regard with limited information pertaining to MPO-ANCA. One-hundred and fifty-six patients from Wegener granulomatosis etanercept (WEGET) study had serum collected every 3 months and the titers of antibodies to mature PR3 (PR3-ANCA) and to pro-PR3 were analyzed in relationship with disease activity and subsequent relapse.[229] In this study, there was only weak association between PR3-ANCA levels. The proportion of patients who had relapse within 1 year of an increase in PR3-ANCA levels was 40% for mature-PR3 and 43% for pro-PR3. These findings lack support for the use of PR3-ANCA levels in guiding immunosuppressive therapy.

Although a rise in ANCA titer may predict recurrent disease, the relapse may not occur for several months. In a study by Cohen Tervaert et al., one third of patients with a rise in titer did not experience clinical signs of relapse even after 18 months.[230] In this context, and considering the toxicities of immunosuppression, the prophylactic use of high-dose corticosteroids or cyclophosphamide to prevent relapse would needlessly expose many patients to their toxic side effects. If alternative, less toxic therapies are shown to be effective in the treatment of ANCA vasculitis, the risk–benefit ratio may make such a preemptive or prophylactic approach more appealing. To date, the evidence does not support the use of preemptive immunosuppressive therapy to prevent a relapse in patients with an increase in ANCA titer. Relapsing ANCA vasculitis responds to immunosuppression with corticosteroids and cytotoxic agents with a similar response rate as the initial disease. The decision regarding the repeated use of pulse methylprednisolone can be based on the total amount of corticosteroid that has been administered to the patient over the course of the disease, as well as the severity of the relapse. Patients with a history of relapsing disease pose a particular challenge because they are particularly subject to the cumulative toxic effects of cytotoxic agents and corticosteroids. Some may require the use of long-term "maintenance" immunosuppressive therapy with either low-dose prednisone or azathioprine. Although

the use of trimethoprim-sulfamethoxazole or cotrimoxazole is beneficial in the prevention of relapses involving the nose and upper respiratory tract, no benefit is seen in disease affecting the kidneys or other organ systems.[231] The concomitant use of trimethoprim-sulfamethoxazole and methotrexate is contraindicated because it may result in severe bone marrow toxicity.

In an effort to limit the exposure to cytotoxic agents, a number of immunomodulatory drugs and antibodies are being evaluated for the treatment of patients with recurrent vasculitis. The various studies can conceptually be divided into two categories: studies aimed at treating patients who are resistant to conventional treatment with cyclophosphamide and corticosteroids, and studies aimed at the prevention of relapse. Table 48.9 summarizes various "novel" therapies that have been or are being evaluated. The efficacy of any such agents is currently not established, and they should not be considered as first-line therapies.

48.9 A Summary of Various "Novel" Therapies That Have Been or Are Being Evaluated in the Treatment of Anca Vasculitis and Glomerulonephritis

Therapy	Possible Role	References
Plasmapheresis	Adjunctive therapy in patients with pulmonary hemorrhage or advanced renal disease	Gaskin, 2001[266]; Frasca, 1992, 1993[267,268]; Pusey, 199[145]; Zauner, 2002[269]; Klemmer, 2003[142]; Cole, 1992[144]; Jayne, 2007; Walters, 2010
Intravenous immunoglobulin	Adjunctive therapy in patients with persistent disease on standard therapy	Jayne et al.,[155] Martinez, 2008
Methotrexate	Alternative to cyclophosphamide in patients with "early disease" and without significant renal or pulmonary disease.	Sneller, 1995[148]; Langford, 2000[270]; DeGroot, 2005[150]
	Prevention of relapse?	Isaacs, 1996[161]; Booth, 2002[167]; Stegeman, 1997[271]
Azathioprine	Prevention of relapse?	Jayne, 2003[147]; Pagnoux, 2008; IMPROVE, 2010
Mycophenolate mofetil	Prevention of relapse?	Nowack, 1999[170]; Langford, 2004[272]; Stassen, 2007; Hu, 2008; Silva, 2010
Leflunomide	Prevention of relapse?	Metzler, 2004[273]
Rituximab	Adjunctive therapy for cyclophosphamide-resistant or relapsing patients?	Specks, 2001[274]; Keogh, 2005[156]; Eriksson, 2005[157]; Jones, 2009; Martinez, 2009
	Induction therapy	RAVE, RITUXVAS (Stone; Jones, 2010)
Infliximab	Adjunctive therapy for cyclophosphamide-resistant or relapsing patients?	Lamprecht, 2002[164]; Bartolucci, 2002[165]; Booth, 2004[166]; D'Haens, 1999[275]
Alemtuzumab	Adjunctive therapy for cyclophosphamide-resistant or relapsing patients?	Kirk, 2003[160]; Walsh, 2008
Etanercept	Shown NOT to be efficacious in the prevention of relapse	WGET[276]
Trimethoprim-sulfamethoxazole	Prevention of relapses that affect the upper respiratory tract	DeRemee, 1985[277]; Reinhold-Keller, 1996[278]; Stegeman, 1996[53]

Potential Adjunctive Treatment for Patients with Resistant Disease or Contraindications to Conventional Therapy

Several agents have been evaluated as adjunctive therapy for patients with resistant forms of ANCA vasculitis. Adjunctive therapy with intravenous immunoglobulin (IVIg) (single course of a total of 2 g per kg) was evaluated in a randomized controlled trial in patients with persistently active ANCA vasculitis despite conventional therapy. Patients treated with IVIg experienced a more rapid decline in disease activity (as measured by a 50% reduction in Birmingham Vasculitis Activity Score [BVAS]) and C-reactive protein at 1 and 3 months, but there was no significant difference between the two groups after 3 months with respect to disease activity or frequency of relapse.[232] The use of IVIg was also evaluated in a prospective, open-label study of 22 patients with relapsing ANCA vasculitis.[233] Patients received IVIg (0.5 g/kg/day for 4 days) administered monthly for 6 months as additional therapy to ongoing corticosteroids and/or immunosuppressants (cyclophosphamide, azathioprine, methotrexate, or MMF). Corticosteroid therapy could be continued or reintroduced with relapse; immunosuppressants could be maintained but could not be reintroduced. Serum creatinine >3.4 mg per dL or rapid rise in creatinine was reason for exclusion. One patient developed renal insufficiency after the first IVIg infusion. Ninety-five percent of patients achieved remission between months 1 and 5 but there was a 32% rate of relapse within 9 months. These results suggest that IVIg may induce remission in patients with relapsing ANCA vasculitis when added to baseline immunosuppression but should be avoided in patients with severe renal disease.

Evidence indicates that rituximab may have a role in the management of ANCA vasculitis that is resistant to or relapsing after standard therapy. As demonstrated in the RAVE trial, patients treated with rituximab for relapse had significantly improved outcome over patients treated with cyclophosphamide and corticosteroids.[216] Small, uncontrolled case series[156–158] used rituximab (375 mg per m^2 IV weekly × 4 or 500 mg IV weekly × 4 fixed doses) in conjunction with corticosteroids, resulting in remission in the majority of patients. In these reports rituximab was generally well tolerated. In contrast, in a fourth open label study of eight patients with severe, refractory GPA, the addition of rituximab (375 mg per m^2 every 4 weeks × 4 doses) to cyclophosphamide, mycophenolate mofetil, or methotrexate was associated with limited benefit.[234] Recent retrospective studies evaluating rituximab for refractory ANCA vasculitis report favorably for achievement of remission.[235]

Alemtuzumab (Campath-1H) is a humanized monoclonal IgG1 antibody directed against the CD52 antigen expressed on the surface of peripheral blood lymphocytes, monocytes, and macrophages.[236] Treatment with alemtuzumab results in complement-mediated lysis, antibody-dependent cellular cytotoxicity, and induction of apoptosis of target cells and results in depletion of T cells and B cells.[237] Alemtuzumab has been used to treat a select group of patients with refractory or relapsing autoimmune diseases, including 70 patients with ANCA vasculitis.[238] These patients received at least one course of 135 mg intravenous alemtuzumab over 5 days. Remission was achieved by 83% of surviving patients. Unfortunately, this treatment regimen was associated with high rates of serious infections and death (18% at 1 year) and a 43% rate of relapse. Recently, a cohort study on alemtuzumab in treatment of refractory or relapsing ANCA vasculitis showed high mortality with 31 deaths out of 71 patients.[239] In this study, 85% of patients entered remission but 72% of those patients had a relapse with a median time of 9.2 months. Mortality and infection risk limit the utility of this therapy.

Similarly, the chimeric monoclonal antibody directed against TNF-α[163] infliximab has been evaluated in four open-label uncontrolled trials of small numbers of patients.[240–243] In these studies, the treatment regimen included infliximab plus corticosteroids, and either cyclophosphamide or other immunosuppressive agents. In the largest of these trials, which included 32 patients with acute or resistant disease, infliximab was associated with a remission rate of 88% and a relapse rate of 20%.[166] These promising results are mitigated, however, by an elevated rate of serious infectious complications.

The immunosuppressant, 15-deoxyspergualin, used in Japan for the treatment of steroid-resistant renal transplant rejection, has also been evaluated for the treatment of refractory GPA.[244,245]

Maintenance Therapy

Azathioprine is the most well-validated maintenance therapy in ANCA vasculitis. In a controlled trial of 144 patients who achieved remission with daily oral cyclophosphamide and corticosteroids, a switch to azathioprine after 3 to 6 months was associated with equivalent relapse rates and long-term outcomes as 12 months of cyclophosphamide.[209]

Methotrexate offers no benefit over azathioprine in the prevention of relapse, and may be associated with a higher rate of serious adverse effects. Maintenance therapy with methotrexate compared to azathioprine in a randomized controlled fashion was evaluated after induction of remission with cyclophosphamide and corticosteroids.[246] The primary outcome measure was serious adverse events rather than the rate of relapse. One-hundred and twenty-six out of 180 treated patients attained remission and were randomized to azathioprine (2 mg/kg/day) or methotrexate (0.3 mg/kg/week initially and progressively increased to 25 mg per week) for 12 months followed by a tapered withdrawal over 3 months. Impaired renal function at randomization was not an exclusion criterion. The two groups were well matched for age, diagnosis, organ involvement, and serum creatinine. The azathioprine group included more patients with risk factors for relapse (PR3-ANCA and alveolar hemorrhage). There was no significant difference in the rate of relapse between the groups (36% and 33% respectively;

P = .71) with a mean randomization-to-relapse interval of 20.6 ± 13.9 months. Methotrexate was associated with a trend toward a higher rate of adverse events when compared to azathioprine (HR 1.65; 95% confidence interval 0.65 to 4.18; P = .29).

Methotrexate was compared to leflunomide for maintenance therapy in ANCA vasculitis in a controlled trial that was terminated early due to the rate of major relapses in the methotrexate limb.[247] Data does not support routine use of methotrexate for the prevention of relapse in ANCA vasculitis. Risk of serious adverse effects precludes the use of methotrexate in patients with decreased renal function.

In a large randomized control trial MMF was compared to AZA in 156 patients with ANCA vasculitis who attained remission with cyclophosphamide and corticosteroids.[248] Randomization was to MMF (2 g per day) versus azathioprine (2 mg/kg/day) and patients were followed for a median of 39 months. Relapses were more common in the MMF group compared to the azathioprine group (unadjusted HR for MMF 1.69, 95% CI 1.06–2.70; P = .03). Adverse events, disease activity score, glomerular filtration rate, and proteinuria did not differ between the groups.

Data is scarce on whether rituximab could be used for the prevention of relapses, but this remains an appealing concept.

Treatment of Eosinophilic Granulomatosis

Treatment of EGPA often parallels the approach to GPA and MPA. In a prospective, randomized open label trial of EGPA patients without renal impairment, cardiomyopathy, gastrointestinal tract, or central nervous system disease, patients entered remission with steroid treatment alone; however, relapse rate was 35%.[249] Attempts to sustain remission and avoid cyclophosphamide by use of azathioprine, MMF, or methotrexate for EGPA without poor prognostic factors have been reported.[249,250]

In five of seven patients with EGPA refractory to standard therapy given interferon-α with steroids went into remission although follow-up time was only 6 months.[250] There is case report evidence for use of the anti-IL-5 antibody mepolizumab and anti-IgE antibody omalizumab in refractory EGPA.[251,252] Interferon-α and mepolizumab have also been studied for maintenance treatment in EGPA.[252,253]

RENAL TRANSPLANTATION

Renal transplantation has been recognized as an option of renal replacement therapy in patients with GPA, MPA, or necrotizing crescentic glomerulonephritis. Although there is a risk of disease recurrence posttransplantation patient and graft outcomes in ANCA vasculitis are similar to those of renal transplant recipients with other causes of renal failure not including diabetes.[254] Successful renal transplantation in patients with ANCA vasculitis has been reported in patients who were in full remission and with negative ANCA test results, in patients with positive ANCA test results,[255,256] and even in patients with evidence of active vasculitis at the time of transplantation.[257] Recurrent vasculitis after transplantation has also been described as occurring as early as a few days posttransplantation and as late as several years posttransplantation. Just as with the initial ANCA vasculitis, reported recurrences after transplantation involve a spectrum of various organs and are not limited to the transplanted kidney.

Based on a pooled analysis,[258] ANCA vasculitis recurs in about 17% of all patients, with an average time from transplantation to relapse of 31 months. Case series report ANCA relapse rates after transplantation to range from 0.02 to 0.1 relapses per patient year.[257,259,260] The presence of ANCA at transplantation does not appear to increase the rate of relapse posttransplantation. Relapse rate was 9% (all extrarenal) at >1 year with no effect on graft function in a population where 80% were transplanted with induction therapy (66% using a depletion agent) and >80% maintenance therapy with tacrolimus or cyclosporine + MMF + prednisone.[261]

Patients with GPA had a relative risk of relapse of 2.75 when compared with patients with MPA or necrotizing crescentic glomerulonephritis alone. Conversely, ANCA pattern (c-ANCA or p-ANCA) or antigen specificity (PR3 or MPO) was not associated with differences in relapse rate posttransplantation.

A review of the reports of recurrent ANCA vasculitis posttransplantation reveal a good response to cyclophosphamide in the treatment of relapsing disease, although recurrent disease can lead to graft loss and even patient death.[262] Rituximab has been reported to be effective in treating posttransplant cyclophosphamide refractory recurrent ANCA disease.[263,264] In summary, renal transplantation is a beneficial option in the management of patients with ESKD associated with ANCA vasculitis. Although the presence of circulating ANCA is not a sufficient contraindication to transplantation, it is current practice not to perform transplantation in patients with active vasculitis, but to delay surgery until the disease is in remission. No data are currently available about the need to wait a certain period of time after remission is attained and before proceeding to transplantation.

BEHÇET DISEASE

Behçet disease is a systemic vasculitic syndrome classically characterized by a triad of recurrent oral ulcerations, genital ulcerations, and ocular lesions usually consisting of uveitis, iritis, or retinal vasculitis. Behçet disease can present with protean manifestations with multiple organ involvement, either concomitantly or consecutively. Other organ system involvement includes the skin, musculoskeletal system with arthralgias and myalgias, central nervous system, and lungs, and gastrointestinal, cardiac, and genitourinary systems. Vascular involvement may affect large blood vessels, capillaries, venules, and veins. The diagnosis of Behçet disease is based on an established set of criteria.[265] The criteria

include the presence of oral ulcerations, and two or more of the following: recurrent genital ulcerations, eye lesions, skin lesions, and positive pathergy test results. The latter test represents a nonspecific skin hyperreactivity induced by intradermal needle prick.

Epidemiology

Although Behçet disease has been reported worldwide, the highest incidence of disease appears to be in Japan, the Middle East, and around the Mediterranean basin. The incidence ranges from 1 to 2 per 10,000 in Japan and Saudi Arabia to as low as 0.3 per 100,000 in Northern Europe. The peak age of onset is within the third decade, and there is a male preponderance in most published case series. Men are also reported to have more severe disease than women.

Pathogenesis

The etiology of Behçet disease remains unknown. Associations with infectious agents such as herpes simplex virus I, Streptococcus sanguis, parvovirus B19, and Mycobacterium tuberculosis have been hypothesized and evaluated to various degrees. However, no direct link has been convincingly established. Human leukocyte antigen (HLA) typing reveals a close association between Behçet disease and HLA-B51 (especially the allelic variants HLA-B*5101)[266] and HLA-B*5108 and HLA-B*57 among Caucasians.[267] Other studies point to an association with a microsatellite located between the HLA-B locus and the TNF gene rather than an association with the HLA-B*51 gene itself.[268] Therefore, the TNF promoter allele TNF-1031 was found to be independently associated with susceptibility to Behçet disease among Caucasians.[267] The presence of antibodies to a number of autoantigens such as alpha-tropomyosin[269] has been described. The role of such autoantibodies in the pathogenesis of the disease is unclear. Similarly, T cells are likely involved in the pathogenesis of Behçet disease as evidenced by an increase in $\gamma\delta$T cells,[270] a predominance of Th1 cell phenotype,[271] and autoreactive T cells.[272]

Renal Involvement

Renal involvement in Behçet disease appears to be more frequent than previously recognized. The spectrum of involvement ranges from subtle urinary abnormalities to end-stage renal disease and can conceptually be divided into five categories: (1) glomerulonephritis, (2) amyloidosis, (3) renal vascular involvement, (4) interstitial nephritis, and (5) other problems, such as complications of drug therapy or genitourinary system abnormalities.[273] The nephrotic syndrome and renal failure occurring in the setting of Behçet disease can be associated with the presence of AA amyloidosis more typically found in patients with long-standing disease.[274] Based on an extensive review of the published case reports (totaling 159 patients), amyloidosis was the most commonly reported lesion (43% of cases), whereas glomerulonephritis accounted for 32% of cases.[273] Although an early study reported the presence of hematuria, proteinuria, or both in about one third of patients,[275] a recent extensive retrospective review of more than 4,200 cases identified such urinary abnormalities in about 11% of patients tested and documented glomerulonephritis in only 7 (0.16%) patients.[276] The pathologic lesions associated with Behçet disease include focal and diffuse proliferative glomerulonephritis, membranoproliferative glomerulonephritis, focal segmental necrotizing glomerulonephritis with crescents, and minimal change disease. In Benekli's review, predominant IgA deposits are reported in 11 of 40 cases of glomerulonephritis associated with Behçet disease. The report of several cases of focal segmental necrotizing and crescentic glomerulonephritis[277] in the absence of immune complex deposition raises the question of an association with ANCA. The presence of such autoantibodies has been reported in rare cases,[278] but not in systematic screening of patients with Behçet disease.[279]

Treatment

A number of immunomodulatory and immunosuppressant agents are used in the treatment of Behçet disease. These include corticosteroids, calcineurin inhibitor, azathioprine, interferon-alpha, and rituximab.[280,281] More recently the use of agents that block the TNF pathway has also been reported.[282] Because of the rarity of glomerular involvement in Behçet disease, no definitive data for treatment are available. The use of corticosteroids has been reported with variable outcomes. In cases of Behçet disease with severe vasculitic disease or glomerulonephritis, the use of corticosteroids and immunosuppressive therapy with azathioprine or cyclophosphamide may be justified.

THERAPEUTIC CONSIDERATIONS COMMON TO ALL VASCULITIC SYNDROMES

As the mainstay of therapy of severe vasculitis remains based on corticosteroids and alkylating agents, it is associated with short- and long-term complications. The most prominent side effects of this form of therapy are infection, ovarian failure (especially with a prolonged course of cyclophosphamide), bone disease, and cataract formation. In addition, the prolonged use of cyclophosphamide is associated with a 15% risk of developing a transitional cell carcinoma of the bladder over the course of 5 to 10 years.[268] Whether the use of monthly pulse intravenous cyclophosphamide (which is associated with a smaller incidence cumulative dose and a lower incidence of hemorrhagic cystitis) can reduce the rate of bladder cancer is not yet ascertained.

The institution of attentive supportive care is crucial in minimizing the short- and long-term complications. Compulsive attention must be paid to the early detection and aggressive treatment of infections, because they remain an important cause of morbidity and death. Whenever possible,

the use of trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia should be considered.

Whenever corticosteroids are used, measures must be taken to minimize the development of osteoporosis. Specific recommendations include calcium (1.2 g per day) and vitamin D supplementation and, in selected patients with established osteoporosis, calcitonin nasal spray or alendronate for patients in whom the drug is not contraindicated (e.g., azotemia or esophagitis). Rigorous control of blood pressure with sodium restriction and antihypertensive therapy is essential to minimize the additive effect of hypertension in loss of renal function after active nephritis. Current research directions include the preservation of gonadal function by hormonal manipulation during cytotoxic therapy. In a small study, the use of testosterone during cyclophosphamide treatment appeared to prevent azoospermia.[283] The gonadotropin-releasing hormone agonist leuprolide appears to be effective in the prevention of cyclophosphamide-induced ovarian failure based on a small prospective uncontrolled trial of patients with lupus nephritis.[284]

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