CHAPTER 21

Vasculitides
A. Giant Cell Arteritis, Polymyalgia Rheumatica, and Takayasu's Arteritis

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- Giant cell arteritis (GCA) and Takayasu's arteritis (TA) are prototypes of large vessel vasculitis, tending to involve the aorta and its branches.
- Giant cell arteritis predominantly affects the second- to fifth-order aortic branches, often in the extracranial arteries of the head.
- Giant cell arteritis occurs exclusively among individuals who are 50 years of age or older. The mean age at diagnosis onset is approximately 72.
- In TA, the aorta and its major branches are the prime disease targets.
- Both GCA and TA are associated with granulomatous inflammation within the blood vessel wall.
- In both GCA and TA, clinical symptoms of vascular inflammation and vascular insufficiency are usually accompanied or preceded by a systemic inflammatory process.
- Visual loss is the most feared complication of GCA. Visual loss may occur through the syndrome of anterior ischemic optic neuropathy, caused by narrowing of the posterior ciliary artery and other vessels to the eye.
- The diagnosis of GCA is made usually by biopsy of the temporal artery.
- Polymyalgia rheumatica (PMR), a syndrome of muscle pain and stiffness in the neck, shoulders, and hips, often occurs with GCA but can occur independently.
- Glucocorticoids are the cornerstone of treatment for GCA, TA, and PMR. Isolated PMR requires a lower dose of prednisone for disease control.

Despite the spatial closeness of blood vessels and inflammatory cells, blood vessel walls are infrequently targeted by inflammation. Giant cell arteritis (GCA) and Takayasu's arteritis (TA) are characterized by inflammation directed against the vessel wall. GCA and TA display stringent tissue tropism and affect defined vascular territories in a preferential manner. GCA predominantly affects the second- to fifth-order aortic branches, often in the extracranial arteries of the head. The aorta itself may also be affected in GCA, albeit less often than other regions. In contrast, in TA, the aorta and its major branches are the prime disease targets.

In both GCA and TA, clinical symptoms of vascular inflammation and vascular insufficiency are usually accompanied or preceded by a systemic inflammatory process not localizable to a single tissue or organ. Systemic inflammation is also characteristic of polymyalgia rheumatica (PMR), a syndrome of muscle pain and stiffness in the neck, shoulders, and hips. PMR can accompany, precede, or follow GCA, but it also occurs independently. In a subset of PMR patients, GCA is present but not clinically evident.

GIANT CELL ARTERITIS

Epidemiology

Giant cell arteritis is the most common primary form of vasculitis among adults in the United States and Europe. The disease occurs almost exclusively in individuals aged 50 years and older, and its incidence increases progressively with age (1). Women are more likely to be affected than men. The prevalence is highest in Scandi-

navian countries and in regions settled by people of Northern European descent, with incidence rates reaching 15 to 25 cases per 100,000 persons aged 50 years and older. GCA occurs much less frequently in Southern Europeans (6 cases per 100,000 individuals) and is rare in blacks and Hispanics (1–2 cases per 100,000 individuals).

The Vasculitic Lesion

The histological hallmark of GCA is a mononuclear cell infiltrate dominated by T lymphocytes and macrophages. The inflammatory infiltrate penetrates all layers of the arterial wall (Figure 21A-1). The infiltrates can be granulomatous with the accumulation of histiocytes and multinucleated giant cells. Granuloma formation is most likely to be observed in the media. Although the presence of multinucleated giant cells inspired the name of the disease, they are often absent, and the mononuclear infiltrates lack a complex organization. If present, giant cells lie in close proximity to the fragmented internal elastic lamina. Their presence correlates with increased risk for ischemic complications. GCA can also present with perivascular cuffing of vasa vasorum or T cell–macrophage infiltrates in the adventitia, sometimes arranged along the external elastic lamina. This finding is consistent with recent studies suggesting that the adventitia is a critical site in the disease process.

The inflammation causes a series of structural changes to the arterial wall. Among the first pathologic changes observed is the finding of a lymphoplasmacytic infiltrate in the adventitia. With progress of the inflammatory process, the media of the arterial wall becomes thinner. As the medial smooth muscle cell layer loses thickness, the intima becomes hyperplastic, compromising or occluding the arterial lumen. Although the vessel lumen may become critically narrowed, thrombosis is not the central event. Hyperplasia of the intimal layer with scarring in the media and fragmentation of the elastic lamina are irreversible changes that persist beyond the stages of active arterial inflammation.

Fibrinoid necrosis is rare and should raise the suspicion for other forms of vasculitis. Polyarteritis nodosa, microscopic polyangiitis, and Wegener's granulomatosis, for example, are known to affect the temporal artery as well as other more typical vascular beds. When these forms of vasculitis affect the temporal artery, their first pathological manifestations may be lymphoplasmacytic infiltrates within the adventitia, indistinguishable at an early stage from GCA.

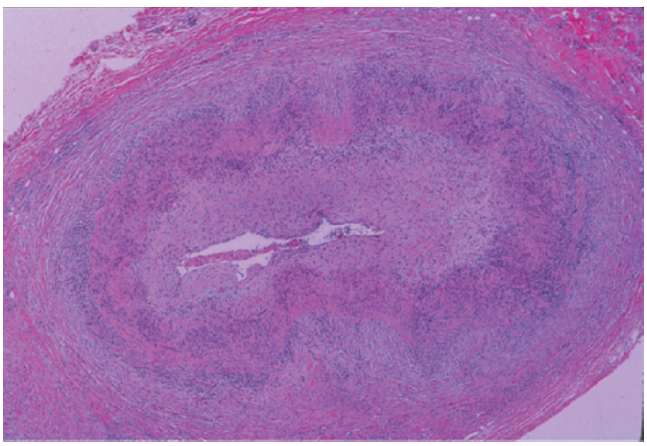


FIGURE 21A-1

Histomorphology of giant cell arteritis. A typical temporal artery biopsy specimen is shown. Characteristic changes include a panmural mononuclear infiltrate, destruction of the internal and external elastic laminae, and concentric intimal hyperplasia.

Pathogenesis

The Immune Response in the Arterial Wall

Experimental evidence supports a T-cell–mediated immunopathology of GCA (2). Humoral immunity does not appear to be important: B cells are not found within the arterial wall; no pathognomic antibodies have been identified; and hypergammaglobulinemia is absent. T cells enter the vessel wall from the vasa vasorum in the adventitia, not from the macroendothelium. Recruitment and activation of tissue-invading T cells is controlled by dendritic cells (DCs) in the adventitia. DCs are an indigenous cell population in normal medium-sized and large vessels. In the adventitia, they are typically localized at the outside of the external elastic lamina, close to the adventitia–media junction. Evidence suggests that these vascular DCs utilize Toll-like receptors (TLRs) to scan their environment for signs of infection, specifically for pathogen-related molecules.

In GCA and PMR, such adventitial DCs are strongly activated, produce chemokines, and express T-cell stimulatory ligands. This model is supported by experiments in human artery mouse chimeras. In these experiments, human temporal arteries from GCA patients are implanted into severe combined immunodeficiency mice. Depletion of either T cells or DCs from the implanted vascular lesions terminates the inflammatory response, with subsequent clearing of the inflammatory infiltrate. In contrast, administration of TLR ligands to chimeras implanted with normal temporal arteries followed by the adoptive transfer of T cells is sufficient to induce the initial steps of vasculitis (3).

Based on these studies, it has been proposed that the vessel wall, in its physiologic state, is an immunoprivileged site. In GCA, activation of vascular DCs by microbial products can break this immunoprivilege and lead to the recruitment and stimulation of T cells. The nature of the peptide antigens recognized by these T cells is

undetermined, but it may be that common self-antigens are sufficiently immunogenic when DCs are activated.

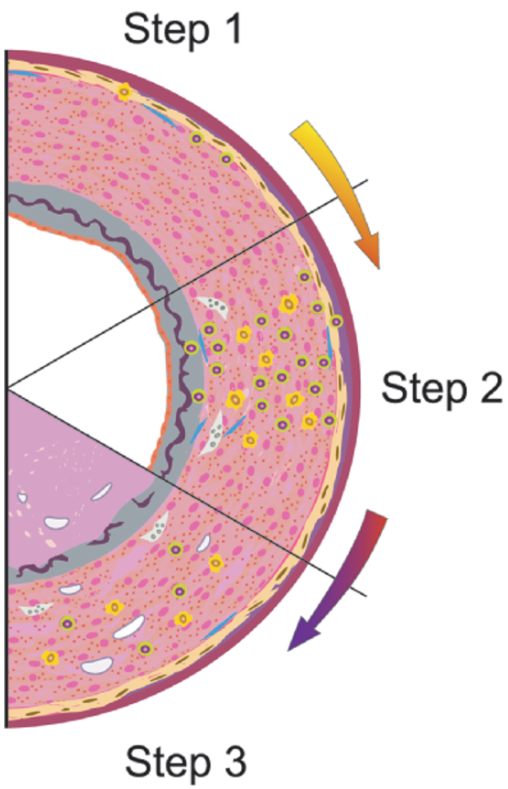
Macrophage function in GCA is known to be multifaceted, with specific commitments of these cells linked closely to their topographical arrangements within the cell wall (4). Interferon (IFN) gamma, a T-cell cytokine, regulates both macrophages and giant cells. Macrophages in the adventitia, intermingling with activated T cells, produce interleukin (IL)-1, IL-6, and transforming growth factor (TGF) beta. Macrophages in the medial layer are specialized in the production of metalloproteinases, and also contribute to oxidative damage. End products of lipid peroxidation, a cell injury mechanism driven by oxygen radicals, are typically found on medial smooth muscle cells (5). Macrophages recruited to the intimal layer are committed to the production of nitric oxide synthase-2. Nitric oxide is suspected to be involved in tissue injury, cellular activation, and vascular remodeling. Multinucleated giant cells, once assumed to function in the removal of indigestible debris, are actually active secretory cells, producing molecular mediators relevant in structurally changing the arterial wall. The presence of giant cells in GCA corresponds with the presence of high adventitial levels of IFN-gamma (6).

The Artery Is an Active Collaborator in Arteritis

The assumption that all pathogenic mechanisms in inflamed arteries are mediated by tissue-infiltrating immune cells is simplistic. T cells and macrophages in the arterial wall do not live and function in isolation, but rather closely interact with stromal components of the blood vessel in a bidirectional pattern (7). The major vascular abnormality leading to clinical disease is a nonthrombotic luminal occlusion, caused by rapid and concentric growth of the intima. These structural alterations result from the response to injury elicited in arterial cells (Figure 21A-2). Intimal hyperplasia is generated by the mobilization of smooth muscle cells, their directed

FIGURE 21A-2

Schematic diagram of the sequence of pathogenetic events in giant cell arteritis. (1) Mononuclear cells enter the adventitia via the vasa vasorum, where T cells recognize antigens and produce IFN-gamma. (2) The infiltrate advances to the media, where macrophages and giant cells undergo differentiation and exert tissue-injurious effector functions. (3) The artery responds with neoangiogenesis and intimal hyperplasia.



Step 1: Immune activation in the adventitia

Activation of vascular dendritic cells by blood-borne microbial products
Chemokine production, recruitment of T cells and monocytes
Stimulation of T cells by activated dendritic cells
Production of IFN-g and other T cell- and macrophage-derived cytokines

Step 2: Persistent T-cell and macrophage activation

Granuloma formation
Macrophage differentiation
Formation of multinucleated giant cells

Production of
- MMPs
- Growth factors/Angiogenesis factors
- Reactive oxygen intermediates

Step 3: Remodeling of the arterial wall with luminal occlusion

Matrix digestion
Fragmentation of elastic membrane
Smooth muscle cell loss
Migration and proliferation of myofibroblasts
Intimal hyperplasia
Neocapillarization of intima/media
Luminal occlusion

migration towards the lumen, and their proliferation and matrix deposition. This process is under the control of growth factors. Platelet-derived growth factor (PDGF), a factor with the capability of supporting the outgrowth of the hyperplastic intima, is present in inflamed arteries. PDGF derives from macrophages and multinucleated giant cells. Patients with low PDGF production have no or minimal lumen-occlusive intimal proliferation. In contrast, those with excessive PDGF production are at a risk for ischemic complications (8).

A second pathway of the arterial injury–response program relates to the formation of new capillaries. The media and intima of normal arteries are avascular, but intense neoangiogenesis is induced in GCA (9). Vascular endothelial growth factor (VEGF) is critical in driving the generation of neovessels in the media and intima. VEGF, like PDGF, originates from macrophages and multinucleated giant cells. The arterial response pattern initiated by the production of PDGF and VEGF leads to profound structural arterial abnormalities with subsequent stenosis and tissue ischemia, emphasizing that the immune system coerces the artery toward a counterproductive pattern of reaction. However, the inflammation also leads to the induction of protective response patterns that are aimed at healing and tissue repair. An example is the upregulation of the enzyme, aldose reductase (10), which metabolizes and detoxifies end products of oxidative damage.

The Systemic Inflammatory Response

The activation of vascular DCs as an early step in the pathogenesis of GCA has two major implications: (1) Inflammation and immune activation are not limited to vascular lesions; and (2) a systemic component of GCA is an independent dimension of the disease process and not simply a spillover from vessel wall inflammation. Further evidence for this systemic component is the activation in GCA patients of circulating monocytes, which produce IL-1 and IL-6. Elevated levels of IL-6, a potent inducer of acute phase responses, are characteristic of GCA. In this model, GCA is a systemic inflammatory disease, with vasculitis of medium and large arteries as a consequence of the disease process.

Risk Factors

Age is the major risk factor for GCA. No other environmental risk factors, including a variety of infectious agents, have been demonstrated convincingly to play important roles in this disease. The high incidence rates of GCA in all geographical regions settled by people of Scandinavian ethnicity strongly suggest inherited risk factors (1). The best available information is for human leukocyte antigen (HLA) genes. HLA-DR4 haplotypes are associated with increased disease risk. Several allelic variants of HLA-DR4 are enriched among patients. Selective binding of antigenic peptides has been proposed as the mechanism underlying this genetic association. In contrast to other HLA-DR4–associated diseases such as rheumatoid arthritis, HLA polymorphisms do not correlate with clinical phenotypes and disease severity. Many other genetic risk factors have been suggested, but none have been proven to date.

Clinical Features

The diagnostic category of GCA encompasses multiple variants (Figure 21A-3). Each of these subtypes has characteristic clinical features (11); however, the clinical manifestations of the different subtypes overlap substantially, and none of the clinical symptoms is unique for any one of the variants. Increased awareness of GCA, a growing population of individuals older than 50 years of age, and improvement in diagnostic procedures (e.g., the availability of magnetic resonance angiography to image the aorta and its branches) have led to increased detection of cases formerly considered to be atypical presentations.

Giant cell arteritis presents with two major symptomatic complexes, signs of vascular insufficiency resulting from impaired blood flow and signs of systemic inflammation. In general, vascular changes are those of occlusion; arterial wall dilatation only occurs when the aorta is involved.

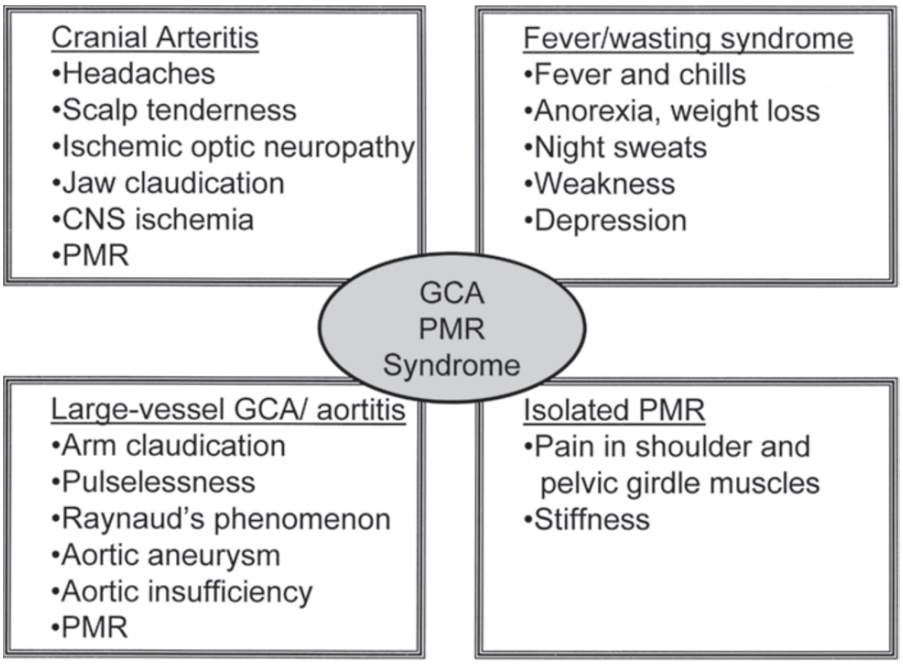
Cranial Giant Cell Arteritis

Giant cell arteritis, also known as temporal arteritis, has a predilection for involving the extracranial branches of the carotid arteries. The temporal artery, which courses just below the skin over the temple region, is the vessel most amenable to biopsy. In 80% to 90% of patients, histopathology of vasculitis is detected in the extracranial arterial tree, most often in the superficial temporal artery; the vertebral, ophthalmic, and posterior ciliary arteries; and, less frequently, the internal and external carotid and central retinal arteries.

Patients complain of throbbing, sharp, or dull headaches that are usually severe enough to prompt clinical evaluation. The headaches may or may not be associated with scalp tenderness. In classic cases, the patients notice temporal tenderness when wearing glasses, grooming, or lying on a pillow. On physical examination, involved vessels may be thickened, tender, and nodular. Pulses may be reduced or absent. Abnormalities are most frequent in the temporal arterial branches, but they can also be detected in the occipital arteries or other superficial scalp vessels. In one third of the patients with biopsy-proven GCA, the temporal arteries are normal on physical examination.

FIGURE 21A-3

Clinical spectrum of the giant cell arteritis/polymyalgia rheumatica syndrome.



Focal arteritic lesions in the ophthalmic artery produce the most feared complication of GCA: vision loss. The disease is an ophthalmological emergency, because prompt recognition and treatment can prevent blindness. Ischemia anywhere along the visual pathway can lead to visual loss, but anterior ischemic optic neuropathy is the most common cause. Visual loss is sudden, painless, and usually permanent. Amaurosis fugax, reported as fleeting visual blurring with heat or exercise or posture-related visual blurring and diplopia, may precede partial or complete blindness. On ophthalmologic examination, anterior ischemic optic neuropathy is recognized by optic disc edema, eventually followed by sectoral or generalized optic atrophy with optic disc cupping. Besides optic neuropathy, the spectrum of ophthalmic complications is wide, ranging from pupillary defects to orbital ischemia and from ocular motor ischemia to anterior and posterior segment ischemia.

A relatively disease-specific manifestation of GCA that is present in about half of the patients is jaw claudication: pain in the masseter or temporalis muscles caused by compromised blood flow in the extracranial branches of the carotid artery. Prolonged talking and chewing produce pain in the muscles of mastication. The onset of jaw claudication following the initiation of chewing is surprisingly swift. Cases of trismus have been described. Claudication of the tongue is less frequent, but tongue infarctions have been reported. Vaso-occlusive disease of the carotid and vertebrobasilar arteries results in ischemia of the central nervous system (CNS), manifesting as transient ischemic attacks or infarcts. Neurologic manifestations are increasingly being recognized and can be expected in 20% to 30% of patients. True intraparenchymal CNS vasculitis in GCA is rare, but reported.

Occult presentations of GCA are common. GCA is the cause of fever of unknown origin in up to 15% of elderly individuals, for example. Nonspecific symptoms of pain in the face, neck, or throat are other warning signs of possible GCA. Chronic nonproductive cough can be an initial presentation of GCA. The involvement of cough receptors (present throughout the repiratory tree) by the vasculitic process is believed to be the cause of cough in GCA.

Giant Cell Arteritis Manifesting as Fever of Unknown Origin

Symptoms related to systemic inflammation are frequently present. Laboratory abnormalities are detectable in more than 90% of patients. In a subset of patients, the disease process is dominated by a systemic inflammatory syndrome. Fever of unknown origin with spiking temperatures and chills usually leads to diagnostic evaluations designed to exclude infections and malignancies. In less dramatic cases, malaise, anorexia, weight loss, low-grade fever, and fatigue eventually become severe enough to prompt medical attention. Physical examination of the scalp arteries is often negative, and symptoms of vascular insufficiency can be absent. Temporal artery biopsy, even if the artery is normal on clinical examination, remains the diagnostic procedure of choice.

Large Vessel Giant Cell Arteritis

In at least 10% to 15% of patients, GCA involves the large arteries in a clinically evident manner. (The percentage of cases with subclinical large vessel disease may be substantially higher.) Preferred vascular beds are the carotid, subclavian, and axillary arteries. Vasculitis of the femoral arteries is infrequent. The major clinical presentation is that of aortic arch syndrome, producing claudication of the arms, absent or asymmetrical pulses, paresthesias, and (rarely) symptoms of digital ischemia. Patients with the large vessel variant of GCA often lack evidence of cranial involvement; they do not complain about headaches, have normal temporal arteries on examination, and almost 50% of temporal artery biopsies are negative for vasculitis (12).

Aortitis in GCA can coexist with cranial arteritis. Whether the patient subset with subclavian–axillary GCA is distinct from the subset progressing to aortic involvement is not known. Overall, the risk of patients with GCA to develop thoracic aortic aneurysm is increased 17-fold (13). The elastic membranes supporting the aortic wall are destroyed and replaced by fibrotic tissue. The resulting histopathology can be indistinguishable from that of TA. Most cases of aortitis have been diagnosed several years after the initial diagnosis of GCA, raising the possibility that smoldering aortitis is more common than previously expected (14). The spectrum of clinical manifestations ranges from silent aneurysm to aortic dissection and fatal rupture.

Diagnosis

In 1990, the American College of Rheumatology (ACR) formulated classification criteria for GCA. These criteria, not intended for the purposes of establishing a clinical diagnosis of GCA, are shown in Appendix I.

The diagnosis of GCA should be considered in patients aged 50 years and older with recent onset of unexplained headache, signs of tissue ischemia in the extracranial vascular territory, loss of vision, symptoms of limb or jaw claudication, or polymyalgia rheumatica. Laboratory evidence of an acute phase response heightens concern about GCA. The diagnostic procedure of choice is the histological verification with the superficial temporal artery. In a recent meta-analysis, positive clinical predictors of a positive biopsy were jaw claudication, diplopia, and abnormalities of the temporal artery biopsy on physical examination (15). All other symptoms, including vision loss, elevated sedimentation rate, headaches, and constitutional symptoms, were not particularly helpful in predicting the results of temporal artery biopsies (i.e., in diagnosing GCA). The presence of synovitis was a negative predictor of GCA, indicative of the fact that most patients with true arthritis have another diagnosis, such as rheumatoid arthritis.

Even the most specific findings for history, physical examination, and routine laboratory testing have sensitivities of only (at best) 50%. In view of the fact that rendering the diagnosis of GCA commits a patient to long-term course of glucocorticoid therapy, confirmation of the diagnosis by temporal artery biopsy is essential whenever possible. True negative results are expected in more than 50% to 70% of all patients undergoing biopsies at most institutions. False-negative biopsies, which occur as frequently as 10% of the time, can be minimized by taking a sufficient length of biopsy, by examining serial sections, and by removing the contralateral temporal artery when the first biopsy is free of arteritis. Short-term glucocorticoid treatment (up to 2 weeks, or even significantly longer) is unlikely to interfere with the results of a temporal artery biopsy. Prednisone should therefore not be withheld if a biopsy cannot be performed immediately.

Laboratory Testing

A pathognomic laboratory test for GCA does not exist. Specific autoantibodies have not been identified. Highly elevated acute phase responses are typical for GCA but are not present in all patients. Although a high erythrocyte sedimentation rate (ESR) is usually considered a hallmark of GCA, in a recent study 25% of all patients with positive temporal artery biopsies had normal ESRs before the initiation of glucocorticoid therapy (16). Other markers of acute phase response, particularly C-reactive protein (CRP), may be more sensitive than ESR in some patients, but studies have not demonstrated this consistently. Some evidence indicates that the most sensitive serum marker for ongoing systemic inflammation in GCA (both before and after glucocorticoid therapy) is IL-6. IL-6, a strong inducer of acute phase reactants, probably functions upstream in the disease process. Unfortunately, reliable IL-6 measurements are not widely available, and knowledge about how (or if) to adjust therapy in the context of changing IL-6 levels remains incomplete. There is currently no evidence that treatment decisions should be predicated upon the results of laboratory tests—ESR, CRP, or IL-6—in the absence of clinical symptoms.

Other laboratory abnormalities in GCA include mild-to-moderate normochromic or hypochromic anemia. Elevated platelet counts are common. Liver function tests, particularly alkaline phosphatase, can be abnormal.

Imaging Studies

Precise mapping of the vaso-occlusive process still requires angiography. Angiography is also essential for patients with significant stenoses in vessels to all four extremities, for the purpose of measuring central aortic

pressure directly. Alternatives to conventional angiography, however, have made great strides in recent years (17). Magnetic resonance angiography (MRA) permits evaluation of vessel wall thickness and perivascular edema—significant advantages over conventional angiograms, which evaluate only the vascular lumen. In the proper clinical context, therefore, certain MRA findings may be diagnostic of large vessel vasculitis. The noninvasive nature of MRA also lends important advantages in serial monitoring. Unfortunately, the appropriate interpretations of some MRA findings, for example, enhancement of the vessel wall following gadolinium administration and the presence of vessel wall edema, remain uncertain and require additional longitudinal studies.

Computed tomography angiography, another promising technique, has not been evaluated thoroughly in large vessel vasculitis. Position emission tomography (PET) with ^{18}F-fluorodeoxyglucose also holds promise for the assessment of the degree of disease activity in large arteries, but has not yet been validated for general clinical use. Other noninvasive vascular studies, including fluorescein angiography, transcranial Doppler flow studies, and Doppler ultrasonography, are useful in assessing certain vascular beds, for example, the retinal, vertebral, or subclavian arteries. These techniques only identify vascular insufficiency in cases with pronounced, lumen-stenosing disease, however, and do not provide specific information useful from the standpoint of diagnosis. Although Doppler ultrasound was once hypothesized to be useful in the diagnosis of GCA, the value of identifying a "hyperechoic halo" on ultrasound in the temporal artery has not been confirmed in subsequent studies (18).

Treatment

Glucocorticoids are explicitly effective in suppressing clinical manifestations of GCA. Since the introduction of glucocorticoids, the rate of GCA-related blindness has declined, documenting the effectiveness of this immunosuppressive approach. In almost all patients, glucocorticoids induce relief within 12 to 48 hours. The excellent response of the disease to this therapy has been suggested by some as a diagnostic criterion.

In view of the severity of GCA-related morbidity, initial doses of 60 mg prednisone or equivalent have been recommended. Glucocorticoids cannot reverse intimal hyperplasia but may help attenuate the ischemic insult by reducing tissue edema. In ophthalmologic emergencies (e.g., amaurosis fugax occurring in suspected GCA), pulse glucocorticoids may be appropriate (19). Initial doses should be maintained until reversible manifestations of the disease have responded and the systemic inflammatory syndrome is suppressed. Subsequently, under close monitoring for clinical signs of disease reactivation, the dose of prednisone generally can be tapered by 10% every 1 to 2 weeks.

So far, the use of glucocorticoid-sparing agents to allow a more rapid taper has been unsuccessful (17). Initial positive results with methotrexate could not be confirmed in a subsequent study (20). A recent randomized, controlled trial of tumor necrosing factor (TNF) alpha blockade found this therapy to be ineffective as a glucocorticoid-sparing medication (21). A recent study suggests that a more aggressive induction therapy at the onset of the disease, including three daily pulses of 1 gram of methylprednisolone, may allow for a rapid tapering of glucocorticoids and, in particular, a discontinuation of glucocorticoids in the second year of disease (22).

Aspirin is an important adjunctive treatment for GCA patients without contraindications. Retrospective studies have indicated strong reductions in the risks of visual loss and central nervous system ischemic events among patients taking aspirin for other reasons at the time their GCA was diagnosed (23). The mechanism of aspirin's efficacy in this setting is not entirely clear, but the medication may exert its effect through the selective suppression of interferon gamma production (17). Although the optimal dose of aspirin has not been established, doses ranging from 81 mg/day to 325 mg/day may be beneficial.

Prognosis

The most significant morbidity of GCA relates to reduced blood flow to the eye and optic nerve as well as hypoperfusion of the brain (19). If diagnosed and treated promptly, progression of the downstream effects of arterial wall inflammation, in particular lumen occlusion with tissue ischemia, can be prevented. Side effects of high doses of glucocorticoids given over a prolonged period of time can be serious, especially in patients older than 50 years, and treatment should therefore only be initiated if the diagnosis is confirmed. In the majority of patients, GCA does not enter remissions that are sustained indefinitely after discontinuation of glucocorticoids. In a prospective study of 25 patients with biopsy-proven GCA, all of the patients responded to 60 mg prednisone with disappearance of clinical signs of the disease (16). However, 60% of patients had disease relapses that occurred throughout the course of treatment. Typically, reactivation of the disease produced symptoms of systemic inflammation or polymyalgic symptoms, but no vascular complications were seen.

POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica is diagnosed in patients presenting with pain and stiffness in the muscles of the neck, shoulder girdle, and pelvic girdle of at least 4

weeks' duration (24). The myalgias are combined with signs of systemic inflammation manifesting clinically as malaise, weight loss, sweats, and low-grade fever. Most patients have laboratory abnormalities such as elevated ESR, elevated CRP, and anemia, which are indicative of a systemic inflammatory syndrome. Upregulation of acute phase reactants is helpful in distinguishing PMR from other pain syndromes, yet (as in GCA and TA) not all patients with active disease have elevated markers of inflammation within their serum. No pathognomic test for PMR is available; exclusion of other diseases with similar clinical presentations is essential. The systemic inflammatory syndrome associated with PMR is exquisitely sensitive to glucocorticoid therapy, such that prompt improvement of clinical symptoms with glucocorticoid therapy has been proposed as a diagnostic criterion. The pathophysiology of PMR is related closely to those of GCA. PMR is now often considered a form of GCA that lacks fully developed vasculitis.

Epidemiology

Because PMR remains a clinical diagnosis, epidemiological studies are difficult. PMR affects the same patient population as GCA, but occurs approximately two to three times more frequently (24). Women are affected more often than men, and the diagnosis is extremely unlikely in individuals younger than 50 years of age. In high-risk populations, such as Scandinavians and other peoples of Northern European descent, annual incidence rates have been estimated at 20 to 53 per 100,000 persons over the age of 50 years. In low-risk populations, such as Italians, the annual incidence rates for individuals aged 50 years and older are only 10 cases per 100,000.

Pathogenesis

Although the sudden onset of intense inflammation is suspicious for an infectious etiology, no causative agent has been identified. Most pathogenic abnormalities in PMR patients are reminiscent of those in GCA, supporting the concept that PMR is a variant of GCA characterized by the dominance of the systemic inflammatory over the vascular component.

Human leukocyte antigen polymorphisms that are genetic risk factors for GCA are also associated with PMR. There is no evidence that the HLA has a role in determining whether the disease process will remain limited to PMR or progress to fully developed GCA.

Polymyalgia rheumatica appears to be associated with a global activation of the innate immune system, including circulating monocytes that produce IL-1 and IL-6. Activated DCs render arteries susceptible to vasculitis. In many patients with PMR, in situ cytokine production can be demonstrated in biopsy specimens, although in lower quantities than in GCA. Of note, IFN-gamma is absent in PMR, but abundant in GCA (25). A subset of PMR patients develops inflammation of periarticular structures, for example, bursae. Whether these patients comprise a different subset from those susceptible to developing frank vasculitis remains unclear.

Clinical Features

Patients complain about aching and pain in the muscles of the neck, shoulders, lower back, hips, thighs, and occasionally the trunk. In typical cases, the onset is abrupt and the myalgias symmetrical; they usually affect the shoulders first. Often the patients have pain during the night and have difficulties rising and dressing themselves. Weight loss, anorexia, malaise, and depression are common. Fever and chills should raise the suspicion of fully developed GCA. PMR is frequently difficult to distinguish from forms of seronegative polyarthritis. In particular, male patients can present with proximal aching and diffuse edema of the hands and feet that is highly glucocorticoid-responsive.

Polymyalgia rheumatica includes patients with mild disease that is promptly responsive to therapy and remits within a few months (26). In many patients, however, reactivation of myalgias occurs when glucocorticoid doses are tapered. Some patients require higher initial doses of glucocorticoids than are usually considered to be effective in PMR.

Patients with PMR must be carefully evaluated for possible GCA. A negative temporal artery biopsy does not exclude the possibility of large vessel vasculitis targeting primarily the subclavian and axillary arteries and the aorta. Signs of vascular insufficiency, including claudication in the extremities, bruits over arteries, and discrepant blood pressure readings should alert the physician to the possibility of GCA (12). MRA can be helpful in confirming the concomitant diagnosis of large vessel vasculitis.

In PMR patients with inflammation of periarticular structures, the most prominent findings are subdeltoid and subacromial bursitis (27). Biceps tendonitis and glenohumeral synovitis may also be present. Ultrasonography reveals fluid accumulation in the bursae; T2-weighted MRI shows thickening and edema. These involved areas show increased uptake on PET scans.

The clinical symptoms of PMR can be mimicked by a number of arthropathies, shoulder disorders, inflammatory myopathies, hypothyroidism, and Parkinson's disease. The differential diagnosis also includes malignancies and infections. No clear guidelines have been developed to determine whether patients with PMR should be screened for occult malignancies. Lack of the typical and impressive improvement upon initiation of

therapy can provide a clue towards reevaluating the diagnosis of PMR.

Treatment

Polymyalgia rheumatica is dramatically responsive to glucocorticoid therapy. Currently there are no data documenting glucocorticoid-sparing effects of other medications. However, almost all patients with PMR can be safely managed with glucocorticoids; doses for long-term treatment are low and unlikely to cause serious side effects.

A critical decision in treating PMR is the dose of glucocorticoids required for successful suppression of symptoms and inflammation. The glucocorticoid requirements may differ quite markedly among patients. Two thirds of patients can be expected to respond with remission of pain and stiffness when started on 20 mg/day or less prednisone (25). Some patients will need doses as high as 40 mg/day for complete clinical control. Such patients may be at higher risk of full-blown GCA. Patients initially controlled on 20 mg/day of prednisone can usually taper the dose by 2.5 mg every 10 to 14 days. More protracted tapering may be necessary once daily doses of 7 to 8 mg prednisone are attained. Dose adjustments should be based mainly on clinical evaluation, not exclusively on laboratory abnormalities. In many patients, PMR can go into long-term remission, and prednisone can be discontinued. Occasionally, successful suppression of recurrent myalgias and stiffness may only be achieved by giving very low doses of prednisone over an extended period. Patients should be warned about the potential of PMR progressing to GCA and should be monitored for vascular complications, particularly when discontinuing glucocorticoid therapy.

Prognosis

The prognosis of patients with PMR is good. In the majority of patients, the condition is self-limited. A proportion of patients will eventually present with typical symmetrical polyarthritis, fulfilling the criteria for the diagnosis of seronegative rheumatoid arthritis. Such patients may require disease-modifying antirheumatic drug (DMARD) therapy.

TAKAYASU'S ARTERITIS

Takayasu's arteritis is a vasculitis of the large elastic arteries, specifically the aorta and its main branches. The disease may also affect the coronary and pulmonary arteries (28). Inflammatory injury to the vessel wall leads to patchy disappearance of the elastica and smooth muscle layer and subsequent intimal hyperplasia, resulting in vascular stenosis in virtually all patients and dilatation and aneurysm in about 25%. Complete occlusion of upper extremity arteries results in the loss of palpable pulses, which is why TA is also termed the *pulseless disease*. The preference for the aorta and its primary branches is signified in another alternative name, *aortic arch syndrome*. The ACR has developed a set of criteria to distinguish TA from other vasculitic syndromes (see Appendix I).

Epidemiology

Takayasu's arteritis is a rare disease that primarily affects adolescent girls and young women. The diagnostic criteria include an age of less than 40 years at disease onset; however, TA can start later in life, particularly in Asians (29). (In addition, the diagnosis is often not made until the patient is older than 40, but symptoms may have begun years before the diagnosis.) Incidence rates are highest in Asia (Japan, Korea, China, India, and Thailand), with estimates of approximately 1 case per 1 million persons annually. TA can occur in all races and geographic regions, but South American countries have recently been recognized as additional areas of relatively high incidence. An international survey among 20 countries has indicated differences in the clinical spectrum of TA in different ethnic groups.

Pathogenesis

Takayasu's arteritis is a granulomatous polyarteritis. The adventitia is characterized by striking thickening, often with intense perivascular infiltrates around the vasa vasorum. Granuloma formation and giant cells are predominantly found in the media of the large elastic arteries. The medial elastic smooth muscle cell layer is destroyed in a centripetal direction and replaced by fibrotic tissue, leading (in the aorta) to vessel wall dilatation and aneurysm formation. Smooth tapering, narrowing, or complete occlusion of the vascular lumen results from proliferation of the intima, occasionally with thrombosis.

The etiology of TA remains unknown. In view of the systemic features of the syndrome, microbial infections have been implicated, but no conclusive evidence for infectious organisms has been provided. CD8 T cells are a major component of vascular infiltrates, setting TA apart from GCA. Cytotoxic activities of tissue infiltrating CD8 T cells, mediated by the release of the pore-forming enzymes perforin and granzyme B, have been suspected of contributing to smooth muscle cell damage (30).

Support for a role of CD8 T-cell–mediated cytolytic tissue injury has come from the observation that selected HLA class I molecules, specifically HLA-B52, are overrepresented among TA patients (31). CD8 T cells recognize antigens when bound to HLA class I molecules.

The role of CD4 T-cell responses and the contribution of macrophage effector functions in the vascular lesions are not understood. The focus of lymphocytic infiltrates on the adventitia and accumulation of T cells around vasa vasorum makes it less likely that the macroendothelium has major involvement in the pathogenesis of TA.

Clinical Features

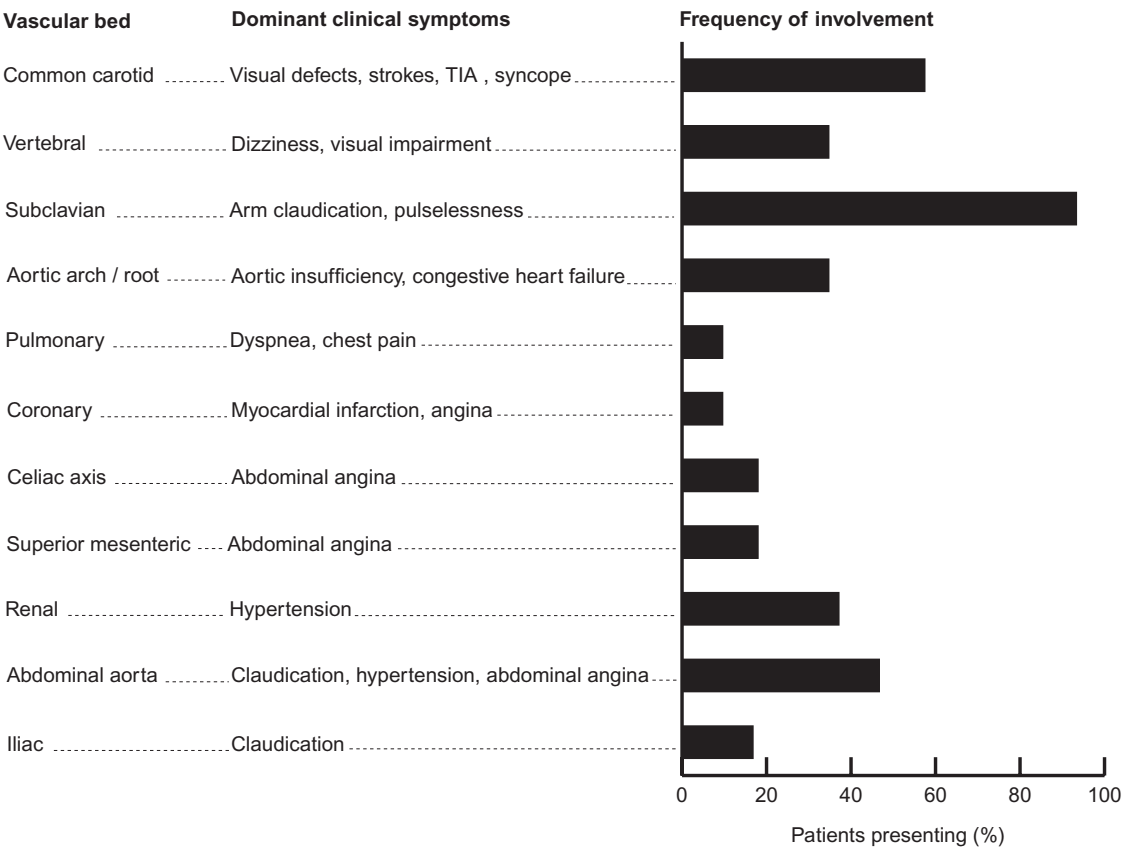
A generalized inflammatory syndrome with fever, night sweats, malaise, anorexia, weight loss, and diffuse myalgias often dominates initial manifestations of TA. These symptoms are frequently misdiagnosed as infection. The clinical pattern of ischemic complications that emerge—often years later—directly reflect the vascular territory targeted by the disease (Figure 21A-4).

Involvement of the carotid and vertebral arteries leads to neurologic and ophthalmologic symptoms, including dizziness, tinnitus, headaches, syncope, stroke, and visual disturbances. Atrophy of facial muscles and jaw claudication are mostly late manifestations. Occlusions of the brachiocephalic and subclavian arteries impair blood flow to the upper extremities, presenting as arm claudication, pulselessness, and discrepant blood pressures. The detection of bruits can be helpful in making the diagnosis.

Cardiac disease, including ischemic coronary disease, arrhythmia, and congestive heart failure, can be related to aortitis of the ascending aorta or severe hypertension. Aortic regurgitation, a serious complication requiring prompt clinical attention, is a consequence of aortic dilatation. Coronary arteries can be involved directly or indirectly, producing classical symptoms of myocardial ischemia. Progressively enlarging aneurysms and possible rupture are a major concern in patients with TA of the aortic arch and the descending thoracic aorta. Patients from India, China, and Korea often have lesions in the abdominal aorta and its branches (particularly the renal arteries, causing renovascular hypertension). The proximal ends of mesenteric arteries are less frequently affected, but gastrointestinal symptoms, such as nausea, vomiting, and ischemic bowel disease can be seen in patients with TA.

FIGURE 21A-4

Clinical spectrum of Takayasu's arteritis in relationship to vascular bed involvement.



Diagnosis

A combination of vaso-occlusive disease and systemic inflammation in a young patient should immediately raise suspicion for TA. Typically, the diagnosis is made by characteristic findings on vascular imaging (32). Tissue is rarely available. The findings on conventional angiography can be diagnostic for TA in the proper clinical setting. Angiography reveals long, smooth taperings of involved vessels, with a remarkable web of collateral blood vessels in advanced cases. As in GCA, conventional angiography is essential in many patients with TA in order to measure accurately the central aortic blood pressure.

Several noninvasive imaging techniques are informative for assessing progression of occlusive disease, but currently lack standardization and are subject to investigator bias and experience. Far more problematic than assessing the degree of stenosis within a given blood vessel is the reliable assessment of inflammatory activity by imaging. MRI/A has largely replaced conventional angiography for serial assessments of the distribution and degree of vessel involvement, and also permits evaluations of the vessel wall as well as the lumen. MRI/A is particularly important in the longitudinal monitoring of TA although, as noted, the correct interpretation of all MRI/A findings is not always clear. MRI/A has clear utility in monitoring the progress or stability of vascular stenoses, provided that serial studies are compared carefully for changes. Doppler ultrasound provides a good assessment of cervical vessels. Computed tomography angiography can be used to survey the aorta and proximal vessels, but rigorous serial studies of its use in TA remain to be performed. The role of PET scanning in gauging the degree of ongoing inflammation (as opposed to uptake that might be related to a process of healing or fibrosis) has not been established.

Treatment

Although some patients with TA have disease that appears to "burn out," becoming quiescent after years of active disease, most patients have progressive or relapsing/remitting disease and require long-term immunosuppressive treatment (33). Glucocorticoids are the therapy of choice for management of TA. Recommendations of initial doses have varied, but 40 to 60 mg of prednisone may be necessary to control vascular as well as systemic inflammation. Monitoring of acute phase reactants (ESR, CRP) is only helpful in a subset of patients. In a National Institutes of Health (NIH) cohort, 50% of patients had active progressing disease despite nonelevated acute phase reactants (34). Prednisone doses are tapered as clinically indicated and tolerated, usually by 5 mg/day every 2 weeks until a maintenance dose of 10 mg/day is reached. Further dose reductions must be tailored to the individual patient. Low-dose aspirin or other antiplatelet agents should complement glucocorticoid therapy. Methotrexate, given in weekly doses of up to 25 mg, has shown promise in improving remission rates and sparing glucocorticoids (35), but has never been tested in a randomized trial (the same is true for all other potential steroid-sparing agents). Azathioprine, mycophenolate mofetil, cyclosporine, and TNF-alpha blockers have been used with reported success in individual patients, but controlled studies are required. Contrary to other vasculitides, cyclophosphamide does not play a major role in this disease because of its toxicity and uncertain efficacy.

Stenotic lesions are irreversible. Surgical management and angioplasty or stent placement have a role in selected patients, but for most patients revascularization attempts of vessels to the extremities are not necessary because of the exuberant collateralization that develops in TA. When revascularization is necessary, bypass grafts are generally successful, while stenting appears to have a high rate of reocclusion (33). Angioplasty is reserved for short stenotic segments. Treatment of hypertension secondary to renal artery stenosis may or may not benefit from revascularization, depending on the location of the lesion leading to renovascular hypertension. Decisions about whether or not to attempt revascularization should be undertaken in consultation with experts accustomed to the management of complex hypertension cases.

Prognosis

For much of the past several decades, TA has been viewed as an inevitably devastating disease. The diagnosis was seldom made before damage from prolonged vascular inflammation was already extensive. More recently, the potential for earlier diagnosis, effective immunosuppressive therapy, and astute surgical management have led to an improved prognosis for many patients. Long-term follow up of almost 1000 Japanese patients found stable clinical conditions in two thirds of the patients and serious complications occurring in only 25% of affected individuals. Cardiac complications, including congestive heart failure and ischemic heart disease, have become the most common cause of death in Japanese patients with TA. Acceleration of atherosclerotic disease emerges as a critical factor in long-term outcome.

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CHAPTER 21

Vasculitides
B. Polyarteritis Nodosa

KEITH T. ROTT, MD, PHD

- Polyarteritis nodosa (PAN) primarily affects medium-sized arteries that supply the skin, gut, nerve, and kidney, but may involve multiple organs.
- Microaneurysms of arteries to or within the kidneys, liver, or gastrointestinal tract are highly characteristic of PAN.
- Polyarteritis nodosa is not associated with antineutrophil cytoplasmic antibodies (ANCA) directed against either proteinase-3 or myeloperoxidase.
- Mononeuritis multiplex, an asymmetric sensory and motor neuropathy due to ischemia and infarction of peripheral nerves, occurs frequently in PAN.
- In mononeuritis multiplex, nerve conduction studies of peripheral nerves reveal a distal, asymmetric, axonal neuropathy involving both motor and sensory nerves.
- Polyarteritis nodosa is characterized pathologically by patchy, transmural inflammation in medium- and small-sized muscular arteries, sparing large arteries, capillaries, and the venous system. The inflammation leads to fibrinoid necrosis, but is not associated with granulomatous features.
- High-dose glucocorticoids are the mainstay of therapy in PAN. In cases that are rapidly progressive or life- or organ-threatening, however, cyclophosphamide is added to glucocorticoid treatment.
- Most cases of idiopathic PAN do not recur once a sound remission has been achieved with 6 to 12 months of therapy.
- A minority of PAN cases (now >10%) are associated with acute hepatitis B infection. Cases associated with hepatitis B are treated with regimens emphasizing antiviral therapy and only short courses of immunosuppression and plasmapheresis.

Polyarteritis nodosa (PAN) is a vasculitis affecting predominantly medium-sized arteries. Clinically, PAN often presents insidiously with nonspecific, constitutional symptoms. The disease has a predilection for medium-sized arteries supplying skin, gut, nerve, and kidney, but may involve multiple organs. The majority of PAN cases have no known cause, but cases secondary to hepatitis B virus infection have been reported.

Described by Kussmaul and Maier in 1866 (1,2), PAN is often regarded as the first reported form of systemic vasculitis. In fact, earlier descriptions of Behcet's disease, Takayasu's arteritis, Henoch–Schönlein purpura, and even PAN itself exist in the medical literature. For nearly a century after the case reported by Kussmaul and Maier, however, most forms of systemic vasculitis were termed *periarteritis nodosa*, and forms of vasculitis recognized later were contrasted and classified in comparison to PAN. The patient described by Kussmaul and Maier was a 27-year-old male with fever, weight loss, abdominal pain, and a polyneuropathy that progressed over the period of 1 month to paralysis. An autopsy revealed microaneurysms ("whitish small tumors up to the size of poppy and hemp seeds") throughout medium-sized arteries, conspicuously sparing both the venous circulation and the lungs.

Before the delineation of vasculitis subsets and the formulation of definitions based principally on vessel size (3), PAN was used to describe two now-distinct forms of vasculitis: the classic PAN described by Kussmaul and Maier, and "microscopic PAN" (now called *microscopic polyangiitis*). According to current convention, and as described in this text, PAN is a vasculitis affecting medium-sized arteries. PAN is also not associated with antineutrophil cytoplasmic antibodies (ANCA), at least not those directed against proteinase-3 (PR3) or myeloperoxidase (MPO) that are such a distinctive feature of the majority of cases of Wegener's granulomatosis, microscopic polyangiitis, and, to a lesser extent, the Churg–Strauss syndrome. Although patients may be P-ANCA-positive on immunofluorescence testing, enzyme immunoassays for PR3- and MPO-ANCA are negative in PAN. Further, in contrast to the ANCA-associated vasculitides (see Chapter 21C), PAN does not involve either the lungs or

blood vessels as small as the renal glomeruli (which are essentially capillaries).

Polyarteritis nodosa affects men and women approximately equally and has a broad age range of patients. Although the incidence of PAN varies according to the population studied, it is rare in all populations, with annual incidence rates generally ranging from 2 to 9 cases per million. Higher rates have been reported in populations with a high burden of hepatitis B virus infection, but with the availability of a vaccine, hepatitis B virus infection now accounts for less than 10% of PAN cases in developed countries (4). PAN has also been reported to occur in conjunction with hairy cell leukemia.

CLINICAL FEAURES

Polyarteritis nodosa can present with nonspecific constitutional symptoms such as fever, fatigue, malaise, myalgias, and arthralgias. This phase of the illness can last weeks or months. The more specific clinical manifestations of PAN are the direct results of inflammation in medium- and small-sized muscular arteries. PAN often has cutaneous involvement, a feature it shares with small vessel vasculitides such as the ANCA-associated disorders. This differentiates it from large vessel vasculitis (e.g., giant cell arteritis and Takayasu's arteritis), in which skin disease is very rare. However, unlike the ANCA-associated vasculitides, PAN is not associated with glomerulonephritis or pulmonary involvement. Common clinical features of PAN and their frequency are listed in Table 21B-1 (5).

In autopsy studies, the most frequently involved organ in PAN is the kidney. Involvement of the medium-sized arteries supplying the renal parenchyma can result in hypertension due to renal ischemia; hypertension is mediated by the renin–angiotensin system. Renal insufficiency, another common manifestation of PAN, is due to ischemia resulting from the involvement of arteries the size of renal arteries and smaller. Microaneurysms, detectable by angiography [Figure 21B-1(A,B)], are a hallmark of PAN.

The gastrointestinal (GI) tract is involved in up to 50% of patients. Postprandial periumbilical pain, or intestinal angina, is the result of mesenteric ischemia. More severe disease can result in bowel infarction and perforation. Other GI symptoms can include nausea, vomiting, diarrhea, and bleeding. While the small intestine is most commonly involved, rare presentations involving ischemia of the gallbladder or appendix have

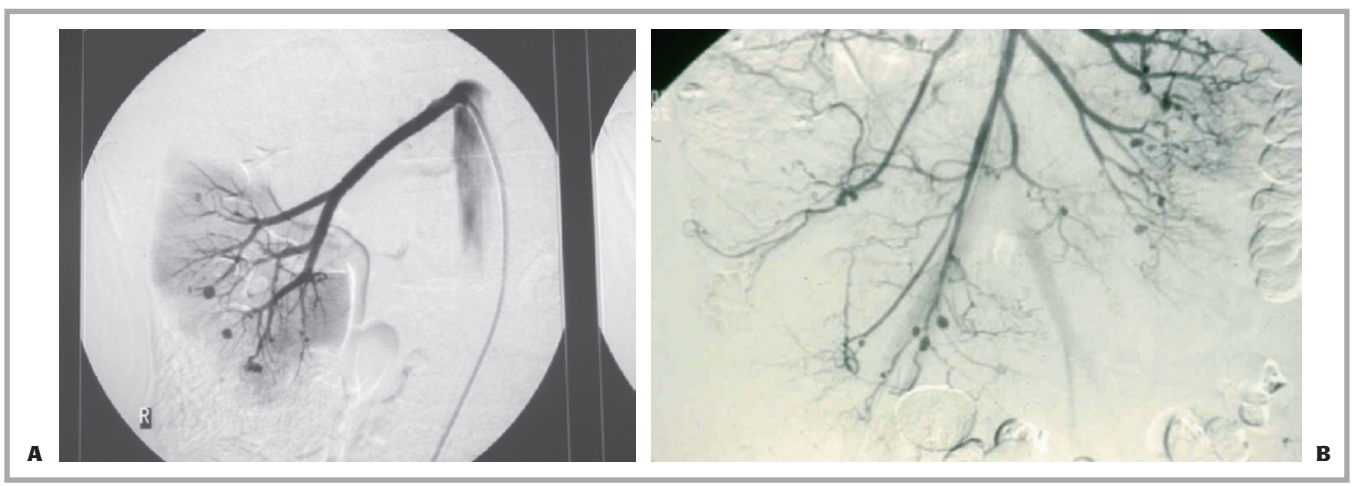
TABLE 21B-1. SELECTED CLINICAL AND DIAGNOSTIC FEATURES OF PAN AND THEIR FREQUENCY.

Clinical Features	
Myalgias, general weakness, or leg muscle tenderness	69%
Weight loss ≥4 kg	67%
Mononeuropathy or polyneuropathy	65%
Azotemia (BUN > 40 mg/dL or Cr > 1.6 mg/dL)	40%
Hypertension (diastolic blood pressure >90 mm Hg)	37%
Testicular pain or tenderness	29%
Skin ulcers, infarction, or peripheral gangrene	27%
Livedo reticularis	25%
Abdominal angina or ischemic perforation	24%
Diagnostic Features	
Visceral arteriogram with aneurysm or occlusion	73%
Biopsy of small-or medium-sized artery with granulocytes	48%
Abnormal arteriogram or characteristic biopsy	92%

SOURCE: From Lightfoot RW, et al. Arthritis Rheum 1990;33:1088–1093, by permission of *Arthritis and Rheumatism*.
ABBREVIATIONS: BUN, serum urea nitrogen; Cr, creatinine.

FIGURE 21B-1

Microaneurysms detected by angiography in polyarteritis nodosa. (A) Renal microaneurysms. (B) Mesenteric vessel microaneurysms. (Courtesy of Dr. John Stone.)



been described (6). Moderately elevated hepatic transaminases often betray liver involvement. Asymptomatic mircoaneurysms within the liver are common; these occasionally rupture.

Involvement of the peripheral nervous system is seen in 50% to 75% of patients, usually as an asymmetric sensory and motor neuropathy due to ischemia of peripheral nerves (7). Infarction of named nerves results in mononeuritis multiplex (Figure 21B-2). Progressive sensory neuropathy has been described less frequently. Central nervous system involvement is much less common, but has been reported in the form of cerebrovascular accidents.

Polyarteritis nodosa can have multiple cutaneous manifestations: livedo reticularis, nodules, ulcerations (Figure 21B-3), and frank ischemia of digits (8). A small group of patients have a form of disease termed *cutaneous PAN*, a variant limited ostensibly to the skin. These patients develop nodules and ulcerations, primarily of the lower legs, which can occur in crops and can be very painful. However, as with any other vasculitis, cutaneous manifestations should prompt a thorough evaluation for evidence of systemic disease.

As with Kawasaki's disease, the other medium vessel vasculitis described in this text, PAN can also involve the coronary arteries. Clinical proof of coronary disease during life is difficult. Myocardial infarction is uncommon, and coronary involvement is usually only seen at autopsy. Contraction band necrosis, indicative of segmental ischemia, is a common finding in the myocardium at autopsy, attesting to the presence of vasculitis below the resolution of conventional angiography. PAN can involve other organs, such as the testicle, ovary, breast, and eye.

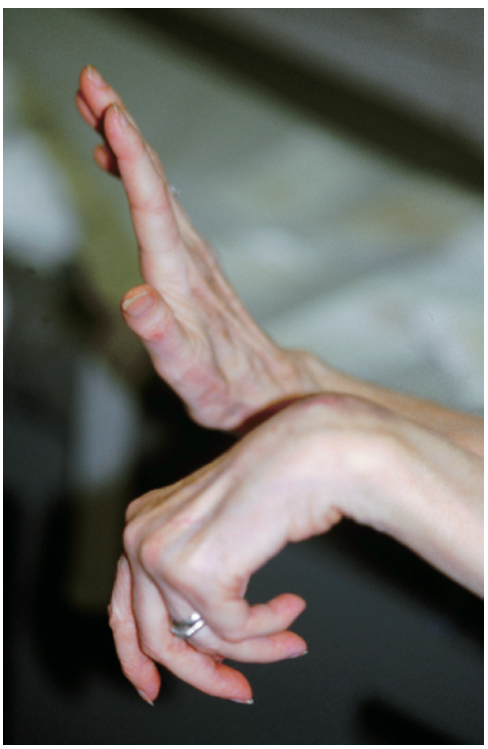


FIGURE 21B-2

Mononeuritis multiplex. (Courtesy of Dr. John Stone.)

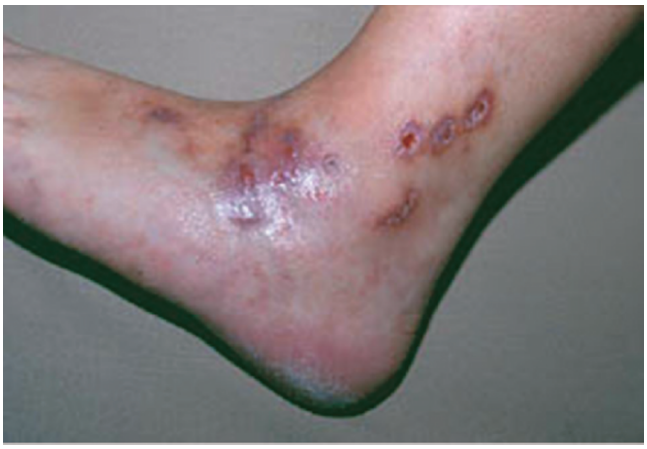


FIGURE 21B-3

Cutaneous ulcerations over both medial malleoli in polyarteritis nodosa. (Courtesy of Dr. John Stone.)

PATHOLOGY

Polyarteritis nodosa is characterized pathologically by patchy, transmural inflammation in medium- and small-sized muscular arteries, sparing large arteries, capillaries, and the venous system. There is a pleomorphic cellular infiltrate and fibrinoid necrosis in the vessel, but no features of granulomatous inflammation. Disruption of the elastic laminae of the vessel wall can lead to aneurysmal dilatation at the site of the lesion. PAN has a predilection for certain organs: arteries to the kidney are estimated to be involved 70% to 80% of the time, the GI tract is involved in 50% of cases, the peripheral nerves are involved in 50% of cases, and the central nervous system is involved in 10% of cases (9).

DIAGNOSIS

Polyarteritis nodosa is diagnosed based on characteristic symptoms, physical examination findings, and compatible laboratory, angiographic, and pathologic data. Because PAN is a rare disease and its treatment can result in serious adverse events, the diagnosis should be supported with either abdominal angiography or biopsy whenever possible. PAN must be differentiated from other forms of vasculitis, such as the ANCA-associated disorders, cryoglobulinemia, and Buerger's disease.

TABLE 21B-2. AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR CLASSIFICATION OF PAN.

At least 3 of 10 criteria:
1. Weight loss ≥4 kg
2. Livedo reticularis
3. Testicular pain or tenderness
4. Myalgias, weakness, or leg tenderness
5. Mononeuropathy or polyneuropathy
6. Diastolic blood pressure >90 mm Hg
7. Elevated serum nitrogen urea (>40 mg/dL) or creatinine (>1.5 mg/dL)
8. Hepatitis B virus infection
9. Arteriographic abnormality
10. Biopsy of small- or medium-sized artery containing polymorphonuclear neutrophils

SOURCE: From Lightfoot RW, et al. Arthritis Rheum 1990;33:1088–1093, by permission of *Arthritis and Rheumatism*.

Common vasculitis mimics, such as viral hepatitis, bacterial endocarditis, or other embolic diseases, should be excluded. Undiagnosed connective tissue diseases, such as systemic lupus erythematosus, rheumatoid arthritis, or systemic sclerosis, must be ruled out, as such diseases can be associated with systemic vasculitis or widespread vascular dysfunction that involves multiple organs. Atrophie blanche, a thrombotic disorder that may lead to lower extremity ulcerations, must be differentiated from PAN by skin biopsy.

The American College of Rheumatology criteria for the classification of PAN are listed in Table 21B-2 (5). The criteria were developed through the selection of clinical findings that identify PAN and distinguish it from other forms of vasculitis. Although the criteria are useful for classifying patients in clinical studies, they were not intended for use in diagnosing individual patients (10).

Laboratory Studies

Routine laboratory studies are often abnormal but nonspecific, such as elevated inflammatory markers (erythrocyte sedimentation rate or C-reactive protein), anemia, and thrombocytosis. The patient may have mild renal insufficiency, with an elevated blood urea nitrogen and creatinine. Non-nephrotic range proteinuria and mild hematuria are also seen, but active urine sediments are not a feature of PAN.

As not, PAN is not associated with ANCA. Indeed, there is no characteristic autoantibody for PAN—a fact that creates one of the diagnostic challenges in this disease. Electromyography/nerve conduction velocity (EMG/NCV) studies may be very useful in confirming patterns of nerve dysfunction consistent with mononeuritis multiplex; namely, a distal, asymmetric, axonal neuropathy involving both motor and sensory nerves.

Imaging

Imaging in a patient with suspected PAN should be guided by symptoms. In patients with abdominal pain, abdominal arteriography often reveals characteristic strictures and aneurysms (beading) of the mesenteric vessels [see Figure 21B-1(B)]. Similar findings can be seen in the renal vasculature.

Biopsy

As with imaging, biopsy should be guided by organ involvement. Blind biopsy of an asymptomatic organ, such as muscle or testicle, is not recommended. Skin biopsy is often the easiest way to confirm this diagnosis, with a biopsy from the center of a nodule or the edge of a vasculitic ulcer. Routine punch biopsy of involved skin reveals leukocytoclastic vasculitis and fibrinoid necrosis within the blood vessel wall. Because punch biopsy samples include only epidermis and superficial dermis, they do not capture medium-sized, muscular-walled arteries whose inflammation is characteristic of PAN. When PAN is suspected and skin biopsy is indicated, a full thickness skin biopsy that includes some subcutaneous fat should be performed (arteries within the fat lobules of subcutaneous tissue are often involved.)

Another option for confirming the diagnosis of PAN is a peripheral nerve biopsy. The sural nerve is biopsied most often because it does not mediate motor function. Whenever the sural nerve is biopsied, a muscle biopsy (of the gastrocnemius) should be performed simultaneously. Because of the highly vascular nature of muscle, biopsies of this organ may yield proof of vasculitis even in the absence of clinical indications of muscle involvement (Figure 21B-4).

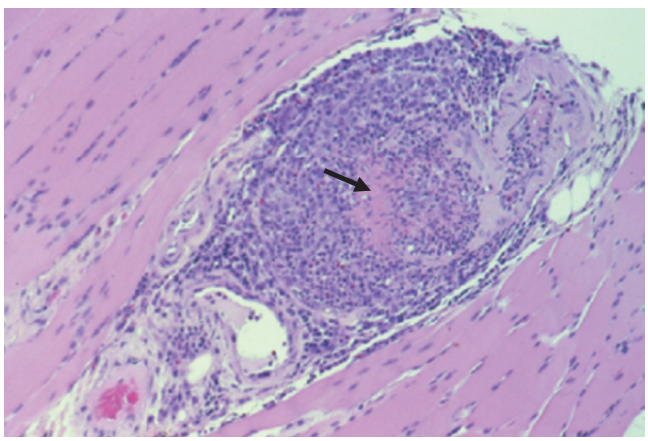


FIGURE 21B-4

Muscle biopsy showing fibrinoid necrosis within the wall of a medium-sized muscular artery. Although the patient had clinical symptoms of a neuropathy and nerve conduction studies were consistent with a mononeuritis multiplex, the nerve biopsy was negative. The diagnosis of polyarteritis was confirmed by the muscle biopsy. (Courtesy of Dr. John Stone.)

PROGNOSIS

Untreated PAN has a high mortality, with an estimated 5-year survival of 13% prior to the introduction of glucocorticoids. With current treatment, survival is greatly improved, approximately 80% at 5 years. In a population of 278 patients enrolled in prospective trials for PAN, MPA, and Churg–Strauss syndrome, approximately 75% of the deaths occurred during the first 18 months after the diagnosis was made and treatment initiated. Of the patients who died, 26% died from progression of their vasculitis, while 13% died of infectious complications related to treatment. No major differences were seen among the three vasculitides studied (11).

Not surprisingly, more severe disease is associated with increased mortality. A Five Factor Score has been used to classify disease severity (12). The five factors are (1) proteinuria >1 g/day, (2) renal insufficiency (Cr > 1.6 mg/dL), (3) cardiomyopathy, (4) gastrointestinal symptoms, and (5) CNS involvement. A Five Factor Score of 0 is associated with a 5-year mortality of only 13% (with not all deaths caused directly by PAN). Five Factor Scores of 1 and 2 or more are associated with mortalities of 26% and 46%, respectively (12).

TREATMENT

The treatment of PAN is guided by both the etiology of the disease (if known) and its severity. PAN cases associated with hepatitis B are treated with a short course of prednisone (1 mg/kg/day) to suppress the inflammation. Patients begin 6-week courses of plasma exchange (approximately three exchanges per week) simultaneously with the start of glucocorticoids. The dose of prednisone is tapered rapidly (over approximately 2 weeks), followed by the initiation of antiviral therapy (e.g., lamivudine 100 mg/day).

For idiopathic PAN, the mainstay of treatment is glucocorticoids, with an initial dose of approximately 1 mg/kg daily of prednisone. Intravenous glucocorticoids can be used in patients with difficulty taking oral medications due to GI involvement. Pulse doses (e.g., methylprednisolone 1 g intravenously each day times three) may be used in severe disease. Glucocorticoids alone may be enough to treat milder cases. Approximately half of all patients with PAN may be cured with glucocorticoids alone.

In cases of PAN that are rapidly progressive or life- or organ-threatening, cyclophosphamide is added to glucocorticoid treatment. Cyclophosphamide should be considered for any patient with a Five Factor Score of 1 or greater. In addition, severe peripheral neuropathy or mononeuritis multiplex is also a strong indication for cyclophosphamide. Although many clinicians still prefer daily oral cyclophosphamide to monthly pulsed intravenous cyclophosphamide, a meta-analysis comparing the two regimens in ANCA-associated vasculitis showed little difference (13). Therapy should be tailored to the individual patient's circumstances.

Most cases of idiopathic PAN do not recur after remission has been achieved and the patient has received 6 to 12 months of cyclophosphamide. Current regimens generally emphasize shorter courses of cyclophosphamide, with durations of therapy closer to 6 months than to 12. After treatment with 6 months of cyclophosphamide, patients in remission—the great majority—should be switched to another immunosuppressive agent for remission maintenance. As with the ANCA-associated vasculitides, azathioprine or methotrexate is often used. After a total treatment length of approximately 18 months, the remission maintenance agent can often be stopped, with a low relapse rate. Patients should continue to be monitored for evidence of recurrence.

Much potential morbidity in PAN relates to adverse events from inappropriate (or overly aggressive) treatment. Conversely, poor outcomes also result from undertreatment, for example, failure to employ cyclophosphamide in a patient clearly failing high-dose glucocorticoids. An important aspect of treatment is avoiding known side effects of agents used. This includes the use of calcium and vitamin D supplementation in all patients on glucocorticoids, along with use of a bisphosphonate in those at high risk for bone loss and monitoring of bone density. Patients on cyclophosphamide should have routine monitoring for cytopenias and hematuria and receive trimethoprim/sulfamethoxazole for prevention of *Pneumocystis jiroveci* (formerly *carinii*) pneumonia. Patients receiving pulsed intravenous cyclophosphamide are also candidates for MESNA (sodium-2-sulfanyl ethanesulfonate) for prevention of hemorrhagic cystitis. Premenopausal females on cyclophosphamide are candidates for leuprolide to suppress the GnRH axis and prevent premature ovarian failure; males may opt to bank sperm. Finally, as a teratogen, patients should not become pregnant or father children on cyclophosphamide.

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CHAPTER 21

Vasculitides

C. The Antineutrophil Cytoplasmic Antibody–Associated Vasculitides: Wegener's Granulomatosis, Microscopic Polyangiitis, and the Churg–Strauss Syndrome

JOHN H. STONE, MD, MPH

- Many patients with Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), or the Churg–Strauss syndrome (CSS) have antineutrophil cytoplasmic antibodies (ANCA) within their serum.
- As a result, these three disorders are termed the *ANCA-associated vasculitides* (AAV), even though not all patients with these conditions have ANCA.
- Multiple antibodies may lead to positive immunofluorescence testing for ANCA in either perinuclear (P-ANCA) or cytoplasmic (C-ANCA) patterns. However, only antibodies to myeloperoxidase (MPO) and proteinase-3 (PR3) are associated with the AAV.
- Wegener's granulomatosis may be associated with destructive upper respiratory tract disease, including saddle-nose deformity, erosive sinusitis, and subglottic stenosis. The CSS is often associated with allergic rhinitis, nasal polyposis, or sinusitis, but is rarely associated with destructive lesions.
- A host of ocular lesions may occur in the AAV, including episcleritis, scleritis, peripheral ulcerative keratitis, and orbital pseudotumor.
- Lung disease is common in the AAV and ranges from asthma (in CSS) to nodular lesions with a tendency to cavitate (in WG) to interstitial lung disease (MPA) to alveolar hemorrhage (all forms of AAV).
- Segmental, necrotizing glomerulonephritis commonly accompanies the AAV, particularly WG and MPA.
- Eosinophilia is the sine qua non of CSS.

In 1954, Godman and Churg observed that Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and the Churg–Strauss syndrome (CSS) share certain pathological similarities despite their clinical distinctions (1). These diseases, Godman and Churg noted, "group themselves into a compass, (ranging from) necrotizing and granulomatous processes with angiitis . . . to vasculitis without granulomata." Validation of the pathological links between these disorders became clear three decades later with the discovery of antineutrophil cytoplasmic antibodies (ANCA) and the finding that most patients with WG, MPA, and (to a lesser extent) CSS have ANCA in their serum. These diseases are commonly termed *ANCA-associated vasculitides* (AAV), even though not all patients with these diseases have detectable ANCA (Table 21C-1).

Anticytoplasmic antibodies directed against neutrophils (i.e., ANCA) were reported in association with segmental necrotizing glomerulonephritis in the early 1980s. In 1985, the presence of diffuse cytoplasmic staining of neutrophils was reported in patients with WG (2). In studies of patients with WG, MPA, or renal-limited vasculitis, Falk and Jennette (3) noted another pattern of immunostaining—perinuclear fluorescence of alcohol-fixed neutrophils. The two types of antibodies associated with AAV are those directed against (1) proteinase-3 (PR3) and (2) myeloperoxidase (MPO). PR3 and MPO, both serine proteases, are constituents of the primary granules of neutrophils and monocytes. Antibodies directed against these antigens are known, respectively, as PR3-ANCA and MPO-ANCA.

TABLE 21C-1. THE 1990 AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA FOR WEGENER'S GRANULOMATOSIS AND CHURG–STRAUSS SYNDROME.

WEGENER'S GRANULOMATOSIS	CHURG–STRAUSS SYNDROME
Nasal or oral inflammation	Asthma
Painful or painless oral ulcers or purulent or bloody nasal discharge	Wheezing or high-pitched rales
Abnormal chest radiograph	Eosinophilia
Nodules, fixed infiltrates, or cavities	>10% of white blood cell differential
Urinary sediment	Mononeuropathy or polyneuropathy
Microhematuria or red cell casts	Mononeuropathy, multiple mononeuropathies, or polyneuropathy attributable to vasculitis
Granulomatous inflammation on biopsy specimen	Pulmonary infiltrates, nonfixed
Granulomatous inflammation within the wall of an artery or in the perivascular area	Migratory or transitory pulmonary infiltrates Paranasal sinus abnormality Acute or chronic paranasal sinus pain, tenderness, or radiographic opacification Extravascular eosinophils Biopsy of artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas

SOURCE: From Leavitt RY et al. Arthritis Rheum 1990;33:1101–1107, and Masi AT et al. Arthritis Rheum 1990;33:1094–1100, by permission of *Arthritis and Rheumatism*.

CLASSIFICATION CRITERIA AND DEFINITIONS

The 1990 American College of Rheumatology classification criteria for WG and the CSS (Table 21C-1) (4,5) were developed to ensure the inclusion of uniform disease populations in research studies (6). These criteria did not address the utility of ANCA for classification or the difference between polyarteritis nodosa and MPA. These limitations were addressed by the Chapel Hill Consensus Conference (Table 21C-2) (7). To date, widely accepted diagnostic criteria for these diseases have not been developed.

EPIDEMIOLOGY

A population-based study from Norfolk, England, reported incidences of 8.5 cases per million for WG, 3.6 cases per million for MPA, and 2.4 cases per million for the CSS (8). In two large U.S. cohorts of patients with WG (9,10), whites comprised more than 90% of all cases, whereas African Americans, Hispanics, and Asians together represented 1% to 4% of cases. The mean age at diagnosis is about 55 years, but cases involving octogenarians are not unusual.

TABLE 21C-2. THE CHAPEL HILL CONSENSUS CONFERENCE DEFINITIONS OF THE ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES–ASSOCIATED VASCULITIDES.

Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Churg–Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, associated with asthma and eosinophilia.

SOURCE: Jennette JC, et al. Arthritis Rheum 1994;37:187–192, by permission of *Arthritis and Rheumatism*.

TABLE 21C-3. CLINICAL FEATURES OF THE PRIMARY ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES–ASSOCIATED VASCULITIDES.

FEATURE	WEGENER'S GRANULOMATOSIS	MICROSCOPIC POLYANGIITIS	CHURG–STRAUSS SYNDROME
ANCA positivity	80%–90%	70%	50%
ANCA antigen specificity	PR3 > MPO	MPO > PR3	MPO > PR3
Fundamental histology	Leukocytoclastic vasculitis; necrotizing, granulomatous inflammation (rarely seen in renal biopsy specimens)	Leukocytoclastic vasculitis; no granulomatous inflammation	Eosinophilic tissue infiltrates and vasculitis; granulomas have eosinophilic necrosis
Ear/nose/throat	Nasal septal perforation; saddle-nose deformity; conductive or sensorineural hearing loss; subglottic stenosis	Absent or mild	Nasal polyps; allergic rhinitis; conductive hearing loss
Eye	Orbital pseudotumor, scleritis (risk of scleromalacia perforans), episcleritis, uveitis	Occasional eye disease: scleritis, episcleritis, uveitis	Occasional eye disease: scleritis, episcleritis, uveitis
Lung	Nodules, infiltrates, or cavitary lesions; alveolar hemorrhage	Alveolar hemorrhage	Asthma; fleeting infiltrates; alveolar hemorrhage
Kidney	Segmental necrotizing glomerulonephritis; rare granulomatous features	Segmental necrotizing glomerulonephritis	Segmental necrotizing glomerulonephritis
Heart	Occasional valvular lesions	Rare	Heart failure
Peripheral nerve	Vasculitic neuropathy (10%)	Vasculitic neuropathy (58%)	Vasculitic neuropathy (78%)
Eosinophilia	Mild eosinophilia occasionally	None	All

SOURCE: Reproduced with permission from Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med 2004;117:39–50.
ABBREVIATIONS: ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

CLINICAL FEATURES

There is substantial overlap in many of the clinical features of the AAVs. In some cases, distinguishing among two or more of these diseases on the basis of clinical features alone is difficult (Table 21C-3).

Upper Respiratory Tract and Ears

Although patients with the CSS or MPA may experience substantial ear, nose, or sinus disease, this pattern of involvement is most characteristic of WG. More than 90% of patients with WG eventually develop upper airway or ear abnormalities. The nasal symptoms of WG include nasal pain and stuffiness, rhinitis, epistaxis, and brown or bloody crusts. Nasal inflammation may lead to septal erosions, septal perforation, or, in many cases, nasal bridge collapse—the "saddle-nose deformity" (Figure 21C-1). The distinction between active WG in the sinuses and secondary infections in the sinuses may be challenging (see Nonmedical Interventions section).

In 60% to 70% of patients with the CSS, allergic rhinitis is the earliest disease manifestation, typically appearing years before the development of full-blown

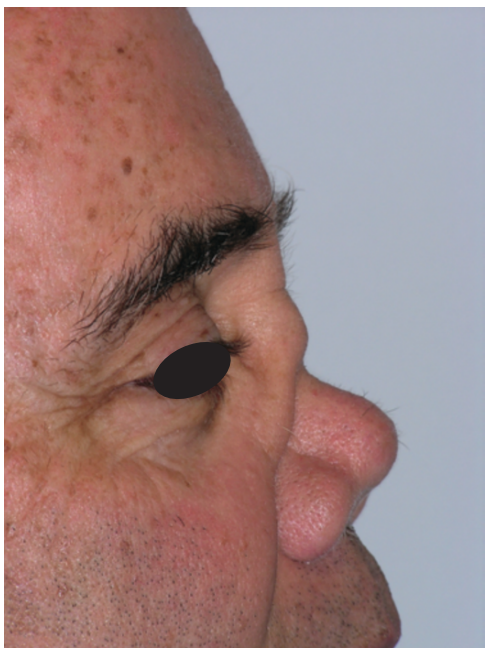


FIGURE 21C-1

Saddle-nose deformity in Wegener's granulomatosis.

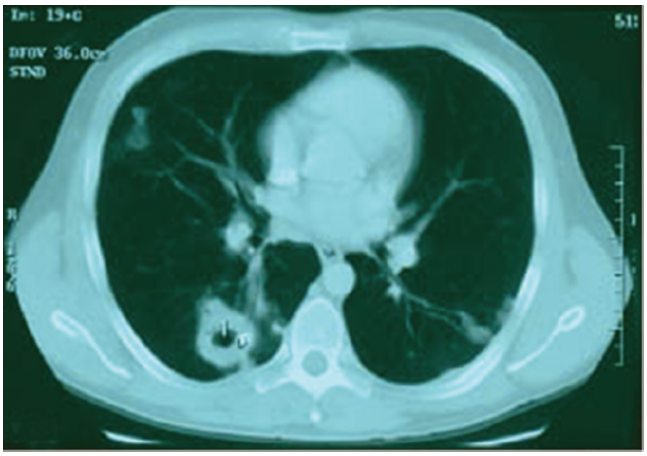


FIGURE 21C-2

Multifocal cavitary nodules in Wegener's granulomatosis.

systemic vasculitis. Rhinitis may be severe and may require serial polypectomies to relieve obstruction and sinusitis. Nasal crusting and conductive hearing loss (due to serous otitis or granulomatous middle ear inflammation) may also occur in the CSS.

Two principal categories of ear disease—conductive and sensorineural hearing loss—are typical of WG. The most common cause of conductive hearing loss may be Eustachian tube dysfunction due to nasopharyngeal disease. Inner ear disease in WG may be associated with sensorineural hearing loss, vestibular dysfunction, or both. In contrast to middle ear disease, the mechanism of inner ear disturbances in WG is poorly understood.

Trachea and Bronchi

Subglottic stenosis and stenotic lesions of the bronchi are potentially serious complications of WG. Subglottic involvement, often asymptomatic initially, becomes apparent as hoarseness, pain, cough, wheezing, or stridor. Thin-cut computed tomographic scans and often direct laryngoscopy are useful in assessing these airway narrowings.

Eyes

Scleritis may lead to necrotizing anterior scleritis (scleromalacia perforans) and blindness. Peripheral ulcerative keratitis may cause the corneal melt syndrome. Other ocular manifestations of AAV include conjunctivitis, episcleritis, and anterior uveitis. In WG, orbital masses termed *pseudotumors* occur in a retrobulbar location in 10% to 15% of patients, causing proptosis, diplopia, or visual loss. Nasolacrimal duct obstruction is most typical of WG.

Lungs

In WG, the pulmonary manifestations range from asymptomatic lung nodules and fleeting (or fixed) pulmonary infiltrates to fulminant alveolar hemorrhage. The nodules are usually multiple, bilateral (Figure 21C-2), and often cavitary. Infiltrates are often misdiagnosed initially as pneumonia.

Pulmonary capillaritis, equally likely to occur in WG and MPA, may lead to lung hemorrhage, hemoptysis, and rapidly changing alveolar infiltrates (Figure 21C-3). Patients with MPA may also develop interstitial fibrosis of the lungs.

Obstructive airway disease and fleeting pulmonary infiltrates are the hallmarks of the CSS. The majority of patients report the new onset of asthma months to years before the appearance of overt vasculitis. Following resolution of the vasculitic phase with treatment, many patients with CSS suffer from steroid-dependent asthma.

Kidneys

The most feared clinical presentation of renal disease among the AAVs is rapidly progressive glomerulonephritis. More than 75% of patients with WG will eventually develop renal involvement. The progression of the disease often appears to accelerate once kidney involvement is apparent. In MPA, renal disease may have a more indolent course, and renal biopsies typically demonstrate more sclerosis and fibrosis than do specimens from patients with WG. Severe renal disease in CSS is very rare. "Renal-limited" vasculitis is pauci-immune glomerulonephritis (see Pathology section) associated with ANCA, usually directed against MPO, without evidence of disease in other organs. ANCA-associated

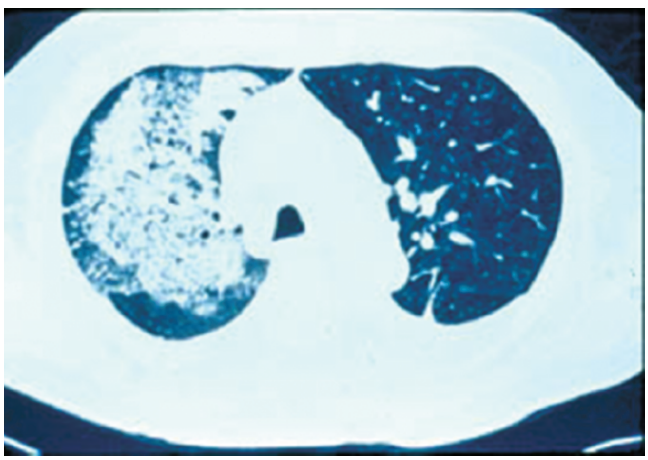


FIGURE 21C-3

Alveolar hemorrhage in microscopic polyangiitis.

renal disease may lead to fibrotic crescents and other scarring within the kidney. Subsequent disease flares and progression of renal dysfunction through hyperfiltration may lead to end-stage renal disease.

Arthritis/Arthralgias

Inflammatory joint complaints, often migratory and oligoarticular in nature, occur in at least 60% of patients with AAV. Joint problems are frequently the presenting complaint, but the diagnosis is seldom made until other symptoms are manifest. The combination of joint complaints, cutaneous nodules (frequently mistaken for rheumatoid nodules), and the high frequency of rheumatoid factor positivity among patients with AAV (approximately one third are rheumatoid factor positive) often lead to the misdiagnosis of rheumatoid arthritis early in the disease course. Arthralgias are more common than frank arthritis. The recurrence of musculoskeletal complaints in a patient in remission often marks the start of a disease flare.

Skin

In both the CSS and WG, cutaneous nodules may occur at sites that are also common locations for rheumatoid nodules, particularly the olecranon region (Figure 21C-4). Skin findings in the AAVs also include all of the potential manifestations of cutaneous vasculitis: palpable purpura, vesiculobullous lesions, papules, ulcers, digital infarctions, and splinter hemorrhages.

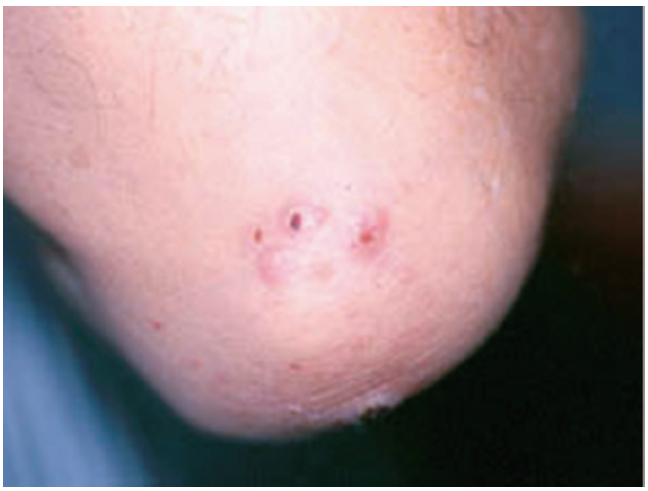


FIGURE 21C-4

Churg–Strauss granulomas, that is, cutaneous extravascular necrotizing granulomas, occurring over the elbow. These lesions may occur in both the Churg–Strauss syndrome and Wegener's granulomatosis, mimicking rheumatoid nodules.

Nervous System

Vasculitic neuropathy may lead to a devastating mononeuritis multiplex or a disabling sensory polyneuropathy. Mononeuritis multiplex occurs more commonly in the CSS [up to 78% of patients (11)] and MPA (up to 58%) than in WG. Central nervous system abnormalities occur in approximately 8% of patients with WG, usually in the form of cranial neuropathies, mass lesions, or pachymeningitis. The frequency of parenchymal brain involvement in AAV, though not yet known with certainty and generally regarded as rare, has been reported. Central nervous system disease generally occurs only when more typical disease manifestations are present elsewhere.

Heart

The CSS is the type of AAV that is most likely to involve the heart, usually in the form of rapid-onset heart failure. Cardiac complications in WG and MPA are both less common and more difficult to attribute with certainty to the underlying disease. Focal cardiac valvular lesions, valvular insufficiency, pericarditis, and coronary arteritis have been described in WG.

Gastrointestinal Tract

Eosinophilic gastroenteritis often precedes the frank vasculitic phase of the CSS. Among patients with either the CSS or MPA, unexplained abdominal pain occurs in up to one third of patients and may lead to ischemic bowel. Gastrointestinal involvement is less common in WG.

Blood

Eosinophilia (before treatment) is a sine qua non of the CSS. Eosinophil counts are usually sensitive markers of disease flares, but respond very quickly (within 24 hours) to treatment with high doses of glucocorticoids. Tissue infiltration by eosinophils, however, may remain. Mild eosinophilia (rarely more than 15% of the total white blood cell count) may also occur in WG. Most patients with CSS also have elevated serum immunoglobulin E levels. In addition to ANCA, nonspecific autoantibodies, such as antinuclear antibodies and rheumatoid factor, also occur in high percentages of patients with AAV.

Other

Antineutrophil cytoplasmic antibodies-associated vasculitides rarely affect the parotid gland, pulmonary artery, breast, or genitourinary organs. Involvement of these organs by AAV is usually an unexpected finding on biopsies performed to exclude other diseases, particularly cancer and infection.

PATHOLOGY

Fibrinoid necrosis, a pathological hallmark of AAV, may be found in a variety of vasculitic (and nonvasculitic) conditions, such as polyarteritis nodosa, scleroderma renal crisis, systemic lupus erythematosus, and malignant hypertension. Both vasculitic and necrotizing granulomatous features, which do not invariably coexist, may be confirmed in lung biopsy specimens. In addition, pulmonary WG frequently demonstrates an extensive, nonspecific inflammatory background. Coalescence of such neutrophilic microabscesses leads to extensive regions of "geographic" necrosis. Palisading granulomas, scattered giant cells, and poorly formed granulomas may also be found in WG.

Churg–Strauss syndrome typically evolves through three phases, with corresponding pathological findings. In the first phase, allergy, asthma, and other atopic symptoms predominate. In the second, eosinophilic infiltration occurs in the lung and other organs (eosinophilic pneumonia, eosinophilic gastroenteritis; Figure 21C-5). In the third phase, vasculitis ensues. Curiously, at the time the vasculitic phase begins, patients' asthma often improves significantly. The histopathological findings in CSS in the lung include eosinophilic infiltrates; extensive areas of necrosis (reminiscent of the geographic necrosis in WG); a granulomatous vasculitis of small arteries and veins, associated with striking eosinophilic infiltration. In contrast to WG and MPA, lymphadenopathy (with overwhelming eosinophilic infiltration into the lymph nodes), is frequently found in CSS.

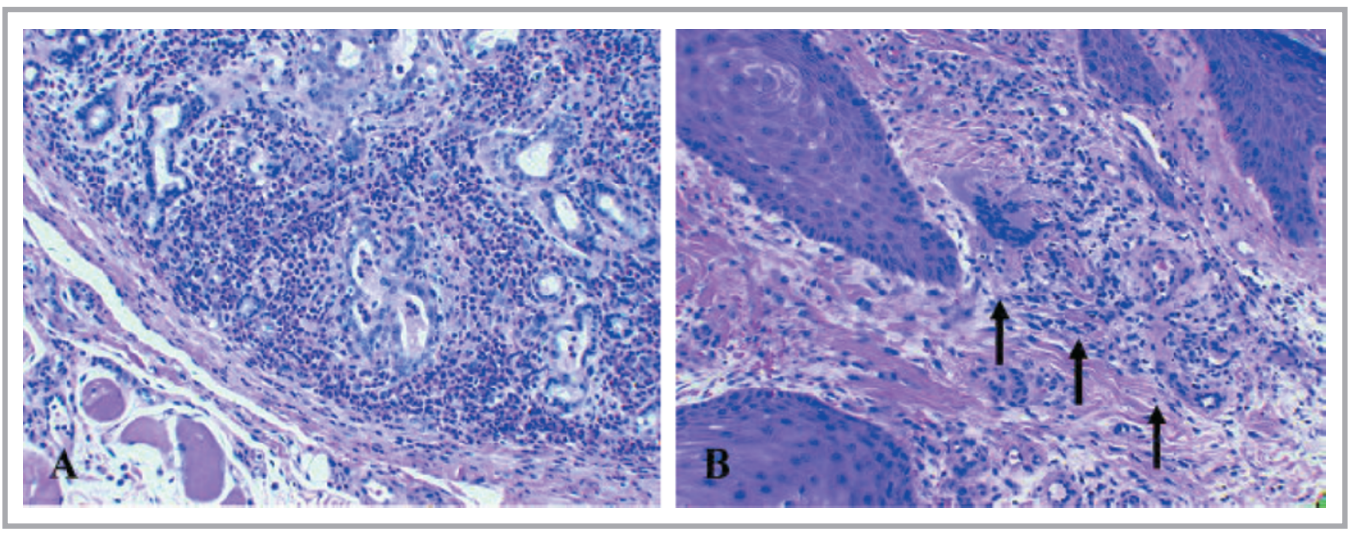
The interstitial lung disease of MPA resembles usual interstitial pneumonitis (UIP), with the exception that necrosis of the alveolar septae and areas of hemorrhage can occur. More characteristic findings in MPA, however, reveal nonspecific infiltrates or alveolar hemorrhage. Vasculitis of the pulmonary capillaries may be difficult to prove.

Renal disease in the AAVs is associated with focal, segmental lysis of glomerular tufts, disruption of the basement membrane, and accumulation of fibrinoid material (i.e., fibrinoid necrosis). Crescents in Bowman's space develop as a result of spillage of inflammatory mediators across the ruptured glomerular capillaries, accumulation of macrophages, and epithelial cell proliferation. Thrombotic changes in the glomerular capillary loops are among the earliest histologic changes. Acute tubular necrosis and tubulointerstitial nephritis are also seen commonly. Immunofluorescence studies of renal biopsy specimens demonstrate scant deposition of immunoglobulin and complement, hence the term pauci-immune glomerulonephritis.

Tissue samples from involved areas of the upper respiratory tract (nose, sinuses, and subglottic region) in WG often reveal only acute and chronic inflammation. Nevertheless, these biopsies are easier to obtain than are biopsies of the lung and kidney. Moreover, the combination of these pathological findings (nondiagnostic in and of themselves) and compatible clinical features (e.g., pulmonary nodules and PR3-ANCA) may yield the diagnosis in some cases. Upper respiratory tract biopsies are therefore worth undertaking in patients with significant upper respiratory involvement.

FIGURE 21C-5

Eosinophilic infiltration of a salivary gland in a patient with the Churg–Strauss syndrome. The arrows in panel B indicate the formation of a Churg-Strauss granuloma, with multinucleated giant cells, palisading histiocytes, and scattered eosinophils.



ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

The Antigens

Proteinase-3, a 29-kDa serine protease, is found in the azurophilic granules of neutrophils and peroxidase-positive lysosomes of monocytes. MPO, which constitutes nearly 5% of the total protein content of the neutrophil, is localized to the same cellular compartments as PR3. The protein is a covalently linked dimer with a molecular weight of 140 kDa. The autoantibodies directed against PR3 and MPO are directed against multiple epitopes. Sera from different patients may recognize different epitopes. All ANCA, however, recognize restricted epitopes of PR3 involving its catalytic site.

Clinical Testing for Antineutrophil Cytoplasmic Antibodies

Two types of assays for ANCA—immunofluorescence and enzyme immunoassay—are now in common use. Capture enzyme immunoassays may offer some advantages over the more widely available tests, but are currently performed only in specialty centers.

With immunofluorescence, three principal patterns of fluorescence are recognized: the cytoplasmic (C-ANCA), perinuclear (P-ANCA), and "atypical" patterns. In patients with vasculitis, the C-ANCA pattern usually corresponds to the detection of PR3-ANCA by enzyme immunoassay. The combination of a C-ANCA pattern on immunofluorescence testing and PR3-ANCA is associated most strongly with WG. The P-ANCA pattern, which usually corresponds to the presence of MPO-ANCA in vasculitis patients, occurs in approximately 10% of patients with WG, but is more typical of MPA, the CSS, and renal-limited vasculitis. The great majority of patients with drug-induced AAVs are P-ANCA positive, often with very high titers of MPO-ANCA.

Regardless of the immunofluorescence pattern, positive immunofluorescence assays should be confirmed by the performance of enzyme immunoassays for the specific antibodies associated with vasculitis: PR3- and MPO-ANCA. Even for C-ANCA, the positive predictive value for WG is only in the range of 45% to 50% (12,13).

Clinical Utility of Antineutrophil Cytoplasmic Antibody Serologies

Despite advances in ANCA testing techniques, the cornerstone of diagnosis in WG remains the rigorous interpretation of histopathological specimens within the overall clinical context. When biopsy specimens are nondiagnostic, ANCA assays provide an important adjunct to diagnosis (Table 21C-4).

In the proper clinical setting, a positive ANCA assay greatly increases the likelihood that a form of AAV is present. Most series indicate that up to 10% to 20% of patients with active, untreated WG are ANCA negative. For patients with limited WG, 30% or more of patients lack ANCA. Approximately 70% of patients with MPA and 50% of those with CSS (higher in some series) have ANCA.

TABLE 21C-4. CLINICAL UTILITY OF ANTINEUTROPHIL CYTOPLASMIC ANTIBODY TESTING.

Positive ANCA serologies are extremely useful in suggesting the diagnosis in the proper clinical setting.
Positive immunofluorescence assays without confirmatory enzyme immunoassays for anti-PR3 or anti-MPO antibodies are of limited utility.
Histopathology remains the gold standard for diagnosis in most cases.
Negative ANCA assays do not exclude ANCA-associated vasculitis because between 10% and 50% of patients with ANCA-associated vasculitis (depending on the particular disease) may be ANCA-negative.
Persistence of ANCA in the absence of clinical indications of active disease does not indicate a need for continued treatment.
In a patient who was ANCA-positive during active disease, persistent ANCA-negativity provides reassurance—but no guarantee—that the disease is not active. If disease flares occur in such patients, they are usually limited.
A patient who becomes ANCA-positive again following a period of clinical quiescence associated with negative ANCA assays may be at an increased risk for a disease flare. The temporal correlation between the return of ANCA and a disease flare, however, is poor.
Treatment of ANCA-associated vasculitis should never be predicated upon ANCA serologies or titers alone.

ABBREVIATIONS: ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

Utility of Antineutrophil Cytoplasmic Antibody Assays following Disease Activity and in Predicting Flares

In general, ANCA titers have imperfect correlations with disease activity. In one study, the positive predictive value of a rise in ANCA titers as measured by immunofluorescence was only 57% in a prospective study, compared with 71% for enzyme immunoassay (14). Moreover, among patients with an elevation of ANCA titers measured by enzyme immunoassay, only 39% suffered disease flares within 6 months. A more recent prospective study (15) showed that increases in PR3-ANCA levels did not predict disease relapses. The proportion of patients who relapsed within 1 year following an increase in ANCA levels was only 40%. Although some studies suggest that a rise in ANCA titer is a risk factor for a flare, the temporal relationship between a rise in ANCA titers and the development of disease activity requiring treatment is very poor, with months to years between these two events. Thus, the adjustment of immunosuppressive medications based solely on the rise or fall of ANCA titers is never justified.

PATHOPHYSIOLOGY

The AAVs are complex disorders mediated by the immune system in which tissue injury results from the interplay between an initiating inflammatory event and a highly specific pathogenic immune response (i.e., the production of ANCA) to previously shielded epitopes of neutrophil granule proteins. ANCAs produce tissue damage via interactions with primed neutrophils and endothelial cells. The hypothesis, supported strongly by in vitro evidence, is that the antibodies induce a necrotizing vasculitis by inciting a respiratory burst and degranulation of leukocytes (neutrophils and monocytes), leading to endothelial injury. The initial events in the process require the priming of leukocytes by cytokines and perhaps other stimuli, leading to the expression of PR3 and MPO on the cell surface. The effects of ANCAs are determined by the state of neutrophil activation. ANCAs may constitutively activate primed neutrophils and promote binding of the primed neutrophils to the vascular endothelium, degranulation, and the release of neutrophil chemoattractants, hence creating an autoamplifying loop.

There is now substantial evidence that ANCAs are directly involved in the widespread tissue damage that is the hallmark of the AAVs. Recombinant activating gene 2 (RAG-2)–deficient mice that receive anti-MPO antibodies develop clinical features consistent with AAV, including crescentic glomerulonephritis and systemic necrotizing vasculitis (16). In humans, the evidence is indirect. Propylthiouracil is known to accumulate within neutrophil granules and may lead to a drug-induced AAV (17), possibly by increasing the immunogenicity of MPO (leading to the characteristically high titers of MPO-ANCA seen in this disease).

In addition to ANCA, multiple other elements of the immune system participate in the pathophysiology of these diseases. If the autoantibody response leading to ANCA production follows the exposure of a cryptic epitope, epitope spreading may then generalize the antibody response to the rest of the molecule. This hypothesis implies a prominent role for the T cell in the pathogenesis of the AAVs. Moreover, most patients with AAVs produce isotype-switched IgG ANCA, implying a secondary immune response driven by T cells. Growing evidence, particularly data from clinical studies (18), now also implicates B cells as important participants in the inflammation of AAV. As the precursors of plasma cells (which produce ANCA), B cells now seem a logical therapeutic target in AAV. In addition to disrupting ANCA production, however, interference with B-cell function may also ameliorate AAV by disabling critical B cell/T cell interactions, by removing the antigen presenting function of B cells, and perhaps other mechanisms. B-cell depletion is the focus of ongoing randomized trials involving patients with WG and MPA.

The pathophysiology of CSS likely bears many similarities to that of WG and MPA, albeit ANCA are less common in CSS. In the CSS, however, relatively little is currently understood about the special role played by the eosinophil in that disease.

DIFFERENTIAL DIAGNOSIS

Because of their multiorgan system nature, the differential diagnosis of AAV is lengthy. One frequently challenging task is the differentiation of these diseases from other forms of vasculitis. Indeed, clear distinctions are often impossible between WG and MPA, because granulomatous inflammation is not detected on all biopsy specimens from patients with WG. Distinguishing the AAVs from other forms of vasculitis is often more critical because the specific treatments differ according to diagnosis. In addition, the AAVs must be distinguished from a host of other disorders associated with inflammation and multiorgan system dysfunction. The differential diagnosis of AAV is shown in Table 21C-5.

Churg–Strauss syndrome has an additional major branch of its differential diagnosis because of the eosinophilia associated with the disease. Allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, eosinophilic gastroenteritis, eosinophilic fasciitis, the hypereosinophil syndrome, and eosinophilic leukemias must all be excluded.

TABLE 21C-5. DIFFERENTIAL DIAGNOSIS OF ANTINEUTROPHIL CYTOPLASMIC ANTIBODY–ASSOCIATED VASCULITIS.

Another form of ANCA-associated vasculitis Wegener's granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis, drug-induced ANCA-associated vasculitis, or renal-limited vasculitis
Another form of vasculitis. Typical vasculitic mimickers: Polyarteritis nodosa, Henoch–Schönlein purpura, cryoglobulinemia, antiglomerular basement membrane disease
Systemic inflammatory disorders associated with autoimmunity Systemic lupus erythematosus, sarcoidosis, inflammatory bowel disease, relapsing polychondritis
Infection Endocarditis, sepsis, deep fungal infections, mycobacteria (*Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare*), actinomycosis, syphilis
Malignancy Lymphomatoid granulomatosis, lymphoma, Castleman's disease, lung tumors
Hypereosinophilic disorders Allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, eosinophilic gastroenteritis, eosinophilic fasciitis, hypereosinophil syndrome, eosinophilic leukemia
Miscellaneous Idiopathic pulmonary alveolar hemorrhage, illicit drug use (intranasal cocaine, smoking of crack)

ABBREVIATION: ANCA, antineutrophil cytoplasmic antibody.

TREATMENT

Current choices for treatment in WG are based on the classification of patients into the categories of either severe or limited disease (19). Severe WG constitutes an immediate threat either to the function of a vital organ or to the patient's life. Conversely, limited WG consists of disease manifestations that do not pose such threats. The practical distinction between severe and limited disease is that under the current standard of care the diagnosis of severe WG mandates the use of cyclophosphamide, whereas milder therapeutic approaches may be appropriate and should be considered for limited disease. The treatment of MPA parallels very closely that of severe WG. Because of the propensity of MPA to involve major organs (lungs, kidneys, peripheral nerves) in a severe fashion, limited forms of the disease are recognized less often. Some cases of CSS can be treated with glucocorticoids alone, but those with vasculitic neuropathy, life-threatening pulmonary involvement, and other sobering organ involvement require cyclophosphamide from the outset of therapy.

In treating severe AAV, the standard approach now is to employ cyclophosphamide [e.g., 2 mg/kg/day, adjusted for renal dysfunction (20)] for 3 to 6 months. Some experts prefer intermittent (intravenous) regimens of cyclophosphamide (e.g., 500–750 mg/m^2 every month). No data yet available strongly endorse one cyclophosphamide regimen over another. Remission induction with cyclophosphamide is usually followed by longer periods of remission maintenance therapy with either azathioprine (11) or methotrexate (21).

For patients who demonstrate propensities to flare, long-term use of the least toxic drug for the maintenance of remission may be appropriate. This may include methotrexate or azathioprine and, for patients with recurrent disease flares, low doses of prednisone (e.g., 5 mg/day). The optimal length of treatment with methotrexate or azathioprine is not clear, but continuation of these medications for at least 1 year after remission is reasonable in most patients. Tumor necrosis factor inhibition (or at least etanercept) does not appear to be effective in WG (22), and its use in combination with cyclophosphamide may heighten the risk of solid malignancies substantially (23).

Among patients with limited WG, remission is induced in approximately three fourths of patients with the use of methotrexate (up to 25 mg/week) and glucocorticoids alone. Patients treated with methotrexate and glucocorticoids must be observed carefully for breakthrough disease, particularly glomerulonephritis.

Other Potential Medical Treatments in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

The use of trimethoprim–sulfamethoxazole as a treatment for WG has fallen increasingly into disfavour. The use of trimethoprim–sulfamethoxazole alone for the treatment of active WG is not appropriate. The medication may have some role in remission maintenance for patients with upper respiratory tract disease, however, its efficacy is uncertain and its mechanism of action unclear. A wide array of other therapies, such as plasmapheresis, intravenous immunoglobulin, mycophenolate mofetil, and leflunomide, have been employed in small numbers of patients, but so far there are insufficient data to judge their efficacy. Rituximab and other strategies for B-cell depletion are now being tested. Interferon-alpha has been reported to have some benefit for CSS.

Nonmedical Interventions

Once scarring and fibrosis are well established in the subglottic region, airway narrowing may be due to the progression of scar tissue rather than to WG-related inflammation. In such cases, subglottic stenosis responds poorly to immunosuppressive therapy, and the most

effective therapeutic approach to this problem is laryngoscopic dilatations of the airway, augmented by intralesional corticosteroid injections (24). Serial procedures are often required. If severe subglottic stenosis precludes a safe dilatation procedure, a patent airway should first be secured by a tracheostomy. WG often leads to chronic nasosinus dysfunction. Regardless of disease activity, most patients require multiple daily saline irrigations to minimize the accumulation of secretions and crusts, and to reduce the incidence of secondary infections. Persistent or recurrent infections may require surgical drainage. Distinguishing between worsening sinus disease caused by active WG and superinfection may be difficult. In the absence of a prompt response to antibiotics, surgical drainage and biopsy are often required for a more definitive diagnosis.

COURSE AND PROGNOSIS

In contrast to the situation in the first 40 years following the descriptions of the AAVs, these diseases are now highly treatable. Unfortunately, disease relapses are a major threat. MPA and the CSS are somewhat less likely than WG to flare after the achievement of remission. The percentages of patients with those diseases who suffer disease flares after appropriate courses of treatment have been estimated to be about 25% to 40%.

Even with therapy, mortality and morbidity are substantial. In a cohort of 158 patients followed at the National Institutes of Health (NIH) from the late 1960s through the early 1990s (9), 12% of deaths were due to either the disease or complications of treatment, and 86% suffered permanent disease-related morbidity, including chronic renal insufficiency (42%), end-stage renal disease requiring dialysis (10%), hearing loss (35%), nasal deformity (28%), tracheal stenosis (13%), and visual loss (8%). Many patients incurred more than one type of permanent morbidity. In a more recent retrospective study of 246 patients with ANCA-associated renal vasculitis (25), cumulative patient survival at 5 years was 76%. There was an 18% mortality rate at 1 year, however, with infections as a major cause of death. In this cohort, mortality was associated with age older than 60 years, the development of end-stage renal failure, and an initial serum creatinine level greater than 2.26 mg/dL.

In the Wegener's Granulomatosis Etanercept Trial (WGET) (22), although >90% of all patients achieved at least a transient disease activity score of zero, fewer than 50% of patients achieved and maintained these disease remissions over the mean 22-month course of follow-up on treatment. Thus, although remissions are achieved in most patients with WG, relapse remains a major threat. Furthermore, 89% of the patients enrolled in the WGET had sustained at least one item of damage from the disease or treatment within 1 year of enrollment (26). The most common items of damage recorded were hearing loss (26%) and proteinuria (19%).

Much of the morbidity in the AAVs relates to prolonged courses of immunosuppression, particularly the need to re-treat patients who suffer multiple relapses. In the 1229 patient-years of follow-up in the NIH series, only 46% of these years were spent in remission. Serious infections occurred in 46%. Other morbidities included drug-induced cystitis caused by cyclophosphamide (43%), increased risk of malignancy (particularly bladder cancer, leukemia, and lymphoma), infertility (57% of women with childbearing potential), and a host of side effects related to the use of glucocorticoids.

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CHAPTER 21

Vasculitides
D. Immune Complex–Mediated Vasculitis

PHILIP SEO, MD, MHS

- Pathogenic immune complexes formed between antigen and antibodies tend to occur during periods of antigen excess. When the immune complexes precipitate into the tissues, they fix complement, leading to an intense immune reaction.
- In immune complex vasculitis, immune complexes deposit in the vascular endothelium or in capillary beds, such as those found in the skin, kidneys, or lungs.
- The most common skin manifestation of small vessel vasculitis is palpable purpura.
- Hypersensitivity vasculitis is characterized by immune complex deposition in capillaries, postcapillary venules, and arterioles. The usual causes are either medications (e.g., penicillins, sulfonamides, or cephalosporins) or infections.
- Cryoglobulinemic vasculitis is usually caused by hepatitis C infections. The antigens involved in cryoglobulinemic vasculitis are portions of the hepatitis C virus (HCV) virion. The relevant antibodies are both IgG and IgM, leading to the designation "mixed" cryoglobulinemia.
- Henoch–Schönlein purpura is associated strongly with IgA deposition within blood vessel walls.
- Hypocomplementemic urticarial vasculitis has many features that overlap with systemic lupus erythematosus.

Exposure to a foreign antigen activates an adaptive immune response that leads to the production of antigen-specific antibodies. The combination of antibody with antigen creates immune complexes that neutralize the foreign antigen, and allow it to be cleared safely by the reticuloendothelial system. This complex system, however, contains within it the potential for failure. If the antibody response is just right, these immune complexes may escape early detection, and instead imbed themselves into joints and blood vessels. These immune complexes can then activate complement, leading to local inflammation. Immune complexes deposited in the kidneys, for example, create glomerulonephritis (1). Those deposited in the synovium lead to arthritis. If the immune complexes are found in the blood vessels, vasculitis is the result.

In pathology, the word *vasculitis* describes inflammation within blood vessel walls. This process frequently leads to cellular destruction, damage to the vascular structures, and compromise of blood flow to organs supplied by the involved vessels, resulting in organ compromise. Several forms of vasculitis are the direct result of immune complex deposition. This chapter outlines several examples of immune complex–mediated vasculitis and highlights some common themes.

PATHOPHYSIOLOGY

In 1903, Maurice Arthus noted that intradermal injection of a rabbit with horse serum resulted in a cutaneous inflammatory reaction that evolved into localized tissue necrosis (2). The reaction was faster, he observed, if the animal had been previously exposed to horse serum. This response, now known as the Arthus reaction, forms the basis of our understanding of immune complex–mediated diseases. In the Arthus model, injection of the horse serum leads to immune complex formation that initiates complement activation and an influx of inflammatory cells. In the areas of most intense inflammation, in situ thrombosis formation can lead to tissue ischemia and hemorrhagic infarction.

In general, immune complexes are not pathogenic. Their immunogenicity is governed by a large number of factors, including antigen load, antibody response, the efficiency of the reticuloendothelial system in the clear-

ance of immune complexes, physical properties of the blood vessels (including flow dynamics and previous endothelial damage), and the solubility of the immune complexes themselves.

Immune complex solubility is determined by the ratio of antibody to antigen. When antibody and antigen are present in equal proportion, large immune complexes are formed, which are identified easily and removed by the reticuloendothelial system. When there is an excess of antibody, small immune complexes are formed, which remain in solution, and do not elicit an immune response. When there is a slight excess of antigen, however, the immune complexes precipitate from solution, and become trapped in characteristic areas—either the capillary beds (such as those found in the skin, kidneys, or lungs), or the endothelium of medium-sized blood vessels previously damaged by turbulent blood flow.

When the immune complexes precipitate into the tissues, they fix complement, leading to an intense immune reaction. Complement fixation and local inflammation recruit neutrophils, which attempt to engulf the immune complexes. During this process, the neutrophils degranulate, releasing lysosomal enzymes and oxygen free radicals that cause tissue necrosis.

The inciting antigen can be from numerous sources. In infective endocarditis, the antibody response, formed against bacterial antigens, can lead to painful cutaneous lesions known as Osler nodes. In systemic lupus erythematosus (SLE), antibodies form against nuclear components (e.g., DNA and histones) that are released during tissue injury. Certain forms of malignancy can be associated with immune complex formation, with antibodies directed against tumor-associated antigens. Immune complexes may also form in response to a large number of drugs, including penicillin and sulfonamides.

CLINICAL SYNDROMES

Hypersensitivity Vasculitis

Definition

Hypersensitivity reactions were first noted in patients who were treated with antitoxin derived from horse serum. Such patients developed an antibody response to the horse antigens, which led to a characteristic syndrome of fever, joint pain, and rash now known as serum sickness.

Hypersensitivity vasculitis refers to a heterogeneous group of syndromes (including serum sickness and drug-induced vasculitis) characterized by immune complex deposition in capillaries, postcapillary venules, and arterioles. This is the most common form of vasculitis. Although multiple agents have been implicated, including penicillins, sulfonamides, and cephalosporins, the inciting agent cannot always be identified.

In 1990, the American College of Rheumatology proposed the following five criteria for the classification of hypersensitivity vasculitis in an adult (3):

- Age >16 years
- Use of a possible offending medication in temporal relation to the symptoms
- Palpable purpura
- Maculopapular rash
- Biopsy of a skin lesion showing neutrophils around an arteriole or venule

The presence of three or more criteria has a sensitivity of 71% and specificity of 84% for the diagnosis of hypersensitivity vasculitis.

Hypersensitivity vasculitis that occurs without systemic manifestations is sometimes referred to as cutaneous vasculitis or *cutaneous leukocytoclastic angiitis*. The term *serum sickness*, on the other hand, is reserved to describe a systemic illness, including rash and arthralgias, which occurs 1 to 2 weeks after exposure to a drug or foreign antigen.

Clinical Presentation

Most patients with hypersensitivity vasculitis will develop cutaneous manifestations, the most common of which is purpura (Figure 21D-1). These lesions are

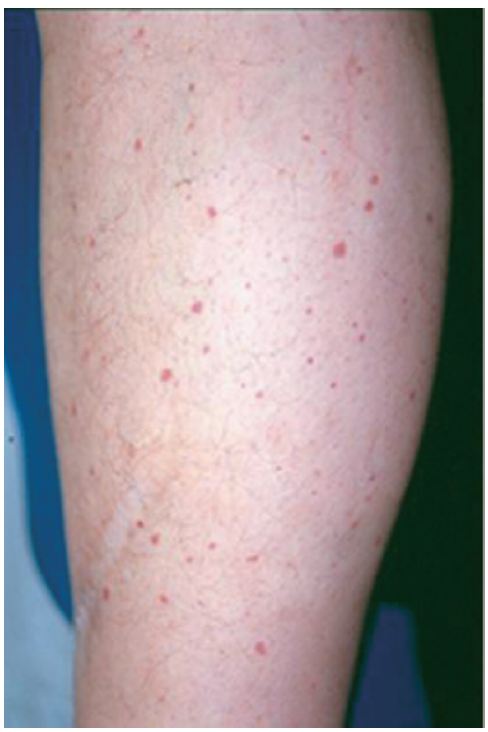

FIGURE 21D-1

Palpable purpura in a patient with hypersensitivity vasculitis. (Courtesy of Dr. John Stone.)

distributed usually in a symmetric fashion over dependent regions of the body, particularly the lower legs (and, in recumbent patients, over the buttocks) because of the increased hydrostatic pressure in such areas. Purpuric lesions are not always palpable to the touch. The term *palpable purpura* is essentially synonymous with small vessel vasculitis, but does not necessarily imply an immune complex–mediated pathophysiology; pauci-immune forms of vasculitis, such as Wegener's granulomatosis, microscopic polyangiitis, and the Churg–Strauss syndrome, for example, may present with identical skin findings (see Chapter 21C).

Diagnosis

Biopsy is the diagnostic method of choice. Cutaneous biopsies are associated with low morbidity, and are generally sufficient to confirm one's clinical suspicion. Light microscopy examination of a hematoxylin and eosin (H&E) preparation will demonstrate an inflammatory infiltrate primarily composed of mononuclear or polymorphonuclear cells, as well as telltale signs of small vessel vasculitis: leukocyte diapedesis, karyorrhexis, and leukocytoclasis. Although H&E preparations are adequate for confirming the presence of vasculitis, they often provide insufficient data for a precise diagnosis. In cases of immune complex–mediated vasculitis, direct immunofluorescence (DIF) studies on the biopsy demonstrate the types of immunoreactants (i.e., immunoglobulin and complement proteins) present at the site of disease. Although direct immunofluorescence requires a biopsy of a second cutaneous site, this procedure is critical in many cases to differentiating the array of conditions associated with cutaneous vasculitis. Biopsy is especially useful to exclude other causes of vascular injury, including embolism and hypercoagulability states, which may demonstrate evidence of erythrocyte extravasation but not immune complex deposition. Of course, the presence of small vessel vasculitis does not always confirm the presence of a primary autoimmune disease; malignancy, for example, can also be associated with leukocytoclastic vasculitis. All biopsies, therefore, must be evaluated in the appropriate clinical context.

Therapy

Removal of the inciting agent is the only reliable therapy. In patients who have been exposed to multiple medications, determining the inciting agent may be difficult, and may require withdrawal of multiple agents simultaneously until the syndrome clears, typically in 1 to 2 weeks. Immunosuppression with glucocorticoids should be reserved for patients with particularly fulminant disease, and may be discontinued usually within several weeks.

Prognosis

The prognosis for patients with hypersensitivity vasculitis depends on the nature of the inciting agent. In the case of drug-induced vasculitis, multiple agents may need to be discontinued and re-introduced gradually. Approximately half of cases of isolated cutaneous angiitis do not have an obvious cause. Many such cases are associated with a relapsing and remitting course, but remain restricted to the skin and do not mandate aggressive immunosuppressive therapy.

Cryoglobulinemic Vasculitis

Definition

In 1933, Wintrobe and Buell noted that when serum from a patient with a hyperviscosity syndrome due to multiple myeloma was held at temperatures less than 37°C, a protein precipitate formed (4). In 1947, this "cold precipitable serum globulin" was referred to for the first time as a "cryoglobulin." Cryoglobulins are immune complexes that are characterized by their tendency to precipitate from serum under conditions of cold. Cryoglobulins, detectable to a varying degree in a wide array of inflammatory conditions, are not invariably pathogenic. In some patients, however, cryoglobulins deposit in the small- and medium-sized blood vessels and activate complement, leading to cryoglobulinemic vasculitis (5).

Three major types of cryoglobulinemia are recognized, defined by the specific kinds of immunoglobulins with which they are associated. Type I cryoglobulinemia, characterized by a monoclonal gammopathy (generally IgG or IgM), can be associated with Waldenström's macroglobulinemia or, less frequently, multiple myeloma. Type I IgA cryoglobulinemia has also been described, although this is quite rare. In contrast to the monoclonal nature of type I cryoglobulinemia, type II and type III cryoglobulinemias are known as "mixed" cryoglobulinemias because they are comprised of both IgG and IgM. In most cases of type II cryoglobulinemia, more than 90% of which are caused by hepatitis C infections, the cryoproteins consist of monoclonal IgM and polyclonal IgG. Cases of type II cryoglobulinemia not associated with hepatitis C infections are sometimes termed "mixed essential" cryoglobulinemia. Such cases may be associated with a still undefined viral infection. Type III cryoglobulinemia, typically associated with polyclonal IgG and polyclonal IgM, is associated with many forms of chronic inflammation, including infection and autoimmune disease. Not every form of cryoglobulinemia fits neatly into this classification system; cryoglobulins can, for example, have an oligoclonal antibody component.

Clinical Presentation

Type I cryoglobulinemia rarely presents with signs and symptoms of vasculitis. When symptomatic, type I cryoglobulinemia may be associated with a hyperviscosity syndrome that can lead to serious neurologic manifestations, including dizziness, confusion, headache, and stroke. Type I cryoglobulinemia can also be associated with other evidence of vascular stasis, including livedo reticularis, acrocyanosis, and digital gangrene (Figure 21D-2).

Type II and type III cryoglobulinemias often present with a triad of signs and symptoms: purpura, arthralgias, and myalgias. The purpura may be extensive and confluent, and sometimes involves the trunk, upper extremities, and even the face (albeit in most cases the rash is confined to the lower extremities). Other common organ system involvement, more common in type II than in type III cryoglobulinemia, includes membranoproliferative glomerulonephritis (Figure 21D-3), peripheral neuropathy, and cutaneous ulcerations (the result of medium vessel vasculitis, in contrast to the small-sized vessel involvement that leads to purpura).

Diagnosis

Biopsy of an affected organ (such as the skin or kidney) may be the most straightforward method of confirming the diagnosis. Light microscopy of purpuric lesions demonstrates leukocytoclastic vasculitis. Direct immunofluorescence studies reveal various types of immunoglobulin and complement deposition, depending on cryoglobulinemia type. In type II cryoglobulinemia, for example, direct immunofluorescence reveals IgG and IgM deposition, as well as complement components.

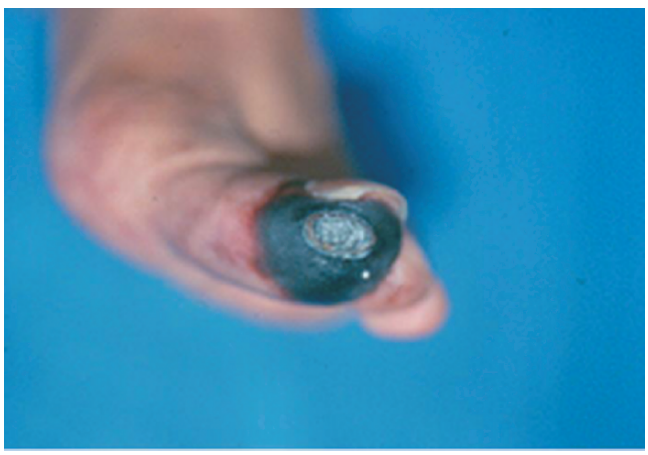

FIGURE 21D-2

Acrocyanosis and digital necrosis in type I cryoglobulinemia associated with multiple myeloma. (Courtesy of Dr. John Stone.)

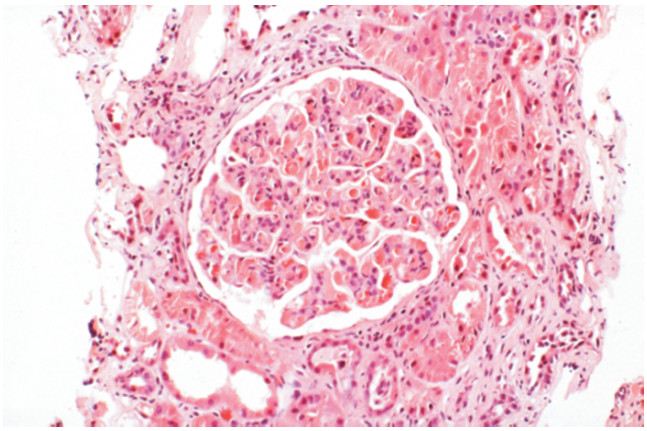

FIGURE 21D-3

Proliferative glomerulonephritis associated with type II cryoglobulinemia. (Courtesy of Dr. Mark Haas.)

Renal biopsies from patients with glomerulonephritis caused by cryoglobulinemia reveal a membranoproliferative glomerulonephritis that must be distinguished from lupus nephritis (another disorder in which immune complexes play a major role).

If biopsy is impractical or impossible, serologic testing may be helpful. The most directly relevant test is a serum cryoglobulin assay, which can give a direct sense of the burden of disease. The serum is allowed to remain at 4°C for several days before interpretation. The percentage of the serum occupied by the cryoprecipitate is commonly referred to as the cryocrit, and may be useful for following such patients longitudinally.

Serum cryoglobulin tests are, unfortunately, notoriously difficult to obtain, largely because the collection apparatus must be prewarmed and the blood must be allowed to clot at 37°C before processing. False-negative assays for cryoglobulins are common, particularly in laboratories not experienced in the collection and processing of samples.

For patients with type II and type III cryoglobulinemia, nonspecific serologic testing may also heighten suspicion. First, a strong clue to the presence of mixed cryoglobulinemia is an extremely low (to almost undetectable) level of C4. For reasons that are not entirely clear, C4 levels are lowered out of proportion to the decrease observed in C3. Second, the monoclonal component of type II cryoglobulins almost invariably has rheumatoid factor activity (i.e., binds to the Fc portion of IgG). Thus, essentially all patients with type II cryoglobulinemia are rheumatoid factor-positive—usually strikingly so. In many cases, rheumatoid factor tests are a more reliable screening test for type II cryoglobulinemia than are assays for cryoglobulins themselves.

Although rheumatoid factor titers correlate with immunoglobulin burden in such patients and can be used in longitudinal follow-up in a manner similar to the cryocrit, the level of clinical symptomatology often correlates poorly with both rheumatoid factor level and cryocrit. Once patients have achieved a state of disease quiescence following treatment, both rheumatoid factor levels and cryocrit often remain elevated. Neither should be used as a gauge of therapy for most patients. Finally, acute-phase reactants such as the erythrocyte sedimentation rate and the C-reactive protein are elevated in many patients with cryoglobulinemia. In patients with type I cryoglobulinemia, for example, the erythrocyte sedimentation rate may be even higher than anticipated because of the excess circulating immunoglobulin.

Therapy

Treatment of the underlying cause of the cryoglobulins is the only approach that may lead to long-term response. Immunosuppression alone will not be sufficient to treat a cryoglobulinemic vasculitis that is driven by malignancy or chronic infection. In the case of hepatitis C–associated cryoglobulinemic vasculitis, for example, the optimal therapy consists of the effective control of the underlying viral infection (typically with interferon-alpha and ribavirin). In patients who experience severe consequences of cryoglobulinemia (such as mononeuritis multiplex, glomerulonephritis, or other forms of tissue necrosis), immunosuppression with high dose glucocorticoids and cyclophosphamide may be necessary to prevent further damage. In patients with rampant systemic vasculitis, anecdotal evidence suggests that the systemic inflammation should be controlled first with glucocorticoids and other immunosuppressive agents, as appropriate, before the institution of antiviral therapy. In some cases of flagrantly active vasculitis, the introduction of antiviral therapy first is believed to have triggered disease exacerbation through an unfavorable alteration of the antigen/antibody ratio.

Prognosis

The prognosis of patients with cryoglobulinemia generally depends on the underlying cause. The outcome of type I cryoglobulinemia relates closely to the efficacy in treating the cause of the cryoglobulin. Type II cryoglobulinemia secondary to hepatitis C may be treated effectively if the viral infection is responsive to therapy. If patients do not tolerate antiviral therapy well or if the treatment is ineffective, however, some patients may require low-to-moderate doses of prednisone to control the disease. Type III cryoglobulinemia is frequently a response to an inflammatory event (such as infection), and may not require specific therapy.

Henoch–Schönlein Purpura

Definition

Henoch–Schönlein purpura (HSP) is an immune complex–mediated form of small vessel vasculitis that is associated strongly with IgA deposition within blood vessel walls. Many cases of HSP are reported to occur after upper respiratory tract infections. Group A streptococci, mycoplasma, Epstein–Barr virus, varicella, and other infectious agents have all been implicated in the pathogenesis of this disease, but the true etiology remains unknown.

In 1990, the American College of Rheumatology proposed the following criteria for the classification of HSP (6):

- Palpable purpura
- Age ≤ 20 years at disease onset
- Bowel angina
- Granulocytes in arteriole or venule walls on biopsy

Meeting two of four criteria is associated with a sensitivity of 87% and a specificity of 88% for this diagnosis.

Clinical Presentation

The hallmarks of HSP include an upper respiratory tract infection followed by a syndrome characterized by a purpuric rash, arthralgias, abdominal pain, and renal disease. HSP is usually viewed as a disease of childhood and, indeed, the majority of cases affect children younger than 5 years of age. Adults, however, can also be affected by HSP, and have a greater tendency toward prolonged disease courses (with recurrent bouts of purpura) than do children (7). Colicky abdominal pain, presumably secondary to gastrointestinal vasculitis, is a common characteristic of HSP, and frequently occurs within a week after the onset of rash. Occasionally the abdominal pain in HSP occurs before the onset of purpura, and may be difficult to distinguish from an acute abdomen. Endoscopy may demonstrate purpura in the upper or lower intestinal tract. Mild glomerulonephritis is common and generally self-limited, although some patients will develop end-stage renal disease.

Diagnosis

In children with mild manifestations, the clinical history alone may be sufficient to confirm the diagnosis. In more serious cases or when there is sufficient doubt about the diagnosis, biopsy of an involved organ is essential. Unlike other forms of immune complex–mediated disease, however, direct immunofluorescence will

reveal florid IgA deposition. In the proper clinical setting, this finding is diagnostic of HSP. Other forms of small vessel vasculitis may have small quantities of IgA within blood vessels, but IgA is not the predominant immunoreactant in such cases.

Therapy

In mild cases of HSP, no specific therapy is necessary. Even for patients with glomerulonephritis, it has been difficult to demonstrate that treatment with glucocorticoids or immunosuppressive agents significantly alters outcomes. Despite this, it may be prudent to treat aggressive renal involvement with an immunosuppressive regimen, including high-dose glucocorticoids and another immunosuppressive agent such as cyclophosphamide, azathioprine, or mycophenolate mofetil, depending on disease severity (8). In patients with renal involvement, anecdotal evidence suggests that plasmapheresis and intravenous immunoglobulin may also be beneficial, particularly in patients who are refractory to standard immunosuppressive regimens.

Prognosis

Recurrences of skin disease, often comprised of multiple episodes occurring over many months, are not unusual. Generally, however, even in patients with recurrent disease, the rule is for the disorder to subside and to resolve completely over a few months to a year. In a minority of patients, some evidence of permanent renal damage persists in the form of proteinuria and hematuria. Only a small minority, probably well under 5%, develop renal failure as a result of HSP.

Hypocomplementemic Urticarial Vasculitis Syndrome

Definition

The study of urticaria is hampered by multiple terms that sound similar but describe different types of diseases. The word *urticaria* is most frequently used to describe *acute urticaria*, an IgE-mediated hypersensitivity reaction to a variety of stimuli, including medications, infection, and other triggers. Acute urticaria manifests as pruritic wheals that resolve days after the allergen is removed. *Chronic urticaria* is an autoimmune condition that is probably driven by an autoantigen. This form of urticaria may require immunosuppressive therapy in addition to antihistamines to prevent recurrence (9).

Urticarial vasculitis describes a form of small vessel vasculitis that is characterized by the appearance of urticarial wheals. *Normocomplementemic urticarial vasculitis* is most often simply an example of hypersensitivity vasculitis in which the principal skin manifestation is urticaria. Normocomplementemic urticarial vasculitis tends to be self-limited, as is the case with hypersensitivity vasculitis. In contrast, urticarial vasculitis associated with hypocomplementemia is much more likely to constitute a significant and persistent clinical problem.

Two categories of urticarial vasculitis associated with hypocomplementemia are recognized. The distinctions between these two categories are not always sharp, and both categories also share a number of features with systemic lupus erythematosus. The first category, known simply as hypocomplementemic urticarial vasculitis, refers to cutaneous vasculitis associated with low levels of serum complement (C3 and C4). The diagnosis of hypocomplementemic urticarial vasculitis is predicated upon the exclusion of other disorders that may present in a similar fashion, particularly cryoglobulinemia and SLE. The second category—a more specific but still loosely defined entity known as the *hypocomplementemic urticarial vasculitis syndrome* (HUVS)—consists of the constellation of low complement levels and urticaria for a period of at least 6 months, as well as some or all of the following: arthritis, glomerulonephritis, uveitis, angioedema, chronic obstructive pulmonary disease, pleurisy, or pericarditis.

Clinical Presentation

Although the lesions associated with chronic urticaria and urticarial vasculitis are similar in appearance, certain differences help differentiate these two conditions. In urticarial vasculitis, the urticaria typically have a purpuric quality, indicative of small blood vessel damage and red blood cell extravasation (Figure 21D-4). Unlike common urticaria, the lesions of urticarial vasculitis are frequently associated with moderate pain, burning, and

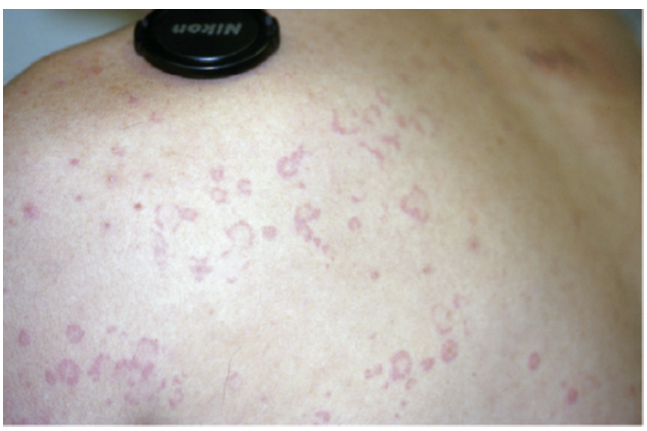

FIGURE 21D-4

Urticarial vasculitis. (Courtesy of Dr. John Stone.)

tenderness, in addition to pruritus. Whereas common urticaria typically resolve completely within 24 to 48 hours, the lesions of urticarial vasculitis may take days to resolve completely and often worsen without therapy. Arthralgias and myalgias are common in urticarial vasculitis. As noted above, patients with HUVS may also develop glomerulonephritis, pulmonary manifestations (particularly obstructive airway disease), and other findings. Gastrointestinal, cardiovascular, and neurologic manifestations are uncommon, but have been reported. There is striking overlap between HUVS and SLE, and patients will frequently have characteristics of both, although angioedema and COPD are more common in HUVS.

Diagnosis

Biopsy of an urticarial wheal in UV will demonstrate evidence of leukocytoclastic vasculitis, including injury to the endothelial cells of the postcapillary venules, erythrocyte extravasation, leukocytoclasis, fibrin deposition, and a perivascular neutrophilic (or less commonly, lymphocytic) infiltrate. Direct immunofluorescence demonstrates immune complex deposition around blood vessels in the superficial dermis and striking deposition of immunoglobulins and complement along the dermal–epidermal junction (Figure 21D-5). The "interface dermatitis" is identical to that observed in lupus—a histopathological finding termed the *lupus band test*. In the proper setting, these findings (interface dermatitis as well as immunoreactant deposition within blood vessels) are diagnostic of hypocomplementemic urticarial vasculitis. HUVS, in contrast, is a clinical diagnosis based not only on the presence of urticarial vasculitis but also the occurrence of typical features in extracutaneous organ systems.

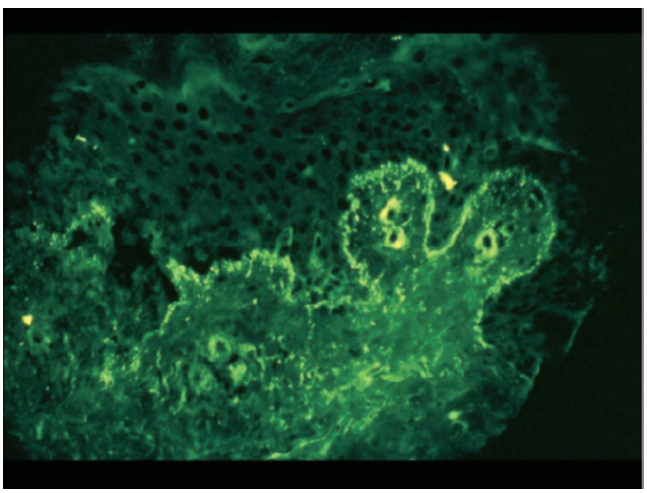

FIGURE 21D-5

Direct immunofluorescence of a skin biopsy in urticarial vasculitis. The immunostaining shows immunoreactant deposition within small blood vessels in the superficial dermis, and florid deposition along the dermal–epidermal junction. (Courtesy of Dr. John Stone.)

Therapy

Some cases of hypocomplementemic urticarial vasculitis respond to therapies commonly used for the treatment of SLE, including low-dose prednisone, hydroxychloroquine, dapsone, or other immunomodulatory agents. There is anecdotal evidence that antihistamines, calcium channel antagonists, doxepin, methotrexate, indomethacin, colchicine, and pentoxifylline are effective in some cases. Serious cases, particularly those presenting with glomerulonephritis or other forms of serious organ involvement, may require treatment with high doses of glucocorticoids and cytotoxic agents. Both chronic obstructive pulmonary disease (COPD) and cardiac valvular abnormalities are associated with HUVS, and may require specific treatment as well.

Prognosis

The prognosis of HUVS is frequently linked to the disorder with which it is associated. SLE, COPD, angioedema, and valvular abnormalities are all known to occur in association with this disorder, and in such cases, may strongly influence both quality and quantity of life.

SUMMARY

The immune complex–mediated vasculitides are a clinically heterogeneous group of disorders linked by inefficient, defective, or dysregulated clearance of immune complexes by the reticuloendothelial system. Biopsy of an involved organ is frequently helpful in establishing the diagnosis. Direct immunofluorescence studies of involved blood vessels demonstrate characteristic patterns of immunoglobulin and complement deposition, which may be particularly useful in distinguishing these diseases. The prognosis of patients with immune complex–mediated vasculitis is tied closely to the ability to identify and to treat the underlying cause of the immune response.

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CHAPTER 21

Vasculitides

E. Miscellaneous Vasculitis (Behçet's Disease, Primary Angiitis of the Central Nervous System, Cogan's Syndrome, and Erythema Elevatum Diutinum)

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- The prevalence of Behçet's disease is highest in countries of the eastern Mediterranean, the Middle East, and East Asia.
- Aphthous oral ulcers are usually the first and most persistent clinical feature of Behçet's disease. Aphthous ulcers also occur frequently on the genitals (e.g., the scrotum or vulva).
- Uveitis—either anterior or posterior—is common in Behçet's disease and a source of major morbidity.
- Many forms of central nervous system disease may occur in Behçet's disease. These include aseptic meningitis and white matter lesions in the brainstem.
- Human leukocyte antigen (HLA)-B51 is a strong risk factor for Behçet's disease.
- The diagnosis of primary angiitis of the central nervous system is predicated upon either biopsy evidence of vasculitis or angiographic findings suggestive of vasculitis in the setting of other compelling features, for example, strokes demonstrated by magnetic resonance imaging or the findings of a cerebrospinal fluid pleocytosis.
- The diagnosis of primary angiitis of the central nervous system should never be made on the basis of an angiogram alone.
- Patients with benign angiopathy of the central nervous system are predominantly female, tend to present acutely with headache (with or without focal symptoms), and have normal or near normal cerebrospinal fluid.
- Cogan's syndrome refers to the association of inflammation in both the eyes and ears: specifically, the occurrence of nonsyphilitic interstitial keratitis and immune-mediated inner ear disease, resulting in audiovestibular dysfunction.
- Any type of ocular inflammation may occur in Cogan's syndrome (e.g., scleritis, uveitis, orbital pseudotumor). The inner ear disease associated with this condition often leads to deafness.
- In erythema elevatum diutinum, skin lesions consist of purple, red, or brown plaques and often have an annular or nodular appearance. The skin lesions have a predilection for the extensor surfaces of the distal extremities and often overlie joints, but may be generalized.

BEHÇET'S DISEASE

Behçet's disease (BD) is a chronic inflammatory disorder of unknown cause. Its manifestations are thought to be caused by an underlying vasculitis. Although this disease is recognized worldwide, the prevalence is highest in countries of the eastern Mediterranean, the Middle East, and East Asia, thus the name Silk Road disease. The disease tends to be more severe in areas where it is more common. Prevalence rates in all areas of the world are increasing, probably because of improved recognition and reporting.

Behçet's disease occurs primarily in young adults. The mean age at onset is between 25 and 30 years. The incidence of disease in males and females with the disease is approximately equal along the Silk Road, but

in Japan, Korea, and Western countries the disease occurs more frequently in women. Familial aggregation and juvenile cases are not common. Case confirmation can be challenging because many patients labeled as having Behçet's disease have oral ulcers as the primary or sole manifestation.

Clinical Manifestations

Aphthous oral ulcers are usually the first and most persistent clinical feature of BD. Lesions occur in crops and some patients may have them during most of the course of the disease. Aphthae occur as ulcers that are 2 to 12 mm or larger. These are discrete, painful, round or oval red-rimmed lesions that affect mainly the nonkeratinized mucosa of the cheeks, the border of the tongue, the soft palate, and the pharynx (Figure 21E-1). Oral ulcers are identical to the lesions of recurrent aphthous stomatitis. The severity and behavior of the oral ulcers in BD often fit the description of complex aphthosis, in which multiple, recurrent, or persisting lesions result in a severe syndrome that may include perianal or genital ulceration.

Genital ulcers resemble oral aphthae but occur less frequently. They occur as single or multiple lesions of the vulva and in the vagina, or on the scrotum or penile shaft (Figure 21E-2). Genital lesions are usually painful and may result in scarring, but vaginal ulcers may be asymptomatic or only produce a discharge. Perianal ulcers may occur.

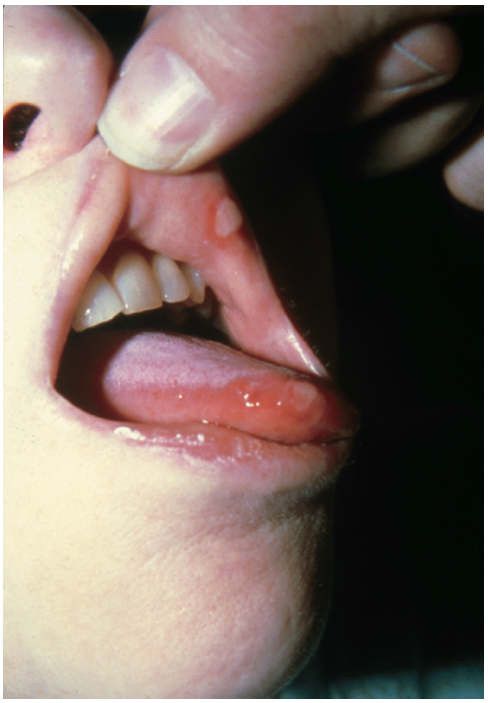

FIGURE 21E-1

Oral aphthous ulceration in Behçet's disease. (Courtesy of J.D. O'Duffy, MB.)

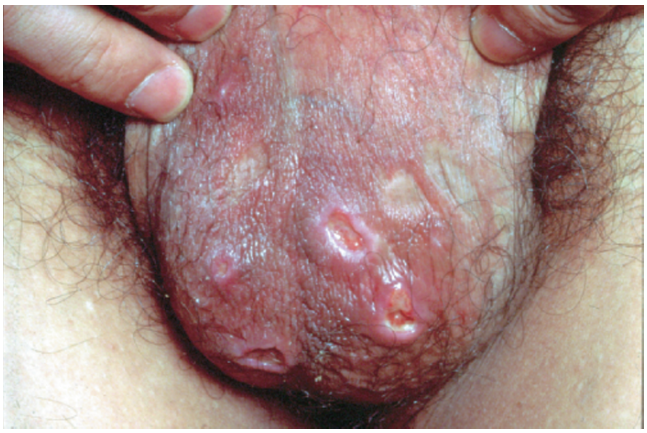

FIGURE 21E-2

Ulcers on the scrotum in a patient with Behçet's disease. (Courtesy of J.D. O'Duffy, MB.)

Skin lesions are common in BD. The International Study Group (ISG) criteria for the diagnosis of BD (Table 21E-1) (1) include the presence of erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneform nodules. Nodular lesions should be distinguished from superficial thrombophlebitis. A neutrophilic vascular reaction characterizes lesions typical of

TABLE 21E-1. INTERNATIONAL STUDY GROUP CRITERIA FOR BEHÇET'S DISEASE.

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period[a]
Plus 2 of:	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient[a]
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions; or acneform nodules observed by physician in postadolescent patients not receiving corticosteroid treatment[a]
Positive pathergy test	Read by physician at 24 to 48 hours

SOURCE: From International Study Group for Behçet's Disease. Lancet 1990;335:1078–1080, by permission of *Lancet*.
[a] Findings applicable only in the absence of other clinical explanations.

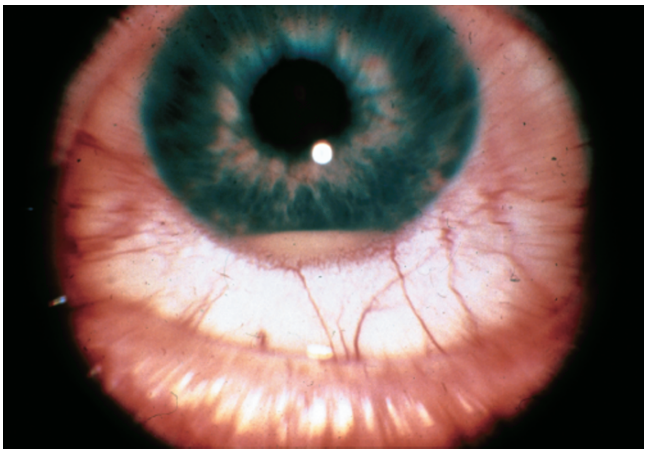

FIGURE 21E-3

Hypopyon in the anterior chamber of a patient with Behçet's disease, caused by anterior uveitis.

BD. A neutrophilic infiltrate is typical of other dermatoses occasionally seen with the disorder, including pyoderma gangrenosum and Sweet's syndrome.

Pathergy is an excessive skin response to trauma, reflecting neutrophil hyperreactivity, and is highly specific for BD. Pathergy is suggested if there is a history of red papules, pustules, or sterile abscesses after therapeutic injections, at intravenous catheter sites, or after minor skin trauma. Testing for pathergy can be done with a sterile 20-gauge needle, used to penetrate the cleansed skin perpendicularly to a depth of approximately one quarter of an inch, rotated briefly on its axis, and then removed. After 48 hours, the appearance of an erythematous papule or pustule at the puncture site constitutes a positive test. The volar forearm is usually chosen for the test and sensitivity is greater when three needle punctures are made. The positivity of the test may vary during the course of the disease and is more likely to be positive at times of active disease. The sensitivity of the test is lower in Western countries than in Silk Road countries, but a positive test adds great support for the diagnosis of BD.

Ocular inflammation typically follows mucocutaneous symptoms by a few years, but it often progresses with a chronic, relapsing course affecting both eyes. The ocular finding in Behçet's original patients was anterior uveitis associated with a hypopyon [the accumulation of an inflammatory cell infiltrate—essentially pus—in the anterior chamber (Figure 21E-3)]. Anterior uveitis that is not treated promptly with a mydriatic agent may result in synechiae formation between the iris and the lens and permanent papillary distortion. The ocular manifestations of Behçet's disease may also include a panuveitis, however, with posterior chamber involvement and retinal vasculitis, the complications of which may extend to visual loss. Retinal vasculitis, which leads to episodes of retinal occlusion and areas of ischemia, may be followed by neovascularization, vitreous hemorrhage and contraction, glaucoma, and retinal detachment. The earliest findings of retinal vasculitis may be detected with fluorescein angiography. Isolated optic disk edema in BD suggests cerebral venous thrombosis rather than ocular disease, but papillitis may occur with ocular inflammation and central nervous system disease. Cranial nerve palsies may result from brain stem lesions, and visual field defects may also be caused by intracranial disease involving the optic pathways.

With cerebral venous thrombosis, patients usually present with symptoms of intracranial pressure: headache, visual obscurations, and papilledema. Magnetic resonance imaging may be used to demonstrate acute or recent clot in the larger dural sinuses, but magnetic resonance venography is more reliable for recognizing clot in the cerebral venous system, especially in the smaller veins and older thromboses.

Central nervous system symptoms in BD may be due to aseptic meningitis or parenchymal lesions, resulting in focal or diffuse brain dysfunction. An increased protein concentration and lymphocytic pleocytosis in the cerebrospinal fluid (CSF) is supportive of the diagnosis. The clinical combination of stroke, aseptic meningitis with CSF pleocytosis, and mucocutaneous lesions can be diagnostic of BD. Focal or multifocal nervous system involvement reflects the predilection of the disease for diencephalon, midbrain, and brainstem (Figure 21E-4). In contrast to multiple sclerosis, there is

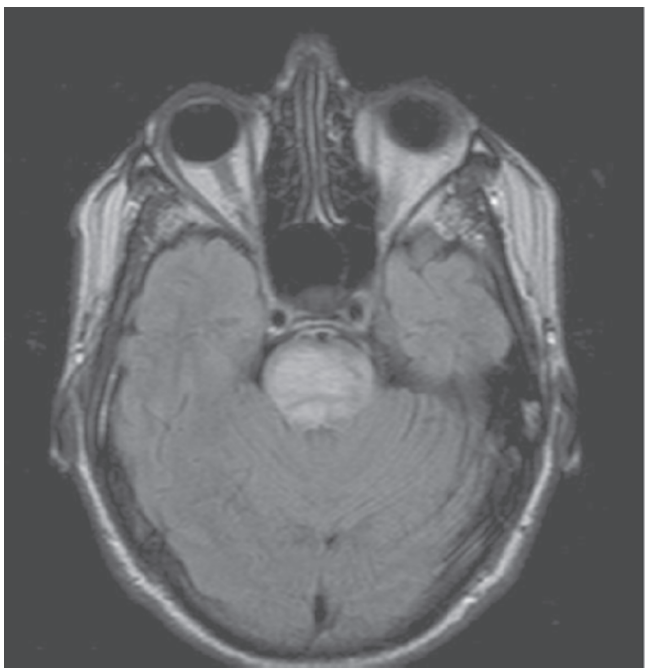

FIGURE 21E-4

Brainstem involvement in a patient with Behçet's disease.

no preference for the periventricular structures (2). Isolated headaches in BD are common but the cause is not well understood. These may represent secondary migraine or may not be related to the disease.

Large vessel involvement, which occurs in about one fourth of patients with BD, is a major cause of morbidity and mortality (3). Patients with vascular disease often have multiple lesions and involvement of both the arterial and venous systems (4). Deep venous thrombosis (DVT) is the most common large vascular lesion. Patients with recurrent DVTs are at risk for chronic stasis changes in the legs. Occlusions of the vena cava, hepatic, and portal veins, other recognized thrombotic complications in BD, are associated with an increased risk of mortality. Chest wall, abdominal, and esophageal varices may occur from deep-seated venous thrombosis. Right ventricular thrombi have been reported, usually in association with pulmonary vasculitis. No primary abnormality of the coagulation, anticoagulation, or fibrinolytic system explaining the thrombotic tendency in BD has been identified consistently.

Arterial complications occur in up to 7% of patients with BD (5). Stenoses, occlusions, and aneurysms occur in the systemic circulation or the pulmonary arterial bed. Arterial aneurysms, caused by vasculitis of the vasa vasorum, involve the aorta or its branches. The risk of rupture is high. Pulmonary artery aneurysms (6) may lead to fistulae between the pulmonary artery and bronchi, presenting with hemoptysis. Anticoagulant treatment for presumed pulmonary emboli can result in massive hemorrhage and death. Clinically apparent cardiac vascular involvement is unusual, but may result in myocardial infarction.

Gastrointestinal symptoms in BD include melena and abdominal pain. Colonoscopic lesions appear as single or multiple ulcerations involving primarily the distal ileum and cecum. Gastrointestinal lesions have a tendency to perforate or to bleed. The lesions in BD should be differentiated from those of Crohn's disease and those due to the use of nonsteroidal anti-inflammatory drugs.

An intermittent, symmetric oligoarthritis of the knees, ankles, hands, or wrists affects one half of the patients with BD; arthralgia is also common. An erosive or destructive arthropathy is unusual. Inflammatory cells of the synovium and synovial fluid are primarily polymorphonuclear leukocytes.

Epididymitis occurs in about 5% of affected patients. Glomerulonephritis and peripheral neuropathy occur much less frequently in BD than in other forms of systemic vasculitis. AA-type amyloidosis, presenting as nephrotic syndrome, can accompany BD. The occasional association of the disorder with ankylosing spondylitis [in human leukocyte antigen (HLA)-B27-positive patients] or relapsing polychondritis (MAGIC syndrome [mouth and genital ulcers with inflamed cartilage]) likely represents the simultaneous occurrence of two disorders.

No laboratory abnormality is diagnostic of BD. Acute-phase reactants may be increased, especially in patients with large vessel vasculitis, but they may be normal in other patients, even those with active eye disease. The histocompatibility antigen HLA-B51 is associated with BD in areas of high prevalence and in patients with ocular disease.

Diagnosis

The multiple manifestations of BD in the same patient may be separated in time, occasionally by several years. For definitive diagnosis, the manifestations must be documented or witnessed by a physician. The ISG criteria for the classification of BD (Table 21E-1) (1) are not meant to replace clinical judgment regarding the diagnosis in individual cases. For patients in Western countries, large vessel disease or acute central nervous system infarction in the setting of aphthosis should suggest the diagnosis (7).

The diagnosis of BD in patients with complex aphthosis requires the presence of other characteristic lesions and the exclusion of other systemic disorders. Inflammatory bowel disease, sprue, cyclic neutropenia or other hematologic disorders, herpes simplex infection, and acquired immune deficiency syndrome may cause similar lesions. Other disorders responsible for orogenital/ocular syndromes include erythema multiforme, mucous membrane pemphigoid, and the vulvovaginal–gingival form of erosive lichen planus. The differential diagnosis can be clarified with the aid of an experienced dermatologist and biopsy findings. In Reiter's disease, mucocutaneous lesions are nonulcerative and painless, and the uveitis is usually limited to the anterior chamber. Similarities between BD and Crohn's disease include gastrointestinal lesions, fever, anemia, oral ulcers, uveitis, arthritis, thrombophlebitis, and erythema nodosum. Granuloma formation in intestinal lesions is not typical in BD, and in Crohn's disease the iritis is typically confined to the anterior chamber. Genital ulcerations and central nervous system disease are rare in Crohn's disease.

Disease Activity

Frequent ophthalmologic examinations are essential for patients with ocular disease, and periodic monitoring of the eyes is recommended for all patients. A careful history and examination, with attention to the vascular and neurologic systems, should be part of the physician's assessment. Standardized forms for scoring disease activity and ocular inflammation have been developed for use in clinical trials and the care of individual patients (8).

Management

Aphthous lesions are treated with topical or intralesional corticosteroids. An empiric trial of dapsone or methotrexate may be appropriate in difficult cases. Colchicine is used in the treatment of mucocutaneous manifestations and as an adjunct in the treatment of more serious manifestations (0.6 mg three times daily may be required to achieve a therapeutic effect; many patients suffer gastrointestinal intolerance of the drug at that dose). The effectiveness of colchicine has been demonstrated for genital ulcers and erythema nodosum in females and for arthritis in both sexes (9). Thalidomide has been used for the treatment of mucosal and follicular lesions, but toxicity is a major concern. Short courses of prednisone are useful in the management of mucocutaneous disease in some patients. In others, low-dose prednisone as maintenance therapy is required.

Cyclosporine can be effective for the control of uveitis. A controlled study has demonstrated the value of azathioprine at a dose of 2.5 mg/kg per day in limiting the progression of ocular disease and preventing new eye disease in males. Combination treatment with cyclosporine and azathioprine can been used when single-agent treatment has failed. Azathioprine can have a beneficial effect on mucosal ulcers, arthritis, deep venous thrombosis, and long-term prognosis (10). Because young males are at the greatest risk for severe disease, especially uveitis, aggressive treatment is warranted in this disease subset. In open trials, interferon-alpha has been found useful for treating mucocutaneous lesions and arthritis and is emerging as an effective treatment for ocular disease (11). Etanercept, a tumor necrosis factor inhibitor, was shown to be beneficial for mucocutaneous manifestations in a controlled study (12). Reports of uncontrolled experience with infliximab for eye inflammation have been positive, but controlled data are lacking. Immunosuppression with chlorambucil or cyclophosphamide is used for uncontrolled ocular disease, central nervous system disease, and large vessel vasculitis, including recurrent deep venous thrombosis. Glucocorticoids are useful in suppression of inflammation in acute phases of the disease, but these agents are insufficient by themselves to treat such severe disease manifestations as posterior uveitis or parenchymal brain disease.

Because of the high risk of rupture, surgical treatment is indicated for systemic arterial aneurysms. Glucocorticoids and alkylating agents should also be used to minimize the high risk of anastomotic recurrences or continued disease. Pulmonary arterial aneurysms may respond to these same medications, but uncontrolled bleeding requires percutaneous embolization or surgical treatment. Cerebral venous thrombosis is treated with anticoagulation and corticosteroids. The treatment of Budd–Chiari syndrome has included anticoagulants or antiaggregants, colchicine, and glucocorticoids. Portocaval shunting should be considered if the inferior vena cava is patent.

Pathogenesis

In many geographic areas, genetic studies have shown a strong association with HLA-B51, but the exact role of this gene in the development of BD is uncertain. Neutrophilic hyperfunction is recognized in BD, in normal subjects with HLA-B51, and in HLA-B51 transgenic mice (13). Evidence also exists for antigen-driven immune mechanisms in the pathogenesis of BD. Cytokine analysis and cellular characterization suggest a T-helper cell (Th1) response by lymphocytes in BD. Molecular techniques have identified herpes simplex viral RNA and DNA in cells from patients with BD, and streptococcal antigens have been proposed as triggers of active disease. Activated gamma-delta T cells are increased in the circulation and in mucosal lesions, but the precise role of these cells in the pathogenesis of BD is uncertain. Peptides from mycobacterial heat shock protein (HSP) and homologous human peptides have been found to stimulate gd+ T cells from patients with BD in a specific fashion (14). Cross-reactivity and molecular mimicry between peptides from streptococcal or viral HSP, homologous human HSP, and mucosal antigens may result in selection of autoreactive T cells (15). More recently, similarities between BD and inflammatory disorders associated with autoimmunity have been recognized (16).

PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

Primary angiitis of the central nervous system (PACNS) is a rare form of vasculitis limited to the brain and spinal cord. The term *granulomatosis angiitis* of the central nervous system was previously applied because of the histopathologic findings observed in arteries from early reported cases. However, an analysis of a larger number of cases supports varied mononuclear cell infiltrates, with fewer than 50% of cases showing granulomatous inflammation (17). Anatomically, the angiitis is multifocal and segmental in distribution and involves the small leptomeningeal and intracerebral arteries. In general, the arteries are involved much more frequently than the veins.

Clinical Manifestations

The disease predominantly affects males. Most patients are young or middle-aged, although patients of a broad

age range are affected. Cases of PACNS in children have also been described. The clinical manifestations of PACNS are not distinctive. The most common symptom is headache. Because virtually every anatomic area of the central nervous system may be affected by the vasculitis, a wide range of neurologic presentations and deficits may be seen, including transient ischemic attacks (TIAs), cerebral infarction, paraparesis, quadriparesis, hemiparesis, ataxia, seizures, aphasia, and visual field defects, among others. Decreased cognitive function or fluctuating levels of consciousness are not uncommon. Progressive multifocal symptoms over time in a younger patient should suggest the possibility of PACNS, particularly in the absence of other risk factors. The spinal cord may occasionally be involved. Presentations with subarachnoid or intracerebral hemorrhage are rare.

Diagnosis

Timely diagnosis of PACNS is critical, before the occurrence of massive brain damage. Preliminary diagnostic criteria for PACNS have been proposed (18) but never validated. The diagnosis of PACNS is usually predicated upon either biopsy evidence of vasculitis or angiographic findings suggestive of vasculitis in the setting of other compelling features, for example, strokes demonstrated by magnetic resonance imaging or the findings of a cerebrospinal fluid pleocytosis (17). Histologic confirmation remains the most specific diagnostic procedure for PACNS, but the sensitivity of brain biopsy is limited because of the focal segmental distribution of the disease. A negative biopsy does not exclude the diagnosis of PACNS, but may be essential to excluding other disorders that mimic PACNS clinically.

In the absence of histologic confirmation, a cerebral angiogram typical of vasculitis in the appropriate clinical settings is frequently used to establish the diagnosis of PACNS. Suggestive angiographic findings include segmental narrowing, dilatation, or occlusion affecting multiple cerebral arteries in the absence of proximal atherosclerotic changes (Figure 21E-5). The findings of narrowing are, however, highly nonspecific, and can be caused by a host of nonvasculitic causes. Angiographic findings compatible with vasculitis are commonly encountered in conditions such as vasospasm, central nervous system infection, cerebral arterial emboli, intravascular lymphomatosis, and atherosclerosis. Furthermore, the sensitivity of angiography is limited if small vessels beyond its resolution are primarily involved. Cerebral angiography has been normal in some biopsy-proven cases.

General laboratory tests, including acute-phase reactants such as C-reactive protein and the erythrocyte sedimentation rate, are not useful in the diagnosis of PACNS. In addition to being nonspecific, in fact, acute-phase reactants are known often to be normal even in the setting of biopsy-proven active disease. Cerebrospinal fluid (CSF) analysis, however, is an essential part of the diagnostic workup of PACNS. The CSF findings are abnormal in 80% to 90% of cases documented pathologically. CSF findings are characterized by a modest pleocytosis and elevated protein levels. CSF analysis should include appropriate stains, cultures, and serologic tests to exclude for CNS infections.

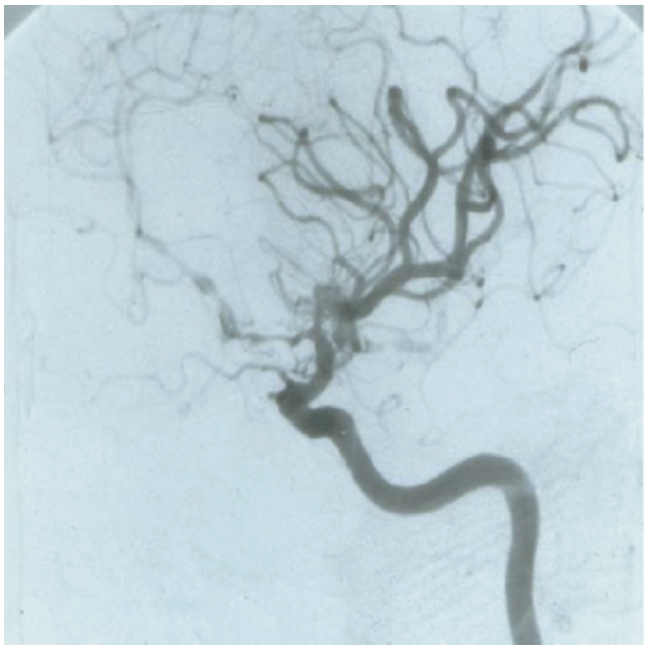

FIGURE 21E-5

Cerebral angiogram in a patient with central nervous system vasculitis. The angiogram reveals multiple segmental stenoses of the A1 and A2 segments of the anterior cerebral artery and the distal segments of the middle cerebral artery.

Magnetic resonance imaging (MRI) is the most sensitive imaging study in the evaluation of PACNS. Only rare cases have no MRI abnormalities. The most common findings are multiple, bilateral, supratentorial infarcts distributed in the cortex, deep white matter, and/or leptomeninges, but the findings lack specificity. Magnetic resonance angiography (MRA) is limited in sensitivity in most cases of PACNS. Angiographically demonstrable lesions are often beyond the resolution of current MRA technology. Thus, a normal MRA does not rule out the disorder.

Management and Outcome

Primary angiitis of the central nervous system is considered a progressive disorder with a fatal course unless treated vigorously with a combination of high-dose glucocorticoids and a cytotoxic agent (usually cyclophos-

phamide). There are no controlled treatment trials on which to base this standard. The optimal duration of therapy is unknown, but in view of the substantial side effects associated with cyclophosphamide and the successful use of shorter courses of therapy in other forms of vasculitis, a 6-month course of cyclophosphamide followed by an additional 1 year of azathioprine appears reasonable. Prednisone should be discontinued in a tapering fashion over 6 to 9 months.

Benign Angiopathy of the Central Nervous System

The presence of a subset of patients with some features suggesting PACNS but demonstrating a more benign course has been suggested (19). This subset of patients is considered to have a disease entity known as benign angiopathy of the central nervous system (BACNS). BACNS patients are predominantly female, primarily present acutely with headache, with or without focal symptoms, and have normal or near normal CSF analysis. The diagnosis in these cases has been established angiographically and appeared to have a monophasic course with a favorable neurologic outcome. Most of these patients recover after only short-term glucocorticoid treatment, often supplemented by a calcium channel blocker to mitigate against vasospasm. Cytotoxic agents are not required for patients with BACNS.

The etiology of the vascular disease in this benign form has not been defined clearly, but could be the result of arteritis or reversible vasospasm. The existence of a benign, angiographically defined subset, however, remains controversial (20). Recently, we identified a subset of patients presenting with evidence of prominent leptomeningeal enhancement on MRI (21). These patients were characterized by normal cerebral angiography, brain biopsy evidence of vasculitis predominantly affecting the small leptomeningeal vessels, and a good response to corticosteroids and/or immunosuppressive therapy with a favorable neurologic course.

COGAN'S SYNDROME

Cogan's syndrome refers to the association of nonsyphilitic interstitial keratitis (Figure 21E-6) and immune-mediated inner ear disease, resulting in audiovestibular dysfunction. The disorder affects men and women equally at any age, but typically in their third and fourth decade. Presenting manifestations include sudden hearing loss, Ménière's-like vertigo and tinnitus, and ocular inflammation, alone or in any combination (22). Other features of the disease, if not present initially, usually follow within several months. Hearing loss is bilateral, shows a downsloping pattern on audiograms, and is often progressive and profound. Vestibular testing shows bilateral cochlear dysfunction, helping to distinguish this disorder from Ménière's syndrome. In comparison to Ménière's syndrome, the damage to hearing from Cogan's syndrome is typically more unremitting. Scleritis, uveitis, or other inflammatory conditions of the eye (Figure 21E-7) may be present initially but often patients will subsequently develop interstitial keratitis if not present initially. Systemic manifestations include headache, fever, arthralgia, and vasculitis, with or without aortitis. The critical evaluation and monitoring

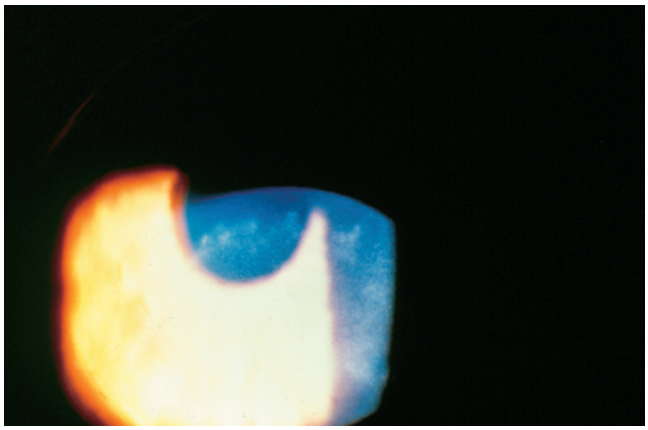

FIGURE 21E-6

Nonsyphilitic interstitial keratitis in a patient with Cogan's syndrome. Retroillumination image of the cornea with the slit lamp reveals a patchy, deep, granular corneal infiltrate characteristic of early Cogan's syndrome in the cornea. (Courtesy of Dr. Thomas J. Liesegang, Mayo Clinic College of Medicine.)

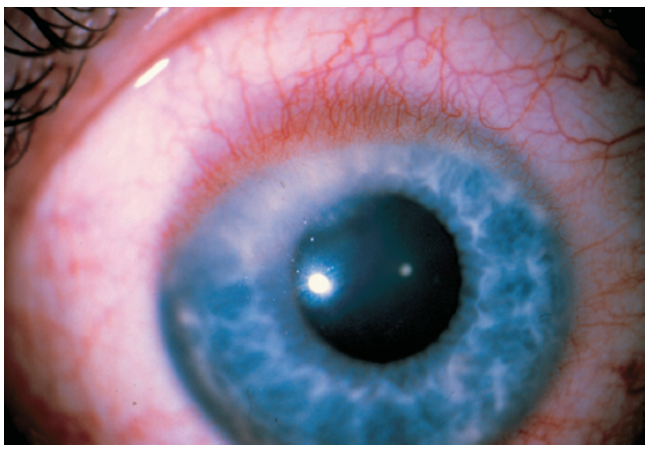

FIGURE 21E-7

Localized corneal edema in Cogan's syndrome. Direct corneal view of classic ocular Cogan's syndrome in an advanced stage. There is localized peripheral corneal edema, mild lipid infiltrate, and moderate vascularization extending from the corneal limbus. (Courtesy of Dr. Thomas J. Liesegang, Mayo Clinic College of Medicine.)

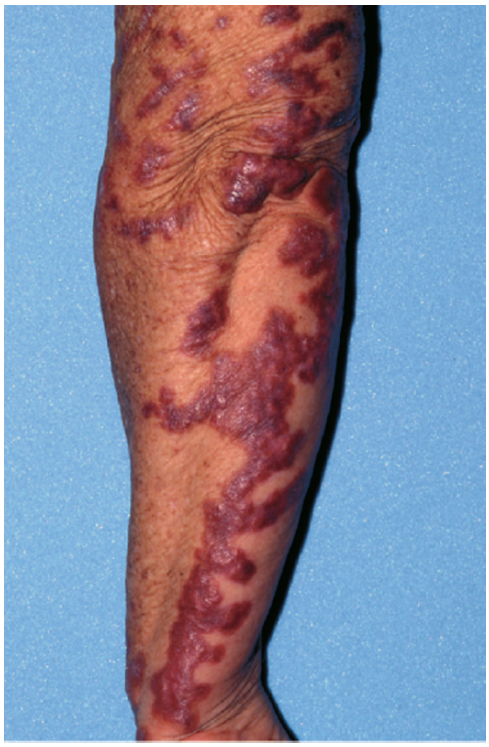

FIGURE 21E-8

Erythema elevatum diutinum.

of Cogan's patients requires the expertise and collaboration of the treating rheumatologist, otolaryngologist, and ophthalmologist (23).

There are no controlled studies on the treatment of Cogan's syndrome. Glucocorticoids are used topically for anterior eye disease and systemically for audiovestibular manifestations, unremitting ocular disease, or when the disorder is complicated by vasculitis or significant systemic manifestations. These agents should be started as soon as the disorder is recognized, in adequate doses (at least 1 mg/kg/day), and for a sufficient duration to initially control the disease or for relapse. Documented improvement in 2 to 3 weeks supports a therapeutic response and can be followed by gradual tapering of the dose and use of immunosuppressive agents if necessary for maintenance. The prognosis for hearing in these patients has been poor (22), but cochlear implants are used successfully in these patients with bilateral deafness.

ERYTHEMA ELEVATUM DIUTINUM

Erythema elevatum diutinum (EED) is an extremely rare, chronic, recurrent vasculitis with distinctive clinical and histopathologic features (24,25). The disorder affects both men and women in middle age. Individual lesions consist of purple, red, or brown plaques that often have an annular or nodular appearance. The skin lesions of EED have a predilection for the extensor surfaces of the distal extremities and often overlie joints, but may be generalized. Older lesions may be dense and coalesce (Figure 21E-8). Erupting lesions may be associated with stinging, burning, or tenderness, and may be accompanied by systemic symptoms. In early lesions, the pathology of EED is one of a leukocytoclastic vasculitis with a perivascular neutrophilic infiltrate. More mature lesions demonstrate perivascular or onion-skin–like fibrosis. Capillary proliferation and cholesterol-containing histiocytes may also be seen. The differential diagnosis includes other neutrophilic dermatoses, primarily Sweet's syndrome.

Erythema elevatum diutinum has been recognized to occur in association with infections diseases, including human immunodecifiency virus infection, hematologic disorders (particularly IgA gammopathies), and several immune-mediated inflammatory diseases, including rheumatoid arthritis. Treatment of any associated disorder may benefit EED. Dapsone (100 mg/day) has been reported to be successful in some patients.

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CHAPTER 21

Vasculitides
F. Kawasaki's Disease

BARRY L. MYONES, MD

- Kawasaki's disease (KD), once known as mucocutaneous lymph node syndrome, is a systemic inflammatory disorder occurring in children that is accompanied by vasculitis and a risk of coronary artery aneurysms.
- Other typical features of KD include spiking fevers, cervical lymphadenopathy, conjunctivitis, erythematous changes on the lips and in the oral cavity, dryness and cracking of the lips, a strawberry appearance to the tongue, and a polymorphous rash.
- Eighty percent of KD cases occur in children less than 5 years of age.
- Attempts to link KD definitively to some types of infection, particularly ones associated with superantigens, have thus far been unsuccessful.
- High dose aspirin and intravenous immune globulin (IVIG) are the cornerstones of therapy in KD. IVIG is essential to the prevention of coronary aneurysms.
- Years after KD has occurred during childhood years, some cases of myocardial infarction caused by thrombosis of coronary aneurysms have been reported.

Kawasaki's disease (KD) is a form of systemic vasculitis that occurs in young children and may be associated with the development of coronary arteritis and aneurysm formation (Figure 21F-1). KD is the leading cause of acquired heart disease of children in the United States. This illness, first recognized to be a new entity by Tomasaku Kawasaki in Japan in 1967 (1,2), was termed for *mucocutaneous lymph node syndrome* (MCLNS) until KD became the accepted designation for this disorder (3). Although the disorder was named after Kawasaki, at least one previous case exists in the medical literature (4). This case, recounted in detail below, is classic in its clinical features of KD.

A 5-year-old girl presented with a sore throat, a fever to 105°F, and an erythematous rash over her trunk, appearing "desperately and acutely ill" (4). Oropharyngeal lesions included an aphthous stomatitis, erythematous lesions of the hard palate, and prominent lingual papillae. On the fifth hospital day the hectic fevers ceased, but low-grade fevers and tachycardia to 140 beats per minute persisted. The skin of her fingers desquamated, but over the ensuing weeks she improved steadily. One month after admission, however, she developed acute chest pain, shortness of breath, and expired. A postmortem examination revealed blood and clots in the pericardial space, and several large aneurysms along the epicardial vessels. One aneurysm, the size of a large ripe cherry in the left coronary artery, was the site of hemorrhage into the pericardium. Although the microscopic appearance of the disease was typical of periarteritis nodosa (i.e., PAN; see Chapter 21B), no hepatic or renal infarctions were present. Indeed, among the internal organs the heart alone was involved. The child's death was attributed to an atypical case of "infantile periarteritis nodosa," now recognized as KD.

CLINICAL FEATURES

Kawasaki's disease strikes quickly, runs a furious course over a few weeks, and then apparently resolves. In all 50 of the patients described initially by Kawasaki, the symptoms resolved without sequelae within 1 month. In subsequent years, however, mortality from cardiac complications (usually coronary artery thrombosis) was reported (5,6). Cardiac complications of KD result from a severe panvasculitis, leading to narrowing of the coronary lumina by the migration of myointimal cells from the media through the fragmented internal elastic lamina. Although catastrophic heart complications occur in only a small minority of patients (<5%), the preponderance of patients with KD appear to have at least some cardiac involvement. Heart lesions may include myocarditis, pericarditis, aneurysmal dilatation

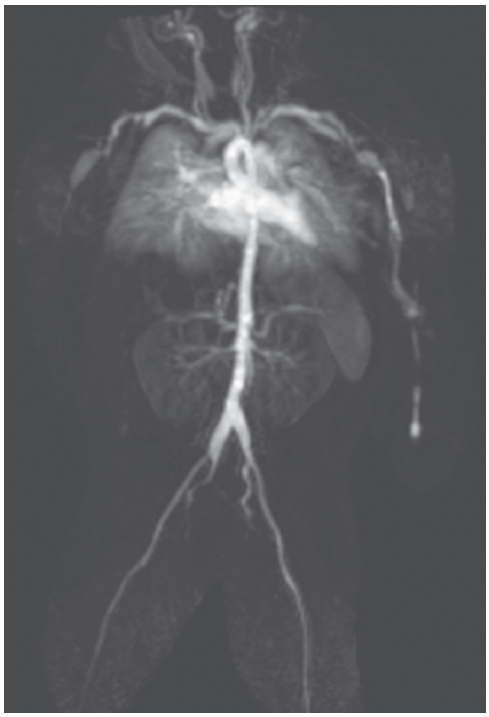

FIGURE 21F-1

Coronary and peripheral aneurysms in Kawasaki's disease (KD). Magnetic resonance angiogram in an infant with KD, revealing irregularities of the subclavian, axillary, and proximal brachial arteries, as well as fusiform dilatation of the right common iliac and right proximal internal iliac arteries. There is also a focal aneurysm of the left internal iliac artery.

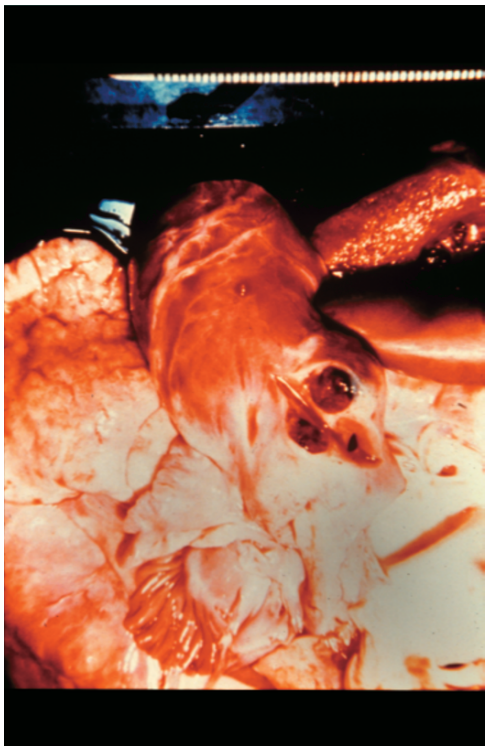

FIGURE 21F-2

Coronary artery thrombosis leading to death in Kawasaki's disease. [Reproduced with permission from the American College of Rheumatology collection, slide 124 (#9406010).]

and thrombosis of the coronary arteries (Figure 21F-2), and myocardial infarction. The tropism of the vascular inflammation for coronary arteries and its unusual propensity to cause aneurysm formation remain unexplained.

In addition to the cardiac findings, KD is associated with a number of other dramatic clinical findings (Table 21F-1). Spiking fevers may last for 5 days or more. The conjunctivae, generally inflamed in a nonpurulent manner, are accompanied by erythematous changes on the lips and in the oral cavity [Figure 21F-3(A)]. The lips become dry and cracked [Figure 21F-3(B)], with a diffuse reddening of the oropharyngeal area and a strawberry appearance to the tongue (Figure 21F-4). A polymorphous rash typically involves the trunk [Figure 21F-3(A)], and there may be extensive lymphadenopathy in the neck region. The palms and soles become erythematous and indurated, followed by desquamation in the skin of these areas during the healing phase (7–9).

The term *atypical KD* has been used to describe both older children and young infants presenting outside the typical age range of 2 to 5 years, as well as those presenting with features other than the classical criteria. *Incomplete KD* has been applied to any patient felt to have KD but who did not fulfill classical criteria. These are often diagnosed by echocardiogram findings of coronary aneurysms and often occur in the older children or young infants (10,11). Coronary aneurysms, in fact, are most likely to occur in infants <6 months of age. Because

TABLE 21F-1. PRINCIPAL CRITERIA FOR THE DIAGNOSIS OF KAWASAKI'S DISEASE (5 OUT OF 6 CRITERIA MET).[a]

Fever lasting 4 days or more
Bilateral nonpurulent conjunctival injection
Changes of the lips and oral cavity (including dry, fissured lips, strawberry tongue, diffuse reddening of the oropharyngeal mucosa)
Polymorphous rash primarily on the trunk
Acute nonpurulent swelling of a cervical lymph node to >1.5 cm
Changes of the peripheral extremities (including reddening of palms and soles, indurative edema of hands and feet, membranous desquamation from the fingertips)

[a] Illness not explained by any other known disease process.

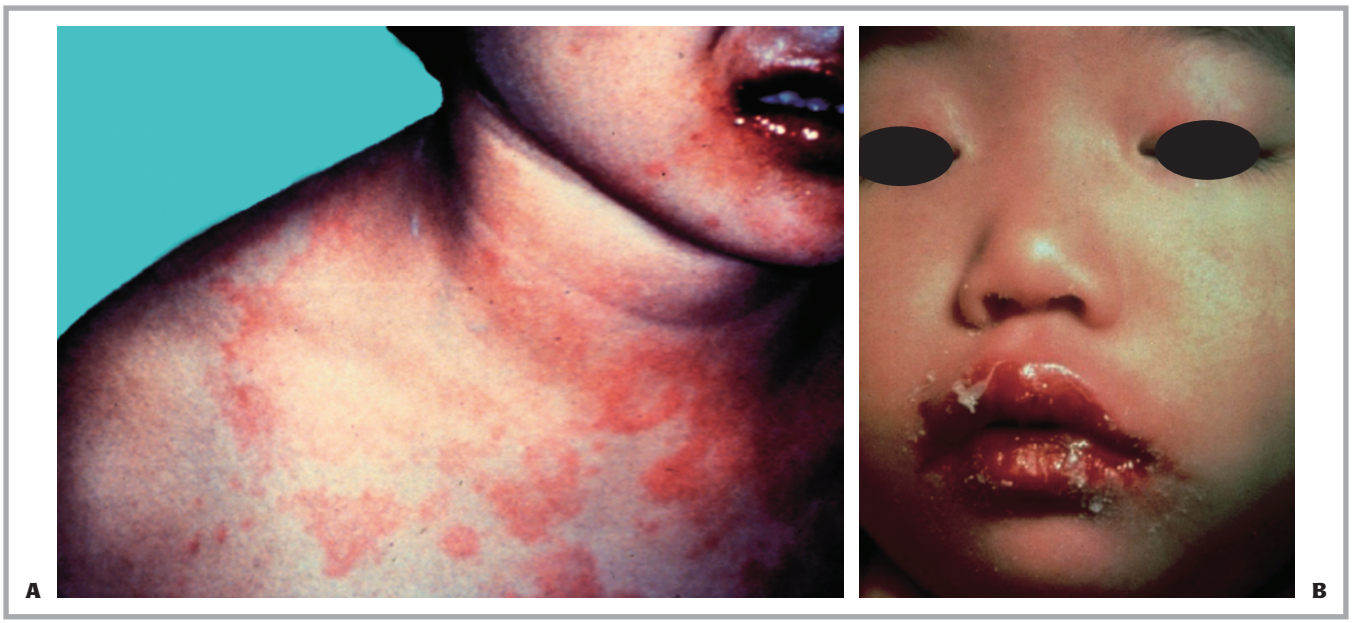

FIGURE 21F-3

Oral and cutaneous manifestations of Kawasaki's disease. (A) Erythema of the lips and an erythematous, annular rash on the skin. (B) Cracking and desquamation of the lips in a patient with Kawasaki's disease. [Reproduced with permission pending from the American College of Rheumatology slide collection. (A) Slide 93 (#9106110). (B) Slide 92 (#9106131).]

FIGURE 21F-4

Strawberry tongue in Kawasaki's disease. [Reproduced with permission pending from the American College of Rheumatology slide collection, Slide 95 (#9106120).]

of confusion (and often inappropriate use) surrounding disease terminology, there have been sentiments among KD experts to phase out the term *atypical* and to expand the term *incomplete*. Unusual disease features known to occur in KD include sterile pyuria and urethritis, arthral-

TABLE 21F-2. REVISED GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF KAWASAKI'S DISEASE.

Expanded epidemiologic case definition includes fever of at least 4 days and ≥4 principal criteria (Table 21F-1) without other explanation OR fever and <4 principal criteria if coronary artery abnormalities are detected by echocardiogram or coronary angiography
An echocardiogram should be performed in any patient ≤6 months of age if fever persists ≥7 days without other explanation and with laboratory measures of inflammation, even in the absence of any principal clinical criteria
The following laboratory parameters may be used to help with diagnosis and determine disease severity: CRP ≥3.0 mg/dL, ESR ≥40 mm/h, albumin ≤3.0 g/dL, anemia for age, ↑ ALT, platelets after 7 days ≥450,000, WBC ≥15,000, urine microscopic ≥10 WBC/high-powered field

SOURCE: From the scientific statement by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Circulation 2004;110:2747–2771 and Pediatrics 2004;114:1708–1733.
ABBREVIATIONS: ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

gia and arthritis, aseptic meningitis, diarrhea, abdominal pain, pericardial effusion, obstructive jaundice, and hydrops of the gallbladder.

Intravenous immune globulin (IVIG), a critical medication in the treatment of KD, is a limited resource in many parts of the world because of its expense. The American Heart Association (AHA), concerned about both the potential for overuse of IVIG as well as the failure to employ this medication in a timely manner in appropriate patients, issued guidelines on the diagnosis and treatment of KD (Tables 21F-2 through 21F-4) (12,13). In these guidelines, the epidemiologic case definition of KD included fever of at least 4 days and four or more principal criteria (Table 21F-1) without other explanation; or fever and less than four principal criteria if coronary artery abnormalities are detected by echocardiogram or coronary angiography.

EPIDEMIOLOGY

In Japan, the illness appears in late winter and spring. The peak age is 6 to 12 months, with 80% of cases occurring in patients younger than 5 years of age. The male: female ratio is 1.5:1. Except for three major pandemics (1979, 1982, 1985/6), the cases have reached a plateau of 5000 to 6000 per year. The endemic annual incidence is 67/100,000 children <5 years old, with a recurrence rate of 6%.

In the United States, there is also a seasonal variation in most places. The peak age is 18 to 24 months, and the illness accounts for 3000 hospitalizations/year. The recurrence rate is 1% to 3%. Data from Hawaii from 1971–1980 show ethnic incidence rate/100,000 children <8 years old per year of 33.6 in Japanese, 11.1 in Chinese, 9.2 in Hawaiians, 2.9 in Filipinos, 2.8 in Caucasians. In Los Angeles from 1980–1983, rates per 100,000 children <14 years old per year include 23.0 in Asians, 2.3 in African Americans, and 1.6 in Caucasians and Hispanics (14–17).

TABLE 21F-3. ECHOCARDIOGRAM CRITERIA INCLUDE ANY OF THE FOLLOWING THREE.

1. LAD[a] or RCA[b] *z* score ≥ 2.5
2. Japanese Ministry of Health Criteria (coronary artery diameter >3 mm in children <5 year or >4 mm in children ≥5 years, lumen diameter ≥1.5× an adjacent segment, coronary lumen is clearly irregular)
3. ≥3 suggestive features: (perivascular brightness, lack of tapering, ↓ left venticular function, mitral regurgitation, pericardial effusion, LAD or RCA *z* scores = 2–2.5)

SOURCE: From the scientific statement by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Circulation 2004;110:2747–2771 and Pediatrics 2004;114:1708–1733.
[a]Left anterior descending coronary artery.
[b]Right coronary artery.

TABLE 21F-4. KAWASAKI'S DISEASE: RECOMMENDED THERAPY.

Acute Stage
Aspirin 80–100 mg/kg/day in 4 divided doses until the 14th day of illness
+
IVIG 2 g/kg in 1 dose over 10–12 hours
Convalescent Stage (>14th illness day; afebrile patient)
ASA at 3–5 mg/kg/day in a single dose
Discontinue 6–8 weeks after onset of illness after verifying that no coronary abnormalities are present by echocardiography
Acute Coronary Thrombosis
Prompt fibrinolytic therapy with streptokinase, urokinase, or tissue plasminogen activator by a tertiary care center under the supervision of a cardiologist
Chronic Treatment for Patients with Coronary Aneurysms
ASA 3–5 mg/kg/day in a single dose
Some physicians add dipyridamole in selected patients deemed at high risk
Some physicians use warfarin or heparin in combination with antiplatelet therapy in patients with severe coronary findings or past evidence of coronary thrombosis

SOURCE: From the scientific statement by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Circulation 1993;87:1776–1780 and Pediatrics 1979;63:175–179.

ETIOLOGY

The epidemiology of KD is consistent with an infectious cause: clinical features that resemble infection (fever, lymphadenopathy), time/space clusters, epidemic occurrences, and alleged proximity of case foci to bodies of water. To date, however, no infectious etiology has been proven. There has been no culture or serologic evidence for conventional viral agents, Mycoplasmae, Rickettsiae, or bacterial agents (*Streptococcus*, *Staphylococcus*). Molecular biologic techniques have provided support, however, for a *Propionibacterium acnes* variant, retroviruses, Rickettsiae, parvovirus B19, Epstein–Barr virus, and coronavirus, as well as for the participation of the *S. aureus* toxin TSST-1 and other superantigens (e.g., *Yersinia pseudotuberulosis*).

Support exists for a superantigen-mediated process both from clinical studies (18–22) and from a murine model for coronary arteritis stimulated by *Lactobacillus casei* cell wall extracts (23). This hypothesis proposes that the etiologic agents—which may differ across geographic sites throughout the world—are capable of evoking immunologic responses via T-cell receptor V beta restriction. An oligoclonal response is supported by the discovery of IgA-secreting plasma cells within

the walls of the affected arteries. This finding lends credence to the hypothesis that the respiratory or gastrointestinal tract may be the portal of entry for the inciting organism, and that the process is antigen-driven (24,25).

PATHOGENESIS

The pathogenesis is characterized by immune activation. A host of immunologic irregularities have been described in KD, not all of which have been confirmed consistently: endothelial cell activation [particularly human leukocyte antigen (HLA)-DR expression on coronary endothelial cells]; autoantibody formation (e.g., anti-endothelial cell antibodies); complement activation and immune complex formation; abnormalities of immunoregulation (lymphocyte infiltration, activated CD4+ and B cells, activated monocyte/macrophages, T lymphopenia, polyclonal B-cell activation); adhesion molecule upregulation (soluble P-, E-, and L-selectins); increased vascular endothelial growth factor; and marked cytokine production with high levels of interferon-gamma, interleukins-1, -4, -6, and -10, and tumor necrosis factor (TNF)-alpha (18,26–28). In severe cases, this "cytokine storm" results in a macrophage activation syndrome (MAS).

TREATMENT

Following the initial recognition of KD, this illness was treated with salicylates, using the same doses of aspirin employed in the treatment of rheumatic fever. Because of the potential for impedance of aspirin absorption caused by vasculitic involvement of the gastrointestinal tract, however, the use of aspirin must be monitored carefully in this setting. If aspirin doses are too high (e.g., 100–150 mg/kg/day), improvement of intestinal absorption with therapy may lead to symptoms of toxicity. In Japan, doses of 30 to 50 mg/kg/day have been employed because of the high incidence of the slow-acetylator gene in the Japanese population. A combined US and Japanese multicenter study demonstrated that 30 to 50 mg/kg of aspirin plus IVIG (see below) was effective at preventing aneurysm formation in most cases (29). Current AHA guidelines, however, endorse aspirin doses of 80 to 100 mg/kg/day, in four divided doses (Table 21F-4).

Furusho studied the use of aspirin alone versus the combination of aspirin plus IVIG (0.4 mg/kg/day × 4 days), using a protocol then in use for immune thrombocytopenic purpura (30). A multicenter study demonstrated a decrease in the incidence of coronary artery abnormalities: only 4% (3 of 68) in the IVIG group, compared with 33% (38 of 119) in the aspirin-only arm (31). No patients in the IVIG arm developed giant coronary artery aneurysms. In contrast, 6% of the aspirin-only group suffered this occurrence. This study established IVIG as the standard of care. Several years later, a follow-up trial compared a single dose of IVIG (2 g/kg) to the traditional 0.4 mg/kg/day × 4 schedule, confirming the superiority (a further lowering of the coronary aneurysm rate) of the single-dose regimen (32). Thereafter, the single-dose regimen became the standard of care recommendation by the AHA (Table 21F-4) (9,33).

The use of glucocorticoids in KD is, surprisingly, controversial. One retrospective study assessed the outcomes of five different treatment regimens, including aspirin alone, aspirin plus prednisolone, prednisolone alone, prednisolone plus warfarin, and no treatment aside from background antibiotic therapy (which all other treatment groups received, as well). Although aspirin alone reduced the aneurysm rate from 20% to 11% compared with the no-treatment group, treatment with prednisolone was associated with an increase in the percentages of patients who developed aneurysm to 67% (34). Of note, the seven patients treated with aspirin plus prednisolone—none of whom developed aneurysm—were not emphasized in the discussion. In addition, the patients in the prednisolone-only group were perhaps the most ill at baseline (and hence were treated with glucocorticoids, presumed empirically to be the most powerful therapy).

After the publication of this study's results, glucocorticoids for the treatment of KD fell into disfavor among pediatricians and in fact were viewed as contraindicated for this disease. More recent case series, evaluating the use of pulse methylprednisolone as rescue therapy for IVIG nonresponders, have been more encouraging with regard to the potential for a beneficial effect of glucocorticoids (35–37). Initial results from a multicenter trial (38) indicate no worsening in the coronary aneurysm rate among patients treated with glucocorticoids, and a decrease in fever, inflammatory markers, length of hospital stay, and IVIG side effects.

A consensus conference at the National Institutes of Health (18) was prompted by the recognition of an ongoing immune activation at microvascular levels in patients treated adequately by the current therapies. Outcome data from Japan with long-term (10–15 year) follow-up demonstrated persistence of disease in some cases, with intravascular ultrasound and ultrafast computed tomography studies demonstrating lingering coronary aneurysms and/or wall fibrosis. Of greatest alarm was the finding of such abnormalities in areas of the vasculature previously documented as normal by echocardiogram and even coronary angiography. Electron microscopy studies of endomyocardial biopsies up to 23 years after the KD episode showed ongoing microaneurysms and small vessel coagulopathy. In a small number

of young adults who have experienced myocardial infarctions in the absence of known cardiac risk factors, angiograms have revealed giant coronary artery aneurysms compatible with old KD. The extent of active KD in such patients, if any, as opposed to the clinical sequelae occurring in arteries damaged years before, is not clear.

Newer treatment modalities have been utilized in selected patients and patient populations. Small studies and anecdotal reports of treatment with the antiglycoprotein IIb/IIIa monoclonal antibody (abciximab) or with low-molecular-weight heparin have suggested more rapid regression of aneurysms and perhaps endothelial cell remodeling. Noninvasive imaging modalities, such as magnetic resonance imaging studies of the chest and abdomen, have identified the extracardiac arterial aneurysms and dilatation (Figure 21F-1). The knowledge of the more widespread nature of the vasculitic involvement has prompted more aggressive and combination therapies (39).

Pentoxifylline, a phosphodiesterase inhibitor, has antiplatelet activity, vasodilatory effects, effects on red blood cell rheology, and the ability to inhibit TNF synthesis. A regimen of 20 mg/kg/day of pentoxifylline in three divided doses demonstrated an improvement in clinical features and the rate of aneurysm formation in KD (40). Further pharmacokinetic studies of a commercial liquid preparation of pentoxifylline demonstrated safety and a reduction in TNF levels in KD patients of 28% with doses up to 25 mg/kg/day (41). Anecdotal reports indicate tolerability of doses of 40 to 60 mg/kg/day in infants with KD. A multicenter trial of infliximab in KD is currently under way (42,43).

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