

VIII SYSTEMIC VASCULITIS SYNDROMES

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The diagnosis of a primary vasculitic syndrome is dependent on documentation of vasculitis and the exclusion of diseases that can cause secondary vasculitis. The diagnosis of a specific primary vasculitic disorder depends on the pattern of organ involvement, the histopathology, and the size of affected blood vessels; diagnosis should not be made on the basis of laboratory studies alone (e.g., findings of serum antineutrophil cytoplasmic antibodies [ANCAs] and cryoglobulins).

The major determinants of prognosis and type of therapy include the specific vasculitic disorder, the severity and extent of critical organ involvement, the rate of disease progression, and the etiology, if identifiable. The inflammatory process is often associated with nonspecific symptoms and laboratory abnormalities (e.g., elevated erythrocyte sedimentation rate [ESR], anemia, and fevers) that do not distinguish vasculitic diseases from other inflammatory, infectious, or neoplastic diseases. The toxic nature of the therapies for systemic vasculitis dictates the need for an accurate diagnosis.

Approach to the Patient Suspected of Having Vasculitis

EVALUATION

The physician should not be reluctant to pursue invasive testing in the diagnostic evaluation of patients with a multisystem illness, but biopsy of clinically uninvolved tissue and the use of less specific tests should be eschewed. An approach directed toward “ruling in” a specific form of vasculitis and ruling out reasonable specific alternatives should be pursued.

The first step in the diagnosis of vasculitis is to perform a detailed patient history and physical examination to document specific organ involvement. Special attention should be paid to the skin, eyes, ears, upper airway, joints, urinalysis, lymph nodes, peripheral nerves, and large vessels. A few laboratory tests [see Table 1] should be selectively included in the initial evaluation. Specialized studies, including serologies, are ideally obtained only after a differential diagnosis is formulated. If the urine dipstick test indicates blood, leukocytes, or protein, the physician must promptly examine several fresh urine sediments. Urine that has been sitting for several hours before analysis is not as useful for identification of cellular casts, which rapidly degenerate ex vivo. The presence of red blood cell casts is virtually diagnostic of glomerulonephritis; white cell casts may also be seen. Glomerulonephritis is usually asymptomatic. On the basis of the pattern of organ involvement, a differential diagnosis that includes specific types of systemic vasculitis and other disorders can then be generated, prompting additional, targeted testing.

CLASSIFICATION

Several classification schemes have been proposed for organizing the systemic vasculitic disorders into a consistent paradigm. These classifications are useful in distinguishing the clinical disorders that have distinct differences in prognosis and response to treatment.1 No scheme is perfect or universally accepted. They all reiterate the characteristics of fulminant or classic disease, placing an emphasis on specificity of diagnosis. If a classification scheme is strictly adhered to, the newly ill patient without fully expressed disease is frequently left without a definitive diagnosis. The physician must recognize that until specific etiologies are defined, these diagnostic entities remain conceptual, and overlap between diseases is not unusual. This must not be a deterrent to instituting therapy in the patient at risk for rapidly progressive organ damage. Nonetheless, classification systems provide useful constructs for communication and the design of research protocols [see Figure 1]. The most widely used classification schemes are based on the caliber of affected blood vessels, the pattern of organ involvement, and the presence or absence of granulomas, significant immune complex deposition, and eosinophilic infiltrates. Some authors have proposed a category of ANCA-associated vasculitis on the basis of the presence or absence of specific serum ANCs, particularly antibodies to proteinase 3 and myeloperoxidase. At present, the appropriate role of ANCA testing is to support a rationally developed clinical diagnosis. In patients who do not fit perfectly into a well-defined diagnostic category, these serologic tests should not supplant an attempt to obtain a tissue diagnosis. The presence of ANCA is not sufficient to make a diagnosis of a primary vasculitic syndrome; ANCA testing is not a screening test.

When the dominant symptoms and findings (i.e., neuropathy and cutaneous vasculitis) do not suggest a single specific vasculitic disorder, targeted physical examination and serologic testing may be helpful. Most valuable is biopsy confirmation of the specific disorder. The value of indiscriminate testing for antinuclear antibodies, ANCs, rheumatoid factor, and angiotensin-converting enzyme is arguable. In contrast, infection with hepatitis B or C can be associated with a broad range of vasculitic syndromes; these infections must be routinely excluded in patients with vasculitis involving small or medium-sized vessels when there is no clear-cut evidence of a defined vasculitic disorder, such as Wegener granulomatosis (WG).2

OVERVIEW OF TREATMENT

The systemic vasculitides are potentially life threatening and may require potent anti-inflammatory and immunosuppressive therapy. Diagnoses should be made with as much certainty as possible. However, questions regarding alternative diagnoses or coexistent diseases frequently linger. Hence, even after therapy is initiated, physicians should maintain a high degree of vigilance to detect unrelated medical problems, complications of therapy, or both. The signs and symptoms of unrecognized infection may transiently resolve with steroid therapy.2 With the initiation of potent immunosuppressive therapy, there is a prolonged window of increased susceptibility to opportunistic infection. The greatest risks occur in patients with marked neutropenia or those receiving high doses of corticosteroids. Physicians must be particularly wary about attributing new problems to “flares” in the underlying disease without first excluding a new or recrudescent infection. Patients with varicella-zoster virus may present with fever and pain before the appearance of the vesicles. Pneumocystis jiroveci, cytomegalovirus, and systemic fungal infections and reactivation of mycobacterial disease are observed more frequently in patients

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with systemic vasculitides than in the general population. Immunosuppression from steroids and other medications is frequently associated with mucosal candidiasis, less commonly associated with molluscum contagiosum, and rarely associated with Kaposi sarcoma.

Methotrexate, azathioprine, and cyclophosphamide may cause leukopenia and, less often, other cytopenias. In patients with decreased renal function, methotrexate must be used with caution, if at all; the dose of cyclophosphamide should be decreased and carefully monitored because the pro-drug (cyclophosphamide) is renally excreted. Bladder-emptying dysfunction is a relative contraindication to the long-term use of cyclophosphamide, because increased exposure to toxic metabolites of the drug may predispose to bladder cancer or cystitis. The trend in the treatment of patients with certain potentially life-threatening systemic vasculitic syndromes has been to introduce therapy with a short course of high-dose corticosteroids along with a second immunosuppressive agent to induce remission and then, depending on the disease, to taper the corticosteroids and continue immunosuppressive therapy with the safest effective immunosuppressant to maintain remission. The noncorticosteroid agent may initially be cyclophosphamide, which is felt to be the most potent of the noncorticosteroidal immunosuppressants, but cyclophosphamide is then replaced with an agent that has a better safety profile (e.g., methotrexate or azathioprine). Therapy with this agent is then continued for many months. Such an approach has been best evaluated in patients with WG and, in this patient group, has been shown to be effective.

Small Vessel Vasculitis

Vasculitis that affects capillaries and venules is the most common form of vasculitis and almost always involves the skin. It can occur at any age and affects men and women with equal frequency.

ETIOLOGY

Small vessel vasculitis can occur as an idiopathic (primary) disorder or secondary to drug allergy, bacterial endocarditis, viral infections such as those caused by hepatitis B or C, disseminated Neisseria, and rickettsiae; it can be part of a defined
systemic autoimmune disorder such as Sjögren syndrome, systemic lupus erythematosus (SLE), or rheumatoid arthritis; or it can occur in association with hematologic, lymphoid, and solid-organ malignancies [see Figure 2]. Small vessel vasculitis can accompany diseases commonly associated with the involvement of larger vessels (e.g., WG).

**DIAGNOSIS**

**Clinical Manifestations**

Cutaneous involvement can occur in many of the primary or secondary vasculitic syndromes. Large, medium-sized, or small vessel occlusion can cause livedo, Raynaud phenomenon, or necrosis. Purpuric lesions that partially blanch under pressure are the most common manifestations of small vessel vasculitis. Small vessel vasculitis, particularly when associated with infections, is frequently associated with immune complex deposition. Vasculitis primarily involving the postcapillary venules was termed hypersensitivity vasculitis in older literature. Primary small vessel vasculitis may be limited to the skin or may be associated with visceral involvement, including alveolar hemorrhage, intestinal ischemia or hemorrhage, and glomerulonephritis.

Purpura tends to occur in recurrent crops of lesions of similar age and is more pronounced in gravity-dependent areas [see Figure 3]. When purpura is not primarily in gravity-dependent areas, cold agglutinin disease, cryoglobulinemia (which may be associated with an infection such as hepatitis C or with lymphoma), embolism, infiltrative diseases, and self-induced injury should be excluded. Cutaneous vasculitis of any etiology may be associated with striking dependent edema.

In a case series of cutaneous small vessel vasculitis, almost 100% of patients younger than 20 years had disease limited to the skin, whereas approximately 40% of the 172 patients older than 20 years had an associated or underlying systemic disorder. Seventeen adults had a systemic necrotizing vasculitis, four had malignancy, four had a bacterial infection causing the vasculitis, 11 had cryoglobulinemia, and 59 had Henoch-Schönlein purpura. The prevalence of infection with hepatitis C...
Palpable purpura of the distal extremities is the most common presentation of small vessel vasculitis. virus, likely the most common cause of mixed cryoglobulinemia, was not reported in this series.

Laboratory Tests

Biopsy is most useful in excluding causes of nonvasculitic purpura such as amyloidosis, leukemia cutis, Kaposi sarcoma, T cell lymphomas, trauma, and cholesterol or myxomatous emboli. Tissue immunofluorescent staining is useful to support the diagnosis of Henoch-Schönlein purpura (specifically, IgA staining), SLE, or infection (the percentage of patients with positive results on immunofluorescent staining is not known). The cells infiltrating and perhaps destroying the vessel wall may be neutrophils or lymphocytes, depending on the etiology. The pathology in most cases of small vessel vasculitis is leukocytoclastic angiitis (LCA). Hepatitis C infection should be excluded routinely in patients who present with unexplained purpura—an important example of the fact that the presence of LCA does not indicate that a patient’s illness is the result of a primary vasculitic syndrome.

Clinical Subsets

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a clinically defined small vessel vasculitic syndrome in which cutaneous features are usually striking and in which significant visceral involvement is less common. Henoch-Schönlein purpura, which occurs less frequently in adults than in children, is usually associated with vascular and renal deposition of IgA-containing immune complexes. Common manifestations of Henoch-Schönlein purpura include purpura; urticaria; abdominal pain; gastrointestinal bleeding or intussusception (mostly in children); arthralgias or arthritis; and glomerulonephritis. Visceral symptoms may precede the skin lesions. Henoch-Schönlein purpura may appear to be precipitated by medications or streptococcal or viral infections. It is usually a self-limited disorder, but the associated glomerulonephritis may, in rare instances (most often in adults), progress to renal failure. In the absence of renal dysfunction, Henoch-Schönlein purpura is often a self-limited but frequently recurrent syndrome that may require only symptomatic therapy; because some visceral involvement may be significant, the patient should be periodically monitored until there is a complete resolution of symptoms.

Urticarial Vasculitis

Urticarial vasculitis represents a peculiar subset of small vessel vasculitis. The clinical presentation is that of wheals or serpentine papules, sometimes with surrounding or geographically separate angioedema. Individual lesions are slow to resolve, often lasting for several days; the disease follows a more prolonged course than typical urticaria. There is frequently a burning, dysesthetic discomfort from the lesions. Like purpura, the lesions of urticarial vasculitis are frequently located in gravity-dependent areas and often heal with skin hyperpigmentation or an ecchymotic area. Most cases are idiopathic, although an association with an underlying systemic autoimmune disorder such as SLE, IgM paraproteinemia, or a viral infection has been described. In rare cases, urticarial vasculitis has been associated with a syndrome that includes hypocomplementemia and interstitial pulmonary disease. This syndrome is distinct from C1 esterase deficiency–associated angioedema, which does not cause urticaria.

Treatment

Therapy for cutaneous vasculitis is first directed at eliminating any underlying precipitant. Infectious etiologies should be sought out and treated. Potential offending drugs should be withdrawn. Association with myelodysplasia and myeloproliferative disease should be considered, especially if cytopenia or abnormal cell forms are evident on peripheral blood smear. If no precipitants are apparent, low-risk therapy can be attempted with nonsteroidal anti-inflammatory drugs, colchicine, pentoxifylline, dapsone, or short-term low-dose corticosteroids. These therapies are not uniformly effective at reducing attack frequency or severity. Long-term corticosteroid therapy should be avoided if at all possible. Compressive support stockings or panty hose may be useful in limiting the significant edema that often accompanies cutaneous vasculitis of the legs.

Visceral involvement with organ dysfunction may necessitate a more aggressive approach than that used in limited cutaneous vasculitis. Moderate-dose corticosteroids are generally effective. In the setting of potential complications from chronic corticosteroid use or the setting of severe visceral involvement, methotrexate, azathioprine, cyclophosphamide, or other immunosuppressive agents may occasionally be required [see Table 2]. Apheresis may be effective in the treatment of severe cryoglobulinemic vasculitis. When treating chronic, refractory small vessel disease that is not organ or life threatening, one must pay close attention to the risk-to-benefit ratio of selected therapies.

Wegener Granulomatosis

WG is a relatively uncommon, potentially lethal disease characterized by necrotizing granulomatous inflammation and vasculitis of small and medium-sized vessels. Males and females of all ages can be affected.

Diagnosis

Clinical Manifestations

WG is characterized by parenchymal necrosis with a variable contributory component of vasculitis. Multiple organs are
often involved; there is a predilection for the upper and lower respiratory tracts, eyes, and kidneys.

**Upper respiratory tract involvement** Upper airway disease may be striking but is often indolent and attributed for months or even years to routine sinus disease until other manifestations of WG are recognized. Even after the diagnosis is made and immunosuppressive treatment is provided, sinus disease may be recalcitrant to therapy. This chronicity may be caused in part by superinfection of damaged tissue by *Staphylococcus aureus*. Anatomic damage can include septic perforations and saddle-nose deformities. Laryngotracheal involvement may result in subglottic stenosis, which is best treated by local corticosteroid injection therapy. Ear involvement is common, particularly otitis media, which may produce conductive hearing loss. Orbital pseudotumors may cause proptosis, ophthalmoplegia, intractable pain, and loss of vision; these inflammatory and fibrous masses may be refractory to anti-inflammatory therapy, immunosuppressive therapy, and even radiation therapy. Conjunctivitis, uveitis, and scleritis alone or in combination commonly occur.

**Lower respiratory tract involvement** Lung involvement may be absent at the onset of disease, may be asymptomatic, or may present dramatically as diffuse alveolar hemorrhage. One third of pulmonary lesions noted on imaging studies [see Figure 4] are asymptomatic (CT scanning is more sensitive than radiography). Nodules may undergo necrosis leading to cavity formation. Bronchospasm is not characteristic of WG. If airway obstruction is suspected, bronchoscopy should be considered to exclude endobronchial or subglottic stenoses. It is frequently necessary to rule out infectious causes of the pulmonary infiltrates, and bronchoscopy with lavage is useful in this regard. However, tissue obtained from transbronchial biopsy is usually of insufficient quantity to confirm the pathologic diagnosis of WG.

Open lung or thoracoscopic biopsy is often the optimal method for demonstrating the typical pathologic findings of WG and for excluding malignancies and atypical infections. Typical open lung biopsy sections’ may contain areas of necrosis, frequently in a broad pattern; giant cells in the parenchymal tissue; and vasculitis. Not all histopathologic features may be present in the same biopsy section, and vasculitis may not be evident. Because pathology similar to WG may be demonstrated in chronic mycobacterial and fungal infections, special stains and cultures for these agents are essential.

**Glomerulonephritis** Glomerulonephritis is a common cause of morbidity and mortality in WG. Its presence or absence distinguishes the generalized from the limited forms of the disease. Glomerulonephritis is often aggressive, but it may be relatively indolent. It may be clinically and pathologically indistinguishable from idiopathic, rapidly progressive, crescentic glomerulonephritis, and it is usually clinically silent. The evolution from subclinical to dialysis-dependent renal disease may occur over several weeks. Glomerulonephritis may be present at the onset of the disease, or it may develop only after the patient has been ill with an apparently limited form of the disease. The importance of frequent microscopic urinalyses in the initial and follow-up evaluation of patients with WG cannot be overemphasized. This monitoring can be done by patients at home using routine dipstick analysis to detect occult hematuria. Especially in elderly or debilitated patients, valuable information may be obtained by occasional 24-hour urine samples.
collections, which can establish a more accurate estimate of the glomerular filtration rate (GFR) than that provided by the serum creatinine measurement. Renal biopsy may reveal focal and segmental glomerulonephritis with variable glomerular proliferative changes, crescent formation, and necrosis, in the absence of significant immune complex deposition (so-called pauci-immune glomerulonephritis). Although supportive of the diagnosis of WG, these findings are not diagnostic of the disease, and renal biopsy is not the preferred study to confirm the specific diagnosis of WG [see Laboratory Tests, below].

**Additional clinical manifestations** Musculoskeletal involvement occurs in over half of patients with WG. Symptoms may include arthralgias or arthritis; these symptoms may be migratory, additive, or of fixed distribution. Rheumatoid factor is frequently present in patients with WG, and it may cause diagnostic confusion with rheumatoid arthritis when joint symptoms are significant. The joint disease of WG only rarely produces bone erosions. Neurologic signs and symptoms occur in fewer than 50% of patients, peripheral neuropathy in fewer than 20%, and involvement of the central nervous system in fewer than 10%. Oculomotor defects may occur because of impingement by a retro-orbital mass or inflammatory sinus disease. Gastrointestinal ischemia and ulcerations are infrequent but may be confused with inflammatory bowel disease, especially because the latter can be associated with ANCA (usually perinuclear ANCA, or p-ANCA). Up to 50% of WG patients exhibit cutaneous involvement with purpura, panniculitis, or ulcerations. If present, the skin disease generally parallels systemic disease activity. Observations from recent clinical trials suggest that patients with WG are predisposed to develop deep vein thrombosis.10

**Laboratory Tests**

Unexplained chronic inflammation of the respiratory tract or eye or the presence of glomerulonephritis is consistent with the diagnosis of WG. The probability of WG is increased when multiple organ involvement is present, upper airway disease is destructive, and pulmonary nodules (especially with cavities) are demonstrated by radiography. Any combination of organ involvement is possible, but most patients exhibit upper airway involvement at the time of diagnosis.

If the entire clinical picture is compatible with WG and if alternative diagnoses have been appropriately ruled out, the finding of circulating cytoplasmic ANCA (c-ANCA) with anti–proteinase 3 specificity is sufficient to make the provisional diagnosis and initiate therapy without a tissue diagnosis. Approximately 20% of patients with WG may have p-ANCA with antmyeloperoxidase specificity. If there are any atypical features or special concerns regarding the initiation of immunosuppressive therapy or if the patient does not respond appropriately to therapy, histopathologic confirmation of the diagnosis should be aggressively pursued. The presence of ANCA is not equivalent to the presence of vasculitis; ANCA can be found in other diseases.

The ANCA level is not a reliable means to follow disease activity.11-13 Because WG generally requires therapy with a corticosteroid plus a second agent to induce remission and limit the likelihood of relapse, it should be distinguished from other inflammatory disorders, including other vasculitic syndromes [see Table 3], which may be effectively treated with a less toxic regimen.

**TREATMENT**

Initial treatment of generalized WG warrants dual-drug immunosuppressive therapy. Corticosteroids may produce symptomatic improvement in the upper airway, lungs, skin, and musculoskeletal system, but tapering usually results in a prompt flare in the disease unless a second agent is administered concurrently. Acutely serious disease, particularly renal disease that is progressing, is treated initially with corticosteroids and daily cyclophosphamide with subsequent tapering of the corticosteroids over several months. Many authors now recommend that once remission is achieved, cyclophosphamide therapy should be promptly replaced by methotrexate or azathioprine therapy for at least an additional 12 months of therapy [see Table 2]. This approach is now supported by several clinical trials.14

There are some strong relative contraindications to the long-term use of cyclophosphamide, including bladder dysfunction (increased risk of drug metabolite–induced cystitis and bladder
**Table 3 Clinical Features of Vasculitis**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Common Target Organs</th>
<th>Special Pathologic Features</th>
<th>Special Laboratory Studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic polyangiitis</td>
<td>Nerve, glomerulus, lung (small vessels), GI tract, skin</td>
<td>No giant cells, vasculitis, proliferative GN (no or rare immune deposits*)</td>
<td>p-ANCA (antineutrophil cytoplasmic antibody)</td>
<td>Rule out hepatitis B and C</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Nerve, GI tract</td>
<td>Arteritis of medium muscular arteries, no giant cells, no GN</td>
<td>No ANCA</td>
<td>No small vessel involvement; rule out hepatitis B and C</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>Upper airway, eye, lung (small vessels), glomerulus, nerve, musculoskeletal system</td>
<td>Giant cells, geographic necrosis, mild eosinophilia, vasculitis, proliferative GN (no or rare immune deposits)</td>
<td>c-ANCA (anti-PR3)</td>
<td>Chronic sinuses or ear disease</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>Nerve, lung infiltrates, heart, skin</td>
<td>Giant cells, eosinophilia, vasculitis, proliferative GN (no or rare immune deposits)</td>
<td>Eosinophilia ± ANCAs</td>
<td>Positive atopic history</td>
</tr>
</tbody>
</table>

*Presence of immune deposits suggests possible hepatitis B or C infection. ANCA—antineutrophil cytoplasmic antibody  c-ANCA—cytoplasmic ANCA  GN—glomerulonephritis  p-ANCA—perinuclear ANCA  PR3—proteinase 3

cancer) and leukopenia; however, even without such contraindications, cyclophosphamide-associated morbidity is significant. In milder or limited WG, weekly doses of methotrexate (0.20 to 0.30 mg/kg, adjusted for renal function) with folic acid or leucovorin may be substituted for cyclophosphamide to induce and maintain remission. Patients undergoing treatment with immunosuppressive agents must be continuously monitored for flares in disease, opportunistic infections, and medication side effects. Flares may be more frequent in patients treated with methotrexate than in those receiving longer courses of cyclophosphamide, and they often occur as the corticosteroids are withdrawn. Side effects of methotrexate include cytopenias and drug-induced pneumonitis. Methotrexate may cause hepatitis, and, on rare occasions, cirrhosis. It should be avoided in the setting of renal insufficiency or alcohol use. Azathioprine can cause a febrile hypersensitivity reaction and leukopenia. Attempts to limit cyclophosphamide side effects by using methotrexate or azathioprine are warranted, but such an approach must be accompanied by careful monitoring for disease flare. Some authors have suggested using trimethoprim-sulfamethoxazole as adjunctive therapy for the treatment of WG because some data suggest that this therapy can decrease the frequency of flares of upper airway disease. However, this approach remains controversial and is not routinely undertaken in conjunction with full-dose methotrexate, because the combination may result in additive antifolate toxicity. Administration of trimethoprim-sulfamethoxazole three times weekly is useful in protecting patients against *P. jiroveci* (formerly *P. carinii*) pneumonia while they are receiving intensive immunosuppressive therapy. Local nasal and sinus toilet and periodic otolaryngoscopic evaluations are a routine part of the care of patients with upper airway disease. Anti–tumor necrosis therapy with etanercept has been shown in a randomized, controlled trial to be ineffective as adjunctive therapy for the treatment of WG. Prophylactic measures to prevent osteoporosis and regular dual-energy x-ray absorptiometry (DXA) scans to measure bone density should always be considered when corticosteroids are used on a long-term basis.

**Churg-Strauss Syndrome**

Churg-Strauss syndrome (CSS), or allergic granulomatosis angitis, is a rare syndrome that affects small to medium-sized arteries and veins in association with bronchial asthma.

**DIAGNOSIS**

**Clinical Manifestations**

The inflammatory component of CSS displays clinical similarities to WG in terms of organ involvement and pathology, especially in patients with upper or lower airway disease or glomerulonephritis. CSS differs most strikingly from WG in that the former occurs in patients with a history of atopy, asthma, or allergic rhinitis, which is often ongoing. In the prevasculitic atopic phase, as well as during the systemic phase of the illness, eosinophilia is characteristic and often of striking degree (≥ 1,000 eosinophils/mm³). When eosinophilia is present in WG, it is usually more modest (~ 500 eosinophils/mm³).

Organ-specific features of CSS include some combination of pulmonary infiltrates, cardiomyopathy, coronary arteritis, polyneuropathy (symmetrical or mononeuritis multiplex), ischemic bowel disease, eosinophilic gastroenteritis, ocular inflammation, nasal perforations, glomerulonephritis, cutaneous nodules, and purpura. Organ-specific features of CSS in asthmatic patients have been reported to have occurred after the introduction of inhibitors of 5-lipoxygenase while these patients were being weaned off corticosteroids. Cardiac disease in CSS can be severe and is a leading cause of mortality. Cardiac infiltration or coronary arteritis can produce heart failure and ischemic syndromes. Valvular heart disease may occur, but it is not as striking or as common in CSS as it is in the idiopathic hypereosinophilic syndrome. Neurologic involvement occurs in more than 60% of patients with CSS. Such involvement may be severe and is generally attributable to arteritis. Cutaneous purpura, urticaria, polymorphous erythematosus eruptions, and nodules occur. Gastrointestinal involvement resulting from ischemic vasculitis, eosinophilic gastrenteritis, or both may cause pain, cramping, and diarrhea.

**Laboratory Tests**

Histopathology typically exhibits extravascular granulomatous inflammation, with a prominent eosinophil infiltrate, and vasculitis is variably present. Granulomas can be found in...
tissue at areas separate from the demonstrable vasculitis. Eosinophilic infiltrates in CSS are more striking than those in WG. Abundant eosinophils, granulomas, and giant cells are not found in classic polyarteritis nodosa (PAN) or microscopic polyangiitis (MPA). The pathology of the nodules is not by itself sufficient to make a diagnosis of CSS, because similar pathology can be seen in lymphoma and sarcoidosis. Glomerulonephritis in CSS is frequently not as severe as it is in WG, but when glomerulonephritis is present in CSS, it is usually focal and segmental and indistinguishable from other forms of pauci-immune glomerulonephritis (i.e., glomerulonephritis that is without significant tissue deposition of immune complexes). Circulating ANCAs may be present, and for this reason, CSS is often included as one of the ANCA-associated vasculitides.

TREATMENT

CSS is often responsive to corticosteroid therapy. For most patients, withdrawal of steroids is possible. Bronchial asthma and sinus disease, however, may require ongoing therapy, even if the vasculitic component of the disease has remitted. Patients with severe or refractory visceral organ involvement are empirically treated with additional agents, such as cyclophosphamide, methotrexate, and azathioprine, depending upon the severity of the organ involvement. Corticosteroids are tapered after remission is achieved [see Table 2].

Polyarteritis Nodosa and Microscopic Polyangiitis

CLASSIFICATION

Early reports of PAN and MPA, two forms of necrotizing medium-sized vessel arteritis, did not adequately distinguish the two entities. An international conference proposed that the distinction between these disorders be based on the absence of granulomatous inflammation in both and by involvement of arterioles, capillaries, venules, and glomerular capillaries in MPA but not in PAN. It is now generally accepted that classic PAN is a rare disorder that is linked to arteritis of medium-sized muscular arteries; small vessels are unaffected. Older studies of patients with PAN did not uniformly make this distinction. Even more important, patients with viral hepatitis B or C were not excluded from older studies. The recognition of viral hepatitis is crucially important because chronic hepatitis B or C can elicit a secondary vasculitic syndrome indistinguishable from PAN or MPA in presentation but distinct in prognosis and response to therapy.  

MPA, unlike PAN, involves smaller vessels ranging in size from capillaries and venules to medium-sized arteries [see Figure 1]. Because of the involvement of small vessels, MPA may manifest itself as glomerulonephritis or alveolar hemorrhage, which further distinguishes it from PAN. Clinically, MPA can mimic WG, although some authors have arbitrarily defined MPA as excluding involvement of the upper airway. The recognition that MPA, but not PAN, is an ANCA-associated vasculitis (in which the ANCAs are almost always directed against myeloperoxidase) further clarifies the distinction between these entities.

DIAGNOSIS

Clinical Manifestations

Glomerulonephritis, particularly rapidly progressive glomerulonephritis, and alveolar hemorrhage are common in MPA and absent, by definition, in classic PAN.

PAN affects the medium-sized muscular arteries and, like MPA, is associated with peripheral neuropathy and bowel ischemia. Azotemia and hypertension in PAN may occur because of arteritis of the renal arteries and ischemic neuropathy but not because of glomerulonephritis. Microaneurysm formation in medium-sized visceral arteries may be striking in PAN, and the arteries may occasionally rupture.

Constitutional symptoms such as fever, asthenia, and myalgias are common in both PAN and MPA. Elevated acute-phase reactants, thrombocytosis, leukocytosis, and the anemia of inflammatory disease are common, although they are not uniformly present.

When the clinical syndrome of PAN or MPA is suspected, chronic bacterial infection (e.g., endocarditis) and viral infection (e.g., hepatitis B or C) must be excluded. The association with hepatitis B or C infection may not dramatically alter some features of the PAN or MPA syndromes, but membranous glomerulonephritis, cryoglobulinemia, immune complex–associated glomerulonephritis, hepatic failure, and thrombocytopenia are more likely to occur with viral hepatitis–associated vasculitis. Significant immune complex deposition does not occur in PAN or MPA.

Antiphospholipid antibody syndrome (APLS) can mimic PAN by presenting as mesenteric ischemia or renal insufficiency caused by thrombotic occlusion of mesenteric and renal vessels. Features of both APLS and arteritis affecting muscular arteries include livedo reticularis [see Figure 5]. Glomerulonephritis, cryoglobulinemia, immune complex–associated glomerulonephritis, and peripheral neuropathy are not expected to occur in APLS unless the patient also has SLE. Thrombocytopenia can occur with APLS but is usually not present in PAN. Cholesterol embolization should also be considered as a cause of livedo, renal insufficiency, eosinophilia, and constitutional symptoms, particularly if the clinical history includes a recent vascular procedure. Tissue biopsy will often establish the diagnosis.

Laboratory Tests

The diagnosis of MPA and PAN should ideally be based on histopathologic demonstration of arteritis and the clinical pattern of disease. A biopsy specimen of clinically involved, non-necrotic tissue that demonstrates the presence of arteritis of muscular arteries is the ideal supportive finding for the diagnosis of arteritis of a medium-sized vessel, but obtaining such a biopsy sample is not always possible. The presence of serum p-ANCA with antимyeloperoxidase specificity (occurring in approximately 60% of MPA patients) supports the clinical diagnosis of MPA, but p-ANCA is not specific for this disease. ANCAs are not characteristically detected in PAN.

MPA is a form of pauci-immune glomerulonephritis; that is, the renal biopsy tissue in MPA, as in WG and CSS, does not contain extensive immune complexes on immunofluorescent staining or electron microscopy. As opposed to WG, parenchymal inflammation in MPA is not striking (apart from areas of ischemic damage), and giant cells are not found in MPA. Lung biopsy in the setting of pulmonary infiltrates or hemorrhage reveals capillaritis, a histopathologic pattern that can also be seen in WG, SLE, and anti–glomerular basement membrane disease. Lung biopsy in patients with suspected MPA is most useful in ruling out alternative pulmonary diagnoses; open lung and thoracoscopic techniques have a higher yield for vasculitis than transbronchial biopsy does. Classic PAN does not cause glomerulonephritis, lung capillaritis, or pulmonary parenchymal disease.
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stenoses that can be visualized by angiography. When angiog-
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less than 30% for the diagnosis of PAN.

cally uninvolved tissue (i.e., asymptomatic muscle) has a yield of
the time. There is notable morbidity associated with sural nerve
biopsy; 13 of 60 patients experienced wound infections or de-
layed healing, and three patients suffered from postprocedure
pain in the sural nerve that underwent biopsy. Biopsy of clini-
cally uninvolved tissue (i.e., asymptomatic muscle) has a yield of
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Abdominal angiography is often performed in the evalua-
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raphy is used in an effort to diagnose systemic necrotizing vas-
culitis in the absence of pathologic evidence of the disease, sev-
eral caveats must be noted. Angiography has limited spatial
resolution; smaller vessels are not well seen. In patients with
primarily smaller vessel disease, the angiogram will not likely
be diagnostic. In one study, angiograms were diagnostic in
only four of 30 patients with MPA, a disease that affects both
small and medium-sized arteries. Different investigators have
reported aneurysms in 60% to 90% of patients with PAN.
Aneurysms take time to develop and may not be present early
in the course of the illness. In addition to being associated with
aneurysms, arteritis may be associated with stenoses, which
may be longer and smoother than typical atherosclerotic les-
sions or occlusion. To maximize the yield from the procedure,
angiography should include the celiac, renal, and mesenteric
vessels. Lack of clinically apparent involvement of an organ
(i.e., no intestinal ischemia) does not exclude the possibility of
finding abnormal vessels on angiography. It has been suggest-
eted that the visualization of aneurysms in PAN denotes more
severe disease; it is unclear whether their presence may alterna-
tively relate to the actual duration of the untreated illness.
Aneurysms may resolve with successful treatment of primary
or viral hepatitis–associated arteritis. The presence of visceral
microaneurysms is not diagnostic of PAN. They have also been
anecdotally described in patients with WG and MPA, likely
representing medium-sized muscular artery involvement in
these diseases. Microaneurysms also occur in nonvasculitic dis-
orders. Isolated case reports have described aneurysms in pa-
tients with atrial myxoma, bacterial endocarditis, peritoneal
carcinomatosis, and severe arterial hypertension, as well as af-
after methamphetamine abuse. Inadequate data are available to
assess the sensitivity and specificity or the predictive value of
abdominal angiography in the diagnosis of necrotizing arteri-
tis. As is the case when interpreting a biopsy result of suspect-
ed vasculitis, imaging studies must be considered in the light of
the entire clinical profile. Angiography is generally avoided in
the setting of progressive or significant renal insufficiency.

**TREATMENT**

Treatment of both PAN and MPA is empirical9 [see Table 2].
Corticosteroids in high doses (1 mg/kg/day of prednisone or
its equivalent) remain the initial mainstay of therapy for both
disorders in the acutely ill patient. Use of corticosteroids alone
may be sufficient in patients with PAN who do not have criti-
cal organ involvement, defined as renal insufficiency (from re-
nal ischemia, as opposed to glomerular nephritis), gastroin-
testinal ischemia, cardiomyopathy, or dense peripheral neu-
ropathy. Therapy with corticosteroids alone fails more frequently
in MPA than in PAN, given the tendency for frequent relapses
in MPA.25 Patients who require long-term corticosteroid ther-
apy for disease control or patients who have clinical markers of
severe disease are usually treated with glucocorticoids and an
additional immunosuppressive agent such as cyclophos-
phamide or methotrexate. The indications for initial combina-
tion therapy have not been sufficiently studied.

When active hepatitis B or C infection is present, a relatively
short course of steroids should be considered on the basis of ex-
trahepatic disease severity and the organs at acute risk for fail-
ure, in conjunction with aggressive antiviral therapy.

**Kawasaki Disease**

Kawasaki disease (KD) was first described in 1967 as muco-
cutaneous lymph node syndrome.9 It typically affects infants
and young children, causing dominant cutaneous and oral mucosal manifestations, fever, and coronary arteritis. It can on rare occasions affect adults.

DIAGNOSIS

The presence of characteristic clinical features has permitted the establishment of diagnostic criteria for KD [see Table 4]. Vasculitis may involve vessels ranging in size from venules to the aorta. Prominent inflammation is noted in the larger coronary arteries, which results in aneurysm formation in approximately 25% of untreated patients. The immediate and delayed life-threatening cardiac complications of the disease, coupled with its unique therapy (aspirin and intravenous γ-globulin), mandate prompt clinical diagnosis. Biopsy is generally not necessary, nor is it likely to yield a specific diagnosis.

High spiking fevers may persist for 1 to 2 weeks if left untreated. Rapid defervescence is usually observed with initiation of appropriate therapy. Nonexudative conjunctivitis often appears with the fever. Aseptic (lymphocytic) meningitis is common. Oral involvement includes erythema, dryness and fissuring of the lips, nonexudative pharyngitis, and tongue erythema with very prominent papillae. Mucosal ulcerations are not characteristic of this illness. Distal limb swelling may appear days after the fever, with erythema and tenderness that are not limited to the joints. Desquamation of the hands and feet, often in sheets, may begin days to a few weeks after the onset of fever. When desquamation occurs early in KD, it may appear concurrently with a truncal rash and eye and lip changes; it may mimic a drug reaction or Stevens-Johnson syndrome. The rash is usually diffuse and polymorphous, with urticarial, morbilliform, annular, or plaque components, but it is not vesicular. Adenopathy, which is present in 75% of patients, is most apparent in the cervical region.

The morbidity and mortality (< 3%) of KD is overwhelmingly associated with the development of inflammatory coronary artery aneurysms, most of which are asymptomatic at the time of formation. Aneurysms may be detected by echocardiography. Thrombosis can occur in the aneurysms, resulting in direct or embolic coronary artery occlusion. Coronary events may occur weeks or even many years after the febrile illness. A baseline echocardiogram should be obtained at the time of the acute illness and repeated 2 and 6 weeks later. Early recognition of the disease and treatment with intravenous immunoglobulin and aspirin have significantly decreased the frequency of aneurysm formation and thrombotic coronary events.

TREATMENT

Treatment of KD should be initiated with intravenous immunoglobulin (2 g/kg as a single dose) and aspirin (80 to 100 mg/kg/day every 6 hours) as soon as the disease is seriously suspected. Aspirin is more effective than corticosteroids in preventing aneurysms. Corticosteroid therapy is usually unnecessary, and some authors feel that it is relatively contraindicated. Symptoms tend to respond within several days after the institution of aspirin and intravenous immunoglobulin. In resistant cases, however, corticosteroids are frequently added to the above therapies.

Large Vessel Arteritis

Temporal, or giant cell, arteritis (GCA) of the elderly and Takayasu arteritis (TA) are the most common inflammatory diseases of the aorta and its major branches. Similar vascular targeting may occur in Behget disease, Cogan syndrome, and sarcoidosis. The last two conditions are distinguished by the pattern of extra-aortic organ involvement. It is uncertain whether TA and GCA are distinct disorders or are the same disorder with modified expression in different age groups.

TEMPORAL OR GIANT CELL ARTERITIS

GCA generally affects persons older than 50 years. In many patients, it is associated with the syndrome of polynynalgia rheumatica (PMR). PMR is characterized by proximal muscle pain, with nocturnal and early-morning worsening. There may be a subjective sense of weakness, without true weakness on examination and without elevation of serum muscle enzyme levels. Synovitis may be present, often making it difficult to distinguish between GCA and elderly-onset rheumatoid arthritis.

GCA is variably associated with fever, scalp tenderness, headache, masticatory muscle claudication, peripheral vascular disease, inflammatory aortic aneurysms, and retinal ischemic syndromes. Oligoarticular arthritis, often in the upper extremity, and acute carpal tunnel syndrome can occasionally occur. The ischemic symptoms and signs may be clinically indistinguishable from those occurring in arteriosclerotic obliterative or atheroembolic disease.

Examination for disparate four-extremity pulses, blood pressure readings, abdominal aneurysms, and bruits in the neck, abdomen, and extremities must be part of the routine follow-up visits of patients with GCA or PMR. Pathologic findings of GCA can occur in superficial temporal arteries of patients with PMR, even without any symptoms of GCA. However, routine biopsy of the superficial temporal arteries in patients with PMR, without any other symptoms or findings of GCA, is not warranted, because patients without any physical findings or symptoms to suggest occlusive disease do not generally develop visual loss.

Levels of acute-phase reactants are elevated in more than 80% of patients with GCA but are not completely reliable markers of disease activity during and after therapy. Definitive diagnosis of GCA is generally made by biopsy of the superficial temporal artery. Pathology in GCA usually reveals chronic mononuclear cell infiltrates, destruction of the internal elastic lamina, and giant cells. The presence of giant cells is not requi-

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Diagnostic Criteria for Kawasaki Disease</th>
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<tbody>
<tr>
<td>Persistent fever (&gt; 5 days)</td>
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<td>plus</td>
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<td>Four of the following five conditions:</td>
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<td>- Nonpurulent bilateral conjunctivitis</td>
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<td>- Oral mucosal involvement</td>
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<td>- Erythematous pharynx</td>
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<td>- Red or fissured lips</td>
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<td>- Strawberry tongue</td>
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<td>- Soft tissue abnormalities of hands and feet</td>
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<td>- Edema/erythema</td>
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<td>- Desquamation</td>
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<tr>
<td>- Polymorphous, nonvesicular rash</td>
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<tr>
<td>- Cervical adenopathy</td>
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ACP Medicine RHEUMATOLOGY: VIII Systemic Vasculitis Syndromes – 10
Takayasu arteritis (pulseless disease) is a chronic inflammatory disease affecting the aorta and its major branches. Usually diagnosed in younger, predominantly female patients of reproductive age, TA can also occur in young children and older patients of either sex. TA is more commonly associated with stenoses and aneurysms of the aorta and aortic branch vessels than is GCA.

The presenting clinical syndrome may include a prolonged flulike illness, including a polymyalgia rheumatica pattern of muscle pain. Many patients initially present with symptoms of limb, cerebral, or cardiac ischemia in the absence of any constitutional features. The characteristic features of the disease reflect the ischemia resulting from inflammatory stenoses of the aorta and its major branches. Renal ischemia can elicit high renin hypertension. Predominant sites of stenosis are the aortic arch vessels, particularly the subclavian arteries [see Figure 6]. Arm claudication with supraclavicular or axillary bruits is common. Superficial artery pain and tenderness (e.g., carotidynia) may be found on examination but are not diagnostic of TA. Severe central hypertension caused by renal artery stenosis may be unrecognized because of coexistent arm artery stenosis; thus, four-extremity blood pressure readings must be evaluated initially and monitored on a frequent basis. Occasionally, stenoses exist in all major vessels of the extremities, and cuff monitoring may be an unreliable measure of central aortic pressures. Stroke is not uncommon and is often related to undetected central hypertension. It is extremely difficult to assess the activity of TA; the presence or absence of constitutional features or elevated acute-phase reactants are poor measures of disease activity. This impression is supported by vessel histopathology obtained during reconstructive surgery. Over 40% of vascular specimens from patients thought to be in remission revealed active inflammation. Thus, regular anatomic monitoring of these vessels by examination and imaging (either on magnetic resonance imaging or angiography) is mandatory.

Diagnosis of TA is usually made by MRI or arteriographic evidence of stenotic lesions; aneurysms are less commonly observed. The entire arch, as well as the abdominal aorta and renal vessels, should be evaluated. It is of paramount importance that central arterial pressure be routinely obtained at the time of angiography and compared with simultaneously obtained arm and leg cuff pressures. The role of sequential vascular MRI and positron emission tomography scanning in the evaluation and follow-up of patients suspected of having TA is currently under investigation; of great interest is whether imaging properties of the vessel wall can contribute to the assessment of disease activity. These imaging techniques may reveal therapy-related changes in vessel wall thickness, inflammation, edema, and changes in lumen size. Pathologic documentation is difficult to obtain in TA, but the histopathology of TA, usually obtained at the time of bypass surgery, is similar to that of GCA. Preoperative discussion with the vascular surgeon is mandatory to ensure that appropriate tissue samples are obtained, if possible.

TREATMENT OF GCA AND TA

Corticosteroids are the initial treatment of both TA and GCA. GCA is generally very responsive to steroid therapy, although the most appropriate initial dose remains controversial. Initial daily doses of between 20 mg and 1 mg/kg have been advocated, with tapering over 8 to 12 months. Most authors are comfortable with a starting dose of 40 mg to 60 mg daily. It is generally recommended (without the support of data from...
controlled trials) that patients with any symptoms of ocular isch-emia be initially treated with high-dose corticosteroids (at least 1 mg/kg of prednisone or its equivalent, with some au-thors, predominantly ophthalmologists, suggesting IV methylprednisolone in doses of up to 1 g daily for several days). A significant proportion of patients with GCA require several years of therapy.

High-dose corticosteroid therapy, especially in the elderly, is associated with significant morbidity. Measurement of acute-phase reactants provides an imperfect index of disease activity and should not be the sole guide for adjustment of steroid dosing. If significant steroid side effects occur or if patients experience relapses during tapering, a second-line agent such as methotrexate is often given on an empirical basis with the corticosteroid therapy. However, the value of adjunctive steroid-sparing agents in GCA has not yet been proved. A large prospective, randomized trial was unable to demonstrate a positive effect from methotrexate therapy, although a second trial suggested a small benefit. In a recently completed trial, anti–tumor necrosis factor therapy was not shown to provide any additional benefit to corticosteroid therapy. The addition of low-dose aspirin to corticosteroid therapy has been demonstrated to reduce the ischemic complications of temporal arteritis. There have been only anecdotal reports of successful adjunctive use of azathioprine, methotrexate, and mycophenolate in the treatment of resistant TA. Special attention must be paid to the prevention of opportunistic infections, osteoporosis, glaucoma, hyperglycemia, and hyperlipidemia.

Vascular reconstructive surgery, angioplasty, and stent placement are adjunctive therapeutic options for some patients. Very preliminary experience, however, suggests a high degree of stent failure at some centers. The frequent involvement of the subclavian vessels in TA must be taken into consideration when choosing the graft implantation site for coronary or carotid bypass procedures; grafting from these vessels should be avoided.

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Cytoxan, corticosteroids, methotrexate, azathioprine, pentoxifylline, colchicine, aspirin, and dapsone have not been approved by the FDA for uses described in this chapter.

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Acknowledgments

Figures 1 and 2 Seward Hung. Figure 6 Gary S. Hoffman.