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.

The major determinants of prognosis and therapy include the type of vasculitis, 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, 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 with Suspected 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, should be obtained only after a differential diagnosis is formulated. If the urine dipstick test indicates blood, leukocytes, or protein, the

Table 1 Selected Laboratory Tests for Patients with Multisystem Disease and Possible Vasculitis

Test	*Comments*
Platelet count	Thrombocytosis may parallel the acute-phase response Thrombocytopenia is not expected in primary vasculitic syndromes; consider SLE, marrow infiltration, hairy-cell leukemia, TTP, DIC, hypersplenism, APLS, HIV, scleroderma renal crisis, and heparin-induced thrombocytopenia
White blood cell count	Leukopenia is not expected in primary vasculitis; consider SLE, leukemia, hypersplenism, sepsis, myelodysplasia, and HIV Eosinophilia is common in Churg-Strauss syndrome; it may occur in WG, rheumatoid arthritis, or normotensive scleroderma renal crisis
Erythrocyte sedimentation rate	Relatively low ESR is seen in DIC, liver failure, and hyperviscosity; ESR is frequently normal in HSP, may be low in Takayasu arteritis, and is normal in ≤ 20% of giant cell arteritis
Transaminases	ALT or AST is elevated in liver disease, myositis, rhabdomyolysis, hemolysis, or myocardial necrosis
Anti–glomerular basement membrane	Useful for evaluation of alveolar hemorrhage, with or without glomerulonephritis; also useful for evaluation of normocomplementemic glomerulonephritis
Antinuclear antibody	Order when there is clinical suspicion of SLE, not as a general screening test for sick patients; negative test makes SLE very unlikely
Antineutrophil cytoplasmic antibody	Order when there is clinical suspicion of WG or MPA; order specific anti-PR3 and antimyeloperoxidase
Drug screen	Order for unexplained CNS symptoms, myocardial ischemia, vascular spasm, panic attacks with systemic features, or tachycardia; urine screen should be done
Blood cultures	Useful for any patient with febrile, multisystem, or wasting illness; pulmonary infiltrates; or focal ischemia/infarction. Cultures are easy to obtain
APLA/PTT/RVVT	Order for unexplained venous or arterial thrombosis or thrombocytopenia
Purified protein derivative (± anergy)	Use in any patient who may require steroid therapy or who has unexplained sterile pyuria or hematuria, granulomatous inflammation, chronic meningitis, or possible exposure to tuberculosis
Examination of fresh urinary sediment	Perform in all patients with an unexplained febrile or multisystem illness
Hepatitis serologies	Order for abnormal transaminases or elevated hepatic alkaline phosphatase; portal hypertension; PAN or MPA syndrome; or unexplained cryoglobulinemia, polyarthritis, or cutaneous vasculitis
Complement C3, C4	Not a screening test for vasculitis; useful in the differential diagnosis of glomerulonephritis; low in cryoglobulinemia; may be low in endocarditis; usually normal in PAN, MPA, HSP, WG; may be low in viral hepatitis–related glomerulonephritis or vasculitis
Aldolase	Aldolase has no organ specificity; it has similar organ distribution as lactic dehydrogenase

ALT—alanine aminotransferase APLA—antiphospholipid antibody APLS—antiphospholipid antibody syndrome AST—aspartate aminotransferase DIC—disseminated intravascular coagulation ESR—erythrocyte sedimentation rate HSP—Henoch-Schönlein purpura MPA—microscopic polyangiitis PAN—polyarteritis nodosa PR3—proteinase 3 PTT—partial thromboplastin time RVVT—Russell viper venom test SLE—systemic lupus erythematosus TTP—thrombotic thombocytopenic purpura WG—Wegener granulomatosis

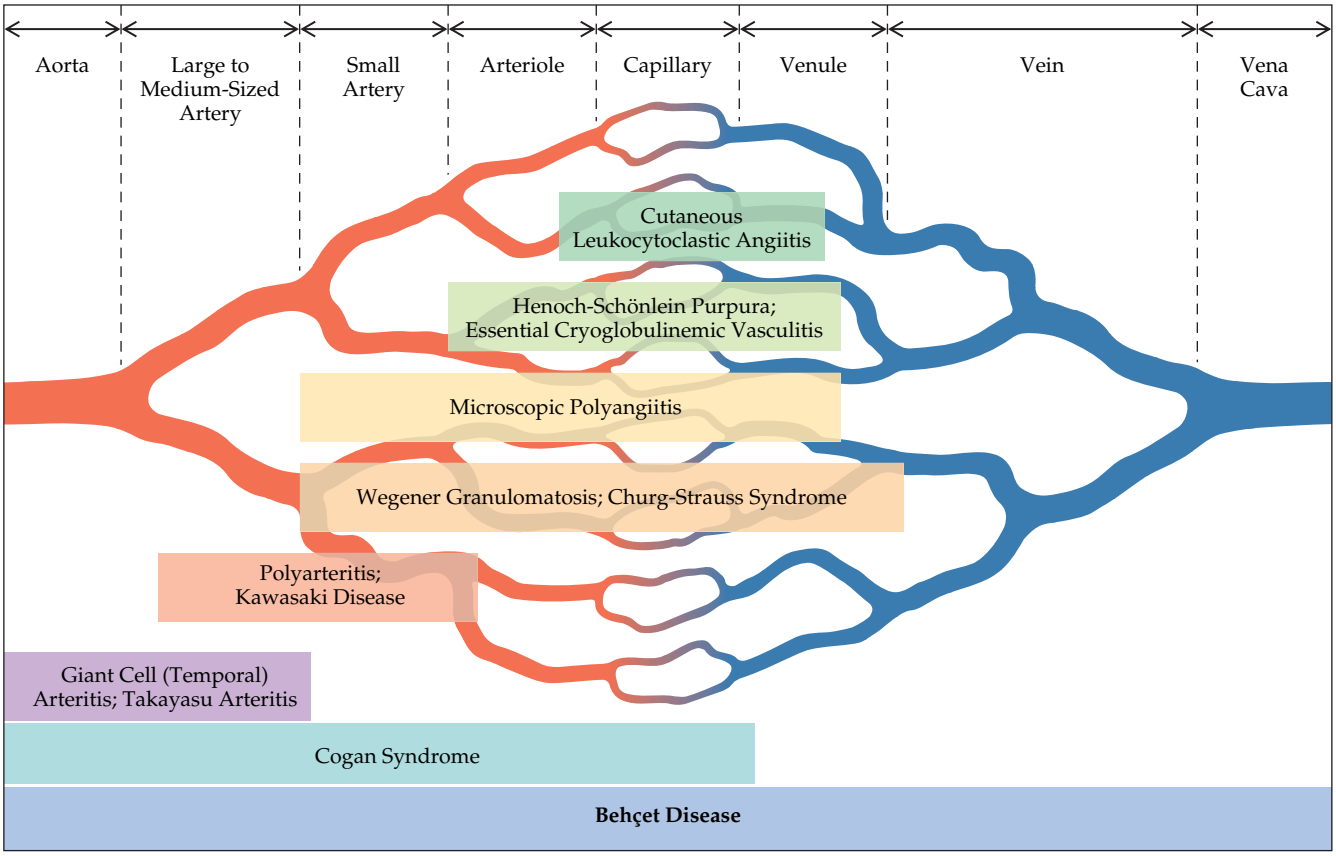

Figure 1 **Classification of the systemic vasculitis syndromes.**[1]

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 highly suggestive of glomerulonephritis, but 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.

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 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, 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 diagnostic role for the presence or absence of specific serum antineutrophil cytoplasmic antibodies (ANCAs), particularly antibodies to proteinase 3 and myeloperoxidase. At present, the appropriate role of these tests is to support a rationally developed clinical diagnosis, not to define one. In patients who do not fit neatly 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 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, ANCA, rheumatoid factor, and angiotensin-converting enzyme is arguable. Alternatively, infection with hepatitis B or C can be associated with a broad range of vasculitic syndromes, and these infections must be routinely excluded.[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 may linger. Hence, even after therapy is initiated, physicians should maintain a high degree of vigilance to detect unrelated medical problems, complications of therapy,

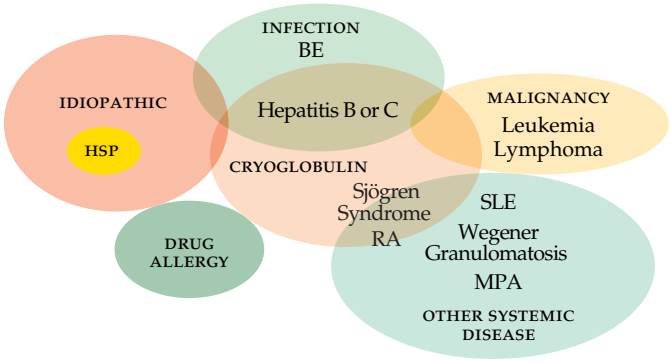

Figure 2 **A Venn diagram illustrates the relations between the causes of small vessel ("hypersensitivity") vasculitis. (BE—bacterial endocarditis; HSP—Henoch-Schönlein purpura; MPA—microscopic polyangiitis; RA—rheumatoid arthritis; SLE—systemic lupus erythematosus)**

or both. The signs and symptoms of unrecognized infection may transiently resolve with steroid therapy.[3] 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 appearance of the vesicles. *Pneumocystis carinii,* cytomegalovirus, and systemic fungal infections and reactivation of mycobacterial disease are observed more frequently in patients 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 recent trend in the treatment of patients with certain potentially life-threatening systemic vasculitic syndromes has been to introduce therapy with a short course of corticosteroids (often with a second immunosuppressive agent), tapered from a high dose to a low dose, to induce remission and then, depending on the disease, to continue immunosuppressive therapy with an alternative regimen of corticosteroids to maintain remission. The second regimen may initially consist of cyclophosphamide, which is felt to be the most potent of these agents, but cyclophosphamide is then replaced with an agent that has a better safety profile (e.g., methotrexate or azathioprine). Therapy with that agent is then continued for many months.

Small Vessel Vasculitis

Vasculitis that affects capillaries and venules is the most common form of vasculitis and almost invariably 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 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., Wegener granulomatosis [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. Purpura is the most common manifestation 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 has been termed hypersensitivity vasculitis in older literature.[4] 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, and infiltrative diseases should be excluded. Cutaneous vasculitis of any etiology may be associated with striking dependent edema.

In a case series of cutaneous small vessel vasculitis,[4] almost 100% of patients younger than 20 years had disease limited to the skin, whereas approximately 40% of the 172 patients older

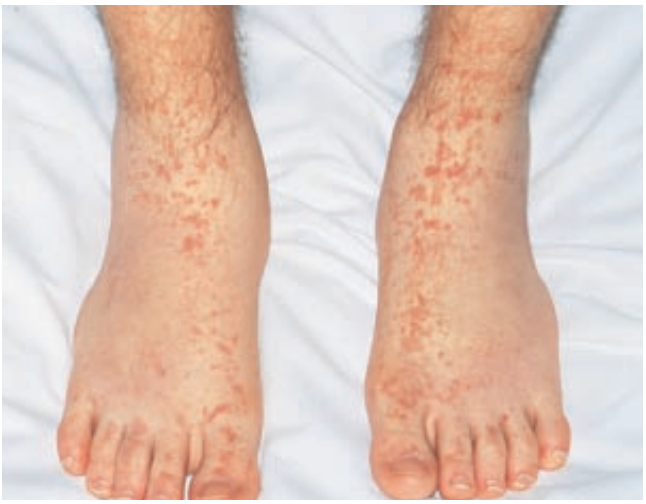

Figure 3 **Palpable purpura of the distal extremities is the most common presentation of small vessel vasculitis.**

Table 2 Immunosuppressive Therapies for Vasculitis

Drug	*Dose*	*Efficacy Rating*	*Comments*
Prednisone	Often used at 1 mg/kg daily (split doses in severe disease) initially; tapered, with goal of discontinuance by 6 months or sooner if possible; utilize other drugs to enable this if possible	Primary therapy in all forms of life- or organ-threatening forms of vasculitis; probably most rapid-acting therapy	Ideally, check baseline PPD status; consider prophylaxis against *Pneumocystis* (when using high doses) and osteoporosis; monitor for development of glaucoma in elderly patients
Cyclophosphamide	1–3 mg/kg p.o. daily; avoid neutropenia; nadir is usually 9–14 days after initiation of therapy or change in dose; decrease dose in setting of renal insufficiency; monthly "pulse" dosing has been used (0.5–1 g/m^2), but there may be greater likelihood of relapse; give pulse dose after dialysis	Most potent nonsteroidal immunosuppressive therapy; unclear onset of action but should be given when severe disease recognized, particularly rapidly progressive glomerulonephritis	Major side effects limit long-term use of this drug: leukopenia, myeloproliferative disease, bladder damage, and malignancy; current trend is to induce remission in WG and other severe forms of vasculitis with prednisone and cyclophosphamide, with tapering of prednisone and change of cyclophosphamide to a less toxic (but likely less effective) medication (e.g., azathioprine or methotrexate)
Azathioprine	2–3 mg/kg daily p.o.	Less potent than cyclophosphamide; useful to maintain remission while trying to spare corticosteroid dosing	Not usually given as primary induction therapy; avoid leukopenia; can cause a confusing hypersensitivity reaction that includes high fever, with or without rash and eosinophilia
Methotrexate	Given once weekly (up to approximately 0.3 mg/kg/dose) along with daily folic acid (1 mg)	Less potent than cyclophosphamide; useful to maintain remission while trying to spare corticosteroid dosing; decrease dose for mild renal insufficiency; *avoid in patients with creatinine > 2.5 mg/dl*	Useful in maintaining remission; has been used as primary induction therapy with prednisone in patients with mild WG; significant frequency of relapse in WG patients maintained on this drug alone; monitor WBC, creatinine and transaminase levels (causes hepatitis and can cause cirrhosis; avoid any ethanol ingestion); can be given orally or by weekly injection; folic acid reduces "nuisance" side effects

PPD—purified protein derivative WBC—white blood cell count WG—Wegener granulomatosis

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 virus, likely the most common cause of mixed cryoglobulinemia,[2] 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, 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 cases 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 even the demonstration 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,[5] 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 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.

Urticarial Vasculitis

Urticarial vasculitis represents a peculiar subset of small vessel vasculitis.[6] 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 eliminat-

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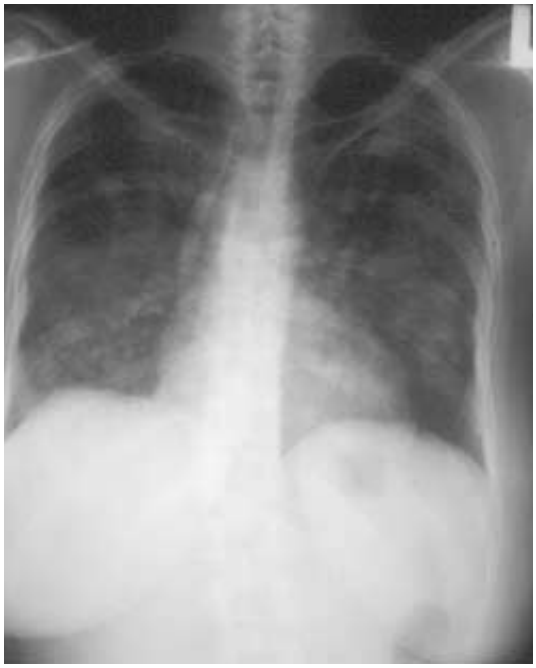

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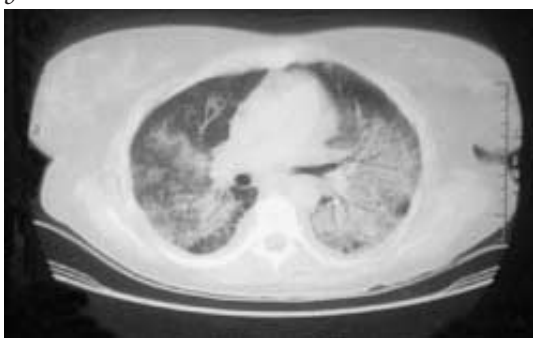

Figure 4 **The nodular infiltrates of the lung in Wegener granulomatosis are shown less extensively in a standard radiograph (*a*) than in a computed tomographic scan (*b*).**

ing 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 there are any hematologic abnormalities. 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. Long-term corticosteroid therapy should be eschewed 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*]. 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.[7,8] 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 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 septal 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 with 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 or 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 often 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 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 biopsy is often the optimal method for demonstrating the typical pathologic findings of WG and for excluding malignancies and atypical infections. Typical open lung biopsies[9] 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. Because these findings may also occur in chronic mycobacterial or 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 defines the generalized or limited forms of the disease.

Table 3 Clinical Features of Vasculitis

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

*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

Glomerulonephritis is often aggressive, or 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 outset 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. Especially in elderly or debilitated patients, valuable information may be obtained by occasional 24-hour urine 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. 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.

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 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. The activity of the skin disease generally parallels systemic disease activity.

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 antimyeloperoxidase 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 is mandatory. The presence of ANCA is not equivalent to the presence of vasculitis; ANCAs can be found in other diseases. The ANCA level is not a reliable means to follow disease activity.[10-12] Because WG generally requires therapy with a glucocorticoid plus a cytotoxic agent, 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 virtually always requires dual-drug immunosuppressive therapy. Corticosteroids may produce symptomatic improvement in the upper airway, lungs, skin, and musculoskeletal system, but tapering usually results in a flare in the disease. 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 recommend that once remission is achieved, cyclophosphamide therapy should be replaced by methotrexate or azathioprine therapy for an additional 12 months of therapy [*see Table 2*]. 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 cancer) and leukopenia. 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. Patients undergoing treatment with immunosuppressives must be continuously monitored for flares

in disease, opportunistic infections, and side effects. Flares may be more frequent in patients treated with methotrexate than in those receiving longer courses of cyclophosphamide.[12] Side effects include cytopenias and drug-induced pneumonitis. Methotrexate may cause hepatitis, marrow suppression, and, on rare occasions, cirrhosis. It should be avoided in the setting of renal insufficiency or alcohol use. Some authors have suggested using trimethoprim-sulfamethoxazole as adjunctive therapy for the treatment of WG and for prevention of bacterial infections that may promote flares of upper airway disease. This approach remains highly controversial. Administration of trimethoprim-sulfamethoxazole three times weekly is useful in protecting patients against *P. carinii* pneumonia while they are receiving intensive immunosuppressive therapy. Local nasal and sinus toilet and otolaryngoscopic evaluations are a routine part of the care of patients with upper airway disease. Prophylactic measures to prevent osteoporosis should always be considered when corticosteroids are used on a long-term basis.

Churg-Strauss Syndrome

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

DIAGNOSIS

Clinical Manifestations

CSS displays clinical similarities to WG in terms of organ involvement and pathology, especially in patients with upper or lower airway disease or glomerulonephritis. It can follow a rapidly progressive course. 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 atopy phase, as well as during the systemic phase of the illness, eosinophilia is characteristic and often of striking degree (≥ 1,000 eosinophils/mm^3). When eosinophilia is present in WG, it is usually more modest (~500 eosinophils/mm^3).

Systemic features of CSS include some combination of pulmonary infiltrates, cardiomyopathy, coronary arteritis, pericarditis, polyneuropathy (symmetrical or mononeuritis multiplex), ischemic bowel disease, eosinophilic gastroenteritis, ocular inflammation, nasal perforations, glomerulonephritis, cutaneous nodules, and purpura.[13,14]

The patchy pulmonary infiltrates of CSS are often transient and may be associated with alveolar hemorrhage. Pulmonary nodules are uncommon and rarely cavitate. Pleural effusions are common and often contain abundant eosinophils. Clinical distinction from hypersensitivity pneumonitis, allergic aspergillosis, and pulmonary lymphoma is at times difficult. Several cases of CSS have been reported to have occurred after the introduction of inhibitors of 5-lipoxygenase and while patients with chronic bronchial asthma are being weaned off corticosteroids.

Cardiac disease can be severe and is a leading cause of mortality. Valvular heart disease is not as striking or as common as it is in the idiopathic hypereosinophilic syndrome. Neurologic involvement occurs in more than 60% of patients. Such involvement may be severe; it is generally attributable to arteritis. Cutaneous purpura, urticaria, polymorphous erythematous eruptions, and nodules occur. Gastrointestinal involvement resulting from ischemic vasculitis, eosinophilic gastroenteritis, or both may cause pain, cramping, and diarrhea.

Laboratory Tests

Histopathology typically exhibits extravascular granulomatous inflammation, with a prominent eosinophilic infiltrate and vasculitis. Vasculitis in a given tissue section may be granulomatous or nongranulomatous. Granulomas can be found in tissue at areas separate from the demonstrable vasculitis. Eosinophilic infiltrates are more striking than in WG. Neither abundant eosinophils, granulomas, nor giant cells are 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 is frequently not as severe as in WG, but when present, it is usually focal and segmental and indistinguishable from other forms of so-called pauci-immune glomerulonephritis (i.e., glomerulonephritis that is without significant tissue deposition of immune complexes).

TREATMENT

CSS is generally responsive to corticosteroid therapy. Most patients are able to be withdrawn from steroids. However, bronchial asthma and sinus disease 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, or azathioprine; the corticosteroids are tapered after remission is achieved [*see Table 2*].

Polyarteritis Nodosa and Microscopic Polyangiitis

CLASSIFICATION

Attempts to separate PAN and MPA, two forms of necrotizing small to medium-sized vessel arteritis, have not been universally accepted. A recent international conference proposed that the diagnosis of 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. 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[2,15] can elicit a secondary vasculitic syndrome indistinguishable from PAN or MPA in presentation but distinct in response to therapy.[16] MPA involves vessels ranging in size from capillaries and venules to medium-sized arteries [*see Figure 1*].[17] Clinically, MPA can mimic WG, although some authors have arbitrarily defined MPA as excluding involvement of the upper airway.

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.[18-20] Azotemia and hypertension in PAN may occur because of arteritis of the renal arteries but not because of glomerulonephritis. Microaneurysm formation in medium-sized visceral arteries may be striking, and they may 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, 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 the presentation of the PAN or MPA syndrome, except that membranous glomerulonephritis, cryoglobulinemia, immune complex–associated glomerulonephritis, hepatic failure, and thrombocytopenia are more likely to occur with viral hepatitis–associated vasculitis.

Antiphospholipid antibody syndrome (APLS) can mimic PAN by presenting as mesenteric ischemia or renal insufficiency caused by thrombotic occlusion of mesenteric and renal vessels.[21] Features of APLS and arteritis affecting muscular arteries include livedo reticularis [*see Figure 5*]. Glomerulonephritis cryoglobulinemia, immune complex–associated glomerulonephritis, and peripheral neuropathy are not expected in APLS unless the patient also has SLE. Thrombocytopenia can occur with APLS but is not expected in PAN. Cholesterol embolization should also be considered as a cause of livedo, renal insufficiency, eosinophilia, and constitutional symptoms[22]; the clinical history of a recent vascular procedure and the performance of a biopsy will help confirm 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, nonnecrotic 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 such a biopsy is not always possible. The presence of serum p-ANCA with antimyeloperoxidase specificity (in 60% of MPA patients) supports the clinical diagnosis of MPA, but p-ANCA is not specific for this disease. ANCAs are not characteristic of 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 and electron microscopy. 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. Biopsy is most useful in ruling out alternative pulmonary diagnoses; open lung and thoracoscopic techniques have a higher yield for demonstrating vasculitis than transbronchial biopsy. Classic PAN does not cause glomerulonephritis or pulmonary parenchymal disease.

The demonstration of arteritis in PAN may be difficult, especially in the setting of dominant constitutional symptoms and the absence of easily accessible, disease-affected tissue. Biopsy efforts should be directed toward tissue that is abnormal as demonstrated by symptoms or objective testing. Sural nerve biopsy has become a popular option when attempting to diagnose an arteritis that is affecting medium-sized muscular vessels. The sural nerve is an accessible pure sensory nerve, and its vasa nervorum contains small as well as medium-sized muscular arteries. Nerve conduction studies can identify a diseased ischemic sural nerve before the appearance of clinical symptoms.[23] Multiple reports have emphasized the low diagnostic yield from the biopsy of asymptomatic and electrically normal nerve. Even nerves exhibiting abnormal conduction have reportedly showed no diagnostic pathology 46% of the time.[24] There is notable morbidity associated with sural nerve biopsy; 13 of 60 patients experienced wound infections or delayed healing, and three patients suffered from new pain in the distribution of the sural nerve that underwent biopsy.[24] Biopsy of clinically uninvolved tissue (i.e., asymptomatic muscle) has a diagnostic yield of less than 30%.

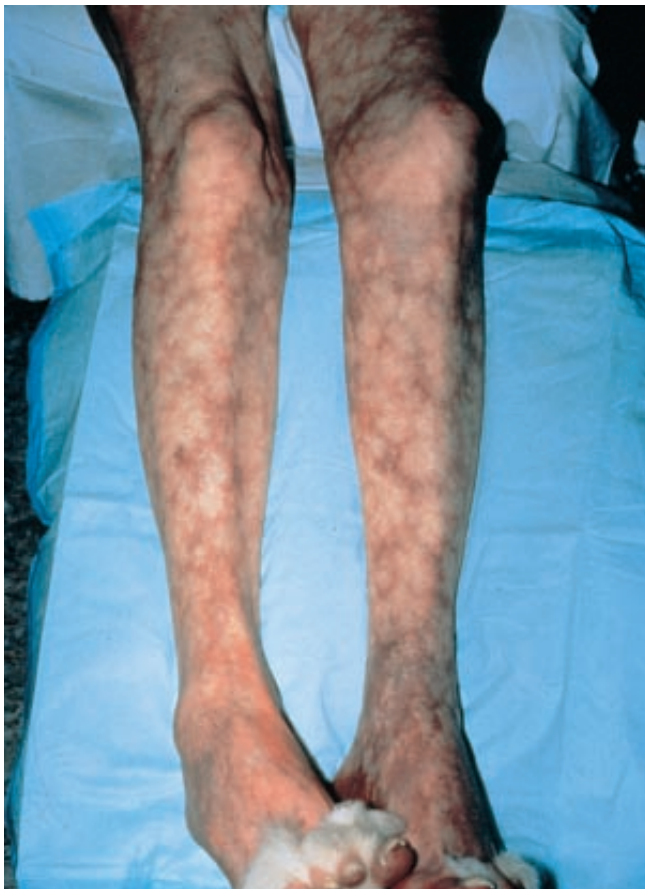

Figure 5 **Livedo reticularis is characterized by reddish-blue mottling of the extremities caused by occlusion of the deep dermal arterioles.**

Abdominal angiography is frequently utilized in the evaluation of patients who may have medium-sized vessel arteritis when biopsy has been unrewarding or is not an option. Arteries affected by polyarteritis nodosa and other disorders of medium-sized muscular arteries may develop microaneurysms or stenoses that can be visualized by angiography. When angiography is used in an effort to diagnose systemic necrotizing vasculitis in the absence of pathologic evidence of the disease, several 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.[17] 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 lesions or occlusion. To maximize the yield from the procedure, angiography should in-

clude the celiac, renal, and mesenteric vessels. Lack of clinical involvement of an organ (i.e., no intestinal ischemia) does not exclude the possibility of finding abnormal vessels on angiography. It has been suggested that the visualization of aneurysms in PAN denotes more severe disease; it is unclear whether their presence may alternatively relate to the actual duration of the untreated illness. Aneurysms may resolve with successful treatment of primary or viral hepatitis–associated disease. 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 disorders. Isolated case reports have described aneurysms in patients with atrial myxoma, bacterial endocarditis, peritoneal carcinomatosis, or severe arterial hypertension and 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 arteritis. As is the case when interpreting a biopsy result of suspected 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 empirical[25] [*see Table 2*]. Corticosteroids in high doses (1 mg/kg daily 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 who do not have critical organ involvement, defined as renal insufficiency, gastrointestinal ischemia, cardiomyopathy, or dense peripheral neuropathy. Therapy with corticosteroids alone may fail more frequently in MPA than in PAN, given the tendency for frequent relapses in MPA.[17] Patients who require long-term corticosteroid therapy for disease control or patients who have clinical markers of severe disease are usually treated with glucocorticoids and an additional immunosuppressive agent such as cyclophosphamide. The indications for initial combination therapy have not been adequately studied.

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

Kawasaki Disease

Kawasaki disease (KD) was first described in 1967 as mucocutaneous lymph node syndrome.[26] It typically affects infants and young children, causing dominant cutaneous 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), mandates 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, 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.[27] 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.

Table 4 Diagnostic Criteria for Kawasaki Disease

- Persistent fever (> 5 days)
  - *plus*
- Four of the following five conditions:
  - Nonpurulent bilateral conjunctivitis
  - Oral mucosal involvement
    - Erythematous pharynx
    - Red or fissured lips
    - Strawberry tongue
  - Soft tissue abnormalities of hands and feet
    - Edema/erythema
    - Desquamation
  - Polymorphous, nonvesicular rash
  - Cervical adenopathy

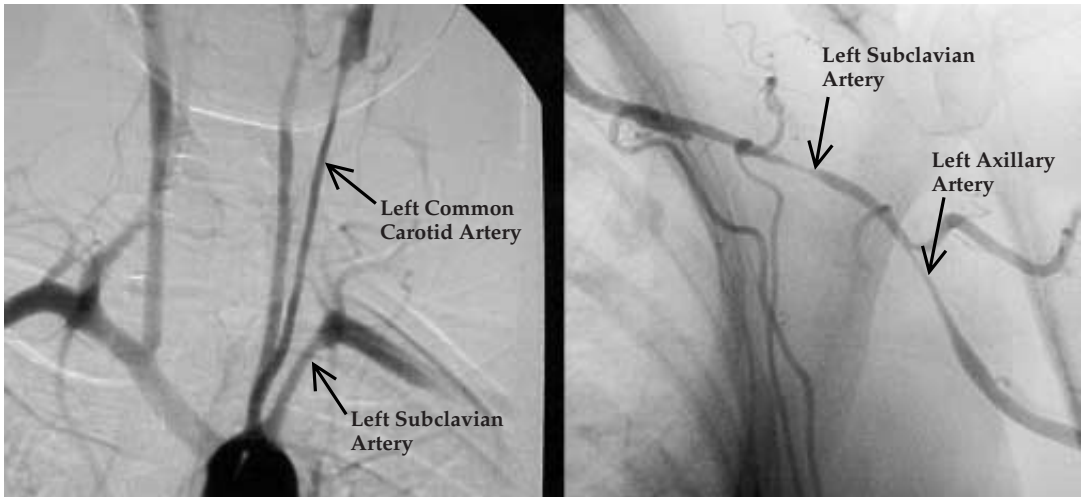

Figure 6 **Angiograms of a patient with Takayasu aortitis demonstrating long, smooth stenotic lesions of the left subclavian artery and involvement of other branches of the aortic arch vessels.**

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 Behçet disease, Cogan syndrome, and sarcoidosis. The last two conditions are recognized 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 individuals older than 50 years.[28,29] In many patients, it is associated with the syndrome of polymyalgia 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.

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 occur. The ischemic symptoms and signs may be clinically indistinguishable from those occurring in arteriosclerotic obliterative disease.

Examination for disparate four-extremity blood pressure readings, abdominal aneurysms, and bruits 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 of GCA, is not warranted.

Levels of acute-phase reactants are elevated in more than 80% of patients. 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 requisite to make the diagnosis. The presence of characteristic clinical features such as new headache and jaw claudication, especially with concurrent PMR, may allow for a presumptive diagnosis in the absence of a biopsy or even when the superficial temporal artery biopsy is negative. However, because other conditions can mimic GCA, including atherosclerosis, an attempt to diagnose GCA by biopsy is warranted in most patients.[30] Corticosteroid therapy will not rapidly affect the biopsy results and should not be withheld from a patient strongly suspected of having GCA who is awaiting biopsy. Bilateral superficial temporal artery biopsy increases the diagnostic yield.

TAKAYASU ARTERITIS

Takayasu arteritis (pulseless disease) is a chronic inflammatory disease affecting the aorta and its major branches.[31] 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 vessel 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 produced by the 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 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 not be recognized 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 ob-

tained during reconstructive surgery. Over 40% of vascular specimens from patients thought to be in remission revealed active inflammation.

Diagnosis of TA is usually made by arteriographic demonstration 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 magnetic resonance imaging in the evaluation and follow-up of these patients is currently under investigation.[32] This technique may reveal therapy-related changes in vessel wall thickness and edema as well as changes in lumen size. Pathologic documentation is difficult to obtain in TA, but the histopathology, usually obtained at the time of bypass surgery, is similar to that for 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 for 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. It is generally recommended (without the support of data from controlled trials) that patients with any symptoms of ocular ischemia be initially treated with high-dose corticosteroids (at least 1 mg/kg of prednisone or its equivalent, with some authors suggesting I.V. methylprednisolone in doses of up to 1 g daily for several days). A significant proportion of patients with GCA require several years of therapy. 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 added on an empirical basis to the corticosteroid therapy. However, the value of adjunctive steroid-sparing agents in GCA is currently unproved. A recent large prospective, randomized trial was unable to demonstrate a positive effect from methotrexate therapy.[33] Vascular reconstructive surgery, angioplasty, and stent placement are adjunctive therapeutic options in some patients. Although very preliminary experience suggests a high degree of stent failure, 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. High-dose corticosteroid therapy, especially in the elderly, has potentially dangerous side effects. Special attention must be paid to the prevention of opportunistic infections, osteoporosis, glaucoma, hyperglycemia, and hyperlipidemia.

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Acknowledgments

Figures 1 and 2 Seward Hung.

Figure 6 Gary S. Hoffman.