H CONT.

S. aureus, vancomycin is often initially used to cover gram-positive cocci. The duration of treatment depends on the causative organism and patient response, but usually lasts 2 to 4 weeks.

An infected joint must also be adequately drained. Needle aspiration is an acceptable approach and should be performed regularly (usually daily) as long as there is an effusion. Ultrasound guidance may improve the ability to fully drain the joint. Surgical drainage is an equally good alternative and is more immediately definitive. Additionally, surgical drainage is required for joints that are not easily accessible for needle aspiration (for example, sternoclavicular, sternomanubrial, shoulder, and hip joints), if there is evidence of soft-tissue extension of infection, or if the clinical response to antimicrobial therapy is inadequate. The goal of surgery is to remove all purulent material and nonviable tissue and, in some cases, to perform synovial biopsy or synovectomy.

Antibiotic treatment is recommended for all patients with Lyme arthritis. Approximately 90% of patients will respond to a 28-day course of oral doxycycline, amoxicillin, or cefuroxime axetil. Patients with incomplete responses may need treatment with a second course or a more aggressive drug regimen, usually intravenous ceftriaxone. Treatment beyond 1 month of ceftriaxone offers no benefit and should not be employed. Antibiotic-refractory Lyme arthritis occurs in ≤10% of patients, probably represents a progression to sterile autoimmune arthritis, and responds to synovectomy or treatment with disease-modifying antirheumatic drugs such as hydroxychloroquine or methotrexate.

Mycobacterial joint infections require at least 6 to 9 months of therapy. Treatment of arthritis associated with viral infections is largely supportive, although specific viral therapy is appropriate for HIV and hepatitis C infection; immunosuppressive therapy with glucocorticoids and rituximab may be needed in refractory hepatitis C–related disease or severe mixed cryoglobulinemia.

Treatment of prosthetic joint infections is challenging and requires early surgical consultation. Orthopedic implants serve as a nidus for microorganisms, and the avascularity of the infected hardware limits antibiotic penetrance. Many patients require removal of the orthopedic device as part of a two-stage procedure, with reimplantation of a new device after an appropriate course of intravenous antibiotics. H

- In patients with suspected infectious arthritis, blood and synovial cultures must be obtained before treatment, but empiric antibiotic therapy should be started while awaiting culture results.
- In addition to antibiotic therapy, an infected joint must also be adequately drained by needle aspiration or surgical drainage.
- Many patients with prosthetic joint infections require removal of the orthopedic device as part of a two-stage procedure, with reimplantation of a new device after an appropriate course of intravenous antibiotics.

Systemic Vasculitis

Overview

Vasculitis is inflammation of blood vessels, including the capillaries, arteries, and veins. Clinical manifestations result from tissue ischemia associated with the involved vessels. Vasculitis may be primary, secondary to an autoimmune disease, or triggered by other causes (**Table 38**). Mimics of vasculitis must also be considered in the differential diagnosis (**Table 39**). Primary autoimmune vasculitis disorders are discussed in this section.

TABLE 38. Causes of Secondary Vasculitis

Medications
Common causes: antimicrobial agents (e.g., minocycline, sulfadiazine); antithyroid agents (mostly propylthiouracil [80%-90%], methimazole, carbimazole, and benzylthiouracil [10%-20%]); other cardiovascular drugs (hydralazine); tumor necrosis factor α inhibitors
Rare causes: vaccines; antiepileptic agents; antiarrhythmic agents; diuretics; anticoagulants; antineoplastic agents; hematopoietic growth factors; NSAIDs; psychotropic drugs; sympathomimetic agents; allopurinol; interferon alfa; levamisole (associated with cocaine)
Infections
Hepatitis A, B, and C viruses; HIV; bacterial endocarditis; parvovirus B19
Neoplasms
Hairy cell leukemia (associated with polyarteritis nodosa); other hematologic and solid malignancies
Autoimmune Diseases
Systemic lupus erythematosus; rheumatoid arthritis; Sjögren syndrome; inflammatory myopathies; systemic sclerosis; relapsing polychondritis; inflammatory bowel disease; primary biliary cirrhosis

TABLE 39. Differential Diagnosis (Mimics) of Vasculitis

Disease	Comments
Infection (sepsis; endocarditis; hepatitis)	Rash and/or musculoskeletal symptoms can occur.
Drug toxicity/poisoning	Cocaine, amphetamines, ephedra alkaloids, and phenylpropanolamine may produce vasospasm, resulting in ischemia.
Coagulopathy	Thrombotic diseases (disseminated intravascular coagulation; antiphospholipid syndrome; thrombotic thrombocytopenic purpura) can produce ischemic symptoms.
Malignancy	Paraneoplastic vasculitis is rare. Any organ system may be affected, but the skin and nervous system are the most common. Vasculitic symptoms may precede, occur simultaneously with, or follow diagnosis of cancer. Lymphoma occasionally may involve the blood vessels and mimic vasculitis. Consider malignancy in patients with incomplete or no response to therapy for idiopathic vasculitis.
Atrial myxoma	Classic triad of symptoms is embolism, intracardiac obstruction leading to pulmonary congestion or heart failure, and constitutional symptoms (fatigue; weight loss; fever). Skin lesions can be identical to those seen in leukocytoclastic vasculitis. Atrial myxomas are rare but are the most common primary intracardiac tumors. Myxomas can also occur in other cardiac chambers.
Cholesterol emboli	Typically seen in patients with severe atherosclerosis. Embolization may occur after abdominal trauma, aortic surgery, or angiography. May also occur after heparin, warfarin, or thrombolytic therapy. Patients may have livedo reticularis, petechiae and purpuric lesions, and localized skin necrosis.

Large-Vessel Vasculitis

Giant Cell Arteritis

Epidemiology and Pathophysiology

Giant cell arteritis (GCA; temporal arteritis) affects patients over 50 years of age (peak incidence between 70 and 80 years). Most patients are women. GCA is more common in white persons; incidence ranges from 10 to 20/100,000 in Europe. An association with HLA-DRB*04 has been identified.

GCA is characterized by granulomatous inflammation of affected vessels with infiltration of lymphocytes, macrophages, and multinucleated giant cells. Involved vessels include the aorta, its major branches off the arch, and secondary branch vessels, including the external carotid, subclavian, axillary, temporal, ophthalmic, ciliary, occipital, and vertebral arteries. The level of vessel involved dictates the clinical symptoms.

Clinical Manifestations and Diagnosis

Common GCA symptoms include headache, scalp pain, and temporal artery tenderness. Symptoms are frequently unilateral but can be bilateral. Aching and fatigue with chewing (jaw claudication) indicates ischemia of the muscles of mastication. Fever, fatigue, and weight loss may be present. The most feared complication is ischemic optic neuropathy, which can cause amaurosis fugax and blindness. Because blindness is usually permanent, early recognition and treatment of any visual change are critical. Subcranial disease involving great vessels in the chest occurs in 25% of cases, resulting in upper extremity claudication. Severe but uncommon complications include aortic aneurysm and dissection. Dilation of the aortic root may cause aortic valve regurgitation and heart failure. Up to 50% of patients with GCA have polymyalgia rheumatica (PMR) that may occur before, concurrent with, or following diagnosis of GCA.

Physical examination may reveal scalp or temporal artery tenderness and induration, reduced pulses and bruits, or aortic regurgitation and heart failure. Laboratory findings may include elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), but some have normal values. Nonspecific evidence of inflammation may include anemia and thrombocytosis.

GCA is suspected on the basis of the clinical presentation and is confirmed by temporal artery biopsy and/or imaging of great vessels. New or atypical headache, jaw claudication, or visual changes in a patient over the age of 50 years, especially with concurrent PMR, should raise suspicion. Temporal artery biopsy is diagnostic, but false-negative results are common; bilateral temporal artery biopsy can increase the yield. Importantly, temporal artery biopsy will remain abnormal for up to 2 weeks after initiation of glucocorticoids. Angiography is used to document and follow subcranial disease.

Management

Suspected GCA must be treated immediately to prevent visual loss. Prednisone, 1 mg/kg/d, is recommended. Intravenous pulse methylprednisolone for 3 days is used for acute visual loss, but established blindness is usually irreversible. Symptoms and inflammatory markers usually respond rapidly to glucocorticoids; lack of response should prompt reconsideration of the diagnosis. High-dose prednisone is maintained for 2 to 4 weeks; after symptoms resolve and inflammatory markers normalize, prednisone is tapered by 10% to 20% every 2 weeks. Once a dose of 10 mg/d is reached, the taper is slowed to 1 mg per month. Patients should be carefully monitored for

symptom recurrence. ESR and/or CRP should be monitored monthly but should not be the sole indication for adjusting the glucocorticoid dose. Mild flares can be managed with increases of prednisone by 10% to 20% and a slower tapering schedule.

Based on limited data, daily low-dose aspirin may help to reduce the risk of blindness and is recommended for those without contraindication. Glucocorticoid-sparing immunosuppressives such as methotrexate are sometimes used, although little data support their efficacy. The IL-6 inhibitor tocilizumab was recently approved by the FDA for treatment of GCA.

The prognosis for properly treated GCA is good unless aortitis is present. GCA may recur.

Polymyalgia Rheumatica

Epidemiology and Pathophysiology

Although not a vasculitis, polymyalgia rheumatica (PMR) is an inflammatory disorder that frequently accompanies GCA. PMR and GCA likely reflect the clinical spectrum of a single disease process, although PMR occurs 3 to 10 times more frequently. Up to 50% of patients presenting with GCA have PMR, and 20% of patients presenting with PMR have GCA symptoms on questioning.

Clinical Manifestations and Diagnosis

PMR is associated with pain and stiffness of the neck, shoulder, and hip girdle. Pain and stiffness are worse after immobility; 1 hour or more of morning stiffness is common. Inflammation is periarticular (bursitis and tenosynovitis). Synovitis in the hands and feet occasionally occurs. Constitutional symptoms and laboratory findings resemble GCA, but temporal artery biopsy should be performed only if GCA is suspected. Diagnosis of PMR is made clinically. Differential diagnosis includes myopathies, metabolic syndromes (thyroid and parathyroid), and musculoskeletal syndromes (capsulitis, cervical spondylosis, or calcium pyrophosphate deposition).

Management

PMR responds dramatically to low-dose prednisone (12.5-20 mg/d); lack of a rapid response should prompt consideration of alternate diagnoses. Prednisone taper is initiated 1 to 2 months after symptom resolution and requires months to years. Monitoring of recurrence is managed similarly to GCA. For relapses, recent guidelines for the management of PMR (developed by a collaborative effort of the American College of Rheumatology and the European League Against Rheumatism) recommend increasing the prednisone to the last pre-relapse dose at which the patient was doing well, followed by a gradual reduction within 4 to 8 weeks back to the relapse dose. Glucocorticoid-sparing therapies are the same as for GCA. Prognosis is good, although periodic recurrences are common.

Takayasu Arteritis

Epidemiology and Pathophysiology

Takayasu arteritis (TA) causes inflammation of the large vessels, most commonly the aorta, followed by the subclavian, common carotid, and renal arteries; the pulmonary arteries may also be involved. TA is rare (40/million in Japan and 4.7 to 8/million elsewhere). In contrast to GCA, TA predominantly affects younger women. Arterial lesions are often stenotic ("pulseless disease"), and one third contain aneurysms. Histopathology is similar to GCA.

Clinical Manifestations and Diagnosis

TA manifestations include carotodynia, limb claudication, reduced pulses, bruits, and blood pressure discrepancies between the arms. Heart failure related to aortic insufficiency or coronary artery disease may occur. Neurologic manifestations include transient ischemic attack, stroke, and mesenteric ischemia. As with GCA, laboratory studies are nonspecific and reveal anemia as well as elevated ESR and CRP. Angiogram may demonstrate arterial stenosis or aneurysm (**Figure 27**).

Management

Primary treatment of TA is high-dose glucocorticoids (1 mg/kg/d) with a slow taper. Glucocorticoid-sparing medications such as disease-modifying antirheumatic drugs are used but without clear evidence for efficacy. Angioplasty, graft placement, and bypass may be necessary but should be avoided during active inflammation. The leading cause of death is heart failure; stroke and cardiovascular disease also contribute to morbidity. The 10-year survival rate is 90%.

FIGURE 27. Aortic angiogram from a patient with Takayasu arteritis. Note the high-grade stenosis of the proximal right subclavian artery (*white arrow*) as well as the left subclavian artery just below the origin of the left vertebral artery (*black arrow*). Incidentally noted is an anatomic variation with a common origin of the right brachiocephalic artery and the left common carotid artery.

KEY POINTS

- Giant cell arteritis should be suspected in a patient over the age of 50 years with new or atypical headache, jaw claudication, or visual changes.

HVC
- Suspected giant cell arteritis should be treated immediately with prednisone because of the risk for visual loss; diagnosis is confirmed with temporal artery biopsy, as pathologic findings will persist for up to 2 weeks after initiation of prednisone.

HVC
- Polymyalgia rheumatica is associated with pain and profound stiffness of the neck, shoulder, and hip girdle; it responds dramatically to low-dose prednisone.
- Takayasu arteritis occurs in younger women and causes inflammation of the aorta and other major noncranial vessels; manifestations include carotodynia, limb claudication, reduced pulses, bruits, and blood pressure discrepancies between the arms.

Medium-Vessel Vasculitis

Polyarteritis Nodosa

Epidemiology and Pathophysiology

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis that affects medium and occasionally small arteries. Prevalence is 31/million but declining. PAN is more common in men than women. Average age of onset is 50 years.

Hepatitis B virus (HBV) infection has been strongly associated with PAN. However, the proportion of patients with HBV-associated PAN has declined from 36% to less than 5% since the advent of the HBV vaccine; thus, most contemporary cases are presumed autoimmune. Activated endothelial cells as well as increased interleukins, T cells, and macrophages have been identified as potential contributors to vessel damage.

Clinical Manifestations and Diagnosis

PAN most commonly affects the skin, neurologic, and musculoskeletal systems. It does not involve the lungs and rarely the heart. Kidney involvement is renovascular rather than glomerular. Cutaneous PAN is a variant confined to the skin. See **Table 40** for the clinical and laboratory findings of PAN.

The gold standard for diagnosis is focal segmental panmural necrotizing inflammation of a medium-sized vessel shown on biopsy. The biopsy is usually performed on an involved, easily accessible area, such as skin or a peripheral nerve/muscle. PAN may also be diagnosed on angiogram; mesenteric or renal arteries show characteristic aneurysms and stenosis, especially at branch points.

Management

Glucocorticoids and cyclophosphamide are indicated for severe organ-threatening disease; glucocorticoids and disease-modifying antirheumatic drugs are used for milder disease. HBV-associated PAN is treated with short-term glucocorticoids, antiviral medication, and plasmapheresis if necessary. The 5-year survival rate for treated PAN is 80%, and the relapse rate is 10% to 20%. H

Primary Angiitis of the Central Nervous System

Epidemiology and Pathophysiology

Primary angiitis of the central nervous system (PACNS) is a rare medium-vessel vasculitis of unknown cause that is confined to the central nervous system. Incidence is 2.4/100,000. Median age at onset is 50 years. There are three histologic

TABLE 40. Clinical Features of Polyarteritis Nodosa

Organ System	Symptoms	Frequency	Comments
Constitutional	Fever; malaise; weight loss	65%	—
Musculoskeletal	Arthralgia; myalgia	55%	—
Skin	Purpura; nodules; necrotic ulcers	50%-60%	—
Neurologic	Mononeuritis multiplex; peripheral neuropathy	79%	Wrist drop; foot drop
Kidney	Hypertension; hematuria; proteinuria	40%	Renal artery microaneurysms with tissue infarct/hematoma; no glomerulonephritis
Gastrointestinal	Mesenteric ischemia; intestinal perforation; pancreatitis; cholecystitis; appendicitis; gastrointestinal bleeding	38%	One third of gastrointestinal cases manifest as acute abdomen
Testicular	Orchitis	17%	Usually unilateral, due to testicular artery involvement
Other	Sensorineural hearing loss	Case reports	Bilateral; symmetric; sudden onset; rapidly progressive
Laboratory	Elevated erythrocyte sedimentation rate in 82%; elevated C-reactive protein; leukocytosis; anemia; thrombocytosis; increased liver chemistry tests in 33%	—	—

presentations, all with patchy distribution: granulomatous (58%), lymphocytic (28%), and necrotizing (14%).

Clinical Manifestations and Diagnosis

Patients with PACNS usually present with gradual and progressive symptoms of headache, cognitive impairment, neurologic deficits, transient ischemic attacks, and strokes. Laboratory studies are normal. Cerebrospinal fluid (CSF) is abnormal in 90%, with elevated protein, lymphocytic pleocytosis, and occasional oligoclonal bands. MRI shows nonspecific white and gray matter changes and infarcts. MR angiography and CT angiography have limited usefulness due to poor resolution. Cerebral angiogram may demonstrate vessel "beading" (alternating dilations and stenoses) but has limited sensitivity and specificity. Brain biopsy is the best test for diagnosis, but the patchy distribution of findings results in a 50% false-negative rate.

Evaluation centers on ruling out other conditions, including infection, malignancy, and reversible cerebral vasoconstriction syndrome.

Management

PACNS is treated with high-dose glucocorticoids and cyclophosphamide. Patients often have permanent disability from neurologic damage, and the recurrence rate is 27%.

Kawasaki Disease

Kawasaki disease (KD) is a medium-vessel vasculitis that affects children and is very rare in adults. KD presents as fever, rash, cervical lymphadenopathy, conjunctival congestion, and mucositis. Coronary vessel vasculitis, aneurysm formation, and other cardiac complications (heart failure, pericarditis, arrhythmias) may develop. Treatment is with intravenous immunoglobulin and aspirin.

Many patients recover fully. However, coronary aneurysms may develop, and adults who had KD in childhood may suffer long-term cardiac sequelae. Chronic low-dose aspirin is indicated for coronary artery abnormalities. Clopidogrel may be added for cases with multiple aneurisms; warfarin prophylaxis is recommended for giant aneurysms.

KEY POINTS

- Polyarteritis nodosa most commonly affects the skin, neurologic, and musculoskeletal systems; the gold standard for diagnosis is focal segmental panmural necrotizing inflammation of a medium-sized vessel on biopsy.
- Patients with primary angiitis of the central nervous system usually present with gradual and progressive symptoms of headache, cognitive impairment, neurologic deficits, transient ischemic attacks, and strokes; treatment consists of high-dose glucocorticoids and cyclophosphamide.

(Continued)

KEY POINTS *(Continued)*

- Kawasaki disease (KD) affects children; many patients recover fully, but coronary aneurysms may develop, and adults who had KD in childhood may suffer long-term cardiac sequelae.

Small-Vessel Vasculitis

ANCA-Associated Vasculitis

ANCA-associated vasculitis includes three diseases characterized by the presence of ANCA: granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, along with ANCA-associated glomerulonephritis.

There are two types of vasculitis-associated ANCA: p-ANCA (perinuclear, directed against the neutrophil enzyme myeloperoxidase) and c-ANCA (cytoplasmic, directed against the neutrophil proteinase 3). Perinuclear and cytoplasmic refer to patterns of immunofluorescent staining; enzyme-linked immunosorbent assays are used to confirm antibody positivity.

ANCA may play a direct role in vessel damage by hyperactivating already primed neutrophils, leading to vessel endothelial inflammation and damage. The presence of granulomatous inflammation in some forms of ANCA-associated vasculitis suggests a role for cell-mediated immunity.

See **Table 41** for a comparison of the features of the three forms of ANCA-associated vasculitis.

See MKSAP 18 Nephrology for details on kidney involvement in ANCA-associated vasculitis.

Granulomatosis with Polyangiitis

Epidemiology and Pathophysiology

Granulomatosis with polyangiitis (GPA) is the most common ANCA-associated vasculitis, with an incidence of 7 to 12/million/year. It is more prevalent in Nordic countries and white persons. Typical age of onset is between 45 and 60 years.

Clinical Manifestations and Diagnosis

GPA affects the upper and lower airways, kidneys, eyes, and ears. At least 50% of patients have constitutional symptoms. More than 95% of patients are ANCA positive, overwhelmingly (>90%) directed against proteinase 3 (anti-PR3 antibodies; c-ANCA).

GPA has two forms: systemic and localized. Systemic is more common, involves major organs, and is anti-PR3 positive. Localized has more granulomatous inflammation, has less vasculitis, and is less likely to be anti-PR3 positive. Patients in the localized group are more likely to be younger and female; have mainly ear, nose, and throat involvement; and be more prone to relapse. See Table 41 for GPA clinical features.

In the setting of a classic clinical presentation and positive c-ANCA/anti-PR3, diagnosis of GPA is straightforward. However, because of significant risks of treatment, biopsy of

TABLE 41. Clinical Features of ANCA-Associated Vasculitis Diseases

	Granulomatosis with Polyangiitis	Microscopic Polyangiitis	Eosinophilic Granulomatosis with Polyangiitis
ANCA	c-ANCA (antiproteinase-3 antibodies) (>95%)	p-ANCA (antimyeloperoxidase antibodies) (50%-75%)	p-ANCA (antimyeloperoxidase antibodies) (~50%)
Vascular Histology	Pauci-immune necrotizing granulomatous vasculitis	Pauci-immune nongranulomatous necrotizing vasculitis	Pauci-immune necrotizing granulomatous vasculitis with eosinophilic infiltration of vessel walls and tissues; extravascular granulomas
Cardiac	Pericarditis; myocarditis; conduction disorder (<10%)	—	Pericarditis; endomyocarditis; conduction disorder; heart failure (27%-47%)
Ears/Nose/Throat	Crusting; rhinorrhea; sinusitis; otitis media; chondritis of ears and nose with saddle nose deformity; septal perforation (70%-100%)	Sinusitis; sensorineural hearing loss (9%-30%)	Nasal polyps; rhinitis; sinusitis (prodromal)
Gastrointestinal	Ulceration; perforation (5%-11%)	Abdominal pain; bleeding (30%-58%)	Abdominal pain; bleeding
Kidney	Pauci-immune necrotizing glomerulonephritis (40%-100%)	Pauci-immune necrotizing glomerulonephritis (80%-100%)	Pauci-immune necrotizing glomerulonephritis (25%)
Lung	Alveolar hemorrhage; nodules; tracheal/subglottic stenosis (50%-90%)	Alveolar hemorrhage; pulmonary infiltrates; pulmonary fibrosis (25%-55%)	Asthma (prodromal, >90%); nodular opacities; infiltrates (25%-86%)
Ocular	Scleritis; episcleritis; retinal vasculitis; retro-orbital pseudotumor; dacryoadenitis (14%-60%)	—	—
Skin	Palpable purpura; nodules; pyoderma gangrenosum; mucosal ulcerations (10%-50%)	Palpable purpura; livedo reticularis; nodules; necrotic skin ulcers (30%-60%)	Palpable purpura; nodules (60%)
Neurologic	Mononeuritis multiplex, sensorimotor peripheral neuropathy (33%)	Distal symmetric polyneuropathy; mononeuritis multiplex (37%-72%)	Sensorimotor peripheral neuropathy, mononeuritis multiplex (70%)
	Central nervous system involvement (pachymeningitis) (<5%)	Central nervous system pachymeningitis; cerebral hemorrhage; infarcts (<20%)	

CONT.

involved tissue is usually recommended. Histopathology of most tissues demonstrates pauci-immune necrotizing granulomatous vasculitis; pauci-immune necrotizing glomerulonephritis without granulomas is seen on kidney biopsy.

Management

For induction of remission in severe organ-threatening or life-threatening disease, treatment of GPA consists of high-dose glucocorticoids plus cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab for at least 12 to 24 months after stable remission has been achieved. Glucocorticoids alone are insufficient to control GPA. Patients with nonsevere forms of GPA (such as arthropathy or upper airway disease) without organ-threatening disease can be treated with glucocorticoids plus either methotrexate or mycophenolate mofetil; such patients should be carefully monitored for treatment failure or the development of renal or other organ-threatening disease, necessitating the more aggressive regimen. Using these approaches, GPA mortality has declined from 90% to around 10%.

Relapses are common (>50% 5 years after initial remission) and may respond better to rituximab than to cyclophosphamide.

Kidney failure and infection are the main causes of mortality.

Microscopic Polyangiitis

Epidemiology and Pathophysiology

The incidence of microscopic polyangiitis (MPA) is estimated at 2.7 to 94/million/year in Europe and lower elsewhere. Average age at onset is between 50 to 60 years with a predilection of men over women (1.8:1). In contrast to GPA, ANCA are less prevalent (50%-75%) and tends to be directed against myeloperoxidase (MPO) rather than PR3.

Clinical Manifestations and Diagnosis

Like GPA, MPA characteristically affects the lungs and kidneys, along with other organ systems. See Table 41 for the clinical features of MPA. Diagnosis is suspected based upon typical clinical findings and positive ANCA, although negative ANCA

does not rule out the diagnosis. The diagnostic gold standard is a biopsy demonstrating nongranulomatous necrotizing pauci-immune vasculitis of small vessels or pauci-immune necrotizing crescentic glomerulonephritis in the kidney. Absence of granulomas distinguishes MPA from GPA.

Management

Like GPA, MPA treatment requires high-dose glucocorticoids plus either cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab.

Prognosis is worse in the setting of pulmonary hemorrhage or rapidly progressive glomerulonephritis. Survival with treatment is 82% at 1 year and 76% at 5 years.

Eosinophilic Granulomatosis with Polyangiitis

Epidemiology and Pathophysiology

Eosinophilic granulomatosis with polyangiitis (EGPA) is the rarest ANCA-associated vasculitis, with an incidence of 0.11 to 2.66/million/year and a prevalence of 10 to 14/million (France). EGPA has no predisposition for gender or ethnicity. In addition to neutrophil activation, eosinophil infiltration, activation, and degranulation participate in the pathogenesis.

Clinical Manifestations and Diagnosis

The typical patient with EGPA has a history of asthma (96%-100%), nasal polyps, rhinitis, sinusitis, and/or atopy. A prodromal phase (months to years) consisting of arthralgia, myalgia, malaise, fever, and weight loss may occur. An eosinophilic phase with increased peripheral and tissue eosinophilia follows, with migratory pulmonary infiltrates and, less commonly, endomyocardial infiltration and gastrointestinal disease. The subsequent acute vasculitic phase includes mononeuritis multiplex or peripheral sensorimotor neuropathy (70%), kidney (25%), and skin involvement (60%). Paradoxically, the vasculitis phase is often associated with improvement of asthma. See Table 41 for the clinical features of EGPA.

Laboratory findings show peripheral eosinophilia of more than 10%, or more than 1500/μL (1.5×10^9/L). Only 50% of patients have a positive ANCA, mostly directed against MPO.

Diagnosis is based upon typical clinical findings, eosinophilia, and biopsy demonstrating fibrinoid necrosis and eosinophilic infiltration of vessel walls, as well as extravascular granuloma formation.

Management

In EGPA, glucocorticoids alone may be sufficient for mild disease without major organ involvement. With kidney, gastrointestinal, cardiac, or neurologic involvement, cyclophosphamide is indicated.

Mortality for EGPA is the lowest of all the forms of ANCA-associated vasculitis. The 5-year survival is 97%, and the relapse rate is 28%.

- Granulomatosis with polyangiitis typically affects the upper and lower airways, kidneys, eyes, and ears; induction of remission in severe organ-threatening or life-threatening disease consists of high-dose glucocorticoids plus cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab.
- Microscopic polyangiitis commonly affects the lungs and kidneys; treatment requires high-dose glucocorticoids plus either cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab.
- Eosinophilic granulomatosis with polyangiitis is associated with asthma, nasal polyps, rhinitis, sinusitis, atopy, peripheral and tissue eosinophilia, migratory pulmonary infiltrates, and mononeuritis multiplex; treatment consists of glucocorticoids for mild disease, with cyclophosphamide added for more severe disease.

Immune Complex-Mediated Vasculitis

Immune complexes form from cross-linking of multiple antigens and antibodies. If not cleared, immune complexes deposit in tissue, leading to complement and neutrophil activation with inflammation and tissue damage. Although any tissue or organ may be affected, the classic finding is invariably in the skin. Inflammation and erythrocyte extravasation from involved vessels result in nonblanching palpable purpura, usually in dependent areas (**Figure 28**). Leukocytoclastic vasculitis refers to disintegration of nuclei (nuclear dust) of dead neutrophils along with fibrinoid necrosis of the vessel wall.

Cryoglobulinemic Vasculitis

Cryoglobulins can cause immune complex-mediated small-vessel vasculitis. There are three types of cryoglobulins;

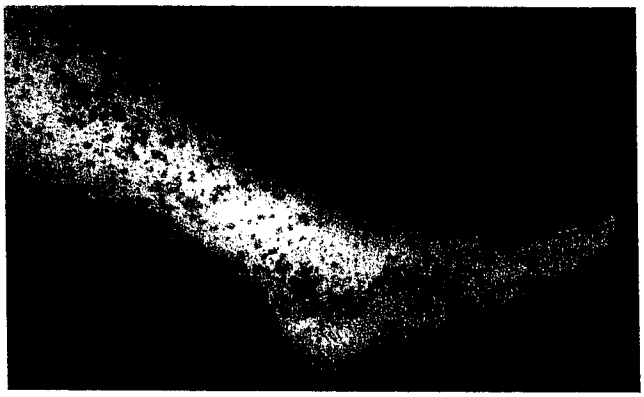

FIGURE 28. Palpable purpura is the classic rash of any small-vessel, immune complex-mediated vasculitis. The lesions are nonblanching and represent extravasations of blood from damaged vessels. Purpuric lesions are typically more prominent on the lower extremities, a consequence of the superimposed effect of gravity on hydrostatic pressure.

discussion here is limited to types II and III ("mixed" types). Both are polyclonal, but type II cryoglobulins include a monoclonal IgM rheumatoid factor, whereas type III cryoglobulins include a polyclonal IgM rheumatoid factor. The ability of rheumatoid factor to directly bind other antibodies facilitates the formation of immune complexes even in the absence of persistent antigen. See MKSAP 18 Hematology and Oncology for details on cryoglobulins and the differentiation from cold agglutinin disease.

Epidemiology and Pathophysiology

Mixed cryoglobulinemia accounts for 85% to 90% of all cases; 90% of mixed cases are related to hepatitis C virus (HCV) infection, which can cause both type II and type III cryoglobulinemia. Autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome cause type III cryoglobulinemia. Onset is usually in the fifth decade, and women slightly outnumber men.

Clinical Manifestations and Diagnosis

Cutaneous symptoms (palpable purpura, Raynaud phenomenon, ulcers, necrosis, and livedo reticularis) predominate in 70% to 90% of patients with mixed cryoglobulinemia, but any organ may be involved. Peripheral neuropathy (60%), arthritis (40%), and glomerulonephritis (40%) are common. In addition to cryoglobulins, a low C4 complement and positive rheumatoid factor are present. A false-negative cryoglobulin result may occur if the serum sample is not maintained at 37.0 °C (98.6 °F) due to ex vivo cryoprecipitation at room temperature.

HCV infection associated with mixed cryoglobulinemia may go unrecognized for many years before the development of vasculitis. It is therefore important to test for HCV infection in patients with cryoglobulinemia.

Management

When possible, treatment of the underlying cause of cryoglobulinemia is the first priority. For HCV-related disease, antiviral medication is the primary therapy. For severe or refractory disease, the vasculitis must be independently addressed. Glucocorticoids and cyclophosphamide have been used in the past; plasmapheresis and rituximab (provided there is no hepatitis B virus infection) have demonstrated efficacy and may carry less toxicity.

IgA Vasculitis

See MKSAP 18 Nephrology for information on IgA nephropathy and on kidney involvement in IgA vasculitis.

Epidemiology and Pathophysiology

IgA vasculitis (Henoch-Schönlein purpura) is a common vasculitis of childhood that occurs rarely in adults. Estimated incidence in adults is 14/million/year. Onset is often preceded by a viral or streptococcal upper respiratory infection.

Clinical Manifestations and Diagnosis

Patients with IgA vasculitis typically present with a palpable purpura in dependent areas. Gastrointestinal symptoms such as abdominal pain or bleeding (65%), arthritis and arthralgia (63%), and glomerulonephritis (40%) may be present. Although rare, life-threatening pulmonary hemorrhage may occur.

There are no specific laboratory tests for diagnosis; serum IgA may be elevated but is not sensitive or specific. Diagnosis is confirmed with biopsy. Skin biopsy demonstrates leukocytoclastic vasculitis with heavy deposits of IgA and complement on immunofluorescent staining. Renal histology is identical to IgA nephropathy.

Management

Although IgA vasculitis in children tends to be self-limited, adults are more likely to develop severe persistent disease, especially nephropathy, and may require glucocorticoids and cyclophosphamide.

Hypersensitivity Vasculitis

Epidemiology and Pathophysiology

Hypersensitivity vasculitis is a small-vessel vasculitis mediated by immune complex deposition confined to the skin. It may be triggered by an antigen such as a drug or infection; in 50% of cases, the antigen is unknown.

Clinical Manifestations and Diagnosis

The most common presentation of hypersensitivity vasculitis is palpable purpura in dependent regions, developing 7 to 10 days after exposure to a triggering antigen; lesions appear in "crops" and resolve over a few weeks after the antigen is removed. Internal organs are unaffected. Skin biopsy with immunofluorescence demonstrates leukocytoclastic vasculitis without heavy IgA deposits. Evaluation should be guided by clinical signs and symptoms, and may only require a complete blood count, basic chemistries, and urinalysis.

Management

Removal of the antigen (if identified) and supportive care are usually sufficient. Resolution within a month is the rule. If symptoms persist or recur, anti-inflammatories, topical or low-dose systemic glucocorticoids, colchicine, or dapsone may be helpful.

KEY POINTS

- Mixed cryoglobulinemia is associated with cutaneous symptoms, peripheral neuropathy, arthritis, and glomerulonephritis, with 90% of cases related to hepatitis C virus infection; treatment of the underlying disorder causing cryoglobulinemia is required.
- IgA vasculitis (Henoch-Schönlein purpura) is characterized by palpable purpura and abdominal pain/bleeding and occurs mainly in children; adult disease is rare but more likely to be severe and/or persistent and to require glucocorticoids and cyclophosphamide.

(Continued)

KEY POINTS *(continued)*

- The most common presentation of hypersensitivity vasculitis is palpable purpura, developing 7 to 10 days after exposure to a triggering antigen; removal of the antigen and supportive care are usually sufficient management.

Other clinical manifestations include venous thrombosis that may affect the large veins, including the vena cava and the dural venous sinuses. Central nervous system (CNS) manifestations include brainstem lesions and aseptic meningitis; the most common CNS symptoms are headache and diplopia. Inflammatory arthritis (usually in the knees), skin lesions, and gastrointestinal inflammation/ulceration indistinguishable