Medium-Vessel Vasculitis

Polyarteritis Nodosa

Epidemiology and Pathophysiology

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis that affects medium-sized and sometimes small-sized arteries. Prevalence is approximately 31 per million but declining. Average age at onset is 50 years.

Historically, PAN has been strongly associated with hepatitis B virus (HBV). Because HBV prevalence has declined with the advent of the HBV vaccine and antiviral treatment, the proportion of patients with HBV-associated PAN has declined from 36% to less than 5% of all PAN cases; most contemporary cases are autoimmune. Pathophysiology is not well understood.

Clinical Manifestations and Diagnosis

PAN most commonly affects the skin and peripheral nervous system, as well as the gastrointestinal tract and kidneys. **Table 40** lists the clinical and laboratory findings of PAN. The disease does not involve the lungs. When present, kidney involvement is renovascular rather than glomerular and often leads to hypertension. Cutaneous PAN is a variant confined to the skin. Cutaneous features of medium-vessel vasculitis include livedo reticularis (**Figure 53**) and painful deep ulcers and skin necrosis due ischemic infarction (**Figure 54**). Because of the intense inflammation of medium-sized vessels, subcutaneous nodules may be palpable.

Related Question

Question 51

Diagnosis is often confirmed via angiography of the mesenteric and/or renal vasculature, which demonstrates saccular microaneurysms and areas of narrowing in medium-sized vessels. The gold standard for diagnosing PAN is histologic identification of focal segmental panmural necrotizing inflammation of a medium-sized vessel, obtained on biopsy of involved, easily accessible tissue (e.g., skin or a superficial nerve).

Management

Intravenous pulse 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%.

Primary Angiitis of the Central Nervous System

Epidemiology and Pathophysiology

Primary angiitis of the central nervous system (PACNS) is a rare small- and medium-vessel vasculitis of the central nervous system; it affects the brain parenchyma, spinal cord, and leptomeninges. Incidence is 2.4 per 100,000. Median age at onset is 50 years. The three histologic presentations have a patchy distribution: granulomatous (most common), lymphocytic, and necrotizing.

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 findings are normal. Cerebrospinal fluid is abnormal but nonspecific in 80% to 90% of patients, with elevated protein, lymphocytic pleocytosis, and occasional oligoclonal bands. MRI shows nonspecific white and gray matter changes and infarcts. Magnetic resonance angiography and CT angiography have limited usefulness because of poor resolution. Cerebral angiography may demonstrate vessel "beading" (alternating dilations and stenoses) but has limited sensitivity and specificity. Brain biopsy should be performed in any patient in whom the diagnosis is seriously considered; however, the patchy distribution of findings results in a 50% false-negative rate.

Evaluation also focuses on ruling out other conditions, including infection, malignancy (e.g., intravascular CNS lymphoma), 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 is a medium-vessel vasculitis and the most common type of vasculitis in children. It presents as fever, rash, cervical lymphadenopathy, conjunctival congestion, and mucositis. Coronary vessel vasculitis is the most feared complication and may leave permanent vasculopathy if not treated promptly. Although Kawasaki disease almost never develops in adulthood, adults who had Kawasaki disease as a child may have residual coronary aneurysms that require monitoring and management. Recently a Kawasaki-like syndrome (multisystem inflammatory syndrome in children) has been identified in patients (rarely, adults) who have been infected with COVID-19.

Key Points

- Polyarteritis nodosa most commonly affects the skin and peripheral nervous system, as well as the gastrointestinal tract and kidneys; 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.
- Adults who had Kawasaki disease as a child may have residual coronary aneurysms that require monitoring and management.

Small-Vessel Vasculitis

ANCA-Associated Vasculitis

ANCA-associated vasculitis includes three diseases characterized by the presence of ANCA (**Table 41**): granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. (ANCA-associated glomerulonephritis is discussed in MKSAP 19 Nephrology.) The presence of ANCA can be detected on serologic testing and helps to define the diseases.

The two types of vasculitis-associated ANCA are 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 against myeloperoxidase and proteinase 3 are used to confirm antibody positivity and in some cases to replace immunofluorescence testing.

ANCA may play a direct role in disease propagation by activating primed endothelial cells and neutrophils, leading to vessel damage. The granulomatous inflammation in some forms of ANCA-associated vasculitis suggests a role for cell-mediated immunity. Although most cases of ANCA-associated vasculitis are idiopathic, a few are drug induced; several drugs can cause this rare reaction, including propylthiouracil and levamisole (an adulterant often found in cocaine).

See MKSAP 19 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 annual incidence of 7 to 12 per million.

Clinical Manifestations and Diagnosis

GPA affects the small vessels of the upper and lower airways (sinuses, lungs), kidneys, eyes (scleritis), skin, and peripheral nerves. At least 50% of patients have constitutional symptoms. More than 95% of patients are ANCA positive, with antibodies overwhelmingly (>90% of cases) directed against proteinase 3 (anti-PR3 antibodies; c-ANCA).

Related Question

Question 4

GPA presents as systemic or localized disease. The systemic form is more common, involves major organs, and is associated with positivity for anti-PR3 antibodies. Patients with localized disease are more likely to be younger and female; have mainly ear, nose, and throat involvement; and are less likely to be PR-3 positive. See **Table 41** for clinical features of GPA.

Cutaneous features of GPA include petechiae or palpable purpura (both of which are nonblanching lesions; **Figure 55**), hemorrhagic bullae, and superficial ulcers. However, any of the small-vessel vasculitides may present with these findings.

In the setting of a classic clinical presentation and positivity for c-ANCA/anti-PR3 antibodies, diagnosis of GPA is straightforward. However, because of significant risks of treatment, biopsy of involved tissue is usually recommended if possible. Histopathology of most tissues demonstrates pauci-immune necrotizing granulomatous vasculitis; pauci-immune necrotizing glomerulonephritis without granulomas is seen on kidney biopsy.

Management

Management

Related Question

Question 33

To induce remission in severe organ-threatening or life-threatening disease, treatment of GPA consists of high-dose oral glucocorticoids or intravenous glucocorticoids plus rituximab (preferred) or cyclophosphamide; selected patients may benefit from plasma exchange. Once remission is achieved, patients should receive maintenance therapy consisting of rituximab, methotrexate, or azathioprine; rituximab appears to be most effective for preventing relapse and is preferred. It remains unclear whether suppressive maintenance therapy can be fully withdrawn because relapse in GPA is common (historically, >50% after initial remission). Glucocorticoids alone are insufficient to control GPA. Patients with limited presentations of GPA (such as arthropathy or upper airway disease) without organ-threatening disease can sometimes be treated with glucocorticoids plus methotrexate; such patients should be carefully monitored for treatment failure or development of kidney or other organ-threatening disease, necessitating a more aggressive regimen. With use of these approaches, GPA mortality has declined from 90% to around 10%. Kidney failure and infection remain the main causes of death.

Microscopic Polyangiitis

Epidemiology and Pathophysiology

The annual incidence of microscopic polyangiitis (MPA) is estimated at 2.7 per million in Europe and lower elsewhere. Average age at onset is 50 to 60 years, with a predilection for men over women (1.8:1). Compared with GPA, ANCAs are less prevalent (50%-75%) and usually directed against myeloperoxidase.

Clinical Manifestations and Diagnosis

Like GPA, MPA characteristically affects the lungs and kidneys, along with other organ systems. In contrast to GPA, MPA tends to spare the upper airways, and lung involvement is not granulomatous on biopsy. See **Table 41** for the clinical features of MPA. Diagnosis is suspected on the basis of typical clinical findings and positivity for myeloperoxidase ANCA, although negativity for ANCA does not rule out the diagnosis. The diagnostic gold standard is a biopsy specimen demonstrating necrotizing pauci-immune vasculitis of small vessels in any affected tissue or pauci-immune necrotizing crescentic glomerulonephritis in the kidney. Absence of granulomas distinguishes MPA from GPA.

Management

Treatment of MPA is similar to that of GPA.

Eosinophilic Granulomatosis With Polyangiitis

Epidemiology and Pathophysiology

Eosinophilic granulomatosis with polyangiitis (EGPA) is the rarest ANCA-associated vasculitis, with an annual incidence of 0.11 to 2.66 per million. Eosinophil infiltration, activation, and degranulation participate in disease pathogenesis.

Clinical Manifestations and Diagnosis

The typical patient with EGPA has a prodromal history of difficult-to-treat asthma (96%-100%), rhinitis, and/or atopy. A 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 involvement (25%), and skin involvement (60%). The vasculitis phase is often associated with improvement of asthma. See **Table 41** for the clinical features of EGPA.

Clinical Manifestations and Diagnosis

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Laboratory findings show peripheral eosinophilia of more than 10%, or more than 1500/μL (1.5×10^9/L). Only about 40% to 60% of patients have a positive ANCA result, mostly directed against myeloperoxidase.

Diagnosis is based on typical clinical findings, eosinophilia, and biopsy specimens 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 had been indicated in the past. However, mepolizumab, a monoclonal antibody that binds interleukin-5, has been FDA approved for EGPA and has a more favorable safety profile than cyclophosphamide.

Mortality for EGPA is the lowest among all forms of ANCA-associated vasculitis. The 5-year survival is 97%, and the relapse rate is 28%. If not treated early, neuropathy may become permanent.

Key Points

- Granulomatosis with polyangiitis affects the upper and lower airways, kidneys, eyes, skin, and peripheral nerves; induction of remission in severe organ-threatening or life-threatening disease consists of high-dose glucocorticoids rituximab (preferred) or cyclophosphamide.
- Microscopic polyangiitis characteristically affects the lungs and kidneys; treatment is the same as that for granulomatosis with polyangiitis.

- Eosinophilic granulomatosis with polyangiitis is associated with asthma, rhinitis, sinusitis, atopy, peripheral and tissue eosinophilia, migratory pulmonary infiltrates, and mononeuritis multiplex or peripheral sensorimotor neuropathy; treatment consists of glucocorticoids for mild disease, with mepolizumab or cyclophosphamide added for more severe disease.

Immune Complex–Mediated Vasculitis

Immune complexes develop from cross-linking of multiple antigens and antibodies. Immune complexes can deposit in small vessels, leading to complement and neutrophil activation, with consequent 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 damaged vessels result in nonblanching palpable purpura, usually in dependent areas (**Figure 56**). The various immune complex–mediated vasculitides are distinguished by the antigen that drives them, the class of antibody generated, and differences in clinical presentations.

Cryoglobulinemic Vasculitis

Related Question

Question 56

Cryoglobulins cause an immune complex–mediated small-vessel vasculitis primarily affecting the skin, peripheral nervous system, and kidneys. CNS involvement may rarely occur. There are three types of cryoglobulins. Type I occurs as a consequence of malignant monoclonal gammopathies and B-cell lymphoma. Types II and III are polyclonal and "mixed" in nature. Each is formed from the interaction of antigen-targeted antibodies with rheumatoid factor; type II cryoglobulins include a monoclonal IgM rheumatoid factor, whereas in type III cryoglobulins the rheumatoid factor is a polyclonal IgM. The ability of rheumatoid factor to directly bind other antibodies facilitates the formation of immune complexes even in the absence of persistent antigen. In addition to their ability to form immune complexes, all cryoglobulins demonstrate the unique feature of precipitating in the cold. See MKSAP 19 Hematology for details on type I cryoglobulins. See MKSAP 19 Hematology for the differentiation of cryoglobulinemia from cold agglutinin disease.

Epidemiology and Pathophysiology

Mixed cryoglobulinemia, which accounts for 75% to 90% of all cases of cryoglobulinemic vasculitis, is rare, with an estimated prevalence of 1 in 100,000. About two thirds of mixed cryoglobulinemia (type II and type III) cases are related to hepatitis C virus infection. Autoimmune diseases, such as systemic lupus erythematosus and Sjögren syndrome, more typically cause type III cryoglobulinemia.

Clinical Manifestations and Diagnosis

Cutaneous symptoms (palpable purpura, digital ischemia, ulcers, necrosis, and livedo reticularis) are seen in about 90% of patients. Other common manifestations include peripheral neuropathy, arthralgia without arthritis, and glomerulonephritis (usually membranoproliferative). Pulmonary and/or gastrointestinal involvement is rare. Testing for cryoglobulins requires that a sample of blood be maintained at 37.0 °C (98.6 °F) until clotting is complete to avoid incorporation of the cryoglobulins into the clot. In addition to detection of cryoglobulins, laboratory abnormalities frequently include depressed C4 complement and low CH50 levels. Patients with type II and type III cryoglobulinemia have positivity for rheumatoid factor. A false-negative cryoglobulin result is not unusual given the complexity of cryoglobulin testing.

Management

Treatment of cryoglobulinemia requires first addressing the cause of the disease, such as instituting antiviral therapy for hepatitis C virus–related cryoglobulinemia. When the consequences of the cryoglobulinemia are severe (e.g., glomerulonephritis, ulcerating cutaneous lesions, digital gangrene), the vasculitis itself must also be treated. Glucocorticoids and rituximab in combination are the standard first-line therapy.

IgA Vasculitis

See MKSAP 19 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 rarely occurs in adults. Estimated annual incidence in adults is 14 per million. Onset is usually preceded by upper respiratory tract infection, often with streptococcal bacteria.

Clinical Manifestations and Diagnosis

Patients with IgA vasculitis typically present with palpable purpura in dependent areas. Other common findings include abdominal pain or gastrointestinal bleeding (50%), arthritis and arthralgia (60%), and glomerulonephritis. Although progressive renal damage may occur, 90% of adults with kidney involvement fully recover.

There are no specific laboratory tests for diagnosis. Diagnosis is confirmed by demonstrating IgA tissue deposition, generally in the skin, by immunofluorescent microscopy. Skin biopsy demonstrates leukocytoclastic vasculitis with heavy deposits of IgA and complement on immunofluorescent staining. Although rarely necessary, renal histology shows IgA deposition within the mesangium.

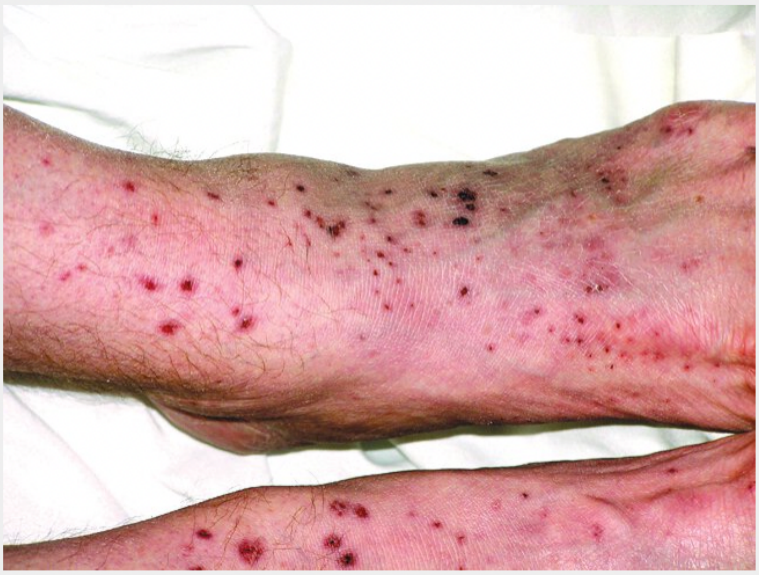
Management

Although IgA vasculitis in children tends to be self-limited, adults are more likely to develop persistent nephropathy and may require glucocorticoids. Despite lack of evidence, some patients may require additional immunosuppression (cyclophosphamide or rituximab).

Question 56

A 63-year-old man is evaluated for an 8-week history of a spreading rash on the feet and legs, fatigue, and arthralgia.

On physical examination, vital signs are normal. The rash is shown. Some lesions are palpable. He cannot extend his left wrist. Findings on pulmonary, cardiac, and gastrointestinal examinations are unremarkable. There are no swollen or tender joints.



Laboratory studies:	
Erythrocyte sedimentation rate	110 mm/h
Alanine aminotransferase	93 U/L
Aspartate aminotransferase	89 U/L
C3 complement	113 mg/dL (1130 mg/L)
C4 complement	Not detected
Creatinine	2.1 mg/dL (185.6 µmol/L)
Rheumatoid factor	118 U/mL (118 kU/L)
Anti–cyclic citrullinated peptide antibodies	Not detected
Urinalysis	2+ blood; 2+ protein; dysmorphic erythrocytes; no casts

Which of the following is the most likely diagnosis?

A Cryoglobulinemic vasculitis

B Hypersensitivity vasculitis

C Polyarteritis nodosa

D Rheumatoid vasculitis

A 53-year-old man is evaluated in the emergency department for abdominal pain. Four weeks ago, fatigue and malaise developed, followed 1 week later by a rash. Two weeks ago, he began tripping over his left foot. Three days ago, he developed abdominal pain after a meal; abdominal pain is now constant.

On physical examination, temperature is 38.0 °C (100.4 °F), and blood pressure is 154/96 mm Hg; other vital signs are normal. The abdomen is soft and nontender. Muscle strength at dorsiflexion of the left ankle is 3/5. Erythematous nodules are present on the lower legs. The remainder of the examination is normal.

Laboratory studies:	
Hemoglobin	8.7 g/dL (87 g/L)
C-reactive protein	13.8 mg/dL (138 mg/L)
Creatinine	1.7 mg/dL (150.3 µmol/L)
Urinalysis	Normal
Hepatitis C virus serology	Negative
HIV testing	Negative

Chest radiograph is normal.

Which of the following is most likely to establish the diagnosis?

A ANCA panel

B Hepatitis A virus serology

C Kidney biopsy

D Magnetic resonance angiography of abdomen

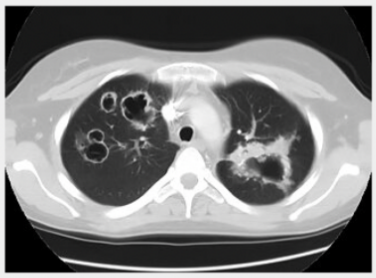
Question 4

A 67-year-old woman is evaluated in the hospital for malaise, fatigue, arthralgia, and rash of 8 weeks' duration; dry cough and sinus congestion of 6 weeks' duration; and painless eye redness and dyspnea that began several days ago.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 122/76 mm Hg, pulse rate is 104/min, respiration rate is 24/min, and oxygen saturation is 92% with the patient breathing ambient air. Bilateral, localized ocular injection is seen. Scattered rhonchi are heard on lung auscultation, and petechiae and purpura are visible on the legs.

Laboratory studies:	
Erythrocyte sedimentation rate	87 mm/h
Creatinine	2.1 mg/dL (185.6 µmol/L)
ANCA	Pending
Urinalysis	3+ blood; 2+ protein; 20-30 dysmorphic erythrocytes/hpf; 5-10 leukocytes/hpf; erythrocyte casts

Chest CT scan is shown.



Which of the following is the most appropriate diagnostic test to perform next?

A Kidney biopsy

B Sinus biopsy

C Skin biopsy