Medium vessel vasculitis

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Abstract

Polyarteritis nodosa (PAN) and Kawasaki's disease are primary systemic vasculitides with predominant medium-sized vessel involvement. PAN typically affects muscular arteries, causing aneurysms (nodosa). There are no specific serological markers, and diagnosis depends on clinical presentation, angiography and tissue biopsy. Exclusion of hepatitis B infection is important. Treatment with corticosteroids and immunosuppressive drugs is usually effective, but PAN can pursue a relapsing course. Kawasaki's disease affects children, usually under the age of 5 years, and presents as an acute, febrile exanthematous disease. Coronary artery involvement predominates and can lead to aneurysm formation and thrombosis. Prompt treatment with intravenous immunoglobulin and aspirin reduces the frequency of these complications. Relapse is rare, although vascular damage results in an increased longer term risk of cardiovascular disease.

Keywords Aneurysm; glucocorticoids; immunosuppression; intravenous immunoglobulin; Kawasaki's disease; MRCP; polyarteritis nodosa; systemic vasculitis

Key points

Polyarteritis nodosa:

- This is now only rarely associated with hepatitis B infection
- Diagnosis is based on biopsy and/or angiography
- Glomerulonephritis and ANCA positivity are not compatible with polyarteritis nodosa
- Corticosteroids and cyclophosphamide are the main therapeutic modalities

Kawasaki's disease:

- There is a sudden onset of a febrile, exanthematous illness
- It is the most common cause of acquired heart disease in children in the developed world
- The frequency of coronary artery aneurysms is reduced to 4% by early diagnosis, intravenous immunoglobulin (a single infusion of 2 g/kg) and aspirin

Introduction

Medium vessel vasculitis predominantly affects medium-sized arteries, defined as the main visceral arteries and their branches, but can involve arteries of any size. It does not involve arterioles, capillaries or venules. The principal medium vessel vasculitides are polyarteritis nodosa (PAN) and Kawasaki's disease (KD). PAN is most common in adults but well recognized in children, whereas KD is almost exclusively a childhood disease and only very rarely reported in adults. The term PAN should not be applied to patients with focal necrotizing glomerulonephritis or other types of capillaritis (including pulmonary capillaritis), who typically have antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis (AAV) microscopic polyangiitis as defined by the Chapel Hill Consensus Conference nomenclature 2012. In general, proteinase 3 or myeloperoxidase-ANCA seropositivity is incompatible with PAN, a useful distinction because necrotizing medium and small vessel arteritis can occur in AAV.

Medium-sized vessels can be involved in other vasculitides, including cryoglobulinaemic vasculitis (another small vessel vasculitis) and 'variable vessel vasculitides' such as Behçet's disease. Similarly, medium vessel vasculitis can be a feature of single-organ vasculitis (e.g. primary central nervous system (CNS) angiitis), and other diseases such as systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, Sjögren's syndrome and relapsing polychondritis.

Polyarteritis nodosa

Epidemiology and pathogenesis

PAN is a rare disease (incidence of 1–2 per million) and much less common than other primary vasculitides, including AAV. It primarily but not exclusively affects individuals of European ancestry, and its aetiology is largely unknown. Before blood products were routinely screened, hepatitis B virus (HBV)-associated PAN was frequent. In the French Vasculitis Study Group Database (1973–2005), 35% of PAN cases are HBV-linked.[1] Typically, PAN develops within 6 months of infection, with HBV antigens detectable in deposited immune complexes. Today, HBV-associated PAN is uncommon, but it remains important to screen all patients for HBs antigenaemia because serum liver enzyme concentrations may be normal. Aggressive immunosuppression without recognition of HBV can cause cirrhosis or hepatocellular carcinoma. More rarely, PAN-like vasculitides occur in hepatitis C and HIV infection and are associated with other diseases including hairy cell leukaemia and familial Mediterranean fever.

Recently, deficiency of adenosine deaminase 2 (ADA2) has been recognized as a cause of childhood-onset PAN and PAN-like vasculopathy.[2] ADA2 is encoded by *CECR1* and appears to be involved in the regulation of macrophages and activated T cells, as well as

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acting as a growth factor that may modulate vascular integrity. ADA2 deficiency is inherited in an autosomal recessive pattern, and PAN can result from either homozygous or compound heterozygous mutations. ADA2 deficiency is phenotypically diverse, and the diagnosis should be considered in patients with a family history of vasculitis, sporadic paediatric cases of PAN and adults with a prior childhood history, including those with neurological involvement (especially stroke). Serum ADA2 activity can be assayed and genetic screening is available through specialized centres. Treatment with anti-tumour necrosis factor (TNF)-α agents may be efficacious, including when other agents have failed.

Cutaneous PAN is a medium and small vessel arteritis limited to the skin that is less common than systemic PAN but can rarely progress to systemic PAN. Cutaneous PAN is an immune complex disease that can be idiopathic or linked to group A β-haemolytic streptococcal infection.

Diagnosis

Typically, PAN presents in adults of around 50 years old, but can occur at any age including childhood.[1] Constitutional or musculoskeletal symptoms and skin involvement predominate (Table 1). Mononeuritis multiplex is also frequent. Severe gastrointestinal disease is less frequent but important to identify. HBV-PAN does not have a distinct presentation, but neurological manifestations (including mononeuritis multiplex and peripheral neuropathy), gastrointestinal disease and hypertension may be more frequent than in idiopathic PAN[1]. Significant kidney disease (renal impairment with active urinary sediment and albuminuria), pulmonary disease (asthma, infiltrates, nodules, cavities, haemorrhage) and ear, nose and throat disease suggest AAV rather than PAN. Inflammatory markers are typically elevated, but ANCA and cryoglobulins are negative and serum complement remains normal.

Confirmation requires demonstration of non-granulomatous necrotizing arteritis (e.g. by skin, nerve or muscle biopsy) or microaneurysms (e.g. in kidneys, spleen, liver) on imaging. Selective conventional angiography (Figure 1) remains the most sensitive modality for detecting micro-aneurysms whereas computed tomography (CT) angiography and MR angiography have lower sensitivities but can detect larger aneurysms. Arterial stenoses and other angiographic features can also be indicative of PAN. Angiography is relevant in patients with suspected cutaneous PAN to rule out systemic disease. Aggressive renal arteritis occasionally provokes renal failure via cortical infarction or malignant hypertension, but patients with active urine sediment or impaired kidney function should usually undergo kidney biopsy before angiography, because focal necrotizing glomerulonephritis in small vessel vasculitis remains the most likely cause of these findings. PAN is often patchy, and both tissue samples and angiography can be non-diagnostic.

PAN: major clinical features

- ☐ Arteritis affecting medium or small arteries (biopsy or microaneurysms on angiography)
- ☐ Hepatitis B infection (now uncommon)
- ☐ ANCA-negative, no cryoglobulinaemia
- ☐ No evidence of glomerulonephritis or capillaritis
- ☐ Constitutional or musculoskeletal: fever, weight loss, arthralgia and myalgia
- ☐ Livedo reticularis, nodules or purpura (occasionally ulcers or gangrene)
- ☐ Mononeuritis multiplex, peripheral neuropathy (occasionally CNS disease)
- ☐ Abdominal pain
- ☐ Gut infarction, haemorrhage or perforation (uncommon but increased mortality)
- ☐ Hypertension
- ☐ Testicular pain and orchitis
- ☐ Retinal vasculitis, uveitis or keratitis (infrequent)
- ☐ Coronary vasculitis (rare)

Table 1

Management

The goals of treatment are to achieve sustained remission, prevent death and minimize treatment-related toxicity. In the absence of HBV infection, the intensity of immunosuppressive therapy should reflect disease severity (Figure 2).[3] PAN typically responds to corticosteroids and, traditionally, monotherapy has been advocated for patients without adverse risk factors. Oral prednisolone (1 mg/kg per day up to 60–80 mg/day and tapering over 9–12 months) ± intravenous methylprednisolone (500

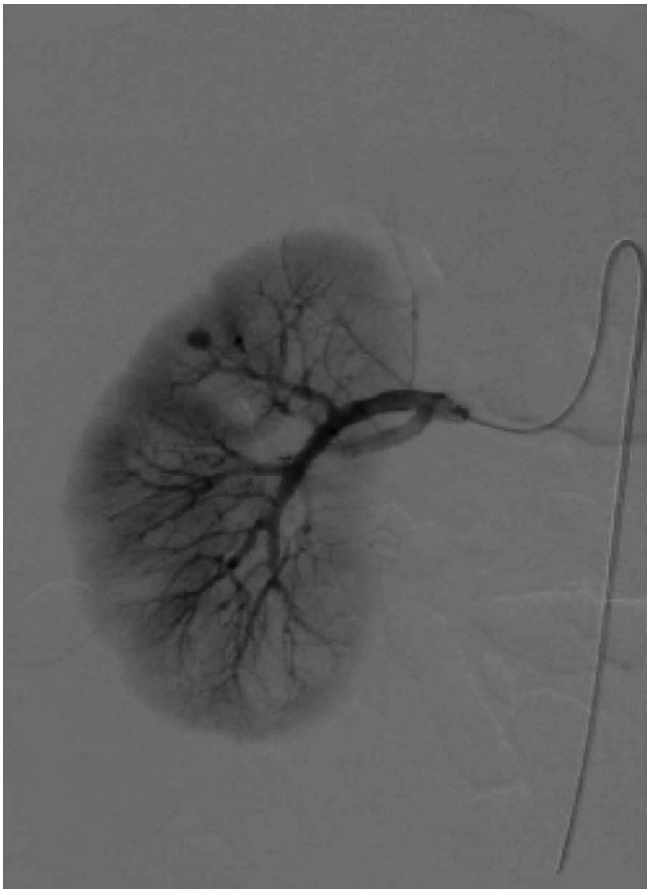

Figure 1 Renal micro-aneurysms in PAN. Image courtesy of Dr Claire Cousins, Addenbrooke's Hospital, Cambridge, UK.

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