Medium vessel vasculitis

Peter Hewins

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 corticosteroid 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 reduce 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; IVIg; Kawasaki's disease; polyarteritis nodosa; systemic vasculitis

Introduction

Medium vessel vasculitis (MVV) predominantly affects medium-sized arteries, defined as the main visceral arteries and their branches, but it can involve arteries of any size.[1] MVV does not involve arterioles, capillaries or venules. The principal MVVs 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.[2,3] The term PAN should not be applied to patients with focal necrotizing glomerulonephritis (FNGN) or other types of capillaritis (including pulmonary capillaritis), who typically have the anti-neutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis (AAV), microscopic polyangiitis (MPA) as defined by the Chapel Hill Consensus Conference nomenclature 2012.[1] In general, PR3- or MPO-ANCA seropositivity is incompatible with PAN, a useful distinction since necrotizing medium and small vessel arteritis can occur in AAV.[4,5]

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.

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Polyarteritis nodosa (PAN)

Epidemiology and pathogenesis

PAN is a rare disease (incidence of 1–2/million) and much less common than other primary vasculitides including AAV.[6,7] It primarily affects individuals of European ancestry but its aetiology is largely unknown.[8] 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.[2] 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 since serum liver enzyme concentrations may be normal. Aggressive immunosuppression without recognition of HBV can cause cirrhosis or hepatocellular carcinoma.[9] More rarely, PAN-like vasculitides occur in hepatitis C infection, HIV infection or associated with other diseases including hairy cell leukaemia and familial Mediterranean fever.[10,11] Cutaneous PAN is a medium and small vessel arteritis limited to the skin that is even less common than systemic PAN in adults but comprises a larger proportion of childhood PAN.[12] Cutaneous PAN is an immune complex disease that can be idiopathic or linked to group A beta-haemolytic streptococcal infection.

Diagnosis

Typically, PAN presents in adults ~50 years and children ~8 years of age.[2,3] Constitutional or musculoskeletal symptoms and skin involvement predominate, but abdominal pain is also frequent (Table 1).[2,3] Mononeuritis multiplex is common in adults. Severe gastrointestinal disease is less frequent but important to identify. HBV-PAN does not have a distinct presentation, but neurological and gastrointestinal disease and hypertension are more frequent than in idiopathic PAN.[2,9] Significant kidney disease (renal impairment with active urinary sediment and albuminuria), pulmonary disease (asthma, infiltrates, nodules, cavities or haemorrhage) and ENT 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 micro-aneurysms (e.g. in kidneys, spleen or liver) on conventional angiography (Figure 1). CT and MR angiography are not sufficiently sensitive. 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 ordinarily undergo kidney biopsy before angiography, since FNGN in SVV remains the most likely cause of these findings. PAN is often patchy and both tissue samples and angiography can be non-diagnostic.

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

Polyarteritis nodosa: major clinical features

Arteritis affecting medium or small arteries (biopsy or micro-aneurysms 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 (occasionally symmetrical polyneuropathy or CNS disease)
Abdominal pain
Gut infarction, haemorrhage or perforation (uncommon but increased mortality)
Hypertension
Testicular pain and orchitis (isolated testicular vasculitis without PAN also occurs)
Retinal vasculitis, uveitis or keratitis (infrequent)
Coronary vasculitis (rare)

Table 1

therapy should reflect disease severity (Figure 2).[8] PAN is typically responsive to corticosteroids and, traditionally, monotherapy has been advocated for patients without adverse risk factors.[8,13] Oral prednisolone (1 mg/kg/day up to 60–80 mg/day and tapering over 9–12 months) ± i.v. methylprednisolone (500–1000 mg for 3 days) can be employed. The 'five-factor score' (FFS) developed for use in patients with PAN and selected SVV has been updated; adverse features are now: age >65, renal insufficiency, cardiac involvement and gastrointestinal manifestations.[14] In PAN, only age and gastrointestinal involvement are independently linked to increased mortality. PAN patients with FFS scores of zero, 1 and ≥2 have 5-year survival rates of 92%, 79% and 60% respectively.[13,14]

Cyclophosphamide is recommended as an adjuvant to corticosteroids where intensification is required although a survival benefit has not been definitively proven.[8,15] Relevant patients include those with gastrointestinal, CNS and cardiac involvement. Additionally, cyclophosphamide is often used to treat mononeuritis multiplex because of the disabling effects of this condition. Patients without adverse features who have failed to respond to corticosteroid monotherapy may also warrant cyclophosphamide. Pulsed cyclophosphamide (15 mg/kg × 6–10 at 2–3 week intervals with dose adjusted for age and/or renal dysfunction) reduces cumulative dosing compared with daily oral therapy. Azathioprine can be adopted as maintenance therapy after cyclophosphamide has induced remission. Anti-tumour necrosis factor (TNF) therapies may be of value in selected patients but there is little evidence base for their use. In contrast to AAV, rituximab has not become established in PAN, nor does its use have an obvious rationale.

Idiopathic PAN is a relapsing disease.[2,8,13] Over 5 years, sustained disease remission occurs in only ~40% of patients treated with corticosteroid monotherapy for baseline FFS = 0.[13]

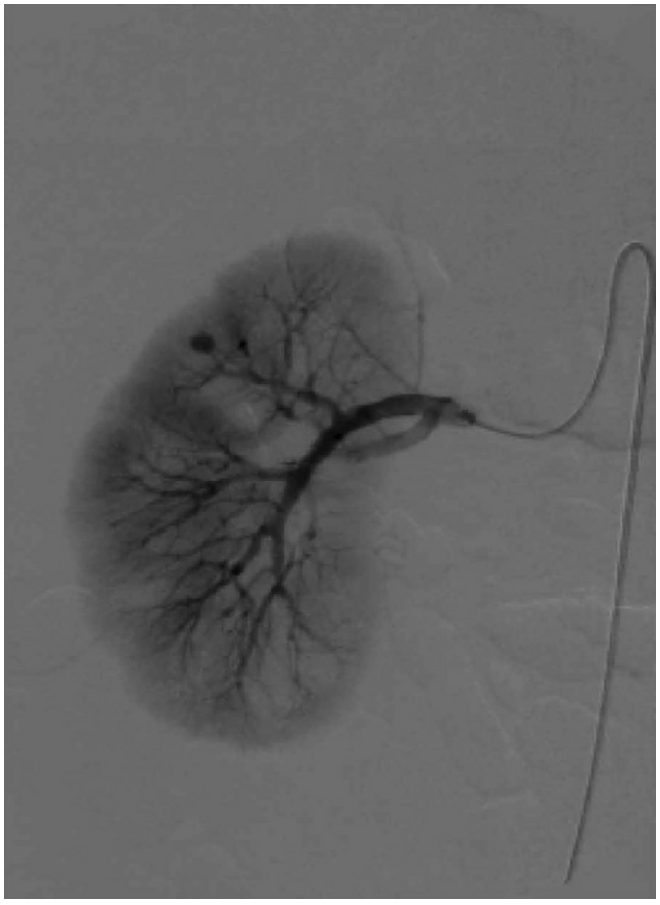

Figure 1 Renal micro-aneurysms in PAN (image courtesy of Dr Claire Cousins, Addenbrooke's Hospital, Cambridge, UK).

A randomized trial (CHUSPAN 2) comparing corticosteroid monotherapy with corticosteroid plus azathioprine in PAN and SSV patients with FFS = 0 has completed recruiting and may influence management of good-prognosis PAN in future (ClinicalTrials.gov: NCT00647166).[8]

HBV-PAN exhibits lower relapse rates but higher mortality than idiopathic PAN (10-year survival rates are 59.6% and 74.0%, respectively).[2] Viral seropositivity is not independently linked to death, but HBV-PAN patients exhibit more severe organ involvement. Antiviral therapy is the mainstay of HBV-PAN treatment, whilst plasma exchange can be used acutely to control vasculitis.[9] Corticosteroids are often administered in HBV-PAN but amplify viral replication. Cyclophosphamide should not be used in HBV-PAN.

NSAIDs, dapsone and hydroxychloroquine are used in cutaneous PAN, but corticosteroids, azathioprine or cyclophosphamide may become necessary to control disease in some patients.[14]

Kawasaki's disease (KD)

Epidemiology

KD is a self-limiting vasculitis, affecting particularly the coronary arteries and complicated by coronary artery aneurysms (CAA) in 15–25% of untreated children (Figure 2).[16,17] Peripheral arteritis can also occur. KD is the leading cause of