Medium vessel vasculitis

Peter Hewins

David Jayne

Abstract

Polyarteritis nodosa (PAN) and Kawasaki disease are primary systemic vasculitides with predominant medium-sized vessel involvement. PAN typically affects muscular arteries causing aneurysms (nodosa) detectable on angiography. There are no specific serological markers and diagnosis depends on clinical presentation, angiography and tissue biopsy. Treatment with corticosteroid and immunosuppressive drugs is usually effective but PAN can pursue a relapsing course. Kawasaki disease affects children, usually under the age of 5 years, and presents as an acute, febrile exanthematous disease. Inflammation and damage of muscular arteries particularly affect the coronary arteries leading to aneurysm formation. Prompt diagnosis and treatment with aspirin and intravenous immunoglobulin have reduced the frequency of this complication. Relapse is rare although vascular damage results in an increased risk of cardiovascular disease later in life. Medium-sized vessels can also be involved in organ-limited vasculitis affecting the skin (cutaneous polyarteritis), gut or brain. Additionally, medium-sized vessels can be involved in vasculitic syndromes defined by the predominant involvement of microscopic or large vessels.

Keywords aneurysm; glucocorticoids; IVIg; immunosuppression; Kawasaki disease; polyarteritis nodosa; systemic vasculitis

Introduction

The term medium vessel vasculitis (MVV) identifies diseases primarily affecting small and medium-sized arteries, but not involving either major branches of the aorta or capillaries. The principal entities are polyarteritis nodosa (PAN) and Kawasaki disease (KD).[1] PAN occurs in both adults and children whereas KD is almost exclusively a childhood disease. Previously, the diagnosis of PAN has been applied to patients with focal necrotizing glomerulonephritis (FNGN). Similarly, the American College of Rheumatology (ACR) classification criteria for PAN did not exclude patients with FNGN.[2] The Chapel Hill Consensus Conference (CHCC) nomenclature, however, defines FNGN and other forms of capillaritis as markers of small vessel vasculitis (SVV), most often microscopic polyangiitis (MPA).[3] The relevance of the distinction is supported by apparently divergent pathogenesis: PR3-ANCA (antineutrophil cytoplasmic antibodies) or MPO-ANCA make PAN improbable and strongly suggest SVV. Two recent classifications (one adult and one paediatric) have emphasized the distinction between PAN and SVV.[4,5]

Involvement of medium-sized vessels can be detected in other vasculitides but these are not classified as MVV since the primary site of injury lies elsewhere. Renal arteritis can occur in ANCA-positive SVV (Wegener's granulomatosis (WG) or MPA) and in type II or III cryoglobulinaemic vasculitis where it is associated with mesangiocapillary glomerulonephritis. Medium vessel vasculitis can also be seen in primary central nervous system (CNS) angiitis, Churg–Strauss syndrome (CSS), Behçet's disease, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and relapsing polychondritis.

Polyarteritis nodosa (PAN)

Pathogenesis

PAN is an uncommon disease (incidence of ~2.5/million in recent reports from Europe) although estimates of prevalence have varied between zero and >30/million.[6–10] Much of this variation is attributable to use of the diagnosis of MPA rather than PAN, but aetiological factors are also relevant. Before the discovery of the hepatitis B virus (HBV), screening of blood products and vaccination programmes, a significant proportion of cases of PAN were HBV-associated, with HBV antigens detectable in deposited immune complexes. Typically, PAN develops within 6 months of HBV infection although diagnosis of hepatitis before the development of vasculitis is by no means commonplace and institution of aggressive immunosuppression without recognition of a viral aetiology can rapidly lead to cirrhosis or hepatocellular carcinoma.[11] Today, HBV-associated PAN is infrequent but it is still important to screen all patients. More rarely, PAN-like vasculitides occur in the context of hepatitis C virus infection, HIV infection or haematological malignancies, particularly hairy cell leukemia, which is more often diagnosed before the onset of vasculitis. The majority of cases of PAN, however, appear to be primary disease and their aetiology remains uncertain.

Diagnosis

Typically, PAN develops in middle-aged or older individuals of European ancestry. Common presentations are weight loss, arthralgia, myalgia, mononeuritis multiplex, gastrointestinal disease (ischaemia, infarction, haemorrhage or perforation), cardiac disease (ischaemic heart disease), hypertension, livedo reticularis and testicular pain.[2,9,12] More severe cutaneous manifestations, including ulceration, also occur in PAN whereas the term 'cutaneous PAN' refers specifically to a limited form of vasculitis, involving arteries in the dermis and subcutaneous tissue, that runs a chronic course but does not progress to a systemic disease. Kidney disease (renal failure, active urinary sediment or significant albuminuria), pulmonary disease (asthma, infiltrates, nodules, cavities or haemorrhage) and ENT disease usually suggest other forms of vasculitis, principally WG, MPA and CSS. Inflammatory markers are typically elevated but tests for ANCA and cryoglobulins are negative while serum complement remains normal. Abnormal liver function tests may signify associated viral hepatitis.

Definitive diagnosis requires demonstration of non-granulomatous necrotizing arteritis in an affected organ (e.g. nerve or

Peter Hewins *PhD MRCP is Consultant Nephrologist in the Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge, UK. Competing interests: none declared.*

David Jayne *MD FRCP is Head of Vasculitis and SLE Services, Addenbrooke's Hospital, and Associate Lecturer in Renal Medicine, University of Cambridge, Cambridge, UK. Competing interests: none declared.*

muscle) or convincing angiographic evidence of micro-aneurysms (e.g. in kidneys, spleen or liver) (Figure 1 and Table 1). Aggressive renal arteritis without glomerulonephritis can occasionally provoke renal failure via cortical infarction or malignant hypertension, but patients with an 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. Like other forms of vasculitis, arteritis in PAN is often patchy and tissue samples can be non-diagnostic. ACR classification criteria have been manipulated for diagnostic purposes but this approach is misconstrued and has an unacceptably low specificity and sensitivity.[13]

Management

In the absence of HBV infection, the intensity of immunosuppressive therapy should reflect organ involvement.[14] PAN is typically responsive to corticosteroids and monotherapy is often sufficient for patients without adverse risk factors. A tapering course of oral prednisolone (starting at 1 mg/kg, 60 mg/day maximum) and supplementary i.v. methylprednisolone (500–1000 mg for 3 days) can be employed. Cyclophosphamide is an effective adjuvant therapy where intensification is required. A 'five-factor score' (proteinuria; renal impairment; CNS involvement; cardiac involvement; and gastrointestinal (GI) involvement) identifies patients with an adverse prognosis: 5-year survival is ~90% when FFS = 0 versus 65% when FFS $\geq$ 2.[15] However, the prominence of glomerular disease parameters in the FFS probably reflects the inclusion of patients with SVV in the original study cohort. Our local practice is to treat patients with mononeuritis multiplex or vasculitis involving the CNS, heart or GI tract with pulsed cyclophosphamide (6–10 IV pulses at 15 mg/kg, maximum 1200 mg adjusted for renal function and age). Azathioprine can be considered as maintenance therapy after cyclophosphamide or as a corticosteroid-sparing agent. Anti-tumour necrosis factor (TNF) therapies (infliximab, adalimumab and etanercept) appear to be of value in selected patients, including those who fail to respond to cyclophosphamide, but there is little evidence base for their use. In patients with HBV-PAN, antiviral therapy is the mainstay of treatment whilst plasma exchange can be used acutely to control the vasculitis.[11] Corticosteroids have been widely administered in HBV-PAN although viral replication will be amplified and caution should be exercised. Historically, relapses were considered to be less common in PAN than in ANCA-positive SVV but more recent data suggest this is true only in HBV-PAN whereas idiopathic PAN does relapse.[9,15] The risks of high cumulative cyclophosphamide exposure are well documented in vasculitis and alternative immunosuppressants may be required for treatment of relapses.

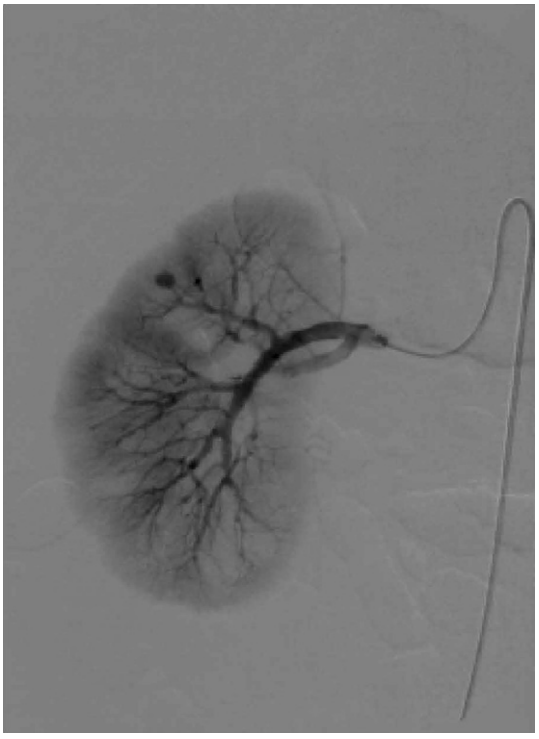

Figure 1 Micro-aneurysms affecting the renal vasculature in PAN (image provided by Dr Claire Cousins, Addenbrooke's Hospital, Cambridge, UK).

Polyarteritis nodosa: major clinical features

Incidence 2.5/million/year
Arteritis affecting medium or small arteries
Micro-aneurysms on angiography
ANCA negative, no cryoglobulinaemia
No evidence of glomerulonephritis or other forms of capillaritis
Hypertension
Neurological involvement (particularly mononeuritis multiplex)
Gastrointestinal vasculitis (infarction, haemorrhage, perforation)
Hepatitis B infection (now in a minority of cases)

ANCA, antineutrophil cytoplasmic antibodies.
See: Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg–Strauss syndrome in a French urban multiethnic population in 2000: a capture–recapture estimate. *Arthritis Rheum* 2004; **51:** 92–9.

Table 1

Kawasaki disease

Kawasaki disease is one of three systemic vasculitides, predominantly involving medium-sized vessels, which affect children – as recognized by the 2005 Consensus Conference of the Pediatric Rheumatology European Society.[5] The other two are childhood PAN and cutaneous polyarteritis. KD is a self-limiting vasculitic syndrome of medium- and small-sized arteries and can be complicated by the development of coronary-artery aneurysms in 25% of untreated patients (Figure 2).[16] Systemic arterial injury can also occur. KD is the leading cause of acquired paediatric heart disease worldwide: it causes myocardial infarction and late coronary-artery disease. The majority of patients are between 3 months and 5 years old. The highest incidence occurs in Japan where it exceeds 120/100,000.[17] The current incidence in the UK is 8/100,000 children.

Pathogenesis

KD is characterized by arteritic lesions at varying stages of progression that begin with endothelial inflammation and proceed to subendothelial oedema and an inflammatory-cell