Polyarteritis nodosa

What is polyarteritis nodosa?

This was the first non-infectious vasculitis to be described and studied in detail,[1] with Kussmaul and Maier's initial case report dating to 1866.[2] The term polyarteritis nodosa (PAN) was adopted in 1992.[3] The current definition of PAN was agreed at the 2012 Chapel Hill Conference:

- PAN is necrotising arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasmic antibodies (ANCAs).[4]

It can affect any organ but, for unknown reasons, it spares the pulmonary and glomerular arteries.[5]

A less severe form called cutaneous polyarteritis nodosa (CPAN) has also been described. Its features include tender subcutaneous nodules, livedo reticularis, cutaneous ulcers and necrosis.[6] It is often associated with streptococcal infection. Although progress to classical PAN at a later stage has been reported, generally it is thought to be unlikely.[7]

How common is polyarteritis nodosa? (Epidemiology)

- PAN's prevalence is approximately 3.1 per 100,000 people.[8]
- It is seen in all ethnic groups and appears to be present throughout the world, although the incidence is higher in areas where hepatitis B is endemic.
- Primary, idiopathic, or 'classical' polyarteritis nodosa is most common.[9]

- Hepatitis B infection is an important cause of secondary polyarteritis nodosa.
- Associations have also been reported with other infectious agents such as group A streptococcus, hepatitis C, HIV and human T cell leukaemia virus 1, but there is a lack of consistent evidence for any specific microbial involvement in idiopathic polyarteritis nodosa.[2] [10]
- A genetic condition, deficiency of adenosine deaminase-2 (DADA2), causes a condition that mimics polyarteritis nodosa, and this is sometimes described as a subtype of the disease. Screening for ADA2 mutations in patients initially considered to have idiopathic polyarteritis nodosa has identified DADA2 in 7% to 31%.[10]
- The average age of onset is approximately 50 years.[2] It can occur, rarely, in childhood, with a mean age at diagnosis of 10 years.[11] [12]
- In both adults and children, males appear to be more commonly affected than females. [10] [12]

Polyarteritis nodosa seems to have become an even rarer disease over time. Historically, polyarteritis nodosa was used to describe any systemic vasculitis of unknown cause; tightening of the diagnostic criteria have contributed to fewer diagnoses being made.[2] Hepatitis B vaccination campaigns and blood transfusion safety measures have substantially reduced the rates of hepatitis B-associated polyarteritis nodosa.[10]

Polyarteritis nodosa symptoms (presentation) [2]

Diagnosis is not easy, as PAN often presents in a vague manner with symptoms including fever, weight loss, headache and myalgia. There is a spectrum of organ involvement ranging from a single organ to multisystem disease.

- Peripheral nerves and skin are the most frequently affected tissues.
- The skin can demonstrate a range of lesions, including purpura, livedoid, subcutaneous nodules and necrotic ulcers.[5]
- Neurologically, mononeuritis multiplex is the most common presentation.

- Involvement of the gastrointestinal tract, kidneys, heart and central nervous system is associated with a higher mortality.[9]
- If there is renal involvement, patients may present with hypertension or acute kidney injury. Renal infarction may produce micro- or macrohaematuria and mild to moderate proteinuria.
- Gastrointestinal symptoms occur in 14-65% of patients and postprandial abdominal pain from ischaemia is the most common symptom.[13] Bowel necrosis and perforation are associated with a poor prognosis.
- Myalgia is reported in 72% of childhood patients.[14]
- The typical presentation in children is one- or two-organ involvement, with constitutional symptoms, and the diagnosis is often based on pathology.[15]

Diagnostic criteria

Diagnosis of polyarteritis nodosa requires the integration of clinical, biopsy, and angiographic findings.

Adult
Historically, these have included the American College of Rheumatology (ACR) and Chapel Hill Consensus criteria.[4] [16] The ACR criteria (10 factors) for classifying a patient with vasculitis within a specific disease entity are useful in clinical practice; however, they were developed before microscopic polyangiitis was reclassified as a separate condition, and make no reference to ANCAs. ANCAs are absent in polyarteritis nodosa, and their presence rules it out.[10]

According to the ACR criteria, polyarteritis nodosa can be diagnosed in a patient with vasculitis if three or more of the following features are present:[16]

- Weight loss greater than 4 kg.
- Livedo reticularis.
- Testicular pain or tenderness.
- Myalgias.

- Mononeuropathy or polyneuropathy.
- New-onset diastolic blood pressure greater than 90 mm Hg.
- Renal dysfunction (blood urea greater than 14.3 mmol/L or creatinine greater than 133 µmol/L).
- Evidence of hepatitis B infection.
- Arteriogram showing the arteries that are dilated or constricted by the blood vessel inflammation.
- On biopsy, presence of granulocyte or mixed leukocyte infiltrate in the wall of a small or medium-sized artery.

Childhood

Classification of childhood PAN requires a systemic inflammatory disease with evidence of necrotising vasculitis or angiographic abnormalities of medium- or small-sized arteries (mandatory criterion) plus one of five criteria:[14]

- Skin involvement.
- Myalgia/muscle tenderness.
- Hypertension.
- Peripheral neuropathy.
- Renal involvement.

Differential diagnosis

As PAN presents with nonspecific symptoms, numerous alternative diagnoses must be considered:

- Fever caused by viral, bacterial and parasitic infections.
- Ulceration due to pyoderma gangrenosum must be excluded (particularly in children).
- Crohn's disease.
- Connective tissue diseases including systemic lupus erythematosus, rheumatoid arthritis, allergic granulomatosis.

- Other vasculitides including giant cell arteritis, Henoch-Schönlein purpura, granulomatosis with polyangiitis, Churg-Strauss syndrome and Kawasaki disease.

Investigations

- Serological testing for hepatitis B, hepatitis C, and HIV should be carried out.
- ANCAs are negative in PAN, and a positive ANCA in the context of necrotising vasculitis strongly suggests an alternative (ANCA-associated) diagnosis, such as microscopic polyangiitis, granulomatosis with polyangiitis, or Churg-Strauss syndrome.[2]
- Inflammatory markers (including ESR and CRP) are elevated - this is nonspecific.
- Biopsy of small arteries will show evidence of necrotising inflammation. Suitable biopsy sites include the skin (including subcutaneous fat with medium-sized arteries); the sural, superficial peroneal, or superficial radial nerves; and muscle. Renal and liver biopsies are best avoided due to a risk of rupture and haemorrhage.[10]
- Arteriography shows microaneurysms in the small-sized and medium-sized arteries of the kidneys and abdominal viscera.[17] Selective renal angiography shows aneurysms in 40% of children.[18]
- FDG-PET/CT is emerging as a potentially useful non-invasive imaging technique for diagnosis.[19]

Associated diseases

Hepatitis B-associated PAN is an important subtype of PAN. The pathogenesis is attributed to immune-complex deposition with antigen excess.[20]

Polyarteritis nodosa treatment and management

Modern trial data are limited, and most current guidelines are based on expert opinion.[21] Therapy depends on the disease's manifestations and severity. The following are taken from the 2021 American College of Rheumatology/Vasculitis Foundation recommendations:[22]

- Newly diagnosed active, severe PAN should be treated with high-dose glucocorticoids plus cyclophosphamide.
- Newly diagnosed, active, nonsevere PAN should be treated with glucocorticoids and other immunosuppressive agents, such as azathioprine or methotrexate.
- Once remission has been obtained, non-glucocorticoid immunosuppressive agents should be continued for 18 months, alongside tapering of glucocorticoid therapy.
- Tumour necrosis factor (TNF) inhibitors appear to be particularly useful in the DADA2 subtype, substantially reducing the risk of stroke.

Management options for other forms of PAN include:

- In patients with active hepatitis B, antivirals and plasma exchanges prevent the development of long-term hepatic complications of hepatitis B viral infection.[20]
- Intravenous immunoglobulin (IV-Ig) and aspirin are effective in childhood PAN but, in resistant cases, either steroid or infliximab has a role.[23]

- In cutaneous polyarteritis nodosa:[6]
    - Mild cases may require only non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine.
    - Prednisolone 30 mg daily or less is often effective in more severe cases but a dosage of 1 mg/kg/day may be required. Unfortunately, exacerbations occur with the tapering of the corticosteroids and adverse effects limit their long-term use.
    - Immunosuppressive agents are frequently effective in CPAN resistant to high-dose corticosteroids and should be reserved for these severe relentless forms.

Complications

Serious complications of polyarteritis nodosa include:[24]

- Stroke.
- Bowel infarction.
- Renal failure.
- Heart failure.
- Encephalopathy.
- Complications of immunosuppressive therapy, such as secondary cancers and opportunistic infections.

Prognosis

Untreated polyarteritis nodosa has a poor prognosis, with a 5-year survival of 13%.

Treatment improves this substantially, with current 5-year survival rates of approximately 80%.[2]

Once remission has been obtained, relapse is relatively uncommon (affecting fewer than 20% of patients).[2] [10]

Prevention

Measures to reduce the incidence of hepatitis B infection, such as vaccination and blood transfusion safety protocols, have made hepatitis B-associated polyarteritis nodosa significantly less common.[10]

Further reading

- Cutaneous polyarteritis nodosa; DermNet NZ

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