Polyarteritis Nodosa (PAN) is a transmural necrotizing vasculitis that affects medium and small-sized arteries. Polyarteritis nodosa is also called Kussmaul disease or Kussmaul-Meier disease.

It is rare in childhood; male to female ratio is 1:1; it has a peak of incidence towards 9 years of age\(^7\), but the incidence and prevalence are not known\(^8\). Polyarteritis nodosa is more common in people with hepatitis B infection.\(^4\)

Etiology is unknown, but it occurs when certain immune cells attack the affected arteries. The presence of IgM and C3 deposits in some cases and of circulating immunocomplexes in others, point towards an autoimmune mechanism: signs and symptoms of this disease are in fact primarily attributable to diffuse vascular inflammation and ischemia of affected organs, probably due to a cytokine dysregulation\(^10\). One hypothesis is that this condition is caused by antibodies against HBV (Hepatitis B Virus), via a type III hypersensitivity reaction.

Histopathologically, PAN is characterized by a segmental, transmural necrotizing inflammation of arteries, most commonly at points of bifurcation and often with the presence of fibrinoid necrosis.

The inflammatory infiltrate contains PMNs and eosinophils, macrophages and lymphocytes.

There is a systemic form (classic PAN), in which any organ can be affected (skin, kidney, peripheral nerves, gut, muscle, testes, heart, and, occasionally, the lung), and a cutaneous form (CPAN), characterized by recurrent episodes of vasculitis limited to skin, muscles and joints, without visceral involvement\(^6\). The clinical appearance is characterized by painful, inflammatory subcutaneous nodules, sometimes ulcerated\(^10\).

These nodules can be isolated or grouped; their color varies from red (initial phase) to blue (during healing phase). The ulcer border is irregular and surrounded by livedo reticularis\(^3\). The presence of fever, anorexia, myalgia, arthralgia or non-destructive arthritis is frequent. There are no specific laboratory tests for diagnosing polyarteritis nodosa. Diagnosis is generally based upon the physical examination and a few laboratory studies that help to confirm the diagnosis:

- CBC (may demonstrate an elevated white blood count)
- ESR (elevated).
- Perinuclear pattern of antineutrophil cytoplasmic antibodies (p-ANCA) - not associated with “classic” polyarteritis nodosa, but is present in a form of the disease affecting smaller blood vessels, known as microscopic polyangiitis or leukocytoclastic angiitis.
- Tissue biopsy (reveals inflammation in small arteries, called arteritis).
- Elevated C-reactive protein.

A patient is said to have polyarteritis nodosa if he or she has 3 of the 10 following signs known as the 1990 ACR (American College of Rheumatology) criteria:

- Weight loss greater than/equal to 4 kg.
- Livedo reticularis (a mottled purplish skin discoloration over the extremities or torso).
- Testicular pain or tenderness. (occasionally, a site biopsied for diagnosis).
- Muscle pain, weakness, or leg tenderness.
- Nerve disease (either single or multiple).
• Diastolic blood pressure greater than 90mmHg (high blood pressure).
• Elevated kidney blood tests (BUN greater than 40 mg/dl or creatinine greater than 1.5 mg/dl).
• Hepatitis B virus tests positive (for surface antigen or antibody).
• Arteriogram (angiogram) showing the arteries that are dilated (aneurysms) or constricted by the blood vessel inflammation.
• Biopsy of tissue showing the arteritis (typically inflamed arteries)\(^9\). It should be underlined that the 1990 ACR criteria were designed for classification purposes only. A biopsy of the lesion showing histopathologic features of cutaneous polyarteritis nodosa is required to establish a precise diagnosis after the exclusion of systemic disease (documented by clinical findings, laboratory tests and instrumental investigations).

Differential diagnosis should be made with other systemic vasculitis such as microscopic polyangiitis, Wegener's granulomatosis and Churg-Strauss syndrome, with vasculitis secondary to infection (Cytomegalovirus, Parvovirus B19, Staphylococcus, Streptococcus, Rickettsiae, Klebsiella, Pseudomonas, Yersinia, Borrelia burgdorferi) and with PAN secondary to haematological or autoimmune diseases. Various diseases that may mimic some clinical aspects of PAN, like atrial myxoma, cholesterol emboli, or infections by Staphylococcus, Gonococcus, Lyme disease, infective endocarditis, malignant neoplasms, ergotism should also be considered in the differential diagnosis. The course is chronic and tends to relapse. Prognosis of the cutaneous form is usually benign\(^1\text{,}^5\) while the systemic form, if untreated is fatal in most cases. Treatment includes medications to suppress the immune system: currently, corticosteroids plus cyclophosphamide is the standard of care for idiopathic PAN, in particular for patients with adverse prognostic factors (more severe disease), in whom this combination prolonged survival. The management of PAN is based on the extent of involvement of target tissues. Corticosteroid therapy has been shown to be beneficial in patients with limited or non-progressive PAN. In rapidly progressive cases that involve the viscera or that cannot be controlled with tolerable doses of prednisone, the addition of cytotoxic agents is necessary (e.g., Cyclophosphamide, Azathioprine, or Metotrexate). The introduction of steroids and Cyclofosfamide results in disease remission in 80% of patients by 3 months and 95% by 6 months.

However, 50% of patients experience disease relapses. Therapy results in remission or cure in 90% of cases. The most serious associated conditions generally involve the kidneys and gastrointestinal tract. When these agents fail, choice of treatment is difficult because appropriately designed trials have not been reported\(^3\). For hepatitis B-related PAN, treatment includes plasmapheresis and antiviral agents. Recent advances in understanding the pathophysiology of the inflammatory response suggest that TNF-\(\alpha\) plays a central role in the pathogenesis of PAN, leading to endothelial and vascular damage, priming neutrophil and endothelial cells\(^6\). Several experiments have demonstrated that there is an increased expression of TNF-\(\alpha\) at sites of vasculitic injury and elevated circulating levels of TNF-\(\alpha\) and TNF-\(\alpha\) receptors during disease activity, that normalize at the time of disease remission\(^7\). Therefore, TNF-\(\alpha\) is a potential therapeutic target.

References


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