166 Childhood Polyarteritis Nodosa

Fatih Ozaltin · Seza Ozen

Definition/Classification

Polyarteritis nodosa (PAN) is a clinical syndrome with a wide variety of signs and symptoms, which are caused by fibrinoid necrosis of small and/or medium-sized arteries. Two disease entities are defined: classical PAN and cutaneous PAN. Microscopic PAN will be discussed in another section. Patients are often classified as PAN based on existing criteria. The recent EULAR/PRINTO/PRES (Ankara) criteria propose the need for a biopsy showing characteristic histological features of PAN or angiography reflecting the mid-size arteritis, as mandatory criteria for the classification of a child as PAN (*Table 166.1*).

Epidemiology

PAN is a rare disease in both children and adults. The disease is seen worldwide. In a large international multicenter study, where 110 patients with PAN were included, it has been reported that mean age at diagnosis was 9.05 ± 3.57 years and that the girl to boy ratio was 56:54.

Etiology, Pathogenesis, and Genetic Background

In most cases, the etiology remains unknown; however, infectious agents have been considered as etiologic or contributing factors. A relationship between hepatitis B infection and PAN has been well described and probably represents an immune complex disease. Streptococcal infections could also be a contributing factor especially in patients with cutaneous PAN.

There is no substantial evidence on genetic predisposition for PAN. Familial occurrence is rare. Recent studies have suggested that PAN is more frequent in patients with familial Mediterranean fever (FMF). It has been suggested that mutations in the gene for FMF provide a susceptibility factor for the development of PAN by forming a proinflammatory state.

Clinical Manifestations

PAN is typically a multisystem disease resulting from vascular inflammation predominantly in skin, abdominal viscera, kidneys, central nervous system (CNS), and muscles. Symptoms may be subtle. However, PAN should be considered in any child with unexplained fever, palpable purpura, myalgia, arthritis, mononeuritis multiplex, or unexplained pulmonary, cardiovascular, or renal disease. Children usually have constitutional symptoms such as fever, malaise, and weight loss. Skin lesions include petechia/purpura, splinter hemorrhages, infarction and ulceration, papules, livedo reticularis, and painful nodules.

Nonspecific abdominal pain occurs in two thirds of patients, usually due to mesenteric and other ischemia caused by vasculitis. Infarction of the gut, gallbladder, or pancreas may develop. Aneurysms of abdominal mid-size arteries have been reported.

Renal involvement (proteinuria, hypertension) has been reported as 45–80%. Renal involvement is classically limited up to the level of spiral arteries, and glomerulonephritis is not seen in this type of PAN.

Clinical findings regarding central nervous system involvement may vary from organic brain syndrome to seizures and hemiparesis. Sensorimotor peripheral neuropathy (mononeuritis multiplex) is quite characteristic.

Cardiovascular involvement including mitral and/or tricuspid valve regurgitation, and impaired left ventricular function may rarely occur.

Testicular or epididymal swelling and tenderness are again rare but important findings for diagnosis in males.

Laboratory Findings

Mild anemia, leukocytosis, thrombocytosis, and elevated acute phase reactants are characteristic features. Autoantibodies are negative and ANCA is frequently negative in this type of PAN.

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Table 166.1
Classification of PAN (Ozen et al. (2010))

Typical histopathology or angiographic abnormality (mandatory) plus one out of five of the following criteria:
1. Skin involvement
2. Myalgia or muscle tenderness
3. Hypertension
4. Peripheral neuropathy
5. Renal involvement

Treatment

Corticosteroids and cyclophosphamide are the mainstay of treatment of systemic necrotizing vasculitides. Oral or intravenous cyclophosphamide is indicated in severe organ involvement. The cumulative dose of cyclophosphamide is a major concern. A number of large studies have shown that a cumulative dose up to 200–250 mg/kg is safe in terms of gonadal toxicity. Azathioprine is used for maintenance treatment.

Prognosis

The prognosis of childhood PAN was guarded in initial series. However, with the judicious use of immunosuppresants, the prognosis, even in children with definite systemic involvement, is better than adults, with reported survival rates.

Cutaneous PAN

Cutaneous PAN (CutPAN) is designated for polyarteritis nodosa limited fundamentally to the skin. It has been described as a distinct clinical entity with benign but relapsing course without systemic involvement. However, there has been much debate on whether or not it can progress to systemic form.

A history of a preceding upper respiratory tract infection, often with streptococcus, is usually present. CutPAN is characterized by purpura, multiple painful subcutaneous nodules, livedo reticularis, and sometimes nonspecific musculoskeletal findings such as myalgia and arthralgia. Constitutional symptoms are not expected to be present and the acute phase reactants are often normal. Nonsteroid antiinflammatory drugs are used in most cases. CutPAN usually responds to short courses of prednisone (0.5–1 mg/kg/day) therapy. Prolonged course and relapses are frequent. Penicillin prophylaxis may be needed if streptococcal infection is implicated as triggering agent. Prognosis is generally good; however, relapses and the chronic course are of concern.

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