Polymyositis

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Creation Date: April 2000
Update: March 2003

Scientific Editor: Professor Loïc Guillevin

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Abstract
Polymyositis (PM) is an inflammatory muscle disease of unknown etiology. Immune disorders are involved to various degrees (according to the type of inflammatory myopathy) in the physiopathogenesis of the disease, as documented by clinical, biological and experimental findings. PM occurs almost exclusively in adults. It is an acquired disorder, even though there may be a predisposing genetic background. Onset may be acute but is more frequently progressive. Clinical signs include proximal muscle weakness (shoulders, arms, thighs), myalgias in 60% of the patients, and possibly inflammation of the pharyngeal muscles responsible for deglutition disorders and requiring emergency hospitalization in specialized units. Other signs, such as arthralgias and palpitations, are less common. Arguments supporting the diagnosis include: clinical findings, sometimes elevated serum muscle enzyme (creatine phosphokinase (CPK) and aldolases) concentrations, , the electromyography tracings and, most importantly, muscle biopsy findings (muscle necrosis, fiber regeneration, diffuse CD8+ T lymphocytes inflitrates) which alone can provide the diagnosis. PM may be associated with other affections, particularly autoimmune diseases, malignancies or viral pathologies, and indeed they should systematically be sought when PM is suspected. PM is a rare connective tissue disease, whose incidence is estimated to be 5-10 cases/million individuals/year with a prevalence of 6-7 cases/100,000 people. Therapeutic management includes immunomodulating agents and physical therapy after the acute inflammatory phase. Corticosteroids are the first-choice treatment, since they are effective on a long-term basis in 60-70% of the patients. In the case of intolerance of or dependence on corticosteroids, or primary or secondary corticoresistance, several immunosuppressants can be tried, with variable efficacy. Many new treatments have recently been used on patients with PM refractory to classical treatments, in particular cyclosporin A and intravenous human polyvalent immunoglobulins. Several clinical, fundamental and therapeutic protocols to treat inflammatory myopathies are currently being assessed.

Keywords
Polymyositis, inflammatory muscle disease, Immune disorders, muscle weakness, inflammation of the pharyngeal muscles, muscle necrosis, diffuse CD8+ T lymphocytes inflitrates, immunomodulating agents.

Introduction

Within primary myositis (or inflammatory myopathies), three main groups can be distinguished, defined according to clinical and immunohistochemical aspects: dermatomyositis (DM), polymyositis (PM) and inclusion body

myositis (IBM). Although these three entities exhibit marked clinical and biological polymorphisms, they have in common an immune dysfunction with inflammatory involvement of striated muscles. Their etiologies, still poorly elucidated, associate environmental and genetic factors. Considerable progress in our understanding and management of these diseases has nonetheless been made in the past few years.

Epidemiology

PM is a rare connective tissue disease, whose annual incidence is estimated to be 5–10 cases/1,000,000 inhabitants with a prevalence of 6–7 cases/100,000 individuals. In the United States, a seasonal character has been reported, notably for certain subgroups of PM. PM preferentially affects females, with a F/M sex ratio of 2/1. It can occur at any age, but primarily affects adults.

Clinical manifestations

Motor deficit

The motor deficit bilaterally, symmetrically and non-selectively affects striated muscle. It is a myogenic deficit, predominantly of proximal muscles, notably the shoulder and pelvic girdles, and cervical muscles. The intensity of the muscle weakness varies from one subject to another, ranging from a simple functional annoyance to a bedridden state. Myalgias, observed in 25–70% of PM patients, can be the major sign. A late mild motor deficit of distal muscles is seen in 25–30% of the patients. Twenty-five to 30% of the patients experience involvement of the striated muscles of the pharynx and the upper part of the esophagus, causing dysphonia, dysphagia and/or deglutition disorders responsible for inhalation pneumopathies that can influence the vital prognosis.

Joint manifestations

Joint manifestations, primarily inflammatory arthralgias and polyarthralgias mainly affecting wrists, knees, shoulders, proximal interphalangeal and metacarpophalangeal joints, occur in 15–30% of the patients with PM. Arthritides are rare, except in the context of an anti-synthetase syndrome.

Cardiac involvement

Cardiac involvement seems to be frequent and is probably underestimated during the course of primary PM. Its frequency varies from 30 to 70% of the patients depending on the criteria applied. Heart disease includes purely electric abnormalities, the most frequent, diverse arrhythmias and, much more rarely, coronary or intramyocardial vasculitis, inflammatory myocarditis and pericarditis. Although clinical cardiac symptoms are seen in only 10–15% of PM patients, they can be responsible for sudden death.

Pulmonary manifestations

Pulmonary manifestations occur in 15–45% of PM patients and can be the result of different mechanisms. Deglutition pneumopathy secondary to pharyngeal muscle involvement is observed in 10–20% of PM patients and represents the second major cause of death after cancers (see Secondary and associated forms). Hypoventilation, as a consequence of weakened respiratory muscles, is seen in 4–8% of the patients. Diffuse interstitial pneumonitis, is the first sign of the disease in 50% of the 10–15% of the patients who develop this manifestation, and sometimes precedes muscular and/or cutaneous signs by several months. It is seen in 50–70% of the patients with anti-synthetase syndrome, which associates, during the course of PM, interstitial pneumopathy, arthritides, Raynaud's phenomenon, and desquamating and splitting hyperkeratosis of the hands. Its appearance compromises the prognosis of PM. Other pulmonary complications are possible [infectious (opportunistic pathogens) or drug induced (methotrexate) pneumonitis].

Complementary examinations

The erythrocyte sedimentation rate is moderately elevated in 50–60% of the patients. Elevated muscle enzyme [creatine (phospho)kinase (CK or CPK), aldolase, lactate dehydrogenase (LDH), transaminases] concentrations attest to muscle necrosis. CPK is the most specific enzyme. Muscle enzymes are elevated in 75–85% of the PM patients. Isolation of CPK isoenzymes MM or MB cannot differentiate possible myocardial involvement, as regenerating muscle fibers secrete the MB isoenzyme.

Rheumatoid factors are positive in 20% of PM patients. Antinuclear and anti-cytoplasm antibodies are present in 30–50% of the patients: antibodies directed against non-specific muscle proteins and antibodies found in numerous autoimmune diseases (anti-ribonucleoprotein (RNP), anti-PM-Scl (scleroderma) anti-Sjögren's syndrome A (SSA), anti-SSB and anti-Ku antibodies). The antibodies most specific to PM can be divided into two major groups of clinical-epidemiological-immunological entities:

- anti-cytoplasm antibodies directed against aminoacyl-tRNA synthetase, which enables each amino acid to bind to its corresponding tRNA during protein synthesis. These antibodies are: anti-Jo1 (histidyl RNA), PL7 (threonyl tRNA), PL12 (alanine tRNA), OJ

(isoleucil tRNA) and EJ (glycyl tRNA). They are found in 10–30% of PM patients, and constitute the anti-Jo1 or anti-synthetase syndrome;
- anti-cytoplasm anti-SRP (signal recognition particle) antibodies are detected in 5% of PM cases associated with myocarditis. This subgroup, poorly responsive to treatment, seems to have a more dismal prognosis (25% survival at 5 years).

Electromyography is able to detect anomalies in clinically affected regions suggestive of the diagnosis (myogenic changes with lower spontaneous activity(low amplitude SA), short-duration motor unit potentials(MUAPs) with polyphasic potentials and short-duration and low-amplitude and polyphasic MUAPs). Furthermore, it is able to objectively demonstrate two important negative signs: the absence of a neurogenic aspect and the normality of the nerve conduction velocity.

Histology and immunohistochemistry

A muscle biopsy can confirm the diagnosis. Certain histological anomalies are common to PM and DM; others are more specific and now can distinguish histologically between the two entities. The shared muscle anomalies typically associate: foci of focal muscle fiber necrosis, foci of regenerating muscle fibers at different stages of regeneration, and inflammatory mononuclear cell infiltrates. The sites of cellular necrosis and inflammatory infiltrates, the possible presence of endothelial lesions and the types of mononucleated cells vary according to the type of myositis.

In PM, the inflammatory infiltrates are mainly located in perinecrotic endomysial regions, with no vascular topography, and contain rare B and CD4+ T cells, but with a predominance of cytotoxic CD8+ T cells and macrophages. CD8+ lymphocytes surround and focally destroy muscle fibers in non-necrotic zones, send spike-like processes into non-necrotic mmuscle fibers, which traverse the basal lamina and focally displace or compresse the muscle fibers. In contrast to DM, microangiopathy, immunoglobulin deposits, immune complexes and ischemic myocytic lesions are not seen. Myocyte destruction is associated with a granular exocytosis phenomenon and the release of perforin by CD8+ cytotoxic lymphocytes in contact with the myocytes. These observations suggested primary involvement of muscle fibers mediated by a cellular cytotoxicity mechanism, selectively directed against myofibrils in PM in adults (no juvenile form described).

Secondary or associated forms of PM

PM is associated with a malignancy in 15–20% of PM patients. And this association is more frequent after 40 years of age. Overlap syndromes and chronic PM do not have a paraneoplastic profile. PM precedes the appearance of the cancer in 70% of the patients.The mean interval between the two diseases is usually less than 1 year. In women, breast, uterine and ovarian cancers are the most common, whereas in men, bronchial epithelial tumors, prostate and digestive tract cancers predominate. The usual lack of parallel evolution of the muscle and malignant pathologies excludes myositis as paraneoplastic syndromes.

The association of a connective tissue disorder characterizes the overlap syndromes. These syndromes affect 10–20% of all PM patients. Scleroderma, Goujerot–Sjögren's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, thryroiditides and primary biliary cirrhosis are the main diseases encountered.

It was postulated that certain enteroviruses, notably Coxsackie B or A19, or Echo virus might trigger PM, primarily in hypogammaglobulinemic patients. However, the polymerase chain reaction (PCR) search for the enterovirus genome never confirmed that hypothesis. More recently, PM have been observed during the course of human immunodeficiency virus (HIV) or human T-lymphocyte virus-1 (HTLV-1) retrovirus infections. Numerous observations of PM induced by certain medications, mainly D-penicillamine and cimetidine or rantitidine, antalgesics (pentazocine), silicone or collagen implants, and certain toxins (cyanoacrylate glues, silica exposure) have been reported. D-Penicillamine is the main medication inducing PM.

Prognosis

Before the era of corticosteroids, myositis PM was a particularly severe disease, whose spontaneous survival rate was less than 40%. In the absence of an underlying malignancy, PM in adults now has a relatively favorable prognosis, with a 5-year survival rate of around 90%. However, only 30–50% of the patients achieve complete recovery, with the majority of patients having a persistent functional deficit.

Treatment

High-dose corticotherapy (1 mg/kg/d of prednisone) constitutes the first-line treatment, which is active in more that 70% of PM patients. Clinical efficacy is slow, with up to 3 months of therapy needed to see improvement. These high doses must be maintained until all clinical signs regress and clear-cut diminution (or even normalization for certain authors) of the muscle

enzyme values is obtained. Only then can slow tapering of the corticosteroid dose be initiated, at a maximum of 10% of the prescribed dose every 15 days, based on evaluation of motor recovery and muscle enzyme values. This decrease should be pursued until the minimal effective dose to be maintained is reached. A clinical relapse should always bring to mind the possibility of an adjunctive myopathy, notably cortisone-induced. Methylprednisolone pulses, prior to oral corticotherapy, even though frequently used in clinical practice, have never been scientifically proven to be effective.

In the case of primary or secondary resistance to, intolerance of or dependence on corticosteroids, different therapeutic alternatives can be attempted. Immunosuppressants are the most prescribed as second-line agents, notably azathioprine and methotrexate, whose efficacy has only been reported in open, non-comparative studies. The authors of several open trials found oral azathioprine, at doses of 2–3 mg/kg/d, to have efficacy in 50% of the PM patients. Methotrexate, administered as weekly intramuscular or intravenous injections of 0.4–0.6 mg/kg/week, has been effective in 50–70% of patients included in published series. Methotrexate seems to be superior to azathioprine in certain subgroups of PM associated with anti-synthetase syndrome. Cyclophosphamide in combination with prednisone has obtained limited success in some PM patients with interstitial pneumopathy. Several small open studies have shown cyclosporine A to be active in 50–70% of PM cases resistant to first-line corticosteroids. Its efficacy seems to better against DM in children. Intravenous immunoglobulins (IVIg) have recently been reported to be active in corticoresistant PM, with their efficacy being estimated at 60–70% of PM. IVIg are given monthly at a dose of 2 g/kg. They are currently prescribed as an alternative to immunosuppressants or when the latter fail. IVIg are extremely well tolerated but their used must be carefully weighed in light of their human biological origin and their high cost.

The occurrence of deglutition disorders imposes that oral intake of food be stopped and enteral or parenteral feeding be initiated with monitoring in intensive care. Prevention of inhalation pneumopathies, physical therapy (passive and mild during inflammatory crises) and ergotherapy are essential for the management of these patients.

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