Dermatomyositis

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Abstract

Dermatomyositis (DM) is an inflammatory muscle disease of unknown etiology. Immune disorders are involved to various degrees (depending on the type of inflammatory myopathy) in the physiopathogenesis of the disease, as documented by clinical, biological and experimental findings. DM occurs at all ages, with, however, two small peaks in frequency: between the ages of 5 and 14 years, when DM is almost exclusively observed, and after 40 years. It is an acquired disorder, even though there may be a predisposing genetic background. Onset is often acute but may be progressive. Clinically, DM is defined by characteristic skin symptoms (photosensitive erythroedema on exposed areas), muscle weakness, inflammation of the pharyngeal muscles causing 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, serum muscle enzymes (creatine phosphokinase (CPK) and aldolases) are often but not always elevated, the electromyogram tracings and, most importantly, muscle biopsy results showing myolysis of ischemic origin, necrosis, regeneration, perivascular B and CD4 inflammatory infiltrates and endothelial membrane attack complex deposits, which alone can confirm the diagnosis. DM may be associated with other affections, especially autoimmune diseases, malignancies (essentially breast, uterine or ovarian cancer in women, whereas bronchial epithelium, prostate or digestive tract tumors in men ) pathologies, and indeed they should systematically be sought when DM is suspected. Therapeutic management includes immunomodulating treatments and physical therapy, once the acute inflammatory phase is over. DM is a rare connective tissue disease, with estimated incidence of 5-10 cases/million inhabitants/year and prevalence of 6-7 cases/100,000 people. Corticotherapy is the first-choice treatment, since it is effective on a long-term basis in 60-70% of the patients. In cases of corticosteroid intolerance or dependence, or primary or secondary corticosteroid resistance, several immunosuppressants can be prescribed, with variable efficacy. Many new treatments have recently been used for patients with DM refractory to classical treatments, in particular cyclosporin A and intravenous human polyvalent immunoglobulins. Several clinical, fundamental and therapeutic protocols applied to inflammatory myopathies are currently being assessed.

Keywords

Dermatomyositis, inflammatory muscle disease, skin symptoms, muscle weakness, inflammation of the pharyngeal muscles, elevated CPK, perivascular B and CD4 inflammatory infiltrates, immunomodulating treatments
Introduction
We can distinguish, within primary myositis (or inflammatory myopathies) three main groups, 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 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
DM are rare connective tissue diseases, whose annual incidence is estimated to be 5–10 cases/1,000,000 inhabitants and its prevalence at 6–7 cases/100,000 individuals. A seasonal character has been reported, notably for certain subgroups of myositis in the United States. DM preferentially affect females, with an F/M sex ratio of 2/1. These diseases can arise at any age, with two small peaks of their frequency: 5–14 years of age and adults in their 5th or 6th decade.

Clinical manifestations
Cutaneous signs
DM are characterized by cutaneous signs that can sometimes precede the myositis by several months or years. The main sign is photosensitive erythroedema occurring predominantly on exposed areas. Orbital erythema like frames of glasses (predominantly lilac-colored upper eyelid) is almost pathognomonic. Myxedematous lichen flat (Gottron) papules are present in 30% of the patients, in the form of erythematous or violaceous plaques on the dorsal surface of interphalangeal and metacarpophalangeal joints and, more rarely, on elbows and knees. Finally, periungual erythema, painful to pressure (manicure sign), is highly suggestive of the diagnosis. Other cutaneous manifestations are possible: calcinosis, vasculitis, Raynaud’s phenomenon.

Motor deficit
The motor deficit affects striated muscles bilaterally, symmetrically and non-selectively. This myogenic deficit predominantly involves proximal muscles, notably shoulder and pelvic girdles, and cervical muscles. The intensity of the muscle weakness varies from one subject to another, ranging from simply annoying to a bedridden state. Myalgias, observed in 25–70% of the DM patients, can be the dominant symptom. A late and mild motor deficit of the distal muscles is seen in 25–30% of the patients. Involvement of the pharyngeal musculature (25–30% of the patients) concerns striated muscles of the pharynx and the upper part of the esophagus, and is responsible for dysphonia, dysphagia, deglutition disorders and pulmonary aspiration affecting the vital prognosis.

Joint manifestations
Joint manifestations are present in 15–30% of the patients with DM. The most common are: inflammatory polyarticular arthralgias primarily affecting wrists, knees, shoulders, and proximal interphalangeal and metacarpophalangeal joints. Arthritis are unusual.

Cardiac involvement
Cardiac involvement appears to be frequent and is probably underestimated. Clinical cardiac symptoms are seen only in 10–15% of DM patients, but nonetheless can be responsible for sudden death. Several types of cardiac manifestations have been reported: the most common are pure conduction abnormalities, diverse arrhythmias and, much more rarely, coronary or intramyocardial vasculitis, inflammatory myocarditis and pericarditis.

Pulmonary manifestations
occur in 15–45% of the DM patients and can be the result of different mechanisms. Aspiration pneumopathy secondary to pharyngeal involvement is seen in 10–20% of the patients and represents the second main cause of death after cancers (see Secondary or associated forms). Hypoventilation because of respiratory muscle weakness is observed in 4–8% of the patients. Diffuse interstitial pneumonitis is the first sign in 50% of the 10–15% of the patients who develop this manifestation, and sometimes precedes muscle and/or cutaneous signs by several months. It is observed in anti-synthetase syndrome, which is rare in DM compared to polymyositis (see chapter). Other pulmonary complications are possible [infectious ( opportunistic pathogens) or drug-induced pneumonitis, (methotrexate)].

Complementary examinations
The erythrocyte sedimentation rate is usually moderately elevated in 50–60% of DM patients. Muscle enzymes (creatine phosphokinase, CK or CPK), aldolase, lactate dehydrogenase (LDH), transaminases) attest to the muscle necrosis. CPK is the most specific enzyme. Muscle enzymes are elevated in 75–85% of PM/DM. Isolation of CPK isoenzymes MM or MB does not distinguish possible myocardial involvement (regenerating muscle fibers secrete isoenzyme MB).

Rheumatoid factors are positive in 20% of the PM/DM. Antinuclear and antineutrophil 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). Antinuclear antibodies directed against a 220-kDa protein of the nuclear complex – anti-Mi-1 and Mi-2 antibodies – seem to be specific to DM. These antibodies are seen in 5–10% of patients with highly corticosensitive classical DM, which has an excellent prognosis. Anti-synthetase antibodies are rare during the course of DM.

Electromyography can 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). It can also objectively demonstrate two important negative signs: absence of a neurogenic aspect and normal nerve conduction velocities.

**Histology and immunohistochemistry**

The histological aspect of a muscle biopsy can provide the diagnosis. Certain histological anomalies are common to PM and DM, while others are more specific and can now be used to distinguish histologically 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. The histological muscle anomalies of DM typically constitute zones of myolysis of ischemic origin with perifascicular atrophy, microinfarction and ischemic vacuoles in the specimen. The lesions and inflammatory infiltrates are mainly located in perivascular areas with a clear predominance of B and CD4+ lymphocytes, as compared to CD8+ T cells. In the perivascular zones predominantly infiltrated by B and CD4+ T cells, capillary endothelial cell lesions are characteristically seen, with destruction of the capillary endomysium, rarefaction of the vascular tree, with a diminished number of capillaries, arterioles and venules. In addition, microthrombi of the small intramuscular vessels, with intravascular deposits of IgG/IgM and or C3 immune complexes and, especially, membrane attack complex (MAC) C5b–9. Myocytes are the site of ischemic lesions with perifascicular myocytic atrophy, microinfarcts and ischemic vacuoles in the specimen (repetition), attesting to primary involvement of the capillaries mediated by a humoral mechanism and responsible for muscle ischemia in DM.

**Secondary or associated forms**

An association between DM and a malignant pathology is found in 15–20% of DM patients. It is more frequent after 40 years of age. Overlap syndromes and juvenile DM do not have a paraneoplastic context. DM precedes the appearance of cancer in 70% of the patients. The mean interval between the onset of the two entities is usually less than 1 year. The malignancy is essentially breast, uterine or ovarian cancer in women, whereas bronchial epithelium, prostate or digestive tract tumors predominate in men. The frequent absence of parallel evolutions of the muscle and malignant pathologies means that DM cannot be considered paraneoplastic syndromes. Cancer is the primary cause of death of adult DM patients, imposing an exhaustive etiological search in patients over 40 years diagnosed with a DM. Association with a connective tissue disease characterizes overlap syndromes. These syndromes represent 10–20% of all DM, with the major associated affections being: systemic sclerosis, Goujerot–Sjögren’s syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), thyroiditides or primary biliary cirrhosis.

**Prognosis**

Before the era of corticotherapy, DM were considered particularly severe affections, for which the spontaneous survival rate was less than 40%. In the absence of an underlying malignancy, adult DM now constitute diseases with relatively favorable prognoses, with a 5-year survival rate around 90%. For children, the vasculitides of DM can be responsible for very severe complications, such as perforations or hemorrhages. The prognosis of disseminated calcinoses is generally pejorative, with progressive aggravation in the majority of cases or, at best, stabilization with residual disability despite different therapies.

**Treatment**

High-dose corticotherapy (1 mg/kg/d of prednisone) constitutes the first-line treatment, which is active in more that 70% of DM. Clinical efficacy is slow, with delayed improvement possible up to 3 months after the start of therapy. In the case of initial failure, increasing the dose to 1.5 or even 2 mg/kg/d is useful in children. 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. The slow tapering of the corticosteroid dose can then 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 proven to be effective in a randomized trial. 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 frequently prescribed second-line agents, notably azathioprine and methotrexate, whose efficacies have 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 DM patients. Methotrexate, administered as weekly intramuscular or intravenous injections of 0.4–0.6 mg/kg, has been effective in 50–70% of patients included in published open studies. Cyclophosphamide in combination with prednisone has obtained limited success in some DM patients with interstitial pneumopathy. Several small open studies have shown cyclosporine A to be active in 50–70% of DM resistant to first-line corticosteroids. Its efficacy seems to better against DM in children. Intravenous immunoglobulins (IVlg) have recently been reported to be active in corticoresistant DM, with their efficacy being estimated at 60–70% of those treated DM. IVlg are given monthly at a dose of 2 g/kg. They are currently prescribed as an alternative to immunosuppressants or when the latter fail. IVlg are extremely well tolerated but their used must be carefully weighed in light of their human biological origin and their high cost. Clinical attenuation of DM symptoms under IVlg is accompanied by reduction of intravascular MAC C5b–9 deposits, less myocyte expression of major histocompatibility complex (MHC) class I antigens and increased vascular density in biopsies taken after IVlg therapy. However, IVlg seem to be less effective as first-line treatment. Plasma exchanges can be indicated for acute, severe and refractory DM, systematically in combination with an immunosuppressive agent or IVlg to prevent any rebound phenomenon when they are stopped. Hydroxychloroquine can be useful for DM cutaneous lesions but has no activity on muscle manifestations. 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.

References
