CHAPTER 9

Clinical Features, Pathogenesis, Diagnosis, and Treatment of the Inflammatory Myopathies

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The inflammatory myopathies comprise three major and distinct subsets: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) (1–8). Although the presence of moderate to severe muscle weakness and endomysial inflammation are common features in all these conditions, unique clinical, immunopathologic, and histologic criteria along with different prognosis and response to therapies characterize each subset.

The cause of PM, DM, and IBM is unknown, but an autoimmune pathogenesis is strongly implicated based on their association with other putative or definite autoimmune diseases or viral infections, evidence of T-cell–mediated myocytotoxicity and complement-mediated microangiopathy, and their varying response to immunotherapies (1–8). In IBM, autoimmune features coexist with degenerative signs consisting of vacuolization, amyloid deposition, and mitochondrial abnormalities. This chapter reviews the main clinical and histologic features of these diseases, their association with autoimmune conditions or viruses, and the underlying immunopathology. It also provides a practical approach to immunotherapeutic interventions.

CLINICAL FEATURES

Dermatomyositis

DM occurs in both children and adults. It is a distinct clinical entity identified by a characteristic rash accompanying or, more often, preceding the muscle weakness. The skin manifestations include blue-purple discoloration on the upper eyelids or heliotrope rash with edema, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption or Gottron rash that later results in scaling of the skin. An erythematous rash also occurs on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest, often in a “V” sign, or on the back and shoulders, the so-called shawl sign; the latter can be exacerbated after exposure to the sun. In some patients the rash is pruritic, especially in the scalp, chest, and back. Dilated capillary loops at the base of the fingernails are characteristic of DM. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular dirty horizontal lines, resembling mechanic’s hands. The degree of weakness can be mild, moderate, or severe, leading to quadraparesis. At times, the muscle strength appears normal, hence the term “dermatomyositis sine myositis.” When muscle biopsy is performed in such cases, however, significant perivascular and perimysial inflammation is seen (9) (Fig. 1). In children, DM resembles the adult disease, except for more frequent extramuscular manifestations. A common early abnormality in children is “misery,” defined as an irritable child that feels uncomfortable, has a red flush on the face, is fatigued, does not feel well to socialize, and has a varying degree of proximal muscle weakness. A tripod gait due to flexion contracture of the ankles is also common. DM usually occurs alone or with systemic sclerosis and mixed connective tissue disease (1,2). Fasciitis and skin changes similar to those found in DM occurred in patients with the eosinophilia-myalgia syndrome associated with the ingestion of contaminated L-tryptophan (1,2).

Polymyositis

The actual onset of PM cannot be easily determined. Unlike in DM, in which the rash secures early recognition, patients with PM do not have unique heralding clinical features. In retrospect, affected patients present with subacute proximal muscle weakness and myalgia that
exists for several months before they seek medical advice. In our judgement, the diagnosis of PM is one of exclusion. It is best diagnosed and defined as an inflammatory myopathy that develops subacutely, usually over weeks to months, and progresses steadily. PM occurs in adults without evidence of a rash, involvement of the extraocular and facial muscles, family history of a neuro-

The disease, history of exposure to myotoxic drugs or toxins, endocrinopathy, neurogenic disease, dystrophy, biochemical muscle disorder, or IBM as determined by muscle enzyme histochemistry and biochemistry (Fig. 2). PM can be viewed as a syndrome of diverse causes that occurs separately or in association with systemic autoimmune or connective tissue diseases and certain known


FIG. 2. Polymyositis. A: A longitudinal section of muscle shows intense cellular infiltration within the fascicle. B: Immunocytochemical staining reveals that the infiltrating cells invading the muscle fiber are mostly CD8+ T cells.
viral or bacterial infections. Other than d-penicillamine and zidovudine, in which the myopathy has endomyal inflammation, myotoxic drugs, such as emetine, chloroquine, steroids, cimetidine, ipecac, and lovastatin, are not a cause of PM. Instead, they can elicit a toxic noninflammatory myopathy that differs histologically from PM and does not require immunosuppressive therapy (1,2).

The animal parasites Toxoplasma, Trypanosoma, cysticerci, and trichinae may produce a focal or diffuse inflammatory myopathy known as parasitic PM. A suppurative myositis, known as tropical PM or pyomyositis, is caused by Staphylococcus aureus, Yersinia, Streptococcus; and other anaerobes. Pyomyositis is seen in rare patients with AIDS. Certain bacteria, such as Borrelia burgdorferi of Lyme disease and Legionella pneumophila of legionnaire’s disease, are an infrequent cause of PM.

Inclusion Body Myositis

IBM affects men more often than women and is the most frequently acquired myopathy in men over age 50 years. It is commonly suspected in patients with presumed PM that do not respond to corticosteroid therapy. The involvement of distal muscles, especially foot extensors and deep finger flexors, which occurs in almost all patients, is a valuable clue to the early clinical diagnosis of IBM (1-7,10). Some patients present with falls and buckling of the knees due to proximal leg weakness. Others present with weakness in the small muscles of the hands, especially finger flexors, and complain of inability to hold certain objects such as golf clubs, play the guitar, turn keys, or tie knots. The weakness and accompanying wasting is often asymmetric with selective involvement of the quadriceps, iliopsoas, triceps, biceps, and finger flexor muscles of the forearm. Dysphagia occurs in up to 60% of patients, especially late in the disease. A lower motor neuron neurogenic disorder may be suspected, especially when the serum creatine kinase (CK) is not elevated. Sensory examination may be normal or show age-related vibratory sensory loss at the ankles. Contrary to early suggestions, distal weakness is not on a neurogenic basis but is a feature of the distal myopathy as shown by macroelectromyography (11). In contrast to PM and DM in which facial muscles are typically spared, mild facial muscle weakness occurs in 60% of patients with IBM (10). The diagnosis is always confirmed when the muscle biopsy shows the characteristic histopathologic changes (Fig. 3).

IBM can be associated with systemic autoimmune or connective tissue diseases in at least 20% of the cases. Inherited cases are often recessively transmitted and less frequently dominantly inherited, sometimes in association with leukoencephalopathy and others with quadriiceps sparing. Hereditary IBM includes a variety of still ill-defined vascular distally greater than proximal myopathies with a clinical profile that differs from the sporadic IBM cases described above (12). Hereditary IBM with sparing of the quadriceps occurs not only in Iranian Jews but in other ethnic groups (13). Detailed description and genetic data on hereditary IBM are not provided in this review because these diseases lack inflammation in their muscles and do not represent a true inflammatory myopathy. There is, however, a subset of patients with familial IBM that have the typical phenotype of sporadic IBM with histologic and immunopathologic features identical to the sporadic form (14).

The progression of IBM is slow and steady, with a degree of disability that is generally related to the duration of the disease, although this has not been systematically studied. A review of 14 randomly chosen patients with symptoms for more than 5 years revealed that 10 required a cane or support for ambulation by the fifth year after onset of dis-

**FIG. 3.** Inclusion body myositis. **A:** A transverse section of muscle shows rimmed vacuoles and small atrophic fibers among big-size fibers. **B:** Characteristic filamentous inclusion seen by electron microscopy in the cytoplasm within one vacuole of myonuclei.
ease, whereas 3 of the remaining 5 with symptoms for 10 years or more required use of a wheelchair. Using quantitative muscle strength testing, we found a 10% drop in muscle strength over a 2-year period. In other studies from our institution, 86 consecutively studied patients showed progression that was faster with late disease onset. The patients whose disease begins in the sixth decade may require assistive devices at a statistically significant later time than those with disease onset in the eighth decade.

EXTRAMUSCULAR MANIFESTATIONS

In addition to the primary disturbance of skeletal muscles, there may be prominent extramuscular manifestations in patients with inflammatory myopathy: dysphagia, most prominent in IBM and DM, due to involvement of striated muscles of the oropharynx and distal esophagus; cardiac abnormalities consisting of atrioventricular conduction defects, tachyarrhythmias, low ejection fraction, and dilated cardiomyopathy alone or associated with hypertension or long-term steroid use; and respiratory involvement, resulting from weakness of chest-cage muscles, drug-induced pneumonitis as for example from methotrexate or interstitial lung disease. Interstitial lung disease can precede the myopathy or occur as an associated feature, overall in up to 10% of patients with PM or DM, most of whom have antinuclear antibodies. The latter may be at times associated with increased fatigue resulting from adult respiratory distress syndrome in those with PM (15), emphasizing the diagnostic importance of these antibodies. Pulmonary capillaritis with varying degree of diffuse alveolar hemorrhage has also been described (16). Subcutaneous calcification, sometimes extruding on the skin and causing ulceration and infection, are found in children and some adults with DM (17). Gastrointestinal ulceration, seen more often in children with DM, is due to vasculitis and infection. Joint contractures are seen, especially in children with DM. General systemic disturbances are seen, such as fever, malaise, weight loss, arthralgia, and Raynaud's phenomenon, when the inflammatory myopathy is associated with a connective tissue disorder. Malignancy is also manifested with increased frequency in those with DM but not PM or IBM. Because tumors are usually uncovered not by a radiologic blind search but by abnormal findings on their medical history and physical examination, it is our practice to recommend only a complete annual physical examination, with breast, pelvic, and rectal examinations; urinalysis; complete blood cell count; blood chemistry tests; and a chest x-ray film.

DIAGNOSIS

The diagnosis of clinically suspected PM, DM, or IBM is confirmed by examination of serum muscle enzymes and compatible findings on electromyography and muscle biopsy.

Serum Muscle Enzymes

The most sensitive serum enzyme is CK, which in the presence of active disease can be elevated sometimes 50-fold or more. Although the CK usually parallels the disease activity, it can be normal in active DM and rarely even in active PM. In IBM, serum CK is usually elevated not more than tenfold, and in some cases may be normal even from the outset of the illness. The CK may also be normal in patients with untreated, even active, childhood DM and in some with PM or DM associated with a connective tissue disease, reflecting the concentration of the pathologic process in the intramuscular vessels and the perimysium. Along with CK, serum aspartate and alanine aminotransferases, lactate dehydrogenase, and aldolase levels may be elevated.

Electromyography

Electromyographic studies are generally useful for excluding neurogenic disorders and confirming either active or inactive myopathy. Needle electromyography shows myopathic potentials characterized by short-duration low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. This pattern also occurs in various acute and active toxic myopathic processes and should not be considered diagnostic for inflammatory myopathy. Polyphasic units of short and long duration suggestive of mixed myopathic and neurogenic disease are more often seen in IBM, but they can be seen in both PM and DM as a consequence of muscle fiber regeneration and the chronicity of the disease. With macroelectromyography, neurogenic involvement alone is not found in IBM (11).

Muscle Biopsy

Muscle biopsy is a potentially definitive test not only to establish the histologic diagnosis of DM, PM, and IBM, but also to exclude other morphologically distinct processes (Figs. 1–3). Although the presence of inflammation is the histologic hallmark for these diseases, there are additional unique histologic features characteristic for each group.

In DM, the endomysial inflammation is predominantly perivascular or in the interfascicular septae, around rather than within the muscle fascicles. Intramuscular blood vessels show endothelial hyperplasia with tubuloreticular profiles, fibrin thrombi especially in children, and obliteration of capillaries (1–6). There is muscle fiber necrosis, degeneration, and phagocytosis, often in groups, involving a portion of a muscle fascicle in a wedge-like shape or at the periphery of the fascicle due to microinfarction. The latter results in perifascicular atrophy, characterized by two to ten layers of atrophic fibers at the periphery of the fascicles (Fig. 1).