CHAPTER 18

Idiopathic Inflammatory Myopathies
A. Clinical Features

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- Idiopathic inflammatory myopathies (IIM) is a heterogeneous group of disorders characterized by chronic inflammation of striated muscle and skin.
- Painless proximal muscle weakness with or without rash is the hallmark feature.
- Increased serum muscle enzymes, muscle biopsy, electromyography (EMG), and magnetic resonance imaging (MRI) can assist in the diagnosis.

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders characterized by symmetric proximal muscle weakness and elevated serum levels of enzymes derived from skeletal muscle. These include creatine phosphokinase (CPK), aldolase, aspartate, and alanine aminotransferases (AST and ALT), and lactate dehydrogenase (LDH). In addition, electromyography (EMG), magnetic resonance imaging (MRI), and muscle histology show changes indicative of nonsupparative inflammation (Table 18A-1) (1).

Today several diseases are included among the IIM (Table 18A-1). The term *polymyositis* refers to patients characterized by the criteria listed above. The term *dermatomyositis* refers to patients who fulfill the criteria for polymyositis but also have a rash. When this occurs in children, the term *juvenile dermatomyositis* (JDM) is employed (2). Further, there is a subset of patients who have the cutaneous manifestations of dermatomyositis but are otherwise normal (good strength and normal enzymes, EMG, and histology), a condition termed *amyopathic dermatomyositis*. The findings of polymyositis or dermatomyositis can be seen in patients with another collagen vascular disease, such as systemic lupus erythematosus (SLE) or scleroderma, or associated with a malignancy. Inclusion body myositis (IBM) occurs in the elderly and is characterized by a polymyositislike presentation (although the specific muscles involved are more variable) and a characteristic histology which includes rimmed vacuoles. Patients with an IIM can be further categorized by the presence or absence of a circulating myositis-specific autoantibody (MSA) (3).

Despite the fact that patients with an IIM share the stated features, the presentations of the different myositis syndromes vary considerably from patient to patient. The usual presentation is insidious, progressive painless symmetric proximal muscle weakness which develops over 3 to 6 months before the patient seeks medical attention. However, some patients (especially children and young adults with dermatomyositis) experience a more acute onset with symptoms developing rapidly over the course of several weeks. In that case, constitutional features such as low-grade fever and fatigue tend to be more common. Myalgias occur in some patients, but are rare. Finally a subset of patients exists where weakness evolves slowly over 1 to 10 years before a diagnosis is made. This presentation is most likely in patients with IBM.

Other findings include pitting edema of the extremities, periorbital regions, or eyelids, as well as hoarseness, dysphagia, nasal regurgitation of liquids, aspiration pneumonia, and dyspnea. Distinctive cutaneous manifestations are often the initial findings in dermatomyositis and may be present for months before muscle weakness develops (4).

CLINICAL FEATURES

Constitutional

Fatigue, fever, and weight loss may occur with any IIM. Weight loss may result from poor caloric intake associated with pharyngeal striated muscle dysfunction or

TABLE 18A-1. IDIOPATHIC INFLAMMATORY MYOPATHIES.

CRITERIA	SUBSETS
1. Symmetric proximal muscle weakness	Polymyositis
2. Muscle biopsy evidence of myositis	Dermatomyositis
3. Increase in serum skeletal muscle enzymes	Myositis with an associated collagen vascular disease
4. Characteristic electromyographic pattern	Cancer-related myositis Juvenile dermatomyositis
5. Typical rash of dermatomyositis	Inclusion body myositis

esophageal dysmotility and dysphagia. If weight loss persists or is severe, an associated malignancy should be considered.

Skeletal Muscle

Typically, skeletal muscle involvement develops insidiously, is bilateral and symmetric in distribution, affects proximal muscles much more than distal muscles, and is painless. An exception is IBM, in which an asymmetric distribution, distal weakness, or atrophy can occur alone or in combination with proximal weakness. In polymyositis and dermatomyositis, the lower extremity (pelvic girdle) is often affected causing difficulty walking up steps or arising from a seated position. Walking on level ground may be fairly normal, but the patients are prone to falls. Upper extremity (shoulder girdle) symptoms, which may lag behind those of the lower extremity, include difficulty raising their arms overhead or combing their hair. Neck flexor weakness may also occur. When myalgias are present, they are more common with exercise. Proximal dysphagia, with nasal regurgitation of liquids and pulmonary aspiration, is a poor prognostic sign and indicates pharyngeal striated muscle involvement. Pharyngeal weakness also results in hoarseness or dysphonia and a nasal quality voice. Ocular or facial muscle weakness is very uncommon in IIM, and their presence should prompt consideration of another diagnosis.

Physical examination using manual muscle testing confirms weakness of individual muscles or muscle groups. In JDM, the Childhood Myositis Assessment Scale has been shown to be reliable and valid for assessing physical function, muscle strength, and endurance. Muscle atrophy and joint contractures are sequelae of disease damage and are late findings in chronic muscle inflammation.

Skin

The skin rash of dermatomyositis may precede, develop simultaneously with, or follow symptoms of myopathy (4). Gottron's papules and the heliotrope rash on eyelids are considered pathognomonic features. Gottron's papules are scaly, erythematous, or violaceous papules and plaques located over bony prominences, particularly over the small joints of the hands, elbows, knees, and ankles. Gottron's sign is a macular erythema that occurs in the same distribution. Photosensitivity with rash on the face or anterior chest, termed the *V sign*, may also be seen. Pruritus is common, particularly in the scalp. Other cutaneous changes include a rash located over the upper back and across both shoulders (the shawl sign), rash on the lateral surface of the thighs and hips (holster sign), erythroderma, cuticular hypertrophy, and periungual erythema. Capillary changes are often present proximal to the cuticles in patients with Raynaud's phenomenon. Cracking, fissuring, or both, of the lateral and palmar digital skin pads is termed *mechanic's hands*. Later in the disease course, skin lesions may become shiny, atrophic, and hypopigmented with telangiectasias. Characteristic changes seen in JDM that are rare in adults include cutaneous necrosis, lipodystrophy, and subcutaneous calcifications.

Joints

Arthralgias or arthritis, if they occur, usually develop early in the disease course. They tend to be rheumatoid-like in distribution and are generally mild. Joint findings are more common with overlap syndromes and in childhood dermatomyositis.

Lung

The lung is the most common extramuscular target in IIM (5,6). Dyspnea may result from interstitial lung disease as well as nonparenchymal problems, such as ventilatory (diaphragmatic and intercostal) muscle weakness or cardiac dysfunction. Pulmonary function testing reveals restrictive physiology, with reduced lung volumes, for example, total lung capacity and forced vital capacity and a parallel decrease in the diffusion capacity for carbon monoxide.

The presence of a "ground glass" appearance on high resolution computed tomography (CT) indicates alveolitis, a potentially treatment-responsive inflammatory condition with a more favorable prognosis. In contrast, the presence of "honeycombing" usually indicates fibrosis (7). The progression of interstitial lung disease is unpredictable but the more favorable histologies include nonspecific interstitial pneumonitis (NSIP) and the organizing pneumonias. In contrast, the finding of usual interstitial pneumonitis (UIP) or diffuse

alveolar damage (DAD) portends a more ominous course.

Patients with progressive interstitial lung disease can develop secondary pulmonary arterial hypertension. Diffuse alveolar hemorrhage with pulmonary capillaritis and pneumomediastinum are rare associations.

Heart

Cardiac involvement is common in IIM but is seldom symptomatic (8). The most common finding is a rhythm disturbance. More ominous complications, such as congestive heart failure and pericardial tamponade, are quite rare.

Gastrointestinal Tract

Swallowing problems (upper dysphagia) manifest as difficulty in the initiation of deglutition or nasal regurgitation of liquids. If severe, aspiration of oral contents leads to chemical pneumonitis. Cricopharyngeal muscle dysfunction is more common in inclusion body myositis, but also occurs in other IIM. This can also cause dysphagia, with the complaint of a "blocking" sensation with swallowing. Patients note a retrosternal "sticking" sensation on swallowing bread or meat and heartburn (reflux) with esophageal body and gastroesophageal sphincter involvement, respectively. Gastrointestinal mucosal ulceration and hemorrhage are rare.

Malignancy and Myositis

There has been considerable controversy regarding the validity and magnitude of the relationship between malignancy and inflammatory myopathy (9). Recent reports strongly support an increased risk of cancer in patients with polymyositis and an even greater risk with dermatomyositis. Amyopathic dermatomyositis patients also have an increased risk of malignancy (10). Patients with pulmonary fibrosis, circulating myositis-specific autoantibodies, or an associated connective tissue disease have a decreased likelihood of cancer. The overall risk of cancer is greatest in the first 3 years after the diagnosis of myositis, but an increased risk of malignancy persists through all years of follow-up, emphasizing the importance of continued surveillance.

In general, the sites of origin of malignancy are typical for the age of the patient (11). The strongest associations are with ovarian, lung, pancreatic, stomach, and colorectal cancer and with non-Hodgkin's lymphoma. However, many other types of cancer occur with myositis, including genitourinary malignancies and melanoma. Ovarian cancer is over-represented in some series. Asian and Chinese patients with dermatomyositis have a clear increase in nasopharyngeal carcinoma.

INVESTIGATIONS

Serum Muscle Enzymes

Enzymes that leak into the serum from injured skeletal muscle include the CK, aldolase, AST, ALT, and LDH (12,13). Which enzymes are elevated and which one is the best to follow varies from patient to patient. Some feel that the CK is the most reliable enzyme to use in routine patient care and best reflects disease activity. The CK is elevated at least at some time during the course of illness in patients with an IIM. Lower values are often seen late in the disease course, in IBM, and in cancer-related myositis. The myocardial fraction of CK (CK-MB) may be increased in myositis without any cardiac involvement because this isoform is also released from regenerating myoblasts.

In contrast, elevated CK levels do not necessarily evidence active inflammation. Previously damaged muscle membranes may remain permeable to CK after the disease has been controlled, resulting in elevated serum levels. In addition, many non–disease-related factors, such as race, may cause an elevated CK (see Chapter 18C for more information on CPK).

Electromyography

Electromyography is a sensitive but nonspecific method of evaluating muscle for evidence of inflammation. Of the 90% of patients with active myositis who have an abnormal EMG, about half show the classic findings of inflammation of fibrillation potentials, complex repetitive discharges, positive sharp waves, and complex motor unit potentials of low amplitude and short duration. In addition to aiding in the diagnosis, EMG is helpful in the selection of a site for muscle biopsy. When this is the case, the study should be performed unilaterally and a contralateral muscle chosen for biopsy to avoid confusion with inflammation artifact that can result from injury caused by the needle.

Later in the course, EMG examination may be helpful for the detection of low grade myositis in the setting of chronic damage from fibrosis or fatty infiltration. It may also be useful in differentiating active inflammation from steroid myopathy.

Muscle Biopsy

Muscle histology remains the gold standard for confirming the diagnosis of an IIM (14). Despite the characteristic features described below, some patients with active myositis have a normal biopsy. Because the disease is patchy in distribution, sampling error precludes 100% sensitivity. Furthermore, the changes in some biopsies may be too nonspecific.

The most characteristic changes in polymyositis include degeneration and regeneration of muscle fibers

and CD8+ T lymphocytes invading non-necrotic fibers. In dermatomyositis, CD4+ T cells and B cells predominate in the perivascular areas and perifascicular atrophy, related to capillary depletion and dropout, is noted. The histology of IBM is characterized by the presence of lined or rimmed vacuoles. Otherwise IBM may appear identical to that of polymyositis, be essentially normal, or show triangulated cells with fiber-type grouping, changes considered to be indicative of a neuropathic process. In chronic myositis, macrophages are seen phagocytosing necrotic fibers and muscle is replaced by fibrous connective tissue or fat (see Chapter 18B for a more detailed discussion of the muscle pathology).

Magnetic Resonance Imaging

Magnetic resonance imaging techniques add an important dimension to our approach to patients with myopathy (15). MRI is noninvasive and can be used to visualize large areas of muscle. T1-weighted images provide excellent anatomic detail, with clear delineation of various muscle groups and are useful in assessing changes resulting from damage and chronicity. T2-weighted images with fat suppression or STIR (short tau inversion recovery) sequences can identify edema, which is indicative of active inflammation. Accordingly, MRI can be used to document myositis or a disease flare, distinguish chronic active from chronic inactive myositis, and noninvasively direct the site of biopsy.

Skin

The characteristic cutaneous histopathologic findings of dermatomyositis include vacuolar alteration of the epidermal basal layer, necrotic keratinocytes, vascular dilatation, and a perivascular lymphocytic infiltrate (4). The pattern is similar to that seen with systemic lupus erythematosus and closely resembles those of chronic graft-versus-host reaction. Vasculitis or vasculopathy may be found in small cutaneous vessels. Capillary changes proximal to the cuticles are often seen in patients with Raynaud's phenomenon (see Chapter 18B for a more detailed discussion of the skin pathology in IIM).

Lung

Chest radiographs may show fibrotic changes in patients with interstitial lung disease, but they are insensitive compared with high resolution CT (HRCT) (16,17). HRCT findings include ground-glass opacities typical of alveolitis and/or consolidation, subpleural lines or bands, traction bronchiectasis, and honeycombing indicating fibrosis. The most common HRCT pattern is a combination of reticular and/or ground glass opacities with or without consolidation and without honeycombing. When honeycombing is present on the initial HRCT, the prognosis is generally poor.

Pulmonary function testing is useful in assessing a variety of potential problems. Reduced ventilatory muscle strength is determined by measuring inspiratory pressures at the mouth. Impaired function results in a weak cough and an increased risk of aspiration. A forced vital capacity of less than 55% of normal predicts carbon dioxide retention that can result when ventilatory muscle function is compromised and interstitial disease is absent. Interstitial lung disease also causes restrictive physiology on pulmonary function testing but is typically accompanied by pulmonary fibrosis. More sensitive indicators of compromised gas exchange include a reduction in the diffusing capacity for carbon monoxide and a decrease in the alveolar–arterial oxygen gradient with exercise.

Heart

Clinically significant cardiac findings are uncommon in IIM. However, electrical disturbances are not uncommon. These include nonspecific ST-T segment changes and conduction system abnormalities. Using sensitive cardiac scintigraphic techniques, increased technitium-99m pyrophosphate uptake and indium-labeled antimyosin binding have been reported.

Intestine

When pharyngeal muscles are involved, a barium swallow may show cricopharyngeal muscle spasm, poorly coordinated motion of the pharyngeal musculature, vallecular pooling of the dye, and, occasionally, aspiration of barium into the trachea (18). Cinesophagrams and manometry are best for evaluation of distal dysphagia resulting from distal esophageal hypomotility.

Serum Autoantibodies

Antinuclear or anticytoplasmic antibodies are present in the majority of patients with IIM, with the exception of IBM, where the frequency is low. Patients with myositis and an associated collagen vascular disease will manifest the antibodies characteristic of that disease [i.e., anti–double-stranded DNA (dsDNA) antibodies and SLE, anti–Scl 70 and scleroderma, etc]. In addition, some antibodies are termed *myositis-specific autoantibodies* (MSAs) because they are found exclusively in patients with features of an inflammatory myopathy (3). Although a few patients have more than one serum autoantibody, several MSAs are rarely detected in the same patient. A negative antinuclear antibody (ANA) test does exclude an MSA, as the latter antigens are cytoplasmic in location and the immunofluorescence staining pattern may be subtle. Testing for serum autoantibodies can both solidify the diagnosis of myositis in patients with atypical clinical features and provide prognostic information regarding the likelihood of future clinical complications.

Although the MSAs are relatively insensitive markers for myositis, the presence of one suggests that the patient will have certain associated features (see Table 18C-1). Anti–Jo 1 antibodies are directed against histidyl-tRNA synthetase. Anti–Jo 1 is the most common MSA and is one of a group of anti–aminoacyl-tRNA synthetases. The clinical associations of the antisynthetase antibodies have been termed the *antisynthetase syndrome*. The muscle involvement in this syndrome is often severe with multiple exacerbations, requiring immunosuppressive agents in addition to corticosteroids. Antibodies against signal recognition particle (anti-SRP) identify patients with polymyositis who may have cardiomyopathy and who often have severe, refractory disease. Anti–Mi 2 is an antinuclear antibody that is almost always associated with dermatomyositis and a good response to immunosuppression.

NATURAL HISTORY AND PROGNOSIS

The clinical course is quite variable among patients with IIM (19). In some, the illness is brief and is followed by remission that does not require continued treatment. That is more common in dermatomyositis than in polymyositis and most common in patients with an associated collagen vascular disease. Other patients with theses diseases experience exacerbations and remissions or persistent disease activity, necessitating chronic use of immunosuppressive drugs, with the frequency of clinical and biochemical relapse varying from 34% to 60% in different series. Patients with IBM do not respond to any known medications. This disease is characterized by a slow and gradual decline in muscle strength, although the level of weakness can plateau for some.

As long as the myositis is active, there is the potential for absolute loss of muscle mass and strength (20). In general, the best functional outcomes occur in dermatomyositis, whereas the worst are seen in IBM, myositis with anti-SRP antibody, cancer-related myositis, and patients with interstitial lung disease. In JDM, predictors of chronic active myositis include delay in diagnosis, failure to regain normal muscle strength after 4 months of corticosteroid treatment, continued increased serum muscle enzyme beyond 3 months, increased plasma von Willebrand factor antigen after 10 months of treatment, and anasarca with hypoalbuminemia.

Factors associated with poor survival include older age, malignancy, delayed initiation of corticosteroid treatment, pharyngeal dysphagia with aspiration pneumonia, ILD, myocardial involvement, and complications of corticosteroid or immunosuppressive treatment. Additional adverse risk factors for survival among patients with JDM are gastrointestinal vasculitis and sepsis.

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