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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CHAPTER 18

Idiopathic Inflammatory Myopathies
B. Pathology and Pathogenesis

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- Major pathology consists of focal inhomogeneous inflammation with injury, death, and repair of muscle cells.
- Each subgroup of myositis has characteristic changes on microscopy and immunochemistry.
- Etiology is still unclear but selected environmental exposures in genetically predisposed hosts have been found.

PATHOLOGY AND IMMUNOPATHOLOGY

The characteristic skeletal muscle pathology in the idiopathic inflammatory myopathies (IIM) consists of chronic inflammation with infiltration by mononuclear cells, including lymphocytes, plasma cells, macrophages and dendritic cells, in the endomysium (between myocytes), perimysium (within fascicles), or perivascular (vessels in interstitium surrounding muscle fibers) areas (Figure 18B-1). The muscle fibers (myocytes), which may be necrotic or non-necrotic, show evidence of degeneration and regeneration, fiber hypertrophy or atrophy, and replacement by fibrosis or fat, and are often accompanied by increased connective tissue or fibrosis in the interstitial areas around the muscle cells (1).

These features collectively are characteristic of myositis, but each feature may be seen as part of the pathology of other muscle disorders, particularly muscular dystrophies. Macrophages may infiltrate to scavenge necrotic muscle as a secondary inflammatory process in dystrophies and other myopathies. Some features of other neuromuscular disorders, such as small angulated fibers, may also be present in myositis. A muscle biopsy is not always diagnostic of myositis. First, the inflammation is often focal and inhomogeneous. Inflammation is also diminished after the initiation of immunosuppressive therapy. A muscle biopsy should also not be performed at the site of an electromyogram (EMG), due to artifactual changes from the EMG. In inclusion body myositis (IBM), the inclusions are not always apparent, either because of their patchy nature or because they may appear later in the course of illness. Paraffin processing also dissolves the vacuoles, so that a Gomori trichrome stain is needed for detection.

A muscle biopsy should be performed, processed, and evaluated by persons experienced in these procedures because careful attention to selection of the biopsy site, to collection of the tissue, and to rapid freezing and appropriate histochemistry is needed to obtain the most informative biopsies. Standard procedure should include hematoxylin and eosin and Gomori trichrome stains to highlight the cellular infiltrates as well as muscle architecture. Alkaline phosphatase positive connective tissue, even in the absence of cellular infiltrates, can also aid in the diagnosis of myositis. A portion of the frozen tissue block should be saved for enzymatic and metabolic stains, as well as immunohistochemistry or detection of muscle sarcolemmal proteins if needed for diagnosis (1).

Each subgroup of myositis has somewhat characteristic changes on routine microscopy and immunohistochemistry. In dermatomyositis (DM), the mononuclear cells are focused more along the vessel walls of perimysial arterioles and venules, with such changes more prominent in the juvenile form of DM (2,3). Vessel thrombosis may also occur. Infarcts from the perifascicular region to the center of the fascicle are

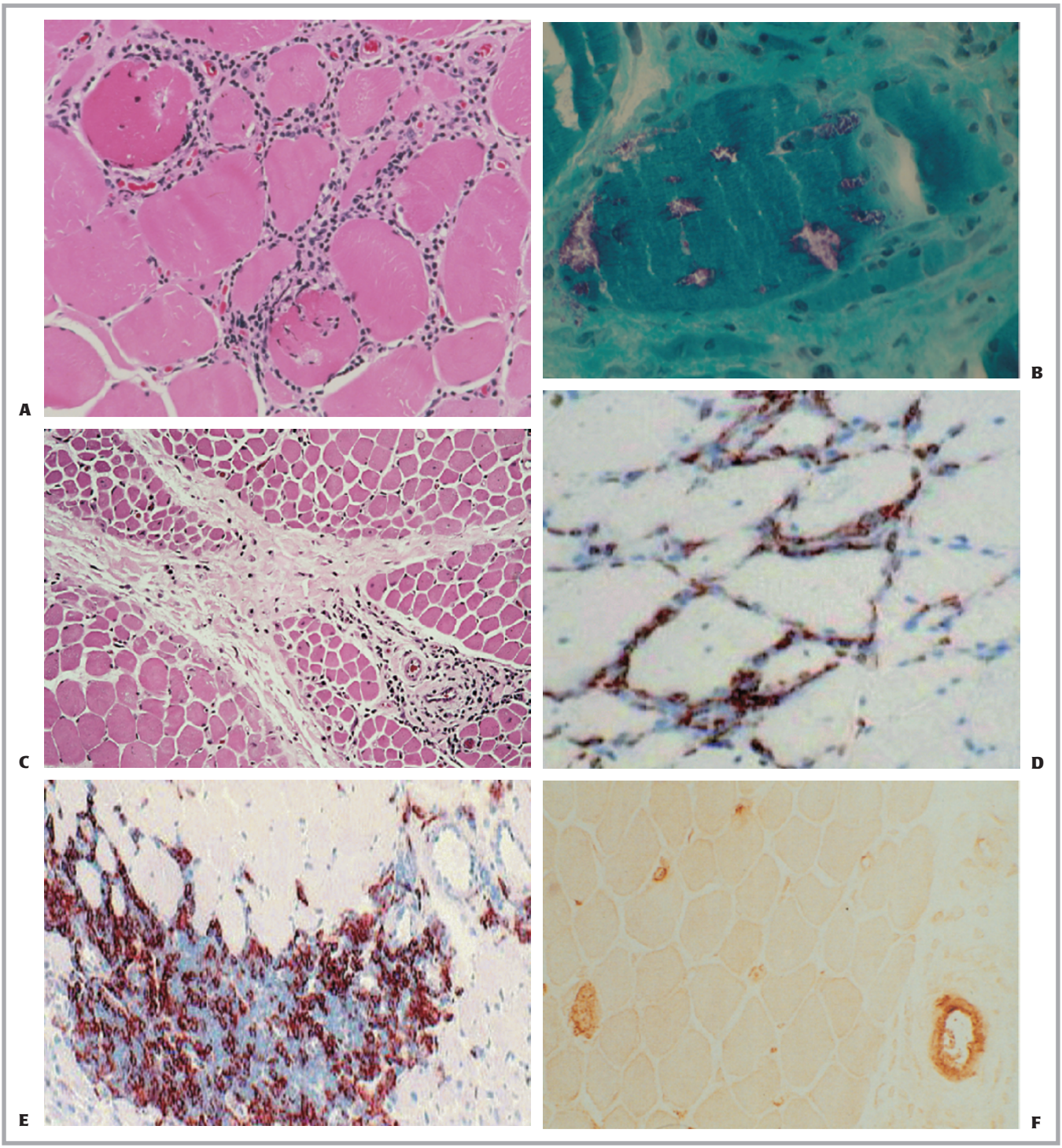

FIGURE 18B-1

Muscle pathology and immunopathology by light microscopy. Cross-sectional views of muscle biopsies showing characteristic changes in IIM. (A) Endomysial mononuclear cell infiltrates surrounding and invading myocytes in a patient with polymyositis (hematoxylin and eosin stain). (B) Similar findings are present in inclusion body myositis, with the exception of typical multiple reddish-rimed vacuoles in myocytes on trichrome staining that define the inclusion bodies (trichrome stain). (C) Dermatomyositis and juvenile dermatomyositis show more prominent vascular changes, including perivascular mononuclear cell infiltration and vessel thrombosis, as well as perifascicular atrophy. (From Rider LG, Targoff IN. In: Lahita RG, Chiorazzi N, Reaves WH, eds. Textbook of autoimmune diseases. Philadelphia: Lippincott Raven; 2000.) (D) Immunohistochemistry demonstrating staining for CD8+ cells that are surrounding myocytes in polymyositis. (From Figarella-Branger D et al., Muscle Nerve 2003;28:659.) (E) Positive immunostaining for B cells in dermatomyositis. (From Figarella-Branger D et al., Muscle Nerve 2003;28:659.) (F) Staining for the C5–C9 membrane attack complex on capillaries and myocytes in dermatomyositis. (Courtesy of Dr. J.T. Kissel.)

particularly present in juvenile DM and less frequently in adult DM (3). Perifascicular atrophy with small fibers at the external rim of a fascicle is also characteristic of DM. In contrast, in polymyositis (PM) and IBM, the inflammatory cells invade non-necrotic muscle fibers in a primarily endomysial distribution (4,5).

Immunohistochemistry also implicates different pathogeneses in the various forms of myositis. In DM, more frequent in the juvenile than adult form, the earliest changes include activation of the complement cascade through C3, deposition of the complement C5b-9 membrane attack complex on the endomysial vasculature, with resultant capillary destruction, muscle ischemia, and dilatation of the remaining capillaries (high endothelial venule formation) (6–8). This leads to resulting inflammation, with the infiltrating cells consisting mainly of B lymphocytes and CD4+ helper T cells in perimysial areas around the muscle fascicles and small blood vessels. MHC class I antigen and intracellular adhesion molecule (ICAM) are upregulated on the cell surfaces of damaged fibers or in perivascular areas, respectively (9). In PM and IBM, the weight of evidence suggests a predominant cytotoxic T lymphocyte–mediated process with CD8+ T cells, accompanied by smaller numbers of macrophages, surrounding and invading otherwise normal-appearing myocytes in endomysial areas (10). MHC class I antigen is upregulated on the surface of the majority of muscle fibers, even those not affected by inflammation, although this is not specific to myositis (1). Necrotic muscle fibers may be scattered in the biopsy, particularly in PM.

In IBM, in addition to these inflammatory findings, there are vacuolated myofibers occurring in the center or periphery of muscle fibers, with wide variation in myofiber size, including scattered atrophic fibers, and prominence of central muscle nuclei. The vacuoles are rimmed by granular eosinophilic material, which on Gomori trichrome stains purple-red and on Congo red staining reveals amyloidlike deposits, including phosphorylated tau, ubiquitin, beta-amyloid, and presinilin 1 (9). Diffuse inflammatory infiltrates and ragged red fibers are sometimes seen. In IBM-characteristic tubulofilaments, 15 to 18 nm in diameter and seen most often in the cytoplasm and less often in the nuclei, are often visible by electron microscopy (1).

In terms of the pathologic features of other organs, the skin in DM demonstrates interface dermatitis, often with basement membrane thickening and mucin deposition. Many of the changes in muscle, including the types of infiltrating cells and the predominance of perivascular inflammation, are also evident in the skin. In the gastrointestinal tract, ischemic ulceration is a potentially life-threatening manifestation and may include a noninflammatory acute endarteropathy with arterial and venous intimal hyperplasia and occlusion of intestinal vessels by fibrin thrombi in the submucosa, muscularis, and serosal layers (3). A chronic endarteropathy characterized by narrowing or complete occlusion of multiple small and medium-sized arteries, subintimal foam cells, fibromyxoid neointimal expansion, and significant luminal compromise and infiltration of macrophages through the muscle layers into the intima may also be seen. The pathology of the interstitial lung disease most commonly is that of nonspecific interstitial pneumonitis (NSIP), but occasionally diffuse alveolar damage, usual interstitial pneumonitis (UIP), and bronchiolitis obliterans organizing pneumonia (BOOP) may be present. The myocardium may demonstrate myocarditis with subsequent fibrosis.

PATHOGENESIS

While the etiology and pathogenesis of the IIM remain unclear, a number of lines of investigation have suggested possible ways in which selected environmental exposures in genetically susceptible individuals may lead to chronic immune activation and the ultimate immunologic attack on muscle and other involved tissues (Figure 18B-2). A number of these mechanisms, which include upregulation of MHC class I on muscle fibers, immune activation, and activation of the endoplasmic reticulum stress response, are processes common to other myopathies besides myositis. While some of the mechanisms are found in all forms of myositis, others are likely unique to selected groups.

Genetic Factors

The finding of families in which two or more blood relatives have myositis and associations of myositis with particular genes support the hypothesis that myositis is at least in part inherited. Polymorphic alleles in the major histocompatibility locus (MHC) are the major immunogenetic risk and protective factors identified for the IIM. The A1-B8-Cw07-DRB1*0301-DQA1*0501 ancestral haplotype is the major immunogenetic risk factor for PM, as well as adult and juvenile DM in Caucasians, with the risk factor likely in the class II HLA region at or near human leucocyte antigen (HLA) DRB1*0301. For IBM, DRB1*0301 and its linked allele DQA1*0501 are risk factors along with the class I Cw*14 allele. HLA DQA1*0201 is protective for all forms of myositis, and other DRB1 or DQA1 alleles are protective for specific clinical groups (11). In the class III MHC region, the tumor necrosis factor alpha (TNF-alpha)-308A allele is a risk factor for adult and juvenile DM and PM in Caucasians, and may also be a severity factor, perhaps related to photosensitive rashes and the development of calcinosis. DMA*0103 and DMB*0102 are possible risk factors for juvenile DM. Outside the HLA region, the IL1 receptor antagonist VNTR A1

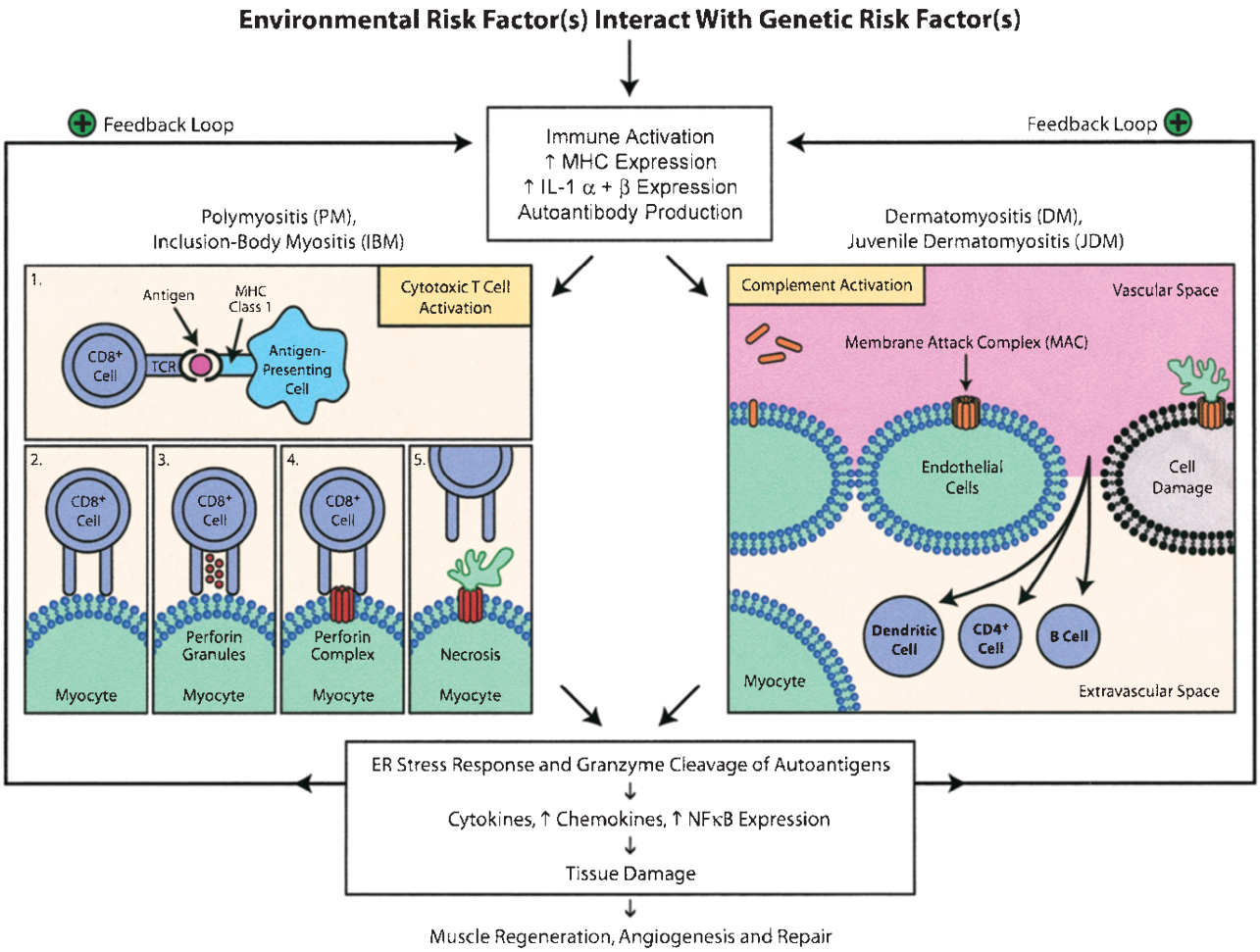

FIGURE 18B-2

Possible pathogenic mechanisms in IIM. All forms of myositis appear likely to involve immune activation following specific exposure to environmental risk factors in genetically susceptible individuals. Common immune activation processes in muscle and other tissues include upregulation of MHC expression and IL-1 alpha and beta, leading to autoantibody production prior to clinical disease onset. Following this, myocyte-directed cytotoxic T-cell mechanisms predominate in PM and IBM, while complement-mediated endothelial damage, leading to CD4, B-cell, and dendritic-cell infiltrations, predominate in DM and JDM. Other general mechanisms may involve hypoxia, activation of the endoplasmic reticulum stress response, and cleavage of autoantigens, resulting in cytokine and chemokine release and positive feedback loops that lead to further immune activation. Later processes include muscle regeneration, angiogenesis, and repair, and in some cases fibrotic changes and other damage in affected tissues.

allele is a risk factor for juvenile DM in Caucasians. The Gm allotypes, serologic markers on the heavy chains of IgG, rather than HLA alleles, are genetic risk or protective factors for myositis in Koreans and Mesoamericans, suggesting that genetics likely varies among ethnic groups (12).

Human leukocyte antigen risk factors are more strongly associated with specific autoantibodies (13). The ancestral haplotype A1-B8-Cw07-DRB1*0301-DQA1*0501 is a strong risk factor for patients with antisynthetase autoantibodies, including Jo1, in Caucasian patients. MHC class II alleles DRB1*0701 and DQA1*0201 are risk factors for Mi 2 autoantibodies. DQA1*0301 is a risk factor for p155, a myositis-associated autoantibody common in adult and juvenile DM.

Environmental Factors

The temporal association of exposure to a number of infectious and noninfectious agents prior to the onset of the IIM in certain individuals, as well as reports documenting temporal, seasonal, or geographic clustering of

IIM cases suggest a role for environmental factors in initiation of disease (12).

Epidemiologic investigations have also suggested a number of environmental factors which may be important in the development of IIM. Most are not proven environmental risk factors, but for some exposures, case-controlled epidemiologic studies, cases of de-challenge and re-challenge, and biomarker assays strengthen the association with illness onset. Of the infectious agents, Group A streptococcus and influenza have the strongest evidence of association with onset of juvenile IIM and toxoplasmosis with adult DM from case-controlled epidemiologic studies. With Group A streptococcus, peripheral blood T lymphocytes from juvenile DM patients react with streptococcal M5 protein and a myosin peptide with homology to M5. The evidence is mixed for coxsackie B virus, with reports of isolation of the virus from some affected muscles but a case-controlled study not supporting an association with onset of juvenile DM. Echoviruses, however, have been clearly associated with a DM-like illness in patients with agammaglobulinemia. Other infections temporally associated with onset of IIM which are not yet defined as definite risk factors for IIM include retroviruses, hepatitis viruses, *Borrelia burgdorferi,* and *Trypanosoma cruzi.* Parvovirus B19 is not associated with onset of juvenile DM in a case-controlled study. A search for viral genomes by sensitive molecular methodology in DM and PM biopsies has failed to identify consistently any viral nucleic acid, suggesting that known viruses are not contributing to the persistent inflammation (12).

Noninfectious agents, including ultraviolet light, physical exertion, psychological stress, medications, and vaccines have been suggested as possible triggers for some forms of IIM. Growing evidence suggests a role for ultraviolet radiation (UV) in the onset of DM. DM patients have a number of photosensitive rashes and, anecdotally, illness may exacerbate following sun exposure. Adult DM patients also have increased sensitivity to UVB as demonstrated by an abnormally low minimal erythema UVB dose. An increase in the proportion of DM relative to PM and an increase in the proportion of patients with the DM-associated Mi 2 autoantibody in areas of the world with higher surface UV radiation suggest that UV light exposure may modulate the clinical and immunologic expression of myositis. Keratinocytes damaged by UV radiation also undergo apoptosis, with increased autoantigen expression on the surface of such cells.

Case-controlled studies support a role for psychological stress, muscular exertion, and collagen implants in the onset of adult DM or PM (14). Exposure to D-penicillamine may induce myositis in 1% to 2% of patients and this has been associated with HLA B18, B35, and DR4 in Caucasians but with DQw1 in patients from India, which are genes distinct from those associated with IIM. Similarly, although there is no epidemiologic evidence from population studies confirming an association between silicone exposure and myositis, Caucasian women who develop myositis following silicone implants do not have the characteristic genetic features seen in IIM, but rather have an increased frequency of HLA DQA1*0102. Temporal associations of onset of the IIM with certain other drugs (including lipid-lowering agents, zidovudine, leuprolide, and local anesthetics), biologic therapies (such as interferon alpha and interleukin 2), and vaccines have been reported, but additional evidence is needed to confirm their potential associations (12). Certain alum-containing vaccines have also been associated with the distinct entity of macrophagic myositis, in which macrophages are the predominant infiltrating cell.

Cytotoxic Mechanisms in Polymyositis and Inclusion Body Myositis

Many lines of evidence suggest that cytotoxic mechanisms play a more important role in PM and IBM than adult or juvenile DM (15). First, as is the case for the quantitation of subsets of lymphocytes in the affected muscle, studies of peripheral mononuclear cells demonstrate that PM and IBM are virtually indistinguishable in showing higher numbers of circulating activated T cells. Second, peripheral blood cells from PM patients have an increased proliferative response to, and demonstrate cytotoxicity to, autologous muscle tissue in vitro. Third, T cells in PM and IBM contain perforin and granzyme granules that are directed towards the surface of the myofibers and that, on release, induce pores in the myocyte membranes (10). Fourth, based on restricted T-cell receptor usage, there is clonal expansion of muscle-infiltrating T cells selected for certain gene families in PM and IBM, implying an antigen-driven process, in contrast to a more polyclonal pattern of T-cell receptor usage in DM. Additionally, the CD8+ cells found in PM and IBM appear to preferentially target MHC class I–expressing myocytes, which would be required for their antigen-specific recognition of cellular targets. These findings, taken together, suggest that in PM and IBM, subpopulations of T cells are selected and expanded in response to as yet uncharacterized antigens and may explain some of the T-cell–mediated pathology seen in these diseases.

Humoral and Endothelial Mechanisms in Adult and Juvenile Dermatomyositis

Humoral and endothelial mechanisms appear to be more important for adult and juvenile DM compared to

PM and IBM (15). First, higher numbers of circulating B and CD4+ T lymphocytes are present in the periphery as well as in the affected muscle. Second, immunoglobulin and the terminal portion of complement are deposited on blood vessels in the earliest phases of illness (6), resulting in a decrease in the number of capillaries and muscle injury, including ischemia. From microarray experiments, in some cases confirmed by immunohistochemistry or real-time polymerase chain reaction (PCR), a number of promoters and inhibitors of angiogenesis are overexpressed in the affected muscle tissue (16,17). There is also increased expression of genes promoting endothelial differentiation and activation, as well as classical and alternative complement pathway regulators that facilitate angiogenesis in the muscle tissue of adult DM patients (16). In juvenile DM, a number of angiostatic ELR-chemokines are increased in expression and correlate with the degree of capillary loss (17). Upregulation of leucocyte adhesion molecules, particularly ICAM-1 on the muscle arterioles and venules in juvenile DM and somewhat in adult DM, results in the infiltration of B and CD4+ T lymphocytes, dendritic cells, and macrophages (9). Proinflammatory cytokines result in damage and further infiltration of cells.

Immune dysregulation is also a key part of the pathogenesis, with upregulation of interferon alpha/beta inducible genes and genes upregulated in a type I interferon response, as well as genes involved in antigen presentation, suggesting either viral initiation of disease or activation of plasmacytoid dendritic cells (18,19). Some of these factors are also angiostatic.

Cytokines, Chemokines, and Related Factors

A growing number of signaling molecules have been discovered to be important in regulating the movement of immune cells from the circulation into different tissues and in altering their subsequent function (9). Immunohistochemistry and array studies have suggested an increased expression of many types of these signaling molecules in the form of cytokines, chemokines, chemokine receptors, and related proteins in muscles of myositis patients. Cytokines frequently found in inflammed muscle include: proinflammatory cytokines, such as interleukin (IL) 1 and tumor necrosis factor alpha (TNF-alpha); cytokines involved in T-cell differentitation, including interferons (IFNs), IL-2, IL-5, and IL-10; and cytokines involved in fibrotic processes, such as transforming growth factor beta (TGF-beta). Chemokines—especially macrophage inflammatory protein-1 alpha (MIP-1 alpha, CCL3), monocyte chemoattractant protein-1 (MCP-1, CCL2) and CCL5 (RANTES)—as well as CXC-chemokine ligands (CXCL 9 and 10) and chemokine receptors (CCR1-5, CCR2A, and CCR2B) are also upregulated in myositis, thus attracting monocytes, macrophages, and T lymphocytes to the inflammatory sites. The molecules that facilitate leukocyte migration from the vasculature into the tissues, including intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), CD142, and CD31 (which facilitate dendritic cell migration), have also been found to be increased in the muscle tissue of myositis patients compared to controls. ICAM-1 is upregulated on perimysial or perivascular areas in DM and on endomysial vessels in PM and IBM. Other studies demonstrate increased expression of interferon alpha/beta–inducible genes as one of the major features differentiating adult and juvenile DM from PM and IBM. Furthermore, an investigation of serial muscle biopsies from three DM and four IBM patients, before and after treatment with intravenous immunoglobulin, suggested decreases in selected chemokine and ICAM-1 genes in those DM patients who responded to therapy (20).

The cytokines present in the muscle biopsies of myositis subjects may be involved in regulating immune responses, but they may also have direct effects on muscle and other target tissues (9). For example, TNF-alpha has been shown to induce many changes in muscle from accelerated catabolism to contractile dysfunction. IL-1 alpha may play a role in direct myotoxicity via its influence on insulinlike growth factor, thereby leading to metabolic disturbances in nutrition supply, and by suppressing myoblast proliferation and fusion. Differences in methodology and patient populations under study, however, have made it difficult to determine if any of these signaling molecules are playing a primary or secondary role in pathogenesis and if there are critical differences in cytokine patterns in the different forms of IIM.

Major Histocompatibility Complex Overexpression and Sequelae

Increased MHC class I antigen expression occurs on scattered myocytes in all forms of IIM, and MHC class I molecules are present even on myocytes far removed from inflammation, suggesting that this may be an early event in pathogenesis (1). How specific this process is to IIM remains unclear because myocytes in muscle biopsies from some muscular dystrophies also show MHC class I expression. Nonetheless, additional evidence that overexpression of MHC class I may be related to myositis comes from an animal model where directed transgenic upregulation in skeletal muscle led to muscle inflammation as well as decreased muscle strength, even before detectable histological damage in the skeletal muscles of these mice (21). The increased MHC class I not only renders muscle a possible target for the recognition by cytotoxic T cells, but it may also

negatively impact cellular metabolism. When there is an imbalance between the load of proteins in the endoplasmic reticulum (ER) and the cell's ability to process that load, signaling pathways are activated that adapt cells to ER stress. This process is called the *ER stress response* and it can be provoked by a variety of conditions, including ischemia, viral infections, mutations that impair protein folding, and excess accumulation of proteins in the ER. The assembly and folding of MHC class I molecules in the ER involves a highly regulated process to assure their proper conformation and to prevent accumulation of unfolded proteins. When excess MHC class I molecules are present, this system can be overloaded to result in many cellular changes, including activation of the NF-κB pathway, as has been demonstrated in both IIM and the transgenic upregulated MHC class I animal model (22,23). This finding suggests that excess production of MHC class I molecules may lead to the ER stress response, which may play a role in IIM pathogenesis via activtaion of NF-κB, resulting in the induction of a number of cytokines, chemokines, adhesion molecules, and further MHC upregulation, thus initiating a self-sustaining positive feedback loop.

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CHAPTER 18

Idiopathic Inflammatory Myopathies
C. Treatment and Assessment

CHESTER V. ODDIS, MD

- Precise diagnosis is essential and muscle biopsy may identify myositis not responsive to therapy.
- Autoantibodies define heterogeneous clinical subsets.
- Steroids are the main pillar of therapy with immunosuppressive drugs, such as methotrexate and azathioprine, utilized as steroid-sparing agents.
- A core set of measures has been developed for assessing disease activity.

ASSESSMENT OF INFLAMMATORY MYOPATHY

Given the rarity of idiopathic inflammatory myopathies (IIM) and the heterogeneity of the myositis syndromes, their management is difficult. There are few well-controlled clinical trials in IIM and many of the reported studies have not adequately distinguished muscle weakness as secondary to irreversible disease damage (muscle atrophy with fatty infiltrate and fibrosis) or disease activity (reversible inflammation) so that assessing treatment response in such reports is problematic. A systematic approach to the assessment and treatment of IIM is essential. This begins with accurately establishing the diagnosis of an immune-mediated myopathy and excluding the various mimics of myositis. This is especially important in polymyositis (PM), which lacks the hallmark cutaneous features of dermatomyositis (DM) that make the latter disease easier to diagnose. A consortium of myositis experts, the International Myositis Assessment and Clinical Studies Group (IMACS), has been organized to address many of these concerns. Recent efforts from this group include the (1) development of core set measures for assessing disease activity in myositis trials (1); (2) proposal of a preliminary definition of improvement in adult and juvenile myositis clinical trials (2); and (3) development of an international consensus document on the conduct of therapeutic trials in adult and juvenile myositis (3). The systematic assessment of the inflammatory myopathies will first be discussed and then a treatment approach will be outlined.

Routine Assessment Tools

Serum Muscle Enzymes

Serum creatine kinase (CK) is generally the most reliable muscle enzyme test to use in the routine care of adult myositis. It tends to predict clinical events as serum CK levels often increase weeks before overt muscle weakness develops during disease flares. Conversely, the CK often decreases to normal prior to an objective improvement in muscle strength. There are exceptions, as some patients with active biopsy-proven myositis (DM > PM and children > adults) have a normal CK. It has been suggested that in children with juvenile DM (JDM) the combination of lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) are the best predictors of disease flare (4). There is considerable racial variation in CK concentrations as persons of Afro-Caribbean descent have an upper limit of normal CK that is higher compared to other ethnic subsets (5). Any form of exercise (anaerobic or aerobic) or trauma (sharp or blunt) can raise CK levels. Many medications and drugs (statins, alcohol, colchicine, cocaine, etc.) can cause increases. Finally, at different times, as many as 30% of people may have an asymptomatic hyper-CK-emia which is of no clinical significance.

In addition to the CK, other serum enzyme activity levels that may be elevated in myositis include the transaminases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and aldolase. When the CK is normal any one or a combination of these enzymes may be elevated and

useful in following disease activity. Elevation of the AST and ALT can often lead to an erroneous diagnosis of liver disease because these enzymes are also released with hepatic injury. A muscle source should be considered when the alkaline phosphatase and gamma-glutamyl transferase (GGT) activity levels are concomitantly normal. From a practical standpoint, if ALT and AST levels do not fall with the CK during treatment, then investigations for hepatic disease should occur. The serum aldolase, although helpful in some patients, is not as specific as the CK. Aldolase is widely distributed and found in more tissue than CK and may be elevated with liver disease, hematologic and other disorders, and with specimen hemolysis.

Electromyography

Although electrical testing is a sensitive but nonspecific method of evaluating muscle inflammation, it allows for several muscle groups to be examined. The typical electromyographic features of myofibril irritability include fibrillation potentials, complex repetitive discharges, and positive sharp waves on needle insertion. Due to its sensitivity nearly all patients with active myositis will have an abnormal electromyography (EMG) such that a normal study indicates inactive disease. Electromyography is often used in the selection of a muscle for biopsy and it should be performed unilaterally to avoid confusion with inflammation artifact resulting from the needle itself. Due to disease symmetry, a contralateral muscle that is abnormal by EMG should be chosen for biopsy. Although corticosteroid myopathy is often difficult to clinically distinguish from active inflammatory disease, the presence of fibrillation potentials suggests active inflammation due to the disease process.

Muscle and Skin Biopsy

Muscle histology can confirm the diagnosis of IIM, but patchy changes within muscle or choosing the wrong muscle to biopsy can limit diagnostic sensitivity. Degeneration and regeneration of myofibrils is the most common finding, while a chronic inflammatory infiltrate in the perivascular and interstitial area is more specific for immune-mediated myositis. PM and inclusion body myositis (IBM) is histologically distinct from DM. The pathognomonic feature of PM (and occasionally IBM) is lymphocytic (cytotoxic T cell) invasion of non-necrotic myofibers. T-helper cells may also be found in the perivascular and perimysial areas but the vasculature is often spared. In contrast, B cells and the terminal component of complement (C5–C9, membrane attack complex) are found in the perivascular area in DM along with CD8+ and CD4+ T cells. The vasculature is commonly targeted in DM and perifascicular myofibril atrophy, likely secondary to an ischemic microangiopathy is noted. Occasionally, overt vasculitis is found in DM. The characteristic cutaneous histopathologic findings of DM include vacuolar degeneration of the epidermal basal layer, vascular dilatation, and a perivascular lymphocytic infiltrate. This interface dermatitis may be similar to that seen with systemic lupus erythematosus (SLE). Microvascular injury is again mediated by the terminal components of complement as in the case of muscle (see Chapter 18B for more detailed discussion on muscle and skin pathology).

Radiographic Assessment of Myositis

The availability of magnetic resonance imaging (MRI) adds another assessment tool to adult and juvenile myositis. (6). MRI is noninvasive, which makes it particularly useful in children where electromyography is painful and poorly tolerated. Large areas of muscle (e.g., the thighs) can be studied and the results used to increase the diagnostic yield of muscle biopsy. The T1-weighted image provides excellent anatomic detail as normal tissue is homogeneously dark with a low signal, while fat (subcutaneous tissue and bone marrow) appears bright. Although muscle is darker on T2-weighted images, inflammation is bright on both T1 and T2 images. Utilizing techniques of fat suppression with short tau inversion recovery (STIR) sequencing with T2 imaging improves the detection of muscle inflammation by enhancing its bright signal and decreasing the darker fat signal. The indications for MRI include (1) documentation of myositis or disease flare in a patient with normal muscle enzymes or a normal EMG and biopsy; (2) confirmation of "amyopathic dermatomyositis" in a patient with normal serum enzymes, dermatologic features, and no apparent muscle involvement; (3) distinguishing chronic active disease from chronic inactive myositis (i.e., damage) where both groups of patients may have muscle weakness but the fat-suppressed technique will distinguish fatty changes from inflammation; (4) directing the site of muscle biopsy particularly in PM where mimics are more of a diagnostic problem; and (5) distinguishing PM from IBM as some useful distinguishing features have been noted in IBM (7). Limitations of MRI include the expense of the procedure and the nonspecificity of edema (even with STIR sequences and T2 imaging) that may be found in other inflammatory processes, toxic myopathies, or dystrophic conditions.

Extramuscular Organ Assessment

Idiopathic inflammatory myopathies are systemic connective tissue disorders and affect patients in ways well beyond the musculoskeletal system. Lung disease can be particularly devastating and patients with antibodies to the aminoacyl-transfer RNA synthetases (see Serum Autoantibodies section) are at risk for interstitial lung

disease (ILD). Involvement of the respiratory musculature is less common but can occur in severe cases of muscle weakness. In the latter instance, reduced ventilatory muscle strength is determined by measuring inspiratory pressures at the mouth. ILD, however, shows restrictive physiology on pulmonary function testing and is accompanied by radiographic evidence of pulmonary fibrosis. Compromised gas exchange leads to a reduction in the diffusing capacity for carbon monoxide and a decrease in the alveolar–arterial oxygen gradient (desaturation) with exercise. The chest radiograph is insensitive compared with high-resolution CT (HRCT) scanning, which reveals "ground glass" opacities (alveolitis), consolidation, subpleural lines or bands, traction bronchiectasis, and honeycombing (fibrosis). Biopsy and autopsy studies of patients with myositis show an interstitial infiltrate of predominantly CD8+ T cells, while bronchoalveolar lavage (BAL) yields mostly CD8+ cells and a minor B-cell component (8). Clinically significant cardiac involvement is uncommon in IIM although autopsy studies detect a higher frequency of myocarditis. Electrical disturbances are commonly reported, including nonspecific ST-T segment changes and various conduction system abnormalities that can be monitored by electrocardiography. The myocardial fraction of CK (CKMB) is increased in patients with active myositis as regenerating myoblasts release this enzyme. However, cardiac troponin I is not influenced by skeletal muscle injury and elevations indicate myocardial damage. In myositis patients with proximal or distal dysphagia, the barium swallow may demonstrate cricopharyngeal hypertrophy or spasm in the case of IBM or poorly coordinated motion of the pharyngeal (striated) musculature, vallecular pooling, or aspiration of barium into the trachea in the case of severe PM or DM. Distal dysphagia reveals distal esophageal (smooth muscle) hypomotility on the cinesophagram or manometry, and occurs most frequently in patients with myositis in overlap with another connective tissue disorder.

Serum Autoantibodies

Antinuclear or anticytoplasmic autoantibodies are found in up to 90% of patients with PM or DM and are useful in defining clinically homogeneous subsets of patients (9). Myositis-specific autoantibodies (MSAs) have been previously reported to occur exclusively in IIM but the presence of MSAs without evidence of an inflammatory myopathy have being reported (10). It is rare for myositis patients to have more than one MSA. Autoantibodies seen in other connective tissue diseases may also be found in patients with myositis and are termed *myositis-associated autoantibodies*. Both groups of autoantibodies and their clinical associations are summarized in Table 18C-1. Although the frequency of autoantibody positivity is low with IBM, 18% (7/38) of IBM patients in one European cohort had identifiable antibodies (10). A negative antinuclear antibody test does not exclude MSA because the antigens targeted by these autoantibodies may be cytoplasmic in location. Testing for serum autoantibodies is helpful and can solidify the diagnosis of myositis in patients with atypical clinical features and provide prognostic information because of the known clinical associations.

Anti–Jo-1 is the most common MSA but the clinical features of the various antisynthetase antibodies are similar, and have been described as comprising the "antisynthetase syndrome" characterized by fever, "mechanic's hands," Raynaud's phenomenon, inflammatory arthritis, ILD, and myositis. Patients with an antisynthetase autoantibody may not manifest all features of the syndrome and some will never develop myositis. For example, anti–PL-12 antibody-positive patients are more likely to have ILD without myositis. Antibodies against signal recognition particle (anti-SRP) comprise a separate subgroup of MSAs targeting a ribonucleoprotein involved in protein translocation. Most patients have PM with severe, refractory disease and the muscle biopsy often does not demonstrate the characteristic lymphocytic endomysial inflammation (11) that is commonly found in PM. Mi-2 is a multi-unit protein complex involved in transcription and, unlike the cytoplasmic location of the synthetases and SRP, anti-Mi-2 is an antinuclear antibody. In general, anti–Mi-2 is associated with the rash of DM and a good response to therapy but it has been observed in PM patients as well as JDM and in malignancy, where the rash can be severe (12).

Anti–polymyositis-Scl is an antinucleolar antibody associated with a good prognosis that can be seen in PM or DM alone, systemic sclerosis alone, or in patients with overlap syndromes. Anti–U1-RNP antibodies should be suspected in patients with a high-titer speckled pattern on routine antinuclear antibody testing and occur in patients with an overlap syndrome of "mixed connective tissue disease" where clinical findings include Raynaud's phenomenon and variable features of SLE, myositis, and/or systemic sclerosis. Antibodies to Ro/SSA are seen in at least 10% of myositis, especially those with antibodies to the aminoacyl-tRNA synthetases.

Malignancy and Myositis

Recent reports strongly support an increased risk of cancer in patients with PM and DM with the greatest risk in DM. In a pooled study from Sweden, Denmark, and Finland, 618 cases of DM were identified, 198 of whom had cancer (13). Fifty-nine percent of the 198 patients developed a malignancy after the diagnosis of DM was made and the most common cancers were ovarian, lung, pancreatic, stomach, colorectal, and non-Hodgkin's lymphoma. A lower but statistically increased

TABLE 18C-1. SERUM AUTOANTIBODIES IN POLYMYOSITIS AND DERMATOMYOSITIS.

AUTOANTIBODY	ANTIGENIC TARGET	FREQUENCY IN IDIOPATHIC INFLAMMATORY MYOPATHIES (%)	CLINICAL ASSOCIATIONS
	MYOSITIS-SPECIFIC AUTOANTIBODIES		
Jo-1	Histidyl-tRNA synthetase	20	Antisynthetase syndrome (fever, interstitial lung disease, arthritis, Raynaud's and mechanic's hands and poor response to Rx)
PL-7	Threonyl-tRNA synthetase	2	Antisynthetase syndrome
PL-12	Alanyl-tRNA synthetase	2	Antisynthetase syndrome; lower frequency of myositis
OJ	Isoleucyl-tRNA synthetase	1	Antisynthetase syndrome
EJ	Glycyl-tRNA synthetase	1	Antisynthetase syndrome; DM > PM
KS	Asparaginyl-tRNA synthetase	<1	Rare; most patients have ILD
Mi-2	Nuclear helicase	5–10	DM (good response to Rx); PM only when ELISA used
SRP	Signal recognition particle	5	PM (with cardiomyopathy and unresponsive to Rx); rare cases of overlapping CTD
	MYOSITIS-ASSOCIATED AUTOANTIBODIES		
PM-Scl	Exosome proteins; multiprotein complex	5–10	Overlap with limited systemic sclerosis; myositis less severe
U1RNP	U1 small nuclear ribonucleoprotein	5–10	"MCTD" or overlapping myositis syndromes
Ku	DNA binding complex	1	PM-SSc overlapping; occasionally SLE
Ro/SSA	Ro60 and Ro52	10–20	Sjögren's; seen with antisynthetases

ABBREVIATIONS: CTD, connective tissue disease; DM, dermatomyositis; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; PM, polymyositis; SSc, systemic sclerosis.

risk of cancer was seen with PM and several case reports note that amyopathic DM may also be associated with malignancy. The overall risk of cancer is greatest in the first 3 years after the diagnosis of myositis, but an increased risk of malignancy continues, emphasizing the importance of ongoing surveillance. Serum CA-125 screening may be useful in women with DM. The presence of myositis-associated or specific serum autoantibodies and/or another connective tissue disease decreases the likelihood of cancer. A cancer screening evaluation of high-risk patients may increase early detection and reduce mortality. In addition to a careful history and physical examination (including a gynecologic evaluation in women) with routine laboratory testing, it is appropriate to complete an age-specific malignancy evaluation given the distribution of tumors noted above. This would include chest, abdominal, and pelvic CT scans, along with colonoscopy and mammography (see Chapter 18A for further discussion of malignancy and myositis).

TREATMENT OF INFLAMMATORY MYOPATHY

General Rehabilitative Measures

After confirming the diagnosis, assessing for systemic involvement and defining the relative contribution of disease activity and damage treatment should commence. Although the timing and aggressiveness of physical therapy is controversial, the overall goal is to improve and preserve existing muscle function and prevent atrophy and muscle contractures. Patients with acute, severe muscle weakness should receive passive exercises including a stretching program to prevent contractures. As muscle strength improves to near 50% to 60% normal then an active, assisted program can be instituted including an isotonic and isometric component involving resistive bands of varying elasticity. A more aggressive approach with free weights and

resistive machines can later be incorporated. Controlled studies utilizing strength training programs in patients with active but stable disease have shown that muscle enzymes do not increase and an improvement in muscle strength and well-being results.

Pharmacologic Therapy

Very few well-designed trials in IIM have been completed over the past 20 years. Although there are only a handful of randomized, blinded, and controlled studies, a pharmacologic approach can be recommended (14).

Corticosteroids

Although fraught with side effects, corticosteroids (CS) remain the agents of choice for the initial empiric treatment of inflammatory myopathy. The dosing depends on the disease severity and risk factors for toxicity because some patients with milder (i.e., overlapping syndromes) disease may benefit from lower CS doses. In general, patients should begin on daily, oral, divided-dose CS equivalent to 60 mg/day of prednisone. After normalization of the serum CK (often within 1–3 months), the prednisone can be consolidated to a once-daily dose and tapered by approximately 20% to 25% of the existing dose every 3 to 4 weeks to a daily morning dose of 5 to 10 mg. This dose should be maintained for several months depending on the clinical course, but patients often flare, necessitating an increase of CS to a previously effective (but not necessarily initial) dose. To evaluate treatment response, patients should be seen at least monthly with measurement of serum muscle enzymes and an assessment of manual muscle testing and functional status. With severe myositis or life-threatening extramuscular manifestations such as ILD, intravenous pulse methylprednisolone should be instituted to effect more rapid disease control. In IBM the use of steroids is controversial but in a patient with new-onset disease an acceptable regimen might include prednisone at 40 to 60 mg/day for 2 to 3 months. A favorable response would include a clear increase in muscle strength with or without a decrease in the serum CK because it is well known that the CK will drop in IBM without any clinical benefit. If improvement occurs, another immunosuppressive agent may be considered as a CS-sparing agent. However, assessing a response in IBM is difficult as the disease progresses insidiously and no studies in IBM have ever established the efficacy of any therapies.

Other Immunosuppressive Agents

Most myositis patients at least partially respond to CS and a complete lack of response in "PM" should prompt a reconsideration of that diagnosis. Methotrexate or azathioprine are often the first IS, steroid-sparing agents chosen and their combination has proven efficacious in refractory myositis (15). Methotrexate can be used in synthetase-positive patients if pulmonary function is carefully monitored. Cyclosporine is useful in both adult and childhood IIM in prospective and retrospective reports and another calcineurin inhibitor, tacrolimus, has efficacy for both myositis and ILD, particularly in Jo-1–positive patients (16). Mycophenolate mofetil has been increasingly reported in both PM and DM as well as the ILD associated with connective tissue diseases including myositis. The use of alkylating agents is controversial and should be reserved for refractory disease or severe systemic complications. In patients presenting with significant extramuscular manifestations or severe disease a CS-sparing agent should be concomitantly administered initially with prednisone. Immunosuppressive (IS) regimens in IBM have generally not been beneficial and treatment expectations with IBM patients should be different than with PM or DM given the greater "damage" at the time of diagnosis. Studies suggest that the inflammatory response in IBM may play a secondary role in disease pathogenesis and although corticosteroid treatment results in a decrease in inflammation in muscle biopsies and improved serum CK levels, muscle strength continues to deteriorate (17).

Intravenous Immune Globulin

Although the mechanism of action is unknown, several prospective trials of intravenous immune globulin (IVIG) have been efficacious in PM, DM, and IBM (18). This agent is often used in JDM early in the disease course in combination with CS and/or another IS agent. It can be utilized as bridge therapy but is unlikely to be helpful without concomitant disease-modifying therapy. It is also useful in the infected myositis where IS agents are contraindicated. IVIG can be administered for 2 consecutive days per month in conventional doses for 3 months and with a positive response, therapy may be continued for 6 months. Limitations include its expense and availability.

Other Therapies

Tumor necrosis factor alpha antagonists are anecdotally helpful and may be considered in the refractory patient but caution should be exercised as alveolitis has been reported with these agents in other rheumatic disease populations. Rituximab has been reported as effective in a small pilot study of DM (19) as well as other isolated cases of both PM and DM. Although one might postulate its improved efficacy in B cell-mediated DM, it is being studied in the largest clinical trial to date in adult and juvenile DM as well as PM.

Extramuscular Manifestations

Pulmonary manifestations significantly contribute to the morbidity and mortality of myositis patients and the most worrisome complication is rapidly progressive diffuse alveolitis manifesting as ground glass on HRCT of the lung. This may rapidly decompensate into adult respiratory distress syndrome, which caries a poor prognosis and an often fatal outcome. The treatment of ILD in such patients is empiric and often unsatisfactory but initial therapy should include pulse solumedrol therapy (1 g daily for 3 consecutive days) followed by daily, divided-dose corticosteroids (60–80 mg) and a second IS agent such as cyclophosphamide, azathioprine, cyclosporine, or tacrolimus. Joint symptoms in IIM often resolve with corticosteroids but the rheumatoidlike disease that may occur with Jo-1–positive patients requires other disease-modifying agents. The rash of DM can be difficult to treat and its course and response to treatment may be discordant with the muscle disease. Hydroxychloroquine (200–400 mg/day) is often effective, but quinacrine (100 mg/day), isotretinoin (0.5–1.0 mg/kg/day), topical tacrolimus, methotrexate, mycophenolate mofetil, or any of the other IS agents should be considered in treating the rash of DM. Subcutaneous or soft tissue calcification is unusual in adults but common in JDM. The soft tissue inflammatory response to calcinosis often responds to oral colchicine and other agents anecdotally reported to benefit calcinosis include low-dose warfarin, aluminum hydroxide, probenecid, bisphosphonates, and diltiazem. However, most clinicians believe that no treatment effectively treats calcinosis.

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