



Immune-Mediated Myopathies

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ABSTRACT

PURPOSE OF REVIEW: This article summarizes the clinical features, diagnostic evaluation, and management of the common immune-mediated myopathies: dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, and overlap myositis.

RECENT FINDINGS: The identification of myositis-specific autoantibodies has improved the characterization of the subtypes of myositis and associated clinical phenotypes, as the severity of muscle involvement, extramuscular manifestations, and risk of malignancy may vary among the subtypes of autoimmune myopathies.

SUMMARY: The understanding and diagnostic accuracy of the subtypes of autoimmune myopathies have been enhanced with careful attention to the key clinical features, the emergence of myositis-specific autoantibodies, the characterization of histopathologic hallmark features, and the aid of muscle imaging. Several immunotherapeutic options now exist that can be selected to target a specific subtype, often with a favorable prognosis, especially when treatment starts early in the disease course.

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INTRODUCTION

Inflammatory myopathies comprise a diverse group of heterogeneous muscle diseases traditionally characterized by muscle weakness, elevation in muscle enzymes, and inflammatory muscle biopsies. The historical classification has evolved over the years, in the past focusing on dermatomyositis, polymyositis, and inclusion body myositis. However, in the past 15 years, the emergence of myositis-specific antibodies within subgroups of patients has resulted in the development of a new classification system for inflammatory myopathies, including dermatomyositis, immune-mediated necrotizing myopathy, inclusion body myositis, antisynthetase syndrome, and overlap myositis.¹ This article will focus on the classification and treatment of the most common immune-mediated myopathies: dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, and overlap myositis. Inclusion body myositis has been removed from the umbrella of immune-mediated myopathies given the lack of response to conventional immunotherapy; refer to the article “Sporadic Inclusion Body Myositis and Other Rimmed Vacuolar Myopathies” by Conrad Wehl, MD, PhD,² in this issue of *Continuum*. Additionally, polymyositis has been recognized as a rare entity.

Muscle Weakness in Immune-Mediated Myopathies

Muscle weakness in patients with dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, overlap myositis, and polymyositis is symmetric and proximal, often involving the proximal shoulder and hip girdle limb muscles; with progression, muscle weakness may also affect the truncal muscles. Patients often describe difficulty with tasks requiring the use of proximal muscles, such as rising from a low-seated chair, climbing stairs, or raising their arms to lift objects. Distal weakness may occur late in the disease process; however, inclusion body myositis should be considered if an early and predominant finding involves finger flexors. Although ocular muscles are typically spared, facial muscle weakness may occur but is usually mild. Neck flexor weakness is more common than neck extensor involvement; however, occasionally neck extensor weakness may be so severe that it results in a dropped head syndrome. Pharyngeal muscles may be affected, causing nasal speech, voice hoarseness, nasal regurgitation, dysphagia, and, if severe, aspiration pneumonia. In advanced cases, weakness of diaphragmatic and accessory muscles may occur, causing dyspnea and respiratory insufficiency that may require noninvasive ventilation. Patients may also report diffuse myalgia or muscle tenderness; however, severe muscle pain is typically not a predominant symptom.

DERMATOMYOSITIS

Dermatomyositis is an inflammatory disease characterized by muscle weakness and skin rash.

Clinical Features

Dermatomyositis presents in children and adults with a subacute onset of proximal muscle weakness that is accompanied or preceded by a distinct skin rash, a cardinal feature of dermatomyositis. The skin involvement may precede the onset of weakness by weeks to months. Early in the course, the rash and muscle enzyme elevations may be the sole manifestations of dermatomyositis. In children, an insidious onset of weakness and myalgia may be preceded by fatigue, low-grade fevers, and rash. Some patients may develop the characteristic rash and never develop the weakness (called *dermatomyositis sine myositis* or *clinically amyopathic dermatomyositis*).

The rash generally occurs in photosensitive areas and is erythematous, edematous, and occasionally pruritic. A pathognomonic heliotrope (or violaceous discoloration) rash often involves the upper eyelids with or without periorbital edema (FIGURE 2-1). The cutaneous manifestations of the rash are characteristically seen over the extensor surfaces of the joints (metacarpophalangeal joints, elbows, and knees), anterior chest (in a V sign) (FIGURE 2-2), back and shoulders (in a “shawl



FIGURE 2-1

Heliotrope rash. Purplish red discoloration of the skin over the upper eyelids in a patient with dermatomyositis. Erythema is also noted over the malar region.

KEY POINTS

- Muscle weakness in patients with dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, overlap myositis, and polymyositis is symmetric and proximal, often involving the proximal shoulder and hip girdle limb muscles; with progression, it may also affect the truncal muscles.
- Dermatomyositis presents in children and adults with a subacute onset of proximal muscle weakness that is accompanied or preceded by a distinct skin rash, a cardinal feature of dermatomyositis.
- A pathognomonic heliotrope (violaceous discoloration) rash often involves the upper eyelids with or without periorbital edema.

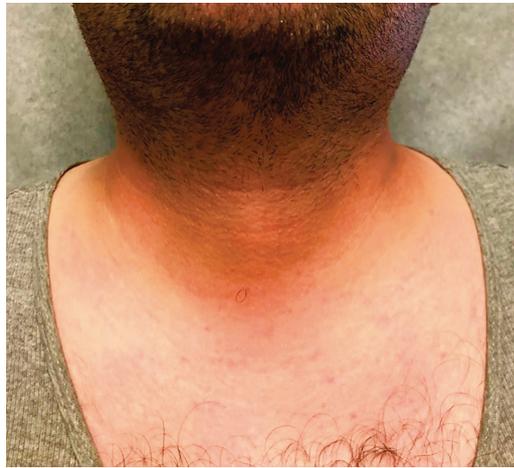


FIGURE 2-2
V sign. Erythematous cutaneous changes seen in a V distribution over the anterior neck in a patient with dermatomyositis.

sign”) (FIGURE 2-3), malar region, and face. Scaling, erythematous eruptions may cover bony prominences, especially metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints (referred to as *Gotttron sign*) (FIGURE 2-4), may be accompanied by raised papules or plaques (*Gotttron papules or plaques*), and can also be noted on the elbows and knees. A rough, cracking appearance of the skin of the fingertips may develop (most prominent on the lateral aspects of the index finger and thumb), known as *mechanic’s hands*. Telangiectasias,

manifested by dilated capillary loops at the nailbeds (periungual abnormalities) with irregular thickened and distorted cuticles can be seen (FIGURE 2-5). Poikiloderma, characterized by areas of hyperpigmentation and hypopigmentation, particularly over the upper back and extensor surfaces of the extremities, may be seen when active skin lesions in dermatomyositis resolve. Itching and scaling lesions may develop on the scalp, resulting in alopecia (FIGURE 2-6). Calcium deposits within the skin (*calcinosis cutis*), may occur in juvenile-onset dermatomyositis but can also be found in adult dermatomyositis, albeit less commonly.

Aside from the cutaneous involvement, other extramuscular manifestations in dermatomyositis include involvement of cardiac, pulmonary, gastrointestinal, and joint systems, as well as malignancy. Although most patients do not develop cardiac symptoms, cardiac arrhythmias or ejection fraction defects may be seen on ECGs and echocardiograms. Pericarditis, myocarditis, and congestive heart failure, while rare, can be lethal because of cardiac muscle involvement in dermatomyositis. Dyspnea and nonproductive cough are the clinical manifestations of interstitial lung disease, which can be a severe complication and the leading cause of death in patients with dermatomyositis. Chest imaging may reveal a diffuse reticulonodular pattern or a diffuse alveolar pattern with a ground-glass appearance seen in more severe pulmonary involvement. Pulmonary function tests reveal a restrictive



FIGURE 2-3
Shawl sign. Erythema noted over the region of the posterior neck and upper back in the distribution of a shawl in a patient with dermatomyositis.



FIGURE 2-4
Gottron sign. Scaling, erythematous cutaneous changes most prominently noted over the metacarpophalangeal joints but also seen over the proximal and distal interphalangeal joints in a patient with dermatomyositis.

defect with reduced diffusing capacity of the lungs for carbon monoxide (DLCO). Skeletal and smooth muscle involvement of the gastrointestinal tract in dermatomyositis can lead to dysphagia, impaired gastric motility, and aspiration pneumonia. Vasculopathy of the gastrointestinal tract, a serious complication seen more commonly in juvenile dermatomyositis than in adult-onset dermatomyositis, can result in ulcers, perforations, and even gastrointestinal hemorrhages. Large-joint and small-joint arthralgias with or without an

underlying arthritis can be a common symptom. An increased incidence of malignancy is noted in adult-onset dermatomyositis patients, especially based on the autoantibody subtype (see below).

Diagnostic Evaluation

Several diagnostic tools are now available for evaluating patients suspected of having a myositis. These include serum muscle enzymes, electrodiagnostic studies, myositis antibodies, muscle biopsy, and muscle MRI.

CREATINE KINASE AND OTHER SERUM ENZYMES. Serum creatine kinase (CK) levels are often elevated as a result of muscle membrane damage and necrosis in patients with myositis. In dermatomyositis, CK levels are often increased; however, they may range from normal to up to thousands of international units per liter. Since CK values in dermatomyositis can be normal, the CK level may not necessarily reflect disease severity or may not always be useful in monitoring disease progression/activity.

Other enzymatic markers that may be elevated when released from damaged skeletal muscle include aldolase, lactate dehydrogenase, as well as the transaminases, aspartate transaminase (AST) and alanine transaminase (ALT) (which are present both in liver and skeletal muscle). In patients with myositis,

KEY POINTS

- Aside from the cutaneous involvement, other extramuscular manifestations in dermatomyositis include involvement of cardiac, pulmonary, gastrointestinal, and joint systems, as well as malignancy.
- In dermatomyositis, creatine kinase levels are often increased; however, they may range from normal to up to thousands of international units per liter.



FIGURE 2-5
Telangiectasia hemorrhages (arrow) at the nailbeds (periungual abnormalities) with irregularly thickened cuticles in a patient with dermatomyositis.

KEY POINTS

- Patients with dermatomyositis with a positive anti-Mi-2 antibody are noted to have more classical cutaneous features of dermatomyositis, confer a good prognosis with a favorable response to steroids, and have a relatively low malignancy risk.
- The anti-TIF-1 γ antibody in dermatomyositis is highly associated with malignancy (in adult dermatomyositis but not in juvenile dermatomyositis) and severe skin manifestations, including diffuse photoerythema and “dusky red face” and unique characteristic cutaneous lesions of hypopigmented and telangiectatic (“red on white”) patches.
- Anti-nuclear matrix protein 2 antibodies are found in up to 25% of patients with juvenile dermatomyositis but are also detected in up to 40% of patients with adult dermatomyositis.



FIGURE 2-6
Alopecia. Focal patches as well as diffuse hair loss seen with erythematous eruptions over the scalp in a patient with dermatomyositis.

elevated levels of AST and ALT may cause confusion, raising a question of liver damage; thus, checking the γ -glutamyltransferase level, which is liver specific (and normal in patients with myositis when the liver is unaffected), can be useful to distinguish liver damage from skeletal muscle inflammation.

ELECTRODIAGNOSTIC STUDIES.

In patients with muscle weakness, electrodiagnostic studies are useful in confirming a myopathic process and ruling out neurogenic conditions with a predilection for proximal muscle weakness (including chronic inflammatory demyelinating polyradiculoneuropathy, spinal muscular atrophy, or other motor neuron disorders). In patients with myositis, sensory

and motor nerve conduction studies are typically normal; however, low-amplitude motor nerve responses can be seen when weakness in myositis is severe and diffuse. Needle EMG may show abnormal spontaneous activity (fibrillation potentials, positive sharp waves) and short-duration, low-amplitude motor unit potentials with an early recruitment pattern consistent with a myopathic process with muscle membrane irritability.

DERMATOMYOSITIS ANTIBODIES. Five known dermatomyositis-specific autoantibodies (including Mi-2, TIF-1 γ , NXP-2, MDA-5, and SAE) have been associated with distinct clinical phenotypes and in some cases serve as useful prognostic markers (TABLE 2-1 and TABLE 2-2). Anti-Mi-2 antibody was the first reported myositis-specific autoantibody associated with rash in 1985.³ Since then, patients with dermatomyositis with a positive anti-Mi-2 antibody are noted to have more classical cutaneous features of dermatomyositis, confer a good prognosis with a favorable response to steroids, and have a relatively low malignancy risk.⁴ However, the anti-TIF-1 γ antibody in dermatomyositis is highly associated with malignancy (in adult dermatomyositis but not in juvenile dermatomyositis)⁵ and severe skin manifestations, including diffuse photoerythema and “dusky red face” and unique characteristic cutaneous lesions of hypopigmented and telangiectatic (“red on white”) patches.⁶ Anti-NXP-2 antibodies are found in up to 25% of patients with juvenile dermatomyositis but are also detected in up to 40% of patients with adult dermatomyositis.⁷ NXP-2 autoantibodies are associated with the development of subcutaneous calcifications in both juvenile and adult dermatomyositis, peripheral edema, and an increased risk of malignancy in adults (CASE 2-1).⁸

Autoantibodies against MDA-5 are reported in higher frequency in Asian patients with dermatomyositis and are associated with minimal muscle

involvement (clinically amyopathic dermatomyositis) yet rapidly progressive interstitial lung disease and a poor prognosis.⁹ Severe skin lesions, including skin ulcerations over interphalangeal joints, tender palmar papules, and oral ulcers, have also been described in patients with dermatomyositis who are anti-MDA-5-positive (FIGURE 2-7).¹⁰ Antibodies against SAE are the least frequent of the dermatomyositis-specific autoantibodies (occurring in less than 10% of adult dermatomyositis cases); patients with dermatomyositis who are

Myositis-Specific Antibodies and Associated Clinical Phenotype

TABLE 2-1

Myositis-Specific Antibodies (Based on Subtype of Myositis)	Characteristic Clinical Features
Dermatomyositis	
Anti-Mi-2	Classical skin rash, moderate muscle involvement, favorable response to immunotherapy
Anti-TIF-1 γ	Strong association with cancer, severe skin rash, hypopigmented red on white patches, variable degree of muscle involvement
Anti-NXP-2	Increased risk of malignancy, classic skin rash, mild-to-moderate muscle involvement, subcutaneous calcifications, peripheral edema
Anti-MDA-5	Severe skin rash, no/minimal muscle involvement, skin ulcerations, rapidly progressive interstitial lung disease
Anti-SAE	Classic rash, mild muscle involvement, dysphagia
Antisynthetase syndrome	
Anti-Jo-1	Muscle involvement common, progressive interstitial lung disease, may have mild skin rash and mechanic's hands
Anti-PL-7	Severe interstitial lung disease, may have moderate muscle involvement
Anti-PL-12	Severe interstitial lung disease, may have mild or no muscle involvement
Anti-glycyl-transfer RNA synthetase (EJ), anti-OJ, anti-KS	High association with interstitial lung disease
Anti-Zo, anti-Ha	Rare, possible interstitial lung disease
Immune-mediated necrotizing myopathy	
Anti-signal recognition particle (SRP)	Severe muscle involvement, rare but occasional lung involvement, no skin involvement
Anti-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase	Severe muscle involvement, prior statin use (but 30% statin naïve), no skin or lung involvement
Antibody-negative immune-mediated necrotizing myopathy	Increased risk of malignancy

positive for anti-SAE antibody may have an initial presentation of amyopathic dermatomyositis, at times with a severe rash, and a high incidence of dysphagia.¹¹

HISTOPATHOLOGY. Perifascicular muscle fiber atrophy is a specific and pathologic hallmark feature of dermatomyositis (FIGURE 2-8).¹² The inflammatory infiltrates (consisting of CD4+ T cells and plasmacytoid dendritic cells) are predominantly located in the perimysium and perivascular regions. Signs of a vasculopathy with a reduction in capillaries and deposition of the membrane attack complex on muscle microvasculature can be seen early in the disease, along with the presence of endothelial microtubular inclusions.¹³ Damage to the capillaries with capillary dropout may cause ischemia with subsequent atrophy and may be an explanation for the perifascicular atrophy pattern seen in dermatomyositis muscle biopsies. Other histologic findings prominent in the perifascicular region include internalized nuclei, fiber necrosis, regeneration, basophilia, increased oxidative enzyme reactivity, endomysial fibrosis, and major histocompatibility complex class-1 upregulation.¹⁴

MUSCLE MRI. Muscle MRI is a useful noninvasive tool more recently used to aid in the diagnosis and management of inflammatory myopathies. MRI scans may demonstrate distribution and severity of muscle involvement (reflecting disease burden), provide guidance to select an affected muscle to biopsy (increasing the yield of the biopsy), and give insight into the response to immunotherapy. MRI is helpful for visualizing muscle edema (an early finding of active disease), muscle atrophy, and fatty replacement (seen in chronic

TABLE 2-2

Myositis-Specific Antibodies and Organ Involvement

Myositis-Specific Antibody	Muscle	Skin	Lung	Cancer
Dermatomyositis				
Mi-2	X	X		
TIF-1γ	X	X		X
NXP-2	X	X		X
MDA-5		X	X	
Antisynthetase				
Jo-1	X		X	
PL-7	X		X	
PL-12			X	
Immune-mediated necrotizing myopathy				
Signal recognition particle (SRP)	X			
3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase	X			
Antibody-negative immune-mediated necrotizing myopathy	X			X

disease), as well as subcutaneous edema and fasciitis. Short tau inversion recovery (STIR) sequences are best used to detect muscle or fascial edema, whereas axial T₁-weighted images are helpful in visualizing fatty atrophy. Distinct patterns of muscle involvement have been described to aid in early diagnosis of the idiopathic inflammatory myopathies.

In dermatomyositis, STIR images commonly demonstrate hyperintensity or edema in a patchy distribution in the muscle, along with edema of the subcutaneous tissues and fascia (an uncommon finding in other inflammatory myopathies) (FIGURE 2-9A), and may mirror the distribution of skin involvement.¹⁵ Fatty

CASE 2-1

A 57-year-old woman presented for a neurologic consultation reporting 2 to 3 months of mild proximal muscle weakness of her legs and arms. Upon questioning, she reported myalgia, fatigue, and a 15-lb weight loss in the preceding few months but denied fevers, cough, or arthralgias. She also had recent mild erythema on her face that she attributed to sun exposure. She was healthy and active at her baseline.

On examination, she was found to have erythematous skin changes on her scalp, malar region of her face, eyelids, anterior neck (V sign), elbows, and metacarpophalangeal joints (Gottron sign). On strength testing, she had weakness predominantly in the following areas: neck flexors 4+/5, shoulder abductors 4/5, elbow flexors and extensors 4/5, hip flexors 4/5, and knee extensors 4+/5.

Her creatine kinase level was mildly elevated at 389 U/L. Needle EMG showed fibrillation potentials with short-duration, low-amplitude motor unit potentials and an early recruitment pattern in proximal muscles. Biceps muscle biopsy showed inflammatory cells, necrosis, and atrophy in a perifascicular distribution. Myositis antibody panel was positive for anti-nuclear matrix protein 2 (NXP-2) antibody. CT of the chest, abdomen, and pelvis and mammogram were negative for malignancy.

The patient was diagnosed with dermatomyositis based on her clinical presentation of proximal muscle weakness, erythematous skin rash on sun-exposed regions, and muscle biopsy hallmark feature of perifascicular atrophy. She was started on oral prednisone and methotrexate, but her symptoms continued to worsen. Given the increased association of malignancy and anti-NXP-2 antibody, despite her negative routine malignancy workup, a positron emission tomography (PET) scan was performed, which revealed a nasal mass found to be a nasopharyngeal carcinoma. She received radiation and chemotherapy for the tumor, was placed on intravenous immunoglobulin (IVIg), prednisone, and methotrexate with improvement in her strength, and continued to be under surveillance 3 years later.

This case exemplifies the increased risk of malignancy associated with the anti-NXP-2 antibody found in patients with dermatomyositis and the importance of vigilant cancer screening because it impacts the treatment and prognosis of these patients.

COMMENT



FIGURE 2-7
Severe skin ulceration affecting the interphalangeal joints in a patient with dermatomyositis associated with antibodies to melanoma differentiation-associated protein 5. Figure courtesy of Luis Chui, MD.

infiltration in dermatomyositis is reportedly mild. MRI has also been useful in detecting the calcinosis deposits seen in dermatomyositis (**FIGURE 2-9B**), as well as in evaluating patients with dermatomyositis who are designated to have clinically amyopathic dermatomyositis because muscle MRI may occasionally show subtle edema along the fascia or subtly affecting the muscle, indicating that there may indeed be mild muscle involvement.

Pathophysiology

The combination of several immunogenetic risk factors,

including class-2 human leukocyte antigen (HLA) alleles, and environmental exposures, have been implicated in the pathogenesis of dermatomyositis.¹⁶ Interferon overproduction has been a proposed mechanism of the pathology seen in dermatomyositis because dermatomyositis muscle has been shown to contain abundant interferon-secreting plasmacytoid dendritic cells.¹⁷ Additionally, interferon-inducible genes are highly upregulated in dermatomyositis, and the gene expression in the blood correlates with dermatomyositis disease activity¹⁸; but the mechanism of interferon overproduction leading to the loss of capillaries and perifascicular atrophy still remains unclear.

ANTISYNTHETASE SYNDROME

Antisynthetase syndrome is an autoimmune condition characterized by a wide variety of clinical manifestations, including myositis and interstitial lung disease, and is associated with serum autoantibodies to the aminoacyl transfer RNA synthetases.

Clinical Features

Patients with antisynthetase syndrome may present with a constellation of all or some of the following clinical features: inflammatory myopathy, interstitial lung disease, arthritis, Raynaud syndrome, fever, and mechanic’s hands. Some patients additionally have skin rashes similar to dermatomyositis. Muscle weakness (secondary to an inflammatory myopathy) is not seen in all patients with antisynthetase syndrome,

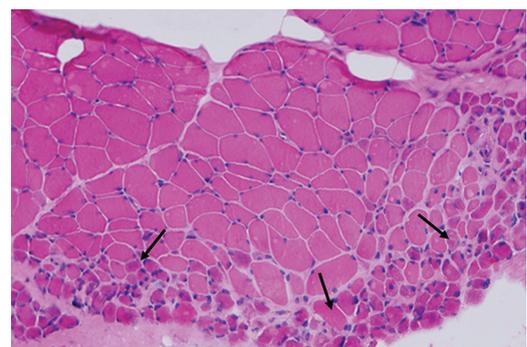


FIGURE 2-8
Muscle biopsy of a patient with dermatomyositis (hematoxylin and eosin stain). Note the characteristic small, atrophic muscle fibers in the perifascicular distribution (arrows).

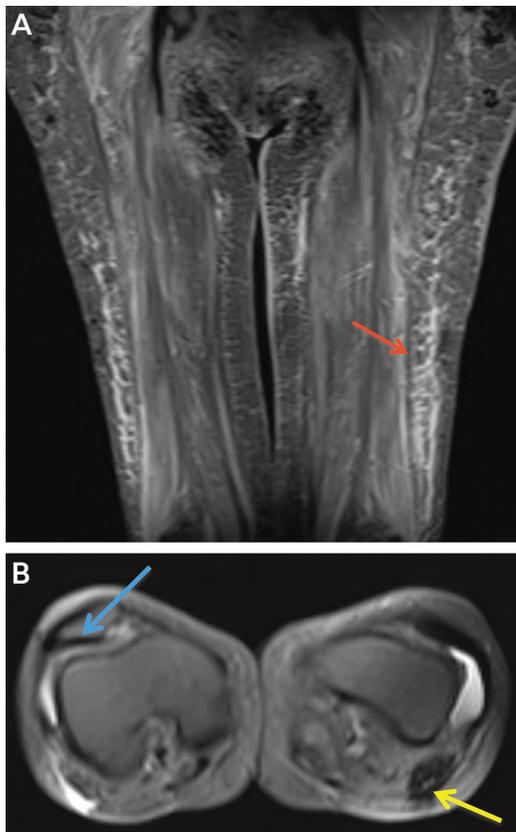


FIGURE 2-9 Thigh muscle MRI of a patient with severe dermatomyositis. *A*, Hyperintensity is seen throughout the subcutaneous tissue (red arrow; coronal section, short tau inversion recovery sequences). *B*, Axial image of the thigh shows marked muscle atrophy (blue arrow) indicating severe disease and subcutaneous calcifications in the posterior thigh (hypointensity, yellow arrow).

but most frequently in patients positive for anti-Jo-1 autoantibodies (CASE 2-2). If myositis is present, the proximal muscle weakness develops subacutely over weeks to months.

Diagnostic Evaluation

The features of myositis in patients with antisynthetase syndrome are similar to those of the myopathic features of dermatomyositis, with similar proximal muscle weakness developing over weeks to months, elevated muscle enzymes, and a myopathic process on EMG.

ANTISYNTHETASE ANTIBODIES.

Aminoacyl transfer RNA (tRNA) synthetases are a group of enzymes that catalyze the binding of a specific amino acid to their cognate tRNA; currently eight antisynthetase myositis-specific autoantibodies (anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-Ha) directed against different tRNA synthetases have been recognized (TABLE 2-1 and TABLE 2-2).^{19,20} Although patients with antisynthetase syndrome

may share a similar constellation of features (inflammatory myopathy, interstitial lung disease, arthritis, Raynaud syndrome, and mechanic's hands), certain antisynthetase autoantibodies have been associated with a greater risk of developing particular characteristics of the syndrome. Anti-Jo-1 (the first to be discovered and most common antisynthetase autoantibody) is associated with the greatest risk of developing a myositis (in contrast to the other antisynthetase antibodies) because up to 90% of patients with Jo-1 antibodies have a myositis; however, the risk of developing interstitial lung disease has been reported in up to 50% of patients with anti-PL-12 antibodies, but they have no muscle involvement.^{19,20} Patients with anti-PL-7 and anti-PL-12 autoantibodies are noted to have more severe lung involvement than muscle weakness.¹⁹

HISTOPATHOLOGY. Muscle biopsies in patients with antisynthetase syndrome share features similar to those of dermatomyositis biopsies (eg, perifascicular atrophy, microvasculature abnormalities). However, other distinct histopathology features described in muscle biopsies from patients with anti-Jo-1 antibodies include necrosis in the perifascicular region,

KEY POINTS

- Perifascicular muscle fiber atrophy is a specific and pathologic hallmark feature of dermatomyositis.
- In dermatomyositis, short tau inversion recovery MRI sequences commonly demonstrate hyperintensity or edema in a patchy distribution in the muscle, along with edema of the subcutaneous tissues and fascia (an uncommon finding in other inflammatory myopathies), and may mirror the distribution of skin involvement.
- Patients with antisynthetase syndrome may present with a constellation of all or some of the following clinical features: inflammatory myopathy, interstitial lung disease, arthritis, Raynaud syndrome, fever, and mechanic's hands.
- Of the antisynthetase antibodies, anti-Jo-1 (the first to be discovered and most frequent antisynthetase autoantibody) is associated with the greatest risk of developing a myositis.
- Up to 90% of patients with Jo-1 antibodies have a myositis; however, the risk of developing interstitial lung disease has been reported in up to 50% of patients with anti-PL-12 antibodies, but they have no muscle involvement.

fragmentation of the perimysium, and increased perimysial alkaline phosphatase activity (FIGURE 2-10).²¹ On electron microscopy, aggregation of nuclear actin is seen, a unique feature that is not seen in other inflammatory myopathies.²²

MUSCLE MRI. MRI scans in patients with antisynthetase syndrome often show intramuscular STIR hyperintensities; however, a specific MRI pattern has not been described.²³

IMMUNE-MEDIATED NECROTIZING MYOPATHIES

Immune-mediated necrotizing myopathies are clinically characterized by severe proximal muscle weakness with rare extramuscular involvement and histopathologically by myofiber necrosis with a lack of inflammatory cell infiltrates.

CASE 2-2

A 51-year-old woman presented with more than 5 months of joint pain and fatigue followed by weakness with difficulty arising from a chair. Within a few months, her muscle weakness had progressed and was accompanied by shortness of breath with exertion and a nonproductive cough. She denied any history of rash but reported mildly dry, cracking skin changes on her fingertips. Her past medical history was notable only for hypertension.

Her neurologic examination revealed proximal muscle weakness of her deltoids and biceps (4/5) and hip flexors (4/5). Examination of her skin showed no erythematous rash over her face or joints but did show signs of mechanic's hands. Her creatine kinase (CK) level was 942 U/L. EMG showed diffuse, small, myopathic units with early recruitment and fibrillation potentials. Muscle biopsy of the biceps showed necrosis in the perifascicular region and fragmentation of the perimysium. Testing for 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase antibody was negative, but the myositis antibody panel was positive for anti-Jo-1 antibody.

The patient was diagnosed with antisynthetase syndrome because she had the constellation of clinical features of myositis, arthralgia, mechanic's hands, and pulmonary symptoms. She was found to have anti-Jo-1 antibody, which has a high association with myositis and lung involvement. CT of her chest showed findings of interstitial lung disease. Methotrexate was avoided because of concern for pulmonary toxicity; thus, she was started on prednisone 40 mg daily and azathioprine at 50 mg a day, titrated to 75 mg 2 times a day (within 6 weeks), with normalization of her strength and CK level within 9 months.

COMMENT

This case portrays the constellation of clinical features seen in antisynthetase syndrome; in addition to the myositis, patients are found to have joint involvement and, importantly, interstitial lung disease, which can be the main prognostic factor. Diagnosis is aided by the identification of one of the antisynthetase autoantibodies, and patients often improve with long-term immunosuppressive therapy.

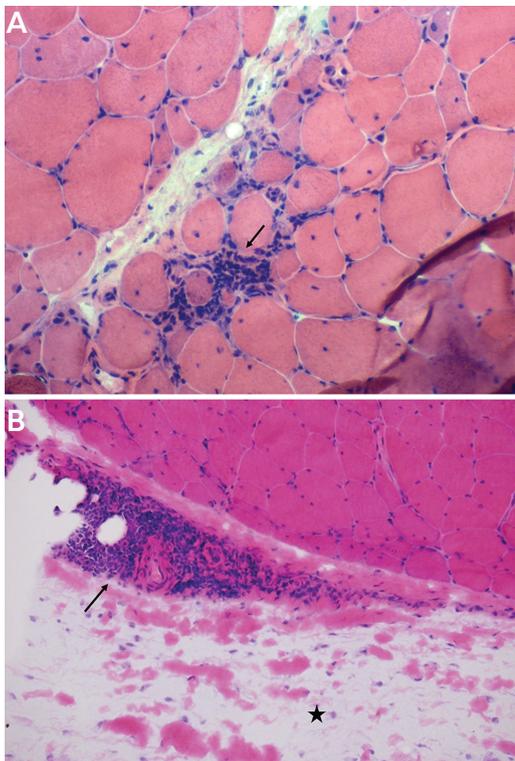


FIGURE 2-10
Muscle biopsy of a patient with anti-Jo-1 antisynthetase syndrome (hematoxylin and eosin stain). **A**, Muscle fiber undergoing necrosis in the perifascicular region of the biopsy (arrow). **B**, Perimysial fragmentation of the connective tissue (star) and inflammation surrounding vessels (arrow).

Clinical Features

Patients presenting with immune-mediated necrotizing myopathies can develop aggressive proximal weakness that may occur acutely or subacutely, often resulting in severe muscle weakness and markedly elevated CK levels (**CASE 2-3**).

The clinical hallmark of immune-mediated necrotizing myopathy is the presence of proximal muscle weakness because significant lung, skin, or extramuscular involvement is rare (occurring in less than 10% of cases) and, if present, should raise concern for another type of inflammatory myopathy.^{24,25} In children affected by immune-mediated necrotizing myopathy, proximal muscle weakness may slowly progress over years, making it difficult to discern from a limb-girdle muscular dystrophy; thus, immune-mediated necrotizing myopathy should be considered

in the differential in patients with a genetically undiagnosed myopathy resembling a limb-girdle muscle dystrophy.²⁶

Diagnostic Evaluation

While similar diagnostic tools are used in evaluating all subtypes of myositis, in patients with immune-mediated necrotizing myopathies the muscle biopsy findings of necrosis (yet lack of inflammation) and presence of an autoantibody often help confirm the diagnosis.

CREATINE KINASE. Serum CK levels in immune-mediated necrotizing myopathy are typically markedly elevated, up to several thousands of international units per liter, with the median peak reported at 4700 U/L.²⁷ Additionally, in immune-mediated necrotizing myopathy, CK elevations may precede the onset of weakness, can be used to detect exacerbations of disease when therapy is being weaned, and can normalize in patients with long-standing disease due to replacement of muscle by fat and atrophy even with ongoing disease activity.

ELECTRODIAGNOSTIC STUDIES. Electrodiagnostic findings in patients with immune-mediated necrotizing myopathy are similar to those in all patients with myositis because the EMG shows a myopathic process with muscle membrane

KEY POINT

- Serum creatine kinase levels in immune-mediated necrotizing myopathy are typically markedly elevated, up to several thousands of international units per liter, with the median peak reported at 4700 U/L.

irritability. The needle EMG in immune-mediated necrotizing myopathy may reveal a “noisier” examination at rest (in comparison with dermatomyositis) with florid abnormal spontaneous activity seen in the form of positive sharp waves, fibrillation potentials, complex repetitive discharges, and even pseudomyotonic discharges, in addition to the myopathic units.

ANTIBODIES. To date, the two main antibodies associated with immune-mediated necrotizing myopathy are the SRP and the anti-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase antibodies,²⁸ which account for approximately two-thirds of immune-mediated necrotizing myopathy cases. Thus, the 2017 European Neuromuscular Centre criteria for immune-mediated necrotizing myopathy describe three subtypes: anti-SRP myopathy, anti-HMG-CoA reductase myopathy, and antibody-negative immune-mediated necrotizing myopathy (TABLE 2-1 and TABLE 2-2).²⁸

Anti-SRP antibodies, although relatively rare (reported in approximately 5% of patients with myositis),²⁹ have been associated with aggressive disease with severe muscle weakness, dysphagia, and strikingly elevated CK levels that may not respond well to conventional immunotherapy. In a large case series of 100 patients with anti-SRP antibody-positive myopathy, 62 of 81 patients (77%)

CASE 2-3

A 49-year-old man presented for evaluation of proximal limb weakness and gait difficulty requiring a wheelchair. He recalled an insidious onset of myalgia with leg weakness and difficulty climbing stairs that started 4 years ago and gradually worsened to affect his proximal legs and arms, without rash, swallowing difficulty, or shortness of breath. At that time, he was seen at an outside facility and found to have a creatine kinase (CK) elevation of 6100 U/L. His statin medication, which he had been on for a few years, was discontinued, but his muscle weakness progressed over months and his CK level increased to 10,300 U/L. A muscle biopsy was performed, and he was diagnosed with polymyositis. Despite 4 years of treatment at an outside facility with courses of IV methylprednisolone, oral prednisone (up to 80 mg daily), and mycophenolate mofetil (1 g 2 times a day), he noted a significant decline resulting in severe proximal muscle weakness and wheelchair use for long distances. He then came to a tertiary neuromuscular disease clinic for a second opinion. His past medical history was notable for hypertension, diabetes mellitus, and hyperlipidemia; he had remained off his lipid-lowering agent for 4 years.

On manual muscle testing, he had severe shoulder and hip girdle weakness, with neck flexors 4/5, shoulder abductors and elbow flexors 3/5, elbow extensors 4-/5, hip flexors and hip adductors 2/5, hip extensors and hip abductors 3/5, and knee extensors 4/5. Facial and distal muscle strength was preserved. He had mild lumbar lordosis and took a few steps with a waddling gait.

EMG showed marked fibrillation potentials and short-duration, low-amplitude motor unit potentials with an early recruitment pattern.

required additional immunotherapy aside from corticosteroids, and despite 2 years of treatment, 27% still had poor neurologic outcomes.³⁰

Anti-HMG-CoA reductase antibody-associated immune-mediated necrotizing myopathy was first described in patients with a history of statin exposure with weakness that continued to progress despite stopping use of the statin medication^{31,32}; however, up to one-third may be statin naïve and may have a more resistant treatment response.³³

The risk of cancer in those patients with an immune-mediated necrotizing myopathy depends on the subtype (based on antibody status). Those with anti-HMG-CoA reductase myopathy have been described to have a relatively weak association with cancer, whereas anti-SRP myopathy is not associated with malignancy. However, autoantibody-negative immune-mediated necrotizing myopathy has been associated with a relatively high risk of malignancy,³⁴ warranting aggressive cancer screening for up to 3 years from the onset of symptoms.

HISTOPATHOLOGY. The muscle histopathology in immune-mediated necrotizing myopathy is characterized by the presence of necrosis of muscle fibers or regeneration with a paucity of (if any) lymphocytic infiltrates (**FIGURE 2-11**).³⁵ Although major histocompatibility complex class-1 upregulation, myofiber

Muscle MRI showed diffuse edema of his thigh muscles. His previous quadriceps muscle biopsy slides were reviewed and showed scattered necrotic and regenerating fibers but no obvious inflammation or perifascicular atrophy. Extensive prior cancer screening and myositis antibody panel including anti-Mi-2, anti-signal recognition particle [SRP], and anti-Jo-1 were negative, and the anti-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase antibody panel was positive.

The patient was diagnosed with anti-HMG-CoA reductase myopathy (ie, immune-mediated necrotizing myopathy). His marked CK elevation (in the thousands of international units per liter), progressive weakness despite stopping his statin medication, and muscle biopsy that showed necrotic fibers without inflammation were clues to the diagnosis. He was started on intravenous immunoglobulin (IVIg) therapy monthly; oral prednisone was gradually tapered over months, and mycophenolate mofetil was discontinued. Within 6 months of IVIg treatment, he noted improvements in strength and his ability to ambulate with a walker and had a CK reduction to 3000 U/L. Two years later, he remained on IVIg monotherapy and had mild residual proximal weakness, but he was able to ambulate unassisted, and his CK normalized (230 U/L).

This case demonstrates that patients with an anti-HMG-CoA reductase myopathy may develop severe progressive proximal limb-girdle distribution of weakness that is accompanied by a marked CK elevation in the thousands of international units per liter, yet they may lack inflammation on muscle biopsy and can have a robust response to IVIg therapy.

COMMENT

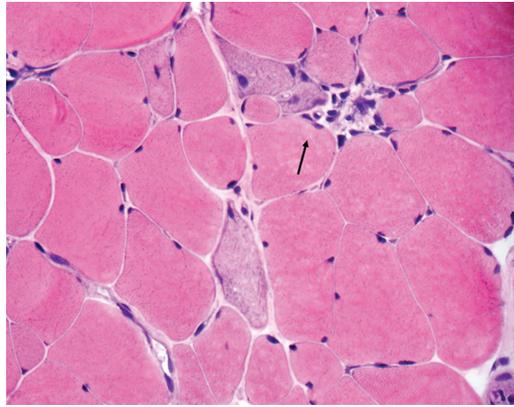


FIGURE 2-11
Muscle biopsy of a patient with anti-3-hydroxy-3-methylglutaryl coenzyme A reductase immune-mediated necrotizing myopathy (hematoxylin and eosin stain). Necrotic and degenerating muscle fibers (arrow) are seen with a lack of lymphocytic endomysial inflammation.



FIGURE 2-12
Thigh muscle MRI of a patient with immune-mediated necrotizing myopathy. Patchy hyperintensity seen throughout the anterior compartment of the thigh (arrow, coronal section, short tau inversion recovery sequences) indicating edema in a patient with immune-mediated necrotizing myopathy and a creatine kinase elevation of 3000 U/L.

degeneration, necrosis, and macrophage infiltration can be seen in immune-mediated necrotizing myopathy (features similar to dermatomyositis), perivascular inflammation and perifascicular atrophy do not occur.²⁸

MUSCLE MRI. Muscle MRI in patients with immune-mediated necrotizing myopathy is useful in demonstrating the distribution of affected muscle and disease burden of both active and chronic disease. Patients with active immune-mediated necrotizing myopathy have MRI findings of generalized muscle edema (seen as hyperintensities on STIR sequences that are associated with ongoing inflammation or myofiber necrosis) (FIGURE 2-12), atrophy and fatty infiltration (seen on T1-weighted images and that can begin early after onset of the disease), with minimal fascial edema (in contrast to patients with dermatomyositis).³⁶ Additionally, patients with immune-mediated necrotizing myopathy may have less involvement of the anterior compartment of the thigh, in comparison to patients with inclusion body myositis.³⁶ In comparison with patients with anti-HMG-CoA reductase myopathy, the muscle MRIs of patients with anti-SRP myopathy reveal higher rates of fatty replacement and atrophy, demonstrating a more severe form of myopathy.³⁶

Pathogenesis

Immunogenetic risk factors have been suggested to play a role in immune-mediated necrotizing myopathy. One study indicated

an association of the class-2 HLA-allele DRB1*08:03 with anti-SRP myopathy.³⁷ Several case-control studies have implicated DRB1*11:01 as a risk factor for anti-HMG-CoA reductase myopathy. DRB1*11:01 has been found in 70% of patients with anti-HMG-CoA reductase antibodies, but only in 15% of the general population, and may play a role in presenting the relevant HMG-CoA reductase peptides with exposure to statins that trigger an immune response.^{37,38}

OVERLAP MYOSITIS

Autoimmune myopathy may be associated with other well-defined autoimmune connective tissue disorders, known as *overlap syndromes* and include systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, and systemic sclerosis. Although significant muscle weakness is not a typical feature in most of these isolated connective tissue conditions (and when present may be the result of disuse atrophy or arthritis), proximal muscle weakness is noted in patients with overlap myositis when a concurrent myositis exists with a known connective tissue disease.

Antibodies

Several myositis-associated antibodies that are nonspecific and seen in immune-mediated inflammatory myopathies and other connective tissue diseases have been identified, including antibodies to Ro52/TRIM21, PMScl, ribonucleoprotein complex (RNP; U1 RNP, U2 RNP, U4/U6 RNP, and U5 RNP), and Ku. The most common myositis-associated antibodies are anti-Ro52 antibodies, which are nonspecific and have been detected in approximately 25% of patients with all types of myositis.³⁹ Anti-PMScl antibodies have been observed in patients with myositis/systemic sclerosis overlap syndrome and have been associated with lung and esophageal involvement.⁴⁰ Anti-Ku antibodies have been identified in up to 55% of cases of myositis/systemic sclerosis overlap syndrome with frequent joint involvement, Raynaud syndrome, and a greater risk of interstitial lung disease.⁴¹ Anti-U1 RNP antibodies have been described in patients with features of myositis, scleroderma, systemic lupus erythematosus, and glomerulonephritis.⁴²

POLYMYOSITIS

Historically, polymyositis has been characterized by a subacute onset of proximal muscle weakness, CK elevation, myopathic EMG, and endomysial inflammation with CD8+ T cell infiltrates seen on muscle biopsy. It has been increasingly recognized that polymyositis is a rare entity because many patients who were initially diagnosed with polymyositis are subsequently diagnosed with inclusion body myositis, antisynthetase syndrome without the rash, or an immune-mediated necrotizing myopathy based on further evaluation of characteristic clinical features, autoantibodies, and histopathology findings.^{43,44} The diagnosis of polymyositis is seen now as a diagnosis of exclusion and patients should be followed closely to assess for the development of clinical findings that may indicate alternative diagnoses.

TREATMENT OF IMMUNE-MEDIATED MYOPATHIES

Several immunotherapeutic agents are available for the treatment of immune-mediated myopathies, often with a favorable response.

KEY POINTS

- The 2017 European Neuromuscular Centre criteria for immune-mediated necrotizing myopathy describe three subtypes: anti-SRP myopathy, anti-3-hydroxy-3-methylglutaryl coenzyme A reductase myopathy, and antibody-negative immune-mediated necrotizing myopathy.

- The anti-3-hydroxy-3-methylglutaryl coenzyme A reductase antibody associated immune-mediated necrotizing myopathy was first described in patients with a history of statin exposure with weakness that continued to progress despite stopping use of the statin medication; however, up to one-third may be statin naïve and may have a more resistant treatment response.

- The muscle histopathology in immune-mediated necrotizing myopathy is characterized by the presence of necrosis of muscle fibers or regeneration with a paucity of (if any) lymphocytic infiltrates.

- The most common myositis-associated antibodies are anti-Ro52 antibodies, which are nonspecific and have been detected in approximately 25% of patients with all types of myositis.

Immunotherapy

Immunosuppressive therapy is widely accepted as the mainstay of treatment for autoimmune myopathies. However, because of the low prevalence of the disease, variability in disease course, and phenotypic differences, only a few randomized controlled treatment trials with a large number of patients have been completed; as a result, standardized consensus guidelines for the treatment of inflammatory myopathies do not exist. Instead, treatment approaches have predominantly been based on anecdotal experience, case series, and the opinions of experts in the field (FIGURE 2-13).

Corticosteroids, commonly prednisone, are the first-line therapy in the treatment of inflammatory myopathies, typically prescribed at a dose of 0.5 mg/kg/d to 1 mg/kg/d, with a maximum dose of 60 mg/d to 80 mg/d. In practice, many experts try not to exceed daily doses of 40 mg/d to 60 mg/d. In cases of severe muscle weakness, IV methylprednisolone (1 g/d for 3 to 5 days) can be given initially, followed by oral prednisone. Prednisone tapering typically should not begin before 4 to 6 weeks and should be individualized based on clinical assessment once patients have shown significant

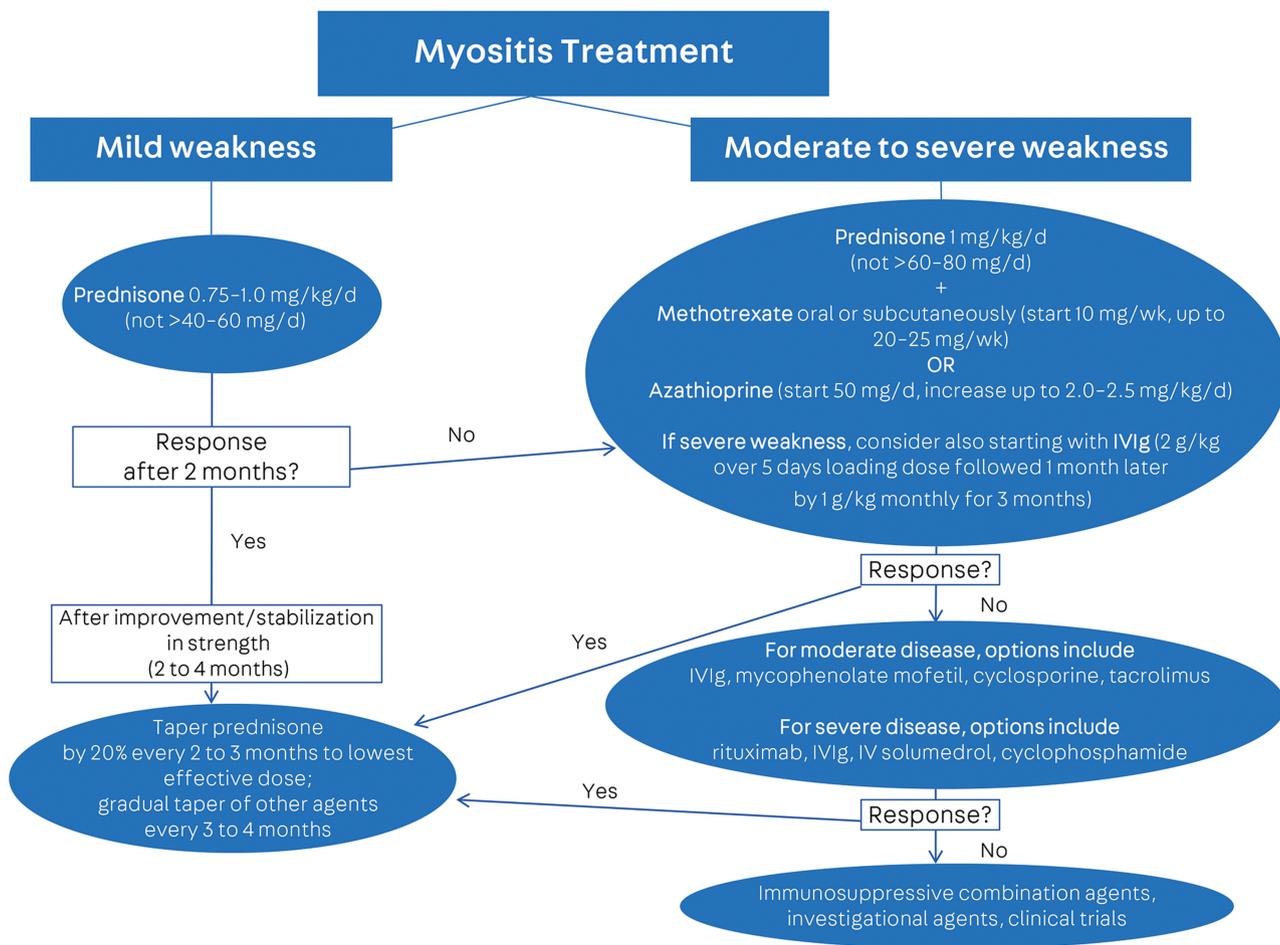


FIGURE 2-13 Treatment algorithm for autoimmune myopathies. The treatment paradigm is based on mild versus moderate-to-severe disease severity.

IV = intravenous; IVIg = intravenous immunoglobulin.

improvement or the slope of improvement has plateaued. Tapers of prednisone that are premature or rapid can lead to exacerbations or clinical worsening of weakness. To reduce the risk of disease flare, a very slow rate of taper is recommended: 5 mg to 10 mg every 2 to 3 months when the prednisone dose is greater than 20 mg/d and even slower tapers, 2.5 mg to 5 mg every 2 to 3 months with prednisone doses of less than 20 mg/d with clinical evaluations performed before each taper and a halt in tapering if subtle signs of worsening of disease appear.

Although many patients have at least a partial, if not robust, response to prednisone, treatment with prednisone is limited by the potentially serious long-term side effects such as osteoporosis, weight gain, hypertension, and elevation of blood sugars. Thus, prednisone monotherapy is rarely used long-term, and it is recommended that a second immunosuppressive steroid-sparing agent should be started early in the course in patients with moderate-to-severe disease. These immunosuppressive agents include methotrexate (10 mg/wk to 25 mg/wk orally or subcutaneously), azathioprine (2 mg/kg/d to 3 mg/kg/d), mycophenolate mofetil (total daily dose of 2 g/d to 3 g/d divided into 2 daily doses), or IV immunoglobulin (IVIg) (1 g/kg/mo to 2 g/kg/mo administered over 2 to 5 consecutive days). Although methotrexate and azathioprine are agents commonly used in conjunction with prednisone, little evidence exists to support the superiority in efficacy of one of these immunosuppressive agents over another in the treatment of autoimmune myopathies. Methotrexate, although beneficial for muscle, skin, and joint involvement, should be cautiously used in patients with myositis with interstitial lung disease because of potential lung toxicity.⁴⁵ For severe or refractory cases, other options include rituximab (an anti-monoclonal CD20 antibody targeting B cells leading to selective peripheral B-cell depletion), which is a well-established biologic agent used in refractory inflammatory myopathy^{46,47}; calcineurin inhibitors, such as cyclosporine and tacrolimus (should be used with caution in the elderly with hypertension because of potential renal toxicity)⁴⁸; and cyclophosphamide (can be used in severe or rapidly progressive interstitial lung disease but can cause infertility).⁴⁹

Recent evidence has suggested that particular subtypes of autoimmune myopathies (based on autoantibodies) may have a robust response to particular immunotherapies. IVIg has shown efficacy in a randomized controlled trial for the management of refractory dermatomyositis⁵⁰ and is effective in immune-mediated necrotizing myopathy, particularly in patients with anti-HMG-CoA reductase antibodies, even as monotherapy.⁵¹ Rituximab has been shown to have beneficial effects in patients with antisynthetase syndrome, primarily anti-Jo-1, and also in anti-Mi-2 autoantibody-positive subjects in a post hoc analysis of a randomized controlled trial of rituximab in refractory dermatomyositis and polymyositis.⁵² Rituximab has also been shown to be effective in treating patients with anti-SRP antibody immune-mediated necrotizing myopathy who were refractory to conventional immunotherapies.^{24,53}

Several biologic agents are under investigation for the treatment of refractory cases of autoimmune inflammatory myopathies. Studies evaluating the use of anti-tumor necrosis factor agents (etanercept and infliximab) have shown conflicting results and, in some cases, concern for inducing or worsening of the myositis.⁵⁴⁻⁵⁶ However, abatacept, a T-cell inhibitor, which inhibits the binding of the costimulatory protein CD28 expressed on effector

KEY POINTS

- Immunosuppressive therapy is widely accepted as the mainstay of treatment for autoimmune myopathies.
- Corticosteroids, commonly prednisone, are the first-line therapy in the treatment of inflammatory myopathies, typically prescribed at a dose of 0.5 mg/kg/d to 1 mg/kg/d, with a maximum dose of 60 mg/d to 80 mg/d.
- Recent evidence has suggested that particular subtypes of autoimmune myopathies (based on autoantibodies) may have a robust response to particular immunotherapies.
- Several biologic agents are under investigation for the treatment of refractory cases of autoimmune inflammatory myopathies.

T cells, was shown to be effective in a randomized phase 2b trial by lowering disease activity at 6 months in patients with refractory dermatomyositis and polymyositis and showed beneficial effects on muscle tissue with an increase in regulatory T cells.⁵⁷ Larger studies evaluating the efficacy of abatacept in inflammatory myopathies are underway. Other novel investigational agents are being explored as therapeutic options. Some case reports of efficacy in immune-mediated myopathies include tocilizumab (a monoclonal antibody that blocks interleukin 6),⁵⁸ sifalimumab (an anti-interferon-alpha monoclonal antibody),⁵⁹ basiliximab (a monoclonal antibody blocking interleukin 2 receptor α -chain, CD25 antigen, present on the surface of activated T lymphocytes),⁶⁰ IMO-8400 (a novel synthetic phosphorothioate oligonucleotide antagonist to Toll-like receptors, which are expressed on muscle cells and keratinocytes that, when activated, are postulated to amplify the inflammatory response), belimumab (to explore whether the B cell-activating factor overexpression plays a role in immune-mediated myopathies),⁶¹ eculizumab (a monoclonal antibody directed against the complement component C5 to prevent cleavage into C5a and C5b-9), and ruxolitinib (Janus kinase inhibitors).⁶²

Although treatment for inflammatory myopathies remains challenging because several therapeutic options are available without consensus guidelines, patients with myositis tend to respond favorably to conventional immunotherapy when started early in the course of the disease. Patients with severe or multisystemic involvement may be better served in multidisciplinary clinics with experienced clinicians familiar with second-line or third-line agents to treat refractory myositis. Supplements, such as vitamin D with calcium and a proton pump inhibitor (for gastric ulcer prophylaxis) when taken with prednisone, and folic acid (1 mg/d), when taken with methotrexate, aid in the overall outcome and well-being of the patient. Physical exercise under the guidance of a physical therapist is an important complementary treatment that improves strength and reduces disability and is safe within 4 weeks of starting medical treatment.⁶³

Cancer Screening

Because the majority of malignancies are identified in the first 3 years of myositis onset, a comprehensive evaluation in search of an underlying malignancy with chest, abdomen, and pelvis CT, as well as age-appropriate cancer screening (eg, mammogram, colonoscopy, gynecologic examination) should be performed, especially in myositis subtypes (based on autoantibody) with an increased risk of malignancy. If negative, the screening should be repeated in those at high risk within the first 3 years of symptom onset. One study demonstrated that a single positron emission tomography (PET) scan may be as sensitive as the combination of all other screening tests in detecting an underlying malignancy in patients with myositis.⁶⁴

CONCLUSION

Over the past decade, the continued discovery of myositis-specific autoantibodies has proven to be useful in improving the understanding of the subtypes of myositis and associated clinical phenotypes. Identifying specific myositis autoantibodies serves as a helpful diagnostic tool early in the evaluation of patients with myositis and, in some cases, ends a diagnostic

odyssey when a prior misdiagnosis has occurred. Accurate subclassification of myositis guides clinical management based on autoantibody subtypes with the associated risks of malignancy, risks of extramuscular/organ involvement, and response to specific types of immunotherapy. These findings have already led to shifts in treatment paradigms and insights into prognosis. With future research focused on the potential role of autoantibodies with respect to the disease mechanisms of autoimmune myopathies, novel therapeutic targets may be discovered.

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KEY POINTS

- Although treatment for inflammatory myopathies remains challenging because several therapeutic options are available without consensus guidelines, patients with myositis tend to respond favorably to conventional immunotherapy when started early in the course of the disease.

- Because the majority of malignancies are identified in the first 3 years of myositis onset, a comprehensive evaluation in search of an underlying malignancy with chest, abdomen, and pelvis CT, as well as age-appropriate cancer screening should be performed, especially in myositis autoantibody subtypes with an increased risk of malignancy.

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