Address correspondence to Dr Andrew L. Mammen, Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Expression, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, 50 South Dr, Room 1146, Bldg 50, MSC 8024, Bethesda, MD 20892, andrew.mammen@nih.gov.

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Autoimmune Myopathies

Andrew L. Mammen, MD, PhD

ABSTRACT

Purpose of Review: This article provides guidelines for diagnosing and treating the different subtypes of autoimmune myopathies.

Recent Findings: The most common subtypes of autoimmune myopathies are dermatomyositis, immune-mediated necrotizing myopathy, antisynthetase syndrome, and overlap syndromes; isolated polymyositis is an exceptionally rare disease. Specific autoantibodies are associated with unique clinical phenotypes and may be used for diagnostic and prognostic purposes, such as to assess the risk of coexisting malignancy.

Summary: Diagnosing the specific subtype of autoimmune myopathy can be achieved by combining relevant features of the history, neuromuscular examination, muscle biopsy, and serologic studies.

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INTRODUCTION

The autoimmune myopathies are a heterogeneous family of diseases that include dermatomyositis, immune-mediated necrotizing myopathy, antisynthetase syndrome, and polymyositis.¹ These diseases, which affect women about twice as often as men, are rare, with an estimated combined incidence of four cases per 100,000 person-years and prevalence of 15 to 32 cases per 100,000.² While patients with autoimmune myopathy typically present with symmetric proximal muscle weakness progressing over weeks or months, each disease subtype is associated with distinct clinical, histopathologic, and pathophysiologic features.

DERMATOMYOSITIS

Patients with dermatomyositis usually present with both skin and muscle involvement. Although long believed to be a single disease, emerging evidence suggests that dermatomyositis may include several clinically distinct subtypes, each associated with a unique autoantibody.

Clinical Features

Patients with dermatomyositis often report difficulty getting up from a seated

position, climbing steps, or raising their arms above their heads as well as other symptoms due to proximal muscle weakness. Patients with more severe disease may have difficulty lifting their heads off the bed because of neck flexor weakness, impaired swallowing due to pharyngeal muscle weakness, or shortness of breath due to diaphragmatic weakness. Tasks requiring distal muscle strength, such as opening a jar, are relatively unaffected.

Unique dermatologic features usually accompany muscle weakness in patients with dermatomyositis (**Case 5-1**). These include scaly erythematous lesions found on the extensor surfaces of the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints known as Gottron papules (**Figure 5-1**³). In addition, patients with dermatomyositis often experience a violaceous eruption on the upper eyelids, sometimes associated with periorbital edema, known as a heliotrope rash (**Figure 5-2**). Gottron papules and the heliotrope rash are pathognomonic for dermatomyositis. In contrast, other types of rashes are less specific, but still common, in dermatomyositis. For example, many patients have an erythematous rash known as a shawl sign covering the upper arms and shoulders or a V-shaped

Case 5-1

A 67-year-old woman developed a rash on the extensor surfaces of her fingers 4 months before presentation, followed over the next few weeks by the development of a rash on her chest, upper back, and over her upper eyelids. Approximately 1 month later, she noticed difficulty going up steps and subsequently noted difficulty raising her arms above her head to wash her hair. She had experienced mild myalgia but no fevers, weight loss, cough, arthralgia, or shortness of breath. Her past medical history was notable for hypertension and hyperlipidemia, for which she took amlodipine and atorvastatin. Clinical examination was revealing for moderate erythema and papules over the extensor surfaces of her fingers (Gottron sign and papules) and an erythematous rash on her upper chest (V-shaped rash) and upper arms and back (shawl sign). Her nail beds had dilated capillary loops. On manual muscle strength testing, she had mild (4+) neck flexion weakness, mild (4+) arm abduction weakness, and moderate (3) hip flexion weakness. Distal muscle strength was intact.

She had a mildly elevated creatine kinase level (247 IU/L). EMG showed positive sharp waves and fibrillation potentials with short-duration polyphasic motor units that recruited early. A left deltoid muscle biopsy showed perifascicular atrophy and some mild perivascular inflammation. Pulmonary function tests were normal. She tested positive for transcriptional intermediary factor 1 γ (TIF1 γ) autoantibodies. Her malignancy workup included a mammogram that revealed a suspicious 2-cm mass. Biopsy showed the mass was an invasive ductal carcinoma, and she was found to have several positive lymph nodes.

Comment. This patient had a classic presentation of dermatomyositis with Gottron sign, heliotrope rash, proximal muscle weakness, mildly elevated muscle enzymes, and perifascicular atrophy on muscle biopsy. Patients with dermatomyositis, especially those with TIF1 γ autoantibodies, have an increased risk of cancer. Evidence-based guidelines for cancer screening are not available. However, most experts agree that patients with newly diagnosed dermatomyositis should undergo age-appropriate screening (eg, mammography and colonoscopy) as well as pelvic ultrasound (in women) and a contrast-enhanced CT scan of the chest, abdomen, and pelvis. Patients at the greatest risk (ie, those with anti-TIF1 γ) may benefit from a positron emission tomography (PET)-CT scan.

rash affecting sun-exposed surfaces on the upper chest. Skin biopsies of a dermatomyositis rash typically reveal interface dermatitis. As they may be indistinguishable from skin biopsy findings in lupus and drug reactions, skin biopsy features alone cannot reliably be used to diagnose dermatomyositis. In addition to skin rashes, some patients also have calcinosis, the progressive deposition of calcium nodules in the subcutaneous tissues (Figure 5-3). These painful lumps occasionally erupt through skin where they can precipitate a skin infection.

While most patients with dermatomyositis have both muscle and skin involvement, a minority have skin disease with no appreciable muscle symptoms. When patients with a dermatomyositis rash have no muscle symptoms and no imaging, laboratory, or electrophysiologic evidence of muscle involvement, the disease is known as *amyopathic dermatomyositis*. *Hypomyopathic dermatomyositis* refers to patients who have no clinical muscle weakness but do have some other evidence of muscle disease (eg, muscle edema on MRI).⁴ Conversely, patients

KEY POINTS

- The different subtypes of autoimmune myopathy include dermatomyositis, immune-mediated necrotizing myopathy, antisynthetase syndrome, and polymyositis.
- Cutaneous manifestations of dermatomyositis include Gottron papules, heliotrope rash, V-shaped rashes on the chest, shawl sign over the shoulders and upper back, and calcinosis.
- Patients with hypomyopathic dermatomyositis or amyopathic dermatomyositis have classic dermatomyositis skin rashes with minimal or no muscle involvement, respectively.

KEY POINT

■ Patients with dermatomyositis have an increased risk of cancer, in particular adenocarcinomas.

FIGURE 5-1 Gottron papules.

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who have no rash but have overt muscle disease and classic histopathologic features of dermatomyositis on muscle biopsy have been described as having *dermatomyositis sine dermatitis*.

In addition to muscle and skin, other organ systems may be targeted in patients with dermatomyositis. Most significantly, 20% to 30% also have interstitial lung disease, a feature most often found in patients with autoantibodies recognizing one of the aminoacyl-tRNA synthetases (eg, Jo-1, discussed later in this article) or the melanoma differentiation-associated protein 5 (MDA5, also discussed later in

this article). The joints and, less often, cardiac muscle may also be affected in patients with dermatomyositis.

Patients with dermatomyositis have an increased risk of malignancy with a standardized incidence ratio of 3.0 to 6.2.^{5,6} Dermatomyositis-associated tumors, often adenocarcinomas, are usually detected within 2 years either before or after the development of muscle weakness or skin rash. In patients with tumors, the autoimmune disease may improve with successful treatment of the cancer.⁷ Still, those with an underlying malignancy have a decreased survival rate (62% of patients) compared to patients with dermatomyositis who do not have a malignancy (92% of patients).⁸

Laboratory Features

In patients with suspected autoimmune myopathy, muscle imaging, electrophysiologic examination, and serologic studies can be used to confirm the diagnosis. When present, dermatomyositis-specific autoantibodies may help to identify patients with different disease subtypes.

Imaging. MRI reveals intramuscular short tau inversion recovery (STIR)-hyperintense regions corresponding to

FIGURE 5-2 Heliotrope rash.

areas of muscle inflammation or necrosis (Figure 5-4). STIR hyperintensities surrounding muscles may be found in patients with fascial involvement (ie, fasciitis). Targeting muscles with abnormalities seen on MRI may increase the diagnostic yield of muscle biopsy.⁹ T1-weighted images can show replacement of muscle by fat and fibrotic tissue, in particular in patients with chronic or especially severe disease. In those who have MRIs showing significant fatty replacement but no features consistent with necrosis or inflammation, persistent muscle weakness may be the result of

FIGURE 5-3 Calcinosis. Calcium deposits eroding the skin over the distal interphalangeal joint.

FIGURE 5-4 Thigh muscle MRI in dermatomyositis. *A*, On T1-weighted MRI, thigh muscles including the quadriceps (*long arrow*) and hamstrings (*short arrow*) are hypointense and fat is hyperintense. *B*, Most muscles reveal hyperintensities on short tau inversion recovery (STIR) imaging, indicating inflammation or necrosis (*long arrow*). Evidence of fascial edema is also noted, particularly in the posterior compartment (*short arrow*).

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KEY POINT

- Short tau inversion recovery hyperintensities on MRI represent areas of active muscle disease in patients with dermatomyositis and other forms of autoimmune myopathy.

KEY POINTS

- Along with creatine kinase (CK) and aldolase, CK-MB and troponin T are released from damaged muscle cells. In contrast, troponin I is only released from damaged cardiac muscle.
- Myositis autoantibodies are found in 60% to 70% of patients with dermatomyositis.
- Anti-transcriptional intermediary factor 1 γ (TIF1 γ) testing has a 58% positive predictive value and 95% negative predictive value for an associated malignancy in patients with dermatomyositis.
- Anti-nuclear matrix protein 2 (NXP2) autoantibodies are associated with calcinosis in dermatomyositis.
- Patients with anti-melanoma differentiation-associated protein 5 (anti-MDA5) autoantibodies often have palmar skin lesions and may develop a severe cardiopulmonary syndrome

permanent muscle injury rather than active disease.

Electromyography. Patients with treated and untreated dermatomyositis typically have small polyphasic motor units that recruit early, consistent with a myopathic process. Most, but not all, untreated patients also have fibrillations and positive sharp waves; one study showed that the prevalence of this spontaneous activity decreased from 78% at the time of diagnosis to 60% with corticosteroid use.¹⁰ In addition, a minority of patients with active dermatomyositis have complex repetitive discharges; in one recent study, complex repetitive discharges were significantly more common in patients with an underlying malignancy.¹¹ Each of these abnormalities is found predominantly in axial and proximal muscles as compared to distal muscle groups.¹⁰ However, it should be noted that fibrillations, positive sharp waves, and complex repetitive discharges resolve when the myositis is in remission.

Blood work. As in other myopathies, disruption of the muscle cell membrane in dermatomyositis allows leakage of intracellular contents into the bloodstream. Consequently, elevated levels of creatine kinase (CK) are common in dermatomyositis. Of note, some patients with muscle weakness and classic dermatomyositis rashes have no CK elevation. This suggests that, at least in some cases, dermatomyositis can cause muscle dysfunction without disrupting the integrity of the myofiber membrane.

In addition to CK, elevated levels of other muscle enzymes, including lactate dehydrogenase, aldolase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), are common in patients with dermatomyositis. Since γ -glutamyltransferase (GGT) is released from damaged liver but not muscle, a normal GGT in the context of elevated AST and ALT levels suggests muscle as the source. Damaged skeletal muscle may also release CK-MB and troponin T into the bloodstream, which can erro-

neously lead to a suspicion of cardiac muscle damage. Testing for troponin I may be helpful as this protein is released from damaged cardiac muscle but not skeletal muscle.¹²

As in patients with other systemic autoimmune diseases, patients with dermatomyositis often have unique autoantibodies that are associated with distinct clinical features (**Table 5-1**). Indeed, one of these myositis-specific autoantibodies is found in 60% to 70% of patients with dermatomyositis.¹³ Among the most common of these, autoantibodies recognizing transcriptional intermediary factor 1 γ (TIF1 γ) have a prevalence of approximately 15% to 40% in dermatomyositis. Those with anti-TIF1 γ autoantibodies are at an especially increased risk of malignancy; a 2012 meta-analysis showed that the positive and negative predictive values for this test to detect an underlying malignancy were 58% and 95%, respectively.¹⁴ In addition, patients with dermatomyositis who are anti-TIF1 γ positive have been noted to have especially severe skin manifestations, including distinctive palmar hyperkeratotic papules, psoriasislike lesions, and hypopigmented and telangiectatic (red on white) patches.¹⁵

Several other dermatomyositis-specific autoantibodies deserve mention. For example, anti-nuclear matrix protein 2 (NXP2) autoantibodies are found in up to 40% of patients with dermatomyositis and are associated with calcinosis, a complication of the disease that can be refractory to immunosuppressive therapy.^{16,17} Approximately 15% of patients have anti-Mi-2 autoantibodies, which are associated with especially severe initial skin manifestations; fortunately, these patients respond well to treatment with glucocorticoids.^{18,19} Patients with autoantibodies recognizing MDA5, found in approximately 5% of cases, usually have modest muscle involvement but rapidly progressive interstitial lung disease and unique cutaneous manifestations including ulcerations, tender palmar papules, and oral pain (**Figure 5-5**).^{20–22}

TABLE 5-1 Myositis Autoantibodies and Associated Clinical Features

Autoantibody	Phenotype Features
Antisynthetase	Myositis, interstitial lung disease, mechanic's hands, arthritis, and Raynaud phenomenon are associated with all types of antisynthetase autoantibodies
Anti-histidyl-tRNA synthetase (anti-Jo-1)	90% with muscle involvement; 50–75% with interstitial lung disease
Anti-threonyl-tRNA synthetase (anti-PL-7)	
Anti-alanyl-tRNA synthetase (anti-PL-12)	52% with muscle involvement; 90% with interstitial lung disease
Anti-glycyl-tRNA synthetase (anti-EJ)	
Anti-isoleucyl-tRNA synthetase (anti-OJ)	
Anti-asparaginyl-tRNA synthetase (anti-KS)	
Anti-tyrosyl-tRNA synthetase (anti-Ha)	
Anti-phenylalanyl-tRNA synthetase (anti-Zo)	
Dermatomyositis	
Anti-Mi-2	Severe initial skin manifestations, but good response to treatment
Anti-transcriptional intermediary factor 1 γ (anti-TIF1 γ)	Especially increased risk of cancer in adults; severe cutaneous involvement in children
Anti-nuclear matrix protein 2 (anti-NXP2)	Increased risk of calcinosis
Anti-melanoma differentiation-associated protein 5 (anti-MDA5)	Skin ulcerations, palmar papules, and severe cardiopulmonary syndrome
Anti-small ubiquitinlike modifier 1	Skin manifestations presenting before muscle manifestations; dysphagia common
Immune-mediated necrotizing myopathy	
Anti-signal recognition particle (anti-SRP)	May be severe and difficult to treat
Anti-3-hydroxy-3-methylglutaryl coenzyme A (anti-HMG-CoA) reductase	Associated with statin exposure in patients older than 50 years of age

tRNA = transfer ribonucleic acid.

Histopathology

Unlike normal muscle fascicles, in which individual myofibers are of a uniform size (Figure 5-6A), the hallmark histo-

logic feature of dermatomyositis is perifascicular atrophy, in which small atrophic fibers line the edges of fascicles that are otherwise composed of relatively

KEY POINT

- Perifascicular atrophy is the hallmark histologic finding in patients with dermatomyositis.

FIGURE 5-5 Cutaneous ulceration on the palmar surface of the index finger in a patient with anti-melanoma differentiation-associated protein 5 (anti-MDA5) autoantibodies.

normal-sized myofibers (Figure 5-6B). While perifascicular atrophy is a very specific feature of dermatomyositis, it is not found in all patients with this disease. For example, a 2015 study showed that among 91 patients with dermatomyositis, only 46 (51%) had perifascicular atrophy.¹³

Perivascular inflammation, a non-specific but more common feature of muscle biopsies of patients with dermatomyositis, is found in approximately 60% of biopsy specimens¹³; the cellular infiltrates surrounding blood vessels and within the perimysium are composed of macrophages, B cells, and plasmacytoid

FIGURE 5-6 Muscle biopsies reveal normal muscle architecture in an individual without muscle disease (A), perifascicular atrophy and perivascular inflammation in a patient with dermatomyositis (B), prominent myofiber necrosis in a patient with immune-mediated necrotizing myopathy (C), and non-necrotic muscle fibers surrounded and invaded by lymphocytes in a patient with polymyositis (D).

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dendritic cells.²³ Other, less common, histologic findings in dermatomyositis muscle biopsies include increased numbers of cytochrome oxidase–deficient fibers suggesting mitochondrial dysfunction, non-necrotic muscle fibers invaded by inflammatory cells (a more typical feature of polymyositis, as discussed later in this article), and a predominantly necrotizing myopathy.¹³

The likelihood of finding characteristic dermatomyositis muscle biopsy features may depend upon which muscle is chosen for biopsy. Indeed, deltoid muscle biopsies may be more likely to show perifascicular atrophy, perivascular inflammation, and mitochondrial dysfunction than biopsies taken from the quadriceps.¹³ Furthermore, while the prevalence of different muscle biopsy features is not significantly associated with the time elapsed between disease onset and the date of biopsy, patients with dermatomyositis on immunosuppressive therapy at the time of biopsy have less perivascular inflammation.¹³

Interestingly, one analysis showed that autoantibody status also influences the relative prevalence of different muscle biopsy features in patients with dermatomyositis.¹³ For example, more muscle biopsies from patients with dermatomyositis who were anti-TIF1γ positive had evidence of mitochondrial dysfunction (47%) than those from patients without this autoantibody (18%). Similarly, whereas half of patients who were anti-Mi-2 positive had non-necrotic muscle fibers invaded by inflammatory cells, none of the patients who were anti-NXP2 positive had this histologic feature. Along with recent studies showing that cancer risk, specific cutaneous manifestations, and lung involvement are each associated with different autoantibodies, these histologic differences underscore the emerging concept that dermatomyositis may be a heterogeneous group of diseases that can be categorized according to autoantibody type rather than a single pathologic entity.

Pathogenesis

Several observations suggest a central role for interferon alfa in the pathogenesis of dermatomyositis: (1) the plasmacytoid dendritic cells infiltrating dermatomyositis muscle biopsies are rich sources of interferon alfa²⁴; (2) genes induced by interferon are expressed at high levels in dermatomyositis muscle and skin cells²³; (3) expression levels of interferon-inducible transcripts in peripheral blood cells are correlated with disease activity^{25,26}; and (4) cultured skeletal muscle cells undergo changes similar to those found in dermatomyositis muscle tissue when they are exposed to interferon. Nonetheless, despite this evidence for interferon playing a role in dermatomyositis disease pathogenesis, it remains unclear how this would explain classic histologic features of the disease, such as perifascicular atrophy. Furthermore, it remains to be shown whether evidence of interferon dysregulation is found in all patients with dermatomyositis or just those with certain autoantibodies.

IMMUNE-MEDIATED NECROTIZING MYOPATHIES

Based on their unique histologic and serologic features, immune-mediated necrotizing myopathies are now considered a distinct category of autoimmune myopathy rather than a form of polymyositis with minimal inflammation on muscle biopsy.

Clinical Features

Patients with immune-mediated necrotizing myopathy are defined by prominent muscle fiber necrosis on biopsy and, usually, by the presence of autoantibodies recognizing the signal recognition particle (SRP) or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the pharmacologic target of statin medications. Like those with other forms of autoimmune myopathy, these patients usually present with a history of proximal muscle weakness progressing over weeks

KEY POINTS

- Patients with dermatomyositis who are already on immunosuppressive therapy may have less inflammation on muscle biopsy.
- Interferon dysregulation may play a role in the pathogenesis of dermatomyositis.
- Patients with immune-mediated necrotizing myopathy often have anti-signal recognition particle (SRP) or anti-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase autoantibodies.

KEY POINTS

- Unlike dermatomyositis and antisynthetase syndrome, immune-mediated necrotizing myopathy most often does not include extramuscular manifestations.
- Statin use is associated with anti-HMG-CoA reductase-positive myopathy in patients older than 50 years of age.

to months. However, unlike patients with dermatomyositis and antisynthetase syndrome, they only rarely have prominent extramuscular involvement such as rash, arthritis, or interstitial lung disease. Future studies including large numbers of patients will be required to determine whether patients with immune-mediated necrotizing myopathy have an increased risk of malignancy.

Laboratory Features

Patients with immune-mediated necrotizing myopathy have many of the same imaging and electrophysiologic findings as patients with other forms of autoimmune myopathy. However, they have unique muscle biopsy and serologic features.

Imaging. Muscle MRI frequently reveals intramuscular edema in patients with immune-mediated necrotizing myopathy. As some of these patients have severe and refractory disease, fatty replacement of muscle tissue may be seen, especially in those with long-standing disease. Unlike in those with dermatomyositis, fascial edema is rare.

Electromyography. Almost all patients with immune-mediated necrotizing myopathy have myopathic motor units and spontaneous activity such as fibrillation potentials and positive sharp waves.

Blood work. Patients with immune-mediated necrotizing myopathy tend to have very high serum levels of muscle enzymes, with a mean peak CK value of about 10,000 IU/L. The high serum muscle enzyme levels probably reflect prominent myofiber necrosis that allows intracellular contents to leak into the bloodstream.

Anti-SRP autoantibodies are found in approximately 5% of patients with autoimmune myopathy and in approximately 16% of patients with a necrotizing muscle biopsy. Patients who are anti-SRP positive tend to be women by a nearly 2 to 1 ratio and have severe proximal muscle weakness, dysphagia, and muscle atrophy.²⁷ Several reports have suggested that younger patients with this autoantibody may also be at risk for cardiac involve-

ment.²⁸ While most patients who are anti-SRP positive respond to immunosuppressive therapy, patients with pediatric onset tend to have worse outcomes.²⁷

Anti-HMG-CoA reductase autoantibodies are found in approximately 40% of patients with a necrotizing muscle biopsy. While these antibodies may be found more commonly in younger women than younger men, this slight female gender predominance is not evident in patients who are anti-HMG-CoA reductase positive and older than 50 years of age.

Statin use has been reported to precede the development of anti-HMG-CoA reductase myopathy in 11% to 100% of cases.^{29,30} It is important to note that the prevalence of statin use among the general population varies with age and between different countries. To date, only one study has compared the prevalence of statin exposure in patients who are anti-HMG-CoA reductase positive to that of age-matched control subjects.³¹ In that study of patients from the United States, among 12 patients who were anti-HMG-CoA reductase positive and older than 50 years of age, 10 (83%) had prior statin exposure. In comparison, only 25% to 35% of patients with dermatomyositis, polymyositis, or inclusion body myositis older than 50 years of age had prior statin exposure. These results, while requiring replication in other cohorts, suggest that statin use in older patients is a risk factor for developing anti-HMG-CoA reductase myopathy.

Unlike patients with self-limited forms of statin myopathy, patients who are exposed to statins who are anti-HMG-CoA reductase positive do not usually improve following discontinuation of statin medications. Rather, these patients develop a progressive myopathic process that requires immunosuppressive therapy to control (**Case 5-2**). Since antibodies recognizing HMG-CoA reductase are not found in healthy controls or those with self-limited statin-related myopathy, testing for these antibodies can help determine whether a patient has self-limited

Case 5-2

A 67-year-old man with a history of diabetes mellitus, hypertension, and hyperlipidemia (for which he had been taking atorvastatin for 2 years) presented with a 6-month history of progressive leg weakness. Three months prior to presentation, he was found to have an elevated creatine kinase (CK) level of 4200 IU/L. The patient's rosuvastatin was stopped, but the CK remained elevated, his leg weakness became worse, and he began to develop weakness in his arms. He had mild myalgia but no arthralgia, rash, cough, or shortness of breath.

His neurologic examination was remarkable for weakness of neck flexors (4-), arm abductors (4-), elbow flexors (4+), hip flexors (2), knee extensors (4+), and knee flexors (4+). He had a mild waddling gait and could not rise from a sitting position with his arms crossed. His serum CK was 6700 IU/L.

A left quadriceps muscle biopsy showed many necrotic fibers with mild perivascular inflammation, but no perifascicular atrophy or non-necrotic muscle fibers surrounded by lymphocytes. Anti-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase autoantibodies were positive. A malignancy workup was negative.

Comment. This patient had an immune-mediated necrotizing myopathy associated with anti-HMG-CoA reductase autoantibodies. Most patients older than 50 years of age with this rare condition have a history of statin exposure. However, the disease usually progresses despite stopping statins and requires immunosuppressive therapy to control. This patient was placed on prednisone 60 mg/d and methotrexate, with the dose of methotrexate escalated from 7.5 mg/wk to 25 mg/wk over 7 weeks with no obvious improvement in strength or CK levels. The patient was subsequently started on IV immunoglobulin (IVIg) 2 g/kg/mo with complete resolution of his weakness over the next 3 months. His CK declined to 900 IU/L but did not return to the normal range. He was able to taper off the prednisone and IVIg, but the disease flared with return of mild weakness and increasing CK levels when the methotrexate dose was decreased. He required chronic methotrexate therapy with periodic IVIg infusions to maintain normal strength.

statin-related myopathy or an autoimmune myopathy.³² In a patient who has been exposed to statins who has proximal muscle weakness and elevated CK levels, a positive anti-HMG-CoA reductase test strongly supports the diagnosis of statin-associated autoimmune myopathy and should lead to both discontinuation of the statin and initiation of immunosuppressive therapy.

Not all patients who are anti-HMG-CoA reductase positive have a history of statin exposure. As expected, this is especially true among younger patients. While younger patients who have not been exposed to statins have identical clinical, laboratory, and histologic features as those who are statin-exposed, they tend to be relatively resistant to treatment, and muscle weakness may

persist and progress despite aggressive therapy.³³

Histopathology

Prominent muscle fiber necrosis is the hallmark of patients with immune-mediated necrotizing myopathy (**Figure 5-6C**). Detailed studies of patients who are anti-HMG-CoA reductase positive reveal that macrophages are the predominant inflammatory cell type infiltrating muscle tissue. Some CD4+, CD8+, and plasmacytoid dendritic cells may also be present in perivascular and endomysial regions.³⁴ However, perifascicular atrophy and conspicuous numbers of B cells, which are common in dermatomyositis, are rarely, if ever, noted in these patients. Similarly, very few patients with anti-SRP or anti-HMG-CoA reductase antibodies have muscle biopsies that show non-necrotic

KEY POINTS

- Anti-HMG-CoA reductase autoantibodies are not found in patients with self-limited statin myopathy.
- Many younger patients who are anti-HMG-CoA reductase positive have no statin exposure and have very difficult-to-control muscle disease.

muscle fibers surrounded and invaded by lymphocytes, as may be seen in polymyositis, inclusion body myositis, and some dystrophies. As do those with other forms of autoimmune muscle disease, patients with immune-mediated necrotizing myopathy often have muscle biopsies revealing upregulation of major histocompatibility complex class I (MHC-I) on the surface of non-necrotic muscle fibers.

Pathogenesis

The mechanisms underlying the initiation and maintenance of autoimmunity in immune-mediated necrotizing myopathies are not understood. However, several clues from studying anti-HMG-CoA reductase myopathy suggest a potential model for those with statin-triggered disease (Figure 5-7). First, HMG-CoA reductase expression is low in

normal cells but is upregulated by statin exposure. Second, a strong immunogenetic risk factor exists for developing anti-HMG-CoA reductase autoimmunity: more than 70% of patients have the DRB1*11:01 class II HLA allele, which is only found in about 10% of the general population. Third, regenerating muscle fibers express high levels of HMG-CoA reductase protein. Taken together, these clues suggest that increased expression of HMG-CoA reductase with statin exposure might lead to aberrant processing of the protein in muscle or some other tissue(s). Cryptic epitopes revealed by aberrant processing or statin binding might be preferentially presented by DRB1*11:01. Once tolerance to HMG-CoA reductase is broken, regenerating muscle cells could serve as a continued source of the autoantigen even after statins are discontinued. While

FIGURE 5-7 A hypothetical model for the initiation and maintenance of autoimmunity in patients with anti-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase myopathy.

appealing, this working model still requires validation.

It remains to be shown how muscle cells are damaged in those with immune-mediated necrotizing myopathies. The observation that anti-SRP and anti-HMG-CoA reductase autoantibody levels are highly correlated with disease activity, along with the presence of complement on non-necrotic muscle fibers, suggests that these autoantibodies could be pathogenic. However, neither SRP nor HMG-CoA reductase is known to be present on the surface of muscle fibers. It could be that the antibodies cross-react with other autoantigens on muscle cells. Alternatively, some other mechanism may mediate cellular necrosis in

those with immune-mediated necrotizing myopathy.

ANTISYNTHEASE SYNDROME

Autoantibodies recognizing histidyl-tRNA synthetase (ie, Jo-1) and several other aminoacyl-tRNA synthetases (**Table 5-1**) are found in approximately 20% of patients with myositis and are associated with a multisystem disease known as antisynthetase syndrome (**Case 5-3**). This syndrome includes two or more of the following: myositis, interstitial lung disease, arthritis, Raynaud phenomenon, fevers, or hyperkeratotic lesions along the radial and palmar surfaces of the fingers, known as *mechanic's bands*

Case 5-3

A 47-year-old previously healthy woman presented with a 6-month history of joint pain in her fingers and a 3-month history of a persistent dry cough that had worsened over time. In the previous 6 weeks, she began to notice shortness of breath with mild exertion, and over the previous month, she noticed difficulty getting up from a toilet seat or off a low couch without help. She did not have fevers, myalgia, or weight loss.

Physical examination was remarkable for crackles at both lung bases and hyperkeratotic skin lesions on the radial surfaces of her fingers (mechanic's hands). She had no other rashes. She had mild (4+) weakness of arm abductors and mild to moderate (4) weakness of hip flexors. Distal strength was intact. Her creatine kinase level was elevated at 642 IU/L. EMG showed small motor units that recruited early, and fibrillation potentials were present. Muscle MRI showed edema in muscles of each thigh. Anti-Jo-1 autoantibodies were positive. Pulmonary function testing revealed a decreased diffusing capacity of the lungs for carbon monoxide (DLCO) at 63% of the predicted value. Chest CT showed ground-glass opacities at the bases of both lobes. A left deltoid muscle MRI showed non-necrotic muscle fibers surrounded and invaded by lymphocytes. A malignancy screen was negative.

Comment. This patient had classic clinical features of the antisynthetase syndrome, including myositis, interstitial lung disease, arthritis, and mechanic's hands. She did not have fevers, which are often part of this syndrome. Of note, not all patients with antisynthetase syndrome have all the typical features of the disease. For example, some patients with anti-Jo-1 antibodies will present with joint and lung involvement, but not myositis.

The patient was started on prednisone at 60 mg/d, and she was started on azathioprine at 50 mg/d, which was increased to 150 mg/d. Her muscle strength and arthritis improved quickly. However, her interstitial lung disease ultimately progressed despite aggressive immunosuppression with cyclophosphamide and IV immunoglobulin (IVIg). She died 9 months after diagnosis from complications of her pulmonary disease, underscoring the seriousness of this manifestation of antisynthetase syndrome, which can be refractory to treatment.

KEY POINT

■ Patients with antisynthetase syndrome may have myositis, interstitial lung disease, arthritis, fevers, mechanic's hands, or erythematous dermatomyositislike rash.

(Figure 5-8).^{35–37} In addition to these features, some patients who are anti-synthetase positive also have erythematous rashes similar or identical to those seen in patients with dermatomyositis. Patients with antisynthetase syndrome are often referred to as having dermatomyositis or polymyositis when such rashes are present or absent, respectively.

Interestingly, one 2015 study showed that patients with anti-Jo-1 antibodies have a unique pattern of perifascicular necrosis with sarcolemmal deposition of complement that can be differentiated from the perifascicular atrophy frequently seen in patients with dermatomyositis.³⁸ Another analysis revealed that muscle biopsies from patients who were anti-Jo-1 positive with and without a rash had indistinguishable histologic features on muscle biopsy.¹³ Taken together with the unique constellation of extramuscular manifestations, these observations support the idea that antisynthetase syndrome is a distinct disease entity that should be recognized as being separate from both dermatomyositis and polymyositis.

POLYMYOSITIS

Bohan and Peter³⁹ defined polymyositis in 1975 based on the presence of symmetric proximal muscle weakness, myopathic features on EMG, elevated serum muscle enzymes, muscle biopsies showing inflammation or necrosis, and the absence of a dermatomyositis rash. However, many of the patients diagnosed with polymyositis using these criteria probably have what would now be recognized as another disease. For example, prior to the recognition of immune-mediated necrotizing myopathy as a distinct form of autoimmune myopathy associated with anti-SRP and anti-HMG-CoA reductase autoantibodies, these patients would have been categorized as having polymyositis. Similarly, most patients with antisynthetase syndrome without a rash would have been diagnosed with polymyositis. Furthermore, patients with perifascicular atrophy on muscle biopsy and no rash would have been labeled as having polymyositis; today they are classified as having dermatomyositis sine dermatitis. In addition, it is now realized that

FIGURE 5-8

This patient with the antisynthetase syndrome has mechanic's hands characterized by hyperkeratotic lesions on the edge of the thumb.

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many patients with inclusion body myositis may have been misdiagnosed as having polymyositis, despite the fact that they have a unique pattern of weakness; the majority of these patients might be identified by testing for antibodies recognizing NT5C1A, which are relatively specific for inclusion body myositis.^{40,41} Finally, a number of patients with limb-girdle muscular dystrophies (eg, dysferlinopathy) have been misdiagnosed as having polymyositis given that their muscle biopsies can reveal infiltrating inflammatory cells. Recent widely accepted diagnostic criteria for polymyositis provide important inclusion criteria (eg, the presence of non-necrotic muscle cells surrounded and invaded by lymphocytes; **Figure 5-6D**) and exclusion criteria (eg, the characteristic muscle weakness pattern seen in inclusion body myositis).⁴² However, in the opinion of this author and other experts, polymyositis is an exceptionally rare diagnosis among patients with autoimmune myopathy.⁴³

OVERLAP SYNDROMES

When autoimmune myopathy occurs in the context of another connective tissue disease, such as systemic sclerosis, lupus erythematosus, or rheumatoid arthritis, the patient is said to have a myositis overlap syndrome. While little is known about these overlap syndromes, one 2015 study showed that more than one-third of muscle biopsies from patients with scleroderma-myositis overlap include endomysial inflammation without evidence of non-necrotic muscle cells surrounded and invaded by lymphocytes⁴⁴; patients with these biopsy findings would be categorized as having nonspecific myositis based on the 2004 European Neuromuscular Centre (ENMC) diagnostic criteria.⁴² Interestingly, approximately one-fifth of patients with scleroderma-myositis had a necrotizing myopathy. Very few patients had muscle biopsy features consistent with dermatomyositis.

Rarely, patients may present with more than one autoimmune neuromuscular condition. For example, a handful of patients with both autoimmune myopathy and myasthenia gravis⁴⁵ were recently described in the context of an improving dermatomyositis rash. Since the majority of patients with myasthenia-myositis overlap had positive anti-acetylcholine receptor (AChR) antibodies, the author now recommends routinely checking for these in patients with autoimmune myopathy.

TREATMENT OF INFLAMMATORY MYOPATHIES

Unfortunately, no Class I evidence exists to support the use of any particular therapy for patients with autoimmune myopathy. However, most experts agree that these diseases do respond to immunosuppressive therapy and that high-dose corticosteroids should be the first-line treatment in the majority of patients (**Table 5-2**^{46,47}). Initial therapy usually includes oral prednisone at a dose of 1 mg/kg/d; in severely affected patients, this may be preceded by 3 days of IV methylprednisolone at a dose of 1 g/d. As with all patients on chronic high-dose steroid therapy, these patients should receive appropriate prophylaxis for *Pneumocystis jirovecii* pneumonia and osteoporosis.

Unless the patient has only mild disease, many experienced clinicians often add another agent, such as methotrexate, azathioprine, or mycophenolate mofetil, at the time of diagnosis. In those who develop very severe weakness or do not respond to the initial combination of medications after 6 to 8 weeks, IV immunoglobulin (IVIg) or another agent, such as rituximab, may be added.

Although little evidence exists for using one drug over another, a few specific recommendations can be given. Given that methotrexate may cause lung toxicity, azathioprine is often considered first in patients with interstitial lung disease. Some evidence from a case series suggests that IVIg may be effective, even

KEY POINTS

- Polymyositis is an exceptionally rare diagnosis made in patients with lymphocytes invading non-necrotic muscle cells who do not have rimmed vacuoles, a dermatomyositis rash, distal weakness, or other features suggesting an inherited or toxic myopathic process.
- Overlap myositis occurs in patients who have another connective tissue disease such as scleroderma, systemic lupus erythematosus, or rheumatoid arthritis.
- Rarely, patients may present with both myositis and myasthenia gravis.
- Patients with autoimmune myopathy usually respond to immunosuppressive therapy, and steroids are often the first-line therapy. Steroid-sparing agents such as methotrexate, azathioprine, and mycophenolate mofetil may also be used.

TABLE 5-2 Immunosuppressive/Immunomodulating Therapy for Inflammatory Myopathies^{a,b}

Therapy	Route	Dose	Side Effects	Monitor
Prednisone	Oral	0.75–1.5 mg/kg/d	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, glaucoma, gastric irritation, osteoporosis, infection, avascular femoral necrosis, steroid myopathy, mood alteration, psychosis	Weight, blood pressure, serum glucose/potassium, cataract formation
Methylprednisolone	IV	1 g in 100 mL normal saline over 1–2 h, daily or every other day for three to six doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection	Heart rate, blood pressure, serum glucose/potassium
Azathioprine	Oral	2–3 mg/kg/d, divided into two daily doses	Flulike illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection	Complete blood cell count, liver enzymes
Methotrexate	Oral	7.5–20 mg weekly, single or divided doses; 1 day/week dosing	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, thrombocytopenia, alopecia, gastric irritation, stomatitis, teratogenicity	Liver enzymes, complete blood cell count, creatinine/blood urea nitrogen
	IV/IM	20–50 mg weekly; 1 day/week dosing	Same as oral route	Same as oral route
Cyclophosphamide	Oral	1.5–2 mg/kg/d, single morning dose	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity	Complete blood cell count, urinalysis
	IV	0.5–1 g/m ² /mo for 6 to 12 months		
Cyclosporine	Oral	4–6 mg/kg/d split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity	Blood pressure, creatinine/blood urea nitrogen, liver enzymes, cyclosporine levels
Tacrolimus	Oral	1–2 mg 2 times a day for a total of 2–4 mg/d	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, headache, insomnia, paresthesia, teratogenicity	Blood pressure, creatinine/blood urea nitrogen, liver enzymes, tacrolimus levels
Mycophenolate mofetil	Oral	Adults: (1–1.5 g 2 times a day) Note: No more than 1 g/d in patients with renal failure Children: 600 mg/m ² per dose 2 times a day (not to exceed 2 g/d)	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia	Complete blood cell count

Continued on page 1867

TABLE 5-2 Immunosuppressive/Immunomodulating Therapy for Inflammatory Myopathies^{a,b}
Continued from page 1866

Therapy	Route	Dose	Side Effects	Monitor
IV immunoglobulin (IVIg)	IV	2 g/kg total dose over 2–5 days, then 1 g/kg every 4–8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, flulike symptoms, aseptic meningitis, anaphylaxis, stroke	Heart rate, blood pressure, creatinine/ blood urea nitrogen
Rituximab	IV	750 mg/m ² (up to 1 g) and repeated in 2 weeks; course is then repeated every 6–18 months	Infusion reactions (as per IVIg), infection, progressive multifocal leukoencephalopathy	Some physicians check B-cell count before subsequent courses, but this may not be warranted

IM = intramuscular; IV = intravenous.

^a Modified with permission from Amato AA, Barohn RJ, Neurol Clin.⁴⁶ © 1997 W. B. Saunders Company. [www.neurologic.theclinics.com/article/S0733-8619\(05\)70337-6/fulltext](http://www.neurologic.theclinics.com/article/S0733-8619(05)70337-6/fulltext).

^b Reprinted with permission from Amato AA, Greenberg, SA, Continuum (Minneapolis).⁴⁷ © 2013 American Academy of Neurology. journals.lww.com/continuum/Fulltext/2013/12000/Inflammatory_Myopathies.12.aspx.

as monotherapy, in patients with statin-associated anti-HMG-CoA reductase myopathy.⁴⁸ Patients with refractory anti-SRP may be responsive to rituximab⁴⁹; indeed, some experienced clinicians use this medication at the time of initial diagnosis in patients with this particularly severe form of autoimmune myopathy.

Once muscle strength returns to normal or has plateaued in the context of a normal CK level, steroids are usually tapered to reduce the occurrence of complications such as osteoporosis, weight gain, and opportunistic infection. To minimize the risk of disease flare, the author recommends a slow tapering schedule, reducing the dose of prednisone by 10 mg/d every 3 to 4 weeks until reaching a dose of 20 mg/d. Further reductions of 5 mg/d can be considered every 4 weeks as long as the disease does not flare. Once the patient reaches a dose of 10 mg/d, reductions are made, as tolerated, in 2.5 mg/d increments every 4 weeks.

In patients who have no evidence of active disease for 6 to 12 months after steroids have been discontinued, consideration may be given to tapering any other therapeutic agents the patient may be taking. As with steroids, this

should be done slowly, often over the course of a year, during which time patients should undergo careful monitoring of strength and CK levels. At the first sign of a disease flare, more aggressive treatment should be reinstated.

Of note, a few treated patients recover full strength even though CK levels remain markedly elevated, suggesting that some underlying disease activity still exists. This may be especially true in patients with anti-HMG-CoA reductase myopathy. Whether therapy should be escalated in this situation has not been established. Other patients have persistent muscle weakness even after muscle enzyme levels have normalized. This may occur in patients with an active disease process in which no muscle necrosis and, therefore, no release of muscle enzymes into the bloodstream is present (often in those with dermatomyositis). This may also occur in patients who have developed fatty replacement of muscle tissue due to a chronic or especially severe myopathic process. Muscle MRI can verify extensive permanent muscle damage that, in the absence of active edema, should discourage the futile escalation of immunosuppressive therapy.

KEY POINTS

- IV immunoglobulin may be effective in patients with anti-HMG-CoA reductase myopathy.
- Rituximab may be effective in patients with refractory anti-SRP.
- Steroids and other immunosuppressive/immunomodulatory agents should be very slowly tapered as tolerated by the patient.
- Patients with extensive fatty replacement of muscle may have permanent muscle damage that will not improve with more aggressive therapy.

CONCLUSION

Dermatomyositis, immune-mediated necrotizing myopathy, and antisynthetase syndrome are recognized to be distinct types of autoimmune myopathy with unique muscle biopsy features. In addition, each of these is often associated with a myositis autoantibody that can be used to further subtype the disease. In contrast, polymyositis is now a very rare diagnosis of exclusion made when muscle biopsy reveals normal-appearing muscle fibers invaded by T cells and when the patient does not have an inclusion body myositis or muscular dystrophy phenotype; no polymyositis-specific autoantibodies are known. Currently, only nonspecific immunosuppressive therapies are available to treat these disorders. As mechanisms underlying disease pathogenesis are elucidated, it is hoped that more targeted therapies will be developed.

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