Inflammatory Myopathies

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **This article outlines the salient clinical, serologic, electrophysiologic, imaging, and histopathologic findings and treatment options for the idiopathic inflammatory myopathies, including those related to immune checkpoint inhibitors and SARS-CoV-2.**

RECENT FINDINGS: **The classification of idiopathic inflammatory myopathies has improved with the integration of myositis-specific antibodies and histopathologic findings. Characteristic features of immune checkpoint inhibitor–related myositis have been identified, allowing early recognition and treatment of the syndrome. The COVID-19 pandemic has had a profound impact on the care of patients with idiopathic inflammatory myopathies, and several mechanisms of virus-related muscle injury have been proposed.**

SUMMARY: **A comprehensive evaluation including clinical examination, EMG, imaging, antibody testing, muscle biopsy, and cancer screening, when appropriate, can lead to an earlier accurate diagnosis and an individualized treatment approach for patients with idiopathic inflammatory myopathies.**

INTRODUCTION

Treatable idiopathic inflammatory myopathies are characterized by the subacute development of proximal more than distal muscle weakness, elevated muscle enzymes, and signs of immune dysfunction on muscle biopsies; inflammation is often but not always present. Multiple classification attempts have been made over the years, beginning with the 1975 Bohan and Peter criteria[1] and evolving into modern schemes that take into account the status of myositis-specific antibodies and histopathologic findings.[2,3]

Acknowledging that no single classification system is perfect, the following idiopathic inflammatory myopathies will be described in this article: dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, and overlap myositis.

Polymyositis is much less common than originally thought; almost 90% of patients diagnosed with this condition based on the Bohan and Peter criteria ended up with an alternative diagnosis, after prolonged follow-up and careful analysis of the clinical phenotype, antibody, and histopathology results.[4,5]

Idiopathic inflammatory myopathies resulting from exposure to immune checkpoint inhibitors and SARS-CoV-2, and the impact of the current COVID-19 pandemic on the care of patients with idiopathic inflammatory myopathies, will

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Manousakis discusses the unlabeled/investigational use of several immunosuppressive agents for the treatment of immune/inflammatory myopathies.

also be discussed in this article. For information on inclusion body myositis and its unique clinical features, lack of response to immunotherapy, and different long-term prognosis compared to the idiopathic inflammatory myopathies discussed in this article, refer to the article "Inclusion Body Myositis" by Namita A. Goyal, MD in this issue of *Continuum*.[6]

CLINICAL FEATURES

The clinical manifestations of idiopathic inflammatory myopathies include muscle weakness and extramuscular symptoms and signs, both of which will be discussed in detail in this section.

Muscle Symptoms and Signs

The pattern of weakness of all treatable idiopathic inflammatory myopathies is similar and involves shoulder and pelvic girdle muscles in a symmetric fashion. Neck flexors are also commonly weak. Neck extensors can be prominently affected in cases of overlap myositis with anti–PM-Scl antibodies.[7] Dysphagia due to weakness of pharyngeal muscles is frequent and can lead to aspiration pneumonia. Diaphragmatic weakness can lead to orthopnea and dyspnea on exertion. Extraocular muscle weakness, manifesting with diplopia and ptosis, is very rare, with the exception of immune checkpoint inhibitor–related myositis and coexistent myasthenia gravis. Marked facial and distal upper extremity weakness are uncommon and suggest the alternative diagnosis of inclusion body myositis.

The tempo of weakness progression varies. In most cases of dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, and overlap myositis, it is subacute, over weeks to months. A more rapid progression over days to weeks is possible in viral myositis and immune-mediated necrotizing myopathy, especially with anti–signal recognition particle (SRP) antibodies. A slower progression, over several months to years, is atypical but may occur in immune-mediated necrotizing myopathy with anti–3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase IgG antibodies. Therefore, anti–HMG-CoA reductase IgG antibody testing should be considered in any case of suspected limb-girdle muscular dystrophy with negative exome sequencing results.[8]

Extramuscular Manifestations

Characteristic skin and nail abnormalities occur in dermatomyositis and antisynthetase syndrome. Hallmark findings of dermatomyositis include the heliotrope sign, with periorbital and upper eyelid violaceous discoloration, and Gottron sign, with erythematous, scaly plaques over the metacarpophalangeal

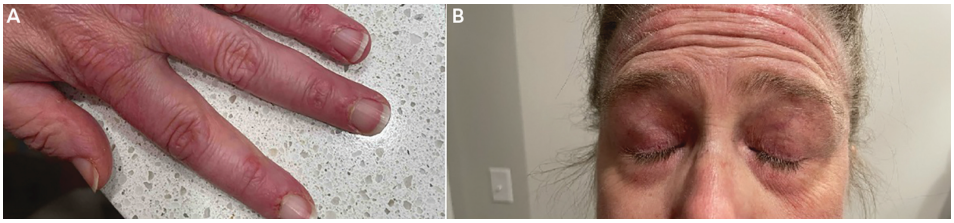

FIGURE 4-1

Characteristic rashes of dermatomyositis. *A,* Gottron sign, with erythematous, scaly papules over the metacarpophalangeal and interphalangeal joints. Note also periungual telangiectasia. *B,* Heliotrope sign.

and interphalangeal joints (FIGURE 4-1). An erythematous rash in sun-exposed areas in the anterior chest (V sign) (FIGURE 4-2), the posterior neck and shoulders (shawl sign), or the lateral thigh (holster sign) may occur. Patients with anti–TIF1-γ antibodies may also show poikiloderma (FIGURE 4-3), with "red on white" patches with coexistent hypopigmented and telangiectatic skin lesions, marked photosensivity with facial erythema, and nonscarring alopecia.[9] Occasionally skin signs will occur in the absence of subjective or objective muscle weakness, known as "amyopathic dermatomyositis"; in most of those cases, imaging, EMG, or biopsy will disclose subclinical muscle involvement.

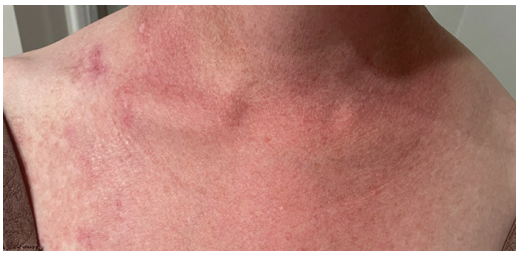

FIGURE 4-2
Anti–TIF1-γ antibody dermatomyositis. Photoerythema and V sign over anterior chest.
Image courtesy of David Pearson, MD.

Subcutaneous calcium deposits, known as calcinosis cutis, occur more often in juvenile dermatomyositis with anti–NXP-2 antibodies and are hard to treat.[10] Nail bed telangiectasias are more common with anti–Mi-2 antibodies; they can be readily identified with capillaroscopy (the technique of visualization of the superficial capillaries within a few millimeters depth of the nail fold, under low power microscope), along with the irregular, "ragged" appearance of the cuticles (Samitz sign) (FIGURE 4-4).

Mechanic's hands refers to a hyperkeratotic eruption over the thumb and the radial aspect of other fingers. It is more often seen in antisynthetase syndrome and overlap myositis with systemic sclerosis than in dermatomyositis.

Anti–melanoma differentiation–associated gene 5 (MDA-5) dermatomyositis manifests with unique lesions, including nail fold and oral ulcers, palmar papules, and alopecia (FIGURE 4-5[11]).[12]

Interstitial lung disease, presenting with dyspnea and nonproductive cough, is a potentially life-threatening comorbidity. Spirometry will show a restrictive pattern with low diffusion capacity of the lungs for carbon monoxide. Chest CT may disclose a reticulonodular pattern or diffuse alveolar injury resembling acute respiratory distress syndrome. The severity of the interstitial lung disease can be independent of the severity of the muscle disease, mortality is high, and treatment is challenging. Interstitial lung disease is a prominent feature of dermatomyositis with anti–MDA-5 antibodies, antisynthetase syndrome, and overlap myositis with systemic sclerosis.

Symptomatic cardiomyopathy is uncommon in idiopathic inflammatory myopathies. When it occurs, patients report dyspnea on exertion, orthopnea, chest pain, and palpitations. Subclinical cardiac involvement can be identified by ECG, echocardiography, or MRI. Pathologic findings include conduction system abnormalities,

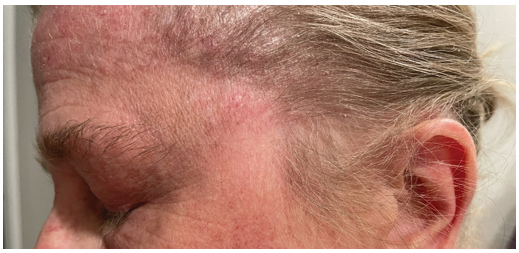

FIGURE 4-3
Scalp poikiloderma and mild alopecia in anti–TIF1-γ antibody dermatomyositis.

KEY POINTS

- **Symmetric proximal upper and lower extremity muscle weakness of subacute onset is common among all treatable idiopathic inflammatory myopathies.**
- **Anti–3-hydroxy-3-methylglutaryl coenzyme A (anti–HMG-CoA) reductase IgG myopathy may evolve slowly and mimic muscular dystrophy; antibody testing should be considered in suspected muscular dystrophy with negative genetic testing.**
- **Heliotrope sign and Gottron sign are the most common skin manifestations of dermatomyositis.**
- **Nail bed telangiectasias and cuticle overgrowth are more common with anti–Mi-2 dermatomyositis.**
- **Palmar papules and fingertip ulcerations are characteristic of anti–MDA-5 dermatomyositis.**
- **The most severe interstitial lung disease occurs with anti–MDA-5 dermatomyositis, antisynthetase syndrome, and overlap myositis with systemic sclerosis. Adding diffusion capacity of the lungs for carbon monoxide to routine spirometry is important to detect this complication.**

KEY POINTS

- Symptomatic cardiac involvement is more likely with anti–signal recognition particle and antimitochrondrial antibody immune-mediated necrotizing myopathy and immune checkpoint inhibitor–related myositis.
- Creatine kinase level can be normal in dermatomyositis and antisynthetase syndrome and is usually very high in immune-mediated necrotizing myopathy. Intermediate-range creatine kinase elevations are not diagnostically helpful and can be seen in myositis mimics, including neurogenic disorders.
- Anti–TIF1-γ and anti–NXP-2 antibodies occur in both juvenile dermatomyositis without cancer and adult dermatomyositis, which has a strong association with cancer.
- Anti–Mi-2 antibody dermatomyositis is associated with typical skin rashes, nail changes, good response to treatment, and no interstitial lung disease or underlying cancer.
- Anti–MDA-5 and anti-SAE antibody dermatomyositis can present without weakness ("amyopathic"), although subclinical muscle involvement is frequently identified on imaging, EMG, or biopsy.

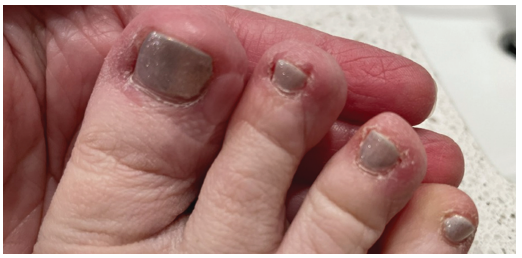

FIGURE 4-4
Toenails with periungual erythema and irregularly thickened, ragged cuticles (Samitz sign).
Image courtesy of David Pearson, MD.

pericarditis, and myocarditis. Immune-mediated necrotizing myopathy with anti-SRP and antimitochondrial antibodies and immune checkpoint inhibitor–related myositis are more likely to cause myocarditis. Pericarditis is a distinctive feature of anti–U1 ribonucleoprotein (RNP) antibody overlap myositis.

Nonerosive arthralgias occur frequently in dermatomyositis, antisynthetase syndrome, and overlap myositis; erosive arthritis is less common. A gastrointestinal vasculopathy may develop in juvenile dermatomyositis, leading to intestinal infarcts or hemorrhage. Glomerulonephritis is seen with anti–U1 RNP antibody overlap myositis. Extramuscular manifestations are rare in immune-mediated necrotizing myopathy.

MUSCLE ENZYMES

Elevated creatine kinase (CK), aldolase, lactate dehydrogenase, aspartate transaminase (AST), and alanine transaminase (ALT) frequently occur in untreated idiopathic inflammatory myopathies. However, CK can be normal in dermatomyositis and antisynthetase syndrome, especially when the inflammation is limited to the perimysium and fascia and muscle fiber pathology is minimal or absent. In those cases, selective aldolase elevation can be diagnostically helpful.[13] Moderate CK elevations are seen in overlap myositis and polymyositis. Extreme CK elevations (>20 times the upper limit of normal) are seen in untreated immune-mediated necrotizing myopathy and some cases of anti–Jo-1 antibody antisynthetase syndrome. CK elevations of less than 10 times the upper limit of normal have limited specificity, as they may also occur with muscle trauma, denervation, and various nonimmune myopathies.

MYOSITIS-SPECIFIC AND MYOSITIS-ASSOCIATED ANTIBODIES

The discovery of several autoantibodies has advanced the classification of idiopathic inflammatory myopathies and allows recognition of syndromes with distinct epidemiologic associations, extramuscular and histopathologic features, and prognosis. A summary of the most important myositis-specific antibodies is presented in TABLE 4-1. The yield of antibody testing in idiopathic inflammatory myopathies is about 65% to 70%.[14]

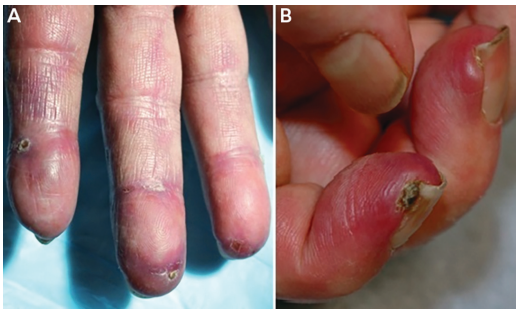

FIGURE 4-5
Anti–MDA-5 antibody dermatomyositis. Typical palmar papules (*A*) and nail fold ulcers (*B*).
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Five antibodies are related to dermatomyositis (anti–NXP-2, anti–TIF1-γ, anti–Mi-2, anti–MDA-5, and anti-SAE). Anti–NXP-2 antibodies are associated

with juvenile dermatomyositis, calcinosis cutis, peripheral edema, and distal weakness, and in adults they confer a higher risk of malignancy.[10,15] Anti–TIF1-γ antibodies have the strongest association with malignancy among dermatomyositis antibodies[16] but can also occur in juvenile forms without cancer.[17] The characteristic skin abnormalities were described in the previous section. Anti–Mi-2 is the most common antibody detected in cohorts of Hispanic patients with dermatomyositis and is characterized by severe muscle weakness, acute onset, typical heliotrope rash and Gottron papules, prominent nail fold pathology, and good prognosis, without elevated risk of cancer or interstitial lung disease.[18,19] Anti–MDA-5 and anti-SAE antibodies were originally described in patients from East Asia, although they were later detected in multiple populations worldwide.[11,20] Anti–MDA-5 antibody syndrome is associated with amyopathic dermatomyositis, but also thrombotic complications, including skin ulceration and palmar papules, and severe, often fatal interstitial lung disease,[11] with clinical and imaging findings that can mimic severe COVID-19. Anti-SAE antibodies are the least common in

Myositis-Specific Antibodies by Myositis Subtype

TABLE 4-1

Syndrome	Antibodies	Typical features
Dermatomyositis	Anti–Mi-2	Acute onset, typical rashes and nail abnormalities, moderate weakness, good prognosis, more common in Hispanic individuals, no cancer or interstitial lung disease
	Anti–TIF1-γ	Bimodal (juvenile and >40 years), strong relationship to cancer in adults, severe photoerythema, V sign, poikiloderma, alopecia; interstitial lung disease rare
	Anti–NXP-2	Bimodal (juvenile and >40 years), related to cancer in adults, calcinosis in juvenile forms, distal weakness and edema; interstitial lung disease rare
	Anti–MDA-5	Predominantly Asian population, amyopathic presentation, palmar papules, nail fold ulcers, alopecia, severe interstitial lung disease; cancer rare
	Anti-SAE	Predominantly Asian population, amyopathic presentation, typical skin rashes, severe dysphagia; cancer association possible
Antisynthetase syndrome	Anti–Jo-1	Muscle involvement can be severe, creatine kinase level occasionally very high, interstitial lung disease, mechanic's hands, Raynaud syndrome and arthralgia, with positivity for anti-Ro52 antibodies
	Anti–PL-7, anti–PL-12, anti-OJ, anti-EJ	Interstitial lung disease more common and severe than muscle involvement
Immune-mediated necrotizing myopathy	Anti–signal recognition particle	Rapid progression, severe weakness, creatine kinase level >10,000 U/L, myocarditis, respiratory failure, poor prognosis if not treated aggressively, more indolent forms possible; cancer and skin lesions rare
	Anti–3-hydroxy-3-methylglutaryl coenzyme A (anti–HMG-CoA) reductase	Variable progression, can be subacute or chronic, creatine kinase level usually >2000 to 3000 U/L, only two-thirds of patients with history of statin use; associated with cancer, no skin lesions
	Antimitochondrial	Slow progression, axial weakness, muscle atrophy, dysphagia, myocarditis, 25% of patients have primary biliary cirrhosis, granulomas sometimes seen on biopsy

dermatomyositis; erythematous rashes and severe dysphagia are characteristic.[20] An elevated cancer risk was recently described.[21]

Anti–aminoacyl transfer RNA (tRNA) synthetase antibodies are found in the antisynthetase syndrome. Those include the most common and well-studied anti–Jo-1 antibody as well as the anti–PL-7, anti–PL-12, anti-OJ, anti-EJ, anti-KS, anti-Zo, and anti-Ha antibodies. Antisynthetase syndrome features myositis plus interstitial lung disease, arthralgias, Raynaud syndrome, and skin manifestations (mechanic's hands). Previously lumped with the diagnosis of dermatomyositis, it is now recognized as a separate syndrome because of the strong association with interstitial lung disease and unique pathologic features, as described in the Muscle Histopathology section. The most striking muscle weakness and CK elevations occur with anti–Jo-1 antibody antisynthetase syndrome; anti–PL-7 and anti–PL-12 antibody antisynthetase syndrome is dominated by interstitial lung disease, often more severe than with the anti–Jo-1 antibody type, but skeletal muscle involvement is milder (CASE 4-1).[22]

Antibodies detected in about 65% of immune-mediated necrotizing myopathy cases include anti-SRP, anti–HMG-CoA reductase IgG, and rarely antimitochondrial M2 antibodies. Anti-SRP antibody syndrome has a seasonal predilection, occurring mostly in the fall; it is characterized by severe and rapidly progressive weakness, extremely high CK levels (typically five-digit),

CASE 4-1

A 49-year-old man presented to his primary care physician with 8 months of dyspnea on exertion and a dry cough without fever or other systemic symptoms. Lung examination showed rales at both bases. ECG and echocardiography were normal. Chest CT showed bilateral interstitial infiltrates and a honeycomb pattern. The results of laboratory testing including complete blood cell count, metabolic panel, antinuclear antibody, rheumatoid factor, antineutrophil cytoplasmic antibody, and C-reactive protein were normal. The patient was treated with oral prednisone, 40 mg daily for 3 months, without improvement.

Neurologic consultation was recommended because of mild proximal weakness, which began 6 months after the initial presentation. Neurologic examination showed mild weakness of hip flexors (4/5) but was otherwise normal. No skin lesions were found. Creatine kinase level was normal (175 U/L), but aldolase was elevated (11.2 U/L). Needle EMG showed a mild irritable myopathy in the lower extremities. Serologic testing was positive for anti–PL-7 antibody. Muscle biopsy showed perimysial thickening and infiltration by macrophages. Tacrolimus, 4 mg daily, led to improvement of muscle weakness and spirometric parameters.

COMMENT

This case demonstrates distinctive features of the antisynthetase syndrome associated with anti-PL-7 antibodies, including severe interstitial lung disease but rather mild muscle involvement, selectively elevated aldolase with normal creatine kinase level, and improvement with use of calcineurin inhibitors such as tacrolimus in steroid-unresponsive cases.

myocarditis, and respiratory failure due to diaphragmatic weakness. If it is not treated early and aggressively, muscle fibrosis and fat replacement can develop within months. Coexistent cancer is infrequent.[23,24] Anti–HMG-CoA reductase IgG myopathy is more common.[25] While the majority of patients with this disorder have a history of exposure to statins, the facts that it is rare among statin users (1:100,000) and at least one-third of patients are statin-naive suggest that additional susceptibility factors exist that lead to the antibody production.[26] The risk of malignancy is increased (CASE 4-2), as is the case with seronegative immune-mediated necrotizing myopathy.[27]

Antimitochondrial antibody–related myositis manifests pathologically as immune-mediated necrotizing myopathy in more than 50% of cases and less often as granulomatous myositis. Myocarditis, axial weakness, dysphagia, and slow course are more common than in other subtypes. A quarter of patients have coexistent primary biliary cirrhosis.[28,29]

Lastly, there is a group of antibodies that can be associated with myositis but are not specific for it, as they can also be detected in numerous connective tissue diseases. The most common is anti-Ro52 (Sjögren syndrome A [SSA]); others include anti–U1 RNP, anti–U2 RNP, anti–PM-Scl, and anti-Ku. Emerging associations include anti-PM-Scl and anti-Ku antibodies, which are present in 60% of cases of systemic sclerosis/overlap myositis syndrome, which includes interstitial lung disease, dysphagia, and Raynaud syndrome. Patients

CASE 4-2

A 57-year-old man presented for a neurologic consultation with a 3-month history of progressive proximal upper and lower extremity weakness and falls. He had been fully independent until 3 months earlier, and he was now unable to rise from a chair without assistance. He also reported dysphagia with liquids, unintentional weight loss of 9 kg (20 lbs), and dyspnea on exertion. He never received statins. He was a former smoker.

Neurologic examination showed muscle strength of 3/5 in the proximal upper and lower extremities and neck flexors. No skin abnormalities were present. Creatine kinase level was 4000 U/L. EMG showed a marked irritable myopathy. MRI of the femur and thighs showed diffuse muscle edema and enhancement, more prominently at the posterior thigh muscles. A left quadriceps biopsy showed necrotizing myopathy. Anti–3-hydroxy-3-methylglutaryl coenzyme A (anti–HMG-CoA) reductase IgG antibodies were strongly positive. He was started on oral prednisone, 60 mg daily, and IV immunoglobulin (IVIg), 0.8 g/kg every 2 weeks, and weakness improved after 1 month. A repeat focused examination by his primary care physician showed mild left-sided submandibular lymphadenopathy confirmed by ultrasonography and a firm mass at the tongue base; biopsy showed squamous cell carcinoma.

COMMENT

This case highlights the association of anti-HMG-CoA reductase IgG antibody myopathy with cancer, which is increasingly recognized, especially in patients who never received statins. IVIg is effective when used as first-line treatment.

positive for anti–PM-Scl-75 and anti–PM-Scl-100 present with prominent weakness of neck extensors (dropped head syndrome) and weakness in proximal upper more than lower extremities.[7] Patients positive for anti-Ku antibodies show more distal weakness than in other idiopathic inflammatory myopathies.[30] Another emerging association is anti–U1 RNP antibodies, which are associated with glomerulonephritis and pericarditis.[31]

ELECTROPHYSIOLOGY

Nerve conduction studies are usually normal in idiopathic inflammatory myopathies unless severe distal muscle involvement causing a decline in distal compound muscle action potential amplitudes occurs. Repetitive nerve stimulation can differentiate myopathies from neuromuscular junction disorders, such as Lambert-Eaton myasthenic syndrome and myasthenia gravis. Needle EMG examination can (1) rule out mimics of myopathies such as motor neuron disorders or polyradiculopathies, (2) determine the extent of muscle involvement, and (3) assist in the selection of muscle for biopsy. Muscles with abnormal spontaneous activity on EMG are more likely to show inflammation, necrosis, or splitting on biopsy (of the contralateral muscle).[32] Muscles with decreased insertional activity, suggesting advanced fibrosis (ie, "end stage"), should be avoided for biopsy. The typical electrophysiologic pattern of untreated idiopathic inflammatory myopathy is the combination of spontaneous activity (fibrillations, positive waves, complex repetitive discharges or true myotonic discharges) and early recruitment of small, short-duration, polyphasic motor unit potentials. This pattern is not specific; it can be seen in many noninflammatory counterparts. After initiation of treatment, subsequent EMG studies can help determine if ongoing weakness is due to active inflammatory myopathy or steroid-induced myopathy; the presence of abnormal spontaneous activity favors the former.

IMAGING

Muscle MRI is the imaging modality of choice for the diagnosis of idiopathic inflammatory myopathies. MRI can assist in distinguishing muscle edema, which is characterized by high T2 and short tau inversion recovery (STIR) signal, from fat infiltration, which is characterized by abnormally high T1 signal due to intramuscular adipose tissue. It can outline the pattern and extent of muscle involvement, help in selecting the optimal target for muscle biopsy, and facilitate assessment of response to therapy. In dermatomyositis, MRI characteristically shows edema in the subcutaneous tissue, epimysium, and perimysium, in addition to patchy muscle edema or contrast enhancement (FIGURE 4-6A). In immune-mediated necrotizing myopathy, severe diffuse edema and enhancement are seen intramuscularly, with little to no fascial involvement; fatty atrophy may occur early, especially in anti-SRP antibody myopathy (FIGURES 4-6B and 4-6C), and pelvic and hip adductor muscles tend to be more severely affected.[33] Note that the MRI finding of edema is not specific for idiopathic inflammatory myopathies, as it can also be seen with muscle trauma, overuse, denervation, toxic rhabdomyolysis, vascular disease, infections (pyomyositis), neoplasms, and other disorders.[34]

MUSCLE HISTOPATHOLOGY

Muscle biopsy remains the most definitive tool to correctly identify the subtypes of idiopathic inflammatory myopathy. In recent years, specific

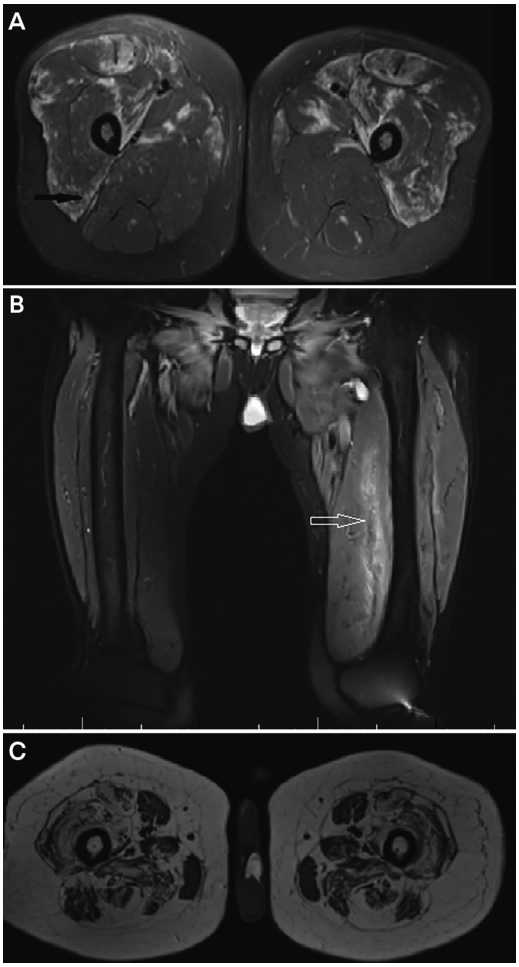

FIGURE 4-6

MRI findings in different inflammatory myopathies. *A,* Axial T2-weighted fat-saturated images showing anti–Mi-2 antibody dermatomyositis. Note patchy intramuscular edema, as well as edema along the perimysium and fascia of the vastus lateralis (*black arrow*). *B,* Coronal T2-weighted short tau inversion recovery (STIR) image showing anti–3-hydroxy-3-methylglutaryl coenzyme A (anti–HMG-CoA) reductase IgG myopathy. Note asymmetric muscle edema of the vastus medialis, left more than right, without fascial or subcutaneous edema (*white outlined arrow*). *C,* Axial T1-weighted images showing advanced-stage anti–signal recognition particle antibody myopathy. Note marked fatty atrophy of anterior and posterior thigh muscles.

correlations of biopsy findings with myositis-specific antibodies have been emphasized.

Key pathogenic events in dermatomyositis are vasculopathy and interferon 1 pathway dysfunction.[35] Capillary dropout is a prominent feature, seen with *Ulex europaeus* agglutinin-1 staining, and membrane attack complex deposition in capillaries is found in 35% of cases.[36] This vasculopathy may lead to ischemia, possibly explaining the pathognomonic finding of perifascicular muscle fiber atrophy. Perifascicular muscle fibers may also show vacuolation, "ghost fibers," and mitochondrial pathology. Those morphologic alterations are most striking in anti–TIF1-γ antibody dermatomyositis.[2] Perifascicular atrophy, however, may be inconspicuous in early dermatomyositis; additional immunohistochemical stains, including major histocompatibility complex (MHC) class I, and interferon-responsive elements like the myxovirus resistance protein A (MxA) may show upregulated perifascicular expression and are more sensitive early pathologic markers of dermatomyositis (FIGURE 4-7).[36] Inflammation in dermatomyositis is perivascular and perimysial and consists of lymphocytes and plasmacytoid dendritic cells. Electron microscopy can show tubuloreticular inclusions in endothelial cells, although this finding is not pathognomonic for dermatomyositis, as it can also be seen with human immunodeficiency virus (HIV) infection and systemic lupus erythematosus.

In antisynthetase syndrome, prominent perimysial thickening, fragmentation, and histiocytic inflammation, identified by alkaline, acid phosphatase, or CD68 stains, are observed. Perifascicular muscle fibers show necrotic or regenerating changes, more often than in dermatomyositis, and capillary pathology is absent.[37]

KEY POINTS

- **Antisynthetase syndrome is the combination of myositis and interstitial lung disease, specific antibodies, mechanic's hands, Raynaud syndrome, and arthralgias. Anti–Jo-1 is the most common antibody involved and is associated with the most severe muscle disease.**
- **Immune-mediated necrotizing myopathy is the most common subtype of immune myopathy. It is related to anti–signal recognition particle, anti–HMG-CoA reductase, or antimitochondrial antibodies. Seronegative cases are often paraneoplastic.**
- **Statins are unlikely to be causally related to anti–HMG-CoA reductase IgG immune-mediated necrotizing myopathy; at least one-third of cases have no history of statin exposure, and many are associated with cancer, regardless of statin use.**
- **Myositis associated with anti–PM-SCl and anti-Ku antibodies overlaps with systemic sclerosis and interstitial lung disease. Anti–PM-SCl antibody myositis presents with dropped head syndrome and upper more than lower extremity weakness.**
- **Spontaneous activity on EMG is predictive of inflammation, necrosis, or splitting on muscle biopsy. After treatment initiation, spontaneous activity can distinguish between active inflammatory myopathy and steroid-induced myopathy.**

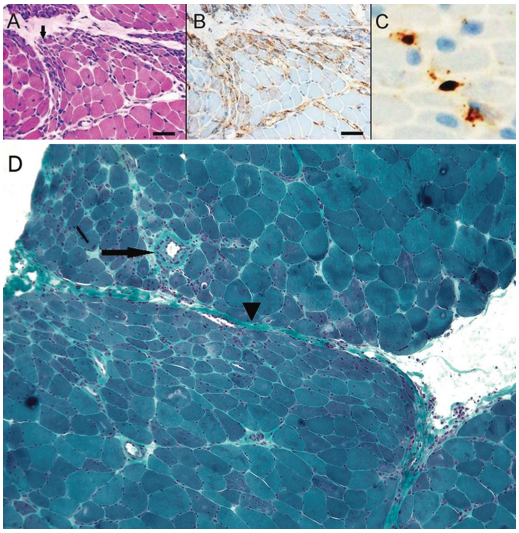

FIGURE 4-7

Characteristic histopathologic features of dermatomyositis. *A,* Hematoxylin and eosin stain showing perifascicular atrophy (*arrow*). *B,* Myxovirus resistance protein A stain. Note increased expression in perifascicular regions. *C,* Membrane attack complex stain. Note increased expression in capillaries. *D,* Gomori trichrome stain showing anti–MDA-5 antibody juvenile dermatomyositis. Note that perifascicular muscle fibers, in addition to atrophy, show multiple internal nuclei with abnormal morphology (*arrowhead*). Perivascular inflammation is also present (*arrow*).

Panels A through C reprinted with permission from Uruha A, et al, Neurology.[35] © 2016 American Academy of Neurology. Panel D courtesy of Peter Karachunski, MD.

Overexpression of MHC class I and MHC class II in the periphery of muscle fibers is common. Actin-like nuclear filaments are identified by electron microscopy in 70% of cases[38] (FIGURE 4-8[2]).

Immune-mediated necrotizing myopathy is the most common pathology among idiopathic inflammatory myopathies. Muscle biopsies show extensive necrosis and regeneration, but inflammation is scant or absent in anti-SRP antibody–positive and seronegative cases. Necrotic fibers are best identified with acid phosphatase (FIGURE 4-9). Membrane attack complex deposition is seen in approximately 50% of cases.[26] MHC class I is upregulated only in necrotic fibers and not diffusely. Recently, a marked increase in fibers staining diffusely with the autophagic markers p62 and LC3 was reported in immune-mediated necrotizing myopathy, in contrast to dermatomyositis and polymyositis.[39] If the condition is untreated, fibrosis can develop within months, especially in anti-SRP antibody myopathy. The pathology of anti–HMG-CoA reductase IgG antibody immune-mediated necrotizing myopathy is more diverse, with frequent perimysial infiltration with macrophages, and perivascular lymphocytic inflammation detected in about 30% of cases.[40]

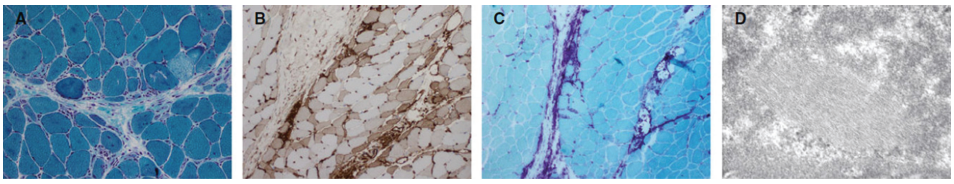

FIGURE 4-8

Characteristic histopathologic features of antisynthetase syndrome. *A,* Gomori trichrome stain showing fragmentation of perimysium and perifascicular muscle fibers with necrotic and regenerating features. *B,* Major histocompatibility complex class II overexpression in perimysial regions. *C,* Prominent staining of perimysium with alkaline phosphatase–positive macrophages. *D,* Electron microscopy showing intranuclear actinlike filaments.

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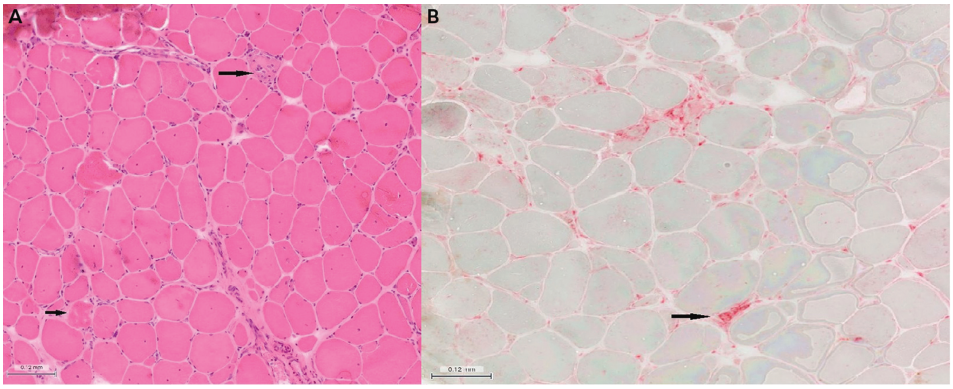

FIGURE 4-9

Immune-mediated necrotizing myopathy with anti–3-hydroxy-3-methylglutaryl coenzyme A (HMG-COA) reductase IgG antibodies. *A,* Scattered necrotic fibers in different stages (*arrows*). *B,* Acid phosphatase stain highlighting necrotic fibers (*arrow*). Note lack of primary inflammation.

Figure courtesy of Grace Taylor.

Overlap myositis does not have a unique pathologic signature. Inflammation can be perivascular, perimysial, or endomysial, and sometimes immune-mediated necrotizing myopathy without inflammation is found. In a 2021 study an association of anti–PM-SCl-100 antibodies with marked endomysial and perivascular inflammation, with large clusters of B cells staining with CD20 marker, was described. This is a rare example of pathologically defined polymyositis.[41]

CANCER ASSOCIATION AND SCREENING

Diverse solid or hematologic malignancies can occur in idiopathic inflammatory myopathies, including lung, breast, ovarian, and gastrointestinal cancers, lymphoma, and melanoma. Most of these will be identified within 3 years of disease onset. Screening for malignancy should be performed in all adults over age 40 with dermatomyositis, especially those who are positive for anti–TIF1-γ[16] and anti–NXP-2 antibodies, and in all adults with seronegative or anti–HMG-CoA reductase IgG antibody–positive immune-mediated necrotizing myopathy. The incidence of underlying cancer in these groups is high and can exceed 40%. With anti–HMG-CoA reductase IgG antibodies, cancer may occur regardless of history of prior statin exposure.[27] The incidence of cancer in individuals with antisynthetase syndrome, anti-SRP antibody immune-mediated necrotizing myopathy, or overlap myositis is low, and routine screening is not recommended.

No consensus exists on the optimal imaging method or required frequency of screening. Specifically, it is not clear whether routine whole-body positron emission tomography (PET) scanning is superior to conventional cancer screening with CT.[42,43] The author screens patients with chest, abdomen, and pelvis CT, gastrointestinal endoscopy, and mammography and pelvic examination for females, and reimages high-risk individuals (eg, those with anti–TIF1-γ antibody–positive dermatomyositis) every 6 months for 2 to 3 years.

PUTTING EVERYTHING TOGETHER TO ARRIVE AT A DIAGNOSIS

An algorithm for the use of the aforementioned diagnostic tools—muscle enzymes, EMG, muscle imaging, antibody testing, and biopsy—to arrive at

KEY POINTS

- MRI of skeletal muscle shows edema in recent-onset inflammatory myopathies and fatty atrophy in chronic cases. Neither edema nor fatty atrophy is pathognomonic.
- Dermatomyositis is pathologically characterized by capillary dropout and complement deposition, perivascular inflammation, perifascicular atrophy, and abnormal perifascicular expression of interferon-responsive elements and major histocompatibility complex class I.
- Antisynthetase syndrome is distinguished from dermatomyositis by the marked perimysial fragmentation and inflammation consisting of macrophages rather than lymphocytes, and lack of capillary pathology.
- Immune-mediated necrotizing myopathy is characterized by multifocal fiber necrosis and regeneration but scant or absent inflammation.
- Cancer screening should be performed in all adults over age 40 with dermatomyositis, especially those who are positive for anti–TIF1-γ or anti–NXP-2 antibodies, and all adults with seronegative or anti–HMG-CoA reductase IgG–positive immune-mediated necrotizing myopathy.

the correct idiopathic inflammatory myopathy diagnosis is proposed in FIGURE 4-10.

TREATMENT OPTIONS

There is a paucity of randomized trials to guide the treatment of idiopathic inflammatory myopathies, and for most agents, the evidence is based on case series or expert opinion. First-line treatment is corticosteroids, either oral prednisone 1 mg/kg/d to 1.5 mg/kg/d or IV methylprednisolone 500 mg/d to 1000 mg/d for 3 to 5 days, when weakness is more severe and a rapid induction of effect is desired. High-dose oral steroid therapy should be continued for at least 4 to 6 weeks or until clinical improvement has plateaued; a slow taper of no faster than 10 mg/month follows. Because of the many systemic side effects of corticosteroids, adjunct second-line treatment is required in all but the mildest cases. Options include oral azathioprine 2 mg/kg/d to 2.5 mg/kg/d, oral or IM methotrexate 20 mg/wk to 25 mg/wk, and mycophenolate mofetil up to 3 g/d in divided doses. For more refractory cases, IV immunoglobulin (IVIg) is a third-line option, supported by a randomized clinical trial in dermatomyositis.[44] Fourth-line treatments include (1) rituximab (the efficacy of rituximab is supported by a randomized trial that did not meet its primary endpoint, yet 83% of participants met the definition of improvement),[45] (2) the calcineurin inhibitors cyclosporine and tacrolimus,[46] and (3) cyclophosphamide.[47] Promising but still experimental

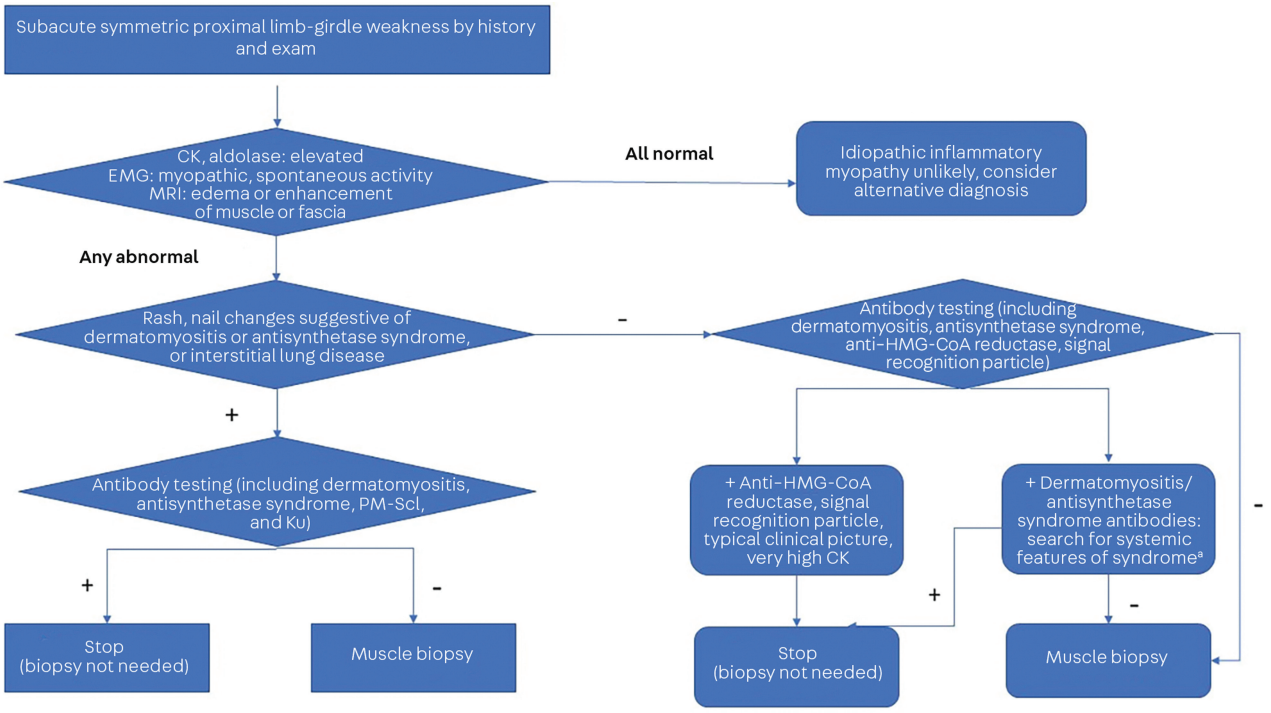

FIGURE 4-10

Stepwise use of clinical findings and laboratory tests to diagnose idiopathic inflammatory myopathy.

CK = creatine kinase.

[a] Systemic features of dermatomyositis/antisynthetase syndrome: cutaneous lesions (see text), Raynaud syndrome, nonerosive arthropathy, interstitial lung disease (order high-resolution chest CT and spirometry with diffusion lung capacity to evaluate for subclinical disease).

approaches include inhibition of complement (eculizumab, zilucoplan), Janus kinase (ruxolitinib, baricitinib), B-cell activating factor (belimumab), interferon alfa (sifalimumab), interleukin 6 (tocilizumab), cannabinoid 2 receptors (lenabasum), and toll-like receptors 7, 8, and 9 (IMO-8400).[48] Anti–tumor necrosis factor agents are avoided because of potential for exacerbation of myositis.[49]

Recent data permit an individualized approach to the treatment of certain subtypes of idiopathic inflammatory myopathies. Immune-mediated necrotizing myopathies require aggressive treatment and earlier use of more than one agent. IVIg may be offered as a first-line treatment in anti–HMG-CoA reductase IgG myopathy, either in combination with corticosteroids and another nonsteroid immunosuppressant or as monotherapy in patients with high risk of steroid complications (eg, those with diabetes).[50] Rituximab has shown promising results in anti-SRP antibody myopathy, anti–Jo-1 antibody antisynthetase syndrome, and anti–Mi-2 antibody dermatomyositis.[51] The combination of steroids and calcineurin inhibitors, especially tacrolimus, or cyclophosphamide may be used early for severe interstitial lung disease complicating antisynthetase syndrome or anti–MDA-5 antibody syndrome.[52] Methotrexate is likely a poor choice for antisynthetase syndrome, as it can exacerbate interstitial lung disease.

IMMUNE CHECKPOINT INHIBITOR–RELATED MYOSITIS

Immune checkpoint inhibitors have revolutionized cancer treatment. By inhibiting apoptotic molecules expressed on cancer cells, such as programmed cell death 1, programmed cell death ligand 1, or cytotoxic T-lymphocyte-associated protein 4, the "brakes" on the immune system are released, and T cells will attack tumor cells.[53] These medications are often used as second- or third-line treatments in recurrent metastatic solid tumors, with impressive results. However, the overactivation of T cells can lead to immune-related adverse events, which include nonneurologic (eg, colitis, skin inflammation, thyroiditis) and neuromuscular syndromes, such as demyelinating or vasculitic neuropathies, myasthenia gravis and myositis, or various combinations of the above.[53] A distinct phenotype of immune checkpoint inhibitor–related myositis was recently characterized.[54] In addition to proximal limb-girdle weakness, occurring within 1 to 2 months after initiation of immune checkpoint inhibitors, features include myositis of ocular muscles, manifesting with diplopia or ptosis, which can be confused with myasthenia gravis (most patients were negative for anti–acetylcholine receptor antibodies and had normal repetitive nerve stimulation studies, making myasthenia unlikely, and biopsies of extraocular muscles showed evidence of inflammation); myocarditis; and lymphopenia. A predilection for axial muscles was noted, especially neck extensor muscles. Muscle biopsies usually showed immune-mediated necrotizing myopathy with clusters of necrotic fibers; inflammation was less common (FIGURE 4-11[54]). CK levels were elevated, yet much lower than those seen in other subtypes of immune-mediated necrotizing myopathy. Corticosteroids represent the most effective treatment; IVIg can be used in refractory cases. In milder cases, immune checkpoint inhibitor treatment does not need to be discontinued (CASE 4-3).

COVID-19 AND MYOSITIS

The COVID-19 pandemic has had a profound impact on the care of patients with idiopathic inflammatory myopathies and our understanding of the relationship between viruses and muscle injury. Muscle involvement in COVID-19 is not

KEY POINTS

- First- and second-line treatments for inflammatory myopathies are corticosteroids and nonsteroidal immunosuppressant drugs such as azathioprine, mycophenolate mofetil, and methotrexate. They often have to be combined.
- Subtypes of idiopathic inflammatory myopathy with better response to IV immunoglobulin and rituximab have been identified.
- Immune checkpoint inhibitor–associated myositis is characterized by ocular myositis with ptosis or diplopia, myocarditis, lymphopenia, and pathologic evidence of immune-mediated necrotizing myopathy with creatine kinase levels lower than those seen in other forms of immune-mediated necrotizing myopathy. Corticosteroids and temporary discontinuation of immune checkpoint inhibitors are the mainstays of treatment.

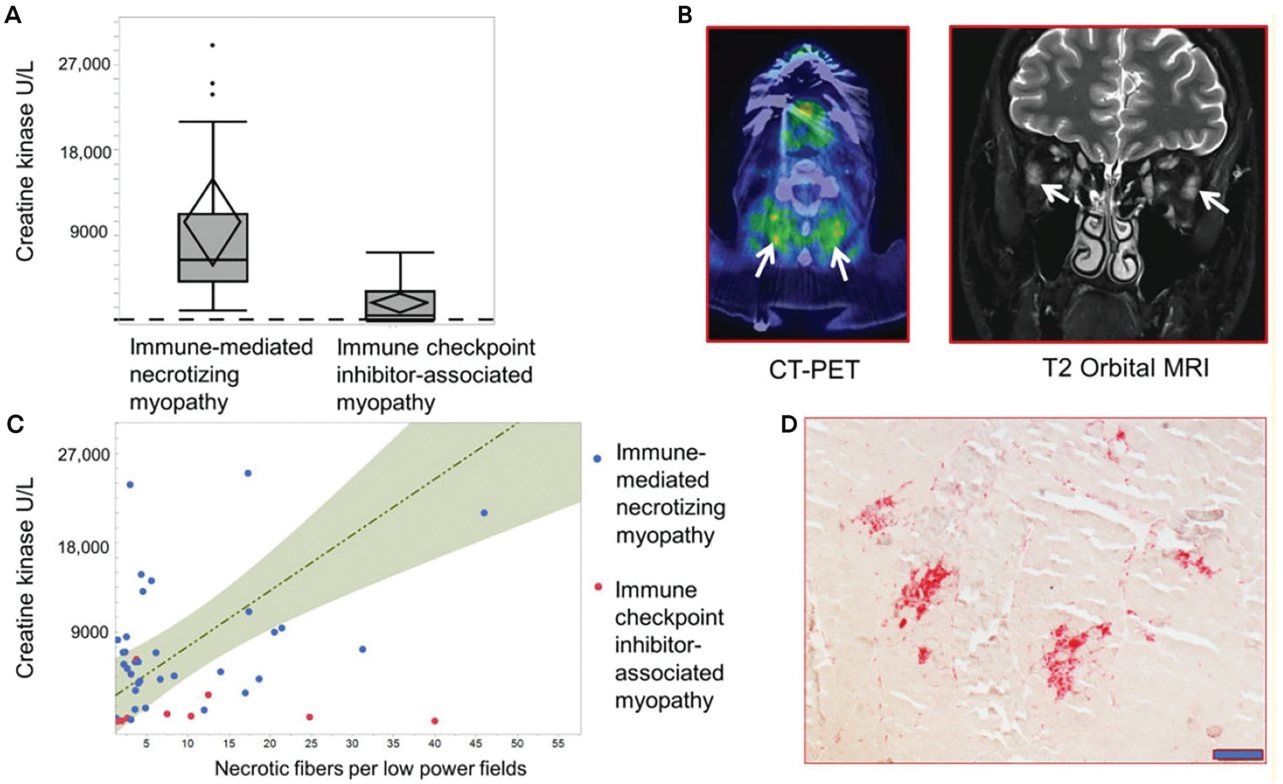

FIGURE 4-11

Summary of characteristic features of immune checkpoint inhibitor–related necrotizing myopathy. *A,* Creatine kinase levels are lower in immune checkpoint inhibitor–related necrotizing myopathy compared with classic immune-mediated necrotizing myopathy. *B,* Fluorodeoxyglucose–positron emission tomography (PET) scan showing increased uptake in posterior scalene muscles (*arrows*), and coronal T2-weighted fat-suppressed orbital MRI showing orbital myositis (*arrows*). *C,* Nonlinear relationship of creatine kinase levels with amount of necrotic fibers on biopsy in immune checkpoint inhibitor–related myositis. *D,* Acid phosphatase stain highlighting clustered necrotic fibers.

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uncommon. Myalgia is reported by 50% of patients, and 16% to 33% show asymptomatic CK elevations, which may be related to increased mortality.[55] Three clinical themes of myopathy have emerged: 1) Rhabdomyolysis. Of 10 reported cases, 4 were fatal. CK levels were markedly elevated, occasionally with accompanying acute kidney injury, and MRI of skeletal muscles showed edema or low T2 signal due to intramuscular hemorrhage. Patients had typical respiratory symptoms of COVID-19, and many were critically ill.[55] 2) Classic dermatomyositis.[56] Five patients were antibody-positive (anti–MDA-5, anti–Mi-2, and anti-SAE antibodies). 3) Isolated paraspinal myositis, identified as increased T2 signal of deep lumbar paraspinal muscles on MRI; nine patients were affected, and most had a prolonged hospital course.[57] The caveat of premortem literature reports is the lack of muscle pathologic findings in most patients. However, two subsequent postmortem studies of 78 patients who died from COVID-19 complications showed that immune-mediated muscle pathology was common, with 25% showing necrotizing myopathy and 20% showing primary inflammation in one series, more than half showing abnormal MHC class I expression, and 15% to 20% showing MxA expression in capillaries

(FIGURE 4-12[58]).[58,59] Importantly, SARS-CoV-2 was not detected in muscle by immunohistochemistry or electron microscopy, arguing against direct viral myocyte invasion. Therefore, the most likely mechanism for muscle injury in SARS-CoV-2 infection is virus-triggered activation of innate and adaptive immunity.[26] An important limitation of the aforementioned studies is that detailed description of clinical symptoms and signs of myopathy, and EMG findings is lacking, and therefore one cannot conclude that those pathological findings are due to a myositis syndrome, versus simply epiphenomena of a systemic inflammatory response to the viral infection. Adaptive immunity abnormalities include T-cell clonal expansion and $CD8^+$ cell overactivation. Innate immunity abnormalities include overexpression of proinflammatory cytokines such as tumor necrosis factor-α, interleukin 1, interleukin 6 (cytokine storm), and dysfunction of the interferon-signaling pathway. A case report of rhabdomyolysis in a COVID-19 patient, whose muscle biopsy showed perifascicular upregulation of MxA protein,[60] supports the latter theory, as does the striking similarity between severe COVID-19 and anti–MDA-5 antibody dermatomyositis, including

CASE 4-3

A 66-year-old woman with metastatic melanoma of the right upper extremity was treated with nivolumab and ipilimumab. Two months later, she developed bilateral ptosis, diplopia, and mild proximal weakness. She was initially evaluated by ophthalmology, who suspected myasthenia gravis; serologic testing including anti–acetylcholine receptor and anti–muscle-specific tyrosine kinase (MuSK) antibodies was negative, and she did not improve with pyridostigmine. She was then referred for neurologic consultation.

Neurologic examination showed nonfatigable right more than left eyelid ptosis, mild to moderate weakness of the orbicularis oculi, and left eye esotropia. Mild (4/5) lower facial, neck flexor, deltoid, and hip flexor weakness was present bilaterally. Creatine kinase was mildly elevated at 620 U/L, and EMG showed an irritable myopathy. Repetitive nerve stimulation studies from the facial and spinal accessory nerves were normal. MRI of the orbits showed edema and postcontrast enhancement of extraocular muscles. Quadriceps muscle biopsy showed multifocal necrosis and regeneration.

The patient was administered high-dose oral prednisone with a gradual taper. Her weakness improved, and immune checkpoint inhibitors were continued.

COMMENT

This case illustrates the characteristic features of immune checkpoint inhibitor–related myositis, which may present with ocular muscle weakness due to orbital myositis and can be diagnostically confused with myasthenia gravis. Biopsies commonly show immune-mediated necrotizing myopathy features, but creatine kinase levels are lower than in other forms of immune-mediated necrotizing myopathy. Steroids are effective in most cases; immune checkpoint inhibitor treatment does not always have to be discontinued.

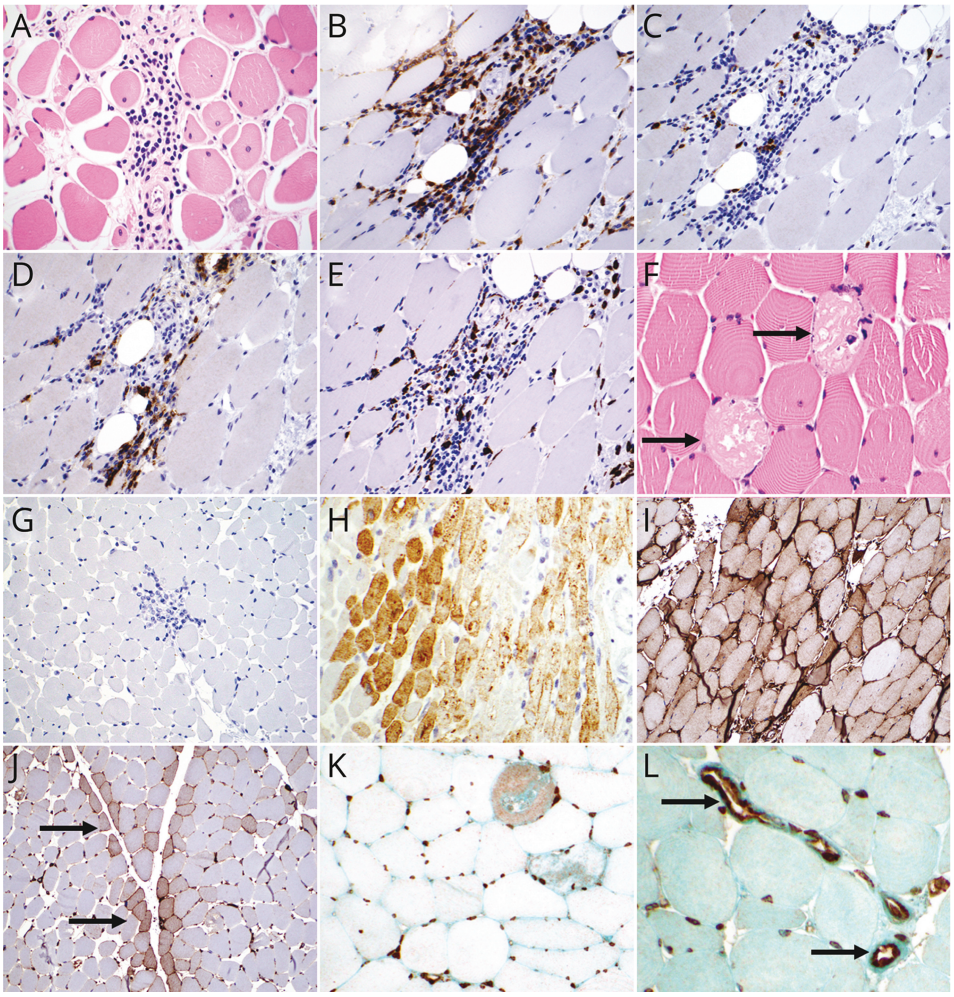

FIGURE 4-12

Histopathologic features of COVID-19 myositis. Autopsy specimen, psoas muscle. Note perivascular and endomysial inflammation on hematoxylin and eosin (H&E) stain (*A*), consisting of $CD4^+$ (*B*) and $CD8^+$ (*C*) cells. H&E stain also shows scattered necrotic fibers (*F, arrows*). SARS-CoV-2 proteins are not detected by immunohistochemistry in skeletal muscle (*G*), in contrast to positive cardiac myocytes (*H*). Major histocompatibility complex class I stain shows either diffuse (*I*) or perifascicular (*J, arrows*) upregulation. Human myxovirus resistance protein A assay shows abnormal expression in necrotic fibers (*K*) or capillaries (*L, arrows*).

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interstitial pneumonitis with peripheral ground-glass opacities, skin findings of thrombosis and ulcerations, fever, hypercytokinemia, and hyperferritinemia. MDA-5 is an intracellular viral RNA detector, activated following release of interferon alfa, and genetic defects in the interferon/MDA-5 signaling pathway have been linked to susceptibility to severe COVID-19.[61]

COVID-19 has undoubtedly disrupted the care of patients with preexisting idiopathic inflammatory myopathy. In a recent survey, 32% of patients with preexisting idiopathic inflammatory myopathy reported issues during the pandemic, including worsening disease activity, hospitalization in 18%, and reduced access to providers and medications.[62] The widespread implementation of telemedicine in the first phase of the pandemic led to limited physical

examinations and less access to ancillary services such as physical therapy. Several solutions—such as the use of patient self-reported outcomes, self–physical assessment tools, mobile apps, teletriaging, and home infusions when feasible—were proposed and implemented. Unanswered questions remain, including the optimal management of immunosuppressive therapies for idiopathic inflammatory myopathy during the pandemic; balancing the risk of severe COVID-19 against the risk of exacerbation of underlying idiopathic inflammatory myopathy; the overall impact of the pandemic on morbidity and mortality of patients with idiopathic inflammatory myopathy; and the possibility of COVID-19 triggering future autoimmune diseases, including idiopathic inflammatory myopathy.[55] Data from large prospective registries are required to answer these questions.

SARS-CoV-2 vaccination is recommended by professional societies for patients with idiopathic inflammatory myopathy.[63] Because different medication regimens may variably affect the immune response to COVID-19 vaccines (eg, rituximab and methotrexate suppress antibody generation to a greater degree than other agents), individualized decisions regarding timing of vaccination in relationship to timing of immunosuppressive treatment have to be made. A recent "practice topic" article from the American Association of Neuromuscular & Electrodiagnostic Medicine serves as a useful guide.[63] Preventive infusion of tixagevimab plus cilgavimab, two long-acting monoclonal antibodies against SARS-CoV-2 spike protein, is recommended for immunosuppressed individuals at risk for poor antibody response to vaccination.[64] Oral (ritonavir-boosted nirmatrelvir, molnupiravir) and IV treatments (eg, bebtelovimab, remdesivir) are also recommended at the earliest signs of SARS-CoV-2 infection in these patients; timely administration can substantially reduce the risk of hospital admission and death.[65]

CONCLUSION

Although all treatable idiopathic inflammatory myopathies share common clinical features, the discovery of myositis-specific and myositis-associated antibodies in the past few decades has allowed the phenotyping of cohorts of patients with idiopathic inflammatory myopathy with distinct serologic-histopathologic correlations, extramuscular manifestations, and associations with cancer. It has also improved the understanding of the pathophysiology of each idiopathic inflammatory myopathy subgroup, hopefully leading to a personalized treatment approach in the near future. Newly recognized triggers for idiopathic inflammatory myopathy, such as immune checkpoint inhibitor drugs and SARS-CoV-2 infection, have further enhanced our insight into idiopathic inflammatory myopathy mechanisms.

KEY POINTS

- **COVID-19 is associated with frequent myalgia and creatine kinase elevations. Rhabdomyolysis, dermatomyositis, and paraspinal myositis have been described. Immune-mediated muscle pathology is a frequent finding on autopsy.**
- **The most likely mechanism of muscle injury in COVID-19 infection is indirect due to adaptive and innate immunity dysfunction rather than direct muscle invasion by the virus.**
- **The care of patients with idiopathic inflammatory myopathies was significantly disrupted by the pandemic. The full impact of SARS-CoV-2 on the morbidity and mortality of patients with idiopathic inflammatory myopathy and the risk of future development of diopathic inflammatory myopathy remain to be determined.**

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