REVIEW ARTICLE

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Toxic Myopathies

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ABSTRACT

PURPOSE OF REVIEW: This article reviews the pathogenesis, clinical features, and management of toxic myopathy related to common medications, critical illness, and illicit substances.

RECENT FINDINGS: Muscle symptoms are common among statin users and are usually reversible after discontinuation of the statin; rarely, however, statins trigger an immune-mediated necrotizing myopathy that persists and requires immunomodulatory therapy. Autoantibodies targeting 3-hydroxy-3-methylglutaryl coenzyme A reductase can distinguish the toxic and immune-mediated forms. Immune checkpoint inhibitors, increasingly used in the treatment of advanced cancer, have recently been associated with the development of inflammatory myositis. A reversible mitochondrial myopathy has long been associated with zidovudine, but recent reports elucidate the risk of myopathy with newer antivirals, such as telbivudine and raltegravir.

SUMMARY: The medications most commonly associated with myopathy include statins, amiodarone, chloroquine, hydroxychloroquine, colchicine, certain antivirals, and corticosteroids, and myopathy can occur with chronic alcoholism. Certain clinical, electrodiagnostic, and histologic features can aid in early recognition. Stopping the use of the offending agent reverses symptoms in most cases, but specific and timely treatment may be required in cases related to agents that trigger immune-mediated muscle injury.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Doughty and Amato discuss the unlabeled/investigational use of immunotherapy for the treatment of drug-induced inflammatory myopathies.

INTRODUCTION

Many drugs and toxic substances cause myopathy with diverse and sometimes poorly understood pathogenic mechanisms (TABLE 10-1). A high index of suspicion is required to recognize the connection because for most drugs this is an infrequent complication. Moreover, the resulting clinical manifestations are quite diverse. Some patients have only mild symptoms, such as myalgia or cramps. Others may develop acute, severe, necrotizing myopathy resulting in weakness or myoglobinuria and life-threatening renal failure. In many cases, symptoms begin soon after initiation of the offending medication, but in others, symptoms develop insidiously only after cumulative exposure over months or even years.

Patients with toxic myopathy often present with subacute proximal weakness, so initially an inflammatory myopathy may be suspected. Clinical clues may facilitate distinguishing the etiology (TABLE 10-2). For example, a concurrent neuropathy is often seen with colchicine or amiodarone, whereas a rash,

concomitant arthritis, or pulmonary involvement or history of other autoimmune disorders may suggest an inflammatory myopathy. Severe muscle pain and myoglobinuria may result from toxic necrotizing myopathy but are unusual in myositis unless there is concurrent fasciitis. However, occasional dystrophies (eg, Becker muscular dystrophy), central core myopathy (caused by a mutation in the *RYR1* gene), and metabolic myopathies can present with myalgia or myoglobinuria. As this illustrates, these clues are frequently nonspecific, so a broad differential diagnosis must usually be entertained. Genetic testing or a muscle biopsy is often required for diagnosis.

Early recognition is important because, in most cases, stopping the offending agent leads to prompt improvement and even resolution of symptoms. In rare cases, however, an immune-mediated response is spurred on by the medication that requires specific treatment to resolve symptoms. Statins, for example, can cause an immune-mediated necrotizing myopathy. Immune-mediated necrotizing myopathy also occurs in non–statin-exposed patients; for more details on this, refer to the article "Immune-Mediated Myopathies" by Namita A. Goyal, MD, FAAN,[1] in this issue of *Continuum*. Recently, immune checkpoint inhibitors used to treat advanced cancer have been associated with an inflammatory myositis. This review will highlight common causes of toxic myopathy, with an emphasis on recent evidence and new agents.

KEY POINTS

- The clinical presentation of toxic myopathy is diverse. Some patients present with severe symptoms soon after initiation of the causative medication, whereas others present with mild symptoms that develop insidiously after months of exposure.
- In most cases, stopping the offending medication leads to improvement and even resolution of symptoms. Statins and immune checkpoint inhibitors, however, can cause an immune-mediated myopathy that may require immunomodulatory treatment.
- The spectrum of myopathic symptoms encountered with cholesterol-lowering agents includes myalgia, cramps, asymptomatic creatine kinase level elevation, proximal muscle weakness, and rhabdomyolysis with myoglobinuria.
- Myalgia and cramps are common among statin users but are not always related to the statin.

NECROTIZING MYOPATHIES

Many drugs can cause a toxic necrotizing myopathy, with cholesterol-lowering agents the most common. Most patients have mild symptoms, such as myalgia or cramps, with some just having asymptomatic creatine kinase (CK) elevation. Rarely, patients experience proximal muscle weakness or, in severe cases, myoglobinuria and renal failure. An elevated serum CK level and EMG demonstrate an irritable myopathy with fibrillation potentials, positive sharp waves, or complex repetitive discharges. Symptoms resolve upon stopping the offending agent, except in the rare cases of statin-associated immune-mediated necrotizing myopathy.

Statins

Statins lower cholesterol through inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in cholesterol synthesis. The pathogenic mechanism by which statins cause myopathy remains uncertain. Hypotheses include destabilization of the muscle membrane due to reduced cholesterol within the membrane and impaired energy production from reduced coenzyme Q10 production (another downstream product of HMG-CoA reductase). Downstream metabolites in the HMG-CoA reductase pathway are also important for glycoprotein synthesis.[2]

Muscle-associated adverse effects occur with all approved statins. Asymptomatic CK elevation occurs in up to 5% of treated patients,[3] and myalgia and cramps affect as many as 20% of statin users.[4] Symptoms may develop at any time but tend to begin a median of 1 to 6 months after initiation.[5–7] Interestingly, in placebo-controlled trials, the incidence of myalgia is similar in placebo and statin arms.[8] For as many as 30% to 50% of patients with myalgia while taking a statin, it has another possible cause.[9] Given the benefit statins offer in terms of lipid lowering and reduction in cardiovascular events, tools are available to help patients and physicians accurately gauge the likelihood that the statin is

causing muscle symptoms, such as one developed by the American College of Cardiology[10] and the Statin-Associated Muscle Symptoms Clinical Index.[11] Statin-related myalgia generally affects large proximal muscle groups symmetrically, whereas cramps affect small muscles in the hands and feet asymmetrically.

Rarely, patients develop severe pain and proximal weakness. The American College of Cardiology estimates the incidence of severe myopathy to be 0.08% for lovastatin, simvastatin, and pravastatin. Concurrent use of medications that affect statin metabolism, including those that inhibit the cytochrome P450 3A4 pathway, increases the risk of toxic myopathy (TABLE 10-3).[8,12,13] The combination of statins with either gemfibrozil or cyclosporine confers especially high risk: the risk of symptomatic rhabdomyolysis among patients with statins is approximately 2 to 3 per 100,000 patient-years, but it is higher in patients taking one of these medications concurrently.[5] When rhabdomyolysis occurs, it is typically early in the course of statin therapy, an average 1.3 months after

TABLE 10-1 **Pathogenic Mechanisms of Toxic Myopathies**

Necrotizing Myopathy

- Statins
- Other cholesterol-lowering agents
- Cyclosporine
- Propofol
- Labetalol
- Alcohol

Inflammatory Myopathy

- Immune checkpoint inhibitors
- D-Penicillamine
- Cimetidine
- Phenytoin
- Interferon alfa
- Tumor necrosis factor inhibitors
- Imatinib
- Hydroxyurea

Amphiphilic

- Amiodarone
- Chloroquine
- Hydroxychloroquine

Antimicrotubular

- Colchicine
- Vincristine

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initiation, but it can also occur after initiation of one of these other medications. The risk of a toxic myopathy is dose dependent. Data from four large, randomized controlled trials suggest a 10-fold increase in myopathy for patients on high-dose therapy compared with those on lower dosages. Additional risk factors include male sex, age older than 65 years, renal or hepatic failure, and hypothyroidism. Finally, a genome-wide association study found that 60% of patients with statin myopathy have a single nucleotide polymorphism located within the *SLCO1B1* gene, which encodes a protein that regulates hepatic processing of statins.[14]

In cases with objective weakness or rhabdomyolysis, the statin should be stopped immediately. CK values may normalize in as quickly as 1 week and rarely remain elevated longer than 2 months.[9,15] Resolution of muscle pain and weakness occurs, on average, 2.3 months after cessation of a statin (**CASE 10-1**).[5]

Rarely, immune-mediated necrotizing myopathy complicates statin therapy.[16,17] This is characterized by proximal muscle weakness with or without myalgia,

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Mitochondrial Myopathy

- Zidovudine
- Telbivudine and other antiretrovirals[a]

Hypokalemic Myopathy

- Diuretics
- Corticosteroids
- Laxatives
- Amphotericin
- Lithium
- Alcohol
- Toluene abuse
- Ingestion of excessive licorice

Unknown

- Emetine
- Febuxostat
- Finasteride
- Isotretinoin
- Levetiracetam
- Omeprazole

[a] The pathogenic mechanism is less clearly established for other HIV and hepatitis B antiviral medications.

typically clinically indistinguishable from the toxic necrotizing form. When the statin is withdrawn, however, the myopathy does not improve; immunomodulatory therapy is required and leads to symptomatic improvement.

CK levels are markedly elevated in patients with weakness from both toxic necrotizing myopathy and immune-mediated necrotizing myopathy. CK values are typically 5000 to 10,000 U/L in patients with immune-mediated necrotizing myopathy. Likewise, EMG will demonstrate an irritable myopathy in proximal muscles in both forms. Myotonic discharges have been reported with statin-induced toxic necrotizing myopathy, but this is not specific.[18] However, most patients with statin-associated immune-mediated necrotizing myopathy develop antibodies against HMG-CoA reductase that are detectable in serum. These anti–HMG-CoA reductase antibodies are quite specific for immune-mediated necrotizing myopathy; statin-exposed healthy control patients and those with self-limited toxic myopathy do not usually have these antibodies.[19,20]

Muscle biopsy can also help distinguish between the toxic necrotizing and immune-mediated forms of statin myopathy. In both cases, necrotic myofibers are a prominent feature. Inflammatory cell infiltration is sparse aside from

TABLE 10-2 **Features That Raise Suspicion for a Toxic Myopathy**

Clinical Features

- **Concomitant polyneuropathy (ie, a neuromyopathy)**
  - Amiodarone
  - Chloroquine/hydroxychloroquine
  - Colchicine
  - Telbivudine
- **Concomitant myasthenia gravis**
  - Immune checkpoint inhibitors
- **Acute, painful myopathy**
  - Statins
  - Other lipid-lowering agents
  - Cyclosporine
  - Labetalol
  - Alcohol (with binge drinking)

EMG Features

- **Myotonic discharges**
  - Chloroquine/hydroxychloroquine
  - Colchicine
  - Cyclosporine
  - Fibrates
  - Statins

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myophagocytosis of necrotic myofibers in both toxic and immune-mediated necrotizing myopathy (FIGURE 10-1). In the toxic form, lipid-filled vacuoles within myofibers and cytochrome oxidase (COX)-negative myofibers have occasionally been noted[21]; however, in the authors' experience, this is not helpful in diagnosis. Increased COX-negative fibers occur with increasing age, which is again a risk factor for developing toxic myopathies. Assessing for increased expression of major histocompatibility complex (MHC)-I and complement membrane attack complex on the sarcolemma of non-necrotic myofibers is more helpful because these are not seen in the toxic myopathies; when noted, this instead suggests immune-mediated necrotizing myopathy.

When patients present with symptomatic hyperCKemia or weakness, the authors' practice is to stop the statin, test for anti–HMG-CoA reductase antibodies, and closely follow the patient. With toxic necrotizing myopathy, the CK level usually begins to improve within a couple of weeks. If the anti–HMG-CoA reductase antibody results are negative and the CK level does not normalize, the authors perform a muscle biopsy. A muscle biopsy can be considered early in severe cases, but histology may reveal only widespread myofiber necrosis. It can

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- **Normal EMG in a patient with clinically suspected myopathy**
  - Corticosteroids
  - Chronic alcoholic myopathy

Muscle Biopsy Features

- **Vacuoles**
  - Amiodarone
  - Chloroquine/hydroxychloroquine
  - Colchicine
- **Mitochondrial abnormalities (eg, many ragged red and cytochrome oxidase–negative fibers)**
  - Nucleoside-analogue reverse transcriptase inhibitors (eg, zidovudine)
- **Type 2 fiber atrophy**
  - Corticosteroids
  - Chronic alcoholic myopathy
- **Sarcolemmal major histocompatibility complex 1 and membrane attack complex expression on non-necrotic fibers**
  - Anti–3-hydroxy-3-methylglutaryl coenzyme A reductase myopathy associated with statins
  - Immune checkpoint inhibitors
  - D-Penicillamine

EMG = electromyography.

TABLE 10-3 **Drugs Associated With an Increased Risk of Statin Muscle Toxicity**

- Amiodarone
- Azole antifungals
- Calcium channel blockers
- Colchicine
- Cyclosporine
- Ezetimibe
- Fibrates (eg, gemfibrozil)
- Niacin
- Protease inhibitors
- Rapamycin
- Sirolimus
- Excessive intake of grapefruit juice

CASE 10-1

An 82-year-old man presented with several weeks of muscle pain and weakness. He had difficulty rising from a seated position. His myalgia was most severe in the thighs bilaterally. His past medical history included polymyalgia rheumatica, chronic kidney disease, and a prior myocardial infarction. He had begun on atorvastatin 40 mg daily 3 months before presentation. He had previously been treated with simvastatin but stopped it because of cramps 5 years ago. He was also being treated with prednisone 5 mg daily for the past 2 years for polymyalgia rheumatica.

Examination revealed 4+/5 weakness of bilateral hip flexion. His serum creatine kinase (CK) level was elevated at 1580 U/L. EMG demonstrated fibrillation potentials and positive sharp waves with early recruitment of low-amplitude, short-duration motor unit action potentials in his right deltoid and right iliopsoas. His statin was stopped, and his symptoms improved and CK level normalized over the next 8 weeks.

COMMENT

Patients in whom toxic myopathy is suspected may be on multiple myotoxic agents. In this case, the muscle pain, elevated CK level, and EMG demonstrating evidence of an irritable myopathy suggest the statin rather than the corticosteroid is to blame. Higher doses of corticosteroids are typically required to produce myopathy, as well. Renal failure, older age, male sex, and history of statin intolerance are all risk factors for statin myopathy. Multiple medications (although not corticosteroids) have been demonstrated to increase the risk of statin myopathy when used concurrently, especially inhibitors of cytochrome P450 3A4.

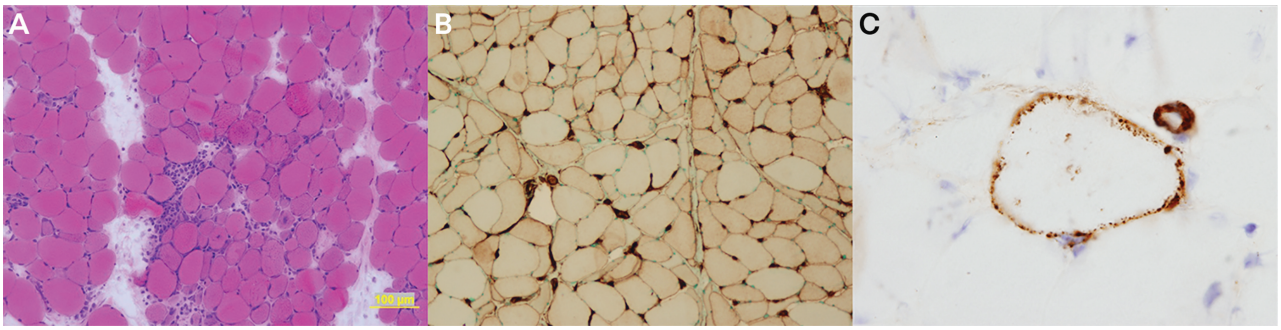

FIGURE 10-1

This muscle biopsy performed in a patient with proximal muscle weakness on a statin revealed necrotic myofibers, regenerating myofibers, and sparse inflammatory cells with myophagocytosis only of necrotic myofibers (*A*). This can be seen in both toxic necrotizing myopathy and statin-associated immune-mediated necrotizing myopathy. However, major histocompatibility complex 1 expression on the sarcolemma of non-necrotic myofibers (*B*) and deposition of complement membrane attack complex on both non-necrotic myofibers and capillaries suggest an immune-mediated pathogenesis (*C*).

be difficult to distinguish between the toxic and immune-mediated forms in such cases, even if MHC-I and membrane attack complex staining are performed because staining can be widespread (MHC-1 is also expressed on regenerating fibers). In cases in which weakness is leading to disability and immune-mediated necrotizing myopathy is suspected (based on the timing of symptoms, for example), the authors often start treatment with IV immunoglobulin (IVIg) and/or prednisone while awaiting results of the anti–HMG-CoA reductase antibody testing. We and others have found that IVIg may be used as monotherapy in anti–HMG-CoA reductase myopathy.[22,23]

Other Lipid-Lowering Agents

A similar spectrum of symptoms occurs in patients treated with fibrates.[24] Fibrates are branched-chain fatty acid esters that limit the availability of free fatty acids for the synthesis of triglycerides in the liver. Their myotoxicity may result from lipophilic membrane destabilization. A higher reported risk is associated with gemfibrozil compared with fenofibrate, but this may be driven by the high frequency of rhabdomyolysis in patients treated concurrently with a statin. Up to 5% of patients treated with gemfibrozil and lovastatin developed a severe myopathy.[25] As with statins, renal failure increases the risk of toxicity. Myotonic discharges have been reported on EMG.

Toxic myopathy has also been reported with niacin and ezetimibe, but most cases have occurred in patients also on a statin.[26,27] Red yeast rice (*Monascus purpureus*), a supplement used for its lipid-lowering effect, has also been reported to cause myopathy, including rhabdomyolysis.[15] In 2015, the US Food and Drug Administration (FDA) approved two proprotein convertase subtilisin/kexin type 9 (PCKS9) inhibitors, alirocumab and evolocumab, for the treatment of elevated low-density lipoprotein in patients who could not meet lipid-lowering goals with diet and other available therapies. These drugs increase low-density lipoprotein clearance from the bloodstream. In the randomized GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3) trial, which enrolled patients with a history of intolerance to two or more statins, no statistical difference was observed in the incidence of

muscle symptoms between ezetimibe (28.8%) and evolocumab (20.7%). Only one of 145 patients taking evolocumab stopped the drug because of muscle symptoms.[28]

INFLAMMATORY MYOPATHIES

Statin-associated immune-mediated necrotizing myopathy (anti–HMG-CoA reductase myopathy) has already been discussed, and case reports have implicated several other medications as triggering autoimmune inflammatory myopathies (TABLE 10-1). D-Penicillamine, used as a chelating agent in the treatment of Wilson disease and rarely in the treatment of rheumatoid arthritis, causes a syndrome clinically and histologically mimicking polymyositis or dermatomyositis (including a skin rash in some) in 0.2% to 1.4% of treated patients.[29] With drug withdrawal and corticosteroids, full recovery is to be expected. With the increasing

CASE 10-2

A 70-year-old woman presented with difficulty walking, head drop, double vision, and dysphagia that was progressive over the past 2 weeks. She had a history of metastatic melanoma; she had undergone surgical excision of a superficial melanoma lesion 4 years previously, but metastatic disease to the lungs and multiple lymph nodes were recently discovered. She began treatment with nivolumab 4 weeks prior to her current presentation and received her second cycle 1 week ago.

Examination revealed asymmetric ptosis and weakness of extraocular muscles, 4/5 strength of neck extensors and symmetric limb-girdle weakness in the arms and legs. Sensory testing was normal.

Her serum creatine kinase level was elevated at 3450 U/L. Acetylcholine receptor and muscle-specific kinase antibodies were negative. EMG revealed fibrillation potentials and positive sharp waves with early recruitment of low-amplitude, short-duration motor unit action potentials in proximal and axial muscles. There was no decremental response to 3-Hz repetitive nerve stimulation.

Nivolumab was stopped, and the patient was treated with methylprednisolone 1000 mg daily for 3 days, followed by prednisone 60 mg daily. In follow-up 4 weeks later, her diplopia and head drop had resolved, and her strength was markedly improved on examination.

COMMENT

Multiple neurologic immune-related adverse events have been reported with immune checkpoint inhibitors, including myositis. Symptoms typically begin after the first or second cycle of treatment. As in this case, ptosis, diplopia, and bulbar weakness frequently occur with immune checkpoint inhibitor myositis, prompting consideration of myasthenia gravis (MG). Myositis and MG can occur concurrently as immune-related adverse events. In this case, negative serology and normal repetitive nerve stimulation argues against myasthenia gravis. Patients typically improve with discontinuation of the immune checkpoint inhibitor and therapy with corticosteroids, but fatal cases have been reported associated with concurrent myocarditis or respiratory muscle weakness.

use of immune checkpoint inhibitors in the treatment of cancer, inflammatory myositis has emerged as one of many potential neurologic complications.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors target mechanisms used by cancer to evade destruction by the immune system. Since the approval of ipilimumab by the FDA in 2011 for the treatment of metastatic melanoma, immune checkpoint inhibitors have been used in the treatment of an increasing number of cancers, sometimes dramatically changing the prognosis for advanced cases. Ipilimumab inhibits cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4); nivolumab and pembrolizumab inhibit the programmed cell death-1 (PD-1) receptor, also on cytotoxic T-lymphocytes; durvalumab and atezolizumab inhibit the ligand of PD-1 (PD-L1) on antigen-presenting cells (**CASE 10-2**).

Although upregulation of the immune system is essential for these drugs' efficacy, it can also lead to off-target immune-related adverse events affecting diverse body systems, including hypophysitis, thyroiditis, pancreatitis, and hepatitis. Moderate to severe neurologic immune-related adverse events including peripheral neuropathy, encephalopathy, and meningitis affect 0.1% to 0.8% of patients treated with anti–PD-1 or anti–CTLA-4 immune checkpoint inhibitors.[30] The incidence of neurologic immune-related adverse events was as high as 2.9% in one cohort of patients treated with anti–PD-1 immune checkpoint inhibitors.[31] Although less common, myopathy is an increasingly reported complication.[30,32,33]

Myositis can occur with CTLA-4, PD-1, or PD-L1 inhibitors. Patients typically develop weakness and myalgia early after immune checkpoint inhibitor initiation, after one or two cycles. In the largest reported cohort, the median onset of symptoms was 25 days after initiation of therapy (range 5 to 87 days).[30] Weakness involves axial muscles (eg, head drop) and the proximal extremities. Although less common, severe respiratory muscle weakness requiring intubation and mechanical ventilation can occur.[34] Bulbar and oculomotor weakness is also very common and can mimic myasthenia gravis (MG) (**FIGURE 10-2**). Interestingly, MG can also occur as a consequence of immune checkpoint inhibitors.[35] Moreover, overlap of myositis and MG appears to be common. For example, 4 of 12 patients with immune checkpoint inhibitor–related MG had clinical myositis in one cohort, and two of six myositis patients had concurrent MG in another.[33,35] When overlap is suspected, an elevated CK level can help establish myositis, whereas a decremental response to slow repetitive nerve stimulation and acetylcholine receptor antibodies suggest MG. Myocarditis can also be seen with or without clinically evident skeletal muscle involvement.[36] For more information about MG occurring as a complication of immune checkpoint inhibitors, refer to the article "Lambert-Eaton Myasthenic Syndrome, Botulism, and Immune Checkpoint Inhibitor–Related Myasthenia Gravis" by Amanda C. Guidon, MD,[37] in this issue of *Continuum*. CK values are almost always elevated in cases of myositis related to immune checkpoint inhibitors and may be greater than 10,000 U/L.[30,33] Myositis-specific antibodies have been negative, but one patient was reported with a positive PM/Scl antibody.[32] Positive anti–striated muscle antibodies have been reported in at least five patients with myositis related to immune checkpoint inhibitors.[32,34,38] EMG demonstrates fibrillation potentials and positive sharp waves and myopathic motor unit action potentials (MUAPs) in most patients.

Muscle biopsies have demonstrated endomysial inflammatory infiltrates composed of CD68+ cells expressing PD-L1 and CD8+ lymphocytes expressing

KEY POINTS

- Rhabdomyolysis in statin-treated patients is a rare event, with an estimated incidence of 2 to 3 per 100,000 patient-years.
- Many drugs interact with statins and increase the risk of muscle toxicity, including rhabdomyolysis, when used concurrently. Important examples include other cholesterol-lowering agents and cyclosporine.
- Higher doses, older age, and renal failure all increase the risk of statin myotoxicity.
- Manifestations of statin-associated toxic necrotizing myopathy resolve within 1 week to 3 months after stopping the statin. Persistent symptoms or creatine kinase level elevations thereafter should prompt consideration of immune-mediated necrotizing myopathy or other underlying disorders.
- A markedly elevated creatine kinase level and EMG demonstrating irritable myopathy are seen in both toxic necrotizing and immune-mediated forms of statin myopathy, but serum anti–3-hydroxy-3-methylglutaryl coenzyme A reductase antibodies are specific for the immune-mediated form.
- Fibrates cause a spectrum of muscle symptoms similar to statins. Myopathy has also been reported with niacin and ezetimibe, but mostly when used together with a statin.

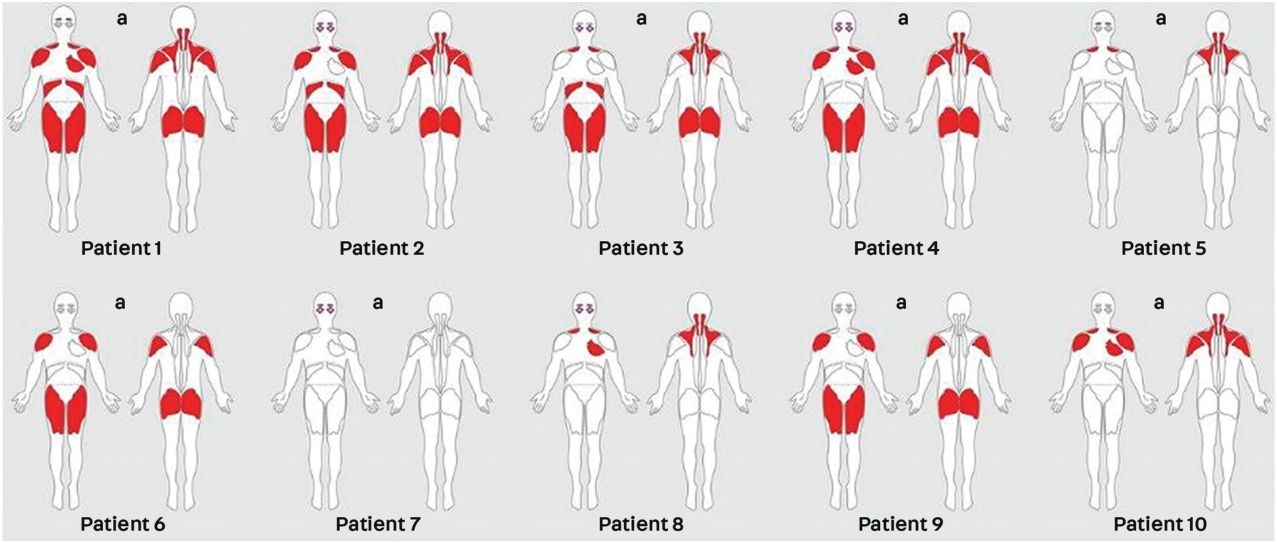

FIGURE 10-2

The distribution of weakness in 10 patients with immune checkpoint inhibitor–related myositis is depicted. Symmetric muscle weakness is indicated in red, asymmetric weakness in purple.

[a] Muscle pain present.

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PD-1 (FIGURE 10-3), along with myophagocytosis and sarcolemmal upregulation of MHC-1.[30] For some patients, muscle biopsy may reveal only necrotic muscle fibers without inflammatory cell infiltrates.

The American Society of Clinical Oncology guidelines for treating immune-related adverse events suggest stopping the immune checkpoint inhibitor for patients with myositis or MG; this alone may be sufficient in mild cases.[39] Most patients require treatment with corticosteroids. IVIg and plasma exchange are used for severe myasthenia. With these strategies, most patients improve over a period of weeks. In one cohort, CK levels normalized in all patients at a median of 44 days.[30] Prednisone is slowly tapered over a few months while patients recover. The American Society of Clinical Oncology guidelines allow considering immune checkpoint inhibitor rechallenge after symptoms resolve if the initial symptoms and signs were mild. Rare reports exist of patients with mild myositis successfully tolerating a rechallenge of

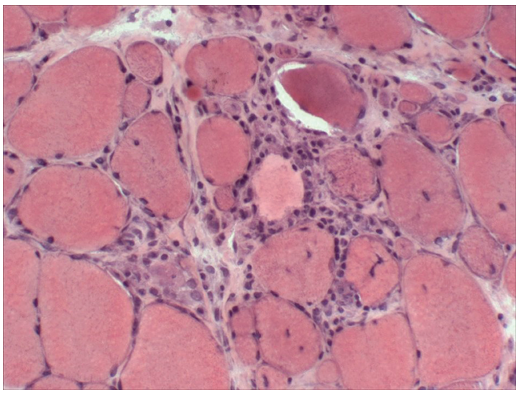

FIGURE 10-3

This is a muscle biopsy from a patient treated with ipilimumab for leukemia cutis after stem cell transplant for acute myeloid leukemia. His course was complicated by graft versus host disease, so he was also treated with steroids. Six months later, he developed neck and proximal weakness. Hematoxylin and eosin (H&E) staining reveals necrotic and atrophic fibers, with prominent endomysial inflammatory cell infiltrate with necrotic fibers and myophagocytosis.

immune checkpoint inhibitor with or without concurrent prophylactic steroid therapy.[33,40]

AMPHIPHILIC MYOPATHIES

Chloroquine, hydroxychloroquine, and amiodarone are amphiphilic molecules containing both hydrophobic and hydrophilic components, allowing them to interact with the lipid bilayer of cells and organelles. Through disruption of lysosomes, they form pathologic autophagic vacuoles filled with myeloid debris in muscle fiber and nerves; the neuropathy can be more severe than the myopathy.

Chloroquine and Hydroxychloroquine

Chloroquine is used to treat malaria, and both chloroquine and hydroxychloroquine are used to treat connective tissue diseases. Patients may develop slowly progressive, painless, proximal weakness, usually after prolonged treatment.[41–43] With chloroquine, a toxic myopathy usually occurs after doses of at least 500 mg daily for 1 year or longer. Renal failure increases the risk. Cardiomyopathy can occur with either medication. Patients may have distal sensory loss and diminished ankle reflexes from concurrent neuropathy. The toxic neuromyopathy is reversible with drug cessation.

Because of the insidious onset of symptoms and normal or only slightly elevated serum CK level, the diagnosis can be elusive. EMG typically demonstrates an irritable myopathy, with fibrillation potentials, positive sharp waves, and occasionally myotonic discharges along with early recruitment of small-amplitude, short-duration MUAPs in weak proximal muscles. Decreased recruitment of neurogenic-appearing MUAPs is present in distal muscles. Biopsies of proximal muscles demonstrate autophagic vacuoles. On electron microscopy, characteristic curvilinear structures are seen within vacuoles.

Amiodarone

Amiodarone is an antiarrhythmic that can also cause neuromyopathy. Symptomatic neuropathy is more common than myopathy; the incidence of any neurotoxicity was 2.8% in one cohort.[44] Duration of treatment and renal failure increase the risk of neurotoxicity. Patients with myopathy develop insidious proximal muscle weakness and can have dysphagia. Amiodarone can also cause hypothyroidism, which can contribute to proximal weakness. Patients with neuropathy may develop ataxia or tremor. Recovery after stopping amiodarone may be partial and take many months.

CK values can be normal. Motor and sensory nerve conduction studies typically reveal low amplitudes and slow-conduction velocities, suggesting a component of demyelination. EMG will reveal an irritable myopathy in proximal muscles, but MUAPs may be large amplitude and long duration in distal muscles due to the neuropathy. Muscle biopsy demonstrates autophagic vacuoles filled with myeloid debris.

ANTIMICROTUBULAR MYOPATHIES

Colchicine is used to treat gout. Like with amphiphilic medications, patients taking colchicine can develop neuromyopathy. The toxicity results from the drug's interaction with tubulin dimers, preventing the formation of microtubules. This likely interferes with the movement and positioning of lysosomes, leading to the accumulation of vacuoles (FIGURE 10-4).[45]

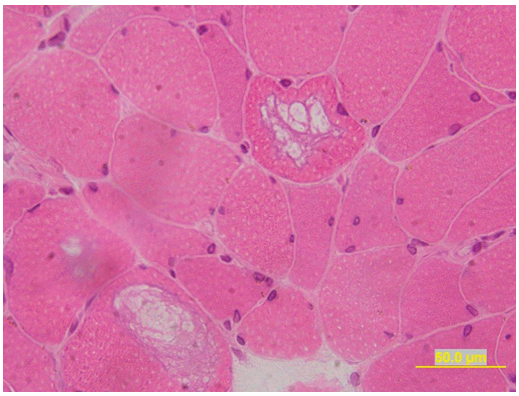

FIGURE 10-4
Muscle biopsy reveals autophagic vacuoles on hematoxylin and eosin (H&E) staining in a patient with myopathy due to colchicine.

Progressive proximal weakness usually occurs after prolonged exposure to colchicine, with doses of 0.6 mg to 4 mg daily. Increased age, renal insufficiency, and concomitant use of cytochrome P450 3A4 inhibitors (eg, statins, cyclosporine) increase the risk of myopathy.[46] CK values are markedly elevated. Nerve conduction studies commonly demonstrate an axonal neuropathy, with signs of an irritable myopathy evident on EMG of proximal muscles. Myotonic discharges can be seen, but only rarely have patients

CASE 10-3

A 63-year-old man presented with 6 months of progressive weakness. He first noted difficulty rising from a chair. Over the past 2 months, he had also noticed numbness in his toes. His past medical history was notable for chronic gout and mild chronic renal insufficiency. He had been treated with colchicine 0.6 mg 2 times a day for the past 3 years.

Examination revealed symmetric 4/5 deltoid and biceps weakness, 3/5 iliopsoas weakness, and 4+/5 ankle dorsiflexion weakness. There was diminished pinprick and vibratory sensation in the toes bilaterally. Deep tendon reflexes were absent at the ankles and diminished elsewhere.

His serum creatine kinase level was elevated at 1710 U/L. Serum creatinine was 1.7 mg/dL. Nerve conduction study demonstrated evidence of a mild, length-dependent, axonal sensorimotor polyneuropathy. EMG demonstrated fibrillation potentials and early recruitment of motor unit action potentials (MUAPs) was noted in proximal muscles with reduced recruitment of high-amplitude, long-duration MUAPs noted in the tibialis anterior.

Colchicine was stopped. Three weeks later, he could rise from a chair without difficulty.

COMMENT

This patient presented with clinical and electrodiagnostic evidence of concurrent myopathy and neuropathy. This pattern can be seen with amphiphilic medications (amiodarone, chloroquine, and hydroxychloroquine) and colchicine. A muscle biopsy can demonstrate characteristic vacuoles but may not be necessary if symptoms promptly resolve with withdrawal of the offending medication. Many patients who develop colchicine neuromyopathy have renal insufficiency, as in this case.

been reported with clinical myotonia.[47] Patients typically improve over weeks to months when colchicine is stopped (CASE 10-3).

MITOCHONDRIAL MYOPATHY FROM ANTIRETROVIRALS

The risk of mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors was exemplified with zidovudine treatment for HIV.[48] Nucleoside analogues work by competing with natural nucleoside substrates of HIV reverse transcriptase but can also impair human mitochondrial DNA expression via inhibition of mitochondrial γ-DNA polymerase. Myopathy affected 17% of patients treated for HIV with zidovudine monotherapy for longer than 9 months.[49] HIV itself can also cause a proximal myopathy, but myalgia is a distinguishing feature common with zidovudine myopathy. Zidovudine has largely been supplanted by newer antiretrovirals in developed countries. When utilized as part of a multidrug, highly active antiretroviral therapy regimen, the required dose is lower, so the incidence of myopathy is lower. CK levels are mildly elevated in affected patients, and EMG demonstrates an irritable myopathy. Muscle biopsy is key for distinguishing between other HIV-associated myopathies. Ragged red fibers on modified Gomori trichrome stain and COX-negative fibers are evident with zidovudine, in contrast with inflammatory cell infiltrates that can be seen in HIV-associated myositis. Both clinical symptoms and these histologic findings are reversible.

Myotoxicity can complicate the use of lamivudine, entecavir, and particularly telbivudine—nucleoside analogues used to treat hepatitis B.[50–52] Asymptomatic CK level elevation occurred in 84.3% of patients over a 3-year period in one cohort.[53] Clinically evident myopathy is less common, with proximal weakness developing after 1 to 2 years of treatment. Muscle biopsies may demonstrate ragged red or COX-negative fibers, necrosis, or inflammatory cell infiltrates. The pathogenic mechanism is less clearly mitochondrial than with zidovudine. Neuropathy has also been reported in association with telbivudine. Neuropathy and myopathy may be particularly common among patients with renal failure after liver transplantation, for whom telbivudine is used to suppress hepatitis B reactivation. In one cohort, 26 of 45 patients stopped taking telbivudine because of symptomatic neuropathy or myopathy.[54]

Other antiretroviral agents have been associated with muscle-related adverse effects distinct from mitochondrial myopathy. Rhabdomyolysis can occur with didanosine, lamivudine, raltegravir, ritonavir, and indinavir. Protease inhibitors increase the risk of statin myotoxicity. Raltegravir, an integrase inhibitor used to treat HIV, is associated with myalgia. Mild proximal muscle weakness, often with a normal CK level, occurred in 3% to 4% of treated patients in two reported series.[55,56] The toxic mechanism is poorly understood at present.

OTHER MECHANISMS

Myopathy can arise in patients treated with corticosteroids or in those who are critically ill. The pathogenic mechanisms in these cases are distinct from the other categories already discussed.

Steroid Myopathy

Proximal muscle weakness can develop in patients with an endogenous (ie, Cushing syndrome) or iatrogenic excess of corticosteroids.[57,58] Corticosteroids regulate transcription, and skeletal muscle toxicity may be due to decreased

KEY POINTS

- Although less common than other neurologic immune-related adverse events, inflammatory myositis can complicate treatment with immune checkpoint inhibitors. Symptoms typically begin after one or two treatment cycles.
- In addition to proximal and axial weakness, oculomotor and bulbar weakness are common with immune checkpoint inhibitor–associated myositis. Myasthenia gravis can develop concurrently.
- Muscle biopsy has demonstrated histiocytic and lymphocytic inflammatory infiltrates in patients with immune checkpoint inhibitor–associated myositis. The creatine kinase level is typically elevated, and EMG will show fibrillation potentials and positive sharp waves in most patients.
- When patients on an immune checkpoint inhibitor develop myositis or myasthenia gravis, the immune checkpoint inhibitor should be stopped. Most patients should also be treated with corticosteroids. Patients' symptoms markedly improve over a period of weeks.
- Chloroquine, hydroxychloroquine, and amiodarone can all cause clinical neuromyopathy. Vacuolar myopathy is evident on muscle biopsy.
- Recovery from amiodarone neuromyopathy may be partial and prolonged over months.

protein synthesis, altered carbohydrate metabolism, mitochondrial alterations, or reduced sarcolemmal excitability.[59] Proximal weakness and atrophy affecting the legs more than the arms develop insidiously. Other features of Cushing syndrome, including facial edema and truncal adiposity, are commonly seen in patients taking corticosteroids. Although weakness can develop within weeks with high-dose therapy, prolonged use of doses equivalent to prednisone 30 mg daily or more is typical. The risk is higher with fluorinated corticosteroids (in order of greater to less risk: triamcinolone, betamethasone, and dexamethasone). Alternate-day dosing and an exercise program to prevent disuse atrophy may mitigate the risk of developing weakness.

Corticosteroids are often used in the treatment of neuromuscular disorders that produce weakness, so distinguishing steroid myopathy from exacerbation of the underlying disorder can be challenging. The pattern of weakness may be a clue because distal, facial, and oculomotor muscles are spared in steroid myopathy. In cases of inflammatory myopathy treated with steroids, the CK level and EMG can be useful. CK values are normal in steroid myopathy; a rising CK level is more indicative of worsening myositis. Likewise, fibrillation potentials and positive sharp waves and early recruitment of small-duration MUAPs are not seen with steroid myopathy, but they are common with active myositis. In cases of diagnostic uncertainty, a gradual steroid taper can be informative because the symptoms of patients with steroid myopathy improve with dose reduction or cessation of therapy. If their symptoms instead worsen, an exacerbation of the underlying disorder is likely. A muscle biopsy is often not required but demonstrates preferential atrophy of type 2 fibers, particularly glycolytic 2B fibers, with steroid myopathy (FIGURE 10-5). Increased lipid droplets may also be seen in type 1 fibers.[60]

Critical Illness Myopathy

Critically ill patients are at risk of developing critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or both. CIM is more common than CIP; when CIP does occur, it usually coexists with CIM.[61] The pathogenesis of muscle injury remains uncertain, but sarcolemmal inexcitability and myosin loss have been demonstrated as key features.[62,63] The first sign of weakness may be the inability to wean the patient from mechanical ventilation. CIM also causes proximally predominant weakness and atrophy but spares bulbar muscles. CIP causes distally predominant weakness and sensory loss. Reflexes can be reduced or absent in either form as weakness progresses. Patients who survive regain strength, but those with CIM recover faster and more completely than those with CIP or CIM/CIP.[64]

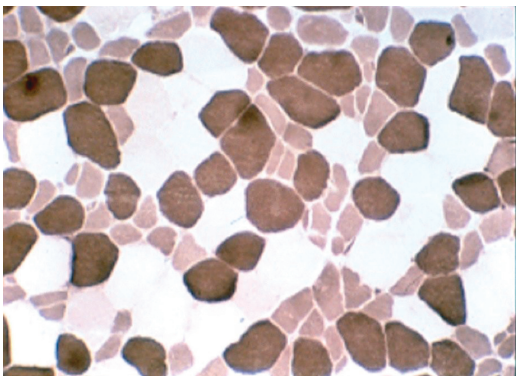

FIGURE 10-5
ATPase stain at pH 4.5 reveals selective atrophy of type 2b muscle fibers (intermediate staining) in a patient with corticosteroid myopathy.

Patients who are critically ill from any process are at risk of CIM/CIP, but those with sepsis and multiorgan system failure are at especially high risk.

Hyperglycemia is another established risk factor. Affected patients have frequently received corticosteroids or neuromuscular blocking agents or both, but CIM/CIP can be seen in patients treated with neither. Despite the traditional assumption that these medications confer an increased risk, data are mixed. A systematic review including 655 reported patients found no association between glucocorticoids or neuromuscular blocking agents and development of CIM or CIP.[65] A randomized, placebo-controlled trial of glucocorticoids in patients with acute respiratory distress syndrome found no difference in the occurrence of CIM/CIP between treatment groups.[66]

The CK level can be normal but is moderately elevated in 50% of patients who are critically ill in the acute stage. Nerve conduction studies reveal low-amplitude compound muscle action potentials (CMAPs) in both CIM and CIP. In CIM, CMAPs may also have prolonged duration.[67] Direct muscle stimulation has been used to help distinguish CIM from CIP; patients with CIP will have a ratio of maximal response achieved via nerve stimulation to that achieved via direct muscle stimulation of less than 0.5, and those with CIM will have a ratio of approximately 1. Low-amplitude or absent sensory nerve action potentials are also noted in patients with CIP. Needle EMG commonly reveals signs of an irritable myopathy in those with CIM. Muscle biopsies may show type 2 fiber atrophy and necrotic muscle fibers. Loss of myosin thick filaments is characteristically seen on electron microscopy or by loss of reactivity on the myosin ATPase stain.

Other Agents

Rare reports exist of rhabdomyolysis with levetiracetam[68] as well as with febuxostat.[69] The risk with febuxostat appears highest in patients with severe renal impairment. Myalgia, muscle stiffness, and asymptomatic CK elevation and rarely weakness may complicate treatment with isotretinoin.[70] Although they do not pose a risk of myopathy for most patients, inhaled anesthetics and depolarizing muscle relaxants (eg, succinylcholine) can cause malignant hyperthermia in susceptible patients.

Muscle symptoms have been reported in association with gemcitabine in patients previously treated with radiation. Muscle pain, edema, and weakness, with or without a skin rash, can develop exclusively in areas previously treated with radiation—a phenomenon termed radiation recall.[71] Radiation recall has been reported with other chemotherapeutic agents such as doxorubicin and taxols, but typically manifests solely with skin rash. Symptom onset occurs a median of 40 days after radiation, but case reports exist of symptoms occurring years after radiation. Muscle biopsy in one case demonstrated thrombosis, endothelial wall thickening, and vascular proliferation, with a focal, perimysial T-lymphocytic infiltrate.[72]

MYOPATHY SECONDARY TO DRUGS OF ABUSE

A chronic proximal myopathy affects up to one-third of patients with chronic alcoholism.[73] An estimated cumulative minimum of 10 kg of ethanol per kilogram of body weight is required to result in myopathy. In one cohort, affected patients consumed, on average, 100 g/d to 300 g/d (approximately 10 to 30 drinks) consistently for 20.5 ± 9.4 years.[74] Myopathy likely results from a combination of the toxic effects of alcohol, nutritional deficiency, and perhaps electrolyte imbalance, but it can develop even in those not obviously

KEY POINTS

- Colchicine causes a neuromyopathy associated with vacuoles on muscle biopsy. Prolonged exposure is typically required, with weakness developing gradually over months.
- Zidovudine commonly caused a reversible mitochondrial myopathy but is used less commonly to treat HIV now. Myopathy has been reported with more contemporary antivirals, as well, including telbivudine, lamivudine, entecavir, and raltegravir.
- Proximal weakness related to steroid myopathy typically occurs after prolonged treatment with the equivalent of prednisone 30 mg daily. Creatine kinase values and EMG are commonly normal.
- Sepsis, multiorgan system failure, and hyperglycemia are associated with a higher risk of developing critical illness myopathy. The risk associated with corticosteroids or neuromuscular blocking agents is much less clear than previously thought.
- Recent reports suggest that levetiracetam, febuxostat, and isotretinoin can all rarely cause rhabdomyolysis and/or myopathy. The mechanism is uncertain.
- Mild proximal myopathy is common among patients with chronic alcoholism. Binge drinking and use of cocaine, amphetamines, and phencyclidine can all result in rhabdomyolysis.

malnourished. Mild painless weakness, sometimes subclinical, develops in the legs more than the arms. Patients with myopathy may have concurrent neuropathy and are also more likely to have alcoholic cirrhosis and cardiomyopathy. About 60% will have elevated CK levels. EMG demonstrates myopathic MUAPs in 10% to 50%, but fibrillation potentials and positive sharp waves are typically absent. Improvement in strength occurs over 2 to 12 months with abstinence.

Alcohol can also precipitate acute weakness and rhabdomyolysis in the setting of binge drinking.[75] Weakness, muscle pain and edema, and a markedly elevated CK level develop over hours to days. Dysphagia and cardiomyopathy can accompany limb weakness. In severe cases, myoglobinuria may lead to renal failure.

Repeated IM heroin injection can lead to focal fibrotic myopathy with years of use.[76] Opiate use is now estimated to be the second most common cause of compartment syndrome (after trauma) due to immobility in the setting of overdose.[77] Rhabdomyolysis can also result from the use of cocaine, amphetamines, and phencyclidine.[78]

CONCLUSION

Myopathy can be encountered as a result of many frequently prescribed medications and other toxic substances, such as alcohol. Although their presentation may at times be nonspecific, certain clinical features and findings on muscle biopsy can allow for diagnosis. Early recognition is key because stopping the use of the offending agent can lead to improvement of symptoms, or in the case of statin-associated immune-mediated necrotizing myopathy and immune checkpoint inhibitor–associated myopathy, appropriate treatment can be initiated.

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