A 76-year-old woman with a medical history notable for hypothyroidism, hyperlipidemia, and coronary artery disease presented to the emergency department a few days after a ground-level fall. The patient was walking in a grocery store parking lot, where she was stung by a wasp on her ankle. She tripped, fell, and was unable to get up without assistance. She was helped up almost immediately after the fall by a bystander, and the patient was assisted walking to her car. At home, she was able to walk unassisted; however, she realized this inability to get up after falling was highly unusual for her given the vigorous workout regimen she had been performing on a daily basis for several years. While previously she had been able to do 60 abdominal crunches a day, the morning of the fall she could only do one. Her husband also noticed that she had been dragging her feet while walking around the house for the past month. Given this history, recent fall, and subacute weakness, the patient presented to her primary care physician, who after reviewing the patient’s initial laboratory work sent her to the Mayo Clinic emergency department.

On evaluation at the emergency department, the patient was in no acute distress and had no concerns other than muscle weakness. She reported no myalgias, muscle cramping, or muscle twitching. The patient did recall that she had felt the sensation of objects getting stuck in her throat while swallowing food and medications for many weeks. On physical examination, the patient’s muscle tone appeared normal throughout without group atrophy. She likewise did not exhibit tremors or muscle fasciculations. Her deltoid, triceps, and biceps strength testing exhibited antigravity with inability to hold against resistance (3 of 5 on a manual muscle strength testing [MMT] scale). Her thigh muscles likewise could activate against gravity with inability to withstand resistance (3 of 5 on MMT) bilaterally. The patient exhibited preserved distal strength in her forearms, fists, fingers, calves, feet, and toes bilaterally against resistance (5 of 5 on MMT). She had decreased neck strength as well as decreased strength with diminished abdominal flexion on examination (both 3 of 5 on MMT). The patient had full passive range of motion of her joints. Reflexes were symmetrically normal in both her upper and lower extremities. The cranial nerves were all intact without unilateral facial droop, ptosis, slurred speech, or decreased facial muscle strength. Skin examination revealed ecchymosis over the right eye lid, left wrist, and left ankle related to the fall but no rashes. The rest of the physical examination was unrevealing.

Her current medications at admission were zoledronic acid, 5-mg annual intravenous (IV) infusion; levothyroxine, 25 mg daily; nortriptyline, 25 mg daily; cholecalciferol, 2000 IU daily; aspirin, 81 mg daily; atorvastatin, 40 mg daily; and cyanocobalamin, 1000 µg daily. Each of these medications, including statin and aspirin, had remained stable in dosage for multiple years.

1. Given this patient’s constellation of symptoms, which one of the following is the most likely diagnosis?
   a. Rhabdomyolysis
   b. Polymyalgia rheumatica
   c. Hypothyroid myopathy
   d. Immune-mediated myopathy
   e. Guillain-Barré syndrome

Because the patient had never experienced myalgias with the evolving weakness
and was quickly helped up after her minor fall with little time on the ground, rhabdomyolysis was less likely. Polymyalgia rheumatica most commonly presents with pain and stiffness in the neck, torso, shoulder, and pelvic girdles accompanied by morning stiffness and gelling phenomenon that improves as the day goes by. It is almost exclusively a disease of older adults. Its prevalence increases with age, and it is more common in women. In the case of our patient, she had not experienced myalgias or any other pain; on the other hand, weakness was an important symptom, making the diagnosis of polymyalgia rheumatica less likely.

Hypothyroid myopathy, or in some rare cases hyperthyroidism, may appear as a polymyositis-like syndrome; hypothyroid myopathy presents with myalgias that are exacerbated by exercise, usually in patients with untreated hypothyroidism. Our patient had a history of treated hypothyroidism with stable doses of levothyroxine for a prolonged period, and she did not experience myalgias, making this diagnosis less likely.

Our patient’s clinical picture best fits an immune-mediated myopathy based on the subacute clinical presentation and proximal muscle weakness with sparing of the distal musculature. The immune-mediated myopathies are a heterogeneous group of acquired muscle disorders characterized by proximal muscle weakness that often requires histopathologic evaluation to clarify differences between them, such as dermatomyositis, polymyositis, inclusion body myositis, and necrotizing autoimmune myopathy. Guillain-Barré syndrome could present similarly with insidious onset of decreased strength, but our patient’s preserved distal strength, normal reflexes, and lack of viral prodrome make this diagnosis less likely.

Laboratory evaluation revealed the following (reference ranges provided parenthetically): creatine kinase (CK), elevated to 10,588 U/L; thyrotropin, 9.5 mIU/L; free thyroxine, 1.1 ng/dL (0.9 to 1.7 ng/dL); triiodothyronine, 115 ng/dL (80 to 200 ng/dL); aspartate aminotransferase, 247 U/L; and creatinine, 0.58 mg/dL. Urinalysis revealed trace hemoglobin but no red blood cells on the urine microscopy, a finding that may be suggestive of myoglobinuria. Erythrocyte sedimentation rate and C-reactive protein were within normal limits.

The work-up for a systemic autoimmune process including antinuclear antibody, anti–Sjögren syndrome–related antigen A, anti–Sjögren syndrome–related antigen B, anti–Jo-1 antibody, anti–topoisomerase 1 antibody, and anti–cyclic citrullinated peptide antibody yielded negative results. Serum and urine myoglobin levels were not checked.

2. Which one of the following is the most appropriate next test for this patient?
   a. Magnetic resonance imaging (MRI) of the affected thigh
   b. Brain MRI
   c. Skin biopsy
   d. Electromyography (EMG)
   e. Muscle biopsy

Although MRI of the patient’s thigh could reveal signs of inflammation, MRI would be nonspecific in distinguishing inflammatory vs metabolic myopathies. If MRI were performed in the setting of inflammatory myositis, T2-weighted imaging would reveal signal abnormalities in muscle and fascia due to inflammation, edema, or muscle replacement by fatty tissue. Magnetic resonance imaging of the brain was not performed because a central neurologic process, such as Parkinson disease or stroke, was unlikely. The patient’s clinical picture, most consistent with an inflammatory myopathy, was unlikely to be dermatomyositis given the lack of skin involvement, rendering a skin biopsy low yield. Normal nailfold capillary examination is another way dermatomyositis could be eliminated from the differential diagnosis, but it was not performed during hospitalization.

Electromyography (EMG) is the best next step for this patient in order to identify if the underlying pathology was neuropathic or myopathic in nature prior to more invasive testing. Furthermore an EMG is helpful to identify which muscle group has the highest yield and can be targeted for a muscle...
biopsy. Muscle biopsy is usually the next step after an EMG has shown a myopathic pattern.

Our patient underwent EMG of the left upper and lower extremity. Results of nerve conduction studies of the left upper and lower limb were within normal limits. Needle examination of the left upper and lower limb and thoracic paraspinal muscles revealed short-duration, low-amplitude, complex motor unit potentials in the majority of the proximal muscles sampled. There were large numbers of fibrillation potentials and myotonic-like discharges in the biceps, triceps, and gluteus medius suggesting evidence of a generalized myopathy with predominantly proximal involvement. Given the patient’s presentation and prevalence of myotonic-like discharges, a necrotizing autoimmune myopathy best fit the clinical picture. Unilateral EMG was performed in order to preserve the contralateral deltoid muscle from iatrogenic artifact in the event of a future muscle biopsy.4

3. Which one of the following is most likely to lead to a diagnosis for this patient?
   a. Serum aldolase measurement
   b. Lumbar puncture
   c. Positron emission tomography/computed tomography
   d. Muscle biopsy
   e. Nerve conduction study

   Aldolase can be a helpful tool in identifying muscle breakdown in patients with symptoms of myositis who present with normal CK levels. This patient’s aldolase level was 83.7 U/L; however, this enzyme is not sensitive or specific in determining what type of myositis our patient has. Lumbar puncture would be applicable in the setting of ascending muscle weakness suggestive of Guillain-Barré syndrome or other findings suggestive of a central neuropathic process such as muscle fasciculation or visible tremors. However, a lumbar puncture would not aid in determining inflammatory myopathy subtype. Polymyositis, dermatomyositis, and necrotizing autoimmune myopathies have been associated with underlying malignancy, which could be identified through positron emission tomography/computed tomography; nevertheless, identification of malignancy, although more likely in dermatomyositis, is not helpful in distinguishing one myopathy from the other. A muscle biopsy would be the most appropriate diagnostic test for our patient with a currently undifferentiated myopathy.5 Nerve conduction study would not be helpful because these studies would have already been performed as a part of the EMG, which previously revealed active myopathy with normal nerve conduction of the left upper and left lower extremity.

   Right deltoid biopsy in our patient revealed the following: necrotic muscle fibers in each fascicle with macrophage replacement; small collections of mononuclear cells at perimysial and perivascular sites with a mild increase in perimysial fibrous and fatty connective tissue; increases of acid phosphatase in macrophages replacing necrotic fibers as well as in scattered cells within the perimysium; one fascicle with mild perifascicular atrophy; and Congo red staining negative for amyloid, indicating inflammatory muscle disease pointing toward the diagnoses of polymyositis or immune-mediated inflammatory myopathy. Immunohistochemical studies were not performed.4

4. Which one of the patient’s home medications is most likely associated with her clinical picture?
   a. Zoledronic acid
   b. Levothyroxine
   c. Aspirin
   d. Nortriptyline
   e. Atorvastatin

   Bisphosphonates are more prone to cause tendinopathy or, in rare cases, severe musculoskeletal pain;6 however, our patient exhibited weakness and elevated CK in the absence of myalgias. Changes in levothyroxine dosing or administration have been a reported trigger of statin-induced myopathy, but this is less likely in our patient with long-standing, stable hypothyroidism and levothyroxine dose.7 Aspirin and nortriptyline were less likely to
be the culprits of this constellation of symptoms in our patient because she was taking low doses of each: 81 mg of aspirin daily and 25 mg of nortriptyline daily at bedtime. Because this patient's clinical presentation and pathologic findings are seen in both polymyositis and statin-associated autoimmune myopathy, further work-up relies on identification of anti–3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) antibodies in order to distinguish the final diagnosis. Commonly, these results may take weeks to return, and atorvastatin should be stopped in the setting of the clinical and laboratory findings of myopathies and elevated CK levels, particularly with elevation above 2000 IU/L as occurs in 90% of cases of statin-associated autoimmune myopathy. Anti–HMGCR antibody was remarkably elevated (>200), and the patient was formally diagnosed as having HMGCR myopathy. Further work-up for necrotizing myopathy including anti–signal recognition particle and other autoimmune myopathy–associated antibodies yielded negative results.

5. Which one of the following is the most appropriate initial treatment for this patient?
   a. IV hydration
   b. IV methylprednisolone
   c. Naproxen sodium
   d. Rituximab
   e. IV immunoglobulin G (IVIG)

Because rhabdomyolysis was less likely, initial IV hydration, which had been started during the admission process, was discontinued. Medical therapy with IV methylprednisolone was administered during the hospital stay with transition to an oral prednisone regimen of 1 mg/kg because this would have been the most appropriate initial treatment given our patient's constellation of symptoms. A nonsteroidal anti-inflammatory drug would have been beneficial in the setting of an atypical presentation of a crystal deposition disease (eg, gout or pseudogout); however, our patient's clinical picture was not indicative of these pathologies. Immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil may be considered as corticosteroid-sparing agents. Rituximab or IVIG may be considered after 8 to 12 weeks without clinical improvement because up to one-half of statin-associated autoimmune myopathy cases require “triple therapy” including IVIG, prednisone, and an immunosuppressive agent. In a recent systematic review, 84% of 100 patients with statin-associated autoimmune myopathy required 2 or more immunosuppressants to induce remission.

After our patient had partial improvement after 1 month of oral corticosteroid therapy, methotrexate and IVIG were added to the medication regimen with dramatic improvement of symptoms and muscle enzyme levels the following month. She received pentamidine for Pneumocystis jiroveci (formerly Pneumocystis carinii) prophylaxis and zoledronic acid with vitamin D and calcium for osteoporosis prophylaxis.

**DISCUSSION**

Lipid-lowering agents are used extensively in the primary care setting as primary prevention for cardiovascular disease. Nearly 40 million individuals in America older than age 40 were prescribed statins between the years 2012 and 2013, an approximate 80% increase of usage in just 10 years' time. Although the vast majority of patients tolerate statin therapy well, nearly 1 in 10,000 will experience some type of myalgia, myopathy, or elevated CK. However, most of these adverse events will spontaneously remit when therapy is stopped. It is further worth noting that these symptoms may occur either during the initiation of statin therapy or spontaneously after many asymptomatic years of treatment. Initial evaluation of patients taking a statin who exhibit muscle-related symptoms should include laboratory work-up to detect elevated CK. This case reveals the importance of a thorough medical reconciliation on hospital admission. A careful review of the patient's
medications helped us narrow the differential diagnosis because this history and presentation can be commonly mistaken for other myopathic syndromes (eg, polymyositis, dermatomyositis). It was likewise important that hospital work-up included infectious, autoimmune, and endocrine laboratory testing to avoid misdiagnosis and delay of immunosuppressive treatment. Evaluation and diagnostic work-up will likely need to include histopathologic evaluation of the affected muscle groups as this will provide clarity in differentiating a necrotizing autoimmune myopathy from other immune-mediated myopathies that impact proximal muscle groups. Most patients will recover with discontinuation of the statin and adequate immunosuppressive therapy.5 Unfortunately, some patients may not fully regain muscular strength if inadequately treated for long periods, allowing fatty tissue to replace muscle, which can be observed with MRI.5 It is important, in particular, for the prescribing physician to bear in mind not only common adverse effects of statins but also the severity of disease, which can in rare instances require hospitalization, respiratory and occupational/physical therapy support, immunosuppressive therapy, and early referral to a rheumatologist or neurologist for continued treatment. Furthermore, as with dermatomyositis and polymyositis, there is some evidence that suggests that HMGCR myopathy may have an association with increased risk of malignancy, and primary care physicians should ensure up-to-date malignancy screening in this population.11

Potential Competing Interests: The authors report no competing interests.

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REFERENCES

CORRECT ANSWERS: 1. d. 2. d. 3. d. 4. e. 5. b