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Case-based Review

A case of statin-associated immune-mediated necrotizing myopathy with atypical biopsy features

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Abstract

Statin-associated immune-mediated necrotizing myopathy (IMNM) is a rare presentation of a statin-associated myopathy. Patients usually present with muscle weakness and pain in the setting of statin use with elevated creatine kinase (CK) levels and a positive anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibody. Muscle biopsies typically show necrosis, CD68+ macrophages, and minimal lymphocytes. We present a case of a 67-year-old woman who had 2 months of progressive weakness and bilateral lower extremity pain after initiating atorvastatin therapy with symptoms persisting after statin cessation. She was found to have high anti-HMGCR antibody titers, and the biopsy of the rectus femoris muscle showed a prominent endomysial inflammatory cell infiltrate with necrotic and regenerative fibers and an atypical extensive inflammatory infiltrate composed of both CD4+ helper T cells and CD8+ cytotoxic T cells. She showed symptom resolution and normalization of CK levels and inflammatory markers with treatment involving a prolonged prednisone taper and a brief course of azathioprine, which was stopped because of the adverse effects.

Keywords: Myopathy, IMNM, statin, anti-HMGCR, autoimmune

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Introduction

Use of statins in reducing cardiovascular risk in patients is effective and ubiquitous (1). Part of the success in statin therapy is because of a fairly safe side-effect profile, although a number of muscle disorders have been widely recognized as potential adverse effects, including myalgia, myositis, and rhabdomyolysis with significant elevations in CK levels (2, 3). Recently, clinicians and investigators have identified a rare immune-mediated necrotizing myopathy (IMNM) characterized by antibodies targeting the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) protein in patients taking statins (4-6). Considering the scarcity of knowledge on this rare condition, we provide a case report on a patient with anti-HMGCR IMNM with atypical pathological features on muscle biopsy.

Case Presentation

A 67-year-old woman from the Dominican Republic presented to the emergency department complaining of 2 months of progressive chronic weakness of the proximal upper and lower extremities accompanied with lower extremity pain.

Two months before her hospitalization, she reported progressive difficulty with walking, rising from a chair, raising her arms above her head, and combing her hair. She also noted a 30-pound weight loss over these 2 months. She denied fever, joint pain, seizures, rash, syncope, chest pain, shortness of breath, abdominal pain, dark urine, or other changes to bowel or bladder habits. Review of her records 2 months before admission revealed elevated liver function tests with an alanine aminotransferase (ALT) level of 454, aspartate aminotransferase (AST) level of 472, and a CK level of 522. At that time, she was instructed by her primary care physician to discontinue statin therapy. After 1 week off statin therapy, outpatient testing showed persistently elevated liver function tests and CK levels. Of note, she was prescribed 40 mg atorvastatin daily for hyperlipidemia 6 months before admission.

Besides atorvastatin, her medication list included 500 mg metformin given orally twice daily, 10 mg lisinopril given orally daily, 50 mg hydrochlorothiazide given orally daily, and 3 mg melatonin given orally each night at bedtime. She denied any known drug allergies and history of alcohol use, tobacco use, or illicit drug use. Her most recent travel was to the Dominican Republic over 8 months before admission.

She denied any family history of malignancy or rheumatic disease.

Her vital signs on initial examination included a temperature of 36.9°C, a heart rate of 114 beats per minute, blood pressure of 185/73, a respiratory rate of 16, and an oxygen saturation of 98% on ambient air. She had no acute distress and was alert and oriented to person, place, and time. She had no rashes on her face or body. She had no oral lesions. She demonstrated no joint swelling or tenderness to palpation. Her cardiovascular, pulmonary, and abdominal examinations were unremarkable without evidence of hepatomegaly or splenomegaly. After 1 deep inspiration, she could count to 25 while exhaling in 1 breath as a proxy for diaphragmatic strength. She did not endorse any tenderness to palpation of her proximal or distal muscles. Her quadriceps was notable for subjective atrophy. Neurological examination revealed 4/5 strength in the neck flexors and proximal upper and lower extremities and 5/5 strength in the distal upper and lower extremities. The remainder of her neurological examination, including cranial nerve testing, gross sensation, coordination, reflexes, and gait, was normal.

Laboratory findings at admission were notable: potassium of 5.7 mEq/L; hemoglobin of 10.8 g/dL; normal mean corpuscular volume and mean corpuscular hemoglobin concentration of 31.7%; ALT level of 414 U/L; AST level of 369 U/L; CK level of 14,909 U/L; uric acid level of 6.6 mg/dL; normal alkaline phosphatase level; normal total bilirubin level; normal thyroid-stimulating hormone level; C-reactive protein (CRP) level of 6.6 mg/L; erythrocyte sedimentation rate of 30 mm/h; and negative human immunodeficiency virus, hepatitis B, and C serologies.

Her electrocardiogram showed sinus tachycardia with minimal T wave peaking. The abdominal ultrasound showed a normal appearing liver with several simple cysts and an incidental non-obstructing 3-mm renal stone in the lower pole of the left kidney.

Hospital course

She was started on intravenous fluids and was admitted to the hospital for further work-up and management. Throughout her admission, she continued to show muscle weakness and pain, predominantly with exertion. Her vital signs remained stable, and examination was unchanged throughout admission.

Laboratory evaluation revealed a negative antinuclear antibody and myositis antibody profile, which included antibodies to histidyl-tRNA synthetase (JO-1), threonyl-tRNA synthetase (PL-7), alanyl-tRNA synthetase (PL-12), glycyl-tRNA synthetase (EJ), isoleucyl-tRNA synthetase (OJ), signal recognition particle (SRP), MI-2 alpha, MI-2 beta, melanoma differentiation-associated gene 5 (MDA-5), transcription intermediary factor 1y (TIF-1y), and nuclear matrix protein 2 (NXP-2). She also had a negative polymyositis antibody 1 (PM-1). An anti-HMGCR antibody test was also performed.

Magnetic resonance imaging (MRI) of the thighs with short-term T1 inversion recovery (STIR) sequencing showed patchy, scattered areas of muscle edema and hyper-enhancement (bilaterally), most conspicuous in the gluteus maximi, rectus femora, and adductor muscles. There was relative sparing of the vastus lateralis, vastus intermedius, and gracilis muscles. There was mild diffuse symmetric muscle atrophy, bilaterally, without imaging evidence of myonecrosis (Figure 1).

Muscle biopsy of her left rectus femoris was performed. The muscle appeared pale upon gross examination. Histological examination revealed skeletal muscle with myopathic changes, including moderate variation in the fiber size, increased internalized nuclei, endomysial inflammatory infiltrates with numerous necrotic myofibers, and scattered regenerative fibers (Figure 2a and 2b). Electron microscopy also demonstrated degenerating fibers occasionally associated with interstitial macrophages, subsarcolemmal collections of endocytic vacuoles and membranous debris, and increased internalized nuclei. There was no increase of intracellular lipid or glycogen. Mitochondria did not increase in number or size. Immunohistochemistry of paraffin-embedded tissue revealed extensive inflammatory infiltrate composed of both CD4+ helper T cells and CD8+ cytotoxic T cells, with only focal perivascular clusters of CD20+ B cells. There were numerous CD68+ monocytes/macrophages within the muscle and interstitial tissue (Figure 2c). Major histocompatibility complex (MHC-1) immunostaining on the frozen tissue showed weak sarcolemmal staining.

With regard to treatment during her hospitalization, her CK reached a plateau at 11,000 after 3 days with intravenous hydration alone and the above work-up was ongoing. After her biopsy was obtained, she was administered 30 mg prednisone twice daily (approximately, 1 mg/kg), and her CK level then gradually decreased to 4,194 on day 7 from a peak of 17,554. She was also administered trimetho-

Main Points

- Immune-mediated necrotizing myopathy (IMNM) is a rare presentation of statin-associated myopathy.
- The presentation of statin-associated IMNM can be similar to that of idiopathic inflammatory myopathies, and a positive anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody can help in confirming the diagnosis.
- Muscle biopsies of statin-associated IMNM often show myonecrosis with a predominance of CD68+ macrophages and occasional T lymphocytes.
- This case is interesting as the muscle biopsy findings showed extensive T and B lymphocytes.
- First-line treatment includes the cessation of statins and initiation of steroid therapy, although there are no standardized guidelines at this time.

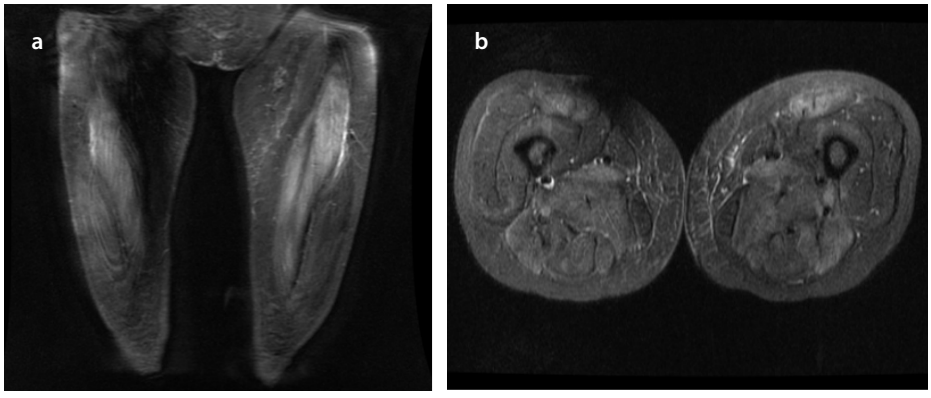

Figure 1. a, b. Representative magnetic resonance imaging scans. Short-term T1 inversion recovery sequencing coronal (a) and axial (b) scans showed patchy, scattered areas of muscle edema and hyper-enhancement (bilaterally), most conspicuous in the gluteus maximi, rectus femora, and adductor muscles. There was relative sparing of the vastus lateralis, vastus intermedius, and gracilis muscles. There was mild diffuse symmetric muscle atrophy (bilaterally), without imaging evidence of myonecrosis.

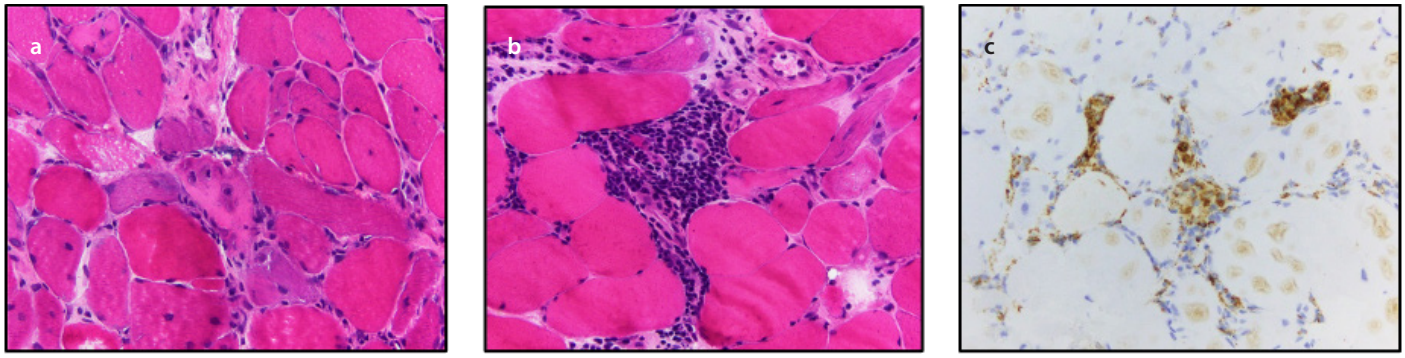

Figure 2. a-c. Skeletal muscle with myopathic changes and myonecrosis. Hematoxylin- and eosin-stained frozen sections revealing variation in the fiber size, increased internalized nuclei, myonecrosis, regenerative fibers, and endomysial inflammatory cell infiltrate (a, b). CD68+ macrophages surrounding and engulfing the myofibers. 200× magnification (c).

prim-sulfamethoxazole for *Pneumocystis jirovec-ci* prophylaxis and Ca/vitamin D for glucocorticoid-induced osteoporosis prophylaxis. She was discharged with planned rheumatology follow-up in the clinic. After 2 weeks, her anti-HMGCR result was positive with a value of 150 U/mL (normal <20 U/mL).

Outpatient follow-up

The patient was seen in rheumatology clinic and initiated on 50 mg azathioprine daily and prednisone was tapered to 20 mg twice daily. She continued to improve symptomatically. In the setting of a short period of non-compliance, her CK level asymptomatically increased. She was eventually up-titrated to 150 mg azathioprine daily (roughly 2 mg/kg), while prednisone was gradually tapered. She subsequently developed nausea and vomiting, which prompted her to discontinue azathioprine. Through joint decision making, it was decided that she would continue solely on a prednisone taper with close follow-up. Her CK level and physical examination remained normalized on 2.5 mg prednisone daily. Informed consent was obtained from the patient to write and publish this case report.

Discussion

We described a case of a 67-year-old woman who presented with progressive weakness and bilateral lower extremity pain after initiating atorvastatin therapy 6 months before and was subsequently diagnosed with autoimmune necrotizing myopathy. Typically, as in our patient, patients present with progressive muscle weakness involving the proximal and symmetric muscles of the upper and lower extremities within several months of initiation of a statin (7, 8).

The history of a patient's presenting symptoms is vital in raising clinical suspicion for IMNM or other myopathies, such as steroid-induced, polymyositis/dermatomyositis (PM/DM), or endocrine myopathy (8). For example, suspicion for IMNM should be raised given the proximity in symptoms in association with statin use and the persistence of these symptoms with the cessation of the statin. The fact that this patient was not on any steroids at the time of presentation makes steroid-induced myopathy unlikely, and the lack of relevant symptoms and normal thyroid-stimulating hormone ruled out thyroid-related myopathy.

Muscle imaging was characteristic of an inflammatory myositis, demonstrating muscle edema on STIR sequencing. These findings of diffuse muscle edema in a proximal muscle distribution, however, do not distinguish among myopathies (9). Nevertheless, they are helpful in identifying the muscles that should be biopsied to avoid false-negative results (9).

Although studies have reported variability in biopsy samples, macrophages are often reported as the most common infiltrating cell, while CD4+ helper T cells and CD8+ cytotoxic T cells are less commonly found in statin-associated IMNM (10, 11). A previous review showed that necrosis alone is present in over 80% of patients, whereas necrosis and concurrent inflammation were observed in 18.51% of patients (12). In cases where inflammatory infiltrates are present, CD68+ macrophages often predominate, and some studies have found scattered CD4+ and CD8+ T cells in the endomysium of 50% of the muscle biopsies of patients with anti-HMGCR myopathy (11, 13). Thus, what appears atypical about this patient's case is that the muscle biopsy showed predominant inflammation and that the inflammatory infiltrate was composed of CD4+ and CD8+ T cells, in addition to the more typically expected CD68+ macrophages. Although the presence of an extensive inflammatory infiltrate characterized by lymphocytes is atypical, there were aspects of the patient's muscle biopsy that were more representative of classical IMNM (10, 12), including scattered necrotic myofibers, sarcolemmal MHC-1 upregulation, and the presence of CD68+ macrophages (10, 11, 13).

That our patient's symptoms had persisted despite discontinuation of her statin, together with MRI and biopsy findings favored a diagnosis of autoimmune necrotizing statin-associated myositis over statin-induced myopathy or PM/DM. Although the clinical and pathological features are helpful, the presence of the anti-HMGCR antibody is integral for the diagnosis of IMNM, especially when other aspects of the clinical presentation are more equivocal (10, 14, 15). A recent study evaluated the detection of anti-HMGCR antibodies by both enzyme-linked immunosorbent assays (ELISAs) and chemiluminescence immunoassays (CIAs) in patients with suspected IMNM and a cohort of patients with different inflammatory and autoimmune rheumatic diseases with a group of healthy controls and showed a strong concordance between the 2 test methods, with high reported sensitivity and specificity for IMNM (e.g., CIA sensitivity of 92.3%; specificity of 100% in n=13 compared with ELISA) (14). Studies have shown that the majority of patients who are positive for the anti-HMGCR antibody have had prior statin exposure (66.6%; 92.3% in patients over the age of 50 years) (5) and that there is a significantly increased frequency of statin use in patients with the anti-HMGCR antibody than in patients with other forms of myositis, such as DM and PM (4). In this case, the positive anti-HMGCR level without other autoantibody positivity or other stigmata of a connective tissue disease in a patient on statins also supports the diagnosis of IMNM.

Although there is a strong association between IMNM and statin exposure, the causal role of statins is still a matter of debate. Pathogenesis of the disease is not well understood. It has been suggested that genetic associations—HLA DRB1*11:01 and DRB1*07:01—combined with statin-mediated overexpression of HMGCR enzyme may lead to a loss of tolerance that

results in autoimmunity (5, 6, 16, 17). Indeed, the role the lymphocytic infiltrate remains unclear in the pathogenesis of the disease or in prognostication of the response to therapy (11). Given that membrane attack complex (MAC) deposition is also a common feature of muscle biopsies in patients with IMNM, a hypothesis suggests that antibody-mediated MAC activation leads to lysis of the myofibers (11).

There have been no clinical trials to standardize the therapeutic guidelines (18). Currently, first-line therapy involves discontinuation of the statin and initiation of steroids (15). As the disease is often refractory upon steroid taper, a steroid sparing agent, such as methotrexate, mycophenolate mofetil, azathioprine, rituximab, or intravenous immunoglobulin (IVIG), is also introduced many times (18, 19).While the use of IVIG has been shown to lower mean CK levels and improve muscle strength, patients on IVIG have continued to show positive anti-HMGCR antibody titers, suggesting that the treatment is unlikely to directly oppose the pathogenesis of the disease (18). IVIG is also sometimes used if symptoms and CK are refractory to steroids (20). Although data regarding long-term prognosis are limited, it is thought that patients with anti-HMGCR antibody IMNM experienced continued weakness despite immunosuppressive therapy (21). Our patient has done well thus far on a protracted steroid taper.

Conclusion

We described a patient presenting with IMNM with anti-HMGCR antibody positivity, likely secondary to statin use. Considering the rarity of the autoimmune statin-associated myositis (2-3/100,000 patients treated with statins), the diagnosis is often considered after other entities are excluded (10, 15). Distinguishing among different myopathies is often first indicated by a thorough history (8). Furthermore, the presence of anti-HMGCR antibodies is central to the diagnosis of statin-associated IMNM (10, 14, 15). In our patient, the muscle biopsy findings were less characteristic, showing extensive inflammatory infiltrates with both CD4+ helper T cells and CD8+ cytotoxic T cells in addition to more common findings of necrotic myofibers, sarcolemmal MHC-1 upregulation, and CD68+ macrophages (13). Although the biopsy findings with IMNM are variable and not considered the standard of reference for diagnosing statin-associated IMNM, it is often still helpful as it can exclude other causes of myositis and specifically suggest an autoimmune pathophysiology. This case highlights the diversity of cell types in an inflammatory infiltrate that, to our knowledge, is atypically encountered in prior reports of statin-associated IMNM. Further studies are thus needed to broaden our understanding of the pathogenesis, histopathological features, and potential treatment options for this illness.

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