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A Case of Statin-Associated Autoimmune Myopathy

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ABSTRACT: A 70-year-old previously independent man developed progressive proximal leg weakness resulting in a fall at home suffering traumatic brain injury. He was prescribed a statin medication two years prior, but this was discontinued on admission to the hospital due to concern for statin myopathy. His weakness continued to progress while in acute rehabilitation, along with the development of dysphagia requiring placement of gastrostomy tube and respiratory failure requiring tracheostomy. Corticosteroids and intravenous immunoglobulin were administered without response. Nerve conduction study demonstrated no evidence of neuropathy; electromyography revealed spontaneous activity suggestive of myopathy. A muscle biopsy was performed and demonstrated myonecrosis. Serology was positive for autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), verifying our diagnosis of statin-associated autoimmune myopathy (SAM). The patient was subsequently treated with rituximab and methotrexate and demonstrated mild clinical improvement. He was eventually liberated from the ventilator. However, later in the course of treatment, he developed respiratory distress and required ventilator support. The patient was discharged to long-term acute care two months after his initial presentation and died due to ventilator-acquired pneumonia three months later. Since their introduction 30 years ago, statin medications have been widely prescribed to prevent cardiovascular diseases. Myalgias and/or myopathic symptoms are among the most recognized side effects of the medication. Statin-associated autoimmune myopathy is a very rare complication of statin use and estimated to affect two to three for every 100,000 patients treated. Clinically, the condition presents as progressive symmetric weakness, muscle enzyme elevations, necrotizing myopathy on muscle biopsy, and the presence of autoantibodies to HMGCR. These findings will often persist and even progress despite discontinuation of the statin. Very few cases of SAM have been described in the literature. Describing this rare condition and the ultimately fatal outcome of our patient, we aim to further understanding of SAM, its presentation and clinical course to promote earlier diagnosis and prompt management.

KEYWORDS: HMGCR, statin complications, statin myopathy, statin failure, statin-associated autoimmune myopathy

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Introduction

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMGCR] inhibitors), since their introduction more than 20 years ago, have been one of the most widely prescribed medications used to treat atherosclerotic disease. Treatment with statins has effectively reduced morbidity and mortality for both cardiovascular and cerebral vascular diseases. Millions of prescriptions are written annually for this class of medication. Given this number of prescriptions written, it is of major importance to closely observe patients for adverse and even life-threatening side effects. Herein, we examine a rare but serious case of statin-associated autoimmune myopathy (SAM).

Case Report

A 70-year-old man presented to the emergency department after sustaining a fall at home. The patient was admitted to the intensive care unit for a large subdural hematoma and required respiratory support with mechanical ventilation. Prior to his fall, the patient had noticed increasing pain and weakness located bilaterally in the proximal shoulder and hip girdle region, but no other focal symptoms. His home medications

for the past two years included, atorvastatin 40 mg once daily and aspirin 81 mg once daily without adverse effects during that time.

His creatine kinase (CK) on presentation was found to be 12 300 IU/L, the statin was discontinued. Despite this, the CK remained persistently elevated, without clinical evidence of improvement in the patient's weakness. The patient was evaluated by several specialists and underwent with extensive testing for neuromyopathies including autoimmune, paraneoplastic, and chronic viral infection—all with negative findings. Tests for autoantibodies were negative, including antinuclear antibody, rheumatoid factor, anti-Ro/SSA, anti-La/SSB, and anti-Jo-1. The myositis panel was negative for PL-7 Ab, PL-12Ab, EJ Ab, OJ Ab, SRP Ab, Mi-2 Ab, and Ku Ab. The patient was also seronegative for HIV and hepatitis A, B, and C infections. A computerized computed tomographic (CT) scan of the chest, abdomen, and pelvis with intravenous (IV) and oral (PO) contrast was unremarkable for malignancy. Nerve conduction study demonstrated no evidence of neuropathy. However, needle electromyography demonstrated features consistent with an active myopathic process with abnormal



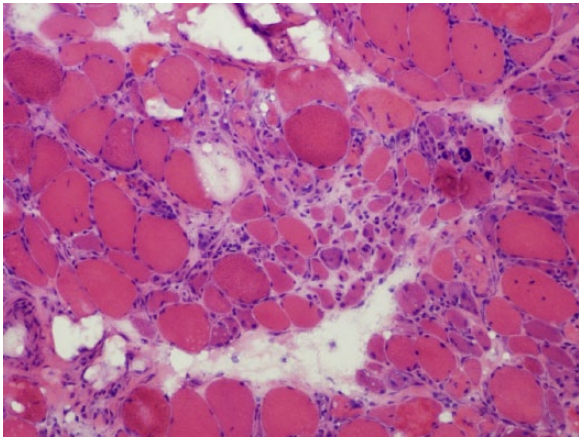


Figure 1. Severe myofiber atrophy with necrosis and myocytolysis not associated with endomysial inflammation. Frozen section (hematoxylin-eosin).

spontaneous activity. Prior to the initiation of corticosteroid and rituximab therapy, a muscle biopsy was performed and revealed a pauci-immune necrotizing myopathy with the absence of macrophage infiltration, inclusion bodies and vascular abnormalities (Figure 1). Serologic testing also revealed HMGCR autoantibodies consistent with an autoimmune process and established the diagnosis of statin-associated autoimmune myopathy.

Initially, the patient was treated with high-dose corticosteroids (IV methylprednisolone, 40 mg every 8hr) but required the addition of rituximab (IV 1000 mg for 3 doses) when no clinical improvement was seen. Of note, it was difficult to assess and quantify the patient's strength, given his dependence on mechanical ventilation and sedation. However, the patient's CK did improve to 1500 IU/L. While continuing rituximab a corticosteroid taper was attempted; however, the CK relapsed toward 9000 IU/L, and he subsequently required an increase in corticosteroid dosing (Figure 2).

The patient had mild clinical improvement with the treatments as described above following the diagnosis of SAM, and was liberated from the ventilator. Unfortunately, he once again developed respiratory distress and ultimately required a tracheostomy and return to ventilator support. After 2 months of his initial presentation, he was discharged to a long-term acute care facility on a drug regime consisting of a high-dose corticosteroid, rituximab, and methotrexate. Eventually, corticosteroids were successfully tapered but rituximab and methotrexate were continued, given incomplete remission. Unfortunately, he died 3 months after being transferred due to ventilator-associated pneumonia.

Discussion

Despite being one of the most commonly prescribed medications, the latest guidelines from the American College of Cardiology and the American Heart Association advocate for increase use; the number of prescriptions for statins is expected to increase substantially. Per the Centers for Disease Control

and Prevention, 36.7% of US adults, 78.1 million people aged 21 years or older, are eligible for statin medication; however, approximately 40 million people are actually taking statins.¹ Statins have been shown to have an acceptable side effect profile and have been found to be generally safe in their indicated patient population. Studies have shown that a wide range (5%-20%) of patients discontinue statin therapy due to intolerance of side effects.^{2,3} Muscle complaints are the most well-known and common side effect of statins and can range from asymptomatic with elevation in CK, mild elevation of CK with myalgia, and profound elevation of CK with frank rhabdomyolysis. In initial clinical trials of statins, myalgia and/or myopathic symptoms (muscle pain without elevation of muscle enzymes) were not identified as common adverse events, with only 1% to 5% of participants reporting muscle-related side effects. However, subsequent observational studies have estimated a much higher incidence of muscle complaints, ranging from 9% to 20%. This illustrates the point that the true side effect profile may not be captured by clinical trials, possibly given their restrictive inclusion criteria.⁴

Myopathy or myositis is generally defined as muscle pain, cramps, soreness, and/or concomitant elevation in CK. It has been estimated to occur in 5 patients per 100 000 person-years, and the incidence of myopathy generally increases with higher dosage of statins.⁵

Rhabdomyolysis is defined as a marked increase in CK levels, more than 10 times the upper limit of normal, which results from massive destruction of muscle fibers and the corresponding release of their contents into the bloodstream. It can induce renal failure and death; however, the rate of occurrence is low, that is, ~1/100 000 or roughly 324 cases per year.⁶ A dose-response relationship is also observed in the incidence of rhabdomyolysis.

Recently, a rare but unique entity has received increasing attention called statin-associated autoimmune myopathy; the clinical spectrum and presentation of statin-induced myotoxicity consist of asymptomatic elevation of CK, muscle pain or weakness, biopsy-proven myositis, and/or rhabdomyolysis with evidence of muscle-cell necrosis on biopsy and the presence of autoantibodies to HMGCR.⁷ The distinct histologic profile consists of profound necrotic, degenerating, or regenerating muscle fibers undergoing phagocytosis with macrophage predominance.⁸ The reported sensitivity and specificity of positive anti-HMGCR for autoimmune statin myopathy are 94.4% and 99.3%, respectively.⁹

Although no prospective clinical trials have yet been completed to allow for evidence-based guidelines for diagnosis or treatment of SAM, the following approach has been advised. Initial workup for patients with current or past statin usage who present with proximal muscle weakness and/or muscle pain begins with obtaining CK levels. CK levels ≥ 10 times the upper limit of normal are suggestive of SAM, whereas levels below this threshold should lead the clinician toward investigation of other causes of weakness and muscle. For

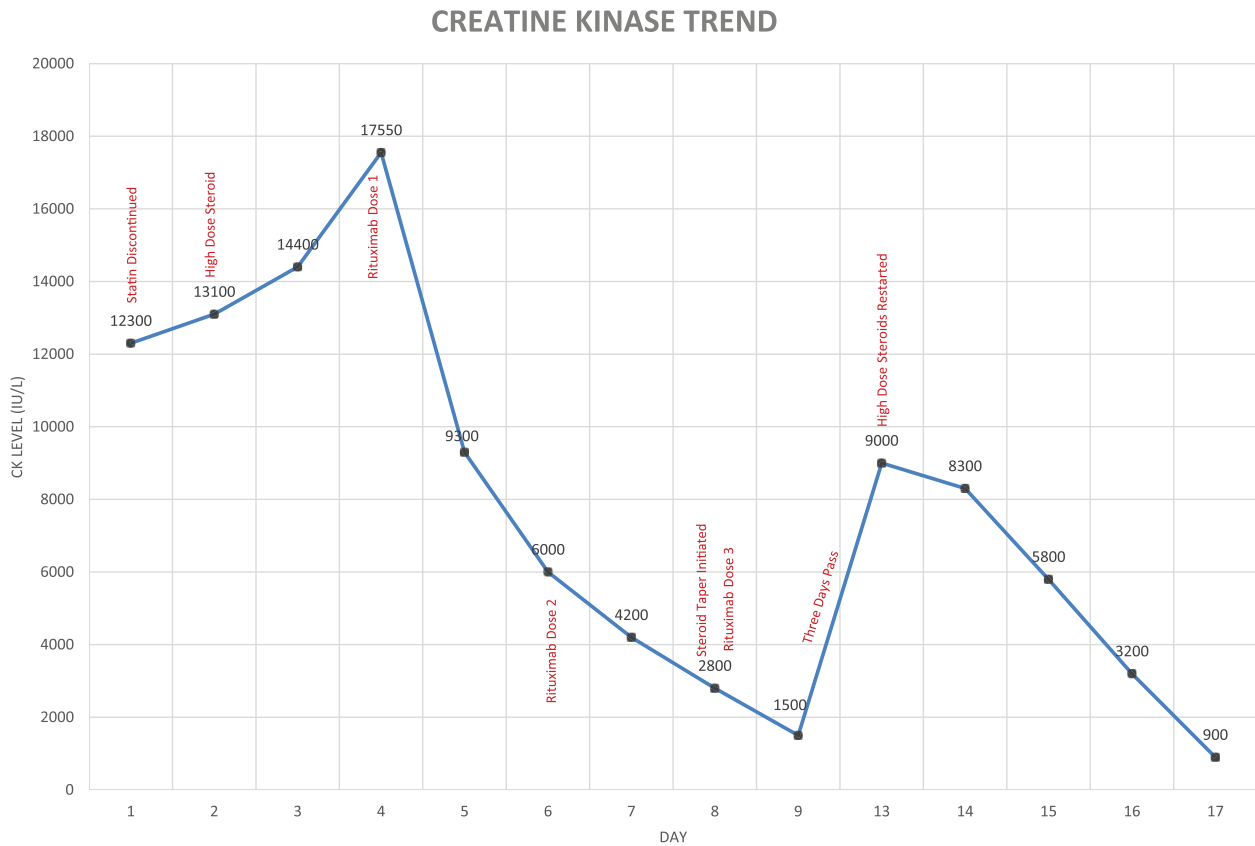


Figure 2. CK trend over the course of days including when particular treatments were implemented.

patients with significantly elevated CK, discontinuation of the statin is indicated, allowing up to 8 weeks for observation of symptoms before repeating CK levels (sooner if symptoms progress). If CK levels remain ≥ 10 times the upper limit of normal 8 weeks after discontinuation of the statin or if symptoms progress after statin discontinuation, the patient should be tested for anti-HMG-CoA reductase autoantibody. A positive test for anti-HMG-CoA reductase autoantibody yields presumptive diagnosis of SAM.⁷

Statin-associated autoimmune myopathy may occur anytime and even long after initial exposure or statin cessation. This is evidenced by elevation of CK and relapse in patients despite discontinuation of the statin. This may occur even while on corticosteroid or immunomodulatory therapy. There are case reports of patients off statin therapy for more than 6 months and then develop the classic characteristic clinical features of SAM.⁹ Patients can have marked weakness, and electrodiagnostic evidence of an active myopathic process and this can be seen up to 11 years after statin cessation. A case series done by Ramanathan et al demonstrated that patients required multiple immunosuppressive agents to achieve clinical remission, and almost all of those that relapsed seemed to be related to de-escalation of high-dose corticosteroids.¹⁰ Therefore, suspicion and early recognition of this diagnosis, use of multiple immunomodulatory agents, and a cautious approach to corticosteroids taper are warranted. At this time, there are no prospective trials with

long-term follow-up evaluating the duration and course of this myopathic process. There has yet to be an optimal definitive induction, maintenance, and remission therapy. Recommendations for treatment of SAM are as follows: first discontinue statin and observe symptoms. If symptoms remain unchanged or clinically worsen, begin initial therapy with oral prednisone. In cases of severe weakness, the clinician may consider a second agent at onset of treatment with prednisone, such as methotrexate, azathioprine, or mycophenolate mofetil. Rituximab or IVIG may be considered after 8 to 12 weeks if no response with prednisone with or without a second agent or sooner in more severe presentations of the condition. IVIG is typically reserved for severe or refractory cases but has been described to be effective as a first-line agent in patients. In a case series, three patients with SAM and underlying diabetes mellitus were treated with IVIG as monotherapy after declining corticosteroid treatment due to potential side effects—partial to full recovery of strength was demonstrated. The combination of prednisone, IVIG, and a steroid-sparing agent was used in nearly one-half of cases described in literature. Treatment of SAM with triple therapy has been recommended. There is also evidence of using IVIG as the sole treatment as depicted by Dr. Mammen in his review article on SAM in the *New England Journal of Medicine*.¹¹ IVIG has been suggested to be first line therapy in severe cases, especially in those who present with an aggressive course.¹²

It is hypothesized that statins may increase the expression of HMGCR autoantibody in regenerating muscle fibers. This self-antigen would perpetuate an immune response. This may explain why patients have a propensity to relapse up on de-escalation of immunosuppression or immunomodulatory therapy.¹³ This is further evidenced in a recent study which demonstrated patients responded well to immunosuppressive treatment, but serum levels of the anti-HMGCR antibody remained high and did not correlate with disease activity.¹⁴

Conclusions

Statin-associated autoimmune myopathy has a unique clinical, histologic, and therapeutic profile that separates it from other inflammatory myopathies. With the new Atherosclerotic Cardiovascular Disease (ASCVD) risk calculator in place and improving access to health care, we expect an increasing use of statin medications. With the benefits of statins with regard to reducing risk of both cardiovascular and cerebrovascular events far outweigh risk and potential adverse effects of these medications; it is crucial for providers to remain aware of possible and even rare side effects of these medications and how to test for them. Statin-associated autoimmune myopathy has been described as an exceedingly rare complication of statin use and is often underrecognized in clinical practice; we urge providers to educate patients to alert their physicians if any signs or symptoms of serious myopathy occur.

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