JCEM Case Reports, 2024, **2**, luae227
https://doi.org/10.1210/jcemcr/luae227
Advance access publication 6 December 2024
Case Report

Statin-Induced Necrotizing Autoimmune Myopathy: Diagnosis and Treatment Approach

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Abstract

The widespread use of statins for cardiovascular diseases has unveiled a new subset of inflammatory myopathy, immune-mediated necrotizing myopathy (IMNM). We describe below an unusual case of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) myopathy. A 64-year-old male individual with type 2 diabetes, hyperlipidemia, and coronary artery disease presented with progressive proximal muscle weakness and pain for 3 months. He took atorvastatin 40 mg for 4 years, which was discontinued due to elevated liver enzymes and resumed treatment with rosuvastatin 5 mg later due to worsening hyperlipidemia. Physical examination showed significant weakness of the hip, shoulder girdle, and biceps/triceps. Creatinine kinase (CK) was found to be 232.48 µkat/L (13 921 IU/L) (normal: 0.833-5.133 µkat/L; 50-308 IU/L). Electromyography and left vastus lateralis muscle biopsy showed findings of myonecrosis. Anti-HMGCR assay was strongly positive with antibodies > 200 chemiluminescent units (CU) (normal: 0-20 CU). He was started on prednisone followed by human-immunoglobulin (IVIG) which led to a decline in CK. Statin-induced necrotizing autoimmune myopathy (SINAM) is an exceptionally rare side effect of statins. Although statins come with a good side-effect profile, one should be aware of marked, persistent elevations in muscle enzyme levels. Prompt confirmation with antibody levels, drug discontinuation, and early initiation of immunosuppression can lead to good outcomes.

Key Words: necrotizing myopathy, statin-induced, SINAM, HMGCR

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IMNM, immune- mediated necrotizing myopathy; IVIG, fluorodeoxyglucose positron emission tomography; SINAM, Statin-induced necrotizing autoimmune myopathy.

Introduction

Statins have been ubiquitously used for their ability to competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase, a crucial step in cholesterol biosynthesis, making them a powerful tool in lowering serum low-density lipoprotein, cholesterol, and triglyceride levels, thereby preventing and reducing mortality due to cardiovascular diseases [1].

On the other hand, it is important to note the adverse effects that have come to light due to their widespread usage. Incidences of myopathy and cognitive, renal, and hepatic dysfunction, as well as type 2 diabetes mellitus, necessitate caution when prescribing these drugs [2].

Increasingly well recognized are the effects of statin on the muscle. Clinically, statin-associated myopathy can be broadly classified as those with myalgia or mild elevation of hyperCKemia (elevation of creatine kinase [CK]), self-limited toxic myopathy, rhabdomyolysis, and immune- mediated necrotizing myopathy (IMNM) [3].

IMNM falls under the spectrum of autoimmune myopathies, along with dermatomyositis and polymyositis. These are a result of direct or indirect injury to the muscle fibers by the immune system. Myositis-specific antibodies (MSA) can be found exclusively in patients with autoimmune myopathies, each MSA corresponding to a unique clinical subtype [4].

IMNM is subdivided based on the presence or absence of unique autoantibodies: anti-signal recognition particle (SRP) myopathy and anti-HMGCoAse reductase (HMGCR) myopathy and seronegative myopathy. The incidence of IMNM is not known with certainty, but it is estimated to occur in approximately 2 or 3 of every 100 000 patients treated with statins. Statin-induced necrotizing autoimmune myopathy (SINAM), a subtype of IMNM, is associated with anti-HMGCR antibody [5].

HMGCR is an enzyme located at the membrane of the endoplasmic reticulum. Antibodies to this enzyme are associated with exposure to statins in half the cases [6]. Although the exact pathogenesis is not known, genetic predisposition and immune system sensitization due to overexpression of HMGCR in muscle tissues following exposure to statins are known to play a role. Individuals with the major histocompatibility complex class II allele, human leukocyte antigen-*DRB111:01** have increased relative odds of developing HMGCR myopathy [7]. Anti-HMGCR myopathy, in contrast to other statin-mediated muscle toxicity, persists long after statin discontinuation [8].

The affected patients show progressive proximal weakness that affects both limb girdles. Creatine kinase (CK) values range from 16.66 to 333.33 µkat/L (1000 to 20 000 IU/L) (normal: 0.833-5.133 µkat/L; 50-308 IU/L). Electromyography and

Received: 24 September 2024. **Editorial Decision:** 21 November 2024. **Corrected and Typeset:** 6 December 2024

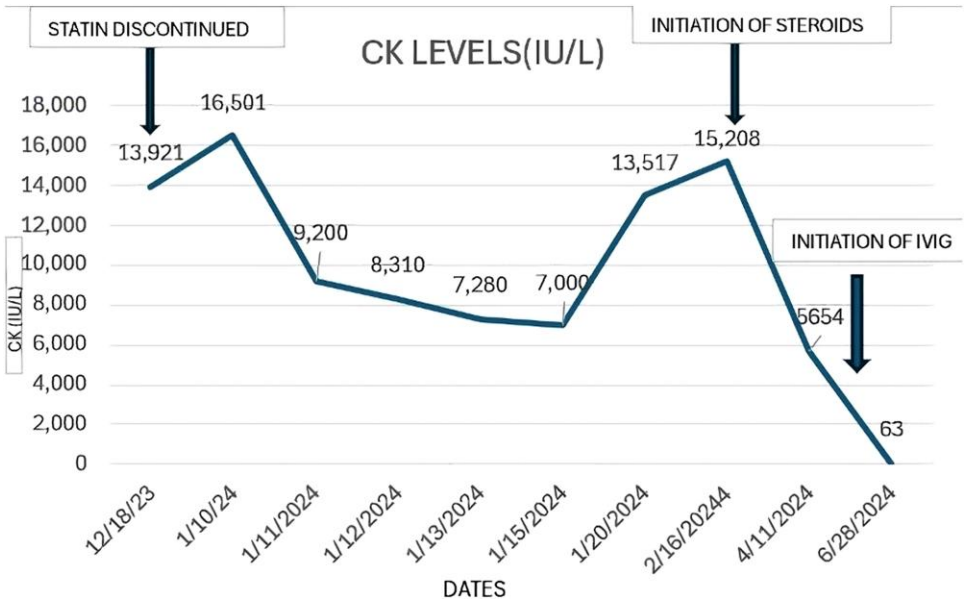

Figure 1. The creatine kinase (CK) levels over the course of this patient's diagnosis and treatment period. This graph shows the trend in the CK levels through the course of events from discontinuing statins to treating the patient with statins and intravenous immunoglobulin.

muscle biopsy characteristically reveals necrosis of muscle fibers and scarce inflammation [3].

This report describes the clinical course of a patient who was diagnosed to have SINAM. This case illustrates the clinical course, various diagnostic tools used, and the challenges in treatment and the response to treatment of this rare condition.

Case Presentation

A 64-year-old Caucasian male patient with a history of type 2 diabetes mellitus, hypertension, hyperlipidemia, metabolic dysfunction-associated steatotic liver disease, Gilbert syndrome, and coronary artery disease presented to the clinic with complaints of progressive proximal muscle weakness over the past 3 months. He also complained of extreme muscle pain, difficulty climbing stairs, and rising from a chair. The patient was initially on atorvastatin 40 mg for 4 years before it was discontinued due to elevated liver enzymes and was then switched to rosuvastatin 5 mg after a 7-month discontinuation of statins due to persistent, worsening hyperlipidemia. He then presented to the clinic after being on medication for 10 months.

Diagnostic Assessment

Physical examination findings were notable for reduced muscle strength. In the upper extremities, there was moderate to significant weakness in the biceps, triceps, and shoulder girdles, but had good strength in the wrists and hands. In the lower extremities, significant weakness was noted in the hip muscles, while strength at the knee and ankles remained good. On further evaluation, his total CK was found to be significantly elevated at 232.48 μkat/L (13 921 IU/L) (normal: 0.833-5.133 μkat/L; 50-308 IU/L), concerning for rhabdomyolysis. He had no history of autoimmune disease. No preceding history of fevers, chills, joint pain, and dysphagia was present.

Laboratory evaluation was also notable for elevated aspartate transaminase (AST): 3.88 μkat/L (233 U/L) (normal: 0.08-0.66 μkat/L; 5-40 U/L), alanine transaminase (ALT): 9.73 μkat/L (584 U/L) (normal: 0.06-0.68 μkat/L; 4-41 U/L), and potassium 5.5 mmol/L (N: 3.5-5 mmol/L). His renal function tests were well within normal limits. Statin and dulaglutide were then subsequently discontinued.

The patient later presented to the emergency room with a syncopal episode without any evidence of a neurological event or ischemia. During workup, his CK level was found to have an increasing trend and reached 275.0167 μkat/L (16 501 IU/L) even after discontinuing statins for almost 3 weeks. His ALT was now 9.71 μkat/L (583 U/L), and AST was 5.35 μkat/L (321 U/L). Aldolase was also elevated at 1.0717 μkat/L (64.3 U/L) (normal: 0.016-0.125 μkat/L; 1.0-7.5 U/L). After aggressive intravenous hydration, CK improved to 153.333 μkat/L (9200 IU/L). The trends in CK levels are depicted in Fig. 1. Right upper quadrant ultrasound and renal and thyroid function tests were normal.

The patient underwent an electromyography, which demonstrated diffuse myopathy with myotonic discharges and findings to support myonecrosis, vacuolization, or fibrous splitting. Findings were abnormal with significant spontaneous activity in the form of fibrillation potentials, complex repetitive discharges, and sharp waves. The pulmonary function test showed a mild decrease in forced expiratory volume and forced vital capacity consistent with neuromuscular weakness. The left vastus lateralis muscle biopsy showed scattered necrotic and regenerating fibers compatible with IMNM.

Additionally, the anti-HMGCR assay completed revealed strongly positive antibody levels at > 200 chemiluminescent units (CU) (normal: 0-20 CU). The Anti Signal Recognition Particle Immunofluorescence (SRP IFA) screen, however, turned out to be negative. Since IMNM can be paraneoplastic, a colonoscopy was undertaken, which was unremarkable. A whole-body fluorodeoxyglucose positron emission tomography/computed tomography was recommended, but the patient could not complete it due to hyperglycemia.

Treatment

He was then empirically started on prednisone 40 mg daily which lowered his CK levels to 94.73 μkat/L (5684 IU/L) (normal: 0.833-5.133 μkat/L; 50-308 IU/L) within a month.

Intravenous immunoglobulin was added for aggressive treatment once the antibody assay confirmed the diagnosis. He was started on 2 grams/kilogram over 5 days (0.4 g/kg of ideal body weight daily for 5 days) monthly for 3 months.

He was started on 10 mg ezetimibe and subsequently 140 mg subcutaneous injections of evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, was added with recommendation to re-evaluate his lipid panel in 2 to 3 months to achieve a goal low-density lipoprotein of < 55 mg/dL in the setting of known coronary artery disease.

Outcome and Follow-Up

CK levels normalized after this and dropped down to 1.05 μkat/L (63 IU/L). Further treatment plan was to continue 2 grams/kilogram intravenous immunoglobulin monthly for 3 more months which would then be decreased to 1 gram/kilogram monthly for months. In addition, prednisone is planned to be slowly tapered and replaced by methotrexate due to poor control of hyperglycemia.

Discussion

Immune-mediated myopathies belong to a family of rare autoimmune disorders that can often be tricky to diagnose due to their rarity and vague nature of their symptoms, ranging from muscle weakness to dysphagia and even respiratory failure. This group of disorders has become known following the widespread use of statins. Proximal progressive weakness as a complaint in statin users who do not respond to initial treatment should prompt consideration of an alternative diagnosis like SINAM.

Muscle weakness, myalgia, and CK levels, which can reach up to 16.70-334 μkat/L (1000 to 20 000 IU/L), do not improve in SINAM after discontinuing treatment, unlike that seen in typical cases of statin toxicity [9]. Symptoms have been found to persist or even progress [10].

In contrast to other myopathies, the sparse inflammatory infiltrates and presence of complement deposits on the sarcolemma of myofibers in IMNMs point to an autoimmune pathophysiology, as opposed to T-cell dependent cytotoxicity seen in cases of dermatomyositis and polymyositis [6]. This can be identified by performing a biopsy of the muscle in affected individuals, which characteristically shows regenerating fibers along with necrosis and no significant inflammation [9]. However, as muscle biopsy is not as specific as the presence of myositis-specific antibodies (MSA), it is therefore, not necessary for diagnosis [11]. In addition, necrotizing myopathy has been found to be a part of paraneoplastic syndromes in rare cases, justifying the use of fluorodeoxyglucose positron emission tomography and colonoscopy to rule out malignancy, but more research is needed to find their true association [12].

Electromyography typically shows findings of myopathic lesions with decreased motor unit potential durations, spontaneous fibrillations, repetitive discharges, and positive sharp waves [4]. The presence of anti-HMGCR antibodies in conjunction with statin use is a characteristic feature of the SINAM subset of IMNM. These individuals are found to be older and have necrosis on biopsy [13].

Immunosuppression is the choice of treatment for SINAM. A trial of glucocorticoids is used as the first line of treatment. SINAM can be especially difficult to treat and achieving remission usually requires the addition of intravenous immune globulin (IVIG) [14]. In our patient, prompt response was observed upon adding IVIG to the steroid, facilitating the tapering of glucocorticoids and eventually switching to methotrexate. This is particularly useful in patients with diabetes and other cardiovascular comorbidities that restrict long-term use of steroids. Even monotherapy with IVIG can be tried in such cases [15]. The finite duration of treatment with IVIG has not been universally defined, due to variations in patient response. Anti-HMGCR antibody levels correlate with higher CK levels and greater disease activity using myositis disease activity assessment (MYOACT scores) [11]. This suggests that antibody monitoring may provide insights into the duration of therapy in individual patients.

For individuals with intermediate or high risk for cardiovascular disease, or in the cases where secondary prevention is needed and this condition develops, alternate lipid-lowering therapy such as ezetimibe and/or subtilisin/kexin type 9 (PCSK9) can be considered. Given the limited number of patients with this condition, there is a lack of data on systematic evaluation of alternate lipid-lowering therapy in this scenario. A case report documenting safety of PCSK9 inhibitor use is available [16].

To conclude, early consideration and prompt diagnosis with anti-HMGCR antibodies should be done in patients with persistent muscle weakness and elevated CK after statin cessation. Early and aggressive immunosuppression is vital to attain remission. Other treatment options for lowering cholesterol should be explored if a patient is found to be susceptible. Techniques to identify genetic susceptibility to statin-induced autoimmune necrotizing myopathy should be further explored and developed.

Learning Points

- Progressive proximal muscle weakness and elevated CK in patients despite discontinuation of statins should prompt the consideration of SINAM as a possible diagnosis.
- Prompt diagnosis with anti-HMGCR antibodies is recommended to be done for confirming diagnosis.
- Early and aggressive treatment with corticosteroids and IVIG is recommended to attain early relief from symptoms and normalization of CK value.

Contributors

All authors made individual contributions to authorship. V.S. and S.P. were involved in writing the initial manuscript draft. K.M. and J.S. were involved in supervising and editing the manuscript. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

The authors declare that there are no financial disclosures or conflicts of interest associated with this case report. Additionally, no external funding was obtained for the preparation or publication of this report.

Informed Patient Consent for Publication

Signed informed consent obtained directly from patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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