

# Necrotizing Autoimmune myopathy: A case report on statin induced rhabdomyolysis requiring immunosuppressive therapy

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## Summary

Statins can cause a wide spectrum of muscular adverse effects ranging from asymptomatic elevation of Creatine Kinase (CK), myalgia and exercise intolerance to rhabdomyolysis. Most of these effects generally resolve on stopping the medication. However, statins can be associated with a unique autoimmune myopathy wherein symptoms persist or even progress after statin discontinuation and require immunosuppressive therapy. The case presented is a 60-year-old woman who was on statin treatment for a period of 2 years. She developed muscle weakness with a limb girdle distribution. She had persistent elevation of CK even after discontinuation of statin therapy. EMG done revealed irritable myopathy and muscle biopsy showed necrosis without inflammation. She subsequently tested positive for anti-3-hydroxy-3-methylglutaryl-coenzyme A (anti-HMG CoA) antibody which is found to be present in patients with statin-associated necrotizing autoimmune myopathy. Patient was started on steroid without much improvement in her symptoms. After a month of follow up, her upper extremity strength was back but lower extremity continued to be weak which prompted us to start her on Methotrexate and Azathioprine. Like our patient, there are rare subgroup of patients with an immune-mediated necrotizing myopathy that does not improve after discontinuation of the drug and requires aggressive treatment with immunosuppressive agents. Awareness and early recognition of this disease is very important in patients who continue to have CK elevation and weakness after discontinuation of statin therapy.

**Keywords:** Necrotizing autoimmune, myopathy, anti-3-hydroxy-3-methylglutaryl-coenzyme A (anti-HMG CoA) antibody

## 1. Introduction

Statins are some of the most widely prescribed medications, and though generally well tolerated, can lead to musculoskeletal side effects, with up to 20% patients experiencing myalgia's (1). There is a wide spectrum of muscular adverse effects associated with statins, from asymptomatic elevation of CK, myalgia and exercise intolerance to toxic necrotizing myopathy and rhabdomyolysis (2). In general, statins produce a self-limited myopathy that resolves within several months of medication cessation; however, they are also

associated with increased incidence of inflammatory myopathies. The present case belongs to the group of inflammatory idiopathic myopathies (IIM), which is divided into four main groups: polymyositis (PM), dermatomyositis (DM), necrotizing autoimmune myopathy (NAM) and sporadic inclusion body myositis (SIBM) (3). NAM can be associated with connective tissue disorder but can also be triggered by viral infections such as HIV or malignancy, be statin induced, or be idiopathic. The absence or relative paucity of an inflammatory lymphocytic infiltrate is described as a pauci-immune necrotizing myopathy and distinguishes NAM from the characteristic histologic findings of PM or DM, which includes CD8+ or CD4+ T lymphocytes and B cells respectively (3). Recently, it has been reported that up to 20% of patients with diagnosis of an IIM have NAM (4). Marked elevations in CK is characteristic of NAM, with a mean value of 10,000 U/

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L compared to the self-limited form (1). NAM affects men and women equally and typically occurs in adults and the elderly (4).

## 2. Case Report

A 60-year-old female with past medical history of hypertension, diabetes and hyperlipidemia (treated with atorvastatin for the last 2 years), presented with proximal muscle weakness. She reported her weakness started 2 years ago mostly in the lower extremity progressing significantly for the past 6 months with recent involvement of her shoulder and arms as well. She initially had trouble getting out of her car seat, climbing steps and getting out of chair. Initially she was advised to lose weight and undergo rehabilitation. Gradually her weakness progressed to where she could barely climb one stair at a time. She was unable to place more than 3 plates in her cupboard above shoulder level due to weakness. She denied any associated muscle or joint pain, fever or chills, rashes, oral ulcers or any recent vision changes.

Physical examination revealed significant proximal upper and lower extremity muscle weakness. Muscle strength examination revealed decreased muscle bulk in the biceps and triceps. She was found to have significantly decreased strength in the hip flexors bilaterally, not capable of lifting her legs against minimal resistance from the examiner. She was unable to rise from a seated position. However, she had no findings on examination suggestive of a systemic autoimmune disorder and no cutaneous manifestations suggestive of DM.

Routine laboratory studies were normal except for a CK level of 12,387 U/L and aldolase of 48.4 U/L. Myoglobin in urine was 3,086 ng/mL. Her CK level remained relatively unchanged despite aggressive intravenous hydration and withholding her atorvastatin. Additional neurologic, serologic and musculoskeletal studies were performed. Thyroid function was normal. Nerve conduction studies and Electromyography (EMG) were consistent with an active, irritable myopathy of the proximal muscles. Given the persistent weakness and CK elevation, there was concern for possible statin associated NAM with consideration for other inflammatory myopathies such as DM and PM. Results for myositis-associated and connective tissue disease antibody including antinuclear antibody, anti-DNA ab, anti-Jo-1 antibody and Myositis panel for MI2 (Mi-2/nucleosome remodeling and deacetylase complex), ku, SRP (signal recognition particle), PL7 (threonyl), PL-12 (alanyl), EJ (glycyl), and OJ (isoleucyl), and Jo 1 (antihistidyl-tRNA synthetase) were negative. The patient was tested for presence of novel anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti HMGCR) antibodies with a positive result. A muscle biopsy from left vastus lateralis was performed that showed

necrotizing myopathy with minimal inflammation with prominent regeneration, necrosis, myophagocytosis, myofiber vacuolation and mild T cell cD3+ component. B cells were absent.

Given the connection between NAM and malignancy, cancer screening was reviewed. Colonoscopy, mammogram and cervical cancer screening performed in the past did not show any significant abnormalities. Computed tomography of the chest and abdomen was negative for malignancy. She was diagnosed with statin-associated NAM and started on prednisone 40 mg daily. After a month of follow up, her upper extremity strength was back but lower extremity continued to be weak. Patient was unable to perform lift off test from chair without hands. She was then started on methotrexate and azathioprine. Her repeat CK was 819 U/L and Aldolase was down to 11 U/L. Myositis specific antibodies were negative for SSA-52, SSA-60 and ribonucleic protein. Patient reported progressive improvement of her weakness to what she considers her baseline. On examination her strength was found to be 5/5 in both upper and lower extremities. Currently, after six months, the patient is on a tapering course of prednisone 30 mg/day. Her latest CK is 108 U/L.

## 3. Discussion

NAM is a recently recognized part of IIM. NAM has been associated with malignancies, HIV, antibodies to signal recognition particle, connective tissue diseases and certain medications, but it can occur in isolation (3). This under recognized condition was recently described in association with statin exposure. Christopher-Stine *et al.* (5) reviewed a cohort of patients with necrotizing myopathy on muscle biopsy and demonstrated that 16/26 patients' sera immune precipitated a pair of proteins with approximate sizes of 200 and 100 kDa. Sixty-three percent of these patients had statin exposure at some point prior to symptom onset. This antigen was later characterized as HMGCR, the pharmacologic target of statins. Further workup by this group has demonstrated that these antibodies are not present in healthy controls; in the majority of patients with DM, PM and SIBM; or in patients with statin exposure and isolated CK, myalgia, or self-limiting statin intolerance, thus suggesting they are highly specific for statin associated NAM (5). The novel anti-HMGCR antibody, which was discovered in 2010, is a promising diagnostic marker for statin-associated NAM (6). The reported sensitivity and specificity are 94.4% and 99.3% (7).

Patients generally present with significant proximal muscle weakness and marked elevation in CK levels, often greater than 10 times the upper limit of normal. EMG shows signs of irritable proximal myopathy, indicative of a severe muscle disease such as immune-mediated myopathy, compared to non-irritable myopathy such as a steroid induced myopathy. Muscle

biopsy has feature of prominent muscle necrosis with myofiber regeneration and minimal inflammation.

Symptoms of statin intolerance may occur at any time after commencement of treatment, with an average of 31 months in 1 series (range 0-84 months) (1). However, the immune-mediated muscle damage initiated in the presence of statins may be sustained long after statin cessation through persistently increased HMGCR expression in regenerating muscle fibers (8). However, once the immune system was activated, discontinuation of the statin at that time would not be sufficient to halt the ensuing muscle destruction. It is not likely to be related to cell mediated destruction of muscle fibers, as inflammatory cell infiltration is not a feature. It may be related to humoral factors such as cytokine or complement-mediated destruction of muscle fibers.

Currently, there are no controlled trials to guide treatment selection; thus all of the data available are from small retrospective studies or case reports. Initial treatment is generally high dose prednisone, but more aggressive immunosuppressive therapy may be needed in up to 77% of patients with this disorder, and an initial response with glucocorticoids takes 2 to 3 months (9). The observation that our patient improved only after addition of immunosuppressive agents suggest that NAM associated with statin use in our patient was also immune mediated. Methotrexate, azathioprine, cyclosporine, tacrolimus, rituximab, plasmapheresis, and IVIG are just a few of the immunosuppressive medications that have been reported to successfully treat anti-HMGCR and anti-SRP antibody-positive NAM (9). Relapses seem to be common when tapering glucocorticoids, potentially providing another reason to consider adding another immunosuppressive medication at disease onset (10). Patient comorbidities such as chronic infection, malignancy, chronic kidney disease, chronic liver disease, or diabetes mellitus may limit immunosuppressive choices.

In conclusion, statin use is associated with a NAM that does not respond to discontinuation of the offending agent. The main problem we have when we initially see a patient who has marked weakness and elevated CK while on statin is how to predict which patient will respond to just stopping the statin and which one will eventually require immunotherapy. We present this case with an aim to highlight that though statin-associated NAM is a relatively rare entity, it is an important consideration for the general internist in patients who

continue to have CK elevation and weakness even after discontinuation of statin therapy. Early recognition of such symptoms is warranted for timely management and prevention of further complication. Awareness of this entity will help physicians who prescribe statins to take action to limit the associated morbidity.

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