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**Case Report**

# Statin induced myopathy: a case report

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## ABSTRACT

Statin-induced necrotizing autoimmune myopathy is an immune-mediated necrotizing myopathy related to the use of statins. It is a very rare disease, which usually presents with proximal muscle weakness and frank elevation in creatine kinase levels. Stopping statin and the use of immunosuppressive therapy are considered the mainstay therapy. Herein, we present a case of a 75-year-old patient with statin-induced myopathy based on the presence of proximal muscle weakness, magnetic resonance findings. The patient was treated with IVIg and corticosteroid therapy with a particularly good response to intravenous immunoglobulin. However, medications are accompanied by the not so friendly adverse events. Through this report we highlight the importance of understanding. This report highlights the importance of timely diagnosis and early use of combined immunosuppressive therapy to improve patients' outcome affected by this rare disease.

**Keywords:** Statins, Creatine kinase, IVIg, Corticosteroid therapy

## INTRODUCTION

Statins have proved to significantly reduce cardiovascular risk in primary and secondary prevention. Myopathy is a frequent adverse effect of statins with an incidence of about 15%.[1] The spectrum of symptoms of statin induced musculoskeletal symptoms varies from a simple muscle pain all the way up to rhabdomyolysis leading to acute kidney failure with the most common symptom being fatigue and muscle weakness. As per a multitude of studies conducted on patients with musculoskeletal symptoms, the incidence due to statins could range from 10-33%.[1]

It is important to differentiate benign muscle pain without biochemical abnormalities from severe myopathies in which discontinuation of statin use is mandatory and in which active therapy could be mandated.

## CASE REPORT

A 75-year-old female with a history of systemic hypertension, type 2 diabetes mellitus on Insulin and an old cerebrovascular accident 12 years back with no residual effect was on atorvastatin 40 mg since 12 years presented to the emergency/ clinic with symmetric proximal muscle weakness and pain in her lower extremities bilaterally and to a lesser extent the upper extremities for a week (unable to walk more than 20 m). She denied any prior trauma, recent strenuous exercise, other neurological symptoms, history of malignancy, auto-immune disease, and no family history of neuromuscular disorders.

On examination a reduced muscle power was noted symmetrically in the upper aspect of her lower extremities (scored 4 out of 5) without any weakening in the upper limbs (strength scored 5 out of 5). There were no fasciculations, swelling of the affected muscles, or

skin rash, reflexes were universally weak and there were no sensory or visual deficits.

Laboratory workup revealed a haemoglobin of 8, PCV 24.7 peripheral blood smear showed normocytic normochromic anaemia. Further, the serum creatinine was 3.63, urea 103.2, serum sodium 139, serum potassium 4.80. Creatine kinase (CK) (17790 U/L, reference value <170 U/L), aspartate transaminase (963U/L, ref. <32 U/L), and alanine transaminase (666 U/L, ref. <31 U/L), C-reactive protein (116 mg/L, ref. <5 mg/L), ESR (104 mm/hour, ref. <20 mm/hr).

Antinuclear antibodies (ANA) profile and serum protein electrophoresis were unremarkable.

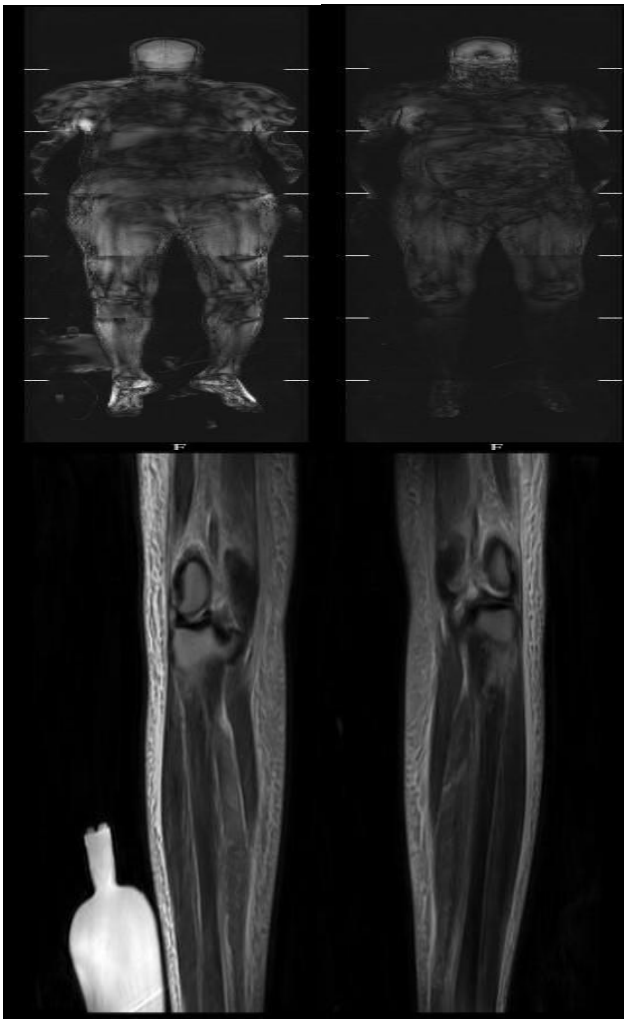

**Figure 1: Diffusely oedematous muscles along the chest wall, abdominal wall, around the shoulder, bilateral lower limbs, proximal arm and neck muscles with diffuse subcutaneous edema-consistent with extensive multi-focal myositis.**

Electrocardiography showed an incomplete right bundle branch block with inverted T waves in leads V1-V5, which were known and were unchanged for this patient. Echocardiography showed no global or regional contractility disorders and no structural abnormalities.

MRI of the whole body showed diffusely oedematous muscles along the chest wall, abdominal wall, around the shoulder, bilateral lower limbs, proximal arm and neck muscles with diffuse subcutaneous oedema-consistent with extensive multi-focal myositis.

The patient was admitted for 10 days to the intensive care unit to monitor diuresis, fluid balances, arterial and urinary pH, electrolytes, and kidney function. Therapy was given for rhabdomyolysis: large amounts of IV crystalloids (2 L per day), mannitol (15% 100 mL four times a day), and sodium bicarbonate (50 mEq $NaHCO_3$ over 15 min followed by 10 mEq/h). Haemodialysis was performed in view of acute kidney injury secondary to rhabdomyolysis. Atorvastatin was discontinued on the 2$^{nd}$ day of admission. Since her EULAR score for myositis was 5.8 which corresponds to about 50-60% probability of having myositis, her myositis profile was unremarkable. The MRI of the skeletal muscles demonstrated features of myositis such as muscle inflammation, fibrosis and calcification which was present in multiple areas on her MRI of the skeletal muscles, however the presence of myositis on MRI is non-specific (could be rhabdomyolysis, myositis, muscular dystrophy or metabolic myopathy). Anti-HMGCR was not available. SRP was negative. In order to find the aetiology? IMNM triggered by statin we recommended a muscle biopsy which the patient denied. Intravenous immunoglobulin of 1 gm per kg was started after which her CK level dropped to 3043, oedema reduced and her muscle weakness improved. Furthermore, pulse therapy with corticosteroids 1gm was given intravenously for 3 days.

She was then shifted to the ward under a maintenance therapy of oral prednisolone. She was gradually symptomatically better with the steroids being tapered 5 days She received intensive physiotherapy. Muscle weakness slowly improved and she was able stand on her own and walk about 10 m at the time of discharge.

## DISCUSSION

Statins are potent hypolipidemic drugs as they have significantly reduced the cardiovascular event and thrombo-embolic episode. But precaution should be taken and cautious use of statin required as it may result in progressive myopathy in genetic susceptible.[2]

Statin-induced blockade of mevalonate biosynthesis and its consequences for skeletal muscle gene expression and myopathy. Potential differences in inter-organ uptake, metabolism and flux of statins in genetically susceptible patients lead to greater skeletal muscle toxicity. Inhibition of mevalonate and its downstream reaction products result in reduced availability of geranyl pyrophosphate and farnesyl-pyrophosphate, needed for

prenylation/lipidation of signaling proteins. Altered signal transduction pathways re-program skeletal muscle gene expression. Genetic polymorphisms and significantly altered genes that putatively underpin skeletal muscle pathology are indicated.[3]

The differential diagnosis of idiopathic inflammatory myopathies comprises polymyositis, dermatomyositis, IMNM, inclusion body myositis, non-specific myositis, and antisynthetase syndrome.[4]

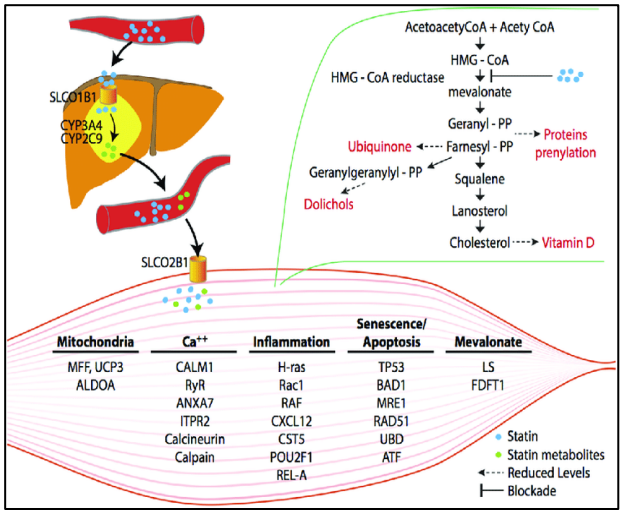


**Figure 2: Hypothesis of statin induced blockade of mevalonate synthesis.**

In a randomized trial, highest risk of myopathy is seen in simvastatin, whilst lower risk is observed in fluvastatin and rosuvastatin. The most severe adverse effect of statin is myotoxicity, in the form of myopathy, myositis or rhabdomyolysis.[5] Rhabdomyolysis is the most severe adverse effect of statins, disseminated intravascular coagulation and death.

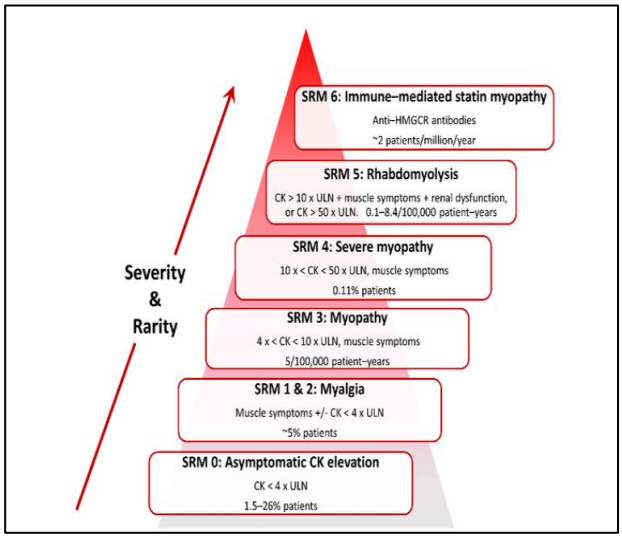


**Figure 3: Classification of statin related myotoxicity.**

Statin-mediated myopathies are diverse and can be divided into benign muscle pain without CK elevation, myopathy/myositis with significant CK elevation, fulminant rhabdomyolysis, and HMGCR antibody-mediated IMNM.[7]

The diagnosis could be made clinically, laboratory evaluation and histopathological findings. Clinically there could be 3 distinct patterns-a history of chronic development of muscle weakness, solely extra muscular findings such as cutaneous eruptions, arthritis, or autoimmune mimicking phenomenon and lastly both muscular and extra muscular findings.[8]

Laboratory parameters could include non-specific or specific. Non-specific findings include elevations in CK, AST, ALT, LDH, with ESR and CRP not being uniformly elevated. ANA is present in up to 60% of patients with DM/PM. with CK being most sensitive and elevated to about 10 times the ULN. However, the association of CK with acute kidney injury in such cases is minimal.

Myositis specific antibodies- anti synthetase antibody-Raynaud, arthritis, inflammatory arthritis, anti-SRP (very specific for necrotizing myopathies and indicate severe disease manifestation), anti-MI 2 antibody (acute onset of DM and indicate a severe form, lower risk for malignancy), anti MDA5 antibody (a protein involved in innate immune response- interstitial lung disease, rapidly progressive disease and high morbidity and mortality), anti- NXP-2 (DM in young with severe disease, edema and calcinosis), anti TIF-1 gamma antibody (cutaneous phenotype and increased risk for malignancy), anti-SAE antibody (5-10% of DM, and CADM they may go on to develop malignancies in the future), anti HMGCR antibody (a key enzyme in cholesterol synthesis-IMNM it is also associated with statin use with about 50% patients with this antibody being statin independent).[9]

The EULAR classification criteria for IIM based on the data from 976 patients with IIM and 634 matched controls, shows 87% sensitivity and 82% specificity and the addition of muscle biopsy increases it to 93% and 88% respectively. This tool for diagnosis is quick and includes clinical findings, laboratory parameters and additionally histopathological findings if any. The level of probability-50%-60% without and 55-75% with muscle biopsy corresponding to a score of >5.5 without muscle biopsy and >6.7 with muscle biopsy is defined as possible IIM and the probability of >90% corresponding to >7.5 without and >8.7 with muscle biopsy and for a patient with a score of <5.3 or 50% it could be classified as non-IIM. Using the web-based calculator our patients score was 5.8 which corresponds to possible IIM.[10]

The treatment of IMNM involves giving immunosuppressants, to deal with the inflammation and further reduce its progression. During the acute phases, Intravenous immunoglobulins are administered to hasten

the process followed by corticosteroids. However, it must be noted to be aware of the pros and cons of glucocorticoids while administering them.

Patients falling in the probability range ≥50% and <55% will be classified as "possible IIM". For a patient to be classified as a non-IIM patient the probability would have to be <50% (score of maximum 5.3 without biopsies; 6.5 with biopsies).

## CONCLUSION

The prevention of statin-related myopathy involves using the lowest statin dose required to achieve therapeutic goals and avoiding polytherapy with drugs known to increase systemic exposure and myopathy risk. Currently, the only effective treatment of statin-induced myopathy is the discontinuation of statin use in patients affected by muscle aches, pain and elevated CK levels.

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