

An Atorvastatin-induced positive anti-HMGCR immune-mediated necrotizing myopathy case

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Introduction

Statin belongs to a medication class of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) inhibitor. It is the most significant drug used for lipid-lowering and cardiovascular disease prevention¹. A wide range of statin myopathy has been reported including myalgia, myopathy, myositis, or rhabdomyolysis. Statin-induced immune-mediated necrotizing myopathy (IMNM) is a relatively rare side effect with an incidence of 2 or 3 of every 100,000 patients taking statins². Many different findings help differentiate toxic non-inflammatory effects from immune-mediated myopathy due to statins¹. We report a case of statin-induced IMNM with oropharyngeal involvement.

Case description

A 56-year-old man with a past medical history of hypertension, and hyperlipidemia, presented with progressive generalized weakness for 4 months. He had been on atorvastatin 40 mg daily for a few months before the symptoms started. Atorvastatin was discontinued when he started having weakness, which started with the slowing of his gait and increased fatigue; and then, progressed to aching shoulders. He noticed difficulty standing from a squatting position and later from a seated position.

Despite stopping Atorvastatin, his symptoms continued to progress to the point he was bed-bound, unable to roll on the bed without assistance. He also complained of dysphagia which led to unintentional 60-pound weight loss since the onset of his symptoms. Physical examination was notable for generalized muscle wasting, proximal muscle weakness grade I-II/V, and distal group grade III-IV/V on both upper and lower extremities.

Methods:

Blood chemistries were significant for elevated creatine kinase (CK) at 4,050 IU/L, c-reactive protein (CRP) at 13.8 mg/dl, erythrocyte sedimentation rate (ESR) at 130 mm/hr, and elevated aldolase at 24 units/L. Liver enzymes were mildly elevated (AST 199 and ALT 119). Creatinine level was low at 0.3 mg/dl. ANA was negative; C3 was normal while C4 was slightly high. Table 1 summarizes the laboratory. The thyroid function test was normal. Workup for idiopathic inflammatory myopathy was negative including anti-Jo-1 (Table 2). MRI of both lower extremities with STIR demonstrated diffuse myositis of the left and right thigh likely related to drug-induced myopathy but other infectious or inflammatory myopathies cannot be excluded (figure 1.1-1.2). No significant muscular fatty atrophy was observed on the MRI (figure 2.1-2.2).

Table 1 Summarization of laboratory during hospitalization.

Lab	Normal range	On admission	At discharge
ESR	0-20 mm/hr	130	45

CRP	0.0-0.5 mg/dl	13.8	0.4
Creatinine kinase	26-308 IU/L	4,050	660
AST	5-37 IU/L	199	81
ALT	5-41 IU/L	119	111
Aldolase	[?] 8.1 unit/L	24	-
C3	90-180 mg/dl	179	-
C4	10-40 mg/dl	57	-

Table 2 Myositis profile

Myositis profile	Result
MI-2 Autoantibodies	NOT DETECTED
PL-7 Autoantibodies	NOT DETECTED
PL-12 Autoantibodies	NOT DETECTED
Ku Autoantibodies	NOT DETECTED
EJ Autoantibodies	NOT DETECTED
OJ Autoantibodies	NOT DETECTED
SRP Autoantibodies	NOT DETECTED
JO-1 Autoantibodies	<1.0 (negative)

A muscle biopsy of his right upper thigh was performed and later revealed many necrotic and regenerating fibers indicating an active myopathy. Small collections of mononuclear cells were present at perivascular sites in the perimysium and a few mononuclear cells were present at the endomysium surrounding necrotic or regenerating fibers. The biopsy findings could represent necrotizing autoimmune myopathy. Regarding the patient’s clinical correlation, anti-body against HMGCR was tested, which returned positive at 139.3 CU. The patient was diagnosed with statin-induced immune-mediated necrotizing myopathy.

Results

He received combination therapy with intravenous immunoglobulin (IVIG) 1g/kg/day for 2 days, methylprednisolone IV high dose up to 500mg every 12 hours and tapering to oral prednisone 60 mg daily, and mycophenolate mofetil titration up to 1,500mg oral twice a day. He was discharged to an inpatient rehabilitation facility with oral prednisone and mycophenolate mofetil. His CK level at discharge was 660 IU/L.

At the 3-month outpatient follow-up, prednisone had been tapered and discontinued but he remained on mycophenolate mofetil. The patient was able to walk and had significant improvement in oropharyngeal dysfunction.

Discussion

Immune-mediated necrotizing myopathy (IMNM) can be caused by cancer, viral infection, connective tissue diseases, and medications, especially statin, anti-HMGCR, and anti-SRP autoantibodies, resulting in skeletal muscle injury³. Antibodies against HMGCR, the statins target, are found more often in patients with necrotizing myopathy with statin exposure; thus, the positive antibody supports the autoimmune process². There have been many proposed mechanisms for the pathogenesis underlying the statin-induced IMNM; however, the true mechanism is not well understood^{2,4}.

Anti-HMGCR IMNM presents clinically as a subacute or chronic progressive symmetrical proximal muscle weakness. Dysphagia, like our patient, occurs in approximately one-third of patients. Muscle weakness persists despite discontinuing statins and CK levels, usually exceeding 10 times the upper normal limit^{1,2}. Extramacular manifestations like those of dermatomyositis can be present⁵. However, malignancy-associated anti-HMGCR IMNM was unclear; there was no statistically significant relation^{6,7}.

Musculoskeletal MRI and EMG can be done prior to antibody assay or muscle biopsy. EMG usually shows signs of irritable myopathic patterns but is not possible to differentiate the type of inflammatory myositis. MRI with STIR sequence in statin-induced IMNM demonstrates diffuse and symmetrical muscle edema and signs of fibro-adipose tissue replacement^{2,3}. A report by Mammen proposed an algorithm for evaluating potential cases of statin-associated autoimmune myopathy². The presence of muscle necrosis and regeneration with sparse inflammatory infiltrates on muscle biopsy are the prominent histologic features².

There is no definite cutoff point on how long after taking statins patients would develop IMNM—it can range from months to years⁸. In our case, the patient developed weakness a few months after statin initiation and continued to deteriorate even after statin discontinuation. Compared to other statins, atorvastatin was more frequently reported to be a cause of statin-induced IMNM, likely due to its high lipophilic property resulting in better penetration to peripheral and liver tissues⁹. Symptoms are milder at onset 50-60 years old while younger patients appear to be more severe and, regardless of statin use, are more recalcitrant to treatment.⁷

Serum levels of the anti-HMGCR antibody are correlated with creatinine kinase and inversely associated with the degree of muscle weakness^{7,10}. However, anti-HMGCR titers remain positive even in the remission of the disease and CK level normalizes. Together with being a more expensive test, there is no need to monitor anti-HMGCR levels practically⁷.

No definite guideline has been available on how long a patient should be on the treatment. The first step is to discontinue statins. Unlike self-limited forms of statin myopathy, statin-induced IMNM very rarely improves spontaneously after stopping statins. Only a few reported statin-induced IMNM patients with positive anti-HMGCR antibodies spontaneously resolved². The most common therapy is prednisolone combined with at least another agent like methotrexate, azathioprine, or mycophenolate mofetil^{5,6,8}. IVIg or rituximab can be added to support the treatment but preferentially IVIG^{3,11,12}. Our case, the patient received triple therapy which comprises IVIg, systemic corticosteroids, and a non-steroidal immunosuppressant, which has been described as in the literature^{2,5}. Symptom resolution time was approximately twelve months and might take longer in females at 16 months⁹. Most of the patients responded well to immunosuppressive treatment. Symptoms monitoring is required following tapering doses of immunosuppressants due to the autoimmunity which may cause disease relapse.

Statins are contraindicated in this group of patients. To substitute the need for statins, aside from fenofibrate or ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be used and are safe in patients with anti-HMGCR myopathy⁹.

Conclusion

A patient presenting with ongoing symmetrical muscle weakness after statin discontinuation with elevated CK levels should have anti-HMG-CoA reductase antibodies checked. Together with positive anti-HMGCR and supporting evidence of MRI or muscle biopsy consistent with necrotizing myopathy, the diagnosis of statin-induced IMNM is highly suspicious. This should lead to the initiation of immunosuppressive therapy and long-term follow-up.

AUTHOR CONTRIBUTIONS

Nattanicha Chairsimaneepan: Resources; writing – original draft; writing – review and editing.

Jerapas Thongpiya: Conceptualization; resources; writing-original draft; supervision

Pitchaporn Yingchoncharoen: validation

Sakditad Saowapa: Validation

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

CONSENT

Verbal and written consent was obtained from the patient to publish this case.

References

1. Tiniakou E. Statin-Associated Autoimmune Myopathy: Current Perspectives. *Ther Clin Risk Manag* . 2020;16:483-492. Published 2020 May 27. doi:10.2147/TCRM.S197941
2. Mammen, A.L., *Statin-Associated Autoimmune Myopathy*. New England Journal of Medicine, 2016. **374** (7): p. 664-669.
3. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Immune-Mediated Necrotizing Myopathy. *Curr Rheumatol Rep* . 2018;20(4):21. Published 2018 Mar 26. doi:10.1007/s11926-018-0732-6
4. Hamann PD, Cooper RG, McHugh NJ, Chinoy H. Statin-induced necrotizing myositis - a discrete autoimmune entity within the "statin-induced myopathy spectrum". *Autoimmun Rev* . 2013;12(12):1177-1181. doi:10.1016/j.autrev.2013.07.001
5. Ramanathan S, Langguth D, Hardy TA, et al. Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. *Neurol Neuroimmunol Neuroinflamm* . 2015;2(3):e96. Published 2015 Apr 2. doi:10.1212/NXI.0000000000000096
6. Aggarwal R, Moghadam-Kia S, Lacomis D, et al. Anti-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibody in necrotizing myopathy: treatment outcomes, cancer risk, and role of autoantibody level. *Scand J Rheumatol* . 2020;49(5):405-411. doi:10.1080/03009742.2019.1672782
7. Tiniakou E, Pinal-Fernandez I, Lloyd TE, et al. More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Rheumatology (Oxford)* . 2017;56(5):787-794. doi:10.1093/rheumatology/kew470
8. Padala S, Thompson PD. Statins as a possible cause of inflammatory and necrotizing myopathies. *Atherosclerosis* . 2012;222(1):15-21. doi:10.1016/j.atherosclerosis.2011.11.005
9. Gagliardo CM, Noto D, Giammanco A, et al. Statin-induced autoimmune myositis: a proposal of an "experience-based" diagnostic algorithm from the analysis of 69 patients. *Intern Emerg Med* . 2023;18(4):1095-1107. doi:10.1007/s11739-023-03278-9
10. Werner JL, Christopher-Stine L, Ghazarian SR, et al. Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Arthritis Rheum* . 2012;64(12):4087-4093. doi:10.1002/art.34673
11. Allenbach Y, Mammen AL, Benveniste O, Stenzel W; Immune-Mediated Necrotizing Myopathies Working Group. 224th ENMC International Workshop:: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord* . 2018;28(1):87-99. doi:10.1016/j.nmd.2017.09.016
12. Meyer A, Troyanov Y, Drouin J, et al. Statin-induced anti-HMGCR myopathy: successful therapeutic strategies for corticosteroid-free remission in 55 patients. *Arthritis Res Ther* . 2020;22(1):5. Published 2020 Jan 8. doi:10.1186/s13075-019-2093-6



