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CASE REPORT

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

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Key Clinical Message

Statins can commonly cause myopathy. Most of the time, stopping the culprit drug should solve the problem. However, if the drug has been discontinued but muscle weakness continues to worsen, immune-mediated myopathy should be taken into consideration.

KEYWORDS

anti-HMGCR, atorvastatin, autoimmune, inflammatory myositis, statin

1 | 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 prevention.[1] A wide range of statin myopathy has been reported including myalgia, myopathy, myositis, or rhabdomyolysis. Immune-mediated necrotizing myopathy (IMNM) can occur as a result of statin exposure evidenced by anti-HMGCR, or anti-SRP autoantibodies which cause skeletal muscle injury.[2,3] Statin-induced IMNM is a relatively rare side effect with an incidence of 2 or 3 of every 100,000 patients taking statins.[2] Patients usually present with subacute onset with progressive symmetric proximal muscle weakness and elevated creatinine kinase level that persists even when the statin is discontinued.[1] Dysphagia occurs in approximately one-third of patients.[1,2] These findings help differentiate toxic noninflammatory effects from immune-mediated myopathy due to statins.[1] We report a case of atorvastatin-induced IMNM with positive anti-HMGCR.

2 | CASE DESCRIPTION

A 56-year-old man with a past medical history of hypertension and hyperlipidemia presented with a 4-month progressive generalized weakness. He had been on atorvastatin 40 mg daily for 3 months when his symptoms developed. He noticed the slowing of gait and increased generalized fatigue. Atorvastatin was discontinued for concern of statin-induced myopathy.

Despite stopping Atorvastatin for 4 months, his muscle weakness progressed in association with bilateral shoulder pain. He developed difficulty standing from a squatting position and a seated position. At presentation to the hospital, the patient was bed-bound; he was unable to roll on the bed without assistance. He also complained of worsening dysphagia which resulted in unintentional 60-pound weight loss. 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.

3 | METHODS

Blood chemistries were significant for elevated creatine kinase (CK) at 4050 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. The thyroid function test was normal. Further investigation to exclude idiopathic inflammatory myopathy was negative including anti-Jo-1. Table 1 summarizes the investigations. 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(Figures 1 and 2). No significant muscular fatty atrophy was observed on the MRI (Figures 3 and 4).

A muscle biopsy of his right upper thigh was performed demonstrating 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 represent necrotizing autoimmune myopathy. Regarding his clinical presentation, anti-body against HMGCR was tested, which returned positive at 139.3 CU. The patient was diagnosed with statin-induced IMNM.

4 | RESULTS

He received combination therapy with intravenous immunoglobulin (IVIG) 1 g/kg/day for 2 days, methylprednisolone intravenously 500 mg every 12 h and tapering to oral prednisone 60 mg daily, and mycophenolate mofetil titration up to 3 g daily. 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, the patient was able to walk, and had significant improvement in oropharyngeal dysfunction. He remained on mycophenolate mofetil while prednisone was tapered and subsequently discontinued.

5 | DISCUSSION

There have been many proposed mechanisms for the pathogenesis underlying the statin-induced IMNM but the true mechanism is not well understood.[2,4] It is believed that statins induce overexpression of HMG-CoA reductase in genetically susceptible patients, HLA allele

TABLE 1 Summarization of laboratory during hospitalization.

Lab	Normal range	On admission	At discharge
Chemistry panel			
ESR	0–20 mm/h	130	45
CRP	0.0–0.5 mg/dL	13.8	0.4
Creatinine kinase	26–308 IU/L	4050	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	–
Myositis profile			
MI-2 autoantibodies	Not detected	Not detected	–
PL-7 autoantibodies	Not detected	Not detected	–
PL-12 autoantibodies	Not detected	Not detected	–
Ku autoantibodies	Not detected	Not detected	–
EJ autoantibodies	Not detected	Not detected	–
OJ autoantibodies	Not detected	Not detected	–
SRP autoantibodies	Not detected	Not detected	–
JO-1 autoantibodies	<1.0 (negative)	<1.0 (negative)	–

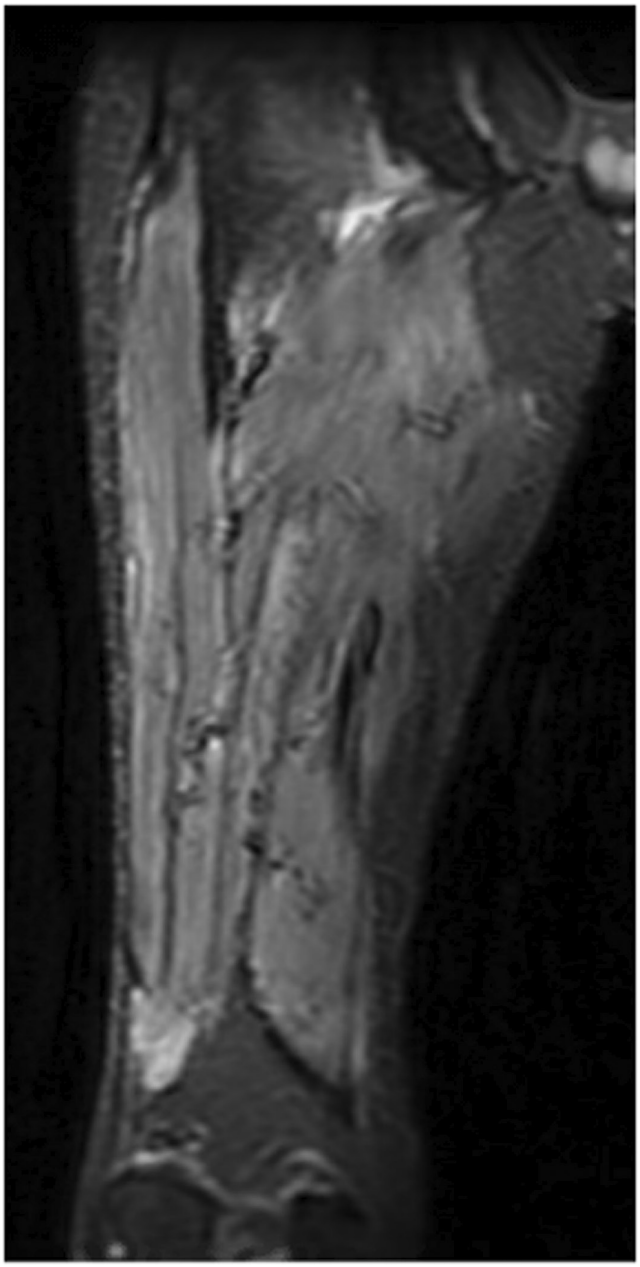

FIGURE 1 FSE STIR MRI of the right thigh in coronal view demonstrating patchy feathery STIR signal intensity seen throughout the right thigh and adductor musculature with minimal superficial perifacial STIR signal within the superficial soft tissues.

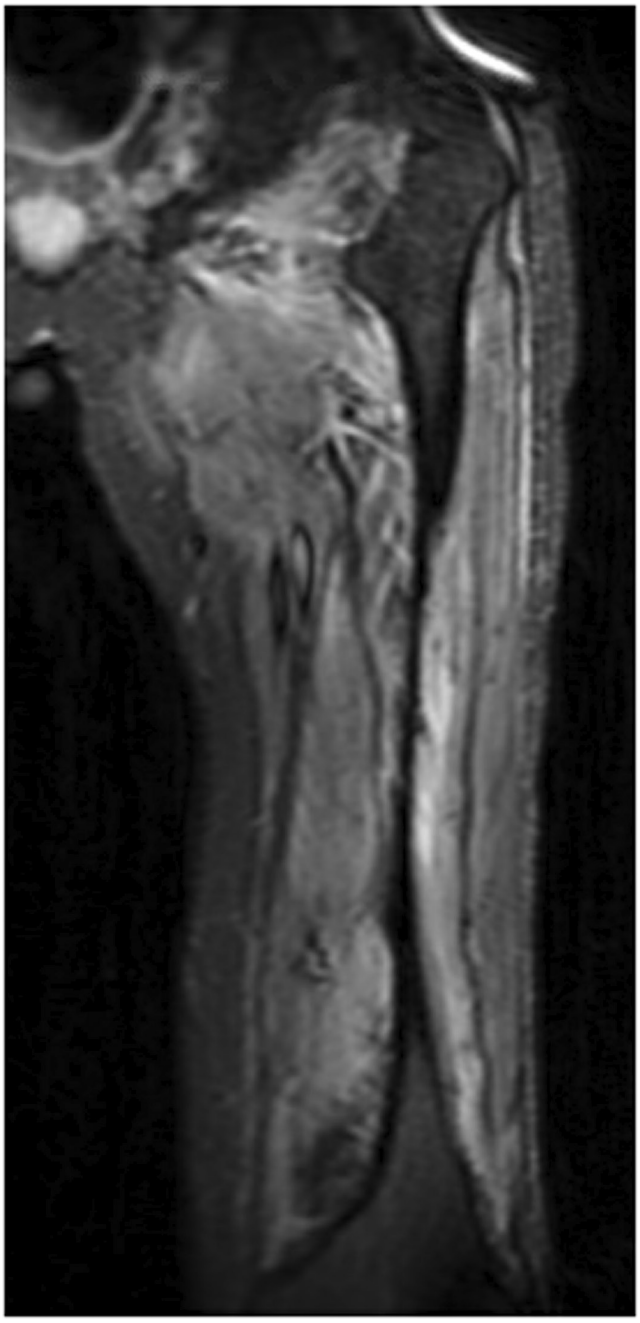

FIGURE 2 FSE STIR MRI of the left thigh in coronal view demonstrating patchy feathery STIR signal intensity seen throughout the left thigh and adductor musculature with minimal superficial perifacial STIR signal within the superficial soft tissues.

DRB1*11:01. The binding of statin to HMG-CoA reductase causes the conformational change of the protein, leading to the generation of neoantigen which is detected by antigen-presenting cells. Thus, autoimmunity is activated.[1–3]

High HMG-CoA reductase levels within regenerating muscle cells possibly continuously drive the autoimmunity process, even after statin is discontinued.[1] However, autoimmunity does not develop in most patients with HLA DRB1*11:01 who are exposed to statins, and patients with HLA allele DRB1*11:01 can also develop autoimmunity without known exposure to statins.[2,3] This has led to an assumption that other genetic risk factors and environmental triggers may play a role in the pathogenesis of statin-induced IMNM.[3]

There is no definite duration on how long after statin exposure a patient will develop IMNM—it can range from months to years.[5] Compared to other statins, atorvastatin was more frequently reported to be a cause of

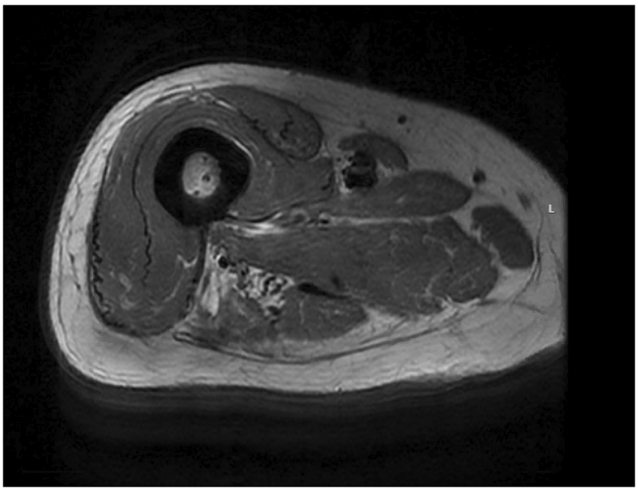

FIGURE 3 T1 MRI of the right thigh demonstrating no significant fatty atrophy seen of the musculature. Tendinous structures are grossly intact.

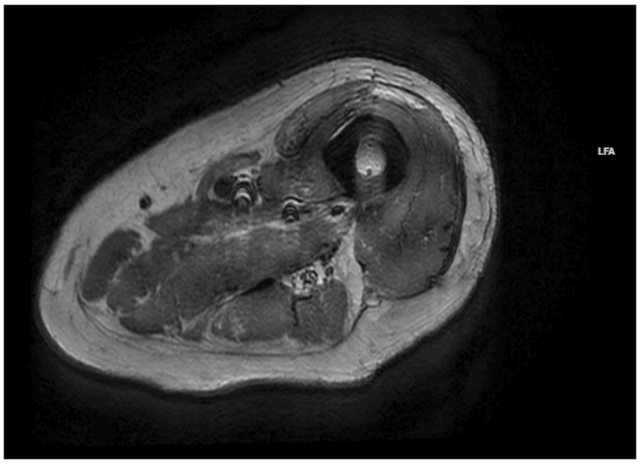

FIGURE 4 T1 MRI of the left thigh demonstrating no significant fatty atrophy seen of the musculature. Tendinous structures are grossly intact.

statin-induced IMNM, likely due to its high lipophilic property resulting in better penetration to peripheral and liver tissues.[6]

Musculoskeletal MRI and EMG can be performed 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] The presence of muscle necrosis and regeneration with sparse inflammatory infiltrates on muscle biopsy are the prominent histologic features.[2] Serum levels of the anti-HMGCR antibody are correlated with creatinine kinase and inversely associated with the degree of muscle weakness.[5,7] Interestingly, anti-HMGCR titers remain positive even in the remission of the disease and CK level normalizes. Therefore, anti-HMGCR levels are not required for monitoring disease activity.[5]

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 resolved.[2] The most common therapy is prednisolone combined with another immunosuppressive agent such as methotrexate, azathioprine, or mycophenolate mofetil.[6,8,9] IVIg or rituximab can be added to support the treatment but preferentially IVIG[3,10,11] Triple therapy given in this case, which comprises IVIg, systemic corticosteroids, and a non-steroidal immunosuppressant, has also been described in the literature.[2,8]

Symptom resolution time was approximately 12 months and might take longer in females at 16 months.[12] Most of the patients responded well to immunosuppressive treatment. Notably, the age of onset determines prognosis; younger patients are more severe and, regardless of statin use, are more recalcitrant to treatment.[1,12] The majority of patients above 60 years old (85%) and less than half of patients below 52 years old recovered full strength within 4 years. Some treated patients recover full strength while some patients' muscle weakness persists even after the muscle enzyme levels have returned to normal due to long-term undertreatment and in whom permanent damage has occurred.[2] This addresses the importance of symptom monitoring, especially following tapering doses of immunosuppressants, due to autoimmunity which may relapse.

6 | CONCLUSION

A patient presenting with unrelenting symmetrical muscle weakness after statin discontinuation with elevated CK levels should be investigated for immune-mediated myopathy. MRI, muscle biopsy, and anti-HMG-CoA reductase antibodies are helpful tools in reaching the diagnosis of statin-induced IMNM. Immunosuppressive therapy must be adequately initiated once the diagnosis is concluded to prevent permanent muscle damage, and a long-term follow-up is required for safe medication tapering.

AUTHOR CONTRIBUTIONS

Nattanicha Chaisrimaneepan: Validation; visualization; writing – original draft; writing – review and editing. **Jerapas Thongpiya:** Resources; validation; visualization; writing – original draft. **Pitchaporn Yingchoncharoen:** Visualization. **Sakditad Saowapa:** Validation.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data underlying the results are available as part of the article and no additional source data are required.

CONSENT

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

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REFERENCES

1. Tiniakou E. Statin-associated autoimmune myopathy: current perspectives. *Therap Clin Risk Manag*. 2020;16:483-492. Published 2020 May 27. doi:10.2147/TCRM.S197941
2. Mammen AL. Statin-associated autoimmune myopathy. *New Eng J Med*. 2016;374(7):664-669. doi:10.1056/NEJMra1515161
3. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Immune-mediated necrotizing myopathy. *Curr Rheumatol Rep*. 2018;20(4) Published 2018 Mar 26:21. 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. 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
6. 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. *Internal Emerg Med*. 2023;18(4):1095-1107. doi:10.1007/s11739-023-03278-9
7. 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
8. 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
9. 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
10. 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. *Neuromuscular Disorders*. 2018;28(1):87-99. doi:10.1016/j.nmd.2017.09.016
11. 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
12. 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

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