Severe Proximal Muscle Weakness Revealing Statin-Associated Autoimmune Necrotizing Myopathy

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Immune-mediated necrotizing myopathy (IMNM) is a rare autoimmune myopathy characterized by severe proximal muscle weakness and elevated creatine kinase, often associated with statin exposure and persisting despite discontinuation of the drug. We present the case of a 65-year-old male with hypertension, diabetes, and hyperlipidemia who developed progressive bilateral lower extremity weakness, resulting in functional decline and inability to ambulate. Initial evaluation excluded acute infarct, spinal cord compression, and metabolic causes. Markedly elevated creatine kinase levels and proximal greater than distal weakness prompted further neuromuscular workup. Muscle biopsy revealed necrotizing myopathy, and serology confirmed a positive anti-HMG-CoA reductase antibody, establishing the diagnosis of IMNM. The patient was initiated on immunosuppressive therapy.

This case underscores the importance of considering IMNM in statin-exposed patients presenting with persistent or progressive weakness. Early recognition and prompt initiation of therapy with corticosteroids, IVIG, and immunosuppressants are critical, as delayed treatment is frequently associated with incomplete recovery. Clinicians should maintain vigilance for this underrecognized complication of statin use, as timely intervention can prevent irreversible disability and improve functional outcomes.

Immune-mediated necrotizing myopathy (IMNM)

Immune-mediated necrotizing myopathy (IMNM) is a rare autoimmune muscle disease characterized by severe muscle weakness, elevated muscle enzymes (such as creatine kinase), and histologic evidence of muscle fiber necrosis with minimal inflammation. Unlike other inflammatory myopathies, IMNM often presents with rapidly progressive, symmetric, proximal muscle weakness that can lead to significant disability, including loss of ambulation if untreated.

A key feature of IMNM is its association with specific autoantibodies, most notably:

- Anti-HMG-CoA reductase (HMGCR) antibodies – strongly linked to prior statin exposure.

- Anti-SRP (signal recognition particle) antibodies – often associated with severe disease and poorer prognosis.

Even after discontinuation of a statin, weakness may persist because the condition becomes self-sustaining through immune activation. Diagnosis typically relies on a combination of clinical presentation, elevated CK levels, autoantibody testing, electromyography (EMG), and muscle biopsy showing necrosis.

Treatment usually requires aggressive immunosuppression, including corticosteroids, intravenous immunoglobulin (IVIG), and additional immunosuppressive agents (e.g., methotrexate, azathioprine, or rituximab). Despite therapy, recovery is often incomplete, especially when treatment is delayed, highlighting the importance of early recognition and intervention.

Case

A 65-year-old male with hypertension, hyperlipidemia, and diabetes presented with progressive bilateral lower extremity weakness and fatigue beginning in late 2024, ultimately resulting in inability to ambulate. Initial evaluation ruled out stroke, spinal cord pathology, and metabolic causes. Lumbar puncture initially suggested cryptococcal infection, but repeat testing was negative. Infectious workup revealed HHV-6 positivity, for which the patient received antiviral therapy. Neurology and rheumatology were consulted, and MRI of the bilateral lower extremities demonstrated diffuse myositis. Muscle biopsy and myositis panel were pursued, with serology positive for anti-HMG-CoA reductase antibody, consistent with immune-mediated necrotizing myopathy (IMNM). The patient was treated with IVIG, high-dose corticosteroids, and mycophenolate, with clinical stabilization and discharge to rehabilitation on a tapering steroid regimen. This case highlights the diagnostic complexity of IMNM and the importance of early recognition and antibody testing in statin-exposed patients presenting with persistent, progressive weakness.

Hospital Course:

- Hospitalized for 18 days.
- CPK trended daily; IV fluids given for rhabdomyolysis risk.
- Neurology and Rheumatology consulted.
- Differential included myopathy, polyneuropathy, myelopathy, radiculopathy.
- Lumbar puncture and CSF studies done (false positive cryptococcal antigen considered).
- Rheumatology ordered extended myositis panel, ANA/ANCA, ENA panel, HMG-CoA reductase antibody.
- Imaging: MRI lower extremities → diffuse myositis.

Diagnostic Confirmation:

- Muscle biopsy performed → consistent with necrotizing myopathy.
- Anti-HMG-CoA reductase antibody positive, confirming immune-mediated necrotizing myopathy (IMNM).

Treatment:

- Started on IVIG ×5 days, high-dose Solumedrol (500 mg ×3 days → 60 mg IV daily), and Cellcept (mycophenolate mofetil).
- Rituximab deferred initially.
- Ongoing monthly IVIG planned.

Discharge & Prognosis:

- Discharged to subacute rehab facility.
- Takeaway: IMNM should be suspected in statin-exposed patients with persistent proximal weakness and high CK.
- Prognosis: less than 50% of patients regain full baseline strength within 1 year; recovery often incomplete, especially with delayed recognition.

Results

Figure 1. CT head demonstrating moderate white matter small vessel ischemic changes and bilateral gangliocapsular lacunar infarcts, where the possibility of a small acute infarct cannot be excluded. MRI revealed small foci of T2 and FLAIR hyperintensities in the bilateral basal ganglia and left cerebellum, consistent with chronic lacunar infarcts.

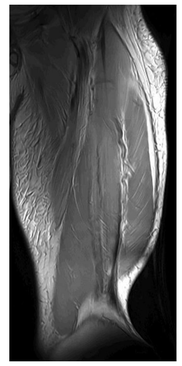

Figure 2. Diffuse **myositis** is demonstrated. No gross muscle atrophy is delineated. Diffuse **edema** is present throughout the subcutaneous fat.

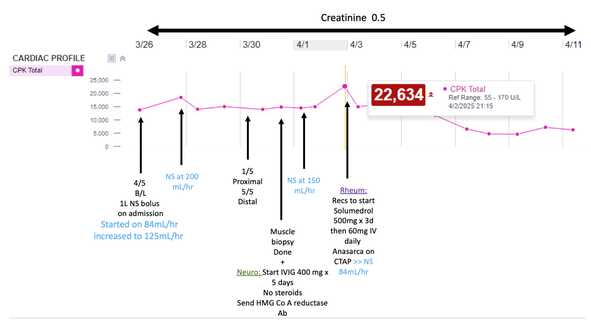

Figure 3. Trend of creatine phosphokinase (CPK) levels.

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HMGCR Ab (IgG)                    281 H          CU  <20


3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase
(HMGCR) Ab is associated with necrotizing myopathy
and is often found with the use of statin
medications. Rarely, HMGCR Ab associated myositis
has also been seen in patients ingesting mushrooms
and other foods.



TISSUE SUBMITTED:
 1. MUSCLE BIOPSY, LEFT, GASTROCNEMIUS
 2. MUSCLE BIOPSY, RIGHT, GASTROCNEMIUS


FINAL DIAGNOSIS:

1. AND 2. LEFT AND RIGHT GASTROCNEMIUS, MUSCLE BIOPSIES:
-IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM), COMPATIBLE WITH
STATIN-ASSOCIATED AUTOIMMUNE MYOPATHY.
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- This case illustrates the diagnostic and therapeutic challenges of statin-associated immune-mediated necrotizing myopathy (IMNM). Progressive proximal weakness with persistently elevated creatine kinase despite statin discontinuation should prompt early antibody testing and consideration of muscle biopsy. Timely initiation of aggressive immunosuppression—including corticosteroids, IVIG, and steroid-sparing agents—is essential to prevent irreversible disability, though complete recovery is not always achieved.
- Clinicians should maintain vigilance for IMNM in statin-exposed patients and recognize the potential for misleading ancillary tests. Early recognition, multidisciplinary management, and a high index of suspicion remain critical to improving patient outcomes.

Special note — Discordant cryptococcal antigen in this case

- CSF analysis revealed high opening pressure and a positive cryptococcal antigen titer, initially suggestive of cryptococcal meningitis. However, serum cryptococcal antigen and HIV serology were negative. Literature describes false-positive serum cryptococcal antigen results in conditions such as SLE, RA, and in cases of insufficient sample dilution, most often at low titers.
- Given the discordant findings, the plan included repeat LP with CSF cryptococcal antigen testing, repeat serologies, and confirmatory evaluation by the microbiology laboratory. Ultimately, results supported a false-positive interpretation, highlighting the need for confirmatory testing and correlation with the clinical picture before committing to antifungal therapy.

- Somagutta MKR, et al. Statin-induced necrotizing autoimmune myopathy. *Cureus*. 2022. PMID: 35664693.
- Khoo T, et al. Anti-HMGCR immune-mediated necrotising myopathy: A narrative review. *Autoimmun Rev.*2023;22(12):103347.
- Selva-O'Callaghan A, et al. Statin-induced myalgia and myositis: an update on pathogenesis and clinical recommendations. *Expert Rev Clin Immunol*. 2018;14(3):215-224.
- Abdalla MS, et al. Statin-induced IMNM: clinical characteristics and disease course. *J Med Cases*. 2023;14(6):237-243.
- Caughey GE, et al. Association of statin exposure with histologically confirmed idiopathic inflammatory myositis. *JAMA Intern Med*. 2018;178(9):1224-1230.
- Chen WY, et al. False positive detection of serum cryptococcal antigens due to insufficient sample dilution: A case series. *World J Clin Cases*. 2023;11(8):1837-1844.
- Harrington KRV, et al. Evaluation of a cryptococcal antigen lateral flow assay and false-positive test results. *Open Forum Infect Dis*. 2021;8(6):ofab123.
- Wang X, et al. Diagnostic accuracy of low CrAg titers in HIV-negative patients: prevalence of false positives. *IMA Fungus*. 2020;11(1):12.