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Case Report

Delayed Recognition of Statin-Induced Immune-Mediated Necrotizing Myopathy in an Older Adult

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Abstract: Statins, widely used for cardiovascular prevention, may rarely induce immune-mediated necrotizing myopathy (IMNM), a severe and potentially disabling condition. We describe a 79-year-old woman with hypertension, dyslipidemia, and obesity who developed progressive proximal weakness and persistent creatine kinase (CPK) elevation after statin discontinuation. Infectious, neoplasms and systemic autoimmune causes were excluded. Strong anti-HMGCR antibody positivity, combined with magnetic resonance imaging (MRI) and electromyographic evidence of inflammatory necrosis, confirmed statin-associated IMNM. The patient improved with corticosteroids, intravenous immunoglobulin (IGIV), and methotrexate. This case highlights the importance of recognizing IMNM in statin users with unexplained weakness and sustained CPK elevation, as early immunosuppressive therapy can prevent long-term disability.

Keywords: Statins; Acute Inflammatory Polyneuropathy; Aged.

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1. Introduction

Statins are the cornerstone of cardiovascular prevention, particularly in the elderly. Muscle-related side effects are common but usually benign. However, they may mask serious disorders such as statin-induced immune-mediated necrotizing myopathy (IMNM), a rare autoimmune disease often underdiagnosed due to its insidious onset and nonspecific symptoms, often misattributed to aging, deconditioning, polypharmacy, or comorbidities, which mask baseline muscle impairment and delay recognition of clinical decline [1].

Creatine kinase (CK) measurement is a valuable tool in the evaluation of muscle complaints but lacks specificity in older adults, as elevations may result from trauma, immobility, renal impairment, or drug interactions. Moreover, CK levels do not always correlate with clinical severity in IMNM. A multimodal diagnostic approach, including antibody testing, imaging, and electromyography, is essential to ensure timely treatment [2].

We report a case of statin-induced IMNM in a 79-year-old woman, illustrating the diagnostic challenges and management strategies in elderly patients with comorbidities.

2. Case Report

A 79-year-old woman cognitively preserved and functionally independent, with mobility limitations secondary to osteoarticular disease, presented with hypoxemic respiratory failure secondary to a viral respiratory infection. Her history included hypertension (treated with angiotensin II receptor blockers and calcium channel blockers), dyslipidemia

(treated with atorvastatin 40 mg for about 10 years), obesity (body mass index 35kg/m2), and cerebrovascular disease. Initial workup revealed thyroid-stimulating hormone (TSH) level of 0.01 μIU/mL and free T4 of 3.8 ng/dL. Neck ultrasound confirmed multinodular goiter, and she was diagnosed with primary hyperthyroidism, managed with propranolol and methimazole.

After resolution of infection, routine testing showed hepatocellular enzyme elevation and markedly elevated CK. Atorvastatin was discontinued, and intravenous fluids were started. Despite this, CK and myoglobin levels continued to rise. Methimazole was stopped as a precaution, but CK remained elevated (Table I). On detailed questioning, the patient reported several months of progressive proximal lower limb myalgias and weakness, previously attributed to osteoarticular disease. Neurological examination revealed proximal weakness (Medical Research Council [MRC] grade 4/5 in the quadriceps femoris muscles and 3/5 in the thigh adductors), with normal strength in the remaining muscle groups. She was still able to ambulate with the aid of a walker.

Table 1: Longitudinal trends in serum enzyme levels over the course of disease progression and treatment.

Day	Creatine Phosphokinase (UI/L)	Myoglobin (ng/mL)	Aspartate Aminotransferase (UI/L)	Alanine Aminotransferase (UI/L)	Interventions
Day 0	1987	-	106	148	Resolution of infection
Day 2	3396	1266	159	187	Statin therapy discontinued
Day 5	3734	1310	151	205	-
Day 6	4176	1587	158	213	-
Day 7	4747	1400	164	210	Methimazole discontinued
Day 8	5418	-	184	236	Methimazole therapy resumed
Day 12	6787	1535	195	288	-
Day 15	10290	2371	305	374	Initiated 3 boluses of intravenous methylprednisolone
Day 16	9792	-	300	370	Underwent MRI
Day 18	10522	2587	345	438	-
Day 20	8673	1641	307	445	-
Day 22	3636	1438	173	405	Initiated prednisolone and trimethoprim-sulfamethoxazole
Day 25	3936	2568	201	373	-
Day 27	3712	2186	202	394	-
Day 29	4094	2844	215	410	-
Day 32	4474	3006	232	444	-
Day 35	5986	2912	410	527	-
Day 36	4418	-	378	455	-
Day 39	4596	-	447	537	-
Day 42	2632	-	402	592	-
Day 44	2619	-	446	698	-
Day 46	2141	-	274	489	-
Day 48	3308	3107	270	438	-

Day 50	1751	-	207	360	-
Day 55	1770	1768	223	358	Initiated methotrexate therapy
Day 76	940	944	105	166	-
Reference range	<149	14.3-65.8	10 - 31	10 – 31	

She denied trauma, skin changes, fever, or dysphagia. Extensive investigation excluded neoplasia, infection, and systemic autoimmune disease. CT scans, mammography and endoscopy were unremarkable. Viral and bacterial serologies were negative. Autoimmune panel (anti-nuclear, anti-mitochondrial and liver kidney microsomal antibodies) was negative; complement and immunoglobulins were normal. She continued to experience muscle weakness despite achieving a euthyroid state.

Myositis antibody panel was non-reactive, but anti-HMGCR antibodies were strongly positive (>200 U/mL). Aldolase was elevated (17.3 U/L). MRI of the thighs revealed hyperintensity on fluid-sensitive sequences in the adductor, biceps femoris, and semimembranosus muscles, consistent with active myositis (Figures 1 to 3). Electromyography of the lower limbs demonstrated some fibrillation potentials, positive sharp waves, and complex repetitive discharges in the biceps femoris and medial gastrocnemius muscles, suggestive of necrotic and inflammatory changes.

Figure 1: A. Longitudinal section of the lower limb. B. Transverse section of the lower limb. T1-weight MRI images showed no abnormalities compared to normal muscle signal.

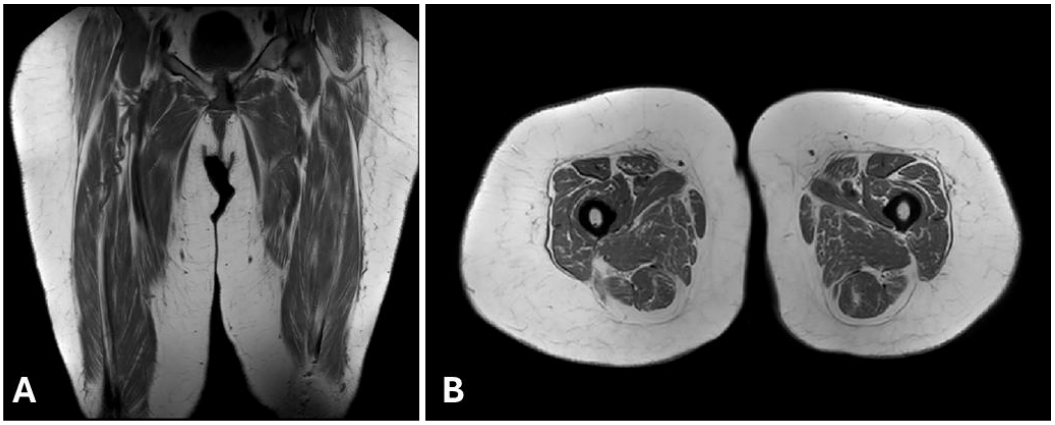


Figure 2: A. Longitudinal section of the lower limb. B. Transverse section of the lower limb. Hyperintense signal on T2-weight MRI sequences consistent with inflammatory edema.

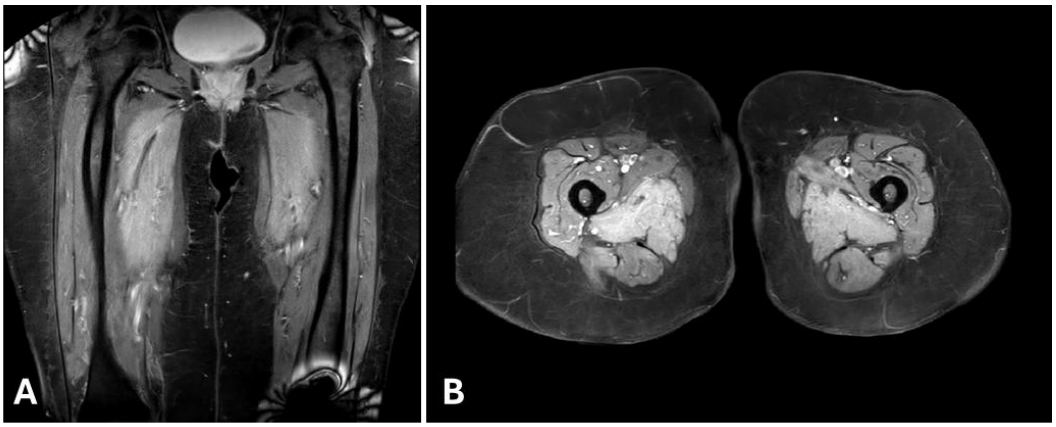
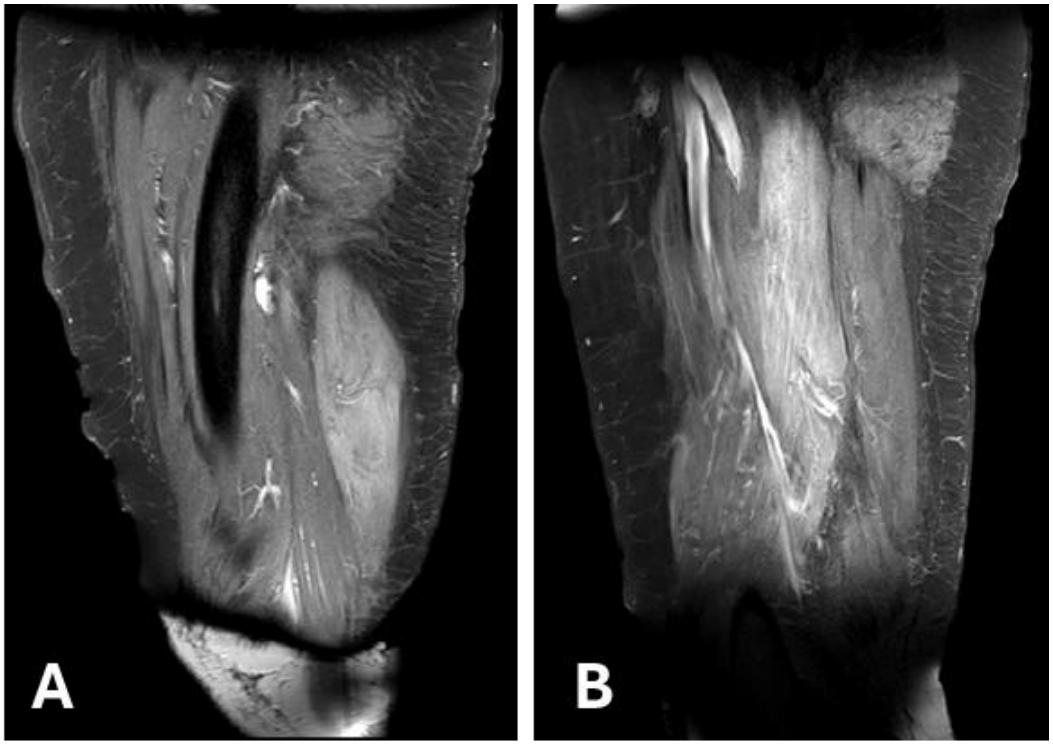


Figure 3: Longitudinal section of the lower limb showing superficial muscles (A) and deep muscles. B. Gadolinium enhancement indicates active inflammation.



A diagnosis of statin-induced IMNM was confirmed. The patient started on IV methylprednisolone pulses, transitioned to high-dose oral prednisone (1mg/kg), and treated with IVIG (2 g/kg administered over 5 days). Initial improvement was followed by relapses during steroid taper. Combination therapy with prednisone (80 mg/day), methotrexate (10 mg in the first week, 15 mg in the second week, and a further 15 mg after one month due to lack of clinical improvement) and IVIG achieved stabilization. A structured rehabilitation program improved functional capacity.

3. Discussion

Idiopathic inflammatory myopathies (IIM) are rare autoimmune muscle diseases with a prevalence of 9–14 per 100,000 individuals. IMNM, one of the main subtypes, is characterized by myofiber necrosis with minimal inflammatory infiltrate and classified into anti-SRP, anti-HMGCR, and seronegative forms [3,4]. Statin exposure is strongly associated with anti-HMGCR IMNM. Although rare (2–3 cases per 100,000 statin users), it predominantly affects women over 50 years-old. Pathogenesis involves immune loss of tolerance to HMG-CoA reductase, the target enzyme of statins, with subsequent T-cell–mediated damage and autoantibody production. Notably, muscle damage often progresses despite statin discontinuation, indicating that IMNM reflects an active immune process rather than a reversible drug-induced toxicity [5].

Clinically, IMNM manifests with progressive symmetrical proximal weakness, often severe and disabling. CK levels are typically elevated, though they may not parallel weakness. Dysphagia and respiratory involvement occur in advanced cases [4,5]. In elderly patients, weakness is often misattributed to sarcopenia, comorbidities, or drug effects. Hyperthyroidism initially confound assessment in this case, yet CK levels persisted after correction [7]. Additional confounders such as beta-blockers, fibrates, antiretrovirals, or angiotensin receptor blockers may raise CK asymptomatically; however, the recently introduced propranolol and metamizole were discontinued without effect, and no association with IMNM has been reported [2].

Anti-HMGCR antibodies provide high diagnostic sensitivity and specificity and may obviate the need for biopsy when clinical and imaging findings are consistent. Even though muscle biopsy has traditionally been considered the diagnostic gold standard, the combination of proximal muscle weakness, marked CPK elevation, prior statin exposure, and anti-HMGCR antibody positivity was deemed sufficient to support the diagnosis [8]. MRI and electromyography further supported the diagnosis, while age-appropriate cancer screening was performed due to a reported, though less consistent, association between anti-HMGCR myopathy and malignancy. Given patient advanced age and comorbidities, an invasive muscle biopsy was avoided, as the results were unlikely to influence the therapeutic approach. Ongoing clinical follow-up during the first years after diagnosis was considered appropriate, as no formal surveillance guidelines exist [9].

Management requires immunosuppression, as statin withdrawal alone is insufficient due to persistent antibody production. Corticosteroids, often combined with IVIG, remain first-line, while early introduction of steroid-sparing agents- such as azathioprine, methotrexate, mycophenolate, tacrolimus, or rituximab, is advised in elderly or comorbid patients to reduce relapses and minimize metabolic and cardiovascular risks. Despite treatment, many patients fail to normalize CK or fully recover strength, reflecting irreversible fatty replacement of necrotic muscle fibers. Rehabilitation is crucial for long-term outcomes [5,6]. Prognosis varies younger patients and those treated early achieve better recovery. In older adults, refractory disease and treatment-related complications are common, with morbidity and mortality rates two to three times higher than in the general population [6].

4. Conclusion

This case highlights the diagnostic complexity of statin-induced IMNM in elderly patients with comorbidities. Persistent CK elevation and proximal weakness in statin-exposed individuals should prompt evaluation for IMNM, especially with positive anti-HMGCR antibodies. Early recognition and immunosuppressive therapy are critical to preventing irreversible disability. A multimodal approach, including clinical evaluation, serology, imaging, electromyography, and rehabilitation, remains essential. Clinicians must remain vigilant for this rare but disabling adverse effect of statins, ensuring individualized management strategies to optimize outcomes.

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Research Ethics Committee Approval: The patient provided written informed consent for participation, and the study was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki.

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Conflicts of Interest: All other authors declare no conflicts of interest.

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