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Statin-Induced Immune-Mediated Necrotizing Myopathy Does Not Always Present With Immediate or Severe Symptoms

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Dear Editor,

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibitors that can cause myalgia or muscle weakness due to their myotoxic effect. These symptoms usually occur within a few weeks of statin initiation.[1-3] Immune-mediated necrotizing myopathy (IMNM) is characterized by severe muscle weakness and marked elevation of creatine kinase (CK), with anti-signal recognition particle or anti-HMGCR antibodies in 88%–90% of patients.[4] Some IMNM subtypes, particularly anti-HMGCR-positive IMNM, can be triggered by statins.[4] We report a case of statin-induced IMNM with an unusually mild presentation and delayed symptom onset that responded well to steroid monotherapy.

A 68-year-old male presented with a 1.5-year history of proximal weakness of both upper and lower extremities and with CK elevated to 657 U/L. He had been taking rosuvastatin at 5 mg daily for 3 years due to hyperlipidemia. Due to muscle weakness, he stopped the medication 4 months before visiting our hospital, but this did not improve his muscle weakness. A neurological examination revealed slight weakness in shoulder abduction (Medical Research Council [MRC] grade 4+) and hip flexion (MRC grade 4) but no other abnormal findings, including for the sensory system, deep tendon reflexes, and coordination. Serum CK was elevated to 440 U/L (normal range <190 U/L), but the findings of other routine laboratory tests were normal, including of thyroid function. Autoimmune profiling for various antibodies was negative. Anti-HMGCR antibody measured by a line immunoassay (Euroimmun, Lübeck, Germany) was strongly positive at 106 U (positive >10 U). Nerve conduction studies were normal and needle electromyography revealed polyphasic motor-unit potentials with small amplitudes and short durations, along with positive sharp waves for the right biceps and rectus femoris muscles. Muscle magnetic resonance imaging revealed that most of the bilateral thigh muscles showed diffuse hyperintense T2-weighted signals (Fig. 1A-D). A muscle biopsy of the left vastus lateralis revealed variation in the fiber size, increased acid phosphatase activity between muscle fibers, and the absence of endomysial inflammation, which increased the probability of IMNM (Fig. 1E and F).[5] No necrotic or regenerating muscle fibers were observed. He was diagnosed with statin-induced IMNM and was treated with intravenous methylprednisolone at 1 g daily for 3 days. After 1 month, the proximal weakness in both upper and lower extremities had almost completely disappeared (MRC grade 5-).

Statin-induced myotoxicity (SIM) usually occurs 4–12 weeks after treatment initiation,[2,3] but its onset can be delayed by months or years in some patients. A previous study involving 45 SIM patients found that the onset delay was highly variable and can be substantial, ranging from 0.25 to 48 months (mean 6.3 months).[6] Among the SIM phenotypes, statin-induced IMNM may take longer to develop. A recent study of statin-induced IMNM found a maximum time to onset of 10 years (mean 3 years).[7] Our patient also had a fairly long period of 1.5 years from the initiation of a statin to the onset of IMNM. The misconception that

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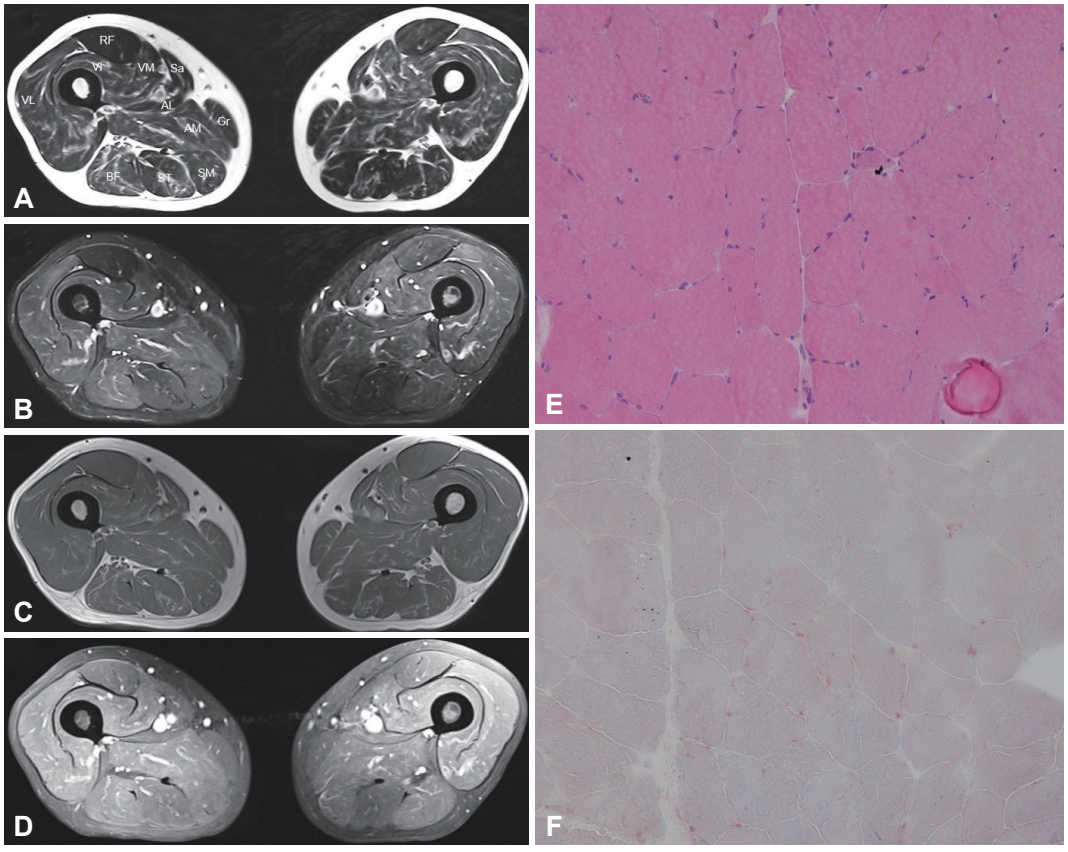

Fig. 1. Findings of axial muscle magnetic resonance imaging of the thighs (A-D) and of a muscle biopsy (E and F). Axial T2-weighted Dixon in-phase (A) and water-only (B) images show that most of the bilateral thigh muscles had diffuse hyperintense T2-weighted signals with relative sparing of the right RF, right AL, bilateral Gr, left BF, and left ST. At the same level, intramuscular signal abnormalities were not seen in the axial unenhanced T1-weighted turbo spin-echo image (C). Thigh muscles with T2-weighted signal changes (A and B) also showed subtle enhancement in an axial fat-saturated gadolinium-enhanced T1-weighted image (D). Microscopic image with hematoxylin and eosin staining (×200) shows slight variations in fiber size but the absence of endomysial inflammation and necrotic/regenerating fibers (E). Acid phosphatase staining (×100) revealed increased activity of acid phosphatase between muscle fibers (red color), indicating the possibility of immune-mediated necrotizing myopathy (F). AL, adductor longus; AM, adductor magnus; BF, biceps femoris; Gr, gracilis; RF, rectus femoris; Sa, sartorius; SM, semimembranosus; ST, semitendinosus; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis.

SIM only occurs soon after statin initiation may lead to a delayed or missed diagnosis, and so clinicians should be aware that SIM can also develop in patients who have tolerated statins well for a long time.

SIM can present with four clinical phenotypes: myalgia and/or slight hyperCKemia, self-limited toxic statin myopathy, rhabdomyolysis, and statin-induced IMNM.[1] The first three phenotypes usually improve after statin discontinuation, while statin-induced IMNM may persist or even progress.[1] For this reason, one study suggested considering a diagnosis of statin-induced IMNM if symptoms of SIM do not improve within 2 weeks of statin discontinuation.[1] In the present case, the patient's symptoms persisted even at 4 months after statin discontinuation. This shows that drug discontinuation might not always be effective (depending on the phenotype of SIM), and so it should not be used as a criterion for excluding statin as a causative agent for myotoxicity.

Statin-induced IMNM typically manifests as severe proximal weakness and very high CK levels of 6,000 U/L or more on average (range 2,000−20,000 U/L).[1,7-9] However, our patient only showed slight weakness, and CK was only slightly elevated at 657 U/L. The present case indicates that the absence of necrotic and regenerating fibers in a muscle biopsy may reflect slight CK elevation, which in turn may lead to mild symptoms. Some recent studies have found asymptomatic statin-induced IMNM in which patients have elevated CK but normal muscle strength.[10] All of these patients were positive for anti-HMGCR antibodies. Therefore, statin-induced IMNM may be a clinically heterogeneous condition with either a severe or mild clinical presentation.

Our case demonstrates that statin-induced IMNM may occur even after years of statin therapy, have a mild clinical manifestation, and persist even after statin discontinuation. Therefore, it is important to consider a diagnosis of statin-induced

IMNM even in patients with delayed onset and mild symptoms.

Ethics Statement

Written informed consent was obtained from the patient.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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