Commentary

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The differential diagnosis for a necrotizing myopathy includes inherited muscle disease and acquired diseases such as toxic myopathies, hypothyroid myopathy, paraneoplastic myopathy, and the autoimmune myopathies. The most common autoimmune myopathies presenting with a necrotizing muscle biopsy are those associated with anti–signal recognition particle (anti-SRP)[2] or anti–3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR) autoantibodies, the latter frequently occurring in the context of statin exposure. In this case, the patient's age, previously normal serum creatine kinase (CK) activities, and rapidly progressive weakness argued against an inherited myopathy. After hypothyroidism and malignancy were excluded, statin myopathy or an autoimmune myopathy were the most likely causes of this patient's condition.

In the acute setting, physical exam, serum CK activities, electromyography, and muscle biopsy may be identical in patients with statin myopathy and a necrotizing autoimmune myopathy. When patients have relatively mild muscle disease, it may be reasonable to discontinue the statin and wait several weeks to see if serum CK activities and strength begin to improve. However, when patients have severe or rapidly progressive weakness, delaying immunosuppressive treatment may not be appropriate.

Although it was not available at the time the patient presented, this case highlights the utility of myositis autoantibody testing. In this clinical context, the presence of either anti-SRP or anti-HMGCR autoantibodies would confirm the diagnosis of autoimmune muscle disease and prompt the immediate initiation of immunosuppressive therapy even if the weakness had been less severe.

Because this patient had anti-HMGCR autoantibodies and statin exposure, the diagnosis was statin-associated immune-mediated necrotizing myopathy (IMNM). This form of autoimmune muscle disease may occur at any time following statin exposure and requires discontinuation of the statin and initiation of immunosuppressive therapy. Although this patient responded to steroids and azathioprine, many patients with statin-associated IMNM require more aggressive therapy, often including intravenous immunoglobulins. Furthermore, the majority of these patients are unable to tolerate complete tapering of immunosuppressive drugs and require chronic therapy.

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[2] Nonstandard abbreviations: SRP, signal recognition particle; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; CK, creatine kinase; IMNM, immune-mediated necrotizing myopathy.

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Commentary

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Statins [3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) inhibitors] have improved the treatment of hypercholesterolemia and associated cardiovascular diseases. However, adverse effects such as myopathy (myalgia, immune-mediated and rhabdomyolysis), hepatotoxicity, and peripheral neuropathy have been reported.

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Advanced age, low body mass index, diabetes mellitus, untreated hypothyroidism, renal or hepatic disease, *SLCO1B1* (solute carrier organic anion transporter family, member 1B1) polymorphisms, statin dose and duration, and interacting medications are associated with increased risk for statin-induced myopathy. Statin-induced immune-mediated necrotizing myopathy is characterized by persistently increased or rising creatine kinase after statin withdrawal, muscle weakness persisting for 12 weeks or longer after statin cessation, electromyogram showing muscle irritability, magnetic resonance imaging showing muscle edema, or a muscle biopsy showing necrotizing myopathy in the absence of significant inflammation. Although guidelines to monitor for statin-induced myopathy have been proposed, diagnosis remains challenging owing to variants of statin-induced myopathy, other causes of myopathy, variable response to statin cessation, varying risk associated with the SLCO1B1*5 allele, and lack of specific diagnostic tests.

Antibodies against HMGCR, the pharmacologic targets of statins, are mainly associated with statin-induced immune-mediated necrotizing myopathy and, less commonly, in statin-unexposed patients. The presence of HMGCR antibodies appears to be helpful in both differential diagnosis and management as reported in this case. Whereas certain statin-induced myopathies may be self-limiting, myopathy associated with HMGCR antibodies may not resolve with discontinuation of the statin and may require immunosuppressive therapy. It may also be helpful to exclude a diagnosis of autoimmune myositis characterized by shared overlapping clinical features and diverse autoantibodies. Nevertheless, a muscle biopsy is necessary to determine the actual pathology and exclude etiologies such as dystrophy and metabolic or inflammatory autoimmune myopathies. This case highlights the importance of understanding the spectrum of statin-induced myopathies, their mimics, and the emerging diagnostic relevance of HMGCR antibodies in screening and monitoring at-risk patients on statin treatment.

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