CASE DESCRIPTION

A 62-year-old woman noticed muscle weakness in the right leg, which was followed a few months later by weakness in the left leg. Over a 6-month period, the muscle weakness progressed to the upper limbs. One year after onset, the patient was referred to a neurologist with a suspected diagnosis of amyotrophic lateral sclerosis. She was taking atorvastatin 40 mg (started approximately 6 years earlier) and l-thyroxine 125 μg (for hypothyroidism after nuclide therapy for Graves disease). Clinical examination revealed a proximal paresis in the arms and legs. Creatine kinase (CK) activity was 7925 U/L (reference interval <145 U/L). Electromyography showed myogenic changes (small and polyphasic motor units). A toxic statin myopathy was considered, although the time span between the start of the statin and onset of the symptoms was long. Late-onset Pompe (glycogen storage) disease was excluded by α-glucosidase activity testing. Further laboratory testing was unremarkable. A biopsy of the right quadriceps muscle was performed and revealed polygonal muscle fibers of varying diameter (and an increase of internal nuclei). There was some evidence of endomysial fibrosis without inflammatory infiltration. Individual muscle fibers showed necrosis with myocyte phagocytosis and without HLA-ABC upregulation.

PATIENT FOLLOW-UP

The muscle weakness was progressive and also affected distal hand muscles and bulbar muscles. The use of statins was discontinued, and high-dose intravenous methylprednisolone was given, followed by oral tapering. Ten days later, there was only minor improvement of the muscle weakness, and azathioprine 100 mg per day was added. Ezetimibe and fenofibrate were started for hypercholesterolemia. The weakness improved, CK activity decreased, and oral methylprednisolone was stopped. The patient fully recovered and was stable at 1-year follow-up after discontinuation of azathioprine. The CK activity normalized.

Quantification of antibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) was not available at the time the patient presented but was performed later (with approval of the local ethics committee) by use of ELISA (Quanta Lite HMGCR, Inova Diagnostics) on 3 banked serum samples obtained (a) before onset of symptoms, (b) when the patient presented with muscle weakness, and (c) after treatment. Anti-HMGCR antibodies were absent before symptoms and increased to 100 U (cutoff 20 U) when the patient presented with symptoms. The antibodies decreased to 0.8 U after immunosuppressive treatment. Fig. 1 shows a timeline of symptoms, treatment, CK, and anti-HMGCR antibodies.

DISCUSSION

Necrotizing myopathy can have a wide differential diagnosis: infectious (e.g., HIV), paraneoplastic, toxic (alcohol and fibrates, HMGCR inhibitors such as statin), genetic disorder, or immune mediated (1, 2). Several antibodies are commonly associated with immune-mediated necrotizing myopathy: antisignal recognition protein and anti-HMGCR antibodies (in statin-exposed patients). In rare cases, antisynthetase antibodies (anti-Jo-1 being the most common) have been associated with necrotizing myopathy (classically, they are associated with inflammatory myopathy) (1). Necrotizing myopathy is also associated with connective tissue diseases, such as systemic sclerosis, although the myopathy in these diseases is most often of the inflammatory type (2). Because of the absence of malignancy, subacute-onset, negative anti-Jo-1 antibodies, and immediate biochemical response to discontinuation of statins in this case, an immune-mediated necrotizing myopathy induced by statins was strongly suspected.
Statins are commonly prescribed and reduce cardiovascular risk in persons with hyperlipidemia. Up to 20% of individuals on statins experience myalgia, which in most cases is mild and transient. Infrequently, myopathy can occur, which usually resolves after discontinuation of the drug. In rare cases (0.44 incidence per 10,000 person-years), severe myopathy that is not self-limiting but worsens despite withdrawal may occur (3). In such severe cases, muscle biopsy typically reveals necrotizing myopathy without inflammation. These patients have autoantibodies to HMGCR, the pharmacologic target of statins that is upregulated in statin-exposed individuals (4). As anti-HMGCR antibody myopathy has been associated with DRB1*11:01 (5), it has been hypothesized that DRB1*11:01 preferentially presents a strongly immunogenic HMGCR-derived peptide that is generated when HMGCR is overexpressed in the presence of statins (6). The mean time interval between the first and second anti-HMGCR antibody testing is approximately 4 years. Future studies might reveal if anti-HMGCR antibodies, like other autoantibodies (7), predate the clinical onset of disease. Anti-HMGCR antibodies are highly specific for patients with an autoimmune myopathy and are not found in statin users or in patients with self-limited intolerance to statins (8). Anti-HMGCR antibodies have also been described in statin-unexposed myositis patients (6).

In this case, the patient had years of statin exposure before development of autoimmune myopathy. During that period, anti-HMGCR antibodies were absent. When the patient developed myopathy, CK activity was markedly increased and anti-HMGCR antibodies were present. After treatment, CK activity normalized, as did the anti-HMGCR antibody concentrations. Although autoimmune myopathy can develop within months after starting statins, most studies report that subjects had years of exposure (up to 9 years) before development of autoimmune myopathy. Once it develops, weakness and increased CK persist and advance until immunosuppressive therapy is initiated (6). Werner et al. (9) evaluated
concentrations of anti-HMGCR antibody and CK activity, as well as proximal muscle strength, in 55 anti-HMGCR-positive patients. Forty of them were exposed to statins. In the statin-exposed group, initial antibody concentrations correlated with CK activity and proximal muscle strength. In a subgroup of 12 statin-exposed patients who were followed during treatment with immunosuppressive agents, CK activity and antibody concentrations declined and arm strength improved. However, the antibody concentrations did not normalize in any patient. In the statin-unexposed patients (n = 5), the antibody concentrations did not reflect disease activity (9).

In conclusion, in statin-exposed patients with myopathy who do not improve after discontinuation of the drug, the possibility of statin-associated immune-mediated necrotizing myopathy needs to be considered. In such patients, a muscle biopsy should be performed. In addition to muscle biopsy, testing for the presence of antibodies to HMGCR (10) may be useful to support the diagnosis and distinguish patients with statin-associated autoimmune necrotizing myopathy from patients with self-limiting statin-associated myopathy. Patients with immune-mediated necrotizing myopathy with antibodies to HMGCR require aggressive immunosuppressive treatment to control the disease.

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References


Clinical Case Study