

## CLINICAL VIGNETTE

# Statin-Induced Necrotizing Autoimmune Myopathy

Maristela B. Garcia, M.D., and Erin Atkinson Cook, M.D.

### *Clinical Vignette*

A 76-year-old man with a history of two prior strokes complicated by residual mild cognitive impairment, atrial fibrillation, coronary artery disease, diabetes mellitus type 2, congestive heart failure, dyslipidemia, and stage 3 chronic kidney disease was admitted for failure to thrive and functional decline. Two months prior, he had been briefly hospitalized for fatigue and inability to walk. At that time, he was found to be dehydrated and was treated for a UTI. His weakness was attributed to exhaustion from overwork and recent travel, and he was subsequently transferred to a skilled nursing facility for rehabilitation. Prior to that hospitalization he had been walking independently and actively working. After a month of rehabilitation therapy, he was able to ambulate with a walker, but he required assistance with his activities of daily living (ADLs). Upon his return home, his function progressively declined despite home physical therapy. He suffered from diarrhea, weight loss, and swallowing difficulties resulting in aspiration with food intake. He was admitted to the hospital and noted to be frail and malnourished. He was found to have liver transaminitis and an elevated creatinine kinase (CK) level of 3095 U/L (reference 63-473 U/L). A modified barium swallow study (MBSS) demonstrated an inefficient oropharyngeal swallow phase with reduced based of tongue contraction and a weak and ineffective cough. It was recommended to give him nothing by mouth (NPO). The patient subsequently aspirated and was transferred to the ICU, where he was supported with high flow nasal O<sub>2</sub> support and was treated with intravenous antibiotics for aspiration pneumonia. Rheumatology and neurology consults were obtained, and both consultants were concerned for an inflammatory or necrotizing myositis. The patient declined components of the recommended work-up including an MRI of the brain and femur and a muscle biopsy. An EMG/NCS could not be performed due to patient fatigue. Because of the lack of objective data to support a diagnosis of necrotizing myopathy, empiric treatment with immunosuppressive agents was not initiated. The patient's respiratory status stabilized, and he was transferred out of the ICU on hospital day 6. A percutaneous endoscopic gastrostomy tube was placed on hospital day 9. On his 11th hospital day, the patient suffered another hypoxic aspiration event and manifested findings consistent with a re-expression of his previous stroke. His respiratory status remained tenuous, and the patient decided that he did not want aggressive treatment or further testing. On his 13th hospital day, he expired. After his death, lab testing for antibody to HMG-CoA reductase result came back significantly elevated, >200 U (reference 0-19 U).

### *Discussion*

Statin therapy has revolutionized the management and outcomes of atherosclerotic cardiovascular disease (ASCVD). Since lovastatin first became commercially available in 1987,<sup>1</sup> statins have become one of the most commonly prescribed drug classes in the US.<sup>2</sup> In 2012-2013, the number of US adults who reported taking a statin was 39.2 million, representing a 79.8% increase from 2002-2003, resulting in an estimated total annual national expenditure for statins of \$16.9 billion.<sup>3</sup> The 2013 AHA/ACC guidelines expanded the indications for statin therapy and are expected to significantly increase these numbers, though the new 2016 USPSTF recommendations on statin use for the primary prevention of cardiovascular disease attempts to curb these indications.<sup>4</sup>

Statin are generally safe and well-tolerated; however, they cause a variety of muscle-related adverse effects, ranging from self-limited myalgia to a serious autoimmune disorder. Patients can experience asymptomatic elevation of creatine kinase (CK), myalgia without CK elevation, muscle weakness, pain with CK elevation, potential for kidney injury, or a rare and progressive autoimmune myopathy that is characterized by muscle necrosis.<sup>5</sup> The true incidence of the statin-associated myopathies is difficult to determine due to the lack of standardized nomenclature and a classification system that predated the recognition of the autoimmune myopathy subset. Myalgia without CK elevation and asymptomatic CK elevation are the most common side effects of these drugs,<sup>6</sup> while the more severe forms of statin myopathy occur with much less frequency. These rare but more serious forms can be classified into two categories, based on their pathophysiologic mechanisms. The first category is the better known, self-limited, non-autoimmune myotoxicity; this is manifested by serious muscle damage and marked elevation of CK that typically resolves with drug cessation and is characterized by the absence of autoantibodies to HMG-CoA reductase.<sup>5,7</sup> In recent years, a second category of a serious but less-recognized statin-related myopathy has emerged with the identification of an autoimmune phenotype. This subset is characterized by muscle necrosis that persists despite discontinuation of statin treatment and has a strong link to HMG-CoA reductase autoantibodies.<sup>6,8,9</sup> This rare but life-threatening myopathy is often referred to in current literature as statin-induced necrotizing autoimmune myopathy (SINAM).

The incidence of SINAM is not known, but it is estimated to occur in about 2 to 3 of every 100,000 treated patients.<sup>10</sup>

Various statins are associated with this condition, which suggests that this phenomenon is a drug class effect and is not specific to any particular statin.<sup>6,11</sup> A recent case-control study showed that atorvastatin has a significantly stronger association with this myopathy compared to rosuvastatin and simvastatin.<sup>12</sup> It is not known whether high-intensity statin therapy affects the risk. Interestingly, diabetes mellitus type 2 appears to be an independent risk factor as well.<sup>12</sup>

Myopathy may occur right after the start of statin therapy, but in most SINAM cases, symptoms developed years after statin initiation. In the series presented by Grable-Esposito et al<sup>13</sup> involving 25 patients, the mean duration of statin exposure before the onset of symptoms was 3 years, and the range was from 2 months to 10 years. The median age of onset was 69.5 years in the retrospective study conducted by Kassardjian et al<sup>14</sup> involving 22 patients with SINAM. The majority of the patients presented with painless, symmetric muscle weakness in the lower extremities; only about a quarter of the patients complained of myalgia. In this series, more than half of the patients also showed weakness of the neck flexors. Other prevalent symptoms included dyspnea (approximately 30%), dysphagia (approximately 18%), and weight loss (approximately 18%). However, in another case series, 63% of patients had dysphagia.<sup>8</sup> Once this form of myopathy develops, symptoms will persist or progress without treatment, despite discontinuation of statin therapy. This is in contrast to other statin-induced inflammatory myopathies, which resolve upon statin discontinuation. Only a few reported patients with mild symptoms of SINAM had spontaneous improvement after stopping statin therapy, without requiring immunosuppressant therapy.<sup>10,15</sup>

Prominent laboratory features of SINAM include elevation of the CK levels to more than 10 times the upper limit of normal, exceeding 2000 IU/L in almost 90% of cases.<sup>8</sup> Electromyography studies show patterns of irritable myopathy.<sup>8,10,16</sup> MRI findings include evidence of muscle edema.<sup>8</sup> The presence of autoantibodies to HMG-CoA reductase in statin-treated patients with necrotizing myopathy is strongly suggestive of SINAM, being found in 92% of patients older than 50 years. Autoantibodies to HMG-CoA reductase are notably absent in patients with self-limited, non-autoimmune forms of statin myopathy, thus an alternative diagnosis must be sought in antibody-negative patients with suspected SINAM.<sup>7,10</sup> Muscle biopsy shows evidence of muscle cell necrosis characterized by a distinctive lack or minimal presence of inflammatory infiltrate, which also distinguishes SINAM from other myositis entities.<sup>17</sup>

The pathophysiologic mechanism causing immune-mediated muscle injury from statins is poorly understood. The findings of both muscle cell necrosis and regeneration with macrophages predominantly noted in the endomysium and perivascular regions suggest ongoing reparative processes.<sup>10</sup> Upregulation of major histocompatibility complex class I molecules is commonly found.<sup>18</sup> Current understanding support the hypothesis that the development of autoimmunity against HMG-CoA reductase is triggered by a statin-induced overexpression of HMG-CoA reductase in genetically vulnerable individuals, possibly in conjunction with other unknown environmental triggers. Whether the autoantibodies

exert direct pathologic effects on the myocyte, or whether some other intermediary factors are involved in causing the muscle injury is presently not known.

To date, there are no clinical trials available to provide specific guidance in the management of SINAM. Patients on statin therapy who present with unexplained muscle weakness or muscle pain should have CK level checked. If the CK level is  $\geq 10$  times the upper limit of normal, the recommendation is to discontinue statin therapy and reassess the patient and CK level in 8 weeks or sooner if the patient's symptoms worsen or do not improve.<sup>10</sup> If the CK elevation persists, the next step is to check for the presence of anti-HMG-CoA reductase antibody. If the latter is present, a presumptive diagnosis of SINAM is made and appropriate referral for consideration of muscle biopsy and immunosuppressant therapy are indicated. These guidelines would not have benefited the patient in this case given the rapid progression of his disease. Moreover, it should be noted that testing for HMG-CoA reductase antibody requires a specialized laboratory; this test is not available at most institutions. The test result in this case took over 1 week. The current approach to treatment is based on clinical experience and relies on the use of immunosuppressive agents similar to the therapeutic management of other autoimmune myopathies. Initial therapy generally starts with prednisone 1mg/kg/day as monotherapy in mild cases or in combination with another drug such as methotrexate, azathioprine, or mycophenolate mofetil.<sup>10</sup> Patients who do not respond to initial therapy or who develop progressive symptoms may require the addition of intravenous immunoglobulin (IVIG) or a monoclonal antibody such as rituximab; more than half of the patients reported in the literature are treated with three agents, which usually includes IVIG.

Most patients experience recovery of muscle strength with treatment; however, some patients relapse and require long-term immunosuppression. CK levels may remain persistently elevated despite full recovery of muscle strength. The optimal therapeutic strategy for this subset of patients remains controversial. Additionally, muscle weakness may persist despite return to normal CK levels. This may be caused by fatty tissue replacement of permanently damaged muscles in patients who are undiagnosed or under-treated for a prolonged period of time.

### **Conclusion**

Statin therapy is one of the therapeutic pillars in the management of atherosclerotic cardiovascular disease and has contributed significant benefits in attenuating ASCVD risk. Statins are well-tolerated, and musculoskeletal side effects, while common, are generally mild. However, a more serious but rare form of an autoimmune myopathy associated with statin use, has been recognized in recent years. While its exact pathophysiologic mechanism is not clearly understood, observations support the possibility of a statin-induced overexpression of HMG-CoA reductase in genetically vulnerable individuals, possibly in conjunction with other unknown environmental factors. Diagnosis is suggested by a triad of muscle weakness, marked elevation of CK, and the presence of anti-HMG-CoA antibody. Assays for HMG-CoA reductase autoantibodies should only be obtained in patients

who have elevated CK levels as they may yield false positive results in 0.7% of cases.<sup>10</sup> Muscle biopsy is also helpful in establishing the diagnosis when accompanied by other supporting data. The myopathy is generally responsive to immunosuppressant therapy, and most patients recover fully with treatment. It is important to note that it may take years of uneventful statin exposure before autoimmune muscle necrosis starts, which highlights the need for clinicians to be aware of this emerging clinical entity and its associated risk factors, especially in view of the expanding indications of statin therapy that will broaden drug exposure to a wider group of the general population.

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