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**Title**

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**Journal**

Proceedings of UCLA Health, 20(1)

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**Publication Date**

2016-01-07

## CLINICAL VIGNETTE

# Statin Induced Necrotizing Myopathy

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### Case Report

A 67-year-old man with diabetes, chronic low back pain, and cognitive impairment presented to the emergency room after a fall. At home, he was unable to stand and remained immobile on the floor for hours. On presentation, he complained of diffuse weakness and difficulty walking that progressed over the course of weeks. He also noted chronic low back pain for years but denied numbness, focal weakness, or incontinence. He had previously been on atorvastatin but had stopped taking all of his medications weeks prior to admission due to losing his medications and not refilling them.

In the emergency room, the patient's vitals included: temperature 36.6, heart rate 89, blood pressure 127/80, and oxygen saturation 98% on room air with a respiratory rate of 18. Physical exam was notable for normal cardiac, respiratory, abdominal, and skin exam with diffuse non-focal weakness with a slight proximal predominance. Neurology initially questioned whether his weakness was true weakness versus volitional in nature. Laboratory testing revealed white blood cells 5.3, hemoglobin 13.8, sodium 132, potassium 4.9, bicarbonate 29, BUN 17 creatinine 0.8, INR 1.1, creatine kinase (CK) 14,764. Urinalysis was positive for blood, but no RBCs were present. MRI spine showed mild degenerative disc disease without significant spinal canal or neural foraminal stenosis. MRI of the brain showed generalized cerebral atrophy.

On admission, he received supportive care, and his rhabdomyolysis was attributed to his fall with trauma and subsequent immobility. After receiving IV fluids and holding his atorvastatin, his symptoms persisted. He had ongoing severe diffuse muscle weakness, myalgias, and CK elevation more than one week later. An electromyogram demonstrated an inflammatory myopathy. His initial laboratory work up was notable for mildly elevated TSH with normal T4, low vitamin D level, and negative ANA/anti-Jo-1. The rheumatology service recommended obtaining an anti-HMGCR antibody test and a muscle biopsy. The patient's anti-HMGCR antibody test was strongly positive, and his muscle biopsy showed active severe necrotizing myopathy with minimal lymphocytic inflammation.

He was treated with prednisone 60mg daily with improvement in his myalgias with a modest decrease in his CK to 4,000 – 5,000. Rheumatology recommended adding methotrexate. Given the patient's improving clinical course and stable treatment regimen, he was discharged to a skilled nursing facility for rehabilitation with Rheumatology follow up. Ten days later, the patient required readmission for septic shock

due to *E. coli* urinary tract infection with bacteremia. He responded to intravenous antibiotics and fluids. At later follow-up, Rheumatology felt his improvement on oral immunosuppression had plateaued and initiated intravenous immunoglobulins. This led to significant improvement in his CK levels to below 600. His symptoms improved, and he returned to rehabilitation with a planned steroid taper.

### Statin-Related Muscle Disease

There is a spectrum of muscle-related side effects attributed to statins, the most common being myalgias (muscle discomfort). Other statin-induced myotoxicities include myopathy (i.e., muscle weakness), myositis (i.e., muscle inflammation; diagnosis confirmed with tissue biopsy or MRI), myonecrosis (i.e., muscle ischemia and/or infarction; accompanied by significant CK elevations), and clinical rhabdomyolysis (myonecrosis with myoglobinuria or acute renal failure). Myalgias can be as common as 1-5% in clinical trials and 11-29% in observational cohorts.<sup>1</sup> The characteristics that suggest statin-induced myalgias include symmetric distribution and early onset symptoms that resolve with statin withdrawal and recur with re-exposure.

Conversely, rhabdomyolysis is rarer. It occurs at a rate of 4.4 per 100,000 person-years in statin randomized, controlled trials and 3.4 per 100,000 person-years in observational cohorts.<sup>2-3</sup> Specific statins carry different risks of rhabdomyolysis; simvastatin and atorvastatin are associated with higher risk, whereas lovastatin, pravastatin, and fluvastatin are associated with lower risk. These differences are most likely due to variances in drug metabolism.<sup>4</sup> Statin myopathies are more likely to occur in the context of pre-existing neuromuscular disorders, hypothyroidism, vitamin D deficiency, and drug interactions. Drugs to be cautious about co-administering with statins are fibrates, niacin, protease inhibitors, nondihydropyridine calcium channel blockers, and azole antifungals.

Management of statin-associated muscle disease begins with discontinuing the statin for those with significant myalgias or CK elevation greater than 5-fold the upper limit of normal.<sup>5</sup> Clinicians should check for potential statin drug interactions and treat risk factors for myopathy including hypothyroidism and vitamin D deficiency. Patients who have not had rhabdomyolysis can undergo a statin re-challenge after muscle symptoms and CK elevation resolve. The majority of patients tolerate re-challenge with the same or different statin.<sup>6</sup> For patients intolerant to multiple statins, clinicians can employ

alternative dosing strategies such as using a statin with a longer half-life (e.g., rosuvastatin or atorvastatin) dosed less frequently or consider newer lower lipid therapies, such as PCSK9 monoclonal antibodies.

### ***Statin-Induced Immune-Mediated Necrotizing Myopathy***

Statin-induced or associated immune-mediated necrotizing myopathy (IMNM) exists at the extreme of the spectrum of statin-related myotoxicity. Unlike other inflammatory myopathies such as dermatomyositis, polymyositis, and inclusion body myositis, IMNM shows muscle necrosis with minimal or absent inflammatory infiltrate on biopsy. Other IMNMs include those associated with paraneoplastic syndromes, mixed connective tissue disorders, viral infections, drug exposures other than statins, and idiopathic forms.

Statin-induced IMNM presents as proximal muscle weakness during statin use or after statin withdrawal, elevated CK levels, and persistent signs and symptoms following discontinuation of the statin.<sup>7</sup> Unlike other inflammatory myopathies associated with mixed connective tissue disease, patients rarely have non-musculoskeletal symptoms or signs of systemic autoimmune disease. In a single study of 45 patients with confirmed disease, 20% of patients also suffered weight loss, the only extra-muscular finding documented.<sup>8</sup>

As this disease becomes more widely recognized, its diagnostic criteria continue to solidify. Currently, diagnosis requires the typical clinical history in addition to biopsy with characteristic histologic patterns (immune-mediated necrotizing myopathy with minimal lymphocytic infiltrate). Also antibodies directed against the pharmacologic target of statins, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) are present.<sup>9</sup> However, etiologies other than statin exposure, especially in younger populations, also cause anti-HMGCR associated myopathies. Anti-HMGCR antibodies in patients with IMNM but without statin exposure accounted for 33% and 56% in two case reviews of 45 patients each.<sup>8,10</sup> Finally, there appears to be a genetic predisposition to anti-HMGCR antibody positivity and statin-induced IMNM. Anti-HMGCR antibody positivity has been strongly associated with HLA DR11.<sup>11</sup>

Treatment of statin-induced IMNM is more aggressive compared to other statin-related myotoxicities. Withdrawal of statins does not improve symptoms. Immunosuppressive therapy is required, often steroids in conjunction with methotrexate and IV immunoglobulin. Anti-HMGCR antibody titers correlate with disease activity, in particular CK levels and muscle strength.<sup>8,12</sup> Antibody levels decline with immunosuppressive therapy, but relapses frequently occur when the immunosuppressive treatment is weaned. Statin-unexposed patients with anti-HMGCR antibodies may be less responsive to immunosuppressive therapy.<sup>12</sup>

### ***Conclusion***

The conditions that comprise statin-induced myotoxicities range from myalgias, myopathy, and rhabdomyolysis—all of which resolve with statin discontinuation—to the rare and more severe statin-induced immune-mediated necrotizing

myopathy. This autoimmune myopathy does not respond to withdrawal of the offending medication, is characterized by characteristic muscle biopsy pattern with muscle necrosis with no or minimal inflammatory infiltrate, and is associated with anti-HMGCR antibodies. Treatment requires immunosuppression. Persistent myalgias or CK elevation that does not resolve with discontinuation of a statin should prompt further diagnostic testing, including anti-HMGCR antibody and muscle biopsy.

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Submitted January 7, 2016