CLINICAL VIGNETTE

Immune-Mediated Necrotizing Myositis in Setting of Statin Use

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A 69-year-old Japanese American female was referred to rheumatology by hematology for evaluation of significantly elevated antinuclear antibody (ANA) level in the setting of thrombocytopenia and red blood cell macrocytosis. The patient's past medical history was significant for polycystic kidney and liver disease, type 2 diabetes mellitus, non-alcoholic steatohepatitis, hypertension, and hyperlipidemia. At consultation, the patient's clinical exam and review of systems were unremarkable for systemic rheumatic disease. Serological testing of ANA subsets revealed a high titer smooth muscle antibody. Due to the association of smooth muscle antibody with autoimmune liver disease, the case was discussed with hepatology, for mild transaminitis, consistent with fatty liver. The hepatology team recommended increased statin to improve dyslipidemia and hyperglycemia.

Her atorvastatin was increased from 40mg nightly, which she had been taking for many years, to 80mg. One month after the dose adjustment, the patient presented to the emergency room with proximal and distal muscle weakness with lower extremity swelling. Laboratory testing showed significantly elevated muscle and liver enzymes, including creatinine kinase, aldolase, AST, and ALT. There was no renal abnormalities a few days after admission and treatment. MRI of the bilateral femur and bilateral tibia/fibula revealed significant muscle edema located primarily in the proximal thighs and pelvis, which were suggestive of myositis. She was admitted and muscle biopsy showed changes consistent with moderate to severe necrotizing myositis. Statin was discontinued and the patient was started on prednisone 50mg daily with significant improvement in her symptoms. Muscle enzymes also dramatically improved. The differentials included statin myopathy, drug/toxic myopathy, and autoimmune myopathy. Serological testing revealed a weakly positive MDA5 autoantibody. Other inflammatory myositis antibodies were negative, including negative anti-HMG CoA reductase antibody. Given her elevated liver enzymes, liver imaging was obtained. Duplex ultrasound CT venogram showed no evidence of fibrosis. Liver biopsy was considered but deferred after improvement in transaminase.

The patient was transitioned to azathioprine therapy over the next few months with gradual lowering of prednisone until completely tapered off. She continues to do physical therapy with improvement in strength. She was transitioned to evolocumab as an outpatient for continued management of dyslipidemia, with improvement in LDL. Muscle and liver enzymes remain normal.

A rare statin-associated condition is immune-mediated necrotizing myositis which requires immunosuppressive therapy. Immune mediated necrotizing myositis is a rare inflammatory myopathy which clinically presents similarly to polymyositis, but with a different pathological presentation. The primary presentation of polymyositis is symmetrical muscle weakness in the proximal muscles, most commonly the deltoids and hip flexors. Weakness is typically insidious, but an acute onset can occur with complaints of trouble ambulating up stairs or opening up high shelves. Serologies revealed weak positive MDA5 antibodies, which are seen more classically in dermatomyositis.[2] The patient did not report any skin findings. Mucocutaneous findings in anti-MDA5 antibody patients include Gottrons papules with overling ulcerations, lateral nailfold changes, non-scaring alopecia, erythematous and painful palmar macules and papules and oral ulcers. Patents often have inflammatory arthritis and interstitial lung disease.

Though widely used, statin therapy has been associated with a variety of muscle-related adverse events, which include myalgia, myopathy, and in rare instances, myositis. The mechanism of statin-mediated muscle toxicity is not well-understood and conflicting studies address whether statins can indirectly decrease ubiquinone (CoQ10) production, which can contribute to the energy production of the muscle cell.

Patient characteristics can increase likelihood of statin side effects. Statins can cause new neuromuscular disorders or unmask symptoms in patients who likely had preclinical disease, including amyotrophic lateral sclerosis (ALS), myasthenia gravis, mitochondrial myopathy and dermatomyositis/ polymyosis.[1] Other untreated metabolic disorders, such as hypothyroidism, hypo-vitaminosis D, acute renal failure or obstructive liver disease can increase the susceptibility to statin-induced myopathy. Side effects typically resolve after treatment of underlying co-morbidity.

Concurrent medications can enhance susceptibility to statin-associated myopathy. These include fibrate therapy and medications that inhibit CYP3A4, including calcium channel blockers, HIV and HCV protease inhibitors, amiodarone, cyclosporine, and grapefruit juice. Statins that are metabolized by CYP3A4, such as simvastatin, lovastatin, and to less extent, atorvastatin, have been associated with increased risk of myopathy. Alternatively, rosuvastatin, pitavastatin, and pravastatin are not cleared by CYP3A4 and have few significant interactions.

Typically, statin-associated myopathy resolves with the cessation of the offending agent. Rarely, statins can induce severe myonecrosis leading to rhabdomyolysis or immune-medicated necrotizing myositis. Rhabdomyolysis requires hospitalization for aggressive intravenous fluids to increase urinary excretion of myoglobin to prevent acute renal failure.

REFERENCES

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