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Statin-Induced Autoimmune Necrotizing Myopathy

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Abstract

Statin therapy is a widely prescribed medication class for hypercholesterolemia. In statin-induced autoimmune myopathy, genetically predisposed and at-risk patients can develop antibodies against hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the key enzyme in the production of cholesterol. As a result, an autoimmune reaction causing weakness, myalgia, with possible severe rhabdomyolysis, renal failure, and myonecrosis also can occur. A 73-year-old female presented to clinic with myalgia and fatigue. She was on atorvastatin 20 mg/day for over 1 year, which she stopped 1 week prior to her initial presentation. Patient did experience rhabdomyolysis as well as a transaminitis. She underwent an autoimmune workup which was positive for HMG-CoA reductase antibodies. Patient was initially treated on a prednisone taper, starting dose 50 mg/day. Without remission of symptoms, methotrexate 15 mg/week was initiated.

Keywords

statin, necrotizing, myopathy, adverse, effects, neurology, hyperlipidemia

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Introduction

Hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is an enzyme that converts HMG-CoA to mevalonate, which is the rate-limiting step in the production of cholesterol products.[1] Statin medications function by acting as competitive inhibitors to this substrate, thus lowering the production of cholesterol. However, the use of statins can cause significant myopathies. The exact cause of statin-induced myopathies is hypothesized to include mechanisms affecting membrane excitability, mitochondrial function, ubiquinone depletion, calcium usage, and apoptosis.[2] In addition to this, antibodies can develop against the primary substrate of statins, HMCR, which can lead to a progressive, debilitating disease known as statin induced necrotizing autoimmune myopathy (SINAM). SINAM's mechanism is currently under investigation but is thought to be due to statins causing the overexpression of HMGCR in patients genetically susceptible to the disease, which in turn increases the production of antibodies against HMGCR.[3] Risk factors for the disease include age >50, African American race, SLCO1B1 genes, decompensated liver disease, severe renal disease, and uncontrolled diabetes mellitus.[4,5]

SINAM is characterized by significant muscle weakness and/or myalgia in multiple muscle groups including legs, arms, shoulder, back, calves, and neck.[6-8] In addition, fatigue, cramping, stiffness, and tendon pain can also be seen.[9] Symptoms can appear at any time following statin initiation, with a mean duration of 6.3 months.[10] Laboratory studies will generally show CK levels greater than 3000 IU/L, and levels greater than 10 times the upper limit of normal could manifest as severe rhabdomyolysis.[11] In addition, histopathologic examination will show myonecrosis without signs of vasculitis, inflammation, or cellular infiltration.

Case Description

A 73-year-old female with secondary hypercholesterolemia presented to her primary care office with complaints of fatigue, myalgia in her thighs, calves and neck, and stiffness in her arms. A few weeks prior, the patient recalled having dark brown urine that resolved on its own. Her only prescribed medications were meloxicam and atorvastatin

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20 mg/day, prescribed 1-year prior for secondary hyperlipidemia without any additional relevant over-the-counter medications or herbal supplements. She admitted stopping this medication 1 week prior to this initial presentation with mild improvement in symptoms. On physical examination, the patient exhibited normal range of motion in her upper and lower extremities, 5/5 muscle strength, and intact sensation. Laboratory results identified elevated creatinine kinase 12635 IU/L (22-198 IU/L), c-reactive protein 9.21 mg/L (<10 mg/L), white blood cell count 12.9 (4.5-11.0 × 109/L) and sedimentation rate 38 mm/h (0-30 mm/h). The patient was subsequently admitted to the hospital for concerns of statin-induced myopathy. Initial treatments included intravenous fluids at a rate of 250 mL/h with her outpatient statin medication held. Creatinine kinase, liver enzymes, and kidney function were monitored throughout her hospital course. Initial admission tests included transaminitis, initially AST 449 and ALT 598 IU/L with creatinine at baseline 0.5 mg/dL. Urinalysis showed large blood without signs of overt infection, indicative of myoglobinuria. Creatinine kinase gradually declined with intravenous fluids to 6733 IU/L. Liver enzymes improved to AST 282 IU/L and ALT 427 IU/L. One-week post discharge, patient obtained a new set of studies which showed worsening of both a creatinine kinase level of 8281 IU/L and transaminitis AST 365 IU/L and ALT 475 IU/L despite discontinuation of the statin medication and initial IV fluid treatment. Given the persistent elevation of creatinine kinase and transaminitis in conjunction with the patient's presentation, an autoimmune pathology was highly suspicious and thus a broader workup was initiated. HMG-CoA reductase antibody was positive. Additionally, other autoimmune lab results were negative, which included cardiolipin antibody, anti-scleroderma antibody, anti-DNA antibody, anti-Jo, and anti-centromere antibodies. MRI of the left thigh with and without contrast revealed diffuse edema and enhancement through the vastus lateralis, vastus intermedius, vastus medialis, hip adductor muscles, biceps femoris, and semimembranosus muscle consistent with myositis. There was no involvement of the neurovascular bundles or muscle atrophy. Once seen in the outpatient rheumatology clinic, patient was placed on a regimen of 50 mg prednisone with plans for a long-term taper. The patient was also placed on immunosuppressive therapy with methotrexate 50 mg per week plus folic acid 1 mg daily. CK continued to trend down to 4908 IU/L, AST 315 IU/L, ALT 455 IU/L, and resolution of ESR. Patient was also seen by Neurology as an outpatient following her hospitalization for further evaluation of her disease. The patient still complained of not being back at complete strength and have difficulty ambulating as well rising from a chair. The patient underwent further testing including testing for MuSK antibody, a Myasthenia Gravis panel testing for acetylcholine binding antibody, acetylcholine blocking antibody, striated muscle IgG and Titin antibody which were all negative. A myositis extended panel testing for SAE1, NXP-2, MDA5 (CADM-140) antibody, TIF-1 Gamma antibody, Mi-2 antibody, P155/140 antibody, PL-12 antibody, PL-7 antibody, OJ antibody, EJ antibody, SRP antibody, Jo-1 IgG, Ku antibody, Sm/RNP antibody, PM/SCL-100 IgG, SSA-52 IgG, SSA-60 (Ro60) IgG, Fibrillarin (U3 RNP) IgG was also negative. Repeat CK level was found to be 1842 IU/L. Since the patient only had a partial response to therapy, the decision was made to trial IVIG with a loading dose of 2 g/kg over 4 days with a subsequent maintenance regimen of 1 g/kg over 2 days monthly, with plans to wean based on response. If response is inadequate, a muscle biopsy would then be pursued.

Discussion

Statins have a variety of muscular side effects including myalgia, myopathy, myositis, myonecrosis, and clinical rhabdomyolysis. SINAM differs from other presentations because of its presentation with severe symmetrical proximal muscle weakness associated with significantly elevated creatine kinase, with symptoms persisting even after discontinuation of the statin. If this occurs, a muscle biopsy can be helpful to elucidate the diagnosis. Early in the course of SINAM, a muscle biopsy will reveal myonecrosis without vasculitis whereas late in the course, rhabdomyolysis will result in mononuclear cell infiltration indicative of inflammatory repairs.[12-14]

This myonecrosis appears to be due to antibodies to HMGCR in regenerating muscle. Though unclear, several hypothetical models have been established to explain the underlying mechanism of development of HMG-CoA reductase autoimmunity.[15] First being the association of class II HLA allele DRB1 × 11:01 with the development of anti-HMG-CoA reductase autoantibodies. Similarly, in genetically predisposed patients, statin exposure significantly increased the expression of HMG-CoA reductase in regenerating myofibers. HMGCR and SRP proteins were found on the sarcolemma of muscle fibers in affected patients along with the presence of classical pathway activation of complement proteins. In addition, interaction of statins and HMG-CoA reductase may lead to generation of non-immune tolerating cryptic epitopes. Hence, once the autoimmune response gets activated, even after stopping the statin, HMG-CoA reductase levels in regenerating muscle could continue to drive autoimmunity.

Immunosuppressive therapies are the mainstays of treatment. Initially, patients may be started on oral prednisone in order to help induce remission of the disease. However, patients may not respond adequately to monotherapy with oral prednisone, and may require pulse dose intravenous methylprednisolone (up to 500 mg) to achieve adequate affect.[16] In those resistant to the above therapies, intravenous immunoglobulin, and/or methotrexate can be used to

ultimately gain induction. Once induction is successfully achieved, patients will need to be started on a suitable maintenance therapy to ensure adequate suppression of the immune response in the future. Patients can have a varied response to maintenance therapy and will need close follow-up to fine tune their final maintenance regimen. Strategies include methotrexate monotherapy or in combination with corticosteroids. In addition, IVIG can be used either as a core of the therapy or can be eventually tapered off the intervention.[16] Refractory patients can be trialed on immunosuppressants azathioprine, mycophenolate mofetil, and/or abatacept to help maintain remission.[16] Once maintenance is properly achieved, patients can be gradually weaned off parts of the regimen as tolerated.

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