

Case Report



Statin-induced rhabdomyolysis in patient with renal failure and underlying undiagnosed hypothyroidism

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Abstract

Rhabdomyolysis is a syndrome characterized by muscle necrosis which causes the release of myoglobin into the bloodstream. The manifestations of this syndrome range from asymptomatic elevation of serum muscle enzymes to life-threatening cases associated with extremely high enzyme levels, electrolyte imbalance, and acute renal failure. Symptoms of rhabdomyolysis include dark urine, muscle weakness, and fatigue. Statins are commonly used drugs for the prevention and management of dyslipidemia. We present an interesting and critical case on statin-induced rhabdomyolysis with renal failure and previously undiagnosed idiopathic hypothyroidism.

Keywords: Atorvastatin, foot drop, myopathy, myositis

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Introduction

Statins have become the most widely prescribed drug worldwide since its introduction in 1987.^[1] They are effective and generally safe. Rhabdomyolysis though rare is the most severe form of myotoxicity, which can occur with all statins, either in monotherapy or in combination therapy.^[2,3] The US Food and Drug Administration Adverse Event Reporting System database reports rates of statin-induced rhabdomyolysis of 0.3–13.5 cases per 1,000,000 statin prescriptions.^[1] We report a case of atorvastatin-induced rhabdomyolysis with renal failure precipitated by underlying undiagnosed hypothyroidism. We also discuss the pathogenesis, clinical features, and management of such cases.

Case Report

A 74-year-old male patient was admitted with complaints of progressive swelling all over the body associated with pain and stiffness in the limbs for 2 weeks. He had history of oliguria and constipation for 4 days. His

past medical history included hypertension, acid peptic disease, and cholecystectomy. Ongoing medications were amlodipine, olmesartan, hydrochlorothiazide, and pantoprazole. Atorvastatin 20 mg was added 15 days prior to his symptom onset. There was no other significant history.

On examination, he had tachypnea, tachycardia, and high blood pressure. Nonpitting subcutaneous edema with severe muscle tightness and rigidity was noted. Reflexes were suppressed. Other systems were unremarkable. Investigations on admission revealed hemoglobin 14.3 g/dl, hematocrit 42.5%, total leukocyte count 22400/mm³ (neutrophil 90, lymphocyte 9), platelet 2.28 lakhs/mm³, erythrocyte sedimentation rate 5, creatinine 1.13 mg/dl, blood urea nitrogen 12.5 mg/dl, sodium 105.1 mmol/L, potassium 4.5 mmol/L, bilirubin 1.1 mg/dl, total protein 5.1 g/dl, albumin 2.94 g/dl, serum glutamic oxaloacetic

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transaminase/serum glutamate pyruvate transaminase 2688/468 U/L, calcium 8.84 mg/dl, creatinine phosphokinase (CPK) 192,000 U/L, thyroid-stimulating hormone 70.5 mIU/L, FT3 1.32 nmol/L, and FT4 <0.88 nmol/L. Urine high-colored, positive for protein and red blood cell, urine myoglobin-positive, serum antinuclear antibody negative, high anti-thyroperoxidase antibody were observed. Leptospirosis IgM and IgG were negative. Vitamin D was normal.

On the basis of history, clinical findings, and laboratory reports – diagnosis of atorvastatin-induced rhabdomyolysis with underlying hypothyroidism was made. Hypothyroidism was diagnosed for the first time on the present admission and it was idiopathic. Eltroxin 75 µg OD was added and then increased to 125 µg OD over a few days.

Magnetic resonance imaging was done which showed diffuse swelling and abnormal signal involving almost all muscles of both lower limbs with increased T2/short tau inversion recovery signal intensity and low T1 signal intensity. Areas of breakdown with liquefied necrosis were seen. All these features were consistent with diffuse myositis with muscle necrosis.

Atorvastatin was discontinued; intravenous hydration with alkalization of urine was initiated with electrolyte correction. He was put on thyroxin supplements and symptomatic treatment. He gradually improved with symptoms resolving over next 2 weeks. His CPK levels were serially monitored which normalized to 116 after 1 month. During the course of illness, creatinine increased to 3.95 which eventually normalized over a period of time. Deranged liver enzymes returned to normal limits within 2 weeks. He developed urosepsis which was successfully treated with appropriate antibiotics. His recovery was uneventful except for bilateral foot drop.

Discussion

The clinical spectrum of statin-induced myopathy ranges from myalgia, myositis, and rhabdomyolysis to asymptomatic increase in the concentration of creatine kinase (CK). Symptoms include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping, and tendon pain.^[2] The muscle symptoms tend to be proximal, generalized, and worse with exercise. The mean duration of statin therapy before onset of symptoms ranges from 1 to 60 days.^[2] The mean duration of myalgia after stopping statin therapy ranges from 1 week to 4 months. Risk factors for precipitating myopathy include advanced age, female sex, low body mass index, diminished hepatic and renal function,

multiple comorbidities (untreated hypothyroidism, diabetes etc.), medications, excess alcohol, intercurrent infections, surgery or trauma, drug interactions, and dietary effect.^[2]

The mechanism of statin-induced myopathy is unknown. Several theories have been proposed which include impaired synthesis of cholesterol leading to changes in the cholesterol in myocyte membranes and behavior of the membrane. Second, impaired synthesis of compounds in the cholesterol pathway – in particular, deficiency of coenzyme Q10 (CoQ₁₀) (ubiquinone) which could lead to impaired enzyme activity in mitochondria.^[4] A third mechanism is depletion of isoprenoids (lipids that are a product of the hydroxymethylglutaryl coenzyme A reductase pathway) which prevents myofibril apoptosis.^[4] Furthermore, pharmacodynamic factors, such as transporters affecting the bioavailability of statins, are probably important in determining toxicity although no direct evidence has been found in humans. Drug responses can also be affected by predisposing genetic factors. *In vitro* and *in vivo* experiments suggest that lipophilic statins (for example, simvastatin, atorvastatin, lovastatin) are more likely to produce muscular effects than are relatively hydrophilic agents (such as pravastatin, rosuvastatin, and fluvastatin). Lipophilic compounds are more likely to penetrate into muscle tissue, enhancing the potential for myotoxic effects.^[3,4] Therefore, it is prudent to use a more hydrophilic agent in patients with preexisting muscle disease.

For most patients, myopathy symptoms induced by statin therapy resolve relatively quickly; however, the results of the PRIMO study showed that it may take up to 2 months for resolution of symptoms.^[5] There is limited evidence regarding the treatment of statin-associated myopathy. While in most cases myopathy caused by statins is mild and can be reversed when the medication is discontinued, it may present as rhabdomyolysis or severe muscle damage as in the case mentioned. The mainstay of treatment consists of cessation of statins; however, it is prudent for clinicians to rule out other conditions that can cause myopathy and/or CK elevations such as hypothyroidism (as in this case), overt physical activity, and alcohol abuse.^[2] Patients who present with clinically significant rhabdomyolysis require hospitalization and intravenous hydration to prevent renal damage.^[6]

Once the patient's muscle symptoms have resolved, clinicians have several options to treat that patient's dyslipidemia, including the use of a lower dose of the same statin, initiation of a different statin, and/or utilization of nonstatin lipid-lowering agents.^[6] Failure to achieve the target low density lipoprotein goal with

statins can be augmented with drugs such as ezetimibe or bile-acid binding resins. The use of fibrates and niacin as monotherapy has been associated with myopathy. Clinical experience indicates that there may be an increased risk of myotoxicity associated with statin and fibrate combination therapy.^[7] Therefore, bile-acid resins may be the optimal choice in those patients without triglyceride abnormalities who cannot tolerate statin therapy.^[8] CoQ₁₀ supplementation is tried in experimental studies and found to be successful in significantly reducing CK and aspartate aminotransferase levels in serum.^[9] There has also been interest in the use of CoQ₁₀, Chinese red rice yeast, and Vitamin D as prevention and/or management of statin-associated myopathy although there is no definite evidence.

A similar case of statin-induced bilateral foot drop in a case of hypothyroidism is published by Chaudhary *et al.*^[10] The present case study highlights the similar findings, thus warrants precautions for use of statins in such patients.

Conclusion

Statin-induced rhabdomyolysis although rare can sometimes present as a life-threatening condition. Thus, clinicians should be vigilant about this critical complication and associated precipitating factors such as hypothyroidism.

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Conflicts of interest

There are no conflicts of interest.

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