CASE REPORT

Atorvastatin-induced Myositis and Drug-induced Liver Injury

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ABSTRACT

Statins are drugs for preventing cardiovascular events in the elderly population. Statins are well tolerated with a lower reported incidence of serious side effects (<0.15%) like myopathy and elevated transaminases (>3× upper limit of normal (ULN)). Serious adverse effects of statins like statin-associated myopathy range from mild muscle pain to rhabdomyolysis. Drug-induced liver injury (DILI) is another adverse effect of statin use, typically presenting with an acute hepatocellular liver injury pattern as mixed or cholestatic injury. Symptoms usually disappear after 3 months of discontinuation of statins. Some patients require immunosuppression with steroids, intravenous immunoglobulin, or rituximab for management of rhabdomyolysis. DILI can be rapidly reversed by the stoppage of the statins if the enzyme elevation is more than twice the normal. Elderly patients are particularly at increased risk of such adverse effects, emphasizing a need for rational prescription of statins in older adults and close monitoring. We report a case of an elderly presenting with paraparesis and later diagnosed to be a case of statin-induced myositis that significantly improved with prompt management.

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INTRODUCTION

More than 100 million prescriptions of statins are written for the management of hypercholesterolemia every year. Although statins are well tolerated with a lower incidence of serious side effects (<0.15%) like myopathy and increased transaminase levels (more than three times the upper limit of normal (ULN)). A meta-analysis of 21 clinical trials with 180,000 person-years of follow-up defined statin-induced myopathy based on muscle symptoms and creatine kinase (CK) levels (>10- to 100-fold ULN), that occurred in five patients per 100,000 person-years. Grades I and II myositis is defined by muscle symptoms with CK levels less than four times ULN, whereas grades III and IV have CK levels between four and 10 times ULN 10–50 times ULN, respectively. Rhabdomyolysis following statin use is usually associated with renal dysfunction due to myoglobinuria. Immune-mediated statin myopathy is another entity associated with increased anti-3-hydroxyl-3-methylglutaryl-coenzyme A reductase autoantibody and Human Leukocyte Antigen associations. Clinically important drug-induced liver injury (DILI) is very rare with statin use. DILI from statins typically presents with an acute hepatocellular liver injury pattern, although mixed or cholestatic injury patterns have also been reported.

Elderly people are at particularly increased risk of these adverse effects due to their advancing age. Multimorbidity and organ dysfunctions like renal insufficiency, hepatic dysfunction, and hypothyroidism are present and, polypharmacy further increases the risk of adverse events. Thus, the rational use of statins while prescribing them to elderly patients is of utmost importance. This is a case of a 68-year-old patient who was admitted with complaints of paraparesis and was eventually diagnosed to be a case of statin-induced myositis with DILI.

Case Summary

A 68-year-old patient who was a known case of coronary artery disease (anterior wall myocardial infarction) with 30% left ventricular ejection fraction underwent percutaneous transluminal coronary angiography twice. The patient was on atorvastatin (80 mg) and aspirin (75 mg) for 8 months and presented with complaints of acute onset weakness in bilateral lower limbs for 20 days. The patient felt a sudden difficulty in getting up from the toilet seat, even with support and had to be carried by the son to the bed. Weakness gradually progressed in terms of difficulty in standing from sitting or lying down. For the next 10 days, the patient started experiencing difficulty in taking turns in bed while lying. However, there were no complaints of any difficulty in wearing slippers, or slippage of sandals from the toes. Simultaneously progressive yellowish discoloration of eyes, without any associated change in his urine or stool color, pain or distension of the abdomen, melena, hematemeses, hematuria, and altered talk was noticed by patients and caregivers. The patient also reported pain along the anterolateral portion of the bilateral thigh, for 15 days which was insidious in onset, dull aching, moderate to severe intensity, pain that aggravated while walking or moving the limbs (hip flexion or extension), with no significant relieving factors. Also, there was mild difficulty in combing hair or lifting the mug while bathing for 7–8 days. There was no difficulty in buttoning the shirt or while eating. There is no history of any radicular pain, back pain, trauma, tingling or numbness over the body, any loss of sensation, loss of appetite or loss of weight, or any bowel or bladder incontinence.

Physical examination revealed icterus and wasting of his proximal muscle groups of both lower limbs. A focused neurological examination showed wasting, significantly diminished power (two-fifths in all flexors, extensors, abductors, and adductors) and tone in proximal muscle groups of lower limbs. The deep tendon reflexes in the lower limbs were absent. Tenderness was present along the anterolateral group of muscles of bilateral thighs. The sensory system and upper limbs and the rest of the examination were unremarkable. Given the history, clinical examination possibilities kept were statin-induced myopathy, polymyositis, or immune-mediated necrotizing myopathy (IMNM).

Hemogram, renal profile, and serum electrolytes were within normal limits. Liver function profile was deranged, aspartate transaminase (AST)—1590 U/L and alanine transaminase (ALT)—1301 U/L, along with an increased total and direct bilirubin (13.1 and 6.7 mg/dL, respectively). N-acetyl cysteine-activated creatine phosphokinase (CPK-NAC level) was 21,650 U/L, lactate dehydrogenase was 3,618 U/L. Magnetic resonance imaging (MRI) of both thighs showed heterogeneous T2/Transverse relaxation time (T2 FS) hyperintensity in muscle fibers of the bilateral adductor group of muscles and muscles of the bilateral anterior compartment of the thigh, bilateral obturator externus and internus,
stopped. After stopping statins, the patient gradually started showing improvement in his muscle power and pain by the 5th day. A repeat AST/ALT and CPK-NAC levels showed 363 U/L, 118 U/L, and 2309 U/L respectively. Bilirubin levels were decreased (total and direct bilirubin—5.91 mg/dL and 5.3 mg/dL, respectively). Clinically jaundice improved.

In light of the clinical history and laboratory findings and observations, we finally diagnosed it to be a case of statin-associated myopathy with DILI. On subsequent follow-up, his power had further improved with a decrease in CPK-NAC levels.

**Discussion**

The incidence of statin-induced myopathy is estimated to be nearly about 0.1–0.5% and rhabdomyolysis to be 0.02–0.04% when the patient is on statin monotherapy.2 Symptoms vary from mild muscle aches to fatal rhabdomyolysis and acute renal failure. They began to occur within a few weeks of starting statin, and sometimes up to a few years
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and their appropriate management should be kept in mind and patients should be monitored with more vigilance. Further studies on myotoxicity will enhance our understanding of these mechanisms and will help in preventing myopathy and in the discovery of lipid-lowering agents free of such adverse effects.

REFERENCES

Conclusions
Discontinuation of statin use in patients with inflammation and elevated CK levels is the currently accepted mode of treatment of statin-myopathy. In patients with liver injury, a different statin can be reinstated with careful and frequent monitoring. Currently, statins are one of the most prescribed medications worldwide, hence the risk of these side effects and their appropriate management should be kept in mind and patients should be monitored with more vigilance. Further studies on myotoxicity will enhance our understanding of these mechanisms and will help in preventing myopathy and in the discovery of lipid-lowering agents free of such adverse effects.