

## Case Report

# **Statin-induced rhabdomyolysis: A cautionary tale for high-dose rosuvastatin**

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## **Abstract**

Statins are a widely prescribed lipid-lowering agent for preventing adverse cardiovascular events. However, a major side effect is rhabdomyolysis, a breakdown of muscle tissue, which can cause acute kidney injury and death. We present a case of a 77-year-old Chinese woman who was started on 40 mg rosuvastatin following percutaneous coronary intervention and ultimately developed rhabdomyolysis and acute kidney injury one month later. This case highlights the need to consider patient risk factors for developing statin-induced rhabdomyolysis when choosing the right dose of statin to prescribe.

**Keywords:** statin, rhabdomyolysis, Asian, stent

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## Introduction

Statins are a class of lipid-lowering medications that inhibit HMG-CoA reductase, the enzyme which catalyzes the rate-limiting reaction in cholesterol synthesis. By reducing cholesterol levels, specifically low-density lipoprotein cholesterol (LDL-C), statins reduce the risk of adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction (MI), ischemic stroke, revascularization, and acute coronary syndromes hospitalizations. In patients with clinical atherosclerosis, the number needed to treat is 20 patients to prevent one adverse cardiovascular event over five years of treatment per 1 mmol/L reduction in LDL-C (1). However, a major side effect of statins is rhabdomyolysis, a breakdown of muscle tissue, which can cause acute kidney injury and death. The mechanism of statin-induced rhabdomyolysis is not well understood. The incidence of rhabdomyolysis is around 1 in 22,000 patients on statin monotherapy per year of therapy (2). Certain pre-disposing patient factors also increase the risk of developing rhabdomyolysis. Here we present a case of a 77-year-old Chinese woman who was started on 40 mg rosuvastatin post-percutaneous coronary intervention and ultimately developed rhabdomyolysis and acute kidney injury one month later.

## Case Report

A 77-year-old Chinese female presented to hospital for a four-day history of severe bilateral lower extremity muscle weakness and pain. The patient had been admitted a month prior at our hospital for ST-elevation MI and an 80% right coronary artery stenosis was found. A drug eluting stent was placed via PCI, and she was started on dual antiplatelet therapy (aspirin 81 mg, clopidogrel 75 mg), and rosuvastatin 40 mg.

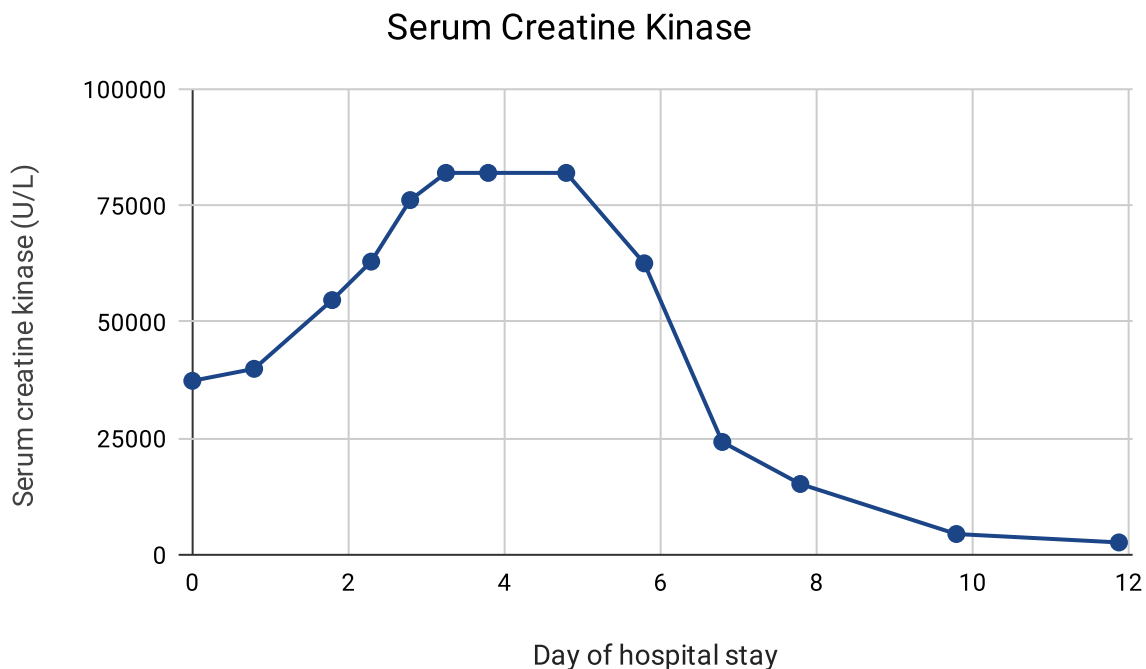
Around four days earlier, the patient had gone on a family trip and walked significantly more than usual. She subsequently developed acute leg muscle weakness. The patient denied any other significant past medical history or known allergies and denied taking regular medications at home. The patient was a nonsmoker and nondrinker. The patient noted poor appetite and weight loss of approximately 3 kg since her procedure a month prior.

On examination, the patient had a small frame and weighed 45 kg. There was muscle weakness with hip flexion, power 3/5 bilaterally. There were no other upper or lower extremity muscle symptoms.

Laboratory test results revealed a markedly elevated serum creatine kinase (CK) at 37345 U/L (0-160 U/L), as well as acute kidney injury (AKI): serum creatinine was 104  $\mu\text{mol/L}$  (46-92  $\mu\text{mol/L}$ ), compared to 64  $\mu\text{mol/L}$  at discharge one month prior. Serum alanine aminotransferase (ALT) was 313 U/L (14-49 U/L), serum potassium was 2.9 mmol/L (3.5-5.0 mmol/L) and serum calcium was 2.02 mmol/L (2.18-2.58 mmol/L). Calculated serum LDL-C was 1.45 mmol/L (target <2.0 mmol/L for high or intermediate cardiovascular disease risk). Urine was dark brown in colour.

The patient was diagnosed with statin-induced rhabdomyolysis and admitted to general internal medicine. Rosuvastatin was held immediately and she was treated with a combination of

intravenous normal saline and 100 mEq sodium bicarbonate at 150 mL/hr. Hypokalemia, hypophosphatemia and hypocalcemia were corrected. By day 5, the patient's serum CK remained above the maximum value reported by our core lab (>82000 U/L); at this point other potential causes were considered including hypothyroidism, inflammatory myositis, and autoimmune myopathy. However, on day 6, the patient's CK started to decrease. Intravenous normal saline was continued in addition to furosemide 40mg IV twice daily. Cardiology assessed the patient and discontinued her statin as her LDL-C level was well below target. The patient was ultimately discharged on day 12 of hospital stay with a serum CK of 2638 U/L and followed up in the outpatient internal medicine clinic.



**Figure 1.** Serum creatine kinase over hospital course. *Note: \* maximum CK value detected by hospital core lab was 82000 U/L*

## Discussion

Rhabdomyolysis is an acute medical condition which results in skeletal muscle cell necrosis. Clinical presentation often involves proximal limb weakness, pain, and swelling, as well as tea-coloured gross pigmenturia. It is characterized by the leakage of muscle cell contents—including myoglobin, CK, and ALT—into the bloodstream. Myoglobin-induced AKI is the most significant complication and can increase mortality. However, long term survival is favourable and majority of patients regain renal function when treated (3).

Statins are an important nontraumatic, nonexertional cause of rhabdomyolysis, accounting for around 2.5% of the etiologies (4). The mechanism of statin-associated muscle symptoms is not well understood. Different statins also have different pharmacokinetics.

Rosuvastatin has maximal effect at 4 weeks, is mainly metabolized by CYP2C9 in the liver and has a half-life elimination time of 19 hours (5).

According to the Canadian Cardiovascular Society, a 50% reduction in LDL-C is recommended following PCI, which usually requires a moderate to high dose of a statin (1). For rosuvastatin, these are typically defined as 5-10 mg and 20-40 mg, respectively. However, Canadian pharmaceutical labelling recommends starting with 5 mg in Asian patients regardless of moderate or high intensity dosing, due to studies that show patients of Asian or Asian-Indian origin have a 2-fold increase in median exposure when compared to a Caucasian control group (5,6). The maximum dose of 40 mg is actually contraindicated in these patients (5). Interestingly, although Asians achieve similar benefits compared to European Americans at lower statin doses, both in terms of LDL-C lowering efficacy and decreased adverse cardiovascular events, evidence to date shows no increased rates of adverse events (myopathy, rhabdomyolysis) in Asian patients taking either lower or higher doses of statins (7).

**Table 1** shows the risk factors that have been associated with statin-associated muscle symptoms, including myalgia and rhabdomyolysis (5,6). In this case, the patient had multiple risk factors including advanced age, frailty, Chinese race, and excessive physical exercise, hence should have been started on a lower dose (5 mg) of rosuvastatin and titrated up as tolerated. Non-statin lipid-lowering agents, such as proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors evolocumab or alirocumab, may also be considered.

This case report highlights the need to consider each patient's risk profile for rhabdomyolysis and individualize dosage appropriately when prescribing statins. Educating patients and caregivers about symptoms is also important for prompt medical treatment.

**Table 1.** Risk factors for statin-associated muscle symptoms

<b>Risk factor</b>	<b>Comment</b>
Pre-existing or family history of muscular disorders	Amyotrophic lateral sclerosis, myasthenia gravis, metabolic myopathy (carnitine palmitoyltransferase 2 deficiency or McArdle's disease)
Previous history of muscle toxicity with another statin	Hypersensitivity syndrome that may include anaphylaxis, angioedema, inflammatory conditions such as polymyalgia rheumatica, fever, chills, dyspnea
Concurrent drug therapy	CYP3A4 inhibitors, fibrates, fusidic acid, niacin
Hypothyroidism	
Hepatic impairment or alcohol abuse	Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal. In patients with severe liver disease (Child-Pugh 8 and 9), systemic exposure was increased by at least 2-fold compared to patients with lower Child-Pugh scores.
Renal impairment	Creatinine clearance < 30 mL/min/1.73 m <sup>2</sup> . Patients have a 3-fold increase in plasma concentration compared to healthy volunteers
Advanced age	Elderly patients >70 years are more susceptible to myopathy
Frailty	Small body frame
Excessive physical exercise	
Diabetes with hepatic fatty change	
Surgery and trauma	
Special populations	Filipino, Chinese, Malaysian, Japanese, Korean, Vietnamese or Asian-Indian patients have around a 2-fold increase in serum concentration

### **Declaration of Interests**

The authors have no potential conflicts of interest to disclose.

### **Consent**

Written consent for this case report was given by the patient's daughter on August 27, 2019.

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