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Pravastatin-induced rhabdomyolysis and purpura fulminans in a patient with chronic renal failure



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ABSTRACT

INTRODUCTION: Rhabdomyolysis associated with the use of pravastatin has been demonstrated to be a rare but potentially life-threatening adverse effect of statins. Here, we report a rare case of rhabdomyolysis and purpura fulminans in a patient who had used pravastatin and developed chronic renal failure (CRF) necessitating the initiation of dialysis.

PRESENTATION OF CASE: We present the case of an 86-year-old man with chronic kidney disease (CKD) treated with dialysis who was admitted with back pain. He was prescribed and took pravastatin for almost 3 years to treat hyperlipidemia. He received hemodialysis therapy 7 times prior to presentation. Laboratory values included a serum creatine concentration of 6.6 mg/dl and a creatinine phosphokinase (CPK) concentration of 2350 IU/L. An abdominal computed tomography scan showed swollen muscles with reduced muscle density and air density in the multifidus muscle. Two days after admission, he had large, tender ecchymotic lesions and purpuric progressive skin necrosis over the back, abdomen, and upper and lower extremities. The patient died 6 days after the initial admission due to disseminated intravascular coagulation (DIC). Based on these findings and the clinical history, a diagnosis of pravastatin-induced rhabdomyolysis and purpura fulminans was made.

DISCUSSION: The long-term use of statin therapy and the initiation of dialysis therapy due to ESRD, followed by a rapid onset of rhabdomyolysis within 6 days, is indicative of an elevated statin concentration. **CONCLUSION:** We report an extremely rare case of pravastatin-induced rhabdomyolysis and purpura fulminans with DIC in a patient with CRF.

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1. Introduction

The ability of statins to reduce the risk of cardiovascular morbidity and mortality in patients with dyslipidemia is well established [1]. In general, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are well tolerated by most users [2]. Statins are also associated with rhabdomyolysis, which may raise concerns about possible adverse drug interactions. The typical clinical presentation of rhabdomyolysis includes muscle weakness, myalgias and dark-colored urine due to myoglobinuria. The diagnosis is usually based on elevated serum skeletal muscle enzyme

levels [3]. Purpura fulminans is an acute illness characterized by rapidly progressive dermal vascular thrombosis and disseminated intravascular coagulation (DIC), leading to hemorrhagic skin necrosis and soft tissue necrosis.

We report an extremely rare case of rhabdomyolysis of the multifidus muscle with pravastatin monotherapy in a patient with chronic renal failure (CRF) that may have resulted in purpura fulminans with DIC. Here, we report this rare case and review the related literature.

2. Presentation of case

The patient was an 86-year-old man with chronic kidney disease (CKD) who also had hyperlipidemia. His past medical history was significant for pravastatin treatment (10 mg once daily) for

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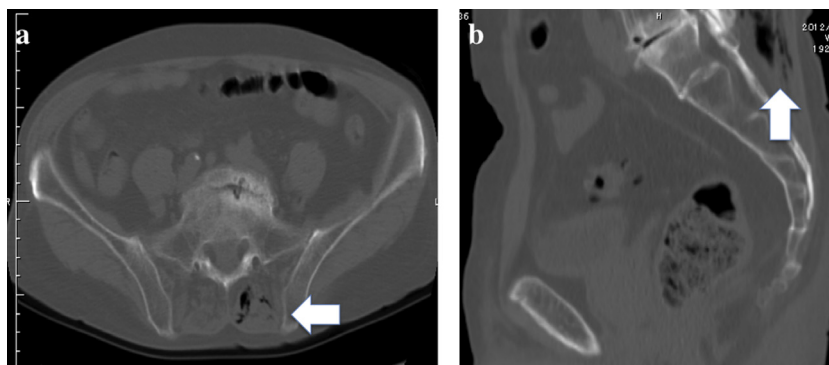


Fig. 1. (a): An abdominal computed tomography (CT) scan showing a large area of low attenuation in the multifidus muscle (arrow). (b): The multifidus muscle was slightly edematous. No calcification was observed.

almost 3 years. He was diagnosed with end stage renal disease (ESRD) and started hemodialysis three times per week. He received hemodialysis therapy 7 times before presentation. Before the initiation of dialysis therapy, the patient's serum creatinine was 4.7 mg/dL, urea 122 mmol/L, and the thyroid-stimulating hormone concentration and liver function were within normal limits. Past medical history included the following pertinent negatives: no recent viral illness, history of trauma, or epilepsy, and the absence of any other medications that could potentially be associated with rhabdomyolysis. Upon admission, the patient had generalized muscle pain and back pain and the following laboratory values: white blood cell count, 7800 mm³; platelet count, 28,000 μ l; Aspartate aminotransferase (AST), 77 U/L; alanine aminotransferase (ALT), 22 U/L; LDH, 356 U/L; triglycerides, 107 mg/dL; total cholesterol, 119 mg/dL; myoglobin, 3000 μ g/mL; creatine, 6.6 mg/dL; and creatine phosphokinase (CPK), 2350 IU/L. The elevated CPK was not cardiac in origin because both electrocardiography and myocardial enzymes markers were within normal limits. Lab values demonstrated evidence of disseminated intravascular coagulation (DIC) and were as follows: prothrombin time, 18.3 s; active partial prothrombin time, 38.5 s; fibrinogen degradation product, 24.1 μ g/mL; and D-dimer, 12.9 mg/mL. Two days after admission, he had large, tender ecchymotic lesions and purpuric, progressive skin necrosis over the back, abdomen, and upper and lower extremities. An abdominal computed tomography (CT) scan showed swollen muscles with reduced muscle density and air density in the multifidus muscle (Fig. 1 a and b) [4]. No calcification was observed in the multifidus muscle. These findings, along with the clinical history, confirmed a diagnosis of pravastatin-induced rhabdomyolysis with purpura fulminans. The patient died 6 days after the initial admission due to DIC (Fig. 2 a and b).

3. Discussion

The most noteworthy adverse reactions associated with statins are elevations in myopathy and rhabdomyolysis, which is characterized by massive muscle necrosis, myoglobinuria, and acute renal failure [5]. In a recently published review, it was suggested that myopathy occurred in 20% of patients receiving statin therapy [6]. The risk of rhabdomyolysis with statin monotherapy is dose related [7,8]. The adverse events submitted to the FDA, including myalgia, rhabdomyolysis, an increase in CPK level and other muscular events, were associated with pravastatin, simvastatin, atorvastatin, and rosuvastatin. These events were more noteworthy for rosuvastatin than pravastatin and atorvastatin [9]. Acute renal failure was also associated with all 4 statins [9].

The clinical manifestations of rhabdomyolysis associated with statins are nonspecific. This condition presents as myalgias, weakness, fatigue, and dark-colored urine, which usually develop within a few days of starting the treatment. Pravastatin monotherapy is associated with the potentially fatal side effect of rhabdomyolysis, which induces DIC and purpura fulminans in our case. Rhabdomyolysis associated with pravastatin monotherapy is extremely rare and may result in myoglobinuria with acute renal failure.

Several factors have been identified that increase the risk for both myopathy and rhabdomyolysis, including advanced age, CRF, metabolic disorders, major surgery, and alcohol abuse [10–12]. Statins are safe and valuable drugs in patients with renal insufficiency. However, it may be prudent to limit the dose of pravastatin (<20 mg/day) as well as simvastatin (<10 mg/day) in patients with a GFR below 10 mL/min and prior to dialysis [13]. The side effects of statin treatment include gastrointestinal complaints, gallstones, and skin reactions, all of which are tolerable and reversible.

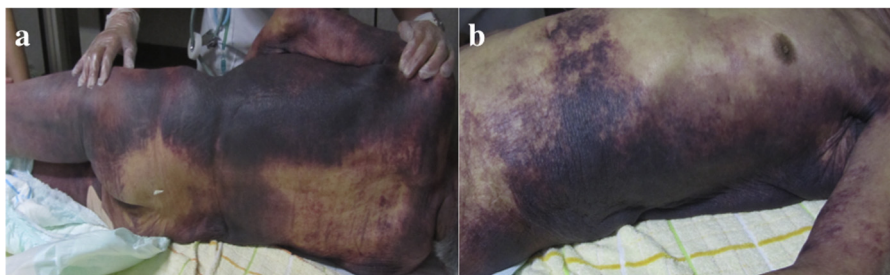


Fig. 2. (a) and (b): Ecchymotic lesions and necrotic purpura on the upper and lower extremities, back, and abdomen.

The mechanism of rhabdomyolysis with statins is poorly defined. The occurrence is known to increase with dose concentration [7,8]. Sakamoto [14] suggested that fluvastatin and pravastatin induced the formation of numerous vacuoles in the myofibers after 72 h of treatment in rats and inactivation of Rab GTPase, which is involved in intracellular membrane transport and is a crucial factor in statin-induced-morphological abnormality in the skeletal muscle fibers. This risk increases in patients taking concomitant drugs that inhibit the cytochrome P450 (mainly CYP2C9 or CYP3A4)-related statin metabolism such as azole antifungals, cyclosporine, fibrates, macrolides, and non-dihydropyridine calcium channel blockers [14,15]. Although pravastatin is primarily eliminated by sulfation, all other available statins are metabolized by the CYP system [15–17]. The metabolic processes include phase I oxidation (mediated by CYP isoenzymes) and phase II glucuronidation (mediated by UDP glucuronosyl transferase). Pravastatin has no phase metabolism and is minimally metabolized by phase II glucuronidation. Most statins are eliminated through biliary excretion; however, pravastatin is partially eliminated by renal excretion. Inhibition of statin metabolism (Phase I or II) and/or active membrane transport may result in elevated statin concentration and has the potential to increase the risk for statin-related adverse events. In our case, the long-term use of statin therapy and the initiation of dialysis therapy due to ESRD, followed by a rapid onset of rhabdomyolysis within 6 days, is indicative of an elevated statin concentration. However, experience with this situation is limited, particularly in a patient with severe impairment of renal function requiring dialysis. It is thought that drug or metabolic accumulation and uremia-related muscle injury increase the risk of myositis.

The CT findings of rhabdomyolysis revealed either focal areas of hypodensity or hyperdensity consistent with calcification in the affected muscles. Focal hypodense areas are usually explained by edematous or necrotic muscles in the acute phase of rhabdomyolysis [4,18]. A CT scan can distinguish normal muscles from abnormal muscles and can clearly demonstrate necrosis in our case.

Purpura fulminans has been reported as a complication of overwhelming infection with *Neisseria meningitidis* or varicella, and more recently *Streptococcus pneumoniae* [19]. Purpura fulminans results in microvascular thrombosis with hemorrhagic skin and soft tissue necrosis. Coagulation abnormalities in sepsis or rhabdomyolysis range from a small decrease in platelet count and subclinical prolongation of global clotting times to fulminant DIC, which is characterized by simultaneous whispered microvascular thrombosis and profuse bleeding from various sites. The pathogenesis of purpura fulminans with digital gangrene is unclear and thought to be related to the development of DIC [19]. The combination of widespread gangrene and laboratory evidence of DIC confirmed the diagnosis of purpura fulminans in our case. In dialysis patients, the situation is different and the risk of drugs and metabolite accumulation is most likely more severe. To the best of our knowledge, this is the first report of pravastatin monotherapy resulting in rhabdomyolysis of the multifidus muscle and purpura fulminans with DIC.

In summary, pravastatin monotherapy is associated with the potentially fatal side effect of rhabdomyolysis in a patient with chronic renal failure. We report an extremely rare case of pravastatin-induced rhabdomyolysis and purpura fulminans with DIC in a patient with CRF. Early diagnosis and treatment are essential to improve the outcome. Diagnosis requires a high degree of clinical suspicion.

Conflicts of interest

None of the authors have identified a conflict interest.

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Consent

Written informed consent was obtained from the patient's relatives for publication of this manuscript and any accompanying images. Copies of the written consent are available for review by the Editor-in-Chief of this journal.

Author contributions

Dr. Kato had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Kato, Sasahara, Onodera.

Acquisition of data: Kato, Ki, Taniguchi, Kawakami.

Analysis and interpretation of data: Kato, Sasahara.

Drafting of the manuscript: Kato, Furukawa.

Critical revision of the manuscript for important intellectual content: Kato, Matsuda.

Administrative, technical, or material support: Sasahara, Higuchi.

Study supervision: Onodera, Furukawa.

Key learning point

- Pravastatin monotherapy is associated with the potentially fatal side effect of rhabdomyolysis in a patient with chronic renal failure.

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