Case report

Rosuvastatin-related rhabdomyolysis causing severe proximal paraparesis and acute kidney injury

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SUMMARY

We describe the case of a 76-year-old man who presented with bilateral lower limb weakness associated with decreased urine output. His initial blood results showed acute kidney injury (AKI) stage 3 with substantially raised serum creatine kinase concentration of 37 950 IU/L (normal range <171 U/L). He had been on high-dose rosuvastatin for 4 years with a recent brand change occurring 1 week prior to onset of symptoms. There was no history of pre-existing neuromuscular disease. Statin-related rhabdomyolysis was suspected and rosuvastatin was withheld. His muscle strength gradually improved. He required haemodialysis for 10 weeks. He was discharged home after a complicated course of hospitalisation. His renal function improved and he became dialysis-independent; however, he was left with residual chronic kidney disease.

BACKGROUND

Statins are the cornerstone therapy in prevention of cardiovascular diseases, and like all medications it comes with its own set of precautions and adverse effects. They are widely prescribed medications and therefore it is important that all medical practitioners involved in its prescription are aware about the profile of adverse effects. Statins are known myotoxins and can cause a spectrum of muscle-related adverse effects ranging from myalgia up to life-threatening rhabdomyolysis that results in significant morbidity. Patients on intensive statin therapy must be monitored closely and attempt must be made to reduce statin dose if low-density lipoprotein (LDL) goals are attainable with lower doses of statin.

CASE PRESENTATION

A 76-year-old man with background of ischaemic heart disease, hypertension and chronic kidney disease (CKD) (stage 3a) presented with 3-week history of progressive muscle pain in his thighs and calves, lower limb weakness and difficulty ambulating. He also noted the presence of dark urine with gradual decrease in his urine output. There was no similar presentation in the past. There was no preceding history of strenuous physical activity or significant trauma. There was no associated fever, rash, influenza symptoms, weight loss or joint pain. There was no history of urinary tract obstructive symptoms. His medical history was significant for ischaemic heart disease for which he underwent triple vessel bypass 4 years ago. He had been commenced on rosuvastatin 40 mg per day by his cardiologist and had been on the same dose for the past 4 years with a recent change of brand occurring 1 week prior to onset of symptoms. He was not on any other concomitant lipid-lowering therapy. His renal and liver function had been stable for the last 2 years. His other medications included telmisartan, aspirin and bisoprolol. There was no history of recent antibiotic or any over-the-counter medication use to explain a possible drug interaction. He consumed three standard alcoholic drinks, three times a week for the last 5 years; however, he denied any alcohol intake over the last 4 weeks. He was a non-smoker. There was no history of illicit drug use.

At the time of presentation, he was alert, afebrile and normotensive. There were no clinical signs of volume overload present. There was no pericardial rub. Neurological examination revealed tender thighs and calves with profound weakness in proximal muscle groups. The power in hip flexors and extensors was 2/5, without any sign of wasting or fasciculation. Deep tendon reflexes and sensory examination were normal. There was no associated joint pain or swelling, or skin changes.

INVESTIGATIONS

The results of initial set of laboratory investigations are outlined in table 1.

He was noted to be anuric at the time of presentation. His blood pressure was preserved at that time and clinically he did not appear hypoperfused. His blood urea nitrogen (BUN)/creatinine ratio was 12. He was initially managed with aggressive intravenous fluid therapy, but failed to produce adequate urine output with volume expansion. We did not use sodium bicarbonate for alkalinising the urine. He subsequently developed signs of fluid overload with refractory hyperkalemia. He was therefore started on continuous renal replacement therapy (CRRT) via a temporary dialysis catheter in high-dependency unit. Electrolyte and metabolic abnormalities were also corrected appropriately. The creatine kinase level gradually declined, however his renal function did not recover. Case was discussed with the nephrology team at a tertiary hospital, and it was decided to transfer him for further management as he would likely require ongoing haemodialysis. This is due to our limited capacity as a regional hospital to initiate haemodialysis for new patients. He had a permacath inserted and was started on regular haemodialysis, as he was dialysis-dependent.

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Table 1 Initial set of laboratory results at admission.

Parameter	Result	Reference range/units
WBC	17.4	(3.6–9.2×10^9)/L
Hb	155	(137–172) g/L
Platelet	204	(140–320×10^9) /L
Urea	47.5	(3.3–7.6) mmol/L
Creatinine	976	(62–106) µmol/L
eGFR	4	(>60) mL/min/1.73 m^2
Sodium	140	(135–145) mmol/L
Potassium	5.7	(3.5–5.2) mmol/L
Venous blood gas		
pH	7.32	(7.34–7.44)
Bicarb	17	(22-28) mmol/L
Base excess	–8	(–3.2–1.8) mmol/L
ESR	34	(0–20) mm/hour
Liver function test		
Bilirubin	17	(<17) µmol/L
Albumin	31	(34–48) g/L
GGT	132	(10–71) U/L
ALT	339	(4–41) U/L
AST	522	(4–37) U/L
ALP	116	(30–110) U/L
Urine analysis	Leucocytes : 30×10^6/L	
	Erythrocytes : 10×10^6/L	
	Epithelial cells :<1×10^6/L	
	Protein/creatinine: 465	mg/mmol
	Albumin/creatinine: 104	<2.5 mg/mmol
Creatine kinase	37 950	(<170) U/L
Troponin T	1099	(<14) ng/L
Serum myoglobin	60	0.02–0.11 mg/L
Corrected calcium	2.28	(2.10–2.60 mmol/L
Phosphate	2.97	(0.75–1.50 mmol/L
Parathyroid hormone	13	(1.6–6.9) pmol/L
Septic workup		
CRP	5	<5.0 mg/L
Blood culture	Negative	
Urine culture	Negative	
Sputum culture	Negative	
Stool PCR	Negative	

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; Hb, haemoglobin; PCR, polymerase chain reaction; WBC, white blood cell.

Table 2 Results of myopathy workup.

Parameter	Result	Range (unit)
Autoimmune workup		
C3	1.35	0.90–1.80 g/L
C4	0.28	0.10–0.40 g/L
IgM	1.74	0.40–2.30 g/L
IgG	7.4	7.00–16.0 g/L
IgA	1.58	0.70–4.00 g/L
ASOT	26	0–200 IU/mL
ANA	Positive (speckled: 80)	
ANCA	Negative	
Anti-GBM	Negative	
Extractable nuclear antigens	Negative	
Myositis antibodies	Negative	
Virology workup		
Respiratory PCR	Negative	
HBsAg	Non-reactive	
HCV Ab	Negative	
HAV Ab	Negative	
HIV	Negative	
EBV, HSV, VZ, CMV PCR	Negative	
Enterovirus antibodies	Negative	
Serum protein electrophoresis		
Kappa free LC	38	(3.3–19.4) mg/L
Lambda free LC	44.9	(5.7–26.3) mg/L
K/L ratio	0.86	(0.26–1.65)
Total protein	56	60–80 g/L
Albumin	22	35–50 g/L
Monoclonal protein	Undetectable	
TSH	5.6	4–6 mIU/L
HBA1c	4.50%	
Vitamin B_{12}	321	(179-660) pmol/L
Folate	10.2	(8.9–45.2) nmol/L
PSA	1.09	(<6.22) ug/L
Vitamin D	40	25–75 ng/mL

ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; Anti-GBM, anti-glomerular basement membrane; ASOT, antistreptolysin O titre; C3, Complement 3; C4, Complement 4; CMV PCR, Cytomegalovirus Polymerase Chain Reaction; EBV, Epstein-Barr virus; HAV Ab, Hepatitis A virus antibody; HBA1c, glycosylated haemoglobin; HBsAg, Hepatitis B surface antigen; HCV Ab, Hepatitis C virus antibody; HIV, Human Immunodeficiency Virus; HSV, Herpes Simplex Virus; IgA, Immunoglobulin A level; IgG, Immunoglobulin G level; IgM, Immunoglobulin M level; LC, light chain; PCR, Polymerase Chain Reaction; TSH, thyroid stimulating hormone; VZ, Varicella Zoster.

After review of the initial laboratory results and subsequent negative renal screen (table 2), it was apparent that he had suffered from rhabdomyolysis resulting in dialysis-dependent acute kidney injury (AKI). The most likely offending agent from an initial assessment was statin. Statin and telmisartan were both withheld and a comprehensive myopathy workup was requested (table 2). All the relevant autoimmune, virology workup was negative. Renal imaging showed normal-sized kidneys with no signs of urinary tract obstruction. CT scans of chest, abdomen and pelvis did not identify any occult malignant process. Echocardiogram showed normal left ventricular size with mild to moderate systolic dysfunction. There was no evidence of interstitial lung disease on high-resolution chest CT scan.

MRI of the extremities was performed. It showed widespread myositis with muscle atrophy throughout the gluteal, pelvis and lower limb muscles. Bilateral lower limb sensory and motor responses were all normal on nerve conduction studies. Electromyographic (EMG) study showed active denervation potentials and polyphasic units with normal duration, consistent with recent rhabdomyolysis with no evidence of pre-existing myopathic changes. Autoantibodies directed against 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase were negative. A neurology consult was sought and they agreed with the diagnosis of rhabdomyolysis. Their recommendation was for ongoing physiotherapy and rehabilitation.

DIFFERENTIAL DIAGNOSIS

Our patient presented with severe rhabdomyolysis that was complicated by AKI. The differentials of non-traumatic and non-exertional rhabdomyolysis are fairly limited. There were no significant electrolyte derangements on his initial metabolic profile to suggest a metabolic cause for rhabdomyolysis. There was no history suggestive of exposure to toxins or snake venom.

Our workup for infectious causes failed to point towards any infectious aetiology. The inflammatory myopathy workup was also negative. Among drug-related causes, the likely offending agent was statin, which is a recognised myotoxin. The muscle-related adverse effect of statin is more profound in advanced age, hypothyroidism, hypovitaminosis D, CKD or obstructive liver disease. Our patient had two of these risk factors and had been on high-dose rosuvastatin.

TREATMENT

Since the muscle strength was noted to improve spontaneously after cessation of statin, it was decided not to proceed with muscle biopsy. No steroids or other immunosuppressive therapy was administered for the myopathy. The myopathy and the complicated course of hospital stay left him significantly deconditioned and he required 3 months stay in rehabilitation ward to facilitate his recovery.

OUTCOME AND FOLLOW-UP

Our patient required regular haemodialysis for 10 weeks. His renal function partially recovered and he was able to come off renal replacement therapy. Nevertheless, he seemed to have suffered an irreversible renal insult after the rhabdomyolysis episode. He was followed-up in the nephrology clinic after discharge. His creatinine level at 6 months after the initial presentation had stabilised at 176 μmol/L with an estimated glomerular filtration rate 30 mL/min/1.73 m^2 from a previous baseline of 120 μmol/L. It was decided to subsequently withhold statin therapy and consider monotherapy with ezetimibe for secondary prevention of ischaemic heart disease.

Retrospectively, we reviewed the previous results of his lipid tests to see if our patient had a compelling indication to remain on high-dose rosuvastatin for the last 4 years. We found that his LDL cholesterol (LDL-C) levels were consistently below 2 mmol/L, but there had been no attempts made on reducing his statin dose. The package insert for rosuvastatin advises caution regarding using 40 mg dose in advanced age (>65 years) and those individuals with CKD. The 40 mg dose of rosuvastatin is only recommended if the LDL-C goals cannot be achieved with the 20 mg dose. Thus we highlight a rare, yet significant complication of high-dose statin therapy. This case serves as an important reminder of individualising medical therapy to suit every individual's unique requirement. Even though high-dose statin has been repeatedly proven to reduce morbidity and mortality in prevention of cardiovascular diseases, yet a vigilant medical practitioner has to consider the benefit versus risk of high-dose statin therapy, especially with older patients who have other risk factors for statin-associated rhabdomyolysis.

DISCUSSION

Statins are most effective and widely prescribed medications that have been demonstrated to significantly lower the risk of cardiovascular disease. For majority of patients, they have been shown to have a good side effect profile.[1]

Rhabdomyolysis is a serious condition that is characterised by rapid breakdown of skeletal muscle fibres and the release of intracellular muscle contents into systemic circulation.[2] It is an important cause of AKI via different mechanisms. With rhabdomyolysis, there is a massive necrosis of the muscle cells that release myoglobin into the circulation. Subsequently, myoglobin precipitates in the glomerular filtrate and causes mechanical obstruction of the tubules. Other contributing factors for AKI are vasoconstriction, hypovolemia and direct renal toxic effect of myoglobin.[3 4] Delayed presentations in cases of severe rhabdomyolysis can lead to acute tubular necrosis. Determinants of slow or no recovery for cases of AKI secondary to acute tubular necrosis include: AKI requiring renal replacement therapy, pre-existing CKD, history of diabetes or heart failure.[5] Our patient had all these features, and this would explain why it took a period of time for the renal function to improve.

The National Lipid Association Statin Muscle Safety Task Force has defined statin-related rhabdomyolysis as myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of at least 44 μmol/L (0.5 mg/dL)).[6] There is great interest in determining the exact pathophysiology related to the myotoxic effect of statin, and clinical research is underway to identifying potential genetic predispositions that confer an individual susceptible to statin-related adverse effects.[7 8]

Fortunately, the profiles of clinically significant adverse effects are uncommon. The incident of rosuvastatin-associated myopathy was reported to be comparable with placebo in trials that extended over a median follow-up interval of 1.9 years.[9] However, statin-associated rhabdomyolysis risk has been described as dose-dependent and concentration-dependent.[10] This association would need to be explored further, given the widespread use of statin in individuals who often have risk factors for statin-associated rhabdomyolysis. These risk factors include older age, female sex, low body mass index, hypothyroidism, diabetes mellitus and impaired renal or hepatic function for statin-associated rhabdomyolysis.[11] Our patient had three of these risk factors present, which when combined with long-term high-dose rosuvastatin therapy resulted in rhabdomyolysis. Whether the recent brand change to an equivalent dose of statin had any influence on the occurrence of this complication cannot be completely ascertained.

The tendency to cause muscle injury varies among different statins. The more hydrophilic statins (such as pravastatin, rosuvastatin and fluvastatin) have lesser penetration into the skeletal muscle fibres, thus less likely to cause muscle injury. Rosuvastatin is hydrophilic in nature and not extensively metabolised by the liver P450 system. In fact, the rates of muscle toxicity with rosuvastatin 20 mg per day were similar to placebo.[9] However, there have been reports of rhabdomyolysis with higher doses of rosuvastatin in myopathy-prone patients. At this stage, we cannot ascertain if the brand change that preceded the occurrence of rhabdomyolysis in our patient is clinically significant or not. To the best of our knowledge, we have not come across any other similar case where a statin brand change caused rhabdomyolysis. It probably needs to be explored further.

The onset of statin-related adverse effects are usually seen within weeks to months after commencing statin therapy but may occur at any time during the course of treatment. Generally the onset seemed to have been triggered by a recent dose change, addition of a new medication or a change in exercise status.[12] Our patient had been on the same dose of rosuvastatin for 4 years and it is unclear what precipitated the sudden rhabdomyolysis. In a review of 45 patients with statin-associated myopathy, Hansen *et al* have shown that 13% were hospitalised for the management of rhabdomyolysis; two had reversible renal dysfunction and one with pre-existing renal insufficiency subsequently began lifelong dialysis.[9]

Renal replacement methods have a supportive role but they are not the first line of treatment for AKI-induced rhabdomyolysis, especially in cases of preserved diuresis.[13] Although various forms of renal replacement have been used in managing patients with rhabdomyolysis-related AKI, there is no specific evidence-based recommendation favouring a

specific form of dialysis.[14 15] The decision to initiate dialysis must not be dictated by the initial serum myoglobin or creatine kinase levels but by the usual metabolic or circulatory complications of AKI. Our patient was started on CRRT and gradually shifted from CRRT to intermittent haemodialysis therapy as his recovery was slow. It took him a period of time for his renal function to recover and he remained on intermittent haemodialysis for 10 weeks. Eventually diuresis ensued, his biochemical parameters progressively improved and we were able to withdraw dialysis.

Immune-mediated necrotising myopathy is an autoimmune myopathy involving statin treatment. Patients classically exhibit progressive proximal muscle weakness, with elevated creatine kinase (CK) values between 10 and 100 times the upper limit, myopathic EMG findings, and muscle biopsy usually showing necrosis with regeneration of muscle fibres and scarce inflammation. There is a degree of clinical overlap between statin-related self-limited toxic myopathy and statin-induced autoimmune myopathy. However, the main differentiating feature is that statin withdrawal does not usually improve the patient's symptoms in autoimmune myopathy and immunosuppressive treatment is required to obtain a clinical response. If patients with severe statin-related rhabdomyolysis do not improve with statin cessation, it is worthwhile to check for anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) antibodies. If the antibodies test positive, immunosuppressive treatment should be considered.[16 17]

In patients with statin-related rhabdomyolysis, statin cessation is the general recommendation. If the patient has high cardiovascular risk factors, then they should be considered for other approved lipid-lowering agents like PCSK9 inhibitors.

In severe cases of rhabdomyolysis, once AKI is established, it requires close monitoring as a significant proportion of these cases may require renal replacement therapy. These patients may progress to developing a residual renal damage and CKD.[18 19]

Prescription of high-potency statins is associated with an increased rate of hospital admission for AKI, compared with lower potency statins. Therefore prescribers should consider this potential risk when contemplating use of high-potency statins in clinical practice, particularly when treatment with a low-potency statin is an option.[20]

Learning points

- Statins are very potent and effective medications, but can also cause significant adverse effects. It is important to individualise statin treatment to each individual.
- Statin-related myotoxicity can range from mild muscle pain up to life-threatening rhabdomyolysis.
- Patients on statin therapy must be monitored for muscle-related adverse effects. Patients treated with statins should be alerted to report the new onset of myalgias or weakness. Statin must be withheld if weakness is noted.
- Statin-related muscle symptoms and/or signs usually begin within weeks to months after starting statins. However, a delayed reaction is also possible. It is recommended to screen for precipitating causes in these cases.
- Patients on intensive statin therapy must be monitored closely and attempt must be made to reduce statin dose if low-density lipoprotein goals are attainable with lower doses of statin.

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