A Rare Presentation of Acute Renal Failure Secondary to Rhabdomyolysis in a Patient Due to Atorvastatin Requiring Short-Term Renal Replacement Therapy

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Abstract

Renal failure secondary to rhabdomyolysis due to statins is quite rare. We present a case of a 57-year-old patient who developed acute renal failure due to rhabdomyolysis secondary to atorvastatin. Interestingly, this patient had a similar presentation 27 years ago requiring dialysis only once resulting in complete resolution of symptoms. He presented to the hospital generally feeling unwell and then developed generalized body ache. He had an extremely elevated creatinine kinase level of 116,000 and it went up to 145,000. His urine dip was negative for nitrites and was positive for blood and protein. He was commenced on intravenous fluids. He also had a computerized tomographic scan of the kidneys, ureters, and bladder, which showed some fat stranding around both kidneys likely inflammatory in origin. His creatinine level continued to rise despite intravenous fluids and was acidic on blood gases. He also tested positive for COVID-19 on day 7 of admission and eventually needed dialysis. His renal functions improved to baseline post dialysis and kidney functions returned to normal. His autoimmune screen was negative and his renal functions remained normal on a follow-up visit.

Introduction

Statins belong to the group hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and have become the most widely prescribed drug worldwide since its introduction in 1987 with approximately, 25 million patients were on statin medications in 2008 [1,2]. Statins are effective lipid-lowering drugs that result in reduced cardiovascular morbidity and mortality, and although they are generally safe but can result in serious adverse effects rarely. As the indications for statins use have increased, so has the prescription and more patients are on statins today than ever before, which has resulted in a higher risk of side effects and there is not a single reliable predictive tool that can provide an accurate estimation of risk of developing these serious adverse effects [2].

Rhabdomyolysis is a very serious but rare complication of lipid-lowering therapy particularly statins, and the risk is increased by combination therapy of statin and fibrates likely due to pharmacodynamic interactions. The risk is also increased by advancing age and comorbidities such as diabetes, hypothyroidism, renal impairment, and polypharmacy due to drug interactions again [3]. The main feature of rhabdomyolysis is the release of myoglobin into the bloodstream by muscle necrosis, which can manifest from an asymptomatic elevation of serum muscle enzymes to serious complications such as renal failure requiring renal replacement therapy (RRT) [1].

Statins in general are quite well-tolerated and have mostly minor side effects however the two serious side effects include hepatotoxicity and injury to skeletal muscles that can range from myalgia to myopathy [4]. In the case of myopathy, the serum creatinine kinase (CK) level can increase more than 10-fold at least and occurs in about 0.5% to 1% of patients and the severity is mostly dose-dependent [4]. About 0.04% to 0.2% of patients from this percentage of patients develop rhabdomyolysis and the death rate from fatal rhabdomyolysis is about 0.15 death per million prescriptions [5,6]. The key features of rhabdomyolysis include acute renal injury secondary to deposition of myoglobin in the renal tubules resulting in case formation and compartment syndrome due to skeletal muscle injury and elevated biomarkers such as CK, myoglobin, deranged renal functions and elevated calcium and phosphate levels [5,6]. On the other hand, according to the US Food and Drug Administration Adverse Event Reporting System database, the incidence of statin-induced rhabdomyolysis is about 0.3–13.5 cases per 1,000,000 statin prescriptions [7].
The key management strategies in patients with rhabdomyolysis include include fluid resuscitation and urine alkalinization and occasionally, these patients with refractory hyperkalaemia, acidosis, fluid overload, or uremic complications require RRT [1].

**Case Presentation**

We present a case of a 57-year-old patient who presented to the hospital feeling unwell for the last couple of days. His past medical history (PMH) includes hypertension (HTN), diet-controlled type 2 diabetes mellitus (T2DM), previous renal failure requiring RRT in 1995 secondary to Ezetimibe, and hypercholesterolaemia. His regular medications include atenolol 50 mg once daily (OD), Felodipine 5 mg OD, and Atorvastatin 40 mg once at night (ON) for the last 20 years. He was triple vaccinated against COVID-19 and he had the last vaccine about 4-5 months ago. His clinical examination was unremarkable. His urine dip showed blood 3+, Protein 3+, leukocytes 3+, and nitrites negative. His lab tests showed creatinine 165 \( \mu \text{mol/L} \), urea 8.5 mmol/L, white cell count 17.5 \( \mu \text{L} \), Neutrophils 16.5 \( \mu \text{L} \), C-reactive protein 39 mg/dL, CK level 28,289 U/L, lactate dehydrogenase (LDH) level >1,800 U/L as shown in Table 1.

| Blood test          | Normal value     | Day 1  | Day 3  | Day 6  | Day 10 | Day 18 |
|---------------------|------------------|--------|--------|--------|--------|--------|
| White cell count    | (4.0-11.0) \( \times 10^9/\text{L} \) | 17.5   | 17.2   | 12.5   | 11.2   | 7.5    |
| Neutrophil          | (1.7-7.5) \( \times 10^9/\text{L} \) | 16.5   | 16.0   | 11.5   | 10.2   | 6.4    |
| Platelet            | (150-400) \( \times 10^9/\text{L} \) | 186    | 172    | 232    | 235    | 250    |
| Sodium              | (133-146) mmol/L | 136    | 138    | 137    | 135    | 139    |
| Potassium           | (3.5-5.3) mmol/L | 4.5    | 4.6    | 4.5    | 4.3    | 4.0    |
| Urea                | (2.5-7.8) mmol/L | 8.5    | 4.5    | 3.2    | 13.5   | 7.2    |
| Creatinine          | (61.9 to 110) \( \mu \text{mol/L} \) | 165    | 350    | 699    | 265    | 85     |
| Bicarbonate         | 22-29 mmol/L     | 17     | 16     | 17     | 18     | 22     |
| Creatinine Kinase   | 40-320 U/L       | 28,289 | 135400 | 22500  | 3250   | 195    |
| C reactive protein  | <5 mg/L          | 39     | 89     | 95     | 55     | 25     |

**TABLE 1: Lab test results trend for patient**

His venous blood gases showed metabolic acidosis with Ph 7.32, PCO\(_2\) 4.55, PO\(_2\) 4.7, Bicarbonate (HCO\(_3\)) 18.0, base excess (BE) -8.2, lactate 1.2, blood sugar (BM) 7.5 as shown in Table 2.

| Blood test | Normal value     | Day 1  | Day 5  | Day 8  |
|------------|------------------|--------|--------|--------|
| Ph         | 7.35-7.45        | 7.32   | 7.33   | 7.31   |
| Bicarbonate| 22-29 mmol/L     | 18     | 17     | 16     |
| Glucose    | 3.6-5.3 mmol/L   | 7.5    | 5.3    | 5.2    |
| Lactate    | 0.5-2.2 mmol/L   | 1.2    | 1.3    | 1.4    |
| PCO\(_2\)  | 4.6-6.4 kPa      | 4.55   | 4.7    | 6.2    |
| PO\(_2\)   | 11.0-14.4 kPa    | 4.7    | 5.4    | 6.2    |
| Base excess| 2-3 mmol/L       | -8.2   | -9.2   | -8.9   |

**TABLE 2: Venous blood gases results**

He had computerized tomographic scan of Kidneys, ureters and bladder (CTKUB) that showed bilateral renal perinephric stranding, particularly in the right kidney and a 6 mm non-obstructing calculus in the upper pole of left kidney as shown in Figures 1, 2.
His chest radiograph did not reveal any abnormality. He was afebrile and his blood pressure (BP) was 113/65, heart rate was 73 beats per minute and oxygen saturation ($\text{SPO}_2$) was 97% on room air (RA). He was commenced on intravenous fluids and was seen by nephrology team. He was also commenced on oral sodium bicarbonate 500 mg BD. His CK level continued to rise and climbed up to 135,400 on day 3 and started to come down on day 5 and came down to 11,500 on day 7. His catheter got blocked on day 5 and did start draining despite flushing and his catheter was changed. An urinary bladder scan showed only 650 mL urine in the bladder and is unlikely to have contributed to any worsening of renal function. The likely
induced renal failure is mannitol and it has been suggested that it improves renal perfusion, improved respiratory or circulatory collapse, and acidosis. It is important to be mindful of the potential problems that may arise with sodium bicarbonate, such as acute kidney injury (AKI) by increasing the urinary pH above 6.5 and can also be used to correct metabolic acidosis. Bicarbonate makes the urine alkaline thus reducing redox-cycling, lipid peroxidation, and myoglobin cast formation using 1.26% or 1.4% sodium bicarbonate solution and occasionally mannitol. Patients who need good hydration and alkalization of urine may be beneficial to minimize the risk of renal failure by hyperkalaemia, and/or do not respond to medical therapy and may require dialysis however a small proportion needs dialysis mainly if they are acidotic, have resistant infection, or trauma, and dietary effects. The risk of myopathy is closely correlated with the dose of statins and is independent of reductions in low-density lipoprotein cholesterol [10]. The most common risk factors associated with myopathy include advanced age, female sex, low body mass index (BMI), impaired renal and hepatic function, polypharmacy or drug interactions or significant comorbidities, alcohol excess, infections, hypothyroidism, surgery or trauma, and dietary effects [10]. The symptoms of myopathy secondary to statins can disappear in about two months and this was also shown in the PRIMO study [11]. Most patients with myopathy do not require dialysis however a small proportion needs dialysis mainly if they are acidic, have resistant hyperkalaemia, and/or do not respond to medical therapy [1]. The mainstay of management is medical or supportive therapy such as fluids and urinary alkalization and patient who have several renal impairments needs good hydration and alkalization of urine may be beneficial to minimize the risk of renal failure by using 1.26% or 1.4% sodium bicarbonate solution and occasionally mannitol. Bicarbonate makes the urine alkaline thus reducing redox-cycling, lipid peroxidation, and myoglobin cast formation [11]. It is possible that urinary alkalization prevents renal failure and it can be used to prevent acute kidney injury (AKI) by increasing the urinary pH above 6.5 and can also be used to correct metabolic acidosis. It is important to be mindful of the potential problems that may arise with sodium bicarbonate such as paradoxical intracellular acidosis and volume overload in patients who are at higher risk of respiratory or circulatory collapse [11,12]. The other medical treatment used in patients with rhabdomyolysis induced renal failure is mannitol and it has been suggested that it improves renal perfusion, improved diuresis, increased renal perfusion, excretion of myoglobin, and a direct antioxidant effect on renal parenchyma [13]. Nevertheless, it’s important to be aware of the potential side effects of mannitol such as

**Discussion**

Rhabdomyolysis secondary to statins leading to renal failure requiring RRT is quite rare. A large United Kingdom (UK) based cohort study based on patients from general practice between 1991 and 1997 reported the mean incidence of statins induced myopathy to be 1.2 per 10,000 person-years [8]. Another large study reported this incidence in patients on monotherapy with atorvastatin, pravastatin, or simvastatin to be 0.44 and for cerivastatin was 5.34 [9]. It is important to mention that the clinical presentation of statins-induced myopathy can vary significantly and may present as myalgia, myositis, rhabdomyolysis, or asymptomatic increase in creatine kinase concentration [10].

The symptoms from statin-induced myopathy can vary from fatigue, muscle pain or tenderness, muscle weakness or cramps and the average duration for the onset of symptoms in patients newly started on statins was about six months in a small retrospective study, and symptoms resolved on average in about two months in patients after stopping statins [10]. The exact mechanism of statin-induced myopathy is unclear and there are three possible proposed mechanisms that could explain this. The first mechanism includes impaired cholesterol synthesis leading to in the myocyte membrane cholesterol structure and behaviour of membrane and the second mechanism is an impaired synthesis of compounds in the cholesterol pathway resulting in impaired enzyme activity in mitochondria. The third possible mechanism includes depletion of isoprenoids, a lipid-based product of the HMG-CoA reductase pathway preventing myofibre apoptosis.

The risk of myopathy is closely correlated with the dose of statins and is independent of reductions in low-density lipoprotein cholesterol [10]. The most common risk factors associated with myopathy include advanced age, female sex, low body mass index (BMI), impaired renal and hepatic function, polypharmacy or drug interactions or significant comorbidities, alcohol excess, infections, hypothyroidism, surgery or trauma, and dietary effects [10]. The symptoms of myopathy secondary to statins can disappear in about two months and this was also shown in the PRIMO study [11]. Most patients with myopathy do not require dialysis however a small proportion needs dialysis mainly if they are acidic, have resistant hyperkalaemia, and/or do not respond to medical therapy [1]. The mainstay of management is medical or supportive therapy such as fluids and urinary alkalization and patient who have several renal impairments needs good hydration and alkalization of urine may be beneficial to minimize the risk of renal failure by using 1.26% or 1.4% sodium bicarbonate solution and occasionally mannitol.
pre-renal azotemia and volume depletion, and should only be in patients in whom fluid intake is not enough to get 300 mL/hour urine daily and should be avoided in anuric patients [12,13].

There are several studies published on statin-induced rhabdomyolysis and renal failure requiring RRT [3,5,7]. The overall incidence of the disease is small and one study suggested the number needed to treat to observe one case of rhabdomyolysis on statin alone is 22,727 and 484 in diabetic patients who were on combined therapy of statin and fibrates. The number needed to treat (NNT) to observe one case of rhabdomyolysis was 22,727 for statin monotherapy and 484 for older patients with diabetes mellitus taking both a statin and a fibrate.

Statin-induced rhabdomyolysis has also been reported in patients with hypothyroidism and one such case report is based on the presentation of a 74-year-old patient who presented with swelling in his lower limbs, stiffness in his muscles and responded to intravenous fluid hydration and urinary alkalization [1]. Another case report is based on the presentation of 72 years old Sri Lankan patient with a background of high cholesterol, type 2 diabetes mellitus, chronic kidney disease, and hypothyroidism. He presented to Emergency Department with rhabdomyolysis secondary to combination therapy of statin and gemfibrozil [2]. Another 67-year-old man who was on atorvastatin after suffering myocardial infarction (MI) four months ago presented with statin-induced hepatitis, rhabdomyolysis, and AKI and unfortunately passed away [15,14].

In patients with severe rhabdomyolysis, conventional haemodialysis is usually not enough due to its failure to remove the bigger size myoglobin particles, and patients with severe acidosis, fluid overload or refractory hyperkalaemia, require intermittent RRT and renal functions usually return to normal after few sessions of RRT without requiring further RRT [5,12].

**Conclusions**

In conclusion, statin-induced rhabdomyolysis is a rare serious adverse effect of statins resulting in renal failure and patients may require RRT. The risk is increased with combination lipid-lowering therapy and these patients may present with severe rhabdomyolysis which results in renal failure. Our patient case is unique due to the fact that he had severe rhabdomyolysis twice in two decades despite being on two different lipid-lowering therapy and required intermittent haemodialysis both times. Our patient recovered well from the episode and his renal functions returned back to a normal level.

**Additional Information**

**Disclosures**

*Human subjects:* Consent was obtained or waived by all participants in this study. *Conflicts of interest:* In compliance with the ICMJE uniform disclosure form, all authors declare the following: *Payment/services info:* All authors have declared that they have no financial relationships with any organizations that might have an interest in the submitted work. *Financial relationships:* All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. *Other relationships:* All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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