



Severe Anuric Renal Failure from Statin-Induced Rhabdomyolysis

Paayal Naidu* and Jenna Paterson

Department of General Medicine, Austin Health, Australia

Abstract

Hydroxymethylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, are well recognized in the management of hyperlipidemia with additional cardiovascular benefits. The adverse effect of rhabdomyolysis, in which there is muscle necrosis, is rare and only occurs in 0.04% to 0.2% of patients using statin as the single lipid lowering agent.

This report reviews a case of a 75 year old lady presenting post three month of high dose statin use, after being stable on a lower dose for several years, with anuric renal failure secondary to severe necrotizing myositis (creatinine kinase >97 500 U/L). She pre-morbidly had a normal renal function, with no documented episodes of acute kidney injury prior to this admission. After five weeks on hemodialysis, she had renal recovery. Histopathology on renal biopsy confirmed tubulo-toxic injury secondary to myoglobin deposition and cast formation. Similarly, muscle biopsy histopathology demonstrated toxin-mediated muscle necrosis.

Though similar cases have previously been reported in literature, there is none of this severity. Usually, there is quick recovery of renal function with statin cessation and intravenous fluid therapy. Also of interest was her apparent lack of risk factors-barring gender and age, this lady had not been on any common cytochrome P450 3A4 inhibitors apart from ticagrelor. Statin and anti-platelet agents are very commonly used together, raising a fascinating learning point both in medication prescribing with attention to medication interactions as well as management of morbidity and mortality within a spectrum of commonly known adverse effects.

Introduction

Hydroxymethylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, are well recognized in the management of hyperlipidemia and are also recognized as having additional cardiovascular benefits [1,2]. Whilst statins are relatively well tolerated, two significant adverse effects are that of hepatotoxicity and skeletal muscle injury which can range from myalgias to myopathy. The latter is defined as an increase in serum creatinine kinase of at least ten-fold, and this occurs in 0.5% to 1% of patients with a dose related effect [1,2].

The progression of myopathy to rhabdomyolysis, in which there is muscle necrosis, occurs in 0.04% to 0.2% of patients using statin as the single lipid lowering agent [3]. The incidence of fatal rhabdomyolysis is reported at the rate of 0.15 deaths per one million prescriptions [3]. Rhabdomyolysis is a clinical and biochemical syndrome encompassing acute renal injury as a result of renal tubule deposition of myoglobin, cardiac abnormalities and compartment syndrome secondary to skeletal muscle damage, and biochemically resulting in release of creatinine kinase, creatinine, potassium, uric acid, myoglobin, calcium and phosphate [1,4].

Here we discuss an interesting case of statin-induced rhabdomyolysis with acute renal failure after increase in statin dose with concurrent use of ticagrelor.

Case Presentation

We present a 75 year old Maltese lady, Ms DC, pre-morbid independent living at home alone admitted after a fall, and with only fifteen minutes spent on the floor before rescue. Past medical history was significant for acute myocardial infarction three months prior which had been managed with percutaneous coronary intervention. She also had a longstanding history of hypertension, osteoarthritis, depression and cataract removal. Her medications consisted of atorvastatin 80 mg, twice daily metoprolol 50 mg and ticagrelor 90 mg twice daily, and daily dosing of amlodipine 5 mg; aspirin 100 mg; amitriptyline 50 mg and perindopril 5 mg. During her admission with myocardial

OPEN ACCESS

*Correspondence:

Paayal Naidu, Department of General Medicine, Austin Health, 145 Studley Road, Heidelberg VIC 3084, Australia, Tel: +61 433365107;

E-mail: Paayal.naidu@austin.org.au

Received Date: 24 Jun 2020

Accepted Date: 16 Jul 2020

Published Date: 24 Jul 2020

Citation:

Naidu P, Paterson J. Severe Anuric Renal Failure from Statin-Induced Rhabdomyolysis. *Ann Clin Case Rep.* 2020; 5: 1864.

ISSN: 2474-1655

Copyright © 2020 Paayal Naidu. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

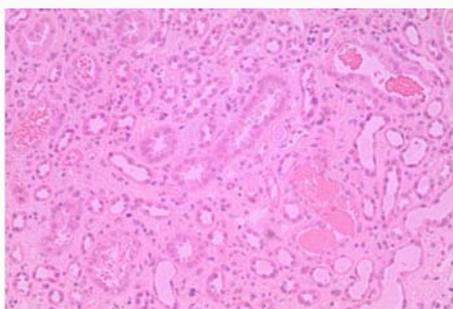


Figure 1: Renal tubular injury with cast formation.

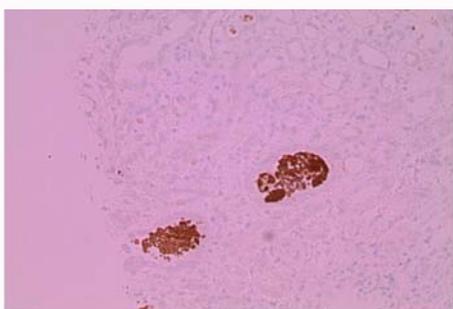


Figure 2: Casts staining positive for myoglobin.

infarction, the atorvastatin dosage had been increased from 40 mg to 80 mg and she had been commenced on ticagrelor. Prior to this she had been tolerating atorvastatin at the dose of 40 mg for many years without any reported side effects and had no previous evidence of acute or chronic kidney disease previously.

Ms DC was referred to her local hospital for further management of progressive generalized weakness. Initial examination demonstrated significant lower limb predominant weakness with 3/5 power bilaterally. Biochemistry showed an acute kidney injury with creatinine 404 $\mu\text{mol/L}$, urea 17 mmol/L and eGFR of 9 with a metabolic acidosis. Urinalysis revealed greater than $1000 \times 10^6/\text{L}$ of both erythrocytes and polymorphonuclear leukocytes. Other results of significance on admission included: Hemoglobin 132 g/L, white cell count $15 \times 10^9/\text{L}$ (neutrophils $11.6 \times 10^9/\text{L}$), CRP 73 mg/L, INR 1.6. Ms DC deteriorated over a period of several days with predominant hypothermia, hypotension and anuria. She was commenced on inotropes and intravenous antibiotics and transferred to a tertiary facility for Intensive Care unit (ICU) admission.

The working diagnosis at the time was acute tubular necrosis secondary to sepsis. She was commenced on Continuous Venovenous Hemodiafiltration (CVVHDF). Creatinine kinase on ICU admission was greater than 25,000 U/L, continuing to rise over the subsequent days to 97,500 U/L. On serial examination, there was progressive bilateral upper and lower limb proximal weakness. Vasculitis and glomerulonephritis screens were negative.

There was concern for a necrotizing myositis given the severity of the renal failure. An MRI-guided muscle biopsy of vastus medialis was done. Histology demonstrated an extensive rhabdomyolysis process most consistent with a toxic pathology rather than autoimmune, and the imaging was also consistent with a myopathic process.

Correlating with this biopsy finding, myositis antibodies (including Ro-52, PM-Scl 100, JO-1 antibodies as well anti SRP)

were negative. HMG-CoA reductase antibody was also negative. Renal biopsy showed a tubulo-toxic process secondary to myoglobin-related cast formation.

After five weeks on dialysis, Ms DC began producing urine with return of renal function to normal. Renal replacement therapy was ceased and the patient was transferred to sub-acute care for rehabilitation (Figure 1 and 2).

Discussion

The severe rhabdomyolysis demonstrated in this case is attributed to the increased dose of atorvastatin and concomitant use of ticagrelor, a medication that also utilizes the CYP450 3A4 pathway.

The cytochrome P450 3A4 pathway allows for statin glucuronidation which is necessary for statin clearance. When this pathway is occupied by other metabolites it leads to increased serum statin levels [3,5]. In a review of cases of rhabdomyolysis submitted to the United States Food and Drug Administration, over 50% of cases were attributable to the additional use of medications which share this pathway [3]. Common medications associated with increased risk of rhabdomyolysis when used in conjunction with statins include fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin and antifungals [3].

Typically, cessation of the statin in combination with intravenous fluids and, in rare cases, a short course of renal replacement therapy is sufficient [6]. Unal et al. [5] describe two cases in which both patients detailed required four to five sessions of hemodialysis before there was renal recovery. Similarly, in another case reported by Ram et al. [7], only seven sessions of hemodialysis were required before adequate urine output was noted. Panchangam et al. [8] presents an account of rhabdomyolysis in a 57 year old male with need for hemodialysis for more than 2 weeks.

A similar case to this has been found, where an elderly female patient presented with statin-induced myositis attributed to commencing ticagrelor and atorvastatin 80 mg daily two months prior to presentation. However, in that case, the patient recovered after statin was withheld and intravenous fluids instituted without need for renal replacement therapy [9].

This case is unusual as Ms DC required prolonged dialysis prior to renal recovery despite early statin cessation. This raised the question of an alternative pathology, leading to further investigation for autoimmune myositis or an immune-mediated necrotizing myopathy. However, serum and histopathological evidence demonstrated only a severe toxin-mediated myositis.

Potential contributors to the severity of this case of rhabdomyolysis included her older age, female sex, increased dose of statin and addition of ticagrelor. Other known risk factors include diabetes, chronic kidney or liver disease and hypothyroidism, though these were not an issue for this patient [1,7]. Atorvastatin at the 80 mg dose is also known to have a higher risk of adverse effects [10].

This case raised a timely reminder to all medical practitioners to be cautious on up-titration of statins. It is important to carefully consider risk factors and potential contraindicated medications, as rarely rhabdomyolysis can be fatal and, as seen in this case, can lead to significant morbidity. However, despite the severity of rhabdomyolysis seen here, when treated early can still lead to good renal recovery.

References

1. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother.* 2001;35(9):1096-107.
2. Holbrook A, Wright M, Sung M, Ribic C, Baker S. Statin-associated rhabdomyolysis: Is there a dose-response relationship? *Can J Cardiol.* 2011;27(2):146-51.
3. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA.* 2003;289(13):1681-90.
4. Melli GV, Chaudhry V, Cornblath DR. Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine.* 2005;84(6):377-85.
5. Unal A, Torun E, Sipahioglu MH, Tokgoz B, Kaya MG, Oymak O, et al. Fenofibrate-induced acute renal failure due to massive rhabdomyolysis after coadministration of statin in two patients. *Intern Med.* 2008;47(11):1017-9.
6. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: From myalgia to rhabdomyolysis. *Curr Opin Lipidol.* 2007;18(4):401-8.
7. Ram R, Swarnalatha G, Ramesh V, Nageswar Rao K, Dakshinamurthy KV. Rhabdomyolysis induced acute renal failure secondary to statins. *Indian J Nephrol.* 2013;23(3):211-3.
8. Panchangam V. Statin-associated acute interstitial nephritis and rhabdomyolysis. *Saudi J Kidney Dis Transpl.* 2014;25(3):659-60.
9. Kido K, Wheeler MB, Seratnahaei A, Bailey A, Bain JA. Rhabdomyolysis precipitated by possible interaction of ticagrelor with high-dose atorvastatin. *J Am Pharm Assoc.* 2015;55(3):320-3.
10. Ronaldson KJ, O'Shea JM, Boyd IW. Risk factors for rhabdomyolysis with simvastatin and atorvastatin. *Drug Saf.* 2006;29(11):1061-7.