Rhabdomyolysis and severe biphasic disturbance of calcium homeostasis secondary to COVID-19 infection

Adrian Po Zhu Li, Stephen Thomas, Refik Gokmen, Dulmini Kariyawasam

Diabetes and Endocrinology, Guy's and St Thomas' Hospitals NHS Trust, London, UK

Correspondence to
Adrian Po Zhu Li;
lipozhu@hotmail.co.uk

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SUMMARY

We report a case of severe hypercalcaemia secondary to rhabdomyolysis in a woman with COVID-19 (SARS CoV-2) infection. The patient presented with myalgia and anuria with an acute kidney injury requiring haemodialysis. Creatine kinase peaked at 760 000 IU/L. A biphasic calcaemic response was observed with initial severe hypocalcaemia followed by severe, symptomatic hypercalcaemia, persistent despite haemodialysis. Control of the calcium levels was achieved by continuous haemofiltration.

BACKGROUND

Rhabdomyolysis is an uncommon cause for hypercalcaemia. Cases can be severe and electrolyte abnormalities difficult to manage.

CASE PRESENTATION

A 22-year-old Black British woman with asthma presented to her local hospital with a recent sore throat, myalgia and 24 hours of anuria. She had no fever, cough or dyspnoea. She denied a history of tetany or weight loss. There was no history of intense exercise and aside from three doses of Ibuprofen (total 600 mg), had not taken any other medications. She did not have any relevant medical history nor history of electrolyte disturbance. There was no family history of autoimmune conditions. She denied any illicit drug use and drank minimal alcohol.

INVESTIGATIONS

Urine dipstick was positive for protein 3+ and blood 3+. She had a creatine kinase (CK) level of 764 470 IU/L (0–159) with a creatinine (Cr) 719 umol/L and acidosis, pH 7.23. She had severe hypocalcaemia with corrected value 1.28 mmol/L and a phosphate level measuring 4.49 mmol/L. A total of 30 mL of 10% calcium gluconate was administered for immediate correction.

She was transferred to a tertiary unit for urgent initiation of haemodialysis as renal replacement. Admission blood tests are shown in table 1.

DIFFERENTIAL DIAGNOSIS

Initial COVID-19 PCR screening was negative. The cause of rhabdomyolysis remained unclear; the history excluded trauma, exercise and drug-induced causes, while there was no evidence of underlying inflammatory myositis and a full autoantibody screen was negative.

During her admission, she developed chest pain and fevers. A CT Pulmonary Angiogram (CTPA) performed in light of elevated d-dimers was negative for pulmonary emboli although bibasal atelectasis was present. Her ferritin was elevated at 1522 ug/L (22–275) and a repeat COVID-19 PCR swab was positive, establishing the diagnosis of COVID-19 infection.

Renal replacement therapy (RRT) was commenced as she remained anuric. Normocalcaemia was achieved on day 6. During her recovery, as her renal function was improving and when withdrawal of her haemodialysis was being considered, she developed progressive severe symptomatic hypercalcaemia with a peak calcium level of 3.39 mmol/L. At this level of calcium, her parathyroid hormone (PTH) level was 5 ng/L excluding parathyroid-driven causes of hypercalcaemia and both 25 hydroxyvitamin D [25(OH) 2D] and 1, 25 dihydroxyvitamin D [1, 25(OH) 2D] were unrecordable at <20 nmol/L and <12 pmol/L respectively, excluding vitamin D toxicity, excess endogenous production or activation of vitamin D.

TREATMENT

RRT was restarted to correct hypercalcaemia. However, this only yielded temporary improvements in calcium, as shown in figure 1—the arrows are explained by the labels in table 2. She was thus switched to continuous haemofiltration using an ultra-low calcium dialysate on day 17. Ionised calcium measurements were taken in intensive care and the fluctuations in calcium are shown in figure 2. A total of 35 hours of haemofiltration was required. No specific treatment was utilised in the management of COVID-19 infection as the case occurred early during the first wave and conservative measures were adequate.

OUTCOME AND FOLLOW-UP

This patient had an excellent outcome; 2 weeks following her discharge, calcium levels remained within normal limits and her creatinine improved to 77 umol/L with an eGFR 81 mL/min. Her vitamin D level is trending towards normalisation with supplementation. She has been discharged from secondary care.

DISCUSSION

Rhabdomyolysis has recently been described as a complication of COVID-19 infection[1] and here we report a case of rhabdomyolysis-associated hypercalcaemia.

In this case, the suppressed PTH at the time of severe hypercalcaemia excludes primary hyperparathyroidism, the the most common cause of

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Table 1 Biochemistry results on admission

Test	Result	Reference range and units
Sodium	129	135–145 mmol/L
Potassium	6.0	3.5–5 mmol/L
Corrected calcium	1.55	2.15–2.55 mmol/L
Creatinine	719	45–84 umol/L
estimated Glomerular Filtration Rate (eGFR)	8	75–130 mL/min
C-Reactive Protein (CRP)	150	0–4 ug/L
Lymphocytes	1.0	1.2–3.5 x 10^9
Alanine Aminotransferase (ALT)	442	4–40 IU/L

hypercalcaemia. Other common causes of hypercalcaemia include malignancy, in particular squamous cell lung carcinoma, but there were no history or examination findings suspicious for any malignancy and the detailed chest imaging showed no evidence of this. Furthermore, there was no history of any medications implicated in hypercalcaemia. The raised CK level renal impairment and positive SARS-CoV 2 test in this case indicate the diagnosis of SARS—CoV 2 infection with associated rhabdomyolysis.

Rhabdomyolysis is striated muscle disintegration.[2] This leads to the release of muscle cell content into the circulation, which can result in multiple electrolyte abnormalities.[3] Other causes of rhabdomyolysis include alcohol, illicit substances and statins, which were excluded from the history. Autoimmune myopathies can cause rhabdomyolysis; however, there were no clinical features of this identified after rheumatological review and an autoimmune screen was normal.

Disturbance in calcium homeostasis has been observed previously in cases of rhabdomyolysis-induced acute renal failure.[4] Initial hypocalcaemia may be observed predominantly due to sequestration of calcium associated with marked hyperphosphatemia on the destroyed muscle cell. Subsequent hypercalcaemia may be severe, as in this case, as this calcium is released back into the circulation possibly exacerbated by an initial temporary rise in PTH levels responding to the initial hypocalcaemia.[5] Additionally, extra-renal and uncontrolled renal production of 1, 25(OH) 2D[6] has also been postulated to contribute. At the time of the severe persistent hypercalcaemia in this case, PTH and 1, 25(OH) 2D were fully suppressed and low.

Treatment of hypercalcaemia is important as severe hypercalcaemia can cause confusion and fatal arrhythmia in the acute phase.

While intermittent haemodialysis can be effective in managing severe hypercalcaemia,[7] the putative ongoing calcium release into the circulation from muscle necrosis necessitated continuous RRT in the form of haemofiltration, which is more effective

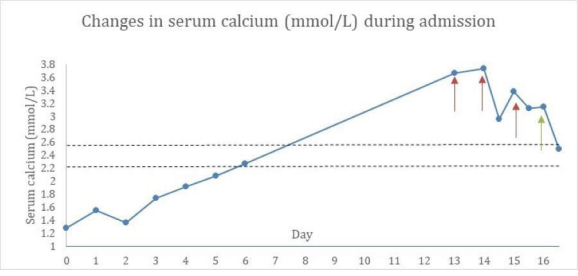

Figure 1 Serum calcium levels from admission to initiation of haemofiltration.

Table 2 Key for figure 1

↑	Haemodialysis to treat hypercalcaemia
↑	Haemofiltration initiated
-------	Denotes normal reference range

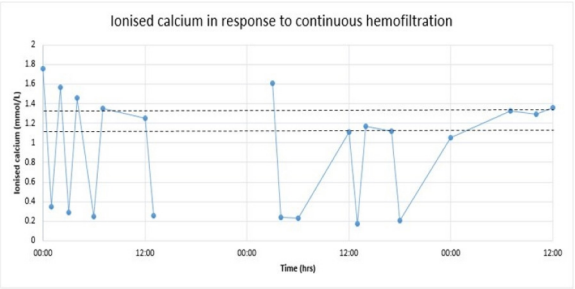

Figure 2 Changes in ionised calcium concentration during continuous haemofiltration.

in solute clearance.[8] In our case, the initial daily haemodialysis utilised an AX225 dialysate, which contains 1.25 mmol/L calcium per litre. This provided a temporary benefit but with a calcium level increasing on cessation of intermittent dialysis. When refractory severe hypercalcaemia occurred, dialysate containing lower calcium concentrations of 1 mmol/L was utilised during continuous haemofiltration to assist with removal of calcium from blood.

Classical treatments of hypercalcaemia such as bisphosphonates and corticosteroids were not used in our case. Bisphosphonates are contraindicated in renal failure and were unlikely to work due to PTH suppression and lack of bone-resorption mechanism. Corticosteroids have been postulated to work via inhibiting, in particular extra-renal 1, 25(OH) 2D production. However, the low 1, 25 (OH) 2D level at the time of severe hypercalcaemia in this case suggests that this would have been unlikely to benefit.

Our case demonstrates the importance of recognising the biphasic calcium response that can occur in rhabdomyolysis and the need for monitoring of the calcium levels throughout the recovery phase. Complications can arise even once urine output and renal function improves. Initial hypocalcaemia may well treatment, but the use of intravenous calcium here should be moderated with knowledge of the subsequent risks of hypercalcaemia. Subsequent hypercalcaemia may be transient but if

Learning points

- Rhabdomyolysis may present initially with severe hypocalcaemia followed by hypercalcaemia.
- Rhabdomyolysis is a recognised complication and may even be the presenting complaint of COVID-19 infection. However, it is important to exclude other common causes of rhabdomyolysis.
- Initial hypocalcaemia is likely secondary to sequestration of calcium into necrotic muscle tissue.
- The cause of subsequent hypercalcaemia is postulated to be due to the release of calcium from muscle necrosis and is not parathyroid hormone mediated thus standard treatments are unlikely to work.
- Hypercalcaemia may be severe and require continuous haemofiltration.

severe, is best treated by haemofiltration against a low calcium concentration in the dialysate.

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