



An Unusual Case of Hypercalcaemia in a Patient with Sarcoidosis

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Abstract

A 37-year old female who was known to have a diagnosis of sarcoidosis which was conservatively managed, presented to the emergency department with a few days history of lethargy, exertional dyspnoea and palpitations. She was noted to be slightly confused and clinically dehydrated on arrival. Her initial investigations showed an adjusted calcium level of 5.5 mmol/L, acute kidney injury, normal phosphate and vitamin D levels with suppressed parathyroid hormone level of 7 ng/L. She also had a raised Angiotensin Converting Enzyme (ACE) level of 169 u/L. She had no abnormalities on her electrocardiogram. Recent radiological investigations had excluded any malignancy. Her calcium and ACE levels had previously been stable, and she denied any vitamin D supplementation prior to this admission. The mechanism of hypercalcaemia in sarcoidosis occurs due to enhanced intestinal calcium absorption and increased endogenous calcitriol production therefore treatment modalities are usually a low calcium diet and corticosteroids which have a peak action within 2-5 days by reducing calcitriol production. This case highlights an atypical presentation of very high calcium levels secondary to sarcoidosis that was resistant to aggressive intravenous fluids, necessitating the use of calcitonin in addition to high dose steroids for a rapid calcium reduction to prevent complications such as renal failure and arrhythmias.

Learning Points

- Acute hypercalcaemia (calcium level of 3.5 mmol/L or more) is a medical emergency which can lead to severe complications such as renal failure, altered mental status, cardiac arrhythmia and death
- Hypercalcaemia is rarely seen as complication of sarcoidosis since calcium is only slightly elevated and stable over time. In such cases, other causes of hypercalcaemic crises should be ruled out
- Calcitonin use in sarcoidosis is controversial but effective for rapid reduction of calcium over a short period of time

Background

Acute hypercalcaemia is a medical emergency. Primary hyperparathyroidism and malignancy are the most common causes of acute hypercalcaemia, accounting for greater than 90 percent of cases while the other causes such as sarcoidosis contribute to the remaining 10% [1,2].

Patients with sarcoidosis, or other granulomatous causes of hypercalcaemia have enhanced intestinal calcium absorption due to increased endogenous calcitriol production. Hypercalcaemia in the context of sarcoidosis is rarely as high as 5.5 mmol/L and can therefore be managed with high dose steroids which though they work over a period of about 2-4 days, in addition to aggressive intravenous fluid therapy are usually effective [3,4].

Case Presentation

A 37-years old female patient, with a background of type 2 diabetes mellitus and sarcoidosis with stable serum calcium level of 2.49 mmol/L (reference range 2.20-2.60 mmol/L) presented to the acute medicine unit with few days history of lethargy, exertional dyspnoea, palpitations and constipation. She was found to be confused, clinically dehydrated while no other abnormality was detected on systemic examination [5]. Blood pressure 154/83, heart rate 108, respiratory rate 17 per min, oxygen saturation 97% and temperature 36.4°C. Her daily medication prior to admission are allogliptin 25 mg, metformin 2 g and sumatriptan 50 mg (when needed). Two months prior to her current admission he was diagnosed with sarcoidosis after discussion in various respiratory MDTs based on CT chest, abdomen and pelvis, NM whole body pet scan and excisional biopsies from cervical lymph node and parotid gland which exclude malignancy and proved sarcoidosis; therefore repeating scans on this admission was not required [6].

Investigation

Initial investigation reported a high calcium level of 5.5 mmol/L (reference range 2.20-2.60 mmol/L), acute kidney injury with creatinine of 100 umol/L (reference range 45-85 umol/L) her baseline creatinine is 31 umol/L, urea 7.1 mmol/L (reference range 2.9-7.5 mmol/L), e GFR 63 (reference range more than 90), only mild inflammatory response noted CRP 42 (reference range (1-10), WBC 10.1 (reference range 4-11 × 10⁹/LN B) and sinus tachycardia on ECG with normal QTC interval of 429 (hypercalcaemic ECG change is of short QTC interval), further investigation elicited normal phosphate and vitamin D with suppressed parathyroid hormone 7 ng/L (reference range 18-80 ng/L) and a high but stable ACE level 169 u/L (reference range 13-64 U/L).

Treatment

The patient initial calcium level upon presentation in emergency department was 4.3 mmol/L; thus, an aggressive treatment with IV fluids was started and then the decision was made to admit her to level 1 unit for cardiac monitoring, and she received a total of 5 L of normal saline 0.9%/24 h, meanwhile prednisolone 40 mg orally was prescribed base on respiratory team advice for 5 days with further tapering plan, however interestingly there was a rebound rise in calcium levels from 4.3 mmol/L to 5.5 mmol/L over 12 hours, which raised concerns, and after further discussion with endocrine team prescribing calcitonin was the next wise and crucial option of management in order to rapidly reduce the high calcium levels and a plan was made to give calcitonin till either calcium level less than 3 mmol/L or for a maximum of 48 hours. Two consecutive dose of calcitonin 100 unit's s/c was given which has led to dramatic reduction in calcium levels From 5.5 mmol/L to 3.4 mmol/L.

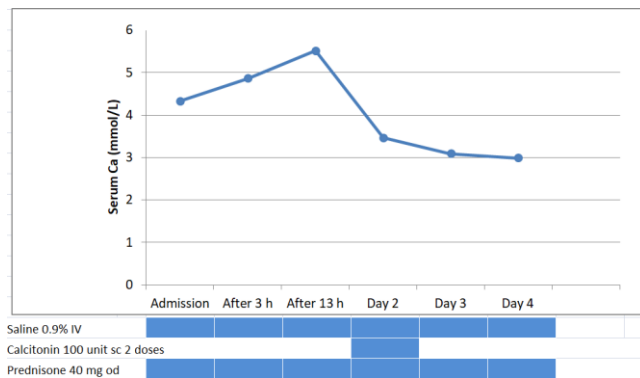


Figure 1: General condition of the patient in 5 days.

Then the general condition of the patient improved and she became more alert. on day 5 her kidney function improved with urea of 4.8 mmol/L, creatinine of 63 μ mol/L and e GFR of >90 and her urine output was in the range of 100 ml–300 ml per hour throughout her admission thus, the haemofiltration was not considered. following that she was continued on regular oral tapering steroids regime, and discharged home in 6 days with calcium level of 2.9 mmol/L on alendronic acid 70 mg orally once a week.

Outcome and Follow-up

The patient is still under follow with regular calcium check up in a arrange of 2.2 mmol/L, in the most recent results almost 2 months after discharge, with a plan of continue steroid tapering and 2 weeks and then 3 monthly calcium checkup.

Discussion

Hypercalcaemia from sarcoidosis is usually mild and usually after vitamin d supplements. Unusual for it to be so high with no obvious cause, if required treatment, corticosteroids are the mainstay of treatment. In this case, the patient didn't require any vitamin D supplements or steroids therapy previously as she had normal vit D and stable ACE level. As per endocrine society guidelines calcium level of <3.0 mmol/L: often asymptomatic and does not usually require urgent correction, 3.0–3.5 mmol/L: may be well tolerated if it has risen slowly, but may be symptomatic and prompt treatment is usually indicated while >3.5 mmol/L: requires urgent correction due to the risk of dysrhythmia and coma. The management as advised by the society is Intravenous 0.9% saline 4–6 L in 24 h and May need to consider dialysis if severe renal failure. If further treatment required after fluids consider intravenous bisphosphonate and the second line of treatment is Glucocorticoids (Prednisolone 40 mg daily usually effective in 2–4 days) in cases of lymphoma, other granulomatous diseases or 25O HD poisoning. In case of poor response to other measures Calcimimetics, denosumab and calcitonin can be considered under specialist supervision. Parathyroidectomy Can be considered in acute presentation of primary hyperparathyroidism if severe hypercalcaemia and poor response to other measures. Isotonic saline restores the volume depletion that invariably occurs in the setting of hypercalcemia-provoked urinary salt wasting. The restoration of intravascular volume results in an increase in the glomerular filtration rate and, thus, an increase in calcium filtration. Furthermore, proximal tubular sodium and calcium re-absorption decrease as the glomerular filtration rate increases. Additionally, an increase in sodium and water

presentation to the distal renal tubular sites provokes a further calciuresis.

It is estimated that with saline hydration, the calcium concentration should decline, at least by the degree to which dehydration raised it, typically in the range of 1.6 mg to 2.4 mg per deciliter for hydration alone, however, rarely leads to normalization of the serum calcium concentration in patients with severe hypercalcemia. bisphosphonates are nonhydrolyzable analogs of inorganic pyrophosphate that adsorb to the surface of bone hydroxyapatite and inhibit calcium release by interfering with osteoclast-mediated bone resorption, and they are more potent than calcitonin and saline for patients with moderate or severe hypercalcemia. As a result, they have become the preferred agents for management of hypercalcemia due to excessive bone resorption from a variety of causes, including malignancy-related hypercalcemia. Their maximum effect occurs in two to four days. Abnormalities of calcium metabolism in sarcoidosis are due to dysregulated production of 1,25-(OH)₂-D₃ (calcitriol) by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation. Corticosteroids cause prompt reversal of the metabolic defect and prednisone in a dose of 20 to 40 mg/day will usually reduce serum calcium concentrations within two to five days by decreasing calcitriol production by the activated mononuclear cells in the lung and lymph nodes and the other modalities of treatment of hypercalcemia in sarcoidosis are Chloroquine, hydroxychloroquine, and ketoconazole are the drugs that should be used if the patient fails to respond or develops dangerous side effects to corticosteroid therapy, providing that corticosteroids require 2 to 5 days to act, and the patient acute presentation with very high calcium level indicate starting calcitonin which acts within 2 hours and limited to the first 48 hours and it lead to rapid reduction of calcium levels by increasing renal calcium excretion and, more importantly, by decreasing bone resorption *via* interference with osteoclast function (lowering the serum calcium concentration by a maximum of 0.3 to 0.5 mmol/L). The efficacy of calcitonin is limited to the first 48 hours, even with repeated doses, indicating the development of tachyphylaxis, perhaps due to receptor down regulation. Haemofiltration was not indicated in this case because of adequate and stable urine output, patient kidney function was not significantly affected and it showed improvement and the patient has no cardiac co morbidities.

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Declaration of Interest

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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All three authors have contributed to the writing and editing of this manuscript and the physician responsible for the patient is one of the authors.

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