CASE REPORT

Antacid abuse: a rare cause of severe hypercalcaemia

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SUMMARY

We discuss a case of an 81-year-old man who presented to hospital with a case of severe hypercalcaemia (5.07 mmol/L). The two most common causes of hypercalcaemia, making up around 90% of the cases, are malignancy and primary hyperparathyroidism. Initial investigations are guided by this knowledge. In this case, no underlying malignancy or evidence of a parathyroid adenoma causing primary hyperparathyroidism was found. Instead, on further history, it was found that this patient had troublesome dyspepsia symptoms for which he had ingested 10–12 calcium carbonate tablets a day for the preceding 2 years. This amounts to 6.6–7.9 g of calcium carbonate per day compared with the guideline daily intake of calcium of 1 g. His presentation of severe hypercalcaemia was therefore diagnosed as milk-alkali syndrome secondary to calcium carbonate tablet abuse.

BACKGROUND

Hypercalcaemia has a wide variety of different causes and it is important to investigate and treat the underlying cause appropriately. The two most common causes are malignancy and primary hyperparathyroidism which make up around 90% of cases.¹ The third most common cause of hypercalcaemia in hospitalised patients is now thought to be milk-alkali syndrome, making up less than 1% of cases.²

Milk-alkali syndrome produces a classical triad of hypercalcaemia, renal failure and metabolic alkalosis and can often be overlooked as a cause of hypercalcaemia. Milk-alkali syndrome was described in the first half of the 20th century and was thought to be related to the introduction of the 'Sippy diet' in 1915, for the treatment of peptic ulcer disease.^{3–4} The diet consisted of hourly ingestion of milk and cream, interspersed with calcinated magnesia and sodium bicarbonate, the idea of which was to neutralise the acidity of stomach with regular consumption of alkaline substances.^{3–5} Since the recognition of the toxic effects of this diet, the incidence of milk-alkali syndrome has decreased but in recent years the incidence has increased due to the use of over-the-counter calcium and vitamin D for the treatment of osteoporosis. Hence, there has been a shift in the demographic from males with peptic ulcer disease to postmenopausal females.^{5–6}

In this case, the level of the calcium was dangerously high and could have been life-threatening without adequate treatment. Hypercalcaemia opens up a wide range of differentials and on initial presentation, it is essential that adequate treatment

and investigations are initiated to find the underlying cause.

CASE PRESENTATION

An 81-year-old Caucasian man presented to the accident and emergency department with gradually worsening leg weakness and self-neglect reported by the grandson. The paramedics noted that the patient was confused and was unable to give a clear history. He was disorientated to time, place and person. He had a medical history of type 2 diabetes, hypertension, polymyalgia rheumatic and a degenerative spine with right L3–L4 disc prolapse and left L4–L5, L5–S1 recess compression. His medication history included aspirin, doxazosin, diltiazem, gliclazide, losartan/hydrochlorothiazide and a low dose of prednisolone 4 mg. He lived at home with his wife who was unable to cope and he usually mobilised with a stick. He did not smoke or drink, and there was no family history of note.

Further collateral history revealed that the patient had multiple episodes of vomiting at home which the relatives described as being 'black', and he had also been complaining of severe indigestion for 2 years for which he had been taking 10–12 calcium carbonate tablets (680 mg/tablet) per day for about 2 years. Examination revealed weakness in the bilateral lower limbs with grade 4/5 power proximally and grade 2/5 power distally. The remainder of his neurological and systemic examination was unremarkable.

His initial blood tests showed an acute-on-chronic kidney injury (creatinine increased from 124 to 344 $\mu\text{mol/L}$), a normocytic anaemia with haemoglobin of 9.9 g/dL (13.3–18.0 g/dL) and raised corrected calcium at 5.07 mmol/L (2.18–2.58 mmol/L). His ECG was in normal sinus rhythm with a normal QT interval. He had a venous blood gas on admission which showed metabolic alkalosis.

In order to investigate the underlying cause of this patient's hypercalcaemia, the parathyroid hormone (PTH) level was checked. The PTH was normal and with such a high level of calcium, it was thought that this should have been suppressed unless there was an element of primary hyperparathyroidism. The patient was investigated further for this with a CT parathyroid single-photon emission computed tomography (SPECT) which showed no evidence of a parathyroid adenoma. The patient also had a myeloma screen, an ultrasound scan of his testes and a CT scan of the neck, thorax, abdomen and pelvis to look for a malignancy. The scans showed no evidence of any malignancy and the myeloma screen was negative.

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The patient also had further investigation for the 'black vomit' with an oesophagogastroduodenoscopy (OGD), the leg weakness with an MRI of the lumbar and sacral spine, and the confusion with a CT head. The OGD showed multiple oesophageal erosions for which he was started on a high-dose proton pump inhibitor. The MRI of the spine showed a slight deterioration in the previous disc disease but there was no evidence of acute vertebral body collapse suggesting metastatic disease. The CT head showed no acute abnormality.

INVESTIGATIONS

- ▶ Plasma PTH 2.45 pmol/L (1.68–9.16 pmol/L)
- ▶ Phosphate 1.27 mmol/L (0.80–1.40 mmol/L)
- ▶ 25-hydroxy vitamin D 50 nmol/L (50–75 nmol/L)
- ▶ Myeloma screen negative
- ▶ Hepatitis B, C, HIV negative
- ▶ OGD
 - ▶ Oesophagus: multiple ulcerated oesophageal erosions
 - ▶ Stomach and duodenum normal
- ▶ MRI spine lumbar and sacral: there has been slight deterioration in features but no evidence of acute vertebral body collapse or metastatic disease is found
- ▶ Ultrasound scan testes and abdomen: no abnormality detected
- ▶ CT head: no acute abnormality seen, mild ischaemic changes
- ▶ CT neck, thorax, abdomen, pelvis: no evidence of any malignancy
- ▶ CT parathyroid SPECT: no evidence of a parathyroid adenoma

DIFFERENTIAL DIAGNOSIS

The underlying cause of the hypercalcaemia was initially thought to be multifactorial due to the very high calcium level. As time went on, more differentials were ruled out; with further investigation there was no evidence of malignancy or primary hyperparathyroidism. The thiazide diuretic and the acute kidney injury helped precipitate the hypercalcaemia but were not thought to be the major cause.

Initial diagnosis:

- ▶ Severe Hypercalcaemia (likely multifactorial)
 - ▶ Milk-alkali syndrome
 - ▶ Thiazide diuretic
 - ▶ Acute kidney injury
 - ▶ Possible paraneoplastic syndrome (further investigation required)

Final diagnosis:

- ▶ Severe hypercalcaemia secondary to milk-alkali Syndrome

TREATMENT

The patient was initially treated with aggressive intravenous fluid resuscitation with 0.9% saline to lower the calcium levels, while he was investigated for the underlying cause. His thiazide diuretic was discontinued as this increases calcium reabsorption in the kidney which could increase the patient's propensity towards developing milk-alkali syndrome. His calcium carbonate tablets were also discontinued and he was started on a proton pump inhibitor instead to treat his oesophagitis.

OUTCOME AND FOLLOW-UP

The patient was discharged home once the calcium had been treated and stable around 2.55 mmol/L. His acute kidney injury had resolved and his renal function was back to baseline at his preadmission level. His leg weakness improved following the treatment of the hypercalcaemia and with physiotherapy. Before discharge he was counselled on his use of antacids and was advised to continue with the proton pump inhibitor. He was discharged for follow-up under endocrinology for a review of calcium levels and symptoms. At 6 months, his corrected calcium level was still stable at 2.54 mmol/L, his 25-hydroxy vitamin D was 30 nmol/L, his phosphate was 1.18 mmol/L and his plasma PTH was 4.18 pmol/L. The normal calcium and PTH levels at 6 months make a diagnosis of primary hyperparathyroidism extremely unlikely and help confirm our final diagnosis of milk-alkali syndrome.

At follow-up, the patient was no longer taking any antacids and his dyspepsia symptoms had completely resolved.

DISCUSSION

Milk-alkali syndrome is characterised by the classical triad of hypercalcaemia, a metabolic alkalosis and renal failure. These develop secondary to the ingestion of large amounts of calcium and absorbable alkali. There are certain factors that put people who ingest large quantities of calcium (4–5 g/day) and absorbable alkali at risk of developing milk-alkali syndrome. These include concomitant use of a thiazide diuretic, underlying renal disease, increasing age, increasing intestinal acidity and excessive vitamin D intake.^{6,7} This patient was ingesting 6.6–7.9 g of calcium carbonate a day, was taking a thiazide diuretic, had an element of chronic kidney disease, was elderly and presumably had increased intestinal acidity due to his multiple ulcerated oesophageal erosions and heavy use of antacids. Altogether these factors most likely contributed to this patient's severely high level of calcium.

The pathophysiology of milk-alkali syndrome can be divided into two stages; the generation phase and the maintenance phase.⁶ The generation phase is the increased calcium absorption in the intestine through increased dietary calcium ingestion, increased vitamin D ingestion or increased acidity in the gut.^{5,6} The maintenance phase is due to the effects of the hypercalcaemia on the body which lead to a self-propagating cycle of increasing plasma calcium levels.^{5,6} The hypercalcaemia causes renal vasoconstriction which leads to a decrease in renal function and in turn a decrease in the amount of calcium excreted.^{3,5,6} The hypercalcaemia also causes nephrogenic diabetes insipidus leading to volume depletion and as a result there is an increased calcium reabsorption in the proximal tubule of the kidney.^{3,6} This reabsorption of calcium in the proximal tubule is also increased by thiazide diuretics and alkalosis.^{3,6,7} Overall, these effects lead to a rise in the calcium level, a decrease in renal function and a worsening alkalosis which is why these three features make up the classical triad of milk-alkali syndrome.

It is important to remember milk-alkali syndrome as the third most common cause of hypercalcaemia following primary hyperparathyroidism and malignancy. There is a case for changing the name of milk-alkali syndrome to calcium-alkali syndrome due to its change in aetiology since its discovery nearly a century ago.^{5,6} Incidence initially declined following the discovery of the relationship between it and the 'Sippy diet' but has increased more recently due to the increasing incidence of over-the-counter calcium and vitamin D replacement.⁵

This patient had a normal PTH with a high plasma calcium level, so it was thought that there was potentially an element of primary hyperparathyroidism because otherwise the PTH level would have been suppressed. However, looking at the literature there are cases of milk-alkali syndrome with both a normal and a suppressed PTH. This is thought to be because in decreased renal function certain assays of PTH are less readily excreted.⁶ So an inappropriately normal PTH does not necessarily mean that there is an underlying primary hyperparathyroidism.^{2,6} At follow-up at 6 months the normal plasma calcium and PTH levels confirmed that there was not an underlying element of primary hyperparathyroidism.

For milk-alkali syndrome, it is important to take a detailed drug history in order to discover if there is an underlying drug cause. Quite often, over-the-counter medication gets forgotten

or neglected in the history taking but this case highlights the importance of detailed drug history taking because that is what led us to the diagnosis.

Of the literature that was reviewed on milk-alkali syndrome, this was the second highest calcium level recorded at 5.07 mmol/L.^{2,3,7–11} The highest of which was a case of calcium-alkali syndrome in postsurgical hypoparathyroidism at a level of 5.6 mmol/L (22.4 mg/dL) and the patient had to be managed on the intensive care unit.² In total, there were 16 cases of milk-alkali syndrome discussed in the literature that was reviewed and in all other cases, calcium levels (apart from one) were far below 5.0 mmol/L. This case is an example of a severely high level of calcium rarely seen elsewhere in the literature, and is the highest level caused by over-the-counter self-medication with a gap of 0.95 mmol/L; the only other levels that came close were from prescribed medication. As a case it can be used to remember the diagnosis, treatment and risk factors for developing milk-alkali syndrome, and can readily be applied to the underlying pathophysiology of the syndrome.

Patient's perspective

"I can't remember anything from my admission. Apparently I was doing stupid things. I was hallucinating and thought I was in a big house in Scotland where my wife's daughter lives. Later on I thought I was out in the street and people were trying to take my wife away. I tried to help her but I couldn't walk, so I shouted for help. It was a terrible, terrible thing."

Learning points

- ▶ The two most common causes of hypercalcaemia making up about 90% of the cases are malignancy and primary hyperparathyroidism.
- ▶ Milk-alkali syndrome is now thought to be the third most common cause of hypercalcaemia.
- ▶ Risk factors for developing milk-alkali syndrome include the use of thiazide diuretics, pre-existing renal disease, increasing age, increased gut acidity and excessive vitamin D intake.
- ▶ The mainstay of treatment is supportive and involves the removal of the offending agent.
- ▶ It is important to take a detailed drug history of regular and over-the-counter medications in hypercalcaemia in order to discover if there is an underlying drug cause for the high calcium.

Competing interests None declared.

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