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Unusual association of diseases/symptoms

Rennies, Crohn's disease and severe hypercalcaemia

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Summary

A 59-year-old lady presented with vomiting and diarrhoea. She was found to have severe hypercalcaemia (5.2 mmol/l) and to be in renal failure. She had a high daily intake of calcium carbonate in the form of Rennies Dual Action, raising the possibility of milk-alkali syndrome. She had ongoing gastrointestinal symptoms after resolution of hypercalcaemia. Further investigation revealed, previously undiagnosed rectal Crohn's disease. Serum 1,25-dihydroxyvitamin D (calcitriol) level was markedly elevated. It is possible that the calcitriol from Crohn's disease tissue facilitated excessive absorption of calcium from the antacid preparation, thus triggering hypercalcaemia.

BACKGROUND

Hypercalcaemia of the severity found in this patient is in itself unusual. Hypercalcaemia associated with active Crohn's disease has only been described in three patients in the literature.[1–3]

Milk-alkali syndrome (MAS) is also uncommon but has in recent years been recognised in association with calcium carbonate containing antacids.[4]

This patient illustrates the potential risks of excessive intake of calcium containing antacids in patients with underlying granulomatous disease in whom excess production of 1,25-dihydroxyvitamin D (calcitriol) can cause increased absorption of calcium and precipitate hypercalcaemia of potentially severe degree.

CASE PRESENTATION

A 59-year-old woman presented as an emergency with diarrhoea, vomiting and dysarthria. She had history of psychiatric illness and had been on sulpiride and orphenadrine long-term. She was vague on direct questioning but admitted to often suffering from heartburn, which had never been formally investigated. On examination, she had orofacial dyskinesia. Clinical examination was normal. Initial laboratory tests revealed corrected calcium (CCa) 5.2 mmol/l and renal impairment. She was initially treated with aggressive intravenous fluid resuscitation while further blood tests and imaging were performed. On further questioning she admitted to excessive use of Rennies Dual Action tablets over many years, typically consuming four to six tablets per day. Recently, and because of worsening gastrointestinal symptoms, she had been taking up to 18 tablets per day. In light of the history, laboratory findings and response to intravenous fluid therapy, she was initially managed as a case of MAS. The diarrhoea persisted and she became feverish with deranged liver function tests and elevated C reactive protein. She was treated with empirical antibiotic therapy. CT and MRI of the abdomen and the pelvis showed thickening of tissues in the rectosigmoid region with perirectal stranding, suggestive of an inflammatory or a tumour mass. Colonoscopy suggested a proximal rectal tumour with an ulcerated appearance. Biopsies revealed no evidence of malignancy and were felt to be compatible with Crohn's disease.

INVESTIGATIONS

The following abnormalities were found on the initial laboratory tests: CCa 5.2 mmol/l, urea 22.2 mmol/l and creatinine 308 µmol/l; potassium 3.2 mmol/l and bicarbonate 32 mmol/l. Phosphate was 1.2 mmol/l and alkaline phosphatase was 242 U/l. Thyroid function tests were normal.

Serum parathyroid hormone (PTH) was normal (2.3 pg/ml) (normal range 0.8–5.0). 25-hydroxyvitamin D concentration was slightly below the normal range at 18 nmol/l (normal range 25–170). Serum 1,25-dihydroxyvitamin D (calcitriol) markedly elevated >250 nmol/l (normal range 20–120). A value of >250 nml/l is very substantially elevated above the upper limit of normal, however, we cannot give a definitive value. Serum ACE 10 mcg/l (normal range <40).

Plain chest and abdominal x-rays were unremarkable. Isotope bone was normal. Abdominal CT showed 'thickening of tissues in rectosigmoid region and some infiltrative shadowing in the presacral fat...? Diverticulitis or alternative pathology', while MRI was suggestive of inflammatory or discrete tumour mass. Subsequent colonoscopy revealed a proximal rectal tumour with ulcerated appearance and performed, however, the tumour biopsies showed 'fragments of colonic mucosa with deep ulceration and histiocytic response; granulation tissue without malignant cells'. In view of high suspicion of malignancy, biopsies were repeated and on this occasion they showed 'deep ulceration and granulomatous areas – suggestive of Crohn's.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypercalcaemia includes primary and secondary hyperparathyroidism, malignancy, MAS, vitamin D toxicity, thyrotoxicosis, granulomatous diseases – sarcoidosis and tuberculosis and drug induced hypercalcaemia.

The differential diagnosis of the rectal mass and ulceration of our patient included adenocarcinoma, Crohn's disease and solitary rectal ulcer syndrome.

TREATMENT

The patient was initially rehydrated with intravenous 0.9% normal saline solution. The serum CCa came in to the normal range after 5 days. Over this period, serum creatinine fell from 308 to 131 and thereafter stabilised to around 90 mnol/l.

After the final diagnosis of Crohn's disease, the patient was commenced on predfoam enemas and mesalazine MR.

OUTCOME AND FOLLOW-UP

Patient's clinical condition rapidly improved. CCa concentration decreased from 5.2 to normal values (2.3 mmol/l) in 5 days and it was achieved after discontinuation of Rennies Duo Action and rehydration with normal saline.

At outpatient follow-up, 2 months after initial presentation, serum calcium remained normal as did the serum PTH. The 1,25-dihydroxyvitamin D (calcitriol) level had returned to normal (39 nmol/l).

At 8-month outpatient review, the patient remained normocalcaemic but there had been some recurrence of symptoms related to Crohn's disease requiring further evaluation.

DISCUSSION

Hypercalcaemia can present with various symptoms: patients with CCa <3.0 mmol/l are often asymptomatic; moderately elevated calcium can present with polyuria, polydipsia, anorexia, nausea and constipation. Higher concentrations of CCa can cause weakness, difficulty concentrating, confusion, stupor and even coma. However, other symptoms from renal, cardiovascular, neurological, musculoskeletal and gastrointestinal systems may occur. The most common causes of hypercalcaemia are primary hyperparathyroidism and malignancy – via multiple mechanisms.[5] Other less common but similarly important causes are listed above, however, the list of conditions precipitating hypercalcaemia is much wider.

MAS is a triad of hypercalcaemia, metabolic alkalosis and renal insufficiency and is associated with the ingestion of large amounts of calcium and absorbable alkali. This diagnostic entity became rare after introduction of histamine H_2 receptor blocker and proton-pump inhibitor therapy for peptic ulcer disease. In recent times, however, MAS has been increasingly recognised again in association with ingestion of absorbable calcium carbonate as a main source of calcium. The 'safe' dose of calcium carbonate is not known, however, it has been claimed that use of 4–5 g per day would be sufficient to cause MAS.[6–7] Our patient was using the excessive amount of up to 18 Rennies Dual Action tablets a day, each containing: calcium carbonate 625 mg, magnesium carbonate 73.5 mg, and alginic acid 150 mg.

Failure to recognise the syndrome has led to significant medical pitfalls including exploratory parathyroid surgery and permanent renal impairment[8–9]

MAS has two forms. Acute MAS, which occurs after 1 week of treatment and its symptoms include hypercalcaemia plus nausea and vomiting, weakness, mental changes and renal impairment. Withdrawal of calcium and alkali leads to rapid and complete recovery. Chronic form of MAS (Burnett's syndrome) occurs in long-term treatment. There is evidence of metastatic calcifications, including band keratopathy and nephrocalcinosis. In the chronic form, even with intensive treatment there is a slow recovery of renal function or persistence of chronic kidney impairment.[8 10]

Pathophysiology of the syndrome involves a number of processes. It is initiated by a large intake of calcium and absorbable alkali. Passive absorption of calcium in the bowel is concentration dependent, active absorption is regulated by vitamin D. Genetic variability has been claimed to play an important role in the development of MAS, with calcium hyper-absorbers being at risk of developing the syndrome.[10] Prolonged hypercalcaemia leads to decreased excretion of calcium by kidneys: afferent arteriole constriction and tubular dysfunction may be implicated. As a result, decreased glomerular filtration rate/creatinine clearance occurs, which presents as a renal failure, but also exacerbates hypercalcaemia by impairing calcium renal excretion. Another important factor in MAS is alkalosis, which inhibits calcium excretion. Volume depletion occurring in hypercalcaemia leads to even more marked alkalosis contributing to the vicious circle of hypercalcaemia.

Abnormalities of calcium metabolism can be found in Crohn's disease. The disease is, however, more associated with hypocalcaemia due to poor calcium intake and malabsorption of minerals and vitamin D. In some cases, however, there is unregulated production of 1,25-dihydrydroxyvitamin D by activated macrophages. A similar mechanism is thought to be responsible for hypercalcaemia in granulomatous diseases like sarcoidosis and tuberculosis. There have been only three case reports of hypercalcaemia with raised 1,25-dihydroxyvitamin D levels related to Crohn's disease.[1–3] Ioachimescu *et al* describes a patient with active Crohn's disease with elevated 1,25-dihydroxyvitamin D (calcitriol) and hypercalcaemia during activity of Crohn's disease which resolved with infliximab.[3] In our patient, the elevated 1,25-dihydroxyvitamin D normalised with steroids.

Our patient had significantly elevated 1,25-dihydroxyvitamin D (calcitriol) levels. There have been reports of elevated 1,25-diydroxyvitamin D (calcitriol) in Crohn's disease even without hypercalcaemia. It has also been noticed previously that 1,25-dihydroxyvitamin D (calcitriol) was not suppressed in patients with MAS.[11]

We therefore believe that there were multiple factors which contributed to the very severe hypercalcaemia. It was initiated by a prolonged excess intake of calcium carbonate and alkali. She then developed Crohn's disease which led to elevated levels of 1,25-dihydroxyvitamin D (calcitriol). She was suffering from gastrointestinal symptoms and therefore increased her self-medication with Rennies Dual Action and therefore further increased her calcium intake. Progressive hypercalcaemia led to renal impairment, which, by decreased calcium excretion, further contributed to hypercalcaemia. All these mechanisms led to disequilibrium hypercalcaemia of this unusually severe degree.

To our knowledge, this combination of factors causing hypercalcaemia has not been previously reported.

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Learning points

- Severe hypercalcaemia is a dangerous condition and often indicates significant underlying pathology.
- Initial management of hypercalcaemia in this situation requires hydration with 0.9% sodium chloride, not bisphosphonates.
- Management of this patient shows how important it is to obtain a thorough history, which includes detailed prescribed and over-the-counter medications.
- While it would have been easy to ascribe this patient's MAS to excessive intake of calcium carbonate and alkali alone; the other ongoing clinical features including increased 1,25-dihydroxyvitamin D (secreted by activated macrophages) led to the correct and more complete diagnosis.
- Several pathogenetic mechanisms likely contributed to this patient's severe hypercalcaemia.

Competing interests None.

Patient consent Obtained.

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