Milk-alkali syndrome

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CASE

A woman, aged 50 years, described experiencing abdominal pain and constipation for five months. Her blood tests showed hypercalcaemia and mild renal dysfunction. Serum calcium was 2.75 mmol/L (reference range [RR] 2.1–2.6 mmol/L), serum creatinine 115 mmol/L (RR 45–90 mmol/L), estimated glomerular filtration rate (eGFR) 48 mL/min/1.73 m^2 (RR >60 mL min/1.73 m^2) and serum bicarbonate 31 mmol/L (RR 22–32 mmol/L). Her vitamin D level was 53 nmol/L (RR >50 nmol/L).

Her past medical history included laparoscopic gastric banding, Hashimoto's thyroiditis and attention deficit hyperactivity disorder. Her medications included thyroxine and methylphenidate.

Proteinuria, haematuria and myeloma were excluded. Renal ultrasound and bone scan were normal. The woman's serum calcium and renal function had been normal four years earlier.

QUESTION 1

What are the most common causes of hypercalcaemia?

QUESTION 2

How does hypercalcaemia typically present?

QUESTION 3

What investigations should be performed?

ANSWER 1

Primary hyperparathyroidism and malignancy account for 54% and 35% of cases of hypercalcaemia, respectively.[1–4] Primary hyperparathyroidism (PHPT) is typically due to a benign adenoma. Hypercalcaemia due to malignancy is mediated by parathyroid hormone-related protein in over 80% of patients.[5] The most common cancers that cause hypercalcaemia are breast, renal, lung and squamous cell cancer, multiple myeloma and lymphoma.[6]

ANSWER 2

Mild and slowly progressive hypercalcaemia (corrected calcium <3 mmol/L) is often asymptomatic or might present with non-specific symptoms such as fatigue and constipation. Severe hypercalcaemia of acute onset can cause polyuria, polydipsia, renal stones, renal impairment, neuropsychiatric symptoms and arrythmias.[1]

ANSWER 3

The key investigation is the parathyroid hormone (PTH) level. A low or low–normal PTH level implies a PTH-independent cause of hypercalcaemia, the causes of which can be remembered using the mnemonic 'VITAMINS TRAP' (see Table 1). A mid- to upper-normal or elevated PTH level is consistent with PTH-dependent hypercalcaemia, which can be due to PHPT or familial hypocalciuric hypercalcaemia (FHH). Urinary fractional excretion of calcium is usually <0.01 in FHH and >0.02 in PHPT.[1] Genetic testing for variants in the calcium-sensing receptor gene can be undertaken if FHH is suspected.

CASE CONTINUED

The woman's PTH was suppressed at 0.9 pmol/L (RR 1.9–9.0 pmol/L).

QUESTION 4

What further history should be taken before performing further investigations?

QUESTION 5

What further investigations are required for PTH-independent hypercalcaemia?

ANSWER 4

Further history should be directed at the causes of PTH-independent hypercalcaemia outlined in Table 1, with a thorough medication history

that includes complementary and over-the-counter medications, as well as cosmetic fillers.

ANSWER 5

Further investigations should target the conditions listed in Table 1. Relevant tests include tumour markers, myeloma screen, imaging, mammogram, pap smear, endoscopy and colonoscopy.[7] Elevation of 25-hydroxyvitamin D might indicate vitamin D intoxication, whereas elevation of 1,25-hydroxyvitamin D could indicate sarcoidosis, lymphoma, granulomatous infection or *CYP24A1* mutation.[1,7]

CASE CONTINUED

On specific questioning, the woman had been taking antacid tablets (Quick-Eze) for gastroesophageal reflux, totalling 6 g calcium carbonate, 1 g magnesium carbonate and 1 g magnesium trisilicate daily, suggestive of milk-alkali syndrome. One week following cessation of antacids, the woman's symptoms resolved, serum calcium was 2.37 mmol/L, PTH 2.7 pmol/L, serum creatinine 82 μmol/L, eGFR 72 mL/min/1.73m^2 and bicarbonate 25 mmol/L. Renal function, bicarbonate and serum calcium remained normal three months later.

Table 1. Causes of parathyroid hormone-independent hypercalcaemia

• **V**itamin D and A excess
• **I**mmobilisation
• **T**hyrotoxicosis
• **A**drenal insufficiency
• **M**ilk-alkali syndrome: antacids, betel nuts, nicotine replacement gum, household cleaners, calcium sulphate beads in orthopaedic surgery
• **I**nflammatory/granulomatous: infections, foreign material-induced granulomas (cosmetic fillers, talc, mineral and paraffin oil)
• **N**eoplastic-related disease (parathyroid hormone related-protein), myeloma, lymphoma
• **S**arcoidosis
• **T**hiazide diuretics, other medications (lithium, heparin, rebound after cessation denosumab, teriparatide)
• **R**habdomyolysis, chronic renal failure, renal transplant, rare (CYP24A1 mutation)
• **A**cquired immunodeficiency syndrome (AIDS)
• **P**aget's disease, parenteral nutrition, phaeochromocytoma, pregnancy/lactation

QUESTION 6

What is milk-alkali syndrome?

ANSWER 6

Milk-alkali syndrome results from the ingestion of large quantities of calcium with absorbable alkali and is characterised by the triad of hypercalcaemia, metabolic alkalosis and renal dysfunction.[8,9] It was first described 100 years ago with the ingestion of milk and bicarbonate for peptic ulcer disease (Sippy regimen). The prevalence of milk-alkali syndrome fell with the availability of histamine H_2 receptor blockers and proton pump inhibitors, but a recent resurgence due to the use of calcium carbonate for gastroesophageal reflux and osteoporosis has resulted in milk-alkali syndrome being the third most common cause of hypercalcaemia. Presentation can be variable, with some patients being asymptomatic, others presenting acutely unwell with symptoms of hypercalcaemia and others presenting with complications of chronic hypercalcaemia, including nephrocalcinosis, chronic kidney disease and metastatic calcification.[9]

Milk-alkali syndrome typically occurs when calcium intake exceeds 4 g/day, although there have been case reports in individuals with calcium intake as low as 1–1.5 g/day.[10] Supportive therapy with isotonic saline and ceasing the offending medication usually leads to normalisation of calcium and renal function.

Key points

- The most common causes of hypercalcaemia are PHPT and malignancy.
- PTH-independent hypercalcaemia should prompt thorough history and investigation because malignancy could potentially be the cause.
- Medication history is important because it might elucidate the cause of PTH-independent hypercalcaemia, such as in this case of milk-alkali syndrome, and avoid extensive unnecessary investigations, as well as patient and health professional anxiety.

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