

A challenging case of hypercalcaemia

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Introduction

Hypercalcaemia is not uncommon in clinical practice. The majority of cases are accounted for by hyperparathyroidism and malignancy. The patient discussed below presented with an unusual case of hypercalcaemia.

Case report

A 56-year-old Caucasian man with a 30-year history of tophaceous gout, initially proven by the aspiration of monosodium urate crystals from an inflamed joint, presented to the nephrology department after being diagnosed with stage 5 chronic kidney disease. He had been diagnosed with hypertension five years prior, by which stage he was already suffering from chronic kidney disease. His presenting complaints included nocturia, constipation without any weight changes and paraesthesia of his feet. At the time of the consultation, his medication included allopurinol 600 mg daily, colchicine 0.5 mg twice daily as needed and Adalat XL® 90 mg daily.

A physical examination revealed multiple gouty tophi and destructive arthropathy of both hands. Decreased vibration, fine touch sensation and diminished ankle reflexes (graded as 1 + bilaterally) were suggestive of a peripheral neuropathy in the lower limbs. A funduscopy revealed grade 1 hypertensive retinopathy. The rest of the physical examination was unremarkable.

Blood tests showed normocytic, normochromic anaemia with a haemoglobin value of 12.1 g/dl. The uric acid level was 0.44 mmol/l and the patient had a normal 24-hour urinary uric acid of 1.6 mmol. Twenty-four-hour creatinine clearance values were 12.4 ml/minute, 11.6 ml/minute and 13.1 ml/minute respectively. Potassium levels and acid-base status were normal. The corrected serum calcium was elevated to 3.05 mmol/l,



L: left, R: right

Figure 1: Plain radiograph of the hands, showing destructive gouty arthritis affecting the wrists and small joints of the hands

which was confirmed by an elevated ionised calcium of 1.68 mmol/l. Phosphate was also elevated to 1.66 mmol/l. Thyroid functions were normal.

A chest X-ray revealed only osteopaenia and kyphosis of the thoracic spine, while an X-ray of the hands evidenced the destructive uric acid arthropathy (Figure 1).

A renal ultrasound showed a left kidney size of 11.1 x 4.9 x 4.7 cm, and a right kidney measuring 10.5 x 4.8 x 5 cm. Both kidneys displayed loss of corticomedullary differentiation, and there was no evidence of hydronephrosis or hydroureter.

A decision was made to conduct further investigations of the patient's hypercalcaemia aetiology. A careful review of the history revealed no medication or supplementation which could have contributed to the hypercalcaemia. The serum parathyroid hormone (PTH) was suppressed to < 0.3 ng/l, excluding hyperparathyroidism as the aetiology for the hyper-

calcaemia. The daily urine calcium excretion was appropriately elevated to 8.9 mmol/24 hours.

In view of the patient's age, the possibility of malignancy-associated hypercalcaemia was considered. It was not possible to perform PTH-related peptide in our laboratory setting. Serum protein electrophoresis was normal, as were prostate-specific antigen values (for his age), while a colonoscopy and gastroscopy did not reveal any malignancy. A computed tomography scan of the patient's chest revealed calcification of the thoracic aorta and bilateral axillary lymph nodes. The largest measured 1 x 1.6 cm. An excision biopsy of one of the nodes was performed and found to be reactive in appearance, with no features of malignancy. The patient underwent fluorodeoxyglucose (FDG)-positron emission tomography scanning, which was consistent with the arthritis and reactive lymph nodes.

Endocrinological causes, including thyrotoxicosis, pheochromocytoma and adrenal insufficiency, were excluded. Consideration was given to granulomatous disease as the aetiology. The patient's 1,25-dihydroxyvitamin D levels were elevated at 70.2 ng/dl, with a normal 25-hydroxyvitamin D level. There was no clinical or radiological evidence to support the diagnosis of sarcoidosis. Induced sputum cultures were negative for tuberculosis.

It was postulated that chronic tophaceous gout was the aetiology for this patient's hypercalcaemia. The mechanism was extrarenal, PTH-independent calcitriol production by activated mononuclear cells within the granuloma.

The patient was treated with prednisone 0.5 mg/kg and two weeks later, his ionised calcium had normalised to 1.18 mmol/l, while his 1,25-dihydroxyvitamin D had normalised to 22 ng/l. This steroid response would be observed with any granulomatous cause of hypercalcaemia.

In the absence of any other cause of the hypercalcaemia, it was postulated that the index patient presented with hypercalcaemia secondary to chronic tophaceous gout. The hypercalcaemia, renal failure and colchicine could have contributed to his peripheral neuropathy.

Discussion

Hypercalcaemia is a relatively common problem in clinical medicine. The majority of cases (over 90%) can be accounted for by hyperparathyroidism or malignancy.¹

The initial step in determining the aetiology of hypercalcaemia is to differentiate PTH-mediated causes thereof (including primary hyperparathyroidism and familial hyperparathyroid syndromes) from non-

PTH-mediated hypercalcaemia (of which malignancy, vitamin D intoxication and granulomatous disease are the most common aetiologies).

Hypercalcaemia that is associated with malignancy is one of the most common causes of non-PTH-mediated hypercalcaemia. Malignancy is generally associated with a more recent onset of hypercalcaemia and is more likely to be symptomatic. The diagnosis of hypercalcaemia of malignancy can be confirmed by demonstrating an elevated serum concentration of PTH-related protein, while levels of PTH and 1,25-dihydroxyvitamin D are generally suppressed.²

The vitamin D metabolite 25-hydroxyvitamin D is generally elevated in vitamin D intoxication.³ The metabolite 1,25-dihydroxyvitamin D may be increased by intake of this metabolite or by extrarenal production in the case of granulomatous disease, such as sarcoidosis or lymphoma.

Rarer causes for hypercalcaemia include bone resorption, like that which occurs in thyrotoxicosis,⁴ multiple myeloma⁵ or immobilisation.⁶ Increased intake of calcium can lead to hypercalcaemia in patients with renal insufficiency.

Other causes of hypercalcaemia include the use of lithium, teriparatide, excess vitamin A⁷ or theophylline toxicity. Endocrine-associated conditions with hypercalcaemia include acromegaly, pheochromocytoma⁸ and adrenal insufficiency.^{9,10} Generally, these are associated with other clinical features of the underlying disease.

Urinary calcium excretion may be decreased in the face of hypercalcaemia if the aetiology is familial hypocalciuric hypercalcaemia, the milk-alkali syndrome associated with calcium carbonate consumption, and with the use of thiazide diuretics.

A case report by Sachdeva et al¹¹ described the presentation of hypercalcaemia in a Caucasian man with chronic tophaceous gout. In this case, as with our patient, extensive workup of the aetiology for the hypercalcaemia revealed a low PTH, negative PTH-related protein, normal thyroid function tests, no evidence of malignancy, and negative blood, urine and sputum cultures. Endocrinological causes of the hypercalcaemia were excluded and a gallium scan revealed increased uptake in areas of gouty arthritis involvement. The authors of this case study postulated that the tophaceous gout was responsible for the hypercalcaemia. The suggested mechanism is extrarenal, PTH-independent calcitriol production by activated mononuclear cells within the granuloma. Monosodium urate crystals are thought to serve as the inciting antigen that leads to an intense inflammatory reaction of macrophages, lymphocytes and giant

cells. The patient was treated with systemic steroids which resulted in normalisation of his serum calcium levels.

In the index patient, none of these usual causes of hypercalcaemia could be established, on grounds of either clinical or special investigation. It would be of interest to test serum calcium levels in all patients with chronic tophaceous gout to establish whether hypercalcaemia is a common association.

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Erratum

Rheeder P, Duim-Beytel MC, Meijer R, Gustavsson T, Danler GKG, Ahmed RA. Carotid intima-media thickness and its associations with type 2 diabetes mellitus in South Africans. *JEMDSA* 2012;17(3):135-140

We hereby wish to apologise for a mistake in the above-mentioned article's abstract. The number of patients in the results paragraph was accidentally printed as "85" instead of "185". The corrected abstract is featured below. Please refer to the full text article on www.jemdsa.co.za

Abstract

Objectives: Carotid intima-media thickness (CIMT) is a surrogate marker of subclinical atherosclerosis and a predictor of cardiovascular events. Few studies in Africa have evaluated CIMT and its associations in people with type 2 diabetes mellitus. This study measured CIMT in a sample of mainly black South African patients with type 2 diabetes mellitus, and evaluated the association of demographic and clinical risk factors with CIMT.

Design: Cross-sectional study.

Setting: Kalafong Hospital, a large community hospital in Pretoria that mainly serves an urban black community.

Subjects: Patients with type 2 diabetes mellitus.

Outcome measures: We evaluated clinical, biochemical and CIMT ultrasound measurements in a standardised fashion.

Results: In 185 patients, the univariate significant predictors of mean far-wall CIMT were age [β 0.007 (standard error 0.001)], systolic blood pressure [β 0.001 (standard error 0.000)] and inverse serum creatinine [β -8.15 (standard error 3.23)]. Low-density lipoprotein cholesterol, apolipoprotein A-1, apolipoprotein B:A-1 ratio and apolipoprotein B:A-1 ratio > 1.2 all had p-values below 0.1, but above 0.05. Age had the largest R-squared (20%). The multivariate models did not explain more of the variation in CIMT than did age alone.

Conclusion: Lipid parameters were related to CIMT in our study population. However, this did not reach statistical significance in this relatively small sample, and lipids added very little to the variability of CIMT compared with age alone.