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Case Report

CASE REPORT

Hypercalcaemic crisis in an elderly patient with pulmonary tuberculosis

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Abstract

Tuberculosis is an uncommon but recognized cause of hypercalcaemia, though calcium levels are seldom severely elevated and rarely result in symptoms. In the elderly patient however, several competing aetiologies may contribute to hypercalcaemia and the diagnostic evaluation may be confounded by polypharmacy as well as multiple co-existing medical conditions. We present here a case of an elderly man who presented with pulmonary tuberculosis and concomitant delirium secondary to hypercalcaemic crisis. Treatment with anti-tuberculous drugs, together with supportive care, eventually led to resolution of hypercalcaemia and restoration of mental function.

INTRODUCTION

Tuberculosis is an infrequent cause of hypercalcaemia [1]. Although the association is well recognized, calcium levels are seldom severely elevated and rarely result in symptoms. We report a case of an 86-year-old man who presented with pulmonary tuberculosis and concomitant delirium secondary to hypercalcaemic crisis. Through this case, we highlight tuberculosis as a potential cause of severe hypercalcaemia, particularly in the elderly, as well as discuss several competing diagnoses specific to this susceptible group of patients.

CASE REPORT

An 86-year-old man presented with productive cough of 2 weeks duration, associated with exertional dyspnoea, fatigue and poor appetite. He also had fever and weight loss. There was no history of night sweats or haemoptysis. His medical history includes hypertension, hyperlipidaemia, previous lacunar strokes and gout. No significant social or family history was reported. On examination, there was a temperature of 39°C and an oxygen saturation of 93% on ambient air. His heart rate was regular at 130 bpm and his blood pressure was 90/40 mmHg. He was ill-looking and confused. A systemic examination revealed bilateral coarse crackles throughout both lung fields, but was otherwise unremarkable. In particular, there were no signs to suggest concomitant congestive heart failure, such as the presence of a raised jugular venous pulse or pedal oedema. There were neither palpable masses nor enlarged lymph nodes.

The laboratory tests are summarized in Table 1. The albumin-corrected serum calcium level at presentation was 3.02 mmol/l, progressing to a peak of 3.13 (normal: 2.1–2.6 mmol/l) despite intravenous fluid therapy. Other significant blood test results at diagnosis included: phosphate 0.82 mmol/l (normal: 0.81–1.45 mmol/l), parathyroid hormone 0.71 pmol/l (normal: 1.3–7.6 pmol/l), alkaline phosphatase 83 U/l (normal: 32–103 U/l) and 25-hydroxyvitamin D 35.7 µg/l (normal: 300–100 µg/l). Serum creatinine level was 197 µmol/l (normal: 37–75 µmol/l). Procalcitonin level was 2.60 µg/l (normal: <0.50 µg/l). A chest radiograph demonstrated ground glass opacities and interstitial infiltrates bilaterally. A diagnosis of severe pneumonia was made, and the

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patient was commenced on intravenous piperacillin and tazobactam, as well as clarithromycin. However, due to the lack of clinical response to initial treatment over a week's duration, computed tomography of the lungs was performed. This revealed patchy infiltrates, tree-in-bud opacities and confluent consolidation bilaterally, including the apices, with more extensive changes on the left. No sinister appearing masses were noted (Fig. 1).

Table 1: Summary of relevant laboratory tests performed

Laboratory test	Values	Normal range
Haemoglobin (g/dl)	12.5	12.0–16.0
Leucocyte (10^9/l)	14.6	4.0–10.0
Platelet (10^9/l)	364	140–440
Urea (mmol/l)	19.6	2.7–6.9
Creatinine (μmol/l)	197	37–75
Sodium (mmol/l)	136	136–146
Potassium (mmol/l)	3.6	3.6–5.0
Phosphate (mmol/l)	0.82	0.81–1.45
Magnesium (mmol/l)	0.75	0.74–0.97
Calcium (mmol/l)	2.62	2.1–2.6
Albumin (g/l)	20	40–51
Parathyroid hormone (pmol/l)	0.71	1.3–7.6
Alkaline phosphatase (U/l)	83	32–103
25-hydroxyvitamin D (μg/l)	35.7	300–100
Erythrocyte sedimentation rate (mm/h)	>120	0–22
C-reactive protein (mg/l)	70.4	0.2–9.1
Procalcitonin (μg/l)	2.60	<0.50
Cortisol (nmol/l)	1077	NA
Free T4 (pmol/l)	12.7	8.8–14.4
Thyroid-stimulating hormone (MU/l)	4.08	0.65–3.70

Several differential diagnoses were considered at this juncture. In our patient, there was neither a reported history of excessive calcium/vitamin D intake nor consumption of thiazides. Laboratory tests (Table 1) and systemic radiological scans, including computed tomography of the abdomen and pelvis, as well as ultrasound of the neck, excluded any malignant processes and endocrinopathies. In view of the severe symptomatology and radiological findings, a diagnosis of hypercalcaemic crisis secondary to pulmonary tuberculosis was formulated.

Two weeks from admission, further investigations revealed sputum samples positive for acid-fast bacilli, which were later confirmed to be *Mycobacterium tuberculosis* on cultures and polymerase chain reaction. Drug-resistant tests for *M. tuberculosis* revealed sensitivity to first-line anti-tuberculous drugs including rifampicin and isoniazid. Based on the patient's weight of 47 kg, he was commenced on a daily anti-tuberculosis antibiotic regimen composed of rifampicin 450 mg, isoniazid 200 mg, ethambutol 800 mg and moxifloxacin 400 mg. Given his medical history of gout, moxifloxacin was used instead to avoid pyrazinamide-induced hyperuricaemia. In terms of treatment for hypercalcaemia, intravenous fluids were administered. Poor cardiac function limited the amount of fluids that could be given safely, and loop diuretics had to be administered intermittently as well.

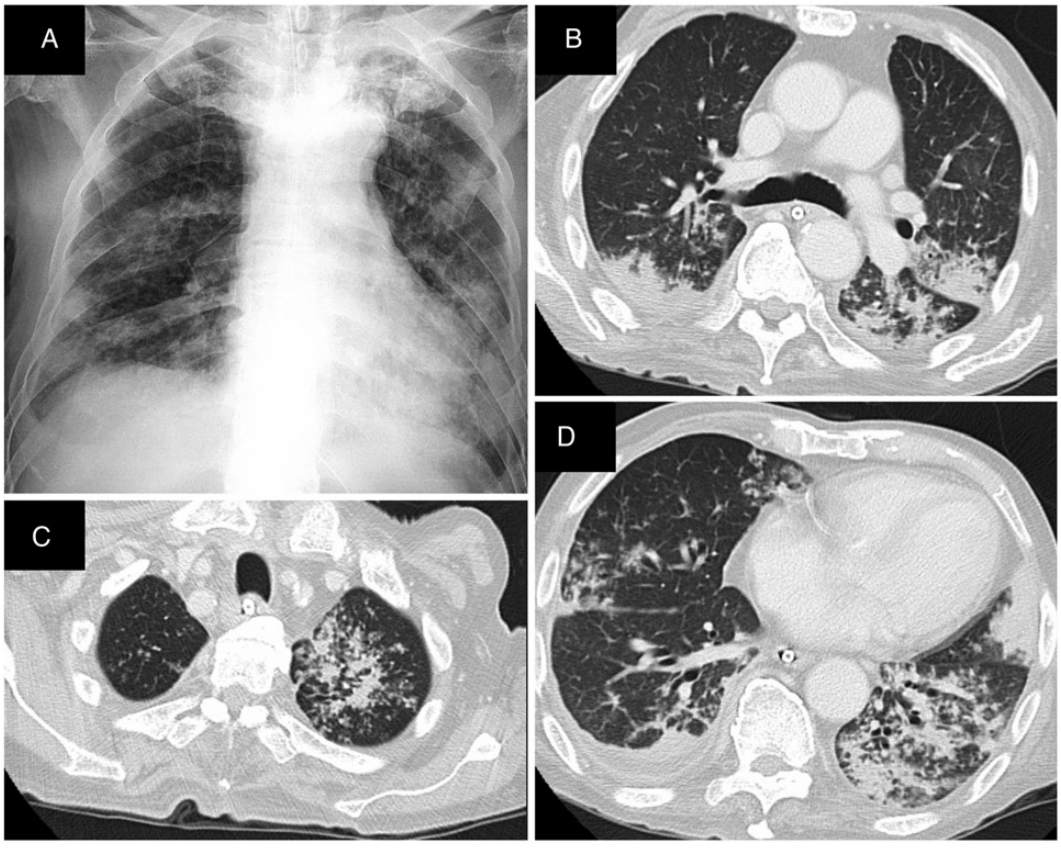

Figure 1: Chest radiography and thoracic computed tomography of the patient with pulmonary tuberculosis. (**A**) A chest radiograph demonstrated ground glass opacities and interstitial infiltrates bilaterally. Computed tomography of the lung revealed patchy infiltrates, tree-in-bud opacities and confluent consolidation bilaterally, including the apices (**B**), with more extensive changes on the left (**C** and **D**).

As calcium levels remained persistently elevated, two doses of intravenous pamidronate were then given, but without a reduction in serum calcium levels or improvement in mental status. Subcutaneous calcitonin was subsequently given with a decrement in serum calcium levels accompanied by resolution of delirium. No steroids were administered. Serum calcium levels eventually normalized with a continued treatment of tuberculosis. Unfortunately, after 3 weeks of inpatient physical rehabilitation, the patient deteriorated from recurrent pneumonia not responding to broad-spectrum antibiotics and eventually passed away while in the hospital.

DISCUSSION

The most important causes of hypercalcaemia in the elderly are hyperparathyroidism, malignant disease and prolonged immobilization. Medications, such as thiazide diuretics and lithium, as well as excessive supplementation with calcium/vitamin D, may precipitate hypercalcaemia. Granulomatous disorders, such as sarcoidosis and tuberculosis, can also potentially present with hypercalcaemia. Other less common causes include familial hypocalcinuric hypercalcaemia and endocrinopathies including thyrotoxicosis and Addison's disease, although the ensuing hypercalcaemia is usually mild in these cases. In the elderly patient, several competing aetiologies may contribute to elevated calcium levels, and the diagnostic evaluation may be confounded by polypharmacy and multiple co-existing medical conditions. Malignancy remains the most common cause of moderate–severe hypercalcaemia in the elderly and must be excluded. Although hypercalcaemia is known to be associated with pulmonary tuberculosis, it is relatively uncommon and is rarely symptomatic. Despite this, moderate–severe elevation in serum calcium levels (>3.0 mmol/l) can occur, predisposing the patient to delirium and acute kidney injury, and immediate treatment is warranted.

The prevalence of hypercalcaemia in patients with active tuberculosis differs widely between countries. This variation has been largely attributed to disparity in vitamin D and calcium intake, the degree of sunlight exposure as well as the criteria for hypercalcaemia [1]. In the elderly patient with tuberculosis, the frequency of hypercalcaemia has not been well documented.

The mechanism of tuberculous hypercalcaemia remains unclear, but has been largely attributed to vitamin D dysregulation (Fig. 2). Patients presenting with active tuberculosis tend to have lower levels of vitamin D than healthy individuals [2]. In patients with tuberculosis, extrarenal synthesis of active vitamin D, 1,25 (OH)2D3, occurs via 1-alpha-hydroxylase produced by gamma interferon-activated T lymphocytes and alveolar macrophages [3, 4], which results in increased enteric absorption of calcium.

In vitro, vitamin D promotes mycobacterial killing in macrophages through production of nitric oxide [5], as well as the antimicrobial peptide cathelicidin LL-37, after activation of macrophages via either Toll-like receptor or gamma interferon release [6, 7], and by inducing phagolysosyme fusion and autophagy [7, 8]. These effects have been shown to be local [9], and does not normally affect overall calcium homeostasis. In addition, 1,25 (OH)2D3 induces 24(OH) hydroxylase expression, which deactivates 1,25(OH)2D3 to calcitroic acid. However, it is believed that if large quantities of 1,25(OH)2D3 are produced, a 'spillover' effect may occur in the circulation and potentially result in hypercalcaemia [10].

Although clinically significant hypercalcaemia from tuberculosis is relatively uncommon, the elderly patient is particularly susceptible, given their advanced age, comorbidities, polypharmacy as well as the frequent use of calcium/vitamin D supplements. Appropriate imaging and laboratory tests should be performed to exclude other competing causes. As seen from our patient, return to normocalcaemia can be achieved with antibiotic and supportive therapy alone, avoiding the usage of steroids. This case report highlights the geriatric population as

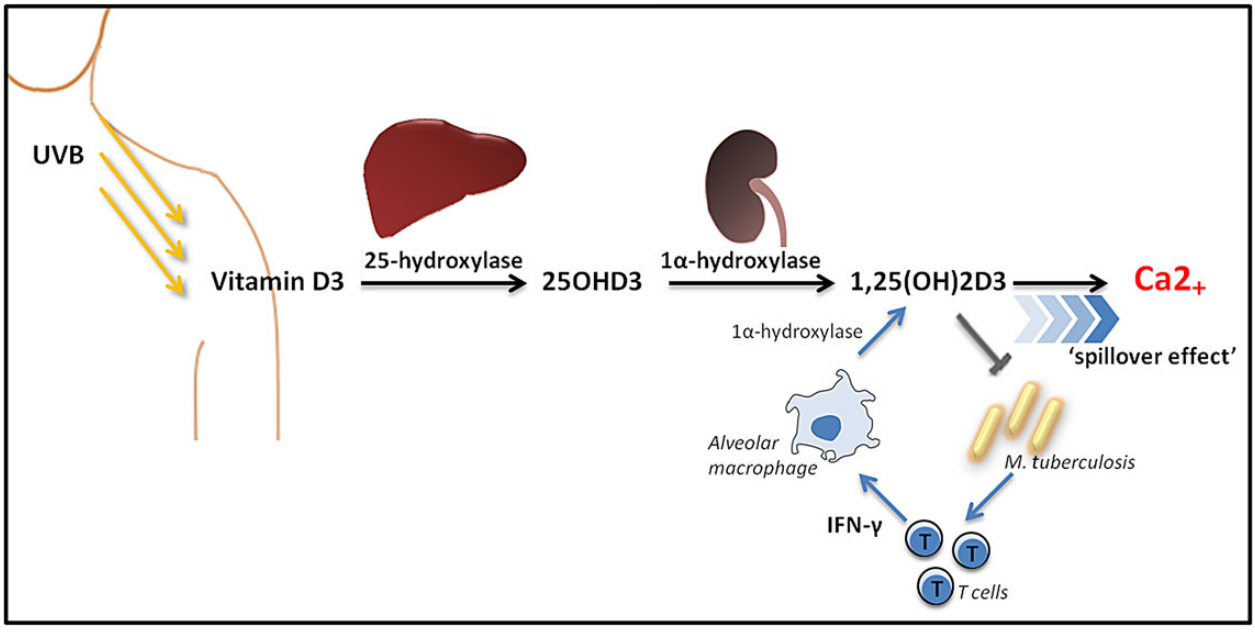

Figure 2: Putative mechanism of tuberculous hypercalcaemia. Vitamin D3 is derived from the skin following the influence of ultraviolet B (UVB) light. Vitamin D3 is first metabolized to 25-hydroxyvitamin D (25OHD3) in the liver, then to 1,25-dihydroxyvitamin D (1,25(OH)2D3) in the kidneys, catalysed via 25-hydroxylase and 1α-hydroxylase, respectively. In patients with tuberculosis, extrarenal synthesis of 1,25(OH)2D3 occurs via 1-alpha-hydroxylase produced by gamma interferon-activated T lymphocytes and alveolar macrophages. Usually, 1,25(OH)2D3 exerts local anti-mycobacterial effects and does not affect overall calcium homeostasis. However, if large quantities of 1,25(OH)2D3 are produced, a 'spillover' effect may occur and potentially result in hypercalcaemia.

a particularly vulnerable group that may be susceptible to hypercalcaemic crises in the setting of active tuberculosis.

This work conforms to standards currently applied in the country of origin and is exempted from any ethics approval. Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-chief of this journal. J.Y.C. and M.K. are guarantors.

CONFLICT OF INTEREST STATEMENT

None declared.

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