CASE REPORT

Fluctuating hypercalcaemia caused by cavitary *Mycobacterium bovis* pulmonary infection

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SUMMARY

Hypercalcaemia occurs in many granulomatous diseases. Among them, sarcoidosis and tuberculosis are the most common causes. Other causes include berylliosis, coccidioidomycosis, histoplasmosis, Crohn's disease, silicone-induced granulomas, cat-scratch disease, Wegener's granulomatosis and *Pneumocystis carinii* pneumonia. Hypercalcaemia in granulomatous disease occurs as a consequence of dysregulated production of 1,25-(OH)₂D₃ (calcitriol) by activated macrophages in granulomas. Hypercalcaemia in patients with *Mycobacterium tuberculosis* infection has been reported in 0%–28% of cases. Uncultured bronchoalveolar lavage cells from patients with *M. tuberculosis* produce greater amounts of calcitriol compared with controls. Although Nayar *et al* described hypercalcaemia in a case of sepsis associated with intravesical Bacille Calmette Guerin therapy, there are no published reports describing hypercalcaemia in patients with pulmonary *M. bovis* infection. We describe a patient with *M. bovis* cavitary pulmonary infection with sustained hypercalcaemia that fluctuated and recurred repeatedly over the course of therapy, ultimately culminating in normalisation of serum calcium when therapy had led to cure. Treatment consisted of antituberculous therapy, oral corticosteroids and intravenous bisphosphonates with a favourable outcome.

BACKGROUND

Hypercalcaemia has been reported in many granulomatous diseases. Among them, sarcoidosis and tuberculosis are the most common causes. Other causes include berylliosis, coccidioidomycosis, histoplasmosis, Crohn's disease, silicone-induced granulomas, cat-scratch disease, Wegener's granulomatosis and *Pneumocystis carinii* pneumonia.^{1–13} Hypercalcaemia occurs as a consequence of the action of 1- α -hydroxylase produced by T lymphocytes and activated macrophages.¹³ This enzyme has the effect of converting 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. Infectious granulomatous diseases are no exception to this phenomenon.¹⁴ Hypercalcaemia in patients with *Mycobacterium tuberculosis* infection at the time of presentation ranges from 0% to 28% in published reports.^{15–17} Nayar *et al* described hypercalcaemia in a case of sepsis associated with intravesical Bacille Calmette Guerin therapy.¹⁸ It has been shown that uncultured bronchial washings cells from patients with *M. tuberculosis*

increase conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol compared with controls.^{4 13}

Mycobacterium tuberculosis is thought to have evolved from *M. bovis* in Neolithic times.¹⁹ *Mycobacterium bovis* infection causes 1.4% of pulmonary tuberculosis (TB) outside Africa and 2.8% within Africa which approximately equates to an annual incidence of *M. bovis* of 7/100 000 worldwide.^{20 21} It leads to a clinical syndrome of pulmonary TB which is phenotypically identical to that caused by *M. tuberculosis*.

CASE PRESENTATION

A 61-year-old man presented with a 3-month history of productive cough, fever and 6 kg weight loss. He had no history of tuberculous contact. He had worked with cattle on a nearby farm in the years prior to presentation. He was a smoker with a 35 pack/year history. He had a history of GOLD (Global Initiative for Chronic Obstructive Lung Disease) Stage B chronic obstructive pulmonary disease, dietary iron deficiency anaemia and alcohol excess. He denied haemoptysis or night sweats.

Figure 1 A chest X-ray showing right upper lobe consolidation with lucent areas suggestive of cavitation.

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Figure 2 CT thorax showing extensive consolidation with areas of cavitation in the right upper lobe.

On examination, he was cachectic (body mass index 14.9 kg/m²) and had scattered wheeze throughout the lung fields. A chest radiograph and CT of thorax demonstrated right upper lobe consolidation and cavitation (figures 1 and 2). Serum calcium (corrected for albumin) was 2.6 mmol/L. Sputum Ziehl Nielsen staining was strongly positive and mycobacterial culture ultimately isolated *M. bovis*. The patient was initially treated with rifampicin, isoniazid, pyrazinamide and ethambutol and treatment was changed to rifampicin, isoniazid and ethambutol when mycobacterial cultures became available.

Fourteen days after presentation, he became confused and was investigated with both CT and MRI of brain to rule out intracranial TB. These showed mild global cerebral atrophy. This confusion resolved with initial antituberculous therapy. After 2 months of antituberculous therapy, he remained unwell, had a persistent spiking fever and serum calcium had increased to 3.22 mmol/L.

INVESTIGATIONS

The patient's serum calcium and albumin were measured regularly and levels throughout his treatment are shown in figure 3.

Parathyroid hormone was suppressed at 5 ng/L (15–65 ng/L). 25-OH Vitamin D was 40 nmol/L (75–200 nmol/L). Serum immunoglobulin (Ig)G and IgA were raised at 27.8 g/L (6–16 g/L) and 4.2 g/L (0.8–4 g/L), respectively. Serum electrophoresis revealed that the gamma band was diffusely raised. Paraprotein screen was negative. Thyroid function test showed a low free T4 with a normal thyroid-stimulating hormone. Bence-Jones proteins were not detected in the urine. Serum ACE was 34 U/L (0–45 U/L). PTHrP (parathyroid hormone related peptide) was in the normal range. On each recurrence of hypercalcaemia, the investigations above were repeated and showed similar results.

Figure 3 Serum calcium, corrected calcium and albumin over the course of antituberculous therapy.

Sputum mycobacterial cultures showed *M. bovis*, resistant to pyrazinamide, but sensitive to other first-line antituberculous drugs, as is constitutive for *M. bovis*.²²

CT of thorax, abdomen and pelvis showed worsening right upper lobe consolidation and cavitation as compared with his initial imaging (figure 3), but no destructive osseous lesions were seen. Radioisotope scanning of the osseous skeleton showed two areas of increased isotope in T10 and the cervical spine; however, these were not felt to be destructive osseous lesions but rather degenerative spine disease which coincided with similar areas on CT scans. Bronchial washings TB cultures at this time were negative.

DIFFERENTIAL DIAGNOSIS

The two most common causes of hypercalcaemia in clinical practice are primary hyperparathyroidism and hypercalcaemia associated with malignancy, accounting for 90% of cases of hypercalcaemia.¹⁵ In this case, parathyroid hormone was suppressed as a response to elevated serum calcium, ruling out hypercalcaemia as a result of primary hyperparathyroidism. A myeloma screen found that the Bence-Jones protein was negative, a diffusely raised gamma band with mildly raised IgA, thought to be secondary to the pulmonary TB. Erythrocyte sedimentation rate was elevated at 104s, also presumed to be as result of the patient's ongoing inflammatory illness. CT of the thorax abdomen and pelvis showed no destructive osseous lesions or evidence of neoplasia. Radioisotope scanning showed no areas of increased uptake throughout the skeletal system.

Thyrotoxicosis was considered as a possible cause of unexpected bone resorption; however, thyroid function tests were also performed and showed no evidence of thyrotoxicosis. 25 hydroxycholecalciferol levels were low at 40 nmol/L (75–200 nmol/L) suggesting that ingestion or absorption of vitamin was not causing elevated serum calcium and thus an intrinsic conversion process was causing the patients to have elevated calcium. 1,25-dihydroxycholecalciferol is not routinely measured due to the short half-life and large daily variation in serum levels.²³

TREATMENT

The patient's first significant hypercalcaemic episode occurred after 75 days of antituberculous therapy and was treated successfully with intravenous fluids. At that time, he was taking rifampicin and isoniazid and he was commenced on three additional antituberculous agents (ethambutol, streptomycin and moxifloxacin) because of the lack of clinical and radiological improvement.

Serum calcium improved but remained elevated and continued to increase over the following weeks, such that after 112 days of antituberculous therapy, serum calcium was 3.14 mmol/L (figure 3). On this occasion, there was an associated KDIGO grade 1 acute kidney injury,²⁴ with a creatinine of 178 mmol/L, increased from a baseline of 95–105 mmol/L. He was treated with intravenous fluids, oral prednisolone and a single dose of intravenous zoledronic acid which normalised serum calcium and renal function after 4 days. Oral glucocorticoid therapy was initialised with prednisolone 30 mg once daily and was then decreased by 5 mg/week. The response to this regime is illustrated in figure 4.

The patient represented on a third occasion after 212 days of antituberculous therapy with a corrected serum calcium level of 2.94 mmol/L (figure 3) and a KDIGO grade 1 acute kidney injury,²² with a serum creatinine of 158 mmol/L. He was treated

Figure 4 Serum calcium and glucocorticoid therapy over the course of antituberculous therapy.

with intravenous fluids and oral steroids and both hypercalcaemia and acute kidney injury resolved after 1 week.

Sputum TB cultures remained negative after 2 months of antituberculous therapy although low-grade spiking fever continued through to 6 months after initiation of therapy.

OUTCOME AND FOLLOW-UP

The patient was treated with antituberculous therapy for a total 257 days. His therapy was complicated by recurrent hypercalcaemic episodes and secondary acute kidney injuries. He was followed for 2 years after the end of his antimycobacterial treatment and had no evidence of recurrence of TB or hypercalcaemia. A chest X-ray taken 4 years after the completion of antituberculous therapy shows residual right upper lobe fibrosis with no evidence of reactivation (figure 5).

DISCUSSION

Hypercalcaemia may occur as a consequence of infectious and noninfectious granulomatous diseases. There are many published reports describing hypercalcaemia in pulmonary TB

Figure 5 A chest X-ray 4 years after completion of antituberculous treatment showing right upper lobe fibrosis.

caused by *M. tuberculosis*; however, hypercalcaemia in patients with *M. bovis* pulmonary disease has not been described and the fluctuating hypercalcaemia seen in our patient over the course of therapy is most unusual.

Intuitively, one would expect that if a patient with TB develops hypercalcaemia, this would be worst at presentation when the disease is at its most extensive and would improve progressively as treatment progresses. Although sputum and bronchial washings mycobacterial cultures remained negative after 2 months of therapy, extensive pulmonary granulomatous inflammation persisted in our patient, facilitating persistent and recurrent hypercalcaemia.

The authors remained concerned about occult malignancy throughout the course of therapy but the ultimate resolution of hypercalcaemia after a protracted course of antituberculous therapy was reassuring.

Learning points

- ▶ Serum calcium should be regularly measured in patients with pulmonary tuberculosis (TB). Insidious, asymptomatic elevations in serum calcium may be seen, even in later stages of treatment.
- ▶ Hypercalcaemia in pulmonary TB should be investigated thoroughly. Although hypercalcaemia is extensively described in patients with granulomatous disease, malignancy, primary hyperparathyroidism and multiple myeloma should be excluded in the differential diagnosis of hypercalcaemia.
- ▶ Treatment of hypercalcaemia should be approached in a stepwise fashion. Increased oral fluid intake and dietary calcium restriction are first line measures. A short course of glucocorticoid treatment may be considered if hypercalcaemia is persistent. Intravenous bisphosphonates may be used when hypercalcaemia is resistant to these treatment modalities.

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Competing interests None declared.

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