HYPERCALCEMIA IN A PATIENT WITH TUBERCULOUS MEDIASTINAL LYMPHADENOPATHY

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ABSTRACT

We describe the case of a 48 year old Indian female with hypercalcemia due to tuberculosis. She presented with symptoms of hypercalcemia and chest radiographs showed bilateral hilar lymphadenopathy with normal lung fields. The diagnosis of tuberculosis was made histologically from biopsy of the enlarged hilar nodes. Her hypercalcemia resolved following one month of anti-tuberculous treatment. The prevalence of hypercalcemia in tuberculosis has been reported to be high in western series. There is, however, a paucity of local data on the subject. The presence of 1-alpha-hydroxylase-like activity in pulmonary alveolar macrophages with resulting increased formation of active vitamin D metabolites is the postulated mechanism of tuberculosis associated hypercalcemia.

Keywords : Tuberculosis, hypercalcemia, Vitamin D metabolism.

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INTRODUCTION

Hypercalcemia has been reported to occur in association with several granulomatous disorders including sarcoidosis, tuberculosis[1-3], and fungal infections[4]. The reported incidence varies from 30% to 50%[1-3]. The problem of tuberculosis associated abnormal calcium metabolism in Malaysia is probably overlooked despite the relatively high prevalence of tuberculosis locally. We report a patient with hypercalcemia due to tuberculosis and discuss its possible pathogeneses.

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CASE REPORT

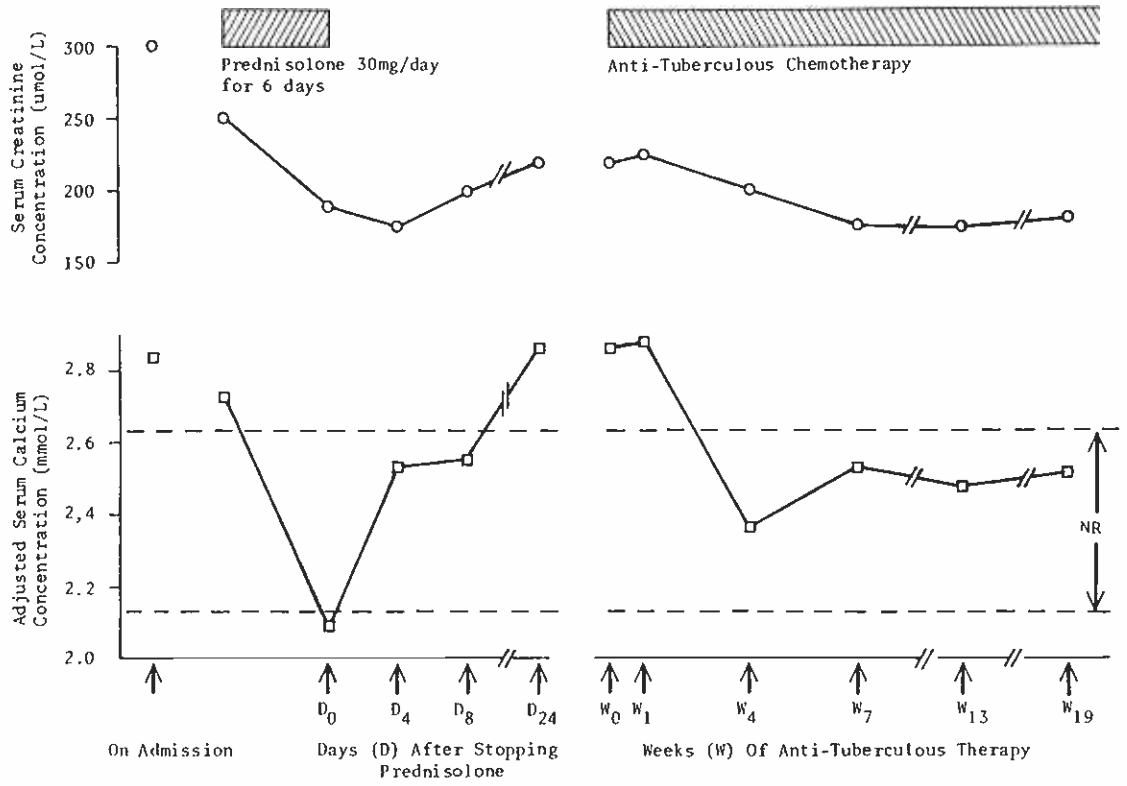
A 48 year old Indian housewife presented to the Endocrinology Unit of Universiti Kebangsaan Malaysia (UKM) with a problem of hypercalcemia and seven months' history of weight loss, constipation, polyuria, polydipsia and anorexia. She had no history of fever, respiratory symptoms or previous history of tuberculosis. She was not on any medication that could induce hypercalcemia. Physical examination revealed a thin lady with obvious proximal muscle wasting and band keratopathy on slit lamp examination. Her supine blood pressure was 130/80 mmHg with no postural drop. Examination of the lungs was normal. There was no bone tenderness or lymphadenopathy. Other systems were normal.

Her serum calcium and albumin levels on admission were 2.85 mmol/L [normal range (NR), 2.13-2.63] and 41g/L (NR, 26-52) respectively. In addition to hypercalcemia, serum levels of creatinine [298 umol/L (NR, 62-124)] and mid-molecule immuno-reactive parathyroid hormone [129 pmol/L (NR, 29-85)] were also raised. Her erythrocyte sedimentation rate (ESR) was 62mm/1st hr (normal < 15). Serum levels of thyroxine, triiodothyronine, alkaline phosphatase, potassium and sodium were all normal. Short synacten test with 250 µg of tetracosactrin given intramuscularly showed normal adrenocortical response.

Radiographs of the skull and hands did not show any evidence of hyperparathyroidism or lytic lesion. Normalisation of serum calcium concentration occurred following 6 days of prednisolone 30mg/day (Fig 1) thus indicating a positive steroid suppression test. The former was associated with a parallel decrease in serum creatinine level. Chest X-ray (Fig 2) and computerised tomographic scan of the thorax showed normal lung fields and bilateral hilar lymphadenopathy. However, both Kveim and Mantoux tests were negative. Sputum, laryngeal swab and bronchial brushings from bronchoscopy were negative for acid fast bacilli (AFB) on direct smears. Serum protein electrophoresis and bone marrow aspirates were normal.

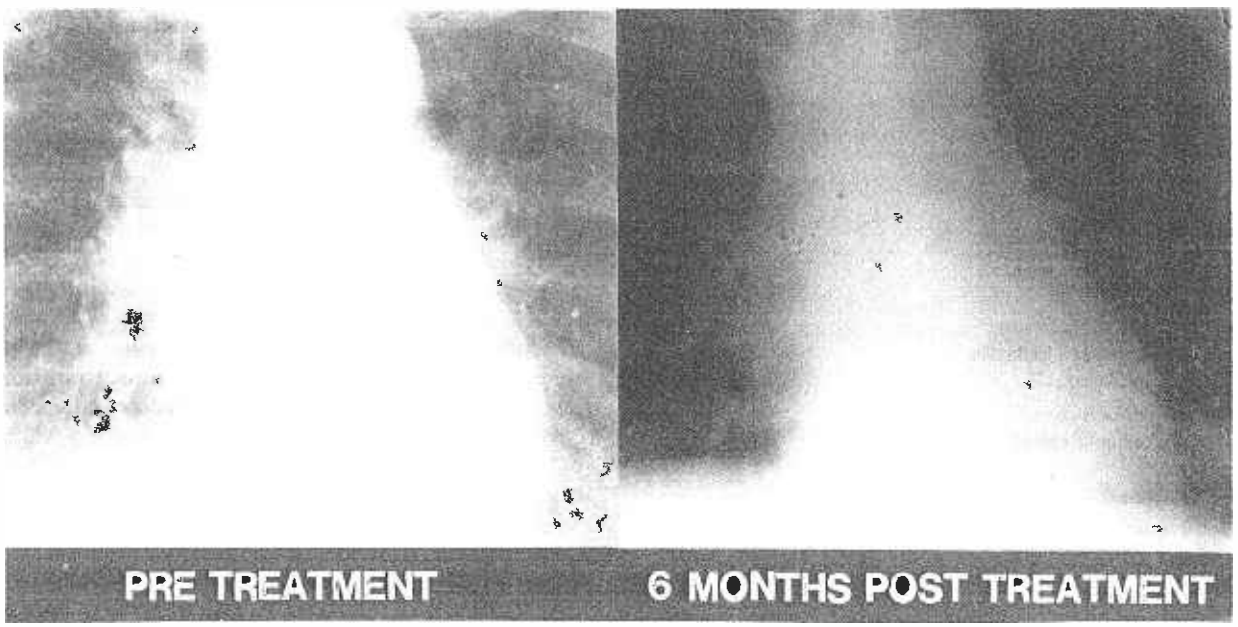
In view of the hilar lymphadenopathy and negative results of previous investigations, a right mini-thoracotomy was performed to obtain tissue for diagnosis. Operative findings were that of adhesions of the right upper lobe to the pleura and mediastinal lymphadenopathy. The right lung parenchyma appeared grossly

Fig 1. – Left panel: Adjusted serum calcium and creatinine concentrations before, during & after withdrawal of prednisolone treatment
Right panel: Normalisation of adjusted serum calcium concentration after 4 weeks of anti-tuberculous treatment.



Adjusted serum calcium = $x + 0.02\,(40 - z)$, x = measured serum calcium concentration in mmol/L and Z = measured serum albumin concentration in g/L

Fig 2. – Chest radiographs of patient showing hilar lymphadenopathy before treatment and its resolution following 5 months of anti-tuberculous therapy



normal. Histology of the lymph node showed non-caseating granulomas and multiple AFB on Ziehl-Neelsen stain. Anti-tuberculous treatment was started with rifampicin 600 mg/day, isoniazid 300 mg/day, ethambutol 600 mg/day and pyrazinamide 1000 mg/day. After 4 weeks of treatment serum calcium adjusted for albumin normalised (2.40 mmol/L) and remained so during subsequent follow-ups (Fig 1). In addition, she felt better generally and had put on weight. The hilar lymphadenopathy resolved following 5 months of treatment (Fig 2). She had not been on corticosteroid since the steroid suppression test.

DISCUSSION

Hypercalcemia was first reported in association with disseminated bone tuberculosis[5]. Subsequent reports, however, showed hypercalcemia in tuberculosis can occur in the absence of

skeletal involvement or hypoadrenalism[1-3]. In this patient there was no evidence of either skeletal or adrenal involvement.

Other possible causes of hypercalcemia such as Vitamin D excess, milk alkali syndrome, thyrotoxicosis and malignancy were not clinically, biochemically or radiologically evident in this patient. The raised parathyroid hormone (PTH) level was due to impaired renal function. The former was in fact relatively low for the degree of renal impairment[6], thus, suggesting appropriate suppression of PTH secretion by the raised serum calcium concentration. Concomitant occurrences of tuberculosis and sarcoidosis had been reported[7]. However, the normalisation of this patient's serum calcium concentration following 4 weeks of anti-tuberculous treatment suggests tuberculosis was the cause of the hypercalcemia.

The prevalence of tuberculosis associated hypercalcemia in Malaysia is probably underestimated. This could be due to one or more of the following reasons: 1) serum calcium may not be part of the liver function test (LFT) in those hospitals without automated multi-channel analyser, 2) in centres in which serum calcium is part of the LFT, it may only received scant attention as the main interest is in the liver enzymes, 3) lack of awareness of the association between tuberculosis and hypercalcemia, and 4) a substantial number of cases of hypercalcemia can be missed if the measured serum calcium concentration is not corrected for the serum albumin level[8]. The latter is often low in patients with chronic illness like pulmonary tuberculosis.

Hypercalcemia had been observed to occur during the first 4 months of anti-tuberculous therapy[1,3]. Improved nutrition and possible effect of the anti-tuberculous drugs on calcium metabolism were among the postulated mechanisms to account for the raised serum calcium level. Need et al.[2], however, demonstrated higher serum calcium levels were present even among untreated bacteriologically proven tuberculosis patients compared to the controls. Most of the tuberculosis associated hypercalcemia reported so far were not severe and usually resolved during the course of anti-tuberculous therapy.

There were individual case reports which demonstrated the presence of elevated 1,25-dihydroxycholecalciferol and low 25-hydroxycholecalciferol in patients with tuberculosis[9]. Interestingly, Gkonos et al[10] also reported the presence of similar changes in the vitamin D metabolites in a patient with end-stage renal disease who also had tuberculosis associated hypercalcemia. These findings suggested the presence of excess 1-alpha-hydroxylase-like activity of extrarenal origin in patient with tuberculosis associated hypercalcemia. Abnormal sensitivity to vitamin D was known to be involved in the pathogenesis of hypercalcemia of sarcoidosis. Latterly, this was found to be related to the presence of excessive 1-alpha-hydroxylase-like activity in the pulmonary alveolar macrophages among sarcoid patients[11]. It is likely that the same mechanism operates in tuberculosis.

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