CASE REPORT

FATAL MILIARY TUBERCULOSIS WITH HYPERCALCEMIA

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Hypercalcemia may occur in patients with tuberculosis. However, the reported incidence in patients not receiving vitamin D supplements varies widely from 25-48% in Sweden (Lind and Ljunghall, 1990) and Greece (Kitrou *et al*, 1982) to 1.6-2.3% in Hong Kong (Chan *et al*, 1992) and Malaysia (Tan *et al*, 1993). Hypercalcemia is uncommon among patients in Hong Kong and Malaysia, possibly because of the low dietary calcium intake in these populations (Chan *et al*, 1994; Chan and Chan, 1994). So far, there has only been one well-documented case of miliary tuberculosis complicated by symptomatic hypercalcemia reported from Hong Kong (Chan *et al*, 1994). Another case is described here to highlight its association with extensive disease.

A 77-year-old Chinese man was admitted to hospital with a 2-month history of anorexia and poor feeding. One week before admission, he was noticed by his family members to be dull. Four months prior to the present admission, he had an operation for intestinal obstruction secondary to a strangulated inguinal hermia. His renal and liver function tests were then within the normal limits. He also had a past history of cerebrovascular accident affecting his left side but he had made a good recovery.

On examination, he looked emaciated and dehydrated. He was dull but obeyed simple commands. He axillary temperature was 36.5°C, blood pressure was 150/90 mmHg and pulse rate was 90 beats/minute. Auscultation revealed coarse crepitations in both sides of his chest. There were surgical scars over the abdomen and right groin. Jerks were more brisk on the left side. Mild contractures of his lower limbs were present. Chest x-ray showed diffuse nodular shadows suggestive of miliary tuberculosis. Biochemical abnormalities included hypernatremia (158 mmol/l), hypoalbuminemia (29 g/l), hypercalcemia (unadjusted calcium 2.9 mmol/l, albumin adjusted calcium 3.2 mmol/l) and raised plasma urea (18.6 mmol/l) and creatinine (139 μmol/l). Plasma alkaline phosphatase (275 IU/l) and alanine transaminase (61 IU/l) were raised but total bilirubin was within the normal limits. He was rehydrated with 3 liters daily of intravenous 5% dextrose and 0.9% saline with potassium supplements. Expectorated sputum was available on day 4 and showed acid-fast bacilli on direct smear examination. He was then started on isoniazid 300 mg daily, ethambutol 800 mg daily and vitamin B_6 10 mg daily. Both his renal function tests (plasma urea 16.1 mmol/l, creatinine 119 μmol/l) and hypercalcemia (unadjusted calcium 2.65 mmol/l) had improved. From day 5, he developed swinging fever and hypotension (systolic blood pressure 90 mmHg) and became more drowsy. On day 6, intravenous ampicillin 500 mg 6 hourly was commenced to cover the catheter-associated urinary tract infection from *E. coli*. His condition continued to deteriorate and died 5 days after admission.

There is now substantial evidence to suggest that extra-renal production of 1, 25$(OH)_2$D is important in producing hypercalcemia in active tuberculosis (Chan and Chan, 1994). High circulating levels of 1, 25$(OH)_2$D were reported in anephric patients with tuberculosis, and increased serum levels of 1, 25$(OH)_2$D were shown in some patients with tuberculosis and hypercalcemia. Fresh total cells and cultured alveolar macrophages obtained by bronchoalveolar lavage in a patient with pulmonary tuberculosis and hypercalcemia were shown to synthesize 1, 25$(OH)_2$D (Cadranel *et al*, 1988). It is also known that 1, 25$(OH)_2$D production by im-

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mune and inflammatory cells occurs in most patients, and is not limited to sites of granulomatous lesions (Cadranel *et al*, 1990). An important source of this active vitamin D metabolite appears to be T lymphocytes, possibly $CD8^+$ T lymphocytes, in the peripheral blood or at the granulomatous sites (Cadranel *et al*, 1990).

Several factors are known to be associated with an increased risk of hypercalcemia in tuberculosis (Chan and Chan, 1994). Increased viamin D intake and increased sun exposure would result in increased circulating vitamin D available for the extra-renal synthesis of 1, $25(OH)_2D$. For a given plasma serum concentration of 1, $25(OH)_2D$, increased absorption of calcium from the gut is expected in the presence of a high calcium intake. The presence or the development of renal failure will reduce the capacity of the kidneys to excrete calcium during hypercalcemic states (Chan *et al*, 1994). In the presence of extensive disease, more extra-renal synthesis of 1, $25(OH)_2D$ by the activated T cells in the granuloma and in the peripheral blood is expected.

The calcium intake for subjects aged 71-80 in Hong Kong is around 300 mg daily (Pun and Chan, 1989). The calcium intake in our patient would be even lower because of the poor feeding. Despite this much reduced calcium intake, he was severely hypercalcemic, possibly because of the presence of extensive disease and development of renal failure. We have previously shown that among patients in Hong Kong, there was a positive correlation between plasma calcium levels and the radiographic extent of disease (Chan *et al*, 1992). Other supporting evidence comes from the fact that most of the recent reports of hypercalcemia concerned patients with miliary tuberculosis (Chan *et al*, 1994; Gerritsen and Knol, 1989; Wyllie *et al*, 1993).

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