HYPERCALCEMIA IN ACTIVE PULMONARY TUBERCULOSIS AND ITS OCCURRENCE IN RELATION TO THE RADIOGRAPHIC EXTENT OF DISEASE

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Abstract. The prevalence of hypercalcemia in tuberculosis in Hong Kong and its occurrence in relation to the radiographic extent of disease were studied in 57 patients with sputum smear (n = 44) and/or culture positive (n = 13) pulmonary tuberculosis and in five patients with military tuberculosis prior to treatment. Only one (1.6%) patient had a corrected plasma calcium level above the reference range for our laboratory. There was a positive relationship between the corrected plasma calcium levels and the radiographic extent of disease ($r = 0.37$), $p < 0.01$). As the occurrence of hypercalcemia in tuberculosis is known to be influenced by the calcium intake, our finding of a low prevalence of "absolute" hypercalcemia in Hong Kong could be related to the low dietary calcium intake in these subjects.

INTRODUCTION

Hypercalcemia has been known to be associated with tuberculosis but the reported prevalence varies widely (Abbasi *et al,* 1979; Chan *et al,* 1991; Davies *et al,* 1987; Kitrou *et al,* 1983; Lind and Ljunghall 1990; Need *et al,* 1980; Shai *et al,* 1972; Sharma 1981; Shek *et al,* 1990). Available evidence indicates that its occurrence is related to the intake of vitamin D (Abbasi *et al,* 1979; Shai *et al,* 1972; Sharma 1981) and calcium (Shai *et al,* 1972) in these patients. It is not clear if the radiographic extent of disease itself is an important determinant as studies so far have yielded conflicting results (Chan *et al,* 1991; Davies *et al,* 1987; Kitrou *et al,* 1983; Need *et al,* 1980).

In Hong Kong, tuberculosis was found to be an important cause of hypercalcemia in the hospital population (Shek *et al,* 1990). However, in a recent survey conducted by our group, none of the 24 patients with active pulmonary tuberculosis had "absolute" hypercalcemia (Chan *et al,* 1991). We have since extended this prospective study in order to ascertain the prevalence of hypercalcemia in these patients and its occurrence in relation to the radiographic extent of disease.

MATERIALS AND METHODS

Consecutive patients presented to the respiratory physicians at the Prince of Wales Hospital, Shatin, Hong Kong in 1989 to 1990 with smear (n = 44) and/or culture positive (n = 13) pulmonary tuberculosis and patients with miliary tuberculosis (n = 5) were entered into the study. Three patients with concurrent bronchogenic carcinoma were excluded.

At entry, before treatment commenced, blood was sent for measurements of plasma albumin, creatinine and calcium. A posteroanterior chest radiograph was taken for the assessment of the extent of disease which was graded 1 to 6 according to the number of one-sixths of the lung field affected (Simon, 1966).

Plasma calcium, albumin and creatinine were measured in a multi-channel analyzer. Plasma calcium was corrected for a change in albumin concentration using the formula of Payne *et al* (1973).

All data are expressed as mean ± SEM. Patients were categorized on the basis of radiographic extent of disease. The significance of difference between groups was tested by Kruskal-Walls one-way ANOVA or Mann-Whitney U test as applicable.

RESULTS

There were 59 Chinese and three Vietnamese subjects. They were 45 men and 17 women, aged from 23 to 86 years (mean 61.8 ± 2.0). None of

Table 1

Patient characteristics and laboratory data according to the radiographic extent of disease.

	Grade 1 (n=11)	Grade 2 (n=21)	Grade 3 (n=15)	Grade 4 (n=4)	Grade 5/6[a] (n=11)	p value (ANOVA)
M : F	8 : 3	15 : 6	9 : 6	4 : 0	9 : 2	
Age (years)	60.1 ± 3.6	60.0 ± 3.4	61.7 ± 5.5	69.5 ± 5.6	64.6 ± 3.0	NS
Plasma creatinine (μmol/l)	86.4 ± 6.0	82.0 ± 4.1	77.0 ± 3.8	77.0 ± 9.8	116.7 ± 23.7[b]	NS
Plasma albumin (g/l)	39.6 ± 1.9	35.2 ± 1.5*	32.9 ± 1.8**	29.0 ± 3.9*	30.5 ± 2.0**	<0.01
Plasma calcium (mmol/l)	2.29 ± 0.04	2.19 ± 0.04	2.14 ± 0.04*	2.08 ± 0.12	2.16 ± 0.06	NS
Plasma calcium (Adjusted) (mmol/l)	2.30 ± 0.02	2.31 ± 0.02	2.32 ± 0.02	2.36 ± 0.04	2.39 ± 0.03*	NS

*p < 0.05, **p < 0.01, when compared to patients with grade 1 disease.
[a]only one patient had grade 6 disease.
[b]including two patients with renal impairment.

these patients had acquired immune deficiency syndrome (AIDS).

Of the 62 patients studied, only one (1.6%) had plasma calcium level above the reference range of this laboratory (2.13 - 2.51 mmol/l). As can be seen in Table 1 and Fig 1, there was a trend for patients with more extensive disease to have a higher adjusted plasma calcium level ($r = 0.37$, $p < 0.01$). A negative correlation between the radiographic extent of disease and the plasma albumin level was observed ($r = -0.40$, $p < 0.01$).

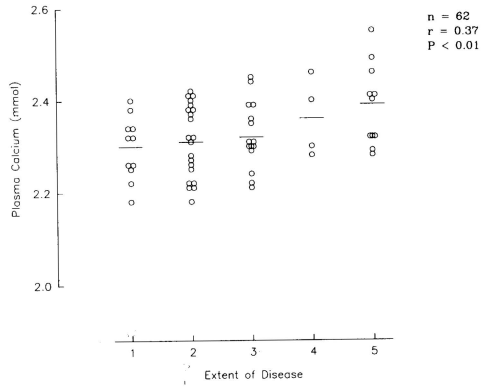

Fig 1—Relationship between the corrected plasma calcium levels and the radiographic extent of disease. Both individual values and the means (——) are shown. Patients with grades 5 and 6 disease are combined.

DISCUSSION

In the present study, we have confirmed our earlier report that "absolute" hypercalcemia was uncommon among patients with active pulmonary tuberculosis in Hong Kong. In comparison, both cross-sectional (Ling and Ljunghall 1990) and longitudinal (Abbasi *et al,* 1979; Kitrou *et al,* 1983; Need *et al,* 1980; Sharma 1981) studies from other countries have generally reported a much higher prevalence of 15.5 to 48%.

One likely explanation for this observed difference in the prevalence of hypercalcemia is the low calcium intake in our patients (Chan *et al,* 1991). It has been demonstrated by others (Felsenfeld *et al,* 1986; Shai *et al,* 1972) that hypercalcemia in tuberculous patients occurs after the administration of vitamin D and/or calcium supplements, and disappears when these are removed from the diet. It therefore appears likely that a low dietary calcium

intake of 300 to 500 mg per day in Hong Kong (Pun *et al,* 1989) might help to prevent hypercalcemia from occurring.

The mechanism for hypercalcemia in tuberculosis is now thought to be extra-renal synthesis of $1,25(OH)_2D_3$ (Felsenfeld *et al,* 1986; Gkonos *et al,* 1984; Peces and Alvares, 1987) resulting in increased gastrointestinal absorption of calcium. Recently, it has been shown that $1,25(OH)_2D_3$ may be produced by inflammatory cells obtained by bronchoalveolar lavage in a patient with pulmonary tuberculosis (Cadranel *et al,* 1988). So it was anticipated that increased hydroxylation of $25(OH)_2D_3$ by the granulomata would occur in the presence of more extensive disease and there would be a correlation between the plasma calcium levels and the extent of disease.

Like others (Kitrou *et al,* 1983; Need *et al,* 1980), we were able to demonstrate a positive relationship between the radiographic extent of disease and the adjusted plasma calcium levels. However, it should be pointed out that this apparent relationship between the two variables could merely reflect the limitations of the calcium adjustment formula used; the formula becomes increasingly unreliable as the deviation of plasma albumin from normal becomes greater. Therefore, measurements of ionized calcium and calcium regulating hormones (parathroid hormone and calcitriol) would be needed to determine whether or not the level of plasma calcium is related to disease severity.

A reduction in plasma albumin is a consistent finding in patients with tuberculosis (Chan *et al,* 1991; Davies *et al,* 1987; Kitrou *et al,* 1983). In the present study, it appeared to a better correlate with disease severity than plasma calcium level. It is likely to be a result of generalized debility caused by disease (Chan *et al,* 1991; Davies *et al,* 1987).

In summary, we confirmed the low prevalence of hypercalcemia in patients with pulmonary tuberculosis in Hong Kong. It is likely that the low dietary calcium intakes in our patients have prevented hypercalcemia from occurring. There was a positive although weak correlation between the plasma calcium levels and the radiographic extent of disease in these patients.

REFERENCES

Abbasi AA, Chemplavil JK, Farah S, Muller BF, Arnstein AR: Hypercalcaemia in active pulmonary tuberculosis. *Ann Intern Med* 1979; 90 : 324-8.

Cadranel J, Hance AJ, Milleraon B, Paillard F, Akoun GM, Garabedian M: Production of $1,25(OH)_2D_3$ by cells recovered by bronchoalveolar lavage and the role of this metabolite in calcium homeostasis. *Am Rev Respir Dis* 1988; 138 : 984-9.

Chan TYK, Poon P, Nisar M, *et al.* Serum calcium and vitamin D in Chinese patients with tuberculosis in Hong Kong. *Am Rev Respir Dis* 1991; 143 : A282. (Abstract)

Davies PDO, Church HA, Brown RC, Woodhead JS: Raised serum calcium in tuberculosis patients in Africa. *Eur J Respir Dis* 1987; 71 : 341-4.

Felsenfeld AJ, Drezner MK, Llach F. Hypercalcaemia and elevated calcitriol in a maintenance dialysis patient with tuberculosis. *Arch Intern Med* 1986; 146 : 1941-5.

Gkonos PJ, London R, Hendler: Hypercalcaemia and elevated 1,25-dihydroxyvitamin D levels in a patient with end-stage renal disease and active tuberculosis. *N Engl J Med* 1984; 311 : 1683-5.

Kitrou MP, Phytou-Pallikari A, Tzannes SE, Virvidakis K, Mountokalakis TD: Serum calcium during chemotherapy for active pulmonary tuberculosis. *Eur J Respir Dis* 1983; 64 : 347-57.

Lind L, Ljunghall S: Hypercalcaemia in pulmonary tuberculosis. *Upsala J Med Sci* 1990; 95 : 157-60.

Need AG, Phillips PJ, Chiu FTS, Prisk HM: Hypercalcaemia associated with tuberculosis. *Br Med J* 1980; 1 : 831.

Payne RB, Little AJ, Williams RB, Milner JR: Interpretation of serum calcium in patients with abnormal serum proteins. *Br Med J* 1973; 4 : 643-6.

Peces R, Alvares J: Hypercalcaemia and elevated $1,25(OH)_2D_3$ levels in a dialysis patient with disseminated tuberculosis. *Nephron* 1987; 46 : 377-9.

Punn KK, Chan LWL, Chung V: The problem of calcium deficiency in Hong Kong. *Hong Kong Pract* 1989; 11 : 287-94.

Shai F, Baker RK, Addrizzo JR, Wallach S: Hypercalcaemia in mycobacterial infection. *J Clin Endocrinol* 1972; 34 : 251-6.

Sharma SC: Serum calcium in pulmonary tuberculosis. *Postgrad Med J* 1981; 57 : 694-6.

Shek CC, Natkunam A, Tsang V, Cockram CS, Swaminathan R: Incidence, causes and mechanism of hypercalcaemia in a hospital population in Hong Kong. *QJ Med* 1990; 284 : 1277-85.

Simon G: Radiology in epidemiological studies and some therapeutic trials. *Br Med J* 1966; 2 : 491-4.