Incomplete suppression of parathyroid hormone activity in sarcoidosis presenting with hypercalcaemia

R. R. GHOSE*
F.R.C.P.

J. S. WOODHEAD†
B.Sc., Ph.D.

R. C. BROWN‡
B.Sc., Ph.D.

*Department of Medicine, Singleton Hospital, Sketty, Swansea, †Welsh National School of Medicine, University Hospital of Wales, Heath Park, Cardiff and ‡Welsh National School of Medicine, University Hospital of Wales, Heath Park, Cardiff

Summary

An adult patient presenting in summertime with sarcoidosis and demonstrating raised levels of serum calcium and 1,25-dihydroxycholecalciferol was observed to have a serum immuno-reactive parathyroid hormone concentration in the mid-normal range. Renal function was normal. Corticosteroid administration quickly depressed serum calcium and 1,25-dihydroxycholecalciferol into the normal range; serum parathyroid hormone also fell to low levels.

It was concluded that corticosteroid suppression, when incorporating measurements of serum calcium and 1,25-dihydroxycholecalciferol concentrations, can distinguish between sarcoidosis-related hypercalcaemia and primary hyperparathyroidism. The significance of the changes in parathyroid hormone concentration is obscure.

KEY WORDS: sarcoidosis, hypercalcaemia, corticosteroid suppression.

Introduction

Hypercalcaemia accompanying sarcoidosis is due to a rise in circulating active vitamin D metabolite, 1,25-dihydroxycholecalciferol (1,25-DHCC). Moreover, corticosteroid administration produces a simultaneous decline in serum calcium and 1,25-DHCC concentrations (Bell *et al.*, 1979; Zerwekh *et al.*, 1980). In these studies, serum immunoreactive parathyroid hormone (PTH) concentration was suppressed to very low levels in the presence of hypercalcaemia. Serum PTH concentration is generally low in sarcoidosis, but may be elevated when there is co-existent primary hyperparathyroidism (Cushard *et al.*, 1972). In hypercalcaemia arising from primary hyperparathyroidism, the serum PTH level may remain within the normal range, particu-

larly when there is no evidence of skeletal involvement (Addison *et al.*, 1971). We report a case of hypercalcaemia associated with sarcoidosis in which the serum PTH level was higher than expected for the level of serum calcium concentration in the absence of primary hyperparathyroidism.

Case report

A 39-year-old female presented in August 1982 with a 2-month history of thirst, anorexia, constipation, and loss of weight of 2 kg. Physical examination revealed a rash on the right forearm, together with hepato-splenomegaly. Blood pressure was 120/80 mmHg.

Investigations: Erythrocyte sedimentation rate (Westergren) 34 mm fall in 1 hr. Serum calcium concentration 3.46 mmol/litre, albumin 39 g/litre, creatinine 106 μ mol/litre. Serum biochemistry was otherwise normal. $^{51}\text{CrEDTA}$ clearance, 90 ml/min/1.73 m². Chest radiograph showed diffuse fibrotic changes in both lung fields. Lung function tests revealed mild obstructive airways disease, but no defect in transfer factor. Skeletal and abdominal X-rays were normal. Skin biopsy of the rash on the forearm revealed non-caseating giant cell systems characteristic of sarcoidosis.

Methods

Serum calcium concentration was measured by Technicon auto-analyser, using venous blood in the fasting state obtained from an unconstricted vein. Serum 25-hydroxycholecalciferol (25-HCC) was measured by radio-immunoassay following protein precipitation with acetone and extraction of the

FIG. 1. Corticosteroids produced a significant fall in serum calcium and 1,25-DHCC concentrations, and serum PTH rose transiently and then fell to very low levels.

vitamin D fraction by reverse phase chromatography (Sep Pak C18 cartridges, Waters Instruments). Serum 25-HCC; 24,25-dihydroxycholecalciferol (24,25-DHCC) and 1,25-DHCC were measured by an adaptation of the technique of Clemens, Hendy and Papapoulos (1979). Serum 25-HCC—mean summer values 22.9 ± 7.6 (s.d.), normal range 11.9 ± 34.1 ng/ml. Serum 24,25-DHCC—mean summer values 1.2 ± 0.59 , normal range 0.36 ± 2.2 ng/ml. Serum 1,25-DHCC—mean summer values 32.5 ± 10.5 , normal range 23.0 ± 61.9 pg/ml.

Serum PTH was measured by an immuno-radiometric radio-immunoassay which estimates the biologically inactive carboxy-terminal fragments—normal range 0–0.8 ng/ml. Between assay coefficients of variation for this technique at serum PTH levels of 0.2 ng/ml. and 1.0 ng/ml. are 13% and 8% respectively (Addison *et al.*, 1971).

Maximum tubular reabsorption of phosphate/glomerular filtration rate (TmP/GFR) was mea-

sured from a 2-hr urine collection, with venous blood obtained at the mid-point, on which calcium, inorganic phosphate and creatinine concentrations were determined. From these variables, TmP/GFR was derived by nomogram (Walton and Bijvoet, 1975) (normal range 0.7–1.4 mmol/litre). ^{47}Ca absorption test was performed according to the technique of Chanard *et al.* (1974) (normal range—40–75%).

Results

The presenting values and the effects of corticosteroid suppression on serum calcium, 25-HCC, 24, 25-DHCC, 1,25-DHCC, and PTH concentrations, together with tubular maximum reabsorption rate with respect to glomerular filtration rate (TmP/GFR), are displayed in Fig. 1. Calcium absorption was measured before and after corticosteroid administration, when fractional calcium absorbed 6 hr after ^{47}Ca was given was 72.5% and 52.5% respectively.

In January 1982, when the patient was off steroids, serum calcium was 2.35 mmol/litre, 25-HCC was 3.9 ng/ml, 24,25-DHCC was 0.30 ng/ml, 1,25-DHCC was 34.4 pg/ml, and PTH was 0.66 ng/ml.

Discussion

1,25-DHCC is generally believed to be synthesized exclusively in the renal cortex by 1 α hydroxylation of 25-HCC (DeLuca and Schnoes, 1976). In sarcoidosis, however, an extra-renal source of 1,25-DHCC has been demonstrated in an anephric patient who developed hypercalcaemia (Barbour *et al.*, 1981). The mechanism and control of this extra-renal synthesis is not understood, but it was speculated that 1,25-DHCC synthesis occurred within active sarcoid tissue. Thus, exposure to sunlight may stimulate 1,25-DHCC production at sites of active sarcoid granuloma formation. In a detailed case-report (Papapoulos *et al.*, 1979) sequential biochemical and hormonal estimations in blood were performed over several years, and it was evident that hypercalcaemia developed in summer and was accompanied by a small rise in serum 25-HCC, which remained within the normal range, and a considerable rise in serum 1,25-DHCC, which far exceeded the normal range. Seasonal hypercalcaemia is well recognized in sarcoidosis (Taylor, Lynch and Wysor, 1963).

In our case, serum calcium and 1,25-DHCC concentrations were raised, while serum 25-HCC was normal. However, a surprising finding was a serum PTH concentration of 0.5 pg/ml. Such a value is inappropriate in the presence of hypercalcaemia. Patients who are hypercalcaemic as a consequence of malignant disease or vitamin D intoxication invari-

ably have serum PTH levels below the detection limit of the assay (0.2 ng/ml), unless marked renal insufficiency is present. While a low TmP/GFR value in itself is of little significance, the observed finding on admission of 0.65 mmol/litre is consistent with inappropriate PTH secretion, and the rise observed after commencing corticosteroid therapy corresponded to a fall in PTH secretion.

The prompt fall in serum calcium and 1,25-DHCC concentration following corticosteroid administration could have resulted from immune suppression of sarcoidosis and inhibition of extra-renal 1,25-DHCC production. The fall in serum 1,25-DHCC levels probably affected gut absorption of calcium. Serum PTH, in this case, rose transiently and then fell to undetectable levels; the mechanism of these changes is obscure. Most PTH antisera cross-react with molecular fragments, while the assay used recognizes in particular the biologically inert carboxy-terminal portion of the PTH molecule. Since PTH degradation occurs in liver and kidney, it is possible that abnormal metabolism of PTH may result from involvement of the liver with sarcoidosis, or to renal-tubular damage secondary to hypercalcaemia, which may have contributed to the inappropriate serum PTH level. Glomerular function was not reduced to an extent that would have caused delayed clearance of the PTH fragments.

The association of sarcoidosis with primary hyperparathyroidism is well known (Dent and Watson, 1966; Winnacker *et al.*, 1969), and a recent report revealed that 23 cases have been described (Robinson, Kerwin and Tsou, 1980). In a patient with biopsy-proven sarcoidosis and hypercalcaemia, in whom bone X-rays fail to demonstrate periosteal reabsorption, the serum PTH level, and the response to corticosteroid administration (Anderson *et al.*, 1954) are important diagnostic aids. Typically the hypercalcaemia of primary hyperparathyroidism is unaffected, whereas the serum calcium returns to normal in sarcoidosis. By extending the test to incorporate measurements of serum 1,25-DHCC and PTH, valuable diagnostic information may be obtained. Similarly high values of serum 1,25-DHCC have been observed in sarcoidosis (Papapoulos *et al.*, 1979), and primary hyperparathyroidism (Broadus *et al.*, 1980), ranging from 40–140 pg/ml. In the present case, corticosteroids reduced serum 1,25-DHCC from 100 to 15 pg/ml; the response in primary hyperparathyroidism is undefined.

Acknowledgment

We are grateful to Miss Julie E. Davies for secretarial assistance.

References

- ADDISON, G.M., HALES, C.N., WOODHEAD, J.S. & O'RIORDAN, J.L.H. (1971) Immunoradiometric assay of parathyroid hormone. *Journal of Endocrinology*, **49**, 521.
- ANDERSON, J., DENT, C.E., HARPER, C. & PHILPOT, G.R. (1954) Effect of cortisone on calcium metabolism in sarcoidosis with hypercalcaemia: Possibly antagonistic actions of cortisone and vitamin D. *Lancet*, **ii**, 720.
- BARBOUR, G.L., COBURN, J.W., SLATOPOLSKY, E., NORMAN, A.W. & HORST, R.L. (1981) Hypercalcaemia in an anephric patient with sarcoidosis: evidence for extra-renal generation of 1,25-dihydroxyvitamin D. *New England Journal of Medicine*, **305**, 440.
- BELL, N.H., STERN, P.H., PANTZER, E., SINHA, T.K. & DELUCA, H.F. (1979) Evidence that increased circulating 1,25-dihydroxyvitamin D is the probable cause for abnormal calcium metabolism in sarcoidosis. *Journal of Clinical Investigation*, **64**, 218.
- BROADUS, A.E., HORST, R.L., LANG, R., LITLEDIKE, E.T., RASMUSSEN, H. (1980) The importance of circulating 1,25-dihydroxyvitamin D in the pathogenesis of hypercalciuria and renal-stone formation in primary hyperparathyroidism. *New England Journal of Medicine*, **302**, 421.
- CHANARD, J., ASSAILLY, J., BADER, C. & FUNCK-BRENTANA, J. (1974) A rapid method for measurement of fractional intestinal absorption of calcium. *Journal of Nuclear Medicine*, **15**, 588.
- CLEMENS, T.L., HENDY, G.N. & PAPAPOULOS, S.E. (1979) Measurement of 1,25-Dihydroxycholecalciferol in man by radioimmunoassay. *Clinical Endocrinology*, **11**, 225.
- CUSHARD, Jr W.G., SIMON, A.B., CANTERBURY, J.M. & REISS, (1972) Parathyroid function in sarcoidosis. *New England Journal of Medicine*, **286**, 395.
- DELUCA, H.F. & SCHNOES, H.K. (1976) Metabolism and mechanism of action of vitamin D. *Annual Review of Biochemistry*, **45**, 631.
- DENT, C.E. & WATSON, L. (1966) Hyperparathyroidism and sarcoidosis. *British Medical Journal*, **1**, 646.
- PAPAPOULOS, S.E., CLEMENS, T.L., FRAHER, L.J., LEWIN, I.C., SANDLER, L.M. & O'RIORDAN, J.L.H. (1979) 1,25-dihydroxycholecalciferol in the pathogenesis of the hypercalcaemia of sarcoidosis. *Lancet*, **i**, 627.
- ROBINSON, R.G., KERWIN, D.M. & TSOU, E. (1980) Parathyroid adenoma with coexistent sarcoid granulomas. *Archives of Internal Medicine*, **140**, 1547.
- TAYLOR, R.L., LYNCH, Jr H.J. & WYSOR, Jr W.G. (1963) Seasonal influence of sunlight on the hypercalcaemia of sarcoidosis. *American Journal of Medicine*, **34**, 221.
- WALTON, R.J. & BLIVOET, O.L.M. (1975) Nomogram for derivation of renal threshold phosphate concentration. *Lancet*, **ii**, 309.
- WINNACKER, J.L., BECKER, K.L., FRIEDLANDER, M., HIGGINS, G. Jr & MOORE, C.F. (1969) Sarcoidosis and hyperparathyroidism. *American Journal of Medicine*, **46**, 305.
- ZERWEKH, J.E., PAK, C.C., KAPLAN, R.A., MCGUIRE, J.L., UCHURCH, K., BRESLAU, N. & JOHNSON, R. (1980) Pathogenic role of 1,25-dihydroxyvitamin D in sarcoidosis and absorptive hypercalcaemia: different response to prednisone therapy. *Journal of Endocrinology and Metabolism*, **51**, 381.

(Accepted 29 December 1982)