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Case Report

Hypercalcaemia and sarcoidosis in an anephric dialysis patient

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Introduction

Dialysis patients develop hypercalcaemia generally because of uncontrollable secondary hyperparathyroidism, inappropriate therapy with vitamin D, or calcium-containing preparations [1]. However, the differential diagnosis of hypercalcaemia in dialysis patients encompasses the entire spectrum of causes, including malignancy, endocrinopathies, and increased intestinal absorption of calcium. We recently managed an anephric dialysis patient who came to end-stage renal disease because of autosomal dominant polycystic kidney disease. We suspected secondary hyperparathyroidism, vitamin D intoxication, or CaCO₃ therapy as likely causes. However, we were surprised when we discovered the presence of sarcoidosis, without pulmonary involvement as the underlying cause.

Case report

The patient is a 44-year-old man with autosomal dominant polycystic kidney disease, who after 18 months of haemodialysis treatments was admitted for persistent hypercalcaemia. He had been treated with 1,25-dihydroxyvitamin D after initiating dialysis; however, the drug was discontinued 6 months prior to admission when his serum calcium concentration increased above the normal range. Hypercalcaemia persisted despite a reduced calcium intake, discontinuation of CaCO₃ and a calcium-free dialysate. The patient noted fatigue, tenderness at the right costal margin, and 'red eyes' in the 2 months prior to admission. Additional pertinent history included hypertension for 10 years, congestive heart failure, and a prior bilateral nephrectomy. The nephrectomy was performed shortly after dialysis treatments were initiated because of uncontrollable suppurative infection in both kidneys.

The blood pressure was 105/65 mmHg, the heart rate was 86/min, the respiratory rate was 18/min, and

the temperature was 37°C. The skin had a sallow brownish color. The conjunctivae were red and injected bilaterally. The retinal arterioles were narrowed and arteriovenous crossing abnormalities were identified. The lungs were clear. A systolic ejection murmur was present. The lower right costal margin was tender, and the liver was slightly enlarged. No neurological abnormalities were found.

On the day after dialysis the haemoglobin was 12 g/dl, there was haematocrit 34 vol%, the white and platelet counts were normal, and the electrolytes were normal. The total protein was 8.4 g/dl, the liver function tests were normal with the exception of a moderately elevated alkaline phosphatase of 189 U/l (normal up to 120 U/l). The serum electrophoresis showed the following: albumin 56%, alpha-1-globulin 3%, alpha-2-globulin 8%, beta-globulin 8% and gamma-globulin 25%. The IgG value was 2250 mg/dl, IgA was 274 mg/dl, and the IgM was 47 mg/dl. The C-reactive protein, serum iron, ferritin and transferrin values were normal. The total serum calcium was 3.69 mmol/l, the serum phosphate was 1.5 mmol/l, the blood urea nitrogen was 28 mg/dl and the plasma creatinine was 7.2 mg/dl. A roentgenogram of the chest was normal; specifically, the patient had no evidence of hilar adenopathy or pulmonary infiltrates. Roentgenograms of the skull, abdomen, and axial skeleton were not revealing.

The total serum parathyroid hormone value was 7.6 pg/ml (normal range 10–55 pg/ml). The parathyroid-hormone-related protein was 4.0 pg/ml (normal less than 5.1 pg/ml). The 1,25 dihydroxyvitamin D was 120 ng/dl (normal 35–90 ng/dl). The 25 monohydroxyvitamin D value was normal as were circulating cAMP values and various tumour markers. The serum angiotensin-converting enzyme concentration was elevated at 89 U/l (normal < 70 U/l).

An abdominal ultrasound examination disclosed an enlarged liver. A neck ultrasound examination identified a normal thyroid gland with no enlarged parathyroids. A bone scan was normal. The bone marrow was biopsied and revealed epithelioid cell granulomata with scattered giant cells consistent with chronic granulomatous disease. The liver biopsy specimen showed

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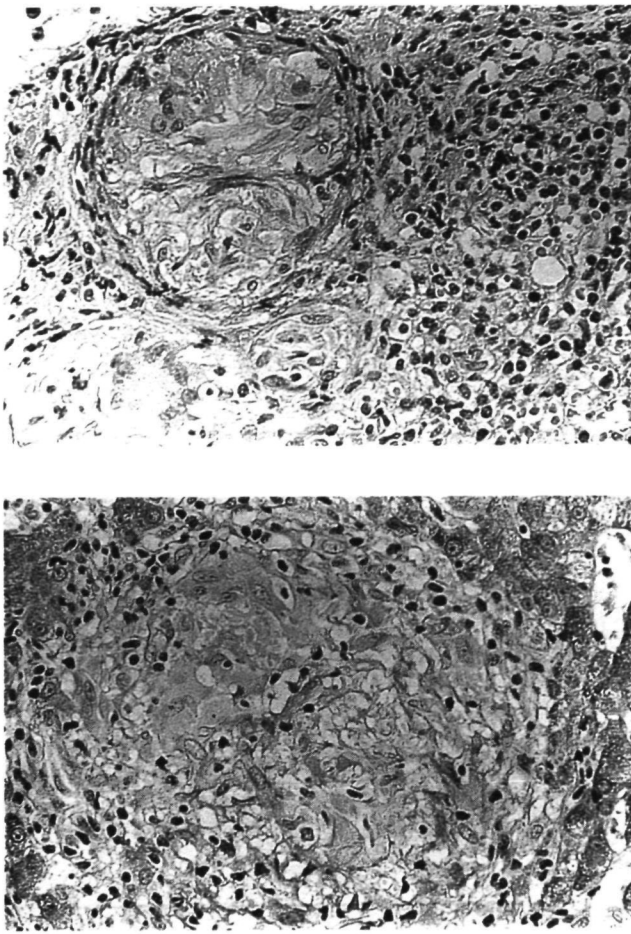


Fig. 1. A Bone marrow biopsy disclosed the presence of lymphocytic infiltration, scattered granulomata with epithelioid and giant cells B Liver biopsy identified non-caseating granulomata as seen in this tissue specimen

non-caseating epithelioid cell granulomas with giant cells. Both are depicted in Figure 1. Adjacent liver tissue was normal. Conventional culture and fluorescence techniques failed to identify acid-fast organisms. The patient's lymphocytes were stimulated with mitogens and showed a decreased tendency to proliferate compared to control lymphocytes [2].

The patient was treated with oral methylprednisolone and rapidly improved. His serum calcium value decreased from 3.27 to 2.77 mmol/l within several days and remained within the normal range thereafter. His sense of wellbeing also improved and he was discharged. A 1-year follow-up shows continued normal calcium values and no additional evidence of granulomatous disease. His chest roentgenogram has also remained free of any disease.

Discussion

Our patient is similar to the patient described by Barbour *et al.* [3], who were the first to provide evidence of extrarenal generation of

1,25-dihydroxyvitamin D. Their patient was an anephric, hypercalcemic dialysis patient with elevated 1,25-dihydroxyvitamin D levels.

The hypercalcemia in sarcoidosis results from the production of 1,25-dihydroxyvitamin D by disease-activated macrophages [4]. Hormone production by the sarcoid macrophage is not subject to regulation by features that normally control 1,25-dihydroxyvitamin D synthesis. Thus, the parathyroid hormone concentration may be low and the serum phosphate concentration may be elevated. Dexamethasone is a potent inhibitor of the macrophage 25-hydroxy-D-1-alpha-hydroxylase reaction [4], which is consistent with the prompt response in serum calcium values we observed after giving methylprednisolone. Ketoconazole, which is an effective inhibitor of cytochrome P-450-lined steroid oxidative enzymes, has also been used to treat hypercalcemia in sarcoidosis [5]. However, ketoconazole may also inhibit overall steroid production, and it is not clear that ketoconazole should replace corticosteroids in the treatment of sarcoid-induced hypercalcemia.

With elevated serum 1,25-dihydroxyvitamin D levels, normal or decreased parathyroid hormone values would be expected in patients with sarcoidosis. Such was the case in our patient. Nevertheless, a patient with sarcoidosis, renal insufficiency, elevated 1,25-dihydroxyvitamin D levels and increased parathyroid hormone values has also been described [6]. In patients with severe renal failure the decreased renal function may be responsible for secondary hyperparathyroidism, which may concomitantly confound the clinical picture.

Sarcoidosis is a multisystem disease of unknown aetiology, characterized by the presence of non-caseating granulomata in various tissues. Sarcoidosis has been known to cause hypercalcaemia for over 50 years [7]. An inverse correlation between the serum calcium level and renal function in sarcoidosis has been described [8,9]. Fewer than 5% of patients with sarcoidosis have a normal chest roentgenograph [4]. Our patient did not undergo bronchoalveolar lavage, a well-accepted diagnostic manoeuvre [4], because of his negative chest roentgenogram. Instead, we examined his peripheral blood lymphocytes, and found that they responded less actively to mitogens than control lymphocytes. This response of peripheral circulating lymphocytes is consistent with sarcoidosis [2].

Our patient underscores the fact that sarcoidosis may cause hypercalcaemia as the sole clinical feature in the absence of clinical signs of pulmonary involvement.

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