

*Case Report***Genitourinary tuberculosis as the cause of unexplained hypercalcaemia in a patient with pre-end-stage renal failure**

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**Key words:** calcitriol; granulomatous diseases; haemodialysis; hypercalcaemia; tuberculosis; uraemia**Introduction**

Hypercalcaemia has been reported in several granulomatous diseases including sarcoidosis [1], tuberculosis [2–6], coccidioidomycosis [7], berylliosis [8], candidiasis [9], histoplasmosis [10], silicone-induced granulomas [11], and eosinophilic granulomas [12]. In all these cases, hypercalcaemia has been linked to the presence of elevated calcitriol levels. Several lines of evidence suggest that extrarenal production of calcitriol is involved in the pathogenesis of the hypercalcaemia of granulomatous disease. The strongest evidence of ectopic synthesis of calcitriol is provided by observations in patients with end-stage renal disease, some of them anephric, who were on haemodialysis and suffered from tuberculosis or sarcoidosis [2–5,13–15].

So far four observations of dialysis patients have been reported who had tuberculosis, hypercalcaemia and elevated calcitriol levels [2–5]. We report a case with genitourinary tuberculosis who developed hypercalcaemia in pre-end-stage renal failure. Inappropriately elevated calcitriol serum levels suggested ectopic production of calcitriol.

**Case report**

A 41-year-old man presented to the hospital for his first admission with a serum creatinine of 8.6 mg/dl and a creatinine clearance of 15 ml/min. He complained of a frequent need to urinate, dysuria and pain referable to epididymis. Sterile pyuria was present in several urine samples. The patient had been treated for orchiepididymitis and prostatitis with several antibiotics, including aminoglycosides, without apparent clinical response. Repeat Ziehl-Neelsen stains of the urine were

negative. An abdominal ultrasound study revealed small irregular kidneys with multiple calcifications. Urinary tract obstruction was excluded. At this time, serum calcium concentration ranged from 10.9 to 13.5 mg/dl, serum phosphorus from 3.3 to 5.2 mg/dl, alkaline phosphatase from 137 to 221 IU/l. Serum albumin remained between 4.4 and 4.6 g/dl. He had intact parathyroid hormone (PTH) levels of 24 pg/ml. The tuberculin test was negative. Tuberculosis was suspected but not confirmed. The patient declined a liver biopsy and any invasive procedure. He received treatment with furosemide, multivitamins, and aluminium hydroxide.

One year later, a follow-up evaluation showed a serum creatinine of 10.5 mg/dl and a creatinine clearance of 5 ml/min. The serum calcium levels ranged from 13.5 to 14.2 mg/dl, serum phosphorus from 4.3 to 5.2 mg/dl, alkaline phosphatase from 120 to 141 IU/l, and serum albumin from 3.5 to 4.4 g/dl. At this time, measurement of PTH levels were: intact molecule 15 pg/ml, carboxy terminal 0.27 ng/ml, and midmolecule 22 pg/ml. Simultaneous levels of calcitriol and 25(OH)D<sub>3</sub> were 41 pg/ml and 18 ng/ml, respectively. The serum angiotensin-converting enzyme concentration was 45.8 U/l (normal 20–60). Serum aluminium was 22.4 µg/l. Radiographs of the chest, skull, abdomen, and axial skeleton were normal. A bone scan was normal. As the renal function deteriorated, thrice weekly maintenance haemodialysis with a dialysate calcium content of 5.5 mg/dl (1.38 mmol/l) was initiated and a low calcium diet was recommended. During the following 18 months, the patient received treatment with haemodialysis in another unit. At that time, the serum calcium concentration ranged from 10.2 to 11.3 mg/dl, serum phosphorus from 4.5 to 5.1 mg/dl, alkaline phosphatase from 90 to 120 IU/l, and intact PTH levels measured on two occasions were 16 and 37 pg/ml, respectively. The patient never received oral calcium or a metabolite of vitamin D.

Thirty months after the first admission, the patient was readmitted because of intermittent fever and malaise. His residual diuresis was ~1000 ml/day. The patient was dialysed against a bath containing 7 mg/dl (1.75 mmol/l) of calcium. At that time, the serum

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calcium concentration ranged from 11.1 to 11.6 mg/dl, serum phosphorus from 5.3 to 5.8 mg/dl, alkaline phosphatase from 77 to 94 IU/l, and serum albumin 3.9 g/dl. Measurement of intact PTH levels were 11 and 13 pg/ml in two consecutive samples. Simultaneous levels of calcitriol and 25(OH)D<sub>3</sub> were 24.5 pg/ml and 18.2 ng/ml, respectively. Thoracic radiographs were normal and abdominal radiographs showed calcification of the aorta. An abdominal ultrasound study showed a calcified granuloma in the liver, and small irregular kidneys with multiple calcifications and irregular parenchymal cavities. These findings were confirmed with computerized tomographs. A Ziehl-Neelsen of the urine was positive. A bone-marrow examination was negative for Ziehl-Neelsen staining. The patient was treated with rifampicin 600 mg/day, ethambutol 800 mg/day, and isoniazid 150 mg/day. After 1 week of antituberculous therapy, serum calcium decreased gradually to 8.8–9.9 mg/dl and remained within the normal range thereafter. One month later the intact PTH levels began to increase and treatment with oral calcitriol was initiated. Ethambutol was discontinued 2 months later and rifampicin and isoniazid maintained for 9 months. The patient has been followed up for 2 years without recurrence.

## Methods

PTH was measured by a radioimmunoassay, which detects the intact molecule (Nichols Institute). Normal values are 10–65 pg/ml. PTH was also determined by radioimmunoassay with antibody directed toward the midmolecule (normal 11–24 pg/ml) and the carboxy-terminal fragment (normal 0.06–0.31 ng/ml). Calcitriol was determined using a radioreceptor assay (INCSTAR) (normal 18–78 pg/ml). Serum 25(OH)D<sub>3</sub> was measured by radioimmunoassay (normal 12–96 ng/ml). Unfortunately, only two determinations of calcitriol and 25(OH)D<sub>3</sub> were available.

In seven patients with advanced chronic renal failure, serum creatinine was from 4.6 to 9.1 mg/dl, these serum calcitriol concentrations by this assay were  $10 \pm 2.2$  pg/ml (mean  $\pm$  SD). In nine patients on maintenance haemodialysis, calcitriol levels were  $4 \pm 0.8$  pg/ml.

## Discussion

Tuberculosis infection is >10–15 times more frequent in haemodialysis patients than in the normal population. Reactivation generally results from old, caseous foci located principally in the lungs, lymph nodes, bone, and genitourinary tract [16]. Genitourinary tract disease can be a particularly occult and insidious form of tuberculosis leading to progressive destruction and caseating of the kidney. Such was the case in our patient. In addition to advanced renal failure associated with genitourinary tuberculosis, the patient pre-

sented with hypercalcaemia that was accompanied by normal PTH values.

Hypercalcaemia was characterized by its occurrence before and after starting treatment with dialysis, and persistence for >30 months. The clinical evolution of hypercalcaemia was associated with relative suppression of PTH, which was initially abnormally low with respect to renal function. One year later, when renal function deteriorated, serum calcium levels became higher, calcitriol level was inappropriately elevated for the uraemic state, and PTH measured by three different assays remained suppressed. These features contrast with what is usually observed in chronic renal failure in the absence of vitamin D and calcium supplements, and suggest abnormal calcitriol production. On the other hand, aluminium loading can result in suppressed PTH, reduced bone turnover, and a tendency to hypercalcaemia. Also, aluminium can have some effect on the renal synthesis of calcitriol and elevated aluminium levels may have been a factor in preventing a further increase in calcitriol levels.

After starting haemodialysis the hypercalcaemia persisted despite a low calcium dialysate and a reduced calcium intake, and the concentration of PTH increased slightly. After 18 months on haemodialysis the hypercalcaemia was also associated with calcitriol

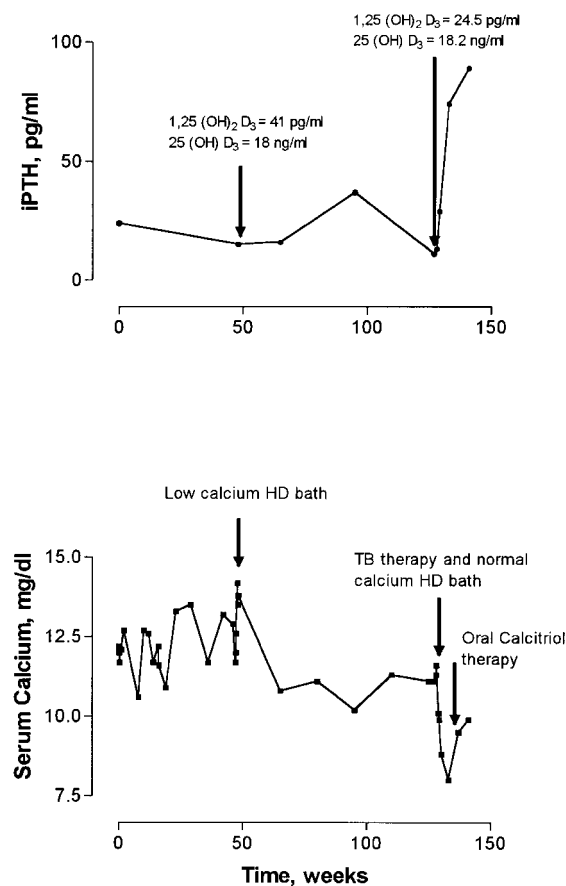


Fig. 1. Concentrations of serum calcium, calcitriol, 25(OH)D<sub>3</sub>, and intact PTH during the clinical course. 'Low' calcium dialysate = 5.5 mg/dl. 'Normal' calcium dialysate = 7 mg/dl.

serum levels inappropriately elevated, and intact PTH suppressed. Therapy with calcitriol or calcium could not have been the cause, since the patient never received a metabolite of vitamin D or oral calcium.

Thus, the presence of inappropriately elevated calcitriol levels in the described patient with genitourinary tuberculosis, suggests abnormal calcitriol production by granulomatous tissue. In addition, in this setting elevated levels of calcitriol were accompanied by low-normal 25(OH)D<sub>3</sub> levels, suggesting an increased rate of conversion of 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub>. This finding that has been previously showed by Gkonos *et al.* [2] suggests that the ectopic production of calcitriol by granulomas is either unregulated, or regulated in ways different from those controlling the normal renal production of the hormone. On the other hand, it has been demonstrated that alveolar macrophages and T lymphocytes recovered by bronchoalveolar lavage are the cellular source for calcitriol in pulmonary tuberculosis [17,18]. However, in this patient with advanced renal failure in the absence of clinical signs of pulmonary involvement, the kidney itself could be involved, suggesting that tuberculous granulomas, whether renal or extrarenal, accounted for the abnormal synthesis of calcitriol [19]. Finally, successful treatment of tuberculosis resulted in resolution of the hypercalcaemia and an adequate PTH response. Figure 1 shows the sequence of events and the patient's serum concentrations of calcium, calcitriol, 25(OH)D<sub>3</sub>, and intact PTH throughout his clinical course.

## References

- Bell NH, Stern PH, Pantzer E, Sinha TK, De Luca HF. Evidence that increased 1 $\alpha$ , 25-dihydroxyvitamin D is the probable cause for abnormal calcium metabolism in sarcoidosis. *J Clin Invest* 1979; 64: 218–225
- Gkonos PJ, London R, Hender ED. Hypercalcemia and elevated 1,25-dihydroxyvitamin D levels in a patient with end-stage renal disease and active tuberculosis. *N Engl J Med* 1984; 311: 1683–1685
- Bell NH, Shary J, Shaw S, Turner RT. Hypercalcemia associated with increased circulatory 1,25-dihydroxyvitamin D in a patient with pulmonary tuberculosis. *Calcif Tissue Int* 1985; 37: 588–591
- Felsenfeld AJ, Drezner MK, Llach F. Hypercalcemia and elevated calcitriol in a maintenance dialysis patient with tuberculosis. *Arch Intern Med* 1986; 146: 1941–1945
- Peces R, Alvarez J. Hypercalcemia and elevated 1,25(OH)<sub>2</sub>D<sub>3</sub> levels in a dialysis patient with disseminated tuberculosis. *Nephron* 1987; 46: 377–379
- Abbasi AA, Chemplavil JK, Farah S, Muller BF, Arnstein AR. Hypercalcemia in active pulmonary tuberculosis. *Ann Intern Med* 1979; 90: 324–328
- Lee JC, Catanzard A, Parthemore Jg, Roach B, Deftos LJ. Hypercalcemia in disseminated coccidioidomycosis. *N Engl J Med* 1977; 297: 431–433
- Stoekle JD, Hardy HL, Weber AL. Chronic beryllium disease. Long-term follow-up of sixty cases and selective review of the literature. *Am J Med* 1969; 46: 545–561
- Kantarjian HM, Saad MF, Esteg EH, Sellin RV, Samaan NA. Hypercalcemia in disseminated candidiasis. *Am J Med* 1983; 74: 721–724
- Murray JJ, Heim CR. Hypercalcemia in disseminated histoplasmosis. Aggravation by vitamin D. *Am J Med* 1985; 78: 881–884
- Kozeny GA, Barbato AL, Bansal VK, Vertuno LL, Hano JE. Hypercalcemia associated with silicone-induced granulomas. *N Engl J Med* 1984; 311: 1103–1105
- Jurney TH. Hypercalcemia in a patient with eosinophilic granuloma. *Am J Med* 1984; 76: 527–528
- Barbour GL, Coburn JW, Slatopolsky E, Norman AW, Horst RL. Hypercalcemia in an anephric patient with sarcoidosis: evidence for extrarenal generation of 1,25-dihydroxyvitamin D. *N Engl J Med* 1981; 305: 440–443
- Maesaka JK, Batuman V, Pablo NC, Shakamuri S. Elevated 1,25-dihydroxyvitamin levels. Occurrence with sarcoidosis with end-stage renal disease. *Arch Intern Med* 1982; 142: 1206–1207
- Kalantar-Zadeh K, Neumayer HH, Wünsch PH, Luft FC. Hypercalcaemia and sarcoidosis in an anephric dialysis patient. *Nephrol Dial Transplant* 1994; 9: 829–831
- García-Leoni ME, Martín-Scarpa C, Rodeno P, Valderrábano F, Moreno S, Bouza E. High incidence of tuberculosis in renal patients. *Eur J Clin Microbiol Inf Dis* 1990; 9: 283–285
- Cadranel J, Hance AJ, Milleron B, Paillard F, Akoun GM, Garabedian M. Vitamin D metabolism in tuberculosis. Production of 1,25(OH)<sub>2</sub>D<sub>3</sub> by cells recovered by bronchoalveolar lavage and the role of this metabolite in calcium homeostasis. *Am Rev Respir Dis* 1988; 138: 984–989
- Cadranel J, Garabedian M, Milleron B, Guillozo H, Akoun GM, Hance AJ. 1,25 (OH)<sub>2</sub> D<sub>3</sub> production by T lymphocytes and alveolar macrophages recovered by lavage from normocalcemic patients with tuberculosis. *J Clin Invest* 1990; 85: 1588–1593
- Pouchot J, Dreyfuss D, Gardin JP, Mier L, Rémy P, Esdaile JM, Coste F, Vinceneux P. Ectopic production of 1,25-dihydroxyvitamin D<sub>3</sub> in tuberculosis. *Nephrol Dial Transplant* 1993; 8: 560–562

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