Case Report

Severe hypercalcaemia with normal serum calcitriol in a diabetic patient with chronic renal failure, autoimmune hepatitis and disseminated tuberculosis

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Keywords: autoimmune hepatitis; calcitriol; disseminated tuberculosis; hypercalcaemia

Introduction

The three most common causes of hypercalcaemia are primary hyperparathyroidism, malignancy and granulomatous disease. Hyperparathyroidism is the most common cause among patients outside of the hospital, while malignancy is the most common cause in hospital patients, hyperparathyroidism being the second [1]. However, Shek et al. found that tuberculosis-associated hypercalcaemia accounts for 6% of all cases of hypercalcaemia, representing, in their study, the second most common cause of hypercalcaemia [1]. Although the tuberculosis-associated hypercalcaemia is always mild, some reports of uraemic patients with disseminated tuberculosis have shown severe hypercalcaemia, which was attributed to elevated calcitriol levels [3–5]. In the present study, we report on an elderly woman with chronic renal insufficiency, autoimmune hepatitis, diabetes mellitus and chronic tophaceous gout who developed severe hypercalcaemia during regular clinical follow-up. Disseminated tuberculosis was diagnosed finally.

Case

A 55-year-old woman had experienced chronic tophaceous arthritis for 4 years. Diabetic mellitus was diagnosed 2 years ago, and blood sugar was controlled with insulin therapy. In September 1999, she had first been admitted to our gastrointestinal ward due to an episode of acute hepatitis. Liver biochemistry study showed aspartate aminotransferase 85 mg/dl, alanine aminotransferase 94 mg/dl, alkaline phosphatase 72 mg/dl, total bilirubin 2.0 mg/dl and GGT 27 mg/dl. During the hospitalization, positive ANA (titre >1:1280, homogenous), positive anti double-stranded (ds)-DNA, negative anti-mitochondrial antibody, negative anti-smooth muscle antibody, negative Coomb’s test, negative rheumatoid factor and normal C3, i.e. 172 mg/dl (reference value 73–134 mg/dl) and C4, i.e. 23.7 mg/dl (reference value 18.2–45.5 mg/dl) were noted. Autoimmune hepatitis was diagnosed initially.

The patient was admitted to our hospital for a second time on October 1998 due to hepatic encephalopathy, which was precipitated by constipation and a high protein diet. Liver biopsy showed chronic active hepatitis, compatible with autoimmune hepatitis. She has been treated with daily prednisolone therapy since then.

The patient was admitted to our nephrology ward in December 1998 due to renal function impairment and bilateral lower leg oedema episodes. Laboratory studies revealed blood urea nitrogen 39 mg/dl and creatinine 1.7 mg/dl. She had moderate proteinuria (1.35 g/24 h) but fundoscopic examination showed no evidence of diabetic retinopathy. Renal biopsy showed sclerotic glomeruli and mesangial hyperplasia with interstitial fibrosis and tubular atrophy. Immunofluorescent microscopy showed 2+ Ig M in mesangium and irregular C3 staining. Electron microscopy showed no deposits.

Thereafter, the patient was regularly followed at our nephrology clinic. Hypercalcaemia and aggravation of chronic renal failure developed in April 1999 (calcium 11.7 mg/dl, creatinine 2.9 mg/dl). Clinically, she had chronic dry cough, anorexia and general weakness. No fever was noted, but she lost 3 kg in 2 months. Serum calcium level rose to 15.3 mg/dl in July 1999 and she was admitted to our institution again.

On arrival, the patient was lethargic and had dry mucous membranes and diminished skin turgor. Moist rales were heard over the right lower lung field. A haemogram showed leukocytosis with left shifting
Severe hypercalcemia in a diabetic patient

Fig. 1. The fluctuation of serum calcium and creatinine before and after diagnosis of disseminated tuberculosis.

(white count 10 100/cmm, segment 96%). Blood urea nitrogen was 67 mg/dl and creatinine was 3.6 mg/dl. There was severe hypercalcaemia (total calcium 13.6 mg/dl, albumin 3.1 g/dl, but normal serum phosphate 3.6 mg/dl). Serum 25-hydroxyvitamin D and calcitriol levels were normal, i.e. 11.9 mg/ml (reference value 9.7–41.7 mg/ml) and 26 pg/ml (reference value 16–42 pg/ml), respectively. A chest X-ray showed a small pleural effusion over the right side. The patient was given intravenous saline immediately, followed by loop diuretic therapy. The calcium level was normalized 4 days later. Plasma i-PTH was normal (19.4 pg/ml, reference value 10–65 pg/ml). Bone scan was negative, as was an abdominal CT.

Intermittent fever without chills occurred after hospitalization. She was treated with empiric antibiotics (cephalothin and gentamicin). A thoracocentesis for the study of pleural effusion revealed a lymphocyte-rich exudate. A pleural biopsy was performed because of the suspicion of pulmonary tuberculosis or malignancy but failed to provide adequate tissue for diagnosis.

The fever persisted. All microbiological examinations (including blood culture, pleural effusion culture, sputum culture and sputum acid fast stain) remained negative. A leukoerythroblastic picture developed 10 days later. Owing to prolonged fever and episodes of decreased consciousness, the patient was given a therapeutic trial of anti-tuberculosis medications, i.e. rifampin plus ethambutol plus pyrazinamide. Tuberculous meningitis was suspected but cerebrospinal fluid analysis was negative. Aspiration pneumonia resulted in hypoxic respiratory failure 8 days later. Endotracheal intubation was performed, whereupon the patient was transferred to our ICU. Oliguric renal failure developed with severe metabolic acidosis and haemodialysis was started. Bronchoalveolar lavage was performed in the ICU, and this time acid fast stain was positive. A bone marrow study revealed tuberculous caseous granuloma. The course was complicated by septic shock, hepatic failure, disseminated intravascular coagulation, upper gastrointestinal bleeding and progressive obtundation. The patient died 1 month after admission.

Discussion

This patient had severe hypercalcemia and dehydration on arrival. Disseminated tuberculosis was diagnosed only after the result of the bone marrow and bronchoalveolar lavage studies became available. The role of tuberculosis in causing severe hypercalcemia was overlooked initially because hypercalcemia in tuberculosis is usually mild and asymptomatic [1,2]. However, it may become severe in some patients, especially in patients with renal insufficiency and disseminated tuberculosis [3,4,5]. Felsenfeld et al. have described a 46-year-old patient on maintenance haemodialysis who had widely disseminated tuberculosis, severe hypercalcemia and elevated levels of calcitriol [3]. Peces et al. have reported a 37-year-old diabetic patient on maintenance haemodialysis who developed
widely disseminated tuberculosis, severe hypercalcaemia and inappropriately elevated serum levels of calcitriol, together with consistently suppressed serum i-PTH levels [4]. Chan et al. have presented a case of severe hypercalcaemia in a patient with miliary tuberculosis and impaired renal function [5]. Thus the serum calcium level should be monitored in all patients with tuberculosis.

The main cause of death in this patient was the delay in diagnosis and treatment of disseminated tuberculosis. Early diagnosis of tuberculosis is still based on acid fast stain of bacilli in secretions or tissue samples. Histopathological studies of bone marrow and liver biopsies are the most reliable methods for the diagnosis of disseminated tuberculosis [6,7]. When performed appropriately, polymerase chain reaction (PCR) is a suitable and reliable method for the detection of mycobacterium tuberculosis in clinical samples in a routine microscopy laboratory [8]. The definite diagnosis of disseminated tuberculosis in this patient was based only on bone marrow biopsy and bronchoalveolar lavage study. PCR could not be performed. Thus, it is imperative to perform bone marrow biopsy if there is a high degree of clinical suspicion of disseminated tuberculosis when the initial acid fast stains of bacilli in secretions or tissue samples are negative. For those hospitals where commercial PCR kits are available, this technique may be very helpful in diagnosing tuberculosis more rapidly.

The pathogenesis of tuberculosis-associated hypercalcaemia is unclear. An abnormal vitamin D metabolism has been incriminated repeatedly. Reports of high circulating levels of calcitriol in two anephric patients with tuberculosis support an extrarenal source of this active vitamin D metabolite [3,4]. Increased extrarenal 1α-hydroxylase activity that causes increased hydroxylation of 25-hydroxyvitamin D to calcitriol has been proposed. Hypercalcaemia in tuberculosis may occur weeks to months after starting anti-tuberculosis chemotherapy. Thus, the hypercalcaemia is not related to the presence of acid fast bacilli but rather to the granulomatous process and associated reactions [2]. Cells obtained from bronchoalveolar lavage in patients with tuberculosis were also found to synthesize calcitriol in vitro. An important source of the active vitamin D metabolite appears to be the CD8+ T lymphocyte at the granulomatous site [9]. If one wonders about the potential benefit of enhanced calcitriol production under these circumstances, the immunomodulatory function of calcitriol could be considered as a beneficial local paracrine factor. Viewed in this context, hypercalcaemia occurs when calcitriol is produced in such quantities that it gains entry into the circulation [2].

Glucocorticoids (40–60 mg of prednisolone or equivalent daily) are the mainstay of therapy for disordered calcium homeostasis resulting from endogenous overproduction of active vitamin D metabolites. Glucocorticoids have a specific antagonistic effect on extrarenal 1α-hydroxylase action. Instigation of glucocorticoid therapy results in prompt decline of the circulating calcitriol concentration within 3–4 days. Glucocorticoids are also useful because they antagonize the effects of calcitriol on calcium absorption in the gastrointestinal tract. Glucocorticoids may also alter hepatic vitamin D metabolism to favour the production of non-active vitamin D metabolites. Finally, glucocorticoids may limit osteoclastic bone resorption [10].

Our case did not show the elevation of calcitriol level seen in previous studies. Serum 25-hydroxyvitamin D and calcitriol were within normal limits. Of note, our patient suffered from autoimmune hepatitis and had received long-term prednisolone therapy (tapered to 10 mg daily before this admission). If our hypothesis regarding the increased production of calcitriol by macrophage cells of granuloma at the extrarenal site is correct, long-term prednisolone therapy should have had a protective effect for hypercalcaemia in the patient; this was not the case.

One possible explanation for this is that the underlying mechanism leading to hypercalcaemia in some tuberculosis patients may not be related to abnormal vitamin D metabolism. In this case the patient would develop hypercalcaemia due to other mechanisms, e.g. the involvement of prostaglandin metabolite or PTHrP (which were not determined in our patient). Even long-term prednisolone therapy would have no protective capacity. At present, the cause of severe hypercalcaemia in patients with disseminated tuberculosis in the absence of elevated serum calcitriol levels remains a mystery and requires further study.

Conclusion

Disseminated tuberculosis should be considered in any renal failure patient who manifests severe hypercalcaemia, after excluding other common causes of hypercalcaemia such as primary hyperparathyroidism and malignancy, especially in endemic areas of tuberculosis. The most reliable diagnostic methods are bone marrow and liver biopsies. When performed appropriately, PCR is a suitable and reliable method for the early detection of mycobacterium tuberculosis in clinical samples. However, it is not routinely available everywhere. Tuberculosis may cause severe hypercalcaemia through an unknown mechanism, unrelated to an elevation of serum calcitriol concentration.

References


Received for publication: 14.4.00
Accepted in revised form: 28.7.00