Secondary hyperparathyroidism resistant to active vitamin D is not unique to renal failure—observation in a patient with distal tubular acidosis and pancreatogenic malabsorption

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Introduction

In recent years nodular hyperplasia of the parathyroid gland has emerged as a major complication of chronic renal failure. Patients with such advanced hyperparathyroidism tend to be hyporesponsive to administration of active vitamin D metabolites [1]. Nodular hyperplasia appears to be the consequence of monoclonal growth and genomic abnormalities as evidenced by loss of heterozygosity analysis [2–5].

Whether similar nodular hyperplasia of the parathyroids occurs in non-renal patients has not been well documented. In the following we report a case of a patient with pancreatogenic malabsorption who developed severe secondary hyperparathyroidism resistant to 1α-hydroxycalciferol therapy. Such hyperparathyroidism was accompanied by marked tubular acidosis.

Case report

A 42-year-old man presented a 3-year history of generalized skeletal pain, nontraumatic fractures of right femur neck, and ischial bone was referred to hospital. For the last 14 years he was treated with insulin due to insulin-dependent diabetes mellitus. A year prior to hospitalization he underwent infiltrative pulmonary tuberculosis therapy. It was evident that he was not avoiding alcohol. The physical examination revealed a malnourished patient (body weight 45 kg, height 174 cm) with anaemia and diffuse bone tenderness. Laboratory findings: haemoglobin, 9.9 g/dl; iron, 84 μg/dl; Na, 145 mmol/l; K, 5.1 mmol/l; total protein, 50.7 g/l; albumin, 23.7 g/l; creatinine, 80 μmol/l. Evaluation of acid-base homeostasis showed hyperchloraemic metabolic acidosis: pH 7.229, HCO3−: 15.8 mmol/l, the anion gap: 10 mmol/l; with respiratory compensation (pCO2, 33.8 mmHg). Serum concentration of calcium was below the normal range (1.9 mmol/l), however, gland has emerged as a major complication of chronic renal failure. Patients with such advanced hyperparathyroidism tend to be hyporesponsive to administration of active vitamin D metabolites [1]. Nodular hyperplasia appears to be the consequence of monoclonal growth and genomic abnormalities as evidenced by loss of heterozygosity analysis [2–5].

Whether similar nodular hyperplasia of the parathyroids occurs in non-renal patients has not been well documented. In the following we report a case of a patient with pancreatogenic malabsorption who developed severe secondary hyperparathyroidism resistant to 1α-hydroxycalciferol therapy. Such hyperparathyroidism was accompanied by marked tubular acidosis.

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Radiologic findings (loss of trabeculae, thinning of cortices) and decreased bone mass density assessed by dual X-ray absorptiometry (lumbar spine 0.34 g/cm2 = 31% of the age-matched norm) indicated severe osteopenia. Bone biopsy made possible to establish the diagnosis of osteomalacia. In order to assess contribution of calcium–phosphate metabolism related hormones in the pathogenesis of bone loss serum 250HD3, calcitriol, and intact PTH were determined. Concentration of 250HD3 was low (8.8 ng/ml; range 10–30), concentration of calcitriol (49 pg/ml; range 20–60) within the
normal range, contrary to substantially elevated iPTH level 1230 pg/ml (range 10–60).

The patient received replacement therapy with natrium bicarbonate (10 g/day), calcium carbonate (10 g/day) and 1α-hydroxyvitamin D₃ (3 μg/day). Insulin therapy was intensified. Under such treatment normalization of systemic acid–base parameters and calcium concentration was obtained. Bone pain subsided gradually.

After 15 months the patient did not complain of skeletal pain, but, remained malnourished (body weight 47 kg). Metabolic acidosis was partially corrected (pH 7.334, HCO₃⁻ 20.1 mmol/l). Serum calcium concentration increased to 2.4–2.5 mmol/l with a high ionized fraction (1.37–1.44 mmol/l). Concentrations of inorganic phosphates, iPTH, and alkaline phosphatase activity as well as bone fraction decreased to 0.88–1.01 mmol/l, 150 pg/ml, and 160/59 U/l, respectively. Bone mass density of lumbar spine ameliorated considerably from 0.34 g/cm² to 1.023 g/cm² (92% of the age matched norm). The 1α-hydroxyvitamin D₃ dose was reduced to 1 μg daily to avoid vitamin D toxicity.

Sixteen months later the patient was readmitted because of rapid deterioration in bone mineralization (lumbar spine 0.808 g/cm²). Hypercalcemia (ionized fraction 1.41 mmol/l), hypophosphataemia (0.76 mmol/l) and increased iPTH concentration (400 pg/ml) disclosed parathyroid overactivity. The diagnosis of refractory hyperparathyroidism was made and patient was referred to the surgeon. Subtotal parathyroidectomy was performed. Parathyroids were markedly enlarged (size 7–15 mm) with histologic pattern of nodular hyperplasia. After surgery a rapid decrease in calcium level was observed. DNA extracted from four paraffin embedded nodules were used for

Fig. 1. Abdominal X-ray showing calcifications within pancreas.

Fig. 2. Results of microsatellite analysis showing loss of heterozygosity at two loci (D1S162 and D1S1656) mapping to both arms of chromosome 1 in the second nodule.
We used microsatellite markers localized to chromosome 1p, 1q, 2q, 6q, 10p, 12q, 13q, 17p regions, which are involved in the genetic of primary parathyroid adenomas and renal hyperparathyroidism. Loss of heterozygosity was detected in one nodule [2] at two loci (D1S162 and D1S1656) localized to the both arms of chromosome 1 (Figure 2).

Discussion

We discuss a patient who has insulin dependent diabetes as well as exocrine pancreatic insufficiency on the basis of chronic alcoholism. The pancreatic insufficiency led to intestinal malabsorption and subsequently to hypocalcaemia and osteomalacia. The ensuing secondary hyperparathyroidism apparently has existed for a long period of time resulting in nodular hyperplasia similar as in chronic renal failure [6]. The loss of heterozygosity in one of the nodules is consistent with monoclonal growth, the findings described in renal secondary hyperparathyroidism [2,4,5].

Of interest, in spite of administration of calcium and 1α-hydroxy vitamin D₃ parathyroid hormone concentration could not be normalized. This is similar to findings reported by other investigators in renal secondary hyperparathyroidism [1,7]. In our case the vitamin D receptor was not measured but it is reasonable to assume that as documented by Fukuda [8] in renal patients, parathyroid nodules had diminished expression of vitamin D receptors and were hyporesponsive to active vitamin D metabolites.

The patient also had distal renal tubular acidosis as evidenced by systemic metabolic acidosis and inability to reduce urine pH following acid load. This may be due to severe hyperparathyroidism. Alternative explanations e.g. alcohol induced liver disease, cannot be excluded.

This case is of interest since it documents that prolonged stimulation of the parathyroids may cause nodular hyperplasia. This process is presumably not unique to renal failure, but is also found in other cases of chronic overstimulation of the parathyroid glands.

References


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