Hypocalcemia due to Spontaneous Infarction of Parathyroid Adenoma and Osteomalacia in a Patient with Primary Hyperparathyroidism

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Abstract. A 49 year-old Japanese woman had subjected enlargement of a cervical tumor, and also suffered two bone fractures in 2 years. The cervical tumor had enlarged further in the month prior to admission, becoming warm and tender. Endocrinological examination revealed that the serum intact PTH concentration was remarkably high at 400 pg/mL despite the low serum calcium concentration, and that the serum vitamin Ds concentration was decreased. Bone roentgenograms revealed severe osteolytic changes compatible with osteitis fibrosa cystica and a pathologic fracture of the humerus. Under a diagnosis of primary hyperparathyroidism, parathyroidectomy was performed, followed by fixation surgery for the pathologic fracture. Histologically, the cervical tumor was a parathyroid chief-cell adenoma with massive necrosis, and the bone pathology by iliac bone biopsy revealed the existence of osteomalacia. She was treated with calcium, vitamins D and K2 and calcitonin after the surgery. This case is a rare condition manifesting hypocalcemia with catastrophic osteoporosis under the coexistence of spontaneous infarction of parathyroid adenoma with osteomalacia, suggesting that the clinical features of hyperparathyroidism are modified by both the autopathyroidectomy and the existence of osteomalacia due to vitamin D deficiency.

Key words: Parathyroid adenoma, Spontaneous infarction, Osteomalacia, Osteoporosis, Hypocalcemia, Vitamin D, Vitamin K2

(Endocrine Journal 45: 617–623, 1998)

PRIMARY hyperparathyroidism is characterized by hypercalcemia and hypophosphatemia due to the action of increased serum PTH. Generally there is a good correlation between serum calcium and PTH concentrations in this disease [1]. In the present patient, serum calcium was low despite the hypersecretion of PTH. This case was diagnosed histologically as spontaneously infarcted parathyroid adenoma associated with osteomalacia.

We present here the clinical course of this complicated case, indicating that both the conditions of parathyroid adenoma and bone mineralization should be evaluated when hypocalcemia is discordant with the PTH level and severe osteoporotic change.

Case Report

A 49-year-old woman was referred to our hospital in April, 1996 for evaluation of a cervical tumor, pathologic right humeral fracture with nonunion, and systemic bone and muscle pain. Although she noticed gradual enlargement of the

Received: December 1, 1997

Accepted: May 25, 1998

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cervical tumor, sometimes associated with warmth and tenderness, she had not undergone further examination for 7 years. In 1994, she suffered a pelvic fracture in a mild collision. In February, 1996 she also sustained a fracture of the right humerus, and there was nonunion despite fixation for 2 months. She had no history of renal stones or bowel disease and took no medication or alcohol, but she has been mildly depressive recently. The family history was not remarkable. Her menarche was at 14 years of age and she gave birth to two children. Her menstruation has been irregular since she was 40 years old and menopause occurred at 48. Physical examination on admission revealed height, 148 cm; weight, 38 kg; blood pressure, 100/60 mm Hg; pulse, 80 bpm, regular; and temperature, 36.8 °C. She was mildly kyphotic and had anemic conjunctivae but no present typical rickets features. A round cervical tumor the size of a small egg was palpable in the left cervical region. Ultrasonography showed a round, cystic lesion with heterogeneous echogenity behind the left thyroid lobe (Fig. 1A). Laboratory examination revealed red blood cell count ($2.23 \times 10^6/\mu\text{L}$; normal: 3.7–4.9), hemoglobin (6.7 g/dL; normal: 11.5–14.5) and hematocrit (20.3%; normal: 35–44) to be decreased; the white blood cell count ($4300/\mu\text{L}$; normal: 3000–9400) and platelets ($291 \times 10^3/\mu\text{L}$; normal: 150–400) were normal; total protein (5.89 g/dL; normal: 6.5–8.0) and serum albumin (3.18 g/dL; normal: 3.9–4.9) were low; serum alkaline phosphatase was high (635 IU/L; normal: 41–127), and isozyme analysis revealed it to be predominantly of bone origin, other liver function tests being normal. The serum iron concentration was noticeably decreased ($32 \mu\text{g/dL}$; normal: 70–130). Endoscopic examinations found no gastrointestinal disorders. The serum calcium concentration was 5.8 mg/dL (corrected value, 6.62 mg/dL; normal: 8.0–10.0) and the serum phosphorus concentration was 2.2 mg/dL (normal: 2.4–4.7). Urea nitrogen (14.8 mg/dL; normal: 8.1–22), serum creatinine (0.98 mg/dL; normal: 0.44–1.04) and uric acid (4.3 mg/dL; normal: 2.4–5.7) were normal. Blood gas analysis demonstrated a slightly metabolic acidosis: pH, 7.34; HCO_3^- , 17.4 mmol/L. Serum chloride was slightly increased to 112 mmol/L (normal: 102–110), with normal sodium (139 mmol/L; normal: 136–144) and slightly lowered potassium (3.3 mmol/L; normal: 3.7–4.9)

Fig. 1. The cervical tumor. A left cervical tumor behind the left thyroid lobe was remarkably large and showed cystic change on cervical ultrasonography (A). Histologically the resected tumor was a parathyroid chief-cell adenoma including massive necrosis and measuring $45 \times 24 \times 21$ mm (HE stain, $\times 338$; B).

concentrations. Urinary excretion of calcium was undetectably low during admission and the urinary phosphorus excretion (0.3 g/day; normal: 0.3–2.2) was at the lower limit of the normal range. Endocrinologic examination data are shown in Table 1. The serum intact PTH concentration was noticeably increased (400 pg/mL). Consistent with this value, nephrogenous cyclic AMP (N-cAMP) was increased (4.73 nmol/dl GFR) and the tubular resorption rate of phosphorus (%TRP) was decreased (69.9%). The serum osteocalcin concentration was noticeably increased, and urinary pyridinoline and deoxypyridinoline excretion were also increased. The serum 1,25-dihydroxyvitamin D concentration was noticeably decreased, and 25-

Table 1. Endocrinologic data on admission

intact PTH	400 pg/mL (14–66)
hs-PTH	7020 pg/mL (230–560)
PTHrP	undetectable
calcitonin	19 pg/mL (27–48)
osteocalcin	214.8 ng/mL (3.5–13.7)
25-hydroxyvitamin D	10 ng/mL (10–55)
1,25-dihydroxyvitamin D	18.3 pg/mL (27.5–68.7)
24,25-dihydroxyvitamin D	1.1 ng/mL (1–4)
nephrogenous cAMP	4.73 nmol/dl GFR (0.8–2.8)
%TRP	69.9% (82–95)
urinary pyridinoline	120 μ mol/mol Cr (13–36)
urinary deoxypyridinoline	14 μ mol/mol Cr (<7)

PTH, parathyroid hormone; hs-, high sensitive; PTHrP, PTH related peptide; %TRP, % tubular resorption of phosphate.

hydroxyvitamin D and 24,25-dihydroxyvitamin D were at the lower limits of the normal ranges. Bone roentgenograms of the skull, hands, femur, pelvic bone and vertebrae revealed a remarkable decrease in bone density with a salt-and-pepper skull appearance (Fig. 2A), periosteal resorption (Fig. 2B) and brown cysts (Fig. 2C) compatible with severely progressed osteitis fibrosa accompanying osteoporosis. In the right humerus, nonunion of the pathologic fracture was also shown (Fig. 2D). No osteomalacial change such as a Looser's zone was observed in these roentgenograms. Bone mineral density in the femur determined by dual energy X-ray absorptiometry (QDR-1000, Hologic) was noticeably decreased to 0.385 g/cm² (49% of young adult mean, 58% of age matched control). Consistent with the echographic findings, cervical computed tomography demonstrated a left-sided cervical tumor corresponding to a parathyroid gland, and tallium-technecium subtraction scintigraphy showed accumulation of tracer in the lower pole of the left thyroid lobe. Following the diagnosis of primary hyperparathyroidism, parathyroidectomy was performed on May 17, 1996 and a massively necrotic chief-cell adenoma (45 × 24 × 21 mm) involving the left lower parathyroid gland was resected (Fig. 1B). The other parathyroid glands were not palpable during the operation. Immediately after the parathyroidectomy, fixation surgery for the right humerus was performed, as well as iliac bone biopsy. The latter specimen revealed increased thickness of osteoid seams with a remarkable decrease in trabecular bone, consistent with osteomalacia, and marked fibrosis in

Fig. 2. Bone roentgenogram. The skull had a typical salt-and-pepper appearance (A), the bones of the hand showed signs of severe periosteal resorptive changes (B) and both femora had multiple cystic lesions (brown tumors; C). In the right humerus, a pathologic fracture with nonunion over 2 months is seen (arrow; D).

peritrabecular marrow probably due to advanced osteitis fibrosa (Fig. 3). After parathyroidectomy, the patient was placed on oral alfacalcidol (1 μ g/day) and calcium lactate (6 to 3 g/day). Additionally, calcitonin injections (20 IU, weekly) and oral vitamin K2 (menatetrenone, 45 mg/day) were administered. The serum PTH concentration gradually decreased and was normal 5 months after surgery. Serum 1,25-dihydroxyvitamin D increased to the normal range after the alfacalcidol administration. Postoperatively, serum ALP was transiently low, subsequently increased, peaked 2 months later, and was normal about 1.5 year after the surgery (Fig. 4). Her bone pain had completely disappeared 2 months after the surgery, and bone mineral density in the femur has increased to the normal range (0.602 g/cm²; 76% of young adult mean, 90% of age matched control) one year later.

Serum calcium and phosphorus concentrations have maintained the normal range since parathyroidectomy, and 1 year later the

Fig. 3. Iliac bone biopsy specimen. Pathologic findings were compatible with osteomalacia, consisting of noticeably increased osteoid with severely diminished trabecular bone, and marked fibrosis in peritrabecular marrow, probably due to developed osteitis fibrosa, is also seen (orange with Villanueva-Goldner staining, $\times 100$).

administration of calcium lactate was discontinued because the serum calcium level has exceeded 10 mg/dL (Fig. 4). Her anemia due to iron deficiency has also completely improved after oral ferrotherapy for 6 months.

Discussion

The increased serum intact PTH and pathologic findings in the resected tumor indicated that this patient had primary hyperparathyroidism, but the serum calcium concentration remained low. Among the bone resorptive markers in this case, increased urinary pyridinoline and deoxypyridinoline, increased N-cAMP and decreased %TRP confirmed the excessive activity of PTH. Although the serum 1,25-dihydroxyvitamin D concentration in patients with hyperparathyroidism is often increased due to the activation of renal 1α -hydroxylase, serum vitamin Ds, especially 1,25-dihydroxyvitamin D, were decreased in the present patient. Because the patient had the habit of having unbalanced diet

Fig. 4. The clinical course. Preoperatively the serum corrected calcium concentration remained low and the inorganic phosphorus concentration was also low. Serum alkaline phosphatase (ALP) gradually decreased after admission. Since parathyroidectomy on May 17, serum intact PTH has gradually decreased, serum 1,25-(OH)₂-D increased, and serum calcium and phosphate levels were normalized with the administration of vitamin D, K2, calcitonin and calcium (Ca-) lactate. Serum ALP was transiently low, subsequently increased and peaked at 2 months after parathyroidectomy, and consequently normalized about 1.5 years after the surgery. One year after surgery, the administration of calcium lactate was discontinued because the serum calcium concentration has exceeded 10 mg/dL. The shadings in the figure show the normal ranges of serum calcium (upper shading: 8.0–10.0 mg/dL) and phosphorus (lower shading: 2.4–4.7 mg/dL).

and not venturing outside, and did not have any evidence of malabsorptive disorders, these habits might have contributed to her deficiency of vitamin D and iron. As a bone formation marker, serum ALP and osteocalcin concentrations were remarkably high in this case, probably affected not only by hyperparathyroidism but also by osteomalacia [2].

The patient's resected parathyroid adenoma showed signs of massive necrosis, which was probably associated with the occasional neck pain with swelling and dysphagia before admission. Taking it into consideration that the serum ALP level has already decreased before the parathyroidectomy, this clinical episode implies the possibility that the spontaneous infarction had occurred in her parathyroid adenoma before admission. The spontaneous infarction of parathyroid adenoma rarely causes the biochemical remission, resulting in normocalcemia [3–6], which is also called as autoperathyroidectomy [6]. The hypocalcemia in the present case might be associated with the hungry bone state after the parathyroid infarction. Although in the literature on the spontaneous infarction of parathyroid adenoma the PTH level has begun to decrease preoperatively, the preoperative serum intact PTH concentration in the present case was remarkably high (400–466 pg/mL) even with hypocalcemia. Considering the slow decrease of the PTH level after the resection of parathyroid adenoma, the PTH excess after the parathyroid infarction might be originated from the other parathyroid glands which has accelerated by hypocalcemia than parathyroid adenoma.

In the literature on the cases showing low or normal serum calcium concentration but high ALP with excessive PTH [7–12], only two cases reported by Keynes *et al.* and Dent *et al.* manifested hypocalcemia [7, 8]. Keynes *et al.* reported a 41-year-old woman with a history of partial gastrectomy, who had suffered hypocalcemia and hypophosphatemia under the condition of both primary hyperparathyroidism and osteomalacia [7]. Dent *et al.* reported a 31-year-old woman with a history of gluten-sensitive enteropathy who had suffered hypocalcemia despite hyperparathyroidism [8]. These patients were first treated with vitamin D administration and followed by parathyroidectomy. The vitamin D

administration to these patients has increased the serum calcium concentration noticeably, which suggests that the action of PTH is blocked as long as vitamin D is deficient (*i.e.* masked hyperparathyroidism) [7, 8]. In these two cases and ours, PTH might not play a role in keeping the serum calcium level normal by bone resorption under the vitamin D deficient condition, resulting in the manifestation of hypocalcemia. It is possible that two pathogeneses were chiefly involved in the coexistence of hyperparathyroidism with osteomalacia. One is that the condition causing osteomalacia, such as vitamin D deficiency, precedes autonomous secretion of parathyroid hormone [13]. The hypocalcemia of osteomalacia due to vitamin D deficiency seems to be a secretory stimulus leading to the progression of the hyperparathyroidism [14]. The other is that hyperparathyroidism precedes the development of osteomalacia, that is to say, hyperparathyroidism causes an increased requirement of vitamin D [9]. As mentioned in similar reports, the cause of osteomalacia accompanied by hyperparathyroidism is recognized to be hypophosphatemia which is induced by increased urinary phosphate excretion due to PTH excess [10, 11]. In the present case, whether hyperparathyroidism or osteomalacia preceded the other is uncertain. Nevertheless, it remains possible that the pathogenesis of both osteomalacia and hyperparathyroidism exacerbate each other in these complicated cases, and moreover, this coexistence might be attributable to catastrophic bone damage resulting in high-graded osteoporosis such as in the present case. Histologically the iliac bone specimen demonstrated not only a remarkable increase in osteoid seams but also severe fibrosis in the peritrabecular marrow which probably was evidence of developed osteitis fibrosa. But no active indication of osteitis fibrosa, such as osteoclasts present within a resorptive cavity in a cluster, was seen. Stanbury said that the failure of normal mineralization on newly formed osteoid seams and the increased bone turnover might result in the histologically mixed features of osteomalacia and osteitis fibrosa cystica in hyperparathyroidism [13].

Since the parathyroidectomy was performed, bone pain and roentgenographic findings have remarkably improved over 2 months. Serum calcium and phosphate concentrations have also

gradually normalized. As regards the therapy, vitamin D was first administered and subsequently parathyroidectomy was reportedly performed, and the serum ALP concentration had already decreased before parathyroidectomy [7–9]. In the present case, whose severe osteoporosis and cervical discomfort had progressed, parathyroidectomy was first performed, followed by the administration of vitamins D and K2 and calcitonin. As in the experimental data on rats, vitamin K2, which is essential for the γ -carboxylation of osteocalcin [15], has been shown to prevent bone loss and bone resorption by osteoclasts in various osteoporotic conditions [16], especially with 1,25-dihydroxyvitamin D [17]. Calcitonin injection was performed to directly suppress the bone resorption by osteoclasts. Because hypocalcemia itself induces the PTH excretion, calcium lactate was also given to normalize and maintain the serum calcium level postoperatively, and the serum PTH level has gradually decreased and normalized in the 5 months since the surgery. Since the parathyroidectomy the serum ALP level has increased for 1.5 years due to hungry bone

syndrome, suggesting that the normalization of bone remodeling required quite a long time in this case. In the present patient, although we cannot completely exclude vitamin D dependent rickets-type I [18], the lack of her family history and the decrease in both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D may permit us to partly eliminate this possibility.

In summary, the present patient had primary hyperparathyroidism accompanied by osteomalacia. Although osteomalacia in this case probably was associated with vitamin D deficiency, these two pathophysiologically related disorders might influence one another, resulting in severe bone damage. Furthermore, the clinical course manifesting hypocalcemia implicates the spontaneous infarction of parathyroid adenoma. This case suggests that various atypical changes in the serum calcium concentration in hyperparathyroidism may indicate the complication of the other bone metabolic disorders, and that the bony expression of hyperparathyroidism is modified by vitamin D deficiency.

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