A Patient with Primary Hyperparathyroidism Associated with Osteomalacia: Markedly Increased Serum Levels of Intact PTH and 1,25-Dihydroxyvitamin D with Normo- and Hypercalcemia

TAKAKO TAKEMIA, KANJI SATO, MARIKO MIYATA, TOSHIHIRO IMAKI, TAMOTSU SHIBASAKI, TOSHI TSUSHIMA, HIROSHI DEMURA, REIKO TANAKA*, TAKAO OBARA*, AND SHIGEKI OGUCHI**

Department of Medicine, *Department of Surgery, Institute of Clinical Endocrinology, **Department of Orthopedic Surgery, Tokyo Women’s Medical College, Tokyo 162, Japan

Abstract. A 65-year-old female patient was admitted with complaining chiefly of lower back pains and arthralgia in the bilateral knee joints of 10-years duration. The serum calcium concentration was normal or only slightly increased, whereas the serum intact PTH and 1,25-dihydroxyvitamin D concentrations were substantially increased. Serum phosphate and 25-hydroxyvitamin D concentrations were decreased. Renal function was normal. Serum alkaline phosphatase activity, the osteocalcin concentration and urinary hydroxyproline excretion were markedly increased. Bone X-ray examination showed severe osteopenia and bone biopsy revealed hyperosteoisodisis without tetracycline deposition, consistent with osteomalacia. A parathyroid adenoma was demonstrated by echography and CT-scan. Surgical exploration of the neck revealed a chief cell adenoma behind the right upper pole of the thyroid gland. After parathyroidectomy, all the abnormal biochemical data gradually normalized and the patient has been doing well without any symptoms for the last 13 months. These clinical data suggest that osteomalacia of the patient was probably induced by hypophosphatemia of prolonged duration. When hypercalcemia is not evident in a patient with primary hyperparathyroidism, in whom serum alkaline phosphatase and intact PTH levels are inappropriately increased, osteomalacia should be taken into consideration.

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PRIMARY hyperparathyroidism is characterized by hypercalcemia, hypophosphatemia, and increased serum concentrations of intact PTH and 1,25-(OH)₂-D. In general, there is a good correlation between the serum calcium and PTH (1–84) concentrations in patients with primary hyperparathyroidism [1]. However, when a patient has vitamin D deficiency or osteomalacia, serum calcium may be within the normal range or only moderately increased [2, 3]. In a few reported cases, the serum calcium values were even subnormal (8 mg/dl), apparently due to hypoproteinemia caused by the associated gluten enteropathy [3, 4].

We report a case of primary hyperparathyroidism with osteomalacia, in whom hypercalcemia was very mild, despite markedly increased serum concentrations of intact PTH and 1,25-(OH)₂-D.
Case Report

A 65-year-old woman presented in April, 1991 with pain in the knees, hips and back of at least 10 years’ duration, which had become progressively worse in the last several months. Eight years ago, when her decayed teeth were extracted, a dentist suggested that the teeth and bones were fragile. It was noticed that she had walked slowly, with her back bent for the previous several years. She had no history of renal stones or colicky pains in the abdomen. She took no medication and did not drink alcohol.

Physical examination was unremarkable except for mild kyphosis and genu varum. Her height was 147cm and body weight 61 kg. No muscle atrophy was detected.

The urine and complete blood count were normal. Total protein was 6.4 g/dl and albumin 3.8 g/dl. The serum calcium concentration was normal at the outpatient clinic (10.1 mg/dl, normal range; 8.8–10.6 mg/dl) or slightly increased during admission (10.5–11.1 mg/dl). The serum phosphate concentration was decreased (1.4 mg/dl, normal range; 2.5–4.3 mg/dl). Alkaline phosphatase was remarkably increased (1249 IU/ml, normal range; 70–260 IU/ml). Isozyme analysis revealed that the enzyme activity was exclusively of bone origin. GOT (40 KU/ml), GPT (52 KU/ml), and total bilirubin (1.2 mg/dl) were slightly increased. Urea nitrogen (12.3 mg/dl), creatinine (0.6 mg/dl) and uric acid (4.3 mg/dl) were normal, with a normal creatinine clearance (67 ml/min). The blood gas analysis demonstrated a metabolic acidosis: PO₂; 78.3 mmHg, pCO₂; 35.1 mmHg, pH 7.365, HCO₃⁻; 19.7 mEq/l. Serum Cl was increased to 115 mEq/l, with normal Na (144 mEq/l) and K (4.3 mEq/l) concentrations. The plasma intact PTH concentration, determined by immunoradiometric assay with an Allegro kit (Nippon Mediphysics, Tokyo), was markedly increased (519 pg/ml, normal range; 23–72 pg/ml) (Fig. 1). Consistent with this value, nephrogenous cyclic AMP excretion was also increased (5.23 nmol/100 ml GFR).

Urinary excretion of calcium was slightly in-
creased (230–300 mg/day), with a slightly decreased phosphate secretion (370 mg/day), which normalized during admission. Urinary hydroxyproline excretion (827 µmol/day, normal range; 83–330) and the serum osteocalcin concentration (59 ng/ml, normal range; 2.5–13 ng/ml) were markedly increased. Serum 25-OH-D (7.9 ng/ml, normal range; 9.0–33.9 ng/ml) was slightly decreased, with a normal 24, 25-(OH)2-D concentration (1.09 ng/ml, normal range; 1.08±0.26 ng/ml) and a marked increase in the serum 1,25-(OH)2-D concentration (226.6 pg/ml, normal range; 20–60 pg/ml).

Bone X-ray examination of the skull, hands, femur, tibiae, and vertebrae revealed marked osteopenia (Fig. 2). A mild compression fracture was observed in the vertebral body of the 5th lumbar spine. The CT scan of the abdomen revealed tiny left renal stones, which had not been detected by a plain X-ray examination.

The echographic study of the cervical region demonstrated a hypoechoic mass of 16 × 8 × 5 mm behind the upper pole of the right thyroid lobe, which was also confirmed by CT scan.

Iliac bone biopsy revealed an increased osteoid surface and increased thickness of the osteoid in the trabecular bone, consistent with osteomalacia (Fig. 3). Although tetracycline had been given for 3 days twice prior to the biopsy, little or no tetracycline label was detected on fluorescence microscopy.

Following the diagnosis of primary hyperparathyroidism with osteomalacia, parathyroidectomy was performed on June 5, 1991 and a chief cell adenoma (1050 mg) of the right upper parathyroid gland was resected. The other parathyroid was histologically normal with no hyperplasia. To prevent post-surgical hypocalcemia, vitamin D2 (1000 U) and calcium lactate (3 g, t.i.d.) were prescribed. After surgery, serum alkaline phosphatase activity rapidly decreased to 700 IU/ml by 6 days, followed by a transient increase to 1135 IU/ml at 4 weeks, reflecting accelerated bone formation (Fig. 4). Consistent with this, urinary phosphate excretion markedly decreased to less than 10 mg/day 6 days after the parathyroidectomy, and then gradually increased to 450–1000 mg/day. The patient was discharged on June 13, 1991.

After discharge, the patient’s complaints such as general fatigue and pains in the knees and back gradually improved. Thirteen months after parathyroidectomy, serum intact PTH and osteocalcin concentrations, alkaline phosphatase activity, and urinary hydroxyproline excretion were within the normal range. Bone X-ray survey revealed a distinct improvement in the osteopenia and the bone mineral density in the lumbar spines (L2–L4) determined by dual energy X-ray absorptiometry (QDR-200, Hologic) was within the normal range (0.765 g/cm²).

Discussion

Increased serum concentrations of calcium, intact PTH and 1,25-(OH)2-D, together with decreased serum phosphate and normal GFR, indicate that this patient had primary hyperparathyroidism. However, her serum calcium concentration was not as high as expected in view of markedly increased serum intact PTH (Fig. 1). Such a discrepancy may occur in a few patients.
with primary hyperparathyroidism who have vitamin D deficiency or osteomalacia [2–9]. Marked hyper-alkaline phosphatase, hypophosphatemia, an increased serum osteocalcin concentration [10], increased urinary hydroxyproline excretion and generalized osteopenia suggested that the patient has osteomalacia [2], which was confirmed by bone biopsy. Although the serum 25-OH-D was slightly decreased, 1,25-(OH)₂-D was markedly increased, certainly due to stimulation of renal 25-OH-D-1 α-hydroxylase by PTH and hypophosphatemia [11]. Decreased urinary phosphate excretion at the time of admission suggests that her daily intake of phosphorus was low. It is well known that phosphorus restriction almost doubles the serum 1,25-(OH)₂-D concentration in normal subjects [12].

Osteomalacia can develop in a few patients with primary hyperparathyroidism [1, 2]. Why a minority of these patients have pure osteomalacia is uncertain [13]. Generally speaking, for bone formation to proceed at the mineralization front, there should be enough calcium, phosphate, active vitamin D and osteoblasts with high alkaline phosphatase activity [12].

In this patient, there was enough calcium and active vitamin D in the circulating blood. The patient’s serum 25-OH-D concentration was decreased, as often seen in the elderly [14]. Since the sample was taken in June, when serum 25-OH-D tends to be high [15], the patient probably had a mild vitamin D deficiency. However, the serum 1,25-(OH)₂-D level in the present case was extremely increased to 226 pg/ml, the highest value among 40 patients with primary hyperparathyroidism in whom the vitamin D metabolites were analyzed in our clinic. This value is much higher than those (42 pg/ml, 31 pg/ml, and 123 pg/ml) reported in other patients with normocalcemic hyperparathyroidism associated with osteomalacia [7, 8, 9].

Furthermore, serum alkaline phosphatase of osteoblast origin was markedly increased. Although it is not alkaline phosphatase in the circulation but alkaline phosphatase on the plasma membrane of osteoblasts that actually induces mineralization of bone matrix [16, 17], we believe

![Fig. 3. Undecalcified bone section from the right iliac crest. The uncalcified region (osteoid), which stains orange with Villanueva-Goldner staining, is markedly increased.](image-url)
that the patient's osteoblast function was not impaired, since her symptoms gradually improved and all the biochemical data normalized after parathyroidectomy, accompanied by normal bone mineral density in the lumbar spine 13 months after surgery.

For many years, chronic hypophosphatemia has been accepted as a critical factor in the pathogenesis of osteomalacia. No matter what the mechanism, chronic phosphorus deficiency interferes with normal osteoblast function, particularly at the mineralization front, leading to osteomalacia [12].

Taking these observations together, we postulate that hypophosphatemia of prolonged duration was at least partly responsible for development of osteomalacia in this patient. It is reasonable to postulate that osteoclasts stimulated by PTH and 1,25-(OH)2-D could not sufficiently mobilize enough calcium from unmineralized bone to increase the serum calcium concentration as expected in view of increased intact PTH levels.

References


