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NOTE

Severe Hyperparathyroidism with Hypercalcemia Associated with Chronic Renal Failure at Pre-Dialysis Stage

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Abstract. We report a case of a 23-year-old Japanese woman who had severe hyperparathyroidism associated with chronic renal failure before the start of dialysis treatment. Her chief complaints were swelling and pain in both shoulders. Laboratory examination revealed renal failure (BUN 134 mg/dl, serum Cr 7.3 mg/dl), severe normocytic normochromic anemia (hemoglobin 4.3 g/dl), hypercalcemia (11.8 mg/dl), and hyperphosphatemia (9.7 mg/dl). Serum PTH levels were extremely increased (intact PTH >1,000 pg/ml: normal range 10–50 pg/ml). X-ray examination of the skull and shoulders showed a salt and pepper appearance, and cauliflower-like deformity of the distal end of both clavicles, respectively. Accelerated ectopic calcification was observed in the costal cartilages, internal carotid arteries, and splenic arteries. Ultrasonographic examination revealed enlargement of the four parathyroid glands. Thallium-technetium subtraction scintigraphy of the parathyroid glands showed increased uptake into the upper two. Renal needle biopsy revealed severe impairment of the interstitium and tubules with much milder changes in glomeruli. The etiology of the renal failure could not be identified. Hemodialysis, total parathyroidectomy and auto-transplantation into the forearm were immediately performed. The pathological diagnosis was chief cell hyperplasia of the parathyroid glands. Based on the presence of chronic renal failure, remarkable hyperphosphatemia with mild hypercalcemia, an unusually high level of serum PTH, and accelerated ectopic calcification, the patient was diagnosed to have severe secondary hyperparathyroidism caused by chronic renal failure with major impairment of the renal interstitium and tubules.

Key words: Secondary hyperparathyroidism, Tertiary hyperparathyroidism, Chronic renal failure, Hypercalcemia, Hyperphosphatemia

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SEVERE secondary hyperparathyroidism which cannot be controlled by medication and requires parathyroidectomy is a complication usually observed in patients with long-term dialysis [1, 2]. Here we report an unusual case of a young Japanese woman who had severe secondary hyperparathyroidism associated with chronic renal failure before the initiation of dialysis treatment.

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Case Report

A 23-year-old Japanese woman started to feel pain and swelling in both shoulders in September, 1995. She had difficulty in raising her arms due to the pain in her shoulders. The first doctor suspected that she might have a malignant bone tumor, and referred her to a specialized center for malignant diseases. As the doctor in this center

found that she had chronic renal failure (BUN 134 mg/dl, serum creatinine 7.3 mg/dl) with hypercalcemia (11.8 mg/dl: corrected for serum albumin), hyperphosphatemia (9.7 mg/dl), and severe normocytic normochromic anemia (hemoglobin 4.3 g/dl), he referred her to our hospital for further examination and treatment in February, 1996.

On admission, her height, body weight, and body mass index were 152 cm, 36.5 kg, and 15.8, respectively. Her blood pressure was 112/78 mmHg, and pulse rate was 100/min with a regular rhythm. Her complexion was pale and anemic. An elastic hard tumor as large as 1 cm in diameter was palpable in the upper pole region of each lobe of her thyroid gland. The surface of these tumors was smooth, and showed no adhesion to the surrounding tissues. The distal ends of both clavicles were swollen to approximately 2.5 cm in diameter, and seemed floating in the shoulder joints. Her heart sound had a systolic ejection murmur due to severe anemia. She had no edema in her extremities. Neurological examination was normal.

Laboratory examination revealed renal failure (BUN 159 mg/dl, serum Cr 8.16 mg/dl), severe normocytic normochromic anemia (hemoglobin 4.5 g/dl) with a low level of erythyropoietin (7.1 mU/ml), hyponatremia (131 mEq/l), hypochloremia (88 mEq/l), normokalemia (4.1 mEq/l), hypercalcemia (10.9 mg/dl: corrected for serum albumin), hyperphosphatemia (9.9 mg/dl), an increase in serum alkaline phosphatase (491 mU/ml: normal range 79–224 mU/ml), a marked increase in plasma renin activity (22.1 ng/ml/h) and the plasma aldosterone concentration (> 4,000 pg/ml). Urinalysis showed proteinuria (812 mg/day), glycosuria (673 mg/day) and increased excretion of β2 microglobulin (36 mg/day) and NAG (8.9 U/day). Serum PTH levels were extremely high (intact PTH >1,000 pg/ml: normal range 10–50 pg/ml, and highly sensitive PTH >340,000 pg/ml: normal range 160–520 pg/ml). Serum osteocalcin was also greatly increased (700 ng/ml: normal range 2.5–13 ng/ml). Plasma levels of calcitonin, anterior pituitary hormones, cortisol, catecholamines and gastrin were normal. Blood gas analysis under room air was almost normal (pH 7.45, pCO_2 34.9 torr, pO_2 106.2 torr, HCO_3^- 24.2 mEq/l, anion gap 20 mEq/l). Normalcy of blood gas data and absence of hyperkalemia in spite of severe renal failure appeared to be the result of a counterbalance caused by the presence of extremely enhanced secondary hyperaldosteronism which was rapidly normalized by the initiation of hemodialysis.

X-ray examination of the skull and shoulders showed a salt and pepper appearance, and cauliflower-like deformity of the distal end of both clavicles (Fig. 1a), respectively. The changes observed in the clavicles did not appear typical of osteitis fibrosa. These changes could be the result of repeated and enhanced bone resorption and bone formation. Chest X-ray revealed accelerated calcification of costal cartilages. CT scan of the head and abdomen revealed calcification of the internal carotid arteries and splenic artery, respectively, although there were no detectable calculi in the kidneys. There was no detectable mass in the pituitary gland, thyroid gland, adrenal gland or pancreas, ruling out the possibility of

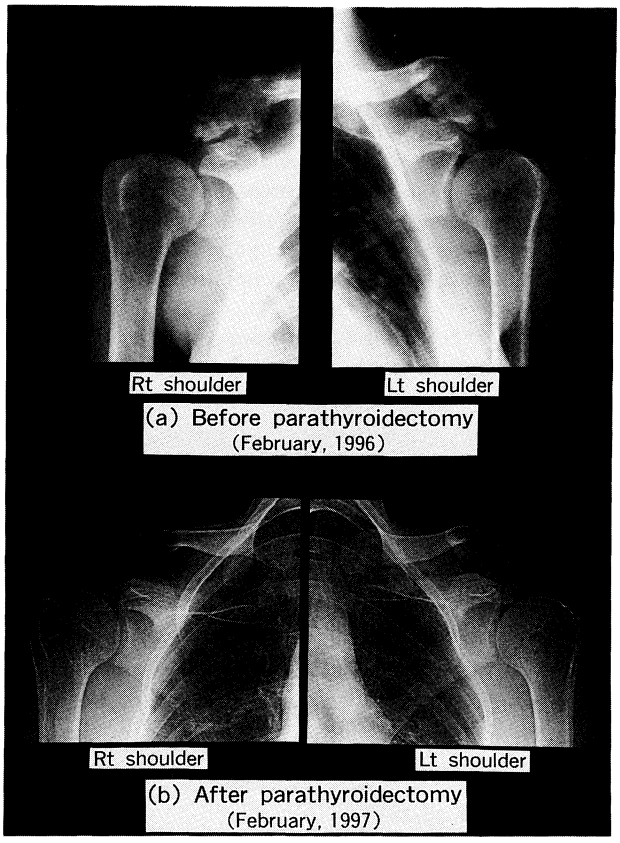
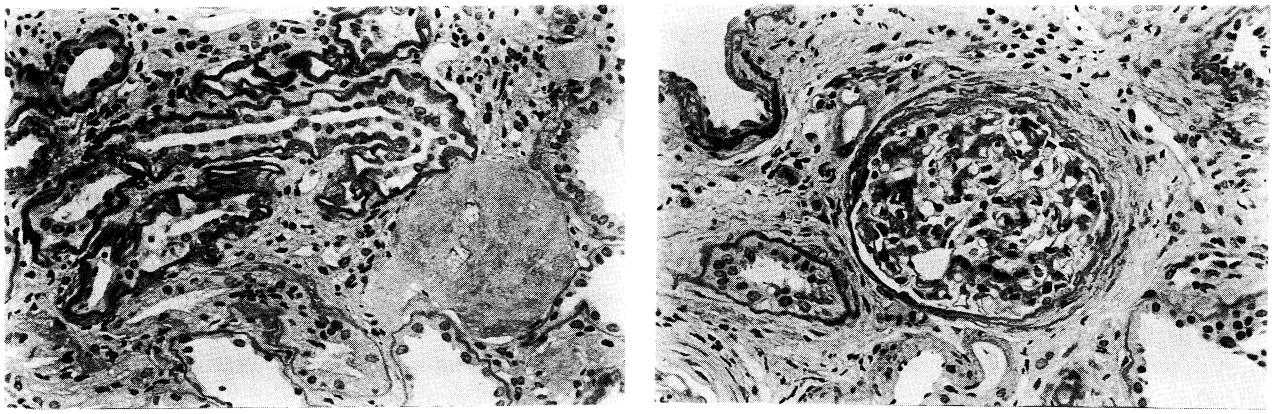


Fig. 1. X-ray examination of the clavicles. (a) Severe destructive changes in the distal end of the clavicles before parathyroidectomy, and (b) dramatic recovery after parathyroidectomy.

multiple endocrine neoplasia, as also indicated by the hormonal data presented above. Bone scintigraphy revealed extremely increased uptake of ^{99m}Tc-phosphorus into the entire skeleton. Ultrasonographic examination revealed four tumors in the frontal neck (upper left: 25.0 mm × 11.2 mm, upper right: 31.3 mm × 11.9 mm, lower left: 13.8 mm × 9.4 mm, lower right: 5.6 mm × 3.5 mm). Thallium-technetium subtraction scintigraphy of the parathyroid glands showed increased uptake into the area corresponding to the upper two parathyroid glands. Pathological examination of the renal tissue obtained by percutaneous renal needle biopsy revealed severe changes in the interstitium and tubules such as tubular atrophy, interstitial fibrosis, infiltration of inflammatory cells, multi-layered changes in the tubular basement membrane, and basophilic calcium-rich liquid retention in the tubules (Fig. 2a). In contrast, changes observed in the glomeruli were much milder, and the collapse of glomeruli was only focal. The surviving glomeruli retained almost a normal structure except for periglomerular fibrosis (Fig. 2b), indicating the unlikelihood of pre-exising glomerular diseases.

The patient received hemodialysis to lower serum calcium and phosphate levels, and blood transfusion for anemia due to chronic renal failure immediately after admission. After the start of hemodialysis, serum calcium and phosphate rapidly returned to the normal range. In addition, PRA, and PAC were dramatically decreased to almost normal levels, although PAC tended to be high, most likely because of chronic renal failure. After the blood transfusion, supplementation of erythropoietin (4,500 IU/week) was also instituted. The hemoglobin level then gradually recovered to 7.8–8.7 g/dl. For the treatment of severe hyperparathyroidism, the four parathyroid glands were removed and a portion of one gland was implanted into a forearm muscle. Macroscopically, the dimensions of the excised glands were 2.3 × 1.0 × 0.5 cm (upper right gland), 3.0 × 2.5 × 1.0 cm (upper left gland), 1.5 × 1.0 × 0.7 cm (lower right gland), and 1.3 × 1.0 × 0.5 cm (lower left gland). Microscopic examination of excised tissue revealed chief cell hyperplasia of the four parathyroid glands, with the right inferior gland having an adenoma-like portion in a fibrous capsule.

Immediately after the operation, intact PTH and calcium levels decreased to 6 pg/ml, and 5.7 mg/dl, respectively. The patient began to take vitamin D_3 (alfacalcidol, 1–4 μg/day) and calcium lactate (6 g/day) soon after the operation, and did not suffer from tetany all through the post-operation period. After the success of the operation, hemodialysis was temporarily withheld to see the effect of dramatically decreased levels of PTH and calcium on the natural course of renal function. BUN and creatinine gradually increased during a one-month observation period from 21 mg/dl, and 3.3 mg/dl (right after the hemodialysis) to 173 mg/dl, and 11.8 mg/dl, respectively. As there was no improvement in renal function after the parathyroidectomy, hemodialysis was restarted and the patient was on maintenance hemodialysis (three



a b

Fig. 2. Microscopic examination of the renal tissue. (a) Severe changes in the tubules and interstitium, and (b) milder changes in the glomerulus (Stained with PAS, original magnification × 200).

times a week) since then. X-ray examination of the skull and shoulders showed dramatic improvement (Fig. 1b) at 10 months after the operation. In March, 1998 she received a kidney transplantation from her mother.

Discussion

The most important and difficult issue in the present case was whether the hyperparathyroidism was primary or secondary to chronic renal failure. Since the patient had not been under medical attention until the present event, it was impossible to know the chronological relationship between renal failure and hyperparathyroidism. Epidemiologically, it is very rare for patients with chronic renal failure to have severe secondary hyperparathyroidism that requires parathyroidectomy before the start of dialysis treatment [1, 2]. Furthermore, the major site of renal impairment in the present case was the interstitium and tubules, which is compatible with secondary changes observed in hypercalcemic nephropathy [3]. In view of these facts, we at first believed that the patient had primary hyperparathyroidism first, which then caused renal interstititial and tubular damage leading to chronic renal failure. The presence of an extremely high level of intact PTH, severe bone and kidney diseases appeared to be compatible with a severe form of primary hyperparathyroidism [4–6].

Nevertheless, based on the literature, the highest level of serum calcium (11.8 mg/d*l*) documented in the present case was not high enough to cause hypercalcemic nephropathy leading to renal failure [7–9]. In addition, the absence of nephrolithiasis, the presence of a high level of serum phosphate (9.9 mg/d*l*) as compared with mild hypercalcemia, accelerated ectopic calcification which is common in secondary hyperparathyroidism, severe normocytic anemia with a low level of erythropoietin, and severe hyperplastic changes in all four parathyroid glands favor concluding that the patient initially had chronic renal failure which then induced severe secondary hyperparathyroidism. The presence of hypercalcemia supports the view that the patient might have developed tertiary hyperparathyroidism [10–12].

As mentioned above, the hyperparathyroidism observed in the present case most likely was secondary to chronic renal failure. The first unsolved problem in this diagnosis is the cause of renal failure. According to the renal pathological findings obtained by the needle biopsy, the major site of renal impairment was not in the glomeruli, but in the interstitium and tubules. There seemed to be no past history related to the renal interstitial and/or tubular diseases, although this is based not on documented records but only on what the patient remembers. The second unsolved problem in this diagnosis is why the patient developed such severe secondary or tertiary hyperparathyroidism before the start of dialysis treatment. Considering that the severe secondary or tertiary hyperparathyroidism is typically a complication in patients on long-term dialysis, the severity of the hyperparathyroidism in this patient is unusual. The patient may have a long history of chronic renal failure which induced secondary hyperparathyroidism. Since the patient had not been examined or treated at all as a patient with chronic renal failure, phosphate retention was left untreated, and serum calcium levels may have been very low in the past, with no calcium or vitamin D_3 supplementation. All these conditions may have further worsened the secondary hyperparathyroidism leading to the severe hyperplasia of all four parathyroid glands. Furthermore, the adenoma-like portion with a fibrous capsule found in the right inferior gland may be an incidental complication of a solitary adenoma producing PTH autonomously.

In summary, we reported an unusual case of severe secondary hyperparathyroidism associated with chronic renal failure before the start of dialysis treatment. Although the chronological relationship of renal failure and hyperparathyroidism was not documented, and the cause of renal failure was not identified, the absence of nephrolithiasis, the presence of severe hyperphosphatemia, severe anemia with low erythyropoietin, ectopic calcification and hyperplastic changes in all four parathyroid glands supported the diagnosis of severe secondary or tertiary hyperparathyroidism due to chronic renal failure.

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