Three Cases of Primary Hyperparathyroidism Associated with Nonmedullary Thyroid Carcinoma

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Nonmedullary thyroid carcinoma was diagnosed in three of nine cases of primary hyperparathyroidism. In all three cases, diagnosis of primary hyperparathyroidism was made before that of thyroid carcinoma. In the first case, follicular carcinoma was incidentally detected during parathyroidectomy. In the second case, thyroid tumor was discovered during imaging studies for hyperparathyroidism. Papillary carcinoma and ectopic parathyroid was diagnosed postoperatively. In the third case, a thyroid lesion had been mistaken for a putative parathyroid lesion, but the diagnosis of papillary carcinoma was obtained. These cases suggest that preoperative examination for hyperparathyroidism should be carefully evaluated, considering possible concomitant thyroid lesions.

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Introduction

The association of medullary thyroid carcinoma and primary hyperparathyroidism is known as multiple endocrine neoplasia type 2A (MEN2A). Ogburn and Black (1) first reported four cases of primary hyperparathyroidism associated with nonmedullary thyroid carcinoma. There have been several other reports discussing the coexistence of these two diseases (2-12), suggesting that the association is not coincidental. Here, we describe three cases of coexisting primary hyperparathyroidism and nonmedullary thyroid carcinoma.

Materials and Methods

Urinary cyclic AMP (cAMP) was measured with commercially available kit (cAMP Kit “Yamasa”, Yamasa Syoyu, Tokyo). Plasma parathyroid hormone (PTH) levels were measured with commercially available kits (C-terminal of PTH (PTH-C): PTH-C “Eiken”, Eiken Kagaku, Tokyo, intact PTH: Allegro Intact PTH Kit, Nichols Institute, and high sensitivity mid-region PTH (HS-PTH): PTH Kit “Yamasa”, with normal range less than 0.6 ng/ml, 23–73 pg/ml and 230–560 pg/ml, respectively). Serum thyroid-stimulating hormone (TSH), free T3 (FT3), cortisol, calcitonin, gastrin were measured with commercially available radioimmunoassay (RIA) kits, respectively (normal range for each, TSH: <10 µU/ml, FT3: 2.6–5.0 pg/ml, cortisol: 5.6–21.3 µg/dl, calcitonin: <170 pg/ml, gastrin: 37–172 pg/ml). Serum adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), osteocalcin were measured with commercially available immunoradiometric assay (IRMA) kits, respectively (normal range for each, ACTH: <60 pg/ml, GH: <5 ng/ml, PRL: 1.4–14.6 ng/ml, LH: 0.4–87.5 µIU/ml, FSH: 1.0–24.0 µIU/ml, osteocalcin: 2.3–9.9 ng/ml).

Case Reports

**Case 1**

A 26-year-old pregnant woman visited our hospital in October 1986. She was referred to our division for further evaluation of hypercalcemia in March 1987. She had been found to have a hydatidiform mole and had it removed in December 1985. Her family history was not contributory. She did not have struma nor surface lymph node swellings. Serum calcium was elevated (6.4 mEq/l), but serum phosphate, creatinine and blood urea nitrogen were normal (2.6 mg/dl, 0.8 mg/dl and 8 mg/dl, respectively). Urinalysis was normal. Total serum cAMP was
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Plasma PTH-C was elevated (0.8 ng/ml). Renal tubular reabsorption of phosphate (TRP) was low (0.81). Serum concentration of ACTH, GH, LH, FSH, PRL, cortisol were all within normal limit for the pregnant woman (37 pg/ml, 6 ng/ml, 204 μIU/ml, 6 μIU/ml, 372 ng/ml, and 32.4 μg/dl, respectively). Serum calcitonin and gastrin were also normal (11 pg/ml and 54 pg/ml, respectively). X-ray showed diffuse thinning and partial disappearance of the dura of alveolar bone. Skull appearance was normal. Microdensitometry (MD) of phalangeal radiographs revealed no definite decalcification. Bone scintigrams were normal. Contrast enhanced image of cervical computed tomography (CT) manifested a small round mass with no enhancement posteromedial to the right lower pole of the thyroid gland (Fig. 1). Thallium-technetium subtraction scintigraphy showed marked thallium accumulation in the same portion. These findings indicated a diagnosis of primary hyperparathyroidism. Hypercalcemia could not be well controlled only by medical treatment and actually signs of bone loss were noted. Considering the effects of hypercalcemia and PTH excess on the fetus, parathyroidectomy was performed in the 25th week of pregnancy. In the exploration of the right lobe, a parathyroid tumor (900 mg) was detected on the posterior surface of the lower pole and resected. The perioperative diagnosis based on frozen specimen of the tumor was parathyroid adenoma, therefore the other parathyroid glands were left intact. The possible diagnosis of parathyroid adenoma was obtained, although the possibility of hyperplasia could not be totally excluded since the histopathology showed the dominant proliferation of oxyphilic cuboidal cells. In addition, another dark gray nodule of 5 mm size was palpated in the parenchyma of the lower pole of the right lobe and resected, which weighed 400 mg. It was proven to be follicular carcinoma. Left lobe exploration revealed no lesions. Postoperatively TRP was normalized (0.91), but total urinary cAMP was low (1.05 nmol/dl GF), plasma PTH-C was normal (0.4 ng/ml). Serum calcium level was low normal (between 4.0 and 4.4 mEq/l) without replacement. Serum calcium, plasma HS-PTH and intact PTH remained normal. No recurrence of thyroid and parathyroid lesion have been found on cervical scintigrams and ultrasonography seven years after the operation.

Case 2

A 76-year-old woman was admitted to our hospital for further examination of hypercalcemia in April 1989. She had a history of hypertension and ischemic heart disease. Her sister had thyroid cancer, and her brother had lung cancer. Physical examination revealed an elastic hard goiter. There were no neurological abnormalities. Serum calcium was elevated (5.6 mEq/l), but serum phosphate, creatinine and blood urea nitrogen were normal (3.7 mg/dl, 0.8 mg/dl and 5 mg/dl, respectively). Serum alkaline phosphatase, plasma HS-PTH, and total urinary cAMP were elevated (180 IU/l, 620 pg/ml, and 6.0 nmol/dl GF, respectively). TRP was in the lower value of normal (0.86). Serum calcitonin and gastrin were within the normal limits. Serum TSH, free T3 were normal (3 μIU/ml and 3.7 pg/ml, respectively). Bone scintigrams indicated slightly enhanced bone turnover. Cervical ultrasonography and CT revealed multiple tumors in the thyroid gland. Thallium-technetium subtraction scintigraphy showed no significant lesion. Contrast enhanced image of chest CT manifested a small poorly enhanced nodule on the posterior surface of the ascending aorta (Fig. 2), which was considered to be an ectopic parathyroid gland. Primary hyperparathyroidism possibly due to an ectopic gland was diagnosed, although it has not been definitely confirmed. Fine needle aspiration of the thyroid did not suggest a malignancy. However the tumor in the left thyroid lobe became...
gradually enlarged and thyroidectomy was performed. The tumor was 3x4 cm in size, and partly invaded trachea. The left lobe and the isthmus of the thyroid gland were resected. Deep cervical lymph nodes were also resected, which had no metastatic lesions. Histological examination indicated a diagnosis of papillary carcinoma and chronic thyroiditis. Serum calcium, alkaline phosphatase, and plasma HS-PTH remained elevated, averaging 5.6 mEq/l, 169 IU/l and 915 pg/dl, respectively.

Case 3

A 59-year-old woman had suffered from recurrent gastric ulcer since 1983, and hypertension since 1986. In April 1990, she was found to have hypercalcemia and admitted to our division. She complained of insomnia. Her family history was not contributory. Struma was not palpable. There were no neurological abnormalities. On laboratory tests, serum calcium was elevated (5.4 mEq/l), but serum phosphate, creatinine and blood urea nitrogen were normal (2.9 mg/dl, 0.8 mg/dl and 17 mg/dl, respectively). Urinalysis was normal. Plasma intact PTH, HS-PTH, osteocalcin were all elevated (124 pg/ml, 1,690 pg/ml, and 13.4 ng/ml, respectively). TRP was slightly low (0.83). There were no bone changes in mandible, hands, or lumbar vertebrae. Bone mineral density of the lumbar spine was slightly decreased, which was 112 mg/cm$^3$ at L2, 107 mg/cm$^3$ at L3 by quantitative CT (QCT), and 0.792 g/cm$^3$ at L2–L4 measured by dual energy X-ray absorptiometry (DEXA). Cervical CT manifested multiple low density tumors in bilateral lobes of the thyroid gland (Fig. 3). Thallium-technetium subtraction scintigraphy showed the thallium accumulation in the left middle lobe and the right lower pole of the thyroid gland (Fig. 4). Primary hyperparathyroidism was diagnosed and parathyroid lesion was expected to exist near the middle portion of the left thyroid lobe. Parathyroidectomy was performed. A thyroid cyst was found in the upper pole of the right lobe. Another tumor of 15 mm size was found below the right lower pole and resected, which weighed 500 mg. The histological examination indicated parathyroid adenoma consisting of water clear cells. In the exploration of the left lobe, two elastic hard tumors of 5 mm and 10 mm size were discovered in the middle portion. Left thyroidectomy and right upper thyroidectomy were performed. Pathological examination of the lesions showed a diagnosis of papillary carcinoma. Postoperatively, serum calcium became low normal (4.4 mEq/l), and plasma intact PTH became within the normal limit (37 pg/ml). Serum calcium has been within the normal limit without replacement. Postoperative hypothyroidism was treated with levothyroxine (75 μg/day). There has been no evidence of recurrent thyroid or parathyroid tumors for four years after the operation.
We treated a total of nine cases with primary hyperparathyroidism over a 5-year period, and nonmedullary thyroid carcinoma was found in the three cases described above (Table 1).

### Discussion

It has been reported that the association of primary hyperparathyroidism and nonmedullary thyroid carcinoma is not rare (2–12). We treated three cases of nonmedullary thyroid carcinoma in a total of nine cases with primary hyperparathyroidism during five years. Attie and Vardhan (12) estimated the incidence of this association was 3.9% (249 out of 6,391). Fujimoto (6) reported that it was 12.3% (9 out of 73) in Japan. Lever et al (9) indicated the prevalence of macroscopic nonmedullary thyroid carcinoma in primary hyperparathyroidism was significantly higher than that of an autopsy group (5.6% vs 0%). As the common etiology of these diseases, several candidates have been suggested, such as radiation history of the head and neck, calcium as a goitrogen, and common genetic factor (2, 5, 13). Low-dose radiation therapy of the head and neck, especially in childhood or adolescence, is well known to induce thyroid and parathyroid tumors (7, 8, 10), but most of the associated cases in the previous reports, including the present three cases, have no history of prior radiotherapy. Although calcium has been reported earlier to be a goitrogen (14), interfering with the uptake of iodine to the thyroid gland (15), there has been no evidence that hypercalcemia causes thyroid neoplasm. As for genetic factors, common oncogenes in both diseases have not been reported to date. It cannot be excluded, however, that the association of the two diseases is coincidental, considering the high frequency of microscopic thyroid carcinoma.

In the present three cases, primary hyperparathyroidism was diagnosed before thyroid malignancy was identified, and it was difficult to locate the parathyroid lesions with the combination of several imaging studies. Although the parathyroid tumor was successfully located in case 1, ectopic parathyroid gland in the mediastinum was suggested only by chest CT in case 2. In addition, the thyroid lesion was mistaken for a parathyroid lesion in case 3. These findings suggest that preoperative examination for hyperparathyroidism should be carefully evaluated considering the possibility of concomitant thyroid lesions.

In summary, we report three cases of primary hyperparathyroidism associated with nonmedullary thyroid carcinoma. These cases suggest that the association of the two disorders may reflect their common etiology or etiological relationship. They also indicate that preoperative location of parathyroid lesions should be carefully made, considering possible concomitant thyroid lesions.

### References