CASE REPORT

Synchronous Parathyroid and Papillary Thyroid Carcinoma

Shi-Dou Lin, Shih-Te Tu*, Shang-Ren Hsu, Julia Heui-Mei Chang¹, Kuang-Tao Yang, Li-Heng Yang

Division of Endocrinology and Metabolism, Department of Internal Medicine,¹ Department of Pathology,² Department of Nuclear Medicine, and ³ Division of General Surgery, Department of Surgery, Changhua Christian Hospital, Changhua, Taiwan, R.O.C.

Concomitant thyroid disease is not unusual among patients with primary hyperparathyroidism. However, the simultaneous occurrence of parathyroid and thyroid carcinoma is extremely rare. We report a 38-year-old man with primary hyperparathyroidism who presented with osteitis fibrosa cystica complicated with pathologic femoral neck fracture. Preoperative investigation for exclusion of multiple endocrine neoplasia did not find evidence of medullary thyroid carcinoma or pheochromocytoma, but imaging studies revealed the presence of nodules in the right lobe and a parathyroid lesion over the left inferior pole of the thyroid gland. Total thyroidectomy, left parathyroidectomy, and bipolar hemiarthroplasty of the left hip were then performed simultaneously. The resected specimens were pathologically identified as papillary thyroid carcinoma and parathyroid carcinoma, respectively. After the operation,¹³¹I ablation therapy was administered at a dose of 120 mCi. Additional doses of 30 mCi were given yearly as serum thyroglobulin level became elevated. Serum calcium level remained normal during yearly follow-up. Although parathyroid carcinoma is an uncommon cause of parathyroid hormone-dependent hypercalcemia, it should nonetheless be given due consideration because its surgical approach differs from that of parathyroid adenoma. As the coexistence of parathyroid and non-medullary thyroid carcinoma has previously been reported, the possibility of both malignancies must also be considered in the setting of primary hyperparathyroidism with thyroid nodules. If confirmed with preoperative parathyroid scintigraphic and other laboratory studies, an optimal outcome may be achieved with complete resection of both tumors at the time of initial operation, followed by adjunctive therapy. [J Chin Med Assoc 2005;68(2):87–91]

Key Words: hypercalcemia, papillary thyroid carcinoma, parathyroid carcinoma, parathyroidectomy, thyroidectomy

Introduction

Since the introduction of routine serum calcium measurement in the 1970s, primary hyperparathyroidism has become one of the most commonly diagnosed endocrine diseases worldwide. Concomitant thyroid disease is not unusual among patients with primary hyperparathyroidism. From published studies, the coexistence of non-medullary thyroid cancer is found in 2.4–3.7% of patients operated on for primary hyperparathyroidism. This high incidence of thyroid cancer, which is greater than that in the general population (< 0.01%), signifies the need for heightened clinical vigilance. Conversely, parathyroid carcinoma is rare and accounts for less than 1% of patients with primary hyperparathyroidism. PubMed and MEDLINE searches yielded only 3 previous reports of synchronous parathyroid and non-medullary thyroid carcinoma. This report is the first in the Chinese medical literature of a case of hyperfunctioning parathyroid carcinoma and concomitant papillary thyroid carcinoma.

Case Report

A 38-year-old man with a history of renal stones requiring lithotripsy 6 years previously was referred to...
our orthopedic clinic because of limping and weakness in both hips. Multiple bone lesions were identified on radiographic studies and bone scan. Biopsy of the pubic bone was pathologically consistent with osteitis fibrosa cystica. Serum biochemistry was significant for hypercalcemia (4.05 mmol/L; normal range, 2.2–2.6 mmol/L). The level of intact parathyroid hormone (PTH) was elevated (107 pmol/L; normal range, 1.8–7.3 pmol/L), whereas the level of thyroid-stimulating hormone was within normal limits (2 mIU/L). Ultrasound demonstrated 2 enlarged parathyroid glands adjoining the right thyroid lobe, and a 4 × 3 cm mass over the left lower thyroid pole. Fine-needle aspiration cytology of this mass revealed marked nuclear pleomorphism with prominent nucleoli, suggesting carcinoma of the parathyroid gland.

A few days later, the patient was admitted to hospital for left femoral neck fracture after falling off a motorcycle. Preoperative screening for evidence of multiple endocrine neoplasia (MEN) showed normal serum levels of calcitonin and carcinoembryonic antigen, and urinary catecholamine concentrations were all within the reference range (Table 1). $^{201}$Tl–$^{99m}$Tc subtraction scintigraphy disclosed a hot spot over the inferior-lateral aspect of the left thyroid gland, and some residual $^{201}$Tl activity over the superior-medial aspect of the right thyroid gland and superior-lateral aspect of the left thyroid gland. In addition, there was a cold area over the superior pole of the right thyroid gland in the $^{99m}$Tc scan when compared with the $^{201}$Tl scan (Figure 1). Computerized tomography (CT) scan of the neck confirmed the presence of a left parathyroid lesion, but also incidentally revealed a calcified lesion in the right thyroid lobe (Figure 2).

During the operation, because the concurrence of both papillary thyroid and parathyroid carcinoma was confirmed by frozen section, it was decided that the

<table>
<thead>
<tr>
<th>Serum parameters</th>
<th>Serum or urinary level</th>
<th>Normal reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin, pmol/L</td>
<td>2.2</td>
<td>&lt; 2.9</td>
</tr>
<tr>
<td>CEA, μg/L</td>
<td>0.6</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.3</td>
<td>3.9–6.1</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>12,683.8 †</td>
<td>894.9–6,212.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary parameters</th>
<th>Serum or urinary level</th>
<th>Normal reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine, mmol/d</td>
<td>177.8</td>
<td>327–2,943</td>
</tr>
<tr>
<td>Epinephrine, mmol/d</td>
<td>43</td>
<td>&lt; 122.3</td>
</tr>
<tr>
<td>Norepinephrine, mmol/d</td>
<td>86.4</td>
<td>65.6–505.3</td>
</tr>
<tr>
<td>VMA, mmol/d</td>
<td>185.8 †</td>
<td>5.9–64.9</td>
</tr>
</tbody>
</table>

$\text{CEA} = \text{carcinoembryonic antigen; VMA} = \text{vanillylmandelic acid; † = elevated.}$

Figure 1. (A) $^{201}$Tl, (B) $^{99m}$Tc, and (C) subtraction scans demonstrating intense uptake in the left lower thyroid pole. Two areas (the left and right upper thyroid gland) had residual thallium activity after subtraction.

Figure 2. A large mass was identified in the left lower thyroid pole on computerized tomography scan of the neck. A calcified lesion was identified in the right thyroid gland.
surgical approach should comprise total thyroidectomy and left parathyroidectomy. Bipolar arthroplasty was also conducted for the left femoral neck fracture. Histologic examination of the resected specimens subsequently confirmed the presence of both parathyroid carcinoma (Figure 3) and papillary thyroid carcinoma (Figure 4), with metastasis demonstrated in 1 lymph node. The postoperative course was uneventful, except for transient hypocalcemia. Three weeks later, the patient received $^{131}$I therapy at an ablative dose of 120 mCi. Thereafter, he was maintained on thyroid hormone replacement therapy and calcium supplementation. Subsequent $^{131}$I therapy at 30 mCi was administered yearly, as the serum thyroglobulin level became elevated after thyroxine withdrawal. Serum levels of calcium and PTH remained normal during yearly follow-up for more than 6 years.

**Discussion**

Although parathyroid carcinoma is an uncommon cause of primary hyperparathyroidism, its incidence may increase in line with an increased incidence of primary hyperparathyroidism. Importantly, parathyroid carcinoma should be considered in the differential diagnosis of PTH-dependent hypercalcemia, as morbidity and mortality associated with this diagnosis are substantial, and optimal outcomes are associated with complete tumor resection (i.e., en bloc removal of the lesion together with the ipsilateral thyroid lobe and isthmus, and removal of any contiguous tissues to which the tumor adheres) at the time of initial operation. All too often, the diagnosis is made retrospectively when hypercalcemia recurs because of local tumor spread or distant metastases. The average time between surgery and first recurrence is approximately 3 years. Once the tumor has recurred, complete cure is unlikely. There are several presenting features of primary hyperparathyroidism that should suggest a malignant rather than benign course. A summary of features that might lead one to suspect parathyroid carcinoma is shown in Table 2. The presence of some of these features in our patient, in particular the excessively high serum calcium, is consistent with the diagnosis of parathyroid carcinoma.

### Table 2. Features suggesting parathyroid carcinoma in primary hyperparathyroidism

- Hypercalcemia: serum calcium > 3.5 mmol/L
- Associated with other signs and symptoms of hypercalcemia
- High serum PTH level: > 3–10 times above the upper limit of normal
- High serum alkaline phosphatase level: above the upper limit of normal
- Elevated levels of $\alpha$- and $\beta$-subunits of hCG
- Palpable neck mass
- Recurrent laryngeal nerve palsy in patients without previous neck surgery
- Simultaneous renal and overt skeletal involvement
- Coexisting with recurrent severe pancreatitis, peptic ulcer disease, and anemia

$hCG = human$ chorionic gonadotropin; PTH = parathyroid hormone. Adapted from reference 4.
high serum calcium and PTH levels, should alert one to the possibility of parathyroid carcinoma. Benign primary hyperparathyroidism usually presents with low serum levels of PTH and calcium, but it should be noted that the distinction between benign and malignant disease may be difficult on clinical grounds in some patients with benign primary hyperparathyroidism who present with high serum levels of PTH and calcium. It is preferable to have a high index of suspicion for parathyroid carcinoma when the above features are present, rather than to miss the opportunity for surgical cure by failing to consider such carcinoma in the differential diagnosis.

In more than 80% of cases, primary hyperparathyroidism is attributable to a solitary parathyroid adenoma. However, up to 10% of cases may result from a hereditary disorder, such as MEN type 1 and type 2A. MEN1 (typically with pituitary, parathyroid and pancreatic tumors) represents 2–4% of all cases of primary hyperparathyroidism, and patients tend to present at a younger age with more severe hypercalcemia than those with sporadic disease, which typically manifests at about 55 years of age. Although our patient was relatively young and had severe hypercalcemia, he has had no evidence of MEN1. His sella turcica appeared of normal size radiographically. Abdominal CT images revealed neither pancreatic nor adrenal tumors. His elevated serum fasting insulin level (12,684 pmol/L) might reflect underlying insulin resistance as he was overweight (body mass index = 25.6 kg/m²).

Primary hyperparathyroidism occurs less commonly in patients with MEN2A (typically with medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism). However, pheochromocytoma occurs in 50% of these patients, which exposes them to the risk of intraoperative hypertensive crisis if alpha-adrenergic blockade is not achieved preoperatively. As for medullary thyroid carcinoma, its exclusion was warranted in this patient because of the thyroid nodule identified via neck CT scan. The possibility of MEN2A warranted in this patient because of the thyroid nodule was low because of the normal serum calcitonin level, although pheochromocytoma and, therefore, of MEN type 2A was unlikely.

There are false-positive and false-negative results of 201Tl and 99mTc subtraction imaging. False-negative results are attributed to the small size of many lesions, abnormal 99mTc uptake by the thyroid gland, attenuation of counts from ectopic glands located deep in the neck or mediastinum, technical factors such as patient movement, and abnormal 99mTc uptake by a parathyroid adenoma. Various lesions may accumulate 201Tl but not 99mTc, resulting in a false-positive subtraction scan. These lesions include the following: papillary, follicular, and anaplastic carcinomas of the thyroid; chronic lymphocytic thyroiditis; benign adenoma and nodules of the thyroid; sarcoïd lymph node; Hodgkin’s lymphoma; and metastatic lymph nodes. The subtraction image of this patient, besides the prominent left parathyroid lesion, also showed 2 areas of residual 201Tl activity. The cold area in the 99mTc scan compared with the 201Tl scan might account for the right residual activity in the subtraction scan. It might represent uptake by the papillary thyroid carcinoma. The left area of residual 201Tl activity might have resulted from patient movement during the procedure, since the subtraction image showed asymmetry of the salivary glands.

There have been only 3 previous case reports of synchronous parathyroid carcinoma and non-medullary thyroid carcinoma. In 1979, a Japanese article described a patient with hyperfunctioning parathyroid carcinoma combined with papillary thyroid carcinoma. In another case, occult parathyroid carcinoma was discovered incidentally after a patient had undergone thyroidectomy for papillary thyroid carcinoma and Hashimoto’s thyroiditis. The third case of hyperfunctioning parathyroid carcinoma and concomitant thyroid carcinoma, without a previous history of neck irradiation, was reported in the English literature. The present case, then, would be the fourth. These cases illustrate the fact that concomitant hyperfunctioning parathyroid carcinoma and non-medullary thyroid carcinoma should not be overlooked, despite the rarity of such occurrence.

In the diagnosis of primary hyperparathyroidism, the association between malignant thyroid disease (medullary or non-medullary thyroid cancer) and neoplastic parathyroid tissue must be given due consideration. Besides the investigations of MEN, an integrated approach using a combination of parathyroid scan, neck ultrasound, and other imaging modalities,
may be required. As prognosis depends largely on successful resection of all malignant tumors at the time of initial operation, any thyroid or parathyroid lesion observed via any imaging study must be taken seriously, even if different imaging studies show discrepant results, as in our case. Failing to consider the malignant potential of all lesions may lead to inadequate surgical resection and, therefore, to a suboptimal outcome.

References


