CASE REPORT

Concurrent Papillary Thyroid Cancer with Pituitary ACTH-secreting Tumor

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Concomitant thyroid cancer with pituitary tumor is uncommon. This study reports a case of advanced papillary thyroid carcinoma with pituitary adrenocorticotropic hormone (ACTH)-secreting tumor. A 58-year-old male patient had thyroid cancer in 1991 and presented with headache caused by pituitary tumor with apoplexy in 1993. Due to hypopituitarism, the patient underwent radioactive iodide (^{131}I) for detection and treatment of metastatic thyroid cancer after the use of recombinant human thyroid-stimulating hormone (rhTSH) in 2000. During follow-up for thyroid cancer, ^{201}thallium scan proved to be an effective tool for detecting metastatic thyroid cancer in the patient without pituitary TSH reserve. Pituitary ACTH-secreting tumor was confirmed in 2001 based on the high serum ACTH level and positive immunohistochemical stain for ACTH. The patient had no Cushingoid features. Moreover, serum ACTH levels were 337 and 232 pg/mL with normal serum cortisol and urine-free cortisol. Although the patient underwent three operations and a total of 370 mCi ^{131}I therapy for recurrent thyroid cancer, the cancer continued to progress. Finally, the patient died of pneumonia with septic shock 12 years after the diagnosis of thyroid cancer. [*J Formos Med Assoc* 2007;106(4):330–335]

Key Words: papillary thyroid carcinoma, pituitary ACTH-secreting tumor, preclinical Cushing's disease, silent corticotroph adenoma, ^{201}thallium scan

Clinical outcome in patients with differentiated thyroid carcinoma is often favorable.[1,2] Papillary thyroid cancer (PTC) is frequently detected by radioactive iodide (^{131}I) scan. The uptake of ^{131}I is thyroid-stimulating hormone (TSH)-dependent. The coexistent hypopituitarism makes ^{131}I treatment more difficult. Among methods of diagnosing metastatic thyroid cancer, ^{201}thallium (^{201}Tl) has been used for detection of locally metastatic thyroid cancer during thyroxine suppressive therapy instead of ^{131}I therapy.[3] This study presents the case of a 58-year-old man with advanced PTC and pituitary adenoma. The role of ^{201}Tl scan in diagnosing metastatic thyroid cancer in hypopituitarism patients is discussed.

Case Report

A 58-year-old male farmer presented to our clinic in 1991 with a firm neck mass that had been present for half a year. Thyroid ultrasonography revealed a 2.7× 2.4 × 2.0 cm right thyroid nodule and fine needle aspiration cytology (FNAC) revealed PTC. He underwent near total thyroidectomy and the pathology result was PTC. The

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patient underwent 100 mCi ^{131}I ablation therapy in 1991 and serum thyroglobulin (Tg) level remained undetectable thereafter under thyroxine suppressive therapy. He had regular follow-up at the endocrine clinic. In 1993, headache and blurred vision occurred and brain magnetic resonance imaging (MRI) and angiography revealed pituitary tumor with suprasellar extension. Serum level of pituitary hormones was low, including luteinizing hormone (LH) < 1 mIU/mL (normal range, 1.9–17.9), follicle-stimulating hormone (FSH) 2.64 mIU/mL (normal range, 3.6–23.7), prolactin (PRL) < 0.1 ng/mL (normal range, 3–14), testosterone < 0.1 ng/mL (normal range, 2.79–8.76), growth hormone (GH) 0.18 ng/mL (normal range, < 5), adrenocorticotropic hormone (ACTH) 13.3 pg/mL (normal range, 9–52), TSH 0.22 μIU/mL (normal range, 0.36–3.25), and cortisol 0.74 μg/dL (normal range, 9–23). The patient was administered cortisone acetate for glucocorticoid replacement thereafter. These hormone assays were determined by radioimmunoassay (RIA) methods. Transsphenoid surgery was conducted for pituitary tumor and revealed pituitary apoplexy (Figure 1). Postoperative thyrotropin-releasing hormone (TRH) stimulation, insulin-induced hypoglycemia, and gonadotropin-releasing hormone (GnRH) stimulation tests revealed low pituitary reserve of GH, ACTH, FSH, LH, PRL, and TSH, which was compatible with pituitary apoplexy with hypopituitarism.

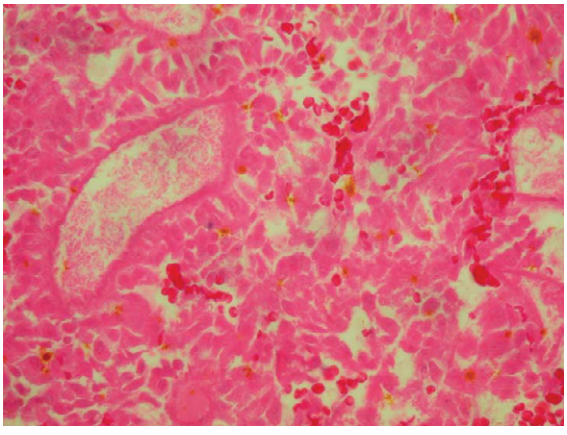

Figure 1. Microscopic examination of the pituitary tumor shows necrotic cells arranged in trabecullar structures (hematoxylin and eosin, 400×).

Because of hypopituitarism and progressively increasing serum Tg level, from less than 1 ng/mL to 7.2 ng/mL in 1999 under thyroxine therapy, the patient underwent ^{201}Tl scan instead of ^{131}I scan, which revealed avid lesions in the neck and anterior superior mediastinal regions. Thyroid ultrasonography was performed and demonstrated a 2.2 × 1.6 × 1.3 cm nodule with cystic component in the left posterior part of the neck. FNAC of the nodule displayed recurrent PTC. The neck nodule was excised and the pathology showed metastatic PTC. However, serum Tg remained high in 2000. The patient was administered 1.1 mg rhTSH for 2 consecutive days and then underwent 100 mCi ^{131}I therapeutic scan, which revealed avid ^{131}I uptake lesions in the upper mediastinum (Figure 2). Nevertheless, the serum Tg level was 92.4 ng/mL 2 days following administration of rhTSH and 98.1 ng/mL 1 month following the therapeutic scan.

The patient complained of blurred vision in November 2001. Visual field examination by an ophthalmologist identified bitemporal hemianopsia. Brain MRI showed recurrent pituitary tumor (Figure 3A). Right frontotemporal craniotomy was performed for decompressive surgery and

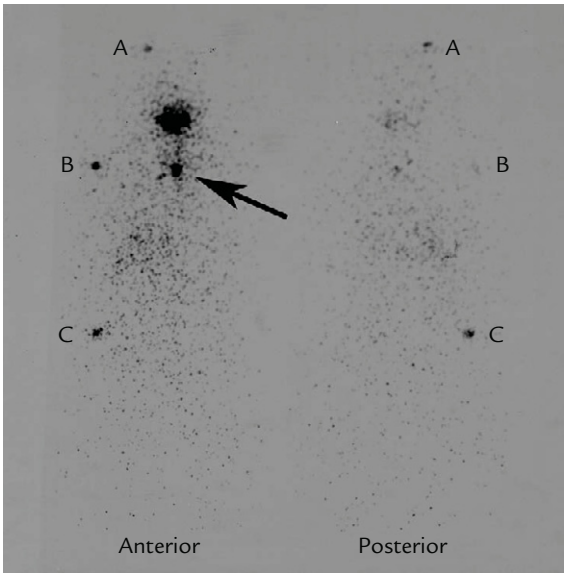

Figure 2. 100 mCi ^{131}I therapeutic scan after preparation of recombinant human thyroid-stimulating hormone shows apparent mediastinum ^{131}I uptake (arrow). A = vertex; B = shoulder; C = iliac crest.

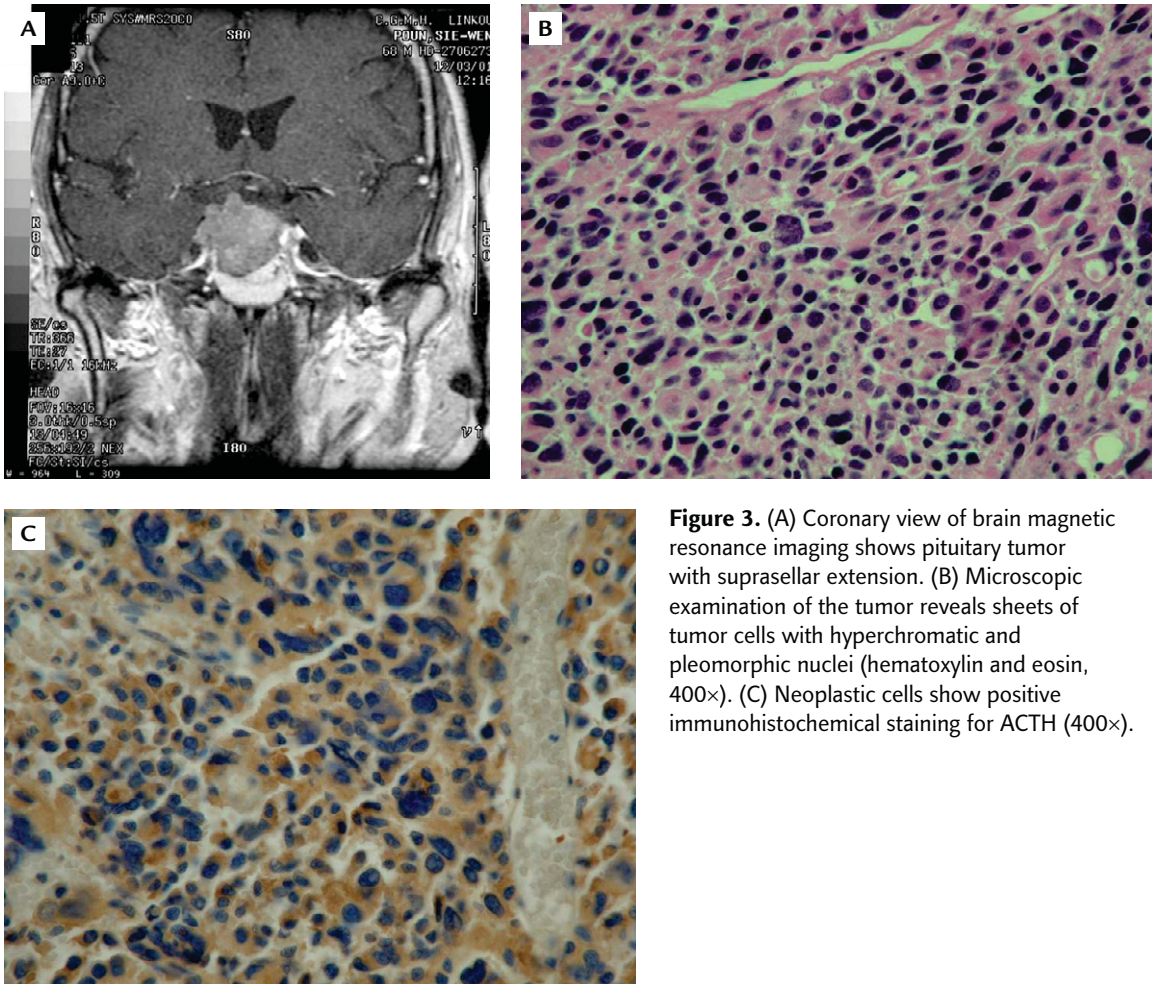

Figure 3. (A) Coronary view of brain magnetic resonance imaging shows pituitary tumor with suprasellar extension. (B) Microscopic examination of the tumor reveals sheets of tumor cells with hyperchromatic and pleomorphic nuclei (hematoxylin and eosin, 400×). (C) Neoplastic cells show positive immunohistochemical staining for ACTH (400×).

the tumor was found to be severely adhesive to the optic chiasm. Pathology showed a recurrent pituitary adenoma (Figure 3B). Immunohistochemically, the tumor cells were positive for ACTH (Dako, Glostrup, Denmark) (Figure 3C) and negative for Tg, TSH, FSH, LH, GH, and PRL. Hormone study revealed high serum ACTH level of 337 and 232 pg/mL (immunoradiometric assay [IRMA]; Nichols Institute Diagnostics, San Clemente, CA, USA) on two separate mornings, associated with extremely low PRL, GH, LH, and FSH, indicating an ACTH-secreting pituitary tumor. The patient had no skin or mucosa pigmentation, and also exhibited no Cushingoid appearance when pituitary ACTH-secreting tumor was identified. The serum 8:00 AM cortisol levels were 27.9 and 10.7 μg/dL (RIA; Diagnostic Systems Laboratories Inc., Webster, TX, USA) (normal range, 9–23), and urine-free cortisol levels were 76.1 and 18.4 μg/day (RIA; Diagnostic Systems Laboratories Inc.) (normal range, 34–122). He stopped taking cortisone acetate as serum cortisol level returned to normal. The higher serum cortisol level (27.9 μg/dL) was detected during his admission to hospital for right clavicular pain because of thyroid cancer metastasis.

^{131}I therapeutic scan with 30 mCi under thyroxine suppressive therapy and ^{201}Tl scan in 2001 both revealed persistent uptake lesion in the upper mediastinum. Subsequent thyroid ultrasonography revealed a large lesion extending from the lower neck to the intrathoracic area. The patient underwent surgery for removal of a 4 × 3 cm metastatic intrathoracic PTC in 2001. However, persistent rise of serum Tg to 1805 ng/mL was detected in August 2002. ^{131}I therapeutic scan with 30 mCi under thyroxine suppression therapy was negative for neck and mediastinum metastasis

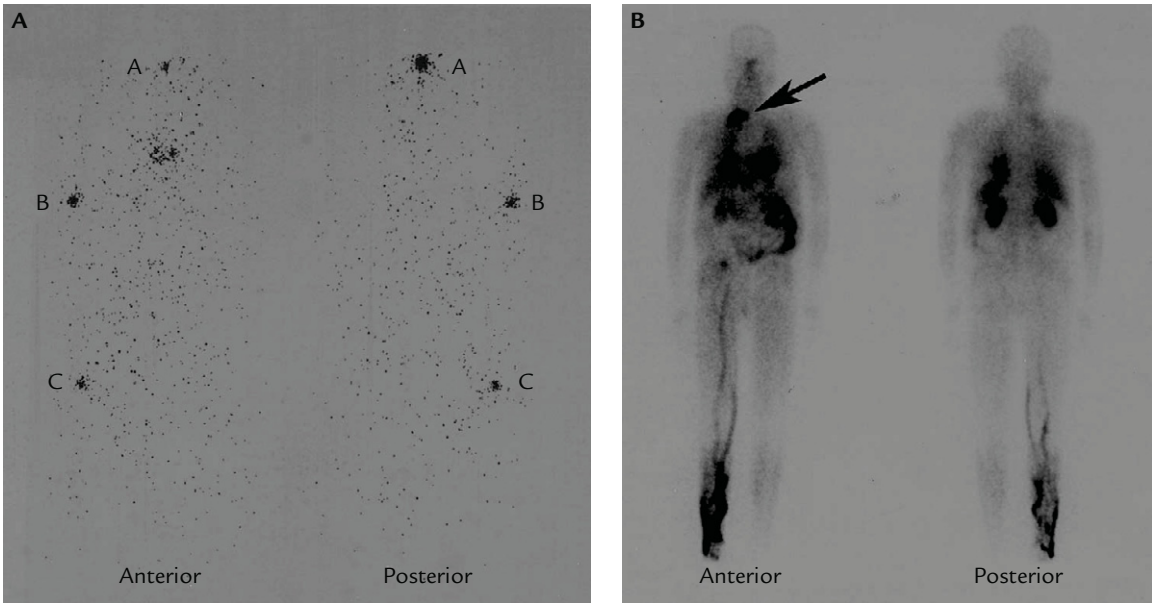

Figure 4. (A) ^{131}I therapeutic scan is negative for neck and mediastinum. A = vertex; B = shoulder; C = iliac crest. (B) ^{201}Tl scan reveals avid uptake lesion in the right lower neck (arrow).

(Figure 4A). Thyroid ultrasonography with FNAC revealed a metastatic lymph node in the right neck, and consequently further surgery to remove the metastatic PTC was conducted. Serum Tg level rose to 2821 ng/mL in January 2003. ^{201}Tl scan revealed avid uptake lesion in the right lower neck region (Figure 4B). During the follow-up period, ^{201}Tl scan proved to be an effective tool for detecting metastatic thyroid cancer in this patient without pituitary TSH reserve. Subsequent computed tomography examination showed a $4 \times 3.5 \times 2.5$ cm metastatic PTC in the lower right of the neck which also destroyed the clavicle and invaded the mediastinum. The patient received a total of 370 mCi ^{131}I throughout the clinical course. Local radiotherapy was performed for pain relief from May 2003. However, the patient died of pneumonia complicated with septic shock which was unrelated to pituitary tumor and thyroid carcinoma in July 2003.

Discussion

Regarding concurrent thyroid cancer with pituitary tumor, no large study has been performed and only case reports can be found. Since TSH can stimulate thyroid cancer cell growth, thyroxine suppressive therapy is administered to patients with differentiated thyroid cancer.[4] Although hyperthyroidism is a typical clinical picture in TSH-secreting pituitary tumor,[5–7] less than five cases of thyroid cancer in TSH-secreting pituitary tumor have been reported.[8,9] In contrast, thyroid cancers in patients with pituitary GH-secreting tumor are not uncommon,[10] and are thought to be associated with increased serum insulin-like growth factor-1 (IGF-1) level.

The English medical literature contains three case reports of thyroid cancer with pituitary ACTH-secreting tumor. The first report describes a patient with substernal metastatic thyroid carcinoma and secondary hypothyroidism because of Cushing's disease, in which the thyroid cancer metastasis was visible on ^{131}I scan after administration of rhTSH or bovine TSH, but was not visible on thyroid hormone withdrawal scan.[11] There are no detailed descriptions of the clinical and pathologic presentations of thyroid cancer and pituitary tumor. The second report describes a patient with preclinical Cushing's disease, accompanied by papillary thyroid carcinoma and adrenal incidentaloma.[12] Finally, the third report describes a case of Cushing's disease with minimally invasive follicular thyroid carcinoma.[13]

Diagnostic and therapeutic ^{131}I scans for differentiated thyroid cancer patients with pituitary tumor may be complicated by coexistent hypopituitarism, because such patients may be unable to generate endogenous TSH. ^{131}I scan following preparation by rhTSH is a good diagnostic method for thyroid cancer patients after operation.[14] The potential efficacy of rhTSH in diagnostic and therapeutic ^{131}I is an important issue that has been studied in a limited number of patients with insufficient pituitary TSH reserve.[5,11] In the present thyroid cancer patient with pituitary apoplexy and hypopituitarism, rhTSH-assisted ^{131}I scan played a role in detecting thyroid cancer metastasis. The ^{131}I scan showed avid ^{131}I uptake, though the therapeutic response was not good according to serum Tg level, which was not suppressed after ^{131}I therapy. ^{201}Tl scan has been used in patients with negative ^{131}I scans together with elevated Tg levels, as in our previous study.[15] The patient described here had positive ^{201}Tl scan but negative ^{131}I scan in the later clinical course during thyroid hormone replacement therapy. ^{131}I therapeutic scan with 30 mCi is not a standard method for treatment of recurrent thyroid cancer patients, especially during thyroxine suppressive therapy, but it probably made no difference in this patient with inadequate pituitary TSH reserve. This is the first case of using ^{201}Tl scan in a metastatic thyroid cancer patient without pituitary TSH reserve. Although rhTSH-stimulated ^{131}I whole body scan and Tg determination is considered to be the standard method, ^{201}Tl scan offered an effective alternative diagnostic tool for this patient.

A silent corticotroph adenoma is an ACTH-secreting tumor which does not induce Cushingoid features. A silent corticotroph adenoma can typically be large because it exhibits no clinical signs. The present patient had a pituitary ACTH tumor without Cushing's syndrome which is compatible with silent corticotroph adenoma. Silent corticotroph adenoma is considered to produce biologically inactive ACTH, which is usually high molecular weight ACTH. The serum ACTH level detected by RIA could be high in patients with silent corticotroph adenoma.[16] However, the serum ACTH level detected by IRMA could also be high in the patient with corticotroph adenoma without Cushing's syndrome.[17] It is thought to be a minor variant of ACTH. The present patient might be an example of similar cases. Alternatively, preclinical Cushing's disease could be likely because the serum cortisol level began returning to normal during pituitary tumor recurrence.

In conclusion, we reported a PTC patient with pituitary ACTH-secreting adenoma. The patient did not display Cushing appearance due to the absence of hypercortisolism. Hypopituitarism complicated by pituitary macroadenoma and apoplexy made the thyroid cancer follow-up difficult. ^{201}Tl scan effectively detected metastatic thyroid cancer in this patient.

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