Thyrotropin-Secreting Pituitary Adenoma with Growth Hormone Hypersecretion

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Key Words
hyperthyroidism; pituitary neoplasm

A 34-year-old woman suffered from palpitation, easy sweating, heat intolerance, increased appetite, irregular menstrual cycle and hand tremor for 1 year. Thyroid function tests showed elevated serum thyroxine (T4), tri-iodothyronine (T3) and thyrotropin (TSH). Computerized tomography (CT) revealed pituitary tumor with suprasellar extension. Thyrotropin releasing hormone (TRH) test showed blunted TSH response with elevated baseline level and paradoxical growth hormone (GH) response with elevated baseline level. T3 suppression test (T3 60 µg per day × 10 days) showed no inhibition of TSH (11.1 µU/mL, normal range < 6.2 µU/mL). She received transphenoidal approach and removal of tumor which measured 0.5 × 0.3 × 0.2 cm. Histopathologically, it was a pituitary adenoma which was immunoreactive for TSH, GH, follicular stimulating hormone (FSH) and luteinizing hormone (LH). To our knowledge, this case is the first case of TSH-secreting pituitary adenoma in Taiwan.

Case Report

A 34-year-old woman suffered from palpitation, easy sweating, heat intolerance, increased appetite, irregular menstrual cycle and hand tremor for 1 year. She was im pressed as having hyperthyroidism at a local clinic in 1987. However, she was re ferred to other hospital due to elevated serum thyroxine (T4), tri-iodothyronine (T3) and TSH. After 3-month antithyroid agent therapy, the thyroid function test showed normal T3 and T4 levels but elevated TSH level. Under the impression of TSH-secreting tumor, she received computed tomography (CT) that revealed pituitary tumor with suprasellar extension (Fig. 1). She was then re ferred to our hospital. Physical examinations revealed body temperature 36.2 °C, respiratory rate 19 time/min, blood pressure 132/76 mmHg, regular heart rate 130 beat/min. Visual field test showed intact. The diffusely enlarged thyroid gland (grade I) was noted. Thyroid function tests showed free T4 > 4.7 ng/dL (normal range, 0.7-2.2 ng/dL); T4, 19.08 µg/dL (normal range, 6.0-12.0...
µg/dL); T3, 259 ng/dl (normal range, 85-165 ng/dl) and ultrasonic TSH (HS-TSH) 5.85 µU/mL (normal range, 0.5-4.0 µU/mL). Thyrotropin releasing hormone (TRH) test showed blunted TSH response with elevated base line level and paradoxical GH response with elevated base line level (Fig. 2). T3 suppression test (T3 60 µg per day ×10 days) showed no inhibition response of TSH (11.1 µU/mL, normal range < 6.2 µU/mL). Follicular stimulating hormone (FSH), 17.22 mU/mL (normal range 1-30 mU/mL); luteinizing hormone (LH), 23.46 mU/mL (normal range, 1-30 mU/mL); estrodiol < 25 pg/mL (normal range, 25-120, 95-250 pg/mL); progesterone 7.71 ng/mL (normal range 4-16 ng/mL). Plurihormonal (TSH and GH) pituitary tumor presenting as hyperthyroidism was impressed. She received transphenoidal approach and removal of tumor on June 23, 1988. Pathology showed a 0.5 × 0.3 × 0.2 cm adenoma, which was immunoreactive for TSH, GH, FSH and LH (Fig. 3). After resection of the tumor, TSH level came into normal range (TSH, 4.97 µU/mL; T4, 6.4 µg/dL; T3, 135 ng/dL) and the GH level was 3.55 ng/mL without paradoxical response of TRH administration. The patient received eltroxine and cortisone replacement for 1 month. She was well without any hormone replacement thereafter. The follow-up CT scan disclosed no evidence of recurrence in 1990.

**Discussion**

TSH-secreting pituitary tumor is a rare disorder accounting for 0.5% of all pituitary adenomas. The progress in measurement of TSH levels has facilitated the diagnosis of central hyperthyroidism since 1970. Misdiagnosis in the past led to inappropriate and frequently harmful therapeutic interventions. Over 280 cases of TSH-secreting pituitary adenoma have been reported in the literature. Hyperthyroidism with elevated TSH level is the key point to suspect this diagnosis. In addition to true TSH-secreting pituitary adenoma, pituitary resistance to thyroid hormone (PRTH) may present as abnormal elevated TSH level. PRTH results from a germline mutation in the carboxyl terminus of the β-thyroid hormone receptor (TRβ). In contrast to PRTH, TSH-secreting pituitary adenoma usually has no family history, no TSH response to TRH or T3 administration, but a tumor is closed by CT or magnetic resonance (MR) scan. A normal induced response to T3 suppression tests has never been recorded in TSH-secreting tumor. There fore, the T3
The suppression test seems to be the most sensitive and specific test for TSH-secreting tumor. Recenly, the somatic mutation of the TRβ gene has been identified in TSH-secreting tumors as the likely mechanism for the defective negative regulation of TSH by T3. The differential diagnosis of TSH-secreting pituitary adenoma and PRTH may be difficult in some rare conditions, for example, PRTH coexisting an incidental pituitary adenoma. More measurements such as α-sub unit and the α/TSH molar ratio, serum sex hormone-binding globulin level, and TRβ gene analysis may be helpful for differential diagnosis. About 90% of TSH-secreting tumors were macroadenoma by imaging and 2/3 were with suprasellar extension or invasion. This case presented as hyperthyroidism and goiter with out mass effect or visual defect. In fact, goiter is the most common (92%) clinical presentations in TSH-secreting tumor as compared with visual field defects (40%) and headache (23%).

The majority of TSH-secreting adenomas secrete only TSH (72.1%). The rest of them co-secrete other anterior pituitary hormones such as GH (15.7%). The clas si fi ca tion between both was made based on hormone secretion and not immunostaining. In our case, immunohistochemistry showed TSH, GH, LH and FSH staining, but base line and dynamic tests revealed only TSH and GH hypersecretion. Patients with plurihormonal pituitary adenoma (TSH and GH) have been reported to have acromegaly and hyperthyroidism. Yet, most patients with plurihormonal pituitary adenoma have symptomatic disease in only one of the hormones, only 7% of them have symptoms related to two hormones. The discrepancy may be due to (1) production of biologically active hormones; (2) activation of the secreted hormone in the circulation; or (3) the abnormal secretion of the particular hormone. In fact, fasting hyperglycemia (115 mg/dL) as presented in our case is one of the clinical presentations of acromegaly. Patients with acromegaly have a
gradual progression of symptoms and signs so that the diagnosis is often delayed as many as 15 to 20 years. It may be one of the reasons why this case presented as hyperthyroidism with out prominent acromegaly.

Plurihormonal adenomas have been divided into monomorphous and plurimorphous tumors by ultrastructural studies. Monomorphous adenomas consist of a cell type capable of producing two or more hormones; while plurimorphous ones are composed of two or more cell types and each produces different hormone. Double-immunostaining results of 167 Taiwanese plurihormonal pituitary adenomas have been reported recently that mixtures of hormones of any combinations were seen in the individual cells in all of the cases. Therefore, our case would likely be monomorphous.

The treatment of choice in most cases is surgical removal of the tumor through the transsphenoidal approach. Surgical alone or in combination of radiation fected a cure in one-third of the patients and notable improvement in another third. The finding of undetectable TSH levels 7 days after surgery was highly predictive of successful outcome. We found undetectable TSH level 14 days after the surgery (no data in 7 days) in this case. The medical chart recorded the detectable TSH level 14 days after the surgery (no data). We found undetectable TSH levels 7 days after surgery was highly predictive of successful outcome. We found undetectable TSH level 14 days after the surgery (no data in 7 days) in this case. The medical chart recorded the detectable TSH level 14 days after the surgery (no data in 7 days) in this case. We found undetectable TSH levels 7 days after surgery was highly predictive of successful outcome.

TSH-secreting tumor is a rare cause of hyperthyroidism. Detection of normal or elevated TSH levels in hyperthyroid patients, measured by ultra-sensitive as say, should raise the suspicion of the rare disorder.

References
