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CASE REPORT

A Case of Pituitary Adenoma with Simultaneous Secretion of TSH and GH

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Thyrotropin (TSH)-secreting pituitary adenoma is a very rare disease. In one-quarter of patients suffering from this disease, the pituitary tumor secretes other anterior pituitary hormones. Herein, we report a case of pituitary adenoma with simultaneous secretion of TSH and growth hormone (GH). A 34-year-old female visitied local hospital complaining of sweating, intermittent palpitation, and weight loss of 8 kg within 1 year. The patient had undergone trans-sphenoidal surgery 3 years prior for resolution of a TSH and GH co-secreting pituitary adenoma. She had been administered somatostatin analogue prior to visiting our hospital. The patient's GH levels were suppressed to below 1 ng/mL on the 75 g oral glucose tolerance test, and her basal insulin-like growth factor-I (IGF-I) level was within normal range. Thyroid function tests demonstrated increased levels of both free thyroxine and TSH. Sella-MRI revealed pituitary adenoma at the floor of the pituitary fossa, approximately 2 cm in height. Therefore, she was diagnosed with residual TSH-secreting pituitary adenoma. The patient again underwent trans-sphenoidal surgery and entered complete remission, based on hormone levels and MRI findings. (*Endocrinol Metab* 26:160-165, 2011)

Key Words: Thyrotropin, Growth hormone, Pituitary adenoma

INTRODUCTION

Thyrotropin (TSH)-secreting pituitary adenomas (TSHomas) are very rare pituitary tumors accounting for less than 2% of all pituitary adenomas [1,2]. TSH-secreting pituitary adenoma (TSHoma) is usually diagnosed when free thyroxine (T4) levels are elevated in the presence of normal to high serum TSH concentration, combined with the presence of a pituitary adenoma [1,2]. The first case of TSHoma was reported in 1960 by measuring serum TSH levels with a bioassay [3], and so far about 350 cases of TSHoma have been reported [4]. Although most benign TSHomas secrete TSH alone, about one-fourth of TSHomas simultaneously secrete TSH and other anterior pituitary hormones. Growth hormone (GH) is the most common co-secreted hormone with TSH (16%), followed by prolactin (PRL) (10.4%) and gonadotropins [2]. Approximately 59 cases of mixed TSH and GH-secreting pituitary adenomas (TSH/GH-omas) and 41 cases of mixed TSH and PRL-secreting pituitary adenomas have been reported [5]. Herein, we report a case of pituitary adenoma with simultaneous secretion of TSH and GH, which was not controlled after trans-sphenoidal surgery (TSA) with long-term somatostatin analogue therapy.

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CASE REPORT

A 34-year-old female visited the hospital complaining of sweating, intermittent palpitation, and weight loss of 8 kg within 1 year. Three years ago, she took a medical examination and was referred to a tertiary hospital for hyperthyroidism with goiter. In magnetic resonance imaging (MRI), huge pituitary adenoma was shown (Fig. 1A, upper panel). She was diagnosed with TSH/GH-oma and underwent TSA. The pituitary tumor was positive to GH, TSH, and PRL on immunohistochemical staining. Plasma insulin-like growth factor-I (IGF-I) levels was normalized after surgery (from 514.5 ng/mL to 233.6 ng/mL; normal, 79-384 ng/mL), but GH was not suppressed to below 1 ng/mL on 75 g oral glucose tolerance test (1.25 ng/mL). Both free T4 and TSH levels were elevated before the surgery and decreased after the surgery for 10 months. Prior to the surgery, free T4 was 2.49 ng/dL (normal, 0.89-1.78 ng/dL) and TSH was 8.0 μIU/mL (normal, 0.17-4.05 μIU/mL). After the surgery, free T4 decreased

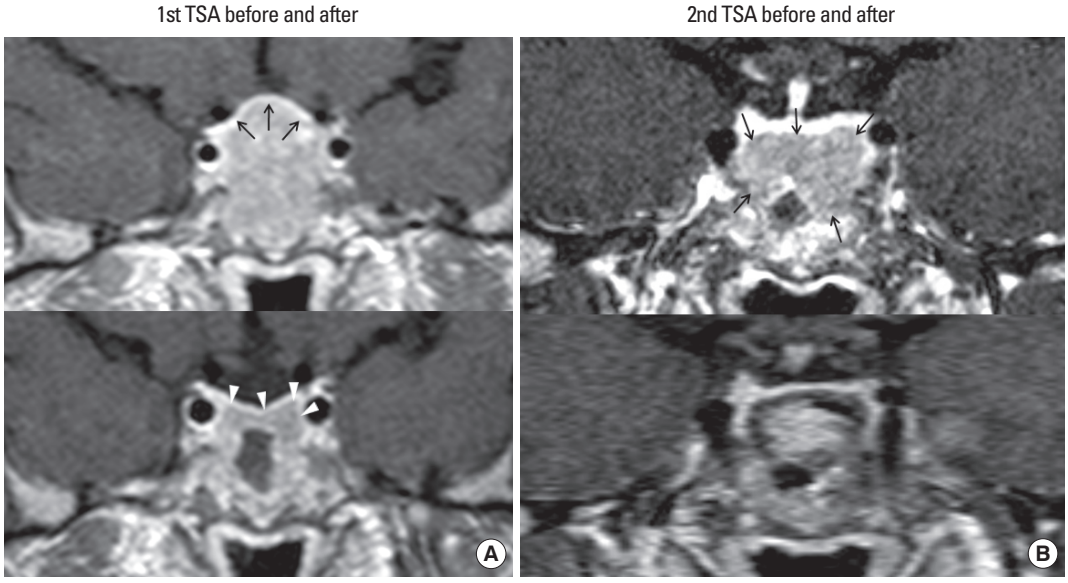

Fig. 1. A coronal view of TSH-secreting macroadenoma by MRI, which was taken before and after the surgery. A. About 30 mm sized macroadenoma displacing the enhanced pituitary gland cranially (arrows) before the first TSA (upper panel) and residual tumor (arrow heads) after the first TSA (lower panel). B. About 20 mm sized macroadenoma (arrows) at the floor of pituitary fossa before the second TSA (upper panel) and completely resected tumor after the second the TSA (lower panel). TSA, trans-sphenoidal surgery; TSH, thyroid stimulating hormone.

Table 1. Results of 75 g glucose-GH suppression test

	Basal	60 min	120 min
Glucose (mg/dL)	82	193	160
GH (ng/mL)	2.66	0.63	0.58

GH normal, 0-9.5 ng/mL. GH, growth hormone.

Table 2. Result of combined pituitary stimulation test (Regular insulin 0.1 U/kg, TRH 400 μg, LHRH 100 μg IV)

	Basal	30 min	60 min	90 min	120 min
Glucose (mg/dL)	83	34	46	59	80
GH (ng/mL)	1.98	9.31	10.87	9.99	5.6
TSH (μIU/mL)	4.84	5.56	5.75	5.38	4.48
Prolactin (ng/mL)	9.32	45.64	50.13	61.5	32.64
Cortisol (μg/dL)	3.64	7.42	18.40	20.09	22.67
ACTH (pg/mL)	3.21	184.50	155.20	114.80	39.57
LH (mIU/mL)	4.15	13.63	24.49	20.55	14.72
FSH (mIU/mL)	2.45	3.38	5.41	5.67	5.51

ACTH, adrenocorticotropic hormone; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone.

to 1.26 ng/dL, and TSH to 2.09 μIU/mL. However, both free T4 and TSH increased 10 months after TSA and peaked to 2.78 ng/dL and 6.3 μIU/mL at 16 months after TSA, respectively. She had been administered long-acting somatostatin analogues (lanreotide SR 60 mg subcutaneous injection, monthly) for 34 months before coming to the hospital. She complained of sweating and intermittent palpitation after the surgery and underwent weight loss of 8 kg over 1 year. She was referred to the hospital for persistently elevated free T4 and TSH levels and symptoms as mentioned above. On admission, her vital signs were as follows: body temperature, 37.2°C; pulse rate 85 beats per minute; blood pressure 119/72 mmHg. Her height and body weight were 158 cm and 54 kg, respectively. Physical examination revealed diffuse goiter without palpable mass, tenderness, or bruit. Primary and secondary sexual developments were normal. There was no tremor or visual defect on the visual field test. Neither ophthalmopathy nor pretibial myxedema was noted.

A complete blood count showed hemoglobin 11.5 g/dL, hematocrit 35.6%, white blood cell count 4870/mL, and platelet count 217,000/mL. Other laboratory tests were within normal range. GH was suppressed to 0.58 ng/mL (normal, 0-9.5 ng/mL) on 75 g oral glucose tolerance test (Table 1) and basal IGF-I was 255.3 ng/mL (normal, 140-405 ng/mL at age 30-40 years). Free T4 increased to 2.50 ng/dL (normal, 0.73-1.95 ng/dL) and TSH also increased to 4.84 μIU/mL (normal, 0.3-4.0 μIU/mL). Combined pituitary function test demonstrated elevated basal TSH level and impaired response of TSH to thyrotropin-releasing hormone (TRH) stimulation. Other hormones such as GH, PRL, luteinizing hormone, follicle stimulating hormone, and cortisol showed normal basal level and proper response to stimulation (Table 2).

The chest X-ray was normal without evidence of hilar lymphade-

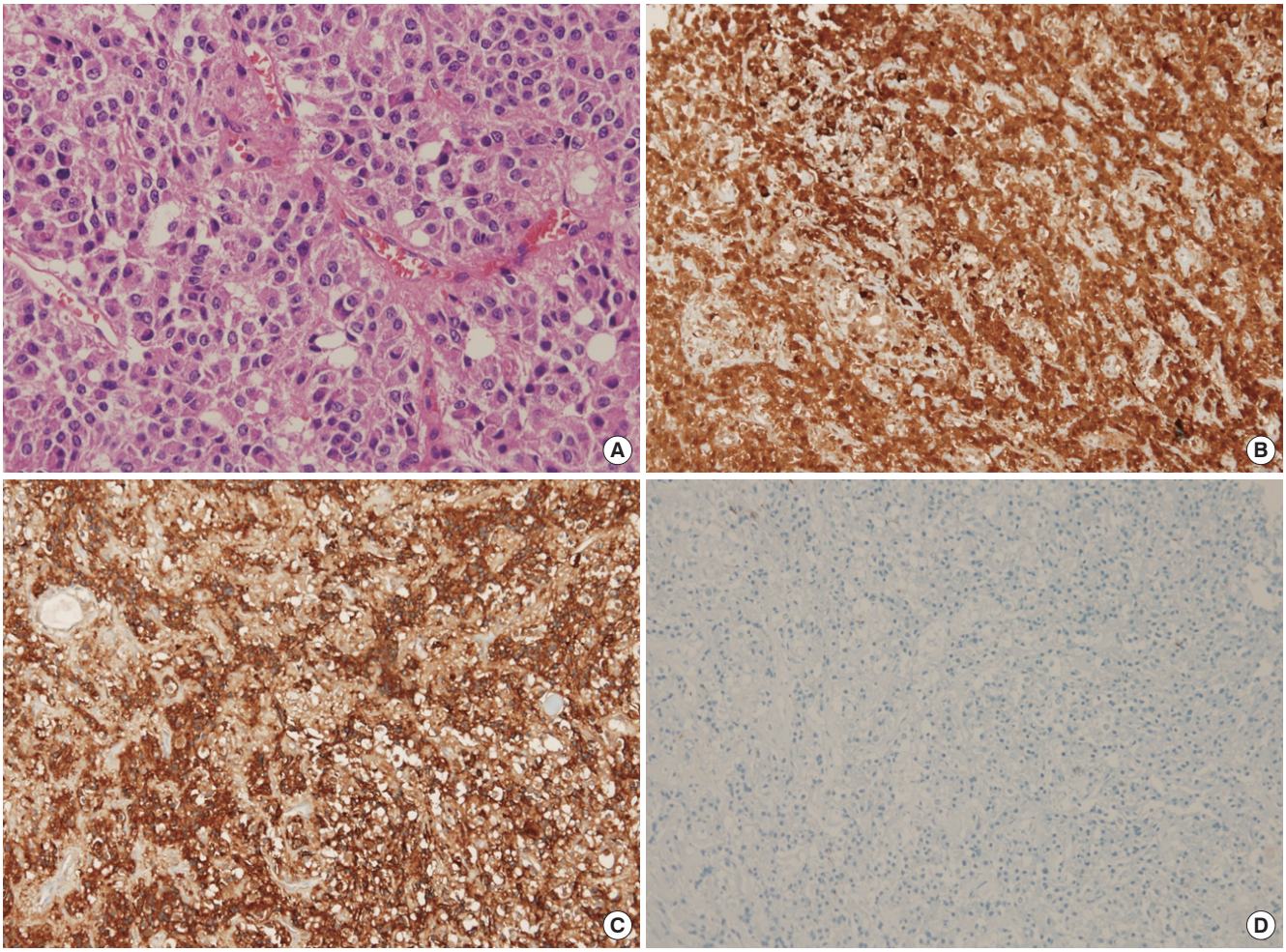

Fig. 2. A high-power view of the pituitary adenoma. A. Tumor tissues show regular thin fibrous septa surrounding tumor cells and chromophobe adenoma (H&E stain, × 200). B-D. Immunohistochemical staining of the tumor cells was positive to TSH (B). and GH (C). and negative to PRL (D). (× 100). GH, growth hormone; RPL, prolactin; TSH, thyroid stimulating hormone.

nopathy. Sella-MRI revealed pituitary adenoma at the floor of the pituitary fossa, approximately 2 cm in height (Fig. 1B, upper panel). There were erosion of the sella floor and invasion of central skull base. There was no invasion of the cavernous sinus or carotid artery. We diagnosed residual TSH-secreting pituitary adenoma. Although she had already undergone trans-sphenoidal adenomectomy, residual pituitary adenoma was observed on MRI. Moreover, long-term somatostatin analogue therapy did not control the hyperthyroidism by TSHoma. Thus, we decided to perform TSA again. Hyperthyroidism was controlled by methimazole of 10 mg per day before surgery. During the operation, fibrotic adhesion and bulging tumor was identified on the floor side. Tumor, which showed yellowish color and slid nature, was penetrating the sphenoid floor bone. Tumor was adherent on the normal pituitary gland and was separated by dissection. After adenomectomy, total resection of tumor was confirmed using an endoscope. Pathologic finding revealed a solid chromophobe adenoma. Immunohistochemical staining results were positive to TSH and GH and negative to PRL (Fig. 2). After the second TSA, MRI showed no residual pituitary tumor (Fig. 1B, lower panel). On the third day after surgery, serum free T4 and TSH levels were normalized also (0.87 ng/dL and 2.40 μIU/mL, respectively) (Fig. 3). She had complete remission, based on hormone levels and MRI findings.

DISCUSSION

TSHomas are very rare pituitary tumors with the prevalence of one case per million [1,2]. The first case of TSHoma was reported in 1960 by measuring the serum TSH levels with a bioassay [3]. The first case of TSHoma by measuring TSH by RIA was reported in

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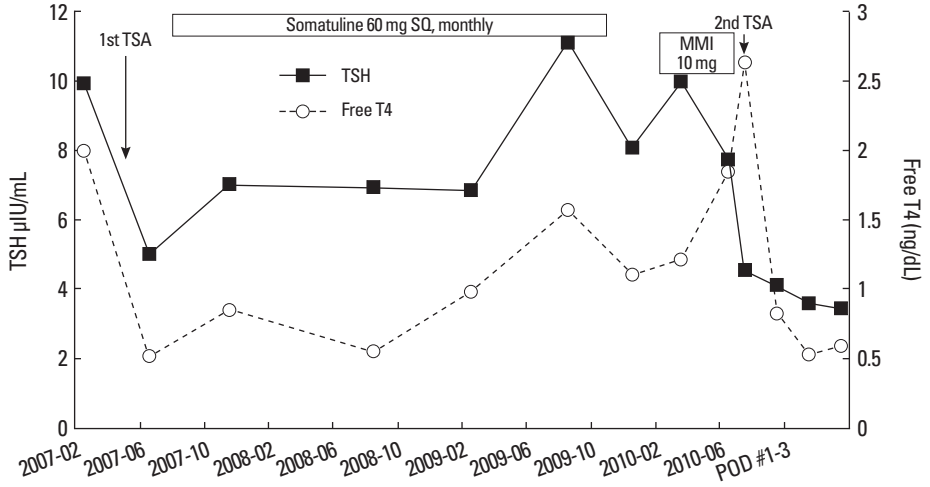

Fig. 3. Clinical course of the patient (changes in free T4 and TSH levels). MMI, methimazole; POD, postoperative days; T4, thyroxine; TSA, trans-sphenoidal surgery; TSH, thyroid stimulating hormone

1970 [6]. The frequencies of reported cases of TSHomas have tripled in the last decade, thanks to the widespread availability of ultrasensitive TSH immunometric assays and the increased awareness by physicians [4,5]. Recently, approximately 350 cases of TSHoma have been reported [4].

TSHoma indiscriminately affects men and women [4]. Most patients with TSHoma are diagnosed in the fifth-sixth decade. However, TSHoma could occur at any age (ranging from 11 to 84 years) [5,7]. TSH levels have no correlation with tumor size [7]. Clinical features vary according to the excessive thyroid hormone and mass effects of the expanding tumor. The most common findings are goiter (more than 90% of patients) and thyrotoxicosis (70% of patients) [2]. In approximately half of patients, presenting symptoms include fatigue, tremor, heat intolerance, weight loss, and diarrhea [4]. Ophthalmopathy, pretibial myxedema, and acropachy are absent [7]. Symptoms due to mass effect, such as visual field defect and headache are present in more than 20% of patients [2]. Menstrual disorders, galactorrhea and acromegalic features may be present at diagnosis [2,7]. In patients with TSHoma with co-secreted GH, typical features of acromegaly may make physicians to overlook the importance of evaluating thyroid function and related symptoms [4]. Our patient was initially recognized by goiter, and acromegalic features were unusually not prominent. After the first TSA, she complained of symptoms associated with thyrotoxicosis. However, ophthalmopathy and pretibial myxedema were not present.

In patients with TSHoma, free T4 levels are elevated, but TSH is not suppressed, and such a condition is called inappropriate TSH secretion [1,2]. Absent or impaired TSH responses to TRH stimulation test are shown in TSHoma [7]. In TSHomas, the hormonal feedback caused by changes in level of peripheral thyroid hormone differs from that in normal condition. Although the negative feedback is impaired, the positive feedback by decrements of thyroid hormone levels is intact or increased [8]. Even with a small reduction of circulating thyroid hormone, the level of TSH can increase abruptly. In our case, the serum TSH level increased rapidly even with the short-term treatment of methimazole (Fig. 3). As TSHomas are often accompanied by hypersecretion of α-subunit, the molar ratio of α-subunit to TSH is one of the diagnostic clues. The molar ratio is calculated using a formula, (α-subunit in μg/L divided by TSH in mU/L) × 10, and an increased molar ratio favors the presence of TSHoma [1,7]. However, in our patient, α-subunit level was 0.49 mIU/mL (normal, 0-0.9 mIU/mL), and molar ratio was very low (0.01). Some cases of TSHomas with low α-subunit level were also reported [9,10]. These results suggest that increased α-subunit level or molar ratio is not always required for the diagnosis of TSHoma.

Most benign TSHomas secrete TSH alone, and about one-fourth of TSHomas simultaneously secrete TSH and other anterior pituitary hormones. GH is the most frequently co-secreted hormone with TSH (n = 59, 16% of all TSHoma cases) at present [5]. Other anterior pituitary hormones, which are co-secreted with TSH, are prolactin (10.4%) and seldom gonadotropins [2]. As somatotroph and lactotroph cells are known to share common transcription factors such as PROP-1, Pit1 and HESX-1 with thyrotrophs, TSHomas seem to be frequently associated with concomitant hypersecretion of GH or PRL [11,12]. In our case, only TSH and GH levels were elevated in plasma, but immunohistochemical staining was positive to PRL, as well as TSH and GH at first.

TSHoma should be differentiated from resistance to thyroid hor-

mone action (RTH) [13]. The main difference between TSHoma and RTH is the presence of signs and symptoms of hyperthyroidism in patients with TSHoma, while RTH patients are in general euthyroid status [2]. Other factors for differential diagnosis are as follows: absence of a family history, normal thyroid hormone levels in family members, and the presence of an elevated glycoprotein α-subunit in patients with pituitary tumor. A definitive diagnosis for RTH requires mutation in the TRb gene [14]. By differentiating TSHoma from RTH, inappropriate thyroid ablation can be avoided for patients with TSHoma or pituitary surgeries for patients with RTH. Moreover, early recognition of TSHoma may help to avoid neurological and endocrine complication and improve the rate of cure [2].

Although TSHomas are benign tumors, and there are only two cases of TSH-secreting carcinoma [11,15], more than 70% of TSHomas are macroadenomas showing an aggressive growth pattern. Most macroadenomas in TSHomas invade into the surrounding structures and extend into the suprasellar area [2,16]. This aggressive growth pattern may be related to highly fibrotic features of TSHomas. One study reported marked interstitial fibrosis of patients with TSHoma was associated with the expression of fibroblast growth factor on the adenoma and elevated levels in the circulation [17]. The patients with previous thyroid ablation by surgery or radioiodine tend to have more invasive macroadenomas [1], which showed aggressive transformation of the tumor. This resembles that occurring in Nelson's syndrome after adrenalectomy for Cushing's disease [2,5].

Most useful imaging modality for evaluating pituitary tumors is known as MRI. MRI using gadolinium contrast shows normal isointense pituitary gland on T1-weighted images before contrast enhancement. Pituitary adenoma shows hypointensity in the sella area after contrast enhancement in MRI. Moreover, MRI displays surrounding structures, as well as pituitary adenoma. A rare but one distinguishing character of TSHoma is extensive and dense calcifications, which is called "pituitary stones" [18].

Trans-sphenoidal or subfrontal adenomectomy is the first choice to treat TSHomas [2]. However, this may be difficult because of an aggressive growth pattern. Thus, TSH-secreting adenomas are less easily controlled by surgery alone than other types of adenomas [7]. Radiotherapy should be considered if clinical remission was not obtained by surgery alone or if surgery is contraindicated. More than one-third TSHoma patients who received combined therapy of surgery and radiotherapy achieved complete cure. Other one-third of patients may be considered to have improved, as normalization of circulating thyroid hormone levels but no complete removal of the adenoma. As a result, approximately more than two thirds of patients with TSHomas are controlled by surgery and/or radiotherapy [1,2,7]. The medical treatment of TSHomas relies on long-acting somatostatin analogues such as octreotide LAR, lanreotide SR or lanreotide Autogel. In *in vitro* studies, most TSHomas express a variable number of somatostatin receptors, and there exists the highest somatostatin-binding site densities in mixed TSH/GH-omas [19]. Treatment with theses analogues was effective to reduce TSH and α-subunit secretion in almost all cases, with recovery of euthyroid state in 75% of patients with TSHoma [1]. Shrinkage of pituitary tumor was observed in 45% of patients. In two-thirds of patients, vision improvement was demonstrated. Goiter size was also reduced in one-fifth of patients [1,2]. Somatostatin analogues may be a useful therapy for long-term treatment of TSHomas and in pregnant women with TSHoma. However, escape from inhibitory effects was documented in about 10-12% of cases and 4% of patients had a true resistance to these analogues [1,7]. Common side effects of these analogues are tachyphylaxis, cholelithiasis and carbohydrate intolerance and should be carefully monitored. Our patient received long-acting somatostatin analogue for more than 2 years, but TSH levels had never decreased to normal. Thus, this case might be considered as true resistance to this analogue.

Although there are no definite criteria for cure of TSHomas because of rarity of the disease, cure has been generally considered as normalization of TSH and the absence of visible tumor on MRI. Pituitary imaging is recommended every 2-3 years after surgery [7]. Losa et al. [20] have proposed the measurement of TSH levels 1-7 days after surgery. Normal thyrotrophs are still suppressed at that time, and measured TSH should reflect TSH levels secreted by the tumor. In our patient, TSH was evaluated before the surgery and subsequently after the surgery for 4 days. TSH level decreased from 10.53 μIU/mL to 2.40 μIU/mL over time.

In our case, the patient had taken TSA and received somatostatin analogue for a long time. Despite this combined treatment, TSH levels were continuously elevated. Moreover, the patient complained of symptoms, such as sweating, palpitation and weight loss. If she received repeated surgical treatment or radiotherapy earlier, her prognosis and quality of life might have been improved. After repeated surgical treatment, she was cured. Although TSHoma is a rare disease, it should be considered in patients with elevated free T4 levels with the presence of normal to high serum TSH concentration. First choice of treatment is TSA. However, most TSHomas show aggressive growth features, with which cure rate by surgery alone tends

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to be low. Thus, combined radiotherapy or medical therapy should be seriously considered. Furthermore, as more than one-fourth of TSHoms simultaneously secrete other anterior pituitary hormones, we should examine and carefully monitor other co-secreted pituitary hormones.

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