

A thyrotropin-secreting macroadenoma with positive growth hormone and prolactin immunostaining: A case report and literature review

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Abstract

Thyrotropin (thyroid stimulating hormone [TSH]) secreting pituitary adenomas (TSHoma) are rare adenomas presenting with hyperthyroidism due to impaired negative feedback of thyroid hormone on the pituitary and inappropriate TSH secretion. This article presents a case of TSH-secreting macroadenoma without any clinical hyperthyroidism symptoms accompanying immunoreaction with growth hormone (GH) and prolactin. A 36-year-old female patient was admitted with complaints of irregular menses and blurred vision. On physical exam, she had bitemporal hemianopsia defect. Magnetic resonance imaging (MRI) evaluation showed suprasellar macroadenoma measuring 33 mm × 26 mm × 28 mm was detected on pituitary MRI. She had no hyperthyroidism symptoms clinically. Although free T4 and free T3 levels were elevated, TSH level was inappropriately within the upper limit of normal. Response to T3 suppression and thyrotropin releasing hormone-stimulation test was inadequate. Other pituitary hormones were normal. Transsphenoidal adenectomy was performed due to parasellar compression findings. Immunohistochemically widespread reaction was observed with TSH, GH and prolactin in the adenoma. The patient underwent a second surgical procedure 2 months later due to macroscopic residual tumor, bitemporal hemianopsia and a suprasellar homogenous uptake with regular borders on indium-111 octreotide scintigraphy. After second surgery; due to ongoing symptoms and residual tumor, she was managed with octreotide and cabergoline treatment. On her follow-up with medical treatment, TSH and free T4 values were within normal limits. Although silent TSHomas are rare, they may arise with compression symptoms as in our case. The differential diagnosis of secondary hyperthyroidism should include TSHomas and thyroid hormone receptor resistance syndrome.

Key words: Inappropriate thyroid stimulating hormone, thyrotropin-secreting pituitary adenoma, thyroid stimulating hormone adenoma

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Introduction

Thyrotropin (thyroid stimulating hormone [TSH]) secreting pituitary adenomas (TSHomas) are an extremely rare cause of hyperthyroidism as well as a rare type of pituitary tumor. TSHomas constitute roughly 1% of all pituitary adenomas.^[1,2] Since the first case described in 1960,^[2] the diagnosis of TSHomas have increased due to the increasing physician awareness and presence of ultrasensitive TSH assays.^[3]

Despite the increase in free thyroid hormones; TSH is not suppressed, but rather inappropriately normal or high which reflects abnormal feedback. The differential diagnosis of secondary hyperthyroidism includes TSHomas and thyroid hormone resistance and primary hyperthyroidism, two conditions that have different pathogenesis and treatment.^[4]

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More than half of the cases of TSHomas present with obvious thyrotoxicosis symptoms, thus TSHomas are usually misdiagnosed as primary hyperthyroidism. Both TSHomas and primary hyperthyroidism may have symptoms of thyrotoxicosis and diffuse enlargement of the thyroid glands, but TSHomas usually present with milder symptoms.^[5] However, patients with this tumor do not exhibit the extrathyroidal systemic findings of Grave's disease such as ophthalmopathy or dermopathy.^[6,7] Rarely, some TSHomas may present with mild hyperthyroidism findings or no symptoms. Diagnosis usually occurs with routine blood tests incidentally or during pituitary imaging performed in order to unravel the etiology of compression symptoms including headache and visual defects.^[7-9] For this reason, they are called silent thyrotropinomas. TSHomas may have active or inactive biological TSH.^[8]

The major aims of the treatment of TSHomas are to provide euthyroid state both clinically and biochemically; as well as to alleviate the symptoms associated with pituitary mass.^[3]

The first therapy of TSHomas is surgical resection; if surgery is unsuccessful or contraindicated; radiotherapy and/or medical treatment with somatostatin-analogs, dopamine agonists, and rarely antithyroid drugs should be considered.^[10,11]

In this report, a case of silent TSHoma that is immunoreactive with growth hormone (GH) and prolactin is presented.

Case Report

A 36-year-old female patient was referred to our clinic from gynecology and ophthalmology departments for irregular menses and blurred vision. Her pelvic and breast examination was normal and no signs of virilization. Her visual defect had started 1-year ago. She had no sign or symptoms of thyrotoxicosis except for irregular menses. She had no acral growth and galactorrhea. She had no personal or family history of thyroid disorder. On the physical examination, her weight was 100 kg and her height was 165 cm. Her blood pressure was 110/70 mmHg, and she had regular heart rate of 88 bpm on auscultation. Thyroid was stage 1b, a moderately firm and mobile nodule measuring 1 cm × 1.5 cm was palpated in the right lobe. Hemianopsia was documented by computational perimetry and was bitemporal. Bitemporal hemianopsia was present.

Hormonal analyses revealed the elevations of free T4 and free T3 levels and TSH within the upper normal limits. Autoantibodies to thyroid peroxidase, thyroglobulin, and TSH receptors were negative. Likewise, whole blood count, urinary analysis, serum biochemistry, renal function tests, liver transaminases and blood electrolytes were within normal ranges. The levels of the other pituitary hormones were also within normal ranges [Table 1]. Level

of insulin-like growth factor 1 (IGF-1) (somatomedin-C) was 198 ng/ml and prolactin (PRL) level was 15 ng/ml. The findings suggested a pituitary adenoma that caused oligomenorrhea and bitemporal hemianopsia. Pituitary

Table 1: Endocrine analyses during the diagnosis of the thyrotropinoma

Parameters	Values	Ranges
TSH (uIU/mL)	4.49	0.34-5.6
Free T4 (ng/dL)	2.39	0.54-1.24
Free T3 (pg/mL)	6.99	1.8-4.7
Prolactin (ng/mL)	15	1.9-25
Estradiol (pg/mL)	49.5	30-119
FSH (mIU/mL)	6.13	1.2-9.0
LH (mIU/mL)	1.71	<14.7
ACTH (pg/mL)	11.5	7.2-63.3
Cortisol (ug/dL)	16	6.7-22.6
Somatomedin-C (IGF-1) (ng/mL)	198	177-382
Parathormon (pg/mL)	28	12-88
SHBG (nmol/L)	91.1	26-110
Ferritin (ng/mL)	85	11-306.8
Alpha subunit of TSH (IU/L)	3	0-0.9

TSH=Thyroid stimulating hormone; IGF-1=Insulin-like growth factor 1; FSH=Follicle-stimulating hormone; ACTH=Adrenocorticotrophic hormone

Table 2: The results of TRH stimulation (500 µ, iv, TRH)

	Baseline	30 min	60 min	90 min	120 min
Prolactin (ng/ml)	21	21.04	20.3	19.8	16.9
TSH (uIU/ml)	5.91	5.23	5.48	5.53	5.34

TSH=Thyroid stimulating hormone; TRH=Thyrotropin releasing hormone

Table 3: The results of T3 suppression

	Baseline	3 days	6 days	9 days
TSH (uIU/mL)	5.30 (0.34-5.6)	4.56	3.98	3.93
Free T4 (ng/dL)	2.20 (0.54-1.24)	1.85	2.07	1.65
Ferritin (ng/mL)	53.9 (11-306.8)	108.2	63.5	55.6
SHBG (nmol/L)	91.6 (26.1-110)	82.4		122.3
Creatin kinase (U/L)	33 (33-211)	30	29	34
Cholesterol (mg/dL)	142 (0-200)	111	104	108

TSH=Thyroid stimulating hormone; SHBG=Sex hormone binding globulin

Table 4: Laboratory values after second operation and long-acting octreotide therapy in follow-up

Parameters	Results	Ranges
TSH (uIU/mL)	1.14	0.34-5.6
Free T4 (ng/dL)	0.67	0.54-1.24
Free T3 (pg/mL)	3.25	1.8-4.7
Prolactin (ng/mL)	15.68	1.9-25
Estradiol (pg/mL)	53	30-119
FSH (mIU/mL)	5.25	1.2-9
LH (mIU/mL)	3.03	<14.7
Cortisol (ug/dL)	11	6.7-22.6
SHBG (nmol/L)	33.50	26-110
Ferritin (ng/mL)	20.8	11-306.8

TSH=Thyroid stimulating hormone; FSH=Follicle-stimulating hormone; SHBG=Sex hormone binding globulin; LH=Luteinizing hormone

magnetic resonance imaging (MRI) showed the presence of a large pituitary macroadenoma that was measured as 33 mm × 26 mm × 28 mm in three dimensions extending to suprasellar region and obliterating the suprasellar cistern

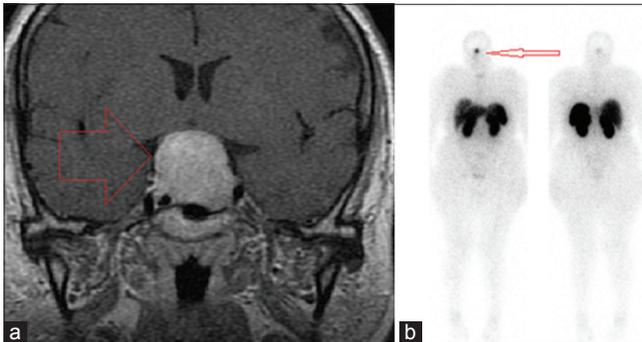


Figure 1: (a) A mass which is measured as 33 mm × 26 mm × 28 mm in three dimensions, extended to suprasellar region and obliterated the suprasellar cistern was shown, (b) Indium-111 octreotide scintigraphy showed a hypophyseal homogenous involvement

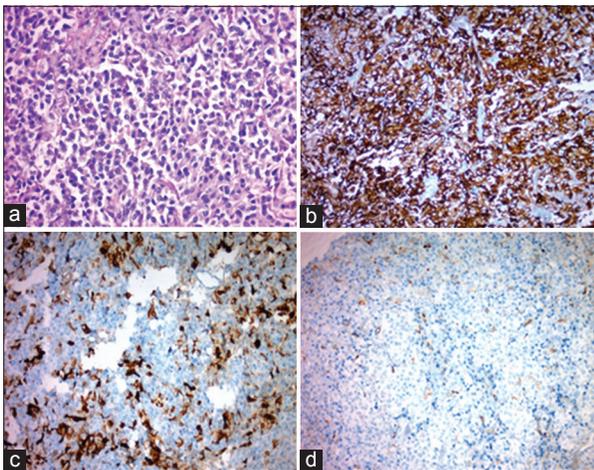


Figure 2: There were a diffuse pattern of cellular proliferations in the surgical samples suggesting a pituitary adenoma (H and E, ×200) (a); the immunohistochemical staining showed that the tumor cells were strongly reactive to thyrotropin stimulating hormone (b) and relatively mildly reactive to growth hormone (c), and focal reactive to prolactin (d)

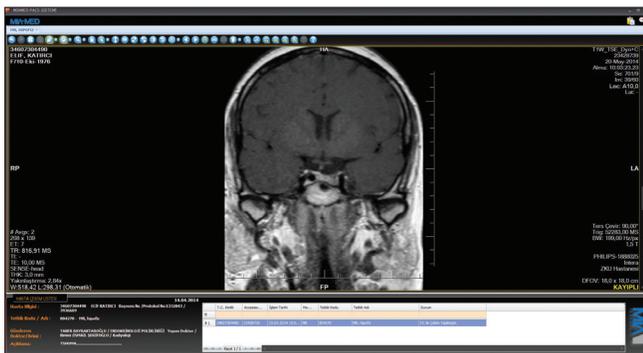


Figure 3: Pituitary magnetic resonance imaging images after 6 months from the second surgery

[Figure 1a]. Because of autonomous secretion in TSHomas, no increase in TSH levels to thyrotropin releasing hormone (TRH) stimulation test and no suppression in TSH levels after T3 administration [Tables 2 and 3]. The alpha subunit of TSH was measured high as 3 IU/L (0–0, 9). The alpha subunit to TSH ratio was high. These findings excluded thyroid hormone resistance and indicated that the pituitary lesion was a thyrotropinoma. A whole-body In-111-octreotide scintigraphy demonstrated an uptake in the pituitary region [Figure 1b]. There was also a nodule in the thyroid gland, it was measured 15 mm in the longest axis and had a cystic component with punctuate echogenities on sonographic evaluation. The samples of the nodule in the fine needle aspiration biopsy was negative for malignancy. Transsphenoidal adenomectomy was performed with steroid protection perioperatively. A widespread reaction with TSH and focal staining with PRL and GH was shown immunohistochemically in the adenoma [Figure 2]. Visual defect was not resolved after neurosurgery, and postoperative MRI showed presence of postoperative residual tumor. Serum TSH, FT4 and FT3 levels were still elevated, hence, a second operation was done 2 months later. The pathology of the resected tumor once again demonstrated widespread TSH in immunohistochemical staining [Figure 2a and b]. In addition, focal staining with PRL and GH was detected [Figure 2c and d], but there was no clinical or biochemical evidence of GH and prolactin co-secretion. Patient was followed-up approximately 4 months. Her visual defect persisted, residual adenoma was shown on MRI, TSH and free thyroid hormones were still high. We decided to administer long-acting octreotide and then cabergoline. After 3-month of treatment with these agents, her vision, menstrual cycles and the levels of serum thyroid hormones recovered [Table 4]. The antitumor and antisecretory response to medical treatment was excellent with significant tumor shrinkage. The treatment was well-tolerated, there were no significant side effects. The size of the adenoma on her last pituitary MRI [Figure 3] was measured as 11 mm. Currently, the patient with residual thyrotropinoma is followed-up on medical treatment without signs and symptoms of hypopituitarism.

Discussion

TSHomas are one of the rare causes of hyperthyroidism arising due to stimulation of the thyroid gland. They are frequently subject to unnecessary antithyroid therapy for years. There are cases who undergo thyroid surgery due to misdiagnosis of toxic nodular goiter or Grave's disease.^[1,9] Thyrotoxicosis is mild in some patients and even asymptomatic similarly to our patient.^[6] In National Institutes of Health series of 25 thyrotropinoma patients, three patients (12%) were asymptomatic although 22 had mild or overt thyrotoxicosis.^[6] They usually present as macroadenomas. While microadenomas in asymptomatic patient group are incidentally detected on routine blood

tests, macroadenomas are reported to be diagnosed as a result of compression symptoms.^[6,8,9,12] They are known as silent TSHomas. In this review, we presented a silent TSHomas with staining with GH and Prolactin immunoreactively.

Previously, a similar case with clinically and biochemically silent thyrotrophic adenoma could only be diagnosed after bilateral optic atrophy.^[9] Our case was in the third decade and was diagnosed as having macroadenoma during the investigations performed for complaints of blurred vision, which was caused by compression of the optic nerve. While the patient was clinically euthyroid, thyroid hormones were inappropriately elevated with normal TSH levels. The elevated alpha subunit ratio to TSH ratio helped to narrow down the diagnosis.

TSHomas are characterized by partial or complete loss of feedback regulation of thyroid hormones and consequently enlargement of the thyroid gland. Major biochemical abnormality is the unsuppressed serum TSH level with elevated free thyroid hormone levels.^[13] Although 75% of thyrotropinomas secrete, only TSH secretion of other pituitary hormones is encountered in 29% of cases; GH secretion was reported in 15% and prolactin secretion in 10%, FSH and LH secretion in 1.4% of cases. Therefore, it may lead to elevations in IGF-1 and prolactin levels.^[4,14,15] Plurihormonal hypophyseal adenomas that secrete TSH and GH are rarely reported.^[16-18] In contrast to case of Berker *et al.*,^[18] our patient had no acromegalic symptoms or elevated GH/IGF-1 levels. In some cases of GH-secreting adenomas, hyperthyroidism can be masked.^[16,19] Although in our case there was no clinical and the biochemical hypersecretory state for GH and prolactin, focal staining with prolactin and GH were detected with immunohistochemistry.

Disappearance of circadian TSH pattern and elevated alpha-subunit value are the most important biochemical abnormalities encountered.^[20,21] Alpha-subunit/TSH molar ratio is used beside to alpha-subunit measurement. This ratio is suggested to be the most useful method for discriminating TSHoma from thyroid hormones resistance. Sex hormone binding globulin and bone turnover markers that are the peripheral markers of thyroid hormone effect are elevated. In addition, dynamic tests like TRH stimulation, T3 suppression and octreotide suppression test are useful in establishing the diagnosis of secondary hyperthyroidism. TSHomas are sporadic cases in contrast to the family history is positive in thyroid resistant cases.^[1,6,8] Our patient had normal TSH levels inappropriately with elevated free thyroid hormone levels. TSH alpha-subunit levels and molar rate were increased. In addition, there was no response to TRH stimulation and T3 suppression test. With all findings, our diagnosis about patient was TSHoma.

Thyrotropinomas may be located in the sphenoid sinus, suprasellar region and rarely nasopharyngeal region when

they are ectopic. Octreotide scintigraphy may be useful for determining the localization of these tumors and to predicting the outcome of octreotide treatment.^[22] In our patient, a hypophyseal homogenous involvement was detected on the imaging with somatostatin receptor scintigraphy.

The first-line therapy of TSHomas is neurosurgery. But generally second surgical procedure is necessary. Only one-third of patients are cured with surgery. External radiotherapy and somatostatin receptor agonist \pm dopamine receptor agonists are the other treatment options in these patients who could not be treated with the initial surgical procedure like in our case or where surgery is contraindicated.^[1,6,8] TSH levels are normalized with somatostatin agonist therapy in 70% of TSHomas and decrease in tumor size is reported in 38% of cases similar to our patient.^[23]

Conclusion

Silent thyrotropinomas are rare neoplasms that may present with compression symptoms. It should be differentiated and diagnosed correctly. Furthermore, it should be kept in mind that the silent TSHomas may be present. Somatostatin-analog \pm dopamin agonists are alternative adjuncts to surgery for residual plurihormonal hypophyseal tumors.

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