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Case Report

Thyrotropin Secreting Pituitary Adenoma Accompanying a Silent Somatotropinoma

Tirotropin Sekrete Eden Pituiter Adenoma Eşlik Eden Sessiz Somatotropinoma

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ABSTRACT

Thyroid stimulating hormone (TSH) secreting pituitary adenomas are rare tumors manifested as hyperthyroidism with goiter in the presence of elevated TSH. We present a case with pituitary adenoma secreting both TSH and growth hormone (GH) with the prominent clinical findings of hyperthyroidism but without clinical findings of acromegaly. Pituitary magnetic resonance imaging revealed a macroadenoma. Transsphenoidal surgery was performed twice. The immunohistochemical staining showed that tumor cells were strongly reactive to GH and relatively mildly reactive to TSH. Control pituitary imaging revealed a residual macroadenoma, and long acting octreotide treatment was administered. After two years of the treatment, tumor size remained the same while thyroid function tests and insulin-like growth factor 1 (IGF-I) values returned to normal ranges. In conclusion, we always recommend hormonal examinations for all patients who have pituitary adenoma without signs and symptoms of acromegaly.

KEYWORDS: Thyrotropin, Pituitary adenoma, Growth hormone, Acromegaly

ÖZ

Tiroid stimule edici hormon (TSH) salgılayan pituiter adenomlar yüksek TSH seviyeleri ile birlikte hipertiroidi ve guatrın görüldüğü nadir tümörlerdir. Akromegali klinik bulgularının görülmediği, ön planda hipertiroidi kliniğinin yer aldığı TSH ve büyüme hormonu (GH) salgılayan piuiter adenomlu bir vakayı sunuyoruz. Pituiter manyetik rezonans görüntülemede makroadenom tespit edilerek iki defa transsfenoidal cerrahi uygulandı. İmmünhistokimyasal incelemede güçlü bir şekilde GH ve daha az oranda TSH ile boyanma izlendi. Kontrol pituiter görüntülemesinde rezidü makroadenom görülmesi nedeniyle uzun etkili oktreotid başlandı. İki yıllık tedavi sonrasında tümor boyutu sabit kalırken tiroid fonksiyon testleri ve insulin benzeri büyüme faktörü 1 (IGF-I) düzeyleri normale döndü. Sonuç olarak akromegali klinik bulguları olmasa dahi her zaman pitüiter adenomu olan hastaların değerlendirilmesinde hormonal incelemelerin yapılmasını öneriyoruz.

ANAHTAR SÖZCÜKLER: Tirotropin, Pituiter adenom, Büyüme hormonu, Akromegali

INTRODUCTION

Thyrotropin (thyroid stimulating hormone, TSH) -secreting adenomas (TSH-oma) are the least common type of tumors representing less than 1% of the total pituitary adenomas (3). Several untreated patients with TSH-oma were described as clinically euthyroid (2). Moreover, hyperthyroid features can be overshadowed by those of acromegaly in patients with mixed TSH/ growth hormone (GH) adenomas (4). We present an unusual case with pituitary adenoma co-secreting TSH and GH with signs of hyperthyroidism but without signs of acromegaly.

CASE REPORT

A 43-year-old man was admitted to the hospital with complaints of excessive sweating, tremor, palpitation and nervousness. He had received antithyroid therapy for thyrotoxicosis two years before referring to our polyclinic and withdraw the therapy seven months ago. No significant past or family history was elicited. On his physical examination, he had a pulse rate of 110/minute, moist and warm skin, and fine tremor of his hands. A goiter was palpated and was visible on neck extension. He had no history of acral growth, arthropathy, glucose intolerance, soft tissue growth, or skin

tags. Examination of the patient's old photographs failed to disclose any facial changes. Thyroid function tests pointed out that free triiodothyronine (FT3) and free thyroxine (FT4) were high in repeated examinations. His laboratory findings are presented in Table I. Radioactive iodine uptake was 25% and 38% at 4th and 24th hours respectively.

Thyroid ultrasonography showed multiple nodules at the right and left lobe and the parenchyma was homogenous. Thyroid fine needle aspirations from the nodules were benign. The alpha subunit to TSH molar ratio were high. Thyrotropin-releasing hormone injection failed to increase TSH and triiodothyronine suppression test failed to suppress TSH (Figure 1A, B). Octreotide (OCT) test suppressed TSH levels.

Growth hormone levels were not suppressed during the glucose-GH suppression test. Dexamethasone suppression test (2 mg) showed a suppressed cortisol level (0.38 µg/dL).

Pituitary magnetic resonance imaging revealed a 23x22x20 mm macroadenoma. The infundibulum was deviated to left and optic chiasm was intact. The patient was given OCT acetate 100 mcg four times daily s.c. for five days for

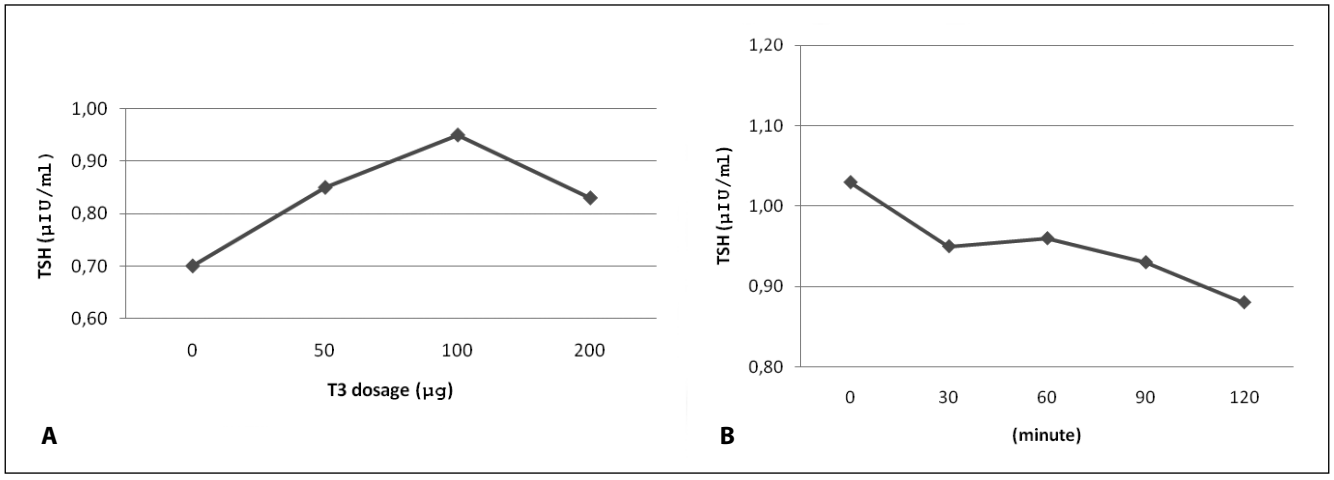

Figure 1: A) T3 suppression test, **B)** TRH stimulation test.

Table I: Results of the Baseline Endocrine Tests

	Normal Range	Patient's Results
Cortisol (µg/dl)	8.7 - 22	18.9
ACTH (pg/dl)	10 - 90	31
FSH (mIU/mL)	1.3 - 13.6	8.62
LH (mIU/mL)	1.2 - 10	6.6
Total testosterone (ng/mL)	2.4 - 9.5	3.27
Prolactin (ng/mL)	2.5 - 18	4.85
GH (ng/mL)	0 - 10	29.6
IGF-I (ng/ml)	119 - 494	927
TSH (µIU/ml)	0.35 - 4.94	1.34
FT3 (pg/ml)	1.7-3.7	6.68
FT4 (ng/dl)	0.7-1.48	2.48
Alpha subunit (µIU/ml)	0-0.8	1.3
Anti-T3 antibodies	<10	<1
Anti-T4 antibodies	<15	<1
SHBG (nmol/l)	10-80	76
Ferritin (ng/mL)	28-265	54
CPK (U/L)	25-200	63

ACTH: *corticotropin;* ***CPK:*** *creatinine phosphokinase;* ***FSH:*** *follicle stimulating hormone;* ***FT3:*** *free triiodothyronine;* ***FT4:*** *free thyroxine;* ***GH:*** *growth hormone;* ***IGF-I:*** *insulin-like growth factor 1;* ***LH:*** *luteinizing hormone;* ***SHBG:*** *sex hormone binding globulin.*

controlling hyperthyroidism preoperatively. Transsphenoidal surgery was then performed. The immunohistochemical staining showed that the tumor cells were strongly reactive to GH and relatively mildly reactive to TSH (Figure 2).

Three months after the operation, the FT3, FT4, GH, IGF-I levels were still high and GH levels were not suppressed in the glucose-GH suppression test (Figure 3A, B). Pituitary magnetic resonance imaging revealed a 16x18x20mm residual macroadenoma. Although the shoe size of the patient did not change during this period of time, mild blunting of the hands was observed. Then second operation was performed transsphenoidally. Three months after operation, IGF-I and FT4 levels were still high (Figure 3A, B). Control pituitary imaging revealed a 14x12x16 mm residual macroadenoma, so long acting OCT treatment (OCT LAR) of 20 mg a month was administered. However, the patient stopped taking medication without consulting his physician due to financial reasons and did not use medication for 1.5 – 2 years, and did not even come to follow-up visits. The patient was still diagnosed as hyperthyroid as a result of examinations performed at the end of the 2nd year. Physical examination of the patient revealed blunting of hands, swelling of nose and mild spacing in teeth, and OCT treatment was started again for the patient who had active acromegaly. After two years of treatment, thyroid function tests and IGF-I values were within normal ranges (Figure 3A, B). Although there was no significant shrinkage in tumor size as a result of two-year OCT LAR treatment, GH levels were suppressed less than 1 ng/ml on the glucose-GH suppression test.

DISCUSSION

Thyrotropin-secreting pituitary adenomas are uncommon neoplasms, accounting for approximately 1% of all pituitary adenomas and usually appear as macroadenomas (11). The first patient with hyperthyroidism secondary to a TSH-oma was diagnosed by measuring serum TSH levels with bioassay in 1960 (8). Recent years, reported TSH-oma cases were increased due to TSH measurement by means of ultrasensitive immunometric methods (2).

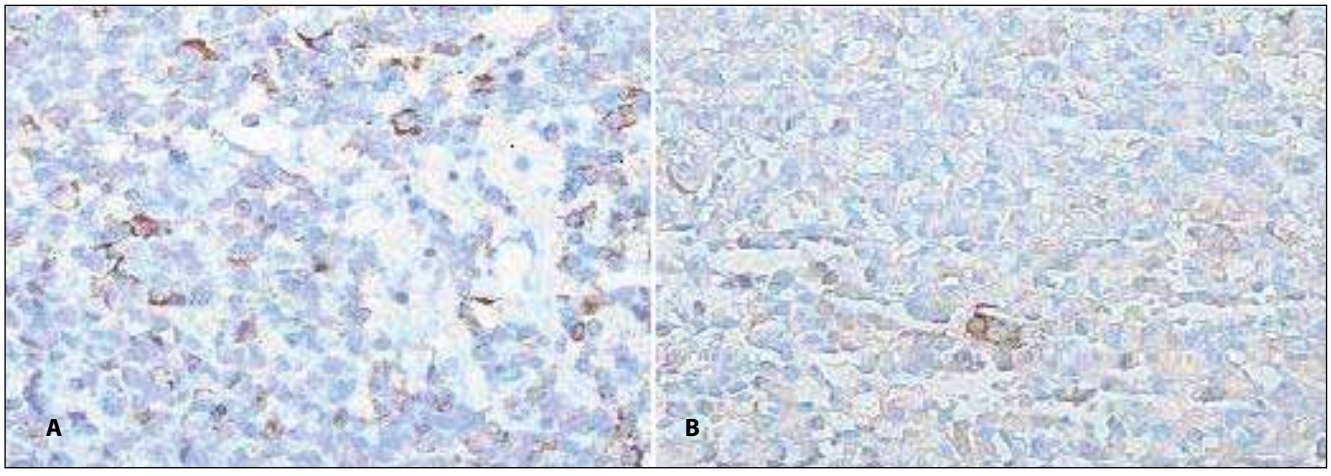

Figure 2: The cells in the surgical specimen showed expression of GH (right) and TSH (left) (x200).

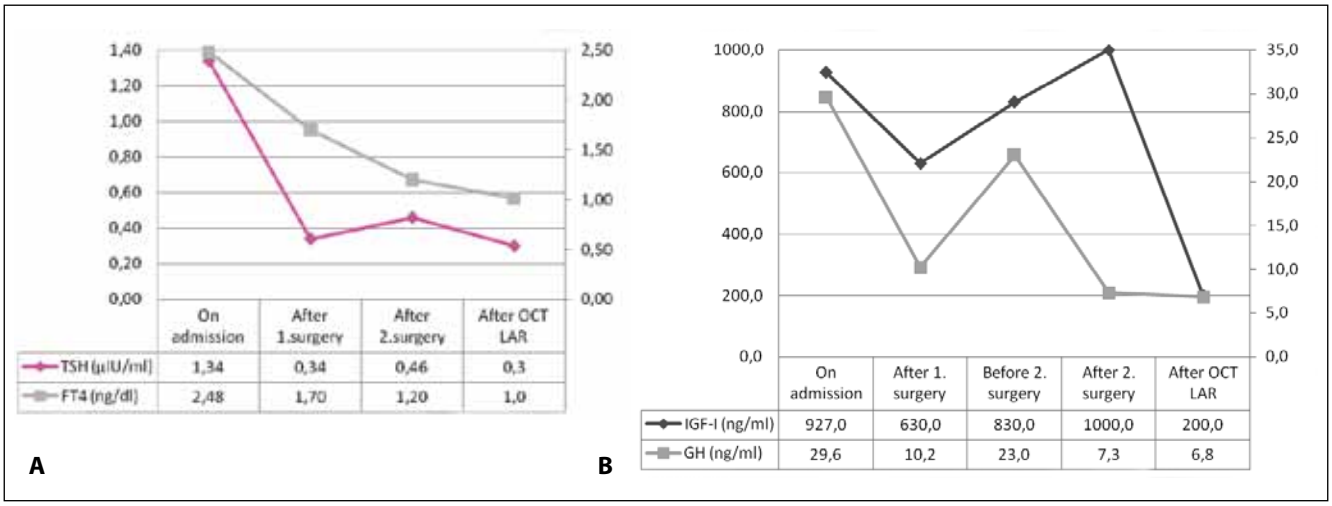

Figure 3: A) Follow-up of thyroid function tests of the patient, **B)** Follow-up of IGF-I levels of the patient

Among TSH-oma patients, 71% show only TSH hypersecretion, and 29% hypersecretion with other pituitary hormones. The most common co-secreted hormone is the GH. The frequency for growth hormone is 16%, prolactin 11%, FSH and LH 1.4% (6). Plurihormonal hypophyseal adenomas that secrete TSH and GH causing hyperthyroidism as in our case were rarely reported in previous years (4, 15).

Measurements of several parameters of peripheral thyroid hormone action have been proposed to quantify the degree of tissue hyperthyroidism. In our case, the bone parameters osteocalcin and deoxypyridinoline were high. The reason sex hormone binding globulin (SHBG) level is not high may be SHBG inhibition by GH that was pointed out previously in GH and TSH-secreting adenomas (2).

In some cases, especially with GH-secreting adenomas, hyperthyroidism can be masked (4, 12). In our case, the clinical signs of thyrotoxicosis were prominent, but the clinical signs of acromegaly were not distinct. Only the patient's nose was slightly enlarged. The admitting complaints "sweating and palpitations" were a result of thyrotoxicosis. Despite high GH and IGF-I levels, there was no clinical picture of acromegaly. Thus, this clinical picture may be due to low GH biological activity as previously reported with silent somatotropinomas (17). However, this theory was disproved by the elevation of serum IGF-I level. The lack of clinical signs then may be related to short duration of GH hypersecretion (9). However our patient had macroadenoma indicating that illness onset was not new and it could not be the reason for the mild clinical picture. However, excessive secretion of GH accompanying TSH-oma may have newly started and clinical findings could not appear yet as development of acromegaly may take a few years. Emergence of clinical findings of acromegaly at follow-up four years after diagnosis supports this theory.

In a study the time of onset of first symptoms and the duration from first symptoms to diagnosis (anamnestic time) were determined retrospectively from clinical, endocrinological, ophthalmological and localizing data in patients with pituitary adenoma (16). It is shown that the median anamnestic time is 5.0 years in women and 5.5 years in men for GH-secreting adenoma. In an epidemiological study analyzing major acromegaly series published between the years 1926 and 1996, the average delay in diagnosis determined from duration of symptoms or changes in photographic appearance was about 8 years (range 6.6–10.2 years) (7).

It has been demonstrated in follow-up of some functional pituitary tumors that they secrete different hormones. A study by Andersen et al. published in 2003 reported acromegaly development in some patients in follow-up of prolactinoma cases and recommended control of IGF-I in annual follow-ups of prolactinoma cases (1). The degree of GH hypersecretion might not have been sufficiently high to cause clinical signs of acromegaly. The answer to this question is still a matter of debate. In 2005 Sen et al. reported high GH and IGF-I levels in a case with silent somatotropinoma as in our patient (14). Otherwise, up to date many studies report slightly high or subnormal growth hormone and IGF-I levels in silent somatotropinomas (10, 13).

The first treatment option in TSH-omas and somatotropinomas is surgery, but generally it is not possible to excise these lesions totally as they are usually diagnosed at the macroadenoma stage. These tumors have fibrotic and invasive properties and only 1/3 of patients are surgically cured (12). Pituitary radiotherapy and/or medical treatment with somatostatin analogs are two valid alternatives if surgery is contraindicated or declined, as well as in the case of surgical failure.

Treatment of TSH-omas by somatostatin analogues revealed that 70% of patients' TSH levels become normal and 38% of patients' tumor sizes diminish by 20% (5). In our case, there was still a residual mass after two operations. There was no suppression by dynamic tests and OCT LAR was started. In the second year of OCT LAR, the patient was in remission with normal hormone levels. However, tumor size remained stable and there was no significant shrinkage in tumor size.

In conclusion, the coexistence of TSH-oma and somatropinoma is very rare and contrary to the literature acromegaly signs may be masked despite high GH and IGF-I levels, thus emphasizing the importance of systematic measurement of GH and IGF-I levels in patients with pituitary adenoma. Somatostatin analogues may be an alternative to surgery with plurihormonal hypophyseal tumors which are not totally excised.

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