CASE REPORT

Thyrotropin-secreting microadenoma and the importance of a prompt diagnosis: A case report

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Abstract

Background: The prevalence of thyrotropin-secreting pituitary adenomas, most being macroadenomas, is one to two cases per million inhabitants. Their differential diagnosis may be challenging, especially for microadenomas.

Case description: We present the case of a 50-year-old male with progressive neck enlargement, hot sudorific hands, anorexia, diarrhea, and weight loss over the preceding three months.

Laboratory evaluation revealed high thyroid hormones, predominantly high free triiodothyronine of 7.74 pg/mL (reference range 2.3-4.2), with a non-suppressed thyroid stimulating hormone (TSH) of 1.73 μIU/mL (reference range 0.55-4.78). A high level of suspicion directed additional evaluation that revealed a high total alpha-subunit of glycoprotein hormones (αGS) and αGS/TSH ratio. Magnetic resonance imaging revealed a six mm pituitary lesion.

A microthyrotropinoma was diagnosed, and long-acting octreotide was initiated before surgery for symptomatic control. Endoscopic transnasal transsphenoidal tumor resection was performed months later. The patient was in remission one year after surgery with no pituitary deficits.

Conclusions: Reaching an accurate diagnosis on time is crucial for deciding the optimal therapeutic approach and preventing and decreasing the frequency of endocrine and neurological complications. HIPPOKRATIA 2022, 26 (4):157-160.

Keywords: Pituitary adenoma, thyroid hormone resistance, somatostatin analogs, transsphenoidal surgery, thyrotropin-secreting pituitary adenoma

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Introduction

Thyrotropin-secreting pituitary adenomas, also known as TSHomas, are extremely rare tumors, comprising approximately one to two percent of all pituitary adenomas[1]. Globally, the prevalence is one to two cases per million inhabitants, although this number is probably underestimated, considering the increased number of reported cases in the past decades[1,2]. The reasons for this increase in prevalence have yet to be established. However, the rise could be attributed to factors such as the use of more sensitive thyroid function assays and advanced imaging techniques. Another possibility is that the actual frequency of this tumor type is increasing[3]. Distinguishing pituitary TSHomas from thyroid hormone resistance (THR) may be challenging, particularly for microadenomas[4]. In order to reduce complications, achieving a timely diagnosis is essential. This reinforces the importance of the present case reporting a microthyrotropinoma with prominent goiter in a 50-year-old man, with a six-year follow-up at our center.

Case report

A 50-year-old man with multinodular goiter was referred to the endocrinology department due to progressive neck enlargement he noticed over the preceding three months, along with hot sudorific hands, anorexia, diarrhea, and non-quantified weight loss. He denied other symptoms. Besides Gilbert's syndrome, his past medical record was unremarkable. He reported no family history of thyroid pathology.

Laboratory evaluation revealed high thyroid hormones, predominantly high free triiodothyronine (FT3) of 7.74 pg/mL (reference range 2.3-4.2), with a non-suppressed thyroid stimulating hormone (TSH) of 1.73 μIU/mL (reference range 0.55-4.78). The subsequent biochemical evaluation showed normal anti-thyroid antibodies, high sex hormone binding globulin (SHBG), chromogranin A, alpha-subunit of glycoprotein hormones (αGS), and αGS/TSH ratio. The remaining pituitary function was also normal (Table 1), and we found no evidence of other endocrine neoplasia. There was no TSH or αGS

Table 1: Baseline endocrine evaluation of the reported patient conducted at various stages of his clinical course.

Parameter	At diagnosis	2 weeks after long-acting octreotide	postop day 1	3 months postop (under levothyroxine 50 mcg/day)	5 years postop (no substitutive therapy)	Reference range
TSH	1.73	0.28	0.07	0.08	0.56	0.55-4.78 µIU/mL
Total T3	2.08					0.60-1.81 pg/mL
Total T4	11.7					4.5-10.9 µg/dL
FT3	7.74	3.63		3.06	3.26	2.3-4.2 pg/mL
FT4	1.93	1.12	1.26	1.14	0.9	0.8-1.76 ng/dL
Total testosterone	650				631	240-830 ng/dL
SHBG	106				69	10-57 nmol/L
Chromogranin A	7.6				1.3	<3 nmol/L
αGS	1.4					<0.8 ng/mL
αGS/TSH molar ratio*	8.09					>1.0 in 75-85% of patients with TSHoma

Postop: after surgery, FT3: free triiodothyronine, FT4: free thyroxine, SHBG: sex hormone binding globulin, αGS: Alpha-subunit of glycoproteic hormones, TSH: thyroid stimulating hormone, *: The αGS/TSH molar ratio is defined as αGS (in ng/mL), divided by TSH (in µIU/mL) and multiplied by 10.

response to the administration of thyrotropin-releasing hormone (TRH) (Table 2). Bone densitometry revealed osteoporosis (femoral neck T score: -1.9; lumbar spine T score: -3.0).

Thyroid ultrasonography showed a remarkably enlarged thyroid gland, with right and left lobe dimensions of 100 x 40 x 40 mm and 120 x 60 x 50 mm, respectively. Two solid nodules of 50 and 70 mm were evident in the left lobe, both with benign cytology.

Pituitary magnetic resonance imaging (MRI) revealed a right-sided pituitary-confined, six mm lesion with regular borders, hypointense in T1-weighted, and hyperintense in T2-weighted images. No deviation of the pituitary stalk was observed (Figure 1).

Based on the baseline thyroid function, the result of the TRH stimulation test, and the MRI images, the most likely diagnosis was a TSHoma. A 20 mg dose of long-acting octreotide was administered, with normalization of thyroid function, followed by transsphenoidal tumor resection. Histopathological examination revealed an adenoma with reticulin fiber disruption in Gomori staining. On immunohistochemistry, the neoplastic cells were positive for TSH antibody (Figure 2), whereas immunostains for GH, prolactin, and adrenocorticotropic hormone (ACTH) were negative, confirming the diagnosis of a TSHoma.

Over the following five months, secondary hypothyroidism was transiently present, requiring levothyroxine replacement. The thyroid function gradually returned to normal. The patient achieved clinical and biochemical remission one year after surgery with no pituitary hormone deficits. Additionally, a slight reduction in the goiter was observed. Subsequently, we conducted follow-up examinations every six months for the next three years. Eventually, we extended the observation intervals to once a year. The thyroid function remained normal, with no pituitary hormone deficits.

Discussion

The hallmark of TSH-producing pituitary tumors is an elevation of thyroid hormone levels in the presence of inappropriately unsuppressed TSH levels. Thereby, distinguishing these tumors from THR may be challenging. Baseline thyroid function alone does not distinguish these entities. In the reported case, the absence of a family history of THR, elevated SHBG, αGS and αGS/TSH ratio, blunted TSH and αGS response to TRH, and FT3/free thyroxine (FT4) normalization with long-acting octreotide, together with a small pituitary adenoma, pointed towards a TSHoma diagnosis.

Below, important features considered in this differential diagnosis are highlighted. TSHomas are rarely associated with familial inheritance. Contrarily, THR results from inherited mutations in the genes of thyroid hormones beta receptors[5]. Serum SHBG is also helpful in the differential diagnosis due to its thyroid hormone-driven increased hepatic synthesis in TSHomas[6]. Exceptionally, in patients with mixed growth hormone (GH)/TSH adenoma, normal SHBG levels can be present due to the inhibitory action of GH on SHBG synthesis and secretion[7]. Moreover, TSHomas are frequently associated with elevated αGS expression and an elevated αGS/TSH

Table 2: Thyrotropin-releasing hormone stimulation test (400 µg) at diagnosis.

	Basal	30´	60´	90´	120´	Reference range
TSH	1.67	1.69	1.92	1.70	1.81	0.55-4.78 µIU/mL
αGS	1.4	1.5	1.3			<0.8 ng/mL

αGS: Alpha-subunit of glycoproteic hormones, TSH: thyroid stimulating hormone.

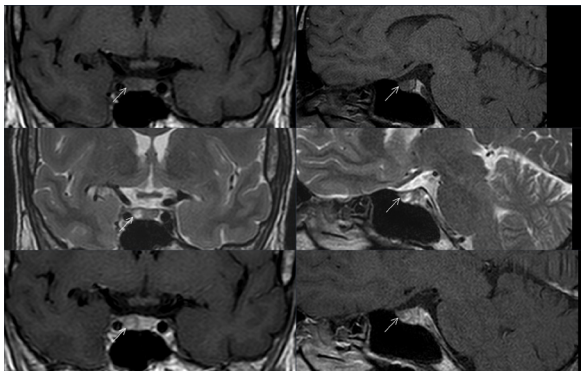

Figure 1: Images of pituitary magnetic resonance imaging at diagnosis revealing a microadenoma (indicated by the arrows).

molar ratio, presumably from excessive and unbalanced αGS formation. TRH stimulation test is also helpful in this differential diagnosis. In TSHomas, the TSH does not respond to TRH, while TSH usually rises in patients with THR. At each point during the TRH test, concurrent measurement of αGS is helpful in establishing the diagnosis, as the molar αGS/TSH ratio is high (>1) in almost 85 % of patients with TSHomas. A blunted TSH and αGS response to the TRH stimulation test also favors the diagnosis. Normalization of the FT3/FT4 ratio with long-acting octreotide therapy is the expected response in 90 % of patients with TSHomas[8].

The clinical presentation of TSHomas is widely variable. Microadenomas are usually silent but can present with symptoms of hyperthyroidism. In approximately half of the patients with TSHomas, fatigue, tremor, heat intolerance, weight loss, and diarrhea are present. Up to 20 % of patients have predominately cardiac symptoms, including palpitations, chest pain, and dyspnea[9]. Our patient reported hot sudorific hands, anorexia, diarrhea, and weight loss. In contrast, macroadenoma patients may present with compressive symptoms such as visual field defects and headaches. Also, compression of the remaining pituitary and pituitary stalk may elicit symptoms of hypopituitarism and hyperprolactinemia, respectively. Goiter is frequently present. Interestingly, the goiter was the symptom our patient described as most significant. Both TSH-producing adenomas and THR may present with goiter. However, contrary to other causes for goiter, a total thyroidectomy is generally not recommended and may worsen the patient's clinical condition.

In contrast to the case we report, TSHomas are usually large, 70 to 90 % being macroadenomas at diagnosis[10,11]. This has been mostly attributed to a delayed diagnosis. Our patient was diagnosed within three months of the onset of symptoms. A TSHoma can go unnoticed if TSH is measured alone as thyroid function screening in a patient with goiter. In fact, this patient's TSH levels were within the reference range; nevertheless, a high index of clinical suspicion and valorization of a discretely but inappropriately elevated FT4 directed the diagnosis and allowed for a prompt diagnosis, resulting in a subsequent reduction of comorbidities.

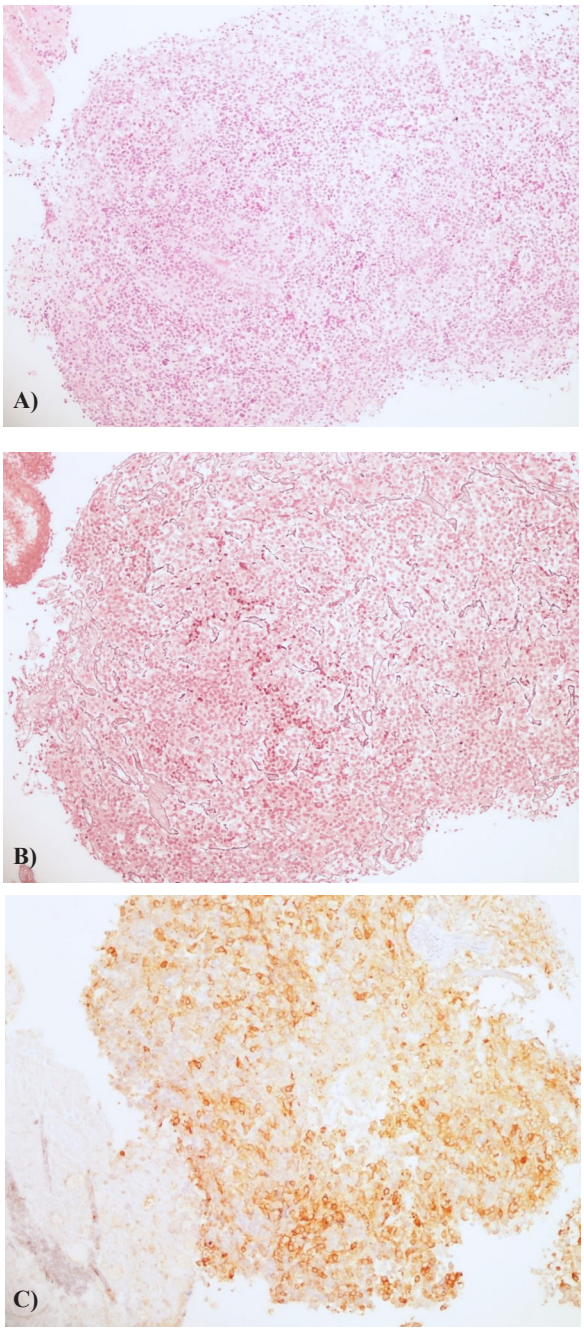

Figure 2: Histopathological images showing a pituitary adenoma, a) Hematoxylin and eosin staining, b) Gomori reticulin staining, and c) immunohistochemistry analysis using the Ventana BenchMark Ultra platform with an antibody specific for thyroid stimulating hormone (TSH) (TSH Rabbit Polyclonal Antibody). Magnification in all images is x100.

Although most TSHomas only secrete TSH (71 %), this secretion is often accompanied by unbalanced hypersecretion of αGS. In this case, the patient displayed isolated production of TSH. In about one-fourth of TSHomas, synchronous hypersecretion of other anterior pituitary hormones is found, mainly GH or PRL, which

are known to share common transcription factors with TSH, such as PROP-1 and Pit-1. Undoubtedly, the most frequent association (18 %) is hypersecretion of TSH and GH, followed by hypersecretion of TSH and PRL (10 %).

Endoscopic transnasal transsphenoidal surgery is the first-line therapy for patients with TSHomas, as it is associated with a low incidence of complications[4]. Somatostatin analogs are typically used as a neoadjuvant treatment before surgery since most TSHomas express a variable number of somatostatin receptors[12]. Administering somatostatin analogs effectively reduces thyroid hormone levels and tumor size[13]. Indeed, our patient responded to the long-acting octreotide therapy administered before surgery, which normalized thyroid function. Radiotherapy is an option for resistant cases[5].

With this case, we aim to raise clinical awareness of the relevance of an adequate interpretation of thyroid function according to the clinical context. Also, we expect to help clinicians in differential diagnosis and treatment decisions in this rare but relevant clinical scenario. We emphasize the crucial importance of promptly reaching the correct diagnosis, as it allows for selecting the optimal therapeutic approach and helps prevent and reduce the frequency of endocrine and neurological complications.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

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