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Case Report

Thyroid-Stimulating Hormone/Growth Hormone Cosecreting Pituitary Adenoma With Normal Thyroid-Stimulating Hormone Level

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Abstract

Thyroid-stimulating hormone (TSH; thyrotropin) adenoma is a rare pituitary tumor that can be missed due to its subtle symptoms. We are reporting a 67-year-old man with history of ventricular fibrillation on amiodarone who presented with acute headache and right third cranial nerve palsy. His computed tomography (CT) scan revealed a 2.2-cm suprasellar mass, consistent with pituitary apoplexy, and he underwent pituitary tumor resection. Preoperational hormonal workup revealed TSH 0.25 mIU/mL (0.25 IU/L) (normal reference range: 0.35-4.94 mIU/mL; 0.35-4.94 IU/L), free thyroxine (T4) 3.17 ng/dL (40.80 pmol/L) (normal reference range: 0.7-1.48 ng/dL; 9.78-19.05 pmol/L), and total triiodothyronine (T3) 91 ng/dL (140 nmol/L) (normal reference range: 58-159 ng/dL; 89-244 nmol/L). Initial differential diagnoses included TSH-producing pituitary adenoma (TSH-oma) and amiodarone-induced thyrotoxicosis. His free T4 declined significantly postoperatively, favoring a TSH-oma diagnosis. The pathology report showed a TSH and growth hormone (GH) cosecreting adenoma. Furthermore, he had a normal thyroid uptake scan, as well as negative thyroid antibodies, making primary thyroid diseases less likely. A high free T4 with normal TSH 3 years ago, prior to the start of amiodarone, suggested a long disease duration. This case demonstrates challenges in diagnosing TSH-oma, especially in patients with normal TSH and concurrent amiodarone use.

Key Words: thyroid-stimulating hormone (TSH) secreting pituitary adenoma (TSH-oma), acromegaly, cosecretion, amiodarone-induced thyrotoxicosis, arrhythmia, pituitary macroadenoma

Abbreviations: ACTH, adrenocorticotropic hormone; AIT, amiodarone-induced thyrotoxicosis; CT, computed tomography; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MIBI, technetium-99m methoxy-isobutyl isonitrile; RTH, resistance to thyroid hormone; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH-oma, thyrotropin-secreting pituitary tumor.

Introduction

Thyrotropin-secreting pituitary tumor (TSH-oma) is a rare pituitary tumor subtype that comprises less than 1% of pituitary adenomas [1]. TSH-oma is often a mono-secreting tumor; however, up to 30% have been found to cosecrete other pituitary hormones [2].

TSH-oma can cause central hyperthyroidism [1]. Symptoms of hyperthyroidism in patients with TSH-oma can be subtler than those with primary hyperthyroidism [3]. This could possibly be explained by a reduction in the biological activity of pituitary-secreted thyroid-stimulating hormone (TSH; thyrotropin) in TSH-oma [4], and the tumor's long-standing duration [1]. Also, in cases of TSH-oma with plurihormonality, symptoms of other hormones can be overlapping or be hidden, making the diagnosis even more challenging [2]. Patients with TSH-oma can also have an enlarged thyroid gland and this may lead to misdiagnosis of primary thyroid diseases [1].

Another challenge in diagnosing TSH-oma is to differentiate it from resistance to thyroid hormone (RTH) because thyroid function tests are similar in both cases with elevated thyroid hormones and high or inappropriately normal TSH [5]. Of note, incidental pituitary adenomas can also be seen in patients with RTH; however, alpha subunit is typically elevated in TSH-oma [1].

First-line treatment for TSH-oma is pituitary tumor resection. However, misdiagnosing a TSH-oma can lead to inappropriate treatment, such as thyroidectomy, radioactive iodine ablation, and/or antithyroid medication use. Infrequently, TSH-oma also accompanies primary thyroid diseases such as Graves disease [4], toxic nodule [6], or thyroid cancer [2], which can pose an even bigger challenge in treatment.

Case Presentation

A 67-year-old man with a complex past medical history of hypertension, ventricular tachycardia, ventricular fibrillation leading to cardiac arrest, atrial fibrillation, non-ischemic cardiomyopathy with heart failure, renal cancer status post resection, and osteoporosis with right hip fracture presented to the emergency room with acute severe headache associated with a right third cranial nerve palsy for 2 days. He had a head

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computed tomography (CT) scan done, which revealed a suprasellar mass, prompting him to have assessment by neurosurgery and endocrinology.

Diagnostic Assessment

His blood pressure was normal at 121/61 mmHg; heart rate was mildly low at 50 beats per minute, while on a beta blocker and amiodarone. Right eye exam revealed loss of function of his superior, medial, and inferior rectus, a complete ptosis, and pupillary dilation of 6 mm with no reaction to light, consistent with right third cranial nerve palsy. The rest of his neurological exam was normal. Humphrey visual test and optical coherence tomography were unremarkable. He did not have acromegalic or cushingoid features.

An emergent head CT scan revealed a $1.4 \times 2.2 \times 2.0$ cm sellar mass extending into the right cavernous sinus and into the suprasellar cistern, abutting the optic chiasm with mild superior displacement of the optic chiasm. The lesion had mild heterogeneity, demonstrating several foci of hyperdensity, which could represent small intralesional hemorrhage (Fig. 1). Magnetic resonance imaging could not be performed due to the presence of an implantable cardioverter-defibrillator. Given the clinical picture with severe acute headache, right cranial nerve palsy, and imaging findings, a diagnosis of pituitary apoplexy was made, and the patient underwent urgent transsphenoidal resection of the sellar mass. Hormonal work up before the surgery is shown in Table 1 and was remarkable for mildly low TSH and high free thyroxine (T4). Insulin-like growth factor 1 (IGF-1), for which results were available later, was high, and alpha subunit was normal. Other pituitary axes showed low prolactin and luteinizing hormone (LH), suggesting hypopituitarism. The initial differential diagnoses included possible TSH-producing pituitary tumor, given very high free T4 and inappropriately detectable TSH; hyperthyroidism due to amiodarone-induced thyrotoxicosis (AIT) type 1 or AIT type 2; and toxic multinodular goiter.

Treatment

Our patient underwent prompt transsphenoidal endoscopic endonasal resection of his pituitary adenoma. The tumor was necrotic and swollen with areas of hemorrhage. Pathology revealed diffuse necrosis consistent with pituitary apoplexy, antigen Kiel 67 (Ki-67) was 1% to 2% in viable cells. Immunohistochemistry revealed diffuse cytoplasmic positivity for synaptophysin, occasional cells staining weakly for TSH (1% staining in the focal area), rare cells staining positive for growth hormone (GH) (7%-8% in very focal area) and focal cells staining for prolactin, weak membranous staining present with somatostatin receptor 2a in 40% to 50% of lesional cells and somatostatin receptor 5 was immunoreactive. Otherwise,

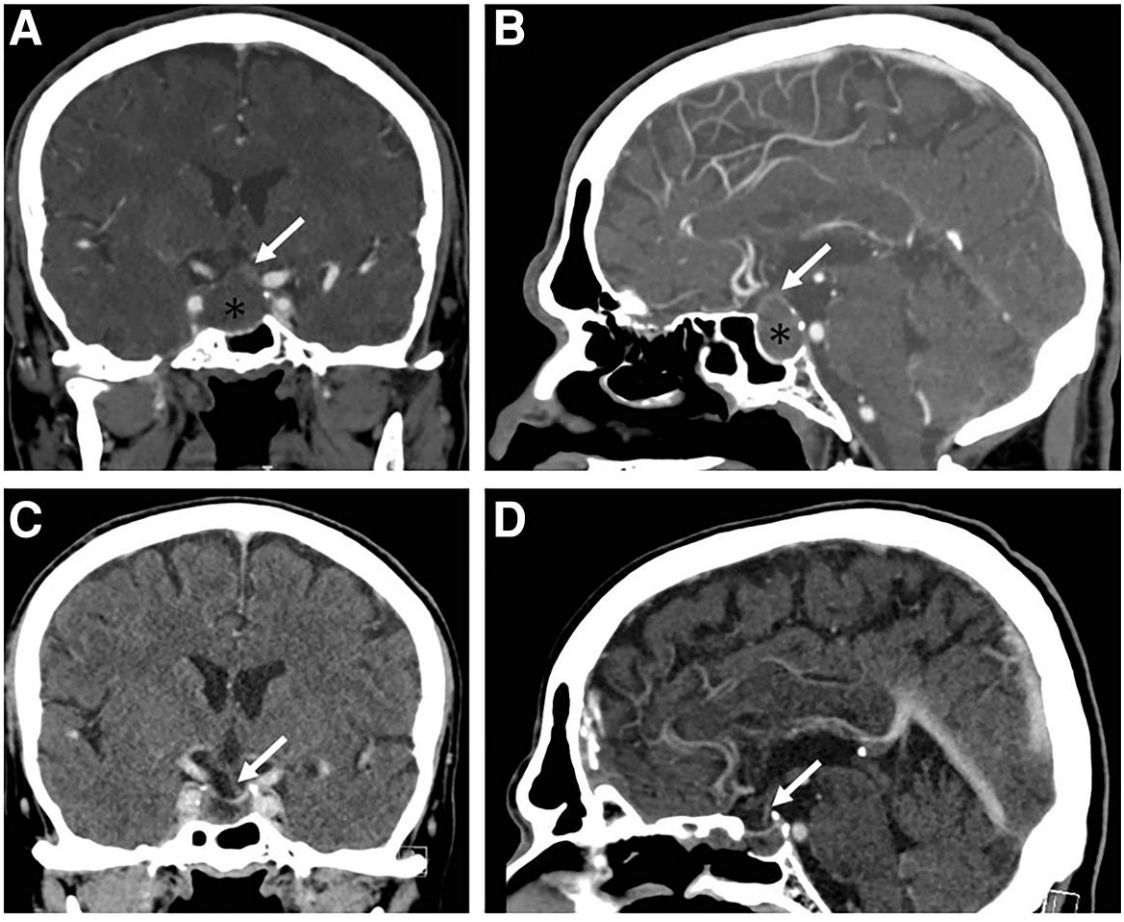

Figure 1. Coronal and sagittal computed tomography imaging (CT) with contrast preoperatively (panels A and B) demonstrating a pituitary macroadenoma (black star; panels A and B) with compression of the normal pituitary and pituitary stalk (white arrow; panels A and B). A 2-year postoperative CT imaging with contrast (panels C and D) demonstrating complete resection of the macroadenoma with preservation of the normal pituitary and pituitary stalk (white arrow). The patient could not have magnetic resonance imaging due to the presence of an implantable cardioverter-defibrillator.

Table 1. Preoperative and postoperative most recent pituitary hormone results

Hormone tested	Presurgery	Normal range	Postsurgery	Normal range
TSH	**0.25 mIU/mL (0.25 IU/L)**	0.35-4.94 mIU/mL (0.35-4.94 IU/)	0.88 mIU/mL (0.88 IU/L) *Postop 23 months*	0.35-4.94 mIU/mL (0.35-4.94 IU/)
Free T4	**3.17 ng/dL (40.80 pmol/L)**	0.7-1.48 ng/dL (9.78-19.05 pmol/L)	1.5 ng/dL (19.3 pmol/L) *Postop 23 months*	0.8-1.8 ng/dL (10.3-23.2 pmol/L)
Total T3	91 ng/dL (140 nmol/L)	58-159 ng/dL (89-244 nmol/L)	83 ng/dL (128 pmol/mL) *Postop 14 months*	76-181 ng/dL (117-278 nmol/L)
Cortisol	6.1 µg/dL (5 PM) (168 nmol/L)	N/A	15.6 µg/dL (8 AM) (430 nmol/L) *Postop 23 months*	>12 µg/dL (>331 nmol/L)
ACTH	9 pg/mL (1.98 pmol/L)	6-50 pg/mL (1.32-11 pmoL/L)	13 pg/mL (2.86 pmol/L) *Postop 1 month*	6-50 pg/mL (1.32-11 pmoL/L)
Prolactin	**1.1 ng/mL (1.1 µ/L)**	2.1-17.7 ng/mL (2.1-17.7 µ/L)	2.5 ng/mL (2.5 µ/L) *Postop 23 months*	2.0-18 ng/mL (2.0-18 µ/L)
LH	**1.4 mIU/mL (1.4 IU/L)**	1.5-9.3 mIU/mL (1.5-9.3 IU/L)	2.9 mIU/mL (2.9 IU/L) *Postop 5 months*	1.6-15.2 mIU/mL (1.6-15.2 IU/L)
FSH	2.9 mIU/mL (2.9 IU/L)	1.4-18.1 mIU/mL (1.4-18.1 IU/L)	3.4 mIU/mL (3.4 IU/L) *Postop 5 months*	1.6-8.0 mIU/mL (1.6-8.0 IU/L)
Testosterone	NA		**41 ng/dL** (1.42 nmol/L) *Postop 5 months*	250-1100 ng/dL (8.67-38.14 nmol/L)
GH	2.3 ng/mL (2.3 µg/L)	≤7.1 ng/mL (≤7.1 µg/L)	0.4 ng/mL (0.4 µg/L) *Postop 14 months*	≤7.1 ng/mL (≤7.1 µg/L)
IGF-1	**396 ng/mL (52 nmol/L)**	41-279 ng/mL (5.4-36.5 nmol/L)	50 ng/mL (6.5 nmol/L) *Postop 23 months*	41-279 ng/mL (5.4-36.5 nmol/L)
Alpha subunit	0.2 ng/mL (0.2 µg/L)	0.1-0.5 ng/mL (0.1-0.5 µg/L)	NA	

Abnormal values are shown in bold font. Values in parenthesis are International System of Units (SI).

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; NA, not available; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine.

adrenocorticotropic hormone (ACTH), p53, and follicle-stimulating hormone (FSH) staining were negative. Staining for transcription factors revealed positivity with pituitary-specific transcription factor 1 (PIT-1), and negative for T-box transcription factor and steroidogenic factor 1. Initial pathology report concluded that this lesion was most likely a somatotroph adenoma. Given the clinical suspicion of TSH-oma, further immunohistochemical staining with GATA-binding protein (GATA) 3 was performed, which came back positive in a subset of viable cells that stained with PIT-1, indicating that this pituitary tumor was a TSH/GH cosecreting pituitary adenoma (Fig. 2).

The patient was treated with stress dose steroid medicines perioperatively and discharged on replacement dose.

Outcome and Follow-Up

After surgery, the patient's headaches and right third cranial nerve palsy resolved. His TSH level immediately decreased, then gradually increased into the normal range. Free T4 decreased to the high end of the normal range and triiodothyronine (T3) stayed in the normal range (Table 2). The significant decline in free T4 after the surgery further confirmed TSH-oma as the cause of his hyperthyroidism. Free T4 was either high normal or mildly higher than the normal range, while the patient was on amiodarone. Mildly high free T4 and normal T3 postoperatively can be explained by amiodarone's inhibition of peripheral conversion of T4 to T3. Most recently, amiodarone was discontinued approximately 2 years after pituitary surgery and free T4 decreased to mid-normal range (Table 2).

To differentiate the hyperthyroidism from primary thyroid diseases, thyroid peroxidase antibody, thyroglobulin antibody, and thyroid-stimulating immunoglobulin were tested, which all resulted negative. A thyroid ultrasound was obtained, revealing a multinodular goiter. To rule out AIT and toxic nodules, a technetium-99m methoxy-isobutyl isonitrile (MIBI) scan was performed and did not show increased or decreased uptake in the thyroid gland.

During follow-up, we received the patient's previous thyroid function tests from an outside hospital from when he had been admitted for ventricle fibrillation cardiac arrest, about 3 years

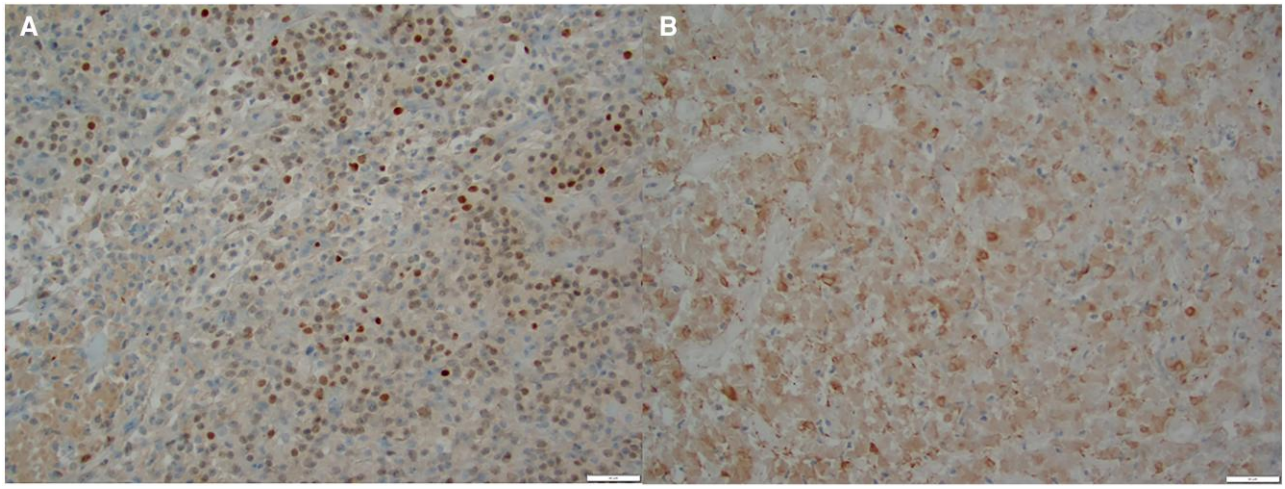

Figure 2. Immunohistochemistry, ×200 magnification, nuclear focal immunopositivity with GATA-3 (A), and patchy cytoplasmic immunopositivity with GH staining (B), scale bar at lower right corner is 50 microns.

prior to the pituitary surgery. The laboratory findings revealed high free T4 4.64 ng/dL (59.72 pmol/L) (normal reference range: 0.76-1.46 ng/dL; 9.78-19.05 pmol/L) and inappropriately normal TSH 1.16 mIU/mL (1.16 IU/L) (normal reference range: 0.358-3.740 mIU/mL; 0.358-3.740 IU/L) (Table 2). These laboratory values were obtained before the initiation of amiodarone, indicating that the patient likely had hyperthyroidism due to TSH-oma for at least 3 years and his abnormal thyroid function tests were unlikely to have been secondary to AIT.

Re-evaluation of morning cortisol and ACTH levels on multiple occasions showed normal values, suggestive of an intact hypothalamus pituitary adrenal axis. IGF-1 and GH levels were normalized after surgery. Free and total testosterone levels were low with inappropriately normal LH and FSH. On repeat, testosterone levels remained low on multiple occasions and given patient's significant fatigue and osteoporosis, he was started on testosterone replacement. The patient's TSH and IGF-1 values continued to stay in normal range. Preoperative and postoperative hormone results are included in Table 1.

Head CT scan 3 months after the surgery revealed a small 6 mm area of nodular enhancement along the right posterior lateral sella, which was not seen on his postoperative 2-year scan. No evidence of recurrence was observed.

We decided to monitor thyroid nodules with imaging after the initial investigation, due to patient's health status, and the most recent follow-up thyroid ultrasound revealed a significant decrease in size of all his nodules, which is explainable because the thyroid stimulation through TSH and GH secretion was already eliminated.

Discussion

Most laboratory assays are designed to reflex abnormal TSH levels to thyroid hormones. Amiodarone treatment requires at least a baseline thyroid function test and routine monitoring afterward; however, we speculate that patient's TSH had always been in the normal range, which led to the failure to diagnose his central hyperthyroidism earlier.

In our case, we have carefully checked for thyroid autoimmune antibodies, but they were all negative, making concomitant primary thyroid diseases less likely. Given that the patient had a goiter and was on amiodarone, we also performed MIBI thyroid scan to rule out AIT. This modality was chosen instead of radioactive iodine uptake and scan out of concern for interference of a high iodine load with amiodarone, and the need for continuing amiodarone in this case. Based on a study by Piga et al, MIBI scan was proposed as an effective tool to differentiate different types of AIT [7].

Although alpha subunit was not elevated in our case, a normal alpha subunit does not exclude a TSH-oma diagnosis [3]. Dynamic tests such as T3 suppression and thyrotropin-releasing hormone (TRH) stimulation tests are recommended to help diagnose TSH-oma and differentiate it from RTH [1]. These were not done in our case due to the urgent need for surgical intervention, and the clinical picture with acute third nerve palsy accompanied by a clear sellar mass on imaging made TSH-oma diagnosis more likely than RTH.

Initial pathological diagnosis in our case was challenged by the presence of necrotic tissue, which compromised the immunostaining evaluation to a certain extent. Further staining with GATA3 helped us confirm TSH/GH cosecreting pituitary adenoma. GATA2 is a transcription factor involved in the development of both thyrotroph and gonadotroph cells. However, GATA2 immunostaining is not widely used. Within the GATA family, GATA3 is highly homologous with GATA2, including the region recognized by the antibody to GATA3. Successful use of GATA3 immunoreactivity to detect gonadotroph tumors or pituitary tumors with TSH expression has been demonstrated [8].

In TSH/GH cosecreting pituitary adenoma, thyroid cancer risk is higher due to both TSH and GH stimulation. In TSH-oma, up to 4.8% of the patients also have thyroid cancer [2]. However, the priority is to treat TSH-oma first, as compared to thyroid cancer. In our case, we carefully performed a thyroid ultrasound, which revealed a multinodular goiter; and on repeated thyroid ultrasound after pituitary tumor removal, his nodules all decreased in size.

Our patient had a good outcome after the pituitary surgery with normalization of IGF-1 and free T4 levels. However, due to the rarity of TSH-omas, there is no well-established biochemical criteria for remission yet. Besides TSH and free T4 levels, other clinical criteria being used are normalization of alpha subunit, disappearance of neurological manifestations, remission from hyperthyroid manifestations, and positive

Table 2. Thyroid function tests trending over time

Thyroid Labs	3 years preop	1 day preop	1 day postop	1 month postop	3 months postop	5 months postop	23 months postop
TSH	1.16 mIU/mL (1.16 IU/L)	**0.25 mIU/mL (0.25 IU/L)**	**0.03 mIU/mL (0.03 IU/L)**	**0.25 mIU/mL (0.25 IU/L)**	**0.27 mIU/mL (0.27 IU/L)**	0.53 mIU/mL (0.53 IU/L)	0.88 mIU/mL (0.88 IU/L)
Normal range	0.358-3.740 mIU/mL (0.358-3.740 IU/L)	0.35-4.94 mIU/mL (0.35-4.94 IU/L)	0.35-4.94 mIU/mL (0.35-4.94 IU/L)	0.35-4.94 mIU/mL (0.35-4.94 IU/L)	0.35-4.94 mIU/mL (0.35-4.94 IU/L)	0.4-4.5 mIU/mL (0.4-4.5 IU/L)	0.35-4.94 mIU/mL (0.35-4.94 IU/L)
Free T4	**4.64 ng/dL (59.72 pmol/L)**	**3.17 ng/dL (40.80 pmol/L)**	**1.71 ng/dL (22.01 pmol/L)**	1.8 ng/dL (23.2 pmol/L)	1.36 ng/dL (17.51 pmol/L)	1.8 ng/dL (23.2 pmol/L)	1.5 ng/dL (19.3 pmol/L)
Normal range	0.76-1.46 ng/dL (9.78-19.05 pmol/L)	0.7-1.48 ng/dL (9.01-19.05 pmol/L)	0.7-1.48 ng/dL (9.01-19.05 pmol/L)	0.8-1.8 ng/dL (10.3-23.2 pmol/L)	0.8-1.8 ng/dL (10.3-23.2 pmol/L)	0.8-1.8 ng/dL (10.3-23.2 pmol/L)	0.8-1.8 ng/dL (10.3-23.2 pmol/L)
Total T3	N/A	91 ng/dL (140 nmol/L)	76 ng/dL (117 nmol/L)	109 ng/dL (167 nmol/L)	99 ng/dL (152 nmol/L)	128 ng/dL (197 nmol/L)	N/A
Normal range		58-159 ng/dL (89-244 nmol/L)	58-159 ng/dL (89-244 nmol/L)	76-181 ng/dL (117-278 nmol/L)	58-159 ng/dL (89-244 nmol/L)	76-181 ng/dL (117-278 nmol/L)	

Abnormal values are shown in bold font. Values in parenthesis are International System of Units (SI).
Abbreviations: TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine.

T3-suppression test with undetectable TSH and no response to TRH. However, these evaluations might be limited if the patient's results were normal before treatment [1].

Learning Points

- It might be challenging to differentiate between hyperthyroidism due to TSH-oma and hyperthyroidism from amiodarone-induced thyrotoxicosis or other primary thyroid diseases.
- TSH-oma can induce arrhythmia, heart failure, and osteoporosis. TSH-oma can be associated with thyroid cancer and special consideration should be made into concurrent monitoring. Management of TSH-oma with associated primary thyroid diseases requires prioritization of treatment/stabilizing of TSH-oma first.
- GATA3 immunostaining, which is more available than GATA2 immunostaining, can be used to help confirm pituitary gonadotroph and TSH-producing tumors.

Contributors

All authors made individual contributions to authorship. V.P. and B.K.: manuscript preparation and involved in care of the patient. F.E.: Diagnosis and management of this patient and review of the manuscript. M.G.S.: Performed transsphenoidal resection of the pituitary adenoma, management of this patient, and review of the manuscript. K.A.: performed the staining of the tumor, review of the manuscript. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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