Thyrotropinoma and multinodular goiter: A diagnostic challenge for hyperthyroidism

Duygu Yazgan Aksoy, Arzu Gedik, Nese Cinar, Figen Soylemezoglu, Mustafa Berker, Omer Alper Gurlek
Department of Internal Medicine, Section of Endocrinology and Metabolism, Departments of Pathology and Neurosurgery, Medical School, Hacettepe University, Ankara, Department of Internal Medicine, Section of Endocrinology and Metabolism, Dokuz Eylul University, Izmir, Turkey

Introduction

Central hyperthyroidism due to a thyrotropin (TSH)-secreting pituitary adenoma (thyrotropinoma) is a rare cause of hyperthyroidism. Thyrotropinomas usually present with signs and symptoms suggestive of hyperthyroidism and mass effects of the pituitary tumor.[1] Hyperthyroidism symptoms are milder compared to those originating from the thyroid itself. Presence of concomitant thyroid pathology may complicate the clinical picture, resulting in unnecessary thyroid ablative procedures.[2-3] Mixed pituitary tumors may co-secrete the growth hormone and prolactin, which may further change the presentation.[4]

Thyroid hormone resistance must be excluded in patients with suspicion of thyrotropinoma, where normal or high serum TSH concentrations accompany an elevated total and/or free thyroid hormone concentrations in both conditions.[5] Markers of peripheral thyroid hormone action and dynamic tests aid in the differential diagnosis.[6] Surgery, radiotherapy, and medical treatment (somatostatin analogs and/or dopamine agonists) are the treatment options.[7]

Presence of thyroid autoimmunity or thyroid nodules may create a diagnostic challenge.[7] We herein present a case with a thyrotropinoma co-secreting growth hormone (GH) with multinodular goiter. She has developed hyperthyroidism due to a toxic nodule after pituitary surgery for adenoma.

Case Report

A 63-year-old female patient was admitted to our university hospital with knee pain. The pain was present for more than ten years, but recently became intense and resistant to analgesics. She had mild hypertension, which was under control. She had exophthalmus and multiple bilateral thyroid nodules on physical examination. There was no family history of thyroid disease.

Thyroid function tests revealed high freeT3 (FT3) and freeT4 (FT4) levels with high TSH, on two consecutive tests. All other laboratory tests including thyroid auto-antibodies were normal except high follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels, indicative of menopause [Table 1]. The GH and age- and sex-matched IGF-1 levels were normal. The alpha subunit level was within normal range. GH suppression was obtained with the oral glucose tolerance test.

On ultrasonography, the right thyroid lobe measured 26 × 28 × 56 mm and the left thyroid lobe measured 29 × 30 × 61 mm. The isthmus was 15 mm and there were multiple nodules with the greatest having a diameter of 28 × 14 × 24 mm, on the right lobe. Thyroid scintigraphy revealed a minimally hyperplastic gland...
with hypoactive nodularity. Thyroid fine needle aspiration biopsy was consistent with benign cytology.

The thyrotropin-releasing hormone (TRH) test before and after the T3 suppression test was applied [Table 2]. There was no response to the TRH and the results did not change after suppression with T3 preparation. An adenoma on the left side, with a 9 x 11 mm diameter, was present on pituitary magnetic resonance imaging (MRI). The tumor was hypointense in T1W Gd (+) and hyperintense in the T2W sequences. The sella basement had widened and the infundibulum was deviated to the right [Figure 1 (A&B)].

Endoscopic endonasal transsphenoidal surgery was performed and the adenoma was removed totally [Figure 1 (C&D)]. Immunohistochemical examination of the tumor showed that it was a plurimorphous plurihormonal adenoma co-secreting TSH and GH [Figure 2 (A&B&C&D)]. The postoperative anterior pituitary hormone levels were within normal reference range, including the thyroid hormones (TSH: 2.41 μIU/mL, FT3: 4.7 pmol/L, FT4 18.2 pmol/L).

Two months after pituitary surgery, the patient developed overt thyrotoxicosis with suppressed TSH levels (TSH was 0.009 uIU/mL). Thyroid scintigraphy revealed a hyperactive nodule. Radioactive iodine treatment was given. The patient was rendered euthyroid, and she is being followed without any recurrence of pituitary tumor or thyrotoxicosis.

**DISCUSSION**

The TSH-secreting adenoma is a rare cause of hyperthyroidism. It is usually benign, arising from the monoclonal expansion of neoplastic thyrotropes. Patients usually present with symptoms of thyrotoxicosis or pituitary mass. Diagnosis is usually delayed, patients present with macroadenoma and cure of the disease becomes almost impossible. Surgery is still the mainstay of the treatment, although somatostatin analogs may be used as medical therapy. Radiotherapy is an option for resistant cases.[8,9]

Thyroid hormone resistance is caused by inherited mutations of the thyroid hormone receptor beta. In this situation, the pituitary gland becomes resistant to inhibitory feedback effects of the circulating thyroid hormones, while the peripheral tissues respond normally.[10]

### Table 1: Laboratory parameters of the patient before surgery

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (μIU/mL)</td>
<td>1.58</td>
<td>0.27-4.2</td>
</tr>
<tr>
<td>FT3 (pmol/L)</td>
<td>8.16</td>
<td>3.1-6.8</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>44.43</td>
<td>12-22</td>
</tr>
<tr>
<td>Anti-thyroid peroxidase Ab (IU/ml)</td>
<td>9.0</td>
<td>0-30</td>
</tr>
<tr>
<td>Anti-thyroglobulin Ab (IU/ml)</td>
<td>&lt;20</td>
<td>0-40</td>
</tr>
<tr>
<td>PRL (ng/mL)</td>
<td>8.29</td>
<td>1.2-29.93</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>15.3</td>
<td>10.39-64.57</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>31.74</td>
<td>2.58-150.53</td>
</tr>
<tr>
<td>Morning cortisol (ug/dL)</td>
<td>13.5</td>
<td>5-25</td>
</tr>
<tr>
<td>ACTH pg/mL</td>
<td>13.1</td>
<td>0-46</td>
</tr>
<tr>
<td>Growth hormone (ng/ml)</td>
<td>0.459</td>
<td>0.06-10</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>232</td>
<td>78-258</td>
</tr>
<tr>
<td>Alpha subunit (mIU/mL)</td>
<td>0.85</td>
<td>0.1-1.6</td>
</tr>
<tr>
<td>SHBG (nM)</td>
<td>171</td>
<td>30-100</td>
</tr>
</tbody>
</table>

TSH = Thyroid stimulating hormone, FT3 = Free triiodothyronine, FT4 = Free thyroxine, PRL = Prolactin, LH = Luteinizing hormone, FSH = Follicle stimulating hormone, ACTH = Adrenocorticotropic hormone, IGF-1 = Insulin like Growth factor-1, SHBG = Sex hormone binding globulin

### Table 2: TRH test before and after T3 suppression test

<table>
<thead>
<tr>
<th></th>
<th>0 minute</th>
<th>20 minutes</th>
<th>40 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>TSH 1.72</td>
<td>1.77</td>
<td>1.82</td>
</tr>
<tr>
<td>After</td>
<td>TSH 1.74</td>
<td>1.72</td>
<td>1.65</td>
</tr>
</tbody>
</table>

TSH (μIU/mL) = Thyroid stimulating hormone

**Figure 2:** (a) Monotonous cellular neoplasm (HE), (b) without a reticulin framework (Reticulin stain), (c) immunohistochemically expressing TSH (c) and GH (d)

**Figure 1:** Preoperative (a and b) and postoperative (c and d) MRI of the patient.
Patients with multiple hormone secreting adenomas may manifest with dominance of one single hormone, but our patient was asymptomatic. She had no symptoms related to thyrotoxicosis or acromegaly.[11,12] High levels of thyroid hormones were incidentally detected. The GH and IGF-1 levels were normal before surgery.

The presence of concomitant thyroid disease complicates the clinical picture in patients with suspicion of central hyperthyroidism.[7,13,14] Patients may undergo unnecessary diagnostic tests and even ablative procedures.

The most specific test for thyrotropinoma is a late response to TRH followed by elevated alpha-subunit, elevated TSH, and an elevated alpha-subunit/TSH ratio. Absolute values of the alpha subunit can be misleading if used alone. We have ruled out thyroid hormone resistance with the TRH test. Unexpectedly, the alpha-subunit level was normal and the alpha-subunit/TSH ratio was less than one. Of late, a patient with GH, TSH, and FSH, along with low alpha-subunit levels has been reported.[15-18] A subgroup of thyrotropinomas with a low alpha-subunit should always be kept in mind when making a differential diagnosis of central hyperthyroidism.

The TSH secretion by thyrotropinomas shares many characteristics of other pituitary hormone-secreting adenomas. Abnormalities in GH and PRL secretion can range between decreased regularity to overt hypersecretion, suggesting tumoral transformation of the thyrotrope lineage cells.[19] The presence of GH positivity with an absence of the clinical findings of acromegaly can be due the inability of the tumor cells to secrete a growth hormone.

The critical point regarding patients with TSH-secreting pituitary adenomas is to discriminate the pathologies originating from the thyroid itself. The presence of ultrasensitive assays for TSH measurement will allow clinicians to recognize central hyperthyroidism from other causes of thyrotoxicosis, where TSH is almost always low in the latter. We have excluded hyperthyroidism originating from the thyroid itself by thyroid imaging and evaluation of thyroid function tests and also thyroid auto-antibodies.

The novelty of this case is the consecutive appearance of two different etiologies of hyperthyroidism in one patient. The first episode of thyrotoxicosis was due to thyrotropinoma and the second episode was due to a thyroid nodule, which became hyperactive later. Clinical presentations like our case may be misleading and puzzling. TSH-secreting adenomas may be kept in mind by an internist as a possible cause of hyperthyroidism. On the other hand, the presence of thyrotropinomas does not exclude the possibility of hyperthyroidism due to the thyroid gland itself.

REFERENCES


