Thyroid storm induced by TSH-secreting pituitary adenoma: a case report

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Abstract. Thyroid stimulating hormone-secreting pituitary adenomas (TSHomas) are uncommon tumors of the anterior pituitary gland. Patients with TSHomas may present with hyperthyroidism, but the incidence of thyroid storm due to TSHomas has yet to be determined. We report a rare case of thyroid storm caused by TSHoma in a 54-year-old woman. Preoperatively she had symptoms of excessive sweating and palpitation. Blood tests showed inappropriate secretion of TSH with blood TSH 6.86 µU/mL, fT3 19.8 pg/mL, and fT4 5.95 ng/dL. Magnetic resonance imaging (MRI) revealed a pituitary tumor with maximum diameter of 13 mm that was extirpated through transsphenoidal route. After operation the patient was stuporous and thyroid storm occurred presenting with hyperthermia, hypertension, and tachycardia. It was well managed with nicardipine, midazolam, steroids, and potassium iodide. Immunohistochemical staining of tumor specimen was positive for TSH and growth hormone (GH). One year after operation, fT3 and fT4 levels were still high. As her tumor was diagnosed to be GH- and TSH-producing adenoma, octreotide injection therapy was started, which normalized thyroid hormone levels. This is the second reported case with thyroid storm due to TSHoma and emphasizes the importance of strategies with interdisciplinary cooperation for prevention of such emergency conditions.

Key words: TSH secreting pituitary adenoma, Thyroid storm, Transsphenoidal surgery

THYROID stimulating hormone-secreting pituitary adenomas (TSHomas) are caused by a clonal expansion of abnormal TSH-producing pituitary cells. Previous data showed that TSHomas account for less than 1% of all pituitary adenomas [1, 2]. Since then, the recorded number of patients with TSHomas appears to have increased along with the introduction of ultrasensitive TSH immunometric assays as the first line test of thyroid function [3, 4]. The recently reported incidence is now much higher at 1-3% among pituitary adenomas [3, 5].

The incidence of thyroid storm has been noted in less than 10% of patients hospitalized for thyrotoxicosis [6, 7]. TSHoma may present with hyperthyroidism [4], but the incidence of thyroid storm due to TSHomas has yet to be determined. So far only one case has been reported [8]. We here report on a patient with thyroid storm induced by transsphenoidal operation for TSHoma.

Case Report

An otherwise healthy woman was found to have thyroid gland enlargement 15 years earlier at a health check. Hyperthyroidism was detected and Graves’ disease was suspected but she was lost to follow-up. At the age of 54, the woman was admitted to a local hospital with chief complaint of palpitation and excessive sweating for a year. Endocrinological tests showed hyperthyroidism and high TSH levels. Magnetic resonance imaging (MRI) of the brain revealed a pituitary tumor of 9x13x8 mm in the sella (Fig. 1).

She was referred to Kagoshima University Hospital...
Physical examination revealed that she was thinly built, 151.2 cm in height, 43.5 kg in weight (BMI: 19.0), and had excessive sweating. Her blood pressure was 135/84 mmHg and heart rate was 107 beats/min with a regular rhythm. She had thyroid gland enlargement but no exophthalmos or acromegalic features. There was also no evidence of visual impairment, congestive heart failure, or neurological deficits. Endocrinological tests suggested syndrome of inappropriate secretion of TSH (SITSH), with TSH 6.86 µU/mL, fT3 19.8 pg/mL, and fT4 5.95 ng/dL. During anterior pituitary stimulation tests using TRH, LHRH, CRH, and GRF, the levels of TSH did not increase. The responses of other hormone levels were normal (Table 1). GHRP-2 test also showed normal response of GH (Table 2) but IGF-1 level was very low (15 ng/mL).

A month later, the patient was readmitted for surgical treatment. At this time, blood fT3, fT4 and TSH levels had further increased (TSH 9.19 µU/mL, fT3 20.2 pg/mL, and fT4 6.98 ng/dL). Excessive sweating and palpitation had worsened with further weight loss. Preoperative use of octreotide was precluded because Japanese health insurance did not cover its use for TSHoma. In this situation, we prepared to treat the emerging thyroid storm with an endocrinologist, anesthesiologist, and intensive care unit team.

First, transsphenoidal surgery (TSS) was performed with 100 mg hydrocortisone intravenously. The tumor was quite fibrotic, but gross total resection was successfully achieved. Immediately after surgery, body for detailed checkup.

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**Table 1** Preoperative and postoperative results of TRH-LHRH-CRH-GRF-loading test

<table>
<thead>
<tr>
<th></th>
<th>Pre-operation</th>
<th>Post-operation</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Peak (60 min)</td>
</tr>
<tr>
<td>TSH (µU/mL)</td>
<td>6.86</td>
<td>7.30</td>
</tr>
<tr>
<td>PRL (ng/mL)</td>
<td>9.3</td>
<td>14.6 (30 min)</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>20.0</td>
<td>77.6 (60 min)</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>19.9</td>
<td>34.3 (90 min)</td>
</tr>
<tr>
<td>GH (ng/mL)</td>
<td>1.7</td>
<td>2.9 (90 min)</td>
</tr>
<tr>
<td>CORT (µg/dL)</td>
<td>3.2</td>
<td>26.2 (90 min)</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>14.9</td>
<td>-</td>
</tr>
</tbody>
</table>

Parenthetical number of (Peak) is time of appearance.

TSH, thyroid-stimulating hormone; PRL, prolactin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; CORT, cortisol; ACTH, adrenocorticotropic hormone

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**Table 2** Preoperative and postoperative results of GHRP-2-loading test

<table>
<thead>
<tr>
<th></th>
<th>Pre-operation</th>
<th>Post-operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Peak (45 min)</td>
</tr>
<tr>
<td>GH (ng/mL)</td>
<td>1.3</td>
<td>26.4 (45 min)</td>
</tr>
<tr>
<td>CORT (µg/dL)</td>
<td>5.2</td>
<td>18.1 (30 min)</td>
</tr>
</tbody>
</table>

Parenthetical number of (Peak) is time of appearance.

GH, growth hormone; CORT, cortisol
Thyroid storm induced by TSHomas

considerably decreased from preoperative levels but remained high (TSH 2.22 µU/mL, fT3 10.4 pg/mL, and fT4 2.32 ng/dL). TSH levels did not increase during the stimulation test, but other hormones were within normal range (Tables 1, 2). IGF-1 levels were very low as before. MRI of brain showed no apparent residual tumor. One year after operation, fT3 and fT4 levels were still high. As her tumor was diagnosed to be GH- and TSH-producing adenoma, long-acting octreotide treatment (octreotide-LAR; 20 mg every 4 weeks) was started, which normalized thyroid hormone levels (TSH 1.46 µU/mL, fT3 2.8 pg/mL, and fT4 1.60 ng/dL).

Discussion

TSHomas are rare pituitary tumors but are often aggressive and invasive in nature [9, 10]. Usually, TSHoma is diagnosed in the fifth and sixth decades of life and occurs more frequently in women [11, 12]. TSHomas are often plurihormonal. Approximately 60% concomitantly secrete GH and/or prolactin (PRL) [13] as in our case. Patients may present with typical temperature rose to 38°C before extubation, systolic blood pressure was 189 mmHg, and the pulse rate increased to 160 beats/min. After extubation the patient was in restless stuporous state (Glasgow Coma Scale: E3V4M6) and body temperature rose to 38.3°C. Based on the diagnosis of thyroid storm, injections of nicardipine (0.5 mg), midazolam (3 mg), and hydrocortisone (100 mg) were administered intravenously. Vital signs returned to normal but patient was still stuporous and was given intravenous steroid injections (three injections of 100 mg hydrocortisone which was followed by two injections of 2 mg betamethasone) during 51 hours after surgery. Per os potassium iodide (100 mg/day) was given twice, at 6 hr and 12 hr after surgery (Fig. 2). By 12 hr after surgery, symptoms had improved. TSH and fT3 levels were normal but fT4 level was slightly high (TSH 0.52 µU/mL, fT3 3.5 pg/mL, and fT4 2.33 ng/dL) on second postoperative day. Immunohistochemically the tumor was positive for TSH and GH (Fig. 3).

At postoperative 3 months, without any adjuvant treatment, basal levels of TSH, fT3, and fT4 levels were considerably decreased from preoperative levels but remained high (TSH 2.22 µU/mL, fT3 10.4 pg/mL, and fT4 2.32 ng/dL). TSH levels did not increase during the stimulation test, but other hormones were within normal range (Tables 1, 2). IGF-1 levels were very low as before. MRI of brain showed no apparent residual tumor. One year after operation, fT3 and fT4 levels were still high. As her tumor was diagnosed to be GH- and TSH-producing adenoma, long-acting octreotide treatment (octreotide-LAR; 20 mg every 4 weeks) was started, which normalized thyroid hormone levels (TSH 1.46 µU/mL, fT3 2.8 pg/mL, and fT4 1.60 ng/dL).

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1134

Fig. 3 Photomicrographs of surgical specimen
A: Hematoxylin and eosin staining showed sheet-like proliferations of round to cuboidal cells with acidophilic or chromophobic cytoplasm among fine vascular network, consistent with pituitary adenoma. There were no malignant findings (A: ×200).
B: Immunostaining for thyroid-stimulating hormone showed universal positivity in neoplastic cells (B: ×200).
C: 20 to 30% of the tumor cells were immunopositive for growth hormone (C: ×200).

clinical signs and symptoms of excessive thyroid hormone production, including thyroid goiter, weight loss, palpitation, tremor, excessive sweating, and fatigue [14]. Some patients may have visual impairment and pituitary insufficiency [4, 11].

Currently, the first line therapy of patients with TSHoma is surgical resection of the tumor [15]. But, as TSHoma are more fibrotic and invasive than other pituitary adenomas [5], surgical remission is limited to 50-70% [5, 11, 16]. Somatostatin analogs (SSAs) including octreotide are commonly used as second-line treatment [15, 17]. Somatostatin receptors are highly expressed on TSHomas [18]. SSAs effectively reduce TSH secretion in more than 80% of patients and induce shrinkage in about 40-80% of the tumors [4, 19, 20].

Thyroid storm, also referred to as thyrotoxic crisis, is an acute and life-threatening hypermetabolic condition requiring emergency treatment. It is triggered by excessive release of thyroid hormones in individuals with thyrotoxicosis. Thyroid storm is usually precipitated by a stressful event such as surgical procedure, trauma, or illness [21, 22]. Its mortality rate is reported to be 9.5-11% [23]. The criteria of thyroid storm in Japan is thyrotoxicosis with at least one central nervous system manifestation and one of the following: fever (≥38°C), tachycardia (≥130 beats/min), congestive heart failure (CHF), or gastro-intestinal (GI)/hepatic manifestations. An alternative criteria is a combination of thyrotoxicosis and at least three combinations of fever (≥38°C), tachycardia (≥130 beats/min), CHF, or GI/hepatic manifestations [22]. In this case, body temperature postoperatively rose to over 38°C, pulse rate increased to 160 beats/min, and also the patient became restless. Thus, the diagnosis of thyroid storm was made. To our knowledge, only one case of thyroid storm due to TSHoma has been previously reported in the literature [8]. An 18-year-old male patient presented with severe headache and was found to have a large suprasellar tumor and a mildly elevated level of TSH. Thyroid storm developed immediately after surgical resection of the pituitary mass. Propylthiouracil and beta-blockers controlled the postoperative acute
symptoms of thyrotoxicosis [8].

In our patient, intravenous administration of hydrocortisone, which inhibits peripheral conversion of T4 to T3 [24], nicardipine, and midazolam at the emergence of thyroid storm suppressed it and prevented further deterioration. Thionamides restore euthyroidism by preventing thyroid hormone synthesis, but several weeks may be needed to completely restore euthyroid status [24]. Potassium iodide was given with the aim of rapid control of overactive thyroid [24].

Antithyroid drugs may lead to a loss of negative feedback control exerted by circulating thyroid hormones on TSHoma cells, increasing TSH secretion and giving rise to the possibility of growth of pituitary tumor [25]. Therefore, somatostatin analog is the recommended treatment for preparing patients with TSHoma before surgery [25, 26], but its use for hormone producing tumors other than GHoma is not currently covered by health insurance in Japan. In hindsight, we should have preoperatively given potassium iodide or beta-blockers, which are used for symptomatic relief to provide cardioprotective benefit for this patient. We hope this case report will serve as another alert to control thyroid status before surgery for TSHoma and that it may also lead to insurance coverage for the use of octreotide for TSHoma in Japan.

In this case, GH response was normal during preoperative and postoperative GHRP-2 test, but the IGF-1 level remained very low. The patient’s liver function was also intact. We suspected that her low BMI and undernutrition by hyperthyroidism had affected her IGF-1 level [27]. We need to perform a prolonged follow-up of her nutritional and metabolic status to determine the exact reason for her low IGF-1 level.

**Conclusion**

This article illustrates a rare case of thyroid storm induced by TSH secreting pituitary adenoma. Preoperative strategies for normalizing thyroid function and interdisciplinary cooperation are needed to avoid catastrophic sequel caused by thyroid storm triggered by surgery on TSH secreting pituitary adenoma.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this research.

**References**

1136


