

# A Thyroid-stimulating Hormone (TSH) Producing Adenoma in a Patient with Severe Hypothyroidism: Thyroxine Replacement Reduced the TSH Level and Tumor Size

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We treated an extremely rare thyroid-stimulating hormone (TSH)-producing pituitary adenoma in a 63-year-old woman with severe hypothyroidism due to autoimmune thyroiditis. She was presented with dizziness and fatigue. The blood level of TSH, prolactin, and fT4 was 288.2  $\mu$ IU/mL, 72.9 ng/mL, and 0.24 ng/dL, respectively. Magnetic resonance imaging demonstrated a large pituitary tumor, 31 mm in height, and a normal pituitary gland. Preoperative thyroxine replacement reduced the TSH level to 2.05  $\mu$ IU/mL and produced a significant reduction in the tumor volume. Histopathologically, the surgically removed tumor was a TSH-producing pituitary adenoma.

**Keywords:** TSHoma, primary hypothyroidism, thyroxine, TRH

## Introduction

Thyroid-stimulating hormone producing pituitary adenomas (TSHomas) are rare types of pituitary adenomas; they account for around 1–3% of all pituitary adenomas.<sup>1,2</sup> The number of TSHomas detected is increasing with the help of ultrasensitive thyroid-stimulating hormone (TSH) immunometric assays and the rapid spread of magnetic resonance imaging (MRI) machines.<sup>1,3</sup> Patients with TSHomas usually exhibit clinical hyperthyroidism; their TSH level tends to be normal to slightly elevated (1–10  $\mu$ IU/mL).<sup>4,5</sup> We encountered a very rare patient with TSHoma accompanied by hypothyroidism whose TSH level was extremely high. Preoperative thyroxine replacement therapy reduced the TSH level and the tumor size.

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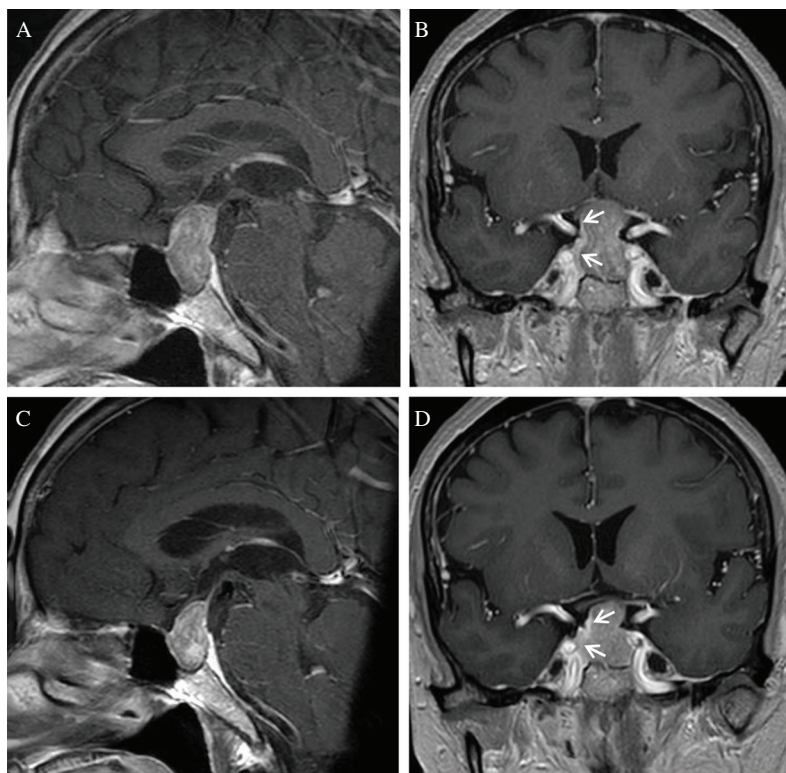
Received: January 4, 2019; Accepted: June 6, 2019  
Online December 18, 2019

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## Case Report

This 63-year-old woman suffering from dizziness and fatigue consulted a neurosurgical clinic. She had stopped taking medication for dyslipidemia and hypertension 3 years earlier. MRI demonstrated a large pituitary tumor extending into the suprasellar space and compressing the optic chiasm upward. Her normal pituitary gland was compressed to the right side (Figs. 1A and 1B). Perimetry denied a visual field deficit.

On admission to our institute, she complained of general fatigue, reduced activity, and dry skin. Anterior pituitary provocation test using a bolus injection of insulin (0.12 U/kg), luteinizing hormone-releasing hormone (LH-RH, 100  $\mu$ g), and thyrotropin-releasing hormone (TRH, 500  $\mu$ g) revealed the marked elevation of TSH which respond well to stimulation (288.2–1465  $\mu$ IU/mL) (Table 1). Her free T4 (fT4) level was very low (0.24 ng/dL); prolactin was elevated and also responded well to the provocation test (72.9–490 ng/mL); the response of luteinizing hormone and cortisol was slightly sluggish. Her insulin-like growth factor 1 level (52 ng/mL) was below the normal range for women of her age (66–194 ng/mL). Thyroid echo revealed glandular atrophy but no mass or goiter; the estimated thyroid weight was 5.7 g. Her anti-thyroglobulin antibody level was extremely high (617 IU/mL, normal  $\leq$ 28 IU/mL). Her blood levels of TSH-receptor antibody (TRAb), thyroid stimulating antibody (TSAb), and thyroid stimulation-blocking antibody (TSBAb) were also elevated (TRAb > 40 IU/L, normal  $\leq$ 2.0 IU/L TSAb 182%, normal  $\leq$ 120%; TSBAb 96.4%, normal  $\leq$ 31.7%). Based on these findings, the diagnosis was autoimmune atrophic thyroiditis. To address her hormonal dysfunction preoperatively, we started thyroxine replacement therapy with incremental doses from 12.5  $\mu$ g. After 2 months, TSH and fT4 levels were normalized (4.32  $\mu$ IU/mL and 1.10 ng/dL, respectively). We continued thyroxine replacement therapy for another 3 months. The maximum dose was 62.5  $\mu$ g. Five months after start of thyroxine, 10 days before the operation, her blood TSH and fT4 levels were still normalized (2.05  $\mu$ IU/mL and 1.04 ng/dL, respectively; Table 1). Her prolactin level also decreased from 72.9 to 48.1 ng/mL. MRI revealed significant tumor shrinkage (Figs. 1C and 1D) and the chiasmal compression had disappeared. Because we were not sure whether the effect of thyroxine



**Fig. 1** Magnetic resonance imaging (MRI) before (A and B) and after (C and D) the start of thyroxine replacement therapy. (A) Sagittal gadolinium-enhanced images showing a heterogeneously enhanced tumor. (B) On coronal gadolinium-enhanced images the pituitary gland is pushed to the right edge of the tumor (arrows). (C) Sagittal gadolinium-enhanced images showing significant tumor shrinkage. Note the absence of compression of the optic chiasm. (D) Coronal gadolinium enhanced images also showing tumor shrinkage. The arrows indicate the pituitary gland.

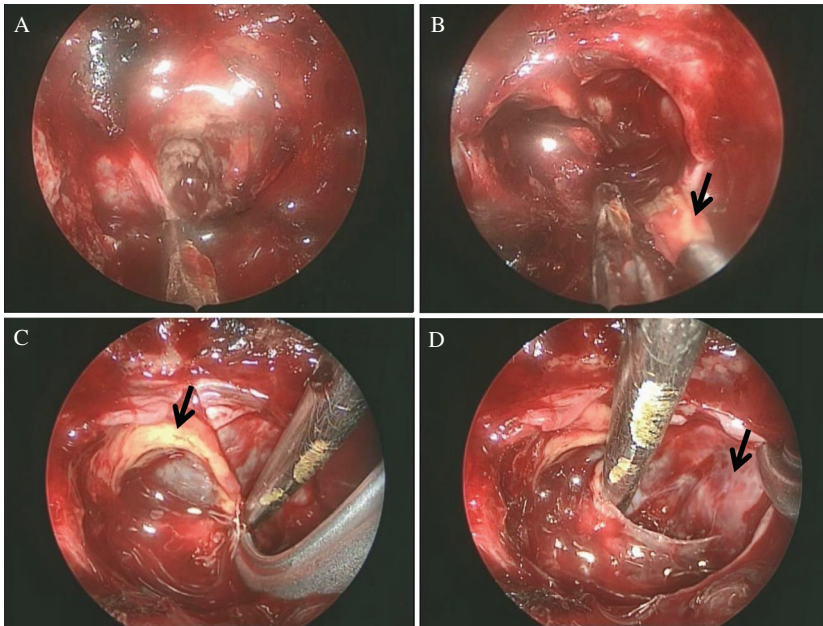
**Table 1** Timeline of changes in hormonal features

Timing	Pre-operation				Post-operation			
	247 Days before operation		10 Days before operation (5 months after start of thyroxine)		8 Days after operation		101 Days after operation	
Provocation	Triple bolus test		TRH–CRH test		Triple bolus test		Triple bolus test	
Hormones	Base	Peak	Base	Peak	Base	Peak	Base	Peak
TSH (μIU/mL)	288.2	1465	2.05	10.75	1.89	5.87	1.35	8.09
Prolactin (ng/mL)	72.9	490	48.1	198.8	17.5	50.3	25.5	62.8
LH (mIU/mL)	2.7	7	–	–	1.2	3.6	1.5	4.2
FSH (mIU/mL)	8	10	–	–	4.5	5.4	4.2	5.9
GH (ng/mL)	0.4	6.7	–	–	0.4	3.6	0.7	3.4
Cortisol (μg/dL)	12.7	15	9.6	17	8.5	15.1	7.6	18.8
ACTH (pg/mL)	21	–	19	64.2	13.4	–	13	78.7
fT4 (ng/dL)	0.24	–	1.04	–	1.21	–	1.12	–
IGF-1 (ng/mL)	52	–	52	–	64	–	50	–

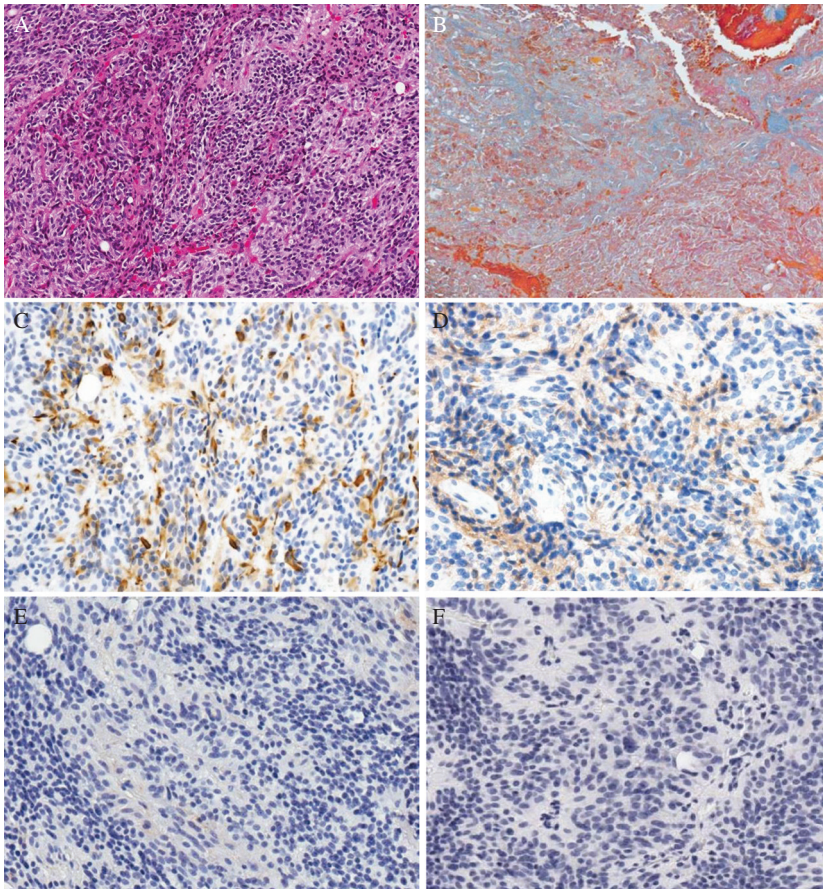
TRH: thyrotropin-releasing hormone, CRH: corticotropin-releasing hormone, TSH: thyroid-stimulating hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, GH: growth hormone, ACTH: adrenocorticotropic hormone, fT4: free thyroxin, IGF-1: insulin-like growth factor 1.

would continue and be cytotoxic, surgical removal was done. Endoscopic transsphenoidal surgery revealed that the tumor was basically soft but intermingled with fibrous tissue in some areas (Fig. 2A). A part of pseudocapsule was detected and removed (Fig. 2B). The pituitary gland located at the upper right corner was slightly yellowish (Fig. 2C). The tumor had not invaded into cavernous sinus, subtotal removal was accomplished (Fig. 2D). Her postoperative course was uneventful except for early postoperative diabetes insipidus.

Repeat provocation test, performed while she received 62.5 μg thyroxine replacement therapy, showed normalization of the TSH and prolactin level and a cortisol response. MRI studies confirmed nearly total tumor removal except for a possible remnant beneath the stalk. Histologically, the tumor was comprised of diffuse or acinar arrangements of ovoid to round chromophobic cells (Fig. 3A). Cellular pleomorphism was rare and the MIB-1 index was under 1%. Stromal fibrosis was frequently observed (Fig. 3B). Immunohistochemically,



**Fig. 2** Intraoperative views. (A) The tumor was basically soft but fibrous areas were also seen. (B) Arrow indicates pseudocapsule of the tumor. (C) The pituitary gland was located at the upper right of the operative field (arrow), which was slightly yellowish. (D) The tumor did not invade into cavernous sinus. The arrow indicates the cavernous sinus wall.

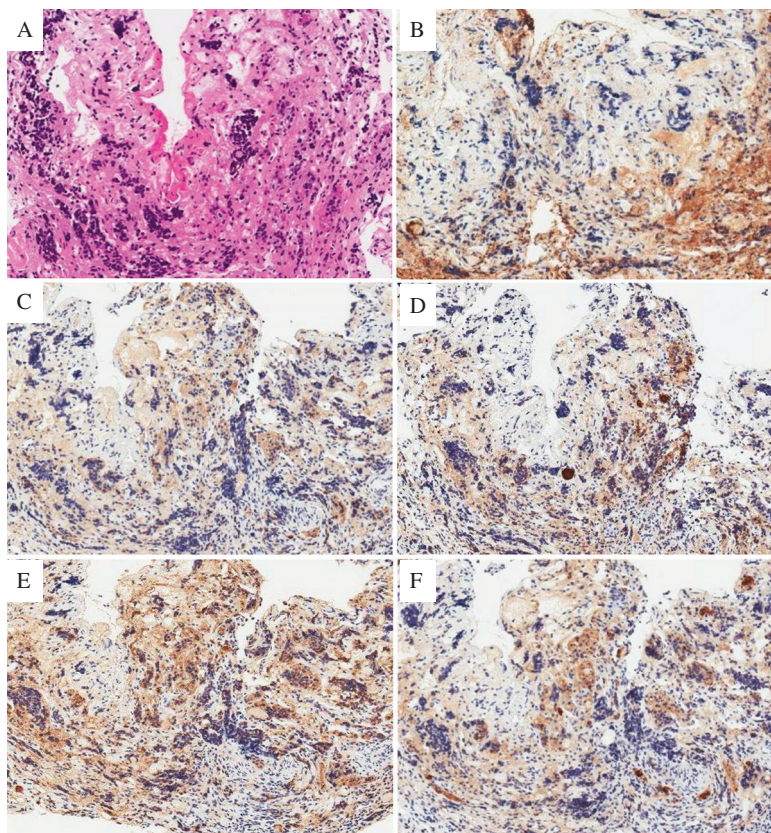


**Fig. 3** Histopathology of the resected tumor. (A) Hematoxylin–Eosin stain showing the proliferation of round or oval chromophobic neoplastic cells in a sheet-like or acinar arrangement. There is scant cellular pleomorphism (150 $\times$ ). (B) Azan-Mallory stain showing well developed collagen fibers (100 $\times$ ). (C and D) The neoplastic cells were positive for thyroid-stimulating hormone (C), and thyrotropin-releasing hormone receptor (D) (200 $\times$ ). (E and F) The tumor was negative for prolactin (E), and growth hormone (F) (200 $\times$ ).

the neoplastic cells were positive for TSH, chromogranin, Pit-1, and TRH receptor (TRH-R) (Figs. 3C and 3D) and negative for prolactin, growth hormone (GH), adrenocorticotropic hormone (ACTH), LH, and follicle-stimulating hormone (Figs. 3E and 3F). A tiny piece of tissue removed from the right edge of the tumor was found to be from the pituitary

gland and positive for GH, ACTH, TSH, prolactin, and gonadotropins (Figs. 4A–4F).

Eight months after the operation, her general condition was good, she continues to be treated with 62.5  $\mu$ g thyroxine replacement therapy, and she is able to pursue the activities of a normal life.



**Fig. 4** Histopathology of a tiny piece of pituitary gland tissue resected from the right lateral edge of the tumor. (A) Hematoxylin–Eosin stain showing acinar arrangement of the cells without pleomorphism (100×). (B–F) Cells were positive for adrenocorticotropic (B), growth hormone (C), thyroid-stimulating hormone (D), prolactin (E), and/or luteinizing hormone (F) (150×).

### Discussion

Histopathologically, the tumor was a TSH-producing adenoma; immunohistochemically it was positive for TSH and distinguishable from the normal pituitary gland positive for all anterior pituitary hormones. The coexistence of primary hypothyroidism, the extremely high TSH level, and the significant reduction in the TSH level and the tumor size by thyroxine replacement therapy render this TSHoma peculiar.

Patients with TSHoma usually present clinical features of hyperthyroidism. Earlier, some TSHomas were mistakenly diagnosed as primary hyperthyroidism (Graves' disease) and patients underwent inappropriate thyroid ablation which led to hypothyroidism.<sup>4,6</sup> Patients with primary hypothyroidism develop marked enlargement of the pituitary gland accompanied by elevated TSH levels; pituitary hyperplasia, a condition that mimics pituitary adenoma.<sup>1</sup> But the true coexistence of TSHoma and hypothyroidism is extremely rare.

Our search of the literature found only seven reports of patients manifesting this coexistence since 1996.<sup>7–13</sup> Their hypothyroidism was attributed to autoimmune thyroiditis in six patients and to thyroid lobectomy to address a benign tumor in one patient. All tumors were macroadenomas including a huge one.<sup>8</sup> The TSH levels were much higher (7.5–3474  $\mu\text{IU/mL}$ ) than that of TSH-producing adenomas without hypothyroidism: the median and interquartile range was 3.08 and 1.82–4.44  $\mu\text{IU/mL}$ , respectively, in a series of 90 patients.<sup>5</sup> A significant reduction in the TSH level elicited by thyroxine replacement therapy was documented in two reports.<sup>7,8</sup> Ghannam et al.<sup>8</sup> obtained a remarkable tumor volume reduction by treatment with thyroxine; the tumor was

initially huge and invaded the bilateral cavernous sinuses and nasal cavity. Ours is the second reported case in which the thyroxine-induced dramatic tumor size reduction was demonstrated by MRI.

The TSH level in TSH-producing adenomas is normal to slightly high.<sup>4,5</sup> Inappropriate thyroid ablation using radioiodine or thyroidectomy to treat patients with TSHoma resulted in the extreme elevation of their TSH level (90–500  $\mu\text{IU/mL}$ )<sup>4,6,14,15</sup> and aggressiveness of the tumor. This was also seen in patients with ACTH-producing adenomas whose bilateral adrenal glands were removed to control hypercortisolism. Their adenomas are much larger and aggressive and their ACTH levels are much higher (Nelson's syndrome)<sup>4</sup> than in patients without adrenalectomy.

The tumor we resected was histologically a TSH-producing adenoma. On high-resolution MRI scans we could see the pituitary gland of normal size on the right side of the adenoma. Although TSH hypersecretion from the pituitary gland may have played a role, we think that the main source of the extremely high TSH level was the adenoma *per se* and attributable to augmented TRH action due to a very low *ft*4 level. We posit that the growth of the adenoma was also TRH-related<sup>16</sup> and that normalization of the *ft*4 level dramatically reduced the TSH level and the tumor volume owing to the cessation of augmented TRH action. The adenoma was removed successfully without new hormonal impairment or neurological sequelae. If the adenoma had been larger and invasive, we would have continued thyroxine replacement therapy to obtain a further reduction in the tumor size.

In terms of the tumorigenicity of TSHoma, autopsy studies and animal hypothyroidism models suggested the development of microscopic TSHomas from pituitary hyperplasia.<sup>17,18)</sup> According to Ma et al.,<sup>10)</sup> their patient's plurihormonal TSH-producing pituitary adenoma developed from pituitary hyperplasia. We think that our patient's adenoma was a primary tumor and not secondary to hyperplasia because, unlike their secondary plurihormonal adenoma, the cells in our adenoma were immunopositive only for TSH. Its singleness and the clear margin separating the pituitary gland from the adenoma support our hypothesis. Because the key genetic alteration(s) that lead to the development of TSHoma remain to be identified,<sup>19)</sup> the genetic differentiation of secondary TSHoma from *de novo* tumors is currently difficult.

Around 10–12% of TSH-secreting adenomas also secrete prolactin.<sup>2,3,5)</sup> In this case, the neoplastic cells were negative for prolactin immunohistochemically. So, the pretreatment elevation of prolactin level was thought to be due to stalk effect.

In conclusion, we reported the rare coexistence of a TSHoma and severe primary hypothyroidism in which preoperative thyroxine replacement therapy reduced the tumor size as well as the blood TSH level. The identification of molecular mechanisms underlying these rapid changes is a future challenge.

### Conflicts of Interest Disclosure

The authors state that they have no conflict of interest.

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