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A case of TSH-producing adenoma treated with octreotide in combination with thiamazole for the control of TSH and thyroid hormones after trans-sphenoidal neurosurgery

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Abstract. While TSH-producing adenoma (TSHoma) is rare, the diagnosis is often delayed because the clinical features are heterogeneous. The patient was a 69-year-old woman who had been referred to the Yachiyo Medical Center in August 2008, because of dyspnea, loss of appetite, weight loss of 10 kg, and diarrhea that lasted 4 years. We diagnosed this patient with pituitary TSH-producing macroadenoma. Thyroid hormone concentration was increasing although the serum TSH level was within a normal range after trans-sphenoidal surgery. We considered that because of enlargement of the thyroid gland due to long-term stimulation by TSH, a low concentration of TSH could stimulate the thyroid gland to produce excess T3 or T4. The somatostatin analogue, octreotide was used to control the TSHoma and serum TSH concentration but not thyroid hormone. The octreotide in combination with thiamazole treatment for 14 months controlled thyroid hormone concentration and decreased the thyroid mass, and ultimately, the thiamazole could be stopped. To date, the use of combination therapy of octreotide with thiamazole in patients with remaining TSH-producing adenoma without Basedow's disease is rare, and we suggest that this treatment is one of the therapeutic means to treat recurrence of TSH-producing adenoma after surgery with progressive complications or large thyroid gland.

Key words: TSH-producing adenoma, Octreotide, Hyperthyroidism, Thiamazole

THYROID-STIMULATING hormone (TSH) -producing pituitary adenomas (TSHoma) are rare, accounting for 0.5-1.1% of all pituitary adenomas [1, 2]. The diagnosis of these adenomas can be delayed and most TSH-producing adenomas are macroadenomas [1]. Herein, we report a patient with chronic heart and renal failure who was diagnosed with TSH-producing adenoma and underwent treatment with octreotide and thiamazole to control the level of TSH and thyroid hormone secretion after pituitary trans-sphenoidal surgery.

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Case Report

The patient was a 69-year-old woman who had been referred to the Yachiyo Medical Center in August 2008, because of dyspnea, loss of appetite, weight loss of 10 kg, and diarrhea that lasted 4 years. She had a history of myoma of the uterus and stenosis of the auditory tube. Upon admission to our hospital, her height was 152.9 cm, body weight was 40.8 kg and her body mass index (BMI) was 17.4 kg/m^2. She had never taken any antihypertensive agents and her blood pressure was 162/67 mmHg. Her heart rate was 142/min, and atrial fibrillation was not observed. Her thyroid was diffusely enlarged but systolic bruit was not audible. Routine laboratory chemical examinations showed marked anemia (Hemoglobin concentration: 4.2 g/dL, Hematocrit: 12.9%) and decreased renal function (serum creatinine

Table 1 Clinical data on admission

[Biochemistry]		[Hormonal examination]	
TP	5.8 g/dL	TSH	8.633 μIU/mL
ALB	2.7 g/dL	fT3	4.25 pg/mL
AST	51 IU/L	fT4	4.22 ng/dL
ALT	35 IU/L	LH	0.5 mIU/mL
LDH	284 IU/L	FSH	25.4 mIU/mL
ALP	379 IU/L	GH	7.01 ng/mL
LAP	54 IU/L	IGF-I	45.5 ng/mL
γ-GTP	64 IU/L	ACTH	38 pg/mL
Ch-E	89 IU/L	Cotisol	21.1 μg/mL
T-BIL	0.5 mg/dL	PRL	57.21 ng/mL
D-BIL	0.2 mg/dL	TgAb	0.3 U/mL
CK	203 IU/L	TPOAb	<0.3 U/mL
AMY	114 IU/L	TRAb	0.5 %
BUN	76.5 mg/dL	TSAb	172 %
CRE	2.56 mg/dL		
UA	14 mg/dL	[hematology]	
Lipase	67 IU/L	WBC	8350 /mm^3
Na	136 mEq/L	RBC	1.41×10^6 /mm^3
K	5.7 mEq/L	Ret	3.1 %
CL	112 mEq/L	HGB	4.2 g/dL
CRP	0.4 mg/dL	HCT	12.9 %
Fe	15 μg/dL	MCV	91.5 fl
UIBC	231 μg/dL	MCH	29.8 pg
TIBC	246 μg/dL	MCHC	32.6 g/dL
Ferritin	54.1 ng/mL	PLT	41×10^4 /mm^3
Vit-B12	>1500 pg/mL		
Folic acid	5.5 ng/mL		

TgAb, thyroglobulin antibody; TPOAb, thyroperoxidase antibody; TRAb, TSH receptor antibody; TSAb, TSH stimulating receptor antibody

concentration:2.56 mg/dL) (Table1). Upper gastrointestinal endoscopy revealed multiple duodenal ulcers (A1 stage). She still exhibited tachycardia after she recovered from the anemia following blood transfusion. Her serum thyroid hormone concentrations were high, and free T3 and free T4 were 4.25 pg/mL and 4.22 ng/dL, respectively, and the serum concentration of thyroid stimulating hormone (TSH) was 8.633 μIU/mL, indicating that hyperthyroidism was caused by inappropriate secretion of TSH (SITSH). Anti-thyroglobulin, antiperoxidase antibodies, TSH receptor antibody (TRAb) and TSH stimulating receptor antibody (TSAb) were negative. Serum TSH concentrations were not increased in response to intravenous administration of TRH (500 μg, iv bolus; 0, 30, 60, 90, and 120 min, 10.537, 11.187, 10.645, 11.818, and 11.580 μIU/mL, respectively; Fig. 1A). Magnetic resonance imaging (MRI) of the head showed a pituitary adenoma (14×27×10 mm), which was not enhanced with gadolinium diethylenetriamine penta-acetic acid (Fig. 2). Based upon these clinical and chemical examinations, we diagnosed this patient with TSH-producing pituitary adenoma. Two weeks after diagnosis, total resection of the pituitary adenoma was performed through trans-sphenoidal neurosurgery in October 2008. Upon immunohistochemical examination, the resected pituitary adenoma cells exhibited positive staining only with the TSH-β antibody (Fig. 3A,B). No other pituitary hormones were detected in the pituitary adenoma. The percentage of positive MIB-1 stain cells is 0.7%, suggesting that the tumor is defined as benign (Fig. 3C). After the operation, TSH, fT3 and fT4 decreased rapidly to a normal range within 1 week. However, 2 weeks after the operation, TSH and thyroid hormone were all increased. We suspected existence of residual TSHoma, but the remaining tumor was not detected clearly by plain MRI as enhancement was not employed due to chronic renal failure. Impaired TSH response to a TRH stimulation test was the similar as before; 6.083, 6.450, 5.944, 6.436 and 6.440 μIU/mL at 0, 30, 60, 90 and 120 min, respectively; Fig. 1B). We selected a dose of 20mg of the somatostatin analog, octreotide, once a month to suppress the TSH concentration and tumor growth. After the octreotide treatment, the TSH concentration was markedly decreased from 6.08 to 0.68μIU/mL initially. However, fT3 and fT4 increased gradually although the TSH was within a

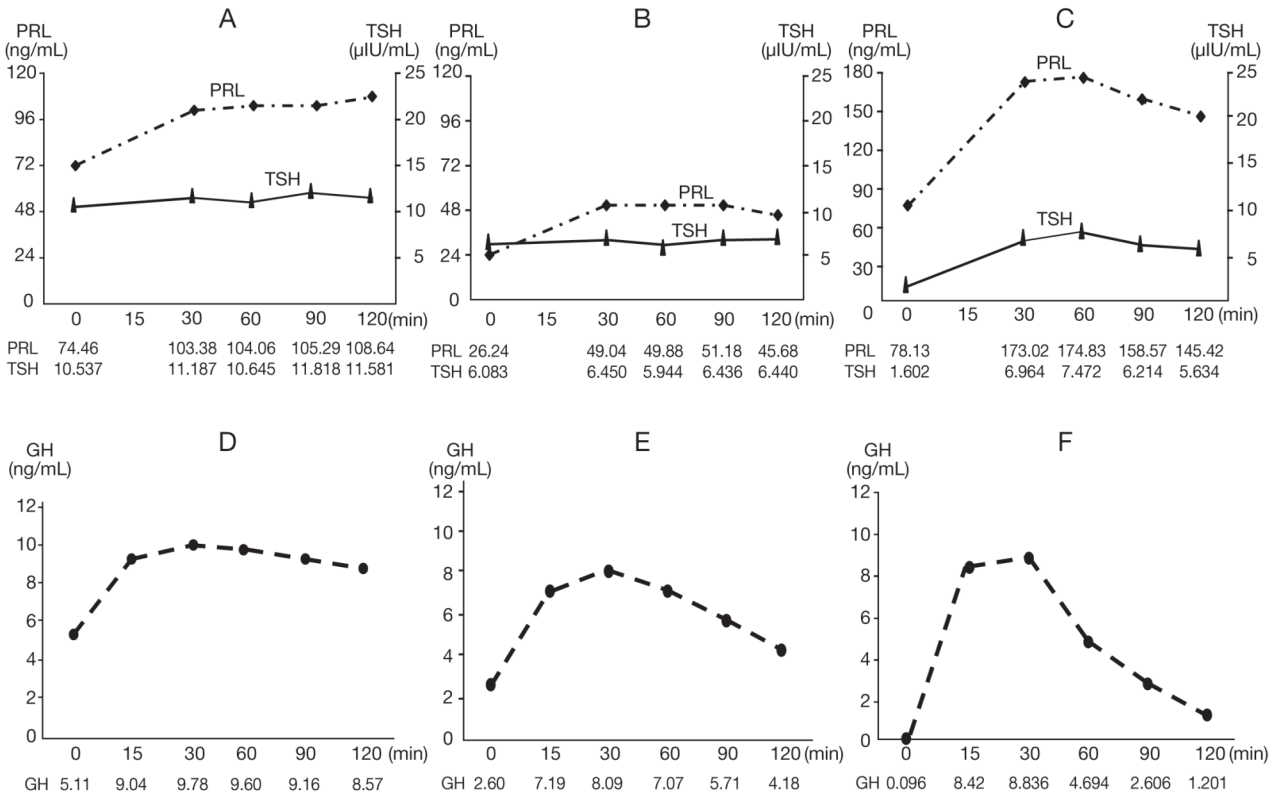


Fig. 1 TSH and PRL response in a TRH stimulation test (A, B and C), and in the GH to GRH stimulation test (D, E and F). A, D; before resection of the TSH-producing pituitary adenoma. B, E; 3 weeks after the resection. C, F; 2 years after the resection

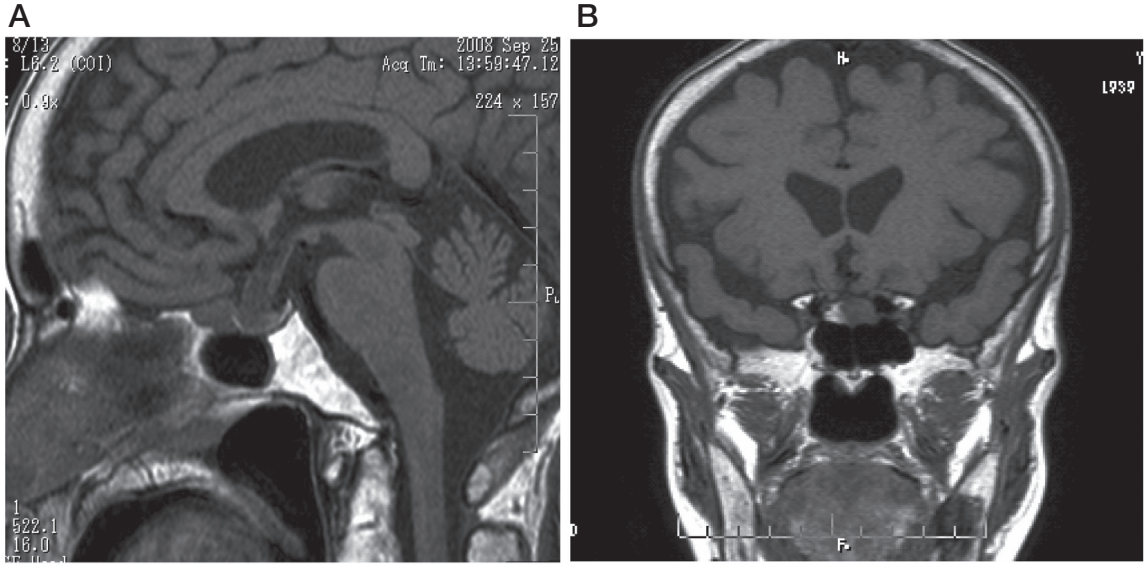


Fig. 2 MR image of the pituitary adenoma enhanced with gadolinium diethylenetriamine penta-acetic acid.. Sagittal (A) and coronal (B) T1-weighted MR image demonstrate a multilocular pituitary adenoma (14×27×10 mm).

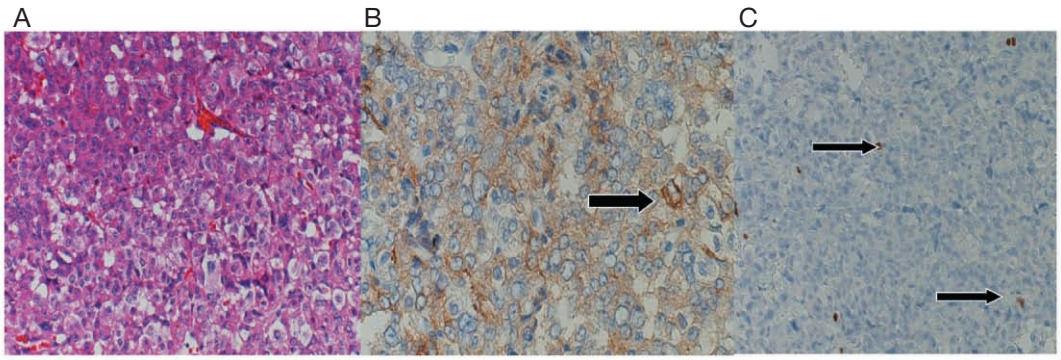
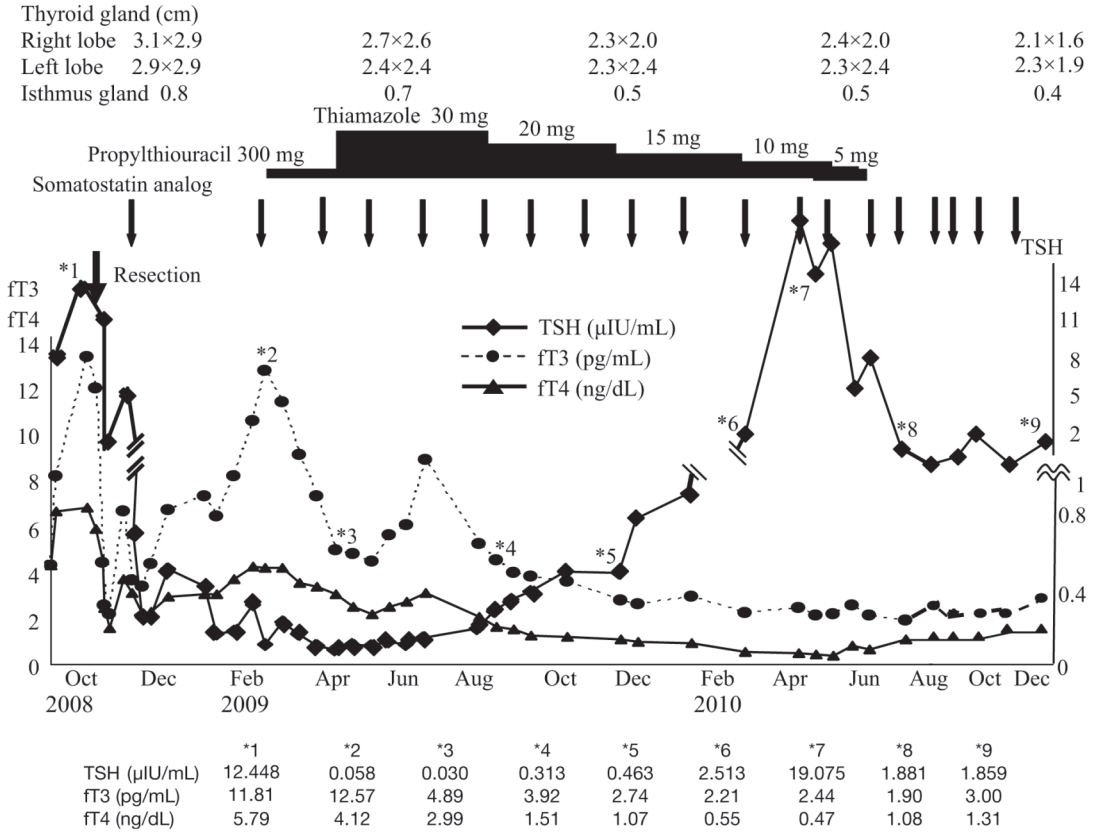


Fig. 3 Histology and immunostaining of pituitary adenoma. A: Hematoxylin and eosin stain. B:TSH stain: black arrow indicates the cells stained with TSH-β. C: MIB-1 stain: The percentage of MIB-1-positive cells, which are indicated by black arrows, is 0.7%. The tumor is defined as benign.



	*1	*2	*3	*4	*5	*6	*7	*8	*9
TSH (μIU/mL)	12.448	0.058	0.030	0.313	0.463	2.513	19.075	1.881	1.859
fT3 (pg/mL)	11.81	12.57	4.89	3.92	2.74	2.21	2.44	1.90	3.00
fT4 (ng/dL)	5.79	4.12	2.99	1.51	1.07	0.55	0.47	1.08	1.31

Fig. 4 Treatment course of pituitary adenoma and changes in TSH, fT3 and fT4 concentrations over time. Thyroid hormone treatment and the size of the thyroid gland are indicated in the upper graph. The size of the thyroid was smaller after the combination treatment with somatostatin and thiamazole.

normal range. We subsequently attempted to treat her with 300mg/day propylthiouracil (PTU) from February 2009 to control the thyroid hormone concentration and suppress the conversion of T4 to T3. Two months later, the thyroid hormone levels were decreased from 12.57 to 4.89 pg/mL for fT3, and from 4.12 to 2.99 ng/dL for fT4. One month after treatment of PTU, she complained of itching eruption all over the body with hypereosinophilia, and we then replaced propylthiouracil with thiamazole. After the change to 30mg/day thiamazole, fT3 and fT4 were controlled after one week (Fig. 4). TRAb and TSAb remained within a normal range (<0.4IU/L,

76 % respectively). Ultrasound studies of the thyroid showed enlargement; 31×29 mm in the right lobe, 29×29 mm in the left lobe, 8 mm in the isthmus glandulae thyroideae 3 weeks after the operation. Five months later, the thyroid was smaller; 27×26 mm in the right lobe, 24×24 mm in the left lobe, 7 mm in the isthmus glandulae thyroideae. As the size of thyroid was smaller and decreasing thyroid hormone and increasing TSH concentration was observed, the dose of thiamazole was decreased. Finally, at 20 months after the operation, treatment with thiamazole could be terminated; at this time the size of thyroid gland was 24×20 mm in the right lobe, 23×24 mm in the left lobe, and 5 mm in the isthmus glandulae thyroideae. Interestingly, TSH secretion in response to TRH was restored to normal, 23months after the operation and the peak value was 7.472 mIU/mL (Fig. 1C). The serum prolactin concentrations in response to TRH were slightly elevated because of the decreased clearance of prolactin in chronic renal failure except just after the operation (Fig. 1A, 1C) [3].

Discussion

Herein, we report a patient who was diagnosed with hyperthyroidism caused by pituitary TSHoma with chronic renal failure. We could not conduct kidney biopsy to further investigate the cause of renal failure, but we considered that this was due to nephrosclerosis as a consequence of the chronic hypertension. In this point, the onset of TSH-producing adenoma with these features in our case was rare. Moreover, she did not complain of visual dysfunction despite the detection of a visual field defect during ophthalmological examination. TSHomas are rare as causes of hyperthyroidism and account for <1% of pituitary adenomas [2, 4]. Biochemical findings showed increased TSH, free T3, free T4, and no response of TSH to TRH injection and MRI findings, suggesting that it was consistent with TSH-producing adenoma. TSHomas are often reported as macroadenomas after a delayed period because the clinical features are heterogeneous and it often takes time to be diagnosed [1, 5].

Regarding the medical treatment of TSHoma, the long-acting somatostatin analog, octreotide, has been generally used. With somatostatin analog therapy, TSH secretion has been reported to be reduced in more than in 90% of patients and normalized in about 75%. Furthermore, circulating thyroid hormone levels were normalized in 96% of patients and goiter size was reduced in 20% of cases [1, 6-8]. The effects of octreotide on suppression of TSH secretion were reported to be due to binding to somatostatin receptors 2 and 5 in TSHoma [9], but in this case we did not examine the expression of the somatostatin receptors. While serum TSH concentration was decreased to a normal range in response to treatment with the somatostatin analog, octreotide, the concentrations of free T3 and free T4 were not normalized and tachycardia continued. Some cases of TSHoma complicated by Graves' disease have been reported [10-12]. TSH is known to repress the expression of interferon-γ-induced Fas antigen [13], intercellular adhesion molecule (ICAM)-1 [14] and class II trans-activator, which is a non-DNA-binding regulator of major histocompatibility complex (MHC) transcription on the thyroid cell surface [11]. Rapid reductions in TSH levels after the treatment of TSHoma may induce Fas-mediated apoptosis, as a result of cell surface Fas expression and expression of both ICAM-1 and MHC class II molecules on the cell surface of thyroid cells. Consequently, autoimmune responses against the thyroid gland may be activated [15]. However, in this case TRAb and TSAb were both negative, even after serum TSH concentration returned to within a normal range after resection, suggesting that normal negative feedback was not observed, and SITSH continued. It was reasonable for us to conclude that the enlarged thyroid cells, caused by long-term stimulation by the TSH-producing adenoma continued to be stimulated in response to the residual pituitary adenoma even though the serum TSH hormone level was within the normal range. There could be a way to select radiation therapy for the thyroid gland, but we expected that the characteristic thyroid hormone levels decrease as the thyroid gland become smaller. Therefore, we attempted to treat this patient with antithyroidal drugs in addition to the somatostatin analog, octreotide, to decrease the thyroid hormone until the thyroid gland was reduced in size. Twenty months after the operation, thiamazole could be stopped, as the TSH concentration and thyroid function were normal. Interestingly several months before the stop of thiamazole, TSH was increased when thyroid function was low in response to thiamazole, and a decrease of the thiamazole dose brought this to within a normal range, suggesting the decrease of autonomic TSH secretion from residual TSHoma by octreotide and the existence of normal TSH secreting pituitary cells that responded

normally to thyroid hormone or TRH. Furthermore, the response of TSH to TRH was restored after cessation of thiamazole treatment. In conclusion, herein, we report a case of hyperthyroidism after the resection of a TSH-producing adenoma, followed by treatment with octreotide in combination with thiamazole to control both the TSH and thyroid hormone concentrations. Finally, the thiamazole treatment could be stopped. We suggest that this treatment is one of the therapeutic means to treat recurrence of TSH-producing adenoma after surgery with progressive complications or large thyroid gland.

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