A Case of Thyrotropin-Secreting Pituitary Macroadenoma†

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Abstract

We present a 49 year old male patient with thyroid stimulating hormone (TSH) producing pituitary macroadenoma. He had been mistakenly diagnosed and treated as Graves' disease for 1 year. Serum TSH level was inappropriately elevated in the presence of high serum total and free thyroid hormone concentrations. Thyrotropin releasing hormone stimulation showed blunt response of TSH but good response for prolactin. The α-subunit level and α-subunit to TSH molar ratio were measured and found to be high before surgery. The sex hormone-binding globulin level was also high. MRI demonstrated a pituitary macroadenoma. Insulin tolerance test and GnRH revealed normal response. The patient was given a high dose of PTU combined with lugol's solution for controlling hyperthyroidism preoperatively. Transfrontal surgery was performed and the tumor was partially removed. The diagnosis was confirmed by tissue pathology and immunohistochemistry staining of the tumor. The immunohistochemistry staining was performed and found that tumor cells were strongly reactive to TSH with a relatively mild degree for follicular stimulating hormone and leutinizing hormone. The tumor cells were not stained for prolactin, growth hormone and ACTH. Supervoltage irradiation by ^{60}Co was delivered to the pituitary area because of persistence of hyperthyroidism. While waiting for the remote effect of radiotherapy, the patient was given an antithyroid drug to control hyperthyroidism.

Key word : Thyrotropin-Secreting Pituitary Adenoma, The Syndrome of Inappropriate Secretion of TSH, TSH Producing Tumor

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The common causes of hyperthyroidism are Graves' disease, autonomously functioning thyroid nodule and toxic multinodular goiter. Serum thyroid stimulating hormone (TSH) levels in primary hyperthyroidism are suppressed primarily due to the negative feedback inhibition of the elevated thyroid hormone concentrations on pituitary thyrotropes[1]. In contrast, in hyperthyroidism caused by TSH-secreting pituitary tumor, serum TSH concentration is inappropriately elevated in the presence of high serum thyroid hormone concentrations. TSH-secreting adenomas are a rare cause of hyperthyroidism, accounting for less than 1 per cent of all pituitary adenomas. So far, more than 270 cases have been reported[2-5]. With the advent of sensitive TSH immunoassay[6], an increasing number of patients are now being recognized who demonstrate normal or elevated immunoreactive TSH in the presence of increased total and free serum thyroid hormone levels. Clinical manifestations of the disease are usually mild and not different from those occurring in the more conventional forms of hyperthyroidism, such as autoimmune Graves' disease and toxic nodular goiter, except for the lack of acropachy and the rare occurrence of ophthalmopathy[7,8]. However, many patients have previously been misdiagnosed as having Graves' disease[9,10]. The diagnostic biochemical hallmark of these tumors is the association of high serum thyroid hormones with an elevated or inappropriately normal serum TSH level [11]. This entity is now termed inappropriate TSH secretion[8,12]. In these conditions there is no intrinsic derangement of the thyroid gland or of the immune system; instead, TSH itself is responsible for thyroid hyperstimulation.

In this paper, we describe a patient with TSH-secreting pituitary macroadenoma who presented with clinical hyperthyroidism and had inappropriately high serum TSH levels. The patient had an increment of serum α-subunit (α-SU) and sex hormone-binding globulin (SHBG) levels. He was treated by transfrontal surgery with partial removal of a pituitary tumor, followed by radiation.

CASE REPORT

The patient was a 49 year old male who went to a private hospital because of goiter and weight loss without anorexia. Physical examination revealed a diffusely enlarged thyroid gland approximately 30 g, smooth surface and no bruit. He had no lid lag, exophthalmos or pretibial myxedema. Examination of heart, lungs and abdomen was normal except for atrial fibrillation. Because of a high serum free thyroxine (FT_4) level of 4.54 ng/dl (normal range 0.7-1.85), he was diagnosed as Graves' disease and he was treated with propylthiouracil (PTU) 300 mg/day and lanoxin 0.125 mg/day. He was referred to a local hospital in a southern part of Thailand to continue treatment. After taking PTU 300 mg/day for 1 year, he went back to the same private hospital. His thyroid gland was markedly enlarged about 100 g in size and his serum FT_4 was normal (1.09 ng/dl) and high serum TSH value of 28.2 uIU/ml (normal range 0.35-5.2). He was diagnosed as PTU induced hypothyroidism and compensated goiter. He was treated with tapazole 5 mg/day and levothyroxine 200 ug/day. Six months later, his serum T_4 was very high at over 30 ug/dl (normal range 4.5-11.5), very high serum T_3 over 800 ng/dl (normal range 65-170). Surprisingly, his serum TSH level was still elevated at 14.3 uIU/ml. Levothyroxine was withdrawn and high dose of PTU (300 mg/day) was given together with lanoxin. His serum TSH levels were still high without negative feedback of high levels of thyroid hormone (Table 1). Since serum TSH levels were inappropriately elevated in the presence of high serum thyroid hormone concentrations, the patient was referred to Rajavithi Hospital for further investigation.

In Rajavithi Hospital, physical examination found thyroid enlargement of 70-80 grams and atrial fibrillation. He had no clinical signs of increased intracranial pressure and fundi were normal. Visual accuity and visual fields were normal in both eyes. He had no symptoms and signs of pituitary hormone excess or deficiency except hyperthyroidism. Liver and renal function tests were normal. Chest X-ray revealed borderline cardiomegaly. Electrocardiogram demonstrated atrial fibrillation and ST-T change at the inferior wall.

Laboratory Investigations Thyroid Function Tests

Serum total T_4 and T_3 concentrations were measured by radioimmunoassays (RIA) (DPC double antibody, Diagnostic Products Corporation, Los Angeles, CA, USA). Serum free T_4 was performed by RIA (Amerlex-M, Amersham International plc, Amersham, UK). Serum TSH concentration was determined by an immunoradiometric assay (Incstar Corporation, Stillwater, MN).

Table 1. Thyroid function tests, α-subunit (α-SU), α-SU/TSH molar ratio, and SHBG of the patient.*

Date		T_4 (ug/dl) (4.5-11.5)	T_3 (ng/dl) (65-170)	FT_4 (ng/dl) (0.7-1.85)	TSH (uIU/ml) (0.35-5.2)	α-SU (ug/L)	α-SU/TSH** molar ratio	SHBG (nmol/L) (10-55)	Treatment***
April	29, '96			**4.54**					PTU 300 mg/d
April	12, '97			1.09	**28.2**				MMI 5 mg/d, T_4 200 ug/d
October	5, '97	**> 30**	**> 800**		**14.3**				PTU, off T_4
December	14, '97	**14**	**184**		**16.1**				PTU
December	6, '98	**15.4**	**554**		**25.1**				PTU 200 mg/d
January	29, '99	11.1	**258**	**2.50**	**20.9**	**1.8**	0.81	**126**	PTU 200 mg/d
February	11, '99	**12.8**	**268**						PTU 200 mg/d
February	23, '99		**306**						PTU 300 mg/d
March	2, '99	**11.9**	**288**						PTU 450 mg/d, lugol's solution
March	8, '99	7.2	147						PTU 450 mg/d, lugol's solution
March	22, '99	3.3	53	0.45	**6.0**	0.5	0.78	**100**	PTU 450 mg/d
April	16, '99	**20.2**	**544**	**7.79**	**7.3**				PTU 300 mg/d
May	25, '99	**13.2**	**263**	**2.91**	**9.7**				PTU 300 mg/d
August	3, '99	10.2	139	**2.51**	**13.2**				PTU 300 mg/d
September	14, '99	**11.6**	**264**	**2.12**	**10.1**				PTU 200 mg/d

* Bold letters are abnormal tests.

** Calculation of the α-SU/TSH molar ratio was based on the following mol wt values: TSH, 28,000 (1 ug TSH corresponds to 4.93 mU); and α-SU, 14,760.

*** Iugol's solution was given from March 2 to 8, 1999; March 17, 99 Transfrontal pituitary surgery was done; March 23, 99 PTU was discontinued; April 20, 99 Radiation therapy was started.

Table 2. Pituitary function test of the patient.

Time* (minute)	TSH (uIU/ml)	Prolactin (ng/ml)	Glucose (mg/dl)	GH (ng/ml)	Cortisol (μg/dl)	FSH (mU/ml)	LH (mU/ml)
0	19.3	5.5	89	0.9	18.1	9.5	7.0
20	21.0	18.3					
30			22**	8.0	15.3	23.7	92.1
45			23**	6.6	21.2		
60	24.9	31.2	23***	4.9	23.0	25.8	82.7
90			158	15.2	24.3	19.6	59.2
120			206	14.8	25.8	19.9	41.0

* After injection TRH 200 μg, GnRH 100 ug, and Humulin R 15 units intravenously.
** Sweating
*** 50% glucose 50 ml was given because of drowsiness.

The serum T_4 concentration was 11.1 ug/dl, T_3 258 ng/dl, FT_4 2.50 ng/dl and high serum TSH 20.9 uIU/ml. Serum antimicrosomal and antithyroglobulin antibodies were non-detectable by hemagglutination assay.

Thyrotropin Releasing Hormone (TRH) Stimulation Test

TRH stimulation test was performed. The result showed blunt response of TSH from the high basal level of 19.3 uIU/ml to the peak level of 24.9 uIU/ml at 60 min after 200 ug of TRH intravenously (Table 2). There was an increment of serum prolactin (PRL) concentration from the basal level of 5.5 ng/ml to the peak level of 31.2 ng/ml at 60 min after TRH injection (Table 2).

α-SU Level, α-SU/TSH Molar Ratio and SHBG Level

Serum α-SU level was measured by a highly specific immunoradiometric assay (Bioclone, Marrickville, Australia) and found to be high at 1.8 ng/ml (normal values in male < 1.1 ng/ml) before surgery and returned to a normal level of 0.5 ng/ml 5 days after transfrontal surgery.

Calculation of the α-SU/TSH molar ratio was based on the following mol wt values: TSH, 28,000 (1 ug TSH corresponds to 4.93 mU); and α-SU, 14,700[13]. The α-SU/TSH molar ratio was calculated using the following formula (α-SU in micrograms per L divided by TSH in milliunits per L) x 10[14]. Using the criteria proposed by Beck-Peccoz et al[15], if TSH is elevated, the ratio should be < 0.7 in normogonadotropic patients and < 1.0 in hypergonadotropic patients. This normogonadotropic patient had high α-SU/TSH molar ratio (0.81) before surgery and returned to normal (0.78) after transfrontal pituitary surgery.

The SHBG level was measured and found to be high at 126 nmol/L (normal values 10-55 nmol/L) before surgery and was 100 nm ol/L 5 days after surgery.

Pituitary Function Tests

Insulin tolerance test (Humulin R 15 units intravenously) revealed normal increment of serum growth hormone (GH) and an increase of serum cortisol from 18.1 ug/dl to 25.8 ug/dl. GnRH stimulation test (Relisorm-L 100 ug intravenously) revealed an increment of serum follicular stimulating hormone (FSH) and leutinizing hormone (LH) from 9.5 mIU/ml and 7.0 mIU/ml to 25.8 mIU/ml and 92.1 mIU/ml, respectively (Table 2).

Roentgenographic Examinations

Film of the skull showed sella enlargement. MRI of pituitary and hypothalamus demonstrated intrapituitary mass size approximately 20 x 13 mm with heterogeneous enhancement after contrast agent injection. Right lateral displacement of the carotid vessel was noted as well as visualized superior displacement of the optic chiasma (Fig. 1A, 1B).

Treatment and the Follow-up Course

The patient was prepared pre-operatively with a high dose of PTU (450 mg/day) combination with lugol's solution for controlling hyperthyroidism. Transfrontal surgery was performed when the patient was euthyroid clinically and biochemically. Because of limitation of the surgical tech-

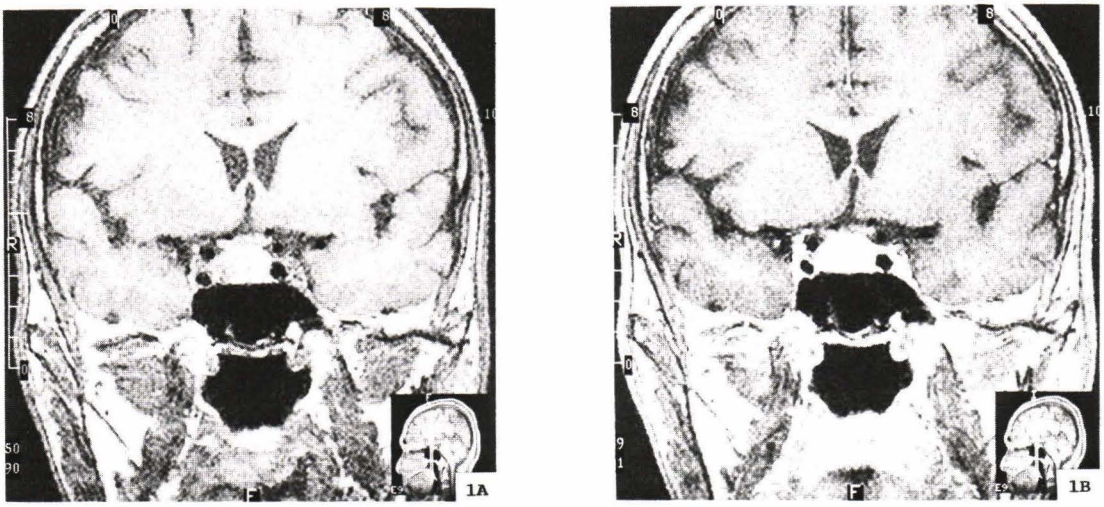

Fig. 1. MRI of pituitary and hypothalamus without contrast agent (1A) and with contrast agent (1B) demonstrates intrapituitary mass size approximately 20 x 13 mm with heterogeneous enhancement after contrast agent injection. The floor slants and superior convexity is noted. Right lateral displacement of carotid vessel is noted as well as visualized superior displacement of optic chiasma. There is no hydrocephalus.

nique and to avoid serious surgical complications, the tumor was only partially removed. The pituitary tumor cells showed pleomorphic activities and large nuclei in H & E staining confirming pituitary adenoma (Fig. 2). Immunoperoxidase staining with anti-TSH, anti-FSH, anti-LH, anti-ACTH, anti-PRL and anti-GH was done in tumor tissue and normal surrounding tissue. The pituitary tumor cells were strongly reactive to TSH (brown staining granules) and relatively mild for FSH and LH (Fig. 2). The tumor cells were not stained for ACTH, PRL and GH. (Fig. 2). As expected, the normal tissue was not stained for TSH.

Five days after surgery, while receiving PTU 450 mg/d, his serum T_4 was 3.3 ug/dl, T_3 53 ng/dl, FT_4 0.45 ng/dl, and TSH 6. 01 uIU/ml. Serum α-SU level was measured and found to be normal at 0.5 ng/ml. Then, PTU was discontinued. Four weeks later, he had clinical hyperthyroidism and his serum T_4 was high at 20.2 ug/dl, T_3 544 ng/dl, FT_4 7.8 ng/dl, and TSH 7.34 uIU/ml. The patient was restarted on PTU 150 mg/d and was considered for radiation. Conventional supervoltage radiation by ^{60}Co was delivered to the pituitary area, with a total tumor dose of 5,000 rad. During the remote effect of radiotherapy, the patient was on an antithyroid drug for control hyperthyroidism.

DISCUSSION

In this case, the patient presented with clinical hyperthyroidism and only FT_4 was investigated and found to be high. Although the most common cause of hyperthyroidism is Graves' disease, the diagnosis of hyperthyroidism should be confirmed by other thyroid function tests such as serum TSH level before starting any treatment. In this case, the patient was diagnosed as Graves' hyperthyroidism because of a high FT_4 level and antithyroid medication was given. During the follow-up period, the thyroid function tests showed high serum T_4, T_3 with inappropriately elevated TSH levels which contradicted the previous diagnosis of Graves' disease.

Inappropriately elevated TSH levels with high serum T_4, T_3 levels could be a differential diagnosis for TSH-secreting tumor, pituitary resistance to thyroid hormone (PRTH), and monoclonal TSH antibodies interfering with the test. PRTH could produce clinical hyperthyroid with high serum T_4, T_3, FT_4 and inappropriately high serum TSH, but the clinical manifestation should appear in the young age group. In this case, he presented with hyperthyroidism at age 49, so it was less likely to be PRTH. Monoclonal TSH antibodies should interfere with some TSH assays that use the same antibodies. TSH antibody was ruled out in

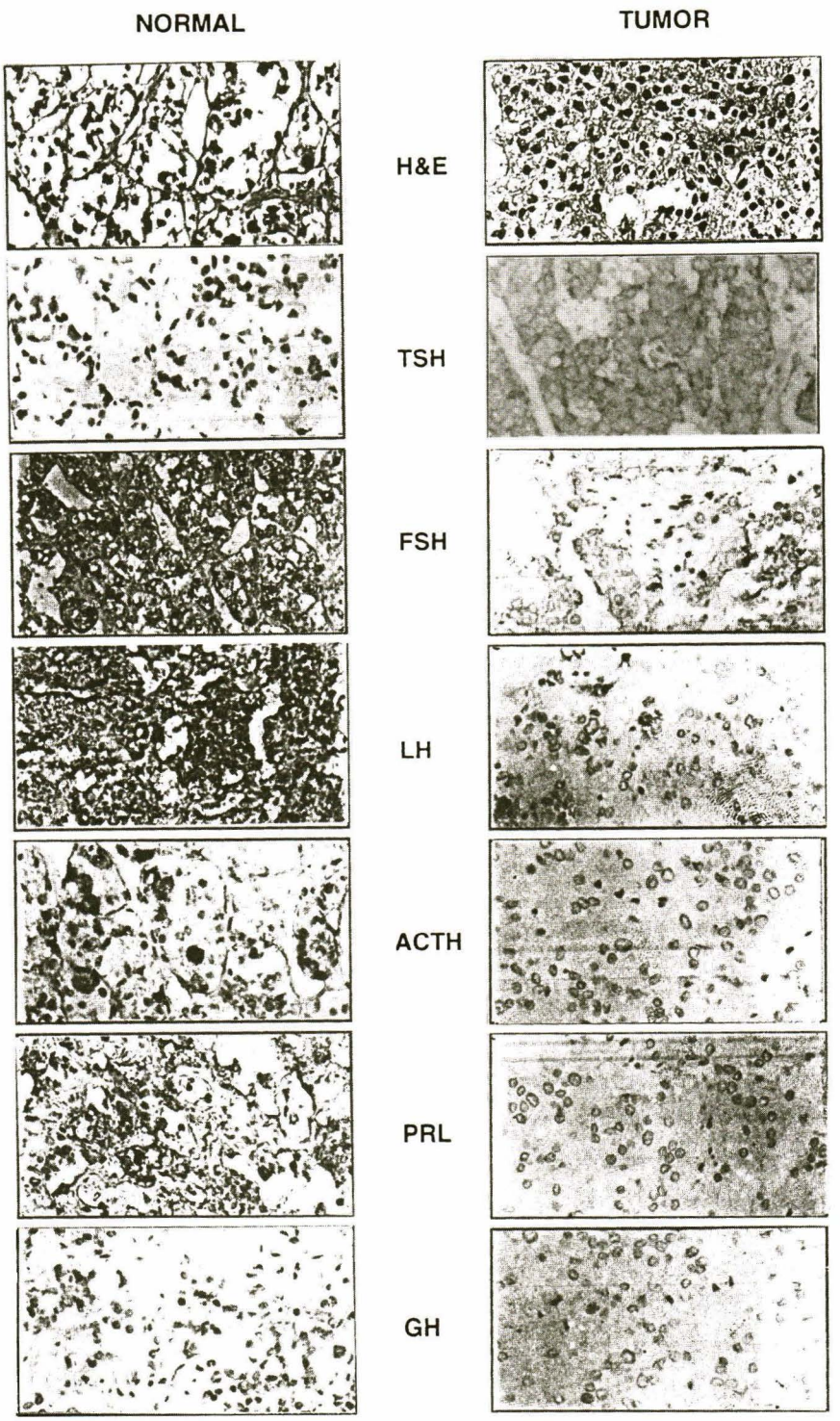

Fig. 2. Photomicrographs of pituitary tumor cells and normal pituitary tissue stained with H & E and immunoperoxidase method with anti-TSH, anti-FSH, anti-LH, anti-ACTH, anti-PRL and anti-GH (x 400). The pituitary tumor cells show pleomorphic activities and large nuclei in H & E staining. The pituitary tumor cells are strongly reactive to TSH (brown staining granules) with a relatively mild degree for FSH and LH. The tumor cells are not stained for ACTH, PRL and GH. The normal pituitary cells are not stained for TSH.

this case because he had goiter and clinical hyperthyroidism and interference by TSH antibody should not occur in many TSH assays as in this patient. Therefore, a TSH-secreting pituitary tumor was the most possible cause of hyperthyroidism in this patient. However, it took more than two years to make the right diagnosis. Although serum T_4, T_3, and Free T_4 concentrations are usually high in hyperthyroidism, serum TSH level is still very important in differentiating the causes of hyperthyroidism. In low serum TSH level, primary hyperthyroidism is the cause of hyperthyroidism. In normal TSH level, euthyroid hyperthyroxinemia should be the differential diagnosis. In secondary hyperthyroidism there could be normal or high TSH concentrations. After antithyroid drug treatment, it would be difficult to find the cause of hyperthyroidism or it would delay the diagnosis as in this case. Beck-Peccoz et al[5] analyzed all reported TSH-secreting pituitary tumors and found two thirds of all patients presented with a long history of thyroid dysfunction, mistakenly diagnosed as Graves' disease and inappropriately treated.

Confirmation by MRI has lead to recognition of TSH-secreting adenoma. Most TSH-secreting tumors have been macroadenomas as in our case. The range of TSH levels that have been reported is broad (1 to 400 mU/L), but approximately one-third of untreated and a quarter of treated patients showed TSH levels within the normal range[5]. Measurements of α-SU and/or α-SU/TSH molar ratio, evaluation of TRH stimulation test, L-T_3 suppression test and SHBG measurement have been advocated as a means of distinguishing TSH-secreting adenomas from other causes of inappropriate TSH secretion[3,4,11,16]. In this case, the additional diagnostic tools that suggested TSH-secreting adenoma were an impaired TSH response to TRH, high levels of α-SU and α-SU/TSH molar ratio, as well as a high level of SHBG. As mentioned before, the interpretation of α-SU/TSH molar ratio depends on basal TSH and gonadotrophin levels. SHBG is also a useful parameter for discriminating between resistance to thyroid hormone and TSH-secreting adenoma because SHBG levels are almost invariably normal in patients with resistance to thyroid hormone but often elevated in patients with TSH-secreting adenoma. Pituitary function test showed normal FSH, LH response to LHRH test, GH and cortisol response to insulin induced hypoglycemia supporting normal reserve of anterior pituitary gland.

The goal of treatment of TSH-secreting pituitary adenomas is to remove the tumor or, alternatively, to block TSH secretion and cell replication, and restore a euthyroid state. So far, surgical removal of TSH-secreting adenomas is the best therapeutic option, leading to prompt clinical and biochemical remission of hyperthyroidism in the majority of patients[13]. Transfrontal surgery was carried out in this case. There was some difficulty in controlling hyperthyroidism although he was receiving a high dose of antithyroid drugs. It was possible that his thyroid gland was quite enlarged. Then, lugol's solution was given to control hyperthyroidism before surgery. Serum TSH levels postoperatively can be used for the prognosis of the patient. Undetectable TSH levels 1 week after surgery are highly predictive of definite cure[13]. In our case, serum TSH levels were still high (6.0 mU/L) 5 days after surgery and hyperthyroidism recurred shortly after surgery. Furthermore, serum T_4, T_3, FT_4 and TSH concentrations were high 4 weeks after surgery. In the case of surgical failure, octreotide treatment is advised due to the high percentage of success obtained with this drug in terms of both restoration of euthyroidism and shrinkage of tumor mass[17]. Modern medical treatment of TSH-secreting adenomas is by the administration of somatostatin analogs, i.e., octreotide or lanreotide[17-19]. In fact, octreotide was effective in reducing TSH and α-SU secretion in 90 per cent of cases, with normalization of TSH in 75 per cent and restoration of the euthyroid state in the majority [5]. However, octreotide treatment would be a costly approach, so we decided to consider radiotherapy by ^{60}Co at pituitary gland. The combination of surgery and radiotherapy has resulted in normalization of circulating thyroid hormone levels and complete removal of tumor mass in 40 per cent of recorded patients[5]. An additional 33 per cent of patients may be judged to have improved, as normalization of circulating thyroid hormone levels was achieved, although there was no complete removal of the adenoma. Approximately one third of TSH-secreting adenomas had TSH hypersecretion after these treatments[5]. Antithyroid medication can be used to control hyperthyroidism while awaiting for the remote effect of radiotherapy.

Immunohistochemistry staining clearly demonstrated that tumor cells were strongly reactive to TSH but normal tissue was not stained for TSH. This would definitely support a TSH secreting adenoma and it showed that the tumor cells produced and secreted TSH into the circulation. High TSH levels would stimulate the thyroid to produce more thyroid hormone. High thyroid hormone concentration would suppress normal thyrotropes which is demonstrated in Fig. 2. Furthermore, the tumor cells exhibited a relatively mild degree of staining for FSH and LH. In approximately 30 per cent of TSH-secreting tumors, the pituitary tumor secretes other hormones, usually GH or PRL[5,7,8,20,21] and follicular stimulating hormone[22]. Acromegaly and/or hyperprolactinemia frequently coexist with TSH-secreting tumors. More than 80 per cent of TSH-secreting tumors oversecreted α-SU. Our case, did not have clinical acromegaly and hormone study and immunohistochemistry staining did not show GH and PRL secretion of tumor cells. Immunohistochemistry staining showed that the tumor cells were strongly reactive to TSH which was compatible with the clinical picture. Furthermore, there was a mild degree of immunohistochemistry staining for FSH and LH, but the secretion of FSH and LH was not high enough to be detected by hormone study. Although, immunohistochemistry staining for FSH and LH has not been found often coexisting with TSH-secreting tumors, there have been some reports [22,23].

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ธัยรอยด์เป็นพิษจากเนื้องอกของต่อมปิตูอิตารีย์ซึ่งหลั่งธัยโรโทรปิน

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ผู้วิจัยได้เสนอรายงานผู้ป่วยธัยรอยด์เป็นพิษจากเนื้องอกต่อมปิตูอิตารีย์ขนาดใหญ่ ซึ่งหลั่ง thyroid stimulating hormone (TSH) ผู้ป่วยได้รับการวินิจฉัยผิดและได้รับการรักษาแบบ Graves' disease มาเป็นเวลา 1 ปี ผู้ป่วยมีระดับ TSH สูงร่วมกับมีระดับธัยรอยด์ฮอร์โมนสูง ผลการกระตุ้น TSH ด้วย Thyrotropin releasing hormone พบว่ามี blunt response แต่ระดับ prolactin ถูกกระตุ้นได้ดี การวัดระดับ α-subunit และ α-subunit ต่อ TSH molar ratio ในผู้ป่วยก่อนผ่าตัด พบว่ามีค่าสูงกว่าปกติ ระดับ sex hormone-binding globulin สูงกว่าปกติเช่นกัน การทำ MRI พบว่ามีเนื้องอกต่อมปิตูอิตารีย์ขนาดใหญ่ การทำ insulin tolerance test และ GnRH test พบว่ามีการตอบสนองเป็นปกติ ผู้ป่วยได้รับ PTU ขนาดสูงร่วมกับ lugol's solution เพื่อคุมภาวะธัยรอยด์เป็นพิษก่อนผ่าตัด transfrontal surgery และได้รับการตัดเนื้องอกต่อมปิตู-อิตารีย์ออกบางส่วน การตรวจทางพยาธิร่วมกับการย้อม immunohistochemistry พบว่าเซลล์ของเนื้องอก ย้อมติด TSH อย่างมาก และย้อมติด FSH และ LH ด้วยในปริมาณเล็กน้อย เซลล์ของเนื้องอกย้อมไม่ติด Prolactin, growth hormone, และ ACTH เลย ผู้ป่วยได้รับการรักษาด้วยการฉายรังสีที่ต่อมปิตูอิตารีย์ด้วย ^{60}Co และตามด้วยการใช้ antithyroid drug ระหว่างที่รอผลการฉายรังสี

คำสำคัญ : ธัยรอยด์เป็นพิษ, เนื้องอกของต่อมปิตูอิตารีย์ซึ่งหลั่งธัยโรโทรปิน

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