A Case of a TSH-secreting Pituitary Adenoma Associated with Evans' Syndrome

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We present a case of a TSH-secreting pituitary adenoma (TSHoma) associated with Evans' syndrome. A 30-year-old woman was referred to our hospital due to purpura and ecchymoses on her limb and body and epistaxis. Evans' syndrome was diagnosed based on idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia. She had a history of malocclusion and thyroid gland enlargement 4 years prior to admission. Endocrinological tests and magnetic resonance imaging also revealed that this patient had hyperthyroidism due to the TSHoma and that this adenoma concomitantly secreted GH. Recently, several cases of Evans' syndrome were associated with hyperthyroidism caused by autoimmune thyroid disease, such as Graves' disease, suggesting that these 2 conditions may have a common immunological basis. To the best of our knowledge, there is no case report of Evans' syndrome associated with hyperthyroidism due to TSHoma. Our report suggests that the excess of thyroid hormone itself promotes autoimmunity in Evans' syndrome. Thus, early treatment for hyperthyroidism is necessary in TSHomas because of the possibility that thyroid hormone normalization may prevent the development of Evans' syndrome.

Key words: TSH-secreting pituitary adenoma, hyperthyroidism, Evans' Syndrome

INTRODUCTION

TSH-secreting pituitary adenomas (TSHomas) are rare tumors, and the TSHoma incidence is 1–3% among pituitary adenomas [1, 2]. TSHomas are diagnosed in the fifth and sixth decades of life, and the spontaneous occurrence of TSHomas is more frequent in women [3, 4]. These tumors may lead to the development of hyperthyroidism through a condition called syndrome of inappropriate secretion of TSH (SITSH) [5]. Approximately 40% of TSHomas are associated with a concomitant production of other pituitary hormones, such as GH and PRL [6]. In the case of TSHomas that concomitantly secrete GH, excessive GH causes acromegalic features, diabetes mellitus, arthropathy, cardiomyopathy and shortened life expectancy [7]. Surgical removal can be curative for small adenomas, whereas incomplete removal is common for large adenomas [8].

In contrast, Evans' syndrome is a rare combination of autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP). Evans reported the first case in 1951, when he presented evidence of a spectrum-like relation between hemolytic anemia and thrombocytopenia [9]. AIHA is a disease in which the products of autoantibodies are directed against red blood cells, leading to premature destruction. ITP involves various autoimmune mechanisms, such as antiplatelet antibodies and tolerance to B-cells and T-cells [10]. Although largely detected in pediatric patients, Evans' syndrome can also occur in maturity [11, 12]. A recent analysis showed a common association of this syndrome with other diseases, such as lymphoproliferative disorders, immune deficiency, and autoimmune disorders. Evans' syndrome patients often benefit from treatment with corticosteroids and second-line treatments consisting of immunosuppressants [13].

Considering the above issues, a relationship between the pathogenesis of TSHomas and Evans' syndrome is unlikely. However, several recent cases of Evans' syndrome associated with hyperthyroidism caused by autoimmune thyroid diseases, such as Graves' disease, suggest that these two conditions may have a common immunological mechanism [14–18]. We report here a case of a TSHoma associated with Evans' syndrome. In our case, the hyperthyroidism is due to TSHoma.

CASE REPORT

A 30-year-old woman was admitted to a nearby hospital due to purpura and ecchymoses on her limbs and body and epistaxis. There was no family history of notable illness, including autoimmune disease. Laboratory results revealed a hemoglobin level of 3.5 g/dL (reference range [RR], 11.5–15.5), white blood

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Table 1 Laboratory data on admission.

Urinalysis		Blood chemistry		Endocrine examination	
color	yellow	CRP	< 0.09 mg/dL	neurohypophysis	
pH	6.0	TP	4.7 g/dL	ADH	2.5 pg/mL
protein	(+)	Alb	2.5 g/dL	adenohypophysis	
occult blood	(2+)	AST	15 IU/L	ACTH	27.8 pg/mL
glucose	(-)	ALT	7 IU/L	F	8.9 μg/dL
ketone body	(-)	LDH	179 IU/L	TSH	4.450 μIU/mL
osmolality	394 mOsm/kg	ALP	262 IU/L	fT3	11.96 pg/mL
		γ-GTP	12 IU/L	fT4	4.03 ng/dL
Hematological examination		CPK	52 IU/L	PRL	6.8 ng/mL
WBC	4900/μL	Na	139 mEq/L	GH	19.5 ng/mL
Neu	68.6%	K	3.1 mEq/L	IGF-1	407 ng/mL
Lym	22.9%	Cl	110 mEq/L	FSH	4.4 mIU/mL
Mo	6.8%	Ca	8.2 mg/dL	LH	< 2.0 mIU/mL
Eo	1.7%	P	3.2 mg/dL	E2	< 25 pg/mL
Ba	0%	BUN	6 mg/dL	Prog	0.2 ng/mL
RBC	143 × 10^4/μL	Cr	0.29 mg/dL		
Hb	3.5 g/dL	UA	4.0 mg/dL		
Ht	12.6%	glucose	118 mg/dL		
Plts	0.1 × 10^4/μL	HbA1c	4.7%		
		plasma osmolality 284 mOsm/kg			

Abbreviations: ADH, antidiuretic hormone; ACTH, adrenocorticotrophic hormone; F, cortisol; TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; PRL, prolactin; GH, growth hormone; IGF-1, insulin-like growth factor-1; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; Prog, progesterone.

cell count of 4900/μL (RR, 4000–8000) and platelet count of 0.5x10^4/μL (RR, 14.0–40.0x10^4). A hematologic disease was suspected, and she was referred to our hospital. She had a history of malocclusion and thyroid gland enlargement 4 years prior to admission.

On physical examination at admission, the patient was 163.0 cm and weighed 49.0 kg. The patient's characteristics were the following: temperature, 37.6 °C; pulse, 148 beats/min; blood pressure, 182/80 mmHg; and respiratory rate, 24 breaths/min. She had anemic conjunctiva and icteric sclera. The patient had no exophthalmos, and the thyroid gland was diffusely enlarged. Acromegalic features were present, such as thickened lips, prognathism of the mandible and enlargement of the fingers. The patient presented with blurred vision. The chest was clear on auscultation. Cardiac examination revealed a normal S1 sound and a physiologically split S2 sound, without a murmur, gallop or rub. The abdomen was not tender, and there was hepatosplenomegaly. She had scattered ecchymoses.

Laboratory analysis at admission revealed low hemoglobin, hematocrit, red blood cell (RBC), and platelet levels (Table 1). The white blood cell (WBC) count was 4900/μL with a normal differential count. Routine laboratory examinations suggested malnutrition, including low levels of the following: TP, 4.7 g/dL (RR, 6.5–8.0); Alb, 2.5 g/dL (RR, 3.9–4.8); K, 3.1 mEq/L (RR, 3.5–4.8); BUN, 6 mg/dL (RR, 8–20); and Cr, 0.29 mg/dL (RR, 0.5–0.8). Urinalysis showed proteinuria and occult blood. Peripheral blood smear examination showed thrombocytopenia and normocytic anemia with anisocytosis and poikilocytes, such as target cells and microcytic and polychromatic RBCs. Reticulocytes were increased in number. The direct/indirect Coombs' test had a positive result. Bone marrow aspiration showed a hypercellular marrow, and the erythroid lineage cells were increased in number. The impression on hematological investigations was hemolytic anemia with thrombocytopenia. The hormonal examination suggested a syndrome of inappropriate secretion of TSH (SITSH), with TSH of 4.450 μIU/mL (RR, 0.27–4.20), fT3 of 11.96 pg/mL (RR, 2.30–4.00), and fT4 of 4.03 ng/dL (RR, 1.00–1.80). The serum levels of GH [19.5 ng/mL (RR, 0.13–9.88)] and IGF-1 [407 ng/mL (RR, 129–304)] were also high. The serum levels of 4.4 mIU/mL FSH (RR, 4.7–21.5), LH < 2.0 mIU/mL (RR, 5–25) and E2 < 25 pg/mL (RR, 50–400) implied central hypogonadism due to compression of the normal pituitary gland by tumor. Magnetic resonance imaging (MRI) of the brain revealed a pituitary tumor of 34x26x28 mm in the sella involving cavernous sinuses and extending inferior to the sphenoid sinus (Fig. 1). Thyroid ultrasonography showed multiple nodules at the right and left lobes and swelling of the thyroid. A 75 g oral glucose tolerance test (OGTT) showed no suppression of GH release (RR, nadir GH level < 1 ng/mL, Table 2). An octreotide suppression test had a positive result (RR, nadir GH level < 2.785 ng/mL, Table 3). We performed some examinations related to autoimmune diseases (Table 4). The serum levels of C3c [37.3 mg/dL (RR, 85–160)] and C4 [< 1.0 mg/dL

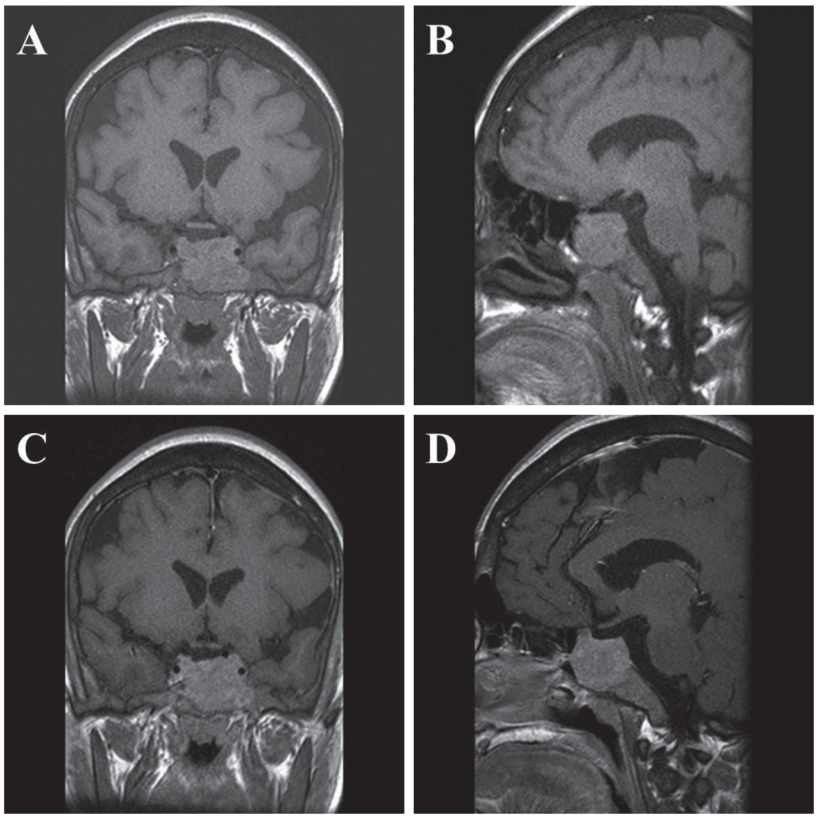

Fig. 1 Magnetic resonance imaging (MRI) findings on admission. MRI revealed a pituitary tumor of 34x26x28 mm in the sella involving cavernous sinuses and extending inferior to the sphenoid sinus (A: unenhanced coronal T1-weighted image, B: unenhanced sagittal T1-weighted image, C: postcontrast coronal T1-weighted image, D: postcontrast sagittal T1-weighted image).

Table 2 Results of 75g glucose tolerance test before surgery.

min	0	30	60	120
glucose (mg/dL)	83	122	142	102
GH (ng/mL)	13.6	10.1	8.21	4.36
[nadir GH level < 1]				

Abbreviations: GH, growth hormone; [ ], reference range.

Table 3 Results of octreotide suppression test.

hour	0	2	4	6	8
GH (ng/mL)	5.57	1.52	1.67	2.13	2.44
[nadir GH level < 2.785]					

Abbreviations: GH, growth hormone; [ ], reference range.

Table 4 Laboratory data on admission.

sIL-2R	2660 U/mL	TPOAb	36 IU/mL
MPO-ANCA	< 10 EU	TgAb	289 IU/mL
PR3-ANCA	< 10 EU	TRAb	0.4%
RF	< 2 IU/mL	anti GAD antibody	< 0.3 U/mL
C3c	37.3 mg/dL	anti SS-A antibody	< 5.0 U/mL
C4	< 1.0 mg/dL	anti SS-B antibody	< 5.0 U/mL
anti nuclear antibody	positive	anti pituitary antibody	negative

Abbreviations: sIL-2R, soluble interleukin-2 receptor; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-ANCA; RF, rheumatoid factor; C3c/4, complement 3c/4 ; TPOAb, anti thyroid peroxidase antibody; TgAb, anti thyroglobulin antibody; TRAb, anti thyroid-stimulating hormone receptor antibody; GAD, glutamic acid decarboxylase.

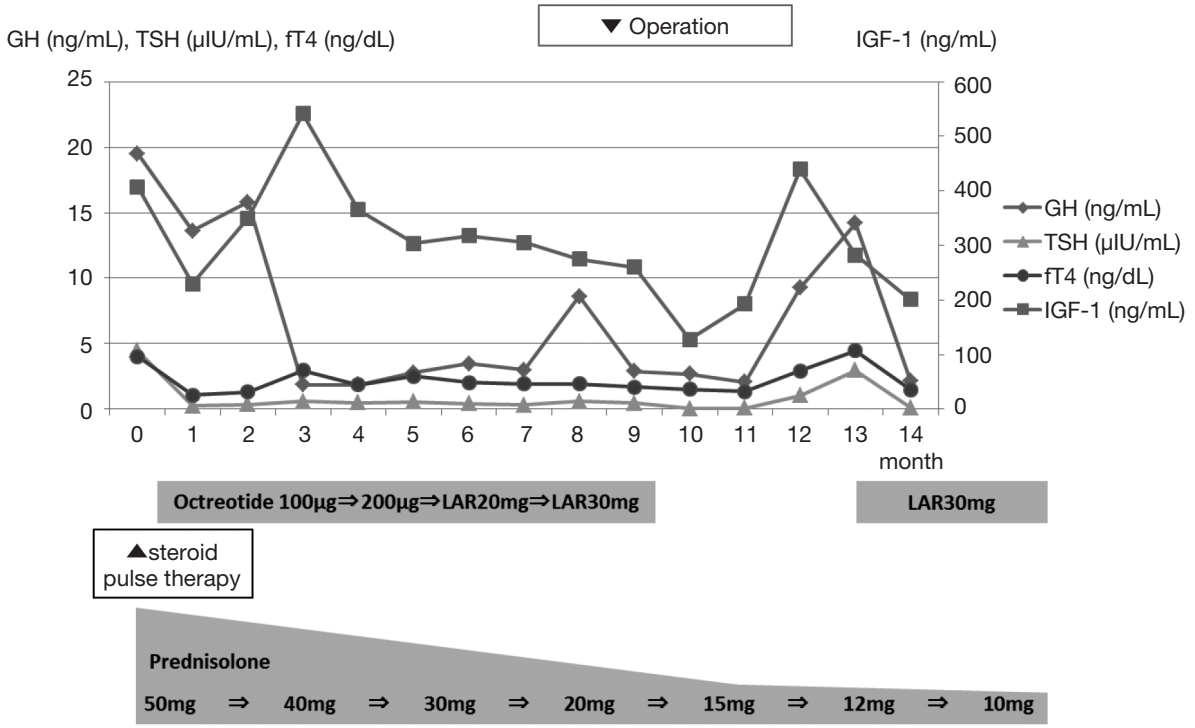

Fig. 2 Clinical course of the patient. Immediately after admission, immunosuppressive therapy with glucocorticoid for Evans' syndrome was started. She was also treated with octreotide to control the hyperthyroidism caused by the TSH-secreting adenoma before the operation. The patients' laboratory data, including hemoglobin, platelet, TSH, fT3, fT4, GH and IGF-1 levels, were normalized before operation. After surgery, octreotide treatment was discontinued, and immunosuppressive therapy was maintained. The patients' laboratory data, including TSH, fT3, fT4, GH and IGF-1 levels, were normalized, but over the next 5 months, these hormone levels increased again. Thus, she was administered a long-acting octreotide treatment again.
Abbreviations: LAR, long-acting release.

(RR, 15–40)] were both decreased, and the antinuclear antibody test was positive. The patient also had an increased sIL-2R of 2660 U/mL (RR, 145–519), anti-thyroid peroxidase antibody of 36 IU/mL (RR, < 16) and anti-thyroglobulin antibody of 289 IU/mL (RR, < 28). Based on these data, we diagnosed the patient with Evans' syndrome and hyperthyroidism due to TSHoma with the adenoma concomitantly secreting GH.

As shown in Fig. 2, we started the patient on high-dose steroids for Evans' syndrome immediately after admission and continued with an oral administration of prednisolone (1 mg/kg). Her hemoglobin and platelet levels were normalized and stabilized within a month after the steroid treatment. The patient was treated with octreotide for 9 months to control hyperthyroidism due to the TSHoma preoperatively. Thereby, the TSH, fT3 and fT4 levels were within the normal limit. Moreover, the GH levels were decreased, and the IGF-1 levels fell into the gender- and age-adjusted normal range. Subsequently, we performed transsphenoidal surgery for the pituitary adenoma. Hematoxylin and eosin staining for the cells in the surgical specimen showed diffuse proliferations of small atypical cells (Fig. 4A). Also they were diffusely positive for chromogranin A (Fig. 4B) and α-subunit (Fig. 4C). Immunostaining for thyroid-stimulating hormone reveals the expression of TSHβ (Fig. 4D). TSHβ-positive cells were not positive for GH (Fig. 4E). GH-positive cells were not observed. Electron microscopy showed that the tumor cells contained secretory granules (50 nm), and we could not find GH-type large secretory granules or fibrous bodies.

After surgery, octreotide treatment was discontinued, and immunosuppressive therapy was maintained. Our patient had an uneventful post-operative course, and her laboratory data, including TSH, fT3, fT4, GH and IGF-1 levels, were normalized. Over the next 5 months, there was a reduction in the size of the pituitary gland compared with the size found using MRI at admission (Fig. 3), but the TSH, fT3, fT4, GH and IGF-1 levels increased again. Furthermore, we performed an OGTT, and GH was not suppressed (RR, nadir GH level < 1 ng/mL, Table 5). We thought that the residual tumor existed because surgical removal can be curative for small adenomas, whereas incomplete removal is common for large adenomas [8]. The patient was administered a long-acting octreotide treatment of 30 mg a month again and was maintained on immunosuppressive therapy of 10 mg/day of oral prednisolone. She is being followed by the Rheumatology and the Nephrology, Endocrinology and Metabolism outpatient division.

DISCUSSION

To the best of our knowledge, there is no case report of Evans' syndrome associated with TSHomas. It would be interesting to determine whether these two diseases exist coincidentally. We presumed that thyroid hormone might influence autoimmune disorders and investigated the etiology using past cases of Evans'

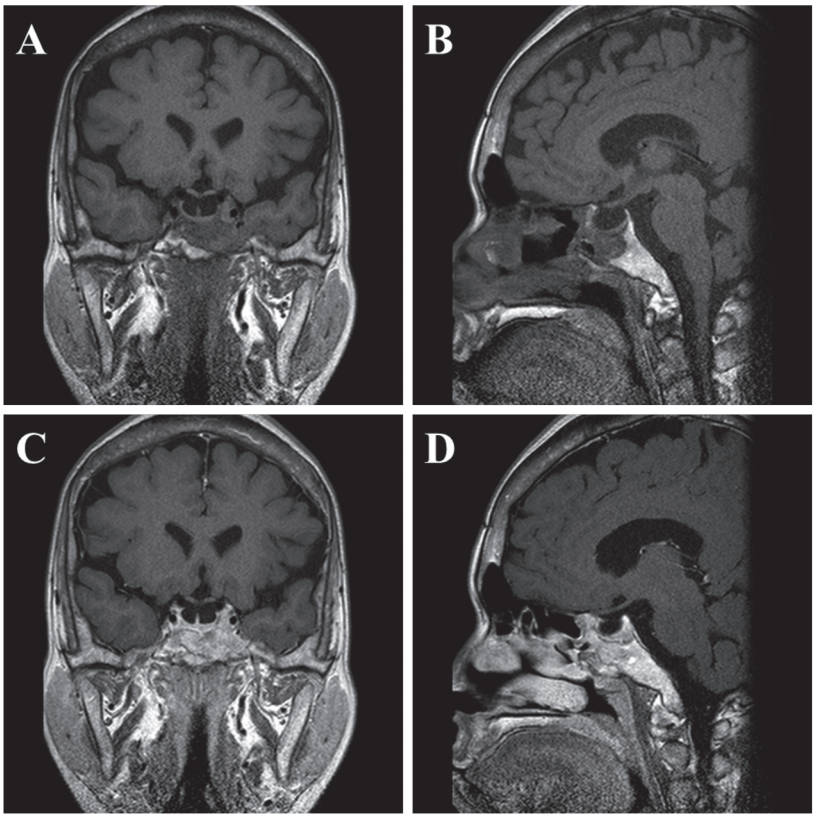

Fig. 3 Postoperative magnetic resonance imaging (MRI) findings at 5 months. MRI revealed a reduction in the size of the pituitary gland compared with the size found using MRI at admission (A: unenhanced coronal T1-weighted image, B: unenhanced sagittal T1-weighted image, C: postcontrast coronal T1-weighted image, D: postcontrast sagittal T1-weighted image).

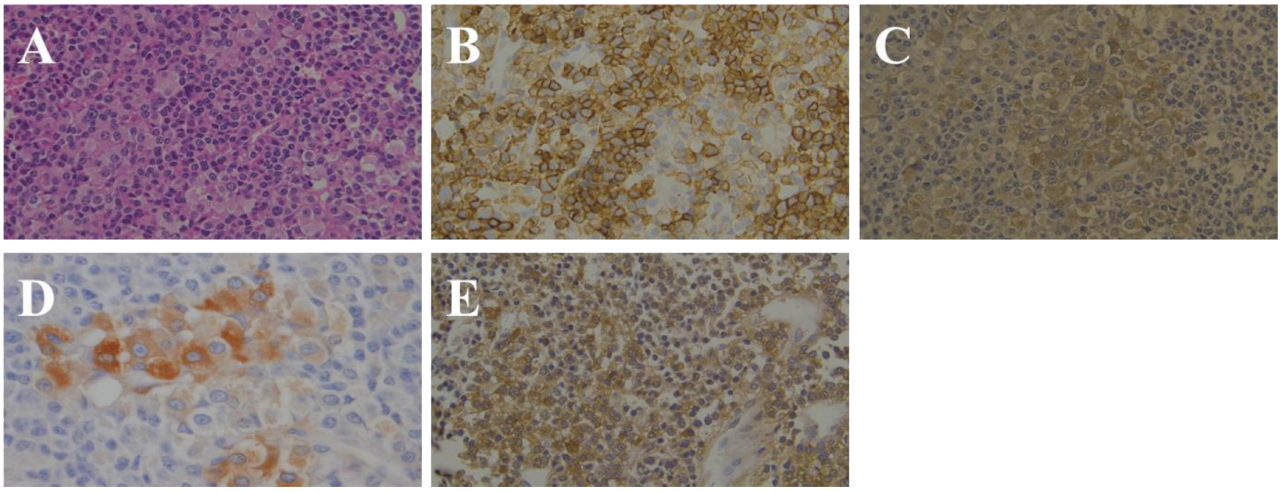

Fig. 4 Histopathological findings. Hematoxylin and eosin staining for the cells in the surgical specimen showed diffuse proliferations of small atypical cells (A, X 400). Also they were diffusely positive for chromogranin A (B, X 400) and α-subunit (C, X 400). Immunostaining for thyroid-stimulating hormone reveals the expression of TSHβ (D, X 800). TSHβ-positive cells were not positive for GH (E, X 400).

Table 5 Results of 75g glucose tolerance test after surgery.

min	0	30	60	120
glucose (mg/dL)	87	160	153	127
GH (ng/mL)	15.6	15.1	8.08	3.27
[nadir GH level < 1]				

Abbreviations: GH, growth hormone; [ ], reference range.

syndrome associated with hyperthyroidism [14–18]. Patients with Graves' disease frequently experience other immunological diseases, such as ITP, AIHA, type 1 diabetes mellitus, and myasthenia gravis [19]. Although the association of Evans' syndrome with Graves' disease is rare [15], it is suggested that both diseases have the same immunological mechanism, including insufficient suppressor T-cell activity [20] and TSH receptor autoantibodies, such as oligoclonal IgG_2 antibodies [21, 22]. Moreover, it was indicated that hemolytic anemia and thrombocytopenia are the results of thyroid hormone stimulation of the activated reticuloendothelial phagocytic system [23]. Increased blood flow, due to hyperthyroidism, accelerates phagocytosis in the reticuloendothelial system [24]. In our patient, the hyperthyroidism is due to the TSHoma and is not associated with autoimmune disorders, such as Graves' disease. Thus, we speculate that the excess of thyroid hormone itself might promote autoimmunity in Evans' syndrome.

An important question, as described above, concerns the extreme rarity of a coincidence between Evans' syndrome and hyperthyroid states, including Grave's disease and TSHomas. It is well known that prolactin (PRL) upregulates immune function and promotes autoimmune responses [25]. Additionally, elevated levels of PRL are common in patients with systemic lupus erythematosus (SLE), which is the same autoimmune disease as Evans' syndrome [26]. Considering the above issues, Li *et al*. speculated that hyperprolactinemia might contribute to the excessive immune response in SLE and investigated patients with SLE and PRLomas [27]. However, there was no clear relationship between the degree of increase in prolactin levels, hormone effectiveness, and autoimmune disease activity [27]. The authors suggested that these results were due to genetic differences in the reactivity to PRL [27]. Similarly, among Evans' syndrome patients, there may be a group of patients with a genetic difference that causes susceptibility to the effects of hyperthyroidism. The accumulation of many cases of TSHomas with Evans' syndrome may be useful to explain the rarety of a coincidence between Evans' syndrome and hyperthyroid states.

Another possible etiology in patients with TSHomas and Evans' syndrome is a genetic polymorphism related to the pituitary tumor-transforming gene (PTTG). Pei and Melmed discovered that PTTG mRNA was expressed in the cells of a rat pituitary tumor cell line [28, 29]. The human gene isoform is named PTTG1, and the protein product was identified to be securin [29]. The protein is an inhibitor of sister chromatid separation, which generally occurs during anaphase of mitosis [29, 30]. The regulation and function of PTTG1 affect DNA damage and repair, cell cycle regulation, metabolism and organ development [29]. This gene is highly expressed in various endocrine-related tumors, for example pituitary, thyroid, uterine, ovarian and breast tumors [31]. PTTG1 overexpression was confirmed to have transforming and tumorigenic activity [29]. In addition, a recent genome-wide study suggested a variant in a region, which was between PTTG1 and the microRNA-146a genes, related to SLE susceptibility [32]. The microRNA-146a is a player in the regulation of the immune system and tumor progression [33]. This study statistically analyzed three single-nucleotide polymorphisms (SNPs) in SLE patients [32]. One SNP was genetically associated with SLE and potentially important in SLE etiology [32]. With this in mind, there is a possibility that a pituitary tumor might be related to an autoimmune disease. Further analysis of these SNPs in patients with TSHomas and Evans' syndrome is necessary to resolve the hypothesis mentioned above.

Finally, we concluded that the TSHoma concomitantly secreted GH in the present case. As shown in case report, acromegaloid features were present and the OGTT showed no suppression of GH release. The level of IGF-1 was high, and MRI showed a pituitary tumor. Based on these findings, we could diagnose this patient with acromegaly according to the "Guideline for Diagnosis and Treatment of Acromegaly 2012." However, the immunohistochemical staining showed that the tumor cells were only reactive to TSH and were not positive for GH. Three possibilities could explain this contradictory situation. The first possibility is a low sensitivity when staining the tumor cells for GH because of a comparatively weak production of GH. In fact, our patient did not express severe acromegaloid features clinically. The second possibility is that we only extracted the tumor sections that produced TSH and did not extract the part that produced GH. The third possibility is influence of octreotide treatment. There was no report of a relationship between excessive GH secretion and the autoimmunity of Evans' syndrome. However, we could not exclude the possibility that GH secretion influenced the onset of Evans' syndrome in addition to hyperthyroidism.

In summary, we described here a case of TSHoma associated with Evans' syndrome. To the best of our knowledge, there is no case report of Evans' syndrome associated with hyperthyroidism due to TSHoma. Our report suggests that an excess of thyroid hormone itself promotes autoimmunity in Evans' syndrome. Thus, early treatment for hyperthyroidism is necessary in TSHomas because thyroid hormone normalization may prevent the development of Evans' syndrome.

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REFERENCES

1) Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. Endocr Rev 1996; 17: 610–638.
2) Sanno N, Teramoto A, Osamura RY. Long-term surgical outcome in 16 patients with thyrotropin pituitary adenoma. J Neurosurg 2000; 93: 194–200.
3) Ónnestam L, Berinder K, Burman P, Dahlqvist P, Engström BE, Wahlberg J, *et al*. National incidence and prevalence of TSH-secreting pituitary adenomas in Sweden. J Clin Endocrinol Metab 2013; 98: 626–635.
4) Mindermann T, Wilson CB. Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol (Oxf) 1994; 41: 359–364.
5) Fukuhara N, Horiguchi K, Nishioka H, Suzuki H, Takeshita A, Takeuchi Y, *et al*. Short-term preoperative octreotide treatment for TSH-secreting pituitary adenoma. Endocr J 2014 Oct 1.
6) Smallridge RC. Thyrotropin-secreting pituitary tumors.

Endocrinol Metab Clin North Am 1987; 16: 765–792.
7) Kumar SS, Ayuk J, Murray RD. Current therapy and drug pipeline for the treatment of patients with acromegaly. Adv Ther 2009; 26: 383–403.
8) McCutcheon IE, Weintraub BD, Oldfield EH. Surgical treatment of thyrotropin-secreting pituitary adenomas. J Neurosurg 1990; 73: 674–683.
9) EVANS RS, TAKAHASHI K, DUANE RT, PAYNE R, LIU C. Primary thrombocytopenic purpura and acquired hemolytic anemia; evidence for a common etiology. AMA Arch Intern Med 1951; 87: 48–65.
10) Koti K, Thumma RR, Nagarajan S, Mathi A. Hashimoto's thyroiditis associated Evans syndrome: A rare case report on the clustered autoimmune disease triad. Indian J Endocrinol Metab 2013; 17: 736–739.
11) Wang WC. Evans syndrome in childhood: pathophysiology, clinical course, and treatment. Am J Pediatr Hematol Oncol 1988; 10: 330–338.
12) Sava¸san S, Warrier I, Ravindranath Y. The spectrum of Evans' syndrome. Arch Dis Child 1997; 77: 245–248.
13) Simon OJ, Kuhlmann T, Bittner S, Müller-Tidow C, Weigt J, Wiendl H, Meuth SG. Evans syndrome associated with sterile inflammation of the central nervous system: a case report. J Med Case Rep 2013; 7: 262.
14) Kuroda H, Kida M, Watanabe H, Matsunaga T, Niitsu Y, Matsumoto M. [Basedow disease associated with Evans syndrome]. Rinsho Ketsueki 2005; 46: 1118–1122.
15) Yashiro M, Nagoshi H, Kasuga Y, Isobe H, Kitajima S, Nakagawa T, *et al*. Evans' syndrome associated with Graves' disease. Intern Med 1996; 35: 987–990.
16) Shimohakamada Y, Fukuda N, Shinohara K, Inoue Y. [Simultaneous occurrence of Basedow's disease and autoimmune hemolytic anemia]. Rinsho Ketsueki 2001; 42: 328–331.
17) Ikeda K, Maruyama Y, Yokoyama M, Kato N, Yamanoto H, Kaguchi Y, *et al*. Association of Graves' disease with Evans' syndrome in a patient with IgA nephropathy. Intern Med 2001; 40: 1004–1010.
18) Ushiki T, Masuko M, Nikkuni K, Terukina-Yoshida J, Momotsu-Nanba A, Morikawa H, *et al*. Successful remission of Evans syndrome associated with Graves' disease by using propylthiouracil monotherapy. Intern Med 2011; 50: 621–625.
19) Biró E, Szekanecz Z, Czirják L, Dankó K, Kiss E, Szabó NA, *et al*. Association of systemic and thyroid autoimmune diseases. Clin Rheumatol 2006; 25: 240–245.
20) Nagaratnam N, et al. Haemolytic anaemia, Graves' disease, autoantibodies, IgM para-proteinemia, lymphoreticular disease and recurrent meningitis: A case report. Asian J Infectious Dis 1978; 2: 271.
21) Michalek K, Morshed SA, Latif R, Davies TF. TSH receptor autoantibodies. Autoimmun Rev 2009; 9: 113–116.
22) Sato A, Zakarija M, McKenzie JM. Characteristics of thyrotropin binding to bovine thyroid plasma membranes and the influence of human IgG. Endocr Res Commun 1977; 4: 95–113.
23) Lamberg BA, Kivikangas V, Pelkonen R, Vuopio P. Thrombocytopenia and decreased life-span of thrombocytes in hyperthyroidism. Ann Clin Res 1971; 3: 98–102.
24) Ogihara T, Katoh H, Yoshitake H, Iyori S, Saito I. Hyperthyroidism associated with autoimmune hemolytic anemia and periodic paralysis: a report of a case in which antihyperthyroid therapy alone was effective against hemolysis. Jpn J Med 1987; 26: 401–403.
25) Peeva E, Venkatesh J, Michael D, Diamond B. Prolactin as a modulator of B cell function: implications for SLE. Biomed Pharmacother 2004; 58: 310–319.
26) Lahita RG. The role of sex hormones in systemic lupus erythematosus. Curr Opin Rheumatol 1999; 11: 352–356.
27) Li M, Keiser HD, Peeva E. Prolactinoma and systemic lupus erythematosus: do serum prolactin levels matter? Clin Rheumatol 2006; 25: 602–605.
28) Pei L, Melmed S. Isolation and characterization of a pituitary tumor-transforming gene (PTTG). Mol Endocrinol 1997; 11: 433–441.
29) Zhao Z, Zhang M. Pituitary tumor-transforming gene 1: perspective on an apoptosis pathway. Cancer Biol Ther 2011; 11: 346–348.
30) Zou H, McGarry TJ, Bernal T, Kirschner MW. Identification of a vertebrate sister-chromatid separation inhibitor involved in transformation and tumorigenesis. Science 1999; 285: 418–422.
31) Vlotides G, Eigler T, Melmed S. Pituitary tumor-transforming gene: physiology and implications for tumorigenesis. Endocr Rev 2007; 28: 165–186.
32) Löfgren SE, Frostegård J, Truedsson L, Pons-Estel BA, D'Alfonso S, Witte T, *et al*. Genetic association of miRNA-146a with systemic lupus erythematosus in Europeans through decreased expression of the gene. Genes Immun 2012; 13: 268–274.
33) Lu LF, Boldin MP, Chaudhry A, Lin LL, Taganov KD, Hanada T, *et al*. Function of miR-146a in controlling Treg cell-mediated regulation of Th1 responses. Cell 2010; 142: 914–929.