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【 CASE REPORT 】

Follicle-stimulating Hormone-secreting Pituitary Adenoma Accompanied by Painful Thyroiditis

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Abstract:
A 30-year-old woman with multiple ovarian cysts presented with high serum estradiol levels. She had a pituitary adenoma, but the follicle-stimulating hormone (FSH) concentration was within the normal range. The patient complained of neck pain and palpitations during the disease course, and laboratory results revealed thyrotoxicosis and a systemic inflammatory response with negative findings for anti-thyroid stimulating hormone (TSH) receptor antibody and positive findings for anti-thyroglobulin and anti-thyroid peroxidase antibodies. Prednisolone improved the symptoms and the thyroid function and was discontinued after two months. A histological examination of the pituitary tumor confirmed it to be FSH-producing pituitary adenoma, with subsequent normalization of the serum estradiol concentration.

Key words: FSH-secreting pituitary tumor, Hashimoto thyroiditis

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Introduction

Gonadotroph adenomas account for approximately 80% of non-functioning pituitary adenomas and 40% of all clinically recognized macroadenomas (1, 2). However, these adenomas are typically poorly differentiated and inefficient producers/secretors and do not increase the serum gonadotropin concentrations. They are thus usually clinically "silent" and cannot be distinguished from other clinically non-functioning adenomas until after surgical pituitary tumor removal and an immunohistochemical evaluation. Therefore, symptomatic follicle-stimulating hormone (FSH)-producing pituitary adenomas are rare.

Hashimoto thyroiditis is an autoimmune thyroid disorder that usually presents as a diffuse, nontender goiter, whereas subacute thyroiditis is an uncommon disease that is characterized by tender thyroid enlargement, transient thyrotoxicosis, and elevated inflammatory markers. Mimicking subacute thyroiditis, patients with Hashimoto thyroiditis rarely but occasionally present with tender goiter and a fever, known as "painful Hashimoto thyroiditis" (3).

We herein report a woman with an FSH-producing pituitary adenoma that caused ovarian hyperstimulation. In addition, the patient developed painful thyroiditis during the disease course that was difficult to confirm as painful Hashimoto thyroiditis or subacute thyroiditis.

Case Report

In December 2014, a 30-year-old woman underwent myomectomy for uterine myomas at the Department of Obstetrics and Gynecology of the University of Yamanashi.

Preoperative laboratory data obtained in the luteal phase showed a normal concentration of serum estradiol (388.1 pg/mL), luteinizing hormone (LH) (13.7 mIU/mL), and FSH (2.2 mIU/mL) levels. Since ovarian cysts had been detected during follow-up visits after the operation, she was diagnosed with functional cysts. In April 2015, she presented to the follow-up appointment with sudden-onset severe upper abdominal pain. A pregnancy test was negative, and transvaginal ultrasonography and computed tomography showed bilateral ovarian enlargements (left: 7×4 cm, right: 11×8 cm). Ovarian torsion was clinically suspected, and emer-

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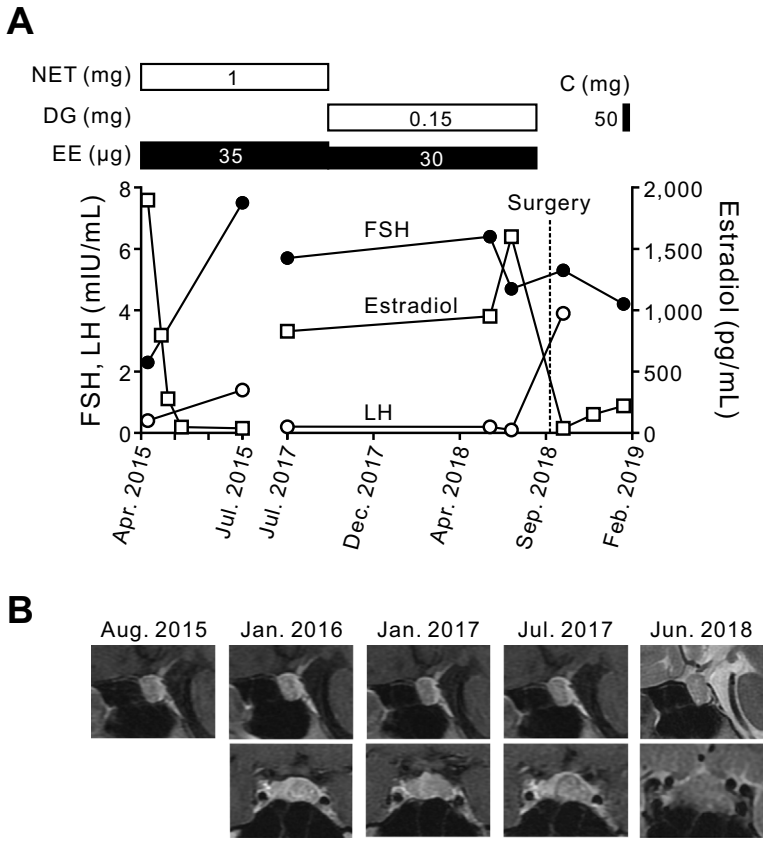

Figure 1. Pituitary tumor and serum gonadotrophins and estradiol concentrations' changes. (A) Changes in the serum FSH, LH, and estradiol concentrations. The dotted line indicates the day of the surgery (September 2018). (B) Changes in the pituitary tumor on sagittal (upper panels) and coronal (lower panels) MRI scans. The image on June 2018 was T2-weighted, while the others were gadolinium-enhanced T1-weighted. The tumor gradually increased in size from January 2017. NET: norethindrone, EE: ethinyl estradiol, DG: desogestrel

gency laparoscopy confirmed left ovarian torsion; the surgeon performed partial left oophorectomy and right ovarian ablation.

The laboratory data just before the operation showed a high serum estradiol concentration (1,897 pg/mL) with a slight elevation of the serum progesterone concentration (1.64 ng/mL) (Fig. 1A). It also revealed normal LH (0.4 mIU/mL), FSH (2.3 mIU/mL), and testosterone (0.44 ng/mL) concentrations (Fig. 1A). The histological diagnosis of the resected ovary was unruptured corpus luteum cysts. Low-dose oral contraceptives (desogestrel ethinylestradiol) were prescribed for the ovarian enlargement, and the serum estradiol and progesterone concentrations decreased after a month to 46.6 pg/mL and 0.26 ng/mL, respectively. The basal concentrations of the pituitary hormones were assessed at the Department of Obstetrics and Gynecology for endocrine screening, and results revealed a low morning plasma adrenocorticotropic hormone (ACTH) concentration (4.11 pg/mL). The patient was referred to the Department of Endocrinology for a further examination in August 2015.

The basal plasma/serum cortisol (8.00 μg/dL), growth hormone (GH) (0.14 ng/mL), and insulin-like growth factor-1 (114 ng/mL) concentrations were within normal ranges but close to the lower limits (Table). However, the insulin tolerance test (0.05 U/kg) demonstrated intact cortisol and GH responses with peak concentrations at 20.50 μg/dL and 18.0 ng/mL, respectively. The basal concentrations of serum LH (1.4 mIU/mL), FSH (7.5 mIU/mL), prolactin (PRL) (13.37 ng/mL), thyroid-stimulating hormone (TSH) (0.68 μIU/mL), and free T3 (2.49 ng/dL) and free T4 (1.31 ng/dL) were within normal ranges. Pituitary magnetic resonance imaging (MRI) revealed a low-enhancement 12-mm pituitary adenoma without suprasellar extensions or optic chiasm compression (Fig. 1B). Given these findings, the patient was clinically diagnosed with a non-functioning pituitary adenoma, and she was followed up with periodic MRI and endocrine examinations. Pituitary MRI in January 2016 did not show any tumoral growth.

In March 2016, the patient complained of neck pain and mild palpitations. Her clinical examination revealed painful palpation of the thyroid and cervical adenopathies. Laboratory examinations showed thyrotoxicosis (TSH 0.029 μIU/mL, free T3 7.26 pg/mL, and free T4 2.69 ng/dL) and a systemic inflammatory response [C-reactive protein (CRP) 13.3 mg/dL], but thyrotropin receptor antibodies (TRAb) was confirmed as negative (Table). Thyroid ultrasonography

Table. Laboratory Data at Onset of Painful Thyroiditis and before Surgery.

	Onset of painful thyroiditis	Before pituitary surgery		Onset of painful thyroiditis	Before pituitary surgery	
WBCs (/μL)	10,690	7,870	TSH (μIU/mL)	0.029	0.68	(0.50-5.00)
Neu (/μL)	8,500	5,380	FT3 (pg/mL)	7.26	2.49	(2.30-4.30)
Eo (/μL)	100	100	FT4 (ng/dL)	2.69	1.31	(0.90-1.70)
Hb (g/dL)	12.1	13.1	Tg (ng/mL)	438.4	8.63	(0-33.7)
RBCs (/μL)	408×10^4	421×10^4	Tg-Ab (IU/mL)	91.78		(0-28.0)
Hct (%)	36.5	39.5	TPO-Ab (IU/mL)	71.43		(0-16.0)
Plt (/μL)	31.5×10^4	22.4×10^4	ACTH (pg/mL)		4.40	(7.2-63.3)
TP (g/dL)	7.5	7.3	Cortisol (μg/dL)		8.00	(3.7-19.4)
Alb (g/dL)	3.8	4.6	GH (ng/mL)		0.14	(0.13-9.88)
Cr (mg/dL)	0.52	0.64	IGF-1 (ng/mL)		116	(59-177)
BUN (mg/dL)	9.8	11.8	PRL (ng/mL)		21.78	(4.9-29.3)
Na (mEq/L)	138	140	LH (mIU/mL)		1.4	(6.7-38.0)
K (mEq/L)	4.5	4.0	FSH (mIU/mL)		7.5	(26.2-113.3)
Cl (mEq/L)	102	105	Estradiol (pg/mL)		1,897.0	
AST (IU/L)	10	12	P (ng/mL)		1.64	
ALT (IU/L)	11	9				
BS (mg/dL)	139					
CRP (mg/dL)	13.3					

WBCs: white blood cells, Neu: neutrophils, Eo: eosinophils, Hb: hemoglobin, RBCs: red blood cells, Hct: hematocrit, Plt: platelets, TP: total protein, Alb: albumin, Cr: creatinine, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BS: blood sugar, Tg: thyroglobulin, Tg-Ab: anti-thyroglobulin antibody, TPO-Ab: anti-thyroid gland peroxisome antibody, IGF-1: insulin-like growth factor-1, P: progesterone. The parentheses show normal concentration ranges.

showed a dyshomogeneous and painful hypoechoic lesion in the right thyroid lobe that exhibited an irregular and poorly defined border, without blood flow enhancement (Fig. 2A). These clinical findings suggested subacute thyroiditis, and the patient was started on treatment with 20 mg prednisolone (Fig. 2B). Anti-thyroglobulin (91.78 IU/mL) and anti-thyroid peroxidase (71.43 IU/mL) antibodies were positive (Table), suggesting Hashimoto thyroiditis as a background disease. Prednisolone effectively improved the symptoms and the thyroid function and was discontinued after two months. In July 2017, the titer of the anti-thyroglobulin antibody (27.58 IU/mL) had decreased to the normal range, but that of anti-thyroid peroxidase antibody (63.83 IU/mL) remained high.

Starting in January 2017, follow-up pituitary MRI revealed a gradual increase in tumor size, and the tumor reached 14 mm in July 2017 (Fig. 1B). In addition, from that point on, regardless of the administration of low-dose oral contraceptives, we observed elevated serum estradiol levels and marked suppression of the serum LH concentration (the serum FSH concentration remained within the normal range) (Fig. 1A). Ultrasonography revealed cystic enlargement of the ovaries (Fig. 3A), suggesting ovarian hyperstimulation due to FSH overproduction from a pituitary tumor. In September 2018, selective complete adenomectomy was performed by an endoscopic endonasal approach. (Fig. 4A).

The tumor cells were composed of eosinophilic adenoma cells and showed marked polarity with elongated cell processes in the areas of pseudorosette formation (Fig. 4B). On an immunohistochemical analysis, most cells were immunopositive for FSH-β, and some scattered cells were immunopositive for LH-β (Fig. 4B), but other anterior hormones were negative (data not shown). The Ki-67 labeling index was 1.8% (Fig. 4C). In addition, SSTR2 was positive (Grade 4) in almost all cells, whereas SSTR5A was weakly positive (Grade 1) (Fig. 4C). Her serum estradiol concentrations dramatically decreased after surgery (Fig. 1A). The multiple ovarian follicles also disappeared (Fig. 3B), and ovulation induction with clomiphene citrate was begun in January 2019.

Discussion

In patients with FSH-producing pituitary adenomas, increased serum estradiol concentrations can suppress the hypothalamus-anterior pituitary gland axis due to a negative feedback mechanism, and consequently, the excessive FSH production can be reduced to the normal range. In contrast, the serum LH concentration may be reduced below the lower limit of the normal range, probably due to the negative feedback mechanism or to compression of the normal pituitary gland by the tumor (4-6). Therefore, a normal FSH value does not always exclude the possibility of FSH-producing pituitary adenomas; instead suppressed LH levels and high estradiol levels can be considered the characteristic endocrinological profile of FSH-secreting gonadotroph adenomas. In our patient, the serum estradiol concentration de-

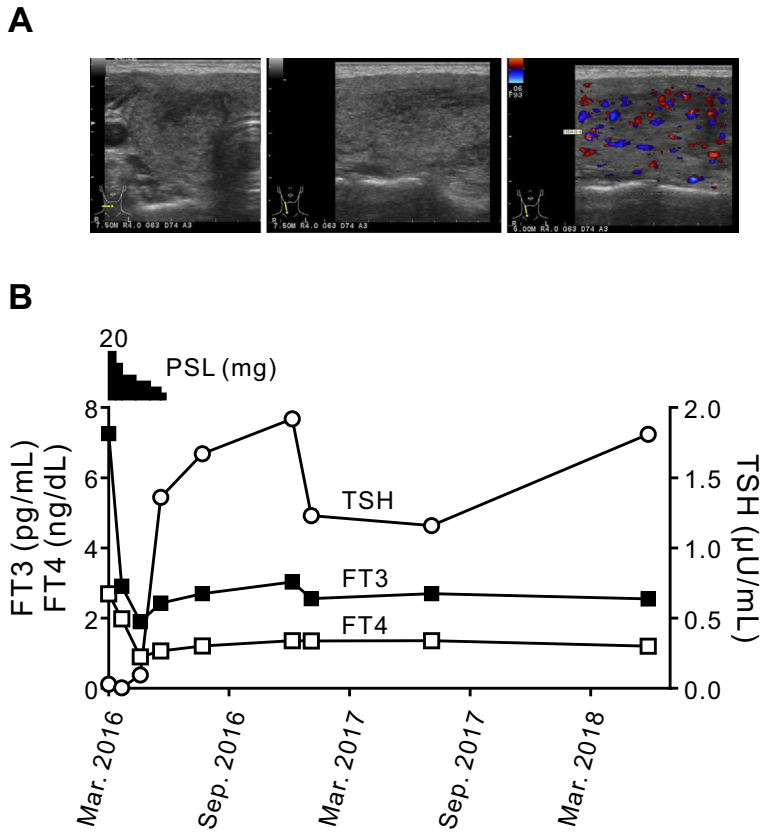

Figure 2. **Clinical course of the thyroid function. (A) (left) Transversal, (middle) longitudinal, and (right) Doppler ultrasonography images of the thyroid at the onset of painful thyroiditis. Heterogeneous echogenicity without a diffuse goiter or increased blood flow was observed. The painful hypoechoic lesion can be seen in the left panel. (B) Changes in the thyroid function and treatment. PSL treatment effectively improved thyrotoxicosis. PSL: prednisolone**

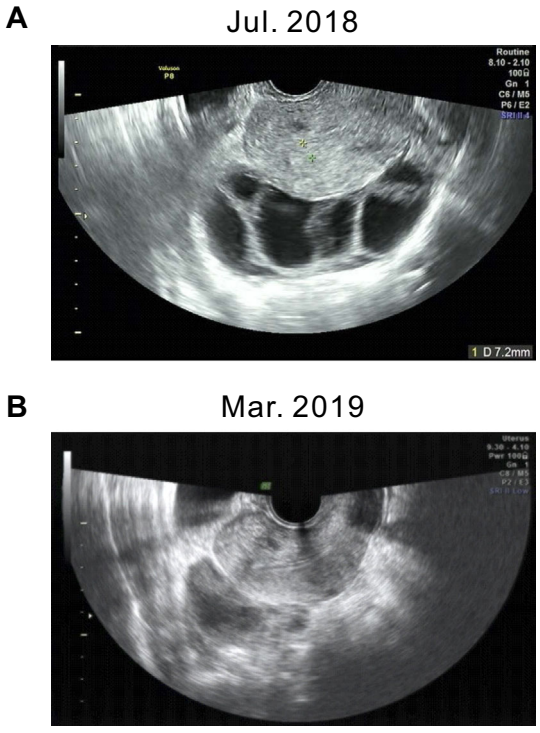

Figure 3. **Transvaginal ultrasonography of the right ovary. (A) The enlarged right ovary with multiple follicles before surgery. (B) The multiple follicles disappeared after surgery.**

creased after partial left oophorectomy and right ovarian ablation and treatment with oral contraceptives; it is therefore conceivable that the decrease in the serum estradiol was caused not only by oral contraceptives but also by the operation. Vargas et al. reported that the administration of oral contraceptives suppressed the elevation of the serum estradiol level, even in cases of elevation due to FSHoma, and masked symptoms related to ovarian hyperstimulation for 10 years (7). Oral contraceptives may be able to suppress serum estradiol levels, even in cases of elevation due to FSHoma. Taken together, these findings suggest that an endocrine assessment should be carefully performed prior to oral contraceptive administration in order to exclude the presence of gonadotrophin overproduction.

Our patient showed a distinct clinical course; painful thyroiditis developed into Hashimoto thyroiditis during the progression of the FSH-producing pituitary adenoma. Most of the findings and the clinical course in the present case suggest that the painful thyroiditis was more likely subacute thyroiditis than painful Hashimoto thyroiditis: the painful hypoechoic lesion, and good therapeutic response to prednisolone were consistent with subacute thyroiditis. Although there were no prior symptoms of upper respiratory infection in the present case, which is typically observed in subacute thyroiditis, these preceding symptoms are only observed in

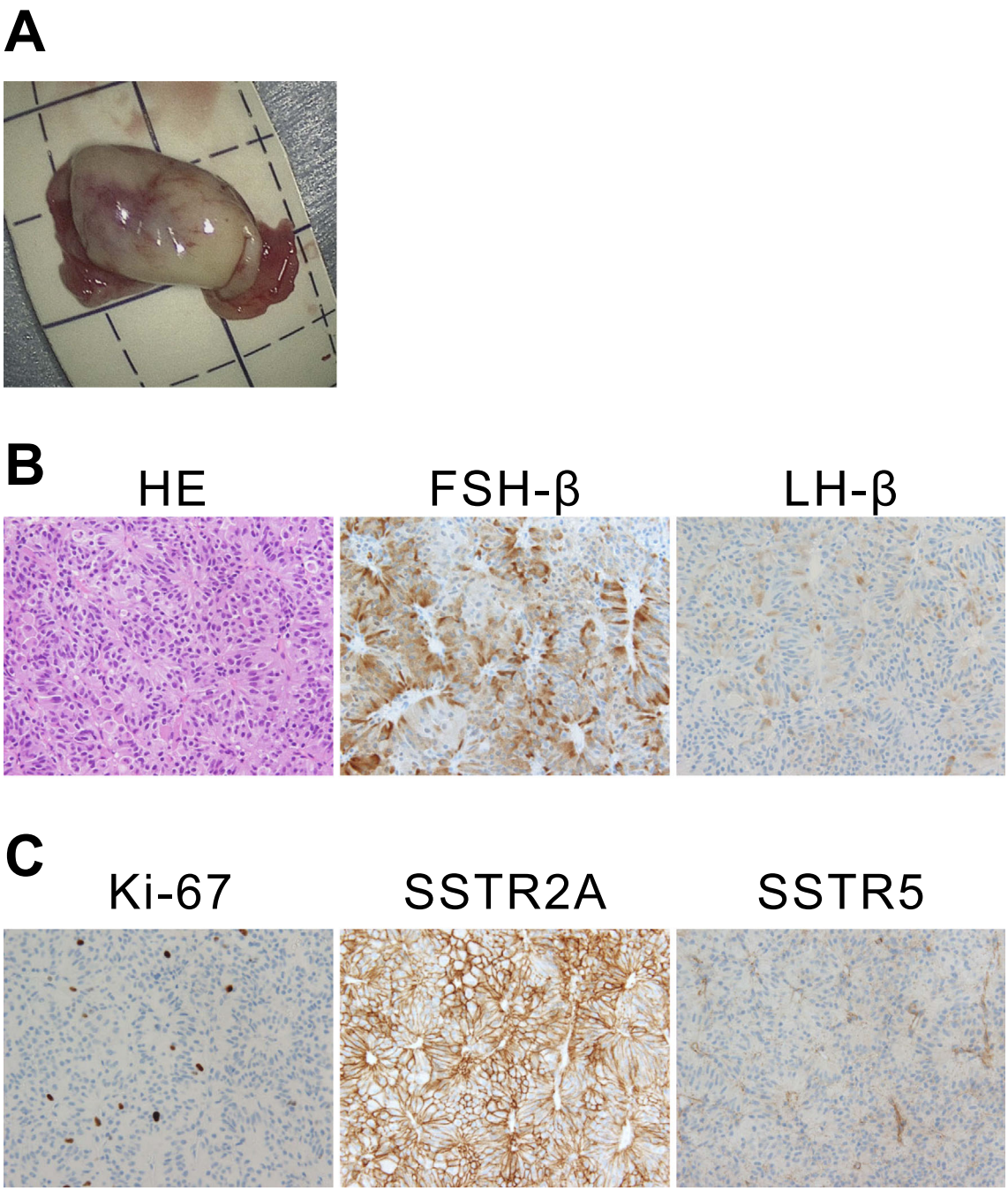

Figure 4. **Gross and histological appearances of the resected pituitary tumor. (A) Gross appearance of the resected pituitary tumor. Solid lines are spaced at 10-mm intervals. (B) Hematoxylin and Eosin (HE) staining and immunohistochemistry of FSH-β and LH-β. The tumor cells were composed of eosinophilic adenoma cells and showed marked polarity with elongated cell processes in the areas of pseudorosette formation. Whereas FSH-β was strongly positive, LH-β was weakly positive. (C) Immunohistochemistry of Ki-67, SSTR2A, and SSTR5. The Ki-67 labeling index was 1.8%. SSTR2 was positive in almost all cells, whereas SSTR5A was weakly positive.**

only in 17% cases of subacute thyroiditis (8, 9). Strictly, painful Hashimoto thyroiditis needs to be distinguished from subacute thyroiditis, especially when painful thyroiditis develops in cases of Hashimoto thyroiditis. However, the incidence, clinical findings, and clinical course in the present case strongly suggest the existence of painful thyroiditis to subacute thyroiditis rather than painful Hashimoto thyroiditis. In cases of painful Hashimoto thyroiditis, the pathology shows lymphocytic thyroiditis with varying degrees of fibrosis, without the giant cells or granulomas characteristic of subacute thyroiditis (10). A thyroid fine-needle aspiration biopsy would have been helpful in making the differential diagnosis in the present case.

The resected tumor was stained positively for LH-β, as well as for FSH-β. However, its immunoreactivity of LH-β was relatively low compared with that for FSH-β, and the

serum LH concentration had been suppressed during the clinical course in response to the excessive estradiol, suggesting that the positive immunoreactivity for LH-β may have been considered clinically "silent." Such immunohistochemical profiles of LH and FSH are reported to be the most common in gonadotroph adenomas, regardless of their function (11). In addition, the tumor strongly expressed SSTR2A, for which octreotide has a high affinity. Although we did not perform an octreotide suppression test, in growth hormone-producing pituitary tumors, the percentage of cell membranes immunopositive for SSTR2A is reportedly associated with the preoperative hormone inhibitory effect by octreotide (12, 13).

In addition to the expression of SSTR2A, various clinical, imaging, histopathology, and molecular factors have been proposed as determinants of resistance of somatostatin receptor ligands in patients with growth hormone-secreting pituitary adenomas (14). There has been no clinical study showing the effects of somatostatin receptor ligands on gonadotropin-producing tumors. A case report demonstrated that octreotide effectively normalized the serum estradiol levels and resolved ovarian hyperstimulation syndrome in a patient with a recurrent FSH/LH-producing pituitary adenoma (15). Therefore, although clinical evidence remains limited, somatostatin receptor ligands may be a viable treatment strategy if the tumor recurs in the present case.

In conclusion, we reported the case of a woman with an FSH-producing pituitary adenoma associated with painful thyroiditis. This case displayed rare endocrine abnormalities and an uncommon clinical course, highlighting the importance of a thorough endocrine assessment and clinical examination in order to identify rare diseases.

Consent for publication: Written informed consent was obtained from the patient for the publication of this Case Report and any accompanying images. A copy of the written consent is available upon request.

The authors state that they have no Conflict of Interest (COI).

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