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CASE STUDY

Response of thyrotropin-secreting pituitary tumors to preoperative lanreotide therapy. Report of two cases

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Abstract

Case 1 was a 51-year-old man diagnosed with thyrotropin (TSH)-secreting pituitary tumor. The octreotide loading test showed suppression of TSH secretion. Treatment with lanreotide preoperatively at 90 mg/month resulted in normalization of thyroid function. Three months after treatment initiation, tumor shrinkage was observed, and pituitary tumor resection was performed through transsphenoidal surgery. Case 2 was a 47-year-old woman in whom the octreotide loading test showed suppressed TSH secretion. Treatment with lanreotide preoperatively at 90 mg/month resulted in normalization of thyroid function. After six months of treatment, tumor reduction was observed, and transsphenoidal surgery was performed. In both cases, lanreotide administration before TSH-secreting pituitary tumor resection achieved normalization of thyroid function and tumor shrinkage. Treatment with lanreotide seems effective in patients who show TSH secretion suppression in the octreotide loading test.

Abbreviations:

ACTH	- adrenocorticotrophic hormone
ATG	- autogel
FSH	- follicle-stimulating hormone
FT	- free triiodothyronine
GH	- growth hormone
LAN	- lanreotide
MRI	- magnetic resonance imaging
SITSH	- syndrome of inappropriate secretion of TSH
SSTR	- somatostatin receptors
TSH	- thyrotropin
TSH-oma	- TSH-secreting pituitary adenomas
TSS	- transsphenoidal surgery

INTRODUCTION

Thyrotropin (TSH)-secreting pituitary adenomas (TSH-omas) are rare, accounting for only 0.5% of all pituitary tumors (Beck-Peccoz *et al.* 1996). There are no established therapeutic strategies for TSH-omas. According to the 2013 European guidelines, the first-line treatment for TSH-omas is surgery. In addition, radiotherapy and hormonal therapy with somatostatin analogues are highly effective and recommended (Beck-Peccoz *et al.* 2013). The American guidelines also recommend surgery as the first-line treatment but also advise radiotherapy and somatostatin analogue

therapy in cases of difficult surgery. In Japan, although three types of somatostatin analogues (octreotide, lanreotide [LAN], and pasireotide) are currently available, their use for TSH-oma treatment is not covered by the National Insurance Scheme. Thus, the use of these three analogues is limited in clinical settings.

Recently, we encountered two patients with TSH-omas who were treated preoperatively with LAN autogel (ATG). The drug improved thyroid function and reduced tumor volume. The octreotide loading test proved effective in determining therapeutic efficacy. We provide here the clinical details of these two cases since LAN ATG therapy for TSH-omas is rarely reported.

CASE REPORT

Clinical summary

Case 1: The patient was a 51-year-old man with difficulty in walking since 26 years of age. He was diagnosed with cerebrotendinous xanthomatosis at 35 years of age. At 44, head magnetic resonance imaging (MRI) identified a pituitary adenoma (approximately 1.5 cm). The free triiodothyronine (FT3), free thyroxine, and TSH levels were 4.6 pg/mL, 2.1 ng/dL, and 2.8 μU/mL, respectively, suggesting syndrome of inappropriate secretion of TSH (SITSH). The levels of other hormones were within the normal ranges. Since no clinical signs or symptoms of hyperthyroidism were evident, the patient was kept under observation without treatment. At 51 ears of age, head MRI showed growth of the pituitary tumor to about 4 cm. He was referred to our department for SITSH and admitted for detailed examination.

On admission, body height was 175 cm and weight 53 kg. The vital signs were normal. Physical examination showed no visual field defects, thyroid enlargement, or finger tremors. Hypertrophic Achilles tendon, hypopallesthesia of the lower extremities, and patellar hyperreflexia were detected. The laboratory findings on admission showed high FT3 and FT4 levels (5.81 pg/mL and 2.48 ng/dL, respectively), without suppression of TSH level (4.12 μIU/mL). The presence of SITSH was confirmed (Table 1).

TSH-oma was diagnosed. A fasting somatostatin loading test was performed under resting conditions in the early morning. After collection of a blood sample, 50 μg of octreotide acetate (Sandostatin) was injected subcutaneously and more blood samples were collected 2, 4, 6, 8, 12, and 24 hours later to measure TSH levels. TSH level decreased from 3.87 to 2.21 μIU/mL at 6 hours after injection. Based on the results of the loading test, somatostatin analogues were anticipated to be therapeutically effective. Treatment with LAN ATG was initiated preoperatively at 90 mg/month and increased to 120 mg/month. This was followed by decrease in TSH level from 4.12 to 2.83 μIU/mL, and in FT4 level from 2.48 to 1.81 ng/dL. These values were near the

Tab. 1. Case 1. Results of laboratory tests.

Peripheral blood		**Endocrinology**	
Leukocyte count	5600/μL	TSH	4.12 μIU/mL
Erythrocyte count	427×10^4/μL	FT3	5.81 pg/mL
Hemoglobin	12.0 g/dL	FT4	2.48 ng/dL
Platelet count	26.0×10^4/L	TRAb	<0.3 U/mL
Blood biochemistry		anti-TG antibody	24 U/mL
Total protein	6.8 g/dL	anti-TPO antibody	15 U/mL
Albumin	4.2 g/dL	PRL	43.1 ng/mL
Aspartate aminotransferase	16 U/L	ACTH	30.1 pg/mL
Alanine aminotransferase	10 U/L	cortisol	6.2 μg/day
γ-glutamyl transpeptidase	10 U/L	GH	1.48 ng/mL
Blood urea nitrogen	10 mg/dL	IGF-1	113 ng/mL
Creatinine	0.74 mg/dL	testosterone	3.81 ng/mL
Sodium	144 mEq/L	LH	4.8 mIU/mL
Chloride	108 mEq/L	FSH	6.3 mIU/mL
Potassium	3.6 mEq/L	Postprandial plasma glucose	98 mg/dL
Serology		HbA1c (NGSP)	5.9 %
CRP	0.02 mg/dL		

HbA1c was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value, which was calculated as HbA1c (NGSP) (%) = HbA1c (Japan Diabetes Society [JDS]) (%) + 0.4 %.
TSH: thyrotropin, FT3: free T3, FT4: free T4, TRAb: TSH receptor antibody

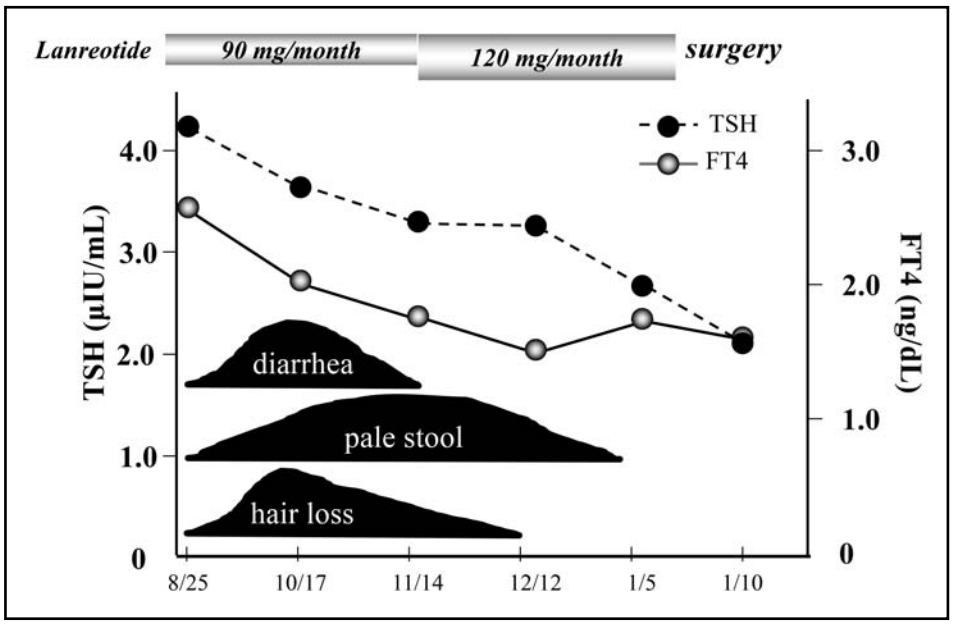

Fig. 1. Case 1. Clinical course. Both thyrotropin and free thyroxine levels started to decrease after administration of lanreotide. Surgery was performed five months after initiation of treatment. Although diarrhea, pale stools, and depilation were detected soon after treatment initiation, these adverse effects resolved gradually and spontaneously.
TSH: thyrotropin, FT4: free T4

normal ranges (Figure 1). Three months after treatment initiation, tumor reduction (from 3.6 to 2.6 cm) was observed (Figure 2). Transsphenoidal surgery (TSS) for pituitary tumor resection was performed. The postoperative course was uneventful. Immunohistochemical examination of the tumor showed staining for TSH and growth hormone (GH) but no staining for adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), and Ki67 (MIB1). Unfortunately, we could not perform somatostatin receptor staining at our facility (Figure 3).

Case 2. The patient was a 47-year-old previously healthy woman. At 47 years of age, she developed headache with feeling of tightness in the area extending from the right temporal to the parietal region. The headache was also noted during sleep. Following failure of response to over-the-counter drugs, she visited the neighborhood neurosurgery clinic. Head MRI showed

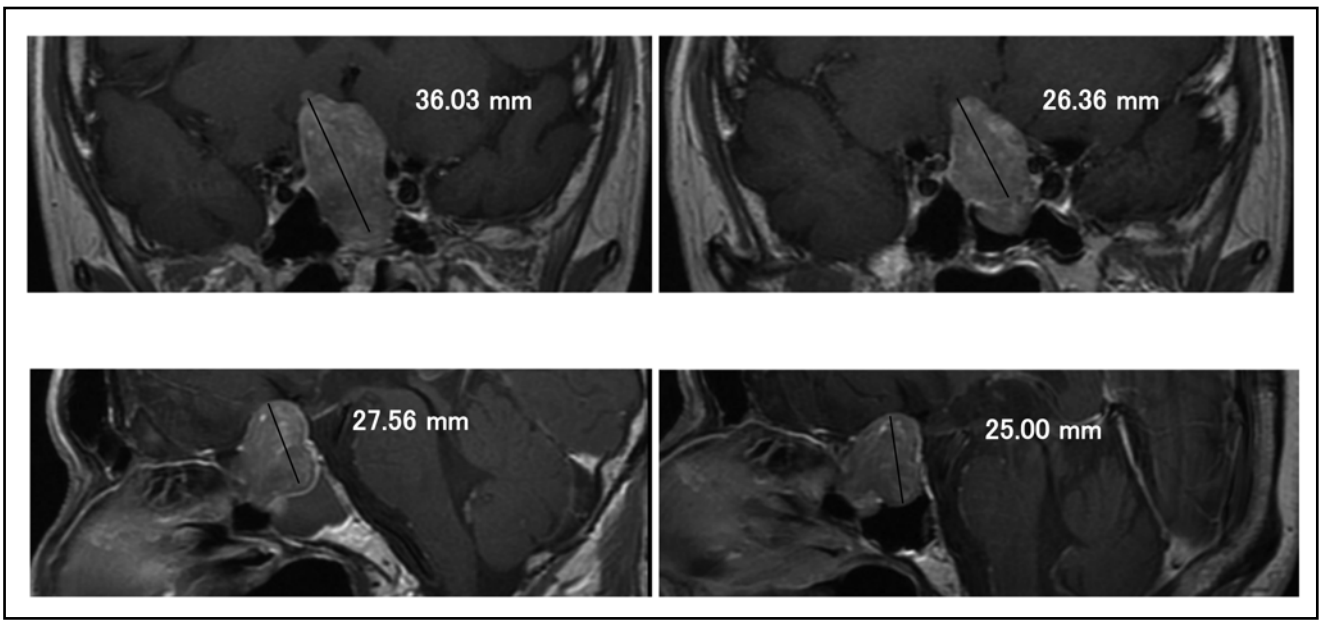

Fig. 2. Case 1. Magnetic resonance imaging using gadolinium-based contrast medium.
The tumor measured 36 mm before treatment, but it shrank to 26 mm at three months after administration of lanreotide.

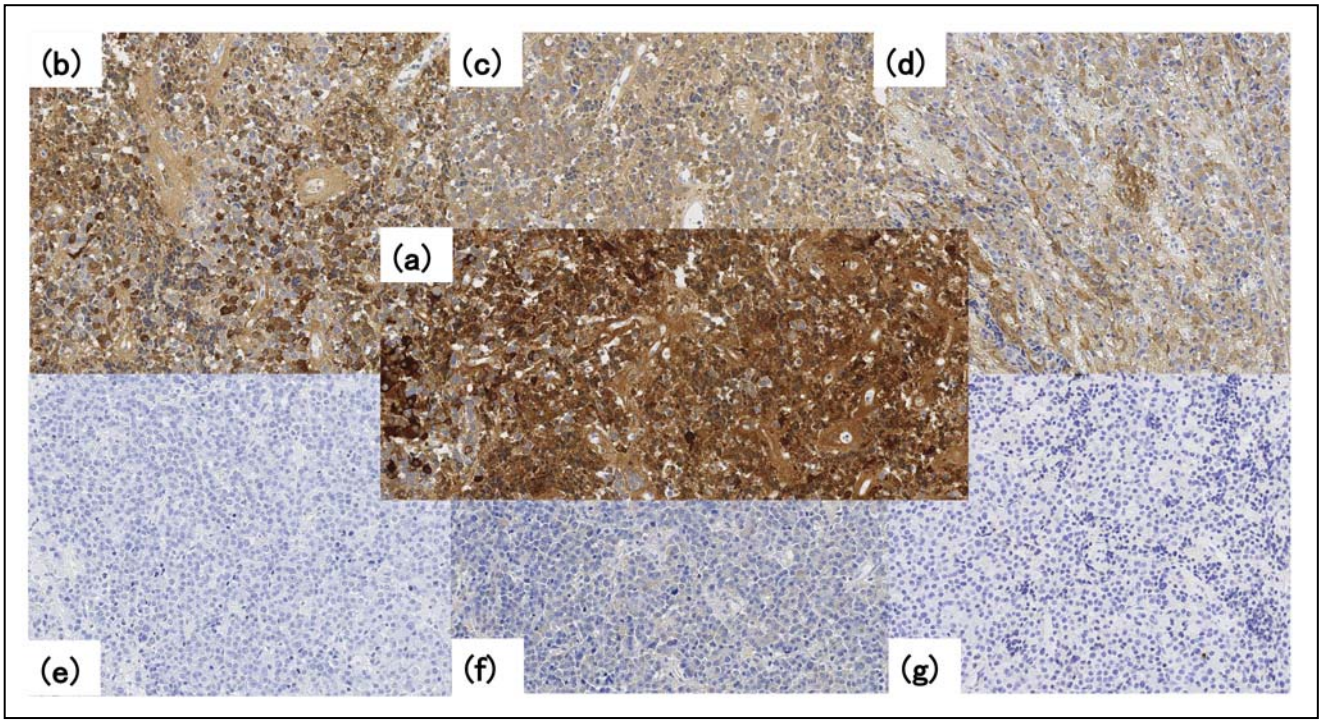

Fig. 3. Case 1. Results of immunostaining of tumor tissue samples. (a) Staining for thyrotropin; (b) staining for growth hormone; (c) no staining for adrenocorticotrophic hormone; (d) no staining for follicle-stimulating hormone; (e) no staining for Ki67 (MIB1) (1%) ×100 magnification.

a pituitary tumor, and she was referred to the neurosurgery department of our hospital. During admission, FT4 level was 2.58 ng/dL, but the TSH level was not suppressed (2.89 μU/mL). Based on the detection of SITSH, TSH-oma was suspected, and surgery was planned. Subsequently, she was referred to our department for detailed medical examination and treatment of hyperthyroidism.

Tab. 2. Case 2. Results of laboratory tests.

Peripheral blood		**Endocrinology**	
Leukocyte count	8600/μL	TSH	3.39 μIU/mL
Erythrocyte count	443×10^4/μL	FT4	2.41 pg/mL
Hemoglobin	11.2 g/dL	TRAb	<0.3 U/mL
Platelet count	32.0×10^4/L	anti-TG antibody	19 U/mL
Blood biochemistry		anti-TPO antibody	10 U/mL
Total protein	7.1 g/dL	PRL	27.3 ng/mL
Albumin	3.9 g/dL	ACTH	23.9 pg/mL
Aspartate aminotransferase	18 U/L	cortisol	11.8 μg/day
Alanine aminotransferase	14 U/L	GH	3.58 ng/mL
γ-glutamyl transpeptidase	21 U/L	IGF-1	142 ng/mL
Blood urea nitrogen	13 mg/dL	estradiol	25.3 pg/mL
Creatinine	0.47 mg/dL	progesterone	0.3 ng/mL
Sodium	137 mEq/L	LH	6.8 mIU/mL
Chloride	104 mEq/L	FSH	11.3 mIU/mL
Potassium	4.5 mEq/L	Fasting plasma glucose	88 mg/dL
Serology		HbA1c (NGSP)	5.8 %
CRP	0.02 mg/dL		

See footnote of Table 1 for abbreviations and estimation of HbA1c.

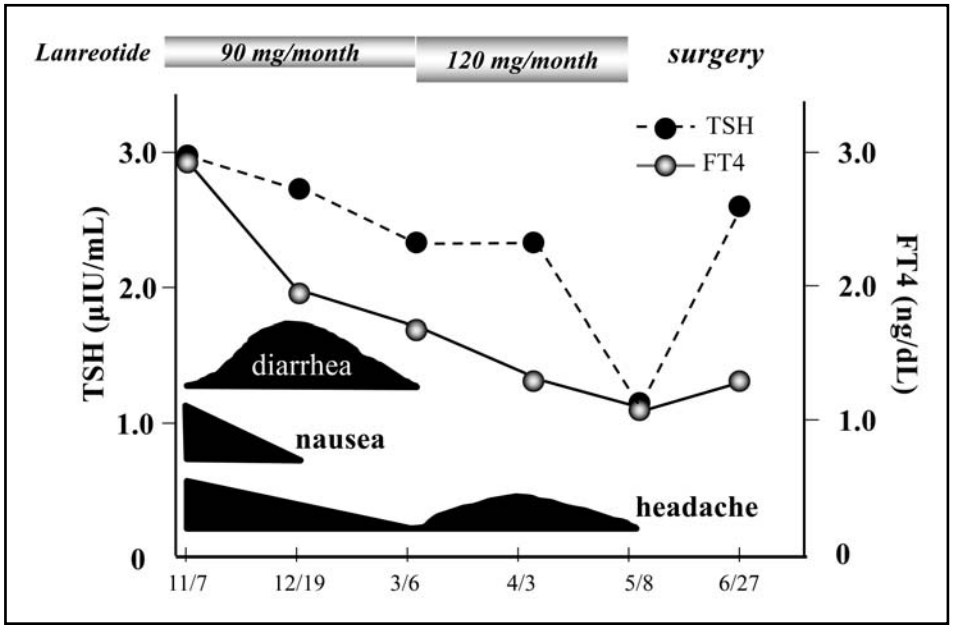

Fig. 4. Case 2. Clinical course. Both thyrotropin and free thyroxine levels started to decrease after administration of lanreotide. Surgery was performed six months after initiation of treatment. Although diarrhea, nausea, and headache were detected soon after treatment initiation, these adverse effects resolved gradually.
TSH: thyrotropin, FT4: free T4

On admission, body height was 160 cm and weight 52 kg. The vital signs were within normal ranges. No visual field defects, thyroid enlargement or finger tremors were noted. Laboratory tests showed high FT4 level (2.41 ng/dL) but no suppression of TSH (3.39 μIU/mL). The presence of SITSH was confirmed (Table 2).

TSH-oma was diagnosed, and the octreotide loading test was performed. As the TSH level decreased from 2.95 to 1.24 μU/mL at 8 hours after the test, the therapeutic effectiveness of somatostatin analogues was anticipated. LAN ATG was initiated preoperatively at 90 mg/month and increased to 120 mg/month. The response to the treatment included decreases in the levels of TSH (from 2.95 to 2.60 μU/mL) and FT4 (from 2.90 to 1.30 ng/dL). These values were within the normal ranges (Figure 4). Furthermore, the tumor size diminished from 2.4 to 1.6 cm at 6 months of treatment (Figure 5). TSS was performed and the postoperative course was uneventful. Immunohistochemical examination of the tumor showed positive staining for

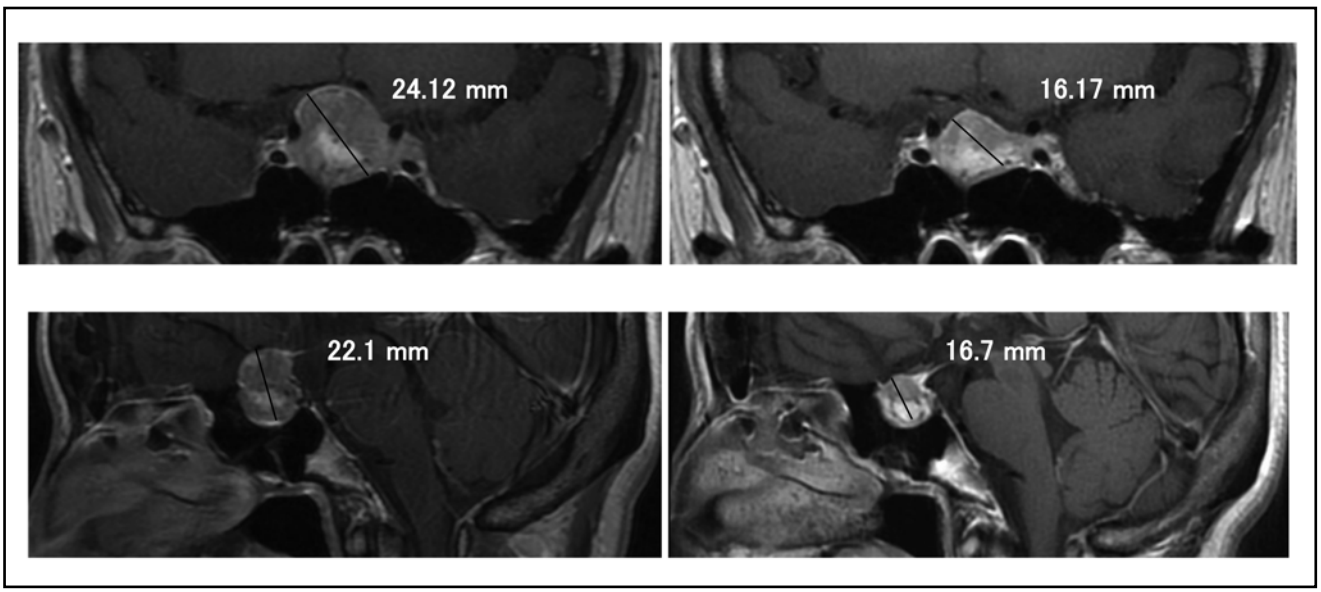

Fig. 5. Case 2. Magnetic resonance imaging using gadolinium-based contrast medium. The tumor measured 24 mm before treatment but shrank to 16 mm at six months after administration of lanreotide.

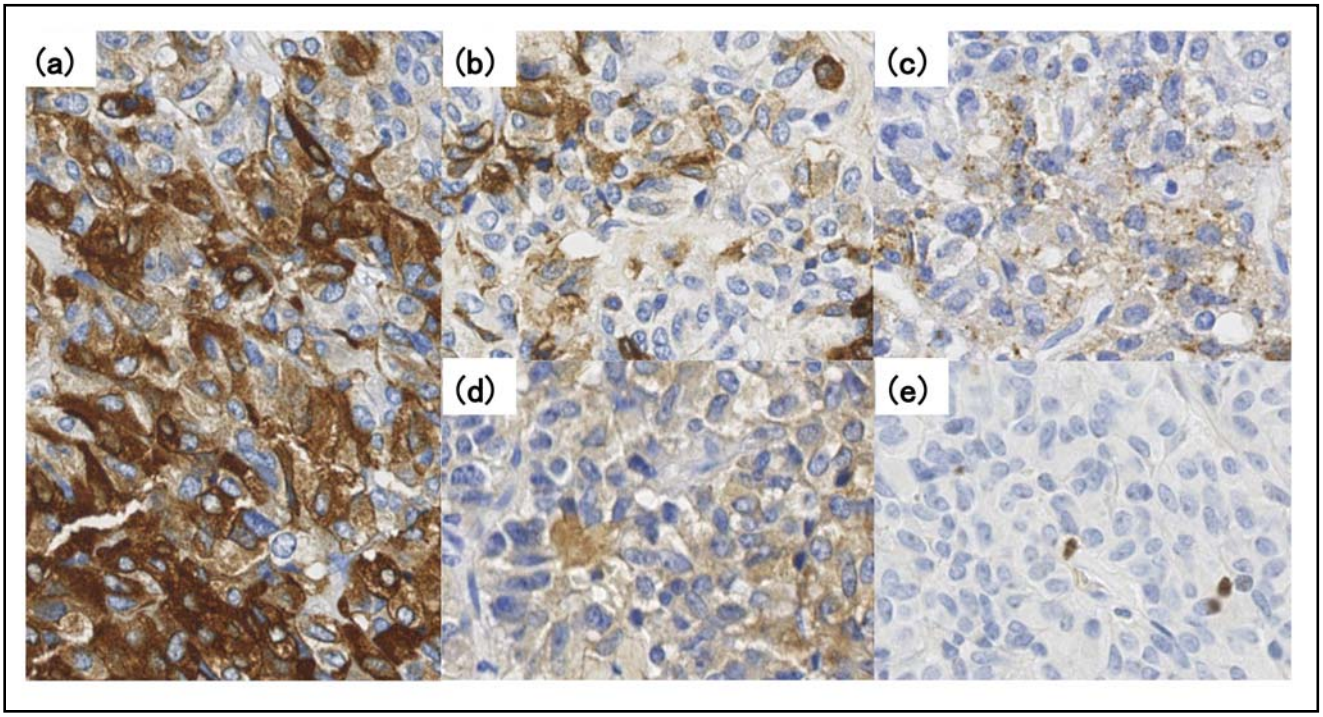

Fig. 6. Case 2. Results of immunostaining of tumor tissue samples. (a) Staining for thyrotropin; (b) weak staining for growth hormone; (c) weak staining for adrenocorticotrophic hormone; (d) weak staining for follicle-stimulating hormone; (e) no staining for Ki67 (MIB1) (1%) ×200 magnification

TSH and weak staining for GH, ACTH, and FSH, and negative staining for Ki67 (MIB1). In this case also, we were unable to perform somatostatin receptor staining (Figure 6).

DISCUSSION

TSH-omas are rare tumors with limited reported evidence. No therapeutic strategies are available at present for TSH-omas. Furthermore, the use of somatostatin analogues for treatment TSH-omas is limited in Japan. In this regard, the efficacy of somatostatin analogues administered preoperatively has not been assessed. We described in this report two patients in whom preoperative treatment with LAN ATG resulted in normalization of thyroid function and pituitary tumor shrinkage. Since the octreotide loading test applied before treatment suppressed TSH secretion in both cases, we suggest its use as a marker for therapeutic efficacy of somatostatin analogues.

In both cases, preoperative LAN ATG therapy for TSH-omas normalized thyroid function. Of the five subtypes of somatostatin receptors (SSTRs, i.e., SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5) in the anterior pituitary gland, SSTR1, SSTR2, and SSTR5 are highly expressed in TSH-omas (Cuevas-Ramos & Fleseriu 2014; Yu *et al.* 2017). Among the five receptor subtypes, LAN has high affinity for SSTR2 and SSTR5 (Ren *et al.* 2003) and suppresses the secretions of TSH and GH by binding to SSTR2 and SSTR5. The effects of somatostatin analogues on the suppression of TSH secretion in TSH-omas have been described in several reports. Furthermore, it has been reported that administration of somatostatin analogues, including LAN, normalizes circulating thyroid hormone levels in 81–85% of cases (Socin *et al.* 2003). In both our cases, administration of LAN ATG resulted in normalization of thyroid hormone levels.

In our cases, preoperative LAN ATG therapy for TSH-omas also resulted in tumor shrinkage. SSTRs are coupled to the G protein, which is involved in regulation of apoptosis and cell proliferation (Strosberg & Kvols 2010). It has been reported that activation of SSTRs coupled to the G protein in tumor cells mediates the induction of apoptosis through steroid receptor coactivator homology 2 domain-containing protein tyrosine phosphatase (SHP)-1 and antiproliferative activity through SHP2 and inhibition of mammalian target of rapamycin by phosphatidyl inositide 3-kinase (Chalabi *et al.* 2014; Florio 2008; Theodoropoulou & Stalla 2013). Although tumor reduction was observed in our cases, Kuhn *et al.* (2000) reported no tumor reduction in any of their 16 cases of TSH-omas treated with slow-release LAN (LAN SR). In their cases, LAN SR at 30 mg was administered every two weeks, and blood LAN levels increased to 1.69±0.65 ng/mL after three months of treatment. In contrast to the above study, the more recent study of Chaplin *et al.* (2014) reported that treatment with 120 mg of LAN ATG, which was used in our patients, was associated with increases in blood LAN levels to 5.0 ng/mL at three months of treatment and 6.1 ng/mL at six months. Considered together, the

above studies suggest that the tumor reduction effect varies with the blood LAN level.

Based on finding of suppression of TSH secretion following administration of octreotide in both of our cases, we advocate the use of this loading test to determine the therapeutic efficacy of somatostatin analogues. For treatment of acromegaly, long-acting release octreotide has been reported to reduce blood levels of GH and insulin like growth factor-1 and to be effective in tumor shrinkage (Cozzi *et al.* 2006). Lamberts *et al.* (1988) suggest that the early finding of suppressed GH secretion in the octreotide loading test could be a predictor for the long-term efficacy of subcutaneous injection of short-acting octreotide. Furthermore, Wang *et al.* (2016), who performed the octreotide loading test in 67 patients newly diagnosed with acromegaly, reported that the test was superior in predicting the efficacy of long-acting somatostatin analogues. Considered together, we anticipate that the octreotide loading test may also be a useful predictor of the efficacy of long-acting somatostatin analogues for TSH-omas.

CONCLUSION

In summary, we encountered two cases who showed normalization of thyroid hormone levels and tumor reduction after preoperative administration of LAN ATG. The report suggests that somatostatin analogues are therapeutically effective in patients with suppressed TSH secretion as demonstrated by the octreotide loading test.

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DISCLOSURE

All authors declare no conflict of interest associated with this research.

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