A Case Report Of Successful Postoperative Treatment With Octreotide For Thyroid-Stimulating Hormone/Growth Hormone-Producing Pituitary Adenoma

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Citation

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Abstract

A 61-year-old man with high levels of alkaline phosphatase was admitted to our hospital presenting SITSH. He was diagnosed as TSH/GH-producing pituitary adenoma. After transsphenoidal adenectomy high serum values of GH, IGF-I, FT3, and FT4 and normal one of TSH still remained because of incomplete resection. In addition to oral administration of cabergoline, 20mg octreotide was administerd. Two months later, his serum TSH and GH levels were well controlled, and the successful response of the patient to octreotide can be attributed to 2 pathological factors, somatostatin-receptor-2-subtype and low Ki-67 SI.

INTRODUCTION

TSH-producing tumors are relatively rare, comprising 0.5–1% of pituitary tumors, and 15% of those secrete growth hormone (GH) 1. Although the primary treatment method for such tumors is resection, the administration of somatostatin analogs such as octreotide and dopaminergic drugs such as cabergoline can be effective in cases where tumors cannot be fully resected 2. Octreotide, in particular, is thought to be effective against tumors with the somatostatin-receptor (SSTR) 2-subtype that exhibit low proliferation potency (Ki-67 SI) 3. We herein report a case of a patient with thyroid-stimulating hormone (TSH)/GH-producing pituitary adenoma treated with transsphenoidal adenomectomy. Postoperative octreotide administration was successful, and both factors that influenced octreotide effectiveness were pathologically confirmed.

CASE REPORT

The patient was a 61-year-old man with hypertension and type 2 diabetes showed high levels of serum alkaline phosphatase, and was diagnosed as a syndrome of inappropriate secretion of TSH (SITSH). He was referred to our hospital for further examination and treatment. He had no other past history or family history of metabolic or endcrinological disorder.

On admission to our hospital, his physical condition was as follows: height, 170 cm; weight, 59.2 kg; body mass index, 20.5 kg/m2; blood pressure, 164/86 mmHg; heart rate, 76/min; and body temperature, 36.6°C. He showed macroglossia and protrusion of the lower jaw without signs of von Graefe nor eyeball protrusion. Diffuse enlargement of thyroid gland (/ Sichijo's classification) was apparent, but no finger tremor was observed. The patient presented macrosis of the hands and feet, but no edema was noted in the lower limbs.

Blood cell counts and serum biochemical data showed normal study (Table 1). His free tiiodothyronine (FT3) and free thyroxine (FT4), as well as TSH levels increased, suggesting SITSH (Table 2). TSH receptor antibody (TRAb), anti-thyrogloblin and anti-thyroid peroxidase antibodies were negative. At the same time, both GH (23.11 ng/mL) and insulin-like growth factor (IGF)-I (627 ng/mL) were significantly high at his age. Chest radiograph revealed that a cardiothoracic ratio (CTR) of 42%.
Electrocardiograms revealed normal sinus rhythm. Thyroid gland echography revealed diffuse swelling of both lobes and isolated small cysts, but internal blood flow was normal. Pituitary gland magnetic resonance imaging (MRI) showed an approximately 30-mm large tumor that bilaterally invaded the cavernous sinus (Figure 1). A thyrotropin releasing

hormone (TRH) loading test revealed TSH unresponsiveness. There was no paradoxical GH elevation by TRH. 75-g oral glucose tolerance test (OGTT) showed that glucose load could not suppress GH secretion from the tumor (GH; 0-min 16.00 ng/mL, 120-min 8.54 ng/mL).

Table 1

Laboratory Findings

《CBC》					
WBC	8400	/μl	T-Bil	0.9	mg/dl
RBC	467×10^4	/μl	ALP	392	U/l
Hb	13.3	g/dl	GOT	18	IU/ml
Ht	40.7	%	GPT	16	IU/ml
Plt	21.0x10^4	/μl	γ-GTP	28	IU/ml
《Blood Chemical Findings》			Amy	56	IU/l
TP	7.3	g/dl	TG	58	mg/dl
Alb	4.6	g/dl	LDL-C	47	mg/dl
BUN	15.4	mg/dl	HDL-C	70	mg/dl
Cr	0.68	mg/dl	BS	110	mg/dl
Na	138	mEq/l	HbA1c(NGSP)	6.2	%
K	3.7	mEq/l	NT-proBNP	108	pg/ml
Cl	103	mEq/l			
Ca	9.7	mg/dl	《Tumor marker》		
P	3.4	mg/dl	CEA	2.7	ng/ml

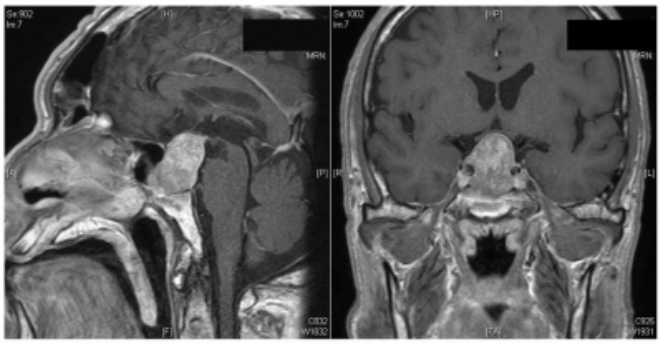
Table 2

Endocrinological examinations

TSH	8.45	μIU/ml	ACTH	49.9	pg/ml
free T4	3.46	ng/dl	cortisol	14.4	μg/dl
free T3	6.05	pg/ml	LH	6.21	mIU/ml
TRAb	0.4	IU/l	FSH	14.65	mIU/ml
Thyroglobulin Ab	12.3	IU/ml	PRL	16.06	ng/ml
TPO Ab	6.0		GH	23.1	ng/ml
			IGF-I	627	ng/ml
			DHEA-S	305	μg/ml

Figure 1

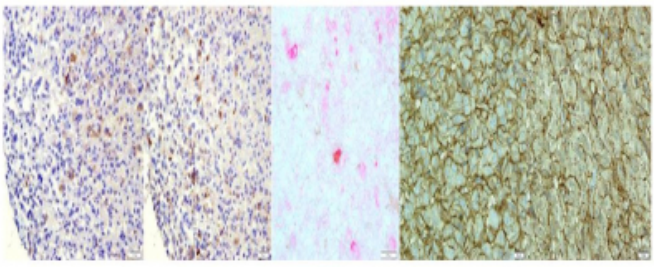
Pituitary gland magnetic resonance imaging. An approximately 30-mm large tumor that bilaterally spanned the cavernous sinus was confirmed.



We diagnosed the patient as TSH/GH-producing pituitary adenoma and performed a transsphenoidal adenectomy. Pathologically, the tumor was a mixed-type and contained eosinophiles and chromophobes. Immunostaining revealed positive and combined staining for GH, TSH, SSTR2 and SSTR5 (Figure 2). Ki67-SI, a tumor proliferation marker, showed low values of approximately 1%. Postoperative head MRI revealed an incomplete resection, although the pituitary tumor was reduced in size. TSH levels returned to normal , but high GH, IGF-I, FT3, and FT4 levels continued. For the first regimen 0.25mg cabergoline was administered, but these hormone levels remained high. Therefore 20mg octreotide was also administered and two months after starting the treatment, all the hormone levels returned to the normal range. Moreover, the size of the remaining pituitary tumor (approximately 17 mm in diameter) reduced to 11 mm at 6 months after octreotide administration.

Figure 2

Left to right: thyroid stimulating hormone (TSH) stain, growth hormone (GH) stain, TSH/GH double stain, somatostatin-receptor (SSTR) 2 stain, SSTR5 stain.



DISCUSSION

We herein report a case with SITSH caused by TSH/GH-producing pituitary adenoma. TSH-producing tumors are relatively rare, comprising 0.5–1% of pituitary tumors, and

15% of them secrete GH 1. Often, TSH-producing tumors are discovered as infiltrating macroadenomas; for example, we found a 30-mm large macroadenoma during a head MRI, although it was unclear whether the adenoma had infiltrated the cavernous sinus or the internal carotid artery. The primary treatment for such tumors is tumor resection, so in this case, a transsphenoidal adenectomy was selected. Pathological studies revealed positive staining for GH and TSH, which did not contradict the preoperative results. Postoperative MRI and endocrinology suggested an incomplete resection, and thus we started cabergoline administration. However, serum values of FT4, FT3, GH, and IGF-I remained high. Therefore octreotide was also administered and at 2 months post-administration, these values had normalized and stabilized. Furthermore, an MRI taken 6 months post-surgery confirmed a decreasing trend in the pituitary tumor size.

The success of octreotide treatment in contributing to the reduction of GH levels is attributed to the fact that the tumor was positive for SSTR2, and that Ki67-SI levels in the tumor were low 3, 5. Mechanistically, hormone-specific transcription factors and transcription cofactors are believed to enhance the functional performance of each hormone, while simultaneously contributing to the differentiation of pituitary hormone-producing cells 6. In particular, the Pit-1 transcription factor is important for the differentiation of TSH/GH production, while on the other hand, in mice, Pit-1 target sequences can be activated by SSTR2 promoter elements 7. Interestingly, the complete response achieved with octreotide could be associated with the effect of Pit-1 on SSTR2 regulation and TSH/GH differentiation. In this case, a postoperative pathological examination revealed that both factors were present. Octreotide has been reported to be effective in reducing tumor size and improving thyroid function in TSH-producing pituitary tumors 8, and SSTR2 and GH expression are equally important for drug sensitivity and reactivity 9. In this case, octreotide treatment was also successful and could be a contributing factor to thyroid function improvement.

CONCLUSION

The successful response of our patient with GH/TSH producing tumor to octreotide can be attributed two pathological factors, SSTR2-subtype and Ki-67 SI.

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

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