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 adnomectomy. 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 endocrinological disorder.
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

<table>
<thead>
<tr>
<th>CBC</th>
<th>T-Bil</th>
<th>ALP</th>
<th>GOT</th>
<th>GPT</th>
<th>TP</th>
<th>TDH-C</th>
<th>BS</th>
<th>NT-pro BNP</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 8400 /μl</td>
<td>0.9 mg/dl</td>
<td>392 U/l</td>
<td>18 IU/mL</td>
<td>16 IU/mL</td>
<td>58 mg/dl</td>
<td>47 mg/dl</td>
<td>70 mg/dl</td>
<td>110 mg/dl</td>
<td>108 pg/mL</td>
</tr>
<tr>
<td>RBC 467x10^6 /μl</td>
<td>13.3 g/dl</td>
<td>4.6 g/dl</td>
<td>15.4 mg/dl</td>
<td>0.68 mg/dl</td>
<td>1.38 mEq/l</td>
<td>3.7 mEq/l</td>
<td>103 mEq/l</td>
<td>9.7 mg/dl</td>
<td>3.4 mg/dl</td>
</tr>
<tr>
<td>Hb</td>
<td>18 IU/mL</td>
<td>16 IU/mL</td>
<td>28 IU/mL</td>
<td>56 IU/mL</td>
<td>6.2 %</td>
<td>6.2 %</td>
<td>3.4 %</td>
<td>2.7 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Ht</td>
<td>40.7 %</td>
<td>21.0x10^3 /μl</td>
<td>13.8 mEq/l</td>
<td>8.6 mEq/l</td>
<td>0.64 mEq/l</td>
<td>12.0 mEq/l</td>
<td>6.0 mEq/l</td>
<td>6.0 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Plt</td>
<td>13.8 mEq/l</td>
<td>8.6 mEq/l</td>
<td>0.64 mEq/l</td>
<td>12.0 mEq/l</td>
<td>6.0 mEq/l</td>
<td>6.0 mEq/l</td>
<td>6.0 mEq/l</td>
<td>6.0 mEq/l</td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Endocrinological examinations

<table>
<thead>
<tr>
<th>TSH</th>
<th>8.40 μIU/ml</th>
<th>ACTH</th>
<th>40.9 pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>free T4</td>
<td>3.40 ng/dl</td>
<td>cortisol</td>
<td>14.4 μg/dl</td>
</tr>
<tr>
<td>free T3</td>
<td>6.05 pg/ml</td>
<td>LH</td>
<td>6.11 mIU/ml</td>
</tr>
<tr>
<td>TR/Ap</td>
<td>0.4 IU/L</td>
<td>FSH</td>
<td>14.05 mIU/L</td>
</tr>
<tr>
<td>ThyroidWide</td>
<td>12.5 IU/L</td>
<td>FT3</td>
<td>10.06 ng/mL</td>
</tr>
<tr>
<td>TSH</td>
<td>6.0 mEq/l</td>
<td>FT4</td>
<td>22.3 ng/mL</td>
</tr>
<tr>
<td>IGF-I</td>
<td>1.67 ng/mL</td>
<td>D-Dias</td>
<td>105 μg/mL</td>
</tr>
</tbody>
</table>

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. 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-1 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. 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. 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. 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, and SSTR2 and GH expression are equally important for drug sensitivity and reactivity. 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 to pathological factors, SSTR2-subtype and Ki-67 SI.

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

**References**

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