CASE REPORT

Thyrotropin-producing pituitary adenoma associated with Graves' disease

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Abstract

Objectives: The examination of potential associations between Graves' disease and thyrotropin-producing pituitary adenoma (TSHoma) after treatment using octreotide, and of the expression of peroxisome proliferator-activated receptor γ (PPARγ).

Design and methods: A specimen of resected TSHoma tissue from our case was immunohistochemically examined for expression of somatostatin receptor 2A (SSTR2A) and PPARγ. Specimens of thyroid tissue from two cases with Hashimoto's thyroiditis were immunohistochemically examined for expression of SSTR2A.

Results: Expression of SSTR2A and PPARγ was identified in TSHoma cells. SSTR2A was also expressed in lymphocytes that had infiltrated thyroid tissue in Hashimoto's thyroiditis. In previous reports, three of four patients with TSHoma displayed Graves' disease after tumor resection, and TSH is also known to play a major role in regulating immunomodulatory gene expression in thyrocytes.

Conclusions: Both the immunomodulatory effects of octreotide on intrathyroidal lymphocytes and rapid reductions in TSH may contribute to the onset of Graves' disease. Patients with TSHoma-associated autoimmune thyroiditis should undergo careful follow-up for development of Graves' disease after treatment. Both octreotide and the PPARγ receptor-activating ligands, thiazolidinediones, may be effective for patients with TSHoma.

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Introduction

Among the disorders causing hyperthyroidism, thyrotropin (TSH)-producing pituitary adenoma (TSHoma) has been considered to be extremely rare. Jailer & Holub (1) reported the first case of TSHoma in 1960, and the tumor is reportedly present in <1% of pituitary adenoma patients (2, 3). Thyrotrophic cells reportedly comprise <5% of all pituitary cells (4), which may help to explain the rarity of TSHoma. Few cases of TSHoma associated with Graves’ disease have been reported (5–8).

TSH is an important hormone that plays critical roles not only in the maintenance of normal physiology, but also in the regulation of immunomodulatory gene expression in thyrocytes (9–11).

A somatostatin analog, octreotide, has been used to treat numerous endocrinological diseases (12, 13); it suppresses TSH secretion and decreases adenoma size in TSHoma (14–16). Recent reports have also indicated that somatostatin is involved in immunomodulation, such as the regulation of proliferative responses to antigens or mitogens in different types of immune cells, or the balance between Th1 and Th2 patterns of cytokine secretion by CD4+ T-lymphocytes (17, 18).

The present report describes the case of a 37-year-old female displaying TSHoma with Graves' disease. Autoimmune thyroiditis was also diagnosed, as positive results were obtained for both anti-thyroglobulin antibody (TgAb) and anti-thyroid peroxidase antibody (TPOAb). Immunohistochemical analysis of TSHoma tissue revealed no production of pituitary hormones other than TSH in the tumor, and expression of somatostatin receptor 2A (SSTR2A), an almost specific octreotide receptor (13), and peroxisome proliferator-activated receptor γ (PPARγ), a member of the nuclear receptor superfamily. After administration of octreotide, to reduce thyroid functions, and subsequent excision of TSHoma, elevation of thyroid-stimulating antibody (TSAb) levels was noted. Expression of SSTR2A by lymphocytes infiltrated into thyroid tissue with autoimmune thyroiditis was confirmed immunohistochemically. Both abrupt decline in TSH and the immunomodulatory effects of octreotide may contribute to the
onset of Graves’ disease, and PPARγ receptor-activating ligands, thiazolidinediones (TZDs), may prove useful in treating patients with TSHoma.

**Case report and methods**

The patient was a 31-year-old woman who had been in good health until 1999, when she consulted her doctor complaining of sweating and weight loss (−3 kg/month). Although serum thyroid hormone levels were markedly increased (free tri-iodothyronine (FT3), 8.8 pg/ml; free thyroxine (FT4), 3.5 ng/dl), TSH levels were within normal limits (2.1 μIU/ml). Magnetic resonance imaging (MRI) of the head revealed a 15 mm macroadenoma of anterior lobe origin in the sellar turcica (not shown). The patient was referred to our hospital for further examination, as inappropriate secretion of TSH due to TSHoma was suggested. Normal ranges are shown in parentheses.

**Endocrinological data** are shown in Table 1. Serum T3, FT3, FT4 and SHBG levels were normal (10.0 pg/ml and 82.8 nmol/l respectively). Serum conmone-binding globulin (SHBG) were normal. Levels of TSH-releasing hormone (TRH) and sex hormones were within normal limits, although serum thyroid hormone levels were increased (2.27 ng/ml, 4.4 ng/dl and 7.2 μIU/ml respectively). TSH levels were increased (2.27 ng/ml, 4.4 ng/dl and 7.2 μIU/ml respectively). Levels of TSH-releasing hormone (TRH) and sex hormone-binding globulin (SHBG) were normal (10.0 pg/ml and 82.8 nmol/l respectively). Serum concentrations of the α-subunit of TSH (αTSH) were also normal (0.8 ng/ml), although the αTSH/TSH molar ratio was elevated (1.1). Positive results were obtained for TgAb and TPOAb (5.9 U/ml and 3.9 U/ml respectively), but negative results were obtained for TSH receptor antibody (TRAb), thyroid stimulation antibody (TSA: 0.3% and 118% respectively), and anti-T3, anti-T4 and anti-TSH antibody. TSH level was reduced from 12.32 μIU/ml to 3.30 μIU/ml with the nadir at 6 h in an octreotide suppression test (100 μg, subcutaneous injection), although no TSH suppression was identified on a bromocriptine suppression test (2.5 mg, oral administration). Impaired TSH response to a TRH stimulation test (500 μg, intravenous injection) was noted. Other anterior pituitary hormones, including corticotropin (ACTH), growth hormone (GH), prolactin (PRL), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), displayed normal responses to stimulation tests by corticotropin-releasing hormone, GH-releasing hormone, TRH and gonadotropin-releasing hormone (data not shown). The 121I-uptake ratio (24 h) was elevated (59.1%) and no defect was demonstrated on 121I-thyroid scintigraphy, and cervical ultrasonography revealed no thyroid tumor (not shown).

TSHoma was diagnosed, and total resection of the pituitary tumor by transphenoidal neurosurgery was performed in January 2000, after restoring thyroid function to normal levels by administering octreotide with 50 μg/day lebothyroxine sodium (Fig. 1). The tumor appeared well defined and was easily aspirated, and no residual tumor was apparent. Immunohistochemically, resected pituitary adenoma cells displayed positive staining only with TSH-β antibody (Fig. 2A). After surgery, TSH levels remained within normal limits, although serum thyroid hormone levels were reduced. Serum thyroid hormones increased beyond normal levels in February 2000 (Fig. 1), although no residual tumor was apparent on MRI (not shown). The clinical course and changes in thyroid function were monitored. In January 2001, antibodies related to the thyroid were checked, as both FT3 and FT4 levels were gradually increasing (7.1 pg/ml and 3.93 ng/dl respectively). Positive results were obtained for TSA: 0.3% but not TRAb. Furthermore, both TgAb and TPOAb were elevated to higher levels than before (9.9 U/ml and 6.4 U/ml respectively). However, TSH levels remained

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**Table 1** Laboratory findings before first operation.

<table>
<thead>
<tr>
<th>Endocrinological data</th>
<th>GH 1.2 ng/ml, LH 4.6 mlU/ml, FSH 3.5 mlU/ml, PRL 21.1 ng/ml, ACTH 49.0 pg/ml, TSH 7.2 μIU/ml, FT3 11.6 pg/ml, FT4 4.4 ng/dl, TRH 10.0 pg/ml (7.8–12.2), Tg 27 ng/ml (&lt;30), SHBG 82.8 nmol/l (20–100), αTSH 0.8 ng/ml (0.2–1.1), αTSH/TSH 1.1 (&lt;1.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH tolerance test</td>
<td>TSH (μIU/ml)</td>
</tr>
<tr>
<td>(500 μg i.v.)</td>
<td>0 min                                            15 min                                        30 min                                         60 min                                         90 min                                         120 min</td>
</tr>
<tr>
<td></td>
<td>9.14                                            12.35                                          11.68                                          12.37                                          11.54                                          12.96</td>
</tr>
<tr>
<td>Bromocriptine tolerance test</td>
<td>TSH (μIU/ml)</td>
</tr>
<tr>
<td>(2.5 mg oral)</td>
<td>0 h                                              1 h                                            2 h                                            4 h                                            6 h                                            8 h                                            12 h                                           24 h</td>
</tr>
<tr>
<td></td>
<td>11.56                                          13.10                                          15.34                                          15.65                                          13.90                                          11.41                                          12.69                                          7.77</td>
</tr>
<tr>
<td>Octreotide tolerance test</td>
<td>TSH (μIU/ml)</td>
</tr>
<tr>
<td>(100 μg s.c.)</td>
<td>0 h                                              1 h                                            2 h                                            4 h                                            6 h                                            8 h                                            12 h                                           24 h</td>
</tr>
<tr>
<td></td>
<td>12.32                                          8.34                                          5.31                                          4.04                                          3.30                                          3.72                                          3.34                                          8.88</td>
</tr>
<tr>
<td>Immunological data</td>
<td>TSA: 118% (&lt;180), TRAb 0.3% (&lt;15), TgAb 5.9 U/ml (&lt;0.3), TPOAb 3.9 U/ml (&lt;0.3), TSHAb (–), T3Ab (–), T4Ab (–)</td>
</tr>
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</table>

Normal ranges are shown in parentheses.

TSHAb, anti-TSH antibody; T3Ab, anti-T3 antibody; T4Ab, anti-T4 antibody.
within the normal range (2.45 μIU/ml) (Fig. 1). Recurrence of TSHoma and occurrence of Graves’ disease were therefore suspected.

After consent was obtained from the patient, she was re-admitted to hospital in August 2002. A re-enlarged pituitary tumor was identified on MRI (not shown). TSAb, TRAb and TSH-stimulation blocking antibody (TSHAB) levels were 263%, 30.6% and 20.9% respectively. Serum FT3 and FT4 levels remained within normal limits, probably due to TSAb, although the TSH level was reduced from 3.21 μIU/ml to 0.17 μIU/ml with the nadir 5 days after octreotide administration (300 μg/day, subcutaneous injection). Supplying FT4 to the patient was therefore unnecessary (Fig. 1). In October 2002, reoperation on the pituitary tumor was performed. The recurrent tumor displayed a soft consistency similar to the first tumor, and was completely resected despite partial fibrosis on
the macroscopic level. Serum FT3, FT4 and TSH levels decreased promptly thereafter (to 2.9 pg/ml, 1.71 ng/dl and 0.22 mIU/ml respectively), but only temporarily. In November 2002, further elevation of TSAb, TRAb, TgAb and TPOAb was revealed (367%, 38.4%, 20.5 U/ml and 26.1 U/ml respectively). Although administration of thiamazole (10 mg/day) was initiated, serum FT3, FT4 and TSH levels continued to increase (Fig. 1). The patient decided against medical advice to discontinue treatment, due to financial reasons and the absence of severe thyrotoxic symptoms. At present, we are observing her clinical course.

Measurements of TRAb, TSAb and TSBAb
Detection of TRAb activity was performed using a commercial radioreceptor assay kit (TRAb, Cosmic III; Cosmic Corp., Tokyo, Japan) with solubilized porcine TSH receptors (TSHRs) as ligand. Assay results were expressed as percentage inhibition of $[^{125}\text{I}]$TSH binding, and were calculated as follows: $[1 - ([^{125}\text{I}]TSH bound in the presence of sample IgG)/[^{125}\text{I}]TSH bound in the presence of normal pooled IgG)] \times 100 \%$. The cutoff value was 15%. The 13.5% (final concentration) polyethylene glycol 6000-precipitated fraction from test serum was dissolved in modified Hanks’ solution without NaCl (Test DF). Porcine thyroid cells were incubated with Test DF in the presence of 1000 mU/ml bovine TSH (bTSH). Production of cAMP was measured to determine TSAb activity, expressed as percentage inhibition of bTSH-stimulated cAMP production by Test DF: $[1 - (c - d)/(a - b)] \times 100 \%$; where a is cAMP produced in the presence of precipitated fraction from normal control sera and bTSH; b is cAMP produced in the presence of a precipitated fraction from normal control sera; c is cAMP produced in the presence of Test DF and bTSH; and d is cAMP produced in the presence of Test DF. The cutoff value was 40%.

Immunolabeling procedure for TSH-β
Tissue sections were treated using 10% normal goat serum (Nichirei Co., Tokyo, Japan) in phosphate-buffered saline (PBS) to block non-specific binding, and incubated overnight at 4°C with polyclonal goat anti-human TSH-β antibody (1:200 dilution; Santa Cruz Biotechnology, Santa Cruz, CA, USA), followed by biotinylated anti-goat immunoglobulin (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min and finally streptavidin peroxidase conjugate (Nichirei Co.) for 30 min. Peroxidase was revealed using 3,3'-diaminobenzidine tetrahydrochloride (DAB; Nacalai Tesque, Kyoto, Japan) with H$_2$O$_2$ in buffered solution.
for 5 min. Sections were counter-stained using hematoxylin (Muto Pure Chemicals, Tokyo, Japan).

**Immunofluorescence procedure for SSTR2A, PPARγ and dopamine D2 receptor (D2R)**

Sections were treated with 5% skimmed milk in PBS to block non-specific binding, and sequentially incubated overnight at 4°C with polyclonal goat anti-human SSTR2A or PPARγ antibody (1:1000 dilution; Santa Cruz Biotechnology), then with anti-goat fluorescein isothiocyanate (FITC)-conjugated secondary antibody (1:50 dilution; DakoCytomation, Glostrup, Denmark) for 60 min at room temperature. In the same way, sections were treated using polyclonal rabbit anti-human D2R antibody (1:1000 dilution; Calbiochem Co., San Diego, CA, USA) and anti-rabbit tetramethylrhodamine-5(6)-isothiocyanate (TRITC)-conjugated secondary antibody (1:50 dilution; DakoCytomation). Each incubation was followed by three washes of 3 min each in TBS with 0.25% BRIJ 35 solution. Mounted slides were observed and photographed using an Axioskop 2 microscope (Zeiss, Germany) under epifluorescence illumination.

**Sequencing of the thyroid receptor (TR)β2 exon 6**

After the patient had provided informed consent, DNA was isolated from resected TSHoma tissue. Amplification of TRβ2 was performed by PCR using 0.4 µg genomic DNA as template and 20 pmol oligonucleotide primers. Details of which have been published previously (19). Initial denaturation was performed at 95°C for 4 min, followed by 50 cycles of denaturation for 1 min at 95°C, annealing for 2 min at 55°C, and extension for 2 min at 72°C, with terminal extension for 7 min at 72°C. Second amplification was performed by PCR using 1 µg first amplified DNA as template and 20 pmol oligonucleotide primers for exon 6, details of which have been reported previously (19), using the same PCR conditions as those described above. Primers for TRβ2 and TRβ2 exon 6 comprised: sense, 5'-ACCAGGGAAACAAAAATGAAGCTAATGC-3' and 5'-CTGCTATTGGAAGGACGATC-3'; antisense, 5'-GGAAATATAGGAAAGGAGCC-3' and 5'-CTGAAAGACATCGGAGGCTGA-3' respectively. PCR products were purified using Micro Bio-Spin P-30 Tris Chromatography Columns (BioRad, Hercules, California, USA) and directly sequenced using a BigDye Terminator Cycle Sequencing kit (ABI PRISM 310, Genetic Analyzer; Applied Biosystems, Tokyo, Japan).

**Discussion**

In our case, the adenoma was immunohistologically confirmed as a pure TSH-producing tumor (Fig. 2A). About 50–70% of TSHomas are reportedly pure TSH-producing tumors (2, 20). Abnormal release of TRH was previously suggested as being responsible for TSHoma development (7). Generation of an abnormal TRβ alternative splicing variant mediated by post-transcriptional mechanisms has recently been considered as a potential cause of the defective negative feedback of thyroid hormone on TSH production, and may also contribute to uncontrolled tumor growth in TSHoma (19, 21). Quite recently, Dupre et al. (22) reported that TRβ isoforms (TRβ1 and TRβ2) are expressed in the hypothalamus and involved in the regulation of hypothalamic TRH. Both inappropriate TSH secretion and uncontrolled tumor growth in TSHoma may be due to defective negative feedback of thyroid hormone on TRH production by abnormal TRβ in the hypothalamus. Ando et al. (19) reported that a 135 bp deletion within exon 6, which encodes the ligand-binding domain of TRβ2, was detected in surgically resected TSHoma, and suggested that this deletion generated an abnormal TR protein that accounted for the defective negative regulation of TSH in the TSHoma (21). We therefore investigated germline mutations within exon 6 of the TRβ2 gene. However, no germline mutations were identified in our case (data not shown). Further studies on the origin of TSHoma are expected. In the present case, TSH levels were unresponsive to rapid administration of exogenous 500 µg TRH (Table 1). Kamoi et al. (8) posited the existence of an abnormal relationship between TRH and TSH secretion in these patients.

In our case, no TSH suppression was identified on the bromocriptine suppression test. We immunohistochemically investigated and identified the expression of D2R in tissues from a resected TSHoma (Fig. 2B). D2R is known to inhibit adenyl cyclase via a Pertussis toxin-sensitive G protein (23). Moreover, Rasolonjanahary et al. (24) reported the existence of direct negative coupling between dopamine (DA)–D2R and phospholipase C via heterotrimeric Gi1/2 proteins in the rat anterior pituitary cell membrane. DA–D2R is thus known to regulate multiple transduction pathways. Conversely, imaging in a patient with TSHoma using radiolabeled D2R radioligand reportedly yielded negative results (25). This may suggest a deterioration in affinity due to structural abnormalities in D2R. We therefore speculate that the downstream signal transduction system of D2R, or perhaps D2R in TSHoma, may differ from that in other D2R agonist-sensitive pituitary tumors.

TSHoma with concomitant Graves’ disease is extremely rare. Previously, only four cases of TSHoma complicated by indisputable Graves’ disease have been reported (5–8). These may have involved incidental association, although three of the four patients developed Graves’ disease after resection of the pituitary tumor resulted in depression of TSH levels (6–8). TSH reportedly upregulates TSHR at the mRNA
level in cultured human thyroid cells (26, 27). Furthermore, TSH is known to repress expression of interferon-γ-induced Fas (9), intercellular adhesion molecule (ICAM)-1 (10) and class II trans-activator, which is a non-DNA-binding regulator of major histocompatibility complex (MHC) class II transcription, on the thyroid cell surface (11). Rapid reductions in TSH levels after tumor resection or administration of octreotide may induce Fas-mediated apoptosis as a result of cell surface Fas expression and expression of both ICAM-1 and MHC class II molecules on the cell surface of thyroid cells. Consequently, autoimmune responses against the thyroid gland may be activated. Many opportunities may therefore exist to develop immunity to TSHRs, which have been upregulated by increased TSH. The existence of a lag between elevation of TSAb and TRAb was recognized in the development of circulating thyroid autoantibodies (Fig. 1). TSAb increased first, with subsequent elevation of TRAb after the first operation. Endo et al. (28, 29) reported that all rabbit antibodies produced toward synthetic peptides corresponding to three different regions of the TSHR possessed TSAb activity, but lacked TSH-binding inhibitor immunoglobulin activity. Our findings may support their theory that antibodies against TSHR in patients with Graves’ disease recognize various regions of the extracellular domain of TSHR in addition to TSHR-specific regions. We speculate that the TSAb in our patient may include some antibodies for various parts of TSHR due to an increasing chance for immunity against upregulated TSHRs following TSH elevation.

Octreotide has been demonstrated to be effective for reducing TSH secretion and causing shrinkage of tumor mass in 92% and 52% of cases with TSHoma respectively (2, 3). In our case, octreotide was again effective, and expression of SSTR2A was immunohistochemically identified in tissues from the resected tumor (Fig. 2C). SSTR2A is expressed at sites of chronic inflammation, like granulomas in murine schistosomiasis (30), rheumatoid synovium (31) and granulomas in sarcoidosis (32). Autoimmune thyroiditis was diagnosed in our case before the first operation. We therefore investigated immunohistochemically whether SSTR2A was expressed in thyroid tissue from patients with Hashimoto’s thyroiditis, and demonstrated for the first time the expression of SSTR2A in lymphocytes that had infiltrated thyroid tissue (Fig. 3). Graves’ disease is caused by the production of circulating TSAb due to Th2-dominated patterns of cytokine secretion from CD4+T-lymphocytes, resulting in acceleration of humoral immune reactions (33). Somatostatin has recently been suggested to be involved in immunomodulation (18, 34). As somatostatin is also reportedly able to induce a Th2-like pattern of cytokine secretion in the absence of mitogens (17), the analog octreotide may trigger a shift in Hashimoto’s thyroiditis-associated Th1 predominant activation (33) by binding to SSTR2A expressed by infiltrated lymphocytes within the thyroid. We actually verified that titers of TRAb and TSAb are increased after octreotide administration (dashed square, Fig. 1).

Tumor resection through transsphenoidal neurosurgery remains the treatment of choice for TSHoma, although tumors are usually huge when discovered (2). Complete surgical removal of macroadenoma is difficult (3). In our case, tumor recurrence developed after the second surgery. Regrowth of residual tumor may be attributable to administration of thiamazole (5 mg/day), as reported by Inukai et al. (35). The patient decided against treatment with octreotide, irradiation or reoperation. Recently, Heaney et al. (36) reported that TZDs inhibit tumor cell growth and GH, PRL and LH secretion both in vitro and in vivo, and proposed TZDs as novel oral medications for managing pituitary tumors. However, whether PPARγ is expressed in TSHoma cell remains in question. PPARγ expression was therefore immunohistochemically confirmed in resected TSHoma cells from our case (Fig. 2D). The efficacy of therapy using TZDs for recurrent TSHoma should be examined.

In conclusion, we have reported herein a rare case of TSHoma associated with Graves’ disease. We speculate that induction of Graves’ disease might have resulted from the rapid reduction of TSH following tumor resection and administration of octreotide. Another contributing factor may have been the shift to a Th2-dominant pattern of cytokine secretion due to octreotide. Patients with TSHoma should undergo careful follow-up for development of Graves’ disease after operative treatment or octreotide, if autoimmune thyroiditis is present. Furthermore, the availability and efficacy of TZDs should be examined in the future for patients with TSHoma who reject other treatments.
Acknowledgements

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