Case Report

A 39-year-old woman was admitted to our hospital on May 8, 1989, because of general fatigue and impaired concentration. She had been in good health until April 1989, when she noticed excessive sweating, palpitations, and finger tremor. She also noticed sleep disturbance and impaired concentration. She had consulted another hospital and was diagnosed as having depression and diabetes mellitus.

Clinically, she appeared to be depressive. On physical examination, her height was 148 cm and weight was 41 kg. Blood pressure was 150/50 mmHg and pulse rate was 104/min and regular. The skin was normal. The right eye was mildly exophthalmic. The thyroid was moderately enlarged and soft with vascular murmur. There was a fine tremor. Reflexes were hyperactive. The remainder of the examination was noncontributory.

Serum levels of FT3, FT4, and TSH were 13.7 pmol/l, 55 pmol/l, and less than 0.1 mU/l, respectively. TGPA and MCPA were both positive (1:802 and 1:1602, respectively). TBII were positive (43.4%). RAIU was 92.3%. A thyroid scintigram (Fig. 1) demonstrated a large cold defect in the right thyroid lobe. A transverse ultrasound of the right lobe (Fig. 2) identified a circumscribed hyperechoic mass with a halo. Fine needle aspiration biopsy of the nodule suggested the presence of thyroid carcinoma. Fasting blood glucose level was 6.7 mmol/l. HbA1c was 5.6% (normal: 4.0–6.0%).

Subtotal thyroidectomy was performed on July 10, 1989, after treatments with methimazole (MMI) and Lugol’s solution (Table 1). Treatments with MMI and Lugol’s solution were started on May 24, 1989, and June 8, 1989, respectively. MMI administration was stopped on June 16 since granulocyte count on June 14 was below 0.3 × 10^9/L. The patient was treated with antibiotics for 6 days and dexamethazone for 2 days from June 16 since she complained of sore throat. White blood cell count on June 26 was 6.9 × 10^9/L with 68% neutrophils. Treatment with Lugol’s solution was stopped on the operative day. The weight of the remaining thyroid was about 6 g. Pathological examination revealed the presence of Graves’ disease associated with follicular thyroid carcinoma (Figs. 3, 4). Lymph node metastasis was not observed. After the operation, synthetic T4 was given to suppress TSH. T4 administration was discontinued in December 1989 since mild thyrotoxic symptoms had developed. TSH, however, was still suppressed after discontinuation of the administration of T4. In 1991, free thyroid hormone levels increased above the normal range. RAIU was 44.5% on July 9, 1991. Therefore, treatment with propylthiouracil was started on July 16, 1991.

As shown in Table 1 and Fig. 5, TBII levels increased above the pretreatment value after the operation. TSAb activity measured using porcine thyroid cells was negative throughout the investigation period. TSAb were negative before and just after the operation. They became positive 3 months after the operation and increased to 84.5% in June 1990. TSAb activity was also negative (114%) in serum obtained on May 31, 1991 even when CHO-K1 cells were used for the assay.
Table 1. Changes in Thyroid Function

<table>
<thead>
<tr>
<th></th>
<th>FT3 (pmol/l)</th>
<th>FT4 (pmol/l)</th>
<th>TSH (mU/l)</th>
<th>TGPA</th>
<th>MCPA</th>
<th>TBII</th>
<th>TSAb# (mU/l)</th>
<th>TSBAb (%)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>89-5-09</td>
<td>13.7</td>
<td>55</td>
<td>&lt;0.1</td>
<td>80°</td>
<td>160°</td>
<td>43.4</td>
<td>&lt;0.3</td>
<td>-4.2</td>
<td>Lugol’s solution</td>
</tr>
<tr>
<td>6-21</td>
<td>2.9</td>
<td>12</td>
<td>&lt;0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lugol’s solution</td>
</tr>
<tr>
<td>7-05</td>
<td>3.2</td>
<td>9</td>
<td>&lt;0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thyroidectomy</td>
</tr>
<tr>
<td>7-10</td>
<td></td>
<td></td>
<td></td>
<td>80°</td>
<td>80°</td>
<td>&lt;0.3</td>
<td>-0.7</td>
<td>-6.2</td>
<td>T4</td>
</tr>
<tr>
<td>8-02</td>
<td>1.8</td>
<td>6</td>
<td>0.49</td>
<td>40°</td>
<td>80°</td>
<td>27.0</td>
<td>&lt;0.3</td>
<td>-84.5</td>
<td>T4</td>
</tr>
<tr>
<td>90-1-19</td>
<td>8.8</td>
<td>22</td>
<td>&lt;0.1</td>
<td>20°</td>
<td>80°</td>
<td>55.1</td>
<td>&lt;0.3</td>
<td>74.9</td>
<td></td>
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<tr>
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<td>6.4</td>
<td>16</td>
<td>&lt;0.1</td>
<td>20°</td>
<td>160°</td>
<td>63.5</td>
<td>&lt;0.3</td>
<td>84.5</td>
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<td>91-1-31</td>
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<td>25</td>
<td>&lt;0.1</td>
<td>40°</td>
<td>160°</td>
<td>62.8</td>
<td>&lt;0.3</td>
<td>76.2</td>
<td></td>
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<tr>
<td>5-31</td>
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<td>35</td>
<td>&lt;0.1</td>
<td>40°</td>
<td>160°</td>
<td>77.2</td>
<td>&lt;0.3</td>
<td>64.1</td>
<td></td>
</tr>
<tr>
<td>8-29</td>
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<td>7</td>
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<td>40°</td>
<td>80°</td>
<td>64.1</td>
<td>&lt;0.3</td>
<td>57.0</td>
<td>PTU</td>
</tr>
</tbody>
</table>

Normal range: FT3: 3.4-7.7 pmol/l, FT4: 11-25 pmol/l, TSH: 0.41-4.10 mU/l, TGPA: <10°, MCPA: <10°, TBII: <15, TSAb: <0.3, TSBAb: -16.1-19.9.

Discussion

The incidence of thyroid carcinoma has been reported to be high in patients with Graves’ disease who have undergone surgery (10). Recently, Belfiore et al (11) reported that differentiated (papillary or follicular) thyroid carcinoma was found in 13 (9.8%) out of 132 Graves’ patients undergoing thyroidectomy. In their study (11), carcinoma was more aggressive in Graves’ disease than in other conditions. They suggested that TSAb detected in Graves’ patients could play a role in the high aggressiveness of the thyroid cancer in these patients. In the present Graves’ disease patient with follicular thyroid carcinoma, TSAb activity has not been detected in the sera to date. Neither metastasis nor relapse of the follicular thyroid carcinoma has been observed.
As shown in Fig. 3, lymphocytic infiltration with a germinal center was seen around the thyroid carcinoma. Volpe (12) suggested that the lymphocytic infiltration results from local response to altered antigen on the carcinoma cells.

Postoperative T4 therapy is recommended for patients with thyroid carcinoma to suppress endogenous TSH in the circulation (13). In the present patient, TSH became detectable 3 weeks after the operation. Therefore, T4 was given. However, TSH was still suppressed by Graves' disease itself even after discontinuation of T4 administration, as shown in Table 1.

TBII activity usually decreases after subtotal (14–16) or total thyroidectomy (16). In the present patient, TBII increased above the pretreatment value after the operation. TSBAb was detected in sera obtained 3 months after the operation and the activity increased thereafter. As shown in Fig. 5, changes in TSBAb activity were similar to those of TBII. These data indicate that elevated TBII observed after the operation is due to the appearance of TSBAb with TBII activity. So far, in Graves' disease, the presence of TSBAb has been reported in untreated patients (3, 4), in patients after 131I therapy (17, 18), and in patients who became hypothyroid after antithyroid drug treatment (19). The present case suggests that subtotal thyroidectomy also could induce and/or modulate the production of TSBAb. The patient was euthyroid or hyperthyroid irrespective of the presence of TSBAb. TSBAb, as measured by the activity of inhibition of TSH-stimulated cAMP increase in prime thyroid cells, might have had little influence on the patients' thyroid function since her TSH levels were suppressed when TSBAb presented in her circulation. Further studies will be required in order to clarify the clinical role of TSBAb in patients with hyperthyroid Graves' disease. TSBAb activity was not demonstrated in our patient even when CHO-K1 cells transfected with human TSH receptor were used for the assay. Regarding the hyperfunction of the patient's thyroid before and after the operation, several explanations are possible: 1) the patients' serum does in fact contain TSBAb, but the activity is masked in vitro by the coexistence of different antibodies against TSH receptor, such as TBII and TSBAb (3, 9); 2) hyperthyroidism is due to the intrathyroidal production of TSBAb acting locally in the thyroid (3); and 3) TSBAb stimulate the human thyroid gland via a TSH-receptor non-mediated pathway (8) and are not detected by the present methods used.

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References


