A Case of Graves’ Disease and Papillary Thyroid Carcinoma with Predominant Production of Thyroid-Stimulation-Blocking Antibodies (TSBAb) Persisted after Total Thyroidectomy

SHIGENORI NAKAMURA, MASAMI ISHIYAMA-TAKUNO, JOHJI KOSAKA, KIMI KONDO*, YOSHIHIRO HORIYA*, SADAO HARA*, HIROTO SHIMA**, AND TSUYOSHI SHIRAKI***

Departments of Internal Medicine, *Surgery and **Pathology, Gifu Red Cross Hospital, Gifu 502, and ***Department of Respiratory Diseases, National Sanatorium Gifu Hospital, Gifu 500, Japan

Abstract. A 42-year-old female with Graves’ disease and papillary thyroid carcinoma with lung metastasis was referred to our hospital. After treatment of thyrotoxicosis with methimazole and Lugol’s solution, she underwent total thyroidectomy. She was then given ¹³¹I twice to treat lung metastasis. However, ¹³¹I uptake into the lung was not clear in the scintigram. Both thyroid-stimulating antibodies (TSAb) and thyroid-stimulation-blocking antibodies (TSBAb) were detected in her sera before and after the treatments. Compared with TSAb activities, TSBAb activities were extremely high. Changes in the titers of these two antibodies were not clear after total thyroidectomy. These results indicate that lymphocytes outside the thyroid gland are the major source of TSAb and TSBAb in this patient.

Key words: Graves’ disease, Papillary thyroid carcinoma, Total thyroidectomy, Thyroid-stimulating antibodies, Thyroid-stimulation-blocking antibodies.

Materials and Methods

Serum samples were stored at −20°C until use. Serum levels of free T₃ (FT₃), free T₄ (FT₄), TSH, and thyroglobulin (Tg) were determined by specific radioimmunoassay (RIA) with commercially available kits (Amerlex-M free T₃ & free T₄ kits, Amersham International, Tokyo; TSH-RIABEAD

Received: September 12, 1991
Accepted: December 20, 1991
Correspondence to: Dr. Shigenori NAKAMURA, Department of Internal Medicine, Gifu Red Cross Hospital, 3-36 Iwakura, Gifu 502, Japan.
TSH-binding inhibitor immunoglobulin (TBII) activity was measured by radioreceptor assay with a commercial kit (Baxter Co., Tokyo). Both TSAb and TSBAb activities were determined with cultured porcine thyroid cells as previously reported by Kasagi et al. [8]. Briefly, a crude immunoglobulin (Ig) fraction was obtained by sedimentation of sera with 15% polyethylene glycol 4000. After incubation of the monolayer cells with this IgG fraction in the absence (TSAb) or presence (TSBAb) of 100 mU/l bovine TSH (bTSH), cAMP released into the medium was measured. The addition of bTSH caused a 30- to 50-fold increase in cAMP [8]. The TSAb activities were expressed as a percentage of values in normal controls. The TSBAb activities were expressed as the percent inhibition of bTSH-stimulated cAMP production calculated as follows: \[ \frac{1-(cAMP\ generated\ in\ the\ presence\ of\ test\ IgG/cAMP\ generated\ in\ the\ presence\ of\ control\ IgG)}{1}\times 100\ (\%) \]. Anti-thyroglobulin (TGPA) and anti-microsomal (MCPA) antibodies were tested by a passive particle-agglutination method (Serodia-ATG and Serodia-AMC, Fujirebio Inc., Tokyo). Normal ranges are shown in Table 1.

**Case Report and Results**

A 42-year-old housewife had been in good health until about 4 years before when she noticed easy fatigability, palpitations, excessive sweating, and finger tremor. She consulted a doctor and was told that her thyroid function was abnormal. The symptoms, however, improved without any treatment. She noticed enlarged goiter in 1987 when these symptoms recurred. In July, 1989, multiple nodular lesions in bilateral lungs were incidentally found by chest x-ray study (Fig. 1). Transbronchial lung biopsy revealed metastatic papillary thyroid carcinoma. She was referred to our hospital in August, 1989 for treatment for thyroid carcinoma with lung metastasis.

On physical examination, her height was 160 cm and weight was 53 kg. Blood pressure was 120/50 mmHg and pulse rate was 88/min with an irregular rhythm. The ECG showed atrial fibrillation. The eyes were normal. On palpation of the thyroid, both lobes were diffusely enlarged and rubbery. In addition, a solitary hard nodule (about 2 × 3 cm) was noted in the lower pole of the right lobe. Several lymph nodes were palpable just lateral to the right lobe. There was no finger tremor. The skin was warm and moist. Reflexes were hyperactive. The muscle strength of the extremities was normal. The remainder of the examination was non-contributory.

Serum levels of FT₃, FT₄, TSH, and Tg were 23.2 pmol/l, 89 pmol/l, less than 0.1 mU/l, and 1160 μg/l, respectively (see Table 1 for changes thereafter). TGPA was negative, while MCPA was positive. TBII was positive with a value of 88.4%. The 24-h thyroidal uptake of ¹²³I was higher than normal (59.9%) (normal: 10–40%). A thyroid scintigram (Fig. 2) showed a cold nodule at the lower pole of the right lobe. No uptake of ¹²³I was observed in either lung field. Fine needle aspiration biopsy of the nodule revealed the presence of papillary thyroid carcinoma. From these results, she was diagnosed as having Graves’ disease and papillary thyroid carcinoma associated with lung metastasis. After treatment with methimazole and Lugol's solution, total thyroidectomy was done on September 11, 1989. The weight of the whole thyroid was 61.4 g. Cervical lymph node metastasis and local invasion through the right jugular vein were noted. Pathological examination of the thyroid (Fig. 3) confirmed the diagnosis. ¹³¹I (3700
TSH RECEPTOR ANTIBODIES AFTER TOTAL THYROIDECTOMY

Table 1. Serial changes in thyroid function results

<table>
<thead>
<tr>
<th>FT₃ (pmol/l)</th>
<th>FT₄ (pmol/l)</th>
<th>TSH (mU/l)</th>
<th>Tg (µg/l)</th>
<th>TGPA</th>
<th>MCPA</th>
<th>TBII (%</th>
<th>TSAb (%)</th>
<th>TSBAb (%)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>89–8–11</td>
<td>23.2</td>
<td>&lt;0.1</td>
<td>1,160</td>
<td>&lt;100</td>
<td>25,600</td>
<td>88.4</td>
<td>221</td>
<td>93</td>
<td>(-)*</td>
</tr>
<tr>
<td>9–11</td>
<td>13.4</td>
<td>&lt;0.1</td>
<td>1,210</td>
<td>&lt;100</td>
<td>6,400</td>
<td>85.7</td>
<td>196</td>
<td>94</td>
<td>Thyroidectomy</td>
</tr>
<tr>
<td>10–09</td>
<td>0.9</td>
<td>&lt;0.1</td>
<td>1,950</td>
<td>&lt;100</td>
<td>6,400</td>
<td>92.2</td>
<td>192</td>
<td>93</td>
<td>¹³¹I (3700 MBq)</td>
</tr>
<tr>
<td>11–06</td>
<td>4.0</td>
<td>0.15</td>
<td>88.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–06</td>
<td>3.5</td>
<td>0.10</td>
<td>1,620</td>
<td>&lt;100</td>
<td>6,400</td>
<td></td>
<td>213</td>
<td>93</td>
<td>T₄ (100 µg/day)</td>
</tr>
<tr>
<td>90–1–05</td>
<td>2.9</td>
<td>0.75</td>
<td>2,160</td>
<td>&lt;100</td>
<td>6,400</td>
<td>89.0</td>
<td>231</td>
<td>93</td>
<td>T₄ (100 µg/day)</td>
</tr>
<tr>
<td>2–13</td>
<td>0.8</td>
<td>2.14</td>
<td>4,500</td>
<td>&lt;100</td>
<td>6,400</td>
<td>91.5</td>
<td>197</td>
<td>94</td>
<td>T₄ (125 µg/day)</td>
</tr>
<tr>
<td>8–23</td>
<td>3.7</td>
<td>14.7</td>
<td>1,790</td>
<td>&lt;100</td>
<td>6,400</td>
<td>91.5</td>
<td>197</td>
<td>94</td>
<td>T₄ (150 µg/day)</td>
</tr>
<tr>
<td>91–1–17</td>
<td>4.0</td>
<td>16.0</td>
<td>3,020</td>
<td>&lt;100</td>
<td>6,400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal range</td>
<td>3.4–11.4</td>
<td>0.41–4.10</td>
<td>&lt;23</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;15</td>
<td>&lt;145</td>
<td>&lt;40</td>
<td></td>
</tr>
</tbody>
</table>

*, Treatments with methimazole and Lugol's solution were started on August 23, 1989 and August 30, 1989, respectively. They were stopped on September 11, 1989.

MBq) was given on October 9, 1989 to destroy the residual thyroid tissue in the neck and lung metastasis. Free thyroid hormone levels were low, but TSH was still suppressed. Slight uptake of ¹³¹I was observed in the thyroid bed (less than 1% one week after the administration of ¹³¹I), but not in the lung metastasis. After then, synthetic T₄ was administered. ¹³¹I (3700 MBq) was given again on February 13, 1990 two weeks after withdrawal of thyroid medication. On that day, TSH was 24.2 mU/l. However, no significant uptake was observed in the lung field or in the neck. Chest x-ray findings in January, 1991 were similar to those obtained before the treatments.

Changes in thyroid functions are shown in Table 1. TGPA was negative throughout the study. Tg levels increased after total thyroidectomy and withdrawal of the thyroid medication, although they were consistently high. Titers of MCPA were decreased after the treatments. Not only TSAb but also TSBAb were detectable in sera obtained before the treatments. Titers of TBII,
TSAb, and TSBAb activities remained unchanged even 16 months after total thyroidectomy. When diluted sera were assayed (Table 2), activities of TBII declined only slightly during the investigation period. However, changes in the titers of TSAb and TSBAb activities were not clear even in this dilution experiment.

**Discussion**

In the present study, we demonstrated a patient with Graves’ disease and papillary thyroid carcinoma with lung metastasis. Belfiore et al. [9] reported that the incidence of thyroid cancer is higher in patients with Graves’ disease than in patients with autonomous thyroid nodule or in euthyroid patients and demonstrated that thyroid carcinomas associated with Graves’ disease are aggressive and frequently metastatic. They suggested that TSAb might play a role in determining the high aggressiveness of thyroid cancer in patients with Graves’ disease. Fletti et al. [10] also reported three cases of Graves’ disease associated with metastatic thy-
TSH RECEPTOR ANTIBODIES AFTER TOTAL THYROIDECTOMY

137

roid carcinoma and demonstrated in vitro that the growth of thyroid carcinoma cells was stimulated by TSAb. These reports suggest that the TSAb affects the development or metastasis of thyroid carcinoma in patients with Graves' disease.

Not only TSAb but also TSBAb were found in the present patient. Furthermore, TSBAb activities were extremely high even after total thyroidectomy. Miyauchi et al. [6] reported the presence of both antibodies in a patient with untreated Graves' disease. During the clinical course, the thyroid function of this patient was dependent on the balance between the two antibodies opposed each other. Concerning TSBAb in Graves' disease, Macchia et al. [11] examined 17 patients with Graves' disease who had TBII but no detectable TSAb and found TSBAb in 15 of them. Fujihara [12] also reported that TSBAb activity was positive in 9 out of 79 patients with untreated or treated Graves' disease. The incidence of TSBAb in Graves' disease is therefore not low when carefully examined. However, coexistence of TSAb and TSBAb seems to be rare in Graves' patients. Fujihara [12] reported that, in only one patient, the simultaneous appearance of both antibodies was observed.

Many reports have shown that TSH receptor antibodies in Graves' disease usually decline slowly and progressively after subtotal thyroidectomy [13-16] and total thyroidectomy [17]. No significant changes in TBII [13, 15] and TSAb [16] after subtotal thyroidectomy have been also observed in some patients with Graves' disease. In the present study, TSBAb activities were so high that we could not find any significant changes in them even after total thyroidectomy (Table 2). As to TSAb, clear changes in them were not observed either since their activities were not so high during the investigation period. In agreement with our results, TSAb activities were also detected after thyroidectomy and 131I therapy in a patient with Graves' disease [18]. In addition, Filetti et al. [10] reported that TSAb titers remained high about 6 months after total thyroidectomy and 131I ablation in a Graves' patient with papillary thyroid carcinoma associated with cervical and mediastinal metastasis. Belfiore et al. [9] detected TSAb activities in 11 out of 12 patients with thyroid cancer and Graves' disease 9-72 months after total thyroidectomy. In their study [9], many patients showed recurrence or persistence of thyroid cancer during the follow-up period. Therefore, there may be some relation between the presence of metastatic thyroid cancer and the production of TSAb. The half-life of IgG is 7 to 23 days [19]. The time course of TSAb and TSBAb activities during the investigation period (Table 1) and the dilution study of them (Table 2) indicate the de novo synthesis of TSAb and TSBAb after the operation. No functioning thyroid tissue could be detected by whole-body scan with 131I in February, 1990. The present results therefore indicate that lymphocytes localized outside the thyroid gland are the major source of TSAb and TSBAb in our patient [18, 20], although it is generally accepted that the thyroid gland is the major site of the production of these antibodies [1].

131I was not effective in our patient even when her TSH was high (24.2 mU/l). Two explanations are possible. One is that TSBAb inhibited the incorporation of 131I into the carcinoma cells through the blocking action of TSH [21]. The other is that cancer tissue itself did not respond to TSH. Suppression of TSAb synthesis has been recommended for Graves' patients with thyroid carcinoma associated with metastasis [9, 22]. Furthermore, the disappearance of TSBAb following glucocorticoid therapy was reported in patients with primary hypothyroidism [23, 24]. Thus, steroid therapy and/or plasmapheresis may be useful in reducing the titers of TSAb and TSBAb in our patient. However, we did not try to reduce the titers of these antibodies, since TSBAb might inhibit the growth of thyroid cells [5, 25].

Acknowledgments

We would like to thank Otsuka Assay Laboratory for measuring TSAb and TSBAb.
References


