Silent Thyroiditis with Thyroid-Stimulation-Blocking Antibodies (TSBAb)

Shigenori NAKAMURA, Miyuki SUGIMOTO, Johji KOSAKA, Hiroshi WATANABE*, Hiroto SHIMA** and Satoru KAWAHIRA***

A 24-year-old man showed thyrotoxic symptoms with hypokalemic periodic paralysis. Serum thyroid hormone levels were high and thyrotropin (TSH) was undetectable. 123I-thyroidal uptake was suppressed. TSH-binding inhibitor immunoglobulin (TBII) was positive. After a month without any treatment, he became hypothyroid. Thyroid hormone level was decreased and TSH was increased to above the normal range. 123I-thyroidal uptake was increased. TBII activity was still positive. From the clinical findings, a diagnosis of silent thyroiditis was made. Sera obtained in the hypothyroid state revealed the presence of thyroid-stimulation-blocking antibodies (TSBAb), but there were no thyroid-stimulating antibodies (TSAb). These results suggest that the hypothyroidism in this patient was due to the presence of TSBAb with TBII activity.

Key words: Periodic paralysis, Hypothyroidism, TSH-inhibitor immunoglobulin, Thyroid-stimulating antibodies

Silent thyroiditis is a well-known disease, characterized by transient thyrotoxicosis, non-tender thyroid gland, and low radioactive iodine uptake (1, 2). Among the patients with silent thyroiditis 30–40% develop transient hypothyroidism after transient thyrotoxicosis (1, 2). Permanent hypothyroidism may occur (3). However, the mechanism(s) which causes transient or permanent hypothyroidism remains unknown. Here, we report a patient with silent thyroiditis whose hypothyroidism might be due to the presence of thyroid-stimulation-blocking antibodies (TSBAb) in the serum (4, 5), as measured by inhibition of the thyrotropin (TSH)-induced cAMP increase using porcine thyroid cells.

CASE REPORT

A 24-year-old man was referred to Gifu Red Cross Hospital on June 3, 1988 for further evaluation of thyroid status. He had been in good health until April 1988, when he noticed finger tremor. On April 25, he had severe muscle weakness in the lower extremities and could not walk for a while. From that time, a similar episode occurred one or two times each week. In the morning of May 19, he was admitted to Owase General Hospital because of flaccid paralysis of the legs and arms. Serum potassium was 2.8 mmol/l. The paralysis was readily resolved by potassium chloride administration. Serum potassium level on the following day was 4.8 mmol/l. His thyroid was enlarged. Serum levels of triiodothyronine (T3), thyroxine (T4), and TSH were 4.8 nmol/l (normal: 1.2–2.8 nmol/l), 236 nmol/l (normal: 59–162 nmol/l), and less than 0.1 mU/l (normal: 0.6–5.1 mU/l), respectively. He did not have neck pain, fever, palpitations, excessive sweating, or diarrhea. He had not previously ingested iodine or thyroid hormones. In order to reduce body weight, he had started to restrict food intake from the beginning of March 1988 and body weight...
weight decreased from 80 to 65 kg in one month. Clinically, he appeared to be euthyroid. On physical examination, his height was 174 cm, and weight was 72 kg. His blood pressure was 140/0 mmHg, and pulse rate was 82/min and regular. There was no finger tremor. The thyroid was slightly enlarged (right lobe 4 x 2 cm, left lobe 5 x 2.5 cm) and soft. Reflexes were hyperactive. Muscle strength of the extremities was normal. The remainder of the examination was non-contributory.

Laboratory data on admission were as follows; potassium 4.4 mmol/l (normal: 3.6-5.0 mmol/l), sodium 145 mmol/l (normal: 135-147 mmol/l), total cholesterol 5.07 mmol/l (normal: 3.16-6.47 mmol/l), and alkaline phosphatase 2.5 μkat/l (normal: 1.3-4.3 μkat/l). CRP was negative and ESR was 2 mm/h. The white blood cell count was 6.5 x 10^9/l with 51% being neutrophils. Serum levels of free T3, free T4 and TSH were 10.1 pmol/l (normal: 3.3-7.7 pmol/l), 15 pmol/l (normal: 14-25 pmol/l), and less than 0.1 mU/l (normal: 0.41-4.10 mU/l), respectively. TSH did not increase with the administration of 500 μg TRH.

Anti-thyroglobulin (Tg-Ab) and anti-microsomal (Mc-Ab) antibodies measured by the passive particle agglutination method (PA method) were both negative (less than 1:100). Tg-Ab measured by radioimmunoassay (RIA) (6) was also negative. TSH-binding inhibitor immunoglobulin (TBII) (7), measured by inhibition of the binding of 123I-labelled TSH to its receptor, was positive (79.2%) (normal <15%). Thyroglobulin (Tg) level was 32 μg/l (normal <45 μg/l). The 24-h thyroidal uptake of 123I was 6.7% (normal: 10-40%). No treatment was given.

Thyroid gland became impalpable in late June 1988 and diastolic pressure became detectable. Clinically hypothyroid symptoms were not clear throughout the study. Changes in thyroid functions are shown in Table 1. Free T3 concentration decreased to below the normal level in July and then fluctuated between below normal and low normal range. Free T4 also decreased and remained below the normal range. On the other hand, TSH increased from an undetectable level to above the normal range. TBIIIs were strongly positive throughout the

### Table 1. Serial changes in thyroid function results.

<table>
<thead>
<tr>
<th></th>
<th>fT3 (pmol/l)</th>
<th>fT4 (pmol/l)</th>
<th>TSH (μU/l)</th>
<th>Tg (μg/l)</th>
<th>TBI (%)</th>
<th>TSAb (%)</th>
<th>TSBAb (%)</th>
<th>Tg-Ab (%)</th>
<th>Mc-Ab (%)</th>
<th>T.C. (mmol/l)</th>
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<tbody>
<tr>
<td>88-6-03</td>
<td>10.1</td>
<td>15</td>
<td>&lt;0.1</td>
<td>32</td>
<td>10</td>
<td>&lt;100</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6-07</td>
<td>3.5</td>
<td>7</td>
<td>0.58</td>
<td>96.4</td>
<td>10</td>
<td>5.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-16</td>
<td>3.5</td>
<td>7</td>
<td>0.58</td>
<td>96.4</td>
<td>10</td>
<td>5.07</td>
<td></td>
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</tr>
<tr>
<td>6-24</td>
<td>4.1</td>
<td>5</td>
<td>23.0</td>
<td>97.5</td>
<td>10</td>
<td>5.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-08</td>
<td>3.0</td>
<td>6</td>
<td>80.0</td>
<td>87.5</td>
<td>&lt;100</td>
<td>7.71</td>
<td></td>
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<td></td>
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<tr>
<td>8-12</td>
<td>3.7</td>
<td>6</td>
<td>88.3</td>
<td>73.2</td>
<td>125</td>
<td>92</td>
<td>8</td>
<td>&lt;100</td>
<td>6.31</td>
<td></td>
</tr>
<tr>
<td>11-18</td>
<td>2.2</td>
<td>6</td>
<td>107.3</td>
<td>84.1</td>
<td>131</td>
<td>92</td>
<td>8</td>
<td>100</td>
<td>5.77</td>
<td></td>
</tr>
<tr>
<td>89-1-20</td>
<td>3.6</td>
<td>7</td>
<td>69.9</td>
<td>88.4</td>
<td>5</td>
<td>400</td>
<td>6.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-08</td>
<td>4.0</td>
<td>11</td>
<td>72.0</td>
<td>86.1</td>
<td>107</td>
<td>99</td>
<td>5</td>
<td>6,400</td>
<td>5.64</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3.3-</td>
<td>14-</td>
<td>0.41-</td>
<td>&lt;45</td>
<td>&lt;15</td>
<td>&lt;145</td>
<td>&lt;40</td>
<td>≥10</td>
<td>&lt;100</td>
<td>3.16-</td>
</tr>
<tr>
<td>range</td>
<td>7.7</td>
<td>25</td>
<td>4.10</td>
<td></td>
<td></td>
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RAIU                  TRH stimulation (88-6-08)

<p>| | | | | | | | |</p>
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<tbody>
<tr>
<td>88-6-14</td>
<td>6.7% (24 h)</td>
<td>TSH (basal)</td>
<td>: &lt;0.1 mU/l</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>89-6-09</td>
<td>14.5% (24 h)</td>
<td>TSH (30 min)</td>
<td>: &lt;0.1 mU/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyrotropin; Tg, thyroglobulin; TBII, thyrotropin-binding inhibitor immunoglobulin; TSAb, thyroid-stimulating antibodies; TSBAb, thyroid-stimulation-blocking antibodies; Tg-Ab, thyroglobulin antibodies; Mc-Ab, microsomal antibodies; T.C., total cholesterol; RIA, radioimmunoassay; PA, particle agglutination; RAIU, radioactive iodine uptake; TRH, thyrotropin-releasing hormone.
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investigation period. Serum Tg levels stayed within the normal range. Tg-Ab, measured by the PA method or RIA remained detectable, whereas Mc-Ab became detectable in November 1988 and the titers of Mc-Ab increased. When he was hypothyroid, TSBAb activity was strongly positive, while thyroid-stimulating antibody (TSAb) activity (8), measured as the increase in cAMP using porcine thyroid cells, was not detectable. We also used diluted sera for the measurement of TSAb and TSBAb activities. However, the results were the same, as shown in Table 2. The patient was prescribed synthetic thyroid hormones, since TSH was constantly high. However, he never complied with the medical regimen. 123I-uptake was normal in June 1989 (14.5%), when free T3, free T4, and TSH were 4.0 pmol/l, 11 pmol/l, and 72.0 mU/l, respectively. As shown in Table 1, serum cholesterol levels increased transiently and then decreased. In order to know the prognosis of this patient, an open biopsy was performed in June 1989. Histology demonstrated distended follicles with slight intrafollicular infoldings as shown in Fig. 1. There were three inflammatory foci in the section examined.

From the clinical course and laboratory findings, a diagnosis of silent thyroiditis was made.

DISCUSSION

The patient showed transient hyperthyroidism followed by hypothyroidism. The first time 123I-thyroidal uptake was tested, free thyroid hormones decreased rapidly and TSH increased from an undetectable level to the normal range as shown in Table 1. Therefore, 123I-uptake in this patient was not as suppressed as that in patients with silent thyroiditis in the thyrotoxic phase (1, 2). It is generally thought that silent thyroiditis is a variant of Hashimoto's thyroiditis (1, 2). In the present study, the microscopic findings of thyroid tissue did not show the typical features of Hashimoto's thyroiditis such as follicular destruction, oxyphilic cell changes, and fibrosis. Concerning this point, Inada et al (9) and Mizukami et al (10) reported that the histological abnormalities, such as lymphocytic infiltration and follicular destruction, can improve spontaneously in the late recovery phase. The present histological findings were in agreement with those of their reports, although our patient was still in the hypothyroid state. From the thyroid histology, it is suggested that his thyroid function could improve if TSBAb activity would decrease or disappear in the future (11).

This patient was first thought to have Graves' disease with periodic paralysis. However, the clinical course and changes in thyroid functions were compatible with the diagnosis of silent thyroiditis, although TBII was strongly positive throughout the study. In 1975, Gluck et al (12) reported a 24-year-old male with silent thyroiditis who had an acute episode of hypokalemic paralysis. Since then, several similar cases have been reported (13-15). These reports suggest that high levels of thyroid hormones alone could play an important role in the develop-

Table 2. TSAb and TSBAb activities in diluted serum.

<table>
<thead>
<tr>
<th>Dilution #</th>
<th>TSAb (%)</th>
<th>TSBAb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>88-11-18</td>
<td>1:5</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>1:25</td>
<td>137</td>
</tr>
<tr>
<td>89-06-08</td>
<td>1:5</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>1:25</td>
<td>120</td>
</tr>
<tr>
<td>Normal range</td>
<td>&lt;145</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

* dilution with normal serum.

Fig. 1. Thyroid specimen shows focal infiltration of lymphocytes and some variation in follicular size. There is no evidence of follicular disruption (x 20).
ment of hypokalemic paralysis, although the early restriction of food intake may have been a contributory factor in the present patient.

Yamamoto et al (16) reported that antimicrobial hemagglutination antibodies are positive in patients with spontaneous silent thyroiditis who develop hypothyroidism and vice versa. Similar results were obtained in patients with postpartum silent thyroiditis (17). Contrary to that report, the present patient developed hypothyroidism even in the absence of such antibodies. Interestingly, during the period he was hypothyroid, TSAb were strongly positive but TSAb were negative. These results suggest that his hypothyroid state was caused by the presence of TSAb with TBII activity. Since sera in the thyrotoxic phase could not be used for the measurement of TSAb or TSAb, it could merely be speculated that TSAb which do not interfere with the action of thyroid hormones liberated from the thyroid gland are present in the thyrotoxic phase, and thus the thyrotoxic symptoms developed.

The presence of TSAb has been demonstrated in patients with Graves' disease who became hypothyroid after antithyroid drug treatment (18). Miyauuchi et al (19) reported a 35-year-old man with Graves' disease who had both TSAb and TSAb in serum at first presentation. TSAb increased and TSAb disappeared when he became hypothyroid after antithyroid drug treatment. Later, TSAb reappeared and TSAb decreased when hyperthyroidism recurred. These reports suggest that thyroid function may vary depending on the balance between TSAb and TSAb activities in the affected patients with anti-TSH receptor antibody. However, we considered that our patient's hyperthyroid state was induced mainly by the destruction of the thyroid gland, and not by the presence of TSAb, since 

uptake was normal when the patient was hypo-

thyroid. Miyauuchi et al (19) also reported a normal 

uptake in a hypothyroid patient with TSAb during treatment with 1-T4. Therefore, TSAb in 

these patients may mainly inhibit a post-process of TSH-stimulated iodine uptake in vivo (21).

In contrast to the reports of Yamamoto et al (16) 

and Smallridge et al (22) wherein serum Tg is high in 

patients with silent thyroiditis during the 

hypothyroid phase, the present patient showed 

normal levels of Tg. The action of TSH which 

stimulates the secretion of Tg from the thyroid gland 

was thought to be inhibited by the presence of 

TSAb, because here microscopic findings revealed 

that the thyroid gland was almost normal. From 

the present study, a normal level of Tg and positive 

results of TBII activity in patients with silent 

thyroiditis during the hypothyroid phase suggest the 

presence of TSAb except when the thyroid gland is 

severely damaged by Hashimoto's thyroiditis and 

does not secrete Tg into the circulation.

ACKNOWLEDGEMENTS: We would like to thank Otsuka Assay Laboratory for measurements of TSAb and TSAb.

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