NOTE

Development of Hypothyroidism with Thyroid Stimulation Blocking Antibody long after Treatment with Antithyroid Drugs in a Patient with Hyperthyroid Graves' Disease: A Case Report

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Abstract. We observed a patient manifesting spontaneous hypothyroidism with thyroid stimulation blocking antibody (TSBAb) long after treatment with antithyroid drugs (ATDs) for hyperthyroid Graves' disease. A 19-year-old female with Graves' disease was treated with ATDs for approximately 2 years; after cessation of ATDs, hyperthyroidism did not recur. Nine years later, she was again seen in our hospital because of symptoms indicative of hypothyroidism. Thyroid hormone replacement was commenced after laboratory confirmation of hypothyroidism. TSH-binding inhibitor immunoglobulin and TSBAb were both positive, while thyroid stimulating antibody (TSAb) was negative, at the time of diagnosis of hypothyroidism. These results indicated that the alterations in thyroid function in this patient appeared to relate to the presumed decline in the activity of TSAb and the appearance of TSBAb years after ATDs administration had been discontinued.

Keywords: Graves' disease, Hypothyroidism, Thyroid stimulation blocking antibody.


IT HAS BEEN reported that thyroid stimulation blocking antibody (TSBAb) may cause hypothyroidism in patients with hyperthyroid Graves' disease previously treated with antithyroid drugs (ATDs) [1–5], although these reports are scanty. We recently observed a patient who developed spontaneous hypothyroidism due to TSBAb approximately nine years after treatment with ATDs for hyperthyroid Graves' disease. The following is a description of this case.

Materials and Methods

Biochemical evaluation of thyroid function included serum levels of butanol-extractable iodine (BEI), tetrasorb and triosorb [6–8]. Serum levels of thyroxine (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) were measured by radioimmunoassay prior to 1986 with commercial kits (Amersham International Inc., Buckinghamshire, U.K.). Serum levels of free thyroxine (FT4), free triiodothyronine (FT3) and TSH were measured after 1986 by radioimmunoassay with commercial kits (Behringwerke AG., Marburg, Germany). TSH-binding inhibitor immunoglobulin (TBI) activity was measured by a radioreceptor assay with a commercial kit (R.S.R. Ltd., Cardiff, U.K.) [9]. Both thyroid stimulating antibody (TSAb) and TSBAb activities were determined with cultured porcine thyroid cells as previously
reported [10, 11]. Antithyroglobulin (TGHA) and antithyroid microsomal (MCHA) antibodies were measured by the tanned red cell hemagglutination technique with commercial kits (Fujizoki Pharmaceutical Co., Tokyo, Japan). Normal ranges are shown in Table 1.

Case Report and Results

A 19-year-old female initially presented to our hospital because of tachycardia, weight loss, excessive sweating and tremor in September, 1975. There was no history of earlier thyroid disease or drug ingestion. Proptosis was minimally present in both eyes, that is, the proptosis was 17 mm or more. The thyroid gland was moderately enlarged (right lobe: 4.7x4.7 cm, left lobe: 4.8x2.8 cm). As shown in Table 1, serum levels of BEI, tetrasorb, triosorb and T3 were in the hyperthyroid range before commencing ATD's administration. Hyperthyroid Graves' disease was thus diagnosed by clinical and laboratory data. Initially, methimazole (MMI) was administered at a dosage of 30 mg/day, continued until 1977, and then withdrawn.

The patient did not return to our hospital between 1978 and 1985, although there was no history suggestive of hyperthyroidism in this interval. However, she was again seen in our hospital because of generalized fatigue, puffy face and constipation in May, 1986. On May 26, 1986, the serum level of TSH was very high, although serum T4 and T3 values were normal. The thyroid gland had spontaneously regressed, with a greater than 50% decrease in goiter size from time of diagnosis of hyperthyroidism; c, normal range before 1986; d, normal range in 1987; e, normal range in 1992.

Table 1. Serial changes in thyroid function results in patient with Graves' disease before, during and after thyroid drug therapy

<table>
<thead>
<tr>
<th>Date</th>
<th>BEI (µg/dl)</th>
<th>Tetrasorb (%)</th>
<th>Triosorb (nmol/L)</th>
<th>T4 (nmol/L)</th>
<th>T3 (pmol/L)</th>
<th>Free T4 (pmol/L)</th>
<th>Free T3 (pmol/L)</th>
<th>TSH (mU/L)</th>
<th>TBII (%)</th>
<th>TSBAb (%)</th>
<th>TSAb (%)</th>
<th>Daily drug dose</th>
<th>Goiter size cm</th>
</tr>
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<tbody>
<tr>
<td>9-18-1975</td>
<td>11.0</td>
<td>25c</td>
<td>40.7</td>
<td>4.04</td>
<td>80²</td>
<td>64j</td>
<td>rt: 4.7</td>
<td>l: 4.8x2.8</td>
<td>MMI (30 mg)</td>
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<tr>
<td>12-3-75</td>
<td>7.9</td>
<td>11.0</td>
<td>44.8</td>
<td>2.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MMI (20 mg)</td>
<td></td>
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<tr>
<td>5-4-76</td>
<td>8.9</td>
<td>50.0</td>
<td>4.2</td>
<td>9.4</td>
<td>MMI (10 mg)</td>
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<tr>
<td>11-3-76</td>
<td>21.4</td>
<td></td>
<td></td>
<td></td>
<td>MMI (5 mg)</td>
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<tr>
<td>10-11-77</td>
<td>5.6</td>
<td>2.15</td>
<td>5.0</td>
<td>22.0</td>
<td>MMI (5 mg)</td>
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<tr>
<td>11-7-77</td>
<td>97.7</td>
<td>1.61</td>
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<tr>
<td>5-28-86</td>
<td>73.3</td>
<td>1.29</td>
<td>21.9</td>
<td>20²</td>
<td>320²</td>
<td>Markedb</td>
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<tr>
<td>8-25-86</td>
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<td>105</td>
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<td>10-18-88</td>
<td>11.7</td>
<td>4.01</td>
<td>21.1</td>
<td>87.8</td>
<td>20²</td>
<td>320²</td>
<td>T4 (100 µg)</td>
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<tr>
<td>9-6-89</td>
<td>17.3</td>
<td>3.64</td>
<td>12.0</td>
<td>13.0</td>
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<td></td>
<td>T4 (100 µg)</td>
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<tr>
<td>9-9-91</td>
<td>15.0</td>
<td>4.19</td>
<td>12.2</td>
<td>10²</td>
<td>320²</td>
<td>T4 (100 µg)</td>
<td></td>
<td></td>
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<tr>
<td>7-22-91</td>
<td>8.8</td>
<td>5.14</td>
<td>20.8</td>
<td>17.8</td>
<td>T4 (50 µg)</td>
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<tr>
<td>5-21-92</td>
<td>19.2</td>
<td>6.51</td>
<td>9.05</td>
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<td>T4 (200 µg)</td>
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<tr>
<td>15.2</td>
<td>3.43</td>
<td></td>
<td>9.95</td>
<td>87.5</td>
<td>64.9</td>
<td>T4 (200 µg)</td>
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<td>Normal</td>
<td>4</td>
<td>4.6</td>
<td>25</td>
<td>65.6</td>
<td>1.08</td>
<td>10.3</td>
<td>3.5</td>
<td>2-10²</td>
<td>10&gt;200d</td>
<td>-40</td>
<td>10²&gt;</td>
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<tr>
<td>range</td>
<td>8</td>
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<td>37</td>
<td>164.6</td>
<td>2.76</td>
<td>25.7</td>
<td>0.1</td>
<td>0.2-4.0</td>
<td>0.25&lt;e</td>
<td>40</td>
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</table>
Discussion

Autoantibodies to TSH receptor, including TSAb and TSBAb, are often found in patients with autoimmune thyroid disease [12]. TSAb and TSBAb are considered to play essential roles in the development of hyperthyroidism [1, 13] and hypothyroidism [11, 14] in autoimmune thyroid disease, respectively.

Tamai et al. [3] reported that TSBAb might account for hypothyroidism in approximately one third of cases of Graves' disease previously treated with ATDs, and the remaining two thirds might be due to autoimmune thyroiditis. A spontaneous decline in thyroid function has been observed in a small minority of Graves' patients following ATDs administration, possibly due to the autoimmune destructive mechanism [3, 15, 16]. Moreover, hypothyroidism due to TSBAb following ATDs administration for hyperthyroid Graves' patients as was observed in our patient has not been frequently reported except the cases of Tamai et al.

In Japan, so far ten patients who manifested a change from hyperthyroidism to hypothyroidism with TSBAb activity after cessation of ATDs treatment have been reported [1-4]. In addition 3 patients developed hypothyroidism from hyperthyroidism with TSBAb activity during ATDs treatment [4, 5].

Tamai et al. [3] reported that hypothyroidism has been diagnosed at 0.5–10 yr after the cessation of ATDs treatment. Our patient was diagnosed as having hypothyroidism at nine years after cessation of ATDs treatment and had positive TSBAb activity at that time. It was therefore of interest that the interval between hyperthyroidism and hypothyroidism in our patient seemed to be quite long when compared with other patients.

On the other hand, Takeda et al. [17] and Cho et al. [18] have reported some rare cases which developed hyperthyroidism following primary hypothyroidism. Miyauchi et al. [19] have reported an unusual case, which showed transient hypothyroidism due to an imbalance of TSAb and TSBAb. The above cases showed hyperthyroidism due to TSAb and hypothyroidism due to TSBAb. These results strongly suggested that some patients with autoimmune thyroid disease might have both stimulating and blocking antibodies. Amino [20] suggested that when the patients have predominantly stimulating antibodies, they develop hyperthyroidism and if they have predominantly blocking antibodies, they progress into hypothyroidism, and the ratio between stimulation and blocking might be interchanged in some patients. Although we were not able to measure the activities of TBII, TSAb and TSBAb during the previous hyperthyroid state of this patient, we strongly felt that the hyperthyroid state was due to positive TSAb. In addition, the observations in the present case suggest that the changes in TSAb and TSBAb resulted in the change in thyroid function over the nine years following the ATDs administration.

It may therefore be necessary to continue to monitor thyroid function, TSAb and TSBAb in this case, as her current status might not prove to be permanent.

Acknowledgments

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References

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