A Case of Graves' Disease with False Hyperthyrotropinemia Who Developed Silent Thyroiditis

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Abstract. We encountered a patient who developed silent thyroiditis during the course of Graves' disease. The diagnosis of silent thyroiditis was made on the basis of a low thyroidal 131I uptake, no response to the thyrotropin releasing hormone (TRH) test, and subsequent hypothyroidism despite the presence of high titers of thyrotropin (TSH) receptor antibody (TRAb) and thyroid stimulating antibody (TSAb). The patient, in addition, had a discrepancy between serum TSH and thyroid hormone values. This was due to the presence of interfering substances that react to mouse IgG in the sera since serum TSH levels were decreased in a dose dependent manner by the addition of increasing amounts of mouse IgG to the sera. It should therefore be noted that silent thyroiditis can develop in patients with Graves' disease. Furthermore, clinicians should be aware that two-site immunoassay kits that use mouse monoclonal antibodies are subject to interference by some substances, possibly antibodies which react to mouse IgG.

Key words: Silent thyroiditis, Graves' disease, Hyperthyrotropinemia, Anti-mouse IgG antibody, Two-site immunometric assay.

Silent Thyroiditis is a transient form of destructive thyrotoxicosis [1–3] of heterogenous etiology [4, 5]. There are several studies suggesting its autoimmune etiology [6–13]. On the other hand, some reports have suggested the importance of environmental factors or agents [14–18]. For clinicians, it is very important but is often very hard to differentiate hyperthyroidism of silent thyroiditis from that of Graves' disease. Although the ratio of serum triiodothyronine (T3) to thyroxine (T4) may be helpful [19], the thyroidal radioactive iodine uptake is the best way to differentiate between the two diseases. It is, however, not routinely done during the course of Graves' disease. We report here a patient who developed silent thyroiditis during the course of her Graves' disease. In addition, this patient had inappropriately high serum TSH values when compared to her serum thyroid hormone values. This appeared to be due to the presence of interfering substances, possibly antibodies that react to mouse IgG in her serum.

Case report

A 43-yr-old woman was referred to Ito hospital in 1980 for the treatment of Graves' disease. Her thyroidal radioactive iodine uptake was 67% and 30 Gy of 131I was administered. She subsequently became subclinically hypothyroid and was prescribed L-T4 intermittently. Her hyperthyroidism relapsed in 1984 and the administration of methi-
Methimazole was commenced. Methimazole was discontinued in February, 1986 when her TRAb titer was 11.3%. In April, 1988 she broke her leg and was admitted to another hospital. She was told that her serum thyroid hormone levels were high and was again prescribed methimazole (10 mg/day). In October, 1988 she presented to Ito hospital with serum free T3 (FT3), TSH, and TRAb values of 0.51 pmol/L, 89.1 mU/L, and 41.9%, respectively. Methimazole was again discontinued. Figure 1 shows the following clinical course of the patient. In November, 1988 her serum FT3, free T4 (FT4), TSH, and TRAb values were 10.0 pmol/L, 27.8 pmol/L, 5.4 mU/L, and 42.0%, respectively. Administration of methimazole was commenced again in January, 1989 when her serum FT3, FT4, TSH, and TRAb levels were 10.6 pmol/L, 27.6 pmol/L, 6.2 mU/L, and 64.8%, respectively. She became hypothyroid again in March (FT3 4.5 pmol/L, FT4 3.5 pmol/L, TSH 99 mU/L) and the drug was accordingly discontinued. In May, 1989 her serum FT3, FT4, TSH, and TRAb levels were 8.1 pmol/L, 21.4 pmol/L, 6.3 mU/L, and 45.1%, respectively. In July the serum FT3 and FT4 values were 7.5 pmol/L and 19.8 pmol/L, respectively and the TSH response to 500 μg of TRH showed little change from 7.5 mU/L before the TRH infusion to 7.6 mU/L at 30 min after the infusion. The titers of TSAb, thyroid stimulation-blocking antibody (TSBAb), and the 24-h thyroid 131I uptake were 1321%, 10%, and 2%, respectively. She became spontaneously hypothyroid in September (FT3 3.3 pmol/L, FT4 6.3 pmol/L, TSH 79.2 mU/L) and L-T4 was started in October. In December, her serum FT3, FT4, TSH, TRAb, and TSAb values were 11.8 pmol/L, 31.5 pmol/L, 8.9 mU/L, 59.8%, and 637.0%, respectively. Specific binding of the serum from the patient to labelled T3, T4, T3 analogue, and T4 analogue was 5.7, 7.1, 5.2, and 6.7%, respectively (all values within the normal range). Computed tomography of the brain revealed no pituitary abnormalities. L-T4 was discontinued in January, 1990 but she developed palpitations and finger tremor in February, 1990 so methimazole was started again. She soon became euthyroid and methimazole was discontinued in May, 1990.

Materials and Methods

Laboratory measurements

Serum FT3 and FT4 concentrations were determined by RIA with commercial kits (Amersham...
International Plc, Buckinghamshire, England). Serum TSH levels were assayed with the Delfia TSH kit (Pharmacia Wallac, Turku, Finland), the Amerlite TSH kit (Amersham), the TSH RIA BeadII kit (Dainabot Co., Tokyo, Japan), the Sucrosep TSH kit (Celltech Diagnostics Ltd, Slough, UK), and the RIAgnost hTSH kit (Behringwerke, Marburg, FRG). The normal ranges of the hormones were as follows; FT3: 3.4–8.6 pmol/L, FT4: 9.7–24.5 pmol/L, and TSH: 0.3–3.5 mU/L (for the Delfia TSH). TRAb was measured by radioreceptor assay (S.R.S. Ltd., Cardiff, UK), while TSAb and TSBAb were measured using porcine thyroid cells as previously described [20–21]. The normal ranges of TSAb and TSBAb were less than 145% and 40%, respectively. Antibodies to thyroid hormones were measured as previously reported [22, 23].

Effect of addition of mouse IgG

Increasing amounts of mouse IgG (Sigma Chemical Co., St. Louis, MO) were added to serum samples obtained from the patient and the serum TSH value was measured in each sample with the Delfia TSH kit.

**Effect of mouse IgG on the Delfia TSH assay**

As shown in Table 1, serum TSH values were decreased in a dose-dependent manner by the addition of increasing amounts of mouse IgG to the patient’s serum. Since FT3 and FT4 values in this serum were 11.8 pmol/L and 31.5 pmol/L, respectively, the serum TSH values after the addition of mouse IgG appeared to be appropriate.

**Serum TSH values measured with various TSH assay kits**

Table 2 shows serum TSH values in the patient’s serum measured with various commercial TSH assay kits. These kits employ a two-site immunometric assay and include mouse serum or IgG to decrease the interference from endogenous anti-mouse IgG antibodies. It is of interest that only the TSH value obtained with the Delfia TSH assay kit was inappropriately high.

**Discussion**

Silent thyroiditis is characterized by transient thyrotoxicosis, a painless and nontender goiter, depressed thyroidal radioiodine uptake, and lymphocytic thyroiditis on biopsy [1–3]. In our case, the presence of silent thyroiditis was diagnosed on the basis of a low radioiodine uptake, no response to TRH, and the subsequent spontaneous onset of hypothyroidism despite high TRAb and TSAb levels; all indicates the preceding destructive process in the thyroid. Since serum TSBAb was negative, the transient hypothyroidism in this patient was unlikely to have been induced by blocking type TSH receptor antibodies.

There are a few reports available on the association of Graves’ disease and silent thyroiditis [2, 9, 12]. One of the patients with silent thyroiditis described by Gluck et al. [2] had an episode of high-uptake thyrotoxicosis followed by low-uptake thyrotoxicosis. Similarly, one of the patients reported by Taylor et al. [9] had alternating episodes of high-uptake and low-uptake thyrotoxicosis with positive thyrotropin displacement activity when she was hyperthyroid. Yamamoto et al. [12] have

**Table 1. Effect of the addition of mouse IgG on the TSH assay of serum samples from the patient**

<table>
<thead>
<tr>
<th>Mouse IgG (g/L) added</th>
<th>0</th>
<th>0.625</th>
<th>1.25</th>
<th>2.5</th>
<th>5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/L)*</td>
<td>6.92</td>
<td>0.22</td>
<td>0.10</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Measured with the Delfia TSH kit.

**Table 2. Serum TSH values determined by various kits**

<table>
<thead>
<tr>
<th>Thyroid hormones (pmol/L)</th>
<th>FT3 11.8</th>
<th>FT4 31.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta TSH (Pharmacia)</td>
<td>6.9</td>
<td>(mU/L)</td>
</tr>
<tr>
<td>Sucrosep TSH (Celltech Diagnostics)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>TSH RIA BeadII (Dainabot)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Amerlite TSH (Amersham)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>
reported a patient who had several thyrotoxic episodes followed by transient hypothyroidism. They showed that serum TRAb was positive when the radioiodine uptake was high and became negative when the radioiodine uptake was low. In contrast, TRAb as well as TSAb were positive throughout in our patient, even when she was hypothyroid. It is very difficult to distinguish the development of silent thyroiditis from an exacerbation of Graves’ disease unless the radioiodine uptake is examined, and this is not routinely done during the course of Graves’ disease after the initial diagnosis. Although the association of silent thyroiditis and Graves’ disease may be rare, clinicians should be aware of the potential for its development in patients with Graves’ disease.

The other interesting point with regard to this patient was factitious increase in TSH due to some interfering substances in her serum. Heterophilic antibodies such as antibodies to rabbit IgG have been known to interfere with the TSH RIA [24–26]. Since the introduction of two-site immunometric assays that use mouse monoclonal antibodies, antibodies which react to mouse IgG in serum from patients or normal individuals have been reported to generate spuriously high results [27–31]. To diminish such interference, non-immune mouse serum or IgG has been added to the reagents in the commercially available TSH assay kits. However, escape from such blockade has been reported [32–34]. It is of interest that antibodies to mouse IgG interfere with some but not all kits that use mouse monoclonal antibodies as demonstrated in the present study and previous reports [32–34]. This may be due to the difference in the absorbing capacity of the kit, or due to the difference in the specificities of mouse monoclonal antibodies used in the kit. In our case, artifactualy increased TSH was corrected by adding more mouse IgG, suggesting that the amount of antibodies that react to mouse IgG in her serum might have exceeded the absorbing capacity of the Delfia TSH kit. As shown here, even kits that contain blocking mouse IgG or serum are still subject to interference by anti-mouse IgG antibodies. It should therefore be noted that antibodies to mouse IgG can give spuriously high values in some determinations in which a two-site immunoassay is used.

References


