NOTE

A Case of Repeated Painless Thyroiditis Followed by Graves' Disease

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Abstract. A fifty-year-old woman was admitted to our hospital because of palpitation and general fatigue. She had received hemithyroidectomy for thyroid papillary adenocarcinoma at 28 years of age. She had experienced episodes of repeated painless thyroiditis five times over the last 12 years. At her sixth episode of thyrotoxicosis, she was suspected to have Graves' disease and admitted to our hospital. Laboratory findings revealed thyrotoxicosis with positive thyroid stimulating antibody and high radioactive iodine uptake, i.e. Graves' disease. Painless thyroiditis often relapses but rarely develops into Graves' disease. This is a rare case in which repeated painless thyroiditis was followed by Graves' disease. The relation between painless thyroiditis and Graves' disease is discussed.

Key words: Painless thyroiditis, Graves' disease, Thyrotoxicosis, TSH-receptor antibody

(PAINLESS thyroiditis is a syndrome that has a clinical course of thyroid dysfunction similar to subacute thyroiditis but involves no inferior neck pain and no tenderness of the thyroid [1]. Initially, patients show signs of a thyrotoxic phase, passing through euthyroidism to hypothyroidism and finally returning to euthyroidism. In recent years, the term silent thyroiditis has also been frequently used [1]. This disorder has been described by various names, such as thyrotoxicosis with painless thyroiditis [2], occult subacute thyroiditis [3], hyperthyroidism [4], lymphocytic thyroiditis with spontaneously resolving hyperthyroidism [5] and transient hyperthyroidism with lymphocytic thyroiditis [6].

The thyrotoxicosis in this disorder is different from that of Graves' disease, and is induced by the leak of intrathyroidal hormones into circulating blood through damage to the thyroid epithelial cells due to autoimmune inflammation [1]. Painless thyroiditis is induced by the aggravation of Hashimoto's disease or autoimmune thyroiditis and parturition is well known as the triggering factor [7]. On the other hand, Graves' thyrotoxicosis is induced by thyroid stimulating antibodies [8], and should be carefully differentiated from painless thyroiditis in clinical practice, since the therapeutic procedures for the two are completely different. The use of antithyroid drugs is rather contraindicated in painless thyroiditis [1].

Painless thyroiditis recurs frequently but rarely develops into Graves' disease [1]. Here we report a very rare case in which painless thyroiditis occurred five times and was finally followed by Graves' disease. The relation between these two diseases is also discussed.

Methods

Before 1988, serum concentrations of total T4, T3 and TSH were measured by conventional radio
immunoassay [9], but since then serum free T4 has been measured by a new free T4 radioimmunoassay (RIA) (Eiken Immunochemical Laboratories, Tokyo, Japan), in which values for free T4 levels are not affected by the concentration of serum albumin or thyroxin-binding globulin [10]. Free T3 was measured by commercially available radioimmunoassay with T3 analogue (Amersham International Ltd, Amersham, Bucks, UK).

Serum TSH was measured with a sensitive immunoradiometric assay kit (Daiichi Radioisotope, Tokyo, Japan). Anti-thyroid microsomal (MCPA) and anti-thyroglobulin antibodies (TGPA) were tested by a passive particle agglutination method (Serodia-AMC and Serodia-ATG; Fujirebio, Tokyo, Japan).

TSH receptor antibodies were assayed by a radioreceptor assay (TSH-binding inhibitor immunoglobulin, TBII) with a commercial kit (Baxter Co., Tokyo, Japan) [11]. The results were expressed as percentage inhibition of the binding of labelled TSH.

Serum thyroid-stimulating antibody (TSAb) was measured as an increase in cyclic adenosine-3′, 5′-monophosphate (cAMP) in FRTL-5 cells as previously described [12, 13].

Results

A fifty-year-old housewife was referred to our hospital for investigation of thyrotoxicosis.

In 1970, she noticed swelling of the left side of her neck and was diagnosed as having papillary thyroid carcinoma. She was treated by hemithyroidectomy with isthmectomy and followed up without any medication. In October, 1980, she noticed swelling of the right thyroid lobe without any pain. She had experienced similar episodes in April, 1983, April, 1986, January, 1989 and January, 1992. There was no recurrence of papillary thyroid carcinoma. Common cold symptoms were observed about a month before the onset in four out of five episodes of thyrotoxicosis. There was no history of papillary thyroid carcinoma. Her height was 153 cm; weight, 48 kg; blood pressure, 130/60 mmHg and pulse rate, 84 per min. She had no proptosis and eye movement was normal. The right side of her neck was enlarged, but her heart and abdomen were normal.

Initial laboratory data on admission are summarized in Table 1. Serum concentrations of FT4, FT3 and TSH were 3.0 ng/dl (normal range: 0.8–1.4), 12.7 pg/ml (normal range: 2.8–5.8) and less than 0.1 μU/ml (normal range: 0.4–5.6), respectively, and the patient had thyrotoxicosis. She had neither

### Table 1. Laboratory data on admission

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Blood chemistry</th>
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<tbody>
<tr>
<td>RBC</td>
<td>475 x 10^6/mm³</td>
</tr>
<tr>
<td>Hb</td>
<td>13.7 g/dl</td>
</tr>
<tr>
<td>WBC</td>
<td>4100/mm³</td>
</tr>
<tr>
<td>Neutro</td>
<td>41.4 %</td>
</tr>
<tr>
<td>Eosino</td>
<td>2.1 %</td>
</tr>
<tr>
<td>Baso</td>
<td>0.4 %</td>
</tr>
<tr>
<td>Lympho</td>
<td>42.7 %</td>
</tr>
<tr>
<td>Mono</td>
<td>10.3 %</td>
</tr>
<tr>
<td>Platelet</td>
<td>23.4 x 10^4/mm³</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Thyroid function test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
</tr>
<tr>
<td>FT3</td>
</tr>
<tr>
<td>TSH</td>
</tr>
<tr>
<td>TGPA</td>
</tr>
<tr>
<td>MCPA</td>
</tr>
<tr>
<td>TBII</td>
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<tr>
<td>TSAb</td>
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</tbody>
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TGPA, Anti-thyroglobulin antibody; MCPA, Anti-thyroid microsomal antibody; TBII, TSH-receptor antibody; TSAb, Thyroid-stimulating antibody.
anti-thyroid microsomal nor anti-thyroglobulin antibodies. The TSH-receptor antibody level slightly increased to 19%. TSAb apparently increased to 4652%. Serum concentrations of GPT and γ-GTP increased slightly. Serum cholesterol was normal and HDL cholesterol was slightly decreased.

The clinical course is shown in Fig. 1. In October, 1980, April, 1983, April, 1986, January, 1989 and January, 1992, thyrotoxicosis was observed. After the occurrence of thyrotoxicosis, transient hypothyroidism developed in association with the increase in the serum TSH concentration. In 1989, observation for the clinical course could not be done, and the serum TSH level was not examined. TSAb was normal in April, 1983: 107.0% and June, 1988: 126.7%. Radioactive iodine uptake (RAIU) was low in April, 1983: 0.8% and February, 1989: 10.5%. The erythrocyte sedimentation rate was normal. Thus the thyrotoxicosis which occurred five times was diagnosed as not due to Graves' disease but due to destructive thyroiditis. The patient was treated with β-adrenergic antagonist for a short period. The clinical course from 1991 is shown in Fig. 2. In February, 1992, the FT4 level was high, and normalized naturally, but after that slowly rose again. In August, 1992, RAIU was apparently high at 60.2%, and thyrotoxicosis was diagnosed as due to Graves' disease. During the clinical course, the TSH level was always suppressed. The MCPA titer, which is a significant marker of autoimmune thyroid disease, was correlated with the activity of TBII. MCPA and TBII were transiently increased in April, 1992 and then slowly decreased. The patient was treated with methimazole (MMI) from August, 1992.

Discussion

In this case, painless thyroiditis recurred every three years. Four times out of five it occurred from January to April when it could easily be due to allergic rhinitis. Recently the association between allergic disease and autoimmune thyroid disease has been noted [14, 15]. Yamamoto et al. pointed out that seasonal recurrence of painless thyroiditis had a causal relationship to allergic diseases [14]. In this case, however, the patient had no allergic

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**Fig. 1.** Clinical course of the patient with repeated painless thyroiditis followed by Graves' thyrotoxicosis. Shaded area indicates the normal range.
rhinitis, and eosinophils and the IgE concentration did not change. RAST (radioallergosorbent test) for various antigens was negative. This case was also unrelated to pregnancy, but this patient had common cold symptoms about one month before the onset of destructive thyrotoxicosis in four out of five episodes. These episodes suggest that some viruses may induce painless thyroiditis in patients with subclinical autoimmune thyroiditis. It is interesting to speculate that the decrease in the titer of antibody to a certain virus may lead to the relapse of the same viral infection and this infection may induce painless thyroiditis every three years.

Painless thyroiditis is induced by the subacute aggravation of Hashimoto's disease or autoimmune thyroiditis [1] and is different from Graves' disease. On the other hand, patients with prior Graves' disease who had remission or near remission, often develop painless thyroiditis, especially after delivery [16]. The important finding in this report is the development of Graves' disease after five episodes of painless thyroiditis. Graves' thyrotoxicosis also developed after silent thyroiditis according to some previous reports [17, 18]. The occurrence of two types of thyrotoxicosis may not be independent and not be coincidental.

It is obvious that both types of thyrotoxicosis often developed after delivery, when the immune reaction is activated [1, 16]. Furthermore it has recently been found that CD5+B cells are related to the production of TSH receptor antibodies in patients with hyperthyroid Graves' disease [19]. CD5+B cells increase against harmful pathogens, such as bacteria and virus [20]. These findings suggest that, in this case, repeated virus infection might have increased CD5+B cells and then stimulated TSAb production, which caused Graves' disease.

It is proposed that Hashimoto's disease and Graves' disease are the same autoimmune disease
occurring in the thyroid gland, and the clinical features depend on the balance between stimulating, blocking and destructive aspects of humoral and cellular immunity. The predominance of destructive or blocking factors, such as blocking antibodies, ADCC, T-lymphocyte cytotoxicity, lymphotoxin (TNF) and cytotoxic antibody, may prevent the immediate development of Graves' disease after the 5th episode of painless thyroiditis, even though, for example, in this case, TBII had already begun to increase in January, 1991 [21]. Recently autoimmune thyroid diseases have been classified into three types, depending on the clinical features and autoimmune laboratory tests [22]. There are two types of thyrotoxicosis: one is painless thyroiditis and the other is Graves' thyrotoxicosis. Both of them develop at the time of aggravation of immune reaction. Thus the aggravating factors or etiologic factors may be related to both types of thyrotoxicosis. In patients with painless thyroiditis, TSH receptor and microsomal antigens are released because of the damage to thyroid epithelial cells. These antigens stimulate helper T cells which induce the production of anti-TSH receptor antibodies and anti-thyroid microsomal antibodies. Actually this patient showed positive TBII two months after the destruction of the thyroid gland in the fifth episode of painless thyroiditis.

These two types of thyrotoxicosis should be carefully differentiated by measurement of TBII and TSAb, since these two types could develop in the same patient.

References


