We report four cases of Graves’ disease that developed after painful Hashimoto’s thyroiditis. All were middle-aged women, who had high titers of anti-thyroid antibodies and thyrotoxicosis at the onset of painful Hashimoto’s thyroiditis. After 2 to 7 years, they developed Graves’ disease with positive antibody against the thyrotropin receptor. Their clinical courses of Graves’ disease went favorably due to the treatment with antithyroid drug or radioactive iodine therapy. Painful Hashimoto’s thyroiditis is an atypical variant of Hashimoto’s thyroiditis and is one form of destructive thyroiditis. Thyroid damage due to painful Hashimoto’s thyroiditis may be associated with the development of Graves’ disease.

Key words: painful Hashimoto’s thyroiditis, Graves’ disease, TSH receptor antibody

Introduction

The pathogenesis of Graves’ disease is still unclear, but by general consensus autoimmunity plays an important role in developing antibodies against the thyrotropin receptor (TRAb), which induces Graves’ hyperthyroidism. A potential trigger that activates the autoimmune system is thyroid gland damage. Several authors reported that Graves’ disease occurs after destruction of the thyroid gland, such as in that due to painless lymphocytic thyroiditis (1-4), subacute thyroiditis (5-12), external head and neck irradiation (13), surgical treatment for thyroid nodules (14), and parathyroidectomy (15). Thyroid destruction releases autoantigens from the thyroid gland, and subsequently some cases undergo autoantibody production.

Painful Hashimoto’s thyroiditis is an atypical variant of Hashimoto’s thyroiditis characterized by thyroid pain and fever. There is no consensus on the definition and guidelines for the diagnosis of painful Hashimoto’s thyroiditis, since not much data is available on this disease (16-21). This is a form of the destructive thyroiditis. Therefore destruction of the thyroid follicular structure due to painful Hashimoto’s thyroiditis can lead to the appearance of TRAb and thus the development of Graves’ disease. Here we report 4 cases with Graves’ disease that developed after painful Hashimoto’s thyroiditis.

Case Report

All 4 patients were middle-aged females. The age at the onset of painful Hashimoto’s thyroiditis ranged from 46 to 50 and the age at the onset of Graves’ disease ranged from 49 to 55. All patients had high titers of anti-microsomal antibody, and one had a high titer of anti-thyroglobulin antibody. The period between the onset of painful Hashimoto’s thyroiditis and that of Graves’ disease ranged from 2 to 7 years. In all of them, their thyroid function after painful Hashimoto’s thyroiditis returned to normal (Tables 1, 2).

Case 1

A 46-year-old woman had pain along her anterior neck, low-grade fever, and an enlarged thyroid gland in June 1990. She went to a local hospital for investigation of her symptoms. Mild thyrotoxicosis and elevated serum C-reactive protein (CRP) were noted at free thyroxine (fT4) 2.6 ng/dl (0.7-2.1), triiodothyronine 181 ng/ml (70-180), and...
Table 1. Pertinent Clinical and Laboratory Data for 4 Cases of Graves’ Disease that Developed after Painful Hashimoto’s Thyroiditis

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age</th>
<th>Time between painful Hashimoto’s thyroiditis and Graves’ disease</th>
<th>Painful Hashimoto’s thyroiditis / Graves’ disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/46</td>
<td>5yrs</td>
<td>1.4 / 43.9</td>
</tr>
<tr>
<td>2</td>
<td>F/48</td>
<td>7yrs</td>
<td>5.3 / 46.1</td>
</tr>
<tr>
<td>3</td>
<td>F/50</td>
<td>2yrs</td>
<td>ND / ND</td>
</tr>
<tr>
<td>4</td>
<td>F/49</td>
<td>2yrs</td>
<td>0.2 / 42.9</td>
</tr>
</tbody>
</table>

| ND: not determined |

*Data obtained at the time of painful Hashimoto’s thyroiditis and Graves’ disease

Table 2. Thyroid Function Tests and Laboratory Data for the Present 4 Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Normal Range</th>
<th>Painful Hashimoto’s thyroiditis / Graves’ disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSH(uIU/ml)</td>
<td>FT4(mg/dl) FT3(pg/ml) CRP(mg/dl) ESR(mm/hr)</td>
</tr>
<tr>
<td></td>
<td>(0.3-5.0)</td>
<td>(0.7-1.6) (1.7-3.7) (&lt;0.5) (&lt;25)</td>
</tr>
<tr>
<td>1</td>
<td>ND / &lt;0.05</td>
<td>2.6 / 6.0 ND / &gt;16.39 53 / ND ND / 25</td>
</tr>
<tr>
<td>2</td>
<td>&lt;0.05 / &lt;0.003</td>
<td>5.65 / 3.37 14.4 / 14.1 64 / &lt;0.1 94 / ND</td>
</tr>
<tr>
<td>3</td>
<td>&lt;0.05 / &lt;0.003</td>
<td>6.94 / 2.41 10.96 / 7.96 ND / 84 94 / ND</td>
</tr>
<tr>
<td>4</td>
<td>0.005 / &lt;0.003</td>
<td>4.20 / 3.24 7.14 / 12.71 5.6 / &lt;0.3 72 / 5</td>
</tr>
</tbody>
</table>

| ND: not determined |

*Data obtained at the time of painful Hashimoto’s thyroiditis and Graves’ disease

CRP 5.3 mg/dl (<0.5). For the following month she took antibiotics. Her fever went down, but tenderness on the right lobe of her thyroid gland remained. She visited our hospital for confirmation of diagnosis in July 1990. Her thyroid function test showed a euthyroid state. However, her 24-hour radioiodine uptake was reduced (1.4%). Her erythrocyte sedimentation rate (ESR) was 24 mm/hour, TRAb was negative and anti-microsomal antibody titer was high. Fine needle aspiration cytology showed lymphocytic infiltration and granulomatous inflammation, which suggested a destructive phase of chronic lymphocytic thyroiditis. From these results, she was diagnosed with painful Hashimoto’s thyroiditis. She thus was given prednisolone at 10 mg/day and this was tapered over the following month. Afterward, her symptoms were relieved, and the treatment was discontinued after 1 month. Her thyroid function was recovered to normal in December 1990. Her thyroid function was then maintained at normal for 60 months. In May 1995, she developed tremors and sweating, but no pain in her thyroid gland. She came to our hospital in June 1995 with severe thyrotoxicosis, positive TRAb, and elevated 24-hour radioiodine uptake. She was diagnosed with Graves’ disease and antithyroid drug therapy involving thiamazole (MMI) at 20 mg/day was started. She had continued MMI by tapering for 2 years and was subsequently cured.

Case 2

A 48-year-old woman had a high-grade fever, pain and tenderness in her thyroid gland, and her body weight had dropped by 2 kg by the end of July 1995. She visited our hospital for investigation of her symptoms in August 1995. Her laboratory data showed thyrotoxicosis, elevated serum CRP and ESR. Her 24-hour radioiodine uptake was reduced, and her anti-microsomal antibody titer was high. Ultrasonography showed low echoic areas in her thyroid gland due to acute inflammation. She was diagnosed with painful Hashimoto’s thyroiditis and prednisolone 20 mg/day was started. During tapering, her symptoms were relieved, and the treatment was discontinued after 1 month. Her thyroid function was recovered to normal in October 1995 and she remained euthyroid for the following 80 months. She then developed tiredness, heat intolerance, palpitations, and shortness of breath in June 2002. Laboratory tests revealed thyrotoxicosis, a high level of TRAb and high 24-hour radioiodine uptake (46.1%), which suggested Graves’ disease. She started to take the antithyroid drug, MMI at 15 mg/day and continued it as tapering for the following 15 months. Afterward her thyroid function remained normal without medication.

Case 3

A 50-year-old woman developed anterior neck pain, high fever, tremor, and headache in June 2001. She went to a local hospital for a check-up. Thyrotoxicosis, elevated ESR, and negative TRAb were noted. Her 99mTc uptake into thyroid gland was normal at 0.8%, but her anti-microsomal antibody titer was high. She visited our hospital to confirm her diagnosis in July 2001. At that time, her clinical symptoms had almost disappeared without medication. She showed transient hypothyroidism in August 2001 and again became euthyroid. From her clinical course and laboratory data, she
was diagnosed with painful Hashimoto’s thyroiditis. For the following 2 years, she remained normal. In November 2003, she developed palpitations, but no pain was noted along her anterior neck. Since her thyroid function test showed thyrotoxicosis and her TRAb was high, she was diagnosed with Graves’ disease. She started taking MMI at 15 mg/day, and after 18 months her thyroid function became normal while taking MMI at 5 mg/3 days.

Case 4

A 48-year-old woman had a fever, tenderness along the right lobe of her thyroid gland, and a diffusely enlarged goiter in August 2001. She went to a nearby hospital and her serum CRP level was found to be elevated at 5.9 mg/dl. She thus took antibiotics for 1 week, but they were not effective. She therefore visited our hospital for investigation of her symptoms. Laboratory data showed thyrotoxicosis, negative TRAb, and high levels of serum CRP and ESR. Her titers of anti-thyroglobulin and microsomal antibodies were also high, and her 24-hour radioiodine uptake was reduced. Ultrasoundography showed low echoic areas in her bilateral lobes due to acute inflammation. Findings of fine needle aspiration cytology were compatible with those of chronic lymphocytic thyroiditis. From these results, we diagnosed her with painful Hashimoto’s thyroiditis and recommended her to start the oral prednisolone therapy. She took prednisolone by tapering for 1.5 months, and her symptoms were relieved. Thereafter, her thyroid function returned to normal via transient hypothyroidism. For the following 17 months, she remained euthyroid. In July 2003, she developed palpitations, body weight loss of 3 kg, and tiredness, but no pain emanated from her the thyroid gland. At that time, her laboratory data showed thyrotoxicosis and high level of TRAb, but her CRP and ESR levels were normal. Also her 24-hour radioactive iodine uptake was high. Thus, she was diagnosed with Graves’ disease, and so antithyroid drug therapy was started. Because of adverse effects involving eruption due to MMI and liver dysfunction due to propylthiouracil, she received radioiodine therapy in September 2003. After 21 months her thyroid function remained normal without taking medication.

Discussion

According to several reports (16-21), painful Hashimoto’s thyroiditis is a form of destructive thyroiditis, but its clinical course is different from that of subacute thyroiditis or painless lymphocytic thyroiditis. The clinical characteristics of painful Hashimoto’s thyroiditis are repeated painful attacks in some patients and a high rate of developing persistent hyperthyroidism. Also, surgical treatment is sometimes required to relieve the symptoms. Most patients originally have a goiter and high titers of antithyroid antibodies. In fact, distinguishing painful Hashimoto’s thyroiditis from subacute thyroiditis is difficult, since the two diseases resemble each other regarding clinical symptoms in the initial phase. In addition, the pathogenesis and causes of both diseases are still unclear. According to the criteria for the diagnosis of subacute thyroiditis established by the Japan Thyroid Association, antithyroid antibodies show a negative or low titer of temporal nature (22). We tentatively made our criteria for painful Hashimoto’s thyroiditis as follows: 1) symptoms of acute inflammation such as pain and/or tenderness in the thyroid gland; 2) high levels of CRP and/or ESR; 3) high titers of anti thyroglobulin and/or microsomal antibody, or cytological evidence of Hashimoto’s thyroiditis from fine needle aspiration biopsy; 4) exclusion involving high levels of thyroid hormones and normal-high radioiodine uptake. Based on these criteria, the four patients in this report had painful Hashimoto’s thyroiditis. For Case 3, the patient’s 99mTc uptake was normal. The 99mTc uptake level is equivocal for determining whether destructive thyroiditis is present or not. Shigemasa et al reported that 99mTc uptake is not completely suppressed in some patients with subacute thyroiditis (23). Hence, this result for 99mTc uptake in Case 3 could be consistent with that of destructive thyroiditis.

Persistent thyroid dysfunction can result from destruction of the thyroid follicular structure. Up to 5% of patients with subacute thyroiditis (24, 25) and 12 to 30% of patients with painless postpartum thyroiditis (26-29) develop permanent hypothyroidism. Thyroid damage can be associated with the development of thyroid autoimmune disease. Some reports describe the onset of Graves’ hyperthyroidism after destructive thyroiditis (1-12) and the destructive condition of the thyroid follicular structure, for example, surgical treatment for thyroid nodules (14), radioiodine therapy for a toxic nodular goiter (30-32), and external irradiation (13). The mechanism responsible for developing Graves’ disease is TSH receptor leakage due to damage to thyroid epithelial cells. These antigens then stimulate helper T cells, which induce the production of anti-TSH receptor antibody (1). Depending on the nature of the antibodies, whether they are stimulatory or inhibitory, hyperthyroidism or hypothyroidism can occur (33). Painful Hashimoto’s thyroiditis is also a type of destructive thyroiditis. Therefore it is no surprise that painful Hashimoto’s thyroiditis can contribute to the development of Graves’ disease, similar to painless or subacute thyroiditis.

In the present 4 cases, the interval of these two diseases was relatively long at approximately 2-7 years. Graves’ disease occurred within one year after an episode of subacute thyroiditis in most reports (5-9, 10, 11). The development of Graves’ disease in our cases might have been fortuitous. However, Fukata et al reported 2 unusual cases who developed Graves’ disease 7-8 years after subacute thyroiditis (9), and Itaka et al reported one case that developed Graves’ disease 18 months after an episode of subacute thyroiditis (12). In addition, Weetman et al revealed the presence of multiple thyroid autoantibodies over a period of up to 39 months after the onset of subacute thyroiditis (34). Considering these observations, destructive thyroiditis could induce Graves’ disease, resulting from the painful Hashimoto’s thy-
Hashimoto’s thyroiditis and developing Graves’ disease is significantly different between the follow-up of 1,697 patients with subacute thyroiditis, 11 (0.6%) developed Graves’ disease (35). The prevalence of developing Graves’ disease is significantly different between the two diseases (p<0.01). Hashimoto’s thyroiditis and Graves’ disease are autoimmune thyroid diseases. In general, subacute thyroiditis is considered to be a non-autoimmune, post-viral inflammatory or genetic disorder. Since patients with painful Hashimoto’s thyroiditis have an immune mechanism abnormality, they may have the tendency to produce another antibody and a higher possibility of developing Graves’ disease than do patients with subacute thyroiditis.

In conclusion, this is the first report on 4 patients who developed Graves’ disease after painful Hashimoto’s thyroiditis, which is an atypical and destructive type of Hashimoto’s thyroiditis. Careful follow-up of patients with painful Hashimoto’s thyroiditis is therefore important.

References

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