Case report

A Case of Lithium-Associated Painless Thyroiditis

Hiroshi Fukazawa1 and Katsumi Yoshida2

1Department of Internal Medicine, Mito General Hospital, Ibaraki, Japan
2Division of Pathophysiology, Tohoku University Graduate School of Medicine, Miyagi, Japan

Abstract

Lithium, prescribed for bipolar disorder, is known to induce thyroid dysfunction, most commonly hypothyroidism. Thyrotoxicosis due to lithium-induced painless thyroiditis is a rare complication. We have previously reported that the serum concentration of immunosuppressive acidic protein (IAP), an α1-acid glycoprotein, increased during the acute phase of subacute thyroiditis, but was within the normal range in patients with painless thyroiditis. In the present case, a 31-year-old woman, receiving long-term lithium therapy for bipolar disorder, had a recurrent episode of painless thyroiditis, and her serum IAP was increased. The pathogenic mechanism for lithium-associated painless thyroiditis may differ from that of autoimmune conditions.

Key words: lithium, painless thyroiditis, immunosuppressive acidic protein

Introduction

Thyroiditis is an inflammation of the thyroid gland that may be painful and tender when caused by infection, radiation, or trauma, or painless when caused by autoimmune conditions or medications. The most common forms are Hashimoto’s disease, subacute thyroiditis, painless thyroiditis, and drug-induced thyroiditis (caused by amiodarone or interferon-alpha). Patients may be euthyroid, hyperthyroid, or hypothyroid, or they may evolve from one condition to another over time. The diagnosis is made by the clinical context and the findings, including the presence or absence of pain, tenderness, and autoantibodies. Painless thyroiditis is usually the term used to describe transient thyrotoxicosis with reduced thyroidal radioactive iodine uptake in patients with Hashimoto’s thyroiditis1). We have previously reported that the serum concentration of immunosuppressive acidic protein (IAP), an α1-acid glycoprotein, increased during the acute phase of subacute thyroiditis2), while it was within the normal range in patients with painless thyroiditis3). In this report, a case of painless thyroiditis on long-term lithium therapy for bipolar disorder is presented; the patient’s serum IAP level was elevated during the thyrotoxic phase of painless thyroiditis. She became permanently hypothyroid after the second episode of painless thyroiditis.

Case Report

A 31-year-old woman, who had been treated with lithium carbonate (900 mg/day) for bipolar disorder for about 5 years, went to K hospital because of weight loss (10 kg in 6 months) and palpitations. Since a thyroid function panel revealed a low thyroid-stimulating hormone level (TSH: less than 0.03 µU/ml; normal, 0.49–4.67 µU/ml), elevated free thyroxine (FT4) (3.3 ng/dl; normal, 0.71–1.85 ng/dl), and elevated free triiodothyronine (FT3) (13.2 pg/ml; normal, 1.45–3.48 pg/ml) levels, she was referred to our hospital.

When first seen, the physical findings included a height of 173.1 cm and a weight of 55.3 kg. Her blood pressure was 112/76 mmHg, and her pulse rate was 104 per minute with a regular rhythm. Her skin was not icteric and not moist, and her thyroid gland was slightly palpable without tenderness. She had no finger tremors or exophthalmos. Both legs were free of edema. No thoracoabdominal or neurological abnormalities were observed. The patient denied having any history of thyroid disease or a family history of thyroid disorder. She denied using alcohol, tobacco, or street drugs.

The patient was diagnosed as having Graves’ disease, and she started receiving treatment with methimazole (MMI) 30 mg/day. However, as shown in Table 1, the MMI had an immediate effect (FT4 decreased from 3.3 to 2.2 ng/dl; FT3 decreased from 13.2 to 5.0 pg/ml within 0.6 months), and anti-TSH receptor antibody (TRAb) was negative. Antithyroglobulin and antithyroid peroxidase antibodies were both
and normal FT4 (1.2 ng/dl) and FT3 (1.8 pg/ml) levels.  The µ123I uptake at 24 h was low (0%).  Thyroid ultrasonography elevated (33.5 U/ml; normal, <0.3 U/ml, and 3.3 U/ml; normal <0.3 U/ml, respectively).  Therefore, a diagnosis of painless thyroiditis was made, and MMI was discontinued. One month after cessation of the MMI, since the FT4 and FT3 levels decreased to 0.4 ng/dl and 1.1 pg/ml, respectively, and the TSH level was elevated (39 µU/ml), 12.5 µg/day treatment with levothyroxine (L-T4) was started. The L-T4 dose was increased to 25 µg/day, and 1 year later, L-T4 was withdrawn (Table 1).

One year later, the patient complained of fatigue and swelling of the thyroid gland, and she visited K hospital. Since her thyroid function tests showed a low TSH (less than 0.03 µU/ml) and elevated FT4 (2.3 ng/dl) and FT3 (5.5 pg/ml) levels, she was again referred to our hospital. She had a diffuse goiter without tenderness and fever. When she visited our hospital, she had a low TSH (less than 0.03 µU/ml) and normal FT4 (1.2 ng/dl) and FT3 (1.8 pg/ml) levels. The 123I uptake at 24 h was low (0%). Thyroid ultrasonography demonstrated a diffuse goiter with heterogeneously reduced signal intensity. No nodular lesion was present in the thyroid. Laboratory studies revealed a slightly increased serum CRP level (0.68 mg/dl) and normal levels of white blood cells, and the serum IAP concentration was increased (675 µg/ml; normal, <500 µg/ml). Antithyroglobulin and antiperoxidase antibodies were both positive (more than 100 U/ml). Painless thyroiditis is usually recognized by a low thyroid 123I uptake in a patient with the symptoms and signs of thyrotoxicosis. An unknown factor apparently causes a sudden onset of inflammation, damaging thyroid follicles and releasing preformed thyroid hormones into the circulation, causing the transient thyrotoxicosis. Painless thyroiditis is often followed by a subsequent hypothyroid phase. Persistent hypothyroidism is less common, but it occurs in patients with Hashimoto’s thyroiditis or prior thyroid irradiation. Lithium is sometimes associated with painless thyroiditis. Miller and Daniels conducted a retrospective review of 123I thyroid scans in cases taking lithium and reported that lithium-associated painless thyroiditis occurred with an incidence rate of approximately 1.3 cases per 1000 person-years, much higher than the reported incidence rates of painless thyroiditis in the general population. Lithium-associated painless thyroiditis may be underreported. As far as we know, however, this is the first case report of recurrence of painless thyroiditis in association with long-term lithium use.

Table 1. Serial changes of thyroid function tests and TRAb during the clinical course

<table>
<thead>
<tr>
<th>Months</th>
<th>FT4</th>
<th>FT3</th>
<th>TSH</th>
<th>L-T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.26</td>
<td>13.2</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>2.15</td>
<td>5.03</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.4</td>
<td>1.1</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>2.0</td>
<td>15.4</td>
<td>12.5</td>
</tr>
<tr>
<td>5</td>
<td>0.91</td>
<td>2.11</td>
<td>2.4</td>
<td>25</td>
</tr>
<tr>
<td>13</td>
<td>1.1</td>
<td>2.49</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>2.25</td>
<td>5.54</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1.17</td>
<td>1.77</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>24.7</td>
<td>0.4</td>
<td>1.1</td>
<td>145.4</td>
<td>25</td>
</tr>
<tr>
<td>25.7</td>
<td>0.41</td>
<td>1.1</td>
<td>165.9</td>
<td>100</td>
</tr>
<tr>
<td>26.7</td>
<td>1.28</td>
<td>1.75</td>
<td>11.15</td>
<td>125</td>
</tr>
</tbody>
</table>

FT4: free thyroxine, FT3: free triiodothyronine, TSH: thyroid-stimulating hormone, L-T4: levothyroxine.

Discussion

Thyroid dysfunction caused by long-term lithium treatment is an important issue, because lithium continues to be one of the first-choice prophylactic treatments for bipolar disorder several decades after its introduction. Unfortunately, despite the large number of published studies of thyroid abnormalities in lithium-treated patients, their relevance is still controversial. Lithium inhibits thyroid hormone release and often causes goiter and hypothyroidism, particularly in patients with autoimmune thyroiditis. Lithium levels have been reported to be much higher in the thyroid than in the blood. However, a cross-sectional study by Baethge et al. reported that long-term lithium treatment did not increase the prevalence of thyroid autoantibodies.

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Painless thyroiditis is usually caused by an autoimmune mechanism in patients with lymphocytic thyroiditis. However, it has been reported that lithium may directly damage thyroid follicular cells, which is the cause of transient thyrotoxicosis in patients with lithium-induced painless thyroiditis. Such follicular destruction has also been reported in amiodarone-induced thyrotoxicosis.
fore, lithium-associated thyrotoxicosis is a heterogeneous condition associated with several thyroid pathologies.

IAP has been shown to be increased in patients with cancer, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and other conditions\(^{12}\). We have previously reported that the serum IAP concentration was increased during the acute phase of subacute thyroiditis\(^3\), and it was normal in 13 patients with painless thyroiditis due to Hashimoto’s thyroiditis\(^3\). In the present case, the serum IAP concentration increased. This increased IAP concentration may reflect a response to inflammation, since the serum CRP level also increased slightly at that time. Although the reason for the elevated IAP level in the present case is unclear, this result suggests that the cause of painless thyroiditis in lithium-treated patients may differ from the usual enhancement of autoimmunity in patients with Hashimoto’s thyroiditis. Measurement of serum IAP levels may be useful in differentiating the cause of painless thyroiditis.

Changes in thyroid function might precipitate, exacerbate, or modify various psychiatric symptoms. Careful monitoring of thyroid function is important during lithium therapy to detect not only hypothyroidism, but also thyrotoxicosis. However, since thyroid diseases are treatable, thyroid function abnormalities should not constitute an absolute contraindication to lithium treatment, and lithium should not be stopped if a patient develops thyroid abnormalities\(^9\).

References