Propylthiouracil-induced Lupus-like Syndrome Developing in a Graves’ Patient with a Sibling with Systemic Lupus Erythematosus

Akemi Yamada, Kanji Sato, Mitsuhiko Hara*, Akiko Tochimoto, Sachiko Takagi, Naomi Hizuka and Kazue Takano

Abstract

A 13-year-old girl with Graves’ disease, whose younger sister had systemic lupus erythematosus, developed polyarthralgia, fever, neutropenia, hypergamma-globulinemia, and microscopic hematuria after treatment with propylthiouracil (PTU) for 2 years. Myeloperoxidase-anti-neutrophil cytoplasmic antibodies were strongly positive. Anti-single- and anti-double-stranded DNA antibodies were positive, whereas LE cells and anti-Sm antibodies were negative. PTU was discontinued and all symptoms subsided gradually. Two years later, the microscopic hematuria had disappeared completely. Both patients had the identical HLA-DR alleles (HLA-DR9). These present two cases in siblings suggest that both sisters had lupus diathesis, and that the elder sister developed a PTU-induced lupus-like syndrome.

Key words: systemic lupus erythematosus (SLE), lupus-like syndrome, Graves’ disease, propylthiouracil (PTU), Anti-neutrophil cytoplasmic antibody (ANCA)

Introduction

In Japan, patients with Graves’ disease are treated routinely with anti-thyroid drugs, particularly propylthiouracil (PTU), in pediatric clinics. Although a number of patients with PTU-induced lupus-like syndrome have been reported (Table 1), most cases developed sporadically without any family history of collagen disease (1–11). There have been only two reports of thionamide-induced lupus-like syndrome developing in families (3, 5). We report here a 13-year-old girl with PTU-induced lupus like syndrome whose younger sister had developed systemic lupus erythematosus (SLE). Since SLE may occur in certain families, genetic susceptibility to SLE has been postulated (12). We speculate that both sisters in the present report had a similar genetic background or lupus diathesis, and that the elder sister developed a drug-induced lupus-like syndrome.

Case Report

An 11-year-old Japanese girl visited Hiroo Hospital, Tokyo, in February 1998, with tachycardia, malaise, excessive sweating and hand tremors. Her 8-year-old sister had developed SLE at 7 years of age and had been treated with prednisolone. Serum levels of free T3 and T4 were elevated and serum levels of TSH were decreased. A diagnosis of Graves’ disease was made and the patient was treated with 300 mg/day PTU (Fig. 1). All symptoms gradually subsided, accompanied with normalization of thyroid function. In October 1999, a low-grade fever appeared and polyarthralgia developed in the shoulder and knee joints. There was no erythema on the face, photosensitivity, or Raynaud’s phenomenon. Because of high-grade fever (38°C) and a lack of response to analgesics, the patient was referred to the Institute of Clinical Endocrinology, Tokyo Women’s Medical University Hospital in March 2000.

At admission, the patient complained of general malaise and polyarthralgia. The girl was well-developed (159.3 cm, 32.8 kg), and her pulse rate (80/min) and blood pressure (104/68) were normal. The thyroid gland was only slightly enlarged. There was no exophthalmos, skin rash, or peripheral edema. The patient complained of polyarthralgia, but no joints were swollen. Chest X-ray and ECG were normal. A computed tomography scan revealed no hepatosplenomegaly.

Hemoglobin was 11.5 g/dl, red blood cell count was 425×10^6/ mm³, and white blood cell count was 3,400/mm³ with 59.5% neutrophils, 1.5% eosinophils, 34.5% lymphocytes, 4.5% monocytes and no basophils. There was slight proteinuria (±) and microscopic hematuria (2+–3+). Serum total protein was markedly elevated (9.1–9.4 g/dl), and the albumin level was...
PTU-induced Lupus-like Syndrome

Table 1. Graves’ Patients Associated with Thionamide-induced Lupus-Like Syndrome

<table>
<thead>
<tr>
<th>Authors (Ref)</th>
<th>Year</th>
<th>Age</th>
<th>sex</th>
<th>F.H.</th>
<th>drug</th>
<th>duration</th>
<th>Anti-N Ab</th>
<th>WBC (/mm³)</th>
<th>ANA</th>
<th>cf</th>
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<tr>
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<td>1964</td>
<td>17</td>
<td>F</td>
<td></td>
<td>PTU</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td>pericarditis+</td>
</tr>
<tr>
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<td>1970</td>
<td>13</td>
<td>M</td>
<td></td>
<td>PTU</td>
<td>8M</td>
<td>ND</td>
<td>(+)</td>
<td></td>
<td>nephritis +</td>
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<tr>
<td>3 Librik et al (3)</td>
<td>1970</td>
<td>13</td>
<td>F</td>
<td>sister</td>
<td>PTU, MMI</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td>LE cells (+)</td>
</tr>
<tr>
<td>4 Hung &amp; August (4)</td>
<td>1973</td>
<td>14</td>
<td>M</td>
<td></td>
<td>PTU, MMI</td>
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<td>M</td>
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<td>2W</td>
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<td>15</td>
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<tr>
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<td>38</td>
<td>M</td>
<td>father</td>
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<td>2W</td>
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<td>15 Imamura et al (15)</td>
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<td>13</td>
<td>F</td>
<td></td>
<td>PTU</td>
<td>(+)***</td>
<td>ND</td>
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<tr>
<td>16 Tanimoto et al (16)</td>
<td>1999</td>
<td>17</td>
<td>F</td>
<td></td>
<td>PTU</td>
<td>1Y</td>
<td>(+)***</td>
<td>(+)</td>
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<tr>
<td>17 Ishigame et al (17)</td>
<td>2001</td>
<td>22</td>
<td>F</td>
<td></td>
<td>PTU</td>
<td>17M</td>
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<td>18 the present case</td>
<td>2000</td>
<td>13</td>
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<td>sister</td>
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<td>2Y</td>
<td>406***</td>
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FH: family history, ND: not described, anti-N Ab: anti-neutrophil antibody, ANA: anti-nuclear antibody, *cytotoxicity testing, **opsonizing antibody, ***MPO-ANCA, AN: autoimmune neutropenia, ISA: insulin autoantibody syndrome.

3.8 g/dl. IgG was increased to 3550 mg/dl (γ-globulin, 35.8%); serum immunoelectrophoresis showed no monoclonal peak of IgG. C-reactive protein was 8.6 mg/dl, and the erythrocyte sedimentation rate was 92 mm/h. Anti-nuclear antibodies were increased 160-fold with diffuse patterns. Anti-single-stranded DNA antibodies were increased to 4.6 U/ml (normal <2 U/ml) and anti-double-stranded DNA antibodies was also positive (3.0 U/ml) (normal <2 U/ml). CH50 (57.2 U/ml), C3 (132.9 mg/dl) and C4 (27.5 mg/dl) were normal. Although SLE was suspected, LE cells, anti-Sm antibody, anti-RNP antibodies, anti-SS-A and anti-SS-B antibodies, and lupus anticoagulant were negative. Myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA) were strongly positive (406 EU/ml, normal <10 EU/ml), whereas proteinase 3-anti-nuclear cytoplasmic antibodies (PR3-ANCA) were negative (<10 EU/ml).

Serum levels of free T4, free T3 and TSH were 1.50 ng/dl (normal range: 0.94–1.71 ng/dl), 3.90 pg/ml (normal range: 2.49–4.11 pg/ml) and 5.0 μU/ml (normal range: 0.530–4.43 μU/ml), respectively. Thyroid-stimulating antibody (TSAb) and TSH receptor antibody (TRAb) were negative. Anti-microsmal antibody was positive (1: 6,400), but anti-thyroglobulin antibody was negative. A delayed lymphocyte stimulation test against PTU was negative (2,649 cpm: control 1,632 cpm, stimulation index 162%).

Under a tentative diagnosis of PTU-induced lupus-like syndrome (13), the anti-thyroid drug was discontinued in March 2000. Thereafter, the fever resolved gradually and arthralgia subsided. The serological data, including anti-nuclear and anti-double-stranded DNA antibodies decreased gradually. Titers of MPO-ANCA decreased steeply as shown in Fig. 1. Proteinuria became constantly negative and microscopic hematuria decreased to 5–10 red blood cells per high power field in April 2001 (Fig. 1). Six months after discontinuation of PTU, serum levels of T4 and T3 increased, with suppressed serum levels of TSH (0.005 μU/ml). Although TSAb and TRAb were constantly negative, recurrence of Graves’ disease was suspected (14). Since methimazole may also elicit similar side effects in a few patients (6, 10, 11), potassium iodide (KI) was given at a daily dose of 50 mg (15). After 4 months, serum levels of TSH increased to 30 μU/ml, and KI was discontinued in January 2001. The patient has been doing well in a euthyroid state, without any symptoms for the last 14 months. In March, 2002, complete blood counts, total protein (8.2 g/dl), albumin (4.8 g/dl), γ-globulin (21.8%), and C-reactive protein were all within the normal range. The microscopic hematuria had disappeared completely, but MPO-ANCA remained slightly positive (34 EU/ml). Anti-single-stranded DNA antibodies remained positive (3.9 U/ml), whereas anti-double-stranded DNA antibodies became negative. After informed consent had been obtained, HLA typing was carried out on the patient and her family. As shown in Table 2, the siblings had identical HLA-DR alleles (HLA-DR9) in homodimers.

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Figure 1. Clinical course of a patient with propylthiouracil (PTU)-induced lupus-like syndrome. Upper panel: ▲ - ▲: serum T3 (ng/dl), ■ - ■: serum T4 (μg/dl), KI: potassium iodide (50 mg/day). Shaded area indicates normal T3 concentration (90-170 ng/dl). Lower panel: ● - ●: WBC (/mm³), ▲ - ▲: MPO-ANCA (EU/ml). Shaded area indicates normal leukocyte counts (4,000-8,000/mm³). TWMU: Tokyo Women’s Medical University.

Table 2. Major Histocompatibility Complex in the Patient and Her Family

<table>
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<tr>
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<th>Mother</th>
<th>Father</th>
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<td>B locus</td>
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<td>B51/B61</td>
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<tr>
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<td>Cw1</td>
<td>#</td>
<td>#</td>
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<td>DR locus</td>
<td>DR6/DR9</td>
<td>DR9*</td>
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*Cw1-Cw7 were not detected. **homozygous.
Discussion

There are as yet no established criteria for the diagnosis of drug-related lupus (13), but it is very clear that the present juvenile Graves’ patient developed a drug-related lupus, since the lupus-like symptoms, including polyarthritis, fever, leukopenia and hypergammaglobulinemia, disappeared completely after discontinuation of PTU. Positive antibodies against double-stranded DNA, which are highly specific for SLE, became negative after discontinuation of PTU, accompanied by the disappearance of microscopic hematuria. Furthermore, the constantly negative anti-Sm-antibodies and LE cells also supported the case for PTU-induced lupus-like syndrome.

Although a number of patients with PTU-induced lupus-like syndrome have been reported, there have been no case reports of siblings developing idiopathic SLE (1–11, 13, 16–22) (Table 1). Drug-related lupus is common in patients taking isoniazid, hydralazine, procainamide and PTU (13). Indeed, familial thionamide-induced lupus-like syndrome in Graves’ patients has been reported in three sisters (3) and in a father and son (5). The latter patients were identical at the HLA-DR locus, suggesting that adverse reactions to thionamides may be controlled by immune response genes. HLA-DR 2, 3 and 4 have been postulated to be susceptible to SLE in Caucasians as well as in Japanese individuals (12, 23). Although both present siblings had the identical HLA-DR (HLA-DR9) in homozygosity, we speculate that both patients probably had similar lupus diathesis. Whether it is associated with the major histocompatibility complex (MHC) class II region (such as HLA-DR) or non-MHC genes on the long arm of chromosome 1 (12) remains to be elucidated.

Since the beginning of 1990, it became possible to routinely measure MPO-ANCA and PR3-ANCA, and an increasing number of ANCA-related lupus-like syndromes, vasculitis and nephritis have been reported in Graves’ patients taking PTU for a prolonged period (24–30). Compared to MPO-ANCA-positive patients who developed pauci-immune necrotizing crescentic glomerulonephritis (25–30), the present PTU-induced lupus-like syndrome was manifested as only mild proteinuria and glomerulonephritis (25–30), the present PTU-induced lupus-like syndrome was manifested as only mild proteinuria and glomerulonephritis (25–30). Since MPO-ANCA was strongly positive and the patient had microscopic hematuria, the patient also developed a mild form of MPO-ANCA-related pauci-immune necrotizing crescentic glomerulonephritis, which has a better prognosis than non-drug-induced ANCA-positive disease (30). Although SLE and drug-induced lupus-like syndrome are different disorders whose pathophysiology is not yet clearly understood, the present cases suggest that both patients had a genetic susceptibility to SLE. Whether the genes responsible reside in the MHC class II locus (HLA-DR) or non-MHC locus remains to be elucidated at the molecular level.

In summary, we have reported a PTU-induced lupus-like syndrome in a 13-year-old girl, whose younger sister developed idiopathic SLE (13). Since MPO-ANCA was strongly positive and the patient had microscopic hematuria, the patient also developed a mild form of MPO-ANCA-related pauci-immune necrotizing crescentic glomerulonephritis, which has a better prognosis than non-drug-induced ANCA-positive disease (30). Although SLE and drug-induced lupus-like syndrome are different disorders whose pathophysiology is not yet clearly understood, the present cases suggest that both patients had a genetic susceptibility to SLE. Whether the genes responsible reside in the MHC class II locus (HLA-DR) or non-MHC locus remains to be elucidated at the molecular level.

In PTU-treated children with Graves’ disease, MPO-ANCA was positive in 16 of 25 patients (64.0%) (36), which is a much higher positivity rate than in adult patients with Graves’ disease (4.1–37.5%) (22, 37), probably due to the longer period of medication in childhood Graves’ disease. Interestingly, more than half of such anti-thyroid drug-induced MPO-ANCA-positive patients with adverse effects were reported in Japan, where Graves’ patients are treated with anti-thyroid drugs, as the first choice of therapy (38). When there are no adverse effects for the first 2-months, the anti-thyroid drugs are prescribed continuously until Graves’ disease goes into remission. MPO-ANCA-related adverse effects, however, may develop so insidiously that the diagnosis may sometimes be delayed (Table 1).

In the present patient, serum levels of T4 and T3 increased gradually 5 months after discontinuation of PTU, accompanied by suppressed serum levels of TSH. Since methimazole may also induce ANCA-related disorders, KI was prescribed at a daily dose of 50 mg (39), which induced transient hypothyroidism after 3 months. At the present time, the patient is doing well without any medication (Fig. 1). If Graves’ disease relapses in the future, it is planned to treat this patient with KI or 131I (40).

In summary, we have reported a PTU-induced lupus-like syndrome in a 13-year-old girl, whose younger sister developed idiopathic SLE (13). Since MPO-ANCA was strongly positive and the patient had microscopic hematuria, the patient also developed a mild form of MPO-ANCA-related pauci-immune necrotizing crescentic glomerulonephritis, which has a better prognosis than non-drug-induced ANCA-positive disease (30). Although SLE and drug-induced lupus-like syndrome are different disorders whose pathophysiology is not yet clearly understood, the present cases suggest that both patients had a genetic susceptibility to SLE. Whether the genes responsible reside in the MHC class II locus (HLA-DR) or non-MHC locus remains to be elucidated at the molecular level.

Part of this case was presented at the 12th International Thyroid Congress in Kyoto, October 2000 (poster viewing).

References


