Successful Remission of Evans Syndrome Associated with Graves' Disease by Using Propylthiouracil Monotherapy

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Abstract

A 46-year-old woman with Graves' disease was admitted for anemia and thrombocytopenia. She had previously been treated with methimazole but she self-discontinued the treatment 6 months prior to admission. She was diagnosed with Evans syndrome associated with Graves' disease and treated with propylthiouracil without corticosteroids, which normalized her thyroglobulin level. Surprisingly, while Evans syndrome is characterized by frequent relapses, this patient has been in remission of Evans syndrome for approximately 4 years. The remission of Evans syndrome associated with Graves' disease in the absence of immunosuppressive therapy suggests that these 2 diseases have a common pathogenetic mechanism.

Key words: Evans syndrome, Graves' disease, soluble IL-2 receptor, propylthiouracil

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Introduction

Evans syndrome is an autoimmune disease characterized by recurrent relapses of autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP) (1). Because spontaneous remissions are very rare, patients require treatment, which usually consists of corticosteroids or intravenous immunoglobulins (2, 3). Cyclosporin therapy, rituximab therapy, or bone marrow transplantation are required in some cases that are refractory to treatment (3).

To date, the etiology of Evans syndrome is unclear. Recently, the findings from several cases of Evans syndrome associated with another autoimmune disease characterized by hyperthyroidism, namely Graves' disease, suggest that these 2 conditions may have a common immunological mechanism (4-7). However, this remains unclear because almost all such patients are treated with antithyroid drugs and immunosuppressive therapies, such as corticosteroids (4).

Here, we report the case of a patient who had Evans syndrome associated with Graves' disease and has been in long-term remission after improvement of thyroid function due to propylthiouracil (PTU) monotherapy.

Case Report

A 46-year-old woman who was diagnosed with Graves' disease 8 years previously was admitted to our hospital with symptoms of anemia, thrombocytopenia, and dyspnea in September 2006. She had been treated with methimazole (MMI) for Graves' disease, but she self-discontinued it 6 months before admission. On the day before admission, she complained of hyperthermia and dyspnea to her doctor. Hematological examination revealed that her hemoglobin concentration was 6.7 g/dL and the platelet count was $20.6 \times 10^4/\mu\text{L}$. MMI treatment for Graves' disease as well as coagulation disturbance with heparin and warfarin for atrial fibrillation were immediately initiated. The following day, however,

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Table 1. Laboratory Findings on Admission

WBC	2500 / μ L	APTT	58.2 seconds
St	5.0 %	(Control	33.7 seconds)
Seg	77.0 %	PT%	57 %
Lym	12.0 %	PT-INR	1.50
Eo	1.0 %	Fib	201 mg/dL
Ba	2.0 %	FDP	3.7 μ g/mL
Mo	3.0 %	D-Dimer	1.2 μ g/mL
RBC	3.9×10^6 / μ L	ATIII	52 %
Hb	7.1 g/dL		
Ht	22.3 %		
MCV	59.1 fL	Thyroid Function Test	
Reticulocyte	25 %		
Plt	5.2×10^4 / μ L	TSH	<0.01 μ IU/mL
GOT	32 IU/L	Free T3	20.34 pg/mL
GPT	20 IU/L	Free T4	>8.0 ng/dL
LDH	196 IU/L		
ALP	478 IU/L	TSH Receptor Antibody	17.4 IU/mL
T-Bil	2.5 mg/dL	Antithyroglobulin Antibody	57.0 U/mL
D-Bil	1.0 mg/dL		
ChE	47 IU/L		
Fe	8 μ g/dL		
Ferritin	24.7 ng/mL		
CRP	0.43 mg/dL		

TSH: thyroid stimulating hormone

her hemoglobin level and platelet count decreased to 6.2 g/dL and 6.8×10^4 / μ L, respectively. A chest radiograph obtained at that time showed cardiomegaly and a lung infiltrate. She was transferred to our hospital on the second day after hospitalization.

Physical examination revealed the following results: pulse rate, 100 beats/min (with atrial fibrillation); blood pressure, 138/66 mmHg; and body temperature, 37.2°C. The palpebral conjunctiva was anemic, and the bulbar conjunctiva was not icteric. A large goiter without nodules was found. Although the cardiac examination yielded normal results, jugular venous distension was observed. On auscultation, moist rales were heard in both the lower lung fields. Her liver, spleen, and superficial lymph nodes were not palpable, and her distal extremities had many petechiae and were edematous.

The patient's initial hemoglobin level and mean corpuscular volume were 7.1 g/dL and 59.1 fL, respectively. The platelet count was 5.2×10^4 / μ L, and the reticulocyte count was 25%. A direct Coombs test was weakly positive, and the warm reactive antibody for AIHA was an immunoglobulin G (IgG) antibody. The haptoglobin type 2-2 level was 69 mg/dL, which is at the lower limit of the normal range. The serum iron and ferritin levels were 8 μ g/dL and 24.7 ng/mL, respectively. The platelet-associated IgG (PA-IgG) level was 67.1 ng/ 10^7 cells, and the lactate dehydrogenase level was 196 IU/L. The total bilirubin and direct bilirubin levels were 2.5 mg/dL and 1.0 mg/dL, respectively, indicating hyperbilirubinemia. A bone marrow biopsy revealed a normocellular marrow and markedly increased number of megakaryocytes with no dysplastic changes. In addition, there was slight erythroid hyperplasia, and the myeloid/erythroid (M/E) ratio was 1.6. A diagnosis of Evans syndrome was made on the basis of a positive Coombs test, hemolytic anemia, and thrombocytopenia with reactive bone marrow changes. In addition, iron-deficiency anemia (IDA) was considered a

complication. Furthermore, the thyroid hormone level was elevated, whereas the thyroid-stimulating hormone (TSH) was suppressed. The tests involving antibodies for the TSH receptor (TSHR) and thyroglobulin also yielded positive results. An initial study of the cell subsets revealed a CD4/CD8 ratio of 2.12. The serum level of soluble interleukin-2 receptor (sIL-2R) was found to be 8,480 U/mL. The brain natriuretic peptide (BNP) level was 682 pg/mL because of acute heart failure secondary to hyperthyroidism. The coagulation test revealed prolongation of the activated partial thromboplastin time (APTT) and prothrombin time (PT) due to a coagulation disturbance.

On admission, the patient underwent a computed tomography (CT) scan of the chest, which showed diffuse infiltrates in both lungs. Because of the presence of hypoxia and bloody phlegm, we performed an emergency fiberoptic bronchoscopy, which revealed diffuse oozing of blood from all lung segments. The bronchoalveolar lavage fluid did not show any evidence of infection, systemic lupus erythematosus, or antineutrophil cytoplasmic antibody-associated vasculitis. The laboratory data did not reveal any findings indicative of Goodpasture's syndrome. Pulmonary hemorrhage was thought to be due to the coagulation disturbances. Detailed laboratory data are shown in Table 1, 2. In addition, no other chronic bleeding point except pulmonary hemorrhage was found throughout the examination. A whole-body CT scan revealed many swollen paraaortic and mesenteric lymph nodes, approximately 1 cm in diameter. These swollen nodes diminished within 1 month of antithyroid therapy.

The patient was diagnosed with Evans syndrome associated with Graves' disease. MMI therapy was changed to PTU therapy (300 mg/day) to prevent the drug-induced pancytopenia and to treat Graves' disease. We then treated the coagulation disturbances due to the pulmonary hemorrhage. The bleeding was arrested, and we began ferrotherapy with

Table 2. Serological Findings

Coombs Test		sIL-2R	8480 U/mL
Direct	(±)	VitB12	>1500 pg/mL
Broad	(weak+)	Folic Acid	6.7 ng/mL
Anti-IgG	(weak+)		
Detachment Test	negative	ANA	40 index
Anti-C3d Ab	(-)	Anti-ds-DNA IgG Ab	<2.0 IU/mL
Anti-C3d,b Ab	(-)	Anti-Sm Ab	<7.0 U/mL
Indirect	(-)	Lupus anticoagulant	negative
		Anti-cardiolipin β2 GPI Ab	negative
PA-IgG	67.1 ng/10 ⁷ cells	Anti-cardiolipin IgG Ab	negative
		Anti-SS-A Ab	<7.0 U/mL
Haptoglobin	69 mg/dL	Anti-SS-B Ab	<7.0 U/mL
		MPO-ANCA	<10 EU
Suger Water Test	(-)	PR3-ANCA	<10 EU
Ham Test	(-)	Anti-GBM Ab	<10 EU
		BNP	682 pg/mL

PA-IgG: Platelet-associated IgG, sIL-2-R: soluble interleukin-2 receptor, ANA: anti-nuclear antibody, GPI: glycoprotein, MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3 antineutrophil cytoplasmic antibody, GBM: glomerular basement membrane, BNP: brain natriuretic peptide, Ab: antibody

Figure 1. Short-term clinical course of the patient. MAP: red blood cells in mannitol-adenine-phosphate, PTU: propylthiouracil, TSHR Ab: TSH receptor antibody, Anti TG Ab: antithyroglobulin antibody

an iron supplement (100 mg/day) for IDA. Surprisingly, when the patient's thyroglobulin level normalized, the direct Coombs test yielded negative results, without corticosteroid treatment (Fig. 1). Moreover, her sIL-2R level decreased with PTU monotherapy alone (Fig. 1). Although her PA-IgG level did not decrease as quickly as did the other measured parameters, her platelet count gradually increased until it was almost normal during long-term observation (Fig. 2). In addition, her BNP level decreased along with the normalization of thyroid function.

The patient has continued PTU therapy for the past 4

years, and we have periodically measured her blood counts and indirect bilirubin levels during this time. Her reticulocyte and bilirubin levels reached the normal range with the normalization of her thyroglobulin function. Her Evans syndrome has been in remission and she has had no relapses to date.

Discussion

Evans syndrome characteristically presents with a chronic and relapsing clinical course (8) after the first-line immuno-

Figure 2. Long-term clinical course of the patient. PTU: propylthiouracil

suppressive therapies (9). Michel et al reported that immunosuppressive therapies could be discontinued in only 22 of 68 patients with Evans syndrome (32%), after a mean follow-up of 4.8 years (10). Patients with AIHA respond well to steroids, but most remain steroid-dependent and many require second-line treatment (11). Patients with ITP usually require treatment at the time of diagnosis, and only 5-9% of such patients achieve spontaneous remission (12). Considering these issues, maintaining remission of AIHA and ITP without immunosuppressive therapies is very rare. Therefore, the present case of a patient who had Evans syndrome associated with Graves' syndrome and has been in remission since 4 years after PTU monotherapy is extremely interesting with regard to the pathogenetic mechanisms underlying Evans syndrome.

We diagnosed this patient with Evans syndrome and IDA. The diagnosis of AIHA was based on the following symptoms: 1) low hemoglobin level, 2) reticulocytosis with slight erythroid hyperplasia of the bone marrow, 3) elevated indirect bilirubin level, 4) haptoglobin level at the lower limit of the normal range, and 5) positive results for broad-spectrum Coombs test.

Because of IDA and the mixed pathological conditions, diagnosing AIHA is complicated. However, the present patient's clinical course was different from that exhibited by patients with IDA alone. First, the patient presented with reticulocytosis on admission, which is not normally associated with IDA. Furthermore, slight erythroid hyperplasia was found in the bone marrow aspiration (M/E, 1.6). Second, emergency reticulocytosis will usually occur after ferrotherapy in IDA patients. In the present case, however, the reticulocyte count decreased to the normal range after ferrotherapy without marked reticulocytosis; this is the clinical course of remitted AIHA. Third, the indirect bilirubin level revealed a normal bilirubin range after normalization of the

thyroid hormone level, which further suggested the remission of AIHA. Collectively, these parameters strongly suggested that the patient had AIHA, rather than IDA alone.

The symptoms of autoimmune thyroiditis, such as Graves' disease and Hashimoto's thyroiditis, often coincide with organ specific disorders, including pernicious anemia, Addison's disease, type 1 diabetes mellitus, ITP, and AIHA (13). However, the association of Evans syndrome with Graves' disease is rare.

In the present case, the direct Coombs test became negative immediately after starting antithyroid drug treatment due to decreasing levels of autoantibodies and the immunosuppressive effects of PTU. Usually, autoimmune diseases require immunosuppressive therapies in order to enter remission. However, in patients taking antithyroid drugs, but not corticosteroids, serum concentrations of autoantibodies decrease along with normalization of thyroid function (14). TSHR autoantibodies, which are associated with Graves' disease, are oligoclonal IgG₂ antibodies (15) that can non-specifically attach to the surface of red blood cells (16). In this particular case study, since the warm reactive antibody for AIHA was an IgG antibody, it is likely that the TSHR autoantibodies cross-reacted with red blood cells, and decreasing TSHR autoantibodies may have contributed to the remission of AIHA. In addition, recent studies show that antithyroid drug therapy increases the number of circulating suppressor T cells and decreases the number of helper T cells and natural killer cells (17). Antithyroid drugs may also induce apoptosis of intrathyroidal lymphocytes (18) and decrease expression of class II human leukocyte antigens (HLA) (19). These results suggest that antithyroid drugs may have had immunosuppressive effects that contribute to remission of not only Graves' disease but also Evans syndrome in this patient. However, further studies are required to elucidate the underlying mechanism.

In hyperthyroidism, thrombocytopenia is the result of thyroid hormone stimulation of the activated reticuloendothelial system (20). Furthermore, increased blood flow, due to hyperthyroidism, increases phagocytosis in the reticuloendothelial system (21). In the present case, the platelet count temporarily increased after PTU therapy and this normalized thyroid function. Although PTU therapy did not significantly change the patient's PA-IgG level, her platelet count increased in proportion to the normalization of thyroid function. The increased platelet counts with normalization of thyroid hormone were thought to be caused by remission of ITP and the decrease in phagocytosis in the reticuloendothelial system.

Furthermore, the patient's sIL-2R level decreased after antithyroid therapy, which is consistent with the findings by Zwirska-Korczala et al, who reported that sIL-2R levels are increased in patients with Graves' disease and decreased after antithyroid therapy (22). Serum IL-2R levels depend on thyroid function because thyroxine stimulates the release of sIL-2R (22). Patients with AIHA also show high levels of sIL-2R, which indicates the hyperactivation of CD4⁺ lymphocytes (23). As a result, sIL-2R is a good biomarker for the state of AIHA.

In conclusion, remission of Evans syndrome without immunosuppressive therapy in this case suggests that Evans syndrome and Graves' disease have a common pathogenetic mechanism. Further studies are required to elucidate the mechanisms underlying Evans syndrome and its association with Graves' disease.

The authors state that they have no Conflict of Interest (COI).

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