Vitiligo Universalis Associated with Evans Syndrome and Antiphospholipid Syndrome
—A Case Report and Review of the Literature—

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The pathogenesis of vitiligo has been proposed as a destruction of melanocytes by autoimmune processes. Evans syndrome is the combination of autoimmune hemolytic anemia and immune-mediated thrombocytopenia. The antiphospholipid syndrome is characterized by arterial/venous thrombosis, recurrent pregnancy loss, or thrombocytopenia in the presence of antiphospholipid antibodies. We present a case of vitiligo universalis associated with Evans syndrome and antiphospholipid syndrome, the association of which has not been reported before. The association of multiple autoimmune diseases in our case also support the theory that vitiligo may result from immune dysregulation. (Dermatol Sinica 22: 93-99, 2004)

Key words: Vitiligo, Evans syndrome, Antiphospholipid syndrome

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INTRODUCTION

Evans syndrome is a chronic hematological condition characterized by simultaneous or sequential occurrence of Coombs' positive autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia purpura (ITP); it is often accompanied by other immunologically mediated disorders. The clinical course is chronic and relapsing, and therapy is generally unsatisfactory. Vitiligo, which is strongly associated with autoimmune or endocrine diseases, also responds poorly to treatments. Both disorders are associated with thyroid diseases. To date, only four patients having vitiligo associated with Evans syndrome have been reported.

Antiphospholipid syndrome (APS) is characterized by arterial/venous thrombosis, recurrent pregnancy loss, or thrombocytopenia in the presence of antiphospholipid antibodies. We herein present a case of vitiligo universalis associated with Evans syndrome and APS.

CASE REPORT

A 29-year-old female visited us for correction of her universal depigmentation in April, 2000. Reviewing her past history, she was diagnosed as having ITP thirteen years previously with the presentation of easy bruise and purpura on her legs. A complete blood count revealed the platelet count was 24,000/ul. Prednisolone therapy was started at 2 mg/kg/day. Splenectomy was performed at the age of 22.

At the age of 27, the patient presented with sudden onset of progressively spreading depigmentation affecting the entire body surface with simultaneous whitening of all hair, including the scalp hair, eyebrows, eyelashes, pubic hair, axillary hair and other vellous hair within one month in April, 1998. There was no family history of vitiligo, immunologic diseases, light sensitivity, or blood dyscrasias. In July, 1999, Coombs' positive AIHA developed with the presentation of generalized malaise, pallor and mild icterus. The combination of ITP and Coombs' positive AIHA led to the diagnosis of Evans syndrome. In March, 2000, at the age of 29, she had painful swelling of both lower legs. Duplex ultrasonography showed total occlusion.

Fig. 1
(a) The skin was diffusely depigmented and the eyelashes were white. Her scalp hair and eyebrows were dyed brown one and half months previously.
(b) The proximal ends of her scalp hair were white.
below the level of distal superficial femoral veins, and partial occlusion of tibial veins and popliteal veins with small calibers. Deep vein thrombosis caused by antiphospholipid syndrome (APS) was diagnosed by the presence of antiphospholipid (aPL) and anticardiolipin (aCL) antibodies. Treatment with heparin infusion (15,000 units/day) for 3 days, then combined with warfarin (5 mg/day) for 7 days, improved the symptoms. There have been no further significant thrombotic episodes since. She has been doing well under the control of oral anticoagulant (warfarin 2.5 mg/day). On physical examination, she had a chalk-white color change over the whole body surface. There were no areas of normal pigmentation (Fig. 1, 2). Her scalp hair and eyebrows were dyed brown one and half months ago. The proximal ends of her scalp hair were white (Fig. 1b). Hair on other body areas was all white. Neither ocular disturbance nor audiological abnormality was noted. Histopathology of the skin biopsy specimen taken from the left upper arm showed absence of melanocytes and melanin in the epidermis (Fig. 3). The Fontana-Masson silver staining demonstrated no melanin pigments (Fig. 4). Immunohistochemically, HMB-45 staining was negative. In electron microscopic examination, there were no identifiable melanocytes. These clinical and histopathological findings were compatible with those of vitiligo universalis.

Laboratory examination data during AIHA attack included a hemoglobin level of 7.6 g/dl (normal 11.3-15.3 g/dl), reticulocyte count, 10.97% (normal 0.5-1.5%), and platelets, 16,000 / ul (normal 120,000-320,000). The blood biochemistry studies and endocrinologic laboratory tests for detecting thyroid disease, adrenal failure, and diabetes mellitus were all within normal limits. Examinations of the peripheral blood smear showed many normochromic and normocytic red blood cells (RBCs). The direct Coombs' test showed a 4+ reaction. Bone marrow examinations during thromocytopenic attacks showed essentially active marrow with a normal to increased number of megakaryocytes. The immunological pro-
file showed positive antinuclear, anticardiolipin and antiphospholipid antibodies. The search for rheumatoid arthritis (RA) factor, as well as antimicrosomal, anti-thyroid, anti-parietal cell, anti-Ro, anti-La, anti-ribonucleoproteins (RNP), and anti-double stranded DNA (dsDNA) antibodies were all negative. Serum immunoglobulin and complement levels were normal.

The patient responded poorly to splenectomy with persistent thrombocytopenia and required further medical therapy. The medical managements consisted of corticosteroids, intravenous gamma globulin, blood transfusions, azathioprine, vinca alkaloids, plasmapheresis for symptoms related to her hematological problems during nine hospitalizations subsequently. All these treatments were all unsatisfactory for

### Table I. Summary of the clinical findings of patients with vitiligo and Evans syndrome

<table>
<thead>
<tr>
<th>Authors/Year of Publication</th>
<th>Age at onset of vitiligo</th>
<th>Location of vitiligo</th>
<th>Type of vitiligo</th>
<th>Antibodies</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walters et al./1978</td>
<td>9y/male</td>
<td>face, trunk, extremities</td>
<td>generalized</td>
<td>N</td>
<td>Evans syndrome</td>
</tr>
<tr>
<td>Marsh et al./1990</td>
<td>24y/female</td>
<td>not mentioned</td>
<td>not mentioned</td>
<td>N</td>
<td>Evans syndrome</td>
</tr>
<tr>
<td>Duru et al./1994</td>
<td>2y/female</td>
<td>hands, face, abdomen</td>
<td>generalized</td>
<td>N</td>
<td>Evans syndrome, Alopecia areata, ↑ Suppressor T cells, ↓ T4/T8 ratio</td>
</tr>
<tr>
<td>Muwakkit et al./2003</td>
<td>9 m/male</td>
<td>face, body</td>
<td>generalized</td>
<td>aCL, aPL, antithyroid antibodies</td>
<td>Evans syndrome</td>
</tr>
<tr>
<td>The presenting case</td>
<td>27y/female</td>
<td>entire body</td>
<td>universal</td>
<td>aCL, aPL, ANA</td>
<td>Evans syndrome, APS</td>
</tr>
</tbody>
</table>

N: negative  
aCL: anticardiolipin antibodies  
aPL: antiphospholipid antibodies  
ANA: antinuclear antibodies  
APS: antiphospholipid syndrome

![Fig. 3](image1.png)  
Histological examination showed absence of melanocytes and melanin in the epidermis.(H & E stain, X200)

![Fig. 4](image2.png)  
Fontana-Masson stain was negative.(Fontana-Masson stain, X200)
Evans syndrome with remissions and exacerbations of thrombocytopenia or anemia or both. Repigmentation of vitiligo universalis and leukotrichia were never noted during the three-year follow-up period.

**DISCUSSION**

The incidence of vitiligo is increased in patients with a variety of abnormal immune states that are characterized by organ-specific antibodies or dysfunction of the immune system, eg, thyroid diseases, pernicious anemia, diabetes, adrenal insufficiency, and myasthenia gravis.\(^3, 4, 9-11\) The association between ITP and AIHA was first reported by Evans et al. in 1949.\(^12\) Since then, the clinical entity has been generally referred to as Evans syndrome. A number of defects in humoral immunity including different antibodies against platelets and RBCs have been described.\(^13\) In the series of Ng et al., the mean age at presentation was 24.8 years (range, 11-34 years) with a marked female preponderance.\(^14\) Most patients require corticosteroid therapies but other therapies including intravenous gamma globulin, danazol, cyclophosphamide, vinca alkaloids, azathioprine, plasmapheresis or splenectomy may be necessary for refractory or recurrent cases.\(^12, 14-15\)

In our case, all these treatments were ever administered.

APS is characterized by arterial/venous thrombosis, recurrent pregnancy loss, or thrombocytopenia in the presence of aPL.\(^16\) These antibodies are identified as lupus anticoagulant, which prolongs phospholipid-dependent coagulation test, or as aCL detected by immunoassays. This entity, first described by Hughes in 1983 in patients with systemic lupus erythematosus (SLE),\(^17\) may appear in patients with no underlying disease - the "primary" PS.\(^18\) There are well-documented associations between these antibodies and abnormalities of specific cellular components of the blood, such as thrombocytopenia, hemolytic anemia, and less commonly, leukopenia.\(^19\) The optimal treatment of patients with APS has not been defined. Depending on the clinical symptoms, patients with APS may need no treatment, or may need anticoagulant or immunosuppressive therapy. Patients with significant thrombotic events (such as deep vein thrombosis, arterial ischemia, or fetal loss) are appropriate candidates for antithrombotic therapy.

The association of vitiligo, Evans syndrome and APS has never been reported before. Only four cases of patients with vitiligo associated with Evans syndrome had been reported.\(^5, 8\) The clinical and autoimmune findings of the 4 cases and our case are summarized in Table I. The previously reported four patients mostly had progressively generalized vitiligo. In our patient, a woman with vitiligo associated with Evans syndrome and APS, the skin involved by vitiligo was universal, much more extensive than the findings of previously reported cases with vitiligo associated with Evans syndrome. Though leukotrichia in vitiliginous areas is not uncommon, the universal leukotrichia in our patient is unique, suggesting the universal destruction of melanocyte precursor cells in the hair follicle. Our case is also featured by the rapidly progressing course of universal vitiligo that resulted in universal depigmentation and leukotrichia within one month.

Walters et al. first described a case of an adolescent with vitiligo and Evans syndrome in 1978.\(^6\) According to Walters' original descriptions, after being treated with the combination of oral psoralens and exposure to ultraviolet light, the patient went into an acute hemolytic crisis and died. Until more information is available, patients with vitiligo and thrombocytopenia should be treated with caution.\(^6\) No treatment specifically aimed at repigmentation was performed in our patient.

The pathogenesis of vitiligo remains obscure but still centers around a mechanism for the destruction of melanocytes. The present report as well as the well-documented association of vitiligo, Evans syndrome or APS with other immunologic diseases have suggested an immunologic basis for vitiligo. The immune hypothesis suggests an aberration of immune surveillance that is destructive to melanocytes.
Muwakkit et al. suggested that both vitiligo and Evans syndrome may be associated with the presence of serum antithyroid antibodies. Given the consequences of hypothyroidism in a developing child, children who have Evans syndrome or vitiligo should be tested for thyroid function and for autoimmune antibodies including antithyroid antibodies. Abnormalities of both humoral and cell-mediated immunity have been described in vitiligo, Evans syndrome and APS. Eighty percent of patients with generalized vitiligo were found to have circulating antibodies to cell surface antigens on normal human melanocytes; these antibodies were cytotoxic to normal melanocytes and to melanoma cells in tissue culture. The concurrent appearance of antibodies targeting melanocytes, RBCs, and platelet antigens might be the mechanism of vitiligo associated with Evans syndrome and APS.

In summary, we present a case of vitiligo universalis associated with Evans syndrome and APS to emphasize the speciality of multiple autoimmunity. In patients with rapidly progressing vitiligo universalis, a survey of possible underlying autoimmune disorders is suggested. Further studies to elucidate the mechanisms of this multiple autoimmune syndrome would give us more insights about the pathophysiology of vitiligo.

REFERENCES


