

*Case report*

**Isoniazid-triggered pure red cell aplasia in systemic lupus erythematosus complicated with myasthenia gravis.**

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***Running title: INH-triggered PRCA in SLE with MG***

## **Abstract**

A 47-year-old woman who had been treated for systemic lupus erythematosus (SLE) with myasthenia gravis (MG), was admitted to our hospital with acute onset of severe anemia after administration of isoniazid. Pure red cell aplasia (PRCA) was confirmed by elevated serum iron levels, reticulocytopenia and bone marrow aspiration showing a remarkable reduction of erythroblasts. Finally, cyclosporine A successfully improved PRCA. Although both SLE and MG have the potential complication of PRCA, we report here a case of isoniazid-triggered PRCA.

**Key words:** Pure red cell aplasia, isoniazid, systemic lupus erythematosus, myasthenia gravis, cyclosporine A

## **Introduction**

Pure red cell aplasia (PRCA) is an uncommon hematological disorder (1). Severe anemia in PRCA is associated with a marked reduction of reticulocytes and an absence of erythroblast in bone marrow (1). Although primary PRCA is a chronic hematological disorder, secondary PRCA can be caused by viral infections, autoimmune disorders or drugs (2). Autoimmune disorders such as systemic lupus erythematosus (SLE) and myasthenia gravis (MG) complicated with thymoma are occasionally reported to be predisposed to PRCA (3). A possible cause is drug-induced PRCA which is reported in up to 5% of cases. Here, we report a rare case of isoniazid-triggered PRCA in a patient with SLE and MG.

## **Case report**

A 47-year-old woman had been diagnosed with SLE and was treated with 20 mg of oral prednisolone in 1995. Although she was taking 2 mg of oral prednisolone daily, she developed ocular type MG with right blepharoptosis that showed a positive tensilon test and positive acetylcholine receptor binding antibodies, without thymoma. Because she experienced diplopia, she began taking 180 mg of pyridostigmine bromide, 10 mg of oral prednisolone and 200 mg of mizoribine in

2001. As of 2006, she was taking 3 mg of tacrolimus and 11 mg of oral prednisolone daily. Because her mother died of pulmonary tuberculosis, she began taking prophylactic isoniazid on September 26<sup>th</sup>, 2008. On October 4<sup>th</sup>, she became extremely fatigued and had heart palpitations while walking the dog. Upon admission to the hospital, she became fatigued with a low grade fever and breathlessness with exertion.

Her hemoglobin level was significantly reduced from 10.8 g/dl on September 3<sup>rd</sup> to 5.8 g/dl on October 24<sup>th</sup> (**Fig. 1**) with remarkable reduction of reticulocytes (1,000/ $\mu$ l; normal: 25,000-75,000/ $\mu$ l), normal leukocyte and platelet counts. An increase in serum iron (225  $\mu$ g/dl; normal: 48-154  $\mu$ g/dl) with a decrease in unsaturated iron binding (13  $\mu$ g/dl; normal: 108-325  $\mu$ g/dl) was found along with normal haptoglobin levels (70.3 mg/dl). Serum folic acid and vitamin B12 levels were within normal limits. IgM and IgG antibodies specific for parvovirus B19 and hepatitis B antigen were negative. Furthermore, both parvovirus B19 and Epstein-Barr virus deoxyribonucleic acid was not detected by polymerase chain reaction. Serum IgG and anti-double-stranded deoxyribonucleic acid antibodies were elevated to 2030 mg/dl (normal: 870-1700 mg/dl) and 88.4 U/ml (normal <12 U/ml) with reduced complement 3 (59.8

mg/dl; normal: 65-135 mg/dl) and normal C-reactive protein (0.04 mg/dl; normal<0.17 mg/dl). Chest computed tomography in September 2008 showed neither thymoma nor swelling of the lymph nodes.

Because acute progression of anemia was observed immediately after taking isoniazid, its administration was ceased on October 24<sup>th</sup>. To conduct the hematological differential diagnosis, bone marrow aspiration was performed on October 29<sup>th</sup>, resulting in the diagnosis of PRCA according to Casadevall criteria (4) accompanied by a decrease in erythroblast. In addition, no malignant cells were observed with normal myeloid cells and megakaryocytes. Although nine cycles of red blood cell transfusion were performed, administration of daily cyclosporine A (CyA) was required due to the protracted recovery of PRCA. When a trough level of 157.3 ng/ml was reached using 300 mg of CyA, the hemoglobin and reticulocyte counts were gradually improved without blood transfusion (**Fig. 1**). On February 20<sup>th</sup>, 2009, reticulocyte counts reached 147,000 with a concomitant improvement of serum iron levels to 130 µg/dl and hemoglobin levels to 8.3 g/dl.

## Discussion

Liver dysfunction and peripheral neuropathy are known to be common adverse side effects of isoniazid, however, isoniazid-induced PRCA has been rarely reported. Some reports (5, 6) showed isoniazid-induced PRCA which was rapidly improved by withdrawal of the drug. Erslev et al. (7) previously reviewed the pathologic condition of PRCA, in which they listed 26 drugs as causative agents including isoniazid for PRCA. Although the detailed mechanism of drug-induced PRCA remains unclear, diphenylhydantoin, an anti-epileptic agent, was shown to be a possible inducer of PRCA through a specific antibody toward the agent (8). Thus, a similar mechanism of antibody-dependent cytotoxicity might account for isoniazid-related PRCA.

Autoimmune diseases such as SLE or MG can be associated with the pathogenesis of PRCA. Mizobuchi et al. (9) reviewed 28 published cases of PRCA that were complicated with MG and thymoma. Although MG could be complicated with PRCA with or without a thymoma, a T cell-mediated immunological response is assumed in both cases. The association between PRCA and SLE is relatively rare. Habib et al. (10) reported that most of the cases of PRCA were diagnosed after, or concomitantly with, the diagnosis of SLE.

However, the characteristics of SLE were reported to be similar despite the diagnosis of PRCA. As to the mechanism of PRCA in SLE, a T cell-mediated immune response is a possibility in both SLE and MG. In support of this idea, Arcasoy et al. (11) conducted hematopoietic progenitor cell assays in which the defect of burst-forming unit-erythroid colony formation was restored by T cell depletion.

Preferential utilization of CyA for treatment of PRCA has been established due to its effectiveness. A nationwide cohort study of CyA treatment for acquired PRCA was done in Japan (12). The results showed a sustained, relapse-free survival in CyA-containing regimens compared to treatment with corticosteroid alone. CyA has the potential to inhibit T cell activation through inhibition of nuclear translocation of the nuclear factor of activated T cells (NF-AT). Thus, in our case, T-cell mediated cytotoxicity of the underlying autoimmune mechanism might be an appropriate indication.

In summary, the present case of PRCA is thought to be triggered by isoniazid due to its clinical course. Considering the prolonged recovery period after administration of isoniazid, we insist that existence of both MG and SLE protracted the course of PRCA based on a T cell-mediated mechanism in our case.

Therefore, isoniazid would be merely an inducer of T cell-mediated cytotoxicity. Additional studies of drug-related PRCA under the presence of autoimmune diseases are required to elucidate the mechanism of action in isoniazid-induced PRCA.

**Abbreviations;** CyA; cyclosporine A, SLE; systemic lupus erythematosus, MG; myasthenia gravis, PRCA; pure red cell aplasia

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**Figure legend**

**Figure 1 Clinical course of pure red cell aplasia (PRCA) of the patient with systemic lupus erythematosus (SLE) combined with myasthenia gravis (MG)**

The patient was pretreated with 11 mg of oral prednisolone and 3mg of tacrolimus for SLE and MG. Immediately thereafter she took 200 mg of isoniazid and severe anemia appeared with remarkable reduction of reticulocytes, which was confirmed as PRCA by bone marrow aspiration. Since discontinuation of isoniazid and repeated blood transfusions were not effective for recovery of anemia, cyclosporine A (CyA) was substituted for tacrolimus. After the trough level of CyA reached 157.3 ng/ml, the reticulocyte and hemoglobin levels were recovered without additional blood transfusions. PSL; prednisolone, MZR; mizoribine, TAC; tacrolimus, INH; isoniazid

