

Successful Treatment of Pure Red Cell Aplasia with Plasmapheresis in a Patient with Systemic Lupus Erythematosus

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Pure red cell aplasia (PRCA) is a rare cause of anemia associated with systemic lupus erythematosus (SLE), and fewer than 20 cases have been reported. The development of PRCA may be mediated by an autoimmune mechanism which is supported by the presence of antibodies that impair various stages and mechanisms of erythropoiesis, by the association with immunological disorders or lymphoma, and by a favorable response to immunosuppressive drugs, antilymphocyte globulin, thymectomy, and splenectomy. However, these therapies have not been successful in all patients with PRCA. We report our experience with a 31-year-old female patient with SLE who developed PRCA that did not respond to immunosuppressive therapies. However, complete normalization of erythropoiesis was achieved after the removal of the autoantibodies by plasmapheresis, and the patient has now maintained a normal hemoglobin level for more than eight months. We suggest that plasmapheresis might be tried in the treatment of PRCA cases before other more aggressive therapies are commenced.

Key Words: Plasmapheresis, pure red cell aplasia, systemic lupus erythematosus

INTRODUCTION

Pure red cell aplasia (PRCA) is an unusual disorder characterized by severe normochromic

normocytic anemia, reticulocytopenia and a markedly decreased number of erythroid progenitor cells, with otherwise normal bone marrow. It develops primary or secondary to infections, tumors, drugs, and autoimmune disorders, such as rheumatoid arthritis or systemic lupus erythematosus (SLE).¹⁻² There have been several reports of PRCA in SLE since 1968,³ and autoantibodies against erythropoietin or erythroid progenitors have been regarded as playing some role in the pathogenesis of PRCA in SLE.⁴⁻⁷ Several treatment methods have been applied to this disorder, including corticosteroids,⁶⁻⁹ immunosuppressive agents,^{7,10} erythropoietin,¹¹ high dose intravenous immunoglobulins,⁶ and plasmapheresis.¹² Especially, corticosteroids are the recommended initial mode of treatment for acquired PRCA. We describe a patient with SLE who developed PRCA that was refractory to immunosuppressive agents, but who was treated successfully with plasmapheresis. To our knowledge, four other cases of PRCA that were treated successfully with plasmapheresis have been reported,¹²⁻¹⁵ and we suggest that plasmapheresis may be attempted first in the treatment of SLE-associated PRCA.

CASE REPORT

A 31-year-old woman was referred to our department due to dizziness and fatigue experienced for three weeks. She had been diagnosed SLE five years earlier in accordance with the ACR criteria¹⁶: malar rash, arthritis, photosensitivity, thrombo-

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cytopenia ($85,000/\text{mm}^3$), and the detection of antinuclear antibody (1:320, speckled pattern) and anti-dsDNA antibodies. She had been treated with low dose prednisolone and hydroxychloroquine (300 mg/day) for five years. On admission she looked pale and moon-faced with faint pink maculopapular rash over the cheeks and she had cardiac systolic murmur. Laboratory results showed a white blood cell count of $6,000/\text{mm}^3$, hemoglobin of 5.5 g/dL, hematocrit of 15.8%, reticulocytes of 0.1%, and platelet count of $286,000/\text{mm}^3$. Serum electrolytes, liver and kidney functions were normal. Coagulation tests were normal, with a prothrombin time of 100% (INR 1.0) and an activated partial thromboplastin time of 38.0 seconds (normal: 29.8 - 41.8). Antinuclear antibody was 1:640 (speckled pattern), anti-dsDNA antibody was 112 IU/ml (normal: < 7), and both anti-Ro and anti-RNP tests were positive. Complement levels were low: C3 was 60.9 mg/dl (normal: 65 - 125) and C4 was 7.19 mg/dl (normal: 12-43). Tests for anticardiolipin antibody (IgG, IgM) and lupus anticoagulant were negative. Serologic tests for the HIV, cytomegalovirus, human B19 parvovirus, and Epstein-Barr virus were negative. Thoracic and abdominal computed tomographic scans revealed no evidence of thymoma, lymphoma or other solid tumors.

Work-ups for the evaluation of the patient's severe anemia were done. Peripheral blood smear revealed normocytic and normochromic anemia. Stool occult blood was negative and serum

haptoglobin level was 117 mg/dl. Iron binding capacity and the levels of serum iron, vitamin B12 and folate were all normal. Ham's test, sucrose lysis test, direct and indirect Coombs' tests were negative. The aspiration and biopsy specimens of bone marrow revealed normal cellularity with severe erythroid hypoplasia (myeloid: erythroid ratio, 45:1); findings compatible with red cell aplasia (Fig. 1). PRCA was diagnosed and the patient was initially treated with the transfusion of 6 units of packed red blood cells and prednisolone (1 mg/kg/day). There was no reticulocyte response after 3 weeks, and 6 units of packed red blood cells supplementation were required during this 3 week period. Then, she was treated with prednisolone (60 mg/day) and azathioprine (100 mg/day) for four weeks, but her Hb level decreased to 8.5g/dl and reticulocyte count remained 0.1%. Subsequently, plasmapheresis was performed 5 times (3 times on the first 3 days and twice more within a week) with a tapering of prednisolone dosage. A modest increase of reticulocyte count (1.3%) occurred after the fourth course of plasmapheresis, and a marked increase in reticulocyte count (3.5%) was observed along with normalization of Hb level (12.3 g/dl) after the fifth course. During eight months of follow-up, she was well maintained normal Hb (12.2 g/dl) and reticulocyte counts (2.5%) with treatment consisting of low dose prednisolone (5 mg/day) and hydroxychloroquine (400 mg/day) (Fig. 2).

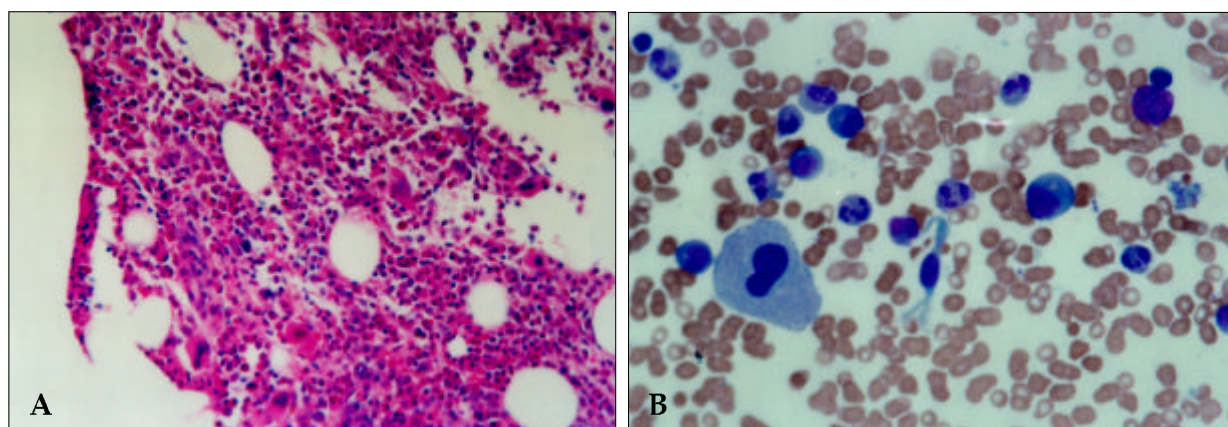


Fig. 1. Bone marrow biopsy specimen revealing that immature erythroid cells are apparently hypoplastic, but that the numbers of myeloid series and megakaryocytes are normal (A) (Hematoxylin-eosin stain, $\times 200$). Bone marrow aspiration specimen also showing scanty erythroblasts with normal myeloid cells and megakaryocytes (B) (Wright stain, $\times 400$).

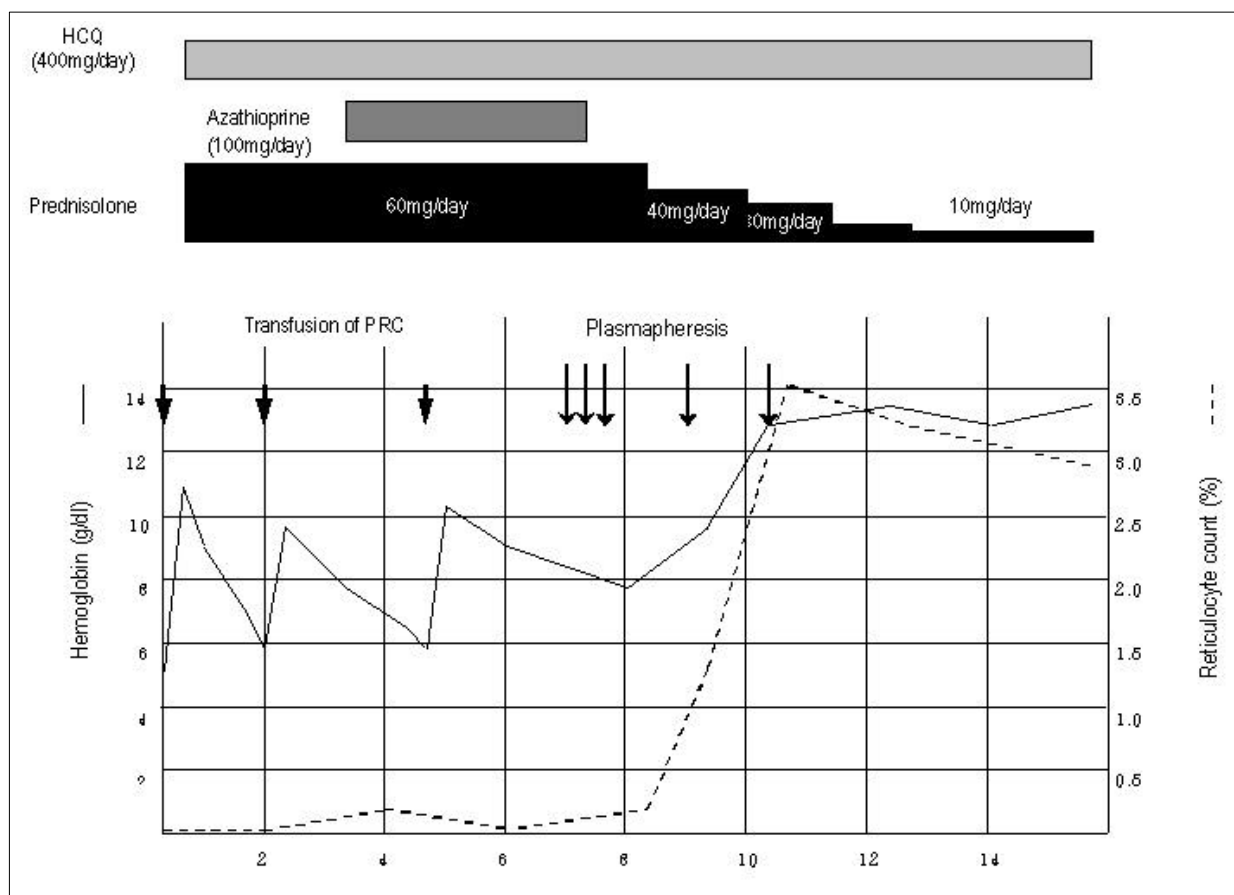


Fig. 2. Effects of therapy on hemoglobin and reticulocyte count. Treatment included transfusions of packed red cells (PRC), prednisolone, hydroxychloroquine (HCQ), azathioprine, and plasmapheresis.

DISCUSSION

SLE is an autoimmune disease that affects the connective tissue of the multisystem, and is characterized by extensive autoantibody production. Anemia is the most common hematologic abnormality seen in SLE and its causes are multiple: secondary to chronic disorder, hemolysis, hypersplenism, iron deficiency, gastrointestinal loss, renal disease and drug intake. PRCA is an unusual cause of anemia in SLE, reported in 18 patients to date.¹⁰ However, there has hitherto been no Korean report of PRCA in a SLE patient. The patient of the present study developed PRCA as a part of SLE. After the failure of high dose glucocorticoid and azathioprine therapy, she was treated with plasmapheresis and showed dramatic and persistent improvement.

PRCA is generally regarded as an autoimmune disorder and associated with autoantibody formation. Erythroid progenitors, erythroblasts, and erythropoietin are all potential targets of erythropoiesis inhibitors in PRCA. Several studies of this disorder have reported the presence of inhibitors of bone marrow erythroblasts, erythroid stem cell differentiation, and erythropoietin-responding cells, along with antibodies against erythropoietin.⁴⁻⁷ T cell mediated inhibition of erythropoiesis may also be involved in the pathogenesis of SLE-associated PRCA.⁶⁻⁷ According to the report of Kiely et al,⁷ culture of T cell-depleted marrow mononuclear cell from a patient with SLE-associated PRCA resulted in increased early erythroid colonies (BFU-E) and granulocyte-macrophage colonies (CFU-GM). The demonstration of an immune pathogenesis in PRCA provides a rationale

for its treatment with immunomodulation. Corticosteroids have been the recommended initial mode of treatment for PRCA, while in patients who are refractory to corticosteroid, cytotoxic drugs such as cyclophosphamide, azathioprine, cyclosporine, and splenectomy have been successfully used. Orbach et al.¹¹ reviewed 6 case reports of PRCA that were treated successfully with human recombinant erythropoietin. Rarely, intravenous immunoglobulin¹⁷ and plasmapheresis¹²⁻¹⁵ have been used as a therapeutic modality for PRCA.

Despite the wide spectrum of diseases currently treated with plasmapheresis such as Guillain-Barre's syndrome, thrombotic thrombocytopenic purpura, myasthenia gravis, Goodpasture's syndrome and other autoimmune diseases, the clinical effectiveness of this treatment has been established only in a few clinical conditions. Considering the pathogenic role of the multiple autoantibodies detected in SLE, their removal by plasmapheresis may result in complete remission of erythropoiesis. To our knowledge, four other cases of PRCA successfully treated with plasmapheresis have been reported previously.¹²⁻¹⁵ In this group complete remission was achieved in three cases and partial response in one case. The plasma of these four patients contained inhibitors against the differentiation of BFU-E or CFU-E. As in the case reported by Khelif A et al.¹⁵ a certain serum inhibitor present in our patient could have reacted against early RBC progenitors, in view of the time of response to plasmapheresis and the estimated maturation time from stem cells to reticulocytes of about 10 days.

However, the mechanisms of persistent remission after plasmapheresis have not been fully explained. Messner et al.¹² suggested that a factor in the plasma substitute may provide or induce the release of erythropoietic stimulators with burst-promoting activity. Complete blockage of antibody production by plasmapheresis was noted during an anamnestic response to bovine albumin in rabbits,¹⁸ and this phenomenon was suggested as another mechanism for the observed persistent remission of PRCA by plasmapheresis. The natural course of this disease may be due to the prolonged effect of plasmapheresis. It is not known whether the characteristic clinical courses and

response to therapy indicate a homogenous subset of the disease, and further clinical and laboratory studies are required.

In summary, SLE-associated PRCA is a rare disorder whose optimal management has remained uncertain. The value of combined treatment with steroids and cytotoxic drugs has been demonstrated by a higher remission rate, but such vigorous immunosuppressive treatment carries increased risks of serious infection, malignancy, sterility and other side effects. In addition, some patients have failed to respond to this modality. Therefore, we suggest that an individualized approach for the management of SLE-associated PRCA is required, and furthermore, that plasmapheresis might be tried in the treatment of autoimmune red cell aplasia before more aggressive therapy is commenced.

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