

Pure red cell aplasia associated with Systemic Lupus Erythematosus

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ABSTRACT

Pure red cell aplasia is a rare condition described in patients with autoimmune diseases such as systemic lupus erythematosus. Bone marrow examination of a 52-year-old female showed selective severe hypoplasia, scarce hematopoietic reserves, and no abnormality in other cell lineages, which are findings compatible with red cell aplasia. This condition has not responded to corticosteroids, cytotoxic drugs or intravenous immunoglobulin. After therapy with high doses of glucocorticoids, cyclophosphamide, and immunoglobulin failed, she was treated with human recombinant erythropoietin, monthly pulses of methylprednisolone, and cyclophosphamide, simultaneously. Data on treatment with erythropoietin for pure red cell aplasia associated with systemic lupus erythematosus is limited, but it appears to be reasonable to try in refractory cases.

Keywords: Aplasia; Treatment; Systemic Lupus Erythematosus; Pure red cell aplasia.

INTRODUCTION

Pure red cell anemia (PRCA) is a generally chronic condition characterized by severe normocytic anemia, reticulocytopenia, and an absence of erythroblasts from an otherwise normal bone marrow¹. It's a rare hematological disorder². PRCA may appear as a congenital disorder or occur as an acquired syndrome. The acquired form of PRCA may present as a primary hematologic disorder in the absence of other diseases, or secondary to various underlying diseases including parvovirus B19 infection, large granular lymphocyte leukemia, other lymphoproliferative disorders, thymoma, autoimmu-

ne disease, certain drugs, and allogeneic hematopoietic stem cell transplantation²⁻⁴. It can arise as a complication of autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE)^{5,6,7}.

We report a case of a patient with SLE-associated PRCA that failed to respond to corticosteroids, cyclophosphamide, and intravenous immunoglobulin and was subsequently treated successfully with combination therapy: pulses of methylprednisolone, cyclophosphamide, and human recombinant erythropoietin (rhEPO), simultaneously.

CASE REPORT

A 52-year-old female had a 20-year history of SLE (established according to the criteria ACR). She was evaluated for malaise, seizures, and acute anemia accompanied by a rapid deterioration in the general condition. At that moment, laboratory exams revealed hemoglobin 4.5 g/L; hematocrit 16%; white blood cell count 6.160/mm³, lymphocytes 2.033 mm³, platelets 307.000 mm³ and ESR 67 mm. First, she had received three pulses of intravenous methylprednisolone and one pulse of cyclophosphamide 1g, but she had required blood transfusions. Initially, it was believed to be autoimmune hemolytic anemia. However, laboratory test revealed negative direct and indirect Coombs test, normal direct and indirect total bilirubin, and reticulocyte count was 1% (normal). Her complement C3 47 mg/dL, C4 11.5 mg/dL was low and CH50 93 mg/dL normal, urinalysis normal, anticardiolipin IgG, IgM, lupus anticoagulant negative, double-stranded DNA positive, complete blood count with severe anemia (normochromic and normocytic anemia), leukocytes and platelets within the normal range, serologic tests for parvovirus B 19, HIV, cytomegalovirus and Epstein-Barr virus were negative, iron binding capacity and the levels of serum iron were normal. The bone marrow aspiration and biopsy showed selective severe hypopla-

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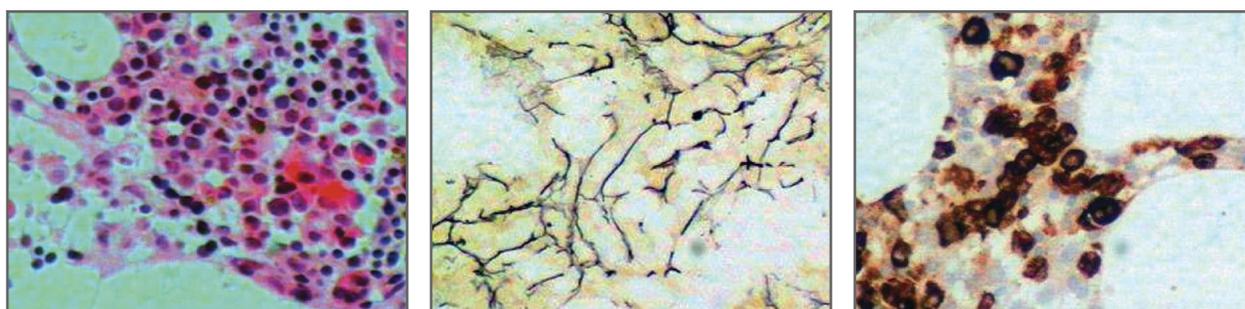


FIGURE 1. Marrow biopsy showed selective severe hypoplasia of the bone marrow, scarce hematopoietic reserves, and no abnormality in other cell lineages; findings compatible with red cell aplasia

sia of the bone marrow, scarce hematopoietic reserves, and no abnormality in other cell lineages, which are findings compatible with red cell aplasia (Figure 1). After clinical stabilization she was discharge for outpatient clinic, but was readmitted three other times due to uncontrolled anemia and fatigue, and was again treated with a single course of intravenous immunoglobulin (IVIG, 400 mg/kg given daily for five days), monthly pulses of methylprednisolone, and cyclophosphamide. However, she still presented with severe anemia (Hb: 4-5 g/dL), without reticulocyte production. During the follow-up, she received 16 units of packed red blood cell supplementation. After failure of therapy with high doses of glucocorticoids, cyclophosphamide, and immunoglobulin, she was treated with rhEPO 6000 IU/week (for recurrent anemia), monthly pulses of methylprednisolone, and cyclophosphamide, simultaneously. Approximately three

months later, we observed a gradual rise in hemoglobin levels that reached 12-13 g/dL. During two years of follow-up, she has been stable, maintained normal Hb 12.7 g/dL (Table I) and is currently using only hydroxychloroquine 400 mg/day.

DISCUSSION

PRCA, a disorder first characterized in 1922, is a syndrome characterized by severe normochromic, normocytic anemia associated with reticulocytopenia, and absence of erythroblasts from an otherwise normal bone marrow. PRCA may appear as a congenital disorder or occur as an acquired syndrome. It may present as a primary haematological disorder in the absence of any other disease, or secondary to parvovirus B19 infection, drugs, and autoimmune disorders, such

TABLE I. TREATMENT OF PURE RED CELL APLASIA

	HB	Pulse CS+CY	BT	Pulse CS+CY + IVIG	Pulse CS+CY+EPO	Pulse CY+EPO
T0	4.5 g/dL	-	-	-	-	-
T1	4.5 g/dL	Yes	Yes	-	-	-
T2	5.0 g/dL	-	Yes	Yes	-	-
T3	4.8 g/dL	-	Yes	Yes	-	-
T4	5.0 g/dL	-	Yes	Yes	-	-
T5	5.0 g/dL	-	Yes	-	Yes	-
T6	7.0 g/dL	-	No	-	Yes	-
T7	9.1 g/dL	-	No	-	-	Yes
T8	11.6 g/dL	-	No	-	-	Yes
T9	12.2 g/dL	-	No	-	-	Yes

BT: blood transfusion; CS: corticosteroids; CY: cyclophosphamide; EPO: human recombinant erythropoietin; HB: hemoglobin; IVIG: intravenous immunoglobulin. T0 at baseline, T1, 2, 3, 4, 5, 6, 7, 8 and 9 is equal to 1, 2, 3, 4, 5, 6, 7, 8 and 9 months after initial treatment.

as rheumatoid arthritis or systemic lupus erythematosus. Depending on the cause, the course can be acute and self-limiting or chronic with rare spontaneous remissions^{2,4,8}.

PRCA is rare cause of anemia associated with systemic lupus erythematosus with less than 28 cases reported, but is probably underdiagnosed^{6,8}. The onset of PRCA did not correlate with symptoms of SLE. In fact, patients with SLE diagnosed previously had clinically inactive disease. Thus, this autoimmune phenomenon occurs independently for unknown reasons. The mechanism for PRCA appears to be multifactorial and is not due to defects in stem cells, but rather to a suppressor effect in the immune system either through humoral or cellular mechanisms acting directly on stem cells or on erythropoietin. A significant proportion of SLE patients have positive anti-EPO antibodies in their serum, and the frequency of these antibodies is significantly higher in patients with severe anemia^{6,9,10}.

Corticosteroids, the initial treatment in PRCA and SLE, have proved efficacious in some cases. However, most patients treated with this medication alone relapse during tapering of therapy^{2,5,11}. The major objective in the treatment of PRCA is to induce a remission with the recovery of erythropoiesis, thus providing relief from transfusions and avoiding transfusion-associated problems. The therapeutic plan usually focuses on the sequential use of various immunosuppressive therapies until a remission is obtained. Remissions have been achieved by treatment with corticosteroids (30-62%), cyclophosphamide (7-20%), cyclosporine A (65-87%), anti-thymocyte globulin, splenectomy, and plasmapheresis. More recently, the efficacies of the anti-CD20 monoclonal antibody, rituximab, and anti-CD52 monoclonal antibody, alemtuzumab, to induce remissions of therapy-resistant PRCA have also been reported^{2,3}.

Although the cyclosporine response rates in the available literature for idiopathic PRCA are better than those following treatment with alkylating agents, we prefer to use cyclophosphamide because the cyclosporine was not at hand¹¹.

The efficacy of a combination of cyclophosphamide and corticosteroids for refractory patients has been reported to be between 40-60%². In this case, the patient did not respond to combined treatment with corticosteroid, cyclophosphamide, and intravenous immunoglobulin. Previous favorable results obtained with rhEPO encouraged us to treat this patient. To our knowledge, another case of PRCA was successfully treated with rhEPO therapy¹².

PCRA 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 erythropoietin⁸. In a recent study, anti-EPO antibodies were detected in SLE patients mainly with severe anemia and active disease. In addition, it has been reported that the frequency of anti-EPO antibodies in patients with SLE is about 15% and that in SLE patients with anemia is 21%^{6,9,10}.

The demonstration of an immune pathogenesis in PCRA provides a rationale for its treatment with immunosuppressants. As one of the possible mechanisms of the pathogenesis of SLE-associated PRCA occurs by the presence of autoantibodies against EPO, it was decided to try to associate immunosuppressive drugs (corticosteroids and cyclophosphamide) with rhEPO to try to control the disease. Immunosuppressive drugs try to minimize or neutralize autoantibodies disease, while the supplied rhEPO will compete with autoantibodies by binding the EPO receptor on immature erythroid cells. What would be better justified if the antibodies against EPO were measured, however there was no availability in service¹².

In summary, PRCA associated with SLE, which is unresponsive to conventional blood transfusion, high dose steroid, and cytotoxic drugs, may respond satisfactorily in combination with rhEPO therapy. Therefore, we suggest that an individualized approach for the management of SLE-associated PRCA is required. Furthermore, that rhEPO might be tried in association with immunosuppressive drugs for treatment of autoimmune red cell aplasia in refractory patients.

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