Primary Sjögren Syndrome Presenting with Hemolytic Anemia and Pure Red Cell Aplasia Following Delivery due to Coombs-negative Autoimmune Hemolytic Anemia and Hemophagocytosis

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Abstract

A 36-year-old woman presented with hemolytic anemia without a reticulocyte response 38 days after delivery. A marked reduction in erythroid cells and an increase in macrophages with active hemophagocytosis were noted in the bone marrow. While conventional Coombs’ tests were negative, the level of red blood cell (RBC)-bound immunoglobulin G (IgG) was increased. The patient was diagnosed with primary Sjögren syndrome (pSS) based on her symptoms, positive anti-SS-A antibodies, Coombs-negative autoimmune hemolytic anemia and pure red cell aplasia associated with RBC-bound IgG and hemophagocytosis. The unique presentation was considered to be a consequence of immunological derangement associated with pSS, pregnancy and delivery.

Key words: Sjögren syndrome, autoimmune hemolytic anemia, hemophagocytosis, pure red cell aplasia, pregnancy, delivery

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Introduction

While various hematological abnormalities have been reported to be associated with primary Sjögren syndrome (pSS) (1, 2), the frequencies and underlying mechanisms of these conditions remain unknown. Similarly, it has been suggested that a variety of changes in the immune system occur in a woman’s body during pregnancy and after delivery; however, the clinical significance of these changes remains unclear.

We herein report a case of pSS in a patient who presented with severe anemia due to hemolytic anemia and pure red cell aplasia (PRCA) caused by Coombs-negative autoimmune hemolytic anemia (AIHA) and hemophagocytosis following delivery. A disturbance in the immune system associated with pSS and additional immunological alterations in the course of pregnancy and delivery were considered to be contributory factors in the pathogenesis of this case.

Case Report

A 36-year-old woman visited our emergency room with the chief complaints of jaundice and fatigue. She had uneventfully delivered her first child in the 40th gestational week 38 days earlier. After the delivery, anemia was noted, and the patient took an oral iron supplement for two weeks. One week before the visit, she noticed yellow-colored skin and dark urine that became gradually prominent. The fatigue worsened to an unbearable level and drove her to our hospital, where she was admitted.

The patient had a history of bronchial asthma in her childhood. She had been suffering from dryness of the mouth and eyes since 32 years of age and had undergone blood testing for autoimmune diseases at 33 years of age, the findings of which were unremarkable. She had no

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known allergies and did not routinely use any drugs. Her father also had a history of bronchial asthma; however, there was no family history of either rheumatic disease or hemolytic anemia.

On admission, the patient’s skin was yellow-colored, and nail fold capillary changes were documented. The conjunctivae were anemic and icteric. A mild systolic ejection heart murmur was audible, and the spleen was palpable 2 cm below the left costal margin. The white blood cell (WBC) count was 3.2×10^9/L with 53.0% neutrophils, 35.0% lymphocytes and 12.0% monocytes. The red blood cell (RBC) count was 1.5×10^12/L, the hemoglobin level was 5.1 g/dL, the hematocrit level was 15.2%, the platelet count was 196×10^9/L and the reticulocyte level was 0.28%. A blood film revealed mild anisocytosis and occasional aggregates of RBCs. The morphology of the individual RBCs appeared to be normal. The blood chemistry tests showed that the total bilirubin level was 2.0 mg/dL, the indirect bilirubin level was 1.5 mg/dL and the lactate dehydrogenase level was 1,704 U/L. The serum ferritin level was 3,183 ng/dL, the soluble interleukin (IL)-2 receptor level was 742 U/mL (reference range: 124-466) and the haptoglobin level was below the limit of detection. Conventional direct and indirect Coombs’ tests were both negative, and serological tests for syphilis, hepatitis B virus, hepatitis C virus, adult T-cell leukemia virus, cytomegalovirus, Epstein-Barr virus and human parvovirus B19 demonstrated unremarkable findings. The serum immunoglobulin G (IgG) level was as high as 3,141 mg/dL. Antinuclear (speckled type) and anti-SS-A antibodies were positive. A quantitative assay of anti-RBC antibodies revealed that 144 IgG molecules were bound to one RBC, which is above the cutoff value for the diagnosis of Coombs-negative AIHA (3). Several cystic changes compatible with lymphoid interstitial pneumonia, a common pulmonary abnormality observed in patients with pSS, were found on chest computed tomography. Based on these characteristic clinical features and the positivity for anti-SS-A antibodies, the patient was diagnosed with pSS. A bone marrow aspiration analysis revealed normocellular bone marrow without abnormalities in megakaryocytes or the myeloid series (Fig. 1A). However, erythroblasts were drastically decreased and consisted of only 0.2% of all nucleated cells. In addition, macrophages were increased in number and actively engulfing mature RBCs and erythroblasts (Fig. 1B, C). However, there were no findings suggesting that cells of the other two lineages were phagocytosed by macrophages. No giant proerythroblasts suggestive of human parvovirus B19 infection were observed. These bone marrow findings were considered to be compatible with those of PRCA with hemophagocytosis. Based on these findings, a diagnosis of pSS with Coombs-negative AIHA and hemophagocytosis with bone marrow findings compatible with PRCA was made. Oral prednisolone therapy was initiated at a dose of 1 mg/kg/day with RBC transfusion support (Fig. 2). The patient’s symptoms improved within a few days, and the anemia recovered rapidly with a marked increase in the reticulocyte count. The spleen was no longer palpable four days after the start of prednisolone. The serum ferritin level also decreased rapidly to 1,123 ng/dL and 670 ng/dL five and 10 days after the start of prednisolone, respectively. The patient was discharged on the twelfth hospital day. She is presently asymptomatic without any signs of
recurrence of anemia after nine months on gradually tapered oral steroid therapy.

**Discussion**

pSS is an autoimmune disorder considered to be caused primarily by hyperreactive lymphocytes. The development of hematological abnormalities in patients with pSS as extraglandular manifestations is not infrequent (4, 5); however, while Coombs’ tests are often positive, active hemolysis is reported to be a rare occurrence (6-8).

It is known that the equilibrium of the human immune system is often disturbed during the course of pregnancy and delivery, since the woman is exposed to a foreign body for a considerably long period. A variety of alterations in the immune system occur during pregnancy. Anti-RBC antibodies are reported to be produced in 0.1% of all pregnancies (9), and the concentrations of various cytokines, such as interferon-γ and IL-4, are elevated during pregnancy (10). In fact, cases of AIHA and hemophagocytic lymphohistiocytosis (HLH) developing during pregnancy have been reported (11, 12). The complex presentation of the present case was therefore considered to be a consequence of hyperactive immune responses, namely the overproduction of self-reactive antibodies and cytokines with the characteristic background of pSS and possibly influenced by pregnancy and delivery, as previously reported (13).

Another distinct feature was that the patient’s bone marrow exhibited the characteristic findings of PRCA with selective phagocytosis of erythroid cells by macrophages. This interesting feature is conspicuously different from that seen in typical HLH in which hematopoietic cells of multiple lineages are phagocytosed by macrophages activated by an endogenous cytokine storm. In general, the presence of cytopenia in at least two lineages is necessary for a diagnosis of HLH (14). Although we do not precisely know the mechanisms underlying the selective hemophagocytosis observed in the present case, we speculate that increased anti-RBC IgG molecules on RBCs may be involved. On the other hand, it has long been recognized that AIHA is sometimes accompanied by aplasia of erythroblasts in the bone marrow (15-17). Some reports have suggested that antierthropoietin antibodies exert suppressive effects on erythroblasts in the bone marrow (18), while others have reported that anti-RBC antibodies affect the differentiation and proliferation of erythroblasts (19, 20). It is assumed that, in our case, anti-RBC antibodies similarly affected erythroblasts and that phagocytosis of erythroblasts with increased IgG molecules on the cell surface, which may have facilitated phagocytosis in a similar manner to opsonization, contributed to the suppression of erythroblasts, thus leading to the bone marrow findings compatible with PRCA, although verification of this hypothesis is required.

To our knowledge, this is the first report of pSS complicated by Coombs-negative AIHA, hemophagocytosis and PRCA that developed following pregnancy and delivery. A disturbance in the immune system due to pSS and further alterations associated with pregnancy and delivery were considered to be responsible for the unique presentation of the current patient. This case also emphasizes the importance of conducting thorough immunological studies, including quantitative assays of RBC-bound IgG and bone marrow examinations, in patients with pSS who present with severe anemia.

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

**References**

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