Pure Red Cell Aplasia After ABO Major-mismatched Allogeneic Peripheral Blood Stem Cell Transplantation Successfully Treated with Plasma Exchange and Low-dose Steroid: Two Case Reports

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Pure red cell aplasia (PRCA) is a complication of ABO-incompatible allogeneic stem cell transplantation. The mechanism is not well known, although the isoagglutinin titer before transplantation or cyclosporine use is considered to be the cause. Patients with this complication require more blood transfusions than those without it. There is no standard treatment. We report two cases of PRCA after allogeneic peripheral blood stem cell transplantation that were successfully treated with plasma exchange and low-dose steroid.

Key Words: pure red cell aplasia (PRCA), ABO major-mismatched allogeneic PBSCT, peripheral blood stem cell transplantation, plasma exchange, low-dose steroid
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Allogeneic bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) from human leukocyte antigen (HLA)-identical related or unrelated donors are used to treat various hematologic diseases. There is ABO incompatibility between donor and recipient in about 20% of HLA-identical BMTs or PBSCTs [1]. Blood group incompatibility does not appear to determine the outcome of BMT or PBSCT, including engraftment of white blood cells (WBCs) and platelets, incidence of graft rejection and graft-versus-host disease (GVHD), and survival [2–4]. Pure red cell aplasia (PRCA) is observed in a minority of ABO major-mismatched BMT or PBSCT recipients [1,4,5]. Various treatment strategies have been used, including cyclosporine discontinuation [4,5], steroid [6], erythropoietin [7,8], antithymocyte globulin [9], donor leukocyte infusion (DLI) [10], anti CD-20 monoclonal antibody [11], plasma exchange [1,4,12], and a combination of any of these. Spontaneous recovery has also been reported [4,13]. However, there is no definitive standard management. We report two cases of PRCA that developed after ABO major-mismatched PBSCT from HLA-identical related donors. Both cases were successfully treated with plasma exchange and low-dose steroid.

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Case Presentations

Case 1

This 20-year-old male with severe aplastic anemia presented in December 2000 with a WBC count of 2,860/μL, a hemoglobin of 5.6 g/dL, and a platelet count of 16,000/μL. He received HLA-identical, ABO major-mismatched (donor: AB, recipient: O) PBSCT from his younger sister in March

2001, with a conditioning regimen of total body irradiation (TBI; 300 cGy) and cyclophosphamide (50 mg/m^2) for 4 days. Prophylaxis for GVHD was provided by intravenous cyclosporine and a short course of methotrexate.

Engraftment of WBCs and platelets was observed on day 14. Stage I GVHD in skin was noted but no treatment was required. Anemia with low reticulocyte counts persisted after transplantation without evidence of hemolysis. Complete donor chimerism was noted on day 26. Bone marrow study on days 14 and 26 showed the absence of erythroid cells. The patient received a blood transfusion of 2 units about every 2 weeks. Isoagglutinin titers were high before transplantation (anti-A/anti-B: 128/128), had transiently declined by day 15 (anti-A/anti-B: 16/8), and were elevated again on day 27 (anti-A/anti-B: 128/64).

Plasma exchange with 18 units (one plasma volume) AB type was performed four times every 2 days from day 27, but anemia and reticulocytopenia persisted even though a low anti-A/anti-B titer (16/2) was achieved by day 170. Blood transfusions were still needed during this period. Plasma exchange was repeated five times every 2 days from day 170, but anemia persisted without transfusion. Cyclosporine was given orally from day 22 (150 mg bid reduced to 125 mg bid, 100 mg bid, and 100 mg qd from days 68, 190, and 309, respectively). It was withheld completely after day 344. Prednisolone (30 mg/day) was prescribed from day 225 (45 days after the last course of plasma exchange).

Reticulocytosis (reticulocyte count > 1%) and elevation of the hemoglobin level were observed on day 268 (43 days after initiation of steroids), with no further blood transfusions required thereafter. Prednisolone was withheld for 8 days during the 43-day period because of fever. Prednisolone was reduced gradually from day 281 with no further drops in hemoglobin level. On day 317, bone marrow showed a normal picture with adequate erythropoiesis. The blood type had also transformed to AB (Figure 1).

Case 2

A 36-year-old male patient suffering from leukocytosis, Ph chromosome positivity, and splenomegaly was diagnosed with chronic myelogenous leukemia (CML) in the chronic phase in April 1999. He received one locus HLA-mismatch, ABO major-mismatched allogeneic PBSCT (donor: A, recipient: O) from his brother in May 2000, with a conditioning regimen of fractionated TBI (200 cGy twice a day for 3 days) and cyclophosphamide (60 mg/m^2 for 2 days). GVHD prophylaxis was provided by intravenous cyclosporine and a short course of methotrexate.

The absolute neutrophil count was more than 500/μL on day 9 and the platelet count was more than 20,000/μL on day 16. The chromosomal abnormality was converted to a normal karyotype (46,XY) using bone marrow aspiration on day 10. Chimerism had shifted to the donor type on day 33. He had persistent anemia and was dependent on blood transfusion, but there was no GVHD. On days 10 and 33, there was a deficit of red blood cell (RBC) precursor cells in the bone marrow compatible with PRCA. Coombs' test, cytomegalovirus polymerase chain reaction (PCR) test, and Parvo B19 PCR test were all negative.

Cyclosporine was given orally from day 26 (150 mg bid reduced to 100 mg bid, 75 mg bid, 50 mg bid, and 75 mg qd from days 61, 82, 103, and 227, respectively). It was withheld completely after day 315. During cyclosporine tapering, there was no evidence of reticulocytosis. Low-dose prednisolone (15 mg/day) was prescribed from day 234. The anti-A titer was 8 at that time. Anemia and reticulocytopenia persisted for 71 days after initiation of steroid therapy. Be-

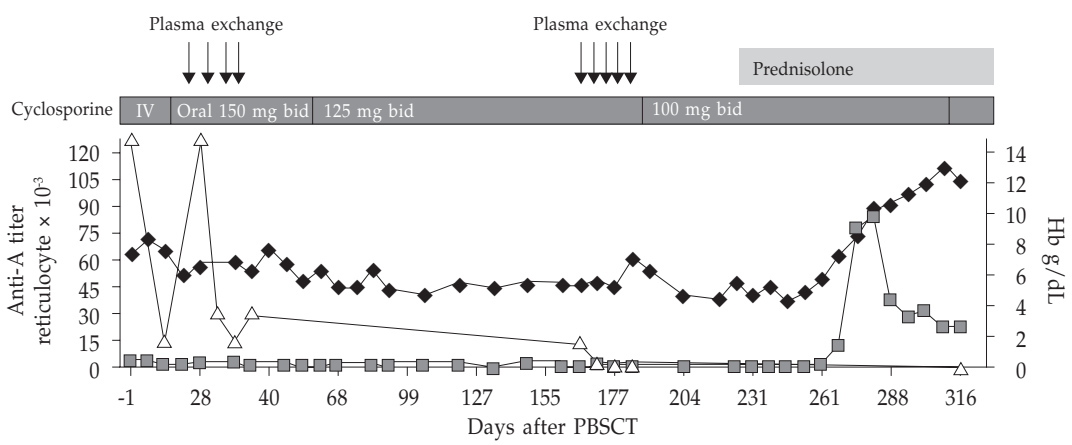

Figure 1. *Case 1: hemoglobin, reticulocyte count, and anti-A titer over time.*
reticulocyte
anti-A titer
Hb

cause there was no response to low-dose steroid, plasma exchange with 18 units (one plasma volume) of AB type was added four times every 2 days from day 305. Reticulocytosis was noted 18 days after the last plasma exchange. No further blood transfusions were needed after discontinuation of prednisolone. On day 809, bone marrow showed a normal picture with adequate red cell series and full chimerism (Figure 2).

Discussion

ABO major-mismatched transplant carries a risk of hemolysis at the time of stem cell transfusion or post transplantation [14], and delayed erythroid engraftment has also been reported. In general, isoagglutinins against RBC precursors are considered responsible for the occurrence of PRCA in patients receiving ABO-incompatible BMT or PBSCT [4,10,12,14]. The mechanism of PRCA after major ABO-incompatible hematopoietic stem cell transplantation is unclear, but the presence of recipient isoagglutinins against ABH antigen on donor red cells may play an important role.

Reticulocytopenia may persist for a long time even when there is a low isoagglutinin titer, with or without management, including vigorous plasma exchange or intravenous immunoglobulin [1,3,7,15]. In our two cases, low isoagglutinin titers after plasma exchange or steroid alone did not achieve effective erythropoiesis. Low isoagglutinin titer alone cannot explain the whole mechanism of erythropoiesis after ABO major-mismatched transplantation. How low an isoagglutinin titer is needed to achieve effective erythropoiesis? Is a mechanism other than isoagglutinin associated with red cell aplasia?

Cyclosporine was thought to be one cause of PRCA. However, although there is an increased incidence of PRCA in patients receiving cyclosporine as GVHD prophylaxis [4], erythropoiesis occurs after discontinuation of cyclosporine [5]. PRCA does not resolve after discontinuation of cyclosporine in all cases [10]. In Case 1, reticulocytosis occurred on day 268, when cyclosporine had been decreased to a steady dose of 100 mg bid for 78 days. Erythropoiesis seemed not to be correlated with cyclosporine tapering because cyclosporine was maintained at the same dosage. In Case 2, cyclosporine was tapered to 50 mg bid, half of the initial dose, from day 103. This continued for 104 days when the dose was decreased to 75 mg qd (on day 227) for 88 days. Cyclosporine was discontinued completely on day 315. Although it seemed that reticulocytosis occurred 14 days after discontinuation of cyclosporine, the 212 days of low-dose cyclosporine seemed too long a period to be the cause of erythropoiesis in this case.

Anti-A isoagglutinin is considered a risk factor for the increased incidence of PRCA [3]. Case 1 had anti-A and anti-B isoagglutinin against donor RBCs and Case 2 had anti-A isoagglutinin against donor RBCs. Some cases with anti-B isoagglutinin alone develop PRCA [1,6,12].

Many treatment options for PRCA after ABO major-mismatched transplantation have been reported. Pulsed and high-dose steroids have been successfully used to treat such cases. To prevent side effects caused by high doses, especially the potential opportunistic infections due to immunosuppression, we decided to use low-dose steroid. This was prescribed initially for Case 2, but no response was observed after 71 days. Plasma exchange was performed concomitantly with steroid administration. In Case 1, plasma exchange was performed initially and a low isoagglutinin titer was achieved, but effective erythropoiesis occurred

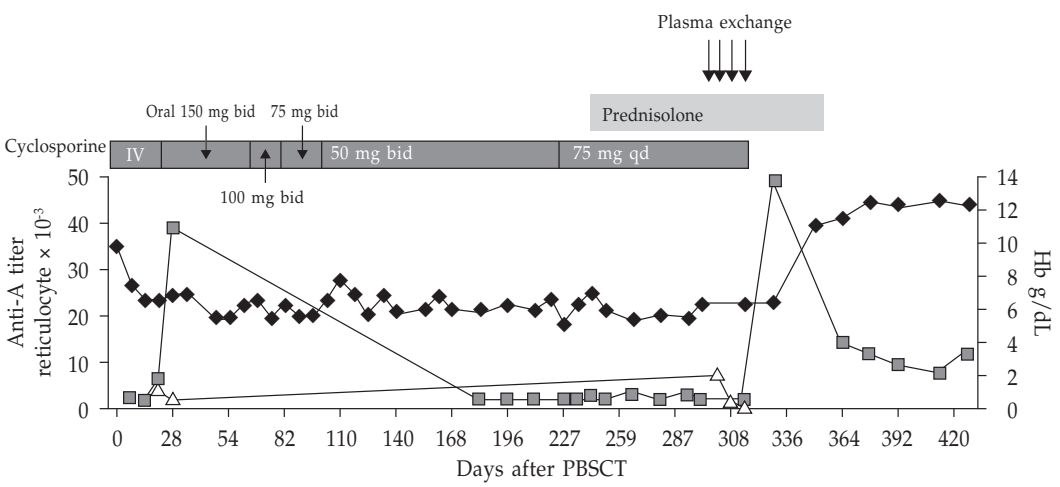

Figure 2. *Case 2: hemoglobin, reticulocyte count, and anti-A titer over time.*

only after low-dose steroid was initiated. Although many cases of PRCA have been successfully treated using plasma exchange alone, it seemed ineffective in our cases, in which combined low-dose steroid and plasma exchange were effective for PRCA after ABO major-mismatched allogeneic PBSCT. We suggest that plasma exchange plays a role in clearing isoagglutinin rapidly and steroid inhibits the production of isoagglutinin by plasma cells derived from residual memory B lymphocytes. However, when plasma exchange should be initiated and how frequently it should be performed, and the adequate dose of steroid to be used remain questions for further investigation. Indeed, delayed erythropoiesis occurred in spite of low isoagglutinin titers in our two cases. It seemed that there must be factors other than isoagglutinins contributing to the development of PRCA, and these need to be investigated.

In conclusion, from our limited two-case experience, PRCA after ABO major-mismatched transplantation can be successfully treated with low-dose steroid and plasma exchange.

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異體骨髓幹細胞移植後血型不合引發純紅血球減少症以血漿交換及低劑量類固醇治療成功之病例報告

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純紅血球減少症是異體骨髓幹細胞移植捐贈者及接受者紅血球血型不合的併症之一，抗紅血球凝集素或環孢黴素之使用被認為和此症有關，但其機轉仍不明確。此類病人比其他無此併發症的病人必須接受較多的輸血，針對此症目前並沒有標準治療方法，我們提出兩個異體骨髓幹細胞移植後發生純紅血球減少症的病例，以血漿交換，及低劑量類固醇治療成功之案例，並加以討論。

關鍵詞：純紅血球減少症（PRCA）；ABO 血型不合之異體骨髓幹細胞移植 PBSCT；外周血干細胞移植；血漿交換；低劑量類固醇

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