

[CASE REPORT]

Recovery of Pure Red Cell Aplasia Following Hematopoietic Stem Cell Transplantation Associated with Interleukin (IL)-6 Elevation Caused by Odontogenic Infection

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Abstract:

We herein report a case of long-lasting pure red cell aplasia (PRCA) after major ABO-incompatible allogeneic stem cell transplantation (SCT) for acute lymphoblastic leukemia. The patient needed red blood cell (RBC) transfusion every week after SCT. On day 236, he was diagnosed with odontogenic infection, and the serum levels of Interleukin (IL)-6 were elevated to 12.1 pg/mL. After that, the numbers of reticulocyte rapidly began to increase, and RBC support was not needed from day 251. No standard care for PRCA following SCT has been established. The IL-6 elevation caused by the odontogenic infection therefore appears to have been affected by the improvement in PRCA.

Key words: pure red cell aplasia, stem cell transplantation, IL-6, odontogenic infection

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Introduction

Pure red cell aplasia (PRCA) is characterized by anemia, reticulocytopenia, and hypoplasia of the erythroblasts in bone marrow. PRCA occurs in about 10-20% of patients following major ABO-incompatible hematopoietic stem cell transplantation (HSCT) (1). Several therapeutic methods have been reported including oral prednisolone, erythropoietin (EPO), donor lymphocyte infusion, tapering immunosuppression drugs, intravenous immunoglobulin, plasma exchange, high dose dexamethasone, rituximab and bortezomib (1-4). However, no standard care for PRCA following allogeneic HSCT has been established.

The risk of iron overload and infections is increased in patients with PRCA due to their requiring transfusion for a long time. A previous study reported that no treatments markedly aided in the recovery of PRCA after allogeneic HSCT from major ABO-incompatible donors (2). Therefore, we still need to clarify the pathophysiology of PRCA after HSCT.

We herein report the clinical course of a patient with pro-

longed PRCA of 244 days after human leukocyte antigen (HLA)-matched major ABO-incompatible HSCT. After the treatment of an odontogenic infection with antibiotics, the patient showed rapid improvement in PRCA.

Case Report

A 51-year-old man with acute lymphoblastic leukemia (ALL) underwent allogeneic peripheral blood stem cell transplantation (PBSCT) from his HLA-matched sibling donor. There was a major blood type mismatch, as the blood type of the recipient was O Rh-positive, while that of the donor was B Rh-positive. The patient had been in complete remission after induction chemotherapy and one cycle of consolidation chemotherapy. PBSCT was performed using cyclophosphamide (60 mg/kg for 2 days) and total-body irradiation (12 Gy) as conditioning therapy. Peripheral blood stem cells were mobilized with granulocyte-colony stimulating factor (G-CSF), and 1×10^6 /kg of CD34-positive cells was infused. Short-term methotrexate and cyclosporine (CsA) were used for graft-versus-host disease (GVHD) prophylaxis.

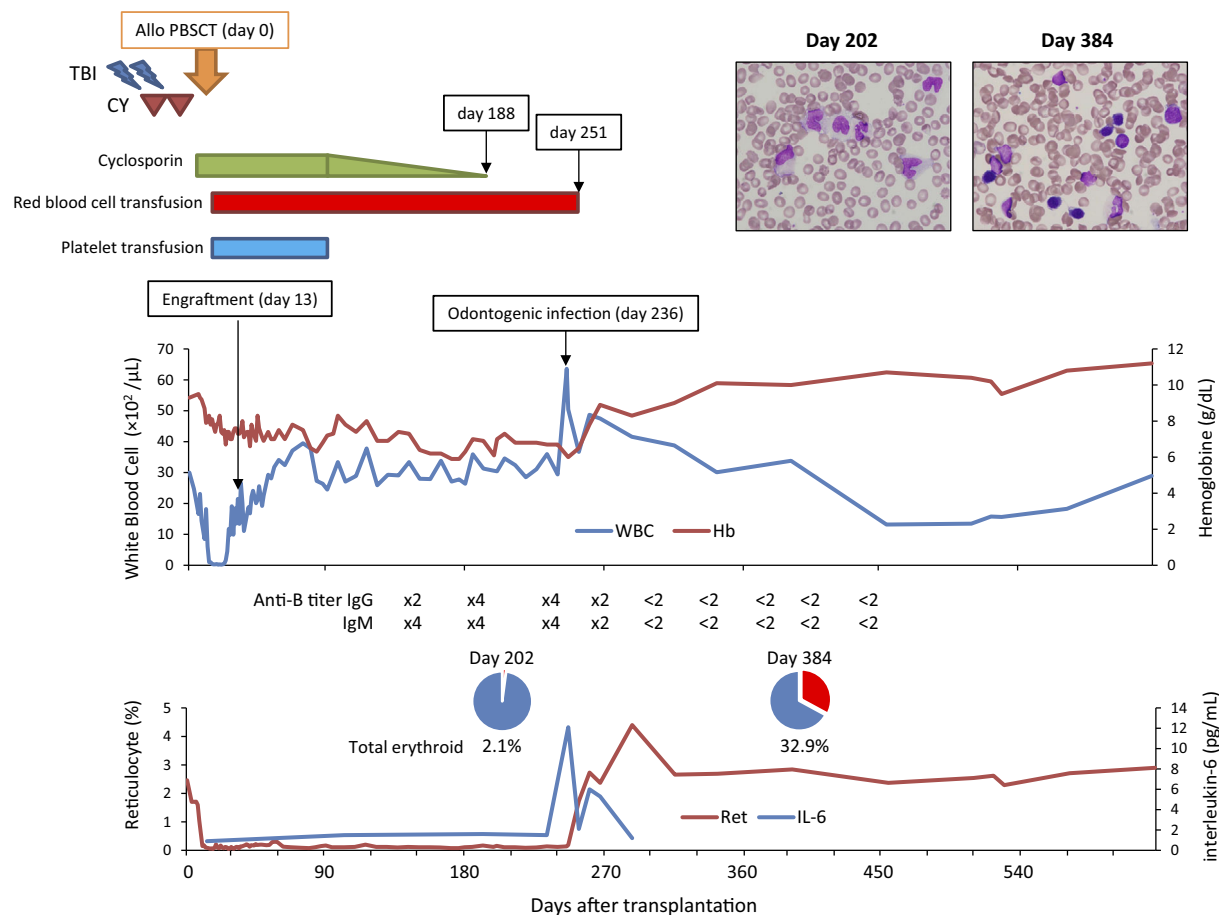


Figure. The clinical course and changes in the reticulocyte count. The proportion of erythroid and bone marrow images on day 202 and 384. Allo PBSCT was performed on day 0.

On day 13 after PBSCT, the number of absolute neutrophils exceeded $500/\mu\text{L}$. Skin acute GVHD grade 1 occurred on day 27 and naturally recovered without any treatment. A cytogenetic analysis of the bone marrow (BM) obtained on day 35 showed 46, XX, and the chimerism was 100% donor type. A BM examination also indicated almost the complete absence of erythroid cells (1%) with normal myeloid and megakaryocytic series. The patient's reticulocyte counts in peripheral blood remained below 0.05%. There were no signs of hemolysis, and a direct Coombs test was negative. The serum EPO on day 70 was 205 mIU/mL, which was within the normal range. Parvovirus B19 and antigenemia of cytomegalovirus were negative. These clinical data led to a diagnosis of PRCA after major ABO-incompatible HSCT. As there were no acute GVHD signs, we began to taper the dose of CsA from day 60 before stopping administration on day 188. However, he still needed to receive red blood cell (RBC) transfusion every 7 days. The titers of anti-B isohemagglutinin were 1:4 (IgM) and 1:4 (IgG) on day 180, and only 2.1% erythroid series was detected in the BM on day 202.

On day 236, he developed a fever and tooth pain, and the white blood cell (WBC) count was elevated to $6,360/\mu\text{L}$. He was diagnosed with an odontogenic infection and treated with antibiotics for 7 days. Although the serum levels of In-

terleukin (IL)-6 had not increased prior to this infection since HSCT, the levels rose to 12.1 pg/mL once the infection hit. After the WBC count recovered, the reticulocyte count rapidly increased to 1.73% on day 244, and the hemoglobin level remained above 10.0 g/dL without RBC transfusion from day 251 (Figure). BM aspiration on day 384 showed 32.9% erythroid series, and his blood type was detected as the donor type (B Rh-positive) after day 370. He continues to be transfusion-independent and disease-free.

Discussion

PRCA following ABO-incompatible allogeneic HSCT is thought to be caused by the remaining recipient plasma cells producing antibodies against the donor RBCs. While several therapeutic methods have been reported, their efficacy has been insufficient (1). PRCA after HSCT is defined as reticulocytopenia lasting more than 60 days after HSCT with a lack of erythroid precursors in the BM and RBC transfusion dependence. Under this definition, our patient was deemed to have PRCA, although the post-transplant anti-donor isohemagglutinin titers did not increase markedly. Lee et al. reported that 7 out of 12 patients whose isohemagglutinin titer against the donor RBCs increased developed PRCA, whereas only 3 out of 23 patients whose isohemagglutinin

did not increase developed PRCA (4). These data suggest that the titer of post-transplant anti-donor isohemagglutinin might be a predictor of PRCA development, although some cases still develop PRCA even with low isohemagglutinin titers (4).

In the present case, calcineurin inhibitor tapering was not effective for treating PRCA. Hirokawa et al. found in their retrospective cohort study of 46 patients that no available treatments of PRCA after allogeneic HSCT from major ABO-incompatible donors led to the recovery of erythropoiesis or ameliorated the need for RBC transfusion support (2). They also showed that the overall survival of PRCA patients who received treatments such as steroids, immune-suppressant, or rapid tapering of calcineurin inhibitors was inferior to that of the patients who did not receive any of these treatments (2). These findings suggest that not all cases of PRCA may be caused by antibodies against the donor RBCs.

The reticulocyte count in the present patient rapidly increased after odontogenic infection, thereby improving PRCA. We therefore measured the serum cytokine levels and found that the serum IL-6 concentration had increased to 12.1 pg/mL during the infection, which was 10 times higher than before the infection. Since half of patients with post-transplant PRCA show an erythropoietic recovery later than six months after HSCT (1), the detection of high serum IL-6 concentrations and the recovery of PRCA might have happened coincidentally. However, IL-6 stimulates an earlier stage of erythropoiesis. Sato et al. previously reported that human IL-6 and soluble IL-6 receptor stimulated the proliferation, differentiation and terminal maturation of erythroid cells from human CD34⁺ cells (5). Patchen et al. reported that the administration of IL-6 stimulated erythroid progenitor cell proliferation in normal mice (6). They also showed that IL-6 was able to accelerate multilineage hematopoietic recovery effectively in mice with radiation-induced hematopoietic injury. Furthermore, IL-6 induced both enhanced hematopoietic repopulation and an enhanced survival in BM-transplanted mice (7). Therefore, some changes in cytokines such as IL-6 under conditions of inflammation may

affect erythropoiesis after HSCT.

To our knowledge, this is the first report showing that elevated IL-6 levels caused by an odontogenic infection triggered the recovery of PRCA. PRCA following major ABO-incompatible allogeneic HSCT in patients whose anti-donor isohemagglutinin titers are not elevated might improve without intensive treatments. In cases of PRCA that improve without any treatments, inflammatory cytokines such as IL-6 secreted during an infection may have stimulated erythropoiesis.

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

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