Successful Allogeneic Stem Cell Transplantation for Severe Aplastic Anemia after Treatment of Lymphoproliferative Disorder Caused by Rabbit Antithymocyte Globulin

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Abstract

Immunosuppressive therapy (IST) with a combination of antithymocyte globulin (ATG) and cyclosporine (CsA) is an effective therapeutic modality for patients with aplastic anemia (AA) who are not eligible for allogeneic stem cell transplantation (Allo-SCT) from a human leukocyte antigen-identical sibling donor. However, there have been reports of some patients developing lymphoproliferative disorder (LPD) after IST for AA. We herein report a case of a 26-year-old man with severe AA (SAA) complicated by LPD after a single course of IST, who was successfully treated with Allo-SCT from an unrelated donor. Two months after starting IST for SAA, he developed LPD in the stomach. CsA was reduced, however, his neutrophil counts decreased, and CsA could not be discontinued. The patient was treated with rituximab monotherapy, and LPD resulted in complete remission. However, he failed IST for SAA and underwent Allo-SCT with reduced-intensity conditioning to recover his hematopoiesis. The patient has achieved complete hematopoietic recovery without the recurrence of LPD for five years after transplantation. This is the first report of successful Allo-SCT for SAA after the treatment of LPD caused by the use of rabbit ATG. This case provides useful information for the management of SAA with the development of LPD after IST.

Key words: severe aplastic anemia, lymphoproliferative disorder, allogeneic stem cell transplantation, antithymocyte globulin


Introduction

Aplastic anemia (AA) is a hematologic disease which is one of the bone marrow failure syndromes (1, 2). The standard specific treatment for a newly diagnosed patient with severe aplastic anemia (SAA) is either allogeneic stem cell transplantation (Allo-SCT) from a human leukocyte antigen (HLA)-identical sibling donor or immunosuppressive therapy (IST) with a combination of antithymocyte globulin (ATG) and cyclosporine (CsA) (3). While there have been reports of patients who developed lymphoproliferative disorder (LPD) after IST for SAA (4-7), to the best of our knowledge, no cases have been reported of patients who underwent Allo-SCT after developing LPD. We herein report the case of a patient with SAA complicated by LPD after a single course of IST who was successfully treated with unrelated bone marrow transplantation (BMT) with reduced-intensity conditioning.

Case Report

A 26-year-old man was diagnosed with acquired SAA in December 2009. Blood analyses showed decreased white
blood cell (WBC) counts of 2.2×10^9/L, neutrophil counts of 0.05×10^9/L, lymphocyte counts of 2.1×10^9/L, hemoglobin level of 12.8 g/dL, reticulocyte counts of 4.2×10^9/L, and platelet counts of 10×10^9/L. Both bone marrow aspiration and trephine biopsy showed severely hypocellular marrow, and cytogenetic analyses of the bone marrow cells were normal. Computed tomography (CT) of the whole body showed slight hepatosplenomegaly. The patient was seropositive for Epstein-Barr virus (EBV)-specific antibodies with a history of EBV infection. Because he did not have an HLA-identical sibling donor, he received IST with a combination of rabbit ATG (3.75 mg/kg for 5 days) and CsA (6 mg/kg orally). Prednisolone (1 mg/kg) was also used as a prophylaxis of ATG-induced allergy.

Two months after starting IST, the patient presented with epigastric discomfort, nausea, and gastrointestinal bleeding. Upper gastrointestinal endoscopy showed multiple ulcerated submucosal tumor-like lesions in the gastric corpus (Fig. 1a). A biopsy specimen of the tumor revealed the proliferation of polymorphic atypical lymphocytes (Fig. 2a, b). An immunohistochemical study demonstrated that these atypical cells were positive for CD20 (Fig. 2c) and EBV-encoded RNA (EBER) according to in situ hybridization (Fig. 2d). According to these findings, the patient was diagnosed with diffuse large B-cell lymphoma. [18F] fluorodeoxyglucose positron emission tomography (FDG-PET) revealed that the abnormal uptake of FDG was limited to the gastric tumor. A bone marrow biopsy revealed hypocellular marrow, and there was no invasion of atypical lymphocytes. The blood analyses showed WBC counts of 2.4×10^9/L, neutrophil counts of 2.1×10^9/L, lymphocyte counts of 0.14×10^9/L, hemoglobin level of 6.3 g/dL, reticulocyte counts of 6.7×10^9/L, and platelet counts of 10×10^9/L. The EBV viral load in the peripheral blood was slightly increased to 120 copies/mL (normal range: <100 copies/mL). The patient was subsequently diagnosed with other iatrogenic immunodeficiency-associated LPDs caused by the treatment of rabbit ATG. Although CsA was reduced after this diagnosis, his neutrophil counts decreased, and CsA could not be discontinued. Because of severe pancytopenia, he was treated with 8 courses of rituximab monotherapy. Upper gastrointestinal endoscopy after 4 courses of rituximab showed the disappearance of gastric tumors leaving scar tissues (Fig. 1b). The biopsy specimens of the scars revealed no evidence of atypical lymphocytes.

Seven months after starting IST, the patient’s LPD remained in complete remission. However, he still depended on regular transfusions and the administration of granulocyte colony-stimulating factor (G-CSF). Because IST resulted in no response to SAA, we performed BMT from an unrelated donor whose HLA was mismatched at the DR locus to recover the patient’s hematopoiesis. The reduced-intensity conditioning regimen comprised total body irradiation (TBI) 4 Gy, cyclophosphamide 60 mg/kg ×2 days, and fludarabine 30 mg/m^2 ×6 days was selected because of mild heart and liver dysfunction due to iron overload. The serum ferritin level was elevated to 1,750 ng/mL (normal range: <200 ng/mL) even though iron chelation therapy was administered. Prophylaxis against graft-versus-host disease (GVHD) consisted of tacrolimus and low-dose methotrexate. The hematological recovery was prompt. He developed heart failure with severe pericardial effusion due to cyclophosphamide on day 3 after transplantation. Both cardiovascular failure and tacrolimus toxicity caused renal failure and tacrolimus was discontinued on day 89. Although the heart failure eventually improved, the patient has had to depend on hemodialysis since day 191. He developed grade 1 acute GVHD that resolved spontaneously. He has not developed any chronic GVHD thus far. The patient has now achieved complete hematopoietic recovery without the recurrence of LPD for five years after transplantation.

**Discussion**

Immunodeficiency-associated LPDs are divided in the clinical setting into 4 categories: 1) LPDs associated with primary immune disorders, 2) lymphomas associated with HIV infection, 3) post-transplant LPDs (PTLDs), and 4)
Figure 2. A biopsy specimen of the gastric tumors. (a) Hematoxylin and Eosin staining, 100× magnification. (b) 400× magnification. The proliferation of polymorphic atypical lymphocytes was seen. (c) Immunohistochemical staining with CD20, 200× magnification. Atypical lymphocytes were diffusely positive for CD20. (d) In situ hybridization with EBER, 200× magnification showed that the cells were positive for EBER.

other iatrogenic immunodeficiency-associated LPDs (8). The most striking clinical characteristic is the high frequency of extranodal diseases (9), as observed in the present case. Although methotrexate and anti-tumor necrosis factor agent are well-known to induce other iatrogenic immunodeficiency-associated LPDs (9), only several cases of LPD induced by IST for SAA have been reported thus far (4-7). Such cases are very rare, however, subclinical EBV reactivation is observed in a majority of patients with SAA who receive IST (10). Once LPD occurs after IST for SAA, it becomes a life-threatening complication for the patients with SAA because IST reduction may worsen their hematopoiesis, and insufficient hematopoiesis may hamper chemotherapy. In the present case, IST could not be discontinued; therefore we added rituximab monotherapy which had a low hematologic toxicity compared to chemotherapy. LPD was controllable by rituximab monotherapy. However, the patient failed IST for SAA and had to undergo Allo-SCT to recover his hematopoiesis.

An optimal dose of rabbit ATG as a first-line therapy for AA has not yet been established (11, 12). A dose of 3.75 mg/kg/day for 5 days is routine in Europe (3), whereas a dose of 2.5 mg/kg/day or 3.75 mg/kg/day for 5 days is recommended by the Pharmaceutical and Medical Devices Agency of Japan (12). The dose of rabbit ATG and the response rate varied according to each study conducted in several countries (13-16). The study in Europe, which used a higher dose of rabbit ATG (3.75 mg/kg/day for 5 days), showed an inferior survival due to infectious complications compared to the study in Korea, which used a lower dose (2.5 mg/kg/day for 5 days). A lower dose of rabbit ATG may therefore be better to prevent developing LPD in addition to infectious complications. However, a randomized prospective study which compares the rabbit ATG doses of 2.5 and 3.75 mg/kg/day is needed to establish the optimal dose of rabbit ATG.

The incidence of PTLD after Allo-SCT has been reported to range between 0.5 and 17% according to single-center experiences or retrospective studies (17). According to a large multi-institutional cohort (18), the risk factors for PTLD were identified to be T-cell depletion of the donor marrow, ATG use, unrelated or HLA-mismatched grafts, age at transplantation of 50 years or older, development of acute and chronic GVHD, and second Allo-SCT. In the present case, we avoided the use of ATG in the conditioning regimen, which was identified as a risk factor for PTLD, and chose low-dose TBI as a substitute in order to minimize the risk of PTLD in the patient who previously developed LPD.

To the best of our knowledge, this is the first report of successful Allo-SCT for SAA after the treatment of LPD.
caused by rabbit ATG. When LPD occurs after IST in patients with SAA, physicians often have trouble in deciding whether they should perform Allo-SCT to recover patients’ hematopoiesis due to the high risk of recurrence of LPD or possible development of another PTLD after transplantation. Our experience with this case provides useful information for the management of SAA with the development of LPD after IST.

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

References


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