

CHINESE MEDICAL SCIENCES JOURNAL

CASE REPORT

Three Times Spontaneous Remission of Severe Aplastic Anemia Following Granulocyte Transfusion from Related Donors: a Case Report and Literature Review[△]

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Key words: aplastic anemia; granulocyte transfusion; spontaneous remission; related donor

APLASTIC anemia (AA) is a bone marrow failure disease caused by abnormal activation of T lymphocytes, resulting in the apoptosis of hematopoietic cells and bone marrow failure.¹ Currently, hematopoietic stem cell transplantation (HSCT), immunosuppressive therapy (IST), and supportive care (e.g. transfusion adjuvant therapy, hematopoietic growth factors, and prevention of infection) are the main treatments of AA. Granulocyte transfusion has recently been accepted as an useful adjuvant therapy of HSCT and intensive IST.² This article reported a severe AA patient who failed to respond to IST, but achieved spontaneous re-

mission three times after granulocyte transfusions from related donors. Such cases have rarely been reported. Existence of human leukocyte antigen (HLA) cross between the patient and his relatives may influence the T cell-mediated immunity, which might explain this patient's recovery.

CASE DESCRIPTION

On November 10, 2009, a 38-year-old male patient was admitted to the First Affiliated Hospital of Soochow University because of cough and fever for two weeks. The blood count showed leukocytes at $0.72 \times 10^9/L$, neutrophils $0.01 \times 10^9/L$, hemoglobin level 84 g/L, and platelets $16 \times 10^9/L$. Sternum bone marrow morphological inspection showed hypocellularity with 0.5% granulocytes, 2% erythroid, 74.5% lymphocytes, and no megakaryocyte. Bone marrow biopsy showed hypocellularity with 34% hematopoietic tissue. The immunophenotype of lymphocytes in peripheral blood was 70.1% CD3⁺, 40.8% CD3⁺CD4⁺, 27.0% CD3⁺CD8⁺, 9.9% CD3⁺CD(16+56)⁺, 0.8% CD3⁺CD25⁺, 3.2% CD3⁺CD69⁺, 18.5% CD3⁺HLA-DR⁺, and 0.2%

Received for publication June 11, 2012.

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△Supported by Key Provincial Talents Program of Jiangsu (H201126), the Natural Science Fund for Colleges and Universities of Jiangsu Province (09KJB320015), Key Projects in the National Science & Technology Pillar Program (2008BAI61B02 and 2008ZX09312-026), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

CD3⁺HLA-DR⁺. Cytogenetic analysis revealed 46, XY[20]. Hemolysis test and antinuclear antibody test both produced negative results. Expression of CD55 and CD59 on white blood cells and red blood cells detected by flow cytometry were normal. Chest computed tomography (CT) suggested pneumonia. The patient was diagnosed as severe AA with pneumonia and received cyclosporine A (CsA) and anti-infective agents. Despite sequential administration of broad-spectrum antimicrobial drugs with imipenem/cilastatin, teicoplanin, caspofungin, and voriconazole, the pneumonia still aggravated, demonstrated by the expanding of pulmonary rales and inflammatory lesions in chest CT. On November 18, 2009, the patient got perianal infection. After obtaining informed consent with the patient and his family, we decided to transfuse granulocytes from his related donor with the same ABO type of red blood cells to control the infection. On November 20 and 23, 2009, he received two times of transfusion of granulocytes from his female cousin. The amounts of transfused granulocytes were $1.79 \times 10^8/\text{kg}$ and $7.7 \times 10^9/\text{kg}$ respectively. After transfusion, his temperature gradually returned to normal. The inflammatory lesions in chest CT on November 25 showed no further expansion. The perianal mucosal ulceration gradually healed. The neutrophil count rose from $0.01 \times 10^9/\text{L}$ to $4.19 \times 10^9/\text{L}$ and transfusion independence was achieved. One month later, CsA was replaced by tacrolimus as IST for the mild increase of creatinine. Three months later, chest CT showed complete recovery of the pneumonia. Sternum bone marrow morphological inspection on March 11, 2010 revealed that the proportion of granulocytes, erythroid, and lymphocytes was 41.5%, 33.5%, and 14.5% respectively, and the number of megakaryocytes was more than 200 per smear. Leukocyte count and hemoglobin level returned to normal, but platelet count was only kept at the level of $50 \times 10^9/\text{L}$.

On August 26, 2010, a month after the withdrawal of tacrolimus, the patient was readmitted to our hospital because of the recurrence of fever and sore throat. The leukocyte count upon readmission was $1.3 \times 10^9/\text{L}$, neutrophil count $0.01 \times 10^9/\text{L}$, hemoglobin level 111 g/L, and platelet count $9 \times 10^9/\text{L}$. Sternum bone marrow morphological inspection showed hypocellularity with 12% granulocyte, 21% erythroid, 56% lymphocyte, and no megakaryocyte. Chest CT showed signs of pneumonia again. In spite of anti-infective therapy, the fever could not be controlled. Granulocyte transfusion was conducted again with granulocytes from his niece with the same ABO blood type. The patient received twice granulocyte transfusions with the amount of transfused granulocytes being $4.14 \times 10^8/\text{kg}$ and $3.74 \times 10^9/\text{kg}$, respectively. The blood count

before transfusion showed leukocytes at $1.26 \times 10^9/\text{L}$ with no neutrophil, hemoglobin 72 g/L, and platelets $8 \times 10^9/\text{L}$. Twenty four days after granulocyte transfusion, the patient achieved transfusion independence again. Thirty eight days after transfusion, the blood count showed leukocytes at $4.54 \times 10^9/\text{L}$ with $3.35 \times 10^9/\text{L}$ neutrophil, hemoglobin 72 g/L, and platelets $33 \times 10^9/\text{L}$. After the cure of pneumonia, the patient was discharged from hospital and took tacrolimus 1 mg twice a day.

Five months later, during the process of tacrolimus reduction before the blood count completely returned to normal, the patient was admitted to hospital once again for fever. The leukocyte count was $0.32 \times 10^9/\text{L}$, hemoglobin level 62 g/L, platelet count $23 \times 10^9/\text{L}$, and the proportion of reticulocytes 0.4%. Pneumonia was revealed again in chest CT. After the third time of granulocyte transfusion with granulocytes from his nephew, the blood count was gradually back to normal and the pneumonia gradually controlled in two months. Two years later, the blood count showed leukocytes at $6.7 \times 10^9/\text{L}$ with $4 \times 10^9/\text{L}$ neutrophils, hemoglobin 124 g/L, platelets $156 \times 10^9/\text{L}$. The patient still received tacrolimus 2 mg twice a day for severe AA after the pneumonia was cured.

DISCUSSION

Immunity-mediated bone marrow damage is a major pathophysiological mechanism of acquired AA. IST is recommended for AA patients who are over 40 years, or younger patients (≤ 40 years) who do not have an HLA identical sibling donor. In the present case, the patient failed to respond to IST and anti-infection treatment, but achieved three times of spontaneous remission after granulocyte transfusions from his related donors.

So far, only a small proportion of patients with AA have been reported to recover spontaneously, and most of them are not severe cases. Ghosh et al³ found that three severe AA patients did not improve after administration of adequate doses of CsA for 4-6 months, but achieved remission after spontaneous bleeding of the thymus. The speculation was that thymic hemorrhage might reduce the abnormal activation of the immune function. Goldstein et al⁴ reported a case of AA in pregnancy who recovered after normal spontaneous delivery. During pregnancy, complicated changes in the immune system could cause changes in hematopoietic microenvironment, possibly leading to the damage of hematopoietic and mesenchymal stem cells. After delivery, with the recovery of hematopoietic microenvironment, a variety of hematopoietic cells could be expected to return to normal status.

The spontaneous remission in this patient may be explained by the following factors. One explanation is that severe infection might cause activation of the immune system by generating immune-stimulating molecules continuously, and the transfusion of neutrophils may reduce the reproduction of these immune-stimulating factors, thus controlling the infection. Another factor may be the natural killer (NK) cells in the transfused granulocytes. NK cell surface contains a kind of inhibitory receptor, killer cell immunoglobulin-like receptor (KIR), the ligand of which is major histocompatibility complex (MHC) I molecules. Binding to MHC I molecules and forming compound with self-peptide may turn off the killing function of NK cells. Because of HLA cross, the binding of MHC molecules on cells from related donors and on inhibitory KIR of NK cells of the recipient may stop the cytotoxicity of NK cells. In alloreactivity, NK cells may kill antigen-presenting cells to reduce the activation of T cells and inhibit T cell immune response.⁵

In this case, the patient relapsed twice, both happening after the withdrawal of immunosuppressant. It was widely accepted that IST should be used for a long term in AA patients. Torres et al⁶ found that the ability of the bone marrow cells in idiopathic severe AA cases to form granulocytic-macrophagic colony-forming units (CFU-GM) or erythroid burst-forming units (BFU-E) was depressed. However, after incubation of the patient's bone marrow cells with antilymphocytic globulin, the number of CFU-GM

and BFU-E returned to normal. In patients with spontaneous remission, maintenance therapy with immunosuppressant was still needed to restore the function of hematopoietic stem/progenitor cells.

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