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## CASE REPORT

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### Haploidentical Allogeneic Hematopoietic Stem Cell Transplantation for Thymoma-associated Severe Aplastic Anemia: a Case Report<sup>△</sup>

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**T**HYMOMA, a relatively rare epithelial neoplasm with unique clinical and pathologic features, is the most usual diagnosis for a mass located in the mediastinum. It is often associated with autoimmune disorders. The myasthenia gravis and pure red cell aplasia are the most common disorders, with the incidences of 40% and 5%, respectively, while the incidence of aplastic anemia is only about 0-1.4%.<sup>1</sup> Thymectomy is hard to perform on patients with severe aplastic anemia

(SAA) due to severe pancytopenia. Immunosuppressive therapy, such as antithymocyte globulin plus cyclosporine A (CsA), might delay the treatment for malignant thymoma, and even cause the tumor progression. Here, we report a patient with malignant thymoma-associated SAA achieved hematologic remission and thymoma controlled after the haploidentical allogeneic hematopoietic stem cell transplantation (allo-HSCT).

#### CASE DESCRIPTION

A 40-year-old female was admitted to hospital on 12th August, 2011 with pyrexia and tonsillitis persisting for three weeks. Except for the mild anemia and adenoids, there were no other obvious abnormalities by physical examination. Her peripheral blood count showed: leukocytes at  $2.59 \times 10^9/L$ , neutrophils at  $0.03 \times 10^9/L$ , platelets at  $12 \times 10^9/L$ , a hemoglobin level of 51 g/L, reticulocytes

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percentage and absolute value were 0.004 and  $19.2 \times 10^9/L$ , respectively. The bone marrow aspirate revealed a markedly hypocellular bone marrow with 2.0% granulocytes, 15.5% erythrocytes, and 73.5% lymphocytes. Bone marrow biopsy showed hypocellular bone marrow and marrow space was mostly filled with adipose tissue. Using flow cytometry to analyze the immunophenotypes of the lymphocytes showed 91.7% CD3<sup>+</sup>, 40.6% CD3<sup>+</sup>CD4<sup>+</sup>, 47.2% CD3<sup>+</sup>CD8<sup>+</sup>, 9.9% CD3<sup>+</sup>CD(16+56)<sup>+</sup>, 3.9% CD3<sup>+</sup>CD25<sup>+</sup>, 0.7% CD3<sup>+</sup>CD69<sup>+</sup>, 5.9% CD3<sup>+</sup>human leukocyte antigen (HLA)DR<sup>+</sup>, and 1.3% CD3<sup>+</sup>HLA DR<sup>+</sup>. Chromosome karyotype was normal. The serum levels of iron and erythropoietin were  $1.02 \times 10^{-4} \mu\text{mol/L}$  and 743.0 mIU/mL, respectively. Other laboratory tests were within the normal limits. The computed tomography (CT) of the chest on 15th August revealed an irregular 57 mm×29 mm mass in the anterior mediastinum was gross extracapsular extension with calcifications. The CT scans of the liver, gallbladder, spleen and pancreas were normal. A diagnosis of malignant thymoma associated with SAA was made.

The patient did not respond to erythropoietin and granulocyte colony stimulating factor. On 7th September, the patient received CT scanning again which demonstrated the mass, being much larger than before, was increased to 66 mm×29 mm in size. The abdominal CT image revealed a 21 mm×13 mm round low-attenuation lesion in the right posterior lobe of the liver. A round low-attenuation mass had clear boundary in the spleen. The thymoma progressed seriously and belonged to Stage IVb according to Masaoka clinical staging.<sup>2</sup>

In order to being treated within the shortest time, the patient underwent allo-HSCT from her sister. The HLAs were as follows: (the receiver) A02/A02, B46/B48, DRB1 (16)/DRB1 (04); (the donor) A02/A02, B15/B48, DRB1 (16)/DRB1 (04). Both of the blood group antigen were A. The patient was treated with conditioning regimen containing busulfan (0.8 mg/kg, q6h, for 4 days, on days -11 to -8), cyclophosphamide [60 mg/(kg·d) for 2 days, on days -7 and -6], rabbit anti-human thymocyte globulin [ATG, 4 mg/(kg·d) for 4 days, on days -5 to -2]. On 23th September, the patient received  $8.3 \times 10^8/\text{kg}$  mononuclear cells and  $2.57 \times 10^6/\text{kg}$  CD34<sup>+</sup> cells. CsA, mycophenolate mofetil, rabbit ATG, and methotrexate were used as graft versus host disease (GVHD) prophylaxis. Neutrophils were  $> 0.5 \times 10^9/L$  10 days after the allo-HSCT, and platelets were  $> 20 \times 10^9/L$  14 days after the allo-HSCT. At 24 days after transplantation, bone marrow aspiration showed hypercellular bone marrow, and the percentages of granulocytes, erythrocytes, and lymphocytes were 46%, 51%, and 1.5%, respectively. The short tandem repeat of bone marrow was

96.8%. The patient reached to complete remission about on day +90 with leukocytes at  $4.62 \times 10^9/L$ , neutrophils at  $2.49 \times 10^9/L$ , platelets at  $170 \times 10^9/L$ , and a hemoglobin level of 104 g/L. During the recovery phase, mild GVHD and hemorrhagic cystitis occurred which were controlled soon by corticosteroid and heteropathy. After the allo-HSCT, the patient was treated with CsA 3 mg/(kg·d), tacrolimus capsules (FK506) 1 mg qd or bid, and the serum concentrations of CsA and FK506 were maintained at  $(1.67-2.49) \times 10^{-1} \mu\text{mol/L}$  and  $(7.30-12.16) \times 10^{-3} \mu\text{mol/L}$ , respectively. Subsequently, the patient was advised to gradually reduce the dosage of immunosuppressants, and now she takes FK506 1 mg qod only.

## DISCUSSION

Thymoma has the capacity to generate mature CD4<sup>+</sup> and CD8<sup>+</sup> T cells from immature precursors, leading to an inverted CD4<sup>+</sup>/CD8<sup>+</sup> ratio towards CD8<sup>+</sup> phenotype, and in doing so produce the auto-reactive T-cell clones responsible for humoral and cytotoxic autoimmune diseases.<sup>3, 4</sup> Although thymectomy is indicated for thymomas with hematologic dyscrasia, hematologic remission is probably less than 20% cases.<sup>5</sup> Only one of 3 patients suffered from thymoma-associated pure red cell aplasia, who underwent thymectomy, had complete remission for two years.<sup>6</sup> Ritchie *et al*<sup>7</sup> reported that a patient with thymoma associated myasthenia gravis was complicated by aplastic anemia 9 months after the eradication of the thymoma, which supported the hypothesis that auto-reactive T cells were exported from the thymoma into the peripheral, where they persist and are capable of initiating auto-immunity at a later stage. Although the patients with thymoma-associated aplastic anemia or SAA may response to immunosuppressants, such as ATG/antilymphocyte globulin, CsA, and intravenous immunoglobulin, most of them cannot reach to permanent hematologic remission.<sup>1, 8, 9</sup> In fact, the overall long-term survival of patients with thymoma is poor once cytopenia occurs. Recently, a patient with thymoma-associated aplastic anemia underwent allogeneic sibling peripheral stem-cell transplantation as without hematologic remission after thymectomy. The bone marrow examination 1 year later demonstrated a normocellular bone marrow with active trilineage hematopoiesis. Thirty-two months after the completion of therapy, there was no evidence of recurrent thymoma.<sup>10</sup>

It is hard to perform thymectomy or radiochemotherapy for thymoma patient with bone marrow aplasia, and immunosuppressive therapy including CsA and/or ATG might cause the progression of thymoma. Taken together, the patient with such a disease should undergo haploidentical allo-HSCT directly. On the one hand, it may lead to hema-

tologic remission, and on the other hand, it may control the progression of thymoma by graft *versus* tumor.

Graft rejection and GVHD are the two common challenges in allo-HSCT. As it has been reported that potent myeloablative regimens, such as thiotepa and busulfan are much more helpful for haploidentical hematopoietic stem cell engraftment.<sup>11</sup> This patient should receive myeloablative drug, busulfan, combined with cyclophosphamide and ATG as the condition regimen.

To date, 12 months have passed since the allo-HSCT, the patient is still in hematologic remission and her latest short tandem repeat of peripheral blood was 97%. CT reexamination revealed that the irregular mass in the anterior mediastinum had shrunk to 50 mm×15 mm, and no low-attenuation was seen in the liver and the spleen. These data suggested that the allo-HSCT was successful and the thymoma was controlled. So, for the patients with thymoma-associated SAA, who are unsuitable for thymectomy, may undergo allo-HSCT directly.

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