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A Case of Successful Allogeneic Hematopoietic Stem Cell Transplantation for HHV8-Positive Castleman's Disease with a Review of the Literature

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Abstract

Objective: To investigate the long-term clinical efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for patients with human herpes virus 8 (HHV8)-positive multicentric Castleman's disease (MCD). **Methods:** A 17-year-old female patient was admitted to Henan Provincial People's Hospital with the complaint of febrile for half a month, headache, and enlarged superficial lymph nodes on October 5, 2010. HHV8-positive mixed cellular Castleman's disease was found by pathological diagnosis of lymph nodes biopsy. After the administration of CHOP and Hyper-CVAD-B, the patient was still febrile, we administrated the followed COAP, two courses of VAD(Vincristine, Adriamycin, Dexamethasone), the patient received CR. Six months after CR, the patient relapsed, we administrated VAD and two courses of bortezomide+dexamethasone chemotherapy, and then the patient received PR. After that, the patient underwent allo-HSCT from his human leukocyte antigen (HLA)-matched unrelated donor after conditioning with Bu/Cy+Etoposide+Smoustin.graft-vs-host disease (GVHD) prophylaxis, which consisted of ATG (7.5 mg/kg, qd, ivdrip) from d-5 to d-2, cyclosporine (3 mg/kg/d, qd, ivdrip, for 24 h) started from day-1, MMF(0.5 g, tid, po.) started from day+1 to +28, and MTX (15 mg per time, ivdrip, d+1,+4,+7,+11). She received 3.5×10^6/L $CD34^+$cells and 8.1×10^8/LMNC. **Results:** Granulocyte engraftment occurred on day+12, platelet engrafted on day+14. Bone marrow biopsy showed normalization of trilineage hematopoiesis on day+33, chimerism: 97.6%. The transplantation was successful and followed up for 7 years with CR. **Conclusion:** Allo-HSCT might cure patients with refractory/relapsed HHV8+ MCD.

Keywords

multicentric type, Castleman's disease, allogeneic, hematopoietic stem cell, transplantation

Introduction

Castleman's disease (CD) is a rare lymphoid proliferative disease with clinical manifestations, including lymphadenopathy and fever. Multicentric Castleman's disease (MCD) might be associated with polyclonal immunoglobulin, anemia, and renal insufficiency. Its clinical manifestations are diverse and are often accompanied by multiple system involvement, while some other cases are associated with POEMS syndrome or progression to Kaposi's sarcoma/malignant lymphoma. Hence, we describe a patient who was diagnosed with refractory MCD with a monoclonal IgG peak and was successfully treated using allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an unrelated

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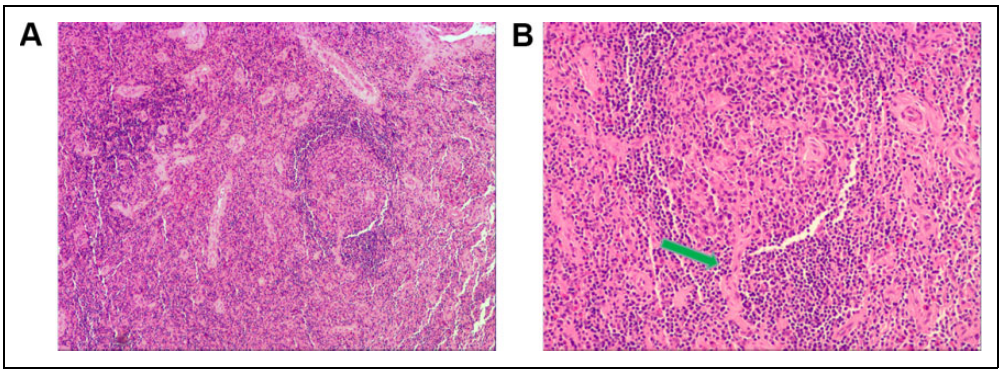

Figure 1. (A) The pathology of the lymph node showed lymphoid follicle was penetrated by a sclerotic blood vessel. Follicular dendritic cells (FDCs) were hyperplastic in lymphoid follicle with small germinal center. The follicle was surrounded by mantle cells (so-called onion skin). The interfollicular regions were expanded by numerous mature plasma cells. (B) The follicle was radially penetrated by a sclerotic blood vessel together with proliferated FDCs, presenting a lollipop-shaped structure. There were plaques distributed in mature plasma cells with abundant red-staining cytoplasm and spoke-like nuclei.

donor. The medical report was obtained following informed patient consent and hospital Institutional Review Board approval. All procedures in this study were conducted in accordance with the Ethics Committee of Henan Provincial People's Hospital and the Institutional Review Board and the Ethics Committee of Zhengzhou University-approved protocols.

Case Report

A 17-year-old female was admitted to our hospital on October 5, 2010, with the chief complaint of a fever lasting for more than two weeks, accompanied by headache, weakness, and muscle soreness. We noticed enlarged lymph nodes in the bilateral supraclavicular and groin regions during physical examination and with a temperature of 37.6°C. The blood tests showed the following results: WBCs 6.61 ×109/L, neutrophils 4.52×109/L, RBCs 3.26×1012/L, PLTs 265×109/L, and Hb 84 g/L. Serum globulin was 48.9 g/L. Viral serology was negative, therefore, HIV infection was ruled out. Additional laboratory values were as follows: PT 13.70, PT% 90, INR 10.7, APTT 44.30, FIB 11.43, TTT 22.50, C-reactive protein 16.6 mg/L, β_2-microglobulin: 2.5 mg/L, IgGκ: single peak, IgG 39.5 g/L, IgA 3.81 g/L, IgM 1.48 g/L, κ 23.2 g/L, λ 10.5 g/L, and 24 h urinary κ light chain 1,560 mg/L. She was found to have splenomegaly by ultrasound. In terms of autoantibodies, her antinuclear antibody titer was 1:100 (nucleolar type), and plasma antineutrophil antibodies were weakly positive. Based on the pathology result from the biopsy of right inguinal lymph nodes combined with immunohistochemistry and histopathology, giant lymphadenopathy (CD) was considered. The immunohistochemical results were as follows: CD34 was positive on vascular structures, F8 was positive on vascular structures, and EBER was negative. After consultation with the Pathology Department of Peking University, it was concluded that the lymphatic follicles were scattered in the lymph nodes. Furthermore, the germinal center was narrowed, inner reticulocytes were dominant, and the surrounding cells were arranged in layers. A large number of plasmacytes were seen proliferating around the follicles, and many Russell bodies were found in the plasma cells. The pathological diagnosis was HHV8-positive, mixed CD (Fig. 1.). Morphological assessment of the bone marrow showed expansion of bone marrow, active granulocyte and erythroid compartments, altered size of mature red blood cells, abnormal pigmentation, and some rouletting of red blood cells. The lymphocyte ratio was decreased, and the monocyte ratio and morphology were normal. The ratio of plasma cells was increased, accounting for 4.4% of the total cells, and binuclear plasma cells were easily observed. Megakaryocytes were seen in the bone marrow. Of 50 classifiable cells, there were 44 granulocytes, 4 platelets, and 2 bare nuclei, and the platelets were easily observed with no obvious morphological abnormalities. The bone marrow biopsy showed active cell proliferation in the bone marrow, including obvious plasma cell proliferation, and binuclear plasma cells were observed. Chromosomal analyses revealed a karyotype of 46, XX. The patient's blood type was A Rh-, and her HLA typing was as follows: HLA-A:30/32, HLA-B: 13/35, HLA-C: 04/06, HLA-DRB1:07/13, and HLA-DQB1:02/06. The patient was treated with three cycles of CHOP (cyclophosphamide, vincristine, methylprednisolone, and epirubicin), hyper-CVAD-B (high-dose methotrexate and cytarabine), COAP (cyclophosphamide, vincristine, methylprednisolone, and cytarabine) after the diagnosis, but symptoms remained uncontrolled. In the two subsequent cycles, we increased the dosage of corticosteroids and added two doses of VAD (vincristine, adriamycin, and dexamethasone). The enlarged lymph nodes disappeared, and her body temperature remained normal for 1 month in response to this treatment protocol. The patient experienced recurrence in June 2011, and she presented with fever accompanied by cervical lymph node enlargement, weight loss, and night

sweating. We repeated the VAD (vincristine 0.5 mg/d, d1-4; doxorubicin and dexamethasone 40 mg/d, d1-4) regimen, but the symptoms remained uncontrolled. We administered two cycles of bortezomib+dexamethasone. After chemotherapy, the lymph nodes shrank, her body temperature decreased, and her fever remained intermittent, fluctuating between 37°C and 38°C. In October 2011, a potential marrow donor was found in the Chinese Medicine Library, and the HLA matching was 10/10. The patient underwent allo-HSCT from an unrelated HLA-matched donor (blood type: AB Rh+; 10/10 HLA-matched) after conditioning with Bu/Cy+etoposide+smoustin. GVHD prophylaxis consisted of ATG (7.5 mg/kg, qd, iv drip) from d-5 to d-2, cyclosporine (3 mg/kg/d, qd, iv drip, for 24 h) started on d-1, MMF (0.5 g, tid, po.) from d+1 to d+28, and MTX (15 mg per dose, iv drip, d+1,+4,+7,+11). The patient received 3.5 ×106 CD34+ cells/L and 8.1 ×108 MNCs/L. Blood levels of cyclosporine were monitored and well-controlled. Granulocyte engraftment occurred on d+12, and platelets engrafted on d+14. Bone marrow biopsy showed normalization of trilineage hematopoiesis on d+33, with chimerism of 97.6%. The patient was regularly checked in the outpatient clinic, the related laboratory tests and body temperature were normal, and fever and lymph node enlargement did not recur. However, the reproductive capacity of the patient was influenced, and she became menopausal.

Discussion

CD is a rare benign lymphoproliferative disorder characterized by lymphoid follicular hyperplasia. It currently exhibits several different histological patterns, including hyaline vascular (HV) variant and a plasma cell type (PC type)[1]. HHV8 (human herpesvirus 8)-related mixed CD cases account for approximately 2.5% of all cases and often occur in HIV-infected patients. These patients have shorter survival and are prone to infection and conversion to lymphoma, which is a common reason for death[2]. There are two types of clinical manifestations: localized/unicentric CD (UCD) and systemic/multicentric Castleman's disease (MCD). UCD is the more common of the two and usually is limited to a lymph node group or region, takes on HV histology, and is cured by surgical removal of asymptomatic local lesions. MCD is the less common type, and most cases are of the PC subtype. MCD can progress to severe pancytopenia, multiple organ failure, and lymphoma. A small number of patients develop a terrible syndrome, including multiple neuropathies, organ enlargement, endocrine disorders, monoclonal gamma globulin disease, and skin changes. The median survival time is approximately 14 months[3,4].

The pathophysiological basis and pathogenesis of CD are still unclear, leading to difficulties in diagnosis and treatment. A large amount of data indicate that CD is associated with viral infections such as those caused by HHV8, cytokine dysregulation such as elevated IL-6 expression, abnormal function of antigen-presenting cells, and angiogenesis. Interactions between inflammatory mediators, primarily IL-6, which in some cases are driven by HHV8, are prominent in MCD, leading to lymphangiogenesis and systemic manifestations of the disease[5]. Also, IL-1, the RAF pathway, epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF) are associated with the pathogenesis of CD in limited studies. Therefore, blocking these pathways represents another attractive treatment strategy for this rare disease[6]. In our patient, the C-reactive protein was higher at disease onset and was positively correlated with the expression of IL-6, suggesting that IL-6 may also be increased. It is speculated that IL-6 plays an important role in cases of concurrent MCD and MM. Of course, the possibility that the polyclonal MCD gradually converts to MM cannot be excluded.

At present, there is no universal treatment for MCD. A combination of various treatments, such as chemotherapy, anti-HHV8 therapy, α-interferon, glucocorticoids, and targeted therapies (thalidomide, rituximab, and bortezomib), is often used[7]. The use of corticosteroids can lead to short-term improvement of symptoms. Similar outcomes can be achieved with CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen or targeted radiotherapy combined with targeted therapy. Q Lin et al. successfully used bortezomib to cure a mixed type of CD patient[8]. Several adult MCD patients have also been successfully treated with IL-6 receptor antibodies (tocilizumab), interferon-α, rituximab, and antiviral drugs[9]. In addition, there are also some less common treatments, such as intravenous immunoglobulin, plasmapheresis, targeted agents, and autologous hematopoietic stem cell transplantation.

In this case, the clinical manifestations of the disease in this patient was fever, fatigue, lymph node enlargement in multiple lymph nodes, increased monoclonal immunoglobulin, and increased C-reactive protein. Morphological analysis of bone marrow cells showed an increase in the PC ratio, accounting for 4.4% of the total cells. Binuclear PCs were easily observed. The patient was diagnosed with HHV8-associated mixed CD, which behaves like a PC disease clinically, and prone to MM. One month after the treatment with bortezomib, the patient developed a relapse.

Considering the generally poor condition of patients with refractory MCD and the importance of quality of life for the young patient, the use of autologous hematopoietic stem cell transplantation is a preferred treatment. However, the patient had constant fever, which led to the failure of the collection of the patient's stem cells. She had no chance to undergo the autologous hematopoietic stem cell transplantation. As there was no sibling to use as a donor, an unrelated donor was selected for the allo-HSCT under the agreement of the patient and her guardians, and the treatment was successful, leading to long-term relief for the patient.

To our knowledge, only one case of a patient with severe MCD who received allo-HSCT after rituximab monotherapy

followed by six months of follow-up has been reported[10]. The reasons why we added the etoposide in the conditioning regimen were as follows: (1) It was reported that both Bu/Cy plus etoposide as conditioning for autologous stem cell transplantation in MM was a safe regimen[11] and treatment of HIV-associated MCD with etoposide[12] had substantial efficacy. (2) The conditioning of aggressive CD is similar to high-grade lymphoma[13,14].

Allo-HSCT is an effective treatment for adolescent patients with nonmalignant hematologic diseases, and the incidence of chronic GVHD was relatively low in this setting[15]. The impact of allo-HSCT on quality of life is different in malignant and nonmalignant hematologic diseases. The patients with nonmalignant hematologic diseases normally have better physical condition. When the recipients developed chronic GVHD, especially after matched unrelated donor allo-HSCT, their body condition declines[16]. In addition, after allo-HSCT, the occurrence of acute and chronic GVHD was associated with reduced overall survival (OS) rates[17]. Studies showed that in the patients with nonmalignant hematological diseases, the removal of T cells in the graft before HSCT can reduce the occurrence of GVHD without increasing the virus-related mortality[18]. Different from the malignant diseases, graft versus tumor effect is unnecessary in the nonmalignant diseases. Thus, complete protection from GVHD is the best strategy for nonmalignant patients receiving allo-HSCT. The experience of GVHD prophylaxis for nonmalignant hematologic disease such as MCD is rare. To avoid the incidence of GVHD, we applied cyclosporine treatment (gradually reduced the dose of cyclosporine) during the first year after allo-HSCT, both acute and chronic GVHD were not observed for over 9 years.

In conclusion, allo-HSCT is the preferred option for the patients with MCD as follows: (1) younger patients desire to have enough quality of life; (2) patients who do not respond to therapeutic monoclonal antibodies or recurrent; (3) patients who had an HLA-matched donor. After 9 years of follow-up, the patient has been living a normal and healthy life as others, and she works as an accountant. Clinical judgment, the doctor's experience, and the patient's wishes played an important role in the treatment planning process. Allo-HSCT can be recommended as an alternative treatment option for patients receiving long-term relief and improved quality of life.

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