SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 2: 515-518, 2011

Kaposi's sarcoma developed after allogeneic hematopoietic stem cell transplantation

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Received December 6, 2010; Accepted January 14, 2011

DOI: 10.3892/ol.2011.259

Abstract. A 33-year-old Chinese male patient with severe aplastic anemia received matched sibling allogeneic hematopoietic stem cell transplantation using antithymocyte globulin containing conditioning regimen after 4 months of unsuccessful treatment with cyclosporine A. Following transplantation, the patient was immunosuppressed demonstrated by intermittent infections, including a varicella 3 months after transplantation. Although DNA-STR results on day +30 confirmed complete donor engraftment, repeat DNA-STR analysis performed more than 3 months after transplantation showed a mosaic phenotype. Cyclosporine tapering commenced early, but the last DNA-STR result confirmed complete graft rejection. On day +198, the patient presented with fever, skin boil in the right temporal region, severe pancytopenia, intrabodominal lymphadenopathy and hepatosplenomegaly. Within 1 month, superficial lymphadenopathy and right exophthalmos developed. Excisional lymph node biopsy pathology confirmed Kaposi's sarcoma (KS). The patient succumbed due to intracranial bleeding as a result of thrombocytopenia. This is the first study of KS that developed following stem cell transplantation for severe aplastic anemia. The precipitating factors underlying KS development in this case and its differentiation from post-transplant lymphoproliferative disorders are analyzed.

Introduction

Treatment for aplastic anemia includes intensive immunosuppressive therapy (IST) and allogeneic hematopoietic stem cell transplantation (AHSCT). AHSCT is the treatment of choice for young adults with severe aplastic anemia (SAA), with cure ranging from 75 to 80% and overall survival at 6 years being more than 90%. Cyclophosphamide (CY) plus antithymocyte globulin (ATG) is the most commonly used regimen in AHSCT for SAA due to a low incidence of graft rejection and chronic graft-versus-host disease (GVHD) (1). However, 5-15% of SAA patients receiving sibling AHSCT are likely to develop graft rejection, particularly those patients that have been heavily transfused (2).

Kaposi's sarcoma (KS) was first described in 1872 by Kaposi as a progressive sarcoma (3). It is a multicentric neoplasm of lymphatic endothelium-derived cells infected with KS-associated herpesvirus (KSHV). Four recognized clinical subsets can be distinguished: the sporadic or classic subtype initially described by Kaposi, the endemic subtype observed in sub-Saharan Africans, the epidemic subtype in patients infected with human immunodeficiency virus (HIV) and the iatrogenic subtype in patients treated by immunosuppressive therapy particularly in organ transplant recipients (4).

The majority of reported post-transplant KS cases occurred in solid organ transplant recipients, and the likelihood of KS developing following hematopoietic stem cell transplantation (HSCT) is low. Only a few cases of KS following allogeneic stem cell transplantation were previously reported (5-11). The majority of these cases had presented with typical KS mucocutaneous lesions. However, no study regarding KS with atypical presentations mimicking those of post-transplant lymphoproliferative disorders (PTLD) after AHSCT for SAA currently exists. This study examined a patient with SAA who developed KS following matched sibling AHSCT and succumbed to bone marrow failure due to graft rejection.

Case report

A 33-year-old Chinese male patient from South China presenting with SAA received AHSCT from his HLA-identical brother using a CY plus busulfan (BU) and ATG conditioning regimen. Prior to the transplantation, the patient had been treated with cyclosporine A (CsA) for 4 months, but without improvement and had to receive red cell and platelet transfusions constantly. Both the patient and the donor were serum-negative for hepatitis B, C, HIV, cytomegalovirus (CMV) or Epstein-Barr virus (EBV). Following transplantation, CsA was administered for GVHD prophylaxis. The patient developed grade I acute GVHD with mucocutaneous

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Key words: aplastic anemia, allogeneic hematopoietic stem cell transplantation, post-transplant lymphoproliferative disorders, Kaposi's sarcoma, graft rejection

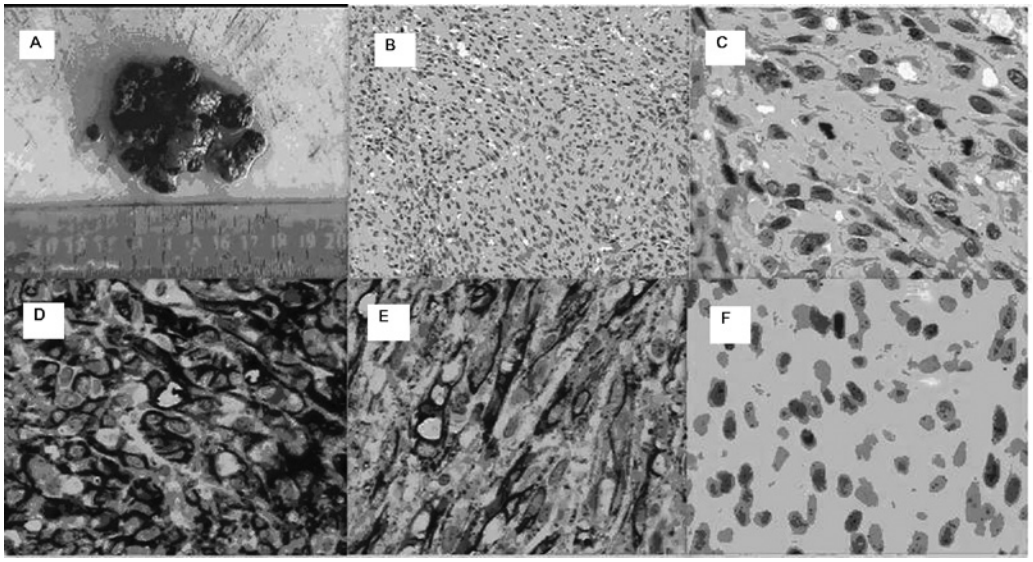

Figure 1. (A) General view of the incised tissue appeared as dark-red multiple nodules. (B) Fascicles of spindled tumor cells with slit-like vascular channels containing erythrocytes (H&E staining). (C) Heteromorphic tumor cells with mitotic figures and plasmic vacuoles. (D) Positive CD31 reactivity in the plasma of tumor cells. (E) Positive CD34 immunohistochemistry reaction in the plasma of tumor cells. (F) Positive immunohistochemistry reaction for HHV-8 in the nuclei of tumor cells.

changes and diarrhea. His neutrophil count increased to >1.5x10^9/l and his platelet count increased to >50x10^9/l on days +10 and +14. Complete donor engraftment was documented on day +30 by blood DNA-STR amplification. A bone marrow examination showed hyperplasia with a megakaryocyte count within normal range, but maturation hindrance was noted. On day +40, the platelet count decreased and 15-30 mg daily of prednisone was given and sustained to improve megakaryocyte maturation. Two months after transplantation, the patient had severe pancytopenia with fever, diarrhea and oral mucositis. Although the symptoms disappeared following treatment with antibiotics, the patient had to receive blood transfusion every week. Three months after transplantation, he got varicella and then fully recovered following treatment with oral acyclovir. Another bone marrow examination at that time showed marrow hypoplasia. The patient then developed fever and respiratory infections twice and recovered. Blood transfusion was not required until 5 months after transplantation. However, a second DNA-STR analysis performed on day +112 revealed partial donor chimerism. CsA was tapered and completely stopped within 6 months of transplantation. On day +156, he was discharged. He was free of infection and did not require blood transfusion.

However, on day +198 he was admitted again complaining of high fever, cough, intermittent epigastric discomfort and progressive emaciation. A physical examination revealed a painful subcutaneous boil of pink color with a diameter of 5 mm in the right temporal region without any other macula, plaque or nodule changes in skin. Severe pancytopenia and platelet transfusion refractoriness with platelet counts of <20x10^9/l even after frequent platelet transfusion were noted. A chest X-ray revealed right pneumonia. The sputum and blood cultures were positive for different gram negative bacteria which responded to treatment with antibiotics. Both abdominal B ultrasound and computer tomography revealed hepatosplenomegaly and multiple hepatic, splenic hilar and intrabdominal lymphadenopathy. Bone marrow smear and biopsy examinations were typical of SAA. The patient remained serum-negative for HIV, hepatitis B virus, hepatitis C virus, CMV or syphilis. Treatment with combined antibiotics and anti-fungal medicine was ineffective. One month later, multiple superficial lymphadenopathy was noted and tender swelling in his right canthal area gradually developed and exacerbated. Within a few days, the right periorbital and right cheek area was badly swollen and right exophthalmos was present resulting in local exudation and ulceration. Blood samples sent for CMV antigen and EBV polymerase chain reaction (PCR) analysis were both negative. Blood DNA-STR analysis on day +190 confirmed complete graft rejection. With the patient's consent and blood transfusion support, excisional biopsy of a cervical lymph node was performed and KS was confirmed by positive morphologic, immunohistochemistry examination results (Fig. 1). The patient then refused further treatment and was discharged against advice. He succumbed to intracranial bleeding as a result of thrombocytopenia on day +230 at home.

Discussion

The patient described in this study received HLA-matched sibling AHSCT with ATG-containing conditioning regimen after 4 months of CsA treatment for SAA. The DNA-STR results on day +30 showed complete donor engraftment. However, repeat DNA-STR analysis performed 4 months after transplantation confirmed a mosaic phenotype which, together with marrow hypoplasia, were indicative of partial graft rejection. Early CsA tapering appeared to have a positive effect, since the blood cell count began to rise and the patient did not require blood transfusion for over 2 months after that. However, graft rejection developed, which was confirmed by the DNA-STR results performed on day +190. It is well-known that AHSCT is curative in SAA. Nevertheless, graft rejection,

infections and GVHD have limited the effectiveness thereof. Graft rejection decreased with the introduction of ATG into conditioning regimen, but it still occurs, particularly in highly transfused patients. The number of prior transfusions is associated with rejection and survival after AHSCT due to the sensitization by the histocompatibility antigens infused with blood products (12). Marsh suggested that SAA patients with eligible sibling bone marrow transplant (BMT) donors should not receive IST, but should receive an early transplant before patients become sensitized to HLA and non-HLA antigens from multiple transfusions (2). Multiple transfusions prior to AHSCT may be the main precipitating factors underlying the graft failure in this patient.

As the patient's hematopoietic function got worse, another attack of mixed infections were observed, which was preceded by KSHV infection resulting in KS and followed by secondary sepsis. The KS lesion firstly presented as an atypical skin boil in the right temporal area together with fever, multiple deep lymphadenopathy and hepatosplenomegaly resembling presentations of PTLD. PTLDs are a heterogeneous group of lymphoproliferative disorders associated with immunosuppression in recipients of solid organ or allogeneic stem cell transplantation. The clinical presentations of PTLD may vary from symptomless or non-specific early symptoms, such as fever, malaise and weight loss in certain patients to typical involvement of lymph nodes and extranodal involvement in other patients. Most cases of PTLD are associated with EBV infection from B-lymphocytes (13). In our case, both the EBV PCR analysis of the patient's blood sample and Epstein-Barr encoded RNA (EBER) *in situ* hybridization test on his pathologic tissue were negative. Although 20-30% of PTLDs were reportedly EBV-negative and a case of HHV-8-positive PTLD has been reported (14), the typical pathological alterations of the lymph node biopsy in this case exclude the diagnosis of PTLD.

Clinical features of KS include mucocutaneous and visceral involvement. Mucocutaneous lesions have been reported in more than 90% of post-transplantation KS cases usually starting as macules that progress and coalesce to form large plaques or nodular and fungiform tumors. These lesions are mainly localized on the lower limbs, but are also frequently observed on the trunk and upper limbs, face, genitalia and oropharyngeal mucosa. Additionally, KS frequently involves lymph nodes and visceral organs, notably the respiratory and gastrointestinal tracts. Other unusual locations of KS involvement include the musculoskeletal system, nervous system, larynx, eye, salivary glands, endocrine glands, heart, thoracic duct, urinary system, breast and wounds (15,16). The development of KS following AHSCT is rare. A review of the current literature shows that only a few KS cases have been reported following AHSCT in patients with sickle cell disease or leukemia. Development of KS following AHSCT for SAA has never been reported. All of the reported KS cases had presented with typical mucosal or skin lesions more than 6 months after AHSCT (5-11). The atypical and complex clinical characteristics of KS in this case made it difficult to make an earlier diagnosis.

KS occurs in patients infected with human herpesvirus type 8 (HHV-8), also known as KSHV, and the level of immunosuppression is the main factor for the development and progression of the disease. HHV-8 belongs to a family of double-stranded DNA viruses involving herpesviruses that are able to escape from complete clearance by the human immune system. The ability of these viruses to become latent is due to their delicate interference with the immune system. Consequently, some of these viruses are regarded as tumor viruses. Herpesviridae comprises three main subfamilies: α- , β- and γ-herpesviruses. α-herpesviruses consist of human herpesvirus-1 (HHV-1), HHV-2 (genital herpes virus) and HHV-3 (varicella-zoster virus; VZV). β-herpesviruses comprise HHV-5 (CMV), HHV-6 and HHV-7. The subfamily of γ-herpesviruses comprises HHV-4 (EBV) and HHV-8 (KSHV) (17). Of note is that during the post-transplant period, the patient in this study got varicella caused by HHV-3 infection during the 2nd post-transplant month. Thus, this patient had infections by two subtypes of herpesvirus at different post-transplant periods. The most frequently reported herpesvirus infections following AHSCT are CMV or EBV (18). Mixed infections of two or three herpesviruses have been reported, mostly CMV and EBV infections. Other herpesviruses include successive EBV/HHV-7, HHV-6/CMV and CMV/HHV-8 infections (10,19,20). Successive VZV and HHV-8 infections in post-transplantation patients have never been reported and may be an indication of sustained immunosuppression in the patient.

The origin of KSHV infection in this patient is unknown as no examination was performed for HHV-8 infection in either the donor or the recipient prior to transplantation. KSHV infection in an immunocompetent host is usually asymptomatic. Therefore, we cannot exclude latent KSHV infection in the donor or the recipient prior to transplantation although neither the donor nor the recipient had presented with any clinical manifestations of KS. In the case reported in this study, KSHV infection may have been transmitted from the donor's latent infection, the result of reactivation of the recipient's previous infection or through blood transfusions. Studies on viral serology suggest that post-transplant KS was primarily due to HHV-8 reactivation in endemic areas and to primary infection in non-endemic areas (10). KS is rare in the majority of Chinese regions, with the exception of Xinjiang. The seroprevalence of KSHV in the general population is 9.5-12.3% and that in volunteer blood donors ranged from 5.65 to 16.2% (21,22). Rosenzwajg *et al* studied the seropositivity of antibodies to HHV-8 latent nuclear antigen in 200 allogeneic BMT recipients and their donors. These authors did not find any association between the presence of antibodies prior to or after transplantation to chronic GVHD or to overall BM transplantation survival. However, their study suggests that blood transfusions increase the risk of HHV-8 infection following BMT (23). It was estimated that KS develops in 0.1-5% of transplant recipients (24). Risk for KS development following organ transplantation is 500 times higher than that in the general population and increases with immunosuppressive therapy. Compared to more frequently reported KS cases following solid organ transplantation, only a few cases of KS following AHSCT have been reported thus far. It has been suggested that the intense cytotoxic conditioning regimens in AHSCT destroy host lymphoid tissues and potential HHV-8 harbouring cells, whereas the immunosuppressive regimens used in solid organ transplants do not eradicate such cells

(10). This may partially explain the reason that KS is rare following AHSCT. The above results indicate that the patient in this study got KSHV infection through blood transfusions as compared to donor-derived infection or reactivation of KSHV infection.

The main treatment of post-transplantation KS involves tapering down immunosuppressive regimens to the lowest possible level. In this case, CsA was discontinued 6 months after transplantation. However, a small dose of prednisone was sustained from 1 month after transplantation to the last month. Moreover, the intractable and progressive graft rejection led to the recurrence of aplastic anemia resulting in refractory neutropenia and secondary infections in the patient. This event combined with sustained immnuosuppression therapy caused severe immunosuppression and rapid progression of KS in the patient. Other treatment choices for KS include cryotherapy, surgical removal or intralesional chemotherapy for localized mucocutaneous lesions and chemotherapies comprising vinblastine, bleomycin, liposomal anthracycline, taxanes or thalidomide for advanced cases with visceral lesions (3). The patient in this study received none of the therapies due to severe pancytopenia, complicating infections and economical reasons. As in the majority of cases with KS, the patient did not succumb to KS, but to marrow failure caused by the recurrence of SAA.

In conclusion, this report examined a patient with KS following AHSCT for SAA presenting with atypical clinical features resembling those of PTLD. Sustained immunosuppression and graft rejection were the main risk factors of KS infection in this case. In post-transplantation patients with PTLD-like presentations, differentiation from KS should be included.

Acknowledgements

The authors would like to thank Professor Qifa Liu from the Department of Hematology of Nanfang hospital for his help in the diagnosis and treatment of the case.

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