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CASE REPORT

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Cytomegalovirus enteritis after autologous peripheral blood stem cell transplantation

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Abstract A 61-year-old male with non-Hodgkin's lymphoma (peripheral T-cell lymphoma, unspecified, clinical stage IVb) received autologous peripheral blood stem cell transplantation (PBSCT) during first remission. He was seropositive for cytomegalovirus (CMV) prior to autologous PBSCT. His posttransplant clinical course was complicated by refractory CMV enteritis, which manifested persistent abdominal pain, diarrhea, and bloody stool. Generally, gastrointestinal CMV disease is relatively rare after autologous PBSCT. However, our case indicates that CMV infection must be considered as a differential diagnosis in cases of unexplained hemorrhagic enteritis following autologous PBSCT.

Keywords Cytomegalovirus disease · Gastrointestinal tract · Hemorrhagic enteritis · Autologous peripheral blood stem cell transplantation · Non-Hodgkin's lymphoma

Introduction

High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) is increasingly used for the treatment of a variety of malignancies. Compared to autologous bone marrow transplantation (BMT), autologous PBSCT provides rapid hematopoietic recovery, which reduces morbidity and mortality from infectious complications. Compared to allogeneic BMT, a risk of viral infection and disease, especially cytomegalovirus (CMV) infection and disease, is apparently decreased after autologous PBSCT.

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CMV infection is a major cause of mortality after allogeneic BMT. Accordingly, significance of CMV viremia, roles of CMV immune responses, and risk factors for CMV pneumonitis have been established in allotransplant patients. However, CMV infection and disease of the gastrointestinal tract have not been well documented following autologous BMT or PBSCT. In this report, we describe a case of refractory CMV enteritis developing after high-dose chemotherapy and autologous PBSCT.

Case report

A 61-year-old Japanese man visited a local hospital because of right cervical lymphadenopathy in 1999. Based on biopsy findings of the right cervical lymph node, he was diagnosed with non-Hodgkin's lymphoma (NHL), peripheral T cell, unspecified. Staging procedures disclosed that the disease was at clinical stage IVb. He was seronegative for adult T-cell leukemia (ATL) virus (HTLV-1) and seropositive for CMV. He was treated with a standard chemotherapy course consisting of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) every 3 weeks. After four courses of CHOP, he achieved complete remission (CR). A regimen of chemotherapy for PBSC mobilization consisted of ifosfamide, dexamethasone, etoposide, and cytosine arabinoside followed by granulocyte colony-stimulating factor (G-CSF) administration, and PBSC collected by apheresis contained 25.2×10^6 $CD34^+$ cells/kg. Since his disease was judged as high-risk according to the international prognostic index (IPI), high-dose chemotherapy facilitated with unmanipulated autologous PBSCT was planned after a further two courses of CHOP. Before transplant, the CD 4/8 ratio of peripheral blood was 2.0 within a normal range ($CD4^+$ cells: 57%, $CD8^+$ cells: 28%). After pretransplant conditioning consisting of ranimustine, carboplatin, etoposide, and cyclophosphamide (MCEC regimen) [1], PBSCT was performed 25 days after achieving CR; 12.6×10^6 $CD34^+$ cells/kg were infused. Rapid trilineage engraftment was observed; a neutrophil count exceeded 0.5×10^9/l on day 9. On day 3, however, he developed high fever, and septic shock was seen on day 7. Stool cultures were positive for methicillin-resistant *Staphylococcus aureus* (MRSA) on day 8. Methylprednisolone (20 mg/kg once daily i.v. for 3 days), panipenem, and vancomycin were started on day 7. Severe watery diarrhea occurred on day 8. On physical examination, there was diffuse and mild unlocalized tenderness in the abdomen without rebound pain or muscle guarding. On day 11, watery diarrhea changed to bloody diarrhea. Stool cultures for MRSA were negative on day 14. Upper gastrointestinal fiberscopy

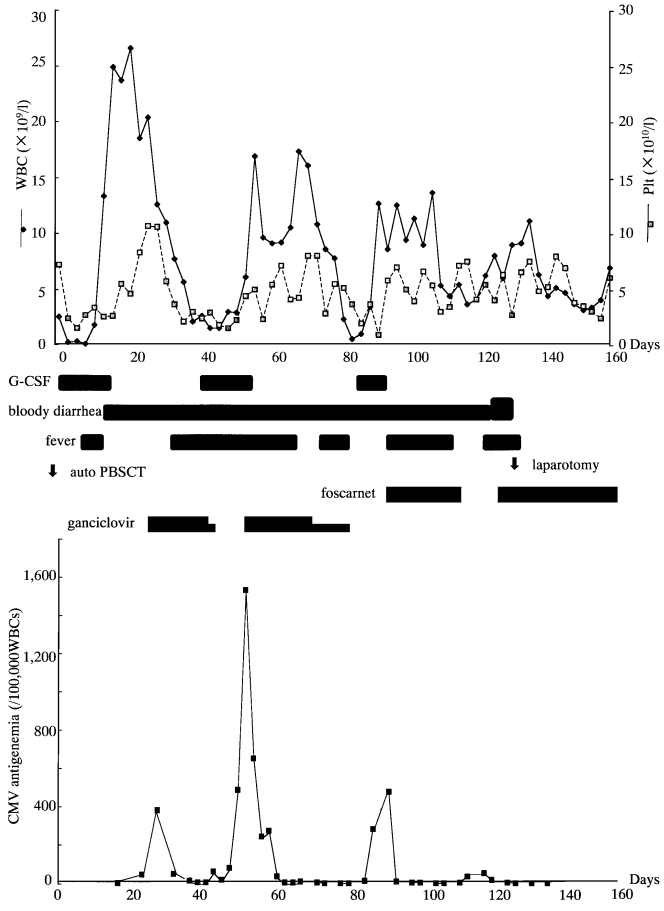

Fig. 1 Clinical course following autologous PBSCT.

and colonoscopy were performed on day 23. Endoscopic findings revealed edematous and inflammatory lesions in the gastric and colonic mucosa. The duodenal mucosa was diffusely and severely injured with pseudopolyposis appearance. On both fiberscopic findings, active bleeding and ulceration were not found. On the same day (day 23), CMV antigenemia was detected by an immunohistochemical assay using a monoclonal antibody for CMV pp65 antigen [2]; 44 positive leukocytes were identified among 100,000 cells examined. At this time, a WBC count was 20.4×10^9/l, a platelet count 107×10^9/l, and serum transaminases were within a normal range. CMV pneumonitis, retinitis, and hepatitis were not diagnosed at that time. Biopsy specimens from gastrointestinal lesions did not reveal cells with an inclusion body or CMV antigen-positive cells or lymphoma cell. However, since severe panenterocolitis induced by high-dose chemotherapy and CMV infection were highly suspected, ganciclovir (5 mg/kg twice daily i.v.) was started, and CMV hyperimmune globulin (100 mg/kg once daily i.v.) was also administered for 3 days. A polymerase chain reaction (PCR) assay of stool specimens revealed positivity for CMV on day 30. Ganciclovir was stopped on day 40 because CMV antigenemia became negative, but diffuse abdominal pain, watery diarrhea, and intermittent bloody diarrhea were persistent. CMV antigenemia became positive again (490/100,000 WBCs) on day 51, and ganciclovir (5 mg/kg twice daily i.v.) was restarted along with CMV hyperimmune globulin (100 mg/kg once daily i.v.). CMV antigenemia disappeared on day 77 with ganciclovir treatment, and administration of ganciclovir was terminated on day 79. On day 78, abdominal computed tomography (CT) scans showed diffuse wall thickness with fluid collection in both small and large intestines. These findings strongly suggested the presence of panenteritis and paralytic ileus. Since CMV antigen-positive leukocytes were increased again (284/100,000 WBCs), foscarnet (45 mg/kg twice daily i.v.) was administered instead of ganciclovir. CMV antigen-positive cells gradually decreased, but bloody diarrhea increased. On day 114, 99mTc-RBC abdominal scintigraphy showed the accumulation of radionuclide in the left side of the abdominal aorta by 2-h delayed scanning. This indicated active bleeding from the small intestine, probably from the jejunum. Small intestinal fiberscopy was performed on day 122. On the fiberscopic findings, there was edematous and irregular mucosa without apparent ulceration and active bleeding in the jejunum. Endoscopic biopsy was performed, but biopsy specimens from these edematous and irregular mucosa failed to identify CMV antigen-positive cells and lymphoma cells. At this time, a WBC count was 9.1×10^9/l, a platelet count 65×10^9/l, and serum transaminases were within a normal range. Since bloody diarrhea continued, he underwent exploratory laparotomy on day 127. A jejunal segment of the small intestine showed segmental ulceration and inflammation. Dark blood clots were seen in the jejunum. The involved area of the jejunum (90 cm in length) was resected. On histologic examination, there were erosion, ulceration, and bleeding of the mucosa; many enlarged cells with cytoplasmic inclusions were observed in the endothelium of the erosive areas. An immunohistochemical stain using a monoclonal antibody for CMV pp65 antigen showed strong positive reactions in the endothelium of erosive lesions. Thus, diagnosis of CMV enteritis was confirmed. There were no lymphoma cell infiltrations on histologic examination. After surgical resection of the jejunum, severe abdominal pain subsided and gastrointestinal bleeding stopped. Since then, CMV antigenemia has remained negative up to the time of this report (Fig. 1).

Discussion

Life-threatening CMV disease has been one of the most common infectious causes of death in allogeneic BMT patients [3], but in autologous PBSCT it is uncommon and its incidence is reported to be 2–7% [4, 5]. The incidence of CMV infection is similar between autograft and allograft recipients, but CMV disease, mainly pneumonitis, is significantly less frequent in autologous than in allogeneic BMT (2% vs 12%, $P<0.001$) [4]. The only definable risk factor for CMV infection in autologous BMT recipients is positive CMV serology before transplantation [5].

Among CMV diseases, pneumonitis is the most common, while gastroenteritis is much less common [6] and rarely reported in patients with hematological malignancy or other immunodeficiency [7, 8]. CMV gastroenteritis in an immunocompromised host may cause hemorrhage, perforation, and peritonitis and be life-threatening [9]. Despite aggressive therapy, the operative mortality rate in patients with acquired immunodeficiency syndrome (AIDS) with intestinal perforation due to CMV disease was 54% and the overall mortality rate was 87% [10].

In the initial course of hemorrhagic enteritis, MRSA infection, mucosal injury caused by the conditioning regimen, especially etoposide, or infiltration of lymphoma cells might be associated with hemorrhagic enteritis. However, while stool cultures for MRSA became negative on day 14, hemorrhagic enteritis persisted. The long-term subsequent course of enteritis weighs against the etiology of hemorrhagic enteritis, due to the condi-

tioning regimen. Histology of a biopsied and resected specimen did not show lymphoma cells. Thus, it is unlikely that MRSA infection, chemotherapy-induced mucosal injury, or lymphoma infiltration was a primary cause of persistent enteritis in this patient.

Immune reconstitution of T cell subsets following autologous PBSCT is faster than allogeneic BMT [11]. Among CMV-seropositive autograft recipients, CMV-specific $CD8^+$CTL and $CD4^+$Th responses are restored in a large proportion of patients in the first 3 months after transplantation, and the presence of a specific $CD8^+$CTL activity could afford protection from subsequent CMV infection [12]. It has been known that the incidence of CMV disease is lower in allogeneic PBSCT compared with that in allogeneic BMT [13] and is markedly higher in CD34-selected autologous PBSCT than in unmanipulated autologous PBSCT [14]. This patient received unmanipulated autologous PBSC and still had refractory CMV enteritis with gastrointestinal bleeding. There are some possible explanations for this unexpected outcome of the patient, which include involvement of a CMV strain resistant to antiviral agents and delayed reconstitution of CMV-specific cellular immunity caused by immune suppression induced by NHL itself and high-dose methylprednisolone administered for septic shock on days 7–9.

In conclusion, CMV enteritis is relatively rare after autologous PBSCT, but it should be one of the differential diagnoses in cases of unexplained gastrointestinal hemorrhage. While the optimal therapeutic approach remains to be determined, not only administration of an antiviral drug, but also an early indication for surgical treatment must be considered when massive gastrointestinal bleeding persists.

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