

The Successful Treatment of a Cord Blood Transplant Recipient with Varicella Zoster Virus Meningitis, Radiculitis and Myelitis with Foscarnet

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Abstract

Infections of the central nervous system (CNS) with varicella zoster virus (VZV) is a rare occurrence after allogeneic hematopoietic stem cell transplantation. We herein report a case of VZV meningitis, radiculitis and myelitis that developed 8 months after cord blood transplantation, shortly after the cessation of cyclosporine and low-dose acyclovir. Although treatment with acyclovir did not achieve a satisfactory response, the patient was successfully treated with foscarnet. Our report indicates that VZV infection should be considered in allo-hematopoietic stem cell transplantation (HSCT) patients with CNS symptoms and that foscarnet may be effective for the treatment of acyclovir-resistant VZV infections of the CNS. The development of optimal prophylactic strategies and vaccination schedules may eradicate post-transplant VZV disease.

Key words: varicella zoster virus, meningitis, myelitis, foscarnet, hematopoietic stem cell transplantation

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Introduction

Varicella zoster virus (VZV) disease is one of the most frequent infectious complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT); during the first year, its incidence ranges from 13 to 55% (1). Although cutaneous herpes zoster is the most common clinical form of reactivation, allo-HSCT recipients may present with fatal systemic dissemination (1, 2). Among the various types of VZV infection, infections of the central nervous system (CNS), especially meningitis and encephalitis, are only rarely reported; however, they represent severely life threatening conditions and may compromise the patient's quality of life (3). We herein report a case of post-transplant VZV meningitis and myelitis that developed after the cessation of immunosuppressant therapy, which was successfully treated with the intravenous administration of foscarnet.

Case Report

A 42-year-old Chinese man with myelodysplastic syndrome (MDS, RAEB-2) underwent cord blood transplantation (CBT) from a Japanese donor in October 2011. The conditioning regimen consisted of total-body irradiation (TBI) (12 Gy), cyclophosphamide (total dose, 120 mg/kg), and cytarabine (total dose, 12 g/m²). Prophylaxis against graft-versus-host disease (GVHD) consisted of cyclosporine (CsA) and a short course of methotrexate. Neutrophil engraftment was prompt, and complete remission was confirmed on day 29. CsA was discontinued on day 189, and no signs of GVHD were observed. Acyclovir (ACV) (1,000 mg/day, orally) was administered from day -7 to 35 as prophylaxis against herpes virus. This was maintained at a reduced dose of 200 mg/day until day 213. The patient's serum immunoglobulin G (IgG) levels remained within the

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normal limits, and his peripheral post-transplant leukocyte counts remained within the normal range.

On day 241 after CBT, the patient presented with blisters on his face and on day 245, a herpes zoster rash developed on his face, body, and extremities. Other than slight numbness on his legs, he presented no neurological symptoms. His body temperature was 37.5°C. The patient was clinically diagnosed with a systemic VZV infection and intravenous ACV (5 mg/kg three times a day) was promptly administered. The cutaneous lesions were reduced on the 8th day after the initiation of ACV treatment, and the treatment was then switched to oral valaciclovir. However, the patient developed a high fever, paralysis of the lower extremities, ischuria, neck stiffness, and spinal automatism on the second day of valaciclovir treatment. His consciousness was alert and there were no signs of recurrent cutaneous lesions. Head computed tomography showed no abnormal findings. The patient's cerebrospinal fluid (CSF) showed an increased number of mononuclear cells (77/μL), an elevated protein level, and a normal glucose level. The enzyme immunoassay (EIA) values in the patient's CSF and serum were 2.56 and 13.5, respectively, for VZV-IgG, and 5.32 and 3.90 for VZV-IgM. VZV-DNA was not detected in a polymerase chain reaction (PCR). At 5.3, the ratio of VZV-IgG in the serum and CSF was relatively low. The presentation of spinal automatism, paralysis of the lower extremities and ischuria led to a diagnosis of VZV meningitis, myelitis, and radiculitis. Intravenous ACV was resumed at an increased dose (10 mg/kg, three times a day), on the 12th day after the initial diagnosis of the VZV infection. Magnetic resonance imaging (MRI) of the thoracic vertebrae and the lumbosacral spinal cord on days 6 and 7 after the resumption of ACV, respectively, revealed no evident abnormalities.

Seventeen days after the resumption of ACV, a high mononuclear cell count (69/μL) was still present in the patient's CSF, and the patient's paralysis and ischuria showed no improvement. ACV was then switched to foscarnet (90 mg/kg, twice a day) on day 20 after the initial diagnosis. After 12 days of foscarnet treatment, the patient showed a complete recovery from ischuria and was able to walk by himself. The patient's CSF showed a significantly decreased cell count, and foscarnet was discontinued after 51 days of treatment. On day 25 after the discontinuation of foscarnet therapy, the VZV-IgM level in the patient's CSF dropped to negative value of 0.78, whereas the VZV-IgG level in the patient's CSF rose to 7.53; in contrast, the value at time of the patient's diagnosis was 2.56. The patient has been in complete remission without recurrent neurological symptoms for 3.5 years since transplantation.

Discussion

The long-term administration of ACV after transplantation has been recommended to reduce the risk of VZV reactivation (1). A large retrospective study showed that the prophylactic administration of ACV for 1 year reduced the inci-

dence of VZV disease, and that the incidence was further decreased by the continuation of prophylaxis in patients who remained on immunosuppressive drugs (4-7). However, the cumulative incidence of VZV disease after the cessation of long-term ACV is reported to be approximately 28.4% at 1 year (8), suggesting that further studies are required to evaluate the optimal duration of low-dose ACV prophylaxis. Our patient had a normal peripheral blood lymphocyte count and serum immunoglobulin levels; thus, we discontinued prophylaxis with low-dose ACV after the cessation of CsA, which may have been associated with the reactivation of VZV. Furthermore, one report described the case of a patient without any known risk factors who developed VZV meningoencephalitis at 22 months after HSCT following the cessation of immunosuppressants and prophylactic treatment with low-dose ACV (9). These rare experiences suggest that VZV meningitis is a complication that may occur in any allo-HSCT recipient at any time after transplantation.

The initial symptoms of VZV meningitis and myelitis in post-transplantation patients vary and may include dermatomal zoster before the onset. Leveque et al. (10) reported two recipients who developed meningitis without skin manifestations. In contrast, Fukuno et al. (11) described a bone marrow transplantation recipient in whom VZV meningoencephalitis occurred suddenly at 21 days after the completion of ACV therapy for a localized cutaneous VZV infection. Our patient's disseminated skin lesions developed first, and his neurological symptoms became obvious as the skin rash disappeared after ACV therapy. Thus, CNS infections should always be considered when CNS symptoms emerge without skin lesions or develop after a cutaneous VZV infection.

Although we could not detect VZV DNA in this patient's CSF, the patient's CSF was positive for anti-VZV IgM and IgG, which was helpful in establishing the diagnoses of VZV meningitis and myelitis. The detection of anti-VZV antibodies in the CSF appears to have greater sensitivity in the diagnosis of VZV infections of the nervous system, than the detection of viral DNA. Gregoire et al. reported that VZV-DNA positivity and the detection of antibodies in the CSF can dramatically change during the clinical course of a viral infection (12). In this report, 0% and 61% of the CSF samples that were collected within the first 7 days after the onset of rash were positive for anti-VZV antibodies and VZV DNA, respectively. However, after 7 days the rate of anti-VZV antibody-positive samples increased to 83%, while the rate of VZV DNA-positive samples decreased to 25%. In our present case, CSF sampling was performed on day 15 after the onset of rash, which was a relatively late time point. We hypothesize that the VZV DNA in the CSF decreased to an undetectable level while the CSF became antibody-positive. Thus, both assays are recommended in the assessment of CSF samples in order to accurately diagnose VZV infections (13).

Vaccination may help decrease the risk of reactivation. Although the data on the safety and efficacy of live-attenuated varicella vaccines in allo-HSCT recipients are lim-

ited (14, 15), no serious adverse events were reported in a previous study involving 110 adult allo-HSCT patients (16). Thus, the guidelines recommend varicella vaccination at 2 or more years after transplantation in allo-HSCT patients without active chronic GVHD or ongoing immunosuppressive therapy (evidenced-based rating: CIII) (17, 18). However, even at 2 years after HSCT, 30-40% of the patients are considered to be ineligible for vaccination (19, 20). For these recipients, the continuation of ACV treatment for an extended period of time may be necessary to decrease the incidence of serious VZV reactivation.

Intravenous ACV (10 mg/kg, every 8 hours), is the recommended treatment for VZV infections of the CNS (21). However, ACV activation is dependent on intracellular virus-encoded thymidine kinase (TK), which implies that TK-deficient VZV strains are resistant to ACV. Tauro et al. described a case in which a patient with VZV encephalitis was successfully treated with the addition of foscarnet to ACV (22). The pharmacological action of foscarnet is TK-independent, which enables the elimination of ACV-resistant VZV (23). In our case, ACV appeared to be insufficient for improving the patient's neurological symptoms, and the patient was then successfully treated when ACV was switched to foscarnet, suggesting that an ACV-resistant VZV strain was involved in the patient's meningitis.

It is possible that the strain of VZV that caused the meningitis was the same strain as that which caused the cutaneous infection, and the present patient might have been a late responder to ACV. However, several reports have shown that the interval between the initiation of ACV treatment and clinical improvement ranged from 3 to 9 days in patients with zoster- or varicella-induced myelitis (24-27). The paralysis and ischuria of the present patient showed no improvement during the 17 days in which he received a sufficient dose of intravenous ACV, and the number of mononuclear cells in the patient's CSF showed a minimal decrease. We therefore hypothesized that the strain of VZV that was responsible for the patient's meningitis was ACV-resistant and that it was unlikely that the patient was a late responder to ACV, and decided to switch the therapy to foscarnet.

In conclusion, we described the case of a patient with VZV meningitis, radiculitis and myelitis after the cessation of immunosuppressant therapy and long-term ACV prophylaxis. VZV CNS infections may be severe life threatening events and have the potential to compromise a patient's quality of life. Thus, when initial ACV therapy is found to be insufficient for the treatment of VZV infections in transplant recipients under long-term ACV prophylaxis, physicians should immediately consider changing to second line therapies, such as foscarnet. Further investigation is necessary to develop optimal prophylactic strategies and effective vaccination schedules may be needed to eradicate post-transplant VZV disease.

The authors state that they have no Conflict of Interest (COI).

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