Case Report

Two Cases of Varicella Zoster Virus Meningitis Found in Pediatric Patients After Bone Marrow Transplantation Despite Valaciclovir Prophylaxis and Without Skin Lesions

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Two cases of varicella zoster virus (VZV) meningitis are described in an 18-year-old girl and an 18-year-old boy. They occurred, respectively, 9 days and 9 months after allogeneic bone marrow transplantation. VZV nucleic acid was detected in the cerebrospinal fluid during the 1st week of illness. This recurrence occurred despite valaciclovir prophylaxis and without skin lesions. The two patients received aciclovir intravenously and immunoglobulins infusion. They responded to treatment and their clinical state improved rapidly.


KEY WORDS: immunodeficient patient; valaciclovir prophylaxis; PCR

INTRODUCTION

Varicella Zoster virus (VZV) infection is a frequent complication occurring after bone marrow transplantation due to a severe impairment in cellular immunity. However, the consequences range from asymptomatic viremia to disseminated visceral infection [Han et al., 1994; Koc et al., 2000]. Most cases occur within a year after bone marrow transplant [Han et al., 1994]. Two cases of VZV meningitis are described in two young bone marrow transplant recipients. This unusual complication happened, respectively, 9 days and 9 months after bone marrow transplantation without vesicular skin lesions and despite antiviral prophylaxis.

CASE REPORTS

Case 1

A 14-year-old girl was diagnosed with pre-B-cell acute lymphoid leukemia in July 1998. Complete remission was achieved after the first course of conventional chemotherapy (EORTC 58881 protocol) [Vilmer et al., 2000]. Because of an unusually delayed relapse in March 2002, she underwent a bone marrow transplantation from her healthy HLA identical brother in June, 2002. Conditioning regimen consisted of total body irradiation (12 Gy), ara-cytine 12 g/m², and melphalan 140 mg/m². Graft versus host disease prophylaxis consisted of cyclosporin (3 mg/kg per day). Donor and recipient were VZV positive. The young girl received standard prophylactic doses of valaciclovir (500 mg twice a day) from the start of conditioning until complete immune reconstitution. On day 9 after bone marrow transplant, she presented hyperthermia (39°C), violent headache, and neck stiffness. Two cerebrospinal fluid analyses were performed on day 10 (white blood cells (WBCs) count was 2/mm³ and proteinorachia was 0.64 g/L) and on day 13 (WBCs count was 39/mm³ and proteinorachia was 0.4 g/L), and showed a positive PCR for VZV DNA. Further PCR analyses for herpes simplex type 1 and 2, enteroviruses, and human herpes virus type-6 were negative. On day 10, a 21-day course of intravenous aciclovir 500 mg/m² three times a day was initiated. Aciclovir treatment was associated with polyclonal immunoglobulins 1 g/kg on days 10 and 11 followed by a weekly perfusion for 4 consecutive weeks. From day 31, valaciclovir 3 g twice a day replaced...
intravenous aciclovir. Lack of consciousness alteration and focal neurological signs pointed towards VZV meningitis. Moreover, lungs X-ray, a retinal examination, and liver enzymes were normal. Recovery to a normal neutrophilic leukocytes count (1,610 per mm$^3$) occurred on day 17 thanks to myeloid hematopoietic growth factor which had been started at the beginning of hyperthermia. The patient’s clinical state quickly improved with regression of meningeal symptomatology within a few days.

**Case 2**

A 14-year-old boy was admitted in July 1998 for T-cell acute lymphoblastic leukemia. Complete remission was achieved after treatment according to the protocol EORTC 58881. In February 2001, he presented a meningeal and medullary relapse. He underwent bone marrow transplant from a phenotypically matched unrelated donor in June 2001. Conditioning was total body irradiation followed by etoposide at 60 mg/kg. Donor’s status towards VZV was anti-T-lymphocyte globulins (10 mg/kg) and ciclosporin (3 mg/kg/day). Donor’s status towards VZV was unknown whereas recipient was positive. Standard prophylactic doses of valaciclovir, co-trimoxazol, and penicillin were used to prevent bacterial, viral, and parasitic infections. In March 2002, 9 months after transplantation, the patient developed meningeal syndrome including headaches, vomiting, asthenia, hyperthermia, photophobia, and ocular burning sensations suggesting ophthalmic herpetic zoster. Cerebrospinal fluid analysis revealed 1 g/L proteinorachia and 230 WBCs per mm$^3$ without lymphoblast. PCR analyses for VZV from the cerebrospinal fluid and ocular samplings were positive while PCR analyses for herpes simplex type 1 and 2, enteroviruses, and human herpes virus type-6 were negative. The CD4 lymphocytes count at the time of infection was 216 per mm$^3$. Intravenous aciclovir treatment (500 mg/m$^2$) associated with polyclonal immunoglobulins (1 g/kg) was initiated and continued for 10 days before a 4 g a day valaciclovir course during 3 weeks. The clinical state of the patient improved rapidly. Cerebrospinal fluid analysis performed after 2 weeks showed no VZV DNA while leukocytosis remained.

**DISCUSSION**

Although VZV infection is one of the most common infectious complication after bone marrow transplant (26% within a year and 45% within 5 years in transplanted children), VZV meningitis is a rare occurrence in pediatric hematology probably because of an efficient antiviral chemoprophylaxis [Leung et al., 2000; Novitzky and Rouskova, 2001]. However, two cases of meningitis related to VZV recurrence occurred at the pediatric bone marrow transplant service within 1 year in an 18-year-old girl and an 18-year-old boy, respectively, 9 days and 9 months after allogeneic transplant. Several risk factors reported in the development of VZV infections were found in these cases: children older than 10 at bone marrow transplant and VZV positive, hematologic malignancy (acute lymphoblastic leukemia), allogeneic transplant, conditioning regimen including total body irradiation. This explains why the two children received a prophylaxis consisting of valaciclovir 500 mg twice a day [Han et al., 1994; Koc et al., 2000; Leung et al., 2000; Steer et al., 2000]. As Steer et al. [2000] showed, either aciclovir (200 mg three times a day) or ganciclovir (5 mg/kg three times a week) prevents VZV infections for the time of maximal immunosuppression estimated at 1 year from bone marrow transplant. Poor observance of prophylactic regimen in the two cases could be the first explanation for VZV meningitis. However, the virus might be able to reach the nervous system by direct spread from sensory ganglia where it remains latent and thus escape from the effect of the antiviral prophylaxis [Echevarria et al., 1997].

An unusual element is the lack of vesicular skin lesions before the onset of meningitis. Ophthalmic zoster was the only cutaneo-mucous symptom in the second case. Indeed, visceral and neurological infections may occur without skin lesions [Grant et al., 2002; Tenenbaum et al., 2002]. Thus, PCR assay for VZV should be carried out on cerebrospinal fluid for all children undergoing bone marrow transplant with neurological complications [Yagi et al., 2000; Grant et al., 2002; Tenenbaum et al., 2002]. PCR should be the reference method for the diagnosis of VZV meningitis in immunocompromised host who receive immunoglobulins. These cases seem to prove that chemoprophylaxis against VZV is an important part of the global treatment of transplanted children and, because of poor specific symptoms, VZV PCR assay should be carried out systematically in order to conduct proper antiviral therapy.

**REFERENCES**


