Involvement of the Esophagus and Stomach as a First Manifestation of Varicella Zoster Virus Infection after Allogeneic Bone Marrow Transplantation

Masaaki TAKATOKU*, Kazuo MUROI**, Chizuru KAWANO-YAMAMOTO**, Tadashi NAGAI*, Norio KOMATSU* and Keiya OZAWA*•**

Abstract

A 46-year-old man with myeloproliferative disorder received a stem cell transplant from an HLA-identical unrelated donor. Eight months status post transplantation, during the course of tacrolimus therapy, the patient developed severe epigastric pain and fever. FGS findings showed eruptions with blisters in the esophagus and ulcers in the stomach. Biopsy specimens revealed acidophilic inclusion bodies in the nuclei. Varicella zoster virus (VZV) DNA copies were detected in the serum. No skin lesions were observed prior to hospital admission. The diagnosis of visceral VZV infection was made and the gastric and esophageal lesions were successfully healed with acyclovir (ACV). Severe abdominal pain is one of the most important signs of VZV infection for recipients of stem cell transplantation.

Key words: visceral varicella zoster, gastric ulcer, BMT, FGS, acyclovir

Introduction

VZV infection is the most common viral disease in the late post-transplant period following allogeneic bone marrow transplantation (BMT), occurring with a frequency of 17% to 50% (1–4). Typically, the infection remains cutaneous, although visceral dissemination is well-recognized, and carries an appreciable risk of mortality. Visceral disease nearly always occurs after skin lesions have been noted (5, 6), although there have been occasional reports of the disease occurring without any cutaneous manifestations.

In our case, we were able to diagnose visceral VZV infection via fiber-gastroscopy (FGS) prior to the appearance of the classical skin rash. Immediate therapy with ACV led to a successful outcome for the patient’s visceral VZV infection.

Case report

A 46-year-old man was diagnosed with a severe myeloproliferative disorder in 1997. The patient developed leukemic cell infiltration in the pulmonary and anal regions in November 1999. Due to a lack of HLA-identical siblings, he received an allogenic bone marrow transplant from an unrelated HLA-identical male donor on February 23, 2001. DRB1 genotype was identical in both the donor and the recipient. The conditioning regimen consisted of total body irradiation at 1,200 cGy in six fractions from days –10 to –8; cytarabine, 1 g/m² twice daily from days –6 to –4; and cyclophosphamide, 60 mg/kg from days –3 and –2. GVHD prophylaxis involved short-term methotrexate and tacrolimus. Serum VZV titer was positive.

The following complications arose during the post-transplant course. On day 26 post-BMT, adult respiratory distress syndrome (ARDS) was diagnosed and was subsequently successfully treated with prednisolone. On day 82, mild GVHD (grade I) developed, and was responsive to a short course of prednisolone. On day 87, steroid and tacrolimus-induced diabetes developed, requiring treatment with insulin. On day 119, pneumocystis carinii pneumonia developed, which was treated with sulfamethoxazole/trimethoprim. On day 140, serum IgG and IgA levels were 652 mg/dl and 98 mg/dl, respectively, and CD4/CD8 ratio was 0.8.
The patient was readmitted on November 4, 2001 (day 255), after reporting a four-day history of progressively worsening severe epigastric pain radiating to the back, and a moderate grade fever (below 39°C). The presence of mild stomatitis strongly suggested chronic GVHD. Tacrolimus had been continued at 1.4 mg/day for treatment of chronic GVHD, and the serum trough level was 9.9 ng/ml the morning after admission. Prior to the onset of abdominal pain, no history of exposure to VZV was reported.

Physical examination revealed marked epigastric tenderness without rigidity. Back pain was exacerbated in the standing position. No eruptions were observed on the face or trunk. Laboratory results were as follows: WBC 4.9×10^9/l, Hb 14.0 g/dl, and platelet count 42×10^9/l. Liver and renal function were normal. C-reactive protein titer was elevated (2.6 mg/dl). VZV DNA was detected in serum at 900 copies/10^9 cells by PCR, while HSV and CMV DNA were not detected. On admission, FGS examination was performed. Several blistering eruptions were noted on the esophageal mucosa (Fig. 1A) and active stage (A2) ulcers were visualized in the mid-portion of the stomach (Fig. 1B). On the same day, initial pathologic examination of biopsied mucosa from the gastric ulcers demonstrated acidophilic nuclear inclusion bodies and cytoplasmic edema (Fig. 1C), typical features of VZV-infected tissue. Serum VZV DNA results were obtained the morning after admission, confirming a diagnosis of visceral dissemination of VZV. Intravenous ACV (5 mg/kg three times daily) was therefore commenced immediately and eruptions appeared on the patient’s face, scalp, trunk, and oral mucosa on the evening of the same day. Shortly after ACV treatment was commenced, the epigastric pain resolved. On the seventh day of admission, the skin lesions had dried and crusted over and by the tenth day healing (H1 stage) of the gastric ulcers was observed (Fig. 1D). The patient was discharged 14 days after admission.

Discussion

Various viral diseases (including CMV, adenovirus, and EBV) are among the important complications that may present months after hematopoietic stem cell transplantation (7). However, as the clinical course is not uniform, it can be very challenging to arrive at a prompt diagnosis from the presenting clinical symptoms seen in the early phase. Although early treatment following immediate diagnosis is very important, diagnosis is often only possible after significant clinical progression of the infectious disease.

In the present case, fever and intense abdominal pain without cutaneous symptoms appeared eight months after allogeneic bone marrow transplantation. At that time, the differential diagnosis was considerable, including acute gastric ulcer, acute enteritis, ileus, mesenteric artery thrombosis, acute pancreatitis, acute cholecystitis, and urinary calculi. In order to evaluate the abdominal distress, we initially performed physical examination, routine laboratory tests, and abdominal roentgenography. It was subsequently recognized that FGS should be urgently performed for diagnosis. On endoscopy, biopsies of the gastric lesions were taken, enabling immediate diagnosis of VZV infection.

The differential diagnosis of abdominal pain after stem cell transplantation is vast and varied, including gram-positive bacterial, fungal, or viral (VZV, HSV, EBV, CMV) infectious disease; enteritis due to chronic GVHD; TMA (thrombotic microangiopathy); and ischemia. In many cases, serologic examination is useful for differentiating between these causes of abdominal pain. While in some cases serum virus antibody titer, ultrasound imaging, or roentgenography are useful for diagnosis, these tests may not enable definitive diagnosis in all cases. When questions remain, digestive tract endoscopy is a very useful modality for quickly arriving at a diagnosis, because it allows direct observation and biopsy of lesions.

The important differential diagnoses are CMV gastritis and Herpes simplex infection. In the present case, ulcer tissue demonstrated VZV-specific findings such as nuclear acidophilic inclusion bodies, cytoplasmic bullous edema, and large cells with multiple nuclei. On November 17, the final pathologic report indicated that immunopositivity was only seen for VZV, with no tissue staining for CMV or Herpes simplex 1. These results thus confirmed the initial diagnosis.

The frequency of VZV infection in recipients of allogeneic BMT ranges from 17% to 50% (1–4). VZV is one of the most common late infections, typically occurring 3–6 months after transplantation. In the majority of patients, VZV infection occurs as a result of reactivation of latent virus, and usually presents as a dermal infection with subsequent cutaneous dissemination (1). Approximately 10–15% of patients progress to further visceral dissemination, which carries a reported mortality of 9% (2). In the present case, VZV infection occurred during tacrolimus administration, on day 255 after BMT. This was unusual, as activation of latent virus generally occurs earlier in the post-transplant course. It is unclear which patients have a high risk of VZV visceral dissemination following BMT. Nevertheless, there is no evidence that chronic GVHD prophylaxis with tacrolimus increases the risk of visceral VZV infection (2, 8).

Recently, Yagi et al (8) reported that seven of nine patients with VZV infection presented with abdominal pain as their initial symptom, prior to the appearance of skin lesions. However, FGS was not performed during the initial diagnostic workup in any of these cases. In this report, we describe a case of visceral VZV infection in which FGS enabled direct diagnosis prior to the manifestation of skin lesions. We believe that the immediate institution of ACV treatment following the prompt diagnosis of visceral VZV infection resulted in attenuation of this infection, which is generally associated with a high risk of mortality.

Severe abdominal pain is one of the most important and earliest signs of VZV infection in immunocompromised hosts, such as recipients of stem cell transplantation (8). We suggest FGS to be the most useful and definitive examina-
tion in these circumstances, allowing immediate diagnosis and rapid institution of antiviral therapy to treat this life-threatening disease.

Figure 1. Fiberscope findings at admission. Eruptions with blisters in the esophagus (A) and an active stage ulcer in the midportion of the stomach (B) were observed. Cells in the stomach ulcer had nuclear acidphilic inclusion bodies (arrows) and cytoplasmic edema (C). The stomach ulcer was in a healing stage after acyclovir treatment (D).

References


