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Case Study

Fatal Visceral Varicella-Zoster Developing Early after Autologous Hematopoietic Stem Cell Transplantation for Refractory Diffuse Large B-Cell Lymphoma

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A middle-aged woman who had undergone autologous hematopoietic stem cell transplantation (HSCT) 1 month previously suffered severe epigastralgia and relapse of lymphoma. The epigastralgia was not relieved by chemotherapy. Thereafter, her pancreatic and hepatic enzyme levels were markedly elevated and disseminated varicella emerged. Despite acyclovir administration, her general condition deteriorated rapidly and she died. Serum varicella zoster virus (VZV) DNA level was shown to be elevated and a diagnosis of disseminated VZV infection was established postmortem. In patients with severe abdominal pain following HSCT, early suspicion and therapeutic intervention for VZV are important, even in the absence of skin lesions. 〔*J Clin Exp Hematop 54(3) : 237-241, 2014*〕

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INTRODUCTION

Varicella zoster virus (VZV) is a common herpes virus and causes two types of disease in immunocompetent populations. First, primary infection results in chickenpox (varicella), an acute infection that usually occurs in children and is characterized by generalized vesicular rash. Second, VZV develops latent infection and causes herpes zoster in adults, which is characterized by grouped painful vesicular lesions in the distribution of some dermatomes.

VZV infection and reactivation occur frequently and can be fatal in immunocompromised patients, especially those who have previously undergone hematopoietic stem cell transplantation (HSCT).[1] In such patients, VZV can develop disseminated infection toward the skin as well as visceral organs, which may mimic acute pancreatitis or hepatitis.[2] Visceral VZV infection is associated with severe and intractable abdominal pain, and can precede the emergence of skin lesions or biochemical and radiological abnormalities suggesting visceral diseases.[2] In such cases, it is difficult to make a diagnosis of VZV infection, and a delayed diagnosis can result in a fatal outcome.

Here, we present a case of fatal visceral disseminated VZV infection that developed early after high-dose chemotherapy and autologous peripheral blood stem cell transplantation for refractory diffuse large B-cell lymphoma. In this case, skin lesions did not appear before visceral VZV infection caused severe pancreatitis and hepatitis, which made it difficult to diagnose the VZV infection earlier.

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CASE REPORT

A 49-year-old woman was diagnosed with diffuse large B-cell lymphoma at clinical stage IIIA in June 2012, and received eight courses of standard chemotherapy (R-CHOP regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). Complete response was achieved, but disease relapse was confirmed in May 2013. She underwent three courses of a salvage chemotherapy regimen consisting of rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP regimen), which resulted in a

partial response. Thereafter, she received high-dose chemotherapy, followed by autologous peripheral blood stem cell transplantation in September 2013. High-dose chemotherapy consisted of melphalan, cyclophosphamide, etoposide, and dexamethasone (LEED regimen). Prophylaxis for VZV (acyclovir 1,000 mg/day) had been performed from 1 week before until 4 weeks after transplantation. Antibody titers for VZV before transplantation were not investigated. Unfortunately, disease relapse was established within a month after transplantation. In addition, she had been suffering from severe abdominal pain from the middle of October 2013, and was readmitted to our department two weeks later.

At the time of readmission, she complained of severe abdominal pain. She was afebrile and had stable vital signs. Her consciousness level was clear and there were no apparent neurological deficits. Physical examination revealed cervical and lymphadenopathy and tenderness of the upper abdomen, without signs of peritoneal irritation. There were no skin eruptions. A complete blood count revealed mild leukopenia (white blood cell count 2,000/μL with 49.5% neutrophils, 35% lymphocytes, and 14% monocytes), without anemia or thrombocytopenia. Biochemical analyses revealed elevation of lactic dehydrogenase (565 IU/L); however, the levels of the other liver enzymes were within normal limits. Renal function and electrolytes were normal. There was no elevation of amylase or lipase. Computed tomography revealed swelling of systemic lymph nodes, including cervical, mediastinal, and intraabdominal areas (Fig. 1a, 1b). No hepatosplenomegaly, ascites, or pleural effusion was detected. In summary, there were no apparent abnormalities except the recurrence and progression of lymphoma, and we initially considered that her abdominal pain was due to rapid progression of lymphoma.

Her clinical course after admission is shown in Fig. 2. For prompt relief of abdominal pain, we initiated salvage chemotherapy consisting of etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisolone (EPOCH regimen) on the second hospital day. Cervical lymphadenopathy decreased rapidly; however, her abdominal pain did not improve. On the third hospital day, serum sodium concentration decreased below 130 mEq/L with serum hypoosmolality. This was considered to be due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), considering the following findings: sustained hyponatremia (121 mEq/L), serum hypoosmolality (244 mOsm/L), urine hyperosmolality (571 mOsm/L), normal renal function (serum creatinine level of 0.34 mg/dL), and sustained urine excretion of sodium (215 mEq/L). SIADH was initially suspected to have been caused by the administration of vincristine. The patient was treated with intravenous sodium supplementation, and hyponatremia was improved by the seventh hospital day. On the ninth day, we detected rapid elevation of serum hepatic and pancreatic enzyme levels and coagulatory disturbance. Serum C-reactive protein level had not been elevated and she remained afebrile throughout the course. Computed tomography revealed swelling of the pancreas, ileus, pleural effusion, and ascites (Fig. 3a-3c). We suspected acute pancreatitis and began intensive care, including protease inhibitor administration. However, the next day, hepatic and liver enzyme levels were further elevated and coagulatory disturbance was also exacerbated, resulting in apparent disseminated intravascular coagulation. At this time, vesicular eruptions emerged, which were scattered around the trunk of her body. Therefore, we strongly suspected disseminated VZV infection and began administration of acyclovir and intravenous immunoglobulin. However, the disease progressed, and she died due to multiple organ failure on the 11th hospital day. After her death, it was ascertained that VZV DNA levels on the 10th hospital day were extremely elevated (10^6 copies/mL). Taking into account previous reports about cases of VZV infection associated with SIADH and visceral zoster in patients after HSCT, we considered that the series of symptoms and signs de-

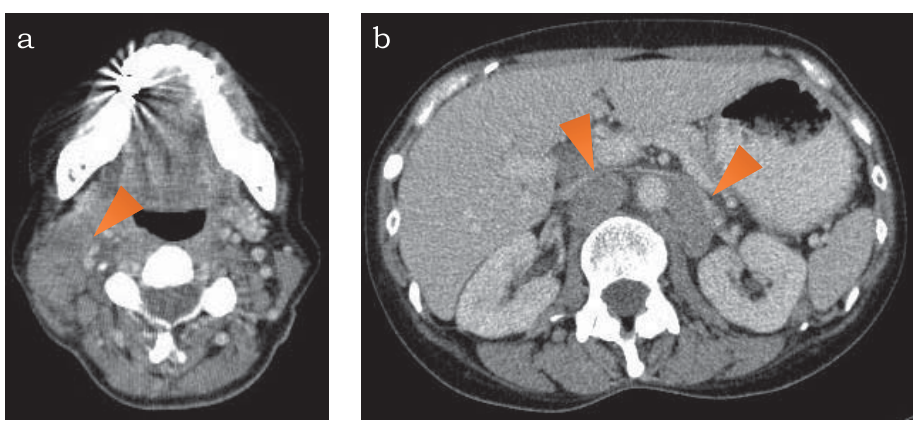

Fig. 1. Computed tomography on admission showed relapse of lymphoma in cervical (*1a*) and intraabdominal (*1b*) lymph nodes.

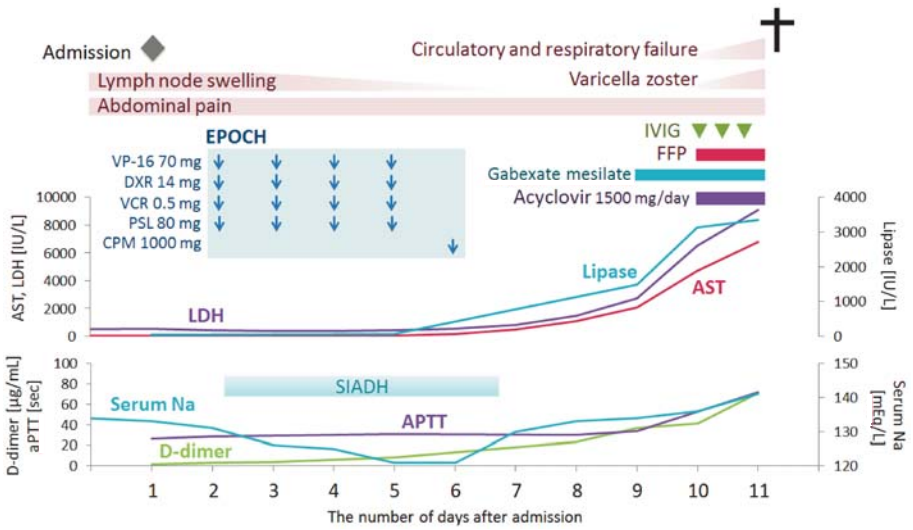

Fig. 2. Clinical course after admission. aPTT, active partial thromboplastin time; AST, aspartate transaminase; CPM, cyclophosphamide; DXR, doxorubicin; FFP, fresh frozen plasma; Hb, hemoglobin; IVIG, intravenous immunoglobulin; LDH, lactic dehydrogenase; PLT, platelet; PSL, prednisolone; VCR, vincristine; VP-16, etoposide; WBC, white blood cell

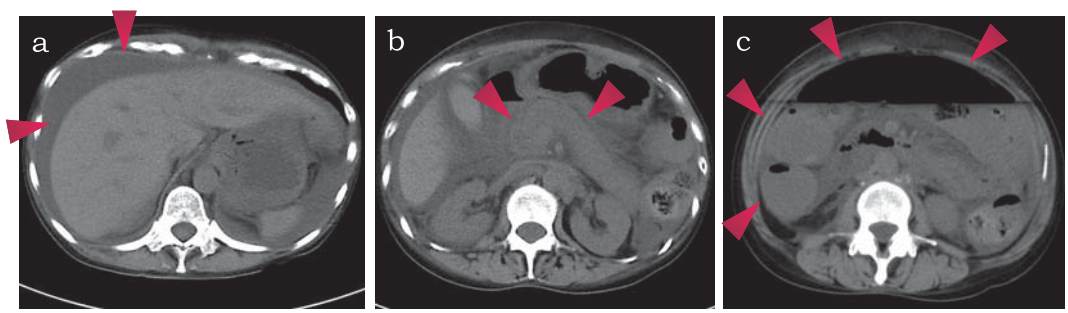

Fig. 3. Computed tomography on the 9th hospital day showed pleural effusion and ascites (*3a*), swelling of the pancreas (*3b*), and ileus (*3c*).

scribed above were caused by disseminated VZV infection. Both anti-VZV-IgG and -IgM proved to be negative on the day before her death, and anti-VZV antibodies had not been examined before.

DISCUSSION

Recurrent infection due to VZV reactivation occurs frequently after HSCT. In most cases, VZV reactivation occurs within 1 or 2 years after transplantation. It has been reported to arise in up to 50% of patients following HSCT.[3] Disseminated infection and visceral infiltration of VZV are not infrequent, and in some cases with visceral spread of VZV infection, skin lesions do not appear, which is called visceral zoster. In many cases of visceral zoster, there are no symptoms or signs except for abdominal pain at presentation, and the patients often develop severe pancreatitis or hepatitis resulting in high mortality rates.[2,3]

Prompt therapeutic intervention is critical to save the lives of these patients. However, it is difficult to make a diagnosis of VZV disease until skin lesions appear. Doki *et al*. analyzed and reported the clinical characteristics and courses of 20 cases of visceral zoster that developed after allogeneic HSCT.[2] They reported that treatment with intravenous acyclovir was performed in most cases, and the overall mortality rate was 20%.[2] It is important to consider VZV disease in cases in which abdominal pain appears following HSCT, which cannot be explained by other factors. Although elevation of VZV DNA copy number is important for diagnosis,[4,5] we should initiate therapy with antiviral drugs at the time of initial suspicion of VZV disease before confirmation of the diagnosis.

It has been reported that disseminated VZV infection after HSCT is sometimes associated with SIADH (Table 1). In

Table 1. Recently reported cases of varicella zoster virus (VZV) infection and inappropriate antidiuretic hormone secretion (SIADH) after autologous hematopoietic stem cell transplantation (HSCT)

Report	Age/Sex	Disease	Donor	Symptoms	Serum Na level (mEq/L)	Time from transplant to VZV disease	Time from onset of VZV disease to emergence of skin lesion	Method of diagnosis	Therapy	Prophylaxis for VZV	Outcome
Szabo, 2000[14]	57/F	CML	Sibling	Abdominal pain, vomiting	120	6 mon	9 days	Culture of vesicular content	ACV, vACV	−	Remission
McIlwaine, 2001[15]	61/F	FL	Autologous	Abdominal pain, somnolence	108	13 mon	10 days	PCR for vesicular content	ACV	−	Death on the 11th day
Au, 2003[8]	38/M	CML	Unrelated	Abdominal pain, vomiting	104	12 mon	10 days	Immunofluorescence for vesicular content	ACV, IVIG	−	Remission
Au, 2003[8]	32/F	ALL	Sibling	Abdominal pain	124	14 mon	7 days	Immunofluorescence for vesicular content	ACV, IVIG	−	Remission
Vinzio, 2005[16]	50/M	AML	Autologous	Abdominal pain, vomiting, fever	123	10 mon	5 days	Antibody titer	ACV	5 months from transplant	Remission
Rau, 2008[4]	19/F	ALL	Unrelated	Abdominal pain	129	16 mon	6 days	Serum PCR (10^5 copies/mL)	ACV	15.5 months from transplant	Remission
This case	50F	DLBCL	Autologous	Abdominal pain	121	1.5 mon	9 days	Serum PCR (10^7 copies/mL)	ACV, IVIG	5 weeks from transplant	Death on the 10th day

ACV, acyclovir; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; FL, follicular lymphoma; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; vACV, valacyclovir

such cases, abdominal pain and SIADH could precede the emergence of skin lesions, and these signs could be strong indicators suggesting VZV infection. It has also been reported that SIADH occurred in cases of localized zoster.[6,7] These observations suggest that there is a certain mechanism by which VZV infection can be associated with SIADH. Some researchers have speculated that VZV infection of the central nervous system would lead to excessive secretion of ADH;[8,9] however, this remains to be confirmed. In the present case, SIADH was initially speculated to be caused by chemotherapy, including vincristine, which was reported to be associated with SIADH;[10] however, considering previous reports about cases of VZV infection associated with SIADH and visceral zoster in patients who underwent HSCT (Table 1), we considered that SIADH was caused by disseminated VZV infection. We could not examine cerebrospinal fluid, and it is not ruled out that VZV infiltration towards the central nervous system could cause SIADH. Moreover, as shown in Table 1, most reported cases of visceral zoster and SIADH developed at least several months after HSCT; in the present case, the diseases emerged atypically early after transplantation.

Prophylaxis for VZV infection after HSCT is important. Especially in the early phase after allogeneic HSCT, acyclovir administration for VZV prevention is well established. Moreover, Kawamura *et al*. reported that long-term administration of low-dose acyclovir (200 mg/day) is effective for the prevention of VZV disease.[11] On the other hand, VZV prophylaxis following autologous HSCT has not been established, but it was recently reported that long-term (12 months) administration of acyclovir or valacyclovir could reduce VZV reactivation.[12] Although it remains to be determined how long prophylactic antiviral drugs should be administered after HSCT, it might be better to perform long-term prophylaxis for VZV because severe VZV disease can occur more than a year after HSCT.[2] In the present case, prophylactic administration of acyclovir was performed for 1 month after transplantation, and VZV disease emerged when acyclovir treatment was stopped. This suggested profound immune dysfunction due to successive and heavy chemotherapy. Furthermore, EPOCH chemotherapy might affect systemic dissemination and advancing severity of VZV disease due to further suppression of immune function.

We could not conclude whether VZV reactivation or primary infection occurred in the present case. Anti-VZV antibodies had not been examined before the admission, and both anti-VZV-IgG and -IgM proved to be negative after the outbreak of VZV disease. These factors cannot prove the primary or recurrent infection of VZV because severe immunodeficiency due to intensively performed chemotherapy and hematopoietic stem cell transplantation can lead to negative conversion of antiviral antibodies.[13]

In conclusion, we encountered a case of fatal VZV infection, which occurred as early as several weeks after autologous transplantation for refractory aggressive lymphoma. Sequential chemotherapy for lymphoma may lead to severe dysfunction of the immune system, which can lead to the emergence of fatal and insidious VZV infection. Long-term

administration of antiviral drugs may prevent such VZV disease.

CONFLICT OF INTEREST

The authors declare no competing interests.

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