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【 CASE REPORT 】

The Efficacy of Amenamevir for the Treatment of Disseminated Herpes Zoster Complicated with Probable Varicella-zoster Pneumonia in an Immunocompromised Patient

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Abstract:

We herein report the case of a 78-year-old woman who was diagnosed as having disseminated herpes zoster (DHZ) complicated with probable varicella-zoster pneumonia during maintenance therapy for microscopic polyangiitis. Because the patient had severe renal dysfunction, amenamevir administration was started to avoid any neurotoxicity of acyclovir, which is suggested to be optimal for treatment. It ameliorated her symptoms without any adverse events. This is the first report suggesting the efficacy of amenamevir in the treatment of severe herpes zoster infection with coexisting DHZ and probable varicella-zoster pneumonia. Amenamevir could thus be a treatment option for severe varicella zoster virus infections.

Key words: disseminated herpes zoster, varicella-zoster pneumonia, amenamevir

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Introduction

Herpes zoster, commonly known as shingles, is characterized by the reactivation of the latent varicella zoster virus (VZV) leading to a painful unilateral vesicular eruption, which has a restricted dermatomal distribution (1). The incidence risk of this condition markedly increases with age and depends on the host's immune status. Immunocompromised patients with impaired T cell-mediated immunity are at increased risk of VZV reactivation, including transplant recipients; patients treated with chemotherapies, immunomodulatory therapies, and/or corticosteroids; and those with human immunodeficiency virus (HIV) infection (2). Disseminated herpes zoster (DHZ) is a rare and serious condition that develops in patients undergoing immunosuppressive treatment. It is characterized by the development of multiple vesicular skin lesions with a generalized distribution distant from dermatomes due to herpes zoster rash. DHZ tends to be accompanied by visceral involvement, such as pneumonia, hepatitis, or encephalitis (3-5).

Amenamevir, a potent helicase-primase inhibitor, is a novel antiviral agent different from major nucleoside compounds such as acyclovir, valacyclovir, and famciclovir. To date, patients with severe herpes zoster infection tend to be treated with intravenous acyclovir, while paying close attention to any associated toxicity, especially in those with renal insufficiency (6, 7). In contrast, amenamevir does not require dosage modification in accordance with creatinine clearance because it is mainly eliminated via the hepatic metabolism (8). To our knowledge, this is the first report of successful treatment of DHZ complicated with probable

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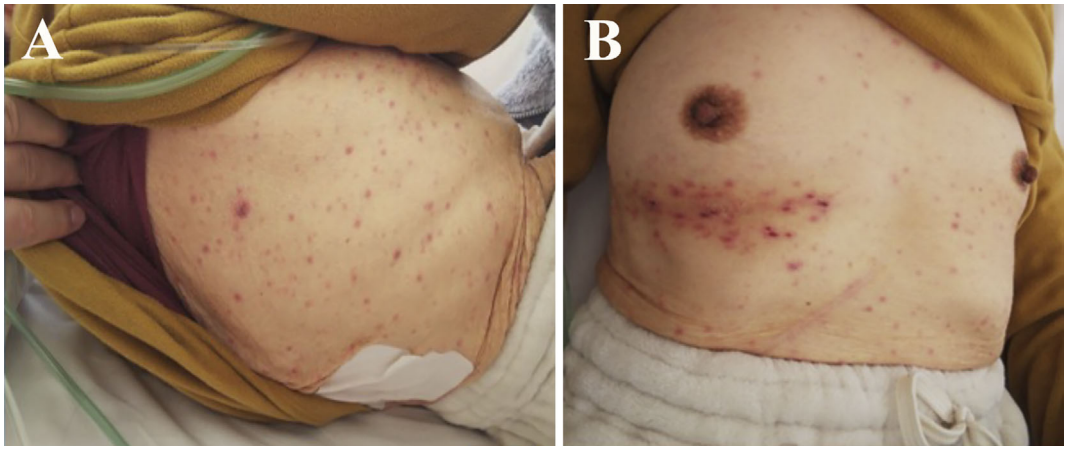

Figure 1. Disseminated eruptions with or without eschar seen on the patient's back (A) and multiple vesicles seen on her right hypochondrium (B).

varicella pneumonia using amenamevir. Our findings indicate that amenamevir could be a treatment option for severe VZV infections, particularly in patients with an impaired renal function.

Case Report

A 78-year-old woman was diagnosed with rapid progressive glomerulonephritis and interstitial pneumonia due to microscopic polyangiitis (MPA) 4 years previously, for which treatment with a combination of high-dose steroids and intravenous cyclophosphamide was started. The induction treatment for MPA successfully improved her signs and symptoms; however, her renal function did not improve to the previous extent, thus resulting in chronic renal failure. As a maintenance treatment for MPA, prednisolone (7 mg/day) and mizoribine (150 mg/day) were continued for more than 2 years. She developed general fatigue and fever 6 and 3 days, respectively, before hospitalization. Subsequent to the development of fatigue and fever, she developed oral ulcers, a rash on her trunk, and a cough. She presented to the emergency department of our hospital because she developed a shortness of breath. She had no history of herpes zoster infection or contact with a person who had chickenpox.

Her vital signs on admission were as follows: blood pressure, 100/64 mmHg; pulse, 107 beats/min; body temperature, 38.7°C; respiratory rate, 24 breaths/min; and oxygen saturation, 94% at room air. Her consciousness was clear. Her height and weight were 152.2 cm and 34.5 kg, respectively. Physical examination revealed coarse crackles in her right lung, multiple skin vesicles on the right hypochondrium, and disseminated punctate eruptions with or without eschar on the trunk, lumbar region, and dorsal thigh (Fig. 1).

The results of the laboratory investigations performed upon admission are shown in Table. Briefly, the investigations revealed lymphopenia, elevated serum levels of acute inflammatory reactants, an impaired renal function, and positivity for both VZV-IgM and IgG. The titer of the anti-neutrophil cytoplasmic antibody specific for myeloperoxidase was low, which was highly positive at the time of the diagnosis of MPA in the patient. The patient's serum Krebs von den Lunge 6 (KL-6) levels were slightly higher than before.

X-ray radiography and computed tomography (CT) of the chest revealed new patchy ground-glass opacities with coalescence of nodules in the right lung (Fig. 2). These findings were comparable to those associated with varicella-zoster pneumonia (9, 10). Since bronchoalveolar lavage fluid test findings were unavailable, it could not be ruled out that the cause of the new lung involvement was something other than a VZV infection, such as an exacerbation of existing interstitial pneumonia due to MPA at that time.

A diagnosis of DHZ was made based on the definition: more than 20 vesicles outside the primary and immediately adjacent dermatomes. Because the patient had severe renal dysfunction (estimated glomerular filtration rate: 14 mL/min/1.73 m^2), amenamevir 400 mg once daily was started to avoid neurotoxicity due to antiviral nucleoside analogs. On the other hand, in the treatment of MPA, the regular dose of prednisolone (7 mg/day) was continued and mizoribine was discontinued. Treatment with amenamevir for 21 days successfully improved the skin eruptions and respiratory symptoms. After the treatment for DHZ, ground-glass opacities in the lung with nodules and serum KL-6 levels improved without the need to administer any immunosuppressive therapies (Fig. 2). Taking these findings into consideration, the patient's condition was clinically diagnosed as varicella-zoster pneumonia complicated with DHZ.

Discussion

DHZ, one of the severe VZV infections, could develop in patients treated with immunosuppressive therapy. The cutaneous dissemination of herpes zoster is followed by visceral involvement, such as that of the lung, liver, and brain, and delays in the treatment can be fatal (3-7). The incidence risk

Table. Laboratory Findings at the Onset of Varicella-zoster Virus Infection.

Complete blood count		BUN (8.0-22.0)	55.9 mg/dL
White blood cells (3,040-8,540)	9,350 /μL	Cre (0.40-0.70)	2.69 mg/dL
Neutrophils (49.7-72.7)	92.5 %	eGFR	14 mL/min/1.73 m^2
Lymphocytes (24.5-38.9)	5.9 %	***Serological tests***	
Monocytes (1.7-8.7)	1.4 %	CRP (<0.2)	14.59 mg/dL
Eosinophils (0.0-5.0)	0.1 %	IgG (870-1,700)	748 mg/dL
Red blood cells (378-499)	352×10^4 /μL	KL-6 (<500)	1,346 U/mL
Hemoglobin (10.8-14.9)	10.1 g/dL	MPO-ANCA (<3.5)	8.2 U/mL
Platelets (15.0-36.0)	18.0×10^4 /μL	PR3-ANCA (<3.5)	<3.5 U/mL
Biochemistry		VZV-IgM	7.09
AST (13-33)	47 U/L	VZV-IgG	≥128
ALT (8-42)	34 U/L	T-SPOT	(-)
LDH (119-229)	557 U/L	CMV antigenemia	(-)
CK (45-163)	110 U/L	β-D glucan	(-)

eGFR: estimated glomerular filtration rate, KL-6: Krebs von den Lunge 6, MPO: myeloperoxidase, ANCA: anti-neutrophil cytoplasmic antibody, PR3: proteinase3, VZV: varicella-zoster virus, CMV: cytomegalovirus

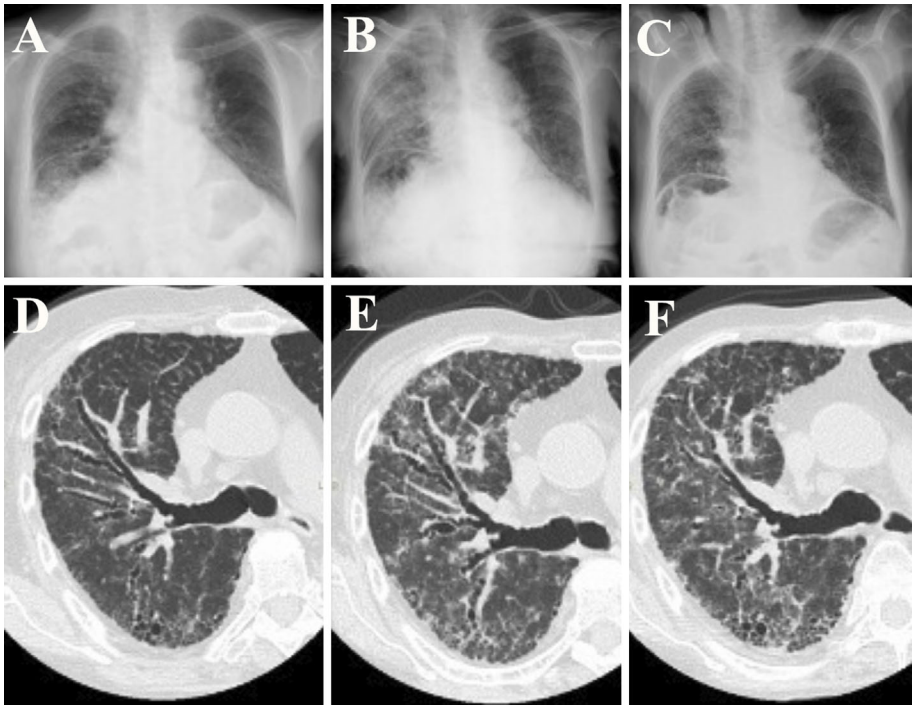

Figure 2. Lung involvement visible on chest X-ray radiography and computed tomography (A, D) before VZV infection, (B, E) at the onset of VZV infection, and (C, F) after treatment with amenamevir. VZV: varicella zoster virus

ratio of DHZ in immunocompromised adults is 32.8 compared to that in immunocompetent adults (11). The clinical course of our case suggests that even patients receiving mild immunosuppressive treatment with low doses of prednisolone and mizoribine may develop a severe VZV infection.

Although intravenous acyclovir is commonly used to treat DHZ or varicella-zoster pneumonia (3-6), the blood concentration of the drug mainly depends on the renal function, and dose adjustment may sometimes be needed. In addition, side effects of acyclovir, such as neurotoxicity and nephrotoxicity, tend to develop in patients with moderate-to-severe renal insufficiency (12, 13). In contrast, amenamevir does not require dosage modification in accordance with creatinine clearance, thus indicating that it is likely a useful treatment option for patients with VZV infection who have renal impairment (8, 14).

A randomized control trial was conducted to demonstrate the efficacy of amenamevir against VZV infection in immunocompetent patients (15). However, there has been little evidence of amenamevir use in immunocompromised patients with DHZ or varicella-zoster pneumonia. One report suggested the efficacy of amenamevir against VZV infection intractable to treatment with valacyclovir in an immunocompromised host (16). Another suggested treatment efficacy

against VZV infection with polyradiculoneuritis in an immunocompromised patient who was treated with a combination of amenamevir and acyclovir (17).

The limitation of our investigation is that the diagnosis of varicella-zoster pneumonia in our patient was not based on histological assessments or the results of polymerase chain reaction using lung specimens. However, the typical CT findings and the improvement of lung involvement and serum KL-6 level with amenamevir treatment suggest that the new lung involvement was related to VZV infection (10). Moreover, a transient increase in the serum KL-6 levels due to viral pneumonia has been previously reported in the literature (18), although it is a useful marker for evaluating the activity of interstitial pneumonia due to collagen diseases (19). In conclusion, to our knowledge, this is the first case report suggesting the effectiveness of amenamevir in the treatment of severe VZV infection complicated with DHZ and probable varicella-zoster pneumonia.

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

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