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Case Report

Time course of skin rash, computed tomography findings, and viral load in a rheumatoid arthritis patient with severe varicella pneumonia

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ABSTRACT

Varicella-zoster virus (VZV) infection in adults or immunocompromised patients has a more severe presentation compared to the mild disease in children. To the best of our knowledge, no reports have described the clinical course of VZV pneumonia focusing on time course of skin rash, chest computed tomography (CT) findings, and viral load. Furthermore, no reports have described the reactivation of human herpes virus 6 (HHV-6) in VZV pneumonia. Here, we report a case of severe VZV pneumonia that resulted in reactivation of HHV-6 in a patient with rheumatoid arthritis (RA). A 66-year-old female treated for RA was admitted to our hospital with papules. Her chest CT showed granular infiltrates, micronodules, and ground-glass opacities. The day after admission, because the typical skin rashes and chest CT findings were observed, she was diagnosed with VZV pneumonia and treated with acyclovir. Her skin rash then crusted over five days and entered the healing process, whereas it took approximately two weeks for her respiratory condition and chest CT findings to improve. In addition, VZV deoxyribonucleic acid (DNA) gradually decreased with treatment. On the 34th day of admission, VZV DNA was not found in the serum sample but remained in the sputum sample. Furthermore, although reactivation of HHV-6 was observed, viremia resolved without treatment. Clinicians should be able to recognize the differences in the improvement of skin rashes, respiratory status, and chest CT findings. In addition, treatment for HHV-6 reactivation should be carefully determined for each case.

Introduction

Although primary varicella-zoster virus (VZV) infection in children is generally mild, VZV infection or reactivation in adults or immunocompromised patients can lead to a severe presentation [1]. Several studies have reported VZV pneumonia in immunocompromised patients [2–4]. However, to the best of our knowledge, none of the reports have described the clinical course of VZV pneumonia focusing on the time course of skin rash, chest computed tomography (CT) findings, viral load, and antibody titer. Furthermore, no reports have described the reactivation of human herpes virus 6 (HHV-6) in VZV pneumonia. Herein, we report a case of severe VZV pneumonia that resulted in HHV-6 reactivation in a patient with rheumatoid arthritis (RA).

Case

A 66-year-old female was admitted to our hospital with papules on her face, anterior chest, and groin along with dyspnea (Fig. 1 A). Her chest CT showed evidence of new pulmonary infiltrates. Her medical history included RA, for which she was being treated with methotrexate (12 mg/week), iguratimod (25 mg/day), and prednisolone (5 mg/day) from the past 7 months.

On admission, she was afebrile (37.3 °C), and her respiratory rate was 18 breaths/min. Her oxygen saturation was 94% with a nasal cannula administering 3 L/min oxygen. Chest CT revealed granular infiltrates, micronodules, and ground-glass opacities (Fig. 2A). Since the initial diagnosis made was bacterial pneumonia or drug-induced interstitial pneumonia, antibiotics were administered and anti-RA drugs were discontinued.

However, the day after admission, her respiratory rate increased to

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30 breaths/min and oxygen saturation decreased to 90% with a reservoir mask administering 15 L/min oxygen. Additionally, vesicular rashes appeared throughout the body, including the head (Fig. 1B). Chest CT at that time showed worsened ground-glass opacities and coalescence of nodular lesions, which are considered characteristic of VZV pneumonia (Fig. 2B) [5]. She had no history of chickenpox and had not been vaccinated against VZV. She lived with her husband and had no contact with children. Although she worked as a health care worker at a facility, no facility user had developed chickenpox or shingles within a month. The titers of VZV-IgM and VZV-IgG detected by enzyme immunoassay were 0.52 and 3.2, respectively, which were slightly increased. Tzanck smear of the vesicular fluid revealed multinucleated giant cells. Based on these results, the patient was diagnosed with VZV pneumonia and treated with acyclovir (10 mg/kg/day intravenously every 8 h). VZV can be transmitted from one person to another via airborne routes. The patient was managed in a negative-pressure room, and all medical staff wore N95 respirators. She was also diagnosed with acute respiratory distress syndrome. Therefore, she was intubated, ventilator management was initiated, and pulse steroid therapy (1000 mg/day) was administered. Since her cardiovascular system was also failing, noradrenaline (0.3 μg/kg/min) and vasopressin (40 U/day) were initiated. Her sequential organ failure assessment score was 8, and laboratory findings revealed a platelet count of 87,000 cells/μL and a prothrombin ratio of 1.08, which led to a diagnosis of sepsis-induced coagulopathy [6]. Therefore, heparin administration (10,000 U/day) was initiated. The creatinine level subsequently increased to 4.87 mg/dL, and she was diagnosed with acute kidney injury due to septic shock. After continued treatment with drug adjustments according to her renal function, the patient's respiratory condition and cardiovascular system gradually improved. She was extubated on the 11th day and discharged on the 19th day of admission. During and after hospitalization, the patient had no symptoms or physical findings suggestive of meningitis or encephalitis, and magnetic resonance imaging findings of her head were normal. The clinical course of this case is summarized in Fig. 3.

The time course of the skin rashes is shown in Fig. 1. On the day of admission, papular skin rashes were observed. (Fig. 1A). The day after admission, the papules changed to vesicles. (Fig. 1B). On the fourth day of admission, majority of the skin lesions appeared crusted (Fig. 1C). On the 12th day of admission, her skin rashes became more pigmented (Fig. 1D). On the 34th day of admission, the skin rashes had almost disappeared (Fig. 1E).

The time course of chest CT findings is shown in Fig. 2. Granular infiltrates, micronodules, and ground-glass opacities were observed on the chest CT at the time of admission (Fig. 2A). The day after admission, worsening of ground-glass opacities and coalescence of nodular lesions were observed (Fig. 2B). On the fourth day of admission, most of the lung fields were filled with ground-glass opacities and infiltrating shadows (Fig. 2C). However, ground-glass opacities and infiltrating shadows disappeared with improvement of the disease. Only small nodules remained on the CT on the 12th day of admission (Fig. 2D). On the 34th day of admission, the nodules had shrunk in size but remained intact. (Fig. 2E).

Multiplex real-time polymerase chain reaction for simultaneous detection of VZV, HHV-6, and herpes simplex virus was performed using blood and sputum samples (Fig. 4). A total of 8.65×10^5 copies/ml of VZV deoxyribonucleic acid (DNA) and 1.04×10^5 copies/ml of HHV-6 DNA were detected on the day of admission in the blood samples. On the 8th day, 2.71×10^4 copies/ml of VZV DNA were detected, while 196 copies/ml were detected on the 15th day. However, the VZV DNA disappeared on the 34th day of admission. On the other hand, HHV-6 DNA were not detected after 8th day of admission. Sputum samples were

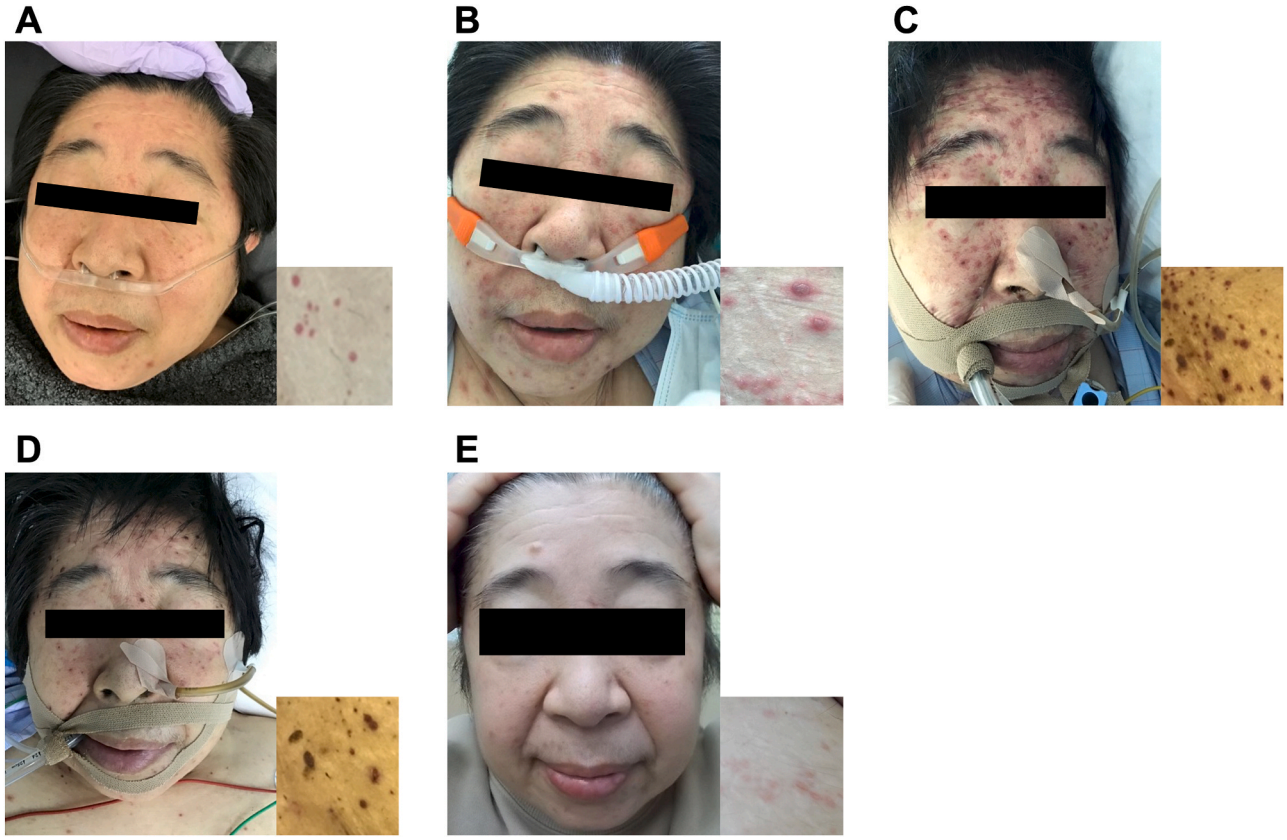

Fig. 1. Time course of skin rash. On the day of admission, papular skin rashes were observed. (A). The day after admission, the papules changed to vesicles. (B). On the fourth day of admission, most of the skin lesions were crusted (C). On the 12th day of admission, her skin rashes became more pigmented (D). On the 34th day of admission, the skin rashes had almost disappeared (E).

collected on days 6, 18 and 34 of admission. Although the quantitativity of the virus in the sputum was not accurate, a total of 2.27×10^4 copies/well and 3.31×10^3 copies/well of VZV and HHV-6 were detected on the 6th day of admission, respectively. On the 18th day of admission, 50 copies/well of VZV DNA were detected, while 27 copies/well were detected on the 34th day of admission. In contrast, HHV-6 DNA was not detected after the 18th day of admission. Herpes simplex virus DNA was not detected at any time point.

VZV-IgM and IgG levels were also measured over the time (Fig. 4). The titers of VZV-IgM and VZV-IgG were 0.52 and 3.2 on the day after admission, 3.76 and 27.6 on the 8th day, 3.22 and 25.3 on the 15th day, 1.77 and 21.3 on the 34th day of admission, respectively. The titer of VZV-IgM increased initially and then decreased, whereas that of VZV-IgG increased and then remained persistently high.

Discussion

Three important findings can be summarized from the patient's clinical course. Improvement in the respiratory condition and chest CT findings occurred subsequent to the healing of skin rashes in a RA patient with VZV pneumonia. In addition, on the 34th day of admission, VZV DNA disappeared from the serum sample, whereas it remained in the sputum sample. Furthermore, although reactivation of HHV-6 was observed, viremia resolved without any treatment in this case.

First, the improvement in the respiratory condition and chest CT findings occurred subsequent to the healing of skin rashes. Several studies have evaluated the chest CT findings of patients at the time of diagnosis of VZV pneumonia [5,7]. In addition, several reports have evaluated the time course of chest CT findings for viral pneumonia other than VZV, with a particular focus on the Coronavirus disease 2019 pneumonia [8–10]. However, there are no reports evaluating the time course of CT findings in patients with VZV pneumonia, along with the course of skin rashes. In the present case, granular infiltrates, small nodules, and ground-glass opacities were observed when dyspnea and papules appeared. In just one day, the vesicular rashes spread to the entire body and rapidly worsened the respiratory condition. In addition, worsening of ground-glass opacities and coalescence of nodular lesions were also observed on the chest CT findings. On the fourth day of admission, despite her skin lesions being mostly crusted, she was in a poor respiratory condition, and her chest CT showed that most of her lung fields were filled with ground-glass opacities and infiltrating shadows. However, on the 12th day of admission, her skin rashes became more pigmented, her respiratory condition improved, and the ground-glass opacities and infiltrating shadows disappeared, leaving only small nodules. On the 34th day of admission, the skin rashes had almost disappeared. On the other hand, CT showed that the nodules had shrunk but remained intact. It is very important for clinicians to recognize that the improvement of respiratory condition and chest CT findings occurred subsequent to the healing of skin rashes.

Second, the viral load of VZV was measured using a multiplex polymerase chain reaction. Although 8.65×10^5 copies/ml of VZV DNA were detected in the blood sample on the day of admission, it decreased steadily with administration of acyclovir. Small amounts of VZV DNA were detected in both blood and sputum samples on the 14th day of admission, when acyclovir was discontinued. However, the treatment was terminated, and follow-up was conducted because the patient recovered well. On the 34th day of admission, VZV DNA disappeared from the serum sample but remained in the sputum sample. VZV DNA detected in the sputum samples may have been those of dead viruses that were not infectious. However, VZV patients with pneumonia may be cautioned to take longer infection control measures than those without pneumonia.

Third, although reactivation of HHV-6 was observed, viremia resolved without treatment in this case. HHV-6 reactivation is often observed after allogeneic stem cell transplantation. However, most patients are asymptomatic, and viremia often resolves without treatment

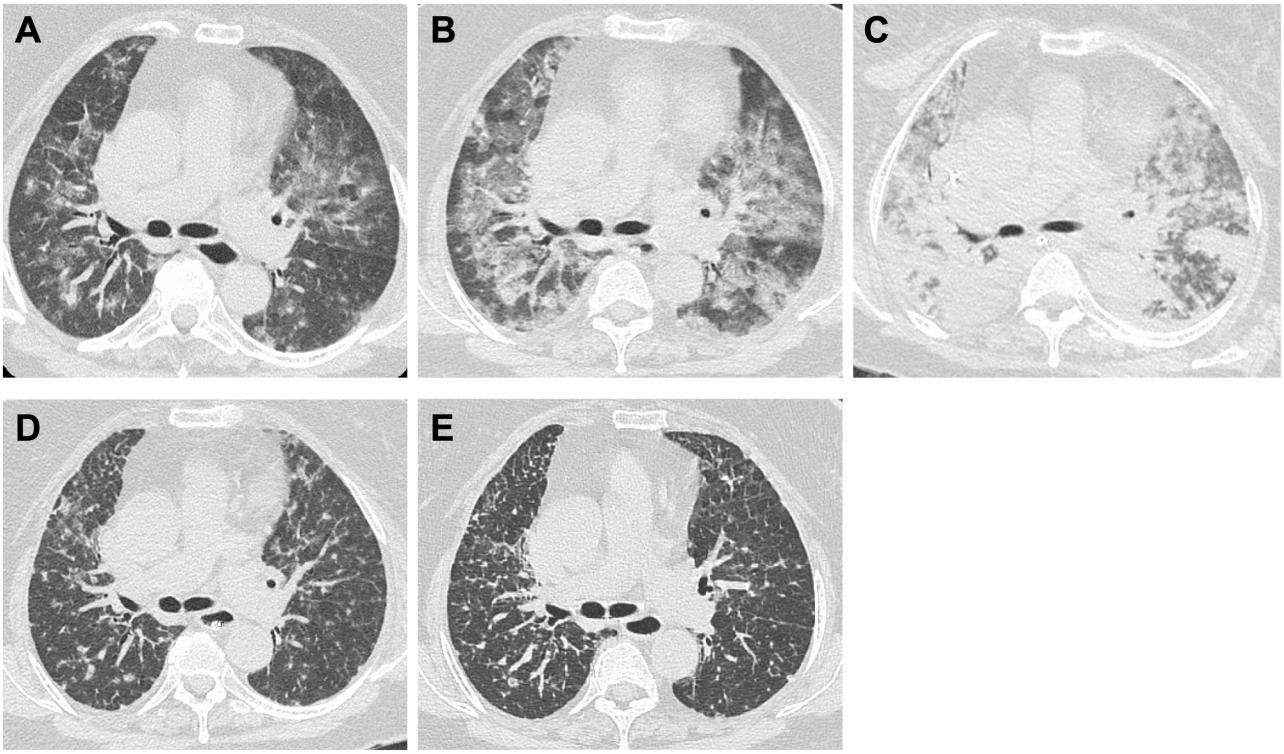

Fig. 2. Time course of chest computed tomography findings. Granular infiltrates, micronodules, and ground-glass opacities were observed on the day of admission (A). Worsening ground-glass opacities and coalescence of the nodular lesions were observed the day after admission (B). On the fourth day of admission, most of the lung fields were filled with ground-glass opacities and infiltrating shadows (C). However, as the disease improved, the ground-glass opacities and infiltrating shadows disappeared, and only small nodules remained on the 12th day of admission (D). On the 34th day of admission, the nodules had shrunk but persisted (E).

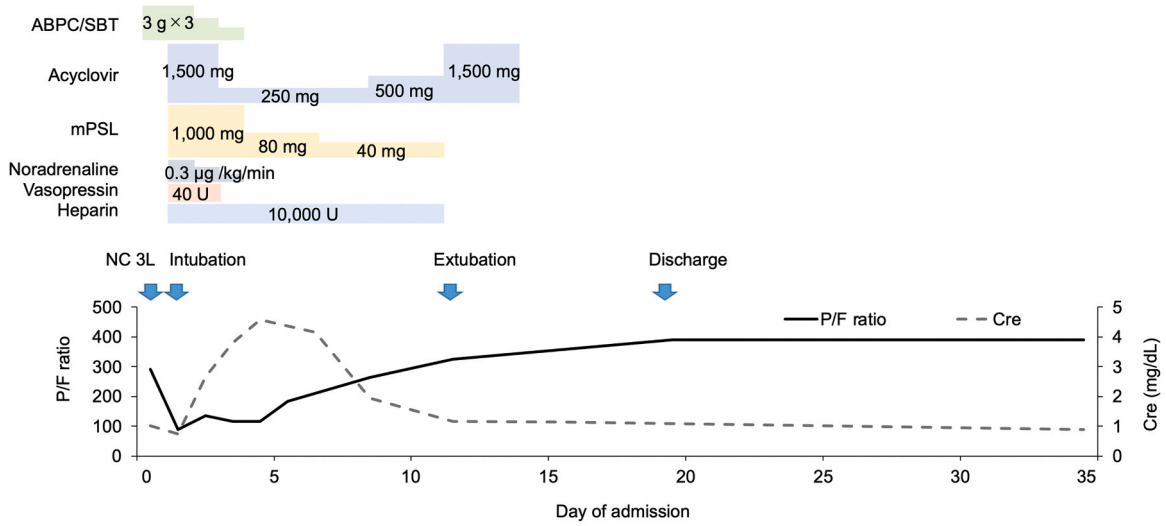

Fig. 3. Clinical course of this case. ABPC/SBT: ampicillin/sulbactam, Cre: creatinine, mPSL: methylprednisolone, NC: nasal cannula, P/F ratio: a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen. Ampicillin/sulbactam was administered upon admission. However, the day after admission, she was diagnosed with VZV pneumonia and treated with acyclovir (14 days) based on the typical skin rash and chest CT findings. Her condition worsened and she developed multiple organ failure. The patient was intubated; ventilator management was initiated; and steroids (10 days), noradrenaline (3 days), vasopressin (2 days), along with heparin (10 days) were administered. After continued treatment with drug adjustments based on the renal function, the patient's respiratory condition and cardiovascular system gradually improved. The patient was extubated on the 11th day and discharged on the 19th day of admission.

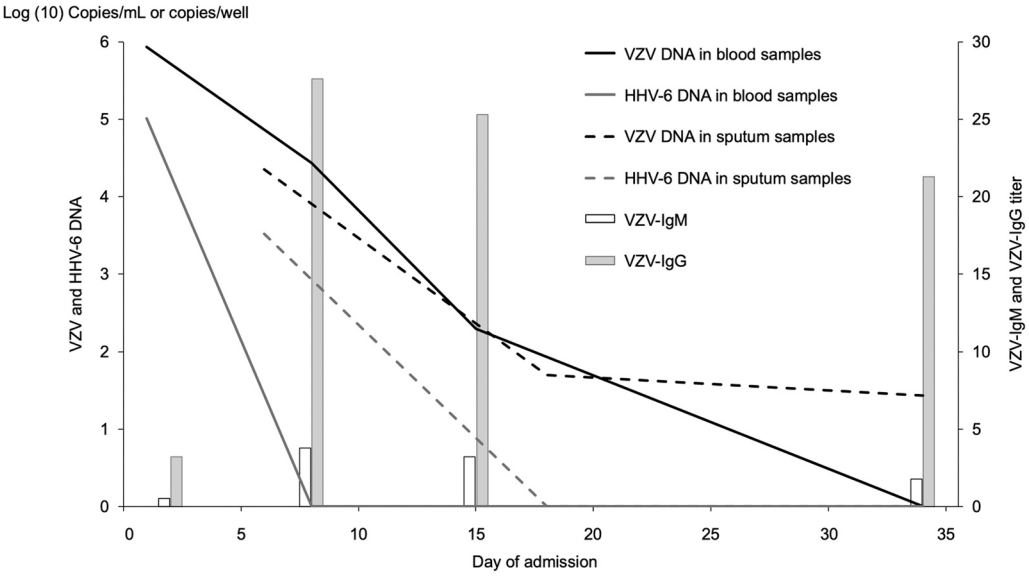

Fig. 4. Time course of polymerase chain reaction of varicella-zoster virus and human herpesvirus 6 and titers of IgM and IgG of varicella-zoster virus. DNA: deoxyribonucleic acid, HHV-6: human herpesvirus 6, PCR: polymerase chain reaction, VZV: varicella-zoster virus. A total of 8.65×10^5 copies/ml of VZV DNA and 1.04×10^5 copies/ml of HHV-6 DNA were detected on the day of admission in the blood samples. VZV DNA was detected at 2.71×10^4 copies/ml on the 8th day and 196 copies/ml on the 15th day, but disappeared on the 34th day of admission. On the other hand, HHV-6 DNA was not detected after the 8th day of admission. In sputum samples, VZV and HHV-6 DNA were detected at 2.27×10^4 copies/well and 3.31×10^3 copies/well, respectively, on the 6th day of admission. VZV DNA was detected at 50 copies/well on the 18th day and 27 copies/well on the 34th day of admission. In contrast, HHV-6 DNA was not detected after the 18th of admission. The titers of both VZV-IgM and VZV-IgG showed little increase upon admission. The titer of VZV-IgM increased initially and then decreased, whereas that of VZV-IgG increased and then remained persistently high.

[11]. In contrast, a case study reported that HHV-6 pneumonia occurred during immunosuppressive therapy [12]. In this case, HHV-6 DNA was detected in the blood and sputum samples, suggesting the development of HHV-6 viremia. However, since the main pathogen was considered to be VZV, foscarnet or ganciclovir, which are recommended as therapeutic agents for HHV-6, were not administered. Subsequently, HHV-6 viremia spontaneously resolved with improvement in VZV pneumonia. These results suggest that the reactivation of HHV-6 in our case was not the main cause of the disease, but occurred secondary to VZV pneumonia. Aggressive treatment for HHV-6 viremia, excluding encephalitis caused by HHV-6, is under discussion, and antiviral therapy should be carefully evaluated in each case [11].

In this case, the time course of the VZV-IgM and VZV-IgG titers suggested primary infection with VZV. However, it has also been reported that VZV-IgM levels are elevated in shingles [13]. In addition, due to vaccination programs for children, the number of varicella cases in Japan has decreased considerably over the past 10 years [14]. Furthermore, the route of infection was unclear from her history; therefore, it was not clear whether this was the first infection or reactivation of VZV.

In conclusion, improvement in the respiratory condition and chest CT findings occurred subsequent to the healing of skin rashes in our case. In addition, on the 34th day of admission, VZV DNA disappeared from the serum sample, whereas it remained in the sputum sample.

Furthermore, although reactivation of HHV-6 was observed, viremia resolved without any treatment. Clinicians should be able to recognize the differences in the improvement of skin rashes, respiratory status, and CT findings. In addition, treatment for HHV-6 reactivation should be carefully determined for each case. These results would contribute to future clinical and basic studies. Further studies are needed to clarify the pathogenesis of VZV pneumonia.

Ethical approval

Not applicable.

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CRediT authorship contribution statement

Hironori Kobayashi: Conceptualization, Writing – original draft, Visualization. **Shunta Takeuchi:** Resources, Writing – review & editing, Visualization. **Yuka Torii:** Investigation, Writing – review & editing. **Tadasuke Ikenouchi:** Writing – review & editing. **Jun-ichi Kawada:** Writing – review & editing. **Keisuke Oka:** Writing – review & editing. **Sayaka Kato:** Writing – review & editing. **Masahiro Ogawa:** Writing – review & editing.

Conflicts of interest

The authors report there are no conflicts of interest to declare.

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Informed consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Authorship statement

All the authors met the ICMJE authorship criteria. All the authors have read and approved the final version of the manuscript.

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