A Case of Varicella due to Primary Varicella Zoster Virus Infection Followed by Cytomegalovirus Reactivation on the Background of an Immunocompromised Condition

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Key Clinical Message

We encountered an immunocompromised patient with cytomegalovirus (CMV) reactivation immediately after varicella. Varicella appears to precede CMV reactivation in cases of reactivation, reinfection, and primary infection of varicella zoster virus.

Introduction

Cytomegalovirus (CMV) reactivation potentially leads to severe conditions, including retinitis, hepatitis, gastrointestinal ulceration, skin ulcers, and pneumonia [1,2]. To prevent these clinical conditions, the reactivation needs to be detected in the early stage. Three cases of CMV reactivation combined with varicella due to the reactivation or reinfection of varicella zoster virus (VZV) in immunocompromised adults have been reported in the English literature in the past 10 years [3-5]. Varicella preceded CMV reactivation in all three cases. Based on these findings, varicella is strongly suggested to lead to CMV reactivation in immunocompromised patients. The reactivation or reinfection of VZV was suggested as the developmental mechanism of varicella

in the cases reported by Kasuya*et al* . [3] and Hioki *et al* .[4], although Qi *et al* . did not definitively indicate the developmental mechanism of varicella [5]. Therefore, it currently remains unclear whether primary infection of VZV is followed by the reactivation of CMV. We encountered a compromised patient with the onset of varicella as primary VZV infection immediately followed by CMV reactivation.

Case Report

A 49-year-old female was referred to us with a 4-day history of cutaneous manifestations on the trunk and extremities. The patient had been diagnosed with systemic lupus erythematosus (SLE) 2 months earlier according to the European League Against Rheumatism and the American College of Rheumatology (2019) criteria [6] and remained hospitalized. SLE was controlled well by a treatment with prednisolone at 0.7 mg/kg/day, mycophenolate mofetil at 2,000 mg/day, and hydroxychloroquine at 200 and 400 mg on alternate days. Four days before presentation, the patient developed red papules on the right lower jaw. Two days before, dyspnea with pyrexia occurred and, thus, the administration of oxygen was initiated. In the first visit, the eruptions became vesicles, which spread over the body (**Figure 1**). The Tzanck test and immunochromatography to detect VZV antigens (DermaQuick VZV; Marho, Osaka, Japan) for vesicles were both positive. In blood tests, VZV-specific IgM and VZV-specific IgG examined using enzyme-linked immunosorbent assays (ELISA) were 0.38 (negative range, <0.8) and <2.0 (negative range, <2.0), respectively, while a CMV antigen-detecting test using the C7 horseradish peroxidase method was positive (4 positive cells per 50,000 white blood cells). Bilateral ground-glass opacities were observed on chest computed tomography (CT) (**Figure 2**).

A histopathological examination revealed intraepidermal blisters with large multinucleated giant cells and intranuclear inclusion bodies (**Figure 3a**). There were no vascular changes in the dermis, such as endothelial swelling suggestive of CMV infection, the so-called owl's eye sign. An immunohistochemical examination of vesicle tissue showed VZV antigens in keratinocytes on the adjacent side of blisters (**Figure 3b**), but failed to detect CMV antigens. Based on these findings, we diagnosed the patient with adult varicella due to primary VZV infection and CMV pneumonia. We administered acyclovir (ACV) at 10 mg/kg/day and added a dose of valganciclovir (VGCV) at 1,800 mg/day.

Eight days after the first visit, vesicles became crusted through the administration of ACV and ELISA for VZV-specific IgM and IgG were 1.50 and 52.6, respectively. Fourteen days later, ELISA for VZV-specific IgM and IgG were 1.25 and 1,080, respectively. Eighteen days later, the attenuation of dyspnea was noted and, thus, oxygen inhalation and VGCV were stopped.

Discussion

The immunocompromised patient was diagnosed with varicella caused by primary VZV infection based on the results of physical, blood, and histopathological examinations. The patient was also diagnosed with CMV pneumonia based on the results of CMV antigen test in the blood and the findings of chest CT; the previous studies reported that CMV pneumonia on CT is mainly detected as ground-glass opacities [7]and varicella pneumonia mainly as nodular lesions [8]. The onset of varicella preceded that of CMV pneumonia by a few days.

Three mechanisms have been proposed for the development of adult-onset varicella: i) the reactivation of latent VZV, ii) reinfection by VZV of a different genotype from that of latent VZV, and iii) primary VZV infection. In the case of varicella caused by the reactivation of latent VZV, VZV-specific IgG potentially increases commonly from a certain level, whereas VZV-specific IgM does not. In the case of varicella due to reinfection by VZV of a different genotype, VZV-specific IgM potentially increases, whereas VZV-specific IgG appears to rapidly increase commonly from a certain level at an early time point from the onset [9]. In the case of varicella caused by primary VZV infection, VZV-specific IgM definitely increases, whereas VZV-specific IgG gradually becomes elevated over 2-3 weeks from a negative level. Increases in VZV-specific IgM were followed by a gradual elevation in VZV-specific IgG over 2 weeks from a negative level in the present case, which was compatible with primary VZV infection.

VZV-specific IgG levels in SLE patients previously infected by VZV were previously reported to be significantly elevated regardless of total IgG levels through the significant activation of B-cells to specific antigens as the pathogenesis of SLE; however, total IgG and complement factor 3 levels sometimes decrease with an increase in the disease activity of SLE [10]. In the present case, the level of VZV-specific IgG in the early stage of varicella was low, which indicated primary VZV infection in our patient.

Cases in which varicella due to the reactivation of or reinfection by VZV preceded CMV reactivation have been reported. In an experiment on monkeys, Ohtaki *et al* . showed that CMV was reactivated after an inoculation with VZV [11]. However, primary VZV infection followed by CMV reactivation has not been reported in humans. This is the first human case of primary VZV infection leading to the reactivation of CMV. Dermatologists need to consider CMV reactivation with the appearance of varicella caused by any type of VZV infection, including reactivation, reinfection, and primary infection.

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Statement of Ethics: This study protocol was approved by The Ethics Committee of The Jikei University School of Medicine and the patient provided written informed consent.

Consent statement: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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Author Contributions

Hizuru Tomita: The author contributed to data curation, resources, and drafting the original manuscript.

Yoshimasa Nobeyama: The author contributed to conceptualization and project administration.

Miya Morishima: The author contributed to resources and preparation for writing of the manuscript.

Akihiko Asahina: The author contributed to review and supervision.

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Figure legends

Figure 1. Clinical manifestations in the first visit

a) Papules, papular vesicles, crusted vesicles, and crusts are mutually intermingled on the back. **b)** Vesicles <6 mm in diameter are shown. Some vesicles have an umbilication representing necrosis in the center.

Figure 2. CT imaging of lungs

Ground-glass opacities are observed in the bilateral lungs; however, no nodules suggestive of varicella pneumonia are found.

Figure 3. Histopathological findings of vesicles

a) Hematoxylin-eosin stain, × 400. Intraepidermal blisters with large multinucleated giant cells and intranuclear inclusion bodies shown as a pale amorphous substance are evident. **b)** Direct immunofluorescence, × 1,000. The nuclei of cells in vesicles are reactive to an anti-VZV antibody (Denka, Tokyo, Japan), as indicated by white arrowheads.