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Varicella zoster virus reinfection in a patient with refractory nephrotic syndrome: A case report

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Abstract

Permanent immunity to varicella zoster virus (VZV) develops following infection in most patients, with reinfections extremely rare. Here, we report a 6-year-old boy with refractory nephrotic syndrome who contracted VZV infection during B-cell depletion after rituximab treatment. Although developing febrile neutropenia, he was promptly treated with acyclovir, which was successful. The VZV immunoglobulin G antibody titer was weakly positive (3.3) by enzyme immunoassay performed 42 days after the initial diagnosis of VZV infection, confirming the presence of VZV, although antibody production was insufficient to prevent reinfection. Three years later, he was diagnosed with VZV infection again, along with the 18th relapse of nephrotic syndrome. Although promptly recovering with acyclovir, he advanced to refractory nephrotic syndrome, which required multiple immunosuppressive therapies to achieve partial remission. The present case illustrates that antibody production can be severely suppressed not only after vaccination but also after viral infection, during rituximab-induced B-cell depletion.

Introduction

In most patients, permanent immunity develops following infection with varicella zoster virus (VZV), and reinfection is extremely rare. Here, we report the unusual case of a pediatric patient with refractory nephrotic syndrome who was infected with VZV during B-cell depletion after rituximab administration and was subsequently reinfected with VZV due to the insufficient production of VZV-specific antibodies.

Case report

The patient was a 6-year-old boy who was diagnosed with refractory steroid-resistant nephrotic syndrome at 1 year of age and achieved remission following treatment with cyclosporine A (CsA), rituximab, steroid pulse, and plasma exchange at the time. By 6 years of age, he had experienced 11 relapses of nephrotic syndrome, including 2 steroid-resistant episodes, requiring 12 doses of rituximab, and continued treatment with CsA and mycophenolate mofetil (MMF). The first kidney biopsy at 1 year of age showed minimal change, whereas a subsequent biopsy at 4 years of age revealed focal segmental glomerulosclerosis. The patient had received the VZV vaccine at 1 year of age, prior to the onset of nephrotic syndrome.

The 11th relapse, which was at the age of 6 years and 3 months, was steroid-sensitive, and the patient received the 12th dose of rituximab (375 mg/m^2 of body surface area) after remission and continued treatment with CsA and MMF thereafter. One month later, he developed a rash covering the entire body, which was scattered across the face, scalp, trunk, and limbs, with some areas forming blisters. He was admitted to our center and diagnosed with VZV infection. Evaluation at admission revealed B-cell depletion (0.1% $CD20^+$ cells), and treatment was initiated with 10 mg/kg/dose acyclovir administered intravenously three times daily. CsA and MMF were discontinued. Five days after admission, the patient developed neutropenic fever, with a neutrophil count of 103 cells/mm^3, and granulocyte colony-stimulating factor was administered. All blisters eventually scabbed, indicating resolution of the

infection. Acyclovir was discontinued, and CsA and MMF were reinitiated. The patient was discharged 10 days after admission following the recovery of the neutrophil count.

Thereafter, the patient experienced several relapses of nephrotic syndrome and continued treatment with CsA, MMF, and rituximab. He received the 14th dose of rituximab at the age of 8 years and 9 months, with the B-cell count recovering 6 months later. At 9 years and 7 months of age, he experienced the 18th relapse of nephrotic syndrome, which was accompanied by the appearance of a rash covering the entire body, again scattered across the face, scalp, trunk, and limbs, with some areas forming blisters; the patient was hospitalized with a diagnosis of VZV reinfection. VZV antigen was recovered from the blisters. Treatment with acyclovir at 10 mg/kg/dose, administered intravenously three times daily, was initiated, and CsA and MMF were discontinued. On day 4 of hospitalization, the blisters were improving, and the patient was switched to oral valacyclovir. However, due to persistent nephrotic-range proteinuria, with a serum albumin of 2.3 g/dL and a urine protein/creatinine ratio of 5.7 g/g, CsA and MMF were reinitiated, and prednisolone was resumed at 60 mg/day. On day 32 of hospitalization, the patient was diagnosed with steroid-resistant nephrotic syndrome and received steroid pulse therapy and rituximab, in addition to CsA, MMF, and oral prednisolone. He achieved partial remission and was discharged 128 days after admission.

Table 1 shows changes in VZV immunoglobulin (Ig) M and G titers, evaluated by enzyme immunoassay, revealing that the VZV IgG titer was weakly positive (3.3) at 42 days after the onset of the first VZV infection, confirming the presence of VZV and suggesting insufficient antibody production due to rituximab-induced B-cell depletion, leading to VZV reinfection.

Table 1
Changes in varicella zoster virus antibody titers during the course of disease

At admission for the first VZV infection	**VZV IgM (EIA)**	**VZV IgG (EIA)**
	0.33 (−)	**< 2.0 (−)**
42 days after the onset of the first VZV infection	Not examined	3.3(±)
30 days after the onset of the second VZV infection	5.65 (+)	18.3 (+)

EIA, enzyme immunoassay; IgG, immunoglobulin G; IgM, immunoglobulin M; VZV, varicella-zoster virus

Discussion

VZV reinfection, which is extremely rare due to lifelong immunity usually acquired after a single infection, can be observed particularly in immunocompromised individuals or elderly adults [1]. This is the first reported case of a patient reinfected with VZV after a 3-year interval, due to insufficient antibody production following rituximab-induced B-cell depletion during the first VZV infection.

Several studies reported extremely poor immune response to vaccination following rituximab-induced B-cell depletion [2–4]. In a study evaluating antibody titers after vaccination for coronavirus disease 2019 in adult patients with rheumatic disease, 28 of 38 patients (74%) whose B-cell numbers recovered after rituximab administration achieved seroconversion, whereas only 1 of 36 patients (3%) with B-cell depletion achieved seroconversion [2]. Similarly, the lack of an increase in the geometric mean of the antibody titer after rituximab administration has also been reported for influenza vaccination [3, 4]. Antibody production can be suppressed not only after vaccination but also following wild-type virus infections during B-cell depletion induced by rituximab.

Concerning the second rash, shingles were unlikely, as the patient did not suffer from pain. Furthermore, the second VZV infection was associated with IgG and IgM positivity, which is observed following primary infection. IgM seroconversion is usually associated with primary infection and is less common in reinfections [5]. In the present case, the lack of an increase in VZV-IgG titer after primary infection suggests IgM seroconversion despite reinfection.

In conclusion, antibody production can be severely suppressed not only after vaccination but also after viral infection during rituximab-induced B-cell depletion. Given that rituximab is expected to be widely used for nephrotic syndrome, with its indications continually expanding, the present case illustrates the need to consider the potential for reduced immunogenicity against viral infections during rituximab-induced B-cell depletion.

Declarations

Competing interests

Koichi Kamei received research funding from the Public Foundation of Vaccination Research Center and the Taiju Life Social Welfare Foundation and donations from Chugai Pharmaceutical, Kyowa Kirin, Taiho Pharmaceutical, and Shionogi. None of the funders had any relationship to this work.

Ethics approval

Ethical approval was waived by the local Ethics Committee of National Center for Child Health and Development in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to publish

Informed consent was obtained from the patient’s parents.

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Author contributions

Koichi Kamei prepared the manuscript. Tomoya Kaneda, Kentaro Nishi, and Masao Ogura were involved in the patient's management. All authors contributed to the work and revised the manuscript.

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Data availability statement

All data generated or analysed during this study are included in this published article

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