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Varicella Zoster Virus Reactivation in Central and Peripheral Nervous Systems Following COVID-19 Vaccination in an Immunocompetent Patient

Seungyon Koh[a,b]
Hong Nam Kim[a]
Yoon Seob Kim[a]
Tae-Joon Kim[a,b]

[a]Department of Neurology, Ajou University Hospital, Suwon, Korea
[b]Department of Neurology, Ajou University School of Medicine, Suwon, Korea

Dear Editor,

The increasing vaccination rate for coronavirus disease 2019 (COVID-19) worldwide is leading to concerns about adverse events. Reactivation of varicella zoster virus (VZV) as herpes zoster (HZ) after COVID-19 vaccination has been reported in a series of adult patients,[1,2] especially in older subjects. VZV reactivation occurs as a wide clinical spectrum, from HZ to a central nervous system manifestation such as meningitis or encephalitis. Here we report a case of an immunocompetent young adult with both VZV meningitis and HZ following COVID-19 vaccination.

A healthy 24-year-old male with normal cognition visited our emergency room (ER) presenting with a headache. His medical history was remarkable, with varicella as a child and aseptic meningitis at 12 years of age. He was vaccinated with the first dose of the Pfizer-BNT162b2 vaccine against SARS-CoV-2 into his left deltoid at 3 days prior to the visit. From the following day, myalgia and fatigue gradually developed. On the 4th day after vaccination, he decided to visit the ER because a headache started and small vesicles had formed on his left upper arm, just below the vaccine injection site.

On presentation, the patient was febrile (37.7°C) with otherwise normal vital signs. He had no neurological deficit, but neck stiffness and positive jolt accentuation were observed. An erythematous patch with grouped vesicles suggestive of HZ was present on his left upper arm within the C5 dermatome (Fig. 1). Laboratory tests revealed a white blood cell (WBC) count of 5,700/μL (21% lymphocytes) in the complete blood count. The findings of other tests including a coagulation panel, electrolyte, chemistry panel, serology, urinalysis, and chest X-ray were within the normal ranges. Anti-VZV IgM/IgG, anti-cytomegalovirus IgM, and anti-HSV IgM antibodies were negative in the blood test. A cerebrospinal fluid (CSF) study was performed, which revealed an opening pressure of 180 mm H_2O, WBC count of 11/μL, 98% lymphocytes, 50.6 mg/dL protein, and 53 mg/dL glucose, while the blood glucose level was 90 mg/dL. CSF polymerase chain reaction for VZV yielded a positive result, and a diagnosis of VZV meningitis was made. He refused admission, and so was treated with oral famciclovir. At the follow-up visit after a week, he reported a mild headache that lasted about 1 week, and then his general condition and fever had improved as the systemic VZV reactivation and meningitis resolved.

This case illustrates the central and peripheral nervous system manifestations of VZV reactivation in an immunocompetent young adult following COVID-19 vaccination. To our knowledge, this is the first report of concomitant VZV meningitis and HZ following COVID-19 vaccination. Cases of HZ reactivation as adverse events following immunization were also observed during the prepandemic era for both inactivated virus vaccines such as influenza vaccines and attenuated virus vaccines such as Japanese encephalitis vac-

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Correspondence
Tae-Joon Kim, MD
Department of Neurology, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Korea
Tel +82-31-219-5175
Fax +82-31-219-5178
E-mail dandy8123@gmail.com

cine.[3] Previous studies of HZ development following COVID-19 vaccination found that patients experienced a mild and treatable course of HZ at 7–20 days, usually after the first dose.[1]

VZV meningitis accompanying HZ rarely occurs in immunocompetent patients. VZV meningitis accounts for 5%–6% of all cases of VZV reactivation,[4] and sometimes progresses to encephalitis or cerebral vasculitis, which are considerably associated with neurological morbidity or even mortality.[5] Reactivation of VZV is largely dependent on T-cell-mediated immunity, which is known to be modulated by COVID-19 vaccination.[6] Immunocompromisation, either by acquired causes of immunodeficiency or immunosenescence, is a major contributor to VZV reactivation.[7] Previous reports have postulated that the mechanism underlying VZV reactivation includes immunomodulation causing a cytokine storm or lymphopenia, similar to the effect of COVID-19 infection[2] or a massive shift of naïve T cells to VZV-specific T cells causing an immune reconstitution inflammatory syndrome (IRIS)-like phenomenon.[1] Although SARS-CoV-2-specific T-cell activity and VZV-specific T-cell activity were not investigated in our patient, we speculate that T-cell shifting caused by the COVID-19 vaccination in a healthy immune system can allow immune escape of the latent VZV infection.

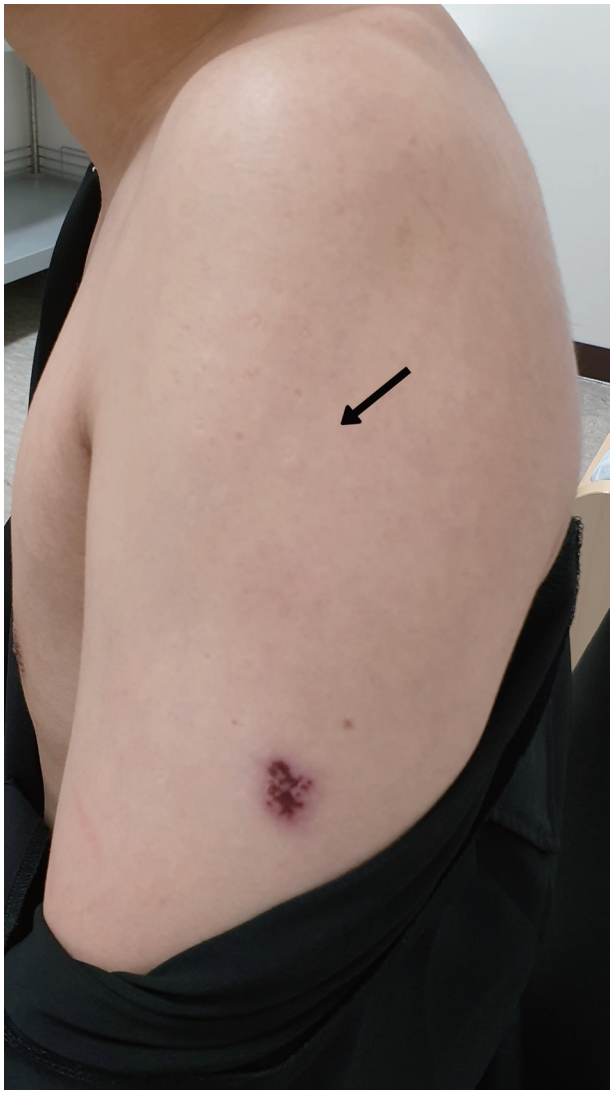

Fig. 1. Clinical photo of the cutaneous lesion taken a week after the symptom onset. Erythematous to violaceous patch with grouped vesicles and crust formation in patient's left upper arm within C5 dermatome is noted, suggestive of herpes zoster. Arrow indicates the site of vaccine injection reported by the patient. No specific cutaneous abnormality was seen at the injection site.

Another outstanding feature in our patient is that the location of HZ coincided with the arm into which the COVID-19 vaccine had been injected. This pattern of HZ dermatomal distribution in the vaccinated arm is sometimes also seen in live attenuated varicella vaccination in children,[8] and was reported in a previous COVID-19-vaccinated patient.[9] In VZV-vaccinated children, the attenuated viruses replicated in the local injected arm are transported to the cervical dorsal root ganglia. Although our patient was actively immunized with VZV by varicella infection as a child, we assume that indolent VZV infection at the cervical ganglia was triggered by the systemic activation of inflammatory cascades by the COVID-19 vaccine. This coincidence observed in our patient also brings attention to the localized cutaneous adverse events of the Pfizer-BNT162b2 vaccine, known as the 'COVID-arm,' which is a delayed hypersensitivity reaction involving perivascular lymphocytic infiltrates.[10]

To our knowledge, this is the first report of central and peripheral nervous system complications of VZV reactivation in a patient vaccinated against COVID-19. This case underpins the importance of diagnostic evaluations of adverse events following immunization, even in immunocompetent patients.

Ethics Statement

This study was reviewed and approved by the Institutional Review Board of Ajou University Medical Center (IRB no. AJIRB-MED-EXP-21-328). The requirement for informed consent was waived by the board due to the retrospective nature of the study.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Seungyon Koh https://orcid.org/0000-0002-5547-6378
Hong Nam Kim https://orcid.org/0000-0002-7064-9409
Yoon Seob Kim https://orcid.org/0000-0002-6363-1999
Tae-Joon Kim https://orcid.org/0000-0001-8451-6634

Author Contributions

Conceptualization: Seungyon Koh, Tae-Joon Kim. Data curation: Seungyon Koh, Tae-Joon Kim. Methodology: Hong Nam Kim, Yoon Seob Kim. Resources: Hong Nam Kim, Yoon Seob Kim. Writing—original draft:

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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