Disseminated varicella-zoster virus infections following messenger RNA–based COVID-19 vaccination

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INTRODUCTION

The novel messenger RNA (mRNA)–based COVID-19 vaccines protect individuals from SARS-CoV-2 infection and severe forms of the disease.[1] Clinical trials data and observational evidence have reported diverse cutaneous responses to these vaccines, including local injection site erythema, urticaria, and morbilliform eruptions.[2] Delayed localized hypersensitive reactions have also been reported; however, these do not preclude subsequent vaccination, emphasizing that serious cutaneous reactions to the vaccines are rare.[3] We report 2 cases of de novo disseminated varicella-zoster virus (VZV) infection, without expansion from a preceding dermatomal presentation, after receiving an mRNA-based COVID-19 vaccine in patients who were not actively on immunosuppression.

Abbreviations used:

mRNA: messenger RNA
VZV: varicella-zoster virus

CASE REPORTS

Case 1

A 58-year-old man with a history of acute myeloid leukemia off immunosuppression for 12 months and in clinical remission following umbilical cord blood stem cell transplantation 20 months ago presented with a new-onset diffuse eruption. Thirty-one days prior, he received the first dose of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine without cutaneous or systemic side effects. Twenty-one days later, he received the second dose, which was followed by 24 hours of fatigue and chills. On day 3 after vaccination, diarrhea and a painful widespread skin eruption developed in him for 24 hours. No previous dermatomal eruption was noted; he denied other systemic or respiratory symptoms.

The skin examination demonstrated discrete round erosions and intact vesicles and pustules on erythematous bases over the scalp, neck, trunk, genitalia, and extremities (Fig 1, *A*). Notably, the patient completed recombinant zoster vaccination (Shingrix, GlaxoSmithKline) 8 months ago. An intact vesicle of the left arm was biopsied (Fig 1, *B*). The patient was started on oral valacyclovir 1000 mg 3 times daily. Laboratory evaluation revealed mild leukocytosis (12.14 K/μL, lymphocyte-predominant), positive findings of polymerase chain reaction for VZV DNA from blood, and elevated VZV immunoglobulin M and IgG antibody titers. Dermatopathology demonstrated extensive epidermal ulceration and a florid, mixed dermal inflammatory infiltrate (Fig 2, *A* and *B*); findings of immunohistochemistry for VZV were positive (Fig 2, *C*). His eruption completely resolved 2 weeks after the initiation of oral valacyclovir.

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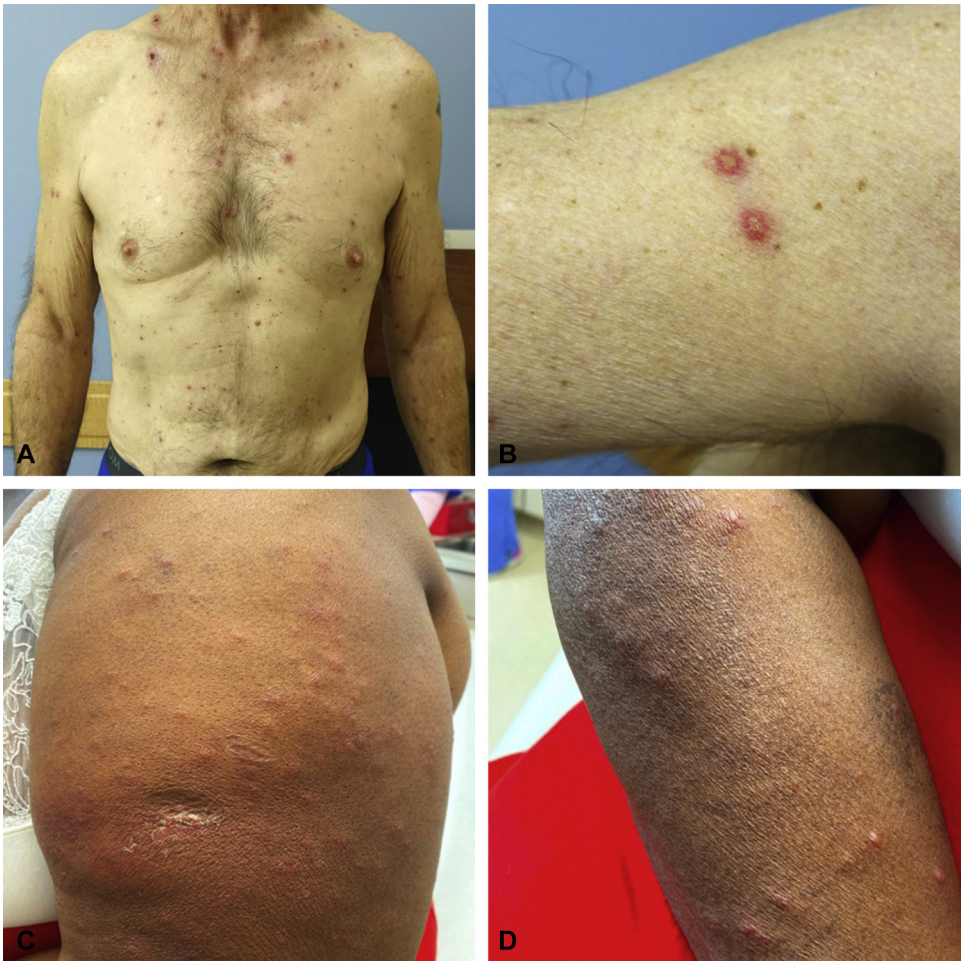

Fig 1. **A**, Diffuse vesicles and erosions on erythematous bases spread over the neck, shoulders, chest, and lower extremities of the patient in case 1. **B**, Two vesicles on erythematous bases on the right arm of the patient in case 1. **C**, Diffuse thin pink and erythematous papules and vesicles on the lateral aspect of the left arm of the patient in case 2. **D**, Scattered erythematous vesicles on the right elbow and forearm of the patient in case 2.

Case 2

A 70-year-old woman with a history of giant cell arteritis and resolved SARS-CoV-2 infection 10 months ago presented with a diffuse erythematous vesicular rash. Eighteen days ago, she completed a 20-week low-dose methylprednisolone taper for giant cell arteritis, initiated at 10 mg daily. Eight days prior to presentation, she received the first dose of the mRNA-1273 (Moderna) COVID-19 vaccine; 5 days later, a pruritic skin eruption with associated daily fevers developed in her.

The examination demonstrated thin erythematous papules and vesicles over the forehead, trunk, and extremities (Fig 1, *C* and *D*). No antecedent dermatomal eruption was noted; of note, the patient had received a live zoster vaccine (Zostavax, Merck) 10 years ago. Dermatopathology demonstrated papillary and mid-dermal lymphocytic infiltrate with admixed neutrophils and foci of lymphocytic vasculitis; findings of VZV immunohistochemistry were negative; however, findings of polymerase chain reaction from a sampled vesicle were positive for VZV DNA. The patient was initiated on oral valacyclovir 1000 mg 3 times daily; the following day, she was admitted to the hospital for intravenous acyclovir (10 mg/kg, every 8 hours for 5 days). One week after hospital discharge, she had a near-complete resolution of her infection with diffuse postinflammatory hyperpigmentation. One week after completing valacyclovir and 4 weeks after her first dose, she received the second vaccine dose without complications.

DISCUSSION

Although dermatome-limited VZV reactivation has been reported as a rare SARS-CoV-2

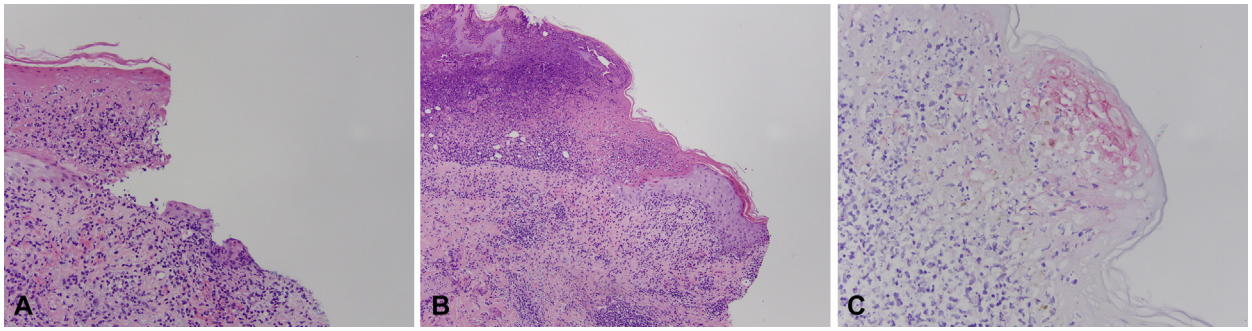

Fig 2. Case 1: dermatopathology images. **A** and **B**, Hematoxylin-eosin staining of intact vesicle of the upper portion of the arm at the papillary (**A**) and reticular (**B**) dermal levels of the patient in case 1. Both sections demonstrate extensive epidermal ulceration with overlying impetiginized scale crust and mixed dermal florid inflammatory infiltrate. **C**, Immunohistochemical staining with alkaline phosphatase (*red*) of the intact epidermis away from the ulcerated area is positive for the varicella-zoster virus in case 1. (**A** and **B**, Hematoxylin-eosin stain; **C**, immunohistochemical stain.)

vaccine—associated adverse event, disseminated VZV infections following SARS-CoV-2 vaccination have yet to be reported. An observational study of 2 large rheumatology departments identified only 6 cases of nondisseminated VZV reactivation following BNT162b2 vaccination.[4] A study of the American Academy of Dermatology registry of postvaccination cutaneous reactions reported 10 VZV infections, none specified as disseminated.[2] To date, at least 52 cases of SARS-CoV-2 mRNA vaccine—associated VZV reactivation have been reported.[5] As of August 11, 2021, the US Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System included only 11 cases of "disseminated varicella zoster virus infection" or "herpes zoster, cutaneous disseminated," emphasizing the rarity of this adverse event.[6]

The relationship between the mRNA-based COVID-19 vaccines and dormant VZV is unknown. VZV reactivation has been documented following influenza, hepatitis A, and rabies vaccination, as well as after live herpes zoster vaccination.[7,8] With the exception of stabilizing salts and buffer solutions, the ingredients in the novel mRNA-based COVID-19 vaccines are largely distinct from those in the aforementioned vaccines, given the use of novel lipid vehicles for mRNA delivery. A consistent ingredient-related mechanism is thus unlikely. This phenomenon is hypothesized to be attributed to vaccine-induced immune system attenuation toward humoral immunity, reducing the suppression of dormant viruses by VZV-specific $CD8^+$ T cells in sensory ganglia.[5,7]

These 2 cases are distinct from previously reported cases of dermatomal herpes zoster following SARS-CoV-2 mRNA—based vaccination, given de novo disseminated disease. Risk factors for disseminated VZV include stem cell transplantation and systemic immunosuppressive/immunomodulatory medications[9]; although both patients had immunomodulating conditions, neither was receiving immunosuppressants when vaccinated. Both patients received adulthood VZV vaccination, yet presented with nondermatomal, acutely disseminated VZV. Patients reported thus far with post-SARS-CoV-2 vaccine VZV reactivation have been highly heterogeneous in terms of sex, childhood VZV infection, and adult VZV vaccination.[5] Considering immunosuppression, a single reported patient was taking ruxolitinib—a Janus kinase 1/2 inhibitor—for polycythemia vera, which may have contributed to VZV reactivation.[10]

These cases were managed with appropriate antiviral therapy; in case 2, valacyclovir between vaccine doses may have been protective against a similar reaction following the second dose. Thus, it is our opinion that disseminated VZV reactivation should not be a contradiction to completing the mRNA-based SARS-CoV-2 vaccine regimens.

A high index of suspicion for disseminated VZV infection should be maintained for diffuse pustular/vesicular eruptions following mRNA-based COVID-19 vaccination. Given the limited number of our reported cases and evolving understanding of SARS-CoV-2 vaccine—associated adverse events, we acknowledge that the disseminated nature of these VZV reactivation cases could be coincidental; however, we emphasize that these patient cases stand in contrast to SARS-CoV-2 vaccine—associated dermatomal VZV reactivation cases reported thus far. Further research is needed to approximate the incidence of this vaccine-associated adverse event, as well as to determine whether

antiviral prophylaxis may be warranted in especially vulnerable populations.

Conflicts of interest

Dr Merola is a consultant and/or investigator for AbbVie, Aclaris, Almirall, Arena, Avotres, Biogen, Celgene, Dermavant, Eli Lilly, EMD Serono, Incyte, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc, Sanofi, Sun Pharma, and UCB. Dr LeBoeuf is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback, and Synox Therapeutics, outside the submitted work. Author Said and Drs Virgen, Lian, and Cutler have no conflicts of interest to declare.

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020; 383(27):2603-2615. https://doi.org/10.1056/NEJMoa2034577
2. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85(1):46-55. https://doi.org/10.1016/j.jaad.2021.03.092
3. Johnston MS, Galan A, Watsky KL, Little AJ. Delayed localized hypersensitivity reactions to the Moderna COVID-19 vaccine: a case series. *JAMA Dermatol*. 2021;157(6):716-720. https://doi.org/10.1001/jamadermatol.2021.1214
4. Furer V, Zisman D, Kibari A, Rimar D, Paran Y, Elkayam O. Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. *Rheumatology (Oxford)*. 2021:keab345. https://doi.org/10.1093/rheumatology/keab345
5. Lladó I, Fernández-Bernáldez A, Rodríguez-Jiménez P. Varicella zoster virus reactivation and mRNA vaccines as a trigger. *JAAD Case Rep*. 2021;15:62-63. https://doi.org/10.1016/j.jdcr.2021.07.011
6. United States Department of Health and Human Services (DHHS), Public Health Service (PHS) C for DC (CDC)/F and DA (FDA). Vaccine Adverse Event Reporting System (VAERS) 1990–4/30/2021, CDC WONDER on-line database. Accessed August 11, 2021. https://wonder.cdc.gov/vaers.html
7. Walter R, Hartmann K, Fleisch F, Reinhart WH, Kuhn M. Reactivation of herpesvirus infections after vaccinations? *Lancet*. 1999;353(9155):810. https://doi.org/10.1016/S0140-6736(99)00623-6
8. Jabbour S, Shekhawat NS, Chen A, Woreta FA. Presumed herpes zoster ophthalmicus reactivation following recombinant zoster vaccination. *Cornea*. 2021;40(2):248-250. https://doi.org/10.1097/ICO.0000000000002537
9. Shingles (Herpes Zoster). Center for Disease Control and Prevention. Accessed August 11, 2021. https://www.cdc.gov/shingles/index.html
10. Lee C, Cotter D, Basa J, Greenberg HL. 20 post-COVID-19 vaccine-related shingles cases seen at the Las Vegas dermatology clinic and sent to us via social media. *J Cosmet Dermatol*. 2021;20(7):1960-1964. https://doi.org/10.1111/jocd.14210