

Disseminated Varicella-Zoster Virus After Vaccination in an Immunocompetent Patient

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Severe adverse events associated with varicella-zoster virus (VZV) vaccination are rare. The authors describe a 53-year-old woman with no known immunodeficiency who presented with diffuse pruritic rash 17 days after receiving the varicella virus vaccine live. She had a low level of white blood cells and received a diagnosis of thrombocytopenia with elevated aminotransferase levels. Punch biopsy demonstrated positive VZV immunostaining and viral culture positive for VZV. After treatment with acyclovir, her rash improved and her white blood cell and platelet counts returned to normal. Mild reactions to vaccines including localized rash are well recognized. Disseminated infections have been reported in patients with congenital and acquired immunodeficiency, but systemic postvaccination infections are rare in immunocompetent adults. This case highlights the importance of recognizing adverse events associated with vaccination.

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Since varicella virus vaccine live became available in the United States in 1995, more than 55 million doses have been distributed.¹ Mild reactions at the injection site and localized rash may be associated with vaccination,² but serious adverse events are rare. Disseminated varicella-zoster virus (VZV) infections after vaccination have been reported in patients with underlying immunodeficiencies, including natural killer T cell defects,^{3,4} or with acquired immunodeficiency caused by HIV,⁵ bone marrow transplant,⁶ or other conditions.^{1,7} Localized rash is the most common adverse event reported in patients receiving the varicella virus vaccine live. Previously undiagnosed immunodeficiencies that were revealed after severe vaccine reactions have been reported in patients receiving live vaccines.^{5,8}

The Vaccine Adverse Events Reporting System is a passive surveillance system administered by the Centers for Disease Control and Prevention and the US Food and Drug Administration that tracks all reported adverse events temporally related to vaccination. Nearly 48 million doses of the varicella virus vaccine live were distributed between 1995 and 2005, and the Vaccine Adverse Events Reporting System reported 8262 cases of rash, of which 197 cases (2.4%) were classified as serious. Of 149 reported cases of thrombocytopenia associated with VZV vaccination, 95 (63.8%) were classified as serious. In addition, 32 cases of hepatic diseases were reported.² Other analyses of adverse events associated with VZV vaccination have come from the Worldwide Adverse Experience

System managed by Merck & Co, Inc, the manufacturer of Varivax (ie, varicella virus vaccine live).^{1,9}

We describe a case of a woman who presented with a diffuse pruritic rash 17 days after receiving the varicella virus vaccine live. This reaction is unique because it occurred in a patient with no known immunocompromise. Physicians must be aware of these potential adverse effects when recommending or administering vaccines to their patients.

Report of Case

A 53-year-old woman presented to the emergency department (ED) with a diffuse pruritic rash 17 days after receiving the varicella virus vaccine live. The rash began on her chest and spread to her face, abdomen, back, and arms within 1 day. Her serologic test results before vaccination were negative for VZV, and she had no history of immunodeficiency or recurrent infections. She also had no other known exposure to VZV before the rash developed. She reported that she recently started taking meloxicam.

Physical examination revealed 1-mm to 2-mm skin-colored vesicles, many with central erosion, located centrally on an edematous pink base on her face, trunk, and extremities (*Figure*). Her palms, soles, and mucous membranes were not affected. The remainder of the physical examination results were within normal limits.

On presentation, the patient's white blood cell count was $1.9 \times 10^9/L$, her absolute neutrophil count was $0.79 \times 10^9/L$, and her platelet count was $68 \times 10^9/L$. Her laboratory results before vaccination demonstrated a normal white blood cell count and platelet count of $127 \times 10^9/L$. Although the patient had a history of non-alcoholic steatohepatitis with mildly elevated aminotransferase levels, at the time of presentation to the ED, she had an alanine aminotransferase level of 86 U/L and an aspartate aminotransferase level of 94 U/L.

The patient reported a headache and mild neck pain for approximately 1 to 2 weeks before presenta-

tion, and a lumbar puncture was performed in the ED that showed normal cerebrospinal fluid cell counts and normal protein and glucose levels. The cerebrospinal fluid polymerase chain reaction was negative for VZV. Chest radiograph results were normal. Serologic test results for HIV, Epstein-Barr virus, and hepatitis B and C were negative.

Two punch biopsies of the affected area were performed for histopathologic analysis and tissue culture. Histopathologic analysis revealed stratum corneum with a basket weave pattern. The epidermis contained single and clustered necrotic keratinocytes, and the dermis was found to have a mixed perivascular lymphohistiocytic infiltrate. Multiple necrotic keratinocytes with ground-glass nuclei were seen in a hair follicle. The VZV immunostain was positive within the necrotic epidermal cells and within the affected hair follicle, and the herpes simplex virus type 1 and type 2 immunostains were negative. Tissue culture was also positive for VZV. The biopsy specimen was cultured in H&V cells containing CV1 African green monkey kidney cells and MRC-5 human fetal lung cells. The live attenuated virus used in preparation of varicella virus vaccine live is propagated in MRC-5 cells and thus should replicate sufficiently in viral culture for detection in case of infection.

On the same day the patient was admitted to the ED, she was treated for a presumed disseminated VZV infection. She received 740 mg of intravenous acyclovir every 8 hours for 2 days, after which her rash improved and her white blood cell and platelet counts increased. She was discharged home and completed 5 more days of oral acyclovir, 800 mg 5 times daily, for a total 7-day course of therapy. On follow-up with her primary care physician 7 days after discharge, her neutropenia and thrombocytopenia had resolved and her rash was almost completely gone. Her aminotransferase levels remained elevated. Given the rare nature of disseminated VZV infections after VZV vaccination in immunocompetent adults, this patient was referred to the immunology clinic for follow-up, but she declined this evaluation.



Figure.

Photographs of a 53-year-old woman who presented to the emergency department with a diffuse pruritic rash 17 days after receiving the varicella virus vaccine live. Physical examination revealed 1-mm to 2-mm skin-colored vesicles, many with central erosion, located centrally on an edematous pink base on her face (A), trunk (B), and extremities (not pictured). The markings on the back indicate where the biopsy was taken.

Discussion

Sharrar et al⁹ described 7963 events reported between 1995 and 1999 from among 16.1 million VZV vaccine doses distributed. The authors⁹ found 1349 rashes that occurred within 42 days of vaccination. Rashes occurring within 2 weeks of vaccination were most likely to contain wild-type VZV, whereas rashes occurring more than 2 weeks after vaccination were most likely to contain the Oka vaccine strain of VZV. The patient in the current case report presented 17 days after vaccination, which suggests that this was more likely a disseminated infection from the vaccine strain of VZV, though we were not able to definitively identify which strain was present in our patient's rash. Sharrar et al⁹ also reported 15 cases of postvaccination thrombocytopenia with platelet counts ranging from $2 \times 10^9/L$ to $120 \times 10^9/L$. The patient in the current case also presented with postvaccination thrombocytopenia, which is a rare adverse event of the vaccine.

Although systemic postvaccination infections are rare in immunocompetent adults, the temporal relationship between the current patient's vaccination and the onset of her symptoms was concerning for disseminated VZV infection. Her diffuse nondermatomal rash, neutropenia, thrombocytopenia, and elevated aminotransferase levels were consistent with systemic infection rather than the localized rash more commonly associated with VZV vaccination.¹ Bernstein et al¹⁰ described a VZV rash caused by the vaccine strain of VZV in an immunocompetent patient who did not demonstrate the laboratory abnormalities noted in the present patient. The present patient possibly had a mild immunodeficiency, such as a natural killer cell defect, of which she was not aware.

The differential diagnosis for the current patient's skin lesions also included a drug reaction or erythema multiforme caused by medications or vaccination. Case reports have been published of erythema multiforme caused by VZV vaccination, either alone or in combination with other medications including amoxicillin and sulfonamides.^{2,8} The current patient had also recently started taking meloxicam, which has been associated with erythema multiforme.¹¹ Positive immunostaining and viral culture confirmed the VZV diagnosis in this patient.

Conclusion

The patient in the present case report had a rare case of disseminated VZV infection after vaccination but no known immunodeficiency. Positive immunostaining and viral culture results confirmed the diagnosis, and the patient responded well to treatment. This type of reaction has not been previously reported after vaccination in an immunocompetent adult. In the setting of concerns with vaccine safety, physicians must be aware of potential adverse reactions such as this in both immunocompromised and immunocompetent patients.

References

1. Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. *J Infect Dis.* 2008;197(suppl 2):S165-S169. doi:10.1086/522125.
2. Chaves SS, Haber P, Walton K, et al. Safety of varicella vaccine after licensure in the United States: experience from reports to the Vaccine Adverse Events Reporting System, 1995-2005. *J Infect Dis.* 2008;197(suppl 2):S170-S177. doi:10.1086/522161.
3. Banovic T, Yanilla M, Simmons R, et al. Disseminated varicella infection caused by varicella vaccine strain in a child with low invariant natural killer T cells and diminished CD1d expression [published online October 31, 2011]. *J Infect Dis.* 2011;204(12):1893-1901. doi:10.1093/infdis/jir660.
4. Levy O, Orange JS, Hibberd P, et al. Disseminated varicella infection due to the vaccine strain of varicella-zoster virus, in a patient with a novel deficiency in natural killer T cells [published online September 26, 2003]. *J Infect Dis.* 2003;188(7):948-953. doi:10.1086/378503.
5. Kramer JM, LaRussa P, Tsai WC, et al. Disseminated vaccine strain varicella as the acquired immunodeficiency syndrome-defining illness in a previously undiagnosed child. *Pediatrics.* 2001;108(2):E39. doi:10.1542/peds.108.2.e39.
6. Bhalla P, Forrest GN, Gershon M, et al. Disseminated, persistent, and fatal infection due to the vaccine strain of varicella-zoster virus in an adult following stem cell transplantation [published online December 1, 2014]. *Clin Infect Dis.* 2015;60(7):1068-1074. doi:10.1093/cid/ciu970.
7. Cheetham TC, Marcy SM, Tseng HF, et al. Risk of herpes zoster and disseminated varicella zoster in patients taking immunosuppressant drugs at the time of zoster vaccination [published online June 4, 2015]. *Mayo Clin Proc.* 2015;90(7):865-873. doi:10.1016/j.mayocp.2015.04.021.
8. Gershon AA. Varicella vaccine: rare serious problems—but the benefits still outweigh the risks [published online September 26, 2003]. *J Infect Dis.* 2003;188(7):945-947. doi:10.1086/378504.
9. Sharrar RG, LaRussa P, Galea SA, et al. The postmarketing safety profile of varicella vaccine. *Vaccine.* 2001;19(7-8):916-923. doi:10.1016/S0264-410X(00)00297-8.
10. Bernstein P, Furuya Y, Steinberg S, Scully B, LaRussa P, Gershon AA. Vaccine-related varicella-zoster rash in a hospitalized immunocompetent patient [published online January 26, 2011]. *Am J Infect Control.* 2011;39(3):247-249. doi:10.1016/j.ajic.2010.06.027.
11. Ward KE, Archambault R, Mersfelder TL. Severe adverse skin reactions to nonsteroidal antiinflammatory drugs: a review of the literature. *Am J Health Syst Pharm.* 2010;67(3):206-213. doi:10.2146/ajhp080603.

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