A Case of Herpes Zoster and Meningitis in a Twice-Vaccinated Healthy Adolescent

Yih-Chieh Chen[1*] Aisha James[1,2*] Emily Kung[3] Vandana Madhavan[3,4]

[1] Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts, United States
[2] Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States
[3] Division of Pediatric Hospitalist Medicine, Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts, United States
[4] Division of Pediatric Infectious Disease, Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts, United States

Address for correspondence Aisha James, MD, MEd, Department of Pediatrics, Massachusetts General Hospital, Boston, MA, United States (e-mail: akjames@partners.org).

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Abstract

Since the adoption of the varicella-zoster virus (VZV) vaccine, the incidence of varicella infections of all types has declined. Although uncommon, local cutaneous herpes zoster secondary to vaccine-strain VZV has been well documented in healthy children. However, there are few reports of vaccine-strain VZV central nervous system disease in this same population. We present a case of a previously healthy twice-VZV vaccinated 14-year-old girl who presented with rash and headache who was found to have herpes zoster complicated by meningitis. Cerebrospinal fluid polymerase chain reaction confirmed zoster infection secondary to reactivation of vaccine-strain VZV. Her disease course and response to therapy are reviewed.

Keywords
- varicella-zoster virus vaccine
- varicella-zoster virus
- herpes zoster
- meningitis

Case Presentation

A previously healthy 14-year-old girl was transferred to our emergency department on day 4 of her illness with worsening headache and rash. Her symptoms had started with a frontal headache noted to be worse in the mornings. On day 3 of illness, she noticed a pruritic rash on her trunk and presented to an outside emergency department. The rash was noted to be vesicular and in a left truncal dermatomal distribution, not crossing midline. She was prescribed an unknown dose of valacyclovir for presumed herpes zoster and discharged home. However, she was unable to tolerate any oral doses of valacyclovir at home due to nausea and she presented again the following day to the same emergency department for evaluation. A review of systems was positive for nausea, weakness, and myalgias, but negative for neck stiffness, fever, chills, vision change, numbness, as well as any respiratory, gastrointestinal, or genitourinary symptoms. A brain magnetic resonance imaging was performed and showed no abnormalities. Lumbar puncture (LP) was attempted but was unsuccessful due to patient discomfort. She was given intravenous (IV) fluids, ketorolac 15 mg IV, metoclopramide 10 mg IV, and morphine 2 mg IV, and subsequently transferred to the Massachusetts General Hospital for Children (MGHfC) for further evaluation. Initial examination at MGHfC revealed a tired, but nontoxic-appearing adolescent with vital signs appropriate for her age. Notably, she was afebrile. She had multiple intact vesicles on an erythematous base with areas of confluence in a T5 dermatomal distribution, from just below her left breast wrapping around to her back. There were no signs of bacterial superinfection with no purulent drainage. Her neurologic exam was overall unremarkable including a

* *These authors contributed equally to this work.*

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fundoscopic exam revealing a sharp disc on the left (right was unable to be visualized), intact cranial nerves 2 to 12, no nystagmus, normal tone and strength, and intact finger-to-nose testing. She denied exposure to, or infection with, primary varicella. Records from her primary care physician indicated that she received doses of varicella-zoster virus (VZV) vaccine at the age of 18 months and 12 years. In addition, she had confirmed immunity with a positive VZV immunoglobulin G (IgG) titer. Initial laboratory studies revealed peripheral white blood cell (WBC) count of 6.53 K/μL (72.8% neutrophils, 13.5% lymphocytes, 12.9% monocytes, and hemoglobin of 9.6 g/dL with MCV 77.9. Inflammatory markers were normal with erythrocyte sedimentation rate 17 mm/h and C-reactive protein 0.3 mg/L. Pediatric neurology was consulted due to concern for possible idiopathic intracranial hypertension given worsening headache in the morning and in a supine position. Pediatric infectious disease was also consulted for diagnostic guidance. Iron studies were obtained for her anemia. The results of these studies were consistent with iron deficiency as ferritin and iron levels were low, 8 and 24 μg/dL, respectively. She was started empirically on IV acyclovir, 10 mg/kg every 8 hours. LP was obtained with the patient lying flat under sedation with an opening pressure of 37 cm H_2O. Cerebrospinal fluid (CSF) was sent for VZV polymerase chain reaction (PCR), herpes simplex virus (HSV) PCR, and cell count. CSF cell count was notable for elevated WBC count at 568 cells/μL, with 92% lymphocytes and 8% monocytes in tube 1. CSF VZV PCR returned positive, while CSF HSV PCR was negative. A CSF sample was subsequently sent to the Centers for Disease Control and Prevention (CDC) for genotyping, which confirmed vaccine-strain Clade 2 VZV genotype. Human immunodeficiency virus (HIV) antibody, VZV IgG, and B and T cells flow cytometry were also sent to assess for coinfection and signs of immunodeficiency. VZV IgG was positive and HIV antibody was negative. The results of flow cytometry showed that the absolute number of T cells, B cells, and NK cells were within normal range. The patient was continued on parenteral acyclovir for a total of 7 days. Her rash completely crusted over by day 10 of illness and her headache resolved on day 11 of illness. She was sent home to complete an additional 14 days of oral valacyclovir 1,000 mg, three times a day. On the day of discharge, she reported complete resolution of her central nervous system (CNS) symptoms and had no new skin lesions. Unfortunately, she did not return for her scheduled follow-up visits in the outpatient pediatric infectious disease clinic, and her family was unable to be reached via telephone.

Discussion

Since adoption of national recommendations for live-attenuated VZV vaccination in 1995, the incidence of primary varicella has dramatically declined. The effectiveness of a single-dose vaccine to prevent disease was found to be 85%, and is estimated to improve to 98% with the two-dose regimen recommended as of 2006.[1] Concurrently, the incidence of herpes zoster has declined in a similar fashion.[2,3] However, the risk of VZV reactivation still remains, and should be considered in the appropriate clinical context. Ten-year postvaccine CDC surveillance data (1995–2005) identified cases of herpes zoster due to both wild-type and vaccine-strain VZVs,[4] and there is a growing body of literature documenting VZV infection in previously immunized individuals.[5–7]

Herpes zoster results from reactivation of dormant VZV after primary infection or vaccination. It typically activates in a single sensory dorsal root ganglion and causes a painful vesicular rash in a dermatomal pattern. Disseminated disease is less common but can include multiple organ systems. CNS manifestations of VZV can range in severity from mild reversible disease to death.

Advances in diagnostic techniques now allow us to easily identify VZV in CSF by PCR DNA amplification. With these improved techniques, there is increasing evidence to suggest that VZV-associated CNS disease is more common than previously thought. Several studies have now established VZV reactivation as a leading cause of viral meningitis and encephalitis.[7,8]

In a statewide study of CNS disease in California, the clinical presentations of VZV CNS infection included meningitis (50%), encephalitis (42%), and acute disseminated encephalomyelitis (8%).[7] A recent retrospective case series from Switzerland detected VZV in the CSF of 11 out of 519 (2.1%) patients with a clinical diagnosis of meningitis or encephalitis. Eight of the patients fully recovered, two suffered chronic neuropsychological sequelae, and one patient died.[8] Our patient developed a severe vesicular rash along a single dermatome and meningitis without focal neurologic deficits. While she was lost to follow-up, her near-complete resolution of symptoms at the time of discharge argues that she will likely have a favorable outcome and full recovery.

In our case, symptoms of meningitis were accompanied by a vesiculopapular rash along a single dermatome, without face and neck involvement; these locations are not always involved in VZV CNS infection. In fact, multiple studies have noted that 11 to 45% of reactivation cases with CNS manifestations do not have any skin findings.[7,8]

Advanced age and immune deficiency are leading risk factors for VZV reactivation; both local herpes zoster and disseminated disease are therefore rare in healthy children. The literature demonstrates increased incidence and severity of VZV infection in children with impaired cell-mediated immunity secondary to disease or medication.[3,7] Our case adds to a growing number of case reports describing immunocompetent children with CNS disease secondary to VZV reactivation.[3–7]

In addition, our patient was previously vaccinated, and VZV genotyping at the CDC identified vaccine-strain virus from her CSF. There are only a small number of reported cases of CNS infection due to vaccine-strain VZV in immunocompetent children.[4–7] To our knowledge, ours is the first reported case in a child who received two doses of the VZV vaccine. Per current CDC guidelines, the first varicella vaccine should be administered between 12 and 15 months and the

second between 4 and 6 years; a minimum of 3 months should elapse between doses, but there is no maximum elapsed time. Our patient did not receive these doses per the recommended U.S. schedule, as she received her doses at the age of 18 months and 12 years.

Her presentation also reflects the likely different CNS manifestations in wild-type and vaccine-strain VZV cases. Similar to cases previously reported, our patient's infection presented with meningitis alone. In contrast, wild-type VZV is most commonly associated with encephalitis. A possible underlying immunologic explanation has not yet been identified.

There are limited data to determine the optimal therapy for VZV CNS infection. The current recommendation by the Infectious Disease Society of America is 10 to 14 days of IV acyclovir for VZV encephalitis, but there are no clear recommendations for VZV meningitis.[9] Our patient was treated for 7 days with IV acyclovir given her lack of viremia, immunocompetent status, and quick symptomatic improvement. In addition, she was discharged with an additional 14 days of oral valacyclovir, for a total of 21 days of antiviral therapy; this agent has been shown to have adequate CSF penetration and clinical efficacy against VZV encephalitis.[10]

In our case, there may have been an inappropriately decreased suspicion for disseminated VZV infection on initial presentation, as headache and rash were the only initial complaints. There was no fever, and she was a fully vaccinated, immunocompetent adolescent. Thus, there was a delay in diagnosis and treatment. Given high rates of routine immunization for VZV, there is likely to be an increase in the incidence of disease secondary to vaccine-strain VZV reactivation among both immunocompetent and immunocompromised children. Our case highlights the importance of considering VZV-related CNS disease in all children with suspicious history and physical exam, regardless of prior vaccination status.

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