Characterization of Virus-specific Immune Response During Varicella Zoster Virus Encephalitis in a Young Adult

Nicole L. Sullivan,^{1,a,b} Christiane S. Eberhardt,^{1,2,a} Andreas Wieland,¹ Rama S. Akondy,¹ Jumi Yi,^{3,c} Anita K. McElroy,^{3,d} and Rafi Ahmed¹

¹Emory Vaccine Center and Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, Georgia; ²Department of Pediatrics and Pathology-Immunology, Center for Vaccinology and Neonatal Immunology, University Hospitals of Geneva and Faculty of Medicine, University of Geneva, Switzerland, and ³Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Georgia

An immunocompetent adult received corticosteroids for chest pain, which later was clinically found to be herpes zoster (HZ). She developed severe disease and rapid viral dissemination that elicited an exceptionally strong varicella zoster virus-specific B-cell and CD8 T-cell response. Clinicians should consider atypical HZ presentation prior to corticosteroid administration.

Keywords. herpes zoster; varicella zoster virus; CD8 T cells; plasmablasts.

Herpes zoster (HZ) is caused by the reactivation of varicella zoster virus (VZV) in sensory nerve ganglia. The annual incidence of HZ is around 1% in the elderly and 10 times lower in young adults [1]. The disease is typically localized and characterized by a cutaneous vesicular rash of the affected dermatome and concomitant neuralgia. However, in immunocompromised individuals, HZ can be severe with neurological and respiratory complications and death.

Here, we present a case of an immunocompetent VZV-vaccinated young adult who initially received corticosteroids for chest pain during a suspected bronchopneumonia. She then developed cutaneous wild-type HZ lesions followed by rapidly disseminated disease with VZV encephalitis. This is one of the few studies to extensively characterize the adaptive

VZV-specific immune response to clinical HZ in an immunocompetent young adult.

Case Description

A 19-year-old female college student, without history of previous hospitalizations or serious illnesses, presented to her primary care provider with a history of 2 days of left-sided chest and back pain. She reported to have received azithromycin as initial treatment for a suspected bacterial bronchopneumonia and muscle relaxants and 3 days of prednisone for chest and back pain. As her chest pain continued over the following days, she also underwent extensive cardiac workup, which was normal. On day 6 of symptoms, she developed a left axillary vesicular rash and was diagnosed with HZ. On day 7, she became febrile (38.5°C), presented with cutaneous disseminated HZ, and was admitted for monitoring and intravenous treatment with antivirals and analgesics (acyclovir and ketorolac). The patient had received 2 doses of Varivax at age 1 year and age 13 years. However, polymerase chain reaction of vesicle fluid confirmed wild-type VZV (National VZV Laboratory, Centers for Disease Control and Prevention [2]) and not the vaccine strain. There was no history of chickenpox, but she was in contact with wild-type VZV during her sibling's chickenpox at age 3 years. On day 8, she deteriorated with signs of encephalopathy. The head computed tomography was unremarkable, and analysis of cerebrospinal fluid showed 404 white blood cells/mm³ (93% lymphocytes), and VZV (6300 copies/mL) was detected. On day 9, she developed tachypnea and respiratory distress and was transferred to the pediatric intensive care unit (PICU) for high-flow nasal cannula. A chest X-ray showed evidence of pulmonary edema and early right posterior lobe consolidation. Her course was complicated by nonoliguric acute renal failure secondary to dehydration and nephrotoxic medications (non-steroidal antiinflammatory drugs and acyclovir), and her treatment was adapted accordingly. She was discharged from PICU on day 13 and completed a 3-week total course of antivirals. Due to difficult pain management and deconditioning, she was not discharged until day 33 after symptom onset. A follow-up appointment after 3 months was normal (Figure 1A).

METHODS

Please refer to [Supplementary Materials](#).

RESULTS

First, we measured antibody responses to VZV and found that the patient mounted a strikingly high antibody response to the infection. Fourteen days after symptom onset, the VZV-specific antibody titers were significantly higher in the patient compared to healthy, latently infected adults. There was a 35-fold

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^aN. L. S. and C. S. E. contributed equally to this work.

^bPresent address: Merck Research Laboratories, Department of Infectious Diseases and Vaccines, Merck & Co., Inc., Kenilworth, New Jersey.

^cPresent address: Division of Pediatric Infectious Disease, University of California–San Francisco Benioff Children's Hospital Oakland.

^dPresent address: Division of Pediatric Infectious Disease, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of UPMC, Pennsylvania.

Correspondence: R. Ahmed, Emory Vaccine Center, Rollins Research Center, Emory University, 1510 Clifton Rd., Atlanta, GA 30322 (rahmed@emory.edu).

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Figure 1. Potent varicella zoster virus (VZV)-specific B-cell and CD8 T-cell response in fulminant zoster encephalitis. (A) Time course of symptom onset, treatment, and hospital stay. Time points of blood sampling are indicated in red. (B) Kinetics of VZV-specific immunoglobulin (Ig) G, IgM, and IgA antibody titers (half maximal effective concentration [EC50]) at days 14, 32, and 106 after onset of symptoms. The solid line represents the mean antibody titer of 7 healthy adults with the corresponding titer range (dashed line). (C) Number of VZV-specific IgG, IgA, and IgM plasmablasts 14 days after onset of symptoms (patient, red) compared to a healthy latently infected adult (black). (D) Flow plots showing expression of HLA-DR+ and CD38+ among CD8+ or CD4+ T cells (left panel, blue gate), and histograms showing Ki-67 expression among activated (HLA-DR+CD38+, blue) and nonactivated T cells (CD38+HLA-DR-, black) in peripheral blood on day 14. (E) Left: Flow plots showing frequency of VZV-specific (ILIEGIFV) tetramer+ CD8 T cells (gated on CD3+CD8+ cells) on days 14, 32, and 106 after onset of rash. Right: Histograms showing expression of activation markers HLA-DR and CD38, proliferation marker Ki-67, and effector molecules perforin, granzyme B, and granzyme K among naïve (CCR7+CD45RA+, black) and HLA-A2-ILI-specific (red) CD8 T cells. (F) Flow plots of cryopreserved peripheral blood mononuclear cells (day 106) after restimulation with ILI peptide showing frequency of interferon- γ , tumor necrosis factor- α , CD107a, and macrophage inflammatory protein-1 β -expressing cells (gated on CD8+ T cells). (G) Flow plot gated on CD3^{neg}CD56^{pos} natural killer (NK) cells (lymphocytes gated using forward and sideward scatter parameters) on day 106. Cytotoxic CD3^{neg}CD56^{br}CD16^{pos} NK cells account for the majority and express higher levels of granzyme B and perforin (blue, histogram) than CD3^{neg}CD56^{dim}CD16^{neg} NK cells (black, histogram). Abbreviations: IFN, interferon; Ig, immunoglobulin; MIP, macrophage inflammatory protein; PBMC, peripheral blood mononuclear cell; TNF, tumor necrosis factor; VZV, varicella zoster virus.

difference in immunoglobulin (Ig) M and IgA isotypes and 180-fold difference in IgG (Figure 1B).

Next, we measured the plasmablast response in the blood. Plasmablasts are derived from recently activated naive or memory B cells that have differentiated into antibody-secreting cells and are an indicator of an active immune response. VZV-specific plasmablasts are thus absent from the blood of healthy latently infected individuals (Figure 1C) [3]. During the acute phase of infection, the patient had a prominent VZV-specific plasmablast response. Although we detected VZV-specific plasmablasts of all 3 isotypes, the majority were IgG secreting (Figure 1C), which coincided with the elevated VZV-specific IgG-antibody levels.

Next, we analyzed the T-cell immune response using the T-cell activation markers CD38 and HLA-DR, which identify activated T cells during the effector phase [4]. On day 14, approximately 17.5% of CD8 T cells in the peripheral blood exhibited an activated CD38+HLA-DR+ phenotype (in healthy adults it is approximately 0.15%–1%), with the majority of these activated cells expressing the proliferation marker Ki-67 (Figure 1D). Among CD4 T cells, approximately 1.7% expressed CD38 and HLA-DR compared to approximately 0.2%–0.6% in healthy adults. The observed T-cell activation was transient and returned to a level comparable to that in healthy adults (approximately 1.8% of CD8 and approximately 0.9% of CD4 T cells) by day 32 (data not shown). To perform a detailed characterization of VZV-specific CD8 T cells during the acute (day 14) and convalescent phases (day 32/106), we used a HLA-A2-tetramer of a recently identified, immunodominant VZV epitope (A2-ILI) from the VZV ribonucleotide reductase subunit 2 protein [5]. Quite strikingly, on day 14, 17% of CD8 T cells were specific for A2-ILI (Figure 1E, left column). These cells expressed markers of activation (CD38+HLA-DR+), proliferation (Ki-67+), and effector function such as granzyme B, K, and perforin, indicative of cytotoxic potential (Figure 1E, histograms). Following this phase of robust activation and expansion, the frequencies of A2-ILI-positive CD8 T cells decreased to 9.5% and to 2.6% on day 32 and day 106, respectively (Figure 1E, left column). A2-ILI-specific CD8 T cells downregulated activation and proliferation markers (CD38, HLA-DR, Ki-67) during the contraction phase but maintained high expression of granzyme B and perforin even on day 106.

Next, we examined the functionality of VZV-specific CD8 T cells in terms of cytokine production after *in vitro* peptide stimulation. We detected CD8 T cells that secreted interferon- γ , tumor necrosis factor- α , macrophage inflammatory protein-1 β , and interleukin-2 (not shown) and had the capacity to degranulate (CD107a) (Figure 1F). Patients with natural killer (NK) cell deficiencies are at risk for complicated VZV infections. On day 106, we detected NK cells that expressed granzyme B and perforin, which suggest a normal NK cell function (Figure 1G). In summary, we show that the patient

mounted a potent VZV-specific B- and T-cell response during the course of infection.

DISCUSSION

Here, we describe the VZV-specific adaptive immune response in a young immunocompetent and previously vaccinated patient with wild-type VZV encephalitis. It remains unknown when the patient was infected with the wild-type virus. She received 2 vaccine doses, the first at age 1 year and the second at age 13 years. There was a reported case of chickenpox in her sibling when she was 3 years old and had only received 1 vaccine dose. She could have acquired a subclinical infection at that time as subclinical VZV infection can occur after 1 dose of vaccine [6, 7]. As an adult, she then presented with symptoms that were clinically more consistent with VZV reactivation. She initially had pain in her left chest, followed by a dermatomal rash in the same area and neuralgia after healing of skin lesions. Subclinical infections before the second vaccine dose may lead to reactivation of wild-type HZ decades later.

The humoral immune response (plasmablasts and antibody titers) to VZV on day 14 after onset of symptoms was much higher compared to the response induced by the live-attenuated Zostavax vaccine, with the initial VZV-specific IgG antibody titer being 100-fold higher than after immunization and about 180-fold higher compared to healthy adults [3]. In addition to a significant B-cell response to VZV, this patient also mounted a large CD8 T-cell response directed against VZV, with 17% of CD8 T cells in the peripheral blood being specific for an immunodominant VZV epitope (ILI) at the peak of the response. The elicited VZV-specific CD8 T cells exhibited a typical effector cell phenotype (CD38+HLA-DR+) and expressed molecules such as granzyme B, K, and perforin, indicative of cytotoxic potential. In contrast to Zostavax vaccination, which fails to induce a significant VZV-specific CD8 T-cell response in the majority of individuals [3], HZ reactivation in this patient resulted in the potent induction of CD8 T cells. Such high frequencies of activated CD8 T cells have previously been reported in other fulminant viral infections [8, 9]. The patient also showed an increase in activated CD4 T cells, which have been shown to play a crucial role in preventing HZ and decreasing clinical symptoms [10].

Disseminated HZ in young immunocompetent individuals is extremely rare. Our patient did not appear to have any NK cell deficiency that is associated with complicated VZV infection. However, prior to the clinical diagnosis of HZ, she received corticosteroid treatment whose immunosuppressive effect is well known [11]. Also, the use of corticosteroids for other indications increases the risk of pediatric HZ [12]. There is limited evidence supporting the benefits of corticosteroids during HZ to decrease post-herpetic neuralgia [13]. If given, simultaneous administration of antivirals is recommended to avoid potential dissemination of disease [14].

It is likely that the short course of corticosteroids initially impaired her antiviral immune response, which allowed for

the abundant and systemic dissemination of the virus. The immune response elicited after cessation of corticosteroid treatment was exceptionally strong, likely due to the high viral load. This case should raise awareness among clinicians of potential HZ in vaccinated young adults. Initial HZ presentation can be atypical and be mistaken for a disease that might warrant corticosteroid treatment. However, keeping in mind the severe complications in case of underlying HZ, corticosteroid treatment should always be carefully evaluated [15].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. *BMC Infect Dis* **2015**; 15:502.
2. Centers for Disease Control and Prevention. Laboratory services provided through the CDC National VZV Laboratory. Available at: <https://www.cdc.gov/chickenpox/lab-testing/cdc-vzv-lab.html>. Accessed 21 October 2018.
3. Li S, Sullivan NL, Roupael N, et al. Metabolic phenotypes of response to vaccination in humans. *Cell* **2017**; 169:862–77 e17.
4. Miller JD, van der Most RG, Akondy RS, et al. Human effector and memory CD8+ T cell responses to smallpox and yellow fever vaccines. *Immunity* **2008**; 28:710–22.
5. Chiu C, McCausland M, Sidney J, et al. Broadly reactive human CD8 T cells that recognize an epitope conserved between VZV, HSV and EBV. *PLoS Pathog* **2014**; 10:e1004008.
6. Siedler A, Rieck T, Tolsdorf K. Strong additional effect of a second varicella vaccine dose in children in Germany, 2009–2014. *J Pediatr* **2016**; 173:202–6 e2.
7. Perella D, Wang C, Civen R, et al. Varicella vaccine effectiveness in preventing community transmission in the 2-dose era. *Pediatrics* **2016**; 137:1–9.
8. McElroy AK, Akondy RS, Davis CW, et al. Human Ebola virus infection results in substantial immune activation. *Proc Natl Acad Sci U S A* **2015**; 112:4719–24.
9. McElroy AK, Akondy RS, Harmon JR, et al. A case of human Lassa virus infection with robust acute T-cell activation and long-term virus-specific T-cell responses. *J Infect Dis* **2017**; 215:1862–72.
10. Haberthur K, Engelmann F, Park B, et al. CD4 T cell immunity is critical for the control of simian varicella virus infection in a nonhuman primate model of VZV infection. *PLoS Pathog* **2011**; 7:e1002367.
11. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol* **2011**; 335:2–13.
12. Ferreira JC, Marques HH, Ferriani MP, et al. Herpes zoster infection in childhood-onset systemic lupus erythematosus patients: a large multicenter study. *Lupus* **2016**; 25:754–9.
13. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev* **2013**; 1–41.
14. Cohen JL. Clinical practice: herpes zoster. *N Engl J Med* **2013**; 369:255–63.
15. Rudinsky DM, Jordan K. Disseminated herpes zoster causing acute respiratory distress syndrome in an immunocompetent patient. *BMJ Case Rep* **2017**; 2017:bcr-2017-220542.