HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2016 December 22.

Published in final edited form as:

Clin Infect Dis. 2009 January 01; 48(1): e1–e2. doi:10.1086/595555.

Encephalitis after Secondary Smallpox Vaccination

Vlada V. Melekhin[1], **Kevin L. Karem**[2], **Inger K. Damon**[2], and **Karen C. Bloch**[1]

[1]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

[2]Centers for Disease Control and Prevention, Poxvirus Program, Atlanta, Georgia

Abstract

We describe a case of post-secondary vaccination encephalitis in a smallpox vaccine recipient and discuss detection of intrathecal antibody to vaccinia virus as a potential diagnostic test.

Encephalitis is a rarely reported complication of smallpox vaccine; the majority of cases are associated with primary vaccination [1–5]. Concern about smallpox virus as a possible bioterrorism agent has led to reinstatement of vaccination for US military personnel and civilian first responders. We report a case of postvaccinia encephalitis (PVE) in a patient revaccinated with smallpox vaccine, with supporting serologic evidence of direct CNS infection.

Case patient

A previously healthy 40-year-old man received hepatitis A vaccine, typhoid vaccine, smallpox vaccine, and FluMist (MedImmune Vaccines) in preparation for active military duty. He had received primary smallpox vaccination 19 years earlier, in 1986, when he joined the military. The patient developed photophobia 5 days after secondary vaccination and was hospitalized 8 days after vaccination, with confusion and agitation. Physical examination revealed a temperature of 38.2°C, increased upper-extremity tone, low-frequency tremor, and a Glasgow coma score of 10. No rash was noted other than at the vaccination site. A lumbar puncture performed 9 days after vaccination revealed an opening pressure of 15 cm of water, a protein concentration of 122 mg/dL, and a WBC count of 294 cells/μL, with 76% lymphocytes and 24% neutrophils. Brain MRI with gadolinium was limited by motion artifact but did not reveal any significant abnormalities. An electroencephalogram revealed diffuse theta-frequency slowing without epileptiform discharges.

The patient began empirical treatment with acyclovir. He developed generalized seizures, which were controlled with phenytoin. Repeat lumbar puncture 11 days after vaccination showed an opening pressure of 19 cm of water, a protein concentration of 95 mg/dL, and a WBC count of 137 cells/μL, with 89% lymphocytes, 1% neutrophils, and 10% monocytes.

Reprints or correspondence: Dr. Vlada V. Melekhin, Vanderbilt University Medical Center, 1161 21st Ave. S., A-2200, Medical Center North, Nashville, TN 37232-2582 (vlada.melekhin@vanderbilt.edu).

Potential conflicts of interest. All authors: no conflicts.

The patient's health gradually improved, and he was discharged from the hospital 16 days after vaccination, at which time formal evaluation indicated that the patient exhibited residual deficits in short-term memory and subjective assessment of impairment in coordination and balance. Results of extensive laboratory testing—including adenovirus CSF PCR, California and eastern equine encephalitis virus serum antibody immu nofluorescence assay (IFA) (<1:20), *Ehrlichia chaffeensis* IgG antibody IFA (<1:64) and whole blood PCR, enterovirus CSF PCR, Epstein-Barr virus CSF PCR, *Herpes simplex* virus CSF PCR, human herpes virus–6 CSF PCR, parvovirus B-19 serum IgM-negative EIA (<0.15), *Rickettsia rickettsii* serum IgG antibody IFA (<1:64), St. Louis encephalitis virus serum IgM and IFA antibody EIA (<1:20), West Nile virus serum IgM EIA (<3.0), and western equine encephalomyelitis serum antibody IFA (<1:20)—were negative for an alternative infectious agent.

Results

Serum and CSF samples collected 11 days after vaccination were sent to the Centers for Disease Control and Prevention, Poxvirus Program (Atlanta, GA), for laboratory testing. Serologic testing was performed using an ELISA as described elsewhere [6, 7]. Controls for CSF testing were an-omyzed diagnostic samples from ruled-out orthopoxvirus cases tested by PCR and ELISA. Vaccinia-specific IgG antibody was detected by ELISA in both serum and CSF samples, whereas IgM antibody was undetectable in both specimens. CSF samples were negative for orthopoxvirus DNA by PCR and for virus by culture. To test for the possibility that the intrathecal vaccinia antibody represented either blood contamination or passive transfer of IgG antibody across the blood-brain barrier, sero-logic testing by ELISA for antibodies to varicella zoster virus was performed with serum and CSF samples. High levels of IgG against varicella zoster virus were observed in serum samples but were undetectable in CSF samples.

Discussion

PVE is an uncommon complication of smallpox vaccination that affects ~3 vaccinees per million primary vaccinees and 0.1 vaccinees per million repeat vaccinees [2, 8]. The pathogenesis of PVE is poorly understood. Although culture of CSF samples may be positive for vaccinia virus in a minority of cases [3], the 5-day lapse to onset of neurological symptoms after secondary smallpox vaccination and lack of evidence of direct CNS infection suggest an autoimmune response to vaccination, as described in other cases [4]. During the time between vaccination and the onset of symptoms, pox-viruses (including vaccinia virus) affect the host immune responses by neutralizing host cytokines [9] and IFNs [9, 10] and by induction of macrophage apoptosis [11].

The patient in this report meets the surveillance case definition for probable PVE [12]. Demonstration of high levels of vaccinia IgG antibody in the absence of IgM supports the history of prior vaccination against smallpox. Although vaccinia virus could not be amplified or isolated from the CSF, elevated levels of vaccinia-specific IgG antibody were detected in the CSF. Intrathecal antibody in the absence of detectable virus has been reported with encephalitis associated with monkeypox, an orthopoxvirus related to smallpox [7]. In

this case, the detection of serum antibody to varicella zoster virus but the absence of such antibody in CSF lends credence to the hypothesis of in-trathecal antivaccinia production rather than blood contamination at the time of lumbar puncture or passive diffusion of proteins across inflamed meninges. Our experience suggests that detection of intrathecal vaccinia antibody may be useful for laboratory confirmation of PVE, particularly in the absence of intrathecal antibody to an unrelated infectious agentto which the host has detectable serum titers.

Acknowledgments

Financial support. National Institutes of Health National Research Service Award Institutional Research Training Grant (T32 AI07474-10 to V.V.M.) and Emerging Infections Program cooperative agreement with the Centers for Disease Control and Prevention (U50/CCU416123-09 to K.C.B.).

References

1. Sejvar JJ, Labutta RJ, Chapman LE, Grabenstein JD, Iskander J, Lane JM. Neurologic adverse events associated with smallpox vaccination in the United States, 2002–2004. JAMA. 2005; 294:2744–50. [PubMed: 16333010]
2. Aragon TJ, Ulrich S, Fernyak S, Rutherford GW. Risks of serious complications and death from smallpox vaccination: a systematic review of the United States experience, 1963–1968. BMC Public Health. 2003; 3:26. [PubMed: 12911836]
3. Gurvich EB, Vilesova IS. Vaccinia virus in postvaccinal encephalitis. Acta Virol. 1983; 27:154–9. [PubMed: 6135334]
4. Miravalle A, Roos KL. Encephalitis complicating smallpox vaccination. Arch Neurol. 2003; 60:925–8. [PubMed: 12873847]
5. Neff J, Modlin J, Birkhead GS, et al. Monitoring the safety of a smallpox vaccination program in the United States: report of the joint Smallpox Vaccine Safety Working Group of the Advisory Committee on Immunization Practices and the Armed Forces Epidemiological Board. Clin Infect Dis. 2008; 46(Suppl 3):S258–70. [PubMed: 18284367]
6. Karem KL, Reynolds M, Braden Z, et al. Characterization of acute-phase humoral immunity to monkeypox: use of immunoglobulin M enzyme-linked immunosorbent assay for detection of monkeypox infection during the 2003 North American outbreak. Clin Diagn Lab Immunol. 2005; 12:867–72. [PubMed: 16002637]
7. Sejvar JJ, Chowdary Y, Schomogyi M, et al. Human monkeypox infection: a family cluster in the midwestern United States. J Infect Dis. 2004; 190:1833–40. [PubMed: 15499541]
8. Sejvar J, Boneva R, Lane JM, Iskander J. Severe headaches following smallpox vaccination. Headache. 2005; 45:87–8. [PubMed: 15663622]
9. Smith GL, Symons JA, Alcami A. Immune modulation by proteins secreted from cells infected by vaccinia virus. Arch Virol. 1999; 15(Suppl):111–29.
10. Symons JA, Tscharke DC, Price N, Smith GL. A study of the vaccinia virus interferon-γ receptor and its contribution to virus virulence. J Gen Virol. 2002; 83:1953–64. [PubMed: 12124459]
11. Humlová Z, Vokurka M, Esteban M, Melková Z. Vaccinia virus induces apoptosis of infected macrophages. J Gen Virol. 2002; 83:2821–32. [PubMed: 12388819]
12. Casey C, Vellozzi C, Mootrey GT, et al. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. MMWR Recomm Rep. 2006; 55(RR-1):1–16.