Herpes Zoster with Skin Lesions and Meningitis Caused by 2 Different Genotypes of the Oka Varicella-Zoster Virus Vaccine

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A previously healthy boy who had received varicella vaccine developed herpes zoster with meningitis. The vaccine strain recovered from scabs of 3 skin lesions had the wild-type allele at position 108111, a vaccine marker never previously associated with vaccine-associated adverse events. The vaccine strain from cerebrospinal fluid also contained mutations never previously observed at vaccine-associated single nucleotide polymorphisms that would alter amino acid sequences in ORF54 and ORF59. The presence of distinct strains in skin lesions and cerebrospinal fluid indicate that >1 variant strain may reactivate to cause herpes zoster.

Most adverse events following the administration of varicella vaccine occur shortly after vaccination, before a vigorous immune response develops [1–3]. Most commonly, these are injection site reactions, but occasionally papulovesicular lesions occur, indicating vaccine virus replication. Rash distant from the injection site occurs during the early period after vaccination in 2%–4% of vaccinees [3]. Less common serious adverse events attributed to varicella vaccine include joint, liver, lung, and central nervous system (CNS) diseases [4]. Following the distribution of 47 million doses of varicella vaccine through 2005, 39 cases of meningitis and 16 cases of encephalopathy were reported to the Vaccine Adverse Events Response System [4]. However, the true incidence of neurologic complications is uncertain because (1) the reporting system was passive, (2) the etiologic cause of these complications was rarely established, (3) some CNS disease was caused by naturally occurring varicella, and (4) other vaccines were often administered concomitantly with varicella vaccine.

Herpes zoster (HZ) caused by reactivation of latent vaccine-strain varicella-zoster virus (VZV) in sensory ganglia constitutes an additional, usually late, complication of varicella vaccination. The frequency of HZ among children who receive varicella vaccine is uncertain, although some experts have suggested that it is much lower than the frequency among children who had had varicella [2, 5, 6]. However, reliable population-based studies are lacking, and varicella vaccine was licensed only in 1995.

Ten cases of viral meningitis attributed to varicella vaccine have been reported with a long interval after vaccination [4]. Only 6 case patients were confirmed to have VZV in cerebrospinal fluid (CSF), with vaccine-strain VZV confirmed only in 2; 1 case occurred in an immunocompromised child. We report a case of laboratory-confirmed HZ with meningitis caused by Oka/Merck strains of VZV in an immunologically healthy child who had received varicella vaccine.

Case report. A healthy 8-year-old boy developed a painless, pruritic papule on his left shoulder. The patient had no past history of atypical infections or recognized exposure to varicella and had received 1 dose of varicella vaccine in the left deltoid region at 1 year of age. The rash evolved into multiple small vesicles over the next 2 days. On day 3, his physician diagnosed HZ with possible bacterial superinfection. On the following day, the patient developed severe headache, meningismus, photophobia, vomiting, and low-grade fever and was subsequently hospitalized. Neurologic examination findings were normal. Findings of computerized tomographic (CT) imaging without contrast were normal. CSF contained lymphocytes with normal levels of glucose and protein (table 1). Polymerase chain reaction (PCR) analysis of a CSF specimen was positive for VZV. Blood counts and results of serum chemistry analyses, including liver function tests, were normal, with the exception of borderline lymphopenia (lymphocyte concentration, 1180 cells/mm³). The patient received acyclovir (15 mg/kg intravenously every 8 h) for...
2 days. After near resolution of symptoms, he was discharged with analgesics but without antiviral therapy.

During the ensuing 3 days, the patient had a recrudescence of severe headache and photophobia, but no fever, as well as intermittent somnolence, and he was rehospitalized. Findings of neurologic examination remained normal. Multiple lesions on the left arm and shoulder were scabbed without erythema, and there were no extradermal lesions. Repeat lumbar puncture revealed persistent lymphocytic pleocytosis without hypoglycorrhachia but with an elevated protein level (table 1). Blood counts and results of serum chemistry analyses, including measurements of liver enzyme levels, were normal. CT imaging with contrast did not show parenchymal abnormalities or meningeal enhancement. PCR analysis of a CSF specimen was negative for herpes simplex virus, enterovirus, and VZV, as were results of viral and bacterial cultures. Quantitative immunoglobulin levels and T and B cell subsets were normal, and the patient tested negative for HIV. Enzyme immunoassays were strongly positive for VZV-specific IgM and IgG antibodies. Intravenous acyclovir (15 mg/kg every 8 h) was administered for 7 days during hospitalization. All symptoms resolved within 48 h. He was discharged to receive valacyclovir for 1 week. Liver enzyme levels were elevated in the hospital (aspartate aminotransferase level, 99 U/L; alanine aminotransferase level, 94 U/L) but were normal 1 week after discharge. Two weeks after discharge, the patient was asymptomatic, and findings of physical examination were normal.

Methods. DNA was extracted and purified as described previously [8]. VZV was identified using Förster resonant energy transfer–based PCR with primers and probes for single nucleotide polymorphisms (SNPs) located in ORF38 (position 69348), ORF54 (94167), and ORF62 (106262 and 107252) [7, 8]. Sequence determination and SNP analysis for the vaccine-associated markers were performed as described previously [8]. Additional known vaccine SNP analyses for ORF6 (position 109137 and 109200) were performed. Strain genotyping was performed using the enhanced method [8]. Targeted amplimers from ORF22 (positions 37902, 38055, 38081, and 38177), ORF21 (33725 and 33728), and ORF50 (87841) were sequenced and evaluated at the indicated variable positions.

Results. For CSF samples obtained during each hospitalization, DNA from a VZV variant in the Oka/Merck vaccine was present in both tubes of a specimen obtained on the third day of illness but was not detected in a specimen obtained 5 days later (table 1). Scabs from 3 individual skin lesions contained an identical VZV variant from the Oka/Merck vaccine, which was different from the variant present in the CSF specimen (table 1 and figure 1A). Variants from both sites carried 3 of the 4 most stable vaccine markers in ORF62 (positions 105705, 106262, and 107252), but the skin lesion scabs had a wild-type variant at the fourth marker (108111). The variant from the CSF specimen carried the vaccine marker at position 108111 but differed at 2 other vaccine-associated markers (94167 and 101089), and it exhibited atypical transversion mutations at these loci that differed from known vaccine and wild-type genotypes. DNA from none of the samples displayed mixed markers at any of the vaccine-associated SNP positions, suggesting that each variant was clonal at its respective site. Standard genotypic analysis indicated that both strains were genotype J, consistent with the Oka vaccine variants (figure 1B).

Discussion. This is 1 of only 3 laboratory-confirmed cases of meningitis caused by a VZV strain in the Oka/Merck vaccine in children and only the second in an immunocompetent child [4]. This case indicates that vaccine-related HZ meningitis can be severe, with clinical and laboratory features similar to those observed with HZ and meningitis caused by wild-type VZV [9], and that recrudescence of symptoms can occur in the absence of VZV in the CSF. The medical history of the child and findings of a limited immunological assessment indicate that he was immunocompetent. This is also indicated by the timely healing of skin lesions and the disappearance of VZV DNA from CSF by day 8 of disease, which contrasts with the delayed VZV clearance from CSF that has been observed in some immunosuppressed patients [10, 11].

The Oka/Merck varicella vaccine is derived from seed cultures that contain a mixture of viruses [12]. Two laboratories have

Table 1. Findings of clinical and polymerase chain reaction (PCR) analyses of cerebrospinal fluid (CSF) and scab specimens.

<table>
<thead>
<tr>
<th>Day of illness</th>
<th>Clinical findings in CSF specimens</th>
<th>PCR findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBC count, cells/μL</td>
<td>Protein level, g/dL</td>
</tr>
<tr>
<td>3</td>
<td>94a</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>245b</td>
<td>41</td>
</tr>
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NOTE. HSV, herpes simplex virus; VZV/Oka, Oka/Merck vaccine strains of varicella-zoster virus.

a A total of 96% of white blood cells (WBCs) were lymphocytes, 2% were monocytes, and 2% were polymorphonuclear leukocytes.

b A total of 80% of WBCs were lymphocytes, 12% were monocytes, 5% were reactive lymphocytes, and 3% were polymorphonuclear leukocytes.
performed targeted DNA sequencing and SNP analysis of VZV isolates from vaccine-associated HZ [8, 13]. Although studies from these laboratories disagree regarding the number of vaccine variants present in HZ lesions, both groups were in initial agreement that no single variant (or small group of variants) is more likely to establish latency after vaccination or to reactivate and cause HZ. However, a recently published analysis of allelic frequencies of SNPs in isolates from persons with vaccine-related HZ or postvaccination rash suggests that a subset of vaccine-virus genotypes is more often associated with rash illness [14]. Our recent analysis of Oka vaccine-strain SNPs in documented cases of rash illness is consistent with these findings to the extent that the SNPs identified by Quinlivan et al. [14] are also present in nearly all strains we recovered from persons with vaccine-associated HZ or postvaccination rash suggests that a subset of vaccine-virus genotypes is more often associated with rash illness [14]. Of the 24 genomic markers examined by both laboratories in VZV isolates from persons with vaccine-associated HZ or postvaccination rash suggests that a subset of vaccine-virus genotypes is more often associated with rash illness [14]. All of the specimens obtained in a given site (scabs or CSF) were identical to each other at the loci we evaluated. The variance at ORF54 and ORF59 in DNA of VZV from CSF specimens represent atypical transversion mutations, with a shift from pyrimidine bases previously identified at position 94167 to a purine (i.e., guanine) and a shift from purine bases at position 101089 to a pyrimidine (i.e., cytosine). All but 1 of 43 SNPs identified between vaccine and parental Oka were transition mutations, specifically a shift from thymidine to guanine at position 39227 (ORF22) [14]. For the ORF54 position, the normally observed sequence difference (cytosine in the strain from the Oka/Merck vaccine and thymine in wild-type VZV) results in no amino acid change. The mutation to guanine results in a shift from leucine to phenylalanine. For the position in ORF59, all 3 polymorphic alleles result in an amino acid shift (leucine in

Analysis of vaccine SNPs from the 5 VZV-positive samples from this case revealed that each contained single clonal vaccine variants; that is, no mixed bases were observed at any of the 34 loci examined. However, the vaccine variant isolated from CSF differed from the variant isolated from scabs of skin lesions at 3 different loci (ORF54 [position 94167], ORF59 [101089], and ORF62 [108111]). All of the specimens obtained in a given site (scabs or CSF) were identical to each other at the loci we evaluated. The variance at ORF54 and ORF59 in DNA of VZV from CSF specimens represent atypical transversion mutations, with a shift from pyrimidine bases previously identified at position 94167 to a purine (i.e., guanine) and a shift from purine bases at position 101089 to a pyrimidine (i.e., cytosine). All but 1 of 43 SNPs identified between vaccine and parental Oka were transition mutations, specifically a shift from thymidine to guanine at position 39227 (ORF22) [14]. For the ORF54 position, the normally observed sequence difference (cytosine in the strain from the Oka/Merck vaccine and thymine in wild-type VZV) results in no amino acid change. The mutation to guanine results in a shift from leucine to phenylalanine. For the position in ORF59, all 3 polymorphic alleles result in an amino acid shift (leucine in
the strain from the Oka vaccine, proline in wild-type VZV, and cysteine in the variant HZ isolate). As such, both of these atypical variants lead to changes in the amino acid sequence of the ORF54 and ORF59 gene products, which could affect protein function. The change at position 108111 in the variant from scabs results in no amino acid change.

Both scab and CSF variants contained wild-type alleles at SNPs located in ORF6, ORF9A, ORF10, ORF21, ORF31, ORF39, and ORF52 and in ORF62 at positions 105310, 107599, 107797, 108838, and the noncoding position 109200. The variant from scabs also carried the wild-type alleles in SNPs located in ORF54 and ORF59. Alleles of VZV in the Oka vaccine were present in SNPs located in ORF51, ORF55, ORF62 (positions 105544, 105705, 106262, 107136, 107252, and [in the CSF isolate only] 108111), a noncoding-region SNP (109137), and ORF64. Each of the wild-type alleles present in these 2 variants encodes a different amino acid than the vaccine allele, with the exception of the noncoding SNP at 109200. Finally, 12 wild-type SNPs in these 2 isolates were recently demonstrated to be present in ≥67% of all vaccine variants isolated from persons with vaccine-associated adverse events [14].

These findings suggest that the number of variant strains in the Oka vaccine may be greater than previously suspected, with some variants present at levels too low to be detected in vaccine preparations. A unique subset of vaccine variants may be selected as variants become latent in the host or because they differ in their capacity to reactivate from latency. The 2 isolates identified in this case, while differing at only 3 of the loci examined, are highly likely to have preexisted in vaccine preparations.

Accumulating evidence suggests that the process of VZV reactivation leading to disease is complex and that activation leading to a given disease manifestation may be determined, at least in part, by virus phenotype. PCR findings from this and a previous study [8] indicate that at least 2 vaccine variants often emerge during reactivation of vaccine-strain VZV during HZ. This might result from initial reactivation of 1 neuron containing >1 vaccine variant, leading to ganglionitis caused by >1 variant, or it might result from the stimulation of multiple neurons, some of which have different latent variants, to reactivate and cause HZ ganglionitis with >1 variant. Moreover, the presence of different variants at distant anatomic sites suggests that these variants (1) may be selected by the path they use to reach an anatomic site, (2) may differ in their ability to replicate at that site, or (3) are influenced by selective pressures in the host.

The relationship between variant varicella vaccine strains from persons with vaccine-related adverse events and pathogenicity remains unclear. Further studies aimed at evaluating individual mutations for differences (e.g., in growth properties) will be needed to elucidate whether there are specific changes in DNA sequence that enhance the extent and the nature of VZV pathogenicity.

References