Disseminated, Persistent, and Fatal Infection Due to the Vaccine Strain of Varicella-Zoster Virus in an Adult Following Stem Cell Transplantation

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Live attenuated varicella vaccine is recommended for healthy individuals who are susceptible to varicella. Although the vaccine is safe, effective, and used worldwide, serious adverse events have been reported, mainly in immunocompromised patients who subsequently recovered. Here, we describe the fatality of an immunocompromised patient who received the varicella vaccine. His medical history provides a cautionary lens through which to view the decision of when vaccination is appropriate.

A middle-aged man with non-Hodgkin lymphoma received chemotherapy and a stem cell transplant. He was vaccinated 4 years post-transplantation, despite diagnosis of a new low-grade lymphoma confined to the lymph nodes. Within 3 months of vaccination, he developed recurrent rashes with fever, malaise, weakness, hepatitis, weight loss, and renal failure. The syndrome was eventually determined to be associated with persistent disseminated zoster caused by the vaccine virus. This case illustrates a circumstance when a live viral vaccine should not be used.

Keywords: zoster; vOka; varicella; vaccine; granulomas.

CASE REPORT

A 47-year-old human immunodeficiency virus (HIV)-negative male was treated for non-Hodgkin lymphoma in 1990. After a recurrence in 1996, he experienced a complete remission. In 2005, at age 62, he was diagnosed with diffuse large B-cell lymphoma (DLBCL) and again received chemotherapy. An autologous stem cell transplant (SCT) was performed in 2006. In 2009, DLBCL recurred but was localized to a few abdominal lymph nodes; additional anticancer therapy was not given. For the next 4 years he was clinically healthy. In March 2010, despite the localized DLBCL, his primary care physician administered measles, mumps, rubella, hepatitis, and varicella vaccines [2]. The patient’s history included childhood varicella.

Three months later, in June 2010, a zosteriform rash appeared on the patient’s forehead that was diagnosed as zoster when varicella zoster virus (VZV) was identified by immunofluorescence; he received valacyclovir (3 g/day) for 10 days. In August 2010, his health...
declined, with progressive weakness and pancytopenia. Repeat abdominal computed tomography (CT) scan showed persistent but stable adenopathy. No evidence of DLBCL was detected in biopsied bone marrow. Zoster reappearing on the patient’s back was treated with valacyclovir for 14 days; prophylaxis followed with oral acyclovir (ACV; 800 mg/day).

Symptoms of fatigue, low-grade fevers, and a functional decline followed the reappearance of zoster, and in September 2010, he was hospitalized with bacteremic pneumococcal pneumonia. Disseminated zoster lesions were present on his right shoulder, chest, and face; he was treated with intravenous ACV (30 mg/kg/day) for 10 days. Three weeks later he had fever (temperature, 39.6°C), multiorgan dysfunction with renal insufficiency, elevated hepatic enzymes, and pancytopenia. Disseminated zoster involving the face, shoulder, chest, forearm, and back was evident. A CT scan showed stable abdominal adenopathy. A bone marrow biopsy revealed mild hypercellularity without lymphoma, but multiple ill-defined large granulomas were seen. Immunocytochemical demonstration of the B-cell marker, CD20, revealed aggregates of B cells surrounding the granulomas and confirmed the absence of B-cell lymphoma in the bone marrow. Extensive testing failed to identify bacterial, fungal, or mycobacterial infection.

Following hospitalization, no bacterial or fungal infections were identified despite further extensive testing. However, multiple skin lesions persisted that, after being biopsied, were found to be cutaneous ulcers with acute and chronic inflammation, rare granulomas, and suspected budding yeast. Fluconazole was given. The patient continued to be a diagnostic problem because fevers persisted, new skin lesions appeared, and fatigue worsened. He was transferred to a university medical center in November 2010. Vesicular lesions of the skin near his eye, forearm, back, and chest were observed. Laboratory data of pancytopenia, creatinine 1.2 g/L, aspartate transaminase (AST) 328 U/L, alanine transaminase (ALT) 372 U/L, alkaline phosphatase 1357 U/L, lactate dehydrogenase 394 U/L, total bilirubin 3.7 g/L, and serum ferritin >15 000 ng/mL were consistent with hemophagocytic lymphohistiocytosis (HLH). His CD4 count was 53 cells/mm³. Liver biopsy revealed portal parenchymal granulomatous inflammation (Figure 1). Cultures, stains, and molecular diagnostics failed to detect bacterial, fungal, and mycobacterial pathogens. VZV was isolated from skin lesions. Epidermal necrosis and multinucleated keratinocytes within granulomas were found in skin biopsies (Figure 2).

The patient was treated again with intravenous ACV. Although no fungal infection was identified, he was given liposomal amphotericin. Despite aggressive treatment with intravenous ACV and amphotericin, vesicular lesions persisted on the face and chest. The patient continued to decline and developed multiorgan failure. Three days prior to death, his total bilirubin was 27 g/L (direct 21.5) AST 227 U/L, ALT 58 U/L, alkaline phosphatase 851 U/L, creatinine 1.9 g/L, and albumin 1.6 g/L. He was anuric, profoundly jaundiced, and encephalopathic. The patient had not been treated for lymphoma in the past 4 years because that illness was quiescent, bone marrow involvement was absent, and minimal abdominal adenopathy on CT remained unchanged for 2 years. He was discharged on hospice care and died 3 days later in December 2010. No autopsy was performed.

**LABORATORY TESTING OF VARICELLA ZOSTER VIRUS**

**Identification of Live Attenuated Varicella Vaccine**

A swab from a vesicle on the patient’s left chest obtained 21 days before death was sent to Columbia University (New York) through the Varicella Zoster Virus Identification Program (VZVIP), part of the Worldwide Adverse Experience System (WAES) of Merck & Co Inc. VZVIP uses polymerase chain reaction (PCR) and single nucleotide polymorphism analyses to identify VZV and distinguish vOka from wild-type (WT) virus [3]. VZV DNA was identified as vOka (Pst1 negative and BglI positive) [3]. Analysis of the viral DNA revealed the vOka characteristic Sma1 restriction site at nucleotide position 106 262 [4]. Moreover, sequencing with Sma1 restriction enzyme revealed that the virus had 3 Sma1-positive sites, further confirming that it was vOka [4]. Additional analysis of the viral sequence revealed that a C instead of a T was also present at position 106 262, confirming that the virus was vOka [5].

**Immunocytochemical Demonstration of Varicella Zoster Virus gE in Skin and Liver Granulomas Postmortem**

Tissues were prepared as described elsewhere [6]. Sections were subjected to antigen retrieval and incubated with affinity-purified rabbit antibodies to ORF63p and monoclonal murine antibodies to VZV gE (Virusys Corp., Taneytown, Maryland). Preparations not exposed to primary antibodies served as controls. Alexa 488- and Alexa 594-conjugated secondary antibodies to VZV gE (Virusys Corp., Taneytown, Maryland) were used to detect sites of antibody binding. Sections were examined with a Leica CTR6000 microscope. Images were captured with a cooled charge-coupled device camera; brightness and contrast were adjusted with a Macintosh computer running Velocity 5 software (Improvision; PerkinElmer, Waltham, Massachusetts).

Granulomas in biopsies of skin and liver obtained 14 days prior to death identified VZV antigens, indicating active ongoing VZV infection (Figures 1 and 2). Coexpression in cells of the lesions of a late protein (gE) and an immediate early protein (ORF63p) indicated VZV infection due to lytic, ongoing viral replication, not latency. PCR of tissue from a slide also demonstrated VZV DNA in the liver.
Detection of Varicella Zoster Virus Resistance to Acyclovir

Following the patient’s death, mutations in the VZV gene encoding thymidine kinase (TK; ORF36) were used to determine whether the patient’s VZV might have acquired resistance to ACV. The coding sequence of ORF36 consists of 1026 nucleotides encoding 342 amino acids. The TK gene was sequenced from 2 overlapping PCR fragments [7]. Both strands of DNA were sequenced and compared with those of WT VZV (Dumas strain; GenBank X04370) and those of known TK mutants [7–9]. One nucleotide substitution, G143A, was found in the 5’ half of the TK gene, resulting in the amino acid change E48G. This mutation is identical to that of the ACV-resistant strain, WStr [8]. Phenotypic data suggested that the nonconservative substitution at residue 48 is sufficient to reduce TK activity. Mutational analysis of ORF36 thus is consistent with the idea that the VZV recovered 21 days before the patient died had become ACV resistant [8].

DISCUSSION

The patient died 7 months after receiving varicella vaccine. Because no disease appeared until 3 months post-vaccination, there was a history of childhood chickenpox, and the lesions were dermatomal, vaccine-related zoster with reactivation in

Figure 1. Granulomatous lesions in the liver express varicella zoster virus (VZV) DNA and gE immunoreactivity. The pathology of the liver was investigated in formalin-fixed paraffin sections of a liver biopsy. A, Hematoxylin and eosin stain. A peribronchial granuloma is evident. An infiltrating mass of mononuclear cells has obscured the normal architecture of the liver. The cuboidal epithelium of an intact small bile duct of a portal area (arrow; magnified approximately 2× in the inset) can still be distinguished. The markers = 60 µm. B, Products of nested polymerase chain reaction (PCR) amplification of DNA encoding ORF67 of VZV. Con (+): a positive control derived from DNA extracted from VZV propagated in human embryonic lung fibroblasts. Con (−): no PCR products were obtained when primers were added to distilled water. Liver: a paraffin section of the liver biopsy was deparaffinized with xylene, hydrated through a graduated series of alcohols, and scraped off of the slide. DNA was extracted and subjected to PCR with nested primers designed to amplify DNA encoding VZV ORF67. The sample contains VZV DNA. C–E, Immunocytochemistry showing the immunoreactivity of gE. The sections are alternate serial sections showing the region illustrated in A and from which DNA was amplified in (B). C, At low power, a gE-immunoreactive lesion is seen within the granuloma. The marker = 50 µm. D, Rarely, isolated individual hepatic cells are gE immunoreactive. The marker = 10 µm. E, At high power, the structure of gE-immunoreactive cells can be seen to be distorted and heterogeneous, suggesting that both parenchymal and stromal cells are infected. Within some cells, small gE-immunoreactive particles with a nearly uniform diameter of 0.2 µm can be discerned; these are consistent with the appearance of virions. The marker = 10 µm.
multiple neurons was suspected. Persistence of zoster despite repeated antiviral therapy suggested ACV resistance. Although the patient had a history of lymphoma, his condition had been stable for years prior to vaccination. Following onset of zoster, there was a rapid deterioration of the patient’s health, with continuing rash, abnormal liver function with jaundice, HLH, renal failure, and encephalopathy. No evidence of lymphoma was found in a liver biopsy or in bone marrow. Although the history of lymphoma may have impeded the immune response to VZV, which could have contributed to the occurrence of zoster, the dramatically uncontrolled multiplication of VZV was more likely than the dormant lymphoma to have caused the patient’s death.

To our knowledge, this is the first reported fatality due to reactivation of latent Oka VZV. In contrast to WT VZV

![Figure 2.](image-url)
infections, death from proven vOka infections is exceedingly rare. Only 2 other such fatalities have been reported, both of immunocompromised children in whom overwhelming varicella followed vaccination [10, 11]. These illnesses, which had characteristics of varicella with pneumonia, were primary infections. An additional child with DiGeorge syndrome died after receiving combined measles, mumps, rubella, and varicella vaccines; however, it was unclear that death was due to VZV [12]. Two patients with vOka resistant to ACV have been reported [13]. Both were immunocompromised due to cancer chemotherapy and both cleared VZV and survived following foscarnet treatment. It seems likely that the vOka our patient acquired through vaccination reactivated from latency and then became resistant to ACV. Both the sequence of the TK gene (ORF36) obtained shortly before death and the clinical history of continuing VZV infection despite treatment suggest resistance to ACV, perhaps as a result of repeated treatment over a prolonged period. Administration of foscarnet would not have been acceptable because of the patient’s poor renal function.

Takahashi attenuated VZV in 1974 [14], and vOka vaccine has been distributed worldwide since 1995. There have been fewer than 25 reported severe adverse events due to vOka; 70% occurred in immunocompromised patients (Table 1).

### Table 1. Reported Severe Adverse Events Following vOka Vaccination, Proven by Polymerase Chain Reaction

<table>
<thead>
<tr>
<th>Age, Sex</th>
<th>Underlying Condition</th>
<th>Complication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactions resembling varicella within 42 d after vaccination (n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 mo, M</td>
<td>ADA deficiency</td>
<td>Hepatitis, respiratory distress</td>
<td>[10, 11]</td>
</tr>
<tr>
<td>13 mo, M</td>
<td>Di George syndrome</td>
<td>Pneumonia</td>
<td>[12]</td>
</tr>
<tr>
<td>15 mo, F</td>
<td>Possible undiagnosed immunodeficiency disease</td>
<td>Severe rash, respiratory compromise, steroids, died</td>
<td>[15]</td>
</tr>
<tr>
<td>16 mo, M</td>
<td>Human immunodeficiency virus, 8 CD4 cells/mm³</td>
<td>Severe rash, encephalopathy</td>
<td>[16]</td>
</tr>
<tr>
<td>18 mo, F</td>
<td>Unidentified cell-mediated immune deficit</td>
<td>Severe rash, pneumonia</td>
<td>[17]</td>
</tr>
<tr>
<td>4 yr, F</td>
<td>Leukemia, remission 5 mo</td>
<td>Pneumonia, multiorgan failure; died</td>
<td>[18]</td>
</tr>
<tr>
<td>5 yr, M</td>
<td>Asthma, cerebral palsy, steroid therapy</td>
<td>Pneumonia</td>
<td>[10, 19]</td>
</tr>
<tr>
<td>6 yr, M</td>
<td>iNK cell deficiency</td>
<td>Severe rash, pneumonia</td>
<td>[20]</td>
</tr>
<tr>
<td>11 yr, F</td>
<td>iNK cell deficiency</td>
<td>Severe rash, pneumonia</td>
<td>[21]</td>
</tr>
<tr>
<td>14 yr, M</td>
<td>Severe combined immunodeficiency</td>
<td>Severe rash, hepatitis</td>
<td>[19]</td>
</tr>
<tr>
<td>48 yr, M</td>
<td>Down’s syndrome</td>
<td>Pneumonia</td>
<td>[19]</td>
</tr>
<tr>
<td>Reactons due to VZV reactivation resembling zoster after vaccination (n = 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 yr, M</td>
<td>Neuroblastoma</td>
<td>HZ thigh, meningitis; ACV resistance</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>21 mo, F</td>
<td>Neuroblastoma</td>
<td>HZ right hand, leg, abdomen, meningitis; ACV resistance</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>3 yr, F</td>
<td>Otherwise healthy</td>
<td>HZ face, meningitis, mild encephalitis</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>4 yr, M</td>
<td>Leukemia; chemotherapy</td>
<td>HZ arm, meningitis</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>4 yr,</td>
<td>Otherwise healthy</td>
<td>HZ arm, meningitis</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>7 yr, M</td>
<td>Otherwise healthy</td>
<td>HZ arm, shoulder, meningitis</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>8 yr, M</td>
<td>Otherwise healthy</td>
<td>HZ shoulder, meningitis</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>9 yr, M</td>
<td>Otherwise healthy</td>
<td>HZ arm, meningitis</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>12 yr, F</td>
<td>Otherwise healthy</td>
<td>HZ neck, meningitis</td>
<td>Reviewed in [13]</td>
</tr>
<tr>
<td>16 yr, M</td>
<td>Otherwise healthy</td>
<td>Hemorrhagic gastric ulcer</td>
<td>Reviewed in [22]</td>
</tr>
<tr>
<td>20 yr,</td>
<td>Common variable immunodeficiency</td>
<td>Progressive outer retinal necrosis</td>
<td>[23]</td>
</tr>
<tr>
<td>6 yr,</td>
<td>DOCK 8 syndrome</td>
<td>VZV vasculopathy</td>
<td>[24]</td>
</tr>
<tr>
<td>67 yr, M</td>
<td>Lymphoma; Stem cell transplant</td>
<td>Disseminated HZ, death</td>
<td>Current patient</td>
</tr>
</tbody>
</table>

Estimate e > 60 million vaccine doses distributed.

Abbreviations: ACV, acyclovir; ADA, adenosine deaminase; DOCK8, dedicator of cytokinesis 8; HZ, herpes zoster; iNK, invariant natural killer cells; vOka, varicella vaccine; VZV, varicella zoster virus.

* VZV Oka DNA demonstrated in cerebral spinal fluid.
These reports are equally divided between patients with varicella and those with zoster.

Both varicella and zoster vaccines are recommended for use in immunocompetent individuals. Neither of these live vaccines is intended for patients whose immune systems are severely suppressed. Whether or not a patient is immunocompromised, however, may not be entirely clear. Current guidelines include administration of varicella vaccine if more than 2 years have elapsed after SCT, there is no graft-versus-host disease, no immunosuppressive medications are being administered, lymphocytes respond in vitro to phytohemagglutinin and/or mitogens, and the CD4 cell count is \( \geq 200/\text{mm}^3 \) [25]. The CD4 cell count of the patient described here was not determined prior to administration of varicella vaccine; however, toward the end of his life, the low CD4 T-cell count (53 cells/\( \mu \)L) indicated that he was significantly immunocompromised. Studies carried out with HIV-infected patients demonstrate that the extent of clinical disease and complications of VZV infection are related to the degree of immunodeficiency, as reflected in a CD4 count \( \leq 200/\text{mm}^3 \) [26, 27]. It is thus plausible that an inadequate number of CD4 lymphocytes enabled VZV to reactivate, disseminate, and persist.

Benign granulomas have occasionally been observed in patients with zoster due to WT VZV [28–33] but rarely during varicella [34, 35]; granulomas are usually in skin and rare in lung [35]. In the patient described here, granulomas due to vOka were observed in both skin and liver. VZV antigens have been reported to be present in cutaneous granulomas that occur during zoster, and viral envelope glycoproteins have been proposed to be responsible for delayed-type hypersensitivity reactions that cause granulomas [31]. It is possible that a mechanism of this type contributed to the granulomas of our patient. More importantly, however, is that gE expression is associated with lytic VZV infection [13]. The presence of gE therefore strongly suggests that active viral multiplication was occurring in granuloma cells in skin and liver. VZV antigen–containing liver granulomas are a novel observation. Their potential for lethality therefore is unknown but possibly substantial. VZV-infected liver granulomas could have contributed to the patient’s death.

The patient appeared to have HLH at the time of his last admission; consistent with HLH were fever, cytopenia involving more than 2 cell lines, hepatitis, and serum ferritin >15 000 ng/mL. The origin of HLH was probably related to the overwhelming VZV infection. HLH has also been reported in immunosuppressed patients infected with other herpes viruses such as Epstein-Barr [36–39]. Although HLH may be self-limited, it can lead to multiorgan failure and death [39]. Thus, HLH may have contributed to the overall decline and death of the patient.

The initial test used to identify VZV included restriction enzymes (Pst1 and BglI) to distinguish between vOka and WT VZV [3]. While useful in screening, this method may not distinguish an Asian WT virus of clade 2 from vOka [40]. Although Asian strains of VZVs are not commonly seen in Western countries, populations are mobile. The restriction analysis and the sequence of the DNA encoding ORF62 at position 106 262 confirmed that the virus recovered from our patient was indeed vOka [40].

The lethal adverse event that followed administration of vOka in our patient should not be considered a reason to withhold vaccination from immunocompetent individuals. The live attenuated varicella vaccine has not become less safe and effective for them. The patient described here was probably immunocompromised when he received vOka. He had a history of chemotherapy, SCT, and a quiescent lymphoma. His vaccination evidently led to a vOka infection that reactivated, disseminated, led to HLH, and became resistant to ACV. This is an extremely rare complication of vaccination. What this case implies is that vOka, like any other live agent, cannot be given to patients without at least a small degree of risk. Clearly, no one should be vaccinated until the possibility of immunodeficiency is minimized or eliminated. If there is any reason to suspect inadequate immunity, vaccination should be avoided. Moreover, in the months that follow vaccination, the occurrence of zoster in immunocompromised patients who were inadvertently vaccinated should be taken seriously. Antiviral therapy should be prompt, aggressive, and not intermittent. Clinical trials are currently underway to evaluate the safety and efficacy of subunit zoster vaccines. While not yet anticipated for prevention of varicella, effective noninfectious subunit vaccines would potentially be useful in preventing zoster in immunocompromised patients.

Notes

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Potential conflicts of interest. A. A. G. has service contracts with Merck and Co. to study complications of varicella and zoster vaccines. She consults when invited for GlaxoSmithKline (GSK) and chairs an independent data monitoring committee for a subunit zoster vaccine for GSK. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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