Disseminated Vaccine Strain Varicella as the Acquired Immunodeficiency Syndrome-Defining Illness in a Previously Undiagnosed Child

J. Michael Kramer, MD; Philip LaRussa, MD; Wan C. Tsai, MD; Paul Carney, MD; Steven M. Leber, MD; Sheila Gahagan, MD; Sharon Steinberg, MD; and R. Alexander Blackwood, MD, PhD

ABSTRACT. The Food and Drug Administration licensed a live-virus varicella vaccine (Varivax; Merck & Co Inc, West Point, PA) in March 1995. Prewave clinical adverse events were minimal; however, since licensure and increased vaccine use, rare previously undetected risks have arisen. Presented here is the clinical course of a previously undiagnosed, human immunodeficiency virus-infected boy who developed dissemination of the vaccine strain of varicella zoster after immunization.

In March 1995, the Food and Drug Administration approved a live-attenuated varicella vaccine for use in healthy individuals 12 months of age and older. The vaccine has been shown to be safe and effective in healthy children and adults, as well as in children with leukemia. The American Academy of Pediatrics does not recommend routine screening of children for human immunodeficiency virus (HIV) infection before vaccination. In addition, routine administration of varicella vaccine is not recommended for all HIV-infected children.

Significant morbidity and mortality is caused by varicella-zoster virus (VZV) in immunocompromised individuals, including those infected with HIV. Postexposure varicella-zoster immune globulin prophylaxis decreases the likelihood and severity of varicella in high-risk individuals, but the breakthrough rate can be as high as 26%. Exposure to varicella are often not recognized, further limiting the utility of postexposure prophylaxis. Immunization, on the other hand, has the potential of establishing permanent immunity. After primary infection in HIV-infected adults, the risk of reactivation remains low well into the progression of acquired immunodeficiency syndrome. These individuals are at risk of developing zoster, but have a relatively low risk of dissemination. This suggests that the immunization of HIV-infected children could prevent primary (wild-type) infection, thereby eliminating viral entry into dorsal root ganglia and subsequent reactivation.

Immunization of immunocompromised patients has been limited to children with leukemia and solid tumors following strict guidelines to limit the potential for serious adverse events. Routine immunization of all healthy children carries the potential risk that unrecognized immunocompromised children could be inadvertently vaccinated. Reported here is a 16-month-old, previously undiagnosed, HIV-infected boy who developed dissemination of the vaccine strain of varicella zoster virus after routine immunization.

CASE REPORT

A previously healthy 16-month-old boy who was admitted to the University of Michigan Mott Children’s Hospital with a 5-day history of increasing respiratory distress, fever (101°F), cough, emesis, and lower extremity weakness. In addition, he had a 1-month history of a progressive erythematous papular rash, which began in the groin and upper right thigh progressing to involve the trunk, axilla, and right knee and foot. The rash was associated with a low-grade fever and the patient had recently been refusing to walk for several days. On admission, he had a pulse of 173 beats/min, and a respiratory rate of 24 breaths/min. Weight (9 kg), height (74 cm), and head circumference (45 cm) were all below the fifth percentile. Physical examination was remarkable for oral thrush, diffuse ronchi, and scattered wheezes, and a confluent macular rash over the trunk and arms. There was also an erythematous zosteriform patch over the right knee showing some clear exudate, eschar formation and a few scattered vesicles. Neurologic examination was remarkable for decreased tone and strength in the right lower extremity, minimal withdrawal to painful stimuli, and a few beats of intermittent left ankle clonus.

Past medical history was remarkable for recurrent oral thrush, beginning 5 months before admission, and lack of appropriate weight gain between the 6- and 13-month well-child visits. Immunizations were up to date, the child having received the measles-rubella and varicella vaccines (right thigh) 3-months before admission, and lack of appropriate weight gain between the 6- and 13-month well-child visits. Immunizations were up to date, the child having received the measles-rubella and varicella vaccines (right thigh) 3-months before admission, and lack of appropriate weight gain between the 6- and 13-month well-child visits. Immunizations were up to date, the child having received the measles-rubella and varicella vaccines (right thigh) 3-months before admission.

A lateral radiograph of the neck revealed tracheal narrowing in the regions of the vocal cords consistent with croup, while a chest retrogram showed multiple small scattered 3- to 5-mm pulmonary opacities throughout both lung fields.
Laboratory studies revealed a hemoglobin of 11.6 mg/dL, hematocrit 34.6%, white blood count 5.3 x 10^3 cells/mm³ with 77% neutrophils, 19% lymphocytes, 4% monocytes and 1% eosinophils, and 275 x 10^3 platelets/mm³. Total lymphocyte count was 800 cell/mm³ with an absolute CD4 count of 8 cell/mm³. Urinalysis was normal. Total protein was 5.7 mg/dL, albumin was 2.9 mg/dL, aspartate aminotransferase was 58 mg/dL, alanine aminotransferase was 44 mg/dL, lactic acid dehydrogenase was 460 mg/dL, alkaline phosphatase was 92 mg/dL, and total bilirubin was 0.4 mg/dL. The patient was anergic, demonstrating no delayed-type hypersensitivity reaction to mumps, tetanus, purified protein derivative, Candida, or Histoplasma. Enzyme-linked immunosorbent assays and Western blot were positive for HIV-1.

The patient’s respiratory distress persisted despite bronchodilator therapy, and a bronchoalveolar lavage was performed on the fourth hospital day. The lavage fluid was negative by direct smear, culture, and/or immunofluorescence for Pneumocystis carinii, acid-fast bacilli, cytomegalovirus, and varicella-zoster, but grew Moraxella catarrhalis and parainfluenza type 2. Intravenous cefuroxime was begun to cover other potential bacterial pathogens. Skin lesions from the chest revealed varicella-zoster virus by VZV-specific direct immunofluorescence and intravenous acyclovir was started. Respiratory symptoms and abnormalities on retrogram persisted and an open lung biopsy was obtained revealing multinucleated giant cells (Fig 1) on histologic examination. VZV-specific polymerase chain reaction of bronchoalveolar lavage fluid and lung biopsy material demonstrated the vaccine strain VZV (Fig 2). (Cerebrospinal fluid [CSF] and samples from the skin lesions were not available to be tested).

Complete loss of the right patellar and ankle stretch reflexes developed within a few days of admission and right calf muscular atrophy became apparent. Magnetic resonance imaging of the brain and lumbar spine on the ninth hospital day showed diffuse mild reduction in brain parenchymal volume without focal lesions. No spinal abnormalities were demonstrated. An electromyogram (EMG) on the fourteenth hospital day was consistent with a lumbar polyradiculopathy on the right with ongoing reinnervation (diminished tibial and peroneal motor responses with small amplitude abnormal spontaneous activity in the right anterior tibialis muscle). The CSF glucose was 77 mg/dL, protein 31 mg/dL, white blood cell count 2 cells/mm³ (41% lymphocytes and 51% histiocytes), and red blood count, zero. The direct smears, including acid-fast bacilli, and cultures were negative for bacteria, viruses, and fungi, and no oligoclonal bands were present. An ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder. The CSF showed (diminished tibial and peroneal motor responses with small amplitude abnormal spontaneous activity in the right anterior tibialis muscle). The CSF glucose was 77 mg/dL, protein 31 mg/dL, white blood cell count 2 cells/mm³ (41% lymphocytes and 51% histiocytes), and red blood count, zero. The direct smears, including acid-fast bacilli, and cultures were negative for bacteria, viruses, and fungi, and no oligoclonal bands were present. An ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder with large postvoid residuals suggestive of a neurogenic bladder. Transabdominal ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder. Transabdominal ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder. Transabdominal ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder. Transabdominal ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder.

A lumbar polyradiculopathy on the right with ongoing reinnervation (diminished tibial and peroneal motor responses with small amplitude abnormal spontaneous activity in the right anterior tibialis muscle). The CSF glucose was 77 mg/dL, protein 31 mg/dL, white blood cell count 2 cells/mm³ (41% lymphocytes and 51% histiocytes), and red blood count, zero. The direct smears, including acid-fast bacilli, and cultures were negative for bacteria, viruses, and fungi, and no oligoclonal bands were present. An ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder. Transabdominal ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder. Transabdominal ultrasound of the kidneys and bladder on the sixteenth hospital day revealed normal-appearing kidneys but a markedly distended bladder.

Commonly recognized adverse reactions to the vaccine included minor injection site reactions (erythema, pain, swelling), and in approximately 5% of vaccinees, a mild vaccine-associated varicella-like rash (localized or generalized, consisting of 6–10 lesions, usually occurring 14–28 days after vaccination with a range of 5–42 days).4,5,11 Headache, upper respiratory infections, pneumonia, neutropenia, and thrombocytopenia have also been reported. Temporal association with erythema multiforme, ataxia, encephalitis, seizures, Stevens-Johnson syndrome, and death have been reported but not confirmed by demonstration of the presence of the vaccine strain.1 Our patient’s rash occurred somewhat later than expected for a typical vaccine-associated rash. However, presentation with a zosteriform rash and lesions outside of that dermatome is consistent with reactivation of vaccine virus and subsequent viremia resulting in disseminated skin lesions and pulmonary involvement. Zoster attributable to the vaccine strain has been reported as early as 25 days after vaccination2 although CSF samples were not available for testing by VZV polymerase chain reaction.

**DISCUSSION**

The varicella vaccine received Food and Drug Administration approval for use in healthy children, adolescents, and adults in 1995. Since its approval, >20 000 000 doses of the vaccine has been distributed. Commonly recognized adverse reactions to the vaccine included minor injection site reactions (erythema, pain, swelling), and in approximately 5% of vaccinees, a mild vaccine-associated varicella-like rash (localized or generalized, consisting of 6–10 lesions, usually occurring 14–28 days after vaccination with a range of 5–42 days).4,5,11 Headache, upper respiratory infections, pneumonia, neutropenia, and thrombocytopenia have also been reported. Temporal association with erythema multiforme, ataxia, encephalitis, seizures, Stevens-Johnson syndrome, and death have been reported but not confirmed by demonstration of the presence of the vaccine strain.1 Our patient’s rash occurred somewhat later than expected for a typical vaccine-associated rash. However, presentation with a zosteriform rash and lesions outside of that dermatome is consistent with reactivation of vaccine virus and subsequent viremia resulting in disseminated skin lesions and pulmonary involvement. Zoster attributable to the vaccine strain has been reported as early as 25 days after vaccination2 although CSF samples were not available for testing by VZV polymerase chain reaction.
CD4 count was only 8 cell/mm³. At the time of presentation, our patient’s absolute inadvertently immunized with the varicella vaccine. severe immunosuppression (failure to thrive and bance, and spontaneous activity on EMG together urinary retention, motor nerve conduction distur- with a lumbosacral polyradiculopathy. The asym- increased tone, strength, and deep tendon reflexes in the right lower extremity. The EMG was consistent the right lower extremity. The EMG was consistent with the onset of the rash and the most af- fected limb was the site of the vaccination suggesting possible lumbar root involvement.

The prevention of varicella in the HIV population is of utmost importance and the varicella vaccine has significant potential utility. However, a potential risk exists when severe T-cell dysfunction is present. The markedly diminished absolute CD4 count⁶ at the time of hospitalization, the presence of oral thrush, and the lack of weight gain for months before vacci- nation are consistent with the hypothesis that the severity of the reaction was attributable to the child’s severely immunocompromised state. To our knowl- edge, this is the only case of a severe, vaccine-assoc- iated, adverse event in a previously undiagnosed HIV-infected child. Current American Academy of Pediatrics guidelines recommend that the use of vari- cella vaccine be considered in asymptomatic or mildly symptomatic HIV-infected children with CD4 counts of 25% or greater. (Centers for Disease Control Class A1 or N1). Given the rarity of the type of vaccine-associated event described above and the presence of signs and symptoms suggestive of severe immunosuppression before vaccination in this pa- tient, we believe that the benefit of vaccination out weighs the risk in asymptomatic or mildly symptomatic HIV-infected children with adequate CD4 cells.

REFERENCES

http://www.pediatrics.org/cgi/content/full/108/2/e39

Downloaded from http://pediatrics.aappublications.org/ by guest on November 13, 2017
Disseminated Vaccine Strain Varicella as the Acquired Immunodeficiency Syndrome-Defining Illness in a Previously Undiagnosed Child
J. Michael Kramer, Philip LaRussa, Wan C. Tsai, Paul Carney, Steven M. Leber, Sheila Gahagan, Sharon Steinberg and R. Alexander Blackwood

*Pediatrics* 2001;108;e39
DOI: 10.1542/peds.108.2.e39

Updated Information & Services
including high resolution figures, can be found at:
[http://pediatrics.aappublications.org/content/108/2/e39](http://pediatrics.aappublications.org/content/108/2/e39)

References
This article cites 27 articles, 4 of which you can access for free at:
[http://pediatrics.aappublications.org/content/108/2/e39.full#ref-list-1](http://pediatrics.aappublications.org/content/108/2/e39.full#ref-list-1)

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
[http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub](http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub)

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
[https://shop.aap.org/licensing-permissions/](https://shop.aap.org/licensing-permissions/)

Reprints
Information about ordering reprints can be found online:
[http://classic.pediatrics.aappublications.org/content/reprints](http://classic.pediatrics.aappublications.org/content/reprints)

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2001 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Disseminated Vaccine Strain Varicella as the Acquired Immunodeficiency Syndrome-Defining Illness in a Previously Undiagnosed Child

J. Michael Kramer, Philip LaRussa, Wan C. Tsai, Paul Carney, Steven M. Leber, Sheila Gahagan, Sharon Steinberg and R. Alexander Blackwood

*Pediatrics* 2001;108;e39
DOI: 10.1542/peds.108.2.e39

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/108/2/e39