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

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ABSTRACT. The Food and Drug Administration licensed a live-virus varicella vaccine (Varivax; Merck & Co Inc, West Point, PA) in March 1995. Prelicensure 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. Pediatrics 2001;108(2). URL: http://www.pediatrics.org/cgi/content/full/108/2/e39; chickenpox, human immunodeficiency virus, pneumonia, encephalopathy, varicella vaccine, adverse events, dissemination.

ABBREVIATIONS. HIV, human immunodeficiency virus; VZV, varicella-zoster virus; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; EMG, electromyelogram; PCR, polymerase chain reaction.

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,1,2 as well as in children with leukemia.3–5 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.6

Significant morbidity and mortality is caused by varicella-zoster virus (VZV) in immunocompromised individuals, including those infected with HIV.7–9 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%.4,5 Exposures 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.8 This suggests that the immunization of HIV-infected children could prevent primary (wild-type) infection, thereby eliminating viral entry into dorsal root ganglia3 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.5 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-mumps-rubella and varicella vaccines (right thigh) 3-months before admission. The past medical history also included 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.

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A lateral radiograph of the neck revealed tracheal narrowing in the regions of the vocal cords consistent with croup, while a chest radiograph 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 10³ cells/mm³ with 77% neutrophils, 19% lymphocytes, 4% monocytes and 1% eosinophils, and 275 x 10⁵ 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 Pseudomonas aeruginosa, 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 with large postvoid residuals suggestive of a neurogenic bladder.

With the diagnosis of HIV (Clinical Category B3), the boy was started on dideoxynosine and zidovudine along with sulfamethoxazole-trimethoprim 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).

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Fig 1. Lung biopsy showing multinucleated giant cells (hematoxylin-eosin, original magnification x250).

Fig 2. Ethidium bromide-stained agarose gel electrophoresis of restriction endonuclease digests of VZV polymerase chain reaction products. Patient’s lung biopsy: lanes 1–3, VZV vaccine strain control: lanes 4–6, VZV wild-type strain control: lanes 7–9. Uncut VZV amplification products: lanes 1, 4, 7. BglI digestion products: lanes 2, 5, 8, PstI digestion products: lanes 3, 6, 9. The expected 350 bp and 222 bp VZV specific amplification products are seen for all 3 samples (lanes 1, 4, and 7). The BglI and PstI digests of the patient’s sample are identical to those of the vaccine control. That is, the 222 bp product is digested by BglI, resulting in 2 fragments of 137 and 85 bps (lanes 2 and 3 respectively) and the 350 bp product is not digested by PstI strain (lanes 3 and 6 respectively). In contrast, the pattern of the digestions of the wild-type control show that the 222 bp product is not digested with BglI (lane 8) but that the 350 bp product is digested with PstI, resulting in 2 fragments of 250 and 100 bp (lane 9).

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). Headache, upper respiratory infections, pneumonia, neutropenia, and thrombocytopenia have also been reported. Temporal association with erythema multiforme, ataxia, encephalitis, seizures, Steven-Johnson syndrome, and death have been reported but not confirmed by demonstration of the presence of the vaccine strain. 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 vaccination. Although CSF samples were not available for testing by VZV polymerase chain reaction...
(PCR), central nervous system involvement by the vaccine strain varicella virus is likely in this patient, given the clinical evidence of neurologic involvement.

The varicella vaccine has been used safely and successfully in other immunocompromised patients, suggesting that under appropriate conditions it may be safely used in HIV-infected children. HIV-positive children, with %CD4 <15 at the time of varicella are at high risk for developing zoster. Although our patient demonstrated evidence of severe immunosuppression (failure to thrive and persistent oral thrush) before vaccination, he was inadvertently immunized with the varicella vaccine. At the time of presentation, our patient’s absolute CD4 count was only 8 cell/mm³.

Clinically, our patient presented with alternating foci of atelectasis and air trapping, significant ventilation-perfusion mismatching, and impairment in gas exchange with subsequent intermittent signs of severe respiratory distress. Bronchoalveolar lavage fluid grew M catarrhalis and parainfluenza type 2. The lung biopsy demonstrated the presence of the varicella virus by in situ hybridization which was identified as the vaccine strain by VZV-PCR. Histopathology from the lung biopsy revealed an interstitial inflammatory reaction with edema and mononuclear cell infiltration of the alveolar septa that was consistent with a viral pneumonia, but not characteristic of varicella (wild-type) pneumonia (overwhelming destruction of the respiratory epithelium from the trachea and small bronchioles to the alveolar walls and the surrounding vasculature). Although M catarrhalis can be associated with pneumonia in HIV-infected patients, the absence of an acute inflammatory reaction, and the persistence of the clinical symptoms despite adequate antimicrobial therapy suggests a more commensal role the organism played in this patient. It is impossible to distinguish the relative roles of the parainfluenza type 2 virus and the vaccine strain varicella virus in our patient’s pulmonary disease.

Neuromuscular involvement with wild-type varicella-zoster virus has been well-documented. In patients with HIV, varicella-zoster virus been has been associated with acute and chronic meningomyelo-radiculitis, chronic progressive varicella-zoster virus encephalitis, transverse myelitis, ventriculitis, focal myelitis, and cerebral infarcts, which may or may not be associated with a typical varicella-like rash. It has been cultured from the CSF and detected in various neurologic specimens using a variety of techniques including PCR, immunocytochemistry, and in situ hybridization. In fact, varicella-zoster must be considered in a HIV-positive child with progressive encephalitis.

Neurologically, our patient presented with decreased tone, strength, and deep tendon reflexes in the right lower extremity. The EMG was consistent with a lumbosacral polyradiculopathy. The asymmetric leg weakness, lower extremity hyporeflexia, urinary retention, motor nerve conduction disturbance, and spontaneous activity on EMG together were not suggestive of other HIV-1-associated neuromuscular complications such as a mononeuritis multiplex, acute/chronic inflammatory demyelinating polyneuropathy, pure sensory neuropathy, or myopathy. The clinical manifestations did not seem to involve the spinal cord, brainstem, or cerebral hemispheres, nor were such abnormalities seen in the magnetic resonance imaging studies. Neuromuscular diseases, usually in association with cytomegalovirus, are common in adults with HIV-1. Peripheral neuropathies, however, are rarely seen in HIV-infected children. Although polyradiculopathy has not been previously associated with the attenuated virus, our patient’s clinical presentation, EMG, and laboratory evidence for dissemination of the vaccine strain of varicella (bronchoalveolar lavage and lung biopsy) implicates it as the causative agent. The onset of the child’s weakness corresponded to the onset of the rash and the most affected 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 count at the time of hospitalization, the presence of oral thrush, and the lack of weight gain for months before vaccination are consistent with the hypothesis that the severity of the reaction was attributable to the child’s severely immunocompromised state. To our knowledge, this is the only case of a severe, vaccine-associated adverse event in a previously undiagnosed HIV-infected child. Current American Academy of Pediatrics guidelines recommend that the use of varicella 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 patient, we believe that the benefit of vaccination outweighs the risk in asymptomatic or mildly symptomatic HIV-infected children with adequate CD4 cells.

REFERENCES

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