ear, neck and throat areas, such as retropharyngeal abscesses.\textsuperscript{9,10} Lemièrre’s syndrome\textsuperscript{11} or meningitis.\textsuperscript{12}

Because of the nonspecific nature of clinical signs with SBO, a high index of suspicion should be maintained for patients with a combination of fever, headache, neck pain or torticollis with or without cranial nerve palsy and in whom no obvious focus can be established. It is quite possible that due to the nonspecific signs and symptoms, highlighted by the 2 cases described in this report, nonotogenic SBO may be more frequent than previously reported in the literature. Imaging modalities that have a role in the investigation of suspected SBO include MRI, CT and bone scan with or without SPECT/CT. MRI has the highest sensitivity and specificity for the diagnosis of osteomyelitis and it has better soft tissue discrimination than CT.\textsuperscript{13} MRI is safe as there is no radiation risk but the prolonged imaging time compared with CT means that some children require general anesthesia before it can be carried out. This was necessary for case 2, and led to a delay in image acquisition and establishing of the diagnosis. Changes seen on MRI and CT can be subtle as demarcations from them regarding the best mode and duration of treatment, severity and etiology that it is hard to draw any conclusions from them regarding the best mode and duration of treatment other than that the clinician should be guided by the individual patient.

There are no definitive guidelines for the treatment of SBO in children, given its rarity and a consequent lack of clinical studies. Both of our cases were treated with intravenous antibiotics for 6 weeks, followed by 6 weeks of oral antibiotics. Both cases responded well to medical management negating the need for surgical treatment. Previous cases reported in the literature vary so greatly in terms of presentation, severity and etiology that it is hard to draw any conclusions from them regarding the best mode and duration of treatment other than that the clinician should be guided by the individual patient.

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\textbf{OPEN}

\textbf{FAILURE OF A SINGLE VARICELLA VACCINATION TO PROTECT CHILDREN WITH CANCER FROM LIFE-THREATENING BREAKTHROUGH VARICELLA}

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\textbf{Abstract:} We report 2 children with life-threatening breakthrough varicella. Both had received 1 varicella vaccination before onset of cancer. Despite treatment with intravenous acyclovir, 1 child died of disseminated varicella. Because similar fatal cases have been reported, high-risk immunocompromised children with 1 varicella vaccination may warrant the same varicella prophylaxis as immunocompromised children who have never been vaccinated.

\textbf{Key Words:} varicella vaccine, varicella deaths, acyclovir

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The live attenuated varicella vaccine was approved by the Food and Drug Administration in the US in March 1995. In July 1996, the vaccine was recommended for all children in the US. Based on the clinical trials, a single dose was recommended by subcutaneous injection to children 12–18 months of age. By the year 2000, investigators in several states had observed a new disease called “breakthrough varicella,” which was wild-type varicella-zoster virus (VZV) infection that occurred in children who had already been given 1 dose of varicella vaccine. Generally, breakthrough varicella was much milder than wild-type varicella, consisting of a rash with <50 maculopapules. Often the papules do not vesiculate. When risk factors for breakthrough varicella were assessed, a common factor was a >5 year interval between vaccinations. This result pointed to waning immunity as a prime cause of breakthrough varicella.

Subsequently, the Advisory Committee on Immunization Practices reviewed the data and in 2007, recommended that all children receive a second dose of varicella vaccine between ages 4 and 6 years before entering primary school. The rate of breakthrough varicella has dropped dramatically in children who have received 2 varicella vaccinations. However, because the majority of states do not have the funds or the infrastructure by which to vaccinate all children currently in the school systems, there remains a large reservoir of older children and young adults in the US who never received a second dose of varicella vaccine. A similar situation exists in Germany, which has a large cohort of children who only received a single varicella vaccination before vaccine policy was changed in 2009. Also, there are many children younger than 4 years who have not yet received their second varicella vaccination. These children remain highly susceptible to breakthrough varicella. Although the disease is mild in otherwise healthy children, breakthrough varicella can be life-threatening in immunocompromised children. This report describes 2 such cases, one of which was fatal.

**TWO CASE REPORTS**

**Case 1**

The patient was a 15-year-old male with T-cell precursor acute lymphoblastic leukemia undergoing reinduction chemotherapy. We defined day 1 as the day when he presented to the emergency department for fever and a sharp stabbing back pain. He had blood cultures drawn and received levofloxacin. On day 2, he presented again with high fever and decreased peripheral perfusion, with prolonged capillary refill time. Thus, he was admitted to the Pediatric Intensive Care Unit and received intravenous antibiotics. Laboratory data on admission showed lymphocytopenia (200 count/mm³). After his general condition was stabilized, the reinduction chemotherapy regimen with vincristine, doxorubicin, asparaginase and dexamethasone was resumed. On day 3, he developed a nonvesiculated cell-like rash, believed to be related to the high dosage of dexamethasone, based on its appearance. On day 7, the rash started to vesiculate. Vesicular fluid was obtained, and VZV DNA was detected with polymerase chain reaction (PCR) analysis. Intravenous acyclovir was started. On day 9, he developed hepatitis, which subsequently progressed to multigener failure and death. His immunization records from school revealed that the boy had received 1 varicella vaccination when he was 5 years old but none thereafter; he was up-to-date on other vaccines. DNA analysis of the PCR product from the vesicle indicated that the virus was wild-type VZV. VZV antibody titers were never obtained.

**Case 2**

The second patient was a 3-year-old girl with hepatoblastoma. She also had a genetic condition, known as mosaic trisomy 17. We defined the day when she developed fever and became critically ill as day 1. About 1 month before this febrile episode, she had been diagnosed with an undifferentiated hepatoblastoma. During her initial chemotherapy regimen, she developed acute kidney injury and a low white blood cell count. She was treated with granulocyte colony stimulation factor. Subsequently, the regimen was switched to vincristine, cisplatin and doxorubicin, leading to a persistent lymphocytopenia (<1000 count/mm³). After she developed fever with neutropenia, she was admitted on day 1 for treatment with antibiotics as per protocol. On day 2, she developed a vesicular rash on the legs. When VZV antigen was identified by immunostaining cells from a vesicle, she was started on intravenous acyclovir (50 mg/kg/day). Despite treatment, the rash worsened and spread over the next 5 days onto the lower abdomen. (The rash, even at onset, never had a zosteriform distribution.) Fevers continued for 5 days. She finally defervesced with no new lesions on day 8. Overall, a prolonged course of intravenous acyclovir was continued until day 19, followed by oral acyclovir (70 mg/kg/day) as suppression therapy for 3 months. Suppressive therapy was lengthy because of a previous case report of recurrence of breakthrough disease in a cancer patient when antiviral therapy was halted too quickly.

As in case 1, the source of the VZV infection was never identified. Of note, she received varicella vaccine when she was 13 months old; however, her screening VZV-specific IgG/IgM (enzyme-linked immunosorbent assay) titers were undetectable when she developed varicella at age 3 years. The diagnosis of VZV infection was confirmed by PCR analysis from DNA extracted from peripheral white blood cells collected on day 3. Testing was performed on blood cells to document a persistent viremia while on antiviral therapy. The strain was confirmed as wild-type VZV.

**DISCUSSION**

The Centers for Disease Control (CDC) recently reported a varicella-associated death of a child with cancer. This 4-year-old child had received 1 varicella vaccination before the cancer diagnosis and had a positive varicella antibody titer at onset of cancer chemotherapy. Of interest, she first presented with fever and abdominal pain before onset of rash. The CDC also recorded a cumulative total of 4 other varicella-associated deaths of children who had received 1 varicella vaccination. All but 1 were immunosuppressed. Recently, we published a related case that described severe breakthrough varicella in a child with cancer who had received 1 varicella vaccination. Similar to the recent CDC case that child also had detectable VZV antibody at onset of diagnosis, but she survived after prolonged antiviral therapy. Altogether, there are a total of 7 life-threatening breakthrough varicella infections in immunosuppressed children who have received only 1 varicella vaccination, 5 of whom died. There may also be other cases that were never reported.

The published experience in the literature is that otherwise healthy children who contract breakthrough varicella after one varicella vaccination have only mildly symptomatic infection, rarely needing any treatment. The chapter on VZV infections in the 2012 Redbook contains a table, which lists candidates for varicella-zoster immune globulin after significant exposure. The first bullet includes immunocompromised children without evidence of immunity. But there is no further information whether to consider children with cancer with one vaccination as nonimmune or immune.
The patient data listed above imply that one varicella vaccination cannot be relied upon as an indicator of protection in an immunocompromised child. Furthermore, VZV antibody titers are of little use after only one immunization because these titers may decline during chemotherapy, a likely explanation for the failure to prevent breakthrough varicella.\(^7\) When all the above cases are considered together, we suggest that children with cancer with a history of only one varicella vaccination, following exposure to wild-type varicella, be considered as candidates for varicella-zoster immune globulin (VarizIG: FFF Enterprises; ASD Specialty Healthcare) or alternatively prophylactic oral acyclovir.\(^3\) Prophylaxis with acyclovir is begun at seven days after exposure and continued for 7 days.

In both cases in this report, the source and date of the VZV exposure were unknown. Therefore, prophylaxis was not possible. Under that scenario, we suggest that children with cancer with only one varicella vaccination be considered in the same high-risk classification as a nonimmune immunosuppressed child with acute wild-type varicella. Having received corticosteroids while incubating varicella may be a particularly high-risk factor.\(^7\) As soon as breakthrough varicella is diagnosed, admission for treatment with intravenous acyclovir is advised.

Finally, we note that presentations of breakthrough varicella may be especially unusual in the immunocompromised child, a further reason for delayed diagnosis. For example, the exanthem may not be as vesicular as seen in primary VZV infection. With regard to our case 1 and the CDC case, severe abdominal and back pain may be an initial symptom of VZV infection before appearance of an exanthem, as has been reported previously.\(^10\)

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