A normally healthy, thriving, fully immunized 14-month-old twin girl with no history of eczema or other medical problems presented with a 2-cm raised erythematous nonpurulent lesion on her right shoulder, associated with a fever to 38.3°C. She was prescribed amoxicillin for a presumed bacterial skin/soft tissue infection (SSTI). The fever resolved after 24 hours, and our patient completed a 10-day course of amoxicillin. Her mother noted initial improvement, but then recurrence of the lesion with the development of coalescing vesicles with clear drainage on the erythematous base.

**Question 1** What is the differential diagnosis for a vesiculopustular skin lesion in a child?

SSTIs can develop after there is a break in the integrity of the skin. They are frequently caused by bacteria, with the 2 most common agents being *Staphylococcus aureus* and group A *Streptococcus*. These infections can manifest as a superficial folliculitis; impetigo, which may have vesicles, crusting, or bullae; or a deeper cellulitis or abscess formation. Fungal infections caused by dermatophytes usually present as focal round skin lesions with scaling but can occasionally have vesicles. Scabies, a reaction to a mite infestation, would also be in the differential for a child presenting with multiple papular lesions and pruritus. Finally, viruses including herpes simplex virus (HSV) types 1 and 2 (HSV-1 and HSV-2), and varicella zoster virus (VZV) may also present with vesicular skin lesions.

In a study published in 2013, 7585 children vaccinated against varicella between 1995 and 2009 were followed to document breakthrough varicella and herpes zoster infections. Over the 14 years of the study, 1935 breakthrough cases of varicella were reported (≥6 weeks after initial vaccination). All cases were after the first dose. Seventy-four percent of patients had mild illness with <50 total lesions.1

HSV (types 1 and 2) is a DNA virus that commonly causes illness in humans. HSV is spread by direct contact with an infected lesion and is highly contagious. HSV-1 is more common than HSV-2 in children older than neonates because HSV-2 has a specific tropism for genital mucosa and most often presents as a sexually transmitted infection or via vertical transmission around the time of delivery from mother to neonate.2

Usual presentations of primary infection with HSV-1 in immunocompetent children include herpetic gingivostomatitis, an illness characterized by high fevers, irritability, and painful oral and perioral lesions, or localized mucocutaneous vesicular lesions, such as herpetic whitlow or herpes labialis. Primary herpetic infection may also be asymptomatic. Less commonly, HSV can present as widespread skin lesions such as herpes gladiatorum, classically seen in wrestlers, and eczema herpeticum in patients with underlying eczema or burn injuries. Eczema herpeticum can be especially severe, and systemic antiviral treatment is recommended.3 The widespread skin lesions sometimes seen with HSV infection are thought to be due to
spread of HSV from a primary site to multiple areas with disrupted integrity of the skin, that is, autoinoculation from a primary site. Intact host defenses (primarily T-cell-mediated immunity) are usually enough to prevent spread to other organs; however, rarely, disseminated disease involving the liver, lungs, and central nervous system can occur even in immunocompetent individuals. Case reports show patients presenting with fever, sore throat, stomatitis, or, in 1 case, acute otitis media. These patients all had persistent fever and progressed within days to fulminant hepatitis, liver failure, renal failure, and death. No evidence of T-cell immunodeficiency (HIV, malignancy, thymic dysplasia) were found, and immunosuppressive medications were not being taken by the patients. Their ages ranged from 11 months to 56 years.4,5

HSV is also the most common cause of acute, nonepidemic viral encephalitis in the United States and can be associated with Bell's palsy. Finally, ocular and genital infections may occur.

Once primary infection resolves, the HSV virus remains dormant in neurons and can reactivate. Recurrences in immunocompetent individuals are commonly less severe than primary infection and are not usually associated with systemic symptoms.2

CASE CONTINUATION

Although inadequate treatment of a staphylococcal impetigo may have been the reason for our patient’s lack of resolution on amoxicillin, the clear drainage prompted the dermatologist to obtain a viral culture and prescribe topical acyclovir. Over the next few days, our patient proceeded to develop multiple lesions on her face, finger, and legs, and she was sent to the emergency department for evaluation. The lesions all began as papules (Fig 1), evolving over 24 hours to single or grouped vesicles on an erythematous base (Fig 2) with copious clear drainage. She was now afebrile but had mild anorexia/malaise. The lesions were neither painful nor pruritic. She had a total of 10 lesions. A bacterial culture, HSV 1 and 2 polymerase chain reaction (HSV-PCR) and VZV-PCR tests were all obtained from 1 of the new lesions. Because of her somewhat unusual presentation with an evolving outbreak after initial fever, persistent mild systemic symptoms, and young age, a concern was raised for disseminated infection with its attendant high morbidity and mortality. Complete blood count and HIV tests were done to help rule out an underlying immune issue, a serum HSV-PCR was sent, and she was admitted for further evaluation and treatment with intravenous acyclovir while awaiting results. Our patient’s viral culture from the original shoulder lesion grew HSV-1. In addition, the HSV-PCR of a secondary lesion was positive for HSV-1, and the bacterial culture and VZV PCR were both negative. Our pediatric infectious disease colleagues felt the multiple lesions were most likely due to autoinoculation; however, her serum HSV-PCR was also positive for HSV-1, indicating viremia present at the time of her secondary outbreak. They had no data to support a specific recommendation for treatment with this positive serum test and a conservative plan, was made to treat with IV acyclovir until there were no new lesions developing and old lesions had crusted over (Fig 3).

**Question 2 What does a positive serum HSV-PCR mean?**

Testing for HSV via DNA-PCR has been replacing the use of viral cultures.

**FIGURE 1** An early papular lesion on patient’s leg.

**FIGURE 2** An evolving lesion, now with more obvious coalescing vesicles.

**FIGURE 3** Crusted, healing lesion.

This evolution of available testing requires us to rethink what HSV “viremia” means. Studies testing for HSV viremia using culture methods have been negative for immunocompetent patients with gingivostomatitis8 or other mucocutaneous lesions.8 In addition, treatment regimens and morbidity have been defined by the presence of HSV viremia or not in neonatal HSV with
distinctions made among skin/eyes/mouth, central nervous system, and disseminated disease. Disseminated HSV has been associated with devastating disease and high mortality in these and other immunocompromised hosts.

Studies dating back to 1992 using the more sensitive HSV-PCR testing have detected the presence of HSV-DNA in the blood of 34% of healthy children with primary HSV gingivostomatitis,9 20% of healthy adults with acute recurrent herpes labialis,9 and in healthy infants from 4 to 36 months of age with and without eczema presenting with vesicles with or without fever.10 HSV DNA has also been found in the brain tissue of “healthy” adults at autopsy11 and in the generalized cutaneous lesions of erythema multiforme after a localized HSV infection.12 None of these patients progressed to multiorgan disease, and none developed evidence of immunodeficiency after presentation.

These findings have implications both for understanding how HSV causes disease and reactivation as well as for treatment regimens for patients who have this “viremia.” These studies show that HSV viremia, as defined by a positive serum PCR, is in fact relatively common during an HSV infection and may be responsible for the spread of mucocutaneous infection to distant sites. However, even in its presence, HSV only rarely leads to true disseminated disease. The DNA detected may not be from productive replicating virus,10 or the viral load may be low enough for intact host defenses to handle.13 Cantey et al noted in their 2012 study that it is their practice to perform a blood HSV-PCR test to optimize diagnosis of infected infants and children. However, they end by noting that “prospective evaluation of blood HSV-PCR testing and assessment of HSV viral load and duration of DNAemia are needed to better understand their relationship to pathogenesis, prognosis, and risk of recurrence.”10 Thus, a positive serum HSV-PCR may be diagnostic of an HSV infection, but it is not necessarily a marker for more severe disease.

**CASE CONTINUATION**

Our patient remained afebrile and well appearing with a normal neurologic exam. Her AST went from 33 U/L initially to 49 U/L 3 days later (normal range 0–32). Her other liver function tests were all within normal limits. She was continued on intravenous acyclovir for 6 days. She was then discharged from the hospital on oral acyclovir for an additional 8 days. Her complete blood count was normal, and an HIV antibody was negative. She was seen in the infectious disease clinic 1 month later with no additional problems. Treatment of recurrences with oral acyclovir was recommended and immune workup planned if there were recurrences at <3-month intervals. Of note, her twin sister developed similar lesions 4 days into her sister’s hospitalization. On day 1, her HSV PCR of lesion and blood were both negative; however, because of the similarity of the lesions, she was treated with a course of oral acyclovir.

**Question 3 Did the patient benefit from the diagnosis of HSV “viremia”? (Was this patient well served?)**

Our case illustrates the lack of utility of a serum HSV-PCR test in an apparently immunocompetent individual. Our initial concern for dissemination due to her widespread lesions without widespread skin disruption should have been tempered by her well appearance, lack of physical or laboratory evidence of immunodeficiency, and her clinical course. The serum test did not help us to identify systemic spread and led to a longer hospital stay and intravenous medication that in retrospect were overtreatment.

Our case also reinforces the call to question the distinctions made between various categories of disease and their implications for treatment. In neonates and other immunocompromised hosts as well as in critically ill immunocompetent hosts with evidence of severe disease (encephalitis, hepatitis, sepsis-like picture), a PCR of lesion/serum/cerebrospinal fluid may be sensitive enough to make a diagnosis otherwise missed with tragic result. Cantey et al10 reviewed the records of 45 patients over 3 years at his institution who had a positive serum HSV-PCR. Ten were older immunocompetent children as noted earlier, 12 were immunocompromised older children, and 21 were neonates. Six neonates (2 with central nervous system disease and 4 with disseminated disease) had a serum PCR as their first positive test. Two of these patients with disseminated disease had a serum PCR as their only positive test. The neonate <21 days old is certainly in a high-risk population that often presents with nonspecific symptoms, lack of skin lesions, and a negative maternal history. However, Cantey also found positive HSV-PCRs in 5 neonates with skin/eyes/mouth disease only. Miller and Bennet also recently reported on the increasing use of HSV-PCR instead of viral culture in neonates both in surface testing and for detection of HSV in serum. They note that even in this population, a positive serum HSV-PCR may lead to overtreatment of localized disease.14

In older immunocompetent, well-appearing children, including our patient, this certainly seems to be the case.

Hospitalists, who are often in the position of evaluating patients in the emergency department and making treatment and admission decisions, should understand the difference in sensitivity between a viral culture and an HSV-PCR. As we continue to learn more about the transmission of HSV and the meaning of viral DNA detection in the serum, we may be better able to make intelligent choices about both the indications for the test and the interpretation of the result. Our goal should be, as always, to avoid both underdiagnosis of serious disease and overtreatment of our patients.

**CONCLUSIONS AND LEARNING POINTS**

1. Although bacteria are responsible for many skin/soft tissue infections in children, it is important to include other agents including HSV in your differential.

2. Testing for HSV has evolved from viral culture to the highly sensitive HSV-PCR test, but the meaning of a positive result for each test is not the same.

3. HSV viremia, defined as the presence of viral DNA, is more common than previously appreciated and may be responsible for spread of the organism without leading to true disseminated disease.
REFERENCES


