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Varicella-Zoster Virus Infection

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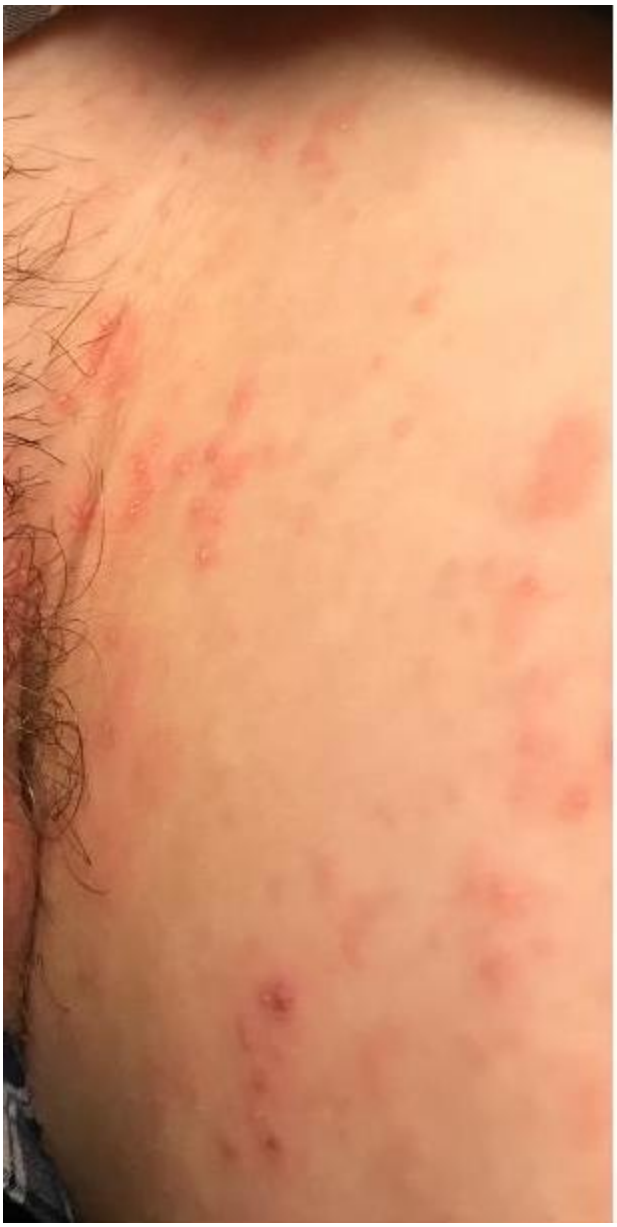
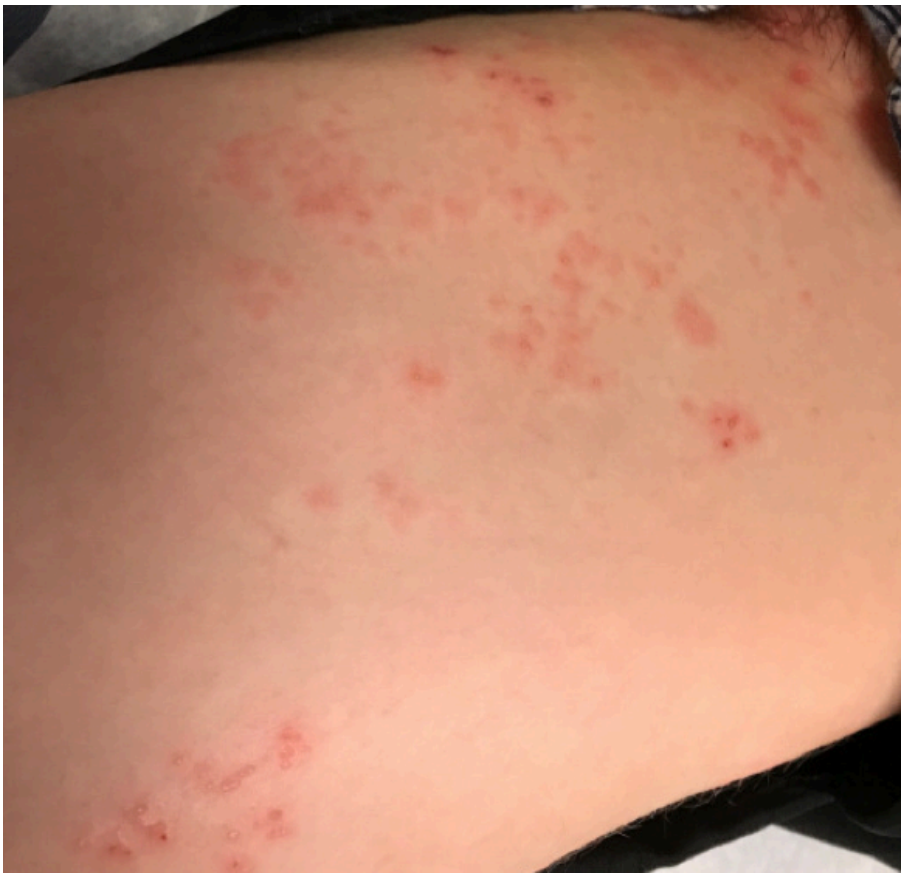
A previously healthy 16-year-old boy presented to an after-hours pediatric clinic with a painful rash. The patient described a burning and tingling sensation along his left inner thigh and across his left lower back that had begun 7 days prior to presentation. He reported that 4 days prior to presentation, a circular, pustular rash had appeared on his lower back, above his waistband, as well as redness and small blisters on his leg and groin. At that time, the pediatrician at the after-hours clinic diagnosed folliculitis and prescribed mupirocin ointment to be applied 3 times a day.

Despite this treatment, the rash and pain continued to worsen for the next 3 days, and he developed low-grade fevers and malaise. He presented for again for reevaluation at the pediatric after-hours clinic. At presentation, he described the pain as “burning” and at an intensity of 8 on a 10-point scale. He also noted that the areas of redness and blisters had continued to progress on his left inner thigh and left lower back. His fevers had a maximum temperature of 38.2°C but were responsive to antipyretics. Findings of a review of systems were otherwise normal.

His medical history was significant only for eczema, which had been well-controlled with emollients. The patient was not immunocompromised and had received all of the recommended immunizations, including the varicella series (vaccinations at 1 and 4 years of age). He had never had a previous varicella infection. Of note, at the patient's 16-year-old well-child visit 4 days prior to initial presentation, he had received his second dose of meningococcal conjugate vaccine without complication. At that visit, his growth, development, and physical examination findings were all within normal limits.

On physical examination, the patient was well-appearing, well-developed, and in no acute distress. Temperature was 36.4°C, and weight was 49.5 kg (10th percentile). Examination findings of the head, eyes, ears, nose, throat, heart, lungs, and abdomen were within normal limits. On skin examination, a vesicular rash in various stages of progression was easily appreciated, extending from the left inguinal crease to the medial and anterior thigh (**Figures 1 and 2**). The vesicles had clear fluid and overlaid an erythematous base. Some vesicles had ruptured, revealing shallow ulcerations with mild yellow crusting. The vesicular rash was also visualized on the patient's left lower back, and several lesions had crusting (**Figure 2**). The unilateral distribution of the lesions correlated with the L1 through L3 dermatomes.





Figures 1 and 2. *The patient's zosteriform rash with clusters of vesicles in a L1-L3 dermatomal distribution, extending from the left inguinal crease to the medial and anterior thigh. The vesicular lesions overlie an erythematous base and are in various stages of development, with several having ruptured, revealing shallow ulcerations.*

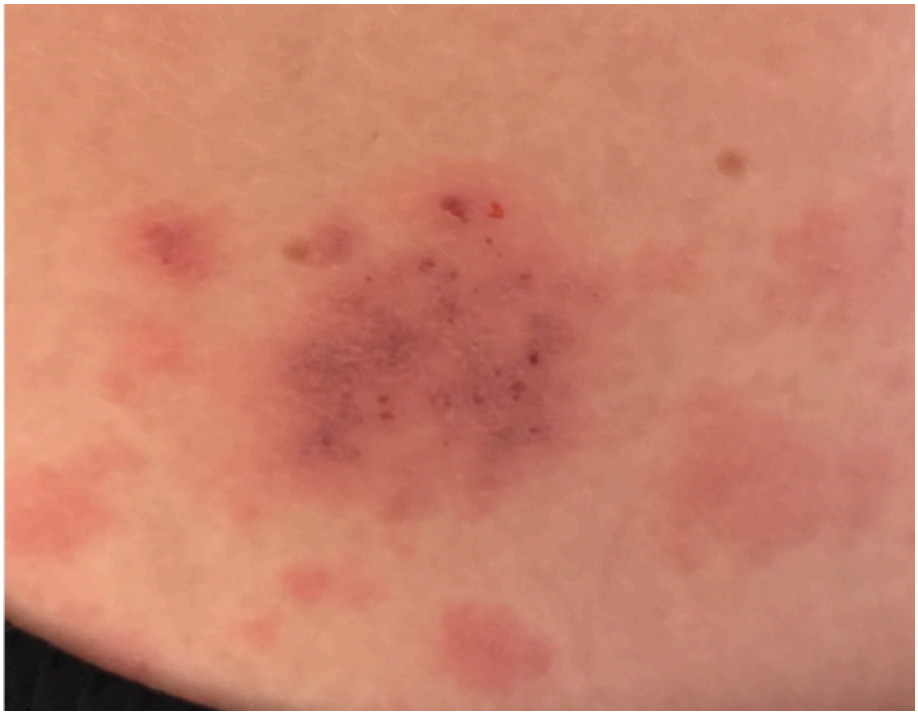


Figure 3. *Extension of the vesicular rash over the left lower back overlying the left iliac crest. A grouping of yellow-crusted, healing lesions surrounded by developing vesicles is present.*

The patient's presentation of a vesicular rash and fever, with neuropathic pain in a unilateral dermatomal distribution, was consistent with a clinical picture of herpes zoster (HZ). For confirmatory testing, an upper thigh vesicle was unroofed, and the exposed fluid was sent for varicella-zoster virus (VZV) polymerase chain reaction (PCR) testing. Due to a high clinical suspicion for HZ, he was started on valacyclovir, 1000 mg, 3 times a day.

Two days after his presentation, PCR test results confirmed VZV infection. Since having presented, his condition had demonstrated clinical improvement, including an afebrile status, decreased pain, and some resolution of the rash, without further new vesicular lesions.

DISCUSSION

VZV is a herpesvirus that causes the diseases of primary varicella and HZ.[1] Primary varicella infection results in the establishment of a latent infection in the dorsal root ganglia.[1] HZ occurs with the reactivation of this latent infection due to a transient, gradual, or chronic waning of cell-mediated immunity against VZV.[1,2] Reactivation occurs as the virus travels in a retrograde direction along axons toward cutaneous sensory nerves and replicates within keratinocytes in skin.

The classic symptomatology of HZ is a unilateral pattern of vesicles, generally along 1 to 3 dermatomes, and most commonly in thoracic and lumbar dermatomal distributions.[1] In adults, these lesions are typically associated with significant neuropathic pain and pruritus, which can precede the development of the rash. However, symptoms tend to be milder in children, characterized by pruritus and fever with little to no prodromal symptoms and few complaints of neuropathic pain.[1] The course typically lasts 1 to 3 weeks with full resolution of disease manifestations.[2] Whereas postherpetic neuralgia (PHN) is a serious and relatively common complication in older adults, affecting 25% to 50% of patients with HZ older than 50 years of age, there is a very low likelihood of PHN in children.[2]

The incidence of HZ typically increases with age, with a marked increase after the age 50, attributed to physiologic waning of cell-mediated immunity against VZV; nonetheless, HZ can occur at any age.[3] Risk factors for the development of HZ in children include immunocompromised states such as HIV infection, acute lymphoblastic leukemia and other malignancies, and organ transplant.[4] Healthy children with a history of a varicella infection before 2 years of age or in utero also demonstrate a 20-fold increased risk of developing HZ, due to a less-developed immune system at time of VZV exposure.[1,2] Although previously considered rare in healthy children, more recent studies report varying incidence rates of HZ, from 42 to 238.5 per 100,000 person-years.[4-6] Importantly, while both the wild-type and vaccine strains of VZV have the capability of latency in the dorsal root ganglia with subsequent reactivation as HZ, varicella vaccination remains effective for decreasing the incidence of HZ in

healthy children, with 79% lower rates of clinical presentation in vaccinated children compared with unvaccinated children.[5]

The definitive diagnosis of HZ is achieved with PCR of VZV DNA from either a skin scraping or vesicular fluid, which is more specific than serology testing for VZV antibodies.[2]

Adequate treatment requires consideration of the patient's symptom severity and duration, immune status, and age. Although low-risk patients do not require pharmacotherapy, outpatient antiviral therapy has been demonstrated to hasten lesion healing and improve symptom resolution in children.[2] Furthermore, in adults, antivirals are known to decrease the risk of PHN. Acyclovir is the most commonly prescribed treatment in uncomplicated, nonrecurrent VZV infection in immunocompetent patients without concern for resistance.[2] However, the dosing frequency and pharmacokinetic profile of acyclovir may lead the provider to select valacyclovir or famciclovir therapy, both of which are considered to be equivalent treatment options for VZV.[1]

The diverse triggers for HZ reactivation in immunocompetent individuals are incompletely understood. The physiologic decline of cell-mediated immunity during aging and in the setting of an immunocompromised state are well-established causes for reactivation and are consistent with the need for virus-specific cell-mediated immunity to prevent VZV reactivation. A more nuanced understanding of causes of reactivation is developing, with elucidation of factors such as trauma, fever, and psychological stress.[7]

Vaccine-linked immunomodulation as a cause of herpes virus reactivation has also been proposed in the literature, including a chart review of 10 cases of HZ in patients from 16 to 60 years of age following immunization,[8] and a case report of a pediatric patient after allogeneic hematopoietic transplant with full recovery of her CD4 and CD8 cell counts who presented with a VZV reactivation following revaccination of routine childhood immunizations (diphtheria, tetanus, and pertussis; inactivated polio vaccine; *Haemophilus influenzae* type b conjugate; and meningococcal C conjugate).[9] This proposed association is particularly interesting in the context of our patient's case, given that he had received a routine meningococcal vaccination less than a week prior to the development of HZ symptoms. Our patient's illness may represent a case of reactivation of vaccine-strain VZV with resulting HZ in the setting of vaccination-linked immunomodulation in a pediatric patient without a clinical history of varicella.

Although further research is needed in this area, it is important to recognize that routine vaccination, which is a known trigger for immunomodulation, may be a possible trigger for VZV reactivation.

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