



Case report

Non-dermatomal cutaneous herpes zoster infection in a solid-organ transplant patient

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ABSTRACT

Diagnosis of atypical generalized forms of herpes zoster can be a challenge and may lead to a delay in treatment. Herpes zoster can present with atypical clinical manifestations, some with higher risk of complications that are potentially life-threatening. We describe a patient that presented with several ulcerated papules and plaques in a non-dermatomal distribution in whom disseminated cutaneous herpes zoster was proven by molecular amplification testing. Patients with disseminated herpes zoster should be treated initially with intravenous antiviral therapy, followed by oral acyclovir, valacyclovir, or famciclovir in most adults, with close follow-up. Earlier treatment may reduce the risk of developing complications and progression of visceral involvement. This case adds to the evolving literature related to herpes zoster, especially regarding patients with immunosuppressed status.

Introduction

During the current pandemic, an increase in herpes zoster (HZ) infections has been reported in association with the COVID-19 outbreak, conceivably due to immune system dysregulation related with physical and mental stress leading to the reactivation of varicella zoster virus (VZV) [1]. Reactivation of VZV from the dorsal roots and autonomic ganglia is usually characterized by a localized skin rash and cutaneous dysesthesias occurring in 5% of individuals but occur more frequently in immunocompromised individuals [2]. Cutaneous dissemination of lesions outside of the primary dermatome has been reported to occur in 10–40% of all immunocompromised patients with HZ and should prompt suspicion for possible visceral involvement through viremic transmission [3]. Nevertheless, patients with compromised immune systems may present with atypical and more severe manifestations of VZV reactivation that is associated with a higher mortality rate, making the early diagnosis and treatment crucial for patient survival [4,5]. Here we report a case of disseminated cutaneous herpes zoster in a solid-organ transplant patient presenting as ulcerated papules and plaques in a non-dermatomal distribution.

Case report

A 32-year-old female presented to our outpatient dermatology clinic

with several eschars scattered over her body of 4 weeks duration. The patient's medical history was notable for type 1 diabetes mellitus, end-stage renal disease status-post simultaneous pancreas and kidney transplant on immunosuppressive therapy consisting of 5 mg/day Everolimus, 10 mg/day Tacrolimus, and 5 mg/day Prednisone. Two years after solid organ transplantation, the patient felt a sudden onset of sharp pain on the right forearm that had developed into two small ulcerations the following day (Fig. 1).

This was thought originally to be a spider bite, but over the course of one week, she developed new similar lesions immediately adjacent to the primary lesion, on the face, trunk, and right arm. She initially experienced pruritus, burning, and stinging around the lesions, which gradually became black and painful without history of any purulent discharge. The patient denied having night sweats or chills, neck stiffness or tightness, neuropathy, or any acute mental status or visual changes, however, she developed a persistent right-sided headache soon after the primary lesion had appeared.

Physical examination revealed erythematous papules and plaques with overlying necrotic eschar and peripheral rim of erythema on the right eyebrow (1 cm; Fig. 2A), right forearm (3 × 2 cm; Fig. 2B), right posterior upper arm, right temple, and right lower quadrant of abdomen (<1 cm) that were nondraining. The patient was afebrile and had no other acute complaints during the clinic visit. There was high suspicion for an atypical infection such as ecthyma, deep fungal or other infectious

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Fig. 1. Two painful and pruritic ulcerated papules with peripheral erythema on the right forearm in an immunosuppressed patient.

etiology given her chronic immunosuppression.

Two punch biopsies were obtained from the larger right forearm lesion for histopathological evaluation and tissue culture. Histology showed epithelial hyperplasia, ulceration, eosinophilic intranuclear inclusions and focal multinucleated keratinocytes surrounded by a dense inflammatory infiltrate (Fig. 3), consistent with varicella or herpesvirus infection. There was no evidence of deep fungal infection or ecthyma identified using Grocott’s Methenamine Silver stain or Gram stain. Tissue cultures for aerobic/anaerobic and acid-fast bacteria, and fungal etiologies were unremarkable. Immunohistochemical staining was not performed.

Because the patient reported a childhood history of chicken pox and had positive serological detection of VZV immunoglobulin G (IgG) antibody three years prior, the possibility of primary varicella was excluded. The differential diagnosis of atypical or disseminated herpes simplex virus (HSV) or herpes zoster (HZ) was entertained. The patient was promptly contacted and advised to be evaluated in our emergency department for additional testing and initiation of antiviral therapy. On admission, the patient was afebrile, normotensive, and had a normal heart rate of 90–100 bpm. Blood data were unremarkable from her baseline, including a reasonable neutrophil-dominant white blood cell

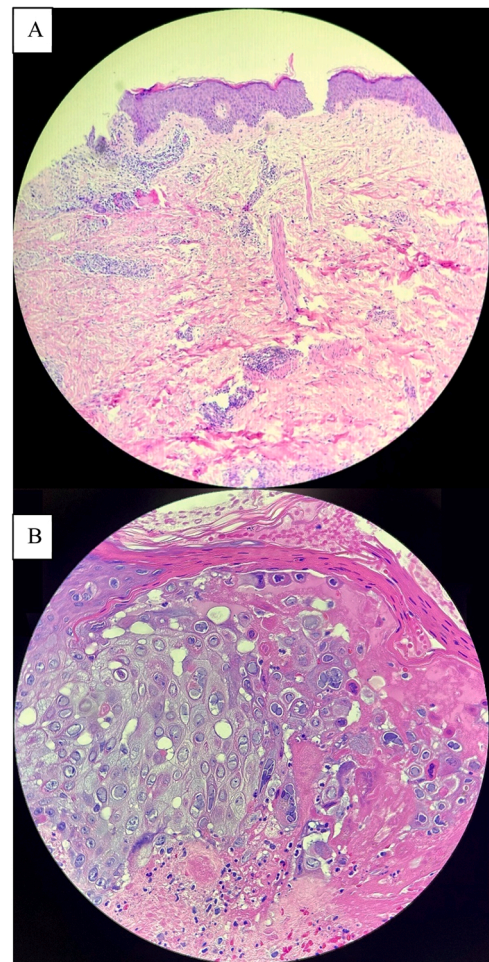


Fig. 3. Punch biopsy obtained from the periphery of the forearm lesion shows epithelial hyperplasia, ulceration, eosinophilic intranuclear inclusions, and multinucleated keratinocytes surrounded by a dense inflammatory infiltrate, typical of varicella or herpesvirus infection. (H&E); Original magnifications: A, x10; B, x40.

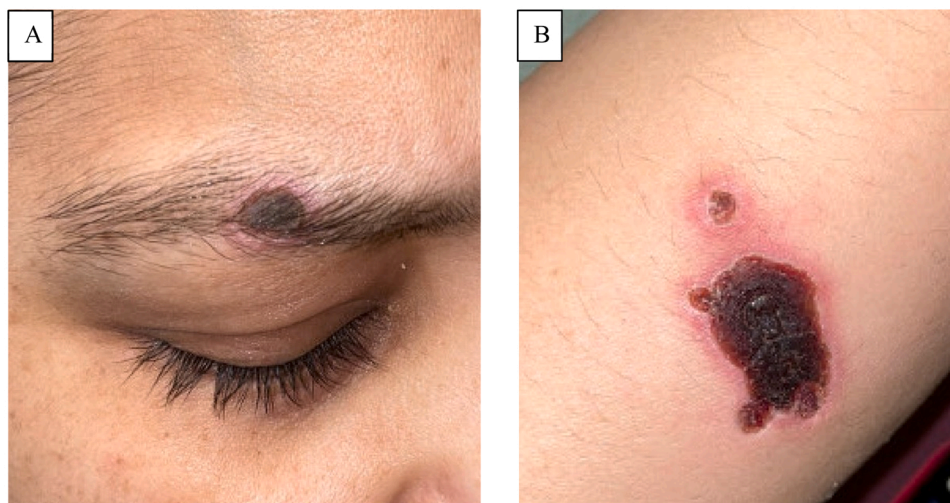


Fig. 2. Erythematous papules and plaques with overlying necrotic eschar and peripheral rim of erythema distributed across the patient’s body without dermatomal pattern: A, Right eyebrow; B, Right forearm.

count (6.4 K/UL), elevated blood urea nitrogen (28 mg/dL) and creatinine (2.0 mg/dL). Lactic acid (1.9 mg/dL) was within the normal range and the patient did not appear to be toxic. Blood cultures and wound swabs from the base of the primary lesion were also collected for microbiological assessment. Antiviral treatment was immediately started with intravenous acyclovir 10 mg/kg, given every 12 h adjusted based on her renal function (creatinine clearance, 33 mL/min), and the immunosuppressive therapy dose was reduced in the setting of infection until outpatient follow-up.

Swab specimens were positive for VZV and negative for HSV-1 and HSV-2 detection on polymerase-chain reaction (PCR). Plasma PCR for VZV deoxyribonucleic acid (DNA) were elevated (400 copies/mL) and undetectable for HSV-1 and HSV-2 DNA. Given the clinicopathologic findings, disseminated cutaneous herpes zoster without dermatomal skin lesions was diagnosed. The patient remained clinically stable throughout the hospital stay and was discharged six days after admission to continue treatment with oral valacyclovir 1 g, given two times daily for 10 days. Upon remote follow-up after completing the antiviral therapy, the patient reported significant improvement in the appearance of the lesions, with most lesions completely healed over. The patient denied any headache, pain or pruritus at the site of previous lesions, or the presence of new lesions. After consultation with the transplant nephrology provider responsible for managing her immunocompromising therapy, it was recommended that she receive two doses of the recombinant zoster vaccine to reduce the risk of recurrent shingles and related complications at her follow-up visit in two weeks.

Discussion

Herpes zoster (HZ), also known as shingles, is a commonly occurring condition in the general population worldwide. After a primary infection with VZV, the herpesvirus enters a latent stage in sensory neurons until there is a stimulus for reactivation such as immunosuppression [3, 7]. The incidence of HZ reactivation is strongly linked to the immune status of the individual. Variables such as advanced age, immunosuppression, metabolic and neoplastic disorders are among the most common risk factors [3,6–8]. Reactivation in immunocompromised patients is usually associated with a more extensive local rash than in healthy individuals and is often accompanied by viremia and a decline in VZV-specific cell-mediated immunity [8]. Visceral involvement in high-risk patients increases the morbidity and mortality associated with VZV requiring prompt diagnosis and treatment of cutaneous VZV infection to reduce the risk of dissemination.

In the setting of immunocompromise, HZ can present as classic zoster (localized rash), dermatomal zoster with dissemination, atypical generalized zoster with or without visceral involvement, and visceral zoster without skin lesions [3,4,7,9]. Disseminated cutaneous HZ is defined as having more than 20 vesicles outside the primary and immediately adjacent dermatomes or affecting three or more dermatomes [3]. Rarely, disseminated cutaneous HZ can occur with an absence of skin lesions in a dermatome [10]. The patient in our case presented with generalized cutaneous HZ without dermatomal skin lesions, making this a clinical diagnostic challenge given the unusual manifestation and distribution initially thought to be caused by an insect bite.

It remains unclear if the VZV infection in this patient was due to a reinfection despite the presence of VZV-specific antibody on serology prior to solid-organ transplantation and having no ill contacts recently, or whether the lesions are due to a reactivation of latent virus that caused atypical disseminated zoster. It is generally considered that specific immunity to VZV will protect against reinfection, although it has been reported that clinical reinfection can occur in patients that are immunologically healthy and unsurprisingly, in immunocompromised patients where reinfection is more common [11]. The cutaneous dissemination of HZ to visceral organs has been reported to occur in over 10% of immunocompromised patients, with the lung being the most

frequent non-cutaneous organ involved regardless of immune status [4, 12]. Dissemination following VZV reactivation can cause pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy, and is associated with a higher mortality rate (approximately 55%) prior to antiviral treatment [3,12]. There was a low threshold to obtain additional testing including diagnostic imaging and lumbar puncture with cerebrospinal fluid analysis in this patient presenting with headache and suspicion for herpes zoster encephalitis. Albeit the patient remained clinically stable without acute deterioration in neurologic status.

Diagnosis of atypical generalized forms of HZ can be a challenge and may lead to a delay in treatment. The possibility of an atypical HSV infection and HZ were both in the clinical differential diagnosis considering that atypical presentations of HSV infection can occur in extragenital locations such as the shoulder [13]. The initial diagnostic test of choice when suspecting a herpesvirus infection is usually a Tzanck smear, which cannot differentiate VZV from HSV infection. However, a skin biopsy should be performed when other etiologies such as deep fungal infection are also considered. Currently, the most reliable and convenient diagnostic tool for detecting HSV and VZV is by PCR testing of skin lesion specimens, which remains superior to viral culture [14]. The use of saliva VZV PCR has recently been suggested as an alternative method and is reported to be more sensitive than that of plasma PCR with a similar specificity for detecting VZV among patients with suspected herpes zoster but with crusted over lesions [15].

Treatment of cutaneous HZ should be initiated promptly to reduce the risk of dissemination, especially in the setting of immunocompromise. Acyclovir (oral and intravenous) has been the drug of choice in the treatment of herpes zoster. If disseminated HZ infection is suspected, intravenous therapy should be given for at least 7 days, but may need to be given for longer in patients with extensive involvement. Adult dosing for disseminated HZ is Acyclovir 30 mg/kg given in three divided doses [16]. Treatment of localized HZ is typically given for at least 7 days or until lesions have crusted over, which may be delayed in immunocompromised patients. Outpatient treatment for localized HZ in adults consists of Acyclovir 800 mg, given five times daily, Valacyclovir 1 gm, given three times daily, or Famciclovir 500 mg, given three times daily [16]. Careful monitoring of renal function is needed while on intravenous or high-dose therapy, and dosing should be adjusted for renal insufficiency. Rates of HZ complications, such as post-herpetic neuralgia are thought to be higher in solid-organ transplant recipients than in immunocompetent populations, thus rapid diagnosis and earlier treatment should be started optimally within 72 h of viral onset [17].

Herpes zoster can present with atypical clinical manifestations, some with higher risk of complications that are potentially life-threatening. Our patient presented with individually scattered ulcerations in over three different dermatomes. The immunosuppression because of her solid-organ transplant made disseminated herpes virus infection likely. This case adds to the evolving literature related to HZ, especially regarding patients with immunosuppressed status.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author statement

All authors discussed the results and contributed to the final manuscript.

CRedit authorship contribution statement

Bao Vincent Ho: Writing – original draft, Writing – review & editing. **Sarah Pourakbar:** Visualization, Investigation, Writing – review & editing. **Christopher Tomassian:** Supervision, Writing – review & editing. **Anand Rajpara:** Investigation, Writing – review & editing.

Declarations of interest

The authors have no conflict of interest to declare.

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