Disseminated Herpes Zoster in an Apparently Healthy Middle-Aged Woman

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Herpes zoster is a characteristic dermatomal maculovesicular rash that results from reactivation of varicella-zoster virus (VZV). Dissemination, or widespread distribution of vesicular lesions beyond the limits of the primarily involved dermatome, occurs almost exclusively in individuals with severe underlying immunodeficiency, such as malignancy, human immunodeficiency virus, and advanced age. Waning cell-mediated immunity is thought to be the final common pathway permitting reactivation and dissemination. Here, however, we present a case of disseminated herpes zoster (DHZ) that occurred in an apparently immunocompetent patient without any traditional risk factors.

Case
Upon returning from a vacation in Palm Springs, California, a 58-year-old white female presented to the emergency department (ED) with a 5-day history of headache and progressive pain, redness, and rash over her right forehead and eyelid. Pain was the initial manifestation, with small vesicles then appearing at her hairline and progressing caudally to involve the eyelid (Figure 1). In addition to significant periorbital edema, she reported a “burning” sensation in her right eye. While still on vacation, on the day prior to her presentation, she had presented to an ED and was given a prescription for acyclovir 800 mg PO five times daily. This patient suffered from hypertension, hypercholesterolemia, a longstanding peripheral sensory neuropathy that had not yet been diagnosed, and chronic ethanol abuse (one bottle of wine per day for at least 10 years) and had a previous 60 pack-year smoking history. She had no known history of immunodeficiency or malignancy. Her medications included a perindopril/indapamide combination tablet and the recently prescribed acyclovir. She reported an allergy to penicillin, the nature of which was unclear.

On examination, she was febrile, with a temperature of 38.4°C; the remainder of her vital signs were within normal limits. An exquisitely tender, erythematous, papulovesicular rash covered her right forehead and eyelid but spared the tip of her nose and did not cross the midline. She had significant periorbital and eyelid edema, effectively closing her right eye. She had jolt accentuation of her headache but no other signs of meningismus. On her torso, back, right arm, and right upper thigh, she had multiple (>30) small erythematous, non-tender

Figure 1. Periorbital distribution of herpes zoster.

Figure 2. Disseminated vesicular lesions on torso and epigastrium.

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Abdominal ultrasonography revealed fatty infiltration of the liver. Further investigations for enterovirus RNA and herpes simplex virus DNA were negative. Blood and cerebrospinal fluid (CSF) cultures were negative, as were CSF mitochondrial and anti-nuclear antibody screens. Complete blood count (WBC) of 12.2 × 10⁶ (0.0–5.0 × 10⁶), composed of 6% neutrophils, 65% lymphocytes, and 29% monocytes; and a protein level of 0.6 g/L (0.15–0.45 g/L), with a normal glucose level and no xanthochromia.

Cerebrospinal fluid (CSF) analysis revealed white blood cell count (WBC) of 12.2 × 10⁶ (0.0–5.0 × 10⁶), composed of 6% neutrophils, 65% lymphocytes, and 29% monocytes; and a protein level of 0.6 g/L (0.15–0.45 g/L), with a normal glucose level and no xanthochromia.

Based upon the characteristic appearance and widespread, multi-dermatomal location of the papulovesicular lesions, a clinical diagnosis of DHZ was made. The patient was admitted to the internal medicine service for IV acyclovir therapy and to complete laboratory investigations for occult malignancy and other immunodeficiency. The clinical diagnosis of DHZ was confirmed by the identification of VZV direct fluorescence antigen positivity in her CSF and fluid from a swab of a torso vesicle. A screen for underlying immunodeficiency was then undertaken. Serologic tests for human immunodeficiency virus (HIV) 1 and 2, hepatitis A, B, and C, and syphilis were negative. However, flow cytometry revealed a mild decrease in the total number of T cells at 0.680 × 10⁹/L (normal 0.800–2.531 × 10⁹/L), and in the CD4 fraction in particular, at 0.371 × 10⁹/L (normal 0.499–0.651 × 10⁹/L). In addition, serum protein electrophoresis; C-reactive protein (CRP); C3 and C4; IgA, IgG, and IgM; anti-smooth muscle, anti-mitochondrial, and anti-nuclear antibody screens were all within normal limits. Blood and CSF cultures were negative, as were CSF studies for enterovirus RNA and herpes simplex virus DNA. Abdominal ultrasonography revealed fatty infiltration of the liver and a mildly enlarged spleen (13.4 cm).

She was treated with 14 days of acyclovir 500 mg IV q8h. At the recommendation of the ophthalmology service, she also received a 9-day course of 1% trifluridine eye drops five times a day, and a 7-day course of 1% prednisolone eye drops. With the resolution of her periorbital edema, a complete ophthalmologic examination was performed and was normal. There was concern regarding a superimposed bacterial cellulitis, and she was treated with ceftriaxone 1 g IV q24h for 9 days.

By the 5th post-admission day, all of the patient’s lesions had crusted over. Unfortunately, she developed diarrhea due to *Clostridium difficile* enteritis, and a 14-day course of oral metronidazole was prescribed. At the time of discharge, the patient was feeling well and the crusts of most of her lesions had sloughed off.

**Discussion**

The characteristic rash of herpes zoster results from the reactivation of latent VZV. During the primary infection with the virus, which manifests as varicella or “chicken pox,” the virus infects peripheral sensory nerves and migrates centripetally, ultimately reaching the dorsal root ganglia. Varicella-zoster-specific cell-mediated immunity (CMI) keeps the virus in a dormant state. As CMI wanes, as a result of aging, malignancy, and immunosuppressive drugs, VZV is permitted to reactivate, resulting in the painful, papulovesicular rash characteristic of herpes zoster. Indeed, whereas the incidence of herpes zoster in the general population is approximately 1.3/1,000 patient-years, it is >10/1,000 patient-years and 29/1,000 patient-years in those over 80 years of age and in those with HIV, respectively.

Herpes zoster is classically restricted to a single dermatome. However, the involvement of discrete lesions removed from the primary dermatome are commonly reported, occurring in 29 of 88 (29%) patients without known malignancy in one prospective series. These ectopic lesions are hypothesized to result from hematogenous seeding. At some critical threshold, the number of these ectopic lesions heralds frank dissemination, a characteristic that has both therapeutic and prognostic significance. Three distinct distributions of herpes zoster have been reported: the classic localized, monodermatomal herpes zoster; herpes zoster with aberrant lesions; and frank dissemination. Unfortunately, dissemination has not been clearly defined in the literature. Of the few studies that report a definition, thresholds range from 10 to 30 lesions. In the absence of any physiological data or rationale, these disparate definitions appear arbitrary.

For dissemination to occur, significant immunocompromise is thought to be necessary. Decline in VZV-specific T-cell function is the final common pathway thought to be necessary to allow reactivation. This decline is most often mediated by increasing age but is also characteristic of T-cell-compromising states such as those resulting from HIV, malignancy, and immunosuppressive therapies. Dissemination occurs in approximately 2% of population-based and prospective studies of general in-patients with herpes zoster. Unfortunately, these studies did not report their definition or threshold for “dissemination,” nor did they report the immune status of the affected patients.

DHZ in apparently immunocompetent, non-elderly patients...
is extremely rare, being limited to three case reports. A review of older cohort studies, with questionable or unstated definitions of dissemination and often unclear or absent assessments for immunocompromise, may yield several more cases. There are no specific guidelines to direct treatment or investigation for occult immunocompromise in patients with DHZ. However, given the degree of immunosuppression implied with dissemination, investigation seems appropriate in these patients.

We present a case of DHZ in an apparently immunocompetent patient. In the absence of known immunodeficiency, a predisposing condition, or advanced age, we propose that ethanol abuse, with a subsequent impact on CMI, may have allowed for the reactivation and dissemination of herpes zoster. There is clear in vitro and in vivo evidence that chronic alcohol consumption impairs cell-mediated immune function. Chronic ethanol use reduces T-cell number and function, which translates into significant increases in infection rates. This effect is thought to be mediated by a combination of ethanol-induced apoptosis and interference with cytokine-mediated T-cell production. Although ethanol abuse has been demonstrated to increase the incidence, and alter the course of, a number of viral infections, including hepatitis C and HIV, only a single study comments on effect of ethanol on VZV reactivation.

In a Brazilian case-control study that sought to determine historical factors that triggered non-DHZ, there was a significantly greater frequency of ethanol consumption in the herpes zoster group (12/30 patients; 40%) as compared with the control group (14/100 patients; 14%). These authors concluded that ethanol consumption may be a factor in triggering herpes zoster. Unfortunately, ethanol consumption was not quantified, nor was it qualified (e.g., as “abuse” or “heavy”).

In conclusion, we present a case of DHZ in an apparently healthy 58-year-old woman. In such apparently healthy patients with DHZ, investigation for occult malignancy and HIV is recommended. If this evaluation ultimately proves to be negative, ethanol abuse should be considered.

References