CLINICAL VIGNETTE

Herpes Zoster Duplex Bilateralis: An Atypical Presentation of Herpes Zoster in an Immunocompromised Patient

Matthew Gonzales, MD and Manuel Eskildsen, MD

An 82-year-old Korean-American woman with a history of EGFR-positive metastatic lung adenocarcinoma, lower extremity deep venous thrombosis, pulmonary embolism, atrial fibrillation, and hypertension presented to her Geriatrician's office for a new facial rash.

The rash was described as initially light pink and indolently becoming dark red in hue over two weeks. The rash first appeared in the right periorbital area, but three days prior to presentation, the rash had spread contralaterally. The patient's family applied mupirocin on the day prior to presentation at the suggestion of a family friend, and the following morning the area of the rash had evolved to include hemorrhagic scabbing and crusting, a change prompting the patient to seek medical attention. The rash had been itchy but not painful, and she noted frequent scratching of the area. There were no vesicles noted, and the patient denied eye pain or visual symptoms. She had never had herpes zoster before. Because of concern about potential herpes zoster ophthalmicus, the patient was sent to the hospital for direct admission.

Her medications were osimertinib, alendronate, mirtazapine, megestrol, rivaroxaban, cholecalciferol, ferrous gluconate, thiamine, oxycodone-acetaminophen as needed, zolpidem as needed, and alprazolam as needed. Osimertinib, which the patient had been taking for metastatic lung adenocarcinoma, had been increased two months prior to presentation because of concern for progressive leptomeningeal carcinomatosis.

On physical examination, patient was cachectic but in no acute distress. Her body-mass index was 12.8 kg/m^2. Her vital signs were within normal limits. Her skin exam was remarkable for crusted, petechial hemorrhages concentrated throughout the glabella symmetrically, with some extension to the nose – including its tip – and the chin. No other rashes were noted. Eye exam was notable only for mildly decreased visual acuity (20/50) in both eyes, and a cranial nerve exam was within normal limits. The remainder of the physical exam was non-contributory.

The patient was placed in contact and airborne isolation and started on oral valacyclovir 1 gram twice daily given the benefits of early treatment of possible disseminated herpes zoster. The risks of intravenous acyclovir therapy were felt to outweigh benefits given a low-to-intermediate suspicion for zoster, presence of mild renal disease, and a reasonable alternative treatment regimen (i.e., oral valacyclovir). The most likely diagnoses were thought to be a hypersensitivity rash secondary to osimertinib, contact dermatitis, or herpes zoster. A detailed ophthalmologic exam did not display evidence of zoster ophthalmicus. A consulting dermatologist unroofed a crusted lesion and sent it for evaluation of herpes simplex virus and varicella zoster virus PCR tests. Given that the lesions were completely crusted, the patient was discharged home to complete a 7-day course of valacyclovir. Just after discharge, varicella zoster PCR test returned positive. At follow up visit, it was noted that patient's rashes had resolved.

Herpes Zoster in the Immunocompromised Patient

The typical cutaneous presentation of herpes zoster is an onset of erythematous papules in a dermatomal distribution, typically with evolution to grouped vesicles that eventually crust over in the time span of approximately one week. Most patients have a burning pain in the area of the rash preceding its appearance. Some patients also report fever and malaise.

Herpes zoster is classified as localized or disseminated depending on whether the rash is localized to one dermatome. The pathophysiology of localized herpes zoster is reactivation of latent varicella zoster virus in previously infected dorsal root ganglia. The most frequent location of reactivation is the trunk, but infection and reactivation can also occur in the cranial nerves. Whereas localized herpes zoster of the trunk carries a benign prognosis, infection of the ophthalmic division of the trigeminal nerve can cause loss of eyesight by mechanisms such as ulcerative keratitis, ischemic optic neuritis, and acute retinal necrosis.[1] Disseminated infection may also have serious consequences, but it is seen much more frequently in immunosuppressed patients, such as in cancer patients receiving chemotherapy and organ transplant recipients.

Herpes zoster has been reported to have atypical presentations, particularly in the immunocompromised patient. A frequently described variant is "zoster sine herpete," in which patients present with dermatomal pain or visceral involvement of zoster without cutaneous manifestations.[2] Rarely, the zoster rash also may remain papular without evolution to the classic vesicular appearance.[3] More typically, appearance of vesicles can be uncharacteristically late, leading to delay in the diagnosis.

Presence of herpes zoster in localized but contralateral dermatomes has been called herpes zoster duplex bilateralis (HZDB). It occurs principally in the immunocompromised and

represents less than 0.1% of all cases.[4] Case reports in the literature have described the appearance of rash as contemporaneous[5,6] or alternatively, in sequence.[7,8] There is little information in the literature regarding the prognosis of HZDB, but it does not appear to have a prognosis any different than unilateral localized herpes zoster. The pathogenesis is presumably reactivation of varicella zoster in two separate dorsal root ganglia, but viral spread from one dermatome to another has also been proposed.[9]

Early recognition of herpes zoster in the immunocompromised patient is paramount. Localized disease can become disseminated (and become life-threatening when visceral organs become involved), but dissemination can be prevented by early recognition and treatment.[10] Moreover, as opposed to immunocompetent individuals, evidence is stronger for therapy after the 72-hour mark of onset of rash.[11] In severely immunocompromised patients (stem cell transplant patients and transplant recipients receiving aggressive antirejection therapy) with local or disseminated disease, intravenous acyclovir with dosing of 10 mg/kg every 8 hours for 7 days is recommended. For less immunosuppressed patients, oral therapy with valacyclovir with dosing of 1000 mg every 8 hours is considered a reasonable alternative, though few data are available to support this approach.[12]

Discussion

Our patient had reactivation of herpes zoster that was atypical in multiple ways: One, it involved symmetric dermatomes with non-synchronous onset; two, the rash was atypical in appearance before the characteristic vesicles and hemorrhagic crusting occurred; and three, the prodromal symptoms that often raise suspicion for the diagnosis were absent. Given that the prevalence of zoster is high in an elderly and immunocompromised individual, the pretest probability of zoster remained high, even though a hypersensitivity reaction to osimertinib or contact dermatitis were attractive alternate diagnoses. Once zoster ophthalmicus was ruled out but before the varicella PCR test returned positive, the patient was started on oral valacyclovir therapy even though clinical suspicion for zoster was low-to-intermediate, given the low probability of valacyclovir toxicity. A more aggressive approach with intravenous acyclovir may also have been justified. Fortunately, our patient had a benign course with oral therapy.

Our case underscores that suspicion for atypical presentations of a disease should remain high in patients with a high disease prevalence, and that it is often justified to start empirical therapy for herpes zoster despite intermediate clinical suspicion given the high prevalence of zoster and the relatively low toxicity of oral treatments.

REFERENCES

1. **Karbassi M, Raizman MB, Schuman JS**. Herpes zoster ophthalmicus. *Surv Ophthalmol*. 1992 May-Jun;36(6):395-410. Review. PubMed PMID: 1589855.
2. **Jantsch J, Schmidt B, Bardutzky J, Bogdan C, Eckardt KU, Raff U**. Lethal varicella-zoster virus reactivation without skin lesions following renal transplantation. *Nephrol Dial Transplant*. 2011 Jan;26(1):365-8. doi:10.1093/ndt/gfq542. Epub 2010 Sep 3. PubMed PMID: 20817667.
3. **Dagrosa AT, Collins LK, Chapman MS**. Atypical herpes zoster presentation in a healthy vaccinated pediatric patient. *Cutis*. 2017 Nov;100(5):303-304. PubMed PMID: 29232420.
4. **Takaoka Y, Miyachi Y, Yoshikawa Y, Tanioka M, Fujisawa A, Endo Y**. Bilateral disseminated herpes zoster in an immunocompetent host. *Dermatol Online J*. 2013 Feb 15;19(2):13. PubMed PMID: 23473283.
5. **Kantaria SM**. Bilateral asymmetrical herpes zoster. *Indian Dermatol Online J*. 2015 May-Jun;6(3):236. doi: 10.4103/2229-5178.156448. PubMed PMID: 26009733; PubMed Central PMCID: PMC4439767.
6. **Leung AK, Barankin B**. Bilateral symmetrical herpes zoster in an immunocompetent 15-year-old adolescent boy. *Case Rep Pediatr*. 2015;2015:121549. doi: 10.1155/2015/121549. Epub 2015 Jan 27. PubMed PMID: 25692062; PubMed Central PMCID: PMC4323070.
7. **Varney HR, Jamieson RC**. A bilateral herpes zoster. *JAMA*. 1910;55(5):372.
8. **Singh KG, Bajaj AK, Dwivedi NC, Merchery A**. Bilateral herpes zoster. *Indian J Dermatol Venereol Leprol*. 1993;59(2):90-2.
9. **Vijay A, Dalela G**. Herpes Zoster Duplex Bilateralis in Immuno-Competent Patients: Report of Two Cases. *J Clin Diagn Res*. 2015 Dec;9(12):WR01-3. doi:10.7860/JCDR/2015/ 15728.6957. Epub 2015 Dec 1. PubMed PMID: 26816979; PubMed Central PMCID: PMC4717711.
10. **Shepp DH, Dandliker PS, Meyers JD**. Treatment of varicella-zoster virus infection in severely immunocompromised patients. A randomized comparison of acyclovir and vidarabine. *N Engl J Med*. 1986 Jan 23;314(4):208-12. PubMed PMID: 3001523.
11. **Balfour HH Jr, Bean B, Laskin OL, Ambinder RF, Meyers JD, Wade JC, Zaia JA, Aeppli D, Kirk LE, Segreti AC, Keeney RE**. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med*. 1983 Jun 16;308(24):1448-53. PubMed PMID: 6343861.
12. **Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, Betts RF, Gershon AA, Haanpaa ML, McKendrick MW, Nurmikko TJ, Oaklander AL, Oxman MN, Pavan-Langston D, Petersen KL, Rowbotham MC, Schmader KE, Stacey BR, Tyring SK, van Wijck AJ, Wallace MS, Wassilew SW, Whitley RJ**. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007 Jan 1;44 Suppl 1:S1-26. Review. PubMed PMID: 17143845.

Submitted June 11, 2018