Beware the Unexpected Infection: Disseminated Varicella Zoster Virus Mimicking A Drug Eruption

Dina Adimora-Onwuka, MD1,2, and Mary Ann Kirkconnell Hall, MPH2

Abstract
Adverse cutaneous reactions to medications are not uncommon and may resemble viral infection and vice versa, complicating diagnosis. We describe the case of a 79-year-old male with cholangiocarcinoma with liver and presumed lung metastasis who presented with abdominal pain and was admitted with ileitis with partial small bowel obstruction. He had a widespread papulovesicular rash with hemorrhagic center, mostly on his face, chest, and back. The rash was initially thought to be a drug eruption, but was eventually diagnosed via dermatopathological examination as disseminated varicella zoster virus (VZV) infection. Steroid treatment was discontinued, and airborne precautions were initiated. Polymerase chain reaction for VZV was obtained and intravenous acyclovir treatment was begun. This case of VZV, initially suspected to be an adverse drug reaction, highlights the importance of early identification of a highly infectious lesion and the importance of early infection control measures, given the implications of exposure to VZV for health care personnel.

Keywords
varicella zoster, herpes zoster, drug eruption, exanthem, infection control

Background
Adverse cutaneous reactions to medications are not uncommon; they occur in as many as 2% to 3% of hospitalized patients.3 While most reactions are mild and self-limiting, they can be severe in &ge;2% of cases.4 Eruptions can take many forms, some of which mimic viral infections; thus, prompt differential diagnosis is needed to ensure that the medication is withdrawn, or treatment for infection is begun as soon as possible.5,7

One such viral illness is varicella zoster virus (VZV).8,9 VZV causes 2 main categories of illnesses: varicella (chicken pox) and herpes zoster (shingles).10-12 VZV causes an acute viremia with incubation period ranging from 8 to 21 days after exposure. VZV is often a clinical diagnosis because of its characteristic diffuse multistage vesicular rash.

Varicella rash presents as papules and within days progresses to grouped vesicles or bullae then becomes pustular. In immunocompromised patients or the elderly, the lesions can be hemorrhagic and severe.13,14 Rashes generally crust within 7 to 10 days in immunocompetent patients, but immunocompromised patients may develop new lesions more than a week after initial presentation. These lesions are infectious until the rashes have fully dried and crusted over.10-12,15

We describe a case in which the patient presented with what was initially thought to be a drug eruption, but was diagnosed via dermatopathological examination as disseminated VZV infection. In this case report, we identify the clinical features of VZV lesions and various laboratory tests used in its diagnosis, and note both infection control recommendations for hospitals for VZV and recommendations to establish immunity in health care personnel, including when and if titers should be checked.

Case Presentation
A 79-year-old gentleman presented with abdominal pain and was admitted with ileitis with partial small bowel obstruction (see Table 1, Case Timeline). He had an intraductal papillary neoplasm of the bile duct, a form of cholangiocarcinoma,
with liver and presumed lung metastasis. He had been on capecitabine, a pyrimidine analogue treatment, for 8 weeks prior to presentation. The patient also had a widespread papulovesicular rash with hemorrhagic center, mostly on his face, chest, and back, which started after his initial capecitabine treatment and progressed with 2 subsequent treatments. Hematologic studies did not initially suggest drug eruption or viral infection. The rash was initially suspected to be due to drug eruption; thus, capecitabine was discontinued and steroids were initiated. Dermatology was consulted. The lesions were biopsied and sent for histological staining and direct immunofluorescence (DIF). Differential diagnoses included paraneoplastic pemphigus, bullous pemphigoid, erythema multiforme (EM) spectrum lesions, and Stevens-Johnson syndrome (SJS). The slides were initially examined by general pathology with preliminary read of nonspecific findings with eosinophilia, seemingly supporting an adverse cutaneous reaction to capecitabine. Negative DIF excluded paraneoplastic pemphigus and bullous pemphigoid. Furthermore, the lesions were not consistent with SJS or EM spectrum rash. Additional dermatopathology review identified cytopathic effects on cells that were consistent with viral etiology: herpes simplex virus (HSV)/VZV. Steroid treatment was discontinued, and airborne precautions were initiated. Infectious disease was consulted and VZV PCR was obtained. The patient was started on intravenous acyclovir. The rash gradually resolved over several weeks. He followed up with his primary care physician, oncologist, and an infectious disease specialist. There were no observed cases of VZV spread to health care providers or their contacts.

**Discussion**

Capecitabine treatment is associated with adverse cutaneous reactions in the literature. As many as 50% of individuals receiving capecitabine chemotherapy experience hand-foot syndrome, and this medication has been associated with skin eruptions in case reports, though dermatological manifestations are usually present in a lichenoid and/or palmo-plantar distribution. Our patient presented with what was initially thought to be a drug eruption. Preliminary findings from his skin biopsy supported this diagnosis, but additional dermatopathological review detected disseminated VZV infection. Laboratory diagnosis for VZV is used when clinical presentation is uncertain or atypical. In these cases, PCR, direct fluorescent antibody (DFA), or enzyme-linked immunosorbent assay (ELISA) testing are used to confirm VZV infection. PCR testing is preferred as it can be used to test lesions of all stages and has a rapid turnaround time. PCR is also preferred as it can be used for noncutaneous specimens such as cerebrospinal fluid. DFA testing can be done on scrapings directly from infectious lesions. ELISA testing is used to determine susceptibility to infection and need for immunization. Viral culture can also be used to diagnose VZV, but is of low yield and requires a longer incubation period.

VZV is highly contagious because it is airborne; thus, infection control is key in health care facilities. Health care workers are at risk of exposure to VZV either via direct contact with infectious lesions or through airborne transmission; airborne precautions are thus advised.

Health care workers should be screened upon employment for immunity to VZV. Immunity is established by (1) 2 doses of varicella vaccine administered 4 to 8 weeks apart, or (2) documented previous diagnosis of varicella disease, or (3) laboratory evidence of immunity via evaluation of titers. Post immunization serology is not recommended after immunization of health care workers because commonly available commercial tests for VZV may not detect the lower antibody levels seen in vaccinated persons as compared with the higher antibody levels seen after natural infection.

This case of VZV, initially suspected to be an adverse drug reaction, highlights the importance of early identification of a highly infectious lesion. It also highlights...
the importance of early infection control measures and the implications of exposure to VZV for health care personnel. Such exposures can require up to 21 days of monitoring, which can be logistically difficult; thus, infection control measures aim to extend protection to the patient and their contact exposures, as well as to the health care team, their exposures, and their loved ones.

Acknowledgments
The authors wish to thank Dr. Gregory Cox and Dr. Kelli Hall for their support and assistance on this work. The authors also wish to acknowledge the Emory University Division of Hospital Medicine Open Access Publishing Fund for supporting dissemination of this work.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors received funding for the open access publication of this article from the Emory University Division of Hospital Medicine Open Access Publishing Fund.

Ethics Approval
Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent
Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD
Mary Ann Kirkconnell Hall https://orcid.org/0000-0002-4188-4768

References
1. Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol. 2001;137(6):765-770.
2. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA. 1986;256(24):3358-3363.
3. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigne R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. Allergy. 1997;52(4):388-393.
4. Hoetzenecker W, Nägeli M, Mehra ET, et al. Adverse cutaneous drug eruptions: current understanding. Semin Immunopathol. 2016;38(1):75-86.
5. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272-1285.
6. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. Am J Clin Dermatol. 2003;4(8):561-572.
7. Wu WH, Chu CY. Annular drug eruptions [published online ahead of print, 2021]. Clin Dermatol. doi:10.1016/j.clindermatol.2021.12.008.
8. Albrecht MA. Epidemiology of varicella-zoster virus infection: chickenpox. UpToDate. https://www.uptodate.com/contents/epidemiology-of-varicella-zoster-virus-infection-chickenpox. Published 2021. Accessed May 19, 2022.
9. Albrecht MA. Diagnosis of varicella-zoster virus infection. UpToDate. https://www.uptodate.com/contents/diagnosis-of-varicella-zoster-virus-infection. Published 2021. Accessed May 19, 2022.
10. Albrecht M, Levin M. Epidemiology, clinical manifestations, and diagnosis of herpes zoster. UpToDate. https://www.uptodate.com/contents/herpes-zoster-epidemiology-clinical-manifestations-and-diagnosis. Published 2021. Accessed May 19, 2022.
11. Dayan RR, Peleg R. Herpes zoster–typical and atypical presentations. Postgrad Med. 2017;129(6):567-571.
12. Khan ZZ. Varicella-zoster virus (VZV) clinical presentation. Medscape. https://emedicine.medscape.com/article/231927-clinical. Published 2021. Accessed May 19, 2022.
13. John AR, Canaday DH. Herpes zoster in the older adult. Infect Dis Clin North Am. 2017;31(4):811-826.
14. Tseng HF, Bruxvoort K, Ackerson B, et al. The epidemiology of herpes zoster in immunocompetent, unvaccinated adults ≥50 years old: incidence, complications, hospitalization, mortality, and recurrence. J Infect Dis. 2019;222(5):798-806.
15. Weber D. Prevention and control of varicella-zoster virus in hospitals. UpToDate. https://www.uptodate.com/contents/prevention-and-control-of-varicella-zoster-virus-in-hospitals. Published 2021. Accessed May 19, 2022.
16. Cobos GA, Nelson CA, Alsarheed A, et al. Capecitabine-related eruption mimicking dermatomyositis in 2 patients with metastatic breast cancer. JAMA Dermatol. 2020;156(1):103-104.
17. Miller KK, Gorcey L, McElhan BN. Chemo-medication induced hand-foot syndrome and nail changes: a review of clinical presentation, etiology, pathogenesis, and management. J Am Acad Dermatol. 2014;71(4):787-794.
18. Advani R, Arad D. Case Report: non-infectious causes of palmar plantar rashes, what to consider. F1000Res. 2018;7:46.
19. García-Lozano JA, Ocampo-Candiani J, González-Ramírez RA. Eruptive palmoplantar lesions induced by capecitabine: report of a case evaluated with dermoscopy. Cir Cir. 2019;87(S1):38-42.
20. Gehlhausen JR, Strausburg MB, Aouthmany M, Katona TM, Turner MJ. Capecitabine-induced lichenoid drug eruption: a case report. Dermatol Online J. 2017;23(2) 13030/qt75n8m2zq.
21. Hauge JS, Ilyshyn A. Lichenoid photosensitive eruption due to capecitabine chemotherapy for metastatic breast cancer. Clin Dermatol. 2020;38(1):102-103.
22. Peccherillo F, Pampena R, Giannetti L, Pellacani G, Longo C. Capecitabine-induced eruptive acral hyperpigmentation: clinical and dermoscopic evaluation of two cases. Dermatol Ther. 2019;32(3):e12853.
23. Shah RA, Bennett DD, Burkard ME. Photosensitive lichenoid skin reaction to capecitabine. BMC Cancer. 2017;17(1):866.
24. Tamer F, Yuksel ME. Generalised lichenoid drug eruption accompanied by hand-foot syndrome due to capecitabine. *Indian J Dermatol*. 2018;63(1):83-84.

25. Walker G, Lane N, Parekh P. Photosensitive lichenoid drug eruption to capecitabine. *J Am Acad Dermatol*. 2014;71(2):e52-3.

26. van Doorn L, Veelenturf S, Binkhorst L, Bins S, Mathijssen R. Capecitabine and the risk of fingerprint loss. *JAMA Oncol*. 2017;3(1):122-123.

27. Tognetti L, Fimiani M, Rubegni P. Benign dermoscopic parallel ridge pattern in plantar hyperpigmentation due to capecitabine. *Dermatol Pract Concept*. 2015;5(2):79-81.