

CASE REPORT

DISSEMINATED HERPES ZOSTER IN AN IMMUNOCOMPETENT PATIENT ON LONG-TERM CLOZAPINE: CASE REPORT

NIKHIL DAS¹, FARZANA HOQUE²

Abstract:

Disseminated herpes zoster is characterized by more than 20 herpetic lesions distributed across other body parts outside the affected dermatome. Disseminated herpes zoster occurs more frequently in immunocompromised patients and only a handful of case reports highlighted its occurrence in immunocompetent individuals. Clozapine use has been linked to decreased immune functioning, but no conclusive evidence to categorize clozapine as an immunosuppressive drug has been published. Here we report a case of a 65-year-old immunocompetent man on long-term clozapine who presented with vesicular lesions in a non-dermatomal distribution and was diagnosed to have disseminated zoster.

Keywords: Disseminated zoster; varicella-zoster virus; herpes zoster; clozapine.

Received: 11.08.2023

Accepted: 16.08.2023

DOI: <https://doi.org/10.3329/bjm.v34i3.68435>

Citation: Das N, Hoque F. Disseminated Herpes Zoster in an Immunocompetent Patient on Long-Term Clozapine: Case Report. *Bangladesh J Medicine* 2023; 34: 241-244.

Introduction:

Reactivation of varicella-zoster virus is known to cause herpes zoster commonly known as shingles. Herpes zoster typically presents as a painful, unilateral, vesicular eruption restricted to a single dermatome.¹ Disseminated herpes zoster is characterized by more than 20 herpetic lesions distributed across other body parts outside the affected dermatome. Dissemination occurs nearly exclusively in immunocompromised patients, but a handful of cases of disseminated zoster in immunocompetent individuals have been reported.²

Clozapine is a highly effective antipsychotic generally reserved for treatment-resistant schizophrenia. This is due to the potential for drug-induced agranulocytosis which requires regular blood count monitoring. The precise mechanism behind this serious adverse effect remains uncertain.³ Clozapine

use has been linked with attenuated immune functioning with studies showing an association with increased risk of pneumonia and tuberculosis,⁴ decreased immunoglobulins in patients taking clozapine compared to those taking other antipsychotics,^{5,6} and suppressed immune function through modulation of the production of multiple cytokines including IFN- α in CD4+ T-cells.^{7,8,9} Prolonged utilization of clozapine may heighten the propensity for immunosuppressive effects.¹⁰ The response in varicella reactivation has been shown to involve similar adaptive immune functions as those that are diminished with clozapine administration.¹¹ However, no prior literature to the authors' knowledge has implicated clozapine use with herpes zoster reactivation. Here we describe a case of disseminated varicella-zoster virus in an immunocompetent individual on long-term clozapine.

1. Saint Louis University School of Medicine, St. Louis, Missouri, USA.

2. Associate Professor of Medicine, Saint Louis University School of Medicine, St. Louis, Missouri, USA.

Address of Correspondence: Dr. Farzana Hoque, Associate Professor of Medicine, Saint Louis University School of Medicine, St. Louis, Missouri, USA. E-mail: farzанаhoquemd@gmail.com

Copyright: © 2023 Association of Physicians of Bangladesh

Case Report:

A 65-year-old deaf and nonverbal black male with a history of schizophrenia on clozapine for over 10 years, seizures, hypertension, history of multiple falls, and cervical myelopathy presented with falls and acute encephalopathy. A right subscapular and flank wound was noted during his admission, and the dermatology team was consulted. He was afebrile and denied any itching or pain associated with the skin lesions. A physical exam revealed a large, ulcerated plaque with irregular and hyperpigmented borders along with peripheral collarette scales on the right subscapular region (Figure 1).



Fig.-1: Large, ulcerated plaque with irregular and hyperpigmented borders along with peripheral collarette scales on the right subscapular region

Hyperpigmented papules with peripheral collarettes of scale, yellow crusting, and peripheral flaccid pseudovesicles were also seen along the right chest (Figure 2). Additionally, scattered vesicles on the left arm and lower legs were noted. Due to the nondermatomal distribution of lesions with more than 20 vesicles outside of the dermatome as well as the presence of intact vesicles, the patient was started on intravenous acyclovir at immunosuppressed dosage (10 mg/kg three times daily) for seven days based on clinical diagnosis. Clozapine levels were normal at 715 ng/mL and the complete blood count was negative for leukopenia. No biopsies of skin lesions were taken. Four days later the

patient's vesicles had crusted over, and he was transitioned to oral valacyclovir 1000 mg three times daily for the remainder of the seven-day course and was later discharged. At follow-up, his rash had resolved three months later, and he complained of postherpetic neuralgia.



Fig.-2: Hyperpigmented papules with peripheral collarettes of scale, yellow crusting, and peripheral flaccid pseudovesicles along the right chest

Discussion:

Disseminated zoster is a rare diagnosis in immunocompetent individuals. A total of 25 cases of disseminated herpes zoster in immunocompetent patients have been reported to date. A recent case review from 2022 detailed 22 prior case reports of disseminated herpes zoster.¹² Since that analysis in 2022 one additional patient has been reported.¹³ A study looking at hospital visits by patients in Canada prior to 2016 found 2 immunocompetent patients per million had disseminated zoster.¹⁴ A phase 3 trial of the recombinant subunit zoster vaccine in immunocompetent subjects found reduced rates of herpes zoster complications with none of the vaccinated individuals developing disseminated zoster and 0.042% of the unvaccinated individuals developing disseminated zoster.¹⁵ This patient received Zostavax (Zoster Vaccine Live; Merck) 14 years prior to presentation, but never received Shingrix (Recombinant Zoster Vaccine; GlaxoSmithKline) which was approved in 2017. However, the live vaccine only provides protection

against herpes zoster for 8 years and is less efficacious than the recombinant vaccine in preventing shingles.¹⁶

Immune function disturbances have been described in patients with schizophrenia¹⁷ as well as those with clozapine use.^{5,7,8,9} Larger doses of clozapine seem to have greater impacts on immune functioning⁸ with one review finding increased clozapine serum levels to be associated with infection.¹⁸ While this patient had normal clozapine levels, he had been receiving clozapine for over 10 years increasing the probability of immunosuppressive effects.¹⁰ This patient's clozapine use could have caused the dissemination of herpes zoster as he had no other clinically significant reason to be immunosuppressed.

Conclusion:

Disseminated varicella is well known to appear in immunocompromised individuals. However, disseminated herpes zoster has been reported to occur rarely in immunocompetent patients. This case report highlights the possibility of developing disseminated zoster in patients on long-term clozapine therapy. Clinicians should keep disseminated zoster in mind when examining non dermatomal skin lesions on an immunocompetent patient, especially in patients that are taking clozapine.

Conflicts of interest: None

Financial support: None

References:

- Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. *Neurology*. 1995 Dec;45(12 Suppl 8):S41-6. doi: 10.1212/wnl.45.12_suppl_8.s41. PMID: 8545018.
- Petrun B, Williams V, Brice S. Disseminated varicella-zoster virus in an immunocompetent adult. *Dermatol Online J*. 2015 Feb 22;21(3):13030/qt3cz2x99b. PMID: 25780980.
- Mijovic A, MacCabe JH. Clozapine-induced agranulocytosis. *Ann Hematol*. 2020 Nov;99(11):2477-2482. doi: 10.1007/s00277-020-04215-y. Epub 2020 Aug 20. PMID: 32815018; PMCID: PMC7536144.
- de Leon J, Ruan CJ, Verdoux H, Wang C. Clozapine is strongly associated with the risk of pneumonia and inflammation. *Gen Psychiatr*. 2020 Apr 16;33(2):e100183. doi: 10.1136/gpsych-2019-100183. PMID: 32420521; PMCID: PMC7199914.
- Lozano R, Marin R, Santacruz MJ, Pascual A. Selective Immunoglobulin M Deficiency Among Clozapine-Treated Patients: A Nested Case-Control Study. *Prim Care Companion CNS Disord*. 2015 Jul 2;17(4):10.4088/PCC.15m01782. doi: 10.4088/PCC.15m01782. PMID: 26693046; PMCID: PMC4664574.
- Ponsford M, Castle D, Tahir T, Robinson R, Wade W, Steven R, Bramhall K, Moody M, Carne E, Ford C, Farewell D, Williams P, El-Shanawany T, Jolles S. Clozapine is associated with secondary antibody deficiency. *Br J Psychiatry*. 2018 Sep 27;214(2):1-7. doi: 10.1192/bjp.2018.152. Epub ahead of print. PMID: 30259827; PMCID: PMC6429246.
- Chen ML, Tsai TC, Lin YY, Tsai YM, Wang LK, Lee MC, Tsai FM. Antipsychotic drugs suppress the AKT/NF- κ B pathway and regulate the differentiation of T-cell subsets. *Immunol Lett*. 2011 Oct 30;140(1-2):81-91. doi: 10.1016/j.imlet.2011.06.011. Epub 2011 Jul 6. PMID: 21763349.
- Song C, Lin Ah, Kenis G, Bosmans E, Maes M. Immunosuppressive effects of clozapine and haloperidol: enhanced production of the interleukin-1 receptor antagonist. *Schizophr Res*. 2000 Apr 7;42(2):157-64. doi: 10.1016/s0920-9964(99)00116-4. PMID: 10742653.
- Leykin I, Mayer R, Shinitzky M. Short and long-term immunosuppressive effects of clozapine and haloperidol. *Immunopharmacology*. 1997 Aug;37(1):75-86. doi: 10.1016/s0162-3109(97)00037-4. PMID: 9285246.
- Jeong SH, Kim YS. Challenges in Prescribing Clozapine in the Era of COVID-19: A Review Focused on Immunological Implications. *Clin Psychopharmacol Neurosci*. 2021 Aug 31;19(3):411-422. doi: 10.9758/cpn.2021.19.3.411. PMID: 34294611; PMCID: PMC8316651.
- Laing KJ, Ouwendijk WJD, Koelle DM, Verjans GMGM. Immunobiology of Varicella-Zoster Virus Infection. *J Infect Dis*. 2018 Sep 22;218(suppl_2):S68-S74. doi: 10.1093/infdis/jiy403. Erratum in: *J Infect Dis*. 2019 Apr 16;219(9):1514. PMID: 30247598; PMCID: PMC6151075.
- Moon YS, Cho WJ, Jung YS, Lee JS. Disseminated Zoster Involving the Whole Body in an Immunocompetent Patient Complaining of Left Leg Radiating Pain and Weakness: A Case Report and Literature Review. *Geriatr Orthop Surg Rehabil*. 2022 Aug 10;13:21514593221119619. doi: 10.1177/21514593221119619. PMID: 35983318; PMCID: PMC9379965.
- Alhayaza G, Al-Omair A, Almohanna HM. Varicella-Zoster Virus Encephalitis in an Immunocompetent Adult with Disseminated Cutaneous Herpes Zoster after Testosterone Booster Supplements: Case Report. *Case Rep Dermatol*. 2022 Jun 27;14(2):164-168. doi: 10.1159/000525252. PMID: 35950142; PMCID: PMC9294947.

14. Buchan SA, Daneman N, Wang J, Garber G, Wormsbecker AE, Wilson SE, Deeks SL. Incidence of Hospitalizations and Emergency Department Visits for Herpes Zoster in Immunocompromised and Immunocompetent Adults in Ontario, Canada, 2002-2016. *Clin Infect Dis*. 2020 Jun 24;71(1):22-29. doi: 10.1093/cid/ciz769. PMID: 31436814.
15. Kovac M, Lal H, Cunningham AL, Levin MJ, Johnson RW, Campora L, Volpi A, Heineman TC; ZOE-50/70 Study Group. Complications of herpes zoster in immunocompetent older adults: Incidence in vaccine and placebo groups in two large phase 3 trials. *Vaccine*. 2018 Mar 14;36(12):1537-1541. doi: 34590136; PMID: 29463421. PMCID: PMC8482024.10.1016/j.vaccine.2018.02.029. Epub 2018 Feb 17. PMID: 29463421.
16. Harbecke R, Cohen JI, Oxman MN. Herpes Zoster Vaccines. *J Infect Dis*. 2021 Sep 30;224(12 Suppl 2):S429-S442. doi: 10.1093/infdis/jiab387. PMID: 34590136; PMCID: PMC8482024.10.1016/j.vaccine.2018.02.029. Epub 2018 Feb 17. PMID: 29463421.
17. Zhang XY, Zhou DF, Cao LY, Zhang PY, Wu GY. Decreased production of interleukin-2 (IL-2), IL-2 secreting cells and CD4+ cells in medication-free patients with schizophrenia. *J Psychiatr Res*. 2002 Sep-Oct;36(5):331-6. doi: 10.1016/s0022-3956(02)00023-7. PMID: 12127601.
18. Clark SR, Warren NS, Kim G, Jankowiak D, Schubert KO, Kisely S, Forrester T, Baune BT, Siskind DJ. Elevated clozapine levels associated with infection: A systematic review. *Schizophr Res*. 2018 Feb;192:50-56. doi: 10.1016/j.schres.2017.03.045. Epub 2017 Apr 6. PMID: 28392207.