

# Varicella Zoster Meningitis in Immunocompetent Hosts: A Case Series and Review of the Literature

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## ABSTRACT

Meningitis caused by varicella zoster virus (VZV) infection is uncommon in immunocompetent patients. We report 3 cases of VZV meningitis with rash in immunocompetent adults from a single academic institution over a 1-year period. The low prevalence of VZV meningitis in this population is attributed to lack of early recognition or underreporting. We highlight the importance of considering VZV as a possible cause of meningitis even in previously healthy young individuals.

## INTRODUCTION

Meningitis is characterized by inflammation of the layers of tissue encasing the brain and spinal cord and is primarily caused by viral infections. Varicella zoster virus (VZV) is one of the common causes of viral meningitis and is rare in otherwise healthy individuals.<sup>1</sup> Following a primary VZV infection, which is often asymptomatic, viral particles may remain latent in cranial nerves, dorsal roots, and autonomic ganglia and can reactivate when cellular immunity is compromised. Reactivation of VZV, known as herpes zoster (HZ), typically presents as painful vesicles in a dermatomal distribution that can be associated with a variety of complications.<sup>2</sup> Risk factors for reactivation include any condition that weakens cell-mediated immunity such as trauma, advanced age, malignancy, chronic kidney or lung disease, and immunosuppression.<sup>3</sup> Acute central nervous system infection or reactivation of VZV in young immunocompetent adults is unusual, and only a few cases have been reported in literature to

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date. This case series describes 2 immunocompetent men and 1 immunocompetent woman who had VZV meningitis associated with rash.

## CASE 1

A 22-year-old man with a past medical history significant for primary varicella as an infant and mononucleosis in 8th grade presented with headache, fever, photophobia, and painful vesicular rash over the scalp. Vital signs were within normal limits except for a low-grade fever of 100.7°F. Physical exam was significant for generalized anterior cervical lymphadenopathy and a 1.5 cm x 3 cm left-sided retro-auricular lymph node. Nuchal rigidity with pain was noted; Brudzinski's and Kernig's signs were negative. The computed tomography (CT) scan of the brain did not show any temporal lobe leptomeningeal enhancement. Cerebrospinal fluid (CSF) analysis was suggestive of possible viral etiology with leukocyte count of 6 cells/μL, 94% lymphocytes, protein of 50 mg/dL, and normal glucose of 60 mg/dL. Subsequent polymerase chain reaction (PCR) analysis of the CSF was negative for herpes simplex virus 1 and 2, cytomegalovirus, enterovirus, and VZV. A skin biopsy of the lesions ultimately returned positive for VZV. Acyclovir and supportive treatment were started due to concern for viral meningitis. By the third day of admission, the patient's pain, nausea, vomiting, photophobia, neck stiffness, and fever improved, and he was subsequently discharged on intravenous (IV) acyclovir 10 mg/kg q8hr for total of 14 days. Upon follow-up, he had improved significantly and reported mild residual headache.

## CASE 2

A 29-year-old man with no past medical history presented to the hospital with a rash over the left side of his scalp, eye swelling, photophobia, headaches, and neck stiffness. He had previously presented to the same hospital a day earlier with a 1-day-old rash

spreading from the left temporal scalp and periorbital skin across to his nasal bridge (Figure), for which the ophthalmologic service diagnosed him with herpes zoster ophthalmicus without corneal or intraocular involvement and discharged him on valacyclovir 1g orally 3 times per day. He was later discovered to be unimmunized for varicella by the Wisconsin Immunization Registry, although his mother stated otherwise. The patient had a history of 2 male partners in the past 5 years but was not currently sexually active and denied any history of sexually transmitted infections. Upon presentation, his vitals were within normal limits and physical exam was remarkable for a confluent vesicular rash with lesions in various stages of healing with crusting, as described above. His left eyelid was edematous (Figure) and the left conjunctiva injected; extraocular muscles and pupils were uninvolved. Brudzinkis and Kernig's signs demonstrated characteristic neck stiffness; the Hutchinson's sign was negative, however. CSF analysis was suggestive of aseptic meningitis with leukocytes of 101/uL, monocytes 61%, glucose and protein within normal limits. Multiplex PCR CSF analysis for common infectious pathogens was positive for VZV. Serum HIV screen was negative. The patient was treated with IV acyclovir 10 mg/kg 8 hourly with complete resolution of symptoms during a week of inpatient admission, and he was discharged with another 7 days of oral valacyclovir.

### CASE 3

A 60-year-old woman with a past medical history significant for diabetes and schizoaffective disorder presented from a behavioral health facility with altered mental status and fever up to 102°F following a fall. Upon presentation, her vital signs were stable and initial lab workup was significant for a lactic acid of 2.8 mmol/L and a positive urinalysis. The CT scan of head was negative for acute changes. She initially was given ceftriaxone for a suspected urinary tract infection and was discharged the next day with a 5-day course of antibiotic. Two days following discharge, she presented to the emergency department with concerns from the facility staff for worsening lethargy and weakness. Physical exam was limited due to the patient's uncooperative state, but vesicles with an erythematous base and punctate healing lesions were noted over her right shoulder. CSF analysis revealed a white blood cell count of 106 cells/ $\mu$ L, 92% lymphocytes, 7% monocytes, protein of 71 mg dl, and glucose of 90 mg/dl. Positive VZV nucleic acid amplification test on CSF PCR analysis confirmed the diagnosis of VZV reactivation complicated by meningitis. She was started on 10 mg/kg IV acyclovir q8h. Once the lesions crusted, her weakness improved and she returned to her baseline mental state, her antiviral was transitioned to oral valacyclovir and she was discharged back to her mental health facility.

### DISCUSSION

The incidence of HZ increases with age with an estimated 2.5 cases per 1,000 for the ages 21 to 50 years and 10.1 per 1,000

**Figure.** Herpes Zoster Rash on Periorbital Skin and Nasal Bridge of Left Eye With Eyelid Edema



Photo consent obtained from patient. Parts of both eyes have been blackened to protect identity.

for those over 80 years.<sup>4</sup> While enteroviruses are the major causative agents, VZV accounts for 2.5% to 8% of cases of aseptic meningitis.<sup>5,6</sup> The exact pathophysiology of VZV meningitis is unknown. It is a rare disease that predominantly affects immunocompromised people, such as the elderly and solid organ transplant recipients. There are only a few reported cases of VZV meningitis in immunocompetent hosts (Table).<sup>4,7-34</sup> Both male sex and a craniocervical dermatomal distribution of the HZ rash are risk factors for the development of aseptic meningitis caused by VZV (30) as seen in 2 of our cases. However, in the majority of patients with VZV meningitis presenting with a dermatomal rash, the meningitis symptoms arose, on average, 6 days before the rash appeared, making rash an unreliable clinical finding to substantiate diagnosis as shown by a retrospective review of data over a 3-year period.<sup>35</sup>

Despite antivirals being the mainstay therapy for VZV meningitis, there is no published data supporting a change in the disease course with the use of antivirals such as acyclovir. One study found that patients receiving IV acyclovir remained hospitalized longer than those not receiving acyclovir; however, 3 of the 4 patients in this study were over 70 years old and other comorbidities likely contributed to their prolonged hospitalization.<sup>35</sup> Early initiation of antivirals may aid in preventing long term sequelae. Symptomatic management through hydration, anti-nausea medication, pain control, antipyretics, and anti-inflammatory medications remain the mainstay of treatment for uncomplicated cases of VZV meningitis in immunocompetent patients. The use of steroids in viral meningitis is controversial because of the resulting delayed immune response and clearance and is therefore reserved only for patients with evidence of increased intracranial pressure.<sup>36</sup> Further studies are needed to determine the efficacy and safety of concurrent steroids and antiviral therapy administration.

**Table.** Available Case Report/Series of Varicella Zoster Meningitis in Immunocompetent Patients, 1997-2018<sup>a</sup>

First Author, Year	Sex	Age (years)	Rash	Ref No.
Moriuchi, 1997	M	37	P	7
Hartzell, 2006	M	21	P	8
Pirounaki, 2007	M	27	P	9
Haargaard, 2008	F	64	P	10
Frantzidou, 2008	F, M	15, 72	NA	11
Mpaka, 2008	M	66	A	12
Leahy, 2008	M	14	A	13
Habib, 2009	F	26	A	14
Iyer, 2009	M	9	P	15
Pena, 2009	M	11	P	16
Spiegel, 2010	F	14	A	17
Klein, 2010	F	53	A	18
Han, 2011	M	7	P	19
Kangath, 2013	F	30	P	5
Mantero, 2013	F	17	A	20
Goyal, 2013	M	27	P	21
Esposito, 2013	M	14	P	22
El-Safadi, 2014	M	39	A	23
Pasedag, 2014	M	18	A	24
Sanguankeo, 2015	M	51	P	25
Abe, 2015	M	57	A	26
Ibrahim, 2015	F	15	A	27
Ganesan, 2016	F	70	P	28
Itoh, 2017	M, M	12, 12	P	29
Kim, 2017	16 M, 8 F	mean age 51.1	P	30
Gnoni, 2018	F	29	P	31
Suri, 2018	F	24	A	32
Spernovasilis, 2018	M	36	A	33
Khaliq, 2018	M	28	P	34

Abbreviations: Ref No., reference number; M, male; F, female; P, present; A, absent; NA, information not available.

<sup>a</sup>As found in the literature (PubMed-indexed).

This case series presents 2 young, immunocompetent men in their 20s and a 60-year-old immunocompetent woman who developed aseptic meningitis from the reactivation of HZ. Our first patient developed varicella in infancy, whereas the second patient is, to our knowledge, the first reported case of an unimmunized individual who developed VZV meningitis. The exact mechanism of illness in the second case is unknown; however, it illustrates an example where a patient was infected without the expected immunologic priming expected with either varicella vaccination or primary infection between the ages of 12 months and 6 years. Our third case demonstrates VZV meningitis in an immunocompetent patient with a HZ rash that started after meningitis symptoms began. This patient's immunization status and previous exposure could not be verified due to lack of records and cooperation by patient. All 3 cases recovered fully with resolution of symptoms and without focal neurological deficits.

In our first case, CSF VZV PCR was negative, but CSF analysis did support aseptic meningitis. Biopsy of rash is not performed

routinely but, given the clinical presentation of meningitis and negative CSF PCR, we did obtain biopsy of scalp rash that supported our presumptive diagnosis of viral meningitis. Although PCR for VZV in the CSF is a useful confirmatory test with 95% specificity, it only has 30% sensitivity, which limits its reliability.<sup>37,38</sup> Based on our findings, we treated the patient appropriately with acyclovir and he had clinical improvement. This unusual presentation makes our case unique.

While these cases are not necessarily novel, the occurrence of 3 cases at our institution in immunocompetent patients suggests that the prevalence of VZV meningitis might be higher than what has been reported previously and highlights the variations in their clinical presentations. Whether VZV meningitis is simply under-reported or misdiagnosed, there clearly exists a dearth of evidence in terms of management of VZV meningitis and further research in this critical area will fulfill this unmet need. While there is no concrete evidence that antivirals reduce mortality or changes disease outcomes in VZV meningitis, timely diagnosis is prudent to shorten length of hospital stay and prevent long-term sequelae associated with the disease.

## CONCLUSION

Central nervous system involvement is a relatively uncommon complication following a VZV infection. Neurologic involvement is a life-threatening sequela and should be assessed early to facilitate prompt and appropriate treatment. VZV meningitis is a rare complication of varicella infection; the low prevalence reported likely suggests a lack of early recognition or reporting. The cases presented here highlight the need for more research to establish standard practice guidelines for the management of VZ meningitis.

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## REFERENCES

- Centers for Disease Control and Prevention. Viral meningitis. Accessed June 4, 2019. <https://www.cdc.gov/meningitis/viral.html>
- Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med.* 2000;342(9):635-645. doi:10.1056/NEJM200003023420906
- Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. *Arch Intern Med.* 1997;157(11):1209-1213. doi:10.1001/archinte.1997.00440320105010
- Kangath RV, Lindeman TE, Brust K. Herpes zoster as a cause of viral meningitis in immunocompetent patients. *BMJ Case Rep.* 2013;2013:bcr2012007575. doi:10.1136/bcr-2012-007575
- Takehisa S, Shiga Y, Himeno T, et al. Clinical, epidemiological and etiological studies of adult aseptic meningitis: report of 11 cases with varicella zoster virus meningitis. *Rinsho Shinkeigaku.* 2017;57(9):492-498. doi:10.5692/clinicalneuro.001054
- Kupila L, Vuorinen T, Vainionpää R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. *Neurology.* 2006;66(1):75-80. doi:10.1212/01.wnl.0000191407.81333.00

7. Moriuchi H, Moriuchi M, Sun CC, Trucksis M. Disseminated cutaneous zoster and aseptic meningitis in a previously healthy patient. *J Infect.* 1997;35(2):183-185. doi:10.1016/s0163-4453(97)91842-9
8. Hartzell JD, Aronson NE, Nagaraja S, Whitman T, Hawkes CA, Wortmann G. Varicella zoster virus meningitis complicating sodium stibogluconate treatment for cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2006;74(4):591-592.
9. Pirounaki M, Liatsos G, Elefsiniotis I, Skounakis M, Moulakakis A. Unusual onset of varicella zoster reactivation with meningoencephalitis, followed by rhabdomyolysis and renal failure in a young, immunocompetent patient. *Scand J Infect Dis.* 2007;39(1):90-93. doi:10.1080/00365540600798809
10. Haargaard B, Lund-Andersen H, Milea D. Central nervous system involvement after herpes zoster ophthalmicus. *Acta Ophthalmol.* 2008;86(7):806-809. doi:10.1111/j.1600-0420.2007.01129.x
11. Frantzidou F, Kamaria F, Dumaidi K, Skoura L, Antoniadis A, Papa A. Aseptic meningitis and encephalitis because of herpesviruses and enteroviruses in an immunocompetent adult population. *Eur J Neurol.* 2008;15(9):995-997. doi:10.1111/j.1468-1331.2008.02233.x
12. Mpaka M, Karantanas AH, Zakyntinos E. Atypical presentation of varicella-zoster virus encephalitis in an immunocompetent adult. *Heart Lung.* 2008;37(1):61-66. doi:10.1016/j.hrtlng.2007.02.009
13. Leahy TR, Webb DW, Hoey H, Butler KM. Varicella zoster virus associated acute aseptic meningitis without exanthem in an immunocompetent 14-year-old boy. *Pediatr Infect Dis J.* 2008;27(4):362-363. doi:10.1097/INF.0b013e318160ee11
14. Habib AA, Gilden D, Schmid DS, Safdieh JE. Varicella zoster virus meningitis with hypoglycorrhachia in the absence of rash in an immunocompetent woman. *J Neurovirol.* 2009;15(2):206-208. doi:10.1080/13550280902725550
15. Iyer S, Mittal MK, Hodinka RL. Herpes zoster and meningitis resulting from reactivation of varicella vaccine virus in an immunocompetent child. *Ann Emerg Med.* 2009;53(6):792-795. doi:10.1016/j.annemergmed.2008.10.023
16. Peña JA, Pirics ML, DiCaprio HS, et al. Varicella reactivation presenting as shingles and aseptic meningitis in an immunocompetent 11-year-old boy. *Clin Pediatr (Phila).* 2009;48(4):435-437. doi:10.1177/0009922808329748
17. Spiegel R, Miron D, Lumelsky D, Horovitz Y. Severe meningoencephalitis due to late reactivation of varicella-zoster virus in an immunocompetent child. *J Child Neurol.* 2010;25(1):87-90. doi:10.1177/0883073809336296
18. Klein NC, McDermott B, Cunha BA. Varicella-zoster virus meningoencephalitis in an immunocompetent patient without a rash. *Scand J Infect Dis.* 2010;42(8):631-633. doi:10.3109/00365540903510716
19. Han JY, Hanson DC, Way SS. Herpes zoster and meningitis due to reactivation of varicella vaccine virus in an immunocompetent child. *Pediatr Infect Dis J.* 2011;30(3):266-268. doi:10.1097/INF.0b013e3181f63cf9
20. Mantero V, De Toni Franceschini L, Lillia N, Guccione A, Santilli I, Agostoni E. Varicella-zoster meningoencephaloradiculoneuropathy in an immunocompetent young woman. *J Clin Virol.* 2013;57(4):361-362. doi:10.1016/j.jcv.2013.04.006
21. Goyal H, Thakkar N, Bagheri F, Srivastava S. Herpes zoster meningitis with multidermatomal rash in an immunocompetent patient. *Am J Emerg Med.* 2013;31(11):1622.e1-e2. doi:10.1016/j.ajem.2013.06.021
22. Esposito S, Bosis S, Pinzani R, Morlacchi L, Senatore L, Principi N. A case of meningitis due to varicella zoster virus reactivation in an immunocompetent child. *Ital J Pediatr.* 2013;39:72. doi:10.1186/1824-7288-39-72
23. El-Safadi L, Arnglim N, Amin FM. Effect of acyclovir and steroid in a young immunocompetent male with herpes zoster myelitis. *Ugeskr Laeger.* 2014;176(25A):V11120681.
24. Pasedag T, Weissenborn K, Wurster U, Ganzenmueller T, Stangel M, Skripuletz T. Varicella zoster virus meningitis in a young immunocompetent adult without rash: a misleading clinical presentation. *Case Rep Neurol Med.* 2014;2014:686218. doi:10.1155/2014/686218
25. Sanguankeo A, Upala S, Sornprom S, Thamcharoen N. Varicella-zoster meningitis with a late-onset of skin eruption. *BMJ Case Rep.* 2015;2015:bcr2014208056. doi:10.1136/bcr-2014-208056
26. Abe M, Araoka H, Kimura M, Yoneyama A. Varicella zoster virus meningoencephalitis presenting with Elsberg syndrome without a rash in an immunocompetent patient. *Intern Med.* 2015;54(16):2065-2067. doi:10.2169/internalmedicine.54.4341
27. Ibrahim W, Elzouki AN, Husain A, Osman L. Varicella zoster aseptic meningitis: report of an atypical case and literature review. *Am J Case Rep.* 2015;16:594-597. doi:10.12659/AJCR.894045
28. Ganesan V, Bandyopadhyay D, Kar SS, Choudhury C, Choudhary V. Herpes zoster infection involving mandibular division of trigeminal nerve and Ramsay Hunt syndrome with meningitis in an immunocompetent patient: a rare association. *J Clin Diagn Res.* 2016;10(6):OD05-07. doi:10.7860/JCDR/2016/19862.7935
29. Itoh N, Motokura K, Kumakura A, Hata D, Hata A. Herpes zoster meningitis in immunocompetent children: two case reports and a literature review. *Pediatr Int.* 2017;59(10):1116-1118. doi:10.1111/ped.13362
30. Kim SH, Choi SM, Kim BC, et al. Risk factors for aseptic meningitis in herpes zoster patients. *Ann Dermatol.* 2017;29(3):283-287. doi:10.5021/ad.2017.29.3.283
31. Gnoni M, Zaheer K, Vasser MM, et al. Varicella zoster aseptic meningitis: report of an atypical case in an immunocompetent patient treated with oral valacyclovir. *IDCases.* 2018;13:e00446. doi:10.1016/j.idcr.2018.e00446
32. Suri V, Mendiratta L, Chatterjee S, Sardana R, Butta H. Unusual presentation of varicella zoster virus meningitis - role of molecular rapid diagnostics in diagnosis and antimicrobial stewardship. *Ann Indian Acad Neurol.* 2018;21(2):168-169. doi:10.4103/aian.AIAN\_438\_17
33. Spernovasilis N, Milioni A, Gialamas I, Kokorakis E, Fanti G. Varicella-zoster virus meningitis with hypoglycorrhachia in a young immunocompetent adult without rash: a case report and literature review. *IDCases.* 2018;12:104-106. doi:10.1016/j.idcr.2018.04.008
34. Khaliq MF, Kochar T, John M. Varicella zoster meningitis: an atypical case of zoster reactivation in immunocompetent young adult. *BMJ Case Rep.* 2018;2018:bcr2017223257. doi:10.1136/bcr-2017-223257
35. Ihekwa UK, Kudesia G, McKendrick MW. Clinical features of viral meningitis in adults: significant differences in cerebrospinal fluid findings among herpes simplex virus, varicella zoster virus, and enterovirus infections. *Clin Infect Dis.* 2008;47(6):783-789. doi:10.1086/591129
36. Fitch MT, van de Beek D. Drug insight: steroids in CNS infectious diseases--new indications for an old therapy. *Nat Clin Pract Neurol.* 2008;4(2):97-104. doi:10.1038/ncpneu0713
37. Nagel MA, Gilden D. Update on varicella zoster virus vasculopathy. *Curr Infect Dis Rep.* 2014;16(6):407. doi:10.1007/s11908-014-0407-z
38. Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology.* 2008;70(11):853-860. doi:10.1212/01.wnl.0000304747.38502.e8.

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