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CASE SERIES

Atypical Bilobed Lymphocytes in CSF: Diagnostic Insights into Varicella Zoster Virus Meningitis and Herpes Zoster with Temporal Presentations

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Background: Varicella-zoster virus (VZV) is a known cause of viral meningitis, which can occur with or without the hallmark vesicular rash. While atypical lymphocytes are commonly described in peripheral blood during primary VZV infection, their presence in cerebrospinal fluid (CSF) during VZV reactivation is rarely reported.

Case Presentation: We describe two cases of VZV meningitis in immunocompromised young adults with atypical lymphocytes identified in the CSF. The first case involved a 19-year-old man with HIV who presented with meningitis symptoms, followed by the appearance of a dermatomal rash three days after initiation of acyclovir, consistent with herpes zoster. The second case involved a 21-year-old woman with systemic lupus erythematosus who presented with a vesicular rash and subsequent headache. In both cases, CSF analysis revealed mononuclear pleocytosis, mildly elevated protein, and the presence of bilobed or binucleated monocytoid lymphocytes on Wright's stain. CSF polymerase chain reaction confirmed VZV infection, and both patients recovered fully following intravenous acyclovir treatment.

Conclusion: These cases highlight the diagnostic value of identifying atypical lymphocytes distinct from Mollaret's cells—specifically bilobed or binucleated monocytoid lymphocytes in CSF cytology. Recognizing these distinct morphological features can aid in differentiating VZV meningitis from other viral etiologies. Although previously associated with primary VZV infection, such cytological findings may also occur in reactivation and should prompt consideration of VZV as an etiology, even in the absence of cutaneous lesions. Early recognition facilitates timely antiviral therapy and favorable clinical outcomes.

Keywords: atypical lymphocytes, CSF cytology, herpes zoster, meningitis, varicella zoster virus, viral reactivation

Introduction

Varicella-zoster virus (VZV) is a double-stranded DNA virus in the order *Herpesvirales*, also known as human alphaherpesvirus 3. Varicella zoster virus is distinct in its ability to persist latently within the neurons of sensory ganglia following a primary infection. In humans, this pathogen drives two primary clinical conditions: the initial acute presentation known as chickenpox (varicella), and a later reactivation known as shingles or herpes zoster (HZ).[1]

Unlike the generally mild nature of the primary infection, HZ typically emerges decades later and is often associated with significant morbidity. The clinical course often begins with a prodromal phase two to three days before any dermatological signs; symptoms include systemic fatigue, headache, and fever, alongside localized sensations of burning or itching.[2] When the active phase begins, a painful rash erupts along the specific dermatome. This can severely impact quality of life, particularly for the estimated 20% of patients who develop post-herpetic neuralgia (PHN), a chronic pain condition that persists long after the rash clears.[2]

While VZV commonly causes chickenpox and herpes zoster, it can also reactivate in the form of encephalitis or meningitis, particularly in immunocompromised individuals. VZV meningitis is an entity that can present as acute meningitis without cutaneous lesions, even in immunocompetent adults, making diagnosis challenging. Prompt

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identification of the viral etiology is essential to initiate empirical antiviral therapy, as delayed treatment carries significant morbidity. While Mollaret's cells are a well-established cytological clue for Herpes Simplex Virus (HSV) meningitis, specific cytological clue for VZV are less defined; to date, atypical lymphocytes in VZV have been reported once.[3] Herein, we describe two cases of VZV meningitis in immunocompromised young adults with atypical lymphocytes identified in the cerebrospinal fluid, presenting in temporal relationship with herpes zoster.

Case Presentation 1

Patient History and Clinical Presentation

A 19-year-old man, diagnosed with HIV infection 5 months prior (naïve CD4 count 315 cells/μL, 14%), presented to the emergency department with a 1-day history of diffuse headache and retro-orbital pain. He had been on combined antiretroviral therapy (cART) with tenofovir disoproxil fumarate/lamivudine/dolutegravir for 4 months, with good compliance, and viral load testing scheduled in the next 2 months. His history included childhood chickenpox, and he had not received the varicella-zoster virus vaccination. Apart from his HIV infection, the patient had no other significant comorbidities, history of opportunistic infections, or recent exposure to other immunosuppressive medications. On examination, he was febrile but showed no signs of meningism, and his neurological exam was normal.

Laboratory Findings

Laboratory investigations were unremarkable except for mild leukocytosis, with a white blood cell count of 11,140 cells/mm^3 (neutrophils 59%, lymphocytes 32.9%, with no atypical lymphocytes). Lumbar puncture revealed a slightly elevated opening pressure of 21 cmH_2O, and cerebrospinal fluid (CSF) analysis showed a white blood cell count of 680 per cubic millimeter, with 95% mononuclear cells. The CSF protein level was slightly elevated at 51 mg/dL, and the CSF/serum glucose ratio was 0.61. CSF Wright's stain revealed mostly lymphocytes, with a few atypical monocytoid lymphocytes that had bilobed nuclei (black arrowhead) (Figure 1). Routine laboratory differential counts in our setting report atypical lymphocytes qualitatively rather than as a specific percentage. Upon manual review, 1 atypical lymphocyte was observed per 20 oil immersion fields (OF).

Imaging Findings

A magnetic resonance imaging (MRI) of the brain with contrast revealed no abnormalities.

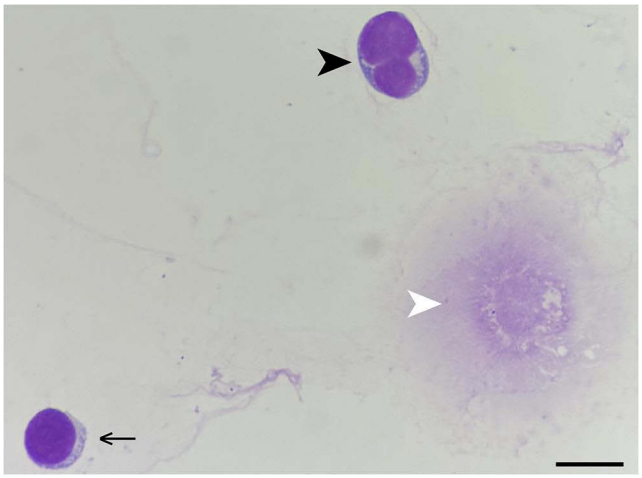

Figure 1 CSF Wright's stain revealed atypical bilobed or binucleated monocytoid lymphocytes (black arrowhead). In the figure, a white arrowhead points to degenerated lymphocyte, and a black arrow points to a normal lymphocyte. The black scale bar indicates 10 μm.

Treatment and Outcome

Empiric therapy for bacterial meningitis was initiated after the lumbar puncture, with ceftriaxone 2 grams intravenously, supplemented by ampicillin to cover *L. monocytogenes*. However, based on the CSF profile results, acyclovir at a dose of 10 mg per kilogram of body weight every 8 hours was started for presumed herpes simplex virus meningitis, and the antibacterial therapy was discontinued. CSF polymerase chain reaction (PCR) was positive for varicella-zoster virus (VZV) at a cycle threshold (Ct) value of 25 and negative for other human herpesviruses. Bacterial and fungal cultures were negative, and serum and CSF cryptococcal antigen tests were negative.

The patient had a resolution of his fever and headache after 2 days of intravenous acyclovir. However, on the third day of treatment, he developed subtle vesicular lesions localized to his right forearm, corresponding to the right T1 dermatome. The lesions consisted of no more than six vesiculopapular eruptions on an erythematous base. Unfortunately, clinical images were not obtained at the time of rash development. The cutaneous lesions regressed within 3 days after their onset.

The final diagnosis was VZV meningitis preceding herpes zoster. After completing 14 days of acyclovir, the patient was discharged without complications. He remained free of neurological symptoms and sequelae at the 1-month follow-up.

Case Presentation 2

Patient History and Clinical Presentation

A 21-year-old female with a history of systemic lupus erythematosus (SLE), currently receiving hydroxychloroquine weekly and prednisolone 5 mg daily, developed a painful vesicular rash over the left T9–T10 dermatomes (Figure 2). Regarding prior VZV exposure, the patient could not recall a history of primary varicella infection (chickenpox). Her vaccination status was uncertain; the varicella vaccine is not included in Thailand's national Expanded Program on Immunization (EPI), and her family could not recall if she had received it privately.

One day after rash onset, she was admitted and initiated on acyclovir for herpes zoster. By the third day, she developed a diffuse headache without neck stiffness. On examination, erythematous vesicular lesions were observed beyond the T9–T10 dermatomes (Figure 2), with 10 discrete lesions scattered across both arms, legs, and face. Kernig's sign was negative, and the rest of the physical examination was unremarkable.

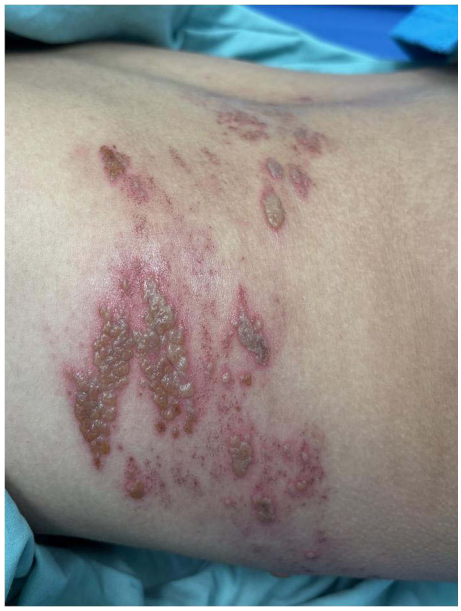

Figure 2 Classic papulovesicular rash on an erythematous base distributed along the T9–T10 dermatomes.

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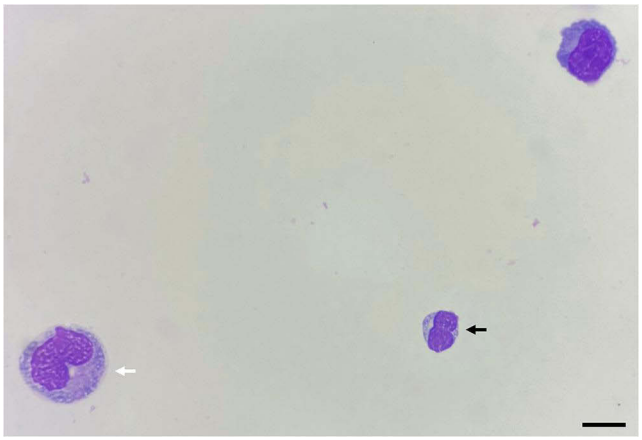

Figure 3 CSF Wright's stain revealed atypical binucleated monocytoid lymphocyte (black arrow). A larger monocyte is indicated by a white arrow. The black scale bar indicates 10 μm.

Laboratory Findings

Cerebrospinal fluid (CSF) analysis revealed a mildly elevated opening pressure of 27 cmH_2O. CSF contained 25 white blood cells/μL (95% mononuclear), no red blood cells, protein of 55 mg/dL, and glucose of 53 mg/dL (serum glucose 100 mg/dL). CSF Wright's stain showed atypical bilobed lymphocytes (Figure 3). CSF polymerase chain reaction (PCR) was positive for varicella-zoster virus (VZV) with a cycle threshold (Ct) value of 30 and negative for other human herpesviruses. Bacterial and fungal cultures, as well as serum and CSF cryptococcal antigens, were negative. Upon manual review, 1 atypical lymphocyte was observed per 30–40 OF.

Imaging Findings

No imaging studies were performed.

Treatment and Outcome

A diagnosis of disseminated herpes zoster and VZV meningitis was made. She was treated with intravenous acyclovir for 14 days. At three months of follow-up, all rashes and symptoms had resolved without complications. She remained on acyclovir secondary prophylaxis. The time course for each case is presented in Figure 4.

Discussion

VZV meningitis is an under-recognized cause of viral meningitis that can affect both immunocompromised and immunocompetent individuals.[4] With the advancement of molecular techniques, an increase in case reports of VZV meningitis in immunocompetent individuals has been observed, implicating it as the third most common cause of viral meningitis in adults.[4–6] Its manifestations range from clinically acute meningitis, with or without cutaneous lesions, to subclinical CSF pleocytosis associated with herpes zoster—the latter being more frequently observed.[7,8] Hence, the diagnosis of VZV meningitis in most cases was established based on a constellation of clinical meningitis with cutaneous manifestation and molecular findings in the CSF. It is noteworthy that in up to 40% of cases, isolated meningitis without herpes zoster has been reported in immunocompetent individuals, with 33% of these cases presenting with meningitis prior to the appearance of cutaneous lesions.[6,7] Therefore, diagnosing VZV meningitis without cutaneous manifestations presents a significant challenge. In these scenarios, while CSF lymphocytic pleocytosis and elevated protein provide initial clues, PCR confirmation remains essential. Outcomes of VZV meningitis after treatment with effective antiviral therapy are generally favorable, though minor neurological sequelae, such as headache, vertigo, and concentration difficulties, have been reported in up to 50% of cases at one month.[7] However, recent case series in immunocompetent adults have shown uneventful recoveries.[7,8] Mortality has not been reported with isolated VZV meningitis, in contrast to VZV encephalitis.[3,5,9,10]

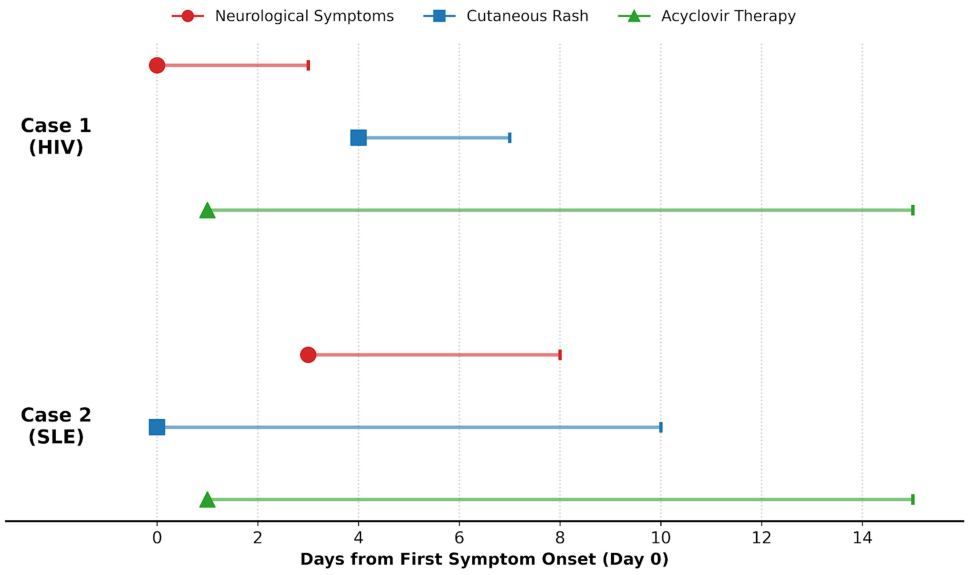

Figure 4 Temporal relationship between neurological symptoms and cutaneous eruption. The timeline illustrates the sequence of clinical events for Case 1 (top) and Case 2 (bottom). The x-axis represents days relative to the onset of the first reported symptom (Day 0). Case 1 demonstrates neurological symptoms (headache and retro-orbital pain) preceding the vesicular rash by 4 days. Conversely, Case 2 demonstrates the onset of vesicular rash 3 days prior to the development of neurological symptoms. Colored markers indicate symptom onset, initiation of acyclovir therapy, and subsequent resolution.

Prompted by our observations, we reviewed the existing literature to characterize the relationship between atypical lymphocytes and VZV infection. To date, only one case report has documented atypical lymphocytes in the CSF during VZV meningitis.[3] No morphological comparison of the atypical lymphocytes in that report was made with those observed in our case. Binucleated or bilobed lymphocytes have been reported in chronic lymphocytic leukemia and in non-neoplastic conditions such as polyclonal B-cell lymphocytosis with binucleated lymphocytes (PPBL).[11,12] However, a plausible mechanism underlying the morphological changes in lymphocytes caused by VZV has yet to be established, nor has their specificity to VZV been proven. It is noteworthy that atypical lymphocytes in the CSF have also been reported in cases of Epstein–Barr virus (EBV), enterovirus, and West Nile virus infections.[13–15] Yet, none of those cases demonstrated the bilobed morphology observed in our patients. Clonal expansion or virus-induced cytopathic effects may explain the atypical CSF morphology, although further immunophenotypic studies would be required to confirm this hypothesis. While atypical lymphocytes are commonly described in the peripheral blood during primary varicella (chickenpox),[16] their presence in the CSF during VZV reactivation, such as herpes zoster, has been documented only once in the literature.[3] In our patient, the appearance of a dermatomal rash after meningitis supports the interpretation that this was a reactivation event rather than primary varicella, similar with the previous report.[3] This finding may suggest that such morphological changes are unique to VZV reactivation and warrant further investigation. Hence, our report suggests that identifying atypical bilobed lymphocytes in the CSF may serve as a simple, early cytomorphological marker. This finding should warrant further molecular testing for herpesviruses and the initiation of empiric antiviral therapy to prevent progression, as observed in Case 1. Reports of neutrophilic and leukemoid reactions in the CSF are very rare, and varicella zoster virus should be considered as a potential etiology, particularly when bacterial causes are not evident.[17–19]

Conclusion

These cases highlight the diagnostic value of identifying atypical lymphocytes distinct from Mollaret's cells—specifically bilobed or binucleated monocytoid lymphocytes in CSF cytology. Although traditionally associated with primary varicella, such findings may also occur in VZV reactivation. Morphological clues in CSF cytology, when interpreted alongside clinical and molecular data, can facilitate early identification of viral etiology—particularly in cases lacking cutaneous manifestations. While treatment of VZV meningitis remains primarily supportive and based on antiviral

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therapy, early suspicion based on cytological findings may prompt earlier initiation of acyclovir, potentially reducing complications or neurological sequelae.

Patient Perspective and Take-Away Message

Both patients provided consent and expressed relief at the successful diagnosis and treatment of their condition. The key take-away message for clinicians is that atypical bilobed lymphocytes in the CSF should raise suspicion of VZV meningitis, even in the absence of a rash. This should encourage the early consideration of acyclovir therapy while awaiting molecular confirmation.

Ethical Approval

This case report was approved by the Ethics Committee of Mahasarakham University, Maha Sarakham, Thailand (no.724-726/2567).

Patient Consent Statement

The patients provided informed consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no competing interests to declare for this work.

References

1. Hasan S, Khan NI, Nakeb AA, Tarranum F. Herpes zoster with oro-facial involvement – report of a case and detailed review of literature. *Indian J Dent*. 2012;3(2):94–101. doi:10.1016/j.ijd.2012.03.011
2. Jayasinghe S, Sheridan S, Macartney K. Herpes zoster vaccination in Australia: what's available and who benefits? *Aust Prescr*. 2020;43(1):2–6. doi:10.18773/austprescr.2020.001
3. Cunha BA, Strollo S, Durie N, Ibrahim MS. Facial herpes zoster complicated by varicella zoster virus (VZV) encephalitis: the diagnostic significance of atypical lymphocytes in cerebrospinal fluid (CSF). *Heart Lung*. 2011;40(2):164–167. doi:10.1016/j.hrtlng.2010.05.059
4. Kupila L, Vuorinen T, Vainionpaa R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. *Neurology*. 2006;66:75–80. doi:10.1212/01.wnl.0000191407.81333.00
5. 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;15:995–997. doi:10.1111/j.1468-1331.2008.02233.x
6. Persson A, Bergstrom T, Lindh M, Namvar L, Studahl M. Varicella-zoster virus CNS disease—viral load, clinical manifestations, and sequels. *J Clin Virol*. 2009;46:249–253. doi:10.1016/j.jcv.2009.07.014
7. Gaudin M, Theïs C, Mrozek N, et al. Varicella zoster virus and meningitis in immunocompetent patients: specificity and questions. *Clin Infect Pr*. 2022;13:100125. doi:10.1016/j.clinpr.2021.100125
8. Becerra JCL, Sieber R, Martinetti G, Costa ST, Meylan P, Bernasconi E. Infection of the central nervous system caused by varicella zoster virus reactivation: a retrospective case series study. *Int J Infect Dis*. 2013;17(7):e529–e534. doi:10.1016/j.ijid.2013.01.031
9. Pahud BA, Glaser CA, Dekker CL, Arvin AM, Schmid DS. Varicella zoster disease of the central nervous system: epidemiological, clinical, and laboratory features 10 years after the introduction of the varicella vaccine. *J Infect Dis*. 2011;203:316–323. doi:10.1093/infdis/jiq066
10. Pollak L, Dovrat S, Book M, Mendelson E, Weinberger M. Varicella zoster vs. herpes simplex meningoencephalitis in the PCR era. A single center study. *J Neurol Sci*. 2012;314:29–36. doi:10.1016/j.jns.2011.11.004
11. Behera G, Chhabra G, Sable MN, Panigrahi A, Shetty D. Multinucleated lymphocytes in chronic lymphocytic leukemia-A rare morphological finding with review. *Int J Lab Hematol*. 2020;42(4):e170–e172. doi:10.1111/ijlh.13220
12. Troussard X, Cornet E, Lesesve JF, Kourel C, Mossafa H. Polyclonal B-cell lymphocytosis with binucleated lymphocytes (PPBL). *Onco Targets Ther*. 2008;1:59–66. doi:10.2147/OTT.S4182

13. Sato Y, Ohta Y, Honda Y, et al. Diagnostic value of atypical lymphocytes in cerebrospinal fluid from adults with enteroviral meningitis. *J Neurol*. 1998;245:598–602. doi:10.1007/s004150050252
14. Kleinschmidt-DeMasters BK, Marder BA, Levi ME, et al. Naturally acquired West Nile virus encephalomyelitis in transplant recipients: clinical, laboratory, diagnostic and neuropathological features. *JAMA*. 2004;292:859–860. doi:10.1001/jama.292.7.859
15. Manucha V, Zhao F, Rodgers W. Atypical lymphoid cells in cerebrospinal fluid in acute Epstein-Barr virus infection: a case report demonstrating a pitfall in cerebrospinal fluid cytology. *Acta Cytol*. 2008;52:334–336. doi:10.1159/000325517
16. Nesr G, Whittaker E, Bain BJ. Atypical lymphocytes-From chickenpox to monkey pox. *Am J Hematol*. 2023;98(8):1333–1334. PMID: 36794460. doi:10.1002/ajh.26883
17. Adachi K, Song SX, Kao RL, Van Dyne E, Kempert P, Deville JG. Herpes zoster meningitis presenting with a cerebrospinal fluid leukemoid reaction in an adolescent with preB-ALL in remission. *J Pediatr Hematol Oncol*. 2016;38(6):476–478. doi:10.1097/MPH.0000000000000614
18. Bhagat RK, Zieske AW, Kamble RT. Cerebrospinal leukemoid reaction secondary to VZV meninigoencephalitis in an AML patient post allogeneic bone marrow transplantation. *Blood*. 2013;122:300–301. doi:10.1182/blood-2013-04-484311
19. Stroiriska-Kusiowa B, Ciszewska L. Polyneuropathy with leukemoid reaction in cerebrospinal fluid as a late complication of zoster [in Polish]. *Neurol Neurochir Pol*. 1974;8:127–130.