



Two Cases of Varicella Zoster Virus Meningitis without Fever and Rash: An Unexpected Clinical Presentation

Ateş ve Döküntü Olmayan İki Varicella Zoster Virüs Menenjit Olgusu: Beklenmeyen Klinik Sunum

  Buket Baddal^{1,2},  Aysegul Bostanci^{1,2},  Kaya Suer³

¹ Department of Medical Microbiology and Clinical Microbiology, Faculty of Medicine, Near East University, Nicosia, Cyprus

² Molecular Microbiology Laboratory, Near East University Hospital, Nicosia, Cyprus

³ Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Near East University, Nicosia, Cyprus

ORCID ID: Buket Baddal: <https://orcid.org/0000-0003-3319-2179>, Aysegul Bostanci: <https://orcid.org/0000-0003-4319-9032>,

Kaya Suer: <https://orcid.org/0000-0002-2565-3425>

*Sorumlu Yazar / Corresponding Author: Buket Baddal, e-posta / e-mail: buket.baddal@neu.edu.tr

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Abstract

Aseptic meningitis caused by varicella-zoster virus (VZV) is a rare phenomenon in the healthy population. Immunocompromised patients are predominantly affected by viral reactivation, characterized by rash and neurological symptoms, and meningitis as a rare complication. Herein, we report two cases of VZV meningitis in adult patients without rash and fever over a 4-month period. The first case was an immunocompetent 37-year-old male who presented with persistent headache, agitation and unclear speech. The second case was an immunocompromised 76-year-old male who was admitted to the emergency department with confusion, disorientation, dizziness, loss of consciousness, pain in the lower left extremities and difficulty in walking. Cerebrospinal fluid (CSF) analysis in both patients revealed a high leukocyte cell count with 97% lymphocytes. CSF gram staining and culture were negative. CSF polymerase chain reaction (PCR) analysis indicated VZV infection. Both patients were administered acyclovir for 14 days and were discharged without any neurological sequela. This case report series highlight the presentation of VZV as aseptic meningitis in both immunocompetent and immunocompromised patients without the typical clinical symptoms and should always be considered by the clinicians.

Keywords Cerebrospinal fluid, rapid diagnosis, PCR, varicella-zoster virus, meningitis

Özet

Varicella-zoster virüsünün (VZV) neden olduğu aseptik menenjit, sağlıklı popülasyonda nadir olarak görülmektedir. Bağışıklığı baskılanmış hastalar ağırlıklı olarak döküntü ve nörolojik semptomlar ile seyrederken, nadir bir komplikasyon olarak menenjit ile karakterize viral reaktivasyondan etkilenir. Bu çalışmada, 4 aylık bir süre içinde tanısı konulan, döküntü ve ateş olmayan iki VZV menenjit vakası sunuldu. İlk olgu baş ağrısı, ajitasyon ve konuşmada güçlük şikâyetleri ile hastanemize başvuran 37 yaşında immünkompetan erkek hasta idi. İkinci olgu ise bilinç bulanıklığı, oryantasyon bozukluğu, baş dönmesi, bilinç kaybı, sol alt ekstremitede ağrı ve yürümeye güçlük şikâyetleri ile acil servise başvuran 76 yaşındaki bağışıklığı baskılanmış erkek hasta idi. Her iki hastanın beyin omurilik sıvısı (BOS) analizinde, %97 lenfosit olmak üzere yüksek lökosit hücre sayısı görüldü. BOS gram boyama ve kültür negatif idi. BOS polimeraz zincir reaksiyonu (PZR) analizi, VZV açısından pozitif olarak sonuçlandı. Her iki hasta 14 gün süreyle asiklovir tedavisi aldı ve herhangi bir nörolojik sekel olmadan taburcu edildi. Bu iki olgu sunumu, VZV'nin tipik klinik semptomlar olmadan hem immünkompetan hem de bağışıklığı baskılanmış hastalarda aseptik menenjit olarak ortaya çıkabileceğini ve klinisyenler tarafından her zaman göz önünde bulundurulması gerektiğini vurgulamaktadır.

Anahtar Kelimeler

Beyin omurilik sıvısı, hızlı tanı, PZR, varicella-zoster virüs, menenjit

INTRODUCTION

Neurotropic herpes viruses [herpes simplex type 1,2 (HSV-1, HSV-2), varicella-zoster virus (VZV)] are commonly seen in humans. A herpes virus family member varicella-zoster virus (VZV), also known as human herpes virus 3 (HHV-3), can spread through droplets, contact and airborne transmission, and causes varicella (chicken pox) in early childhood and herpes zoster (shingles).^{1,2} Neurotropic viruses remain latent on dorsal roots, autonomic ganglia, and cranial nerves where they cause latent infections with the potential for reactivation.³ When cellular immunity is compromised in the case of malignancy, trauma, co-morbidities, advanced age, and immunosuppression, the latent viral particles have the ability to reactivate. Similar to other herpesviruses, VZV can infect the central nervous system (CNS) and is responsible for CNS infections such as meningitis, angiitis, myelitis, or encephalitis due to its retrograde travel. Meningitis and other neurological complications due to VZV are commonly observed in the immunocompromised population with unfavourable outcomes. These complications are rarely seen in healthy immunocompetent people with primary features of rash and neurological symptoms.⁴ VZV meningitis, which was originally identified in healthy patients in the 1980s, is currently regarded as the third most common type of viral meningitis following enterovirus and HSV.⁵ Early diagnosis is critical for the prevention of morbidity and mortality. Diagnosis using the polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) is a rapid and sensitive method for the detection VZV-related neurological complications.

Here we present two cases of unusual, atypical cases of adults presenting with aseptic meningitis with VZV without evidence of rash, which was primarily diagnosed with PCR using patients' CSF.

CASE REPORT

Case 1

A 37-year-old male was admitted to the emergency department by ambulance, after experiencing an unremit-

ting headache for 6 days. He reported unresponsiveness, confusion and slurred speech on the morning of the admission day. He had a dermatomal varicella-zoster virus infection (chickenpox) history and he had received a varicella vaccination during his childhood.

On the day of admission, his blood tests were normal (Table 1.) and COVID-19 antigen test was negative. Patient's C-reactive protein (CRP) test result was 0.17 mg/dL (normal range 0.00-0.50). Hemogram results indicated white blood cell count ($6.4 \times 10^3/\mu\text{L}$) and neutrophil count ($5.13 \times 10^3/\mu\text{L}$) within the normal range. On examination, his vital signs were stable (temperature: 36°C ; blood pressure: 100/60 mmHg; Glasgow coma scale: 15; spO_2 : 98; pulse: 50). On neurological examination the patient did not present with signs of meningeal irritation. His chest X-ray was normal. No pathological findings were present in the cranial magnetic resonance imaging (MRI). Particularly, a stiff neck as a typical sign of meningitis was not found and he did not show any rash. He was admitted to the intensive care unit and a lumbar puncture was performed. The patient CSF biochemical analysis indicated an elevated protein level of 98.4 mg/dL (normal range: 15-45 mg/dL) (Table 2) and cellular analysis of the CSF revealed a high leukocyte cell count of 147,000 cells/ μL with 97% lymphocytes and 3% polymorphonuclear neutrophils (PMNs), suggestive of a possible viral aetiology. The bacterial culture of CSF yielded no growth and no bacteria were detected in the CSF Gram staining. The molecular analysis of the CSF was performed using Qiastat-DX Meningitis/Encephalitis Panel (Qiagen, Hilden, Germany) (including bacterial, viral, and fungal pathogens) and was positive for VZV (Figure 1.).

The patient was immediately administered 750 mg of acyclovir intravenously three times daily for 14 days. On day two of hospital admission, his symptoms improved and he started his nutrition regimen. The patient's headache resolved gradually and he was discharged after 2 weeks. The patient was followed up after discharge and had complete

resolution of symptoms and no neurological sequelae.

Table 1. Biochemical analysis of blood samples for both patients upon admission

Test	Case 1	Case 2	Reference
Creatinine (mg/dL)	0.87	1.49	0.72-1.25
Urea (mg/dL)	28	93	19-44
Glucose (mg/dL)	114	n/a	<140
AST (SGOT) (U/L)	18	11	5-34
ALT (SGPT) (U/L)	17	8	0-55
Sodium (mmol/L)	137	131	136-145
Potassium (mmol/L)	3.5	5.8	3.5-5.1
CRP (sensitive) (mg/dL)	0.17	12.70	0.00-0.50

AST (SGOT): aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
 ALT (SGPT): alanine transaminase (serum glutamic-pyruvic transaminase)
 CRP: C-reactive protein
 n/a: Not available

Table 2. Biochemical analysis of CSF samples for both patients upon admission

Test	Case 1	Case 2	Reference
Glucose (mg/dL)	49	45	40-70
Total protein (mg/dL)	98.4	271.6	15-45
Sodium (mmol/L)	139	131	142-150
Potassium (mmol/L)	3.1	n/a	2.2-3.3
Chlorine (mmol/L)	120	98	118-132

n/a: Not available

Case 2

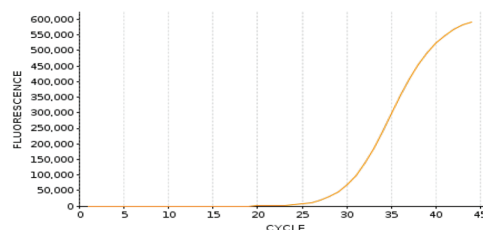
A 76-year-old male was admitted to the emergency department with confusion, disorientation, dizziness, loss of consciousness, pain in the lower left extremities and difficulty in walking. His COVID-19 PCR test was negative. On admission, the patient was reported to have type 2 diabetes and interstitial lung disease as underlying conditions.

The patient's blood test results were analyzed. His serum creatinine and urea levels were found to be 1.49 mg/dL (normal range: 0.72-1.25 mg/dL) and 93 mg/dL (normal range: 18-55 mg/dL), respectively. His CRP levels were elevated at 12.70 mg/dL (normal range: 0.00-0.50 mg/dL) (Table 1). Hemogram results indicated high white blood

cell count ($12.4 \times 10^3/\mu\text{L}$) and high neutrophil count ($9.61 \times 10^3/\mu\text{L}$). Patient's tentative diagnosis was encephalomyelitis. A lumbar puncture was performed and patient's CSF sample was collected. CSF was analyzed using limbic encephalitis panel (LGI1, CASPR2, AMPA1, AMPA2 GABA B, NMDA antibodies) as well as paraneoplastic panel and concluded as negative for both tests. IgG index panel revealed elevated CSF albumin levels at 183 mg/dL (normal range: 15-40 mg/dL) as well as high CSF IgG at 52.40 mg/dL (normal range: 4.20-6.40 mg/dL). In addition, serum albumin levels were low at 29.20 g/L (normal range: 35.00-49.00). CSF oligoclonal electrophoresis result was positive for type 3, which may indicate systemic disease/multiple sclerosis. CSF culture result was negative with scarce polymorphonuclear neutrophilic leukocytes. CSF cell count was 293.000 cells/ μL with 97% lymphocytes. The PCR analysis of the CSF was also performed using Qiastat-DX Meningitis/Encephalitis Panel and was found to be positive for VZV (Figure 1).

The patient was immediately administered 750 mg of acyclovir intravenously three times daily for 14 days and was discharged successfully.

Case 1



Case 2

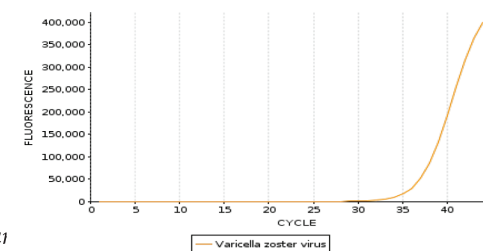


Figure 1
 DNA in both patient's CSF sample

DISCUSSION

VZV, a member of Herpesviridae, is a common pathogen which spreads via airborne droplets or via direct contact with the virus.^{2,6} It causes varicella (chicken pox) in childhood and zoster (shingles) in the adulthood. There are different clinical manifestations for VZV infections. VZV can cause vesicular rash by infecting the epidermis, may infect the neuronal tissues and reactivate after periods of time leading to various neurological complications. Meningoencephalitis, vasculopathy, cerebellitis vasculopathy, postherpetic neuralgia, zoster paresis, cranial nerve palsies, myelopathy and ocular disorders can be seen after zoster or shingle reactivation.⁷ In rare conditions, the VZV can compromise the meninges nerves and cause aseptic meningitis, characterized with a negative CSF bacterial culture. Headache, high fever and vesicular rash are the predominant symptoms of VZV meningitis. Phonophobia, photophobia, neck pain and rigidity are less commonly seen with Kerning's and Brudzinski's sign. Absence of dermatomal rash in VZV meningitis is called Zoster Sine Herpete. More rarely, as reported in our case study, some patients develop VZV meningitis without any fever or rash. In our patient's case, the sole symptom was a persistent headache. VZV meningitis without rash was previously reported in literature.^{6,8} Becerra et al. stated that in CNS cases, vesicular rash is absent in one third of the cases. The lack of rash can be defined by the pathophysiology. In this condition, low viral load and delayed neurological disease are observed in some cases.^{5,6} Signs of meningitis, as described in the literature, were not observed in our patient, however he had elevated CSF protein levels (98.4 mg/dL (range:15-45 mg/dL)) and mononuclear cell predominance (97%), consistent with the literature.⁷

Suppressed cellular immunity have been associated with the disease. Immunosuppression such as advanced age, chemotherapy, autoimmune diseases and stress are risk factors VZV reactivation.⁶ Apart from the immunosuppressed patients, meningitis due to VZV can be also observed in immunocompetent healthy individuals.^{8,9} Here,

we present two atypical cases of VZV meningitis in both immunocompetent and immunosuppressed patients without fever, rash or other neurological signs.

Molecular detection of the causative agent in CSF is considered as the gold standard for the diagnosis of VZV meningitis due to its high sensitivity and specificity. The third most common agent of CNS is VZV in adults after enterovirus and HSV. Therefore, it is imperative to identify the causative agent in a CNS infection. Additionally, meningitis without classical symptoms such as rash was previously confirmed by PCR and reported by Echevarria et al. These cases highlight the importance of molecular tests for VZV detection.^{9,10} VZV PCR testing has enabled the detection of more cases, particularly when the skin manifestation is absent. Furthermore, the differentiation of HSV and VZV is crucial when a viral agent is suspected.

CONCLUSIONS

VZV is capable of causing CNS infections with varying complications both in immunocompetent and immunocompromised individuals. As highlighted by the two cases presented in this study, VZV meningitis can occur in both immunocompetent adults and individuals with underlying conditions and should always be considered by the clinicians even in the absence of rash, fever or neck stiffness.

Ethics Approval

Due to the nature of this retrospective study and the preserved anonymity of the patient, a waiver of ethics committee approval was obtained from Near East University. All methods were carried out in accordance with the guidelines and regulations of Declaration of Helsinki.

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.B, Design: B.B., A.B., Data Collection or Processing: B.B., A.B., K.S., Analysis or Interpretation: B.B,

K.S., Literature Search: A.B., Writing: B.B., A.B., K.S.

Conflict of Interest

No conflict of interest was declared by the authors.

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Informed Consent

The patient was sampled through convenient sampling technique and enrolled after obtaining written informed consent.

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