Case Report

Journal of Emergency Medicine Case Reports

HSV-2 Associated Meningitis Case: A Challenging Diagnosis in An Immunocompetent Woman

Buket Baddal[1,2], Aysegul Bostanci[1,2], Kaya Suer[3]

[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.

Abstract

Herpes simplex virus (HSV), is a member of the herpesviridae family which is transmitted through close contact and can result in lifelong latent infections. Herpes simplex virus type-2 (HSV-2) infections occur through sexual contact and the primary infection of HSV-2 is usually asymptomatic in immunocompetent adolescents. HSV-2-associated aseptic meningitis is rarely seen in healthy individuals. Herein, we report a rare case of meningitis, associated with HSV-2, without the presence of genital lesions. A healthy, 40-year-old female presented to the emergency service with unremitting headache, vomiting, and nausea. Her cerebrospinal fluid (CSF) analysis revealed elevated protein level, increased cell count with lymphocyte predominance, and positive quantitative real-time polymerase reaction (HSV-2) but negative bacterial culture and gram staining. The cranial MRI revealed meningeal contrast enhancement. The patient was administered acyclovir for 10 days during her hospital stay and she was discharged without any neurological sequela. This case report shows that HSV-2 meningitis can occur in immunocompetent individuals via re-activation and should always be considered by clinicians even in the absence of genital lesions.

Keywords: Herpes simplex virus type 2, meningitis, CSF, molecular testing

Introduction

Herpes simplex virus (HSV), a member of the *herpesviridae* family, is a double-stranded DNA virus that spreads through hematogenous dissemination and primarily affects epithelial cells. HSV transmission occurs through close contact and causes latent lifelong infections. The infections associated with HSV can be asymptomatic, mild, or life-threatening. HSV and the host immune system interaction define the infection outcome. HSV affects the epithelial cells in the mucosa or skin during the primary infection [1]. Clinical presentation of HSV infections can be orofacial, and genital ulcers [2]. Herpes simplex virus type 1 (HSV-1) is predominantly found in the oral region, while herpes simplex virus type 2 (HSV-2) causes recurrent genital ulcers [3]. HSV-2 infections occur through sexual contact and the primary infection of HSV-2 is usually asymptomatic in immunocompetent adolescents. Most patients who have HSV-2 infection are likely unaware of their infection and subclinical viral shedding. Meningitis can develop without a known genital herpetic lesion or prior history of genital herpes infection. HSV-2 is currently regarded as the second cause of viral meningitis after varicella zoster virus (VZV) [4].

HSV is able to establish latency in neurons and cause persistent infections in the neuronal ganglia, where it can periodically reactivate and cause recurrent infections after entering the host. HSV is responsible for different central nervous system (CNS) clinical presentations like myelitis, brainstem encephalitis, and aseptic meningitis due to its neurotropic structure. CNS infection could result in acute infection and inflammation leading to high morbidity and mortality. Generally, HSV-1 causes encephalitis whereas HSV-2 is responsible from meningitis. Neurological diseases, associated with HSV-2, arise from the primary infection or latent infection of HSV-2, through reactivation after becoming dormant within the sensory ganglia [5]. In HSV-2 infection, different components of neuroaxis including the retina, cranial nerves, spinal cord, brain, brainstem, and nerve roots can be affected apart from the meninges. Headache, neck stiffness, fever, nausea, vomiting, myalgia, photophobia, and phonophobia are symptoms observed in HSV-2 associated meningitis. HSV-2-associated aseptic meningitis, due to primary genital herpes, occurs in 36% of women and 11% of men, and hospitalization is required in one in six of these individuals. Occasionally, the only clinical manifestation of lately acquired HSV-2 infection is aseptic meningitis.

Diagnosis of HSV-2 could be performed using serum antigen detection, viral culture, detection of the virus using electron microscopy and polymerase chain reaction (PCR). Viral isolation of HSV-2 is rarely used; therefore, PCR is the gold standard for diagnosis of HSV-2-DNA in the

Corresponding Author: Buket Baddal **e-mail:** buket.baddal@neu.edu.tr
Received: 06.04.2023 • **Revision:** 18.05.2023 • **Accepted:** 19.06.2023
DOI: 10.33706/jemcr.1278277
©Copyright 2020 by Emergency Physicians Association of Turkey - Available online at www.jemcr.com
Cite this article as: Baddal B, Bostanci A, Suer K. HSV-2 associated meningitis case: A challenging diagnosis in an immunocompetent woman. Journal of Emergency Medicine Case Reports. 2023;14(3): 60-62

cerebral spinal fluid (CSF). It has high specificity (100%) and sensitivity (95%).

In this report, an aseptic meningitis case confirmed by CSF RT-PCR for HSV-2 in the absence of genital lesions was presented.

Case Report

A 40-year-old woman was admitted to the emergency department of Near East University Hospital with complaints of headache over the previous 10 days. On admission day, she reported myalgia beginning that day. During examination in the emergency department, her vitals were stable and her body temperature was normal (temperature: 36°C, Glasgow Coma Scale:15; blood pressure: 130/70 mmHg). Biochemical blood analysis results indicated CRP was mildly elevated (2,55 mg/dL), whereas urea, creatinine and liver function tests (AST and ALT) were normal.

Neurological examination revealed no meningeal irritation. Following her examination, MRI was suggested and she was discharged. Due to unremitting headache, the patient was admitted to another medical centre and she reported being prescribed antibiotics, although she could not remember the exact medication. The patient was relieved after medication but her headache got worse and she reported repeated nausea and vomiting throughout the night. Next morning, she was re-admitted to the first hospital for a detailed neurological examination in which neck stiffness, phonophobia and osmophobia were found to be positive. The patient's cranial MRI revealed meningeal contrast enhancement (Figure 1).

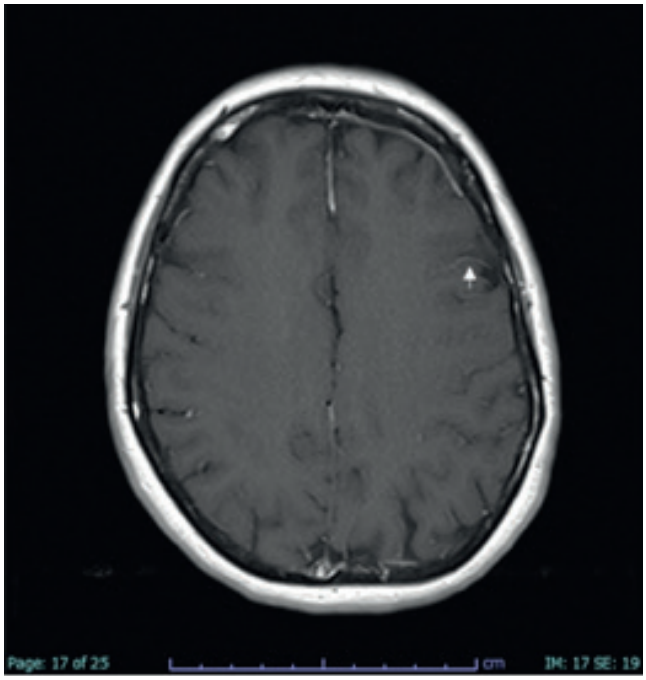

Figure 1. Patient cranial MRI indicating meningeal contrast enhancement (shown with an arrow)

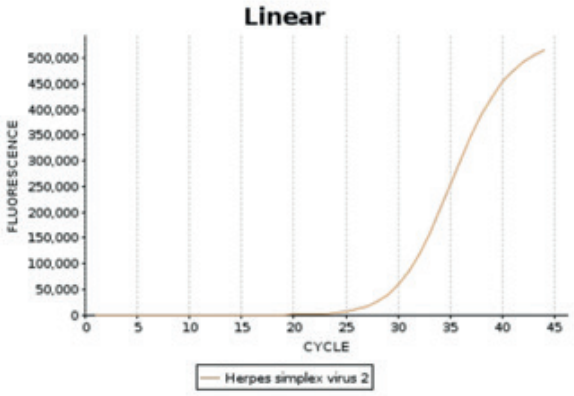

Figure 2. RT-qPCR amplification of Herpes Simplex Virus-2 DNA in the patient CSF sample

She was referred to the inpatient ward and an immediate lumber puncture was performed. The patient's CSF was clear and contained a high leukocyte cell count of 1,118 cells/µL with 98% lymphocytes and 2% polymorphonuclear neutrophils (PMNs), elevated protein level (308,2 mg/dL) and decreased glucose (38 mg/dL) and sodium levels (139 mmol/L). The chlorine level was in normal range (121 mmol/L). The gram staining was negative and the bacterial culture of CSF yielded no growth. Qiastat-DX Meningitis/Encephalitis Panel, including bacterial, viral, and fungal pathogens, was used for the molecular analysis of the CSF and was positive for HSV-2 with a cycle threshold (Ct) of 27.6 (Figure 2).

The patient was immediately administered acyclovir intravenously three times a day for 10 days. Following administration of acyclovir, the patient's symptoms started to improve on day 2. The patient's headache gradually resolved and she was discharged in 2 weeks. After discharge, the patient was followed up till complete resolution of symptoms and no neurological sequelae was observed.

Discussion

The patient presented in this case showed symptoms of unremitting headache, neck stiffness, and symptoms lasted two weeks. Investigation of laboratory results indicated a CSF pleocytosis with mononuclear predominance, and positive RT-qPCR test results for HSV-2, indicating early infection or reactivation, and resulting in the diagnosis of HSV-2 meningitis.

The wide range of neurological symptoms, including myelitis, encephalitis, meningitis, and polyradiculopathy, are associated with HSV infections. CNS can be invaded both by HSV-1 and HSV-2. Rarely, HSV-2 infections cause pulmonary infections, esophagitis, and meningitis and can be seen in immunocompetent individuals. The neurological manifestations of HSV-2 are caused by primary infection of HSV-2 or reactivation of latent HSV-2 [6]. Aseptic meningitis

DOI: 10.33706/jemcr.1278277
Journal of emergency medicine case reports. 2023;14(3): 60-62

has been linked to HSV-2 in both sporadic cases as well as in recurrent cases, termed Mollaret's meningitis [7]. HSV-2 is capable of staying dormant in the sensory neurons of the dorsal root ganglia after primary infection, and retrograde seeding of the virus causes recurrent meningitis [8]. HSV-2 frequently results in benign meningitis due to primary genital infection. However, more than 80% of cases do not have a genital lesion, and HSV-2 meningitis could occur in the absence of the genital rash [9]. The molecular analysis of CSF aids in rapid diagnosis and characterization of HSV infection. The PCR test for HSV-2 has a high sensitivity and specificity; therefore, it can be a useful diagnostic marker. Diagnosis of HSV-2 increases via multiplex-PCR diagnostic systems, and excessive empiric antimicrobial therapy rate decreases due to the use of multiplex-PCR systems. Many HSV-CNS diseases, including mild infections, can be diagnosed by PCR testing. Detection of HSV, even in patients without herpetic shedding, enables the identification of more HSV patients.

The case presented in this report is an example of HSV-2-associated meningitis without genital rash. Consistent with the literature, the patient presented here did not have a genital rash at the time of admission, although the patient stated having a genital herpes infection earlier in life. The elevated protein concentration and normal glucose levels are consistent with a typical CSF profile of viral meningitis. Moreover, elevated CSF protein levels have been observed in patients with herpesviruses [10]. The elevated protein levels observed in the patient has been commonly detected in HSV-2-associated meningitis cases. HSV-1 infection is reported to be mostly presented in 50 to 60 years of age, whereas HSV-2 infected patients usually belong to the 20-40 age group. The patient in this case report is 40 years old and immunocompetent individual.

In the current case study, differential CSF count was suggestive of a viral cause, and it was confirmed via PCR testing. Predisposing factors in HSV-2 meningitis are not clear but HSV-2 should be suspected even in the absence of genital symptoms. The availability of CSF PCR assays aids in rapid diagnosis and immediate care. In HSV-2 associated meningitis cases, treatment should immediately begin for 14 days to prevent any neurological sequelae.

Conclusion

In conclusion, HSV-2 can present as various CNS infections and may lead to meningitis following primary infection both in immunocompetent and immunocompromised individuals. As highlighted by the current case report, HSV-2 meningitis can occur in immunocompetent individuals and should always be considered by the clinicians even in the absence of genital lesions.

References

1. Zhu S and Viejo-Borbolla A. (2021) Pathogenesis and virulence of herpes simplex virus. *Virulence*, 12(1); 2670-2702.
2. Omland LH, Vestergaard BF and Wandall JH (2008) Herpes simplex virus type 2 infections of the central nervous system: A retrospective study of 49 patients. *Scandinavian Journal of Infectious Diseases*, 40; 59-62.
3. Miller S, Mateen FJ, Aksamit Jr AJ (2013) Herpes simplex virus 2 meningitis: a retrospective cohort study. *J. Neurovirol*, 19; 166-71.
4. Grinney, M and Mohseni MM (2022) Recurrent bening lymphocytic (Mollaret's) meningitis due to herpes simplex virus type 2. *Bayl Univ Med Cent*, 35 (6); 820-821.
5. Berger JR and Houff S (2008) Neurological Complications of Herpes Simplex Virus Type 2 Infection. *Arch Neurol,* 65(5), 596-600.
6. Kadayakkara DK, Candelaria A, Kwak YE and Loeser C (2016) Herpes Simplex Virus-2 Esophagitis in a Young Immunocompetent Adult. *Case Rep Gastrointest Med.*, doi: 10.1155/2016/7603484 .
7. Chand S, Thapa S, Gautam K, Twayana AR, Laguio-Vila MR and Elsourbagy T. (2021) Bening Recurrent Aseptic Meningitis (Mollaret's Meningitis) in an Elderley Male: A Case Report. *J Nepal Med Assoc*, 59 (241): 916-918.
8. Sherchan R, Shrestha J, Omotosho YB, Dyatlova N and Nepomuceno JS. (2021) Herpes Simplex Virus-2 Meningitis Masquerading as Pseudotumor Cerebri. *Cureus*, 13(6); 1-5.
9. Davies N, Tang J and Ward KN (2004) Herpes simplex virus type 2 and recurrent meningits. *Lancet,* 364, 501-502.
10. O'Sullivan CE, Aksamit AJ, Harrington JR, Harmnsen WS, Mitchell S and Patel R (2003) Clinical Spectrum and Laboratory Characteristics Associated with Detection of Herpes Simplex Virus DNA in Cerebrospinal Fluid. *Mayo Clin Proc*, 78; 1347-1352.