

CASE REPORT

FROM THE SKIN TO THE BRAIN: A HINT TO DIAGNOSE HERPES SIMPLEX VIRUS TYPE 2 MENINGITIS

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ABSTRACT

Introduction. Herpes simplex virus type 2 (HSV-2) is recognized as one of the most common causes of aseptic meningitis, that is also a well-known complication of genital herpes. We report a case of recurrent HSV-2 meningitis without genital lesions, but with simultaneous skin lesions that were a clue for diagnosis.

Case presentation. A 21-year-old man had two episodes of aseptic meningitis in 2019 and 2021, respectively. During both episodes, the neurological manifestations were preceded by recurrent herpetic skin lesions on the right arm. HSV-2 deoxyribonucleic acid (DNA) was detected in the spinal fluid only in the first episode. However, due to the possibility that the lesions and simultaneous episodes of meningitis were caused by HSV-2, systemic acyclovir was initiated. Each time, the treatment was followed by rapid symptoms' resolution. After the second episode, the patient was put on indefinite suppressive therapy with valacyclovir.

RÉSUMÉ

De la peau au cerveau: une suggestion pour diagnostiquer la méningite à virus de l'herpès simplex de type 2

Introduction. Le virus de l'herpès simplex de type 2 est reconnu comme l'une des causes les plus fréquentes de méningite aseptique. C'est aussi une complication bien connue de l'herpès génital. Nous rapportons un cas de méningite récidivante à virus de l'herpès simplex de type 2 sans séquelles génitales mais aux lésions cutanées simultanées qui ont constitué un indice de diagnostic.

Présentation du cas. Un jeune homme a connu deux épisodes de méningite aseptique en 2019 et 2021, respectivement. Dans les deux épisodes, les manifestations neurologiques ont été précédées de lésions cutanées herpétiques récurrentes sur son bras droit. L'ADN du virus de l'herpès simplex de type 2 n'a été dépisté dans le liquide céphalo-rachidien que lors du

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Conclusions. Recurrent skin lesions can suggest the probability of HSV-2 etiology of concomitant meningitis and justify the initiation of acyclovir. In all confirmed meningitis cases with HSV-2, counseling on this genital infection and the possibility of sexual spread should be considered.

Keywords: herpes simplex virus type 2, recurrent meningitis, herpetic skin lesions.

List of abbreviations:

HSV-1 – herpes simplex virus type 1
 HSV-2 – herpes simplex virus type 2
 VZV – varicella-zoster virus
 DNA – deoxyribonucleic acid
 PCR – polymerase chain reaction
 WBC – white blood cell
 CSF – cerebrospinal fluid
 CT – computed tomography
 ELISA – enzyme-linked immunosorbent assay
 HIV – human immunodeficiency virus

INTRODUCTION

Among the human herpes viruses' family, herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are notorious for their propensity to latency, frequent reactivation, and ability to cause neurological infections¹. After the primary mucocutaneous infection, they establish lifelong dormancy in the peripheral sensory ganglia until their reactivation. Viral reactivation can result in recurrent local mucocutaneous diseases (herpes labialis or keratitis for HSV-1 and genital herpes for HSV-2). However, HSV-1 and HSV-2 can involve almost all mucocutaneous surfaces. More commonly, reactivation can be asymptomatic and thus contribute to unintentional spread of both viruses².

The major central nervous system consequences of HSV reactivation are encephalitis in case of HSV-1 and meningitis in case of HSV-2³. With polymerase chain reaction (PCR) technology, HSV-2 is increasingly recognized as one of the most common causes of aseptic meningitis alongside enteroviruses. HSV-2 meningitis is easily distinguishable when accompanied by genital herpes. However, in the absence of clinically apparent genital lesions, HSV-2 etiology may not be obvious⁴.

Here we describe a patient with recurrent HSV-2 aseptic meningitis and discuss the diagnostic difficulties in the absence of genital herpes.

CASE PRESENTATION

A 21-year-old man presented in January 2019 with a two-days history of fever, severe headache

premier épisode. Cependant, en raison de la possibilité que les lésions et les épisodes simultanés de méningite aient été causés par le virus de l'herpès simplex de type 2, l'acyclovir systémique a été initié. Chaque fois, le traitement a été suivi d'une résolution rapide des symptômes. Après le deuxième épisode, le patient a été mis sous traitement suppressif indéfini avec du valacyclovir.

Conclusions. Des lésions cutanées récurrentes peuvent suggérer une étiologie probable de méningite concomitante par le virus de l'herpès simplex de type 2 et justifier l'initiation de l'acyclovir. Dans tous les cas confirmés de méningite avec le virus de l'herpès simplex 2, des conseils sur cette infection génitale et la possibilité de propagation sexuelle doivent être envisagés

Mots-clés: virus de l'herpès simplex type 2, méningite récurrente, lésions cutanées hérpétiques.

with neck pain and skin lesions on the right forearm, which had appeared 10 days previously. He reported recurrent episodes of skin lesions every 6-7 months for the last 4 years, not accompanied by associated systemic symptoms, each time with spontaneous resolution. The patient didn't have a history of genital herpes. He was admitted to the infectious disease department with presumptive varicella-zoster virus (VZV) meningitis. At the physical examination, the patient was febrile, with marked nuchal rigidity and positive Kerning's sign, but without focal neurological abnormalities. There was a slight discoloration on the right medial forearm. Laboratory tests, such as complete blood count, electrolytes, renal and liver function tests were within normal limits. Enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) was nonreactive. The cerebrospinal fluid (CSF) analysis showed white blood cell (WBC) count of 502.109/L, with 87% mononuclears, raised protein of 0.88 g/L and normal glucose level. HSV-2 deoxyribonucleic acid (DNA) from the CSF was detected on multiplex PCR (FilmArray, BioMerieux, France). The findings of a brain computed tomography (CT) scan were normal. Blood and CSF cultures were sterile. The patient was treated with acyclovir (3x 750 mg) intravenously (i.v.) for 10 days, ceftriaxone (2x2.0 g) i.v. for 10 days and dexamethasone (3x 4 mg) i.v. for 7 days. He was discharged 10 days later, fully recovered, with a prescription for a two-week course of oral valacyclovir 3x1.0 g daily. One month later, the results of ELISA for HSV-1 and HSV-2 (National reference laboratory

“Cell cultures, Rickettsia and Oncogenic Viruses“, National Centre of Infectious and Parasitic Diseases, Sofia), were as follows: IgM negative for HSV-1 and HSV-2 and IgG positive for HSV-1 and HSV-2, indicative of previous exposure to both viruses.

The patient was readmitted in July 2020 with one-day history of similar, but milder symptoms of meningitis, and a recurrent rash on the same body site, preceding the symptoms by 7 days. The vesicles on the right forearm were covered with crusts. The CSF analysis showed WBC count of 277.109/L, with 61% mononuclears, normal protein and glucose level. Therapy with systemic acyclovir was started. CSF was sent to the above laboratory and returned negative for HSV-1/2 DNA (IONTEK Inc., Istanbul, Turkey). CSF was also negative for enteroviruses. The findings of a brain CT were again normal. The patient was treated with acyclovir (3x 750 mg) i.v. for 7 days, dexamethasone (3x 4 mg) i.v. for 4 days and recovered uneventfully. Lymphocyte flow cytometry on a follow-up visit after the patient’s recovery showed normal cellular and humoral immunity.

In July 2021, the skin lesions recurred on his right forearm (Figure 1), but without neurological symptoms, while being evaluated and treated for glomerulonephritis in another hospital. He was put on indefinite suppressive therapy with oral valacyclovir 3x1.0 g daily.

DISCUSSION

We presented the case of a patient with HSV-2 meningitis, without symptomatic genital herpes, but with apparent recurrent herpetic skin lesions. The patient experienced a second episode of meningitis

one year and a half later. These lesions preceding the episodes of meningitis raised the suspicion of a probable HSV-2 etiology.

HSV-2 meningitis is the third most common cause of identified viral meningitis in Northern Europe⁵ and HSV-2 is the leading pathogen of benign recurrent lymphocytic meningitis⁶. HSV-2 meningitis is known as a frequent neurological complication of primary genital herpes infection, as approximately one fifth of patients develop meningitis during initial genital herpes⁷. In addition, after the onset of HSV-2 meningitis, there is a similar chance of meningitis’ recurrence⁸. Clinically, it is indistinguishable from aseptic meningitis, caused by other common viruses, such as enteroviruses. The CSF analysis in the recurrent HSV-2 meningitis is typical for aseptic meningitis, with lymphocytic pleocytosis, mild protein elevation and normal glucose level.

During the first meningitis episode in our patient, HSV-2 DNA was detected in the CSF by PCR. However, during the second episode, the PCR result for HSV-2 was negative. Regardless of the earlier HSV-2 DNA positive episodes, HSV DNA was not always detected in the subsequent CSF³. These false negative results may be attributable to a lower viral load, or earlier timing of CSF sample in the recurrent episode⁹. Some authors consider a period from 2 to 5 days after symptoms’ onset as the optimal timing for CSF testing⁹. During the second meningitis episode, in our patient CSF was collected one day after symptoms’ onset. In addition, PCR testing was inconsistent, as apart from HSV-2 and enteroviruses no other coinfecting viruses were tested. However, coinfection is very unlikely, unless there is severe immunosuppression, as reported by Cinque et al¹⁰.



Figure 1. Group of vesicles on the right forearm.

Notably, the Danish Society of Infectious Diseases defined HSV-2 meningitis not only when HSV-2 is detected by PCR in CSF or genital lesions, but also when HSV-2 has been previously documented, and no other diagnoses are established¹¹.

Our patient experienced two meningitis episodes so far and does not meet the definition of Mollaret's meningitis. Historically, the Mollaret's meningitis, or recently named recurrent benign lymphocytic meningitis, is characterized by recurrent episodes (at least three) of aseptic lymphocytic meningitis in otherwise healthy individuals. These episodes are mild and self-limiting, alternating with symptoms-free period and no long-term neurological sequelae¹². HSV-2 is by far the most common etiological agent³.

Our patient did not disclose a history of genital herpes. However, primary, as well as recurrent HSV-2 meningitis, may frequently appear without characteristic genital herpes, thus making it difficult to suspect an underlying HSV-2 etiology¹³. The typical genital lesions of primary infection occur only in a very few patients and even less commonly during recurrences. The lesions remain undiagnosed if they have a transient atypical presentation or are asymptomatic¹⁴. Furthermore, self-reporting by the patients is not completely reliable if they may be healed at the onset of meningitis. Additionally, the lesions may be misinterpreted by the patients themselves as minor abrasions or fissures. Unfortunately, these lesions might be misdiagnosed by physicians, as well. And finally, as reported by other authors¹⁵, pre-existing HSV-1 immunity, such as in this patient, may confer a partial protection against symptomatic genital infection with HSV-2.

As such, the non-recognition of genital herpes does not rule out the presence of genital HSV-2 infection. As suggested by Tedder et al³, when HSV-2 DNA in CSF is negative but the clinical suspicion of HSV infection is still high, it seems rational to complete genital exam and obtain swabs for HSV DNA. Nevertheless, physicians are unwilling to ask about sexual transmitted disease, even after a positive HSV-2 CSF result is reported.

A cluster of resolving vesicles on the right forearm was observed in the latest skin recurrence in this case. Because the lesions were resolving, no skin scraping was obtained to detect HSV-2 DNA. However, as previously reported¹⁶, HSV-2 was confirmed from such a rare location. This place is far distant from sacral ganglia, the usual site of HSV-2 dormancy. Latency of HSV-2 has also been demonstrated in trigeminal ganglia¹⁷. A widespread latency of HSV-2 implies that the virus may spread within the nervous system to distant ganglia away from those initially infected⁸. Such lesions are more commonly seen in HSV-1 infection than in HSV-2 infection

and appear more often on the face, hands, and arms in HSV-1 infection and on the buttock and legs in HSV-2 infection. In addition, extragenital skin HSV lesions recur more frequently than the sole inapparent genital lesions and, more importantly, they are clinically symptomatic⁷. Thus, the awareness of the presence of undiagnosed and/or asymptomatic genital lesions when the genital herpes remains obscure is the key to suspect the HSV-2 etiology of aseptic meningitis. Regarding the possibility that the skin lesions and concurrent episodes of meningitis were caused by HSV-2, the patient described was started on systemic administration of acyclovir, and both times the treatment was followed by a rapid resolution of symptoms.

The skin recurrence pattern in this case was the reason for the admission misdiagnosis of VZV infection, in particular shingles. However, recurrent VZV infection is rare, except for patients with severe immune deficiency, who require immediate HIV testing. Conversely, HSV infection recurs frequently, as our patient had experienced more than 20 recurrences. Both HSV and VZV infections respond well to intravenous acyclovir. However, the accurate diagnosis is still important, as their susceptibility to various antiviral agents when further given orally may vary considerably. Another reason for a precise diagnosis is the need for a proper infection control. Patients with VZV infection require respiratory isolation, while those hospitalized with HSV infection need only contact precautions¹⁸.

There are not clear treatment recommendations for acute HSV-2 meningitis, due to its rarity and benign course. However, most physicians use acyclovir, as encephalitis and meningitis might clinically overlap early in the patient's evolution. In addition, in many hospitals, including our, the PCR results become available within a week after a lumbar puncture is performed. All these justify acyclovir therapy. Furthermore, according to the Danish guidelines¹¹, acyclovir or valacyclovir are recommended if HSV or VZV are confirmed as the etiology of meningitis.

Like frequently recurrent genital herpes, suppressive therapy for HSV-2 meningitis has been attempted in anecdotal cases¹⁹. A recent double-blind randomized controlled trial of valacyclovir suppression after HSV-2 meningitis did not show a benefit in preventing recurrences. However, only a half of the intervention arm were recurrent cases²⁰. Antiviral suppressive therapy is offered by most experts, but the exact dosage and real benefits are yet to be determined.

CONCLUSIONS

HSV-2 meningitis remains underestimated and undiagnosed, particularly in the absence of genital

HSV-2 infection. Recurrent skin lesions can suggest the probable HSV-2 etiology of concomitant meningitis and justify the initiation of acyclovir. In all confirmed meningitis cases with this virus, counseling on the genital infection and the possibility of sexual spread should be considered.

Author Contributions

R.K. is responsible for the conception, design and writing the manuscript. J.K. and P.K. were responsible for the data acquisition, microbiological investigations and data analysing. K.C. aided to the design, reviewed, and edited the manuscript. All authors contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

“The authors declare no conflict of interest regarding this article“

“The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study“

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