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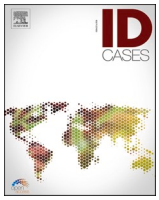

Case report

A case of viral meningitis due to Varicella Zoster virus infection in a young adult male

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ABSTRACT

A 36-year-old male with headaches was empirically treated for herpes simplex virus meningitis; CSF PCR testing later confirmed varicella zoster virus meningitis. Valacyclovir was increased to 2 g QID for remaining duration of therapy with full recovery. This case highlights the importance of comprehensive testing and proper treatment adjustment for rarer etiologies of aseptic meningitis.

Case history

A 36-year-old male with no prior medical history presented to the Baltimore VA Medical Center with a six day history of frontotemporal headache associated with one day of emesis. The patient reported a mild headache at onset, which did not disrupt his ability to go to work or complete his normal activities of daily living. That evening, however, the patient's headache intensified. The patient described the headache as frontotemporal and throbbing, worse with movement and positional change. He stayed home the following day, but the headache did not resolve with rest or oral acetaminophen. He then presented to the emergency department (ED) and was evaluated with no acute abnormalities noted on head CT or on CBC or chemistry panel. The patient was discharged home with strict return precautions, and was admitted two days later after developing nausea and emesis.

The patient had a lumbar puncture performed in the ED, which showed a glucose of 47 mg/100 mL (serum glucose 89 mg/100 mL), evidence of leukocytosis (507 WBC/microL) and elevated protein levels (192 mg/dL), raising a concern for aseptic meningitis. When the patient was evaluated on hospitalization day (HD) 1, he endorsed continued headaches of unchanged character and five episodes of emesis overnight. He remained afebrile throughout the entire prehospital and hospital course. He denied photophobia and did not exhibit any alteration of his mental status. On physical exam patient did not have any rashes or skin lesions on his body and his neurological exam was non-focal.

A broad differential for his aseptic meningitis was considered, including viral, autoimmune and drug induced. The patient reported avoiding non-steroidal anti-inflammatory drugs (NSAIDs) because they upset his stomach. He had no history of autoimmune disease, nor did he have any risk factors for non-viral etiologies. The patient was on pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir due to high-risk sexual behaviors. He reported full compliance with his PrEP and routinely followed in the Baltimore VA ID clinic for monitoring with no history of sexually transmitted infections (STIs). The patient was presumed to have viral meningitis, was started on acyclovir IV therapy (800 mg TID) and continued on it for three days at which point he had improved symptomatically and was deemed stable for discharge. He was discharged home on the morning of HD3 with a presumptive diagnosis of herpes simplex meningitis and plans to continue therapy with valacyclovir 1 g TID, for a total of fourteen days of therapy. The afternoon after discharge, the cerebrospinal fluid (CSF) polymerase chain reaction (PCR) resulted positive for varicella zoster virus (VZV) DNA. The patient was promptly contacted via phone, informed of the result, and the data supporting oral treatment with valacyclovir and his dose was accordingly increased to 2 g QID without a change to duration of therapy. One week after his discharge, the patient was seen in clinic; he did not report any additional symptoms and endorsed being back at his baseline health level.

Discussion

Aseptic meningitis is characterized by clinical symptoms of meningeal inflammation, such as headache, emesis and a negative CSF gram stain and culture. It is the most common form of meningitis, with an

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incidence rate of 7.6 per 100,000 adults; thankfully the condition is usually benign and self-resolving [1]. Viral etiologies, including enteroviruses, arboviruses, and herpes simplex viruses, are most common. Additional etiologies include other infectious causes (spirochetes, mycobacteria, fungi), medication (most commonly NSAIDs) and malignancy. In a retrospective study of aseptic meningitis cases at 9 hospitals in Houston, TX from 2005 to 2010, 81% of patients with aseptic meningitis did not have a confirmed etiology via laboratory testing [2]. This number will likely decrease as the prevalence of newer molecular diagnostic tools increases in clinical settings, but does reinforce the potential etiological heterogeneity of this condition. In the Shukla et al. study, of the 404 adults tested, 10 were human immunodeficiency virus (HIV) serology positive, 36 were herpes simplex virus (HSV) CSF PCR positive and only 1 patient was VZV CSF PCR positive. In an earlier study by Kupila et al. in a hospital in Finland from 1999 to 2003, 66% of patients had a confirmed etiology, with 8% of those cases being due to VZV [3].

A broad differential was considered for our patient prior to arriving to the diagnosis of viral meningitis, aided by a thorough history. Bacterial meningitis was ruled out as the patient did not have altered mental status or focal neurological deficits and a negative Gram's stain and culture from CSF. Fungal meningitis was considered unlikely, given lack of recent travel to endemic areas. The patient had no history of tuberculosis exposure, was born in the United States and had no additional risk factors for exposure. Additionally, the patient had no recent tick exposures, making Lyme disease unlikely. Iatrogenic or medication-induced meningitis was unlikely as the patient's medication combination of emtricitabine/tenofovir is not associated with meningitis, the patient avoided NSAIDs and had no history of sulfamethoxazole/trimethoprim use. While an autoimmune syndrome was considered, the patient had no history of autoimmune disease and no findings such as rash or arthralgias suggestive of an autoimmune disorder. Therefore, viral meningitis was our primary diagnosis. Arboviruses and Enteroviruses were considered but given the patient had no plausible exposures (mosquito bites or sick contacts, respectively) and as he presented in early spring this diagnosis was considered less likely.

A serious concern for our patient was a new acute HIV infection with an emtricitabine/tenofovir resistant viral strain. In reviews of the literature, 6 cases have been described of patients acquiring HIV despite confirmation of consistent PrEP use [4] making this a very rare but devastating possible etiology. Our patient reported 100% compliance with his PrEP regimen and does not recall missing a dose since starting the therapy. He also followed with the Baltimore VA Infectious Disease clinic and was routinely screened for STIs. On the day of his first headache, he was seen in clinic without complaints and a 4th generation HIV Ag/Ab collected at that visit would return negative during his hospitalization.

Prior to the CSF PCR results, in consideration of the patient's clinical exam, CSF findings and lack of epidemiological risk factors, the etiology of the aseptic meningitis was presumed to be HSV type 1 or 2. The patient denied any recent cold sores, or history of painful orolabial or genital ulcers. Upon exam he did not have any genital or oral lesions. He also denied having come in contact with such lesions recently. A particular concern with patients presenting with suspected herpes meningitis is progression to herpes encephalitis, which can be severe and fatal. Our patient did not meet the clinical criteria for encephalitis, as he did not have altered mental status, was afebrile throughout his disease course, and had no seizures or focal neurological findings [5]. While uncomplicated VZV meningitis could be symptomatically managed without antiviral therapy this does leave the possibility of long term sequalae from infection as well as worsening of the symptoms or progression to encephalitis. In our patient he had already had a decompensation and developed worsening nausea and emesis and therefore antiviral treatment was considered necessary to prevent further symptom progression.

The patient was started on appropriate empiric acyclovir therapy while in the ED, and this was continued throughout his hospitalization with the patient showing a good clinical response. Due to his clinical improvement, the patient was discharged with a presumptive diagnosis of HSV meningitis and valacyclovir therapy (1 g TID). The presence of a rash would have raised our concerns for VZV meningitis however, this appears to be a variable clinical finding and in a recent review of VZV meningitis cases in immunocompetent adults only 57% of cases had a rash present [6].

After the patient's CSF PCR resulted as VZV positive we had to consider if our chosen treatment approach was adequate. Due to the under recognition of this virus as an etiology of viral meningitis, no clear empiric guidelines exist and the pharmacokinetics of acyclovir and valacyclovir had to be considered closely. The 50% inhibitory concentrations (IC_{50}) of acyclovir for VZV isolates is broad, ranging from .12 μ to 10.8 μg/mL and CSF concentrations correspond to roughly ~50% of plasma drug concentrations [7]. Since valacyclovir is an acyclovir prodrug their IC_{50} is identical, however valacyclovir is more bioavailable at 55%, compared to acyclovir's 30%, and a single 1 g dose of valacyclovir results in a peak acyclovir concentration of 5–6 μg/mL with a multiple dosing regimen (2 g given four times daily), resulting in a steady-state acyclovir plasma concentration of 8.4 μg/mL [8]. Based off these parameters, the proposed optimal treatment of VZV meningitis is valacyclovir 2 g every 6 h for a total two-week duration of therapy [9]. This approach was shown to successfully treat a female patient previously who did not want to remain hospitalized for further IV acyclovir treatment [10]. Another case report highlights a patient who initially presented with a VZV rash and progressed to VZV meningitis despite being on 1 g valacyclovir TID [11].

Conclusions

This case highlights the role of herpes zoster virus as a causative agent of aseptic meningitis. While not an uncommon occurrence, it is rare as HSV type 1 or 2 are usually the more common etiology. This reinforces the need for paired testing for all three viruses when analyzing CSF via molecular diagnostic methods. In situations where CSF PCR results are not available but patients are clinically stable for discharge it may be prudent to empirically treat with a higher dose of valacyclovir (2 g) until results are available to guide management. This approach could also be useful in situations where a patient may not be amenable to a hospitalization, and furthermore, an oral option for confirmed cases of VZV meningitis would allow providers to avoid placing a PICC line for continuous IV acyclovir therapy as currently recommended. This would of course have to be weighed against the risk of side effects, primarily renal ones and would only be applicable in certain patient populations. While most immunocompetent patients with VZV meningitis are likely to recover on their own with symptomatic management antiviral therapy can help avoid long term sequalae of infection and progression to encephalitis. Further epidemiological surveillance is likely required to determine the baseline rates of HSV and VZV meningitis respectively and to see if there any variations in their prevalence overtime or within specific geographical regions globally and domestically.

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Ethical approval

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by request.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by request.

CRediT authorship contribution statement

Nazary Nebeluk: Data collection, Data analysis, Writing. **Robert Lukin:** Data collection, Writing. **Talal Alkayali:** data Collection, Writing. **Rohit Talwani:** Data collection, Data analysis, Writing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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