

CLINICAL VIGNETTE

Recurrent HSV-2 Meningitis in a Female on Suppressive Valacyclovir

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A 57-year-old female presented to the emergency department with 2 days of a progressive, global headache associated with fever, nausea, neck pain and photophobia. Her past medical history included recurrent HSV-2 meningitis for which she was on prophylactic valacyclovir, 500 milligrams twice a day. The patient had no eye pain, diplopia, lacrimation, facial rash, oral lesions or sick contacts. Just prior to her symptoms worsening, she developed a genital sore which resolved. The patient stated she had been compliant with her valacyclovir since her last episode of HSV-2 meningitis a year prior, but missed 3 doses the week of her presentation. The patient reported a total of four episodes of HSV-2 meningitis since her initial presentation in 2001.

On admission, her exam was unremarkable other than minimal meningismus. There were no facial or mucocutaneous skin lesions, nor any focal neurologic deficits. She did not have a leukocytosis and her basic metabolic panel was unremarkable. Lumbar puncture demonstrated 140 nucleated cells with 1% segmented neutrophils, 93% lymphocytes and 6% monocytes/histiocytes. Cerebrospinal fluid (CSF) glucose was 142mg/dL, protein was 63 mg/dL, and her CSF was positive for HSV-2 via PCR. The patient's CSF PCR meningitis/encephalitis panel was also negative. However, gram stain of her CSF demonstrated gram positive cocci. Infectious Disease was consulted and she was empirically treated for bacterial meningitis while CSF cultures were pending. She was also empirically treated with IV acyclovir and her home valacyclovir was held. The CSF bacterial culture finalized without any growth, as did her blood cultures. The gram positive cocci seen on her gram stain were felt to be contaminants. Her CSF bacterial panel PCR was also negative and IV antibiotics were discontinued. The patient's headache slowly improved and she was transitioned to oral valacyclovir at 1 gram every 8 hours for a total 2-week course, after which she changed to her suppressive dosing of valacyclovir at 500 milligrams twice daily indefinitely.

Discussion

Herpes simplex virus (HSV) is a double-stranded DNA virus consisting of two common clinical subtypes causing oral and genital mucocutaneous symptoms. Furthermore, both subtypes are also neurotropic. HSV-1 often causes encephalitis while HSV-2 typically causes aseptic meningitis. However, there are cases of HSV-1 resulting in meningitis and HSV-2 resulting in encephalitis, with HSV-2 being the identifiable etiology of herpes simplex encephalitis less than 10% of the time.¹ Follow-

ing primary infection, HSV infections become lifelong due to persistence within the neural root ganglia where the virus can remain latent for years. Intermittently, periods of HSV-2 viral reactivation occur manifesting most often as genital sores (and less frequently oral sores), or as recurrent benign lymphocytic meningitis (RBLM).^{2,3} RBLM is also known as Mollaret's meningitis, named after the physician who described the clinical prodrome of idiopathic recurrent meningitis prior to the development of PCR. The most common cause is HSV-2.^{1,4} RBLM may be secondary to various etiologies such as fungi, mycobacterium, malignancy, autoimmunity, intracranial anatomic abnormalities and viruses. It is characterized by more than 3 episodes of fever and meningismus lasting 2-5 days, which resolve completely and spontaneously. The symptoms in RBLM are self-limiting and less severe than bacterial meningitis. Patients are usually symptom free between attacks with complete remission of symptoms. Recurrent meningitis secondary to HSV-2 often includes symptoms of headache, photophobia, phonophobia, fever and nuchal rigidity.² The most common etiology of RBLM is HSV-2 and recurrence occurs in 20-30% of patients following primary HSV meningitis.^{4,5} The frequency of meningitis recurrences varies unpredictably in each patient and may happen within weeks, or up to years later.^{2,3} Mucocutaneous lesions are not required for diagnosing RBLM due to HSV-2, and up to 50% of patients who experience RBLM secondary to HSV-2 do not report prior genital herpetic lesions.⁴ Diagnosis of HSV-2 meningitis is confirmed by PCR of patient's CSF for HSV DNA.²

Studies investigating antiviral therapy for suppression of HSV genital lesions have found treatment effective. Valacyclovir 0.5 grams daily is effective in reducing recurrent HSV genital herpes. In patients who continue to have frequent recurrences of HSV genital sores on daily valacyclovir, twice daily dosage can be more effective.⁵ Unfortunately, there is little data on the effectiveness of suppressive antivirals for treatment of recurrent meningitis secondary to HSV-2.

One randomized, double-blind placebo-controlled trial evaluated suppressive therapy with valacyclovir 500 milligrams twice daily for a year versus placebo in patients with a history of recurrent meningitis (herpetic or unknown origin) or with a prior diagnosis of meningitis secondary to HSV-2. In the second year of the study, patients initiated on valacyclovir were given placebo and valacyclovir was held. The study was limited by a small sample size (n=101), the use of symptoms rather than PCR for diagnosis at times, and some patients not having a

definitive etiology of their recurrent meningitis during patient selection.^{3,5} Additionally, it is possible the dose used may not have penetrated the CNS enough to reach therapeutic concentrations. During the first year, HSV-2 genital sore recurrences were lower in the treatment arm, but treatment with valacyclovir did not reduce the number of episodes of meningitis with greater recurrences in the treatment arm than placebo, though this was not statistically significant. In the second year of the study when valacyclovir was withdrawn from the treatment group, the risk of recurrence of verified or probable HSV-2 meningitis was higher among patients previously on valacyclovir suppression. It was noted that a cluster of episodes occurred after drug cessation in the treatment arm.⁵

RBLM is a rare disease which is self-limiting and most patients do not experience enduring neurologic sequelae after episodes. Given the lack of data, its rarity and its self-limiting nature, guidelines for treating recurrent HSV-2 meningitis are lacking. For HSV-2 meningitis, the CDC suggests IV acyclovir dosed 5-10 milligrams per kilogram every 8 hours until the patient improves, then switching to oral therapy with valacyclovir at 1 gram 3 times daily for 10-14 days. The CDC suggests using oral valacyclovir alone from presentation to completion of treatment in patients with prior documented meningitis recurrence from HSV-2, and does not recommend suppressive therapy with valacyclovir.⁶ Despite its self-limiting nature and usual clinical course of spontaneous resolution, withholding IV acyclovir and giving only supportive treatment on presentation is not necessarily appropriate in certain clinical circumstances. For example, instances like a patient's first or second recurrence when no prior confirmation of diagnosis exists, and cases in the immunocompromised. A physician must consider herpes simplex encephalitis (HSE) on the differential, which is a neurologic emergency and IV acyclovir has been shown to decrease morbidity and mortality.¹ Additionally, data supports administering IV acyclovir in immunocompromised patients with HSV-2 meningitis as this may reduce the risk of their neurologic sequelae.^{2,4}

Conclusions

This is a classic case of recurrent HSV-2 meningitis. The patient had episodes of recurrent HSV-2 meningitis in irregular intervals lasting months to years. Her symptoms were more mild than bacterial meningitis and completely resolved between episodes. In this instance, she presented after missing several doses of her suppressive valacyclovir therapy. Data from one small trial suggests missing suppressive valacyclovir for RBLM could result in a rebound effect, and suppressive valacyclovir may not reduce the frequency of recurrent meningitis in these patients. During her acute presentation, she was treated with empiric IV acyclovir only until HSV-2 recurrence was confirmed by PCR, then given supportive measures and treated with PO valacyclovir for an additional two weeks. The foundation of treatment in confirmed HSV-2 recurrent meningitis is supportive care, with or without oral valacyclovir in immunocompetent patients. Caution must be used before withholding IV acyclovir. Missed herpes simplex encephalitis could result

in catastrophic consequences, which can occur due to HSV-1 and HSV-2. Withholding IV acyclovir in HSV-2 meningitis in an immunosuppressed patient may result in worse neurologic outcomes. After a patient's acute presentation, prescribing suppressive valacyclovir for HSV-2 recurrent meningitis may result in more frequent recurrences of aseptic meningitis if treatment is stopped or missed, as one aforementioned trial suggests. Overall, data is lacking for this disease and its treatment, but physicians should consider the possible implications of starting suppressive valacyclovir to reduce episodes of recurrent aseptic meningitis, as there is no strong data supporting patient benefit for this indication, and further research is needed.

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