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Recurrent benign lymphocytic meningitis in a 66-year-old male diagnosed with Mollaret syndrome. Is suppressive therapy necessary?

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Recurrent benign lymphocytic meningitis in a 66-year-old male diagnosed with Mollaret syndrome. Is suppressive therapy necessary?

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Abstract

Mollaret syndrome is a rare form of recurrent lymphocytic meningitis. It is defined as recurrent episodes of acute attacks that usually last for a few days and are separated by symptom-free periods that can last months to years. Herpes simplex virus 2 (HSV-2) is responsible for the majority of cases. Diagnosis is usually made by isolating the viral DNA from the cerebrospinal fluid analysis (CSF). Treatment with antivirals as a herpetic infection has been used and showed some success.

Here we present a 66-year-old male with past medical history of genital herpes who presented with his third episode of meningitis. Patient presented with low grade fevers, chills, vomiting and occipital headache. He had no active genital lesions. He had similar presentation 15 and 25 years ago. His CSF was consistent with viral meningitis and HSV-2 DNA was detected in the CSF. Antiviral therapy was initiated, and he had significant improvement in his symptoms. Suppressive therapy was not started on that patient due to infrequency of attacks. He remains symptoms free after 16 months follow up.

Mollaret syndrome is a rarely encountered medical condition. Its prevalence is estimated to be 2.2/100,000. It has an unpredictable recurrence rate and the risk of permanent neurologic damage increases with each recurrence. Treatment for acute attacks has been shown to decrease severity and duration of symptoms. One study showed that suppressive therapy with Valacyclovir had no benefits. Whether suppressive therapy would decrease recurrence rate or protect from neurologic damage still needs to be evaluated.

Introduction

Mollaret's meningitis is a form of recurrent benign lymphocytic meningitis that was first described by the French neurologist Pierre Mollaret in 1944 (1). At that time, he described characteristic monocytes and lymphocytes with variable bean-shaped nuclei in the cerebral spinal fluid (CSF) of three patients with recurrent meningitis that were later called Mollaret's cells (**Figure 1**) (2). The disease is defined as three or more episodes of recurrent aseptic meningitis that last two to five days and are typically followed by spontaneous resolution (1). These meningeal episodes are separated by symptoms-free periods that vary from patient-to-patient and can last anywhere from weeks to months to years (3).

In one study, it was reported that the mean age of onset was 40 years old with female predominance (1). Patients usually present with the typical aseptic meningitis symptoms such as fever, headache, photophobia and neck stiffness. Almost 50% of patients have transient neurologic manifestations such as altered mental status, seizures, diplopia, or cranial nerve palsies, and the risk of permanent neurologic damage increases with each attack (5). Diagnosis is usually made by CSF analysis showing viral meningitis. Polymerase Chain Reaction (PCR) of the CSF sample is used to identify the presence of viral particles that may be the etiology of the meningitis.

The relationship between Mollaret's meningitis and herpes simplex virus (HSV) was not established until the late 1990's. HSV-2 is responsible for the majority of cases and can present with or without genital lesions (3-8). Additionally, HSV-1, Epstein Barr Virus (EBV), and Varicella Zoster virus (VZV) have all also been associated with Mollaret's meningitis as well (9-10).

Case Description

Our patient is a 66-year-old male who presented with a worsening headache, stiff neck, and vomiting. His pain had radiated to his neck, shoulder, and back, and was associated with lightheadedness, chills and low grade fever. He had no improvement with NSAIDs. He denied changes in vision, photophobia, weakness, seizures, numbness, tingling, abdominal pain, urinary symptoms, incontinence, recent dental work, travel history, or sick contacts. He admitted to having a history of genital herpetic lesions but denied recent or current eruptions. Additionally, he had a history of similar meningeal symptoms both 25 and 15 years ago and at both times he was diagnosed with viral meningitis but unfortunately we couldn't obtain the records.

Physical exam revealed positive kernig and brudzinski signs. The remaining exam was benign including mental status and cranial nerve function. There was no evidence of skin rash or active genital lesions.

Initial routine labs were unremarkable. CSF sample was taken and revealed results shown in **Table 1**. PCR of the CSF detected HSV-2, without evidence of HSV-1. CSF cytology revealed lymphocytic pleocytosis with no evidence of malignant cells. CSF culture did not grow any bacteria for 5 days.

Patient was initially started on IV vancomycin, ceftriaxone, ampicillin, and acyclovir for both bacterial and viral meningitis management. Patient was continued on only acyclovir after CSF results returned to reveal viral meningitis. Symptoms greatly improved within 12 hours, with complete resolution of symptoms within 24 hours on IV acyclovir. Patient was ultimately discharged on oral valacyclovir for five more days and was told to follow up with infectious disease. After much discussion, it was decided that the patient would not benefit from low dose antiviral prophylaxis given the relatively infrequent and mild nature of his meningeal attacks.

Figures and Tables

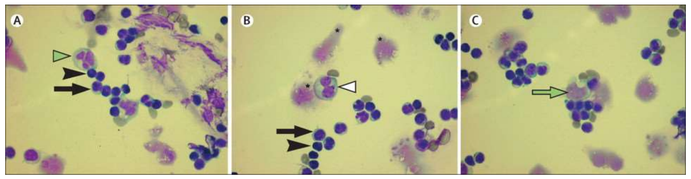

Figure 1: A. CSF cytomorphological image of large monocytes with variable shapes of nuclei (Mollaret's cells); **B.** ghost cells; **C.** normal monocytes and lymphocytes

Green arrowhead=cloverleaf nucleus. Black arrowhead=normal monocytes. Black arrow=normal lymphocytes. White arrowhead=footprint-shaped nucleus. Green arrow=bean-shaped nucleus. *=ghost cells. (2)

Tube number	3
Volume	4.0
Color	Colorless
Clarity	Clear
Glucose	48
Protein	**120**
RBC	2
WBC	**127**
Neutrophils	2
Basophils	0
Eosinophils	1
Lymphocytes	80
Monocytes	17

Table 1: Results of the CSF sample for the patient is shown here. The values highlighted in red are known to be outside the normal ranges. The presence of increased proteins and WBC counts as well as being a clear and colorless sample point towards the diagnosis of acute aseptic viral meningitis.

For reference, a normal range for CSF protein is 15-60 mg/100mL and normal CSF WBC is 0-5 per cubic mL. Normal value for RBC and eosinophils is 0.

Discussion

Although the majority of Mollaret's syndrome cases are self-limiting, most patients become hospitalized and thus given antiviral therapy to aid in recovery. Acyclovir, Valacyclovir and Famciclovir have all been used with success in acute attacks but there is limited information on their efficacy. Suppressive therapy has been used in the past but there is no general consensus on initiating such therapy in patients.

We were able to find only one study on suppressive therapy in Mollaret patients. In a double-blinded randomized clinical trial on 101 patients, 50 patients in the treatment group received 500 mg of Valacyclovir twice a day for prophylaxis and 51 patients in the control group received placebo. Results showed that there was no significant difference between the two groups in the first year in terms of recurrence rate, although genital HSV-2 recurrence rate was lower in treatment group compared to placebo. However, in the second year of the study, no study drug was given and recurrence rate of confirmed and probable cases of HSV-2 meningitis was higher in the treatment group (hazard ratio, 3.29 [95% confidence interval]) (11).

Although this data shows that the risks outweigh the benefits for suppressive therapy, there are also many limitations to this study including sample size, use of symptoms only to diagnose recurrent meningitis, and using patients without a clear etiologic diagnosis at study onset. Additionally, there is much overlap between meningeal symptoms and migraine headaches and thus, a CSF cell count and PCR analysis to confirm the diagnosis would be superior in analyzing the primary outcome (recurrence of HSV-2 meningitis) in this study. As mentioned earlier, our patient had mild symptoms with no neurologic deficits and his attacks were very infrequent, thus the decision was not to start him on suppressive therapy.

In contrast to the clinical trial mentioned earlier, we found a case of a 52-year-old female presenting with her 21st episode of documented aseptic HSV-2 meningitis within 20 years, all of which required hospitalizations and treatment. The patient was treated with IV acyclovir, with resolution of symptoms. She was then started on 800 mg of acyclovir twice a day to be taken as prophylactic therapy upon discharge. She was free of acute attacks after a 2 year follow up. (12).

There were also other reported cases that showed decrease in severity and frequency of acute attacks after initiating suppressive therapy (13) (14). In conclusion, we can say that treatment with antivirals during acute attacks can be beneficial, but due to the rarity of the disease and the variation of recurrence rates in patients, clinical trials to assess suppressive therapy have been very limited. In light of what was mentioned earlier, we feel that acute therapy is warranted but suppressive therapy should be determined on an individual basis, depending on the severity and frequency of attacks, until further clinical trials are conducted and characteristics of patients who would benefit from such therapy could be identified.

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