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ABSTRACT

Mollaret's meningitis, a rare condition primarily caused by HSV-2, presents with sudden aseptic meningitis episodes followed by complete recovery and unpredictable recurrences. Diagnosis is based on clinical history and PCR confirmation of the virus. Two patients with similar histories of headaches and prior aseptic meningitis episodes were studied. Both had neck stiffness and elevated white blood cell counts in their CSF, which tested positive for HSV-2. They were treated with IV acyclovir and discharged in good health with preventive oral treatment. Recurrent meningitis involves at least two episodes separated by full recovery. HSV-2 remains dormant in neural ganglia and can reactivate, often triggered by stress. Early antiviral therapy is recommended to reduce complications, though it can be withheld for noninfectious cases of Mollaret's meningitis. Recognizing and following up with these patients can improve treatment and reduce hospitalization time.

KEYWORDS: Mollaret cells, recurrent meningitis, HSV2 virus, acyclovir.**INTRODUCTION**

Benign recurrent lymphocytic meningitis, also called Mollaret's Meningitis is a rare disease most commonly due to HSV-2 virus.^[1] The most common presentation is characterized by attacks of sudden onset aseptic (viral) meningitis followed by complete recovery and unpredictable recurrences.^[2] Diagnosis is established through clinical history and PCR confirmation of viral infection. We present two cases of patient experiencing their third episode of aseptic meningitis in a stressful context.

OBSERVATIONS**Case n°1**

A 26 year old patient was admitted to the hospital in 2021 with a two day history of frontal headache, photophobia and nausea. His past medical history was significant for two previous episodes of documented aseptic meningitis in 2017 and 2018, respectively. On his previous admission in 2018, he was given preventive treatment (Aciclovir) but the patient stopped it in 2019. The family also reports stressful situations preceding the episodes of meningitis by a few days.

On arrival, his temperature was 37.3°C, blood pressure was 116/70 mmHg. Physical examination found neck stiffness with no deficits. Kernig's sign and Brudzinski sign were mildly positive. There were no signs of genital herpes infection, notable skin rashes or mouth ulcers.

Laboratory results showed leukocytosis (11.2 K/uL). Brain MRI was normal. Cerebrospinal fluid analysis revealed a value of 150 cells/mm³ (98% lymphocytes), hyperproteinorachia (0.86 g/l) and normal level of glucose CSF/serum ratio. Meningitis/encephalitis panel was positive for HSV-2, confirmed with CSF PCR once more. After discussed with the patient regarding the controversial use of antiviral agents, IV acyclovir 700 mg every eight hours was instituted.

The patient responded to treatment with acyclovir and was discharged a week later feeling well with a preventive oral antiviral treatment.

Case n°2

A 24-years-old, with a past history of two previous episodes of documented aseptic meningitis in 2021 treated with aciclovir and January 2022, respectively. She presented to the emergency room with meningeal syndrome and neck stiffness. Her vitals were normal but she had a fever (38.5°C).

Neurologically, Muscular strength of the bilateral upper and lower extremities was nevertheless preserved and sensory function remained intact. Initial diagnostic evaluation included a complete blood count which demonstrated a preserved white blood cell count (10 k/uL). The CT of the head without contrast were unremarkable.

In the emergency department, lumbar puncture revealed colorless clear fluid, normal CSF pressure. CSF analysis showed 230 WBCs (predominately lymphocytes), elevated protein of 1.11 g/l, and normal glucose. Meningitis/encephalitis panel was positive for HSV-2. Additional investigation into autoimmune etiologies was negative given his positive CSF findings consistent with aseptic meningitis. The patient was treated with intravenous Acyclovir 10 mg/kg three times a day. One week later, she felt better and was discharged with an oral treatment.

DISCUSSION

Recurrent meningitis is defined as at least two episodes of headache, fever, and meningismus with associated cerebrospinal fluid (CSF) pleocytosis, separated by a period of full recovery.^[3] Symptoms were noted to resolve within days to several weeks without neurologic sequelae, specifically in the absence of antibiotic/antiviral therapy. First reported by Pierre Mollaret in 1944, the diagnostic evaluation of Mollaret's meningitis revealed the presence of large mononuclear cells, termed "Mollaret cells" within the first 24 hours that is followed by lymphocytic pleocytosis within the CSF.^{[4][5]} This syndrome has also been termed benign recurrent endothelial meningitis, benign recurrent endothelial-leukocytic meningitis, benign recurrent aseptic meningitis and recurrent benign lymphocytic meningitis (RBLM). Most often, this form of aseptic meningitis is secondary to HSV-2, confirmed with PCR of CSF.

HSV-2 infections are lifelong, with viruses lying dormant within neural ganglia. By expressing latency-associated transcript (LAT) RNA, the programmed cell death mechanisms are downregulated and the virus is able to survive for many years within host cells without replication. While the current causes of viral reactivation are relatively unknown, periods of stress tend to cause reactivation of these previously quiescent infections.

Like any meningeal infection, extreme caution must be used until CSF analysis rules out bacterial etiologies. Thus, most patients are treated empirically with empiric antibiotics. There is a lack of consensus regarding empiric treatment of suspected Mollaret's meningitis in those with pending viral PCR results. As the clinical presentation and CSF findings of aseptic meningitis can be similar to that of HSV encephalitis, a life-threatening condition, there is a recommendation to empirically start antiviral therapy in those with consistent presentation and CSF findings to reduce morbidity and mortality associated with potential HSV encephalitis.^[6]

Given the rarity of this diagnosis, recommendations on definitive therapies are limited. Use of acyclovir in case reports is frequently reported, but benign and spontaneous recovery is a hallmark of RBLM even without use of antiviral therapy.^[7] Intravenous

administration of acyclovir dosed at 10 mg/kg every 8 hours during the inpatient stay, similar to the regimen in our patient's case, has been shown to help resolve symptoms.^[8] Furthermore, prophylaxis with oral antiviral therapy either continuously or intermittently can be considered in patients with more frequent episodes, as was prescribed to our patient upon discharge from the hospital.^{[9][10]}

In a more recent prospective study, however, no benefit in recurrence prevention was noted in patients placed on suppressive valacyclovir regimens after HSV-2 meningitis, but this study was not limited exclusively to patients with RBLM.^[11]

CONCLUSION

The recognition and follow up of patients with Mollaret's meningitis may contribute to establishing better treatment that could decrease the duration of hospitalization and avoid unnecessary medications.

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