

## Recurrent Aseptic (Mollaret's) Meningitis in a Patient with HIV

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### INTRODUCTION

Pierre Mollaret first described recurrent episodes of aseptic meningitis in 1944.<sup>1</sup> Since it was first noted, several etiologies have been suggested, however, with the development of polymerase chain reaction (PCR), it is now known that patients with Mollaret's meningitis contain Herpes Simplex Virus type 2 (HSV-2) in their cerebrospinal fluid (CSF) and the recurrent symptoms are due to reactivation of the virus.<sup>2</sup> The CSF analysis often reveals a polymorphonuclear pleocytosis with large (Mollaret) cells early in the course of illness, followed by a lymphocytic predominance found later.<sup>3</sup>

Patients commonly present with meningeal symptoms, including fever, headache, and neck stiffness, and signs including positive Kernig and Brudzinski signs.<sup>4</sup> They also often present with a recurrence of these symptoms, but the recurrence rate and previous medical history is extremely variable.<sup>5,6</sup> In patients with human immunodeficiency virus (HIV), given their immunosuppressive state, meningitis can be caused by various etiologies, including bacterial, fungal, and viral pathogens, including HIV itself. While cryptococcal meningitis is the most common cause of meningitis, opportunistic infections such as cryptococcus primarily infect individuals with a CD4 count less than 350.<sup>7</sup>

In this case, a patient with HIV and aseptic meningitis is presented.

### CASE REPORT

A 34-year-old female with a history significant for HIV since age 12 treated with bicitgravir/emtricitabine/tenofovir alafenamide (Biktarvy®), oral and genital HSV, and two prior episodes of HSV meningitis was admitted to the hospital for new-onset headache with associated neck pain. The patient reported a one-day history of worsening headache radiating down her posterior neck and into her spine that was worse with neck flexion. She endorsed phonophobia but denied photophobia. Notably, she reported a history of meningitis due to HSV-2 and stated that her current symptoms were the same as prior episodes.

Physical exam was significant for positive meningeal signs including positive Kernig and Brudzinski signs. She was intact neurologically with no alteration in mental status or other signs of encephalopathy. Vital signs revealed she was afebrile with a temperature of 35°C, blood pressure of 130/80 mmHg, and a pulse rate of 85 beats per minute.

Laboratory examination revealed no leukocytosis with a white blood cell (WBC) count of  $7.4 \times 10^3/L$  and a normal hemoglobin and platelet count. The metabolic panel was unremarkable. A non-contrast computed tomography scan of the head and cervical spine revealed no acute pathology. A lumbar puncture (LP) was obtained, and CSF analysis revealed an elevated WBC count with a lymphocytic predominance and elevated proteins, consistent with aseptic meningitis (Table 1). A fluid culture revealed no growth, and CSF PCR was positive for HSV-2. A CD4 count obtained during her stay was 588 cells/mm<sup>3</sup> and the HIV viral load was undetectable. The infectious disease team was consulted and recommended acyclovir given recurrent episodes. The patient

symptomatically improved over the course of four days and was discharged home with oral acyclovir for chronic HSV suppression.

**Table 1. Cerebrospinal fluid analysis.**

Appearance	Clear, colorless
WBC (K/mm <sup>3</sup> )	218
RBC (K/mm <sup>3</sup> )	< 2000
Segmented Neutrophils (%)	1
Lymphocytes (%)	93
Monocytes (%)	6
Glucose (mg/dL)	43
Protein (mg/dL)	81
Meningitis PCR	HSV-2
Cryptococcal Antigen	Negative
Fluid Culture	No Growth

### DISCUSSION

Neurologic signs and symptoms in an HIV positive patient should be evaluated cautiously with a wide differential including malignancy, infectious, psychiatric, and primary neurologic etiologies. The most common neurologic syndrome associated with a primary HIV infection is acute aseptic meningitis from HIV.<sup>8</sup> In patients with established HIV, causes of meningitis include opportunistic pathogens including toxoplasma, tuberculosis, and cryptococcus.<sup>9</sup> Notably, cryptococcal meningitis is recognized as the leading cause of meningitis in HIV-infected individuals.<sup>10</sup> However, meningitis related to opportunistic infections should be considered in patients with a CD4 count less than 350 cells/mm<sup>3</sup>, with most central nervous system (CNS) opportunistic infections occurring when the CD4 count is less than 200 cells/mm<sup>3</sup>.<sup>9</sup> In immunocompetent individuals with a CD4 count greater than 500 cells/mm<sup>3</sup>, such as in our patient, it is important to recognize and explore non-opportunistic sources of meningitis, notably HSV.

HSV co-infection is found in 30-70% of HIV-infected individuals in the U.S.<sup>11</sup> In the patient presented, HSV CNS infection was high on the differential when considering a high prevalence and increased risk of HSV-2 recurrence, in addition to an immunocompetent state.

Viral meningitis is suggested by CSF fluid analysis revealing a WBC count of 50-500 per mm<sup>3</sup> with a predominance of lymphocytes, a mildly elevated protein ranging from 30-150 mg/dL, and a glucose level of 30-70 mg/dL. Similarly, fungal meningitis, such as cryptococcus, will have a WBC count of 50-500 per mm<sup>3</sup> with a lymphocytic predominance, protein ranging from 40-150 mg/dL, and a glucose level of 30-70 mg/dL.<sup>12</sup> In contrast, fungal meningitis will have an elevated opening pressure greater than 250 mm H<sub>2</sub>O, while viral meningitis has a variable opening pressure. CSF studies in bacterial meningitis are differentiated from viral and fungal meningitides by a significant WBC elevation ranging from 100-20,000 per mm<sup>3</sup> with a polymorphonuclear predominance. Also, bacterial meningitis is noted to have low glucose, typically less than 40 mg/dL, and elevated protein ranging from 100-500 mg/dL.

Aseptic meningitis is multifactorial and can be caused by fungi, mycobacterium, malignancy, and, most commonly, viruses.<sup>13</sup> Mollaret's meningitis is an aseptic lymphocytic meningitis characterized by recurrent attacks that are separated by symptom-free periods, with intervals lasting anywhere from weeks to years.<sup>14</sup> In the first 24 hours, CSF evaluation will reveal a polymorphonuclear pleocytosis with up to several thousand cells/mL and large cells with distinct nuclear shapes known as "Mollaret cells".<sup>3</sup> Mollaret cells are characteristically fragile and easily lyse, which is why their presence most commonly is noted early in the disease process.<sup>15</sup> Thus, exemplifying the importance of a prompt LP with PCR testing to confirm the diagnosis.

The prevalence of HIV in the world continues to increase, with 30.8 million cases in 2010 to 38.4 million cases in 2021.<sup>16</sup> The increase in prevalence likely is due to continued new infections and longer life spans of individuals with HIV due to improvements in treatment. As the prevalence of HIV increases, cases of Mollaret's meningitis are likely to present more frequently. HSV-2 prevalence in HIV-infected individuals is three times that of the general population in the United States.<sup>17</sup> Thus, with an increased risk of HSV-2 infection, and increasing prevalence of HIV, the ability to recognize, diagnose, and treat Mollaret's meningitis will remain important.

## CONCLUSIONS

In HIV-infected individuals presenting with signs and symptoms of meningitis, Mollaret's meningitis should be suspected, particularly if meningitis is recurrent. HSV-2 has been found to be the leading cause of recurrent aseptic meningitis. As HIV prevalence increases, recognizing and diagnosing Mollaret's meningitis will become increasingly important to reduce cost and prevent unnecessary procedures and hospitalizations.

## REFERENCES

- 1 Saint-Martin M, Duplantis F, Laverdière M, et al. La Méningite de Mollaret. *Can J Neurol Sci* 1982; 9(1):41-43. PMID: 7093824.
- 2 Shalabi M, Whitley RJ. Recurrent benign lymphocytic meningitis. *Clin Infect Dis* 2006; 43(9):1194-1197. PMID: 17029141.
- 3 Livingston RA, Harrison CJ. Recurrent Meningitis. In: SS Long, LK Pickering, CG Prober (Eds.). *Principles and Practice of Pediatric Infectious Diseases*. Fourth Edition. Edinburgh: Elsevier, 2012, pp 287-292.e2. ISBN 978143772702.
- 4 Sehgal A, Pokhrel E, Castro WR, Haas CJ. Mollaret's meningitis: A rare entity. *Cureus* 2021; 13(5):e15264. PMID: 34189002.
- 5 Gadhiya KP, Nookala V. A rare case of Mollaret's meningitis complicated by chronic intractable migraine and papilledema: Case report and review of literature. *Cureus* 2020; 12(2):e7026. PMID: 32211261.
- 6 Ruben SJ. Mollaret's meningitis. *West J Med* 1994; 160(5):459-462. PMID: 8048238.
- 7 Vigil KJ, Zhang R, Hasbun R. Community-acquired meningitis in HIV-infected patients: Etiology, clinical features, and outcomes. *Open Forum Infect Dis* 2016; 3(Suppl 1):2173.
- 8 Singer EJ, Valdes-Sueiras M, Commins D, Levine A. Neurologic presentations of AIDS. *Neurol Clin* 2010; 28(1):253-275. PMID: 19932385.
- 9 Tan IL, Smith BR, von Geldern G, Mateen FJ, McArthur JC. HIV-associated opportunistic infections of the CNS. *Lancet Neurol* 2012; 11(7):605-617. PMID: 22710754.
- 10 Vigil KJ, Zhang R, Hasbun R. Community-acquired meningitis in HIV-infected patients: Etiology, clinical features, and outcomes. *Open Forum Infect Dis* 2016; 3(Suppl 1):2173.

<sup>11</sup> Romanowski B, Myziuk LN, Walmsley SL, et al. Seroprevalence and risk factors for herpes simplex virus infection in a population of HIV-infected patients in Canada. *Sex Transm Dis* 2009; 36(3):165-169. PMID: 19098690.

<sup>12</sup> Erdman SM, Burgos RM, Rodvold KA. *Infectious Diseases*. In: M Lee (Ed.). *Basic Skills in Interpreting Laboratory Data*. 5th Edition. Bethesda MD: American Society of Health-System Pharmacists, 2013, pp. 401-468. ISBN: 9781585283439.

<sup>13</sup> Irani DN. Aseptic meningitis and viral myelitis. *Neurol Clin* 2008; 26(3):635-655. PMID: 18657719.

<sup>14</sup> Poulidakos P, Sergi E, Margaritis A, et al. A case of recurrent benign lymphocytic (Mollaret's) meningitis and review of the literature. *J Infect Public Health* 2010; 3(4):192-195. PMID: 21126724.

<sup>15</sup> Gluck L, Robbins M, Galen B. Mollaret cells in recurrent benign lymphocytic meningitis. *Neurohospitalist* 2018; 9(1):49-50. PMID: 30671166.

<sup>16</sup> Joint United Nations Programme on HIV/AIDS. *In Danger: UNAIDS Global Aids Update 2022*. 2022. <https://www.aidsdatahub.org/resource/danger-unaid-global-aids-update-2022>. Accessed October 10, 2022.

<sup>17</sup> Patel P, Bush T, Mayer KH, et al. Prevalence and risk factors associated with herpes simplex virus-2 infection in a contemporary cohort of HIV-infected persons in the United States. *Sex Transm Dis* 2012; 39(2):154-160. PMID: 22249305.

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