

CLINICAL VIGNETTE

A Real Headache

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A 55-year-old female with a history of recurrent cutaneous lesions and chronic headaches presented with a headache and a rash. She reported her first episode of painful rash on her back in 2001 following a trigger point injection over the same location. Since that time, she reported frequent recurrences; she was intermittently treated with valacyclovir at treatment dosing (1000mg TID) and prophylactic dosing (1000mg BID) but continued to have frequent recurrences. In the 6-8 months leading up to this presentation, she reported going no more than 7 consecutive days without rash and headache-free. Breakouts in her rash were associated with acute worsening of her chronic headaches. She described her headaches as daily, associated with neck stiffness, photophobia, phonophobia, and nausea. There was no history of documented fever.

Social history revealed extensive travel in her employment as a nurse with the Red Cross. Prior to this hospitalization, she had tested negative for the presence of Lyme antibodies, Rickettsial antibodies, syphilis, complement deficiency, and HIV. Her quantitative immunoglobulins were within normal limits.

On physical exam, she was afebrile with a normal heart rate and blood pressure. Her skin exam on initial evaluation was notable for no rashes; neurologic exam showed no focal deficits with cranial nerves II-XII intact. On hospital day 2, an erythematous rash with 3-4 <0.5cm macules appeared over the left low back with a single associated vesicle. The vesicle was swabbed and returned HSV-2 (herpes simplex virus type 2) positive. She was started on intravenous acyclovir. Due to persistent headache, she underwent a lumbar puncture revealing 14 WBC/cm³ (77% lymphocytes, 22% monocytes), 7 RBC/cm³, glucose 68 mg/dL, protein 51 mg/dL. On her cerebrospinal fluid, HSV-2 PCR (polymerase chain reaction) returned negative and HSV-2 IgG returned positive. Cerebrospinal fluid cultures otherwise showed no bacterial growth. She was diagnosed with recurrent cutaneous lesions secondary to HSV-2 and suspected Mollaret's meningitis.

Discussion

Mollaret's meningitis is an entity first described in 1944 by Pierre Mollaret in a Parisian journal of Neurology.¹ In modern medical literature, it is commonly referred to as recurrent benign lymphocytic meningitis.² In his original paper, Mollaret described three patients who suffered from recurrent attacks of fever, headache, and meningismus with sterile cerebrospinal fluid containing "cell ghosts." These "cell ghosts" were identified by microscopic examination of the affected patient's cerebrospinal fluid and present within the first 24 hours of symptom onset. The cells were described as large monocytes

with characteristic bilobed nuclei; Mollaret's meningitis thus came to designate the syndrome of recurrent aseptic meningitis with the previously described symptoms lasting anywhere from several days to weeks without an identifiable pathogen. Additionally, these patients experienced interim periods free of symptoms.¹

Since the time of Mollaret, diagnostic modalities for meningitis have evolved. With increasing incidence, this syndrome has largely come to be associated with HSV-2 meningitis, typically confirmed with HSV-2 PCR (polymerase chain reaction) testing on the cerebrospinal fluid. Additionally, other viruses (echo, coxsackie) causing aseptic meningitis have also been labeled as Mollaret's meningitis when they are recurrent.³ However, in its original conception, the term was employed to describe aseptic meningitis with no identifiable pathogen present in the CSF.¹ Our case is unique in that despite her positive PCR from her skin lesions (confirming active HSV-2 infection outside the blood brain barrier), and her CSF with lymphocytosis consistent with viral meningitis, her HSV-2 PCR test on the cerebrospinal fluid remained negative. This is potentially confounded by her late presentation, that she was treated with valacyclovir prior to hospitalization, and received a dose of intravenous acyclovir prior to the lumbar puncture. One previous study showed that for patients with a diagnosis of recurrent benign lymphocytic meningitis, HSV-2 DNA was present in 46% of LP samples obtained in the first 24-48 hours of symptom onset and in 82% of samples obtained within 2-5 days of symptom onset.⁴ However, PCR is an exquisitely sensitive test, and a negative result is generally accepted as ruling out active HSV-2 infection in the meninges.

The clinical presentation in the modern conception of Mollaret's is characterized as recurrent episodes of meningismus, headache, and fever. These episodes are separated by symptom-free periods. Individual recurrences can last from days to weeks and resolve without intervention. CSF findings reveal pleocytosis with cells characterized by the "ghost-like" description above; no causative agent is identified.⁵ These make up the Bruyn criteria from a 1962 paper by the same.⁶ There are other case reports of associated skin lesions at the time of symptom occurrence. The clinical course may persist up to 5 years in total duration. Mollaret's is often described as a diagnosis of exclusion; computed tomography, intracranial angiography, and magnetic resonance imaging of the brain are typically normal before the diagnosis is entertained.⁷

Our patient's headaches and neck pain were consistently worse at the time of her cutaneous eruptions, furthering our suspicion

that meningeal inflammation in her case is driven by the same pathology causing her cutaneous lesions. Our patient fits the original definition of Mollaret's meningitis, wherein no pathogen in the CSF is identified.

REFERENCES

1. **Pearce JM.** Mollaret's meningitis. *Eur Neurol.* 2008;60(6):316-7. doi:10.1159/000159930. Epub 2008 Oct 3. PubMed PMID: 18832846.
2. **Tedder DG, Ashley R, Tyler KL, Levin MJ.** Herpes simplex virus infection as a cause of benign recurrent lymphocytic meningitis. *Ann Intern Med.* 1994 Sep 1;121(5):334-8. PubMed PMID: 8042822.
3. **Shalabi M, Whitley RJ.** Recurrent benign lymphocytic meningitis. *Clin Infect Dis.* 2006 Nov 1;43(9):1194-7. Epub 2006 Sep 26. PubMed PMID: 17029141.
4. **Kallio-Laine K, Seppänen M, Kautiainen H, Lokki ML, Lappalainen M, Valtonen V, Färkkilä M, Kalso E.** Recurrent lymphocytic meningitis positive for herpes simplex virus type 2. *Emerg Infect Dis.* 2009 Jul;15(7):1119-22. doi:10.3201/eid1507.080716. PubMed PMID: 19624935; PubMed Central PMCID: PMC2744243.
5. **Abu Khattab M, Al Soub H, Al Maslamani M, Al Khuwaiter J, El Deeb Y.** Herpes simplex virus type 2 (Mollaret's) meningitis: a case report. *Int J Infect Dis.* 2009 Nov;13(6):e476-9. doi: 10.1016/j.ijid.2009.01.003. Epub 2009 Mar 28. PubMed PMID: 19329344.
6. **BRUYN GW, STRAATHOF LJ, RAYMAKERS GM.** Mollaret's meningitis. Differential diagnosis and diagnostic pitfalls. *Neurology.* 1962 Nov;12:745-53. PubMed PMID:14016408.
7. **Mirakhur B, McKenna M.** Recurrent herpes simplex type 2 virus (Mollaret) meningitis. *J Am Board Fam Pract.* 2004 Jul-Aug;17(4):303-5. PubMed PMID: 15243021.

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