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HSV-2–Associated Mollaret's Meningitis in a Patient with History of Prior Episodes: A Case Report

Zubair Ahmed[1,*], Falak Naz[2], Asadullah[3], Paghunda Ehsan[4], Shaista Ali[5], Barkha[6], Farhan Ali[3], Laksh Kumar Ahuja[3], Saadullah[3], Muhammad Rizwan[7]

1-Department of Internal Medicine, Richmond University Medical Center, Staten Island, New York, USA
2-Research Department, Richmond University Medical Center, Staten Island, New York, USA
3-Department of Internal Medicine, Chandka Medical College, Larkana, Sindh, Pakistan
4-Holzer Health System, Gallipolis, Ohio, USA
5-Department of Internal Medicine, Shifa International Hospital, Islamabad, Pakistan
6-Department of Internal Medicine, Dow International Hospital, Karachi, Pakistan
7-Shaheed Zulfiqar Ali Bhutto Medical University Islamabad, Islamabad, Pakistan

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ABSTRACT

Mollaret meningitis is a rare, recurrent form of aseptic lymphocytic meningitis, most commonly caused by herpes simplex virus type 2 infection. The clinical presentation includes sudden, recurring attacks of headache, meningismus, and lymphocytic cerebrospinal fluid pleocytosis that resolve spontaneously. We report a case of a 45-year-old woman with known HSV-2 infection and two prior episodes of presumed viral meningitis who presented with progressive bitemporal headache, photophobia, nausea, vomiting, and fever.

Neurologic examination was intact, and brain CT and MRI were unremarkable. Lumbar puncture revealed an opening pressure of 42cm HO. CSF analysis showed WBC 441/μL (92% lymphocytes), protein 77.2mg/dL, glucose 72 mg/dL (serum 116mg/dL), and negative Gram stain and culture. A multiplex meningitis PCR panel was negative; however, targeted testing detected HSV-2 DNA in CSF, confirming the diagnosis. Empiric dexamethasone (8mg IV q6hr), ceftriaxone (2G IV q12hr), vancomycin (1G IV q12hr), and acyclovir (10mg/kg/dose IV q8hr) were initiated, and antibacterial therapy was discontinued once HSV-2 PCR positivity was established. The patient improved with supportive care. Her headache partially improved after CSF drainage and progressively resolved over the course of the hospitalization. She remained neurologically stable without visual changes and was discharged with outpatient neurology and ophthalmology follow-up to monitor for recurrent symptoms or signs of intracranial hypertension.

This case highlights HSV-2–associated Mollaret meningitis presenting with markedly elevated CSF opening pressure, underscoring the importance of targeted CSF PCR during symptomatic episodes and the need for structured follow-up, given the risk of recurrence and the potential for intracranial hypertension.

1. Introduction

Mollaret meningitis is a rare condition characterized by recurrent, sudden-onset episodes of aseptic lymphocytic meningitis that resolve spontaneously between attacks. Since Pierre Mollaret's initial report in 1944, it has remained generally consistent with the classic clinical picture of sudden-onset headaches, fever, and meningismus, with associated lymphocytic pleocytosis and sterile CSF cultures. HSV-2 is now recognized as the most commonly identified cause, as confirmed by PCR testing of CSF during symptomatic episodes [1–3].

Definitions of Mollaret meningitis vary across studies; a cohort study reports that a minimum of two episodes of meningitis were required for diagnosis, rather than the usual three. The authors, only considering HSV-2-associated Mollaret meningitis, reported an annual incidence of 1.2 cases per 1,000,000 adults [4]. Recent reports across diverse populations have shown that recurrences may be sporadic or occur years apart, affecting a broader demographic range than previously appreciated, including both sexes, various age groups, and immunocompetent and immunocompromised individuals [3, 5, 6].

Although Mollaret meningitis is traditionally described as benign, recent reports note that some episodes may be accompanied by significant inflammatory changes, including elevated intracranial pressure [3, 7]. In this case, we describe a patient with a history of prior two meningitis episodes who presented with headaches and photophobia and PCR-confirmed HSV-2 meningitis and a markedly elevated CSF opening pressure. This unusual but clinically important combination underscores the need for careful diagnostic evaluation and close follow-up.

* Corresponding author: Zubair Ahmed, Department of Internal Medicine, Richmond University Medical Center, Staten Island, New York, USA. Email: dbahmed.zubair@gmail.com

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2. Case Presentation

A 45-year-old female patient emigrated from China 10 – 15 years ago, with a past medical history of migraines, HSV-2 infection, and two self-reported prior episodes of viral meningitis (Records unavailable), presented with a mild bitemporal headache rated 4/10. The headache progressively worsened throughout the day, typically absent in the morning and intensifying at night. The pain remained localized to the temporal regions without radiation and was associated with mild nausea. She had been prescribed sumatriptan as an outpatient, but her symptoms did not improve. Several days later, on the day of presentation to the emergency department, her headache had escalated to 10/10, remained bitemporal, and was now associated with photophobia and right shoulder pain. Her immune risk evaluation was unremarkable, with negative HIV testing and no immunosuppressive conditions or medications. She was not pregnant or postpartum and denied use of corticosteroids, biologics, chemotherapy, or other immunosuppressive agents.

On arrival, vital signs included temperature 101.5°F, blood pressure 128/74 mmHg, heart rate 92 bpm, respiratory rate 18/min, and oxygen saturation 97% on room air. Given the combination of fever, severe headache, photophobia, and shoulder pain, meningitis was considered. Neurologic examination revealed the patient to be awake, alert, and oriented ×3 with intact attention, memory, and fluent speech. Cranial nerves II – XII were intact: pupils equal and reactive; visual fields full; extraocular movements full without nystagmus; facial strength symmetric; palate elevating midline; tongue midline. Motor examination showed 5-/5 strength diffusely with normal bulk and tone, and no pronator drift. Sensation to light touch was intact throughout. Reflexes were 2+ and symmetric, and coordination testing was normal. No focal neurological deficits were present. Kernig and Brudzinski signs were absent. CT head without contrast and MRI head with and without contrast showed no acute intracranial abnormality, with no diffusion restriction or meningeal enhancement. Lumbar puncture was performed in the left lateral decubitus position with the patient's legs flexed and without sedation or Valsalva maneuvers. The CSF opening pressure was 42 cm HO. Approximately 15 – 20 mL of CSF was removed; the patient experienced immediate relief of her headache, with gradual improvement thereafter. No closing pressure was documented. Bedside fundoscopy demonstrated no papilledema. Given the markedly elevated opening pressure, cerebral venous sinus thrombosis was considered; however, clinical suspicion remained low in the absence of focal deficits, prothrombotic risk factors, or suggestive imaging findings, and MR venography was deferred. After the lumbar puncture, the patient was started empirically on dexamethasone (8 mg IV q6hr), ceftriaxone (2 G IV q12hr), vancomycin (1 G IV q12hr), and acyclovir (10 mg/kg/dose IV q8hr, based on the patient's actual body weight: 53 Kg) for presumed meningitis. Baseline renal function was normal, with a serum creatinine of 0.7mg/dL and no evidence of chronic kidney disease. The patient received adequate IV hydration throughout therapy to reduce the risk of acyclovir-associated nephrotoxicity. Renal function was monitored daily; creatinine levels remained stable, and no dose adjustments were required during treatment. Dexamethasone was initiated due to concern for bacterial meningitis (particularly pneumococcal).

CSF studies **(Table 1)** demonstrated an elevated WBC count with lymphocytic predominance. A diagnosis of aseptic lymphocytic meningitis was made. The initial CSF multiplex panel was negative **(Table 2)**. Targeted CSF HSV PCR **(Table 3)** confirmed HSV-2-associated aseptic meningitis (Mollaret's Meningitis).

Table 1: CSF studies

Parameter	Value	Reference
Opening pressure	42 cm H_2O	Normal 6–20
CSF Appearance	Cloudy	Clear
CSF White Blood Cells (WBC)	441	0–8
CSF Red Blood Cells (RBC)	12	0–5
CSF Lymphocytes (%)	92%	40–80%
CSF Polymorph Cells (%)	5%	0–6%
CSF Glucose	72 mg/dL	40–70 mg/dL
Serum glucose (drawn at time of LP)	116 mg/dL	70–140 mg/dL
CSF Total Protein	77.2 mg/dL	15–45 mg/dL
CSF VDRL	Nonreactive	No syphilis detected

CSF, cerebrospinal fluid; LP, lumbar puncture; VDRL, Venereal Disease Research Laboratory test.

Table 2: Initial CSF multiplex panel (Day 0)

Test / Organism	Result
Neisseria meningitidis	Not detected
Streptococcus agalactiae	Not detected
Streptococcus pneumoniae	Not detected
Listeria monocytogenes	Not detected
Cryptococcus neoformans	Not detected
Cytomegalovirus	Not detected
Human parechovirus	Not detected
Enterovirus	Not detected
Escherichia coli K1	Not detected
Haemophilus influenzae	Not detected

Table 3: Targeted HSV PCR (Day 3)

Test / Organism	Result
Herpes simplex virus 1	Not detected
Herpes simplex virus 2	Detected
Herpes simplex virus 6	Not detected
Varicella zoster virus	Not detected

Blood and CSF cultures had been obtained before the initiation of antibiotics, and CSF cultures showed no growth at 72 hours (with blood cultures later finalizing as no growth at 5 days). During this period, the patient demonstrated clinical improvement, and CSF analysis revealed lymphocytic-predominant pleocytosis consistent with viral meningitis; ceftriaxone, vancomycin, and dexamethasone were discontinued. Once targeted HSV CSF PCR confirmed HSV-2, Acyclovir was also discontinued, and the patient was managed with supportive care in accordance with current guidelines.

She was discharged with neurology and ophthalmology follow-up for interval reassessment of headaches and visual symptoms,

Table 4: Timeline of events and findings.

Day	Events and Findings
Pre-Hospitalization (Day −7 to −5)	Gradual onset of bitemporal headache (4/10 → 10/10) with mild nausea; worsened in evenings. Trial of sumatriptan without relief. New photophobia and vomiting 1–2 days before ED visit; brief fever at home.
Day 0 — Emergency Department	Presented with 10/10 bitemporal headache, photophobia, and fever 101.5°F. Neurologic exam normal. CT head (non-contrast) and MRI brain (with/without contrast) showed no acute intracranial abnormality, no diffusion restriction, and no meningeal enhancement. LP: opening pressure 42 cm H_2O; CSF WBC 441/μL (92% lymphocytes), protein 77 mg/dL, glucose 72 mg/dL. Partial immediate headache relief after CSF removal. Empiric therapy started: ceftriaxone, vancomycin, acyclovir (10 mg/kg q8hr; weight 53 kg), and dexamethasone. Baseline renal function normal (Cr 0.7 mg/dL); IV hydration initiated for acyclovir safety.
Day 1	Headache improving; afebrile. Continued empiric antimicrobials and supportive care. Renal function monitored—stable.
Day 2	Clinically stable; headache continues to improve.
Day 3	MRI brain confirmed no acute pathology. CSF culture showed no growth. Targeted CSF PCR positive for HSV-2 → ceftriaxone, vancomycin, and dexamethasone discontinued. Acyclovir was discontinued after confirmation of HSV-2 meningitis (Mollaret meningitis) and clinical improvement.
Day 4	Significant symptomatic improvement; no photophobia; eating well; neurologically intact.
Day 5 — Discharge	Fully improved, no visual symptoms. No oral antiviral step-down was prescribed, as short-course IV therapy and spontaneous resolution are consistent with benign recurrent lymphphocytic meningitis. Discharged with acetaminophen and ondansetron PRN. Neurology and ophthalmology follow-up arranged to monitor headaches and visual symptoms and to assess for recurrence. Return precautions reviewed.

CT, computed tomography; MRI, magnetic resonance imaging; LP, lumbar puncture; CSF, cerebrospinal fluid; HSV-2, herpes simplex virus type 2; Cr, creatinine; PRN, as needed.

including repeat funduscopic evaluation if symptoms recurred or persisted. Return precautions were emphasized for worsening headache, vomiting, visual obscurations, or diplopia. She was also counselled on the natural course of HSV-2 meningitis/Mollaret's syndrome, including the possibility of recurrent episodes of aseptic lymphocytic meningitis that typically resolve spontaneously over several days. Timeline of events and findings shown in **(Table 4)**.

3. Discussion

The clinical profile of our patient, severe headache with photophobia and fever, lymphocytic CSF pleocytosis, and HSV-2 PCR positivity, supports the diagnosis of Mollaret's meningitis. Episodes are typically abrupt and self-limited over several days, followed by symptom-free intervals. Studies suggested that viral infections may potentially cause Mollaret's meningitis. In particular, HSV-2 has been implicated in causing recurrent meningitis episodes in some individuals [1–3].

Diagnostic criteria and epidemiology continue to evolve. Bruyn et al. published criteria for the diagnosis of Mollaret meningitis, defined as recurring episodes presenting with severe headache, meningismus, and fever in the absence of a detectable etiological agent [8]. Recent cohorts focused on HSV 2 – associated disease have applied less stringent thresholds (e.g., ≥2 episodes) and quantified rarity: a nationwide Danish cohort estimated an annual incidence of ˜1.2 per 1,000,000 adults, underscoring how easily this condition is underrecognized [4, 9].

Pathophysiologically, the prevailing model posits that HSV-2 latency and reactivation are linked to host susceptibility. The viral component is supported by repeated PCR confirmation during symptomatic windows and the consistency of the clinical phenotype [1–3]. Mechanistically, host factors now feature prominently: whole exome sequencing and functional immunologic studies in recurrent HSV-2 meningitis (Mollaret meningitis) demonstrate possible defects in interferon signaling and autophagy/ubiquitin pathways, which may help explain why inflammatory changes can persist beyond symptom resolution in some patients [7].

Differential diagnosis remains important whenever presentation or testing is atypical. Although HSV-2 is most frequently implicated, HSV-1, VZV, EBV, HHV-6, and even enteroviruses have been documented in recurrent aseptic meningitis with Mollaret features, and non-infectious mimics, such as epidermoid cyst leakage, can also produce recurrent lymphocytic CSF with "Mollaret cells" [1, 5, 10]. Recognizing these alternatives prevents premature anchoring and encourages repeat CSF analysis and appropriately timed virologic testing during symptomatic windows, particularly when initial multiplex panels are negative, as occurred in our patient before targeted HSV PCR established the diagnosis [1–3, 10]. In our case, the differential was addressed by (i) normal non contrast head CT and brain MRI without mass lesion or extra axial process, (ii) a CSF profile demonstrating lymphocytic pleocytosis with elevated protein and normal to slightly high glucose, (iii) negative Gram stain, bacterial cultures, and a comprehensive CSF meningitis/encephalitis multiplex PCR panel for bacterial and non HSV viral pathogens, and (iv) a subsequently positive targeted CSF HSV 2 PCR obtained during the symptomatic window. Collectively, these findings render alternative viral etiologies (HSV-1, VZV, enterovirus, HHV-6), bacterial meningitis, and non-infectious mimics unlikely, while CSF HSV-2 PCR positivity provides a specific etiologic diagnosis consistent with Mollaret's meningitis.

Management is primarily supportive during acute episodes (analgesia, hydration, antiemetics), with many clinicians administering acyclovir/valacyclovir to expedite symptom control, consistent with case-based practice and guideline-consistent care [1–3]. The role of long-term suppressive antivirals remains controversial. A pivotal randomized, double blind trial of valacyclovir suppression after HSV-2 meningitis did not demonstrate a reduction in recurrences, suggesting that routine suppressive therapy should be individualized rather than reflexive [11]. The heterogeneity in recurrence frequency, symptom burden, and patient comorbidities supports a tailored approach that emphasizes patient education on early re-presentation and the avoidance of unnecessary antibiotics once bacterial etiologies are excluded [2, 4, 6, 11].

Finally, neuroophthalmic manifestations (e.g., papilledema, cranial nerve palsies) have been described in Mollaret's meningitis and may reflect intracranial pressure dynamics and transient inflammatory effects on the visual pathways [12], which are relevant to the photophobia and severe headache prominent in our case. These features, together with our patient's raised opening pressure, underscore that Mollaret meningitis, while often self-limited, can exert meaningful physiological impact during and beyond the symptomatic window.

4. Conclusion

In summary, this case demonstrates an episode of HSV-2-associated aseptic meningitis confirmed by CSF PCR in a patient with a history of prior meningitis and a markedly elevated opening pressure. Two key clinical takeaways emerge from this presentation: (1) HSV 2 should be considered in patients with recurrent aseptic lymphocytic meningitis, particularly when CSF demonstrates a lymphocytic profile with a compatible clinical history; and (2) significant intracranial hypertension can accompany HSV-2 meningitis and warrants a structured evaluation and follow-up plan. The patient was discharged with neurology and ophthalmology follow-up to monitor for recurrent symptoms, reassess for papilledema, and provide early evaluation should future episodes occur.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Informed Consent

Written informed consent for publication was obtained from the patient.

Large Language Model

None.

Authors Contribution

ZA provided supervision, editing, reviewing, writing the original draft, and critical revision of the manuscript. FN contributed to conceptualization, data collection, writing the original draft, and reviewing. A contributed to the literature review, writing, reviewing, and visualization. PE contributed to the literature review and editing. SA provided editing, reviewing, and the literature review. B contributed to the literature review and writing the draft manuscript. FA contributed to the literature review, writing the draft manuscript, and editing. LKA provided reviewing and the literature review. S contributed to writing the original draft and the literature review. RA contributed to the literature review and editing.

Data Availability

The data supporting this case report are contained within the article. Additional details are not publicly available due to patient privacy and confidentiality considerations.

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