



## Case Report

# Mollaret's Meningitis : A Case Report and Review of the Literature

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### Abstract

Mollaret's meningitis is defined as a benign recurrent aseptic meningitis characterized by three to ten episodes of fever and signs of meningeal irritation lasting between 2 to 5 days, associated with spontaneous recovery. Mollaret<sup>1</sup> in 1944 described this rare form of self limiting aseptic recurrent benign meningitis. It is an extremely rare condition. Till 2002 approximately 50 cases of recurrent HSV meningitis have been described in the United States and in Europe. Here a report of a patient with recurrent meningitis, which resembles the criteria of Mollaret's Meningitis, is presented.

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### Introduction

Meningitis is an acute medical emergency which is caused by different organisms. Viral meningitis is one of the commonest forms of meningitis in our clinical practice. In rare instances there may be recurrent attacks of viral meningitis in an individual. Mollaret<sup>1</sup> in 1944 described a rare form of self limiting aseptic recurrent benign meningitis which has been termed as Mollaret's Meningitis. In 1962, Brynn<sup>2</sup> proposed the following clinical diagnostic criteria for diagnosis of Mollaret's Meningitis:

- Recurrent episodes of severe headache, meningism and fever;
- Attacks separated by symptom free interval of weeks to months;
- Cerebrospinal fluid (CSF) pleocytosis with large "endothelial" cells, neutrophils, and lymphocytes;

- Spontaneous remission of symptoms and signs; and
- No causative etiologic agent detected.

Mollaret's meningitis is an extremely rare condition. Till 2002 approximately 50 cases of recurrent HSV meningitis have been described in the United States and in Europe<sup>3</sup>. Here a report of a patient with recurrent meningitis, fulfilling the criteria of Mollaret's Meningitis, is presented.

### Case Report

Mr. S I, a 24 years old student from Mohonpur, Rajshahi presented with fever, severe headache, and photophobia for 3 days. The fever was continued with no chill and rigor. The headache was unremitting and severe. He also complained of vesicular eruptions around the lip for the last 6 to 7 days.

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There was no feature of pharyngitis, conjunctivitis, cough, myalgia, arthralgia or gastrointestinal upset and there was no history of genital ulcer or exposure. He denied any recent travel, insect bite, animal contact or head trauma and there was no history of similar symptoms in the family or in the vicinity.

He stated that he experienced three episodes of same type of symptoms (i.e. fever, headache, neck rigidity and vesicular eruptions on the lips) during the last nine years. Each time he got admitted into hospital and recovered completely within 4 to 7 days.

On examination the patient was febrile ( $>101^{\circ}\text{F}$ ), not anaemic with average body build and nutrition. The patient was weak but conscious, oriented and co-operative. Vesicular eruptions over the upper lip resembled Herpes labialis. There was neck rigidity and Kernig's sign was positive. Examination of the nervous system did not reveal any other abnormality. There was no lymphadenopathy, parotid gland swelling, organomegaly or jaundice. There was no bony tenderness. External genitalia were normal as was the ear, nose and throat. Examination of the other systems also revealed no abnormality.

The patient remained febrile for about five days. After that the fever gradually came down as also the other symptoms of the patient. By ten days the patient fully recovered and was discharged with complete cure.

Routine blood, urine and chest skiagram revealed no significant abnormality. Sonogram of the abdomen was normal. CSF was clear with a cell count of 15 lymphocytes/mm<sup>3</sup>. CSF protein level was 24 mg/dl and sugar- was 70 mg/dl. Anti-nuclear factor was negative.

Blood immunoglobulin level was estimated. I revealed that total IgG level was 1875 (Normal: 800 to 1500 mg %). Serum complement level estimation showed that C<sub>3</sub> was 195 mg% (Normal: 55 to 120 mg%) and C<sub>4</sub> was 34 mg% (Normal: 20 to 50 mg%). Blood for Anti HSV- Ab (by ELISA) showed the following picture:

Anti HSV 1- IgM: Positive (Ratio: 2.44)

Anti HSV 1- IgG: Positive (Ratio: 1.52)

Anti HSV 2- IgM: Negative (Ratio: 0.62)

Anti HSV 2- IgG: Borderline (Ratio: 0.91)

PCR assay of CSF to detect HSV 1 and HSV 2- was negative.

## Discussion

Mollaret's meningitis is defined as a benign recurrent aseptic meningitis characterized by three to ten episodes of fever and signs of meningeal irritation lasting between 2 to 5 days, associated with spontaneous recovery.<sup>4</sup> Each episode of illness resembles individual attacks of meningitis. There is fever (up to  $104^{\circ}\text{F}$ ) with headache and neck rigidity. Individual attacks are sudden with symptoms and signs reaching maximum intensity within few hours. These usually persist for one to three days but may be present for up to three weeks. Recurrences can span a period of more than a decade and then suddenly disappear. The long term health of the patient is not adversely affected. Transient neurologic abnormalities (seizures, diplopia, pathologic reflexes, cranial nerve paresis, hallucinations, and coma) occur in as many as 50% of cases. However, persistence of neurologic defects calls the diagnosis into question.

Cerebrospinal Fluid (CSF) examination is the cornerstone for diagnosis of meningitis and is usually performed at the earliest opportunity whenever suspected. CSF obtained early in the course of a patient with Mollaret's meningitis may demonstrate large, friable "endothelial" cells termed Mollaret's cells. Mollaret's cells can be demonstrated by the Papanicolaou stain, and are now considered to be large activated cells of monocyte/macrophage lineage. Mollaret's cells are considered by many to be the hallmark of Mollaret's meningitis, and may comprise 60% to 70% of the CSF cells in early cases. These cells are usually present for only the first 24 hours and can be missed easily. Controversy continues about the importance of Mollaret's cells for the diagnosis of Mollaret meningitis.<sup>5</sup> Tedder et al<sup>6</sup> reported on thirteen patients with benign recurrent

lymphocytic meningitis which fit most of the clinical diagnostic criteria for Mollaret's meningitis, but none had Mollaret's cells demonstrated in their CSF.

As a rule, the glucose content of the CSF remains normal. This is important because a low glucose concentration in conjunction with a lymphocytic or mononuclear pleocytosis usually signifies tuberculous or fungal meningitis or certain noninfectious disorders such as metastatic carcinoma, lymphoma, or sarcoidosis of the meninges.<sup>7</sup> Infrequently, a mild depression of the CSF glucose (never below 25 mg/dL) has been reported with the meningitis caused by mumps, HSV-2, lymphocytic choriomeningitis, or the VZ virus. There is a small and variable increase in CSF protein, especially the gamma globulin fraction.

Mollaret Suggested that disease in some of these patients might be caused by viruses.<sup>8</sup> In patients with Mollaret's meningitis microorganisms cannot be demonstrated by conventional smear or bacterial culture of the CSF or blood. So these patients are said to be suffering from "aseptic" meningitis. The term aseptic meningitis was first introduced to designate what was thought to be a specific disease- "aseptic" because bacterial cultures were negative. The term is now applied to a symptom complex that can be produced by any one of numerous infective agents, the majority of which are viral, but a few of which are bacterial like, mycoplasma, Q fever, other rickettsial infection, etc., but which cannot be grown in normal culture media. In brief, the clinical syndrome of aseptic meningitis consists of fever, headache, signs of meningeal irritation, and a predominantly lymphocytic pleocytosis with normal cerebrospinal fluid (CSF) glucose. Aseptic meningitis is mainly a benign, self-limiting condition, although exceptions may occur.

Recurrent aseptic meningitis has been described following exposure to a number of drugs including non-steroidal anti-inflammatory analgesics, antibiotics including penicillin, immune globulin, OKT3 monoclonal antibody, cytosine arabinoside,

and azathioprine.<sup>9</sup> Newer drugs and chemicals are continually being added to this list. Clinical features are similar to acute pyogenic meningitis and some may have a rash. CSF examination reveals a polymorphonuclear response with no organisms. Diagnosis is historical and it is essential to obtain a full and exhaustive drug history in all cases of recurrent meningitis. Demonstration that a particular drug is the cause can be confirmed by re-challenge, but this is not without hazard to the patient.

Immune deficiency due to any cause may give rise to recurrent attacks of meningitis, both 'aseptic' and septic. Kojima et al<sup>3</sup> in their patient of Mollaret's meningitis found that the serum IgE level was elevated to two times the normal range, whereas serum IgG, IgA, IgM and complement levels were within the normal range. They also excluded asymptomatic Human Immunodeficiency Virus infection by estimation of the CD4/CD8 cell ratio which was normal. We also estimated the total IgG level and the complement C3 and C4 of our patient which were normal.

In Mollaret's meningitis the cause of the meningitis was not known initially and specific infectious agents had rarely been identified in patients with benign recurrent meningitis.<sup>11, 12, 13</sup> Yamamoto et al<sup>14</sup> in 1991 were the first to report a case of Mollaret's meningitis with polymerase chain reaction (PCR) confirmation of HSV type 1 DNA in the CSF. Since then, HSV DNA, mostly HSV type 2, has also been detected in the CSF by PCR amplification technique in patients with HSV Mollaret's meningitis.<sup>15, 16, 17, 18, 19, 20, 21, 22, 23</sup>

The pathogenesis of Mollaret's meningitis remains obscure. It is not known how HSV reaches the central nervous system from the primary site of infection. Proposed hypotheses suggest either possible neural or haematogenous routes. HSV usually stays in the latent phase or at a low level of infectivity after the primary infection. Once it is reactivated, it can cause recurrent mucocutaneous illness through peripheral nerve spread from the ganglia. Venot et al<sup>21</sup> demonstrated that the same HSV type 2 strain caused meningitis in a patient

with recurrent genital herpes by using PCR analysis together with a restriction enzyme technique. Kojima et al<sup>3</sup> and Picard et al<sup>17</sup> detected HSV genome in the CSF, but not in the blood samples. This evidence supports the hypothesis of centripetal spread from the peripheral reactivation in the sensory ganglia to the meninges, and refutes claims of hematogenous spread.

The patient presented in this case report had four attacks of illnesses having meningitis like features during the last nine years. In their study of 13 consecutive patients with a provisional diagnosis of benign recurrent lymphocytic meningitis Tedder et al<sup>6</sup> found that the mean number of attacks was 4.6, ranging from 3 to 9, during periods ranging from 2 to 21 years with a mean of 8.4 years. So our patient had the mean number of attacks within the mean number of years. With regard to the reported cases of HSV type 2 Mollaret's meningitis, women are typically more frequently affected than men.<sup>3</sup> In Tedder's series of 13 patients also there were 9 women, but our patients was a male. Attacks of meningitis lasted 3 to 14 days with a mean of 6.3 days in the 13 patients which also corresponds to the duration of illness of our patient whose recovery was complete within 7 days during all the 4 episodes. In our patient CSF examination revealed 15 lymphocytes/mm<sup>3</sup> and no polymorphs which is less than the mean of 443 cells/mm<sup>3</sup> with 58% to 98% lymphocytes reported in the 13 patients. So our protein content of 24 mg% is also less than the mean of 122 mg/dL (range of 41 to 240 mg/dL) reported in the above series of patients. Sugar content of CSF in our patient was not reduced below normal (70 mg%) which is what is expected in patients of Mollaret's meningitis. Gonzales et al<sup>18</sup> in their patient of recurrent dermatomal vesicular skin lesions with meningitis examined the CSF and found 345 white blood cells, 96% monocuclear; the protein level was 150 gm/dL and the glucose level was 56 mg/dl. Kojima et al<sup>3</sup> examined the CSF of their patient of Mollaret's meningitis and found mononuclear pleocytosis (735/mm<sup>3</sup>, 87% lymphocytes and monocytes, and 13% neutrophils without Mollaret's cells) and an increased protein

level (184mg/dL) but a normal glucose level (51mg/dl). Thus it is evident that examination of the CSF reveals varied biochemical and cytological findings in patients of Mollaret's meningitis, though there was always an increase of cells with predominance of mononuclear cells.

Mollaret in his initial report of the patient with recurrent meningitis had detected presence of large friable 'endothelial' cells in the CSF which were termed "Mollaret's cells". Though initially a lot of importance was given to the finding of Mollaret's cells in the CSF, most of the later case reports did not mention presence of such cells in the CSF<sup>3,6,23</sup>. In our patient also Mollaret's cells were not detected in the CSF.

Unfortunately the blood or the CSF of our patient was not cultured to detect the presence of any bacteria. The biochemical and cytological report of the CSF examination of our patient was strongly against a bacterial infection as there was neither a pleocytosis or polymorphonuclear leucocytosis, nor decrease in the sugar content or increase in the protein content.

A very significant point in the history of our patient is that during each episode of his illness he had the vesicular eruptions on his lips. So his history suggests that he had reactivation of Herpes Simplex Virus 1 infection during each attack and it is logical to assume that each attack of meningitis was precipitated by the reactivation of the HSV-1 virus. Meningitis and encephalitis caused by HSV infection may be difficult to recognize because they are only rarely associated with clinical evidence of extraneural infection. Even when meningitis results from reactivation of latent HSV type 2 infection in patients with known genital herpes, coincident herpetic skin lesions are seldom documented. Kojima et al<sup>3</sup> in their case report of a patient of Mollaret's meningitis in which there were 7 episodes of recurrent meningitis within a 7 year period, found that genital herpes preceded or was associated with recurrent meningitis during the first, third and fourth attacks, while the patient did not notice genital herpes in the second attack and after the fifth attack. They deduce that "after

the earliest attacks, recurrent meningitis often lacks an association with genital herpes". In Japan, HSV type 1 rather than HSV type 2 is the primary cause of genital herpes;<sup>27</sup> however, recurrent cases of genital herpes are primarily caused by HSV type 2, as is the case in other countries. In Tedder's series,<sup>6</sup> only 3 of the 11 patients with HSV DNA and antibody in their cerebrospinal fluid had a history of recurrent genital HSV infection. The 3 patients studied for that series who had recurrent genital HSV did not have mucocutaneous manifestations at the time of the meningitis attack, and fewer than 50% of their previous attacks were associated with herpes genitalis. The single patient with HSV type 1 antibody had a history of oral HSV infection. From review of the literature and our experience, we may conclude that in Mollaret's meningitis caused by HSV-2, mucocutaneous manifestations may not be present, while in HSV-1 infection the cutaneous manifestations are mostly present.

Blood examination of our patient revealed presence of both IgM and IgG antibodies by ELISA method against Herpes Simplex virus type 1. IgM antibodies by ELISA were negative for HSV 2 and Borderline for IgG. Presence of antibodies in blood against HSV 1 indicates infection by this virus confirming the clinical presentation as there was presence of vesicular eruptions on the lips of the patient which is usually a presentation of Herpes Labialis caused by HSV1.

The CSF of our patient was examined at the International Centre for Diarrhoeal Diseases Research in Bangladesh, (ICDDR, B) Dhaka, by Polymerase Chain Reaction (PCR) for the presence of HSV DNA. Unfortunately PCR failed to detect HSV-1 & HSV-2 DNA in the CSF of our patient. The PCR assay is extremely sensitive and highly specific for the diagnosis of HSV infection of the central nervous system.<sup>6</sup> In 11 out of the 13 patients of Tedder et al<sup>6</sup>, HSV DNA was detected by PCR; the amplified sequence of DNA in 10 of these specimens was HSV type 2. In all of the cerebrospinal fluid specimens with HSV type 2 DNA, HSV type 2 antibody was also present. The

cerebrospinal fluid from one patient had HSV type 1 DNA and HSV type 1 antibodies. Herpes simplex virus DNA could not be detected in cerebrospinal fluid specimens from two patients, although both contained antibody to HSV type 2. Thus only 2 of 13 patients had benign recurrent lymphocytic meningitis that was not associated with an HSV infection in the central nervous system, as defined by the presence of HSV DNA. So our patient is similar to these two patients of Tedder's series<sup>6</sup> as he also had antibody present in the blood against HSV-1 but CSF was negative for presence of HSV DNA by PCR assay.

As Mollaret's meningitis is a self limiting benign condition no specific treatment was recommended. But with the recognition of a causative agent like the HSV, against which specific antiviral therapy is available, in most of the recent case reports acyclovir and/or valacyclovir therapy was started as treatment.<sup>3,23</sup> However, treatment with acyclovir had not been shown to definitively alter the natural history of the disease.<sup>28</sup> Moreover the failure of treatment of either primary or recurrent disease to reduce the frequency of subsequent recurrences has indicated that acyclovir is ineffective in eliminating latent infection also. Chronic oral administration of acyclovir for periods of 1 to 6 years or longer or of valacyclovir for up to 1 year has reduced the frequency of recurrences markedly during therapy but once the drug is discontinued, lesions recur. Valacyclovir is approved for the treatment of initial and recurrent episodes of genital HSV infections in immunocompetent adults as well as for suppressive treatment of genital herpes.<sup>29</sup> When patients present with HSV Mollaret's meningitis, long-term suppressive therapy or patient initiated therapy with oral valacyclovir should nonetheless be considered.<sup>3</sup>

Mollaret's meningitis is an extremely rare condition. This case report highlights the fact that such an uncommon condition is present in our patients also. Physicians should consider this diagnosis whenever they are confronted with a patient of recurrent meningitis, when other causes of such condition have excluded.

## References

1. Mollaret P. La meningite endothelio-leucocytaire multirecurrente benigne. Syndrome nouveau ou maladie nouvelle? Documents clinique. *Rev. Neurol.* 1944; 76: 57-76.
2. Bruyn GW, Staathof LJ, Raymakers GMJ. Mollaret's meningitis. Differential diagnosis and diagnostic pitfalls. *Neurol* 1962; 12:745-53.
3. Kojima Y, Hashiguchi H, Hashimoto T, et al. Recurrent Herpes Simplex Virus Type 2 Meningitis: A case report of Mollaret's Meningitis. *Jpn J Infect Dis* 2002; 55:85-88.
4. Galdi A. Benign recurrent aseptic meningitis (Mollaret's meningitis). *Arch Neurol* 1979; 36: 657-658.
5. Achard JM, Duverlies G, Schmit JL, Lebon P, Veyssier P, Fournier A. Mollaret's meningitis and herpes simplex virus type 1 (Letter). *N Engl J Med* 1992; 326: 893-94.
6. Tedder DG, Ashely R, Tyler KL, Levin MJ. Herpes simplex virus infection as a cause of benign recurrent lymphocytic meningitis. *Ann Intern Med* 1994; 121:334-338.
7. Victor M, Ropper AH. Adams and Victor's Principles of Neurology 7th ed. McGraw-Hill, New York. 2001: 786.
8. Mollaret P, Tournier P. Un type special de meningite endothelio-leucocytaire multirecurrente benigne avec fluxions parotidiennes synchrones. Isolement d'un ultra-virus en embryon de poulet. *Bulletins et Memoires de la Societe Meidcale des Hopitaux de Paris.* 1952; 68:946-54.
9. Gordon MF, Allon M, Coyle PK. Drug induced meningitis. *Neurology* 1990; 40: 163-64.
10. Milne Anderson. Meningitis. In: *Brain's Diseases of the Nervous System.* Ed. Michael Donaghy. Oxford University Press, New York 2001; 1097-1116.
11. Steel JG, Dix RD, Baringer JR. Isolation of herpes simplex virus type 1 in recurrent (Mollaret) meningitis. *Ann Neurol* 1982; 11:17-21.
12. Pal GS, Baker JT, Humphrey PR. Lyme disease presenting as recurrent acute meningitis. *Br Med J* 1987; 295:367.
13. Graman PS. Mollaret's meningitis associated with acute Epstein-Barr virus mononucleosis. *Arch Neurol* 1987; 44(11): 1204-05.
14. Yamamoto LJ, Tedder DG, Ashle R, and Levin MJ. Herpes simplex virus type 1 DNA in cerebrospinal fluid of a patient with Mollaret's meningitis. *N Rngl J Med* 1991; 325:1082-85.
15. Bergstrom T, Vahine A, Alestig K, Jeansson S, Forsgren M, Lycke E. Primary and recurrent herpes simplex virus type 2 induced meningitis. *J Infect Dis* 1990; 162: 322-330.
16. Berger JR. Benign aseptic (Mollaret's) meningitis after genital herpes. *Lancet* 1991; 337:1360-1361.
17. Picard FJ, Dekaban GA, Silva J, Rice GP. Mollaret's meningitis associated with herpes simplex type 2 infection. *Neurology* 1993; 43: 1722-1727.
18. Lortholary O, Rozenberg F, Personne C, djebbour S, Lelport C, Vilde JL. Herpes simplex virus type 2 DNA in cerebrospinal fluid of a woman with recurrent meningitis. *Clin Infect Dis* 1993; 17:941-942.
19. Cohen BA, Rowley AH, Long CM. Herpes Simplex type 2 in a patient with Mollaret's meningitis: demonstration by polymerase chain reaction. *Ann Neurol* 1994; 35: 112-116.
20. Bachmeyer R, de la Blanchardiere A, Lepercq J, Dhote R, Grateau G, et al. Recurring episodes of meningitis (Mollaret's meningitis) with one showing an association with herpes simplex virus type 2. *J Infect* 1996; 32:247-248.
21. Venot C, Beby A, Bourgoin A, Giraudeau G, Becq Giraudon B, Agius G. Genital recurrent infection occurring 6 months after meningitis due to the same herpes simplex virus type 2 (HSV-2) strain evidence by restriction endonuclease analysis. *J Infect* 1998; 36: 233-2335.
22. Jensenius M, Myrvang B, Storvold G, Bucher A, Hellum KB, Bruu AL. Herpes simplex virus type 2 DNA detected in cerebrospinal fluid of 9 patients with Mollaret's meningitis. *Acta Neurol Scand* 1998; 98: 209-212.
23. Gonzales N, Tyler KL, Gilden DH. Recurrent Dermatoma Vesicular Skin Lesions. A clue to diagnosis of Herpes Simplex Virus 2 Meningitis. *Arch Neurol* 2003; 60: 868-69.
24. Plummer G. Isolation of herpes viruses from trigeminal ganglia of man, monkeys and cats. *J Infect Dis* 1973; 128:345-47.
25. Warren KG, Devlin M, Gilden DH, et al. Isolation of herpes simplex virus from trigeminal ganglia, including ganglia from one patient with multiple sclerosis. *Lancet* 1977; 2:637-69.
26. Baringer JR. Recovery of herpes simplex virus from human sacral ganglions. *N Engl J Med* 1974; 291: 828-30.
27. Kawaka T, Kawaguchi T, and Sakamoto S. Clinical and biological studies on genital herpes. *Lancet* 1976; II:964.
28. Bergstrom T, Alestig K. Treatment of primary and recurrent herpes simplex virus type 2 induced meningitis with acyclovir. *Scand J Infect Dis* 1990; 22: 239-40.
29. Dolin R. Antiviral chemotherapy excluding antiretroviral drugs. In: *Harrison's Principles of Internal Medicine, 15th edition.* Eds: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, McGraw Hill, New York. 2001: 1092-1100.

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