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Mollaret Meningitis Associated With an Intraspinal Epidermoid Cyst

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ABSTRACT

Mollaret meningitis, a benign recurrent aseptic disease, is known to be associated with intracranial epidermoid cysts. In this report, we describe a case of Mollaret meningitis caused by an intraspinal epidermoid cyst located at thoracic level 12. The patient’s clinical manifestations and cerebrospinal fluid features were similar to those with bacterial meningitis characterized by predominant polymorphonuclear leukocytes. However, Mollaret cells, not bacteria, were identified in the patient’s cerebrospinal fluid. The illness ceased after surgical resection of the cyst, and the cyst tissue was pathologically diagnosed as epidermoid. Therefore, an intraspinal epidermoid cyst can be etiologically associated with Mollaret meningitis and should be included in the differential diagnosis of recurrent aseptic meningitis.

MOLLARET MENINGITIS was initially described by Mollaret1 in 1944 as a form of aseptic meningitis without identifiable infecting agents. It is characterized as recurrent, aseptic, mild, and self-limiting. To date, ~50 cases have been reported in the world, and most have been associated with viral infection, especially herpes simplex type 2.2-5 Other reported etiologies include Vogt-Koyanagi syndrome, Harada syndrome, Behçet disease,6 allergic, systemic lupus erythematosus, familial Mediterranean fever,7 glioblastoma, and Whipple disease, as well as intracranial hydatid, sarcoidosis, and epidermoid cysts.8

In 1962, Bruyn6 proposed criteria for the clinical diagnosis of Mollaret meningitis: (1) recurrent episodes of severe headache, meningismus, and fever; (2) cerebrospinal fluid (CSF) pleocytosis with large “endothelial” cells, neutrophils, and lymphocytes; (3) attacks separated by symptom-free periods that last weeks to months; (4) spontaneous remission of symptoms and signs; and (5) no causative etiologic agent. The so-called large endothelial cells were confirmed in subsequent studies to be enlarged monocytes/macrophages in origin.9 On the basis of these criteria, we recently identified a case of recurrent Mollaret meningitis that was associated with an intraspinal epidermoid cyst. Intraspinal epidermoid cysts in children frequently cause recurrent episodes of bacterial meningitis associated with a dermal sinus tract. The connection between intraspinal epidermoid cysts and the skin surface provides direct access for bacteria on the skin to reach the interior cysts and may result in meningitis. However, the epidermoid cyst in our patient was concealed in the spinal subarachnoid, and no such sinus tract was found. We believe this to be the first case of Mollaret meningitis secondary to an intraspinal epidermal cyst that was not associated with a communicating dermal sinus.

CASE REPORT

An 8-year-old girl presented with repeated episodes of malaise, fever, nausea, vomiting, and headache. In the previous 27 months, she had suffered 38 episodes of “meningitis,” each with similar clinical manifestations.

During the first episode, she had a temperature of 38.5 to 40.5°C, headache, and vomiting. Her physical examination revealed a stiff neck, positive Brudzinski sign, and positive Kernig sign. Her CSF was colorless with a hazy appearance and had a white blood cell count of 100. The CSF analysis revealed a predominance of lymphocytes (85%), with a few neutrophils (15%). The protein level was 77 mg/dL, and the glucose level was 44 mg/dL, both of which were normal. The Gram stain and culture of the CSF were negative. The MRI scan of the brain showed a hypointense area at the level of the conus medullaris, consistent with an intraspinal epidermoid cyst. The patient was treated with intravenous antibiotics and antipyretics, and her symptoms improved gradually. After 2 weeks, the fever and headache subsided, and the patient returned to her normal daily activities.

Key Words: Mollaret meningitis, epidermoid cyst

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell; PMN, polymorphonuclear leukocyte; T12, thoracic level 12

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The WBC differential count was 12% lymphocytes, 2% monocytes, and 86% neutrophils. Glucose was 56 mg/dL, and protein was 106 mg/dL. A CSF stain was negative for acid-fast bacteria and fungus. A peripheral WBC count was 15 000/mm³, with 72% neutrophils and 18% lymphocytes. Blood and CSF bacterial cultures were negative. Brain MRI results were normal. The patient was admitted to a local hospital, and penicillin and cefazidime were given for presumed bacterial meningitis. The symptoms and signs disappeared without any local neurologic signs 7 days later. A repeat lumbar puncture performed on the 15th day of hospitalization revealed nearly normal CSF parameters (WBC count of 7/mm³, with 2 neutrophils). She was discharged 20 days postadmission. Subsequently, the girl experienced 37 episodes of “recurrent meningitis” with symptom-free intervals between episodes. Although she experienced these episodes of recurrent meningitis, the patient was otherwise healthy, and no neurologic sequelae were discovered. During every episode, the symptoms, signs, and recovery process were nearly the same. Laboratory results were similar to those of bacterial meningitis in many respects. There was a CSF pleocytosis with 1000 to 3500 WBC per mm³ and 56% to 99% neutrophils. The CSF protein was mildly elevated, and glucose was slightly decreased. The CSF usually became normal after 2 weeks of treatment. No known specific infectious cause was identified. Every episode was diagnosed as recurrent meningitis and treated with antibiotics, dexamethasone, and a dehydrating agent such as mannitol. The symptom-free periods ranged from 2 to 6 months in the early period. During the last 3 months of her illness, the attacks became more frequent, with intervals of 3 to 7 days between episodes.

On May 11, 2005, she came to our hospital complaining of headache, fever, and stiff neck. Physical examination on admission revealed a temperature of 39.6°C, heart rate of 112 beats per minute, respiratory rate of 25 breaths per minute, and blood pressure of 96/65 mm Hg. No rash, lymphadenopathy, or skin sinuses were found. Neurologic examination revealed a stiff neck, positive Brudzinski sign, and positive Kernig sign. No other focal neurologic signs were discovered. A lumbar puncture was performed on admission and revealed a hazy CSF. The CSF contained no red blood cells and 2520 WBCs per mm³. The WBC differential count was 12% lymphocytes, 2% monocytes, and 86% neutrophils. Glucose was 56 mg/dL, and protein was 106 mg/dL. A CSF stain was negative for acid-fast bacteria and fungus. A peripheral WBC count was 15 000/mm³, with 72% neutrophils and 18% lymphocytes. Blood and CSF bacterial cultures were negative. Brain MRI results were normal. The patient was admitted to a local hospital, and penicillin and cefazidime were given for presumed bacterial meningitis. The symptoms and signs disappeared without any local neurologic signs 7 days later. A repeat lumbar puncture performed on the 15th day of hospitalization revealed nearly normal CSF parameters (WBC count of 7/mm³, with 2 neutrophils). She was discharged 20 days postadmission. Subsequently, the girl experienced 37 episodes of “recurrent meningitis” with symptom-free intervals between episodes. Although she experienced these episodes of recurrent meningitis, the patient was otherwise healthy, and no neurologic sequelae were discovered. During every episode, the symptoms, signs, and recovery process were nearly the same. Laboratory results were similar to those of bacterial meningitis in many respects. There was a CSF pleocytosis with 1000 to 3500 WBC per mm³ and 56% to 99% neutrophils. The CSF protein was mildly elevated, and glucose was slightly decreased. The CSF usually became normal after 2 weeks of treatment. No known specific infectious cause was identified. Every episode was diagnosed as recurrent meningitis and treated with antibiotics, dexamethasone, and a dehydrating agent such as mannitol. The symptom-free periods ranged from 2 to 6 months in the early period. During the last 3 months of her illness, the attacks became more frequent, with intervals of 3 to 7 days between episodes.

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inflammation reaction was observed in the cyst wall (Fig 3 B and C). Cellular debris and keratin were observed within the cyst, but there were no inflammatory cells. Gram-staining and bacterial cultures of the cyst liquid were negative (data not shown), as were acid-fast bacteria and fungi cultures. The cyst tissue was pathologically diagnosed as epidermoid.

Postoperative MRI showed that the cyst was removed completely, and the spinal cord was integrated (Fig 2). The child recovered completely after the operation, and no additional episodes of meningitis have occurred during the next 15 months.

DISCUSSION
Mollaret meningitis was first described as a benign recurrent aseptic meningitis of suspected viral etiology. In particular, herpes simplex virus type 2 was frequently reported to be associated with this disease. However, our laboratory testing (blood and CSF examination) in this patient did not reveal the presence of herpes simplex virus type 2 or other viruses. Instead, MRI revealed a spinal cyst at T12, with pathologic epidermoid confirmation (Figs 2 and 3). Its association with Mollaret meningitis was demonstrated by the cessation of symptoms and signs after surgical removal of the cyst. Therefore, in suspected cases of Mollaret meningitis, imaging of the spinal cord should be considered despite the absence of spinal cord symptomatology.

Our patient had a similar clinical presentation and CSF profile to other cases reported to be caused by intracranial cysts. Analysis of the CSF in this patient and other patients with Mollaret meningitis associated with epidermoid cysts revealed a feature distinct from viral Mollaret during the acute phase (Tables 1 and 2). Although the CSF of patients with Mollaret meningitis caused by herpes simplex virus type 2 displays the same features as other viral meningitis (a mild increase in WBCs and neutrophils), the CSF of those with epidermoid cysts shows more marked CSF pleocytosis with a predominance of PMNs. In addition, frequent recurrence of meningitis without neurologic sequela is another clinical feature of Mollaret meningitis that is different from bacterial meningitis. Thus, we suggest that, among patients with clinical symptoms indicative of Mollaret meningitis, increased levels of WBCs and PMNs in the CSF at the acute phase create speculative evidence that an epidermoid cyst may be the cause of this disorder.

The similarities in the CSF profile between epidermoid cyst–associated Mollaret meningitis and bacterial meningitis make the differential diagnosis difficult in the acute phase. In addition, it has been reported that intraspinal epidermoid cysts in children frequently cause recurrent episodes of bacterial meningitis associated with a dermal sinus tract. The sinus provides a pathway for bacterial entry into the subarachnoid space. However, no such sinus tract was found in our patient, and no bacterium was detected in the cyst liquid, blood, or CSF through culture and Gram-staining. Therefore, aseptic recurrent meningitis in our case is etiologically attributed to an intraspinal epidermoid cyst. This statement is further supported by the cessation of the illness after removal of the cyst from this patient.

The mechanisms by which an intraspinal epidermoid cyst forms or triggers meningitis are unclear. Intracranial
epidermoid cysts are usually congenital and arise from ectodermal cell rests. It remains unclear whether intraspinal epidermoid cysts are also congenitally originated. In addition, it has been reported that lumbar puncture can result in the formation of spinal epidermoid cysts. However, this is not likely the case for our patient, because the cyst was situated ventral to the spinal cord, where it is unlikely to have been caused by puncture. In addition, the patient had no history of receiving a lumbar puncture before the symptoms. As for the pathogenesis of epidermoid cyst–associated meningitis, a proposed hypothesis suggests that the spontaneous rupture of the epidermoid cyst, on repeated occasions, may release contents into the subarachnoid space, causing relapsing chemical meningitis. The wall of the cyst might be closed and the cyst replenished after the rupture; we observed an intact wall around the cyst during surgery, when the patient was asymptomatic (Fig 3A).

Mollaret meningitis has been considered a “self-limiting disease.” Unfortunately, the self-limited trend was not observed in the case reported here. On the contrary, the frequency of attacks increased over time. The symptom-free periods decreased from 2 to 6 months in the

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Source</th>
<th>Age</th>
<th>Gender</th>
<th>No. of Episodes</th>
<th>CSF Analysis</th>
</tr>
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<tr>
<td>1</td>
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<tr>
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<td>Epidermoid cyst</td>
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<tr>
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<td>Ref 12</td>
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<td>F</td>
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<tr>
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<td>Ref 10</td>
<td>7 y</td>
<td>M</td>
<td>5</td>
<td>Epidermoid cyst</td>
</tr>
<tr>
<td>6</td>
<td>Ref 13</td>
<td>5 y</td>
<td>M</td>
<td>2</td>
<td>Epidermoid cyst</td>
</tr>
<tr>
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<td>32 y</td>
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<td>30</td>
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<tr>
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<td>F</td>
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<tr>
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<tr>
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<td>Ref 17</td>
<td>14 mo</td>
<td>F</td>
<td>4</td>
<td>Epidermoid cyst</td>
</tr>
</tbody>
</table>

NA indicates not available; F, female; M, male.
early period to 3 to 7 days in the last 3 months of her illness. One possible explanation for this increasing frequency is that repeated cyst rupture causes an incomplete repair of the cyst wall, which becomes thinner over time and thereby ruptures more easily. Thus, it seems that so called self-limited Mollaret meningitis may not be a clinical feature of the disease as caused by the epidermoid cyst.

CONCLUSIONS
Our clinical data, laboratory results, and imaging analysis support intraspinal epidermoid cyst as one of the etiologies of Mollaret meningitis. Intraspinal and intracranial epidermoid cyst–caused Mollaret meningitis have similar clinical manifestations and CSF features during an attack. Because of the importance of surgical treatment for this disease, spinal neuroimaging studies (computed tomography or MRI) should be performed for patients suspected of having epidermoid cyst–caused Mollaret meningitis when no lesion has been observed in the intracranial contents.

REFERENCES
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