Recurrent Aseptic Meningitis for 24 Years: Diagnosis and Treatment of an Associated Lesion

THOMAS R. FRIEDEN, M.D., M.P.H., JOSEPH PIEPMEIER, M.D., GEOFFREY H. MURDOCH, M.D., AND FRANK J. BIA, M.D., M.P.H.

Department of Medicine, Section of Infectious Diseases, Department of Surgery, Division of Neurosurgery, and Department of Surgery (Neuropathology), Yale University School of Medicine, New Haven, Connecticut

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Recurrent meningitis in the absence of an identifiable causative organism or anatomical source is a difficult diagnostic challenge for any infectious disease consultant. We evaluated a 49-year-old woman with episodes of meningitis which occurred on at least nine separate occasions for over 24 years. No causative organism, physical agent, or underlying disease process was identified as the source of this patient’s recurrent lymphocytic meningitis. When computerized tomographic head scanning was first performed in 1977, a prominence of the left lateral ventricle was evident. It was not until the area was subsequently evaluated with magnetic resonance imaging techniques 13 years later that a lesion could be clearly identified, removed, and evaluated at pathology. Time alone will tell whether the lesion, a cavernous hemangioma, was truly the cause of this patient’s recurrent aseptic meningitis for 24 years.

CASE PRESENTATION

DR. THOMAS FRIEDEN (Fellow, Section of Infectious Diseases): The patient is a 49-year-old woman with a previous history of hypertension. Her chief complaint was simply, “when I can’t touch my chin to my chest I know I should come to the hospital for a spinal tap.” Upon presentation to the Yale–New Haven Hospital, she had a fever (103°F) with severe neck stiffness and photophobia. Her peripheral white blood cell count was 8,900 cells/mm³ with 64 percent polymorphonuclear cells and 3 percent band forms. A spinal tap consistently revealed 136 red blood cells/mm³ and 736 white cells/mm³, of which 6 percent were granulocytes, 80 percent lymphocytes, and 14 percent monocytes. Her cerebrospinal fluid (CSF) glucose concentration was 97 mg/dL with a peripheral blood glucose concentration of 120 mg/dL, and her CSF protein concentration was 93 mg/dL.

Prior medical history and many old volumes of her medical records revealed similar episodes of meningitis in the past (Table 1). These began in August of 1965, when she was 25 years old. On at least eight occasions she had presented with fever, headache, photophobia, elevated CSF protein, and borderline low CSF glucose concentration associated with a lymphocytic CSF pleocytosis. Bacterial and viral cultures were always negative, and she invariably improved within three to four days, with or without administration of antibiotics. Following her second episode in 1965, an evaluation was

Abbreviations: CSF: cerebrospinal fluid CT: computerized tomography MRI: magnetic resonance imaging

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Address reprint requests to: Dr. Thomas Frieden, 125 Worth Street, Box 22, New York, NY 10013

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TABLE 1
Cerebrospinal Fluid Parameters During Recurrent Episodes of Aseptic Meningitis

| Date (month/year) | CSF Protein (mg/dL) | CSF Glucose/Serum Glucose (mg/dL) | Cell Count (wbc/mm³) | Differential Counts |
|-------------------|---------------------|----------------------------------|----------------------|---------------------|
| 8/65              | 194                 | 25/75                            | 98                   | 93 lymphs, 5 PMNs   |
| 10/65             | 116                 | 40/109                           | 310                  | 98 lymphs, 2 PMNs   |
| 10/65             | 40                  | NA                               | 128                  | 100 lymphs          |
| 9/66              | 32                  | 39/66                            | 470                  | 98 lymphs, 2 PMNs   |
| 8/72              | NA                  | NA                               | NA                   | NA                  |
| 6/73              | NA                  | NA                               | 290                  | 83 lymphs, 2 PMNs   |
| 6/74              | 11                  | 60/NA                            | 7                    | 100 lymphs          |
| 1/77              | 14                  | 54/93                            | 2                    | 100 lymphs          |
| 8/89              | 93                  | 97/120                           | 736                  | 80 lymphs, 6 PMNs   |

NA, data not available

performed which included cultures for leptospira, serology for syphilis (VDRL), and a brain scan, all of which were negative. Tuberculin skin test was negative, with a positive control. India ink stains for cryptococcal organisms, acid-fast smears, and viral and mycobacterial cultures of the CSF were also negative. After her third episode in 1966, she had additional laboratory evaluation, including serum complement levels and serum protein electrophoresis, which were completely normal. She was quite well for the next six years.

A PHYSICIAN: Did she have a history of head trauma? Chronic osteomyelitis of bones in the skull could conceivably cause a clinical picture like this.

DR. FRIEDEN: There was no prior history of either head trauma or infections such as chronic sinusitis.

A PHYSICIAN: There is an entity called Mollaret's meningitis which may present in this way. It is associated with recurrent episodes of sterile meningitis and negative CSF cultures. It can go on for many years. Was she ill between episodes?

DR. FRIEDEN: No, she was completely healthy without focal neurological findings between episodes.

A PHYSICIAN: Connective tissue diseases can cause recurrent meningitis. Did she have a serum antinuclear antibody determination done during this time?

DR. FRIEDEN: The antinuclear antibody and latex fixation for rheumatoid factor were negative during the current admission, and her erythrocyte sedimentation rate was 44 mm/hour. In 1977, she again presented with meningitis. A computerized tomographic (CT) head scan was done, both with and without contrast enhancement. It was read as normal except for prominence of the left lateral ventricle.

In summary, we have a patient who experienced at least eight prior episodes of meningitis, all associated with a CSF lymphocytic pleocytosis, occasionally with a relatively low glucose concentration and usually with elevated protein concentrations. Extensive laboratory evaluation had been unrevealing, including a negative serology for Lyme disease. She does provide two additional intriguing pieces of information. One is that she had been receiving nonsteroidal anti-inflammatory agents before some of these episodes. She also scratched her elbow two days before the current episode and
went to a local doctor who prescribed oral ciprofloxacin. We have considered Mollaret's meningitis, viral infections, chronic osteomyelitis of the bones of the skull, connective tissue diseases, and we can add idiosyncratic drug hypersensitivity to the list. Are there any other suggestions for the differential diagnosis?

DR. ROBERT BALTIMORE (Associate Professor of Pediatrics and Epidemiology): One problem that usually begins in infancy is a communication between the cerebrospinal fluid and the outside world; however, this would produce recurrent bacterial meningitis, rather than recurrent culture-negative meningitis. There are also various types of dermoid cysts and tumors involving the spinal cord. These can be missed on a routine examination, especially if the lesion is located in the lower spine. There may be a small dermoid cyst with a sinus that occasionally leaks into the central nervous system. The only thing about this case that wouldn't fit is the lack of a predominance of granulocytes in CSF.

A PHYSICIAN: Had she been abroad?

DR. FRIEDEN: She had not traveled outside of the United States. What would you think of if she had traveled?

A PHYSICIAN: Perhaps a chronic parasitic infection. You did mention that she had a prominent left lateral ventricle.

DR. FRANK BIA (Associate Professor of Medicine and Laboratory Medicine): There are several possibilities to consider. Cysticercosis would be more likely than echinococcosis because the latter usually presents as a large, expanding cyst. If there were cysticerci in the ventricles, we might expect the patient to have developed hydrocephalus.

DR. FRIEDEN: The patient is black, and the diagnosis of sarcoidosis was considered. Sarcoidosis can produce a low CSF glucose concentration but is usually associated with cranial nerve abnormalities [1,2]. Serum angiotensin converting enzyme level was within normal limits. In addition, the course of sarcoid meningitis tends to be chronic and progressive, rather than intermittent. At this point, what would you do to evaluate her illness further?

A PHYSICIAN: Was a cytologic examination performed on cells found in the CSF to rule out Mollaret's meningitis? One looks specifically for large characteristic endothelial cells containing irregular nuclear and cytoplasmic membranes.

DR. FRIEDEN: Mollaret cells were looked for in CSF, and none were found.

DR. BIA: It was time for the patient to go home, and we suggested a magnetic resonance imaging (MRI) brain scan be done. We felt that any person with recurrent meningitis for 24 years deserved the latest technology, but we were clearly looking for clues rather than entertaining a specific diagnosis.

DR. FRIEDEN: An MRI scan was performed one month after discharge. It showed a two-centimeter lesion in the atrium of the left lateral ventricle. The lesion was located precisely where a fullness had been noted twelve years earlier on CT scan. At that time the lesion had not enhanced with contrast. Twenty-four years earlier it had not been apparent on a technetium brain scan. The lesion did enhance on the MRI scan performed with gadolinium and was located in the choroid plexus (Fig. 1). The radiologists provided the following differential diagnosis: meningioma, ependymoma, choroid plexus epitheloma, lymphoma, or metastatic lesion. The patient opted to have the potentially offending lesion removed.
FIG. 1. MRI scan obtained prior to surgery demonstrates a gadolinium-enhancing lesion (arrow) in the left lateral ventricle.

A PHYSICIAN: I would rather experience benign episodes of meningitis every few years than have brain surgery. I am curious about what led to your referring her for surgery.

DR. FRIEDEN: She had severe chronic headaches and was willing to undergo the procedure in the hopes that her headaches would resolve. The patient was evaluated and operated upon by Dr. Joseph Piepmeier. A right parietal craniotomy was performed for resection of the lesion in the left lateral ventricle. In the anterior portion of the ventricle a large vascular structure was found attached to the choroid plexus. This became tangled posteriorly and was attached to a more globular structure which was purple in color and quite vascular. The choroid was stripped from the choroidal fissure and was removed with the lesion as a single block of tissue. Frozen section revealed tissue suggesting a vascular malformation.

DR. GEOFFREY H. MURDOCH (Associate Research Scientist, Neuropathology): This lesion, a cavernous hemangioma, is not uncommon, but its intraventricular location is somewhat rare. None of the attendings in neuropathology have previously seen one in this location. A recent review described a total of only 19 cases [3]. The lesion measured two centimeters in diameter. It was bright red in color with a raspberry-like appearance and was attached to a stalk of choroid plexus. Microscopic examination revealed the characteristic features of a cavernous hemangioma: blood-filled cystic spaces separated by endothelial-lined thin fibrous septae. There are some feeding
arteries with characteristic elastic laminae, but the lesion itself does not consist of conventional vascular structures (Fig. 2).

Vascular lesions of the choroid plexus are not particularly uncommon. In the older literature they are simply referred to as angiomas without specific details or type mentioned. The majority are arterio-venous malformations or venous angiomas, both of which usually have sufficient blood flow to be detected by angiography or contrast-enhanced computerized tomography. Cavernous hemangiomas, which are less common, have relatively stagnant blood flow and often escape detection by these techniques. Gadolinium-enhanced MRI scanning appears more sensitive but is still being evaluated.

FIG. 2. Cavernous hemangioma. A. Low-power profile, showing entire lesion: a raspberry-like mass of dilated vascular channels, some filled with blood and others drained, arising from a stalk of fibrovascular stroma of the choroid plexus. B. High-power micrograph, showing dilated vascular channels separated by walls of delicate fibrous tissue. Note difference between these channels and the feeder artery (a) at bottom with thick muscular walls and an elastic lamina (arrow). Elastin Van Gieson (EVG) original magnification: A × 1, B × 20.
Cavernous hemangiomas usually present with acute hemorrhage or seizures. When located within brain parenchyma, they are surrounded by reactive gliosis and hemosiderin deposition indicative of previous leakage. Sometimes there is a nonspecific mononuclear cell infiltrate, which was not present in this case. Intraventricular cavernous hemangiomas present similarly: non-localizing signs of a mass lesion, hemorrhage, or seizures. Spinal fluid often has increased protein concentration with red cells or xanthochromia present. An elevated white cell count in CSF is not a characteristic feature of such lesions. In this case, the localization of the lesion within the choroid plexus and ventricle may have simply made the inflammatory response more evident.

**DISCUSSION**

**DR. FRIEDEN:** The differential diagnosis for recurrent aseptic meningitis includes Mollaret's meningitis, connective tissue diseases [4,5], Lyme disease [6], drug-induced aseptic meningitis [7], and various tumors. Tumors which may present in this fashion include meningiomas, teratomas, and hemangiomas.

Mollaret's meningitis is an unusual syndrome during which patients have recurrent episodes of fever, headache, and meningismus, which usually resolve within two to four days after onset. Most patients are febrile during episodes, and half have recurrent neurological symptoms. Endothelial “Mollaret” cells are present for a few hours during an attack and are visualized only with Papanicolaou or other special stains [8,9]. Whether many patients with Mollaret's meningitis also have a structural lesion which cannot be visualized by current imaging techniques remains an intriguing but unanswered question.

Tumors can also cause recurrent meningitis. Larbisseau et al. reported recurrent chemical meningitis in a patient with an intraspinal teratoma [10]. The patient experienced five distinct episodes of aseptic meningitis. These were characterized by polymorphonuclear pleocytosis with elevated CSF protein and low CSF glucose concentrations associated with a cystic teratoma at the level of the conus medullaris. Kelleher et al. described recurrent meningitis associated with a meningioma located in the mastoid cavity [11]; however, the recurrent meningitis was of bacterial origin.

In the review by Chadduck et al. [3], they reported 19 cases of intraventricular cavernous hemangioma, but there were no patients who presented with meningitis. Two patients described elsewhere resemble our patient, however. Dell'Acqua described a patient with recurrent meningitis associated with a hemangioma of the third ventricle [12]. This 36-year-old woman had two episodes of fever, meningismus, and CSF pleocytosis. Three years previously she had developed a left seventh nerve palsy and chronic headaches. Her CSF showed lymphocytic pleocytosis. The patient apparently died of complications resulting from obstructing hydrocephalus. Tegeris and Brandiss described a patient with what appears to have been a cavernous hemangioma [13]. The patient presented with chronic meningitis, elevated CSF protein (277–2,100 mg/dL), markedly low glucose (0–64 mg/dL), and up to 30 lymphocytes/mm³. Autopsy revealed a 2.5 cm hemangioma arising at the cerebellum and located in the cerebello-medullary cistern.

Although we have removed a pathological cerebral lesion, we do not have definitive proof that it was the cause of recurrent meningitis over the past 24 years. The patient was healthy for as long as seven years between episodes, and we will have to wait at least that long before concluding that we have eradicated the cause of her symptoms.
Nine months after her resection she remains healthy, and her chronic headaches have resolved. The case clearly demonstrates the benefits of applying newly developed, more sensitive imaging techniques to a long-standing case of recurrent aseptic meningitis.

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REFERENCES

1. Delaney P: Neurological manifestations in sarcoidosis: Review of the literature, with a report of 23 cases. Ann Int Med 87:336–345, 1977
2. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J: Sarcoidosis and its neurological manifestations. Arch Neurol 42(9):909–917, 1985
3. Chadduck WM, Binet EF, Farrell FW, Araoz CA, Reding DL: Intraventricular cavernous hemangioma: Report of three cases and review of the literature. Neurosurgery 16(2):189–197, 1985
4. Harris GJ, Franson TR, Ryan LM: Recurrent aseptic meningitis as a manifestation of mixed connective tissue disease. Wis Med J 86(3):31–33, 1987
5. Sands ML, Ryczak M, Brown RB: Recurrent aseptic meningitis followed by transverse myelitis as a presentation of systemic lupus erythematosus. J Rheumatol 15(5):862–864, 1988
6. Pal GS, Baker JT, Humphrey PR: Lyme disease presenting as recurrent acute meningitis. Br Med J 295(6594):367, 1987
7. Ballas ZK, Donta ST: Sulindac-induced aseptic meningitis. Ann Int Med 142:165–166, 1982
8. Galdi AP: Benign recurrent aseptic meningitis (Mollaret's meningitis): Case report and clinical review. Arch Neurol 36(10):657–658, 1979
9. Kwong YL, Woo E, Fong PC, Yung RW, Yu YL: Mollaret's meningitis revisited. Report of a case with a review of the literature. Clin Neurol Neurosurg 90(2):163–167, 1988
10. Larbrisseau A, Renevey F, Brochu P, Decarie M, Mathieu JP: Recurrent chemical meningitis due to an intraspinal cystic teratoma: Case report. J Neurosurg 52(5):715–717, 1980
11. Kelleher RJ, Murray JA, Welsby PD: Recurrent meningitis associated with meningioma of the mastoid cavity. J Laryngol Otol 103(1):99–100, 1989
12. Dell'Acqua GB: Sindrome meningitica ricorrente de emangioma del pavimento del terzo ventricolo. Minerva Med 59(3):57–62, 1968
13. Tegeris AS, Brandiss MW: Hypoglycorrhachia associated with solitary intracranial tumor. Neurology 13:336–340, 1963