Case Report from The New York-New Jersey Intercity Infectious Disease Rounds
Edited by Donald B. Louria, MD

Recurrent Meningitis in a 38-Year-Old Man with Cirrhosis

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A 38-year-old Hispanic man, who had been admitted to hospital 22 days previously for aseptic meningitis, returned to the hospital with fever, photophobia, and neck stiffness. His first admission followed 3 days of progressive fever and neck stiffness, without headache. An oral temperature of 102.4°F was noted; he had a nonfocal neurologic examination. At that time, computed tomographic (CT) scan of the head was unremarkable. Table 1 presents lumbar puncture (LP) results on admission (LP 1). Ceftriaxone was administered intravenously, and the patient's symptoms resolved after the first hospital day. He received antibiotics for 4 days. Blood and cerebrospinal fluid (CSF) cultures remained negative, and the patient was discharged with the diagnosis of aseptic meningitis, presumed to be of viral etiology. He remained well until a few days prior to the second admission when his symptoms recurred.

The patient had a history of heavy alcohol use, hepatitis C infection, and liver cirrhosis and had undergone portocaval shunt placement 2 years prior to the first admission for aseptic meningitis. He was a former injection drug user. Enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) had been negative 4 months prior to admission. A tuberculin skin test (PPD) had been positive 12 years earlier, at which time he received prophylactic therapy. He had been born in New York City and had traveled to Puerto Rico three times, the last time being several years earlier. On physical examination at the second admission his temperature was 103°F, his neck was supple, and there was no indication of adenopathy, papilledema, or sinus tenderness. The patient was alert and oriented, according to a nonfocal neurologic examination. The white blood cell count was 5100/mm^3 with a normal differential, the hematocrit was 33%, and the platelet count was 123,000/mm^3. The serum total protein and albumin were 6.5 and 2.5 mg/dL, respectively. Other routine laboratory values were within normal range, including serum glucose, coagulation studies, and urinalysis. Chest radiograph and repeat CT scan of the head were unremarkable. Lumbar puncture revealed an elevated white cell count and a low glucose level (see Table 1, LP 2). Serum rapid plasma reagin test (RPR) and cryptococcal latex agglutination test (CLAT) were negative. The infectious disease service was consulted.

DIFFERENTIAL DIAGNOSIS

There are numerous possible causes of recurrent lymphocytic meningitis with hypoglycorrhachia in a 38-year-old cirrhotic with prior injection drug use and a positive PPD. The most likely infectious agents in this case include *Mycobacterium tuberculosis* or fungi (especially *Cryptococcus*; less likely *Histoplasma*, coccidioidomycosis, *Blastomyces*, *Sporotrichum*, *Candida*, and *Aspergillus*). The possibility of partially treated bacterial meningitis or parameningeal focus, such as sinusitis, mastoiditis, or intracranial abscess, was raised, since the patient's meningeal symptoms improved after a short course of ceftriaxone. However, the CSF bacterial culture and assay for bacterial antigens were negative from the first admission, there was no prior antibiotic use, and both CT scans

Table 1. Data from Lumbar Punctures Obtained at First Hospitalization (LP 1) and 22 days later, at Second Admission (LP 2)*

	LP 1	*LP 2*
Appearance	Clear	Clear
Cells (per mm^3)		
Red	20	10
White	29	244
Differential (%)		
Neutrophils	4	
Lymphocytes	94	100
Monocytes	2	
Glucose (mg/dL)†	51	19
Protein (mg/dL)	32	44
VDRL	Negative	ND
Cryptococcal antigen	Negative	Negative
Gram stain	Negative	Negative
AFB stain	Negative	Negative
India ink	Negative	Negative
Bacterial antigens‡	Negative	ND
Bacterial culture	Negative	Negative

*Opening pressure was not obtained on either occasion. †To convert values for glucose to millimoles per liter, multiply by 0.0555. ‡By latex fixation. ND = Not done.

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of the head were unremarkable. Meningitis due to *Listeria* typically causes a neutrophilic pleocytosis, but a lymphocyte predominance can be seen. Although the CSF profile in this patient is typical of secondary syphilis or neurosyphilis, the CSF Venerial Disease Research Laboratories test (VDRL) and serum RPR were negative. Many viruses can cause the aseptic meningitis syndrome, including herpes simplex, enteroviruses, lymphocytic choriomeningitis virus, mumps, and HIV. Mild hypoglycorrhachia is occasionally seen in meningitis associated with most viral agents, but a CSF glucose of 19 mg/dL (as seen in LP 2) is unlikely to be seen in such cases. Noninfectious causes of meningitis to consider in this case include carcinomatous meningitis and sarcoidosis.

WORKING DIAGNOSIS

The patient was presumed to have tuberculous meningitis, and treatment was started with isoniazid, rifampin, pyrazinamide, and ethambutol.

CLINICAL COURSE

Four days into the second hospitalization, the CSF fungal culture from LP 2 grew many colonies of *Cryptococcus neoformans*. Two days later, CSF culture from the first admission grew a single colony of the same organism. Anti-tuberculous medications were stopped; the patient was treated with intravenous amphotericin B and all symptoms resolved rapidly. A repeat HIV ELISA was negative (for both HIV-1 and HIV-2), but T-cell subset analysis showed a CD4 count of 105/mm^3 and a CD4:CD8 ratio of 1.3. Lumbar puncture 12 days after initiating antifungal therapy revealed normalization of CSF parameters. After 14 days of amphotericin B (total dose 660 mg), therapy was switched to oral fluconazole, 400 mg/day. Two months later, still on fluconazole, the patient was asymptomatic, and his CD4 count was 380/mm^3 with a CD4:CD8 ratio of 1.9.

DISCUSSION

Cryptococcus neoformans is now the most common CSF isolate at many New York City hospitals.[1] Most cases occur in HIV-infected patients with CD4 counts less than 100/mm^3. Prior to 1980, most cases of cryptococcal meningitis occurred in patients with altered cellular immunity from other causes, including organ transplantation, chronic corticosteroid use, lymphoreticular neoplasms (especially Hodgkin's disease), and sarcoidosis.[2-5] In the case described here, the patient had a history of heavy alcohol use and hepatic cirrhosis, which, along with diabetes and pregnancy, have been associated with cryptococcal meningitis.[6] Before the AIDS epidemic, almost half of the patients with cryptococcal meningitis lacked clinically apparent immunologic defects.

Smith et al and others have recently described several patients with opportunistic infections and depressed CD4 counts without evidence of HIV infection, so-called idiopathic CD4 lymphocytopenia.[7,8] Cryptococcal meningitis was seen in several of these patients, raising the possibility that many patients with cryptococcal meningitis previously thought to lack immunologic defects may have also had decreased CD4 levels. Few data have been published on patients with idiopathic CD4 lymphocytopenia; this syndrome may result from a variety of rare defects in CD4 cell regulation, production, or destruction. The patient described in this report had a depressed CD4 count and a negative ELISA for HIV-1 and HIV-2, consistent with idiopathic CD4 lymphocytopenia. However, he did not meet established criteria for this syndrome because other tests to rule out HIV infection, such as p24 antigen or polymerase chain reaction (PCR) were not performed, and T-cell subsets were not rechecked until 2 months into recovery, at which time the CD4 count had risen (albeit not into the normal range).

Cryptococcal meningitis has been reported in patients infected with human T-cell lymphotropic virus type 1 (HTLV-1).[9,10] In many of these patients, the development of opportunistic infections such as cryptococcal meningitis can be a harbinger for the onset of T-cell leukemia.[9] Analysis for HTLV-1 infection was not done in this case.

Diagnosing cryptococcal meningitis in patients without underlying immunodeficiency can be challenging.[2-4,11-13] History of exposure to *Cryptococcus neoformans* is rarely helpful because the organism is ubiquitous. Symptoms may be chronic, subacute, or acute in onset, and can range from headache, fever, meningismus, nausea, and vomiting to confusion, dementia, cranial nerve palsies, and coma. Lumbar puncture is essential for diagnosis, and typically shows elevated opening pressure, lymphocytic pleocytosis, elevated protein, and hypoglycorrhachia. Cerebrospinal fluid India ink stain is a rapid test, but is inoculum-dependent and therefore often negative in low grade infections. False positive India ink stains are common; red cells, lymphocytes, and talc powder may be confused for *Cryptococcus neoformans* (which is 2-12 μm in diameter). The CSF CLAT can be performed rapidly and is highly specific (97-100%) and sensitive (98-100%);[14] therefore, it is the single best test for diagnosing crytococcal meningitis. Cerebrospinal fluid fungal culture is positive in most cases but may take several weeks to grow. Blood cultures and the serum CLAT also can be helpful in establishing the diagnosis; however, these indicate active extrameningeal disease, which is unusual in the non-AIDS patient.

Amphotericin B, with or without flucytosine, is the mainstay of therapy for cryptococcal meningitis. Fluconazole is an effective alternative although it has not

been studied in patients without AIDS.[15] To prevent relapse following treatment, suppressive therapy with oral fluconazole is indicated in patients with chronic severe immunosuppression (secondary to AIDS, organ transplantation, or immunosuppressive drugs) where the relapse rate can be 40 to 60%.[16-19] Traditionally, no suppressive therapy is given to patients without severe immunosuppression, in whom the relapse rate is approximately 10%. Factors associated with poor outcome include mental deterioration, elevated CSF pressure, lack of inflammatory cells in the CSF, positive India ink stain, and hypoglycorrhachia.[2] Procedures that will reduce high CSF pressures may also be required, such as therapeutic LPs or shunt placement.[20]

This case illuminates the difficulties in establishing the diagnosis of cryptococcal meningitis in the non-AIDS patient. The initial LP was nonspecific, and although the second LP was more helpful, both of the rapid tests (India ink and CLAT) were negative. The pathology of cryptococcal meningitis has many similarities to tuberculous meningitis.[21] Recurrence of symptoms after several weeks with a high colony count in CSF culture could represent rupture of a cryptococcal granuloma into the subarachnoid space. This patient's first episode may be more analogous to the "serous tuberculous meningitis" first described by Edith Lincoln, presumably attributable to abortive rupture of a cryptococcal granuloma into the subarachnoid space.[22]

In patients with moderately intact cellular immunity the burden of organisms is often low, and in this situation the India ink is usually negative; the culture, if positive, may take several weeks to grow, and the CLAT may be negative.[14,23] The CLAT also may be negative due to the lower sensitivity of some commercially available cryptococcal antigen kits.[14] In these kits, false negative CLATs may be related to a higher negative cutoff chosen to minimize false positive results.

Cryptococci with relatively small capsules are sometimes seen in tissue specimens and in India ink stain of fresh CSF and primary cultures.[24-26] Because culture conditions can greatly influence capsular elaboration, the significance of this finding is unclear.[27,28] Some reports have correlated infection with poorly or nonencapsulated *Cryptococcus neoformans* and low or undetectable antigen titers.[29,30] In the patient presented here, CSF India ink was negative and India ink stain of the primary culture revealed normal capsule size.

In summary, cryptococcal meningitis should be suspected in any patient with altered cellular immunity, and appropriate diagnostic tests of the CSF should be performed, including India ink, CLAT, and fungal culture. In patients without AIDS or other severe immunosuppression, the diagnosis may be more difficult to make, because both the India ink stain and the CLAT, which are dependent on the number of organisms, are likely to be negative, and the culture may take longer to grow. Therapy consists of amphotericin B with or without flucytosine; fluconazole is a frequently used alternative especially after initial control of symptoms and signs. Chronic suppression with oral fluconazole is required in the setting of severe immunodeficiency to prevent relapse.

ACKNOWLEDGMENTS

The authors thank Neal Steigbigel and Brian P. Currie for their helpful comments.

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