BACKGROUND
The patient was a 71-year-old man with a history of severe chronic obstructive pulmonary disease (COPD), asthmatic bronchitis, and an autoimmune bleeding disorder. He was taking oral corticosteroids at the time of his presentation and had taken other immunosuppressant medications. He also had a history of treatment for sinus infections, cellulitis, and urinary tract infections (UTI) over the past 2 years. He reported having had a rash approximately 3 months before his initial visit, followed by chronic, daily, diffuse headaches. The patient was admitted to the hospital for a recent onset of confusion and fever. After approximately 3 weeks, the patient died from multiorgan failure.

MEDICAL HISTORY
His medical history included COPD, asthmatic bronchitis, autoimmune bleeding disorder, sinusitis, cellulitis of the lower extremities, and UTIs.

FAMILY HISTORY
There was no history of migraine or other headache types among family members.

SOCIAL HISTORY
The patient was married with a 40-pack/year history of smoking and moderate alcohol use.

MEDICATIONS
Medications included 20-mg prednisone daily and albuterol inhaler as needed.

PHYSICAL EXAMINATION AND DIAGNOSTIC TESTS
On physical examination, the patient had a temperature of 101.8°F. A computerized axial tomography scan of the brain was unremarkable. Electroencephalogram demonstrated some mild diffuse slowing. A lumbar puncture (LP) was performed, and the cerebrospinal fluid (CSF) revealed pleocytosis, predominantly lymphocytes. CSF also was significant for elevated protein and decreased glucose levels; Gram stain was negative. One fungal culture from the LP indicated growth at 2 weeks. A second LP was performed approximately 12 days later, but fungal cultures were not ordered.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis for this case includes chronic migraine (CM), subarachnoid hemorrhage, bacterial, viral, and aseptic meningitis. However, CM is unlikely, as is subarachnoid hemorrhage given the lack of red blood cells in the CSF. Because of its chronic rather than acute presentation, viral or aseptic meningitis are more likely than bacterial etiologies.

BACKGROUND INFORMATION
Causes of chronic meningitis encompass infectious and noninfectious etiologies. Prominent among infectious agents are Mycobacterium tuberculosis, Treponema pallidum, Borrelia burgdorferi, Leptospira interrogans, Cryptococcus neoformans, and Coccidioides immitis. In addition, malignancies, such as lymphomas and leukemias, may lead to chronic meningitis, as can systemic inflammatory conditions, such as sarcoidosis.

Tubercular meningitis is an important consideration in patients who are immunocompromised, such as those living with AIDS. This type of meningitis is a diagnostic challenge because it causes nonspecific changes in the CSF, and there may not be a positive, confirmatory acid-fast bacilli stain. Similar to this case, patients with tubercular meningitis may report headache, fever, and meningismus; LP will show an increase in the number of white blood cells and decreased glucose levels. Aside from HIV-positive populations, immigrants, especially from Southeast Asia, are at high risk, and one may consider empirical treat-
ment for individuals fitting the clinical picture. Again, among the HIV-positive population, syphilis (generally secondary, rarely tertiary) should be considered.

In certain geographic regions, predominantly the northeastern United States, *B. burgdorferi* infection may cause lymphocytic meningitis. These patients generally demonstrate radicular and/or cranial neuropathies. In addition, they have bilateral Bell’s palsy or seventh nerve palsies as their presenting symptomatology beyond the usual headache, meningismus, and the lymphocytic CSF findings. Similar to Lyme disease, leptospirosis causes lymphocytic meningitis and occurs in geographic regions that harbor infected domestic and wild animals (i.e., possums, skunks, raccoons, and rats). Humans acquire the disease through contact with the infected urine or tissue of these animals, such as by swimming in a lake and accidentally swallowing contaminated water.

In terms of fungal meningitis, *Cryptococcus* must always be considered in the HIV-positive population with neurologic symptoms, such as dementia and headache. The fungus, *C. immitis*, causes coccidiomycosis meningitis. It needs to be ruled out in patients residing or traveling in the southwestern United States and northwestern Mexico (Figure). The fungal spores inhabit the soil, and during intermittent dust storms, they become airborne and are inhaled.

Ultimately, it was determined that this patient had developed meningitis secondary to infection with coccidiomycosis. The majority of cases of coccidiomycosis are mild or asymptomatic, with more severe cases most commonly occurring among individuals who are immunocompromised, such as individuals like this patient, who are taking corticosteroid therapy. The most common symptoms are fatigue, cough, chest pain, fever, rash, headache, and joint aches. Five percent to 10% of patients develop serious complications, including pneumonia, pulmonary nodules, pulmonary cavitation, and meningitis. Diagnosis at times is difficult to confirm, but evidence of the fungus may be present in tissue, sputum, or other body fluid cultures. Antibodies to the fungus also may be detected in blood samples. Most cases (90%) require no treatment; however, antifungal therapy with ketoconazole or similar drugs may be indicated for disseminated cases with more severe pulmonary involvement. Intravenous or intrathecal amphotericin B is prescribed for meningitis cases, although the drug has serious side effects.

Parameningeal infections, including spinal or intracranial abscess or venous sinus thrombosis, also may cause chronic meningitis and headache. This diagnosis should be considered in patients with congenital defects (i.e., skull base defect or dural sinuses along the vertebral column), and/or for patients who have a history of trauma, such as a cribiform plate fracture.

Although patients with a malignant form of meningitis, such as lymphoma or leukemia, will have the same or similar clinical presentation as patients with an infectious etiology, the patient with cancer will have CSF glucose levels that are low to nonexistent. Sarcoidosis and other chronic inflammatory diseases also may result in chronic meningitis. Other chronic inflammatory diseases that may cause meningitis include Behçet’s syndrome, systemic lupus erythematosus, vasculitis, and Mollaret’s meningitis. Patients with Mollaret’s meningitis may experience intermittent episodes of meningeal symptoms. There may be fever and meningismus for 3 to 4 days, seizures, and/or focal neurologic deficits that spontaneously resolve. The underlying cause is unclear, but this may be a type of herpes simplex type 2 infection; therefore, treatment with antiviral medications, such as acyclovir, may be beneficial.

Finally, medications may be a cause of aseptic meningitis. Intrathecal agents, nonsteroidal anti-inflammatory drugs, certain antibiotics (i.e., trimethoprim, amoxicillin, and cephalosporins), and some immunosuppressant medications (i.e., azathioprine) are the most commonly responsible drugs.

View highlights from panel discussion that followed this presentation: www.jhasim.com/cdb.

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**Figure. Endemic Areas for Coccidiomycosis**

![Endemic Areas for Coccidiomycosis](http://example.com/cocci_endemic_areas.png)

*Courtesy of University of Arizona Valley Fever Center for Excellence, May 2003.*