Diagnostic Dilemma of a Young Man With Fever and Headaches

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A 23-year-old man was admitted to the hospital in the fall because of fever and headache. He had been well until 5 days earlier when he developed headaches associated with photophobia, neck pain, nausea, and vomiting. He had no significant medical history and took no medications. He lived with his parents in Seattle, Washington, and took classes at a local college. He had immigrated from China in 2007.

The patient was alert and interactive. The temperature was 40.0°C, blood pressure was 161/92 mm Hg, pulse was 91 beats/min, and oxygen saturation was 100% on room air. His general examination revealed anicteric sclerae and no skin rash. Pain was noted with passive neck flexion. On neurologic examination, the patient was oriented with fluent speech and no dysarthria. Visual fields and extraocular movements were full. The remaining cranial nerve functions were intact. Muscle bulk and strength were normal. Sensation was preserved with no extinction detected. The tendon reflexes were equal at 2+, and plantar responses were flexor. There was no dysmetria on finger-to-nose testing. The gait was normal.

Laboratory studies including a basic metabolic panel, liver function tests, coagulation studies, and urinalysis were notable only for a low sodium of 135 mEq/L (ref 136-145 mEq/L) and an elevated white blood cell count of 13 000/ μ L (ref 4.30-10.00 thousand/ μ L). Blood cultures were obtained. Chest radiograph revealed clear lungs and pleural spaces. Computed tomography (CT) of the head showed no abnormalities. The results of cerebrospinal fluid (CSF) analysis are shown in Table 1.

Dexamethasone, vancomycin, ceftriaxone, and acyclovir were started for possible bacterial or viral meningitis but discontinued once the blood cultures, CSF Gram stain and bacterial cultures, and viral polymerase chain reaction (PCR) tests were negative. Contrast-enhanced magnetic resonance imaging (MRI) of the brain was normal. The patient was discharged home after 3 days with a diagnosis of viral meningitis.

Five days after initial discharge, the patient returned to the hospital with lethargy and confusion. His mother reported that he was less responsive, intermittently mumbling in response to questions, and requiring assistance with basic daily functions.

The patient was drowsy and disoriented. The temperature was 38.2°C, blood pressure 119/90 mm Hg, and pulse 116 beats/minute. On examination, he exhibited neck stiffness, incoherent speech, and impaired comprehension.

Serum sodium was 121 mEq/L and white blood cell count was 15 500/ μ L. Head CT showed mild dilatation of the third and lateral ventricles compared to the study 5 days before. Contrast-enhanced brain MRI demonstrated abnormal enhancement of the prepontine and interpeduncular cisterns (see Figure 1). Human immunodeficiency virus (HIV) test was negative. Repeat CSF analysis is shown in Table 1.

Antibiotics and antiviral medications were restarted. On hospital day 2, the patient had a witnessed convulsive seizure. Repeat head CT showed worsening hydrocephalus. An external ventricular drain was placed, and the patient was given a loading dose of phenytoin. The patient's mother reported that the patient may have been exposed to an uncle with active pulmonary tuberculosis, leading to the initiation of antituberculous medications, including rifampin, isoniazid, pyrazinamide, and ethambutol.

Three days after readmission, a presumptive mold grew in the CSF bacterial cultures. A rash was also noted on the patient's right flank, consisting of plaques and papules with a central pearly pink color. A skin punch biopsy and additional laboratory studies were obtained, including antinuclear antibody (negative), rheumatoid factor (<13 IU/mL; negative), aspergillus galactomannan assay (0.114; negative), and Quantiferon-TB Gold (indeterminate). Upon further questioning, the patient's mother reported the patient had spent 8 months in California 1½ years before. Liposomal amphotericin B was started. Six days after readmission, the results of 2 diagnostic tests were received.

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Table 1. Cerebrospinal Fluid Analysis

Variable	Reference Range, Adults	Initial Admission	Readmission, 5 Days Later
Opening Pressure	60-250 mm H ₂ O	345 mm H ₂ O	Not recorded
Color	Colorless	Colorless	Slightly orange
Red cells (per μ L)	None	18	485
White cells (per μ L)	0-5	1,050	1,748
Differential count		17% Neutrophils, 52% lymphocytes, 23% monocytes, 4% eosinophils, 4% basophils	40% Neutrophils, 41% lymphocytes, 7% reactive lymphocytes, 10% monocytes, 2% eosinophils
Protein (mg/dL)	15-45	163	210
Glucose (mg/dL)	40-80	38; 41% of serum glucose of 93	7; 5% of serum glucose of 135
Gram stain	Negative	2+ Polymorphonuclear lymphocytes, 2+ monocytes, no organisms	2+ Polymorphonuclear lymphocytes, no organisms
Herpes simplex virus (HSV) 1 and 2 polymerase chain reaction (PCR)	Negative	Negative	Negative
Varicella zoster virus (VZV) PCR	Negative	Negative	Negative
Enterovirus PCR	Negative	Negative	
Parechovirus PCR	Negative	Negative	
West Nile PCR	Negative		Negative
Broad range mycobacterium primer	Negative		No acid fast bacilli (AFB) DNA, no <i>Mycobacterium avium</i> complex DNA, no <i>Mycobacterium tuberculosis</i> complex DNA
Venereal disease research laboratory (VDRL)	Nonreactive		Nonreactive
Flow cytometry	Negative		No abnormal B or T cell population
Cryptococcal antigen	Negative		Negative

Figure 1. Magnetic resonance scans of the brain. A, T1 fat-saturation postcontrast axial magnetic resonance image on initial presentation shows normal contrast enhancement. B, T1 postcontrast axial image 5 days later shows mild enhancement of the interpeduncular cistern. C, T1 postcontrast axial image on hospital day 26 shows marked basilar enhancement.

Differential Diagnosis

Discussant: Dr Sandeep Khot

Neurohospitalists are often called upon to evaluate patients with possible meningitis. Clinical, imaging, and laboratory testing may suggest an alternative diagnosis, such as delirium or a toxic-metabolic encephalopathy; but in the febrile patient who is confused and complaining of headache, a diagnostic lumbar puncture is needed early in the clinical course to evaluate for a central nervous system infection. The patient's laboratory studies were consistent with a diagnosis of meningitis or inflammation of the meninges, evidenced by an elevated number of white blood cells in the CSF, and the foremost concern was for acute bacterial meningitis. Patients with acute bacterial meningitis may not develop the classic triad of fever, neck stiffness, and altered mental status—seen in only 44% of patients in 1 nationwide prospective study¹—but often present with impairment in consciousness. In this study, a Glasgow Coma scale of less than 14 was seen in 69% of cases of adults with acute community-acquired bacterial meningitis and 95% of patients had at least 2 of headache, fever, neck stiffness, and altered mental status.

The laboratory evaluation of patients with suspected acute bacterial meningitis should include CSF cell count, Gram stain, and bacterial cultures, as well as blood cultures; blood cultures should always be drawn before the antibiotics are administered. In untreated bacterial meningitis, the CSF WBC count typically is between 1000 and 5000 cells/ μ L with a neutrophilic predominance on the order of 80% to 95%, although about 10% of the patients may present with a lymphocytic predominance.² Other typical CSF findings in bacterial meningitis include low glucose concentration of less than 40 mg/dL in 50% to 60% of patients and an elevated protein concentration in virtually all patients (usually 100-500mg/dL). In patients who do not receive prior antimicrobial therapy, the CSF Gram stain is positive in 60% to 90% of patients and the CSF culture is positive in 70% to 85% of patients. Broad-spectrum PCR on CSF may be useful in some instances where Gram stain and culture are negative. A study using bacterial PCR primers demonstrated a sensitivity of 100% and a specificity of 98.2% for the diagnosis of bacterial meningitis.³

The initial CSF findings in this patient were consistent with bacterial meningitis. Antimicrobials and dexamethasone were appropriately discontinued when CSF and blood cultures did not show any growth. The presumptive diagnosis of acute aseptic meningitis was given. Viruses are the major cause of acute aseptic meningitis and most cases are caused by enteroviruses.⁴ Bacterial causes of aseptic meningitis include *Mycobacterium tuberculosis* (TB), spirochetes such as *Treponema pallidum* subspecies *pallidum* (the bacterium that causes syphilis) or *Borrelia burgdorferi* (the bacterium that causes Lyme disease). Fungal causes of aseptic meningitis include *Cryptococcus neoformans*, *Cryptococcus gatii*, *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*. Tuberculous and fungal meningitis are

typically associated with a CSF lymphocytic pleocytosis, an elevated CSF protein level and decreased CSF glucose level. In HIV-infected patients with aseptic meningitis, tuberculosis, syphilis, and cryptococcal should be given particular attention. Many noninfectious etiologies should also be considered in the differential of aseptic meningitis. These include inflammatory diseases (systemic lupus erythematosus, sarcoidosis, Behçets disease, Sjögren's syndrome), drug-induced aseptic meningitis (due to nonsteroidal anti-inflammatory agents and certain antimicrobial agents), and carcinomatous or lymphomatous meningitis.

The patient's exposure history was initially self-reported to include only his immigration from China; no history of travel within the United States was obtained. When he was readmitted, the patient's family reported possible exposure to a family member with tuberculosis leading to the initiation of antituberculous medications. The persistent CSF lymphocytic pleocytosis with low glucose and elevated protein helped to narrow the differential to tuberculous or fungal meningitis. Patients with tuberculous meningitis compared to patients with bacterial meningitis typically have a longer duration of illness (≥ 6 days) and a lymphocytic CSF pleocytosis with a low glucose.⁵ Fungal meningitis is more likely to present as either subacute or chronic meningitis. The additional travel exposure of a remote trip to California was obtained only after the discovery of mold in the CSF bacterial culture.

Diagnostic Challenges

One of the difficulties in this case was confirming the diagnosis of either tuberculous or fungal meningitis. Diagnostic certainty remains difficult with these infections due to the poor sensitivity of available diagnostic tests. As seen in this case, treatment decisions can be particularly challenging in patients with clinical worsening or complications related to basilar meningitis.

Diagnosis of Tuberculous Meningitis

Delay in treatment of tuberculous meningitis is strongly associated with death.⁶ When the diagnosis is suspected, treatment should be instituted immediately, even without a confirmed diagnosis. A history of TB exposure or known extrameningeal TB is helpful in suggesting the diagnosis, although confirmation of the diagnosis requires demonstration of *M tuberculosis* in culture.

In patients with a history of TB exposure, evaluation often starts with tuberculin skin testing or interferon- γ release assays, such as the Quantiferon-TB gold. Both of these tests are based on the patient's cellular immune response to *M tuberculosis*. However, these tests are not able to distinguish between latent and active tuberculosis, and so while they might establish that a patient is at risk for tuberculous infection, they cannot confirm a diagnosis of TB meningitis.⁷

Cerebrospinal fluid smear is a rapid presumptive diagnostic method for TB meningitis, but it is variably positive, ranging between 12.5% and 87%^{6,8} and does not distinguish between TB and other acid fast bacilli (AFB). Cerebrospinal fluid culture is also relatively insensitive and can delay the diagnosis, as results are typically not available for weeks and are often negative. In one study, a diagnosis was made by CSF smear or culture in 81% of adults with TB meningitis, with AFB seen on smear in 77 (58%) of 132 and on culture in 94 (71%) of 132 patients.⁹ Successful smear diagnosis was associated with the duration of microscopy (at least 30 minutes) and culture diagnosis was associated with the larger volumes of CSF (at least 6 mL).

Other diagnostic techniques in TB meningitis also have limited utility. Molecular diagnosis with nucleic acid amplification (NAA), including PCR testing, is performed by the amplification of target nucleic acid regions unique to *M tuberculosis*. The NAA tests provide rapid results and can better detect mycobacterial DNA after treatment initiation compared to CSF microscopy and culture. However, the sensitivity of NAA is poor and a negative result cannot exclude the diagnosis of TB meningitis. A meta-analysis evaluating commercially available NAA tests on CSF found a sensitivity of only 56% compared to a specificity of 98%.¹⁰

Diagnosis of Coccidioidomycosis Meningitis

Both *C immitis* and *C posadasii* are soil-dwelling fungi endemic in the desert of the southwestern United States, including the southern and central valley of California. Primary infection, usually due to inhalation, may be asymptomatic or present with a nonspecific pulmonary infection. Extrapulmonary dissemination is rare, typically occurring within the first 6 months of infection, although it can occur years later.¹¹ Sites of disseminated coccidioides most commonly include the skin or subcutaneous soft tissue, bones, and the meninges.¹²

Isolating coccidioides from the CSF provides a definitive diagnosis, but the culture is positive in only 20% to 38% of cases.^{13,14} Serologic testing or histopathological identification of coccidioides spherules in tissues can offer additional means of diagnosing coccidioides infection. Coccidioides serologic testing is more reliable than such testing in other mycoses, but the sensitivity is dependent on a number of variables, including the time duration since infection, host immune status, extent of infection, and the method of serologic testing. One study compared 3 commonly used serum serologic tests: immunodiffusion (ID), enzyme immunoassay (EIA), and complement fixation (CF).¹⁵ Among the immunocompetent patients within 1-year of symptom onset and with confirmed or probable pulmonary, thoracic cavity, or extrathoracic disseminated coccidioides, EIA was positive in 87%, CF in 75%, and ID in 73%; at least 1 test was positive in 95% of patients. Reactive serological tests can indicate recent or remote infection. The serology of CSF tends to be less sensitive than serum serology. One recent study of 30 patients with coccidioides

meningitis identified antibody in CSF by CF in 59% compared to the detection of immunoglobulin G (IgG) antibody by EIA in 71%.¹⁴ The CF, which measures the later IgG antibody response, may not be detectable early in infection. Nonetheless, CF is considered a mainstay of CSF diagnosis in coccidioides meningitis; results can be expressed as quantitative titers and a decrease in titer can be used as a marker of response to antifungal treatment.¹⁶

Diagnosis of Histoplasmosis Meningitis

Histoplasma capsulatum is endemic in the soil of southeastern states and the upper Midwestern states bordering the Ohio and Mississippi river valley (Arkansas, Kentucky, Mississippi, North Carolina, Tennessee, Louisiana, Illinois, and Wisconsin).¹⁷ The most common site of primary infection is the lung through inhalation with a wide spectrum of disease depending on the intensity of exposure and the host's immunity. Acute exposure can result in asymptomatic infection or acute pulmonary histoplasmosis with severe pneumonitis and respiratory compromise.¹⁸ Disseminated histoplasmosis is rare, occurring mostly in immunocompromised patients. Isolated chronic meningitis occurs in approximately a quarter of these patients.¹⁹ Diagnosis can be made from blood culture or, in patients with disseminated histoplasmosis, antigens can be detected in the urine in >90% of patients and in serum in 80% of patients.¹⁸ Antibodies to *H. capsulatum* can be detected using CF or ID in the CSF of patients with CNS disease.^{17,20}

Diagnosis of Blastomyces Meningitis

The geographic distribution of *Blastomyces dermatitidis* also includes the states that border the Ohio and Mississippi river valleys, especially the northern Wisconsin. Lungs are most commonly involved, typically presenting with a pulmonary infiltrate and dissemination of infection is rare. Neurologic involvement, characterized by CNS mass lesions or meningitis, in individuals with disseminated blastomycosis is rare. However, in 1 small series of 15 patients with acquired immune deficiency syndrome (AIDS), 40% of patients had CNS disease.²¹ Similar to histoplasmosis, blastomycosis is relatively easy to detect in blood culture in patients with disseminated disease but antibody testing through ID or CF techniques can be unreliable for diagnosis.¹⁷ There are few cases of isolated blastomyces meningitis.²² Isolation of *B dermatitidis* from CSF culture obtained via lumbar puncture is uncommon, though the culture of ventricular fluid may have a higher sensitivity.²³

Diagnostic Results

Six days after readmission, fungal CSF cultures grew *C immitis*. The skin punch biopsy also showed budding yeast, consistent with coccidioides (see Figure 2) and AFB stains were negative.

Figure 2. Skin biopsy (images and interpretation courtesy of Dr Funda Vakar-Lopez). A, Grocott's methenamine silver (GMS) stain, $\times 200$ magnification, demonstrates a budding yeast (arrow). B, hematoxylin and eosin (H&E) stain, $\times 100$ magnification, shows granulomatous inflammation surrounding the tip of a presumed hair follicle with multinucleated giant cells (long arrows) and a coccidioides spherule (short arrow).

Coccidioidomycosis Meningitis

Discussant: Dr Arielle Davis

Coccidioidomycosis meningitis is a rare but dreaded form of disseminated coccidioides infection that is nearly uniformly fatal within 2 years if left untreated.¹¹ The Centers for Disease Control and Prevention reported that the number of annually reported coccidioidomycoses cases in California more than tripled in the time periods between 1995–2000 and 2000–2006 (incidence of 2.5 per 100 000 to 8.0 per 100 000).²⁴ Risk factors for extrapulmonary dissemination include male gender, certain racial or ethnic groups (especially African American, Hispanic, and Asian), pregnancy, and immunosuppression due to HIV, malignancy, or medications.

The differentiation of coccidioid meningitis from meningitis due to other endemic mycoses or tuberculous meningitis remains challenging, due to similar clinical presentations and CSF profiles. The diagnosis often rests on a detailed travel history. In this case, the travel history to California was initially missed as the patient was not explicitly asked about travel within the United States. Only after clinical worsening was the additional information obtained from the patient's family.

Complications of Disseminated Meningeal Disease

Encephalitis can ensue from extension of coccidioid meningitis into brain parenchyma from the perivascular spaces.²⁵ Meningeal infection typically affects the basilar meninges. Severe meningeal inflammation may cause extensive arachnoidal fibrosis that can result in communicating or noncommunicating hydrocephalus.²⁶ Hydrocephalus occurs in approximately 40% of patients with coccidioid meningitis²⁷ and is associated with a 12-fold increased risk of mortality.²⁸ Early neurosurgical intervention for ventricular decompression is often necessary, as occurred in our

patient. Complications of coccidioid meningitis can result in depressed consciousness, confusion, seizures, and focal neurologic deficits.

Coccidioidomycosis-induced vasculitis may develop in up to 40% of cases and is the most common cause of death among patients with coccidioid meningitis.^{25,26} Similar to hydrocephalus, the risk of vasculitis is related to the degree of meningeal inflammation.²⁶ A localized vasculitis from basilar meningitis can cause cerebral infarction by direct invasion of the artery, leading to occlusion or distal embolization. Resulting strokes can occur in apparently stable patients.²⁹ Other rare complications of coccidioid meningitis include lumbosacral arachnoiditis or myelitis and cerebral venous or dural sinus thrombosis.^{26,30}

Treatment of Coccidioid Meningitis

Over the past 20 years, azoles have largely replaced intrathecal amphotericin B as the first-line treatment for coccidioid meningitis. Intravenous (IV) amphotericin has poor CSF penetration and has a limited role as monotherapy in the treatment of coccidioid meningitis.²⁶ High doses of fluconazole, typically with an initial dose of between 800 and 1000 mg/d orally or IV, are effective and better tolerated than intrathecal amphotericin B.^{26,31} Lower doses of fluconazole (400 mg/d orally) can also be effective, but some clinicians prefer early high-dose therapy.³¹ Itraconazole and posaconazole are oral azoles that are as effective as fluconazole.^{31,32} Azoles are fungistatic and are therefore not curative for coccidioid meningitis; lifelong treatment is necessary to prevent relapse. In one study, 78% of patients treated with azoles for coccidioid meningitis had a relapse because they stopped their therapy.³³ The azoles are also not always effective in maintaining remission in the long term, even when maintained at high doses.²⁵ A recent study found that the newer agents, voriconazole and

posaconazole, were reasonable options for salvage treatment of refractory pulmonary, skin or soft tissue, bone or joint, or meningeal coccidioidomycosis, although few patients treated in the study had coccidioid meningitis.³⁴ Intrathecal amphotericin B therapy with or without continuation of azole treatment should be considered in patients with severe disease or clinical relapse.³¹ Although it has the potential advantage of being curative or offering long-term control, intrathecal amphotericin B may cause meningeal irritation, arachnoiditis, and transverse myelitis and is limited by significant side effects (nausea, vomiting, headaches, fever, and abdominal pain).²⁶

Hydrocephalus is a serious complication of coccidioid meningitis that can develop during treatment and does not necessitate switching to an alternative therapy.³¹ The optimal management of other complications, such as lumbar arachnoiditis or vasculitis with stroke, remains unclear.²⁶ Some authorities recommend a trial of corticosteroids in patients with acute stroke and severe meningeal inflammation^{35,36} though this approach remains unproven.

Case Follow-Up

Once a mold was found growing in the CSF culture, TB therapy was discontinued and intravenous liposomal amphotericin B was initiated. Amphotericin was discontinued and oral fluconazole 800 mg orally daily was started after confirmation of coccidioid meningitis. On hospital day 65, the patient began intensive inpatient rehabilitation and subsequently returned home with his parents. After a year from the initial admission, he reported considerable improvement in function and had returned to his college classes although with persistent memory deficits. He remains on chronic suppression with oral fluconazole at a dose of 400 mg orally daily.

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