64-Year-Old Man With Subacute Altered Mental Status and Headache

Nandini S. Mehra, MD; Robert C. Ward, MD; and Meltiady Issa, MD, MBA

A 64-year-old man from Iowa with a medical history of sarcoidosis, managed with prednisone, 20 mg/d, for the past 5 months, presented to the emergency department with gradual-onset, progressive altered mental status and headaches of 1 month's duration. Previously, he was cognitively intact according to his daughter. He had become unable to perform normal daily tasks such as unlocking doors and holding normal conversations. Additionally, he reported a generalized, throbbing, constant headache associated with intermittent blurry vision. About 1 week before presentation, he also experienced severe fatigue and lethargy in addition to a few falls. He had no fever, weight loss, syncope, seizures, or neck stiffness, no exposure to birds or their droppings, no history of travel to the American Southwest or elsewhere, and no sick contacts.

On presentation, his vital signs revealed a temperature of 36.6°C; blood pressure, 148/103 mm Hg; heart rate, 104 beats/min; and oxygen saturation, 98% while breathing room air. He appeared intermittently confused but had no meningismus, papilledema, or focal neurologic deficits on physical examination.

Initial laboratory evaluation revealed the following (reference ranges provided parenthetically): hemoglobin, 16.8 g/dL (13.2-16.6 g/dL); leukocytes, 10.2 × 10^9/L (3.4-9.6 × 10^9/L); platelets, 261 × 10^9/L (135-317 × 10^9/L); electrolytes within normal limits; thyrotropin, 1.8 mIU/L (0.3-4.2 mIU/L); and prothrombin time, 13.3 seconds (9.4-12.5 seconds). Urinalysis results were normal. Acetaminophen and salicylate levels were undetectable. Computed tomography of the head revealed no bleeding, masses, or other changes that would explain the clinical picture.

1. **Based on this patient's presentation, which *one* of the following diagnostic tests should be performed *next*?**
   a. Magnetic resonance imaging (MRI) of the brain
   b. Electroencephalography
   c. Lumbar puncture (LP)
   d. Angiotensin-converting enzyme measurement
   e. Electromyography

Magnetic resonance imaging of the brain is a good test to evaluate changes within the brain parenchyma and can also help in the diagnosis of herpes simplex virus (HSV) encephalitis. However, it is expensive, time consuming, and not readily available in all practice settings. The criterion standard for diagnosis of HSV encephalitis is the detection of HSV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR). Although brain MRI might be needed later on, it is not the best next step in this patient's situation. Electroencephalography could help evaluate for seizure activity or epilepsy, but the patient has no history suggestive of such disorders at this presentation. The best diagnostic step in evaluating a patient, especially if immunocompromised, with subacute altered mental status, headaches, and no focal neurologic deficit is LP. Meningitis and encephalitis must be high on the differential diagnosis and would require CSF analysis for diagnosis. Lumbar puncture can be performed easily by many physicians in different practice settings, has a low complication risk, and is less expensive than MRI. The differential diagnosis may include neurosarcoidosis as well, but it usually presents with cranial nerve palsies and less commonly with headaches.[1] Furthermore, angiotensin-converting

See end of article for correct answers to questions.

Resident in Internal Medicine, Mayo Clinic School of Graduate Medical Education, Rochester, MN (N.S.M., R.C.W.); Advisor to residents and Consultant in Hospital Internal Medicine, Mayo Clinic, Rochester, MN (M.I.).

enzyme levels have low sensitivity and specificity in diagnosing sarcoidosis.[2] Electromyography may be useful for evaluating proximal muscle weakness or the presence of peripheral neuropathy, which are absent in this patient.

Lumbar puncture yielded clear CSF. Initial CSF analysis revealed the following (reference ranges provided parenthetically): opening pressure, 25 cm H_2O (7-18 cm H_2O); total protein, 107 mg/dL (0-35 mg/dL); glucose, 35 mg/dL, with a serum glucose level of 102 mg/dL (CSF glucose should be 60% of serum glucose when drawn concurrently); total nucleated cells, 34/μL (0-5/μL); erythrocytes, 0% (0%); neutrophils, 3% (0%-6%); lymphocytes, 69% (40%-80%); and monocytes, 28% (15%-45%).

2. Given the overall presentation so far, which *one* of the following additional CSF tests would provide the *highest* diagnostic yield?

a. *Streptococcus pneumoniae* PCR
b. *Neisseria meningitidis* PCR
c. Enterovirus PCR
d. Coccidioidomycosis antigen test
e. Cryptococcal antigen test

Streptococcus pneumoniae and *N meningitides* are common pathogens in acute bacterial meningitis, which presents with fever, nuchal rigidity, and characteristic CSF findings of pleocytosis (cell count over 100), low glucose level, and high protein value.[3] This scenario does not fit with our patient's subacute/chronic disease course nor with results of his CSF analysis. Enterovirus causes aseptic meningitis, characterized by a rapid onset (within hours) as opposed to the month-long course our patient experienced. Additionally, the cost and lack of actionable treatment, combined with generally good outcomes, makes the clinical utility of enterovirus PCR low in many cases.[4] Coccidioidal meningitis can present with subacute headache and mental status changes, but it is primarily found in the southwestern United States. Our patient is from Iowa and had no recent travel. Cryptococcal antigen testing would provide the highest diagnostic yield in this patient. First, his clinical course is consistent with subacute meningoencephalitis, characterized by a subacute headache and gradual mental status changes over 2 to 4 weeks, which is seen with cryptococcal meningitis (CM).[5] Second, his initial CSF findings of mildly elevated nucleated cell count with a lymphocyte predominance, low glucose concentration, and high protein level are suggestive of a fungal or mycobacterial infection, the latter being less common. When CM is suspected, sending the CSF for cryptococcal antigen testing is the appropriate next step. It can be analyzed quickly and has a sensitivity of 93% to 100% and a specificity of 93% to 98%.[6,7]

Our patient was admitted to the hospital. His CSF studies were positive for cryptococcal antigen, with a high titer of greater than 1:2560. Cerebrospinal fluid cultures grew *Cryptococcus neoformans* after 25 days of inoculation. Results of human immunodeficiency virus (HIV) serology and CSF mycobacterial cultures were negative. With a confirmed diagnosis of CM, input from the infectious disease department was sought to provide recommendations for treatment.

3. Which *one* of the following is the *preferred* induction therapy for CM in this patient?

a. Flucytosine for at least 2 weeks
b. Liposomal amphotericin B for at least 2 weeks
c. Fluconazole for at least 2 weeks
d. Liposomal amphotericin B and flucytosine for at least 2 weeks
e. Liposomal amphotericin B and fluconazole for at least 2 weeks

A quick and effective reduction of the yeast burden within the central nervous system (CNS) is the goal of induction therapy. Each one of the first 3 medications—flucytosine, liposomal amphotericin B, and fluconazole—may be active in vitro against cryptococcosis, but monotherapy with any one of them is not recommended given the better and faster fungicidal activity of combination therapy. For patients with CM who are HIV negative and have not had a

Mayo Clin Proc. ■ April 2019;94(4):709-713 ■ https://doi.org/10.1016/j.mayocp.2018.05.040
www.mayoclinicproceedings.org

transplant, the current clinical practice guidelines recommend induction therapy with amphotericin B deoxycholate (0.7-1.0 mg/kg per day intravenously [IV]) and flucytosine (100 mg/kg per day orally in 4 divided doses).[8] This combination is associated with improved survival compared with amphotericin B monotherapy. No survival benefit of amphotericin B plus fluconazole was found in a recent randomized trial.[9] Given the higher toxicity with amphotericin B deoxycholate, lipid formulations including liposomal amphotericin B (3-4 mg/kg per day IV) and amphotericin B lipid complex (5 mg/kg per day IV) are often substituted for amphotericin B deoxycholate in the United States. Induction therapy is recommended for at least 4 weeks if there are no neurologic complications. In patients who are at low risk for therapeutic failure, induction therapy can be shortened to only 2 weeks. Such patients include those who have an early diagnosis by history, no uncontrolled underlying disease or immunocompromised state, and excellent clinical response to initial 2-week induction therapy. Conversely, in patients who do exhibit focal neurologic complications, induction therapy can be extended to 6 weeks. Following induction therapy, consolidation therapy with fluconazole (800 mg/d orally) should be given for 8 weeks. After induction and consolidation therapy, patients should receive maintenance therapy with fluconazole (200 mg/d orally) for 6 to 12 months.[8]

Liposomal amphotericin B and flucytosine were administered, but the patient continued to have morning headaches a few days later.

4. **Which *one* of the following is the *preferred* first step in the management of this patient's morning headaches?**
   a. Acetazolamide
   b. Mannitol
   c. Corticosteroids
   d. Serial LPs
   e. Ventriculoperitoneal shunt

Our patient has an elevated intracranial pressure (ICP), supported by an opening pressure of 25 cm H_2O during his LP. This common complication of CM is responsible for his morning headaches. Acetazolamide, mannitol, and corticosteroids have no proven benefit in this setting, so they are not recommended.[8] The preferred first step in management is serial LPs to reduce his opening pressure to a normal of less than 20 cm H_2O. Ventriculoperitoneal shunts can be placed only if more conservative measures to control increased ICP have failed.[7,8]

After induction therapy with liposomal amphotericin B and flucytosine and repeated LP, the patient's symptoms improved dramatically. Morning headaches resolved, and mental status returned to his baseline. He was being prepared for hospital dismissal with appropriate follow-up.

5. **Which *one* of the following would be the *preferred* follow-up after starting induction therapy for CM in this patient?**
   a. Daily measurement of electrolytes and magnesium
   b. Weekly measurement of electrolytes and magnesium
   c. Daily measurement of serum cryptococcal antigen
   d. Weekly measurement of CSF cryptococcal antigen
   e. Weekly measurement of CD4 and CD3 counts

Although induction therapy with liposomal amphotericin B and flucytosine has been found to improve mortality in CM, it is important to recognize the severe adverse effects these medications can have. Amphotericin B deoxycholate in particular is known to be nephrotoxic and causes major electrolyte abnormalities that can be life-threatening. Although lipid formulations of amphotericin B are less nephrotoxic, they still require monitoring of creatinine and electrolyte levels. Potassium and magnesium wasting typically begins after 5 days of amphotericin therapy.[7] Flucytosine also has hematologic adverse effects, including leukopenia and thrombocytopenia, that can worsen in acute-on-chronic kidney disease. As such, it is important to obtain daily

electrolyte measurements to monitor for and treat these abnormalities. Daily measurement of serum cryptococcal antigen and weekly measurement of CSF cryptococcal antigen are not reliable measures to provide therapeutic monitoring and thus are not routinely recommended for that purpose.[10] Because CM can be seen in apparently immunocompetent individuals, measurement of CD4 and CD3 counts would not help predict response to therapy.

DISCUSSION

Cryptococcal meningitis is a devastating opportunistic infection caused by the encapsulated yeast *C neoformans*. It is often considered in HIV-infected patients, but it can occur in patients with impaired cell-mediated immunity from other etiologies.[11] In a US study of more than 300 HIV-negative patients with cryptococcal infection, half had CNS involvement, and of these, 25% had received corticosteroid therapy, 24% had chronic liver, kidney, or lung disease, 16% had a malignancy, 15% had received solid organ transplants, and 30% had no apparent underlying condition.[5] These findings are important given the considerable morbidity and mortality regardless of HIV status, making early recognition key to expedite management.[12] Our patient has 2 risk factors that impair cell-mediated immunity, including sarcoidosis and corticosteroid therapy, which predisposes him to CM.

Patients with CM usually present with subacute or chronic meningitis symptoms of a few weeks' duration. However, these symptoms, such as headache and altered mental status, are not specific. When suspected, LP is the best first step in diagnosing CM. Typically, CSF studies will reveal a high opening pressure, lymphocytic pleocytosis, low glucose concentration, and high protein level. In general, CM should be considered in all cases of lymphocytic meningitis. Cerebrospinal fluid cryptococcal antigen testing has a rapid turnaround time and can establish the diagnosis with high specificity and sensitivity.[6,7] Serum cryptococcal antigen testing is helpful especially in situations in which CSF assessment is delayed for any reason. Additionally, fungal cultures of blood and CSF specimens can be helpful in the diagnostic work-up.

The cryptococcal polysaccharide capsule causes a physical obstruction of the arachnoid villi, which leads to a failure to resorb CSF and in turn elevated ICP.[12] Interestingly, the elevation in ICP is positively correlated with an increased number of organisms in the CSF. One feared complication of intracranial hypertension is cerebral edema. Common symptoms and signs include headaches, vomiting, visual changes, papilledema, abducens nerve palsy, altered mental status, and ultimately coma. Increased ICP in patients with CM should be managed aggressively to decrease morbidity and mortality and is usually achieved using serial LPs.[8]

Once the diagnosis of CM is confirmed, it is important to promptly initiate appropriate antifungal therapy. Although fluconazole monotherapy can be used for mild cryptococcal disease not involving the CNS, treatment of CM is lengthy and arduous and includes 3 stages: induction, consolidation, and maintenance. Induction therapy consists of deoxycholate or lipid formulations of amphotericin B plus flucytosine for 4 to 6 weeks. Subsequently, consolidation therapy should be initiated with fluconazole (800 mg/d orally) for 8 weeks. Following that, maintenance therapy with fluconazole (200 mg/d orally) should be given for 6 to 12 months.[8] Of note, all these medications can have serious adverse effects. Amphotericin B products in particular can lead to nephrotoxicity, in addition to potassium and magnesium wasting. Flucytosine can also cause neutropenia, especially in patients with chronic kidney disease. Therefore, it is extremely important to monitor electrolyte levels and complete blood cell counts closely. In addition, patients should be monitored clinically for infusion-related reactions during and following each administration. Lumbar puncture is repeated 2 weeks after induction therapy in immunocompromised hosts to assess response to therapy by the presence or absence of fungal growth.

Mayo Clin Proc. ■ April 2019;94(4):709-713 ■ https://doi.org/10.1016/j.mayocp.2018.05.040
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CONCLUSION

It is important to recognize CM at an early stage given its high morbidity and mortality if adequate treatment is not started promptly. The HIV-negative status may lead to a delay in diagnosis, so it is helpful to consider other risk factors that impair cell-mediated immunity, especially prednisone use, which in turn predisposes patients to CM.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Meltiady Issa, MD, MBA, Division of Hospital Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (issa.meltiady@mayo.edu).

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CORRECT ANSWERS: 1. c. 2. e. 3. d. 4. d. 5. a