CLINICAL VIGNETTE

Coccidioidal Meningitis Presenting as Post-operative Altered Mental Status

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Case

A 65-year-old male with clear cell renal cell carcinoma (RCC) status post recent partial left nephrectomy six weeks prior, presented with headaches and persistent confusion. Prior to his partial nephrectomy he was independent with all activities of daily living. After surgery, his family noticed that he was more confused and forgetful. He was seen in the Emergency Room two weeks after the surgery for these symptoms. Evaluation included no evidence of infection and the neurological exam revealed only limited orientation, and CT head showed prominence of the lateral ventricles. The patient was discharged with outpatient follow-up for possible early development of dementia. After discharge, his confusion worsened, which led to the patient's current presentation. Family reported that he may have developed a headache after the surgery. Review of systems was negative for fevers, cough, head trauma, viral prodrome, or urinary incontinence.

On presentation, he was afebrile. His exam was significant for white plaques on the tongue, halitosis, and no skin lesions. He was alert but oriented only to himself. His neurological exam was otherwise normal. Initial labs showed a normal basic metabolic panel, complete blood count, liver function tests, ESR, CRP, urinalysis, and chest x-ray. Repeat CT head showed unchanged prominence of the temporal horns of the lateral ventricles and an old left thalamic infarct. MRI head was nondiagnostic due to severe motion artifact.

The differential for the patient's encephalopathy was broad, which included infectious etiologies, reversible causes of dementia, metastatic disease from his RCC, and progressive hydrocephalus given CT head findings. Initial labs revealed a positive serum coccidioidal IgM and IgG and serum coccidioidal complement fixation titer of 1:64. The patient was started on empiric treatment with IV acyclovir and fluconazole for atypical meningitis/encephalitis and suspected coccidioidal meningitis. Under anesthesia sedation, CT chest, MRI brain, and lumbar puncture (LP) were performed. Chest imaging revealed a 9 mm apical nodule with central cavitation, prompting sputum collections with negative acid fast bacillus sputum stains. MRI brain demonstrated leptomeningeal enhancement. LP in the fetal position revealed an opening pressure of 90 mm H_2O. Initial cerebral spinal fluid (CSF) studies showed RBC of 1 per cubic mm, a nucleated cell count of 209 per cubic mm, 17% segmented neutrophils, 69% lymphocytes, 11% monocytes, and 2% eosinophils, with a glucose of 25 mg/dL (serum glucose approximately 100 mg/dL), and protein of 240 mg/dL. The following day, CSF coccidioidal IgM and IgG antibodies returned positive, confirming the diagnosis of acute coccidioidomycosis meningoencephalitis.

The patient had persistent confusion while on oral fluconazole, concerning for treatment failure. Repeat LP showed a normal opening pressure, an improved CSF nucleated cell count to 51 per cubic mm, protein to 221 mg/dL, and a CSF coccidioidal complement fixation ratio of 1:16. After a multidisciplinary discussion, it was felt that the patient's mentation may not respond dramatically and continued therapeutic trial on fluconazole advised with close follow-up.

Six weeks after his discharge, the patient had only minimal improvement in his mental status. He had developed stroke-like symptoms which were felt to be thalamic infarcts, concerning for treatment failure. A third LP outpatient demonstrated persistent nucleated cell count of 41 per cubic mm, protein of 168 mg/dL, increased eosinophil to 8%, and a persistently elevated complement fixation titer of 1:16. Serum complement fixation titer was 1:128. He was switched from oral fluconazole to longterm voriconazole, 200mg BID. His Mini-Mental Status Exam improved from a score of 19 to 27 out of 30 over the next three months following the medication change and the serum titer improved to 1:16.

Discussion

Coccidioidal meningitis is a deadly complication of coccidioidomycosis, a fungal infection caused by the dimorphic fungi of the Coccidioides genus. The CDC notes over 14,000 reported cases of coccidioidomycosis in the United States.[1] Also known as "valley fever," it is endemic to the southwestern United States (including California), northwestern Mexico, and parts of Central and South America.[2,3] Coccidioidomycosis most commonly manifests as a pulmonary infection and can be self-limiting. But, it can also disseminate, leading to extrapulmonary manifestations, including cutaneous, musculoskeletal, and neurological.

Coccidioidal meningitis usually develops within weeks to months of a primary pulmonary infection via hematogenous spread. The most common symptom is a persistent headache, present in 75% of cases. This can confound the clinical suspicion for meningitis, as up to 20% of primary pulmonary coccidioidomycosis can also have headache without menin-

gitis.[4] Other associated symptoms include cognitive dysfunction, emotional lability, gait disturbances, diplopia, and lethargy. On exam, most will have a non-focal neurological exam outside of mental status changes, neck stiffness, and papilledema if hydrocephalus is present.[5] Lab abnormalities are usually identified in the CSF, showing increased WBC's with usually a lymphocytic predominance and sometimes eosinophilia. CSF WBC count usually ranges from a few to several hundred. Typically, CSF glucose is depressed and the CSF protein is elevated (up to 250mg/dL).[4] Of note, the CSF abnormalities can be persistent for weeks to months after azole antifungal treatment is initiated.[5]

Diagnosis of meningitis is made via LP and CSF analysis for antibodies, antigens, and/or growing the organism in culture. CSF antibodies are positive in over 95% of CSF samples, but can sometimes be undetectable early in the disease.[4,5] One retrospective study in Arizona involving 36 patients with 42 episodes of coccidioidal meningitis showed a 93% sensitivity and 100% specificity.[6] The organism itself is only recovered from the CSF about 15-30% of the time. CSF polymerase chain reaction testing has been employed as a rapid means of diagnosis, but with varying degrees of sensitivity.[4,5] Positive serum antibody serology and MRI head findings typical for coccidioidal meningitis such as hydrocephalus (a common complication), basilar leptomeningeal enhancement, cerebral infarct, and focal parenchymal lesions support the diagnosis.[7]

All patients diagnosed with coccidioidal meningitis should be initiated on treatment. The prognosis without treatment is generally fatal, with >91% mortality at two years.[8] Historically, amphotericin B has been used as treatment for coccidioidal meningitis before use of azoles in the 1990's. Since amphotericin B is fungicidal, it is the only pharmacological option with curative potential.[3] The Infection Diseases Society of America (IDSA) 2016 guidelines recommend treatment with azoles, specifically oral fluconazole at 400-1200mg (most starting at 800mg).[4,9] Given that azoles are considered fungistatic, treatment is only suppressive and not curative, leading to the recommendation for lifelong treatment with fluconazole at 400-800mg/day. One study reported 14 out of 18 patients with meningitis relapsing after discontinuing treatment.[10] An alternative to fluconazole is itraconazole, although the CSF penetration is poor (0.2-12% of serum concentrations) as compared to fluconazole (50-90% of serum concentrations).[3] In pregnancy, intrathecal amphotericin B is utilized instead of azoles during the first trimester because of the teratogenic effects of azoles.[4] In situations where there is a plateau in disease control on fluconazole, changing the regimen to voriconazole or posaconazole as salvage therapy appear to provide clinical improvement.[11] With this, voriconazole can cause visual disturbances and dermal photosensitivity, while posaconazole can interfere with the hypothalamic-pituitary axis. Thus, the decision to switch must be considered carefully on a case by case basis.

With appropriate treatment, patients should see a gradual improvement in symptoms within several weeks with most having an uncomplicated course. Some may have residual deficits from mild memory loss to coma.[3,4] Managing coccidioidal meningitis complications, included increased intracranial pressure (ICP), hydrocephalus, vasculitic infarcts, arachnoiditis, syrinx, and rarely abscesses and mass lesions.

With the initial LP, opening pressure should be measured in the lateral decubitus position to assess for increased ICP (which may or may not be associated with hydrocephalus). Elevated opening pressures of 180-250 mm H_2O should be monitored, while pressures $\geq$250 mm H_2O require intervention. The IDSA recommends lowering pressures by removing enough CSF fluid to reduce the pressure by 50% of the initial opening pressure or to <= 200 mm H_2O, whichever is greater. CSF removal should be done daily for at least the first four days until the pressures are <250 mm H_2O. A shunt may be required if pressures cannot be reduced via CSF removal or pharmacological treatment of the meningitis.[9]

Hydrocephalus can be seen with the initial diagnosis of coccidioidal meningitis or as a complication. MRI imaging will show dilated ventricles. It may be associated with an increase in ICP and with symptoms such as headaches, mental status changes, abnormal gait, urinary incontinence, nausea, or vomiting. Those with radiographic findings of hydrocephalus who are asymptomatic, treatment can be medical management with antifungal therapy and serial imaging every three to six months. If symptoms are present, a neurosurgical consult should be pursued for shunt options.[3,9]

Conclusion

Coccidioidal meningitis was once a lethal complication of coccidioidomycosis before the advent of intrathecal amphotericin B and now azoles. Unlike bacterial meningitis, where symptoms are acute and easier to recognize, coccidioidal meningitis can be insidious, often leading to delays in diagnosis. Coccidioidomycosis is a manageable chronic disease, but recovery can be a long process. Coccidioidal meningitis should be considered on the differential for anyone from an endemic region presenting with acute to subacute mental status changes, especially in the absence of infectious symptoms.

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