CLINICAL VIGNETTE

Coccidioidal Meningitis Complicated By Hydrocephalus

Nam Kim, M.D.

Case Report

A 37-year old Hispanic female with diabetes type 2 presented to the emergency department with worsening headache and confusion. She initially presented to a community hospital three weeks before with headache and cough. CXR showed right upper lobe infiltrates and she was treated with azithromycin for presumed community acquired pneumonia. Her symptoms worsened and she returned ten days later and was admitted with worsening pneumonia. Her PPD was positive and lumbar puncture showed lymphocytic pleocytosis and elevated protein and she was started on four drug antituberculous therapy for presumed pulmonary and meningeal TB. Her symptoms continued to worsen after discharge and she developed increasing confusion and was taken to the University hospital. She had nuchal rigidity with positive Brudzinski's sign. Repeat LP was remarkable for lymphocytic pleocytosis, further elevation in protein to 340 mg/dl and glucose 77 mg/dL. CSF AFB stain as well as CSF mycobacterium tuberculosis nucleic acid amplification test were negative. CSF coccidioidal antibody by complement fixation returned positive with a titer 1:16. Brain MRI with gadolinium showed significant basal meningitis. She was diagnosed with disseminated coccidioidomycosis with pulmonary and meningeal involvement. Serum coccidioides antibody titer by complement fixation returned positive at 1:128. HIV test was negative. Her TB treatment was stopped, and she was discharged home on fluconazole 400mg bid. Despite taking Fluconazole daily, her headache, nausea and vomiting did not improve, so the patient was readmitted 2 weeks later. Head CT and MRI showed mild hydrocephalus and basilar meningitis. LP was repeated with very high opening pressure of > 350 mmH2O and persistent lymphocyte-predominant pleocytosis. CSF coccidioides antibody by complement fixation was again positive with a titer 1:16. Neurosurgery was consulted and placed a ventriculoperitoneal (VP) shunt. After VP shunt placement, the headache and nausea improved, and a repeat CT of the brain showed improvement of hydrocephalus. She was discharged home, but she returned to the emergency department 2 weeks later for recurrence of severe headache and nausea. CT of brain showed recurrent hydrocephalus, and nuclear medicine shunt evaluation showed good passage of radionucleotide through the VP shunt, but accumulation in a pocket at the distal tip of the shunt without passage into the abdomen. The patient was taken to surgery for laparoscopic revision of the VP shunt and a CSF pseudocyst was found at the distal tip of the VP shunt. The pseudocyst was drained and the distal tip of VP shunt was repositioned. The patient did well after the procedure with improvement of headache and nausea. Since the discharge, she has been regularly followed as an outpatient with resolution of hydrocephalus and substantially improved headache.

Discussion

Coccidioidomycosisis is caused by inhaling the spores (arthroconidia) of Coccidioides species, (C. immitis or C. posadasii). These fungi are endemic in the southwestern part of the United States and parts of Mexico and South America. However, as people from other areas frequently travel to endemic regions, it is important to know about these infections even in non-endemic areas. One study which examined geographic distribution of fungal infections in elderly patients found 10 percent of fungal infections were diagnosed in patients whose primary residencies are outside of typical endemic regions[1].

The overall incidence of coccidioidomycosis has been increasing with a recent report showing about 60% of the infection occurring in Arizona[2]. The majority of primary coccidiomycosis is subclinical, and less than half of the cases come to medical attention. When patients develop clinically significant infection, the most common presentation is acute or subacute community-acquired pneumonia known as valley fever. It is usually self-limited and does not require specific antifungal treatment except in patients who have immunosuppression, significant co-morbidities such as preexisting cardiopulmonary disease or diabetes, or severe presentation of pul-

monary infection. A small proportion of all the cases of coccidioidomycosis disseminates outside the lungs. When it occurs, any part of the body can be involved, but most frequently affects the skin, skeletal system and the meninges. Risk of extrapulmonary disseminated infection is especially high in immunocompromised patients including those with AIDS, lymphoma, solid organ transplantation or taking immunosuppressive therapy[3]. It is also more common in patients with African, Filipino, Asian or Hispanic ancestry[3]. Pregnancy is also a risk factor for disseminated disease.

Meningitis is the most serious and potentially lethal form of dissemination and occurs in almost half of the patients with disseminated disease. It is estimated that approximately 200 to 300 cases of coccidioidal meningitis occur within the endemic areas of the United States in nonepidemic years[4]. Delays in diagnosis are common because the clinical presentation is frequently insidious and nonspecific, and clinicians often fail to consider it as a diagnostic possibility. If untreated, most patients with meningitis die within 2 years[5]. Most cases of dissemination including meningitis usually occur within weeks to months after primary pulmonary infection[6]. Occasionally meningitis may be the initial presentation of coccidioidal infection without clinically evident pulmonary disease[4]. Coccidioidal meningitis can present in many different ways. Headache is the most common presenting symptom, but patients can present with altered mental status, personality changes, nausea, vomiting, gait abnormalities and focal neurologic deficits[6]. As seen in our patient, some degree of meningismus is present in about 50% of cases[6].

Hydrocephalus is the most common complication of coccidioidal meningitis and it can be a presenting manifestation or a late complication[6]. Most of the morbidity from coccidioidal meningitis results from hydrocephalus[5]. Another common life-threatening complication is CNS vasculitis, which can lead to cerebral ischemia, infarction and hemorrhage[3]. Occasionally stroke or altered mental status from vasculitis can be the presenting manifestation[4]. Rarely, spinal arachnoiditis can occur, especially as a complication of treatment, and it can present as back pain, numbness and tingling, or spastic paraparesis[7]. Also rarely, coccidiodial meningitis can also cause mycotic aneurysms and subsequent subarachnoid hemorrhage[8].

CSF evaluations show findings consistent with chronic meningitis, and the degree of pleocytosis is usually modest ranging from a few to several hundred cells, majority of which are typically lymphocytic. Eosinophils are not common but when present, they are highly suggestive of this diagnosis[6]. Protein level is almost always elevated, usually > 150mg/dL. CSF glucose level is usually low, occasionally profoundly low.

Neuroimaging in patients with coccidioidal meningitis can be helpful in suggesting diagnosis and estimating prognosis as well. The most common abnormalities detected on neuroimaging studies are hydrocephalus, basilar meningitis and cerebral infarction. Hydrocephalus can be seen in 30-50% of patients at some point in their disease courses, and 15-20% of patients can have vasculitic infarction[6]. CT is excellent for detecting hydrocephalus, but MRI is more sensitive in detecting basilar meningitis or cerebral infarction. In one study, significantly elevated mortality rates were associated with neuroimaging finding of hydrocephalus and hydrocephalus with infarction[9].

Confirming the diagnosis is generally based on positive CSF serologic tests. Histopathologic examination such as meningeal biopsy is rarely done, and CSF fungal culture is diagnostic but positive in only about 15% of initial evaluations. The most reliable serologic tests are the immunodiffusion tests for IgM and IgG, and the complement fixation test for IgG[6]. When patients have lymphocytic meningitis but negative CSF fungal culture and negative CSF serology for coccidioides, the diagnosis is sometimes presumed based on serum serology for coccidioides, which is more sensitive but less specific for this condition. Some experts believe it is important to repeat CSF analysis to establish a firm diagnosis.

Intrathecal amphotericin B was the mainstay of treatment until the advent of azole agents in the 1980s[10]. Azole agents, especially fluconazole are safer and more convenient than amphotericin B, which requires intrathecal administration and is associated with significant toxicity. Treatment guidelines for coccidioidomycosis were published by the Infectious Diseases Society of America (IDSA) in 2005[3]. For coccidioidal meningitis, most clinicians favor starting therapy with high-dose fluconazole, 800-1200 mg once per day until clinical improvement is achieved and then decreasing the dose slowly to maintenance doses of around 400 mg daily. Others prefer 400 mg daily as a starting dose and escalate upward if there is suboptimal response to therapy. In addition to fluconazole, some clinicians also initiate therapy with intrathecal amphotericin B based upon their belief that responses are more prompt with this approach[3]. Itraconazole 200 mg twice or three times daily has been reported to be comparably effective[3,6]. Patients who respond to azole therapy should

continue this treatment for life. Patients who do not respond to fluconazole or itraconazole are candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment[3]. There are also reports of possible benefit of voriconazole as a rescue therapy for cases of therapeutic failure with fluconazole. Despite its convenience and better safety profile, fluconazole has not necessarily led to better survival from coccidioidal meningitis. In one report, mortality was similar in those patients treated with intrathecal amphotericin B before the advent of azole therapy with those more recently treated with fluconazole[10].

The complication of hydrocephalus usually requires ventriculoperitoneal (VP) shunting. Development of hydrocephalus may occur regardless of the therapy being used and does not in itself require switching to alternative therapy[3]. In many patients, VP shunting can be very effective, but some develop complications such as obstruction, infection and overdrainage of CSF. Peritoneal CSF pseudocyst formation as seen in our patient is not common[11]. However, any recurrent or persistent headache, nausea and vomiting, gait disturbance, mental status change or any neurologic deficit should be evaluated by CT or MRI for VP shunt malfunction[6].

After starting treatment, patients should be followed closely to monitor clinical response and repeat CSF evaluation as needed. The degree of CSF pleocytosis and CSF serology titer can be monitored for treatment response or relapse. Serum coccidioidal IgG levels should not be used to guide treatment of meningeal illness, as it is with primary and nonmeningeal disseminated disease[6]. Therapy is lifelong, and patients should be educated about the importance of adherence to treatment as non-compliance can result in serious, potentially fatal consequences.

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