CLINICAL VIGNETTE

A 25-Year-Old Male with Eosinophilic Meningitis

Noah (Naomi) Duncan, MD and Vindeep Bhandari, DO

Case

A 25-year-old man with no significant past medical history presented to his primary care physician (PCP) for 3 days of headache. The headache was posterior and bilateral and radiated to his neck and to the top of his head. He reported some photophobia but denied phonophobia, nausea, vomiting or any focal neurologic symptoms. He reported an episode of fever to 101F without reoccurrence. He also noted a recent rash on his left wrist with several hyperpigmented papules that was beginning to resolve. He denied any sick contacts and worked as a delivery driver in the San Fernando Valley. He had no recent travel other than to the Coachella Valley earlier in the year. His primary care physician ordered a non-contrast Head CT, blood work and prescribed ibuprofen. CT head was negative. HIV screening, RPR, CRP, and urine G/C were all negative. Metabolic panel did not show significant abnormalities and CBC had normal WBC, Hemoglobin, Hematocrit, and platelet count. WBC Differential noted elevated eosinophils at 5.8% with elevated absolute eosinophil count of 0.57 thousand/ uL. ESR was mildly elevated at 21mm/hr and HSV serologies showed positive HSV-1 IgG.

The headache did not improve and the patient \ presented to the ED one week later. His headache was now associated with phonophobia as well as photophobia. He also reported fevers with Tmax of 103F. He denied neck stiffness, nausea, vomiting and cardiac, respiratory, or GI symptoms. Physical exam showed no nuchal rigidity. Neurologic examination was again unremarkable. BMP was notable for serum Sodium of 131. Repeat CBC remained normal. A lumbar puncture was done in the ED. Opening pressure was not measured. CSF protein was 58 mg/dL. CSF glucose was low at 36 mg/dL. CSF RBC count was 1 per mm^3. CSF WBC count was elevated at 129 per mm^3 with a differential of 9% neutrophils, 55% lymphocytes, 7% monocytes, and 29% eosinophils. Gram stain showed 1+ PMNs and no organisms. After lumbar puncture the patient was given Ceftriaxone 2g IV x1 and dexamethasone 10mg IV x1 and admitted for meningitis. Infectious disease and neurology were consulted. The patient continued on ceftriaxone and empiric vancomycin was added. He also started IV acyclovir for empiric HSV meningitis coverage. There was concern for possible coccidioidal meningitis and empiric fluconazole was added. CSF bacterial, fungal, and AFB cultures remained negative. CSF HSV, VZV, and EBV PCR were all negative as well as CSF VDRL and Treponemal antibody. Serum Cryptococcal antigen was negative as week as CSF West Nile Virus studies. Acyclovir, ceftriaxone, and vancomycin were stopped. Serum Coccidioides antibody by complement fixation (CF) returned positive with titer of 1:128. Serum Coccidioides IgM antibody was elevated at 1.2 and IgG was elevated at 6.7. MRI brain was unremarkable with no evidence of hydrocephalus. Chest XR showed a lesion in the left upper chest and CT Chest showed a 1.7 x 1.2 cm nodule in the left upper lobe with peripheral, small nodular calcifications compatible with coccidioidomycosis. CSF Coccidioides studies from the initial LP were not sent and there was not enough CSF left. A second lumbar puncture was done 4 days after the initial LP. CSF Coccidioides antibodies by CF were positive with a titer of 1:2. Of note the second LP also showed an elevated CSF protein at 77 mg/dL.

The patient's symptoms improved and he was discharged on fluconazole. At outpatient follow up headaches continued to improve and serum Coccidioides antibodies by CF have decreased to 1:16.

Discussion

This patient's CSF studies noted an eosinophilic meningitis. This is defined by either a CSF eosinophil count greater than 10 eosinophils/uL or greater than 10% of CSF WBCs.[1] The cause of his eosinophilic meningitis was coccidioidal meningitis (CM). Other potential causes of eosinophilic meningitis include parasitic infections, atypical bacterial infections such as tuberculosis and neurosyphilis, and noninfectious etiologies such as malignancy and medications.[1] While parasitic infection may be the most common cause of eosinophilic meningitis in other parts of the world,[2] in the United States, Coccidioides infection is the most common etiology.[1]

Coccidioides is a dimorphic fungus found in the soil, Coccidioides spores can become airborne and cause disease when inhaled.[3] It is endemic to the southwestern United States as well as Mexico and parts of Central and South America.[3] The primary site of infection is usually pulmonary[4,5] and most cases are asymptomatic.[4] This patient presented with had pulmonary disease identified on imaging, but never had any respiratory symptoms. Coccidioides can disseminate to other sites and can cause extra-pulmonary infections in the absence of primary pulmonary infection.[4,5] An epidemiologic study of 364 cases of Coccidioidomycosis in southern Utah found 1.1% of patients had meningitis.[5] Meningitis is a very serious potential complication of Coccidioides infection. Prior to the availability of

effective treatment, cases were usually fatal.[4] The first case of CM was reported in San Francisco in 1901 and resulted in death.[6] Meningitis usually develops soon after primary infection, but rarely CM has been reported years after the initial infection.[4]

The most common presenting symptom of CM is headache,[4] and fever may be present.[4] Other potential symptoms include nausea, vomiting, changes in personality, and focal neurological deficits.[4] CM typically causes a CSF WBC count in the teens to hundreds, but less commonly can cause WBC counts in the thousands.[7] CSF differentials typically shows a lymphocyte predominance.[4] CM can cause an eosinophilic meningitis in a minority of cases with a larger percentage with CSF eosinophil pleocytosis that does not meet criteria for eosinophilic meningitis.[8] CSF protein is typically elevated, often greater than 150 mg/dL, and may be high enough to be measured in grams.[4] Our patient's initial CSF protein was within normal limits and only mildly elevated on the second LP. The patient's symptoms suggest he presented relatively early in the course of disease. Normal or near normal CSF protein can be seen early on in CM.[7] CSF glucose is typically low.[4,7] There is an association between CM and SIADH,[9] which could explain our patient's hyponatremia. Diagnosis is typically established by identification of antibodies by CF or immunodiffusion.[7] Coccidioides on CSF culture is also diagnostic but uncommon.[7]

The mainstay of treatment for CM is fluconazole.[4] Itraconazole and Voriconazole have also been used.[7] Duration of treatment with azoles is life-long.[4] Intrathecal Amphotericin B can also be effective but is mainly used in azole treatment failure.[7] Potential complications of CM include hydrocephalus, arachnoiditis, syrinx, cranial neuropathy, and vasculitic infarction.[7] Hydrocephalus is the most common CM complication and may be present at diagnosis or develop later in the course and is treated with VP shunting.[7] Vasculitic infarction is reported more commonly on imaging than is recognized clinically.[7] A retrospective study of CM stroke due to vascultic infarction reports that glucocorticoid therapy may reduce the risk of further strokes.[10] Currently there is no consensus on the use of glucocorticoids in this clinical scenario.[7] Glucocorticoid therapy may also increase risk of disseminated coccidioidomycosis.[11]

Conclusion

CM is the most common cause of eosinophilic meningitis in the United States. It is a very serious complication of coccidioidomycosis that is often fatal if untreated. Even with lifelong treatment it carries significant risk of morbidity and mortality. It should be considered included in the differential for undifferentiated meningitis in areas where Coccidioides is reported as well as in patients with new headache, neurologic symptoms, or psychiatric symptoms.

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