CLINICAL VIGNETTE

Disseminated Coccidioidomycosis with Fungal Meningitis, CNS Vasculitis, and Recurrent Cerebrovascular Accidents

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Case

A 28-year-old female with disseminated coccidioidomycosis presented with acute left sided weakness of upper and lower extremities. She has chronic low back pain with spinal stimulant or placement and right hip replacement for congenital hip dysplasia. The patient was in her usual state of health until 2 weeks prior when she developed intractable headaches, severe fatigue, shortness of breath, and new skin lesions on her torso and extremities. She also reported neck pain, but denied photophobia, nausea, vomiting, fevers, or night sweats. On presentation, she was afebrile with normal vital signs. Physical exam was notable for normal mental status, and normal cardiorespiratory and abdominal exam. She was alert and oriented with congruent speech and fund of knowledge. Her cranial nerve exam revealed decreased sensation to light touch and pinprick on the left face with left sided facial droop. Her deep tendon reflexes were normal. She reported full compliance with chronic fluconazole and Dupilumab.

The patient was initially diagnosed with disseminated coccidioidomycosis infection 7 months prior with pulmonary and cutaneous involvement. Her chest CT showed diffuse pulmonary tree-in-bud nodules with a right upper lobe consolidative mass (Figure 1a, 1b). Skin findings included a right nasal lesion (Figure 2) described as an Ill-defined, verrucous, nodular plaque composed of vesiculopustules and overlying serous crust. Nasal shave biopsy revealed PAS-D and GMS stains positive for spherules within a multi-nucleated giant cell in the dermis. These pathologic features are consistent with cutaneous coccidioidomycosis. Lab testing showed elevated coccidioides IgG/IgM EIA, positive coccidioidomycosis antibody immunodiffusion and complement fixation. She was discharged on fluconazole but was lost to follow-up. She was re-hospitalized 3 months after her initial diagnosis with intractable headaches and photophobia. There was concern for neurologic involvement from disseminated coccidioidomycosis given missed fluconazole therapy. CT and MRI brain scans demonstrated a right basal ganglia infarct with concern for coccidioidomycosis associated vasculitis. Cerebrospinal fluid studies (CSF) from lumbar puncture included a positive coccidioides antibody complement fixation, consistent with coccidioidomycosis meningitis. She was treated with liposomal amphotericin B and fluconazole. Amphotericin B was discontinued after she developed acute kidney injury. She also completed a dexamethasone taper for CNS vasculitis. The patient's mother provided additional medical history from childhood that included frequent fungal skin infections and a family history of recurrent infections. This raised suspicion of an underlying primary immunodeficiency. She underwent extensive immunologic testing to assess for deficiencies that could explain her history of infections. She was discharged on indefinite fluconazole treatment and dupilumab.

On this admission she underwent a brain stroke protocol CT scan that showed right hemisphere hypoperfusion with multifocal stenosis and irregularity of right MCA M1 branch and diminutive R MCA M2 branch concerning for infectious vasculitis (Figure 3). tPA was not administered because she was outside the 4.5hour window per stroke treatment guidelines. The neurology and infectious disease consult teams evaluated the patient and recommended observation in the intensive care unit and initiation of liposomal amphotericin B and steroids. Brain MRI was also completed that showed small recent lacunar infarcts in the right basal ganglia, as well as right MCA M1 segment stenosis, consistent with fungal basilar meningitis (Figure 4a, 4b). Lumbar puncture was performed with CSF labs including elevated protein, decreased glucose, and lymphocytic predominant differential consistent with a fungal infection. Coccidioides antigen EIA from CSF was also positive. Blood labs revealed coccidioides serologies had again turned positive. Her repeat neurological exam on the second day of admission was notable for improvement in left sided strength and a decrease in left sided facial droop. Her clinical presentation and brain imaging findings were consistent with disease progression despite treatment with fluconazole adherence confirmed by fluconazole levels, thus the patient was switched to voriconazole. Treatment with ambisome B again was again limited due to development of an acute kidney injury. Given the extent of her disease with worsening CNS involvement interferon-gamma (IFN-γ) therapy was added to her therapeutic regimen.

Discussion

Coccidioidomycosis, commonly known as valley fever, is a fungal infection endemic to the southwestern United States (1-

3).[1-3] Coccidioidomycosis infection ranges from asymptomatic or self-limited lung infections to disseminated disease often involving bones, skin, and the central nervous system.[4-6] Approximately 1% of coccidioidomycosis infections are complicated by dissemination.[4] An immunosuppressed state is one of the main risk factors that predispose patients to disseminated coccidioidomycosis.[4] Disseminated coccidioidomycosis can result in a prolonged disease course and significant damage to affected organs. Despite anti-fungal treatments, disseminated coccidioidomycosis may be chronic or incompletely cleared therefore can require lifelong therapy.[7]

The rates of coccidioidomycosis infection have been increasing in California over the past several years likely related to increased temperatures, recent increased rains after prolonged drought, wildfires and increased population in the desert areas of California. Rates of coccidioidomycosis infection have more than tripled in California from 6 cases/100,000 in 2014 to 20.1 cases/100,000 in 2021.[8] Recent research from UC Berkeley suggests there will be an increase in the number of cocci infections this year related to the recent prolonged drought followed by increased rains over the past winter.[9]

The diagnosis of coccidioidomycosis infection is based on clinical presentation, chest imaging and serologic tests for antibodies to coccidioidomycosis. The organism can also be cultured from biological samples including sputum and pleural fluid, and rarely from blood or CSF. The CBC can be notable for peripheral eosinophilia, although this finding is neither sensitive or specific for coccidioidomycosis. The antibody testing is primarily for IgM and IgG with enzyme immunoassay (EIA). Occasionally there can be false positive test results which need to be interpreted in the context of the clinical scenario.[10] The complement fixation (CF) testing is equivalent to measuring IgG and the immunodiffusion (ID) is equivalent to measuring IgM. CF levels are quantified and are followed at regular intervals to evaluate response to treatment.

Fluconazole is the treatment of choice for coccidioidomycosis infections based on extensive data, experience and safety profile.[11] If there is CNS involvement with coccidioidomycosis then fluconazole remains the primary treatment with the addition of systemic and/or intrathecal (IT) amphotericin. The decision of when to start amphotericin is based on the severity and extent of disease and is often limited by the potential side effect of kidney injury. If extended courses of IT amphotericin are planned patients can undergo placement of Ommaya reservoir for further IT injections of amphotericin. If there is progression of disease while on fluconazole or intolerance of fluconazole the treatment can be switched to another azole including itraconazole, voriconazole, posaconazole or isavuconazole.[1] The treatment course for cocci infections varies from 3-6 months for severe pneumonia to longer than 12 months for bone and joint infections and often longer for CNS involvement. Patients with coccidioidomycosis meningitis should remain on lifelong fluconazole as there remains a significant risk of relapse with recurrent disease.[1]

Coccidioidomycosis has the potential to disseminate to multiple organ systems including lungs, skin, and central nervous system. Mortality rates for disseminated coccidioidomycosis can exceed 40% despite medical or surgical therapies.[8] Monitoring for disease progression in the outpatient setting is needed once a patient receives a diagnosis of coccidioidomycosis. Our patient's clinical presentation was concerning for disease progression despite aggressive medical therapies. For this reason, she was placed on immunologic therapies to bolster her cellular immune response.

Certain primary immunodeficiencies can increase the risk of infection due to defects in the interleukin-12 (IL-12)/IFN-γ pathway which is important in the innate and adaptive immune response in eradicating intracellular bacteria (i.e. mycobacteria) and fungi.[8] This patient's evaluation, summarized below, did not demonstrate the presence of a primary immunodeficiency.

Immunologic evaluation:

- Normal immunoglobulin levels (IgG, IgA, IgM)
- Peripheral eosinophilia and elevated IgE
- Normal tetanus titers
- Low streptococcus pneumoniae titers (patient does not recall vaccination with pneumovax)
- No lymphopenia
- T-cell qualitative function intact in mitogen/antigen assay
- Normal complement levels and normal complement function in CH50 and AH50
- Mendelian susceptibility to mycobacterial disease (MSMD) demonstrated normal IFN-γR expression on monocytes
- Normal phosphorylation of STAT1 and IL-12 production in response to IFN-γ
- Normal IL-12R expression on NK cells and phosphorylation of STAT4
- Dihidrorhodamine (DHR) test normal
- Genetic testing demonstrated deletions in STAT1 gene of unclear significance
- Low NK activity (likely 2/2 to acute infection) and increased memory/switched/immature B-cells

T-helper 2 cell (Th2) skewing was suspected due to initial presentation with eosinophilia and elevated IgE level. This is an important finding because a relative insufficiency of type 1 immunity combined with a strong type 2 immune response is suspected to increase risk of disseminated coccidioidomycosis.[9] IFN-γ produced by Th1 cells enhances response to microbes by macrophages and other innate cells and has been shown to assist in resolution of disseminated coccidioidomycosis.[10] Tsai et al. proposed that inhibiting the Th2 milieu could halt the dissemination of the disease.[11] They found that the combination of dupilumab and IFN-γ treatments in addition to antifungal therapy successfully controlled a severe case of disseminated coccidioidomycosis.[10] Dupilumab is a monoclonal antibody that blocks the alpha chain common to the IL-4 and IL-13 receptors, and down-regulates Th2. The medication is FDA

approved for several atopic indications such as severe asthma and atopic dermatitis.
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Figures

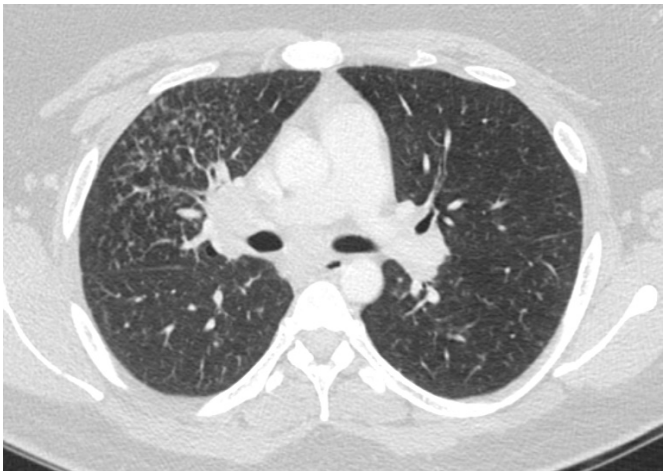

Figure 1a: Chest CT scan without contrast.
Multiple tree-in-bud lung micronodules at right upper lobe

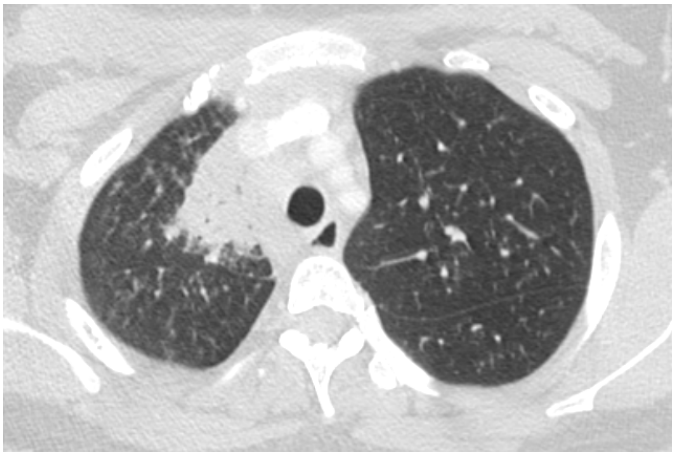

Figure 1b: Chest CT scan without contrast.
Right upper lobe paramediastinal spiculated mass

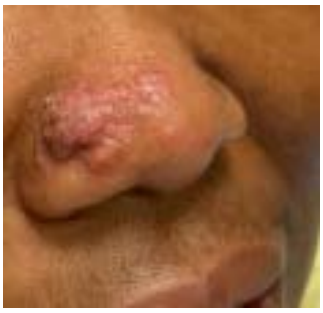

Figure 2: Right nasal lesion.
Ill-defined, verrucous, nodular plaque composed of vesiculopustules and overlying serous crust with surrounding smaller vesiculopustules.

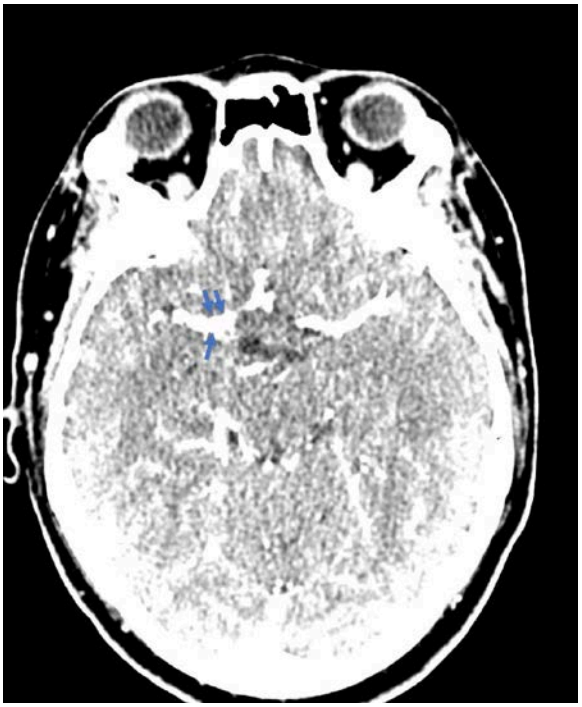

Figure 3: Brain CT with and without contrast.
Irregularity and multifocal stenosis of the right MCA M1 branch with increased surrounding hazy enhancement. There is also a diminutive right MCA M2 branch with segmental severe caliber attenuation. In the setting of known coccidioidomycosis, these findings reflect infectious vasculitis

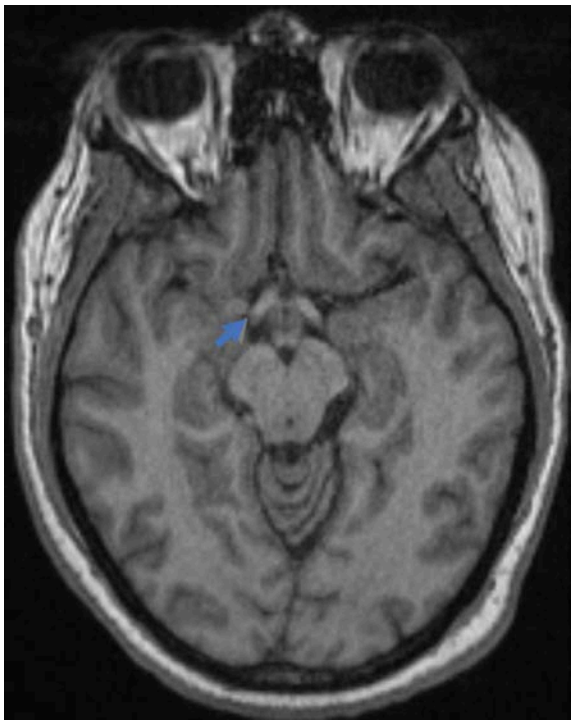

Figure 4a: Brain MRI brain without contrast, axial
Focal T1 hyperintensity in the right aspect of the suprasellar cistern, corresponding to the region of right MCA M1 segment stenosis visualized on the prior brain CTA study. Abuts or nearly abuts the right optic tract

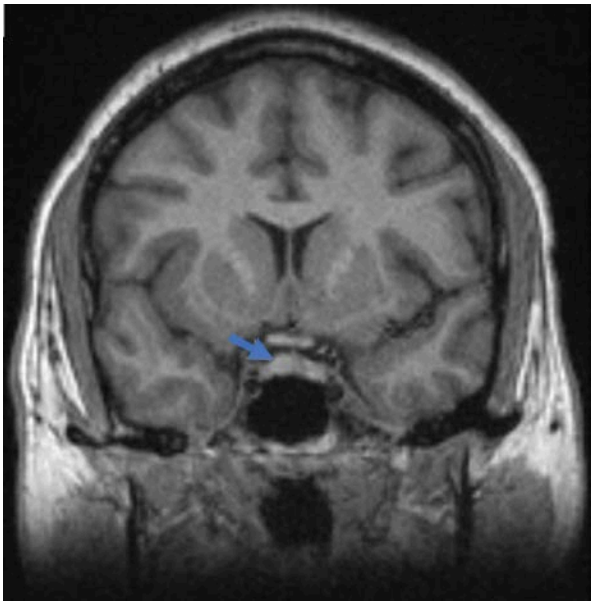

Figure 4b: Brain MRI brain without contrast, coronal.
Mild nodular asymmetric T1 hyperintensity in the right aspect of the sella

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