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Case Report

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A Rare Case of Coccidioidomycosis Meningitis

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Abstract

Disseminated coccidioidomycosis is a fungal disease endemic to the Southwest United States as well as South and Central America. This dimorphic fungus typically manifests as pulmonary infection; however, there are very rare instances of extrapulmonary disseminated disease especially in immunocompromised hosts. Here, we present a 46-year-old immunocompromised patient with a recent diagnosis of pulmonary coccidioidomycosis that initially presented with acute respiratory failure and was found to have coccidioidomycosis meningitis. This case highlights that despite early and adequate treatment of a known pulmonary coccidioidomycosis infection, dissemination of the disease can still ensue and should be considered in cases of acute encephalopathy.

Keywords: Coccidioidomycosis; Fungal infection; HIV; Immunocompromised; Disseminated

Introduction

Coccidioidomycosis is known as valley fever due to its geographic prevalence of California, Arizona, Mexico, Central, and South America. It is mainly caused by *Coccidioides immitis* or *C. posadasii* fungus [1]. This rare disease is commonly acquired through inhalation of arthroconidia, which is found in dust or soil.

Once inhaled into the lungs, this fungus will then transform into endospore containing spherules [2]. It is believed that the affected region is the terminal and respiratory bronchioles, mainly due to the size of the inhaled spores, ranging from 3 to 5 µm [1]. In the immunocompetent host, a delayed-type hypersensitivity reaction (DTHR) helps control the infection. Due to the DTHR, symptoms in approximately 60% of the cases are absent [2].

If the fungus is not treated appropriately or is found in an immunocompromised host, coccidioidomycosis can spread to the lungs, brain, and meninges, leading to respiratory failure, sepsis, shock, or even death. One of the more life-threatening forms is when it spreads to the meninges, causing coccidioidomycosis meningitis (CM) [1]. It affects both immunocompetent and immunocompromised individual, but risk of dissemination is higher in immunocompromised host. We present a case of a 46-year-old human immunodeficiency virus (HIV)-positive male diagnosed with CM.

Case Report

Investigations

We present a case of a 46-year-old male with a recent diagnosis of coccidioidomycosis who presented to the emergency room for shortness of breath and cough of 2 months duration. This was associated with pleuritic chest pain, malaise, diffuse joint pain and intermittent fevers for 2 months. He denied any hemoptysis, recent travel, incarceration history or homelessness. Patient worked as a farmer in Bakersfield for the past 3 years. Two weeks prior to this hospitalization, the patient was seen at an outside facility for fatigue, fevers, and forearm lesions. He tested positive for *Coccidioides* antibody IgG.

On arrival, the patient was tachycardic at 133 beats per minute, tachypneic with a respiratory rate of 47, afebrile, normotensive and hypoxic with an oxygen saturation of 85% on room air. On initial examination, he had coarse bilateral breath sounds and labored breathing. There were 1- to 2-cm palpable subcutaneous nodules in the patients forearms bilaterally. He had no notable rashes, joint effusions, or neurologic deficits. The patient was cooperative, alert, oriented and able to answer questions appropriately with limitations due to shortness of breath.

The patient was transitioned to non-invasive mechanical ventilation due to increased work of breathing and was admitted to the intensive care unit (ICU) for acute hypoxemic respiratory failure and severe sepsis.

Diagnosis

A computer tomography (CT) scan of the chest with intravenous (IV) contrast on admission was notable for diffuse

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Table 1. Significant Laboratory Results From the Cerebrospinal Fluid

Spinal fluid	Patient value (units)	Reference range
Glucose, CSF	81 mg/dL	40 - 70 mg/dL
Protein, CSF	146 mg/dL	15 - 45 md/dL
RBC, CSF	10,000 µL	0 µL
WBC, CSF	4 µL	0 µL
Coccidioides, CSF	1:1	< 1:1
Opening pressure, CSF	43 mL	

µL: microliter, dL: deciliter, mg: milligram, RBCs: red blood cells; WBCs: white blood cells; CSF: cerebrospinal fluid.

multifocal nodular consolidations and ground glass opacities. Patient also had right upper lobe dense consolidations and prominent mediastinal and hilar lymph nodes. He had clear central airways with no evidence of pulmonary embolism.

Treatment

During the first day, the patient was started on IV trimethoprim sulfamethoxazole 15 mg/kg daily, IV cefepime 2 g every 8 h, oral fluconazole 400 mg daily, IV liposomal amphotericin B 5 mg/kg daily, and oral prednisone 40 mg daily. The patient however decompensated overnight and required mechanical ventilation for airway protection. The night of admission, the patient decompensated further into septic shock requiring norepinephrine for blood pressure support.

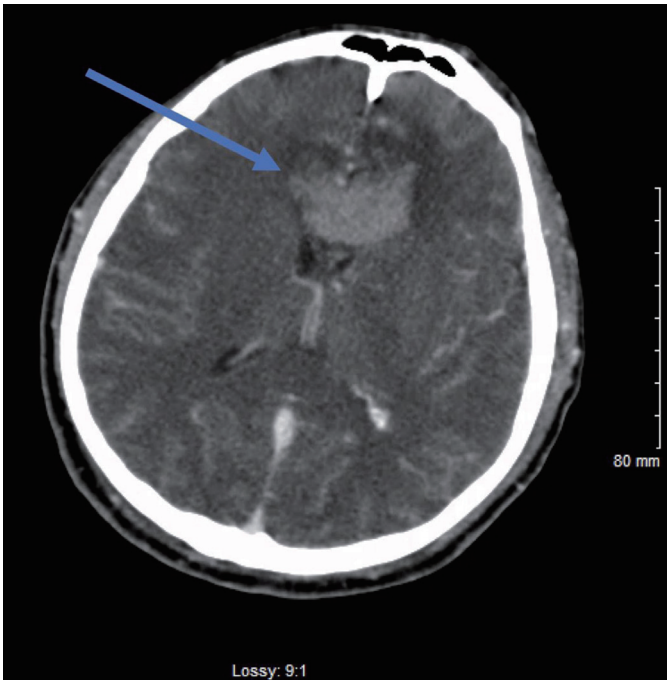

Figure 1. Computed tomography (CT) scan of the head with intravenous (IV) contrast, showing focal hemorrhage versus enhancing mass (blue arrow) involving the genu of the corpus callosum measuring 1.1 × 1.8 × 3.9 cm.

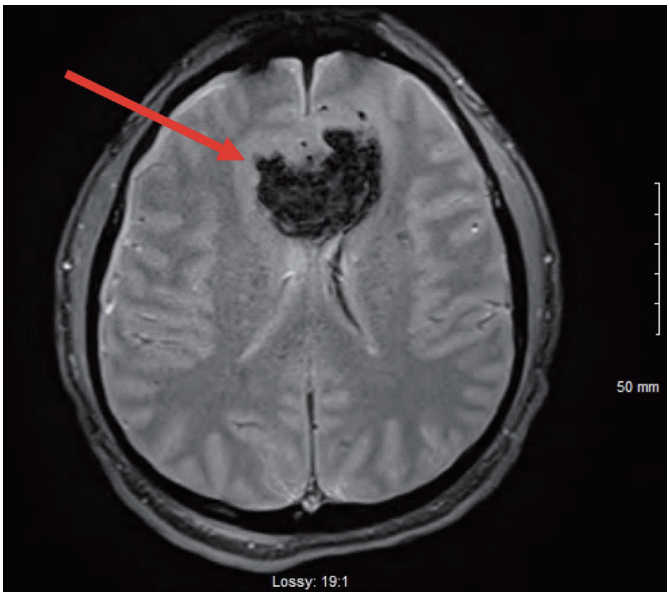

Figure 2. Magnetic resonance imaging (MRI) of the brain without intravenous (IV) contrast, showing large hemorrhagic mass extending across the splenium of the corpus callosum measuring 4.7 cm (red arrow) with surrounding edema.

Throughout his hospitalization, his blood cultures were negative. Tuberculosis (TB) was ruled out and fungal studies were negative for pneumocystis, cryptococcus, and toxoplasmosis, and were notable for coccidiomycosis with titer levels of 1:64 in the blood and 1:1 titer level in the cerebrospinal fluid, seen in Table 1. Infectious disease was consulted during this course. His antiretroviral therapy was held until cryptococcus and TB were ruled out. The patient's hospital course was complicated by declining mentation, worsening respiratory status despite several different ventilator adjustments, minimal response to proning, and intermittent severe metabolic acidosis with renal failure which improved with dialysis and bicarbonate drips.

Due to declining mentation, CT scan of the head with IV contrast (Fig. 1) was performed showing a corpus callosum mass extending into the left lateral ventricle with features consistent with primary central nervous system (CNS) lymphoma. Magnetic resonance imaging (MRI) of the brain showed a 4.7 cm hemorrhagic mass located at the corpus callosum, with surrounding edema with high-grade glioma features, as seen on Figure 2. Echocardiogram showed a right ventricular mobile mass representing vegetation, papillary fibroelastoma versus a thrombus. Workups for cardiac and CNS pathologies were not performed due to unstable patient hemodynamics. The patient was later started on IV flucytosine 25 mg/kg daily for 3 days. As the patient lacked clinical improvement, he was switched to IV fluconazole 1,200 mg daily for 6 days.

Follow-up and outcomes

After a 24-day hospital course, given the critical nature of the

patient's condition and lack of improvement, the decision to place the patient on comfort care was made by his surrogate decision maker. The patient was compassionately extubated and expired soon after.

Discussion

Coccidioidomycosis is an infection caused by the *Coccidioides* species. It usually exists as mycelia which use true septae as their mechanism of invasion and pathology. These cells take different forms to become infectious. Initially the mycelial cells autolyze and thin their cell walls while others are transformed into barrel-shaped, loosely adherent arthroconidia [3]. Hence, due to the loose adherence, the cells are easily airborne at any slight disturbance of the soil. The small size (2 to 5 µm) of the arthroconidia enables them to reach the right terminal bronchiole when inhaled [3]. Once inhaled, the arthroconidia transform into spherules. These spherules then mature and proceed to endosporulation stage forming multiple endospores which release upon rupture. These endospores mature into another endospore filled spherules which then rupture repeating the parasitic cycle. When endospore released in the environment they can transform into mycelial growth [3].

In susceptible/immunocompromised patients, the host response is subacute, compared to healthy individuals who are able to contain the infection within the lungs, which allows further extrapulmonary infection with the *Coccidioides* species [3]. The dissemination into extrapulmonary regions occurs through macrophage trafficking carrying the spores to different body areas. Interferon-γ, produced by Th1, is an integral part of the immune system's defense against disseminated coccidioidomycosis. This is due to a direct correlation noticed amongst resolution of the disease and production of interferon-γ by lymphocytes. Microbial killing is achieved by through production of macrophages and other innate cells as a direct response to the *Coccidioides* antigen [4].

Due to the patient's instability, we were unable to biopsy the corpus callosum mass extending into the left lateral ventricle; however, it presented with features consistent with primary CNS lymphoma. However, this brain mass could have also been a CNS lymphoma, glioblastoma or even a cryptococcoma. The cerebrospinal fluid (CSF) findings of *Coccidioides* IgG antibodies were consistent with CM. CNS dissemination is serious and usually presents as coccidioidal meningitis as well as encephalitis, mass-occupying lesions, brain abscesses, and aneurysms [5]. As per the CDC, a thorough workup includes serologic testing for IgM and IgG antibodies against *Coccidioides* in addition to obtaining cultures from blood, sputum, CSF and urine [6].

To bring into perspective the rarity of this infectious disease, a literature review was conducted on the number of case reports that have been published about patients with CM. We performed a systematic review for eligible case reports through a search on PubMed using the following terms "coccidioidomycosis meningitis". The case reports included were published in English, between the years of January 2012 and December 2022 for subjects 19 years or older.

We found a total of 20 articles that were evaluated, which can be seen in Table 2 [7-17]. Five were excluded as they did not meet our inclusion criteria. One case was excluded as the diagnosis was never confirmed. Three were removed as they did not have meningeal spread. Here we review 14 individual cases of CM.

We examined the age of the infected individuals and noticed the mean age of diagnosis was 42 years old. Four out of the 14 eligible cases were females (28.57%), with the remaining 10 of the 14 being males (71.42%). Many of the cases identified were located in California; however, values were unable to be calculated as some of the case reports did not highlight geographical locations. Out of the 14 cases, 13 were in HIV-negative individuals (92.8%), while only one was in an HIV-positive individual (7.14%). The recovery rate out of these 14 individuals was 10 (71.42%), while three expired (21.4%), and one was comatose (7.14%). There was one case highlighted by Patel et al, who described a 30-year-old pregnant female diagnosed with CM. With appropriate treatment, she had a full recovery. Interestingly enough, the placenta was found to have evidence of *Coccidioides*; however, the newborn had no signs of infection.

It is important to pursue a myriad of differential diagnoses when considering a severely immunocompromised patient. A differential diagnosis we considered on admission was TB. Given his immunocompromised state, appropriate testing for TB yielded negative results. Histoplasmosis, a dimorphic fungus, was a differential that was considered. Commonly found in soils and yeast forms, its portal of entry is through inhalation [18]. Patient was tested for histoplasmosis through urine studies and was found to be negative. Pneumocystis species are a type of fungus that are found in many people's lungs and are generally under control in those individuals who are immunocompetent. However, in those patients who are immunocompromised, it can cause a severe pneumonia [19]. In our patient, we did a bronchoalveolar lavage and pneumocystis was not found within the secretions. Cryptococcus and aspergillus can also severely affect immunocompromised patients. These were also considered in our immunocompromised patient; however, tests for both fungi were found to be negative.

Before the highly active antiretroviral therapy (HAART) medication becoming an effective medication of HIV/AIDs, *Coccidioides* was a significant opportunistic infection for patients with HIV living in endemic regions as their immune responses were unable to control the viral replication and immune reconstitution without the use of HAART [18]. It is suggested in data that a peripheral CD4 count ≥ 250/µL can maintain an immune response against any coccidioidal manifestations [2]. Hence patients with HIV and a CD4 count ≥ 250/µL can be managed in the same way as immunocompetent individuals. The general treatment includes treatment with either fluconazole or itraconazole at a daily dose of 400 mg; however, itraconazole is not the drug of choice for coccidioidal meningitis, although there are some case series has been placed on oral itraconazole with stable disease [2].

Patients with CD4 count lower than 250/µL should receive antifungal rather than potent antifungal therapy [2]. More significantly, patients who have low CD4 count requiring hospitalization with severe disease require initial therapy with am-

Table 2. Demographic Details, Diagnostic Information, Human Immunodeficiency Virus Status, and Outcomes for Patients Diagnosed With Coccidioidomycosis Meningitis (Review of Literature)

Reference	Age	Sex	Geographic location	HIV status	Comorbid conditions	Initial presentation	Plasma titer	CSF titer	Treatments	Outcome
[7]	49	F	LA, CA, USA	Negative	None	Headaches, fevers, vomiting, and maculopapular rashes (1.5 × 1.5 cm) on the face and back	N/a	N/a	IV fluconazole (800 mg intravenously daily), IV ceftriaxone (4 g q24h), and IV mannitol (125 mL intravenously q8h).	Recovered
[8]	66	M	N/a	Negative	None	Facial pain, fever	1:128	1:32	PO fluconazole 400 mg daily. IV liposomal amphotericin, high-dose fluconazole, intrathecal (IT) amphotericin B and voriconazole. IV isavuconazole (372 mg every 8 h for six doses, then every 24 h thereafter) (35-day therapy).	Recovered
[8]	33	F	N/a	Negative	None	Found down	N/a	1:8	Intravenous high-dose fluconazole 400 mg twice daily. High-dose fluconazole, IV LAmB and concomitant IT amphotericin B. IV isavuconazole (372 mg every 8 h for six doses, then every 24 h thereafter) (23-day therapy).	Comatose
[8]	22	M	N/a	Negative	None	3 months of headaches	N/a	1:8	PO posaconazole 300 - 600 mg QD (34-day therapy). PO voriconazole 300 mg BID (17-day therapy). PO fluconazole 600 mg BID (11-day therapy). IV voriconazole 300 mg BID (13-day therapy). PO itraconazole suspension 200 mg TID (204-day therapy). PO isavuconazole 372 mg QD (55-day therapy). PO fluconazole 600 mg BID, IV amphotericin B 5 - 10 mg/kg QD, IT amphotericin B (295-day therapy).	Recovered
[9]	36	M	Central Valley, CA, USA	Negative	None	Headache, nausea, vomiting	1:256	1:8	PO 1,200 mg daily fluconazole and IV liposomal amphotericin-B 5 mg/kg QD, followed by a PO dexamethasone for 15 days and PO fluconazole 800 mg daily. IV liposomal amphotericin-B 5 mg/kg QD and PO voriconazole 400 mg BID, IV dexamethasone 3 mg IV every 6 h, with a 5-day taper to 1 mg IV every 12 h, IV posaconazole 300 mg QD.	Expired
[10]	42	M	Hobbs, New Mexico, USA	Negative	None	3-week history of headache, malaise, low-grade fevers, photophobia, phonophobia, and vomiting	N/a	N/a	IV acyclovir 900 mg every 8 h, IV vancomycin 2 g every 8 h, IV ceftriaxone 2 gram every 12 hours, and IV dexamethasone 10 mg × 1 dose. PO isoniazid 3 mg daily, PO rifampin 100 mg daily, PO ethambutol 1,600 mg daily, PO pyrazinamide 2,000 mg daily, IV dexamethasone 8 mg every 8 h, IV LAmB 200 mg daily. PO fluconazole 800 mg daily, dexamethasone taper.	Recovered
[11]	26	M	Southwest, USA	Negative	None	Persistent fevers, headache, nausea, and vomiting	High	N/a	IV fluconazole 1,200 mg daily. IV LAmB 10 mg/kg daily, dexamethasone. fluconazole was replaced with IV voriconazole with loading dose of 6 mg/kg IV BID for two doses; then maintenance dose of 4 mg/kg IV BID. Lifelong triazole therapy.	Recovered

Table 2. Demographic Details, Diagnostic Information, Human Immunodeficiency Virus Status, and Outcomes for Patients Diagnosed With Coccidioidomycosis Meningitis (Review of Literature) - *(continued)*

Reference	Age	Sex	Geographic location	HIV status	Comorbid conditions	Initial presentation	Plasma titer	CSF titer	Treatments	Outcome
[12]	53	M	N/a	Negative	Coccidioidal meningitis diagnosed 3 years prior	New onset diplopia secondary to a right-sided CN VI palsy that followed 2 weeks of progressively severe worsening headaches	1:16	1:4	PO fluconazole 800 mg daily. IV LAmB 5 mg/kg/day × 14 days, then transitioned to PO voriconazole 200 mg QD.	Recovered
[12]	27	M	N/a	Negative	5-year history of coccidioidal meningitis	Severe headache, meningismus, and normal mentation	N/a	1:4	5-year history of PO fluconazole 1,000 mg QD. IV LAmB 5 mg/kg/day × 14 days, then transitioned to PO voriconazole 200 mg QD.	Recovered
[13]	39	M	Central Valley, CA, USA	Negative	21 years of heavy alcohol use	Weight loss, night sweats	Negative	Positive	PO fluconazole 400 mg daily.	Recovered
[14]	53	F	N/a	Negative	Coccidioidal meningitis	Gait instability, confusion, and headache	N/a	N/a	IV fluconazole, then switched to PO fluconazole.	Recovered
[15]	55	M	Mexico	Negative	None	Bilateral upper extremities weakness	1:128	Positive	High-dose steroids, IV LAmB.	Expired
[16]	30	F	San Joaquin Valley, CA, USA	Negative	14 weeks' gestation	Headaches, nausea, vomiting, joint pain, fevers, circular erythematous lesions on her right thumb and back	N/a	N/a	intravenous LAmB, intrathecal amphotericin B, and intrathecal hydrocortisone.	Recovered
[17]	59	M	Atlanta, GA, USA	Positive	HIV, epididymitis	Headache, photophobia, neck stiffness, fevers, chills, weight loss, dyspnea, cough, scant hemoptysis	N/a	N/a	Four-drug therapy (PO isoniazid daily, PO rifampin daily, PO ethambutol daily, PO pyrazinamide daily) and dexamethasone for tuberculous meningitis.	Expired

F: female; M: male; LA: Los Angeles; CA: California; USA: United States of America; CSF: cerebrospinal fluid; GA: Georgia; N/a: not available; IV: intravenous; PO: oral QD: daily; BID: twice daily; TID: three times a day; LAmB: liposomal amphotericin.

photericin B combined with triazole [2]. Furthermore, because only a few cases of immune response inflammatory syndrome (IRIS) occurred during HIV and coccidioidal infection, it is crucial to initiate potent antiretroviral therapy alongside the antifungal therapy which was done here for our patient when he started showing symptoms and lab values consistent with coccidioidal IRIS [2]. The most effective method in reducing the incidence and severity of coccidioidomycosis in HIV-infected patients is to start and maintain HAART therapy [2].

Learning points

We would like to highlight the importance of disseminated coccidioidomycosis and its appropriate workup. In an immunocompromised patient, if the suspicion for opportunistic infections exists, we suggest obtaining cultures of blood, urine, and CSF. We recommend obtaining an extensive workup to exclude other causes with similar presentations to coccidioidomycosis, such as tuberculosis, pneumocystis, cryptococcus, and toxoplasmosis.

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Conflict of Interest

The authors declare that they have no competing interests.

Informed Consent

Written informed consent was obtained from the patient.

Author Contributions

HG participated in patient care, writing of the case report, revisions, and submission process. BO participated in patient care, writing of the case report and revisions. MG participated in patient care, writing of the case report and revisions. BM participated in patient care, writing of the case report and revisions. MH participated in patient care and revisions.

Data Availability

All data in our report was obtained from the patient's hospitalization. Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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