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Authors

McCullough, Matthew

Tai, Jody

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CLINICAL VIGNETTE

Diagnostic Challenges in Cavitary Pulmonary Coccidioidomycosis

Matthew McCullough, MD and Jody Tai, DO

Introduction

Coccidioidomycosis is a fungus endemic to the Southwestern region of the United States. Pulmonary sequelae are the most common manifestation of coccidioidomycosis infections and are found in up to 95% of patients. Of these cases, up to 15% will develop a pulmonary cavity¹ which can progress into mycetoma formation. Cavitary pulmonary coccidioidomycosis (PC) can be difficult to diagnose given the low sensitivity of serological testing, false negative sputum cultures, and varied histologic presentations.² Clinical presentation may be further complicated by overlying fungal infections that can contribute to mycetoma creation. We present a patient with chronic cavitary PC initially diagnosed and treated as superimposed aspergillosis.

Case Description

A 48-year-old male with known chronic cavitary PC and uncontrolled diabetes with an A1c of 16.3% presented with worsening cough and hemoptysis for the past month. He had initially been diagnosed with PC seven years prior based on clinical presentation, a *Coccidioides* titer of 1:4 and computed tomography (CT) findings showing a right upper lobe cavitary mass. He finished a one-month course of fluconazole, but was then lost to follow-up multiple times. He represented to the hospital twice with a peak *Coccidioides* titer of 1:152 and completed three separate courses of fluconazole, most recently 3 years prior to current presentation.

The patient stated that symptoms started one month ago with mild cough and sputum production that gradually became blood-tinged. He denied fever, chills, night sweats, unintentional weight loss, chest pain, or dyspnea. He also reported not taking insulin for the past year after running out of his medications. He is a construction worker without any tobacco history, alcohol consumption, or illicit drug use. There was no tuberculosis (TB) exposures, or history of incarceration or homelessness. He also denied recent travel or known sick contacts.

Upon presentation to the emergency room, the patient had a temperature of 37.1°C, blood pressure 164/84, heart rate 116, respiratory rate 20, and oxygen saturation of 98% on room air. He appeared anxious but without respiratory distress. Physical exam was notable for bilateral rales in the lower lung fields, right worse than left and vesicular lung sounds in all posterior fields. Labs included a white count of 11.9×10^3 , glucose of

408 mg/dL with positive beta-hydroxybutyrate but no acidosis or anion gap. Complete blood count with differential showed normal absolute eosinophil count compared to a prior elevated level of 0.8×10^9 /L five years ago. Chest x-ray showed a large consolidation in the right mid to upper lung zone with a rounded opacity in the right mediastinum, suspicious for superimposed acute pneumonia (Figure 1). CT chest showed interval increase in size of a complex multiloculated cavitary lesion in the right upper lobe now measuring 7.6 x 11.1cm, two cystic cavitary lesions in the right lower lobe, and multiple partially cavitary lesions in the left lung that were new compared to prior CT in 2020 (Figure 2).

The patient was admitted for treatment of possible invasive aspergillosis due to the interval increase in multiloculated cavitary lesion seen in the right upper lobe concerning for a worsening mycetoma. He was treated with voriconazole and started on ampicillin-sulbactam to cover for a post-obstructive pneumonia. During the admission, the patient had an episode of frank hemoptysis but with stable vitals and hemoglobin count. He had no skin rash findings, headache, vision changes, or joint aches to suggest disseminated *Coccidioides* infection. Although the main consideration was overlying aspergillosis causing worsening of the patient's known PC, other fungal infections such as cryptococcus, or histoplasmosis as well as superimposed TB were considered. Induced sputum for acid fast bacterium and returned negative. Malignancy was considered due to hilar lymphadenopathy but did not fit the clinical presentation due to the lack of B-symptoms and normal complete blood count. Pneumocystis was also considered but was deemed less likely given the patient's immunocompetent status despite chronic PC.

Given a highly positive beta-D-glucan with pending fungal serologies and negative acid-fast bacilli (AFB) culture, the patient was presumed to have superimposed aspergillosis. He was discharged on voriconazole as well as amoxicillin-clavulanic acid. Post-discharge labs eventually revealed negative Aspergillosis, Histoplasma, Cryptococci serologies, negative AFB sputum x3 but elevated *Coccidioides* complement fixation titer of 1:512 most consistent with chronic cavitary pulmonary coccidiomycosis. The patient was switched from voriconazole to fluconazole for an anticipated life-long course and is continuing to follow closely with infectious disease and pulmonology.

Discussion

Coccidioides is a dimorphic fungus endemic to California, Arizona, Utah, Nevada, and New Mexico. According to the California Department of Public Health, the rate of infection in 2019 was about 23 cases per 100,000 people, which is 18% higher than in 2018, when the rate was 19 cases per 100,000 people.³

The pathophysiology of *Coccidioides* infection and cavity formation is due to this fungus existing as mycelia in the environment. These mycelia autolyse and transform into arthroconidia, which are the appropriate size (2 to 5 microns) that can reach the terminal bronchioles when inhaled.⁴ Once inside the lung, arthroconidia remodel into spherules which develop internal septae and grow endospores that can rupture and trigger a host response with alveolar macrophages that encapsulate these endospores⁴ causing a fibrocaseous nodule or necrotizing granuloma. Severe cases can result in a broncho-pleural fistula.² Dissemination can occur due to macrophage trafficking of these encapsulated endospores to other parts of the body, such as the mediastinal lymphadenopathy seen in this patient. The defense against *Coccidioides* species is mainly via T-helper2 lymphocytes (Th2). Th2 dysfunction or deficiency has been found in patients presenting with extrapulmonary or disseminated disease, which is why *Coccidioides* infections can be considered an AIDS-defining disease.⁵

Cavitary PC can be difficult to diagnose due to poor sensitivity of serologic testing and rarity of culture from sputum. Even fine needle aspiration and bronchoalveolar lavage can have poor diagnostic yield due to the rarity of microorganisms and the variability in histopathology of these lesions. Therefore, one of the most reliable tools is the complement fixing test expressed in titers with enzyme immunoassay (EIA). This tests the IgG antibody against the chitinase antigen produced by *Coccidioides*. Polymerase chain reaction (PCR) probes are 98% sensitive and 100% specific, but are not currently available commercially.⁴

Oftentimes diagnosing *Coccidioides* can become a diagnosis of exclusion given nonspecific symptoms of fever, cough, dyspnea, and chest pain⁴ that can often be mistaken for community-acquired pneumonia and appear seven to 21 days post-exposure. However, extrapulmonary *Coccidioides* infection includes a triad of symptoms known as desert rheumatism or valley fever⁴: erythema nodosum or multifforme frequently seen in women, migratory arthralgias, and fever. Laboratory findings can be notable for eosinophilia, although absence of it does not exclude *Coccidioides* as seen in this patient, as well as elevated erythrocyte sedimentation rate (ESR). In cavitary pulmonary coccidioidomycosis, chest radiographs can show peripheral solitary thin-walled cavities. These can be located peripherally, along the pleura, or upper and lower lung lobes in contrast to TB which often forms apical cavities.

Per the Infectious Disease Society of America, treatment of choice is fluconazole from a range of 400mg to 1200mg daily depending on the severity of the disease. Other antifungal drugs like itraconazole can be considered, but drug-drug interactions should be taken into consideration. Primary pulmonary infections should be treated with three months of an oral azole, cavitary infections treated for three to six months, and fibrocavitary disease treated for a year.⁶ Serial imaging is recommended for asymptomatic pulmonary nodules, but surgical resection is recommended if these nodules are enlarging, persisting over 2 years, or near to the pleura.⁴ Patients with cavitary PC should avoid aggressive chest physiotherapy and treatment with inhaled hypertonic saline or N-acetylcysteine as these lesions are prone to significant bleeding.

Conclusion

Diagnosing cavitary PC infections can be complicated due to the possibility of superimposed fungal infections such as Aspergillosis or bacterial infections such as *Mycobacterium*. These superinfections may present with similar chest x-ray findings or preexisting mycetomas. Even in patients who live in non-endemic areas, *Coccidioides* infection should be considered due to winds that carry the infectious mycelia over long distances. Ultimately, cavitary PC can become a diagnosis of exclusion due to the low sensitivity of serology tests and nonspecific chest x-ray or CT findings. *Coccidioides* EIA with complement fixation can be an appropriate first diagnostic step along with concomitant fungal and TB testing to rule out superimposed infections, and early pulmonary and infectious disease consultation should be considered.

Figures



Figure 1. Chest x-ray showing a large consolidation in the right mid to upper lung zone with a rounded opacity in the right mediastinum, suspicious for superimposed acute pneumonia.

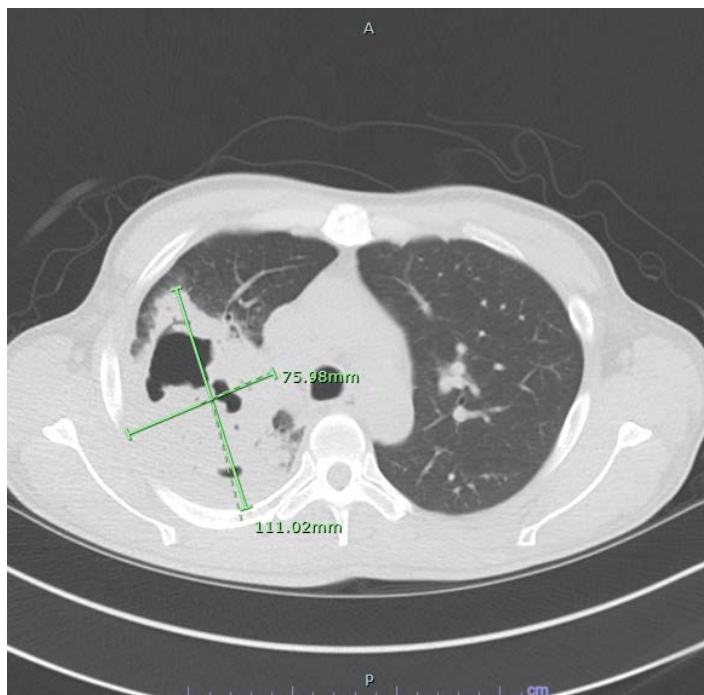


Figure 2. CT chest showed an interval enlargement of 7.6 x 11.1cm complex multiloculated cavitary lesion in the right upper lobe.

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