Coccidioidomycosis in Nonendemic Area: Case Series and Review of Literature

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Four cases of coccidioidomycosis, diagnosed in New Orleans, are described to illustrate the varied clinical presentation of this infection. The first is an immunocompromised elderly patient presenting with a cavitary lung lesion after travel to Utah. The second, a young immunocompetent patient presenting with acute respiratory distress syndrome after moving from Arizona. The third and fourth, young Hispanic immigrants with acquired immunodeficiency syndrome presenting with respiratory distress and sepsis. These are examples of different presentations, depending on immune competency, and illustrate the challenges in making this diagnosis in non-endemic areas. For two of the three patients who died an autopsy was obtained. We present the cases, show radiographic and pathological findings, and review the current literature on coccidioidomycosis.

INTRODUCTION

Coccidioidomycosis, also known as San Joaquin Valley fever, is caused by inhaled spores of the Coccidioides species (immitis or posadasii) and is endemic in the southwest of the United States.1 Clinical manifestations vary from a mild form seen in immunocompetent individuals to a severe, life threatening illness causing respiratory failure, observed primarily in the immunocompromised host. Diagnosis can be delayed when the clinical suspicion is low, as is often the case in non-endemic areas such as New Orleans. Four cases of severe coccidioidomycosis are described; three patients were immunocompromised and died; one was immunocompetent and was cured after one year of treatment. These cases illustrate a wide variety of radiographic appearances ranging from cavitary lesions to pulmonary fibrosis and diffuse nodularity.

CASE REPORTS

Case 1

A 59-year-old white man was seen in the pulmonary clinic for a productive cough and 50-pound weight loss over the previous five months. He was a native of Louisiana and was receiving chemotherapy for diffuse large B-cell non-Hodgkin’s lymphoma. However he had traveled to Utah one year prior to his pulmonary clinic visit. Physical examination revealed cachexia, a port-a-cath on the left anterior upper chest. Laboratory data were all within normal limits except for an albumin of 2.3 g/dL (3.4- 4.0 g/dL). The chest radiograph is shown in Figure 1A. Computed tomography (CT) of the chest with contrast demonstrated the thin-walled cavity seen in Figure 1B. Positron emission tomography (PET) scan of the chest revealed enhancement around the wall of the cavity. Flexible bronchoscopy showed no endobronchial lesions. Transbronchial biopsies and bronchoalveolar lavage (BAL) were performed. After the procedure, the patient became severely hypoxemic, requiring intubation and mechanical ventilation. Broad spectrum antibiotics and antifungal treatment were initiated (initially Amphotericin B, subsequently Voriconazole). BAL revealed a predominantly acute inflammatory pattern with numerous fungal hyphae. Budding yeast were seen on Gomori methenamine silver (GMS stain) (Figure 2). Fungal cultures from bronchial washings grew Coccidioides spp. Despite our therapeutic efforts, the patient’s condition continued to deteriorate, and he died after the family opted for comfort care only.

Case 2

A 35-year-old African American man presented with cough and shortness of breath for two months. He moved to New Orleans from Arizona where he was recently treated for pneumonia with levofloxacin. Having failed outpatient treatment, he was admitted for intravenous antibiotic therapy. He subsequently developed hypoxemic respiratory failure requiring intubation and mechanical ventilation. Hematological data revealed a white blood...
A cell count of 17,000 and Hgb of 9.6 g/dL; HIV-ELISA was negative. The chest radiograph and CT showed diffuse parenchymal opacities suggestive of the adult respiratory distress syndrome (ARDS), as seen in Figures 3A and 3B. Flexible bronchoscopy was done and BAL fluid was obtained. Multiple small erythematous nodules were seen in the right lower lobe bronchus. Fungal cultures from the BAL grew *Coccidioides* spp. Serum *Coccidioides* IgM by immunodiffusion was also positive. A combination of anidulafungin, fluconazole and steroids was started. The patient was successfully liberated from mechanical ventilation, and anidulafungin was discontinued after seven days, while steroids were tapered over ten days. Fluconazole was continued for one year.

**Case 3**

A 25-year-old Hispanic man with AIDS (CD4 count 2 per mm$^3$) had a remote history of incompletely treated pulmonary tuberculosis, and was recently diagnosed with *Mycobacterium avium intracellulare* (MAI) lung infection. He presented to the emergency room with a productive cough and fever. His current medications included azithromycin, ethambutol, rifabutin and trimethoprim-sulfamethoxazole. He was born in Honduras, moved to the United States six years before and resided in New Orleans for nine months while working in construction. His temperature was 103.5°F, and he had diffuse bilateral crackles on lung auscultation. His chest radiograph and CT, as shown in Figures 4A and 4B, showed right upper lobe fibrosis and multiple bilateral small pulmonary nodules. He was admitted and was placed on respiratory isolation. BAL fungal cultures grew *Coccidioides* spp. as well as MAI, and blood fungal cultures were positive for *Coccidioides* spp. Initially liposomal amphotericin B was given, later Voriconazole was added. He developed respiratory failure requiring mechanical ventilation, refractory septic shock, and died on hospital day 30. An autopsy showed disseminated coccidioidomycosis involving his lungs, lymph nodes, liver, spleen, kidneys and omentum (Figure 5.)

**Case 4**

A 34-year-old Hispanic man presented with right upper quadrant abdominal pain, fever, chills, night sweats, cough, and malaise for two months. He moved to New Orleans from Nicaragua two years prior to his presentation and was working as a painter. His temperature was 103.2°F. He had bilateral lung crackles and mid-epigastric tenderness. His chest radiograph and CT are shown in Figures 6A and 6B. He was subsequently diagnosed with AIDS (CD4 count of 18 per mm$^3$). Abdominal ultrasound showed acalculous cholecystitis. BAL revealed filamentous fungi on direct GMS stain, and no microorganisms on acid fast stains. Mycobacterial, viral and bacterial blood cultures were all negative. Initially empirical broad spectrum antibiotics, antitubercular therapy and steroids were employed. Later voriconazole and caspofungin were added. He developed respiratory failure requiring mechanical ventilation and died of refractory shock on hospital day 21. An autopsy revealed disseminated coccidioidomycosis involving the lungs, liver, spleen, kidneys, pancreas and bone marrow (Figure 7A-C).
Coccidioidomycosis was first described in 1892 in a soldier. In 1896 Rixford and Gilchrist called the causative organism Coccidioides (resembling the protozoan coccidia) immitis (not mild). Coccidioides is a dimorphic, soil dwelling fungus endemic in the Southwest US, and is found in certain regions of Arizona, south central California, Nevada, Utah, New Mexico, western Texas. The fungus is also endemic in areas of Central and South America. The risk of infection is increased by direct exposure to soil that harbors Coccidioides. Climatic factors, such as periods of drought following rainy seasons, have been linked to an increased number of cases. In soil, Coccidioides exists as a filamentous mold with branching septate hyphae that fragment into barrel-shaped spores called arthroconidia, measuring 2-8 microns, and hence they have the capacity to aerosolize and reach pulmonary alveoli. Once inhaled, the arthroconidia enlarge to become round, double-walled spherules ranging in size from 20-100 microns in diameter and containing up to thousands of endospore offspring. Each endospore can spread and form additional spherules.

**RISK FACTORS**

Risk factors for infection include travel to endemic regions and occupations that involve handling soil, such as operating excavators, and working in agriculture or archaeology. The disease has a more severe course in immunocompromised patients such as those with AIDS, receiving chemotherapy (especially for hematologic malignancies), immunosuppressive drugs to prevent organ rejection or to treat chronic inflammatory conditions. Reports indicate that in the immunocompromised host there is a 30%-50% risk of dissemination. Mortality rates in such cases are as high as 70%. Pregnant women and women in the early postpartum period are also at higher risk of more severe disease. For unclear reasons, Filipinos and African Americans are also at increased risk of disseminated coccidioidomycosis.

**CLINICAL PRESENTATION AND CHEST IMAGING**

Sixty percent of people infected with Coccidioides spp. are asymptomatic. In the remaining 40%, respiratory symptoms vary widely, from chest pain and wheezing to lobar pneumonia and pleural effusions. Acute illness may develop one to three weeks after exposure, some patients...
presenting with the classic “valley fever” prodrome including fever, chills, headache, weakness, arthralgias, cough, and chest pain. Extrapulmonary findings may include erythema nodosum or erythema multiforme and arthritis. In disseminated coccidioidomycosis, findings may also include weight loss, persistent fever and malaise, synovitis, chronic osteomyelitis, and central nervous system involvement.\(^4,5,9\)

Pleural involvement is common with the primary infection, usually in the form of an exudative lymphocytic pleuritis.\(^5,10\) In the majority of cases with primary lung involvement, chest radiography is nonspecific, showing infiltrates, unilateral or bilateral hilar and paratracheal lymphadenopathy, pleural effusions.\(^9\) Lung manifestations resolve without sequelae in 90%-95% of cases, but in 5%-10% of cases an evolution to persistent pulmonary nodules or cavitary lesions is seen. A radiographic pattern of diffuse pulmonary nodular densities and lymphadenopathy may be difficult to attribute to coccidioidomycosis, due to resemblance with malignancy or other infectious processes.\(^4\) Cavities are usually single, 2 to 4 cm in size, thin walled, without air fluid levels, and usually located peripherally in the upper lobes.\(^1,5,11\) Patients with a small cavity are generally asymptomatic and have a 50% spontaneous resolution rate of the cystic lesion after several years.\(^4\)

Large cavitary lesions, similar to the radiographs of Case 1, are unusual and seldom resolve spontaneously. Airway coccidioidomycosis can present either as erythematous nodules similar to those seen in Case 2, or as granules or papillary excrescences.\(^12\) The miliary form of pulmonary coccidioidomycosis can be seen as part of the acute primary infection, the late stage of the chronic progressive infection, or in cases of fatal coccidioidomycosis in immunocompromised patients.\(^1,13,14,15\) It can also occur as a co-infection with tuberculosis and atypical mycobacteria as seen in Cases 3 and 4. Acute respiratory distress syndrome (ARDS) is an uncommon sequela of pulmonary coccidioidomycosis, but has a mortality rate that approaches 100%. In these cases coccidioidomycosis may be difficult to differentiate clinically from other causes of ARDS.\(^9\)

**DIAGNOSIS**

Definitive diagnosis of coccidioidomycosis is made when the organism is recovered from respiratory secretions, body fluids or tissue especially detecting the characteristic spherules with endospores.\(^9\) Fungal hyphae can be recovered from specimens obtained from boundaries of old cavitary lung lesions and skin lesions. KOH staining is rarely helpful. Examination of specimens with either Papanicolau or GMS stains has a better diagnostic yield. Sputum has a low yield, with a positivity rate reported to be 10%-20% in known cases.\(^16\) The yield of specimens obtained by bronchoscopy is higher especially in patients with parenchymal opacities or cavitary lesions and has been reported to be 31%-53%.\(^16,17\)

Coccidioides grows in culture usually within four to seven days at 37°C and on all laboratory media. As cultures grow, and the Coccidioides spherules convert to their infectious arthroconidium form, the laboratory should be alerted and precautions taken to protect personnel from inhalation. Further diagnostic confirmation can quickly be made with a specific DNA probe.\(^18\) Serologic testing is mainly helpful in detecting early or acute infections. IgM antibodies to coccidioidal antigens develop within one to three weeks after onset of symptoms while the IgG response is more common after three months. Three major techniques are available for measuring the serologic response are enzyme immunoassay (EIA), immunodiffusion (ID), and complement fixation (CF). Tube precipitation and latex agglutination tests have been replaced by enzyme immunoassay (EIA).
and immunodiffusion (ID) IgM and IgG tests. EIA can detect both IgM and IgG and is the most sensitive test. In one study this test was found to have sensitivity of 94.8% and specificity of 98.5%. A negative test can rule out infection. Isolated specific IgM detected by EIA may represent a false positive and diagnosis should be confirmed by ID testing. In one study EIA IgM had a false positive rate of 18%. ID can detect IgM and IgG but may take longer. ID has lower sensitivity to detect IgM than EIA but is more specific. False positive cases with ID are rare and are reported to be close to zero. CF can measure IgG antibody and is less sensitive than ID and EIA. CF can be used quantitatively and higher titers indicate more severe infection and can also be helpful in follow up as the titers decrease as the clinical disease improves. Isolated specific IgM detected by EIA may represent a false positive and diagnosis should be confirmed by ID testing. In one study EIA IgM had a false positive rate of 18%. ID can detect IgM and IgG but may take longer. ID has lower sensitivity to detect IgM than EIA but is more specific. False positive cases with ID are rare and are reported to be close to zero. CF can measure IgG antibody and is less sensitive than ID and EIA. CF can be used quantitatively and higher titers indicate more severe infection and can also be helpful in follow up as the titers decrease as the clinical disease improves.

Figure 5. Cut lung tissue from postmortem examination showing diffuse nodules, vascular congestion, and pulmonary edema.

TREATMENT AND FOLLOW UP

Most patients with primary coccidioidal pneumonia or mild respiratory illness will improve without treatment. Specific therapy is recommended in immunocompromised patients such as individuals with AIDS, organ transplant or hematologic malignancy, pregnant women (especially in the third trimester), in patients with severe pneumonia or extra-pulmonary involvement, and those with chronic progressive and disseminated disease. Patients need to be monitored, during treatment, at one to three month intervals for one year or longer, to ensure resolution of the infection. Antifungal agents such as amphotericin B deoxycholate (0.5-0.7 mg/kg/d), liposomal amphotericin B (3-5 mg/kg/d), fluconazole (400-1200mg/d), itraconazole (400 mg
-800mg/d), posaconazole (400mg q12h), and voriconazole (4mg/kg q12h) have all been successfully used to treat the infection. In severe infections amphotericin B or liposomal amphotericin B are the preferred agents. There are no randomized controlled trials directly comparing the efficacy of amphotericin B to that of azoles. Intravenous therapy is preferred initially for severe illness, followed by an oral agent for a total of one year. Oral therapy is usually with azoles such as fluconazole and itraconazole. A study comparing treatment with itraconazole versus fluconazole in nonmeningeal disease demonstrated after 12 months of treatment a response rate of 72% using itraconazole compared to 57% using fluconazole (p-value 0.05); relapse rate was 18% in those treated with itraconazole compared to 28% in the fluconazole group. A combination of amphotericin B with an azole has been used especially in disseminated disease, though there is paucity of data and no definite evidence that supports its use. In AIDS patients, therapy should be continued for as long as the CD4 count is <250 cells/µL. The use of steroids has been reported in case series of patients with coccidioidomycosis and ARDS and may provide some benefit, but no definite recommendations can be made. Surgery may be necessary for severe and recurrent hemoptysis or large peripheral cavities but is not usually performed as an adjunct to medical treatment. In one study, patients undergoing orthotopic liver transplants with either positive history or serologic tests received prophylaxis. Four out of 76 patients received prophylaxis with fluconazole. None of the four cases had reactivation of coccidioidomycosis.

In conclusion, coccidioidomycosis is endemic in certain regions and can be seen in travelers returning from endemic areas. As shown by our case series, the initial infection can be overwhelming and can occur even in the immunocompetent host, such as Case 2. Three of the four cases we report died and all three of them were immunocompromised. Two patients, both with AIDS, had disseminated disease at autopsy and one (Case 3) had coexistent atypical mycobacterial infection. The ability to diagnose coccidioidomycosis in nonendemic regions such as Case 1 is also documented.
as ours relies upon an high index of suspicion when travel histories and clinical presentation suggest to include this infection in the differential diagnosis.

REFERENCES


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