CLINICAL VIGNETTE

Acute Pulmonary Coccidioidomycosis in Pregnancy: A Case Report

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Introduction

Pregnancy is a well-established risk factor for developing severe or disseminated coccidioidomycosis infection. Disseminated disease in pregnancy is associated with higher maternal and fetal mortality, congenital fetal anomalies and other developmental sequelae.[1] Women who were initially diagnosed with coccidioidomycosis during the third trimester of pregnancy were more likely to develop a severe course.[2] Pregnancy alters the maternal immune system which potentially increases maternal and fetal vulnerability to common infections. However, not all pregnant women who develop coccidioidomycosis are at risk for disseminated disease. Epidemiologic studies suggest that many pregnant patients have mild infection that remain undetected. This case report illustrates important challenges in management of coccidioidomycosis in pregnant patients.

Case Report

A 31-year-old female with an intrauterine pregnancy at 36 weeks presented to an ambulatory clinic with productive cough and fever for 2 weeks. She was diagnosed with community-acquired pneumonia and treated with oral antibiotics. Her cough improved and she subsequently delivered a healthy newborn at 38 weeks gestation. She returned to her primary care physician 1 week after delivery complaining of worsening productive cough with hemoptysis, fever and shortness of breath. Chest radiograph showed a 4 cm mediastinal mass concerning for malignancy (Figure 1). CT of the chest revealed left upper lobe lung mass with left hilar and mediastinal lymphadenopathy concerning for primary bronchogenic carcinoma. Left upper lobe bronchial brush, EBUS-guided transbronchial biopsy and bronchoalveolar lavage were all negative for malignant cells. EBUS-guided transbronchial fine needle aspiration was consistent with coccidioidomycosis infection. Left upper lobe transbronchial tissue biopsy and bronchoalveolar lavage were negative for Nocardia, mycoplasma pneumonia, acid fast bacilli, fungal culture and legionella.

She is of African descent and was born in San Bernardino, California. She has lived in California, New York and a region in Costa Rica. Her travel history within 2 years of diagnosis include frequent trips to San Francisco, California driving in Interstate Highway 5 through Kern County. Other trips included Redlands, CA, Lake Tahoe, NV and Vegas, NV. She has no history of smoking and denied tuberculosis exposure.

Physical examination: She had a temperature of 103.5ºF, a pulse of 104 beats/minute, BP 138/89 and oxygen saturation of 95% on room air. Lung exam revealed coarse breath sounds over left upper lobe. She had no skin lesions or lymphadenopathy.

Laboratory results: She had a white cell count of 12.4 x10E3/ microliter, hemoglobin12.1 g/dl, platelet of 320 x 10E3/ microliter, normal eosinophil count. Sputum culture and smear were negative for acid fast bacilli. A serum fungal panel was positive for coccidioidomycosis. Chest radiograph (see Fig. 1).

Treatment: She was treated with oral fluconazole for 12 months. Her cough improved after 3 months of fluconazole with resolution of left upper lobe consolidation after 6 months of treatment. In addition to her presenting symptoms, she developed fatigue 6 months after initiation of treatment. She underwent physical rehabilitation with improvement of her symptoms. She will be followed for further surveillance and monitoring up to 2 years after completing treatment.

Discussion

Coccidioidomycosis also known as Valley Fever is usually a self-limited infection resulting in lifelong immunity. An estimated 150,000 coccidioidal infections occur annually in the United States.[3] These result in about 50,000 illnesses, and of these patients, only few experience progressive pneumonia or disseminated disease. Some factors that have been associated with severe disease include patients with HIV/AIDS, solid organ transplantation, hematologic malignancies, glucocorticoid and immunosuppressive therapies for autoimmune disease, a specific gene mutation and pregnancy.

Microbiology

Coccidioidomycosis is the infection caused by the fungi of the genus *Coccidioides* which include both *Coccidioides immitis* and *Coccidioides posadasii*.[4] *Coccidioides* species are dimorphic, soil-dwelling fungi known to cause a broad spectrum of symptoms ranging from a mild febrile illness to severe pulmonary manifestations and disseminated disease. *C. immitis* isolates are geographically distributed predominantly in California. *C. posadasii* isolates are distributed in Arizona, Utah, Texas and other endemic regions throughout the western hemisphere. *Coccidioides* infection has increased from 5.3

cases per 100,000 population in 1998 to 42.6 cases per 100,000 population in 2011.[5] Arizona and California account for 66 and 31% respectively of all reported cases in the United States. Individuals who live in or travel to endemic areas are at risk of acquiring coccidioidal infection. The groups at risk for developing severe forms of coccidioidal infection include immunecompromised individuals, pregnant women, and people of African-American or Filipino origin.

The risk of infection due to endemic exposure to *Coccidioides* spp is approximately 3% per year.[6] According to a 2007 Arizona study, patients who were diagnosed with Valley Fever in 2007 had an average residency of 16 years. Therefore, confirmed risk of new infection persists in individual living endemic regions. [13]

Coccidioidomycosis infection is acquired by inhaling a single fungal spore. Inside the lung, the spores convert to large tissue-invasive spherules. As spherules mature and enlarge, they rupture, releasing thousands of small endospores which form new spherules.

Clinical Manifestations

Studies show more than 50% of all infections are subclinical and never come to medical attention. Those who develop symptoms present with a wide spectrum of manifestations from cough, fever, chest pains to more systemic symptoms such as fatigue, nights sweats or weight loss. Some patients present with pulmonary infections whereas others present with dermatologic or rheumatologic complaints.

Routine laboratory findings are typically normal. A common abnormality is mild elevation of white cell count. Approximately 25% of patients have eosinophilia and the erythrocyte sedimentation rate may be slightly elevated. Approximately 50% of patients have a normal chest radiograph. Common abnormalities include unilateral infiltrate with hilar adenopathy. Parapneumonic effusion, pulmonary cavities, nodules or empyema may be rarely present.[8]

The diagnosis of coccidioidomycosis is considered in patients with endemic exposure and a persistent lower respiratory illness lasting more than a week. The incubation period for symptom onset is 7-21 days. Primary coccidioidal infection is also suspected in patients with endemic exposure, symmetrical arthralgias, and erythema nodosum or erythema multiforme. Because exposure typically occurs in endemic regions an accurate travel history is key.[9] Even brief exposure as in changing planes in Phoenix or traveling on the freeway in the Central Valley have been linked to infection.

The isolation of *Coccidioide*s species in culture provides a definitive diagnosis of the condition. In addition, serologic testing and direct examination of the smear can be helpful.

Treatment

Healthy patients with mild disease and those without evidence of extensive coccidioidal infection or risk factors for more serious infection usually do not need antifungal therapy and recover completely with supportive measures.

Antifungal treatment is recommended for patients with severe illness and increased risk of dissemination or complications.

Indicators for severe disease include: symptoms lasting more than 2 months, night sweats longer than 3 weeks, inability to work, infiltrates affecting more than half of one lung or portions of both lungs, prominent hilar adenopathy, anti-coccidioidal complement fixing antibody concentrations greater than 1:16 and significant weight loss.

Risk factors for developing severe or complicated disease include: suppression of cellular immunity as with (HIV infection, solid organ transplantation and high-dose glucocorticoid administration), hematologic malignancies, anti-tumor necrosis factor therapy, chemotherapy, diabetes mellitus, pregnancy especially when disease develops in third trimester, cardiopulmonary conditions, elderly patients, African or Philippine descent due to increased risk of extrapulmonary complications.

Treatment

Fluconazole or itraconazole are the drugs of choice for most non-pregnant patients.

Fluconazole dosage is 400 mg daily. Immunocompetent patients are treated for 3-6 months. It has fewer drug interactions. Fluconazole is the recommended treatment while breastfeeding. Her diagnosis immediately after delivery as well the need for breastfeeding required that the antifungal of choice be safe during breastfeeding. Fluconazole is also the recommended treatment for acute pulmonary coccidioidomycosis while breastfeeding.

Itraconazole 200 mg twice daily can be used for immunocompetent patients who are treated for 3-6 months. It has less drying effects on skin and mucous membranes.

Amphotericin B (deoxylate formulation 0.3-0.6 mg/kg daily; lipid formulation 3-5 mg/kg daily) is the therapy of choice for treatment of pregnant women during the first trimester. It is used only in the most severe cases due to its toxicity and problems with administration. Once stable, these patients are transitioned to oral azole for the duration of treatment which is typically 12 months of total therapy.

Patients with coccidioidal infection should be followed for 1-3 years to monitor the development of complications. For patients who were not treated with antifungal therapy, follow up is complete after 12 months. However, patients treated with

antifungal therapy are followed annually for at least 2 years after completion of therapy due to risk of late recurrences.

Patients with positive *Coccidioides* antigen tests, are recommended to repeat this test every 1-2 months until it becomes negative. This information is used to determine response to treatment but is not used to determine timing of discontinuation of therapy because patients require continued therapy even after this test has become negative.

Radiographic monitoring should be performed in the first 2 to 3 months following diagnosis and then again several months to a year later to determine if the findings have resolved or if there is a residual nodule or cavitary lesion.

Special Consideration Regarding Coccidioidomycosis During Pregnancy

The later the acquisition of coccidioidal infection during pregnancy the more severe the maternal disease. This observation was thought to represent immune inflammatory response syndrome.[10]

Black race has been shown to be a potential risk factor for worse disease in pregnancy.[11]

Women with a resolved pulmonary coccidioidomycosis have a minimal risk of reactivation during pregnancy while women with a history of disseminated coccidioidomycosis have some risk of reactivation if they become pregnant.

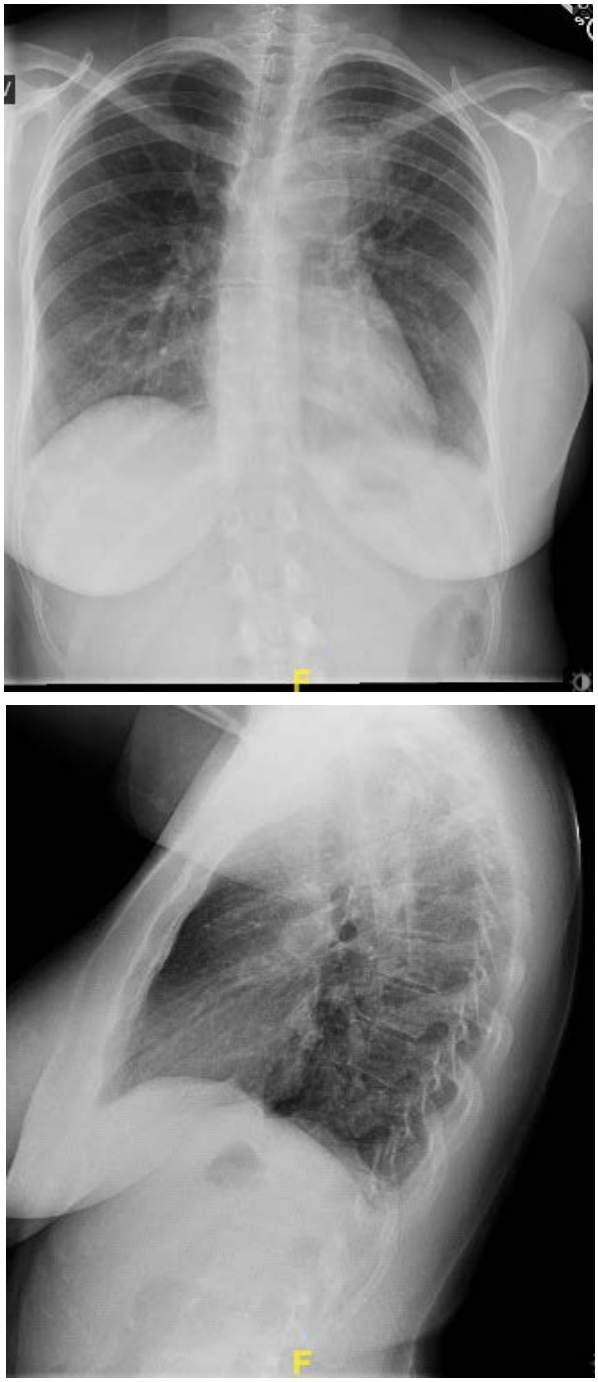
Amphoteracin B is the recommended treatment for coccidioidomycosis during pregnancy. However due to its toxicity, restriction to an IV formulation, and lack of efficacy for coccidioidal meningitis except when directly instilled into the cerebrospinal fluid, its usefulness during pregnancy has been limited.

Ketoconazole was the first available oral azole antifungal therapy for coccidioidomycosis. It was replaced by the triazole antifungals fluconazole and itraconazole as both are effective treatment for coccidioidal meningitis.[12]

Azole antifungals fluconazole and itraconazole may be considered during the second and third trimester pregnancy. Azole antifungals are associated with teratogenicity during the first trimester of pregnancy. There are few data on safety of fluconazole after the first trimester in humans but reports published suggest that exposure later in pregnancy may be safe.

The American Academy of Pediatrics considers fluconazole to be compatible with breastfeeding. Itraconazole is not recommended while breastfeeding whereas Amphoteracin B may be safe while breastfeeding.

Figure 1. 32-year-old female presented 2 weeks postpartum with a productive cough, hemoptysis and shortness of breath. CXR showed a 4 cm mediastinal mass.



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