Final Diagnosis:
Pulmonary Cryptococcosis in a Pan-allergic Immunocompetent Woman

Contributed by:
Amanda A. Valvano, DO  Garden State Infectious Disease Associates/ University of Medicine and Dentistry of New Jersey/Kennedy Health System Voorhees, NJ
Judith A. Lightfoot, DO  Garden State Infectious Disease Associates/ University of Medicine and Dentistry of New Jersey/Kennedy Health System Voorhees, NJ
Images provided by: Michael de la Cruz, MD  Pathology Department-Kennedy Health System Voorhees, NJ

History of the Present Illness:
A 26 year old Caucasian female, who is 5 months post-partum, presents with a four day history of dyspnea and a nonproductive cough. Initially, she had rhinorrhea, nasal congestion and pleuritic chest pain that was relieved with NSAIDs. She denied any fevers, chills or hemoptysis.

Past Medical History:
asthma, juvenile T-wave inversions on her electrocardiogram, tricuspid and mitral valve regurgitation, irritable bowel syndrome and endometriosis
She had a diagnostic laparoscopy to diagnose endometriosis, an endoscopy and a colonoscopy
No known drug allergies.

Key Medications:
Aciphex 20 mg, Zoloft 25 mg, prenatal vitamin

Epidemiological history:
She lives at home. She is married. She has one child. She works as a medical receptionist. She denies any alcohol or drug use. She has a history of smoking approximately 1-1/2 packs per day for 10 years, quitting back in March 2007. She denied any history of TB or asbestos exposure.

Physical Examination:
Her blood pressure is 95/67, heart rate 80, respiratory rate 18, pulse ox 95% on room air. Temperature is 98.1. She is in no acute distress.

HEENT examination: Nasopharynx is clear. Neck exhibits no JVD or lymphadenopathy.
Heart is regular with no murmur.
Lungs demonstrate coarse breath sounds bilaterally.

Abdomen is soft and nontender.

Extremities reveal no clubbing, cyanosis, or edema.

Neurologic exam is grossly nonfocal.

Skin has no obvious rash.

Studies:

Urine HCG is negative.

ABG showed pH 7.42, pCO2 of 42, pAO2 of 75, bicarb 27, 97% sat on room air.

Glucose 115, sodium 138, potassium 3.7, chloride 104, CO2 26, BUN 7, creatinine 0.77, calcium 9.2, phos 3.7, mag is 2.0.

CRP is 3.2.

Cardiac enzymes are negative. BNP is 19.

WBC count is 9.4, hemoglobin 13.4, MCV 81.6, platelet count 344,000

PT/PTT is normal. D-dimer is 0.86.

UA is negative.

Mycoplasma IgM is positive.

EKG demonstrated normal sinus rhythm at 69 beats per minute, nonspecific anterior T-wave changes.

CAT scan of the chest demonstrated some scattered upper lobe alveolar ground-glass inflammatory changes. They were also noted in the lingual, the left lower lobe and right lower lobe. More focal alveolar consolidation was noted in the left lower lobe just above the left hemidiaphragm. There was no significant lymphadenopathy. There was no pulmonary embolism. (see Image 1)

Clinical Course Prior to Diagnosis:

The patient was discharged home with a course of Azithromycin 500 mg daily for 7 days and a Prednisone taper. She was given a prescription for a repeat CAT scan of the chest without contrast in 2 weeks to document radiographic clearing of the infiltrates.

She represented to the Emergency room twelve days later with symptoms of shortness of breath. She completed the antibiotics and had significant improvement, however her symptoms returned. She called her Pulmonologist who advised a hospital evaluation. The patient denied current fever, chills, hemoptysis or night sweats but her cough and dyspnea had returned.
A repeat CAT scan of the chest showed extensive bilateral infiltrates predominantly in the left upper lobe. There was some involvement in the left lower lobe. Bilateral hilar adenopathy was also noted and a small degree of mediastinal lymph nodes were appreciated. No pleural effusions were noted. (see Image 2)

Differential Diagnosis:

1. Community acquired Pneumonia
2. Sarcoidosis
3. Autoimmune vasculitis
4. hyper IgE deficiency syndrome
5. Complement deficiency
6. Malignancy

Repeat Mycoplasma IgM was negative. ACE level was normal at 46. ANCA screen was negative. Scleroderma antibodies were negative. She was placed on intravenous steroids and underwent a bronchoscopy.

Diagnostic Procedure(s) and Result(s):

Bronchoscopy - Bronchial washing of the left upper lobe was negative for malignancy with benign bronchial cells and bronchoalveolar macrophages present. All AFB and respiratory cultures were negative. A tissue biopsy was obtained.

Treatment/Follow-up:

With a working diagnosis of Sarcoidosis, she was again discharged home with Prednisone 40 mg daily and a prescription for a repeat chest x-ray in three weeks.

Subsequently, the pathologist reported non-caseating granulomas on the lung biopsy. Special stains for fungus and AFB were obtained and were consistent with Cryptococcal neoformans. Cryptococcal titers were positive at 1:128.

The patient was diagnosed with Cryptococcal pneumonia and started on amphotericin B. She tolerated the medication for a week and a half, but then developed pruritus and chest tightness. Her therapy was changed to IV Fluconazole 400 mg IV q.12, but after two weeks before she had a similar adverse reaction. She was then switched to Voriconazole but experienced similar symptoms within a few days. Third-line treatment was attempted with caspofungin, but also had to be stopped due to intolerance.

The therapy for the patient was ceased since she had reacted strongly to all classes of antifungals, including liposomal amphotericin B, the azoles, and the echinocandins. While on antifungals, her chest CT had clinically improved (see image 4) and her cryptococcal titers trended down to zero. However,
when off therapy for two weeks, her titers increased back to 1-64. As a result of rising titers, the patient was admitted to the ICU for rapid desensitization to amphotericin B. The patient had a PICC line placed and was receiving IV amphotericin B via a home infusion service.

Weekly blood work revealed electrolyte abnormalities which remained uncorrected despite replacement. As a result, Amphotericin was discontinued and the patient was changed to oral Fluconazole to complete her course. While on Fluconazole, the patient became pregnant and was told to stop the Fluconazole due to warnings of Azole use in pregnancy. The patient remained off therapy with close followup for the remainder of her pregnancy. She had an uncomplicated delivery of a healthy baby boy and remains unsymptomatic.

Brief Discussion of Differential/Major Teaching points of case:

Cryptococcosis is a pulmonary or disseminated infection acquired by inhalation of soil contaminated with the encapsulated yeast Cryptococcus neoformans. It is a worldwide infection that only rarely causes dissemination in healthy individuals. The lungs are the initial site of almost all infections and following inhalation, C. neoformans causes a small focal pneumonitis. The immune status of the affected individual then determines whether the infection disseminates or resolves.

The presentation of pulmonary cryptococcosis can range from asymptomatic nodular disease to severe acute respiratory distress syndrome (ARDS). Classic symptoms of pneumonitis, including cough, fever, and sputum production, may be present. Chest radiographic features of pulmonary cryptococcus varies; most common being solitary or few well-defined, non-calcified nodules. Cavitation is rare, but lobar infiltrates, hilar and mediastinal adenopathy, and pleural effusions may be seen.

Diagnosis is based on culture and histology. Expectorated sputum samples can be positive, but higher yields are obtained using bronchoscopic sampling. The yeast form is identified using the methenamine silver stain.

Pulmonary cryptococcosis should be considered during differential diagnosis as a possible cause of abnormal chest shadow in pregnant and postpartum patients. Naturally occurring maternal immunosuppression increases the risk of various infections, including Cryptococcus, during pregnancy and the postpartum period. This case emphasizes the need for heightened awareness of cryptococcosis in the differential diagnosis of pneumonia, chest pain, and hypoxemia in women of childbearing age.

Cryptococcosis during pregnancy presents a special challenge to the clinician. The risk of congenital cryptococcosis to the unborn fetus is low, and the most likely mechanism whereby neonates acquire invasive fungal pulmonary infection is through aspiration. While it is unclear whether there is any real increased risk of spontaneous abortion, but the overall fetal outcome depends on effective treatment of maternal infection.

A balanced therapeutic approach holds great promise for successful maternal and fetal outcomes. Similar to normal hosts, for pregnant women with limited pulmonary cryptococcosis and no evidence of
dissemination, close follow-up without antifungal therapy is recommended. It is prudent to use frequent physical examinations, every 1-2 months, combined with chest imaging and serum cryptococcal antigens to monitor disease progression.

For patients with dense consolidation, progressive pulmonary disease, or dissemination, antifungal therapy is necessary. Amphotericin B with or without flucytosine represents the choice for initial treatment of the more acutely ill patient. Immunocompetent patients with mild-to-moderate symptoms should be treated with fluconazole 400 mg daily for 6–12 months. In cases where fluconazole is not an option, an acceptable alternative regimen is itraconazole, 400 mg/d, for 6–12 months. If oral azole therapy cannot be given, or the pulmonary disease is severe or progressive, amphotericin B is recommended, 0.7 mg/kg/d for a total dose of 1000–2000 mg.

Careful consideration of the benefit to the mother and the risk to the fetus is required when prescribing antifungal therapy in pregnancy. The systemic antifungal drug with which there has been the most experience in pregnancy is amphotericin B. There have been no reports of teratogenesis attributed to this agent. There is evidence to suggest that fluconazole exhibits dose-dependent teratogenic effects; however, it appears to be safe at lower doses (150mg/day). Fluconazole exposure should be avoided during pregnancy, however it can be started during the postpartum period.

The Infectious Diseases Society of America 2000 guidelines recommend 3 to 6 months of fluconazole for immunocompetent patients who are symptomatic with serum cryptococcal antigen titers >1:8. In asymptomatic immunocompetent patients, careful observation only may be warranted.

Final Diagnosis:

Pulmonary Cryptococcosis

References:


IMAGES:

Figure #1- slide  Pathology slide of tissue biopsy- GMS Silver stain showing small black yeast
Figure #2 slide  initial CT chest, scattered alveolar ground-glass inflammatory changes. More focal alveolar consolidation was noted in the left lower lobe.