**CLINICAL VIGNETTE**

# A Case of Cryptococcal Pneumonia in an Immunocompetent Patient

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## *Introduction*

*Cryptococcus* variants *neoformans* and *gattii* are encapsulated yeasts that are ubiquitous. *Neoformans* is found in soil and pigeon droppings whereas *gattii* is associated with Eucalyptus and other types of trees mainly found in tropical and subtropical regions. The majority of patients affected by cryptococcosis have underlying predisposing factors that affect their immune system, such as human immunodeficiency virus (HIV), solid-organ transplantation, glucocorticoid treatment, hematologic malignancy, or other disorders associated with cell-mediated immune dysfunction.[1] In immunocompromised patients, inhalation of the fungus usually causes symptomatic pulmonary cryptococcosis, which can then easily spread to the central nervous system resulting in meningitis or meningoencephalitis.[1,2] Pulmonary cryptococcosis involving immunocompetent patients is not common. Immunocompetent patients may be asymptomatic or present with symptoms such as cough, chest pain, fever and hemoptysis. Additionally, immunocompetent patients are also typically found to have pulmonary lesions on chest radiography.[3,4] This is a case of an immunocompetent patient presenting with pulmonary cryptococcosis.

## *Case Report*

A 74-year-old male with a history of Type II diabetes mellitus (DM), hypertension, hyperlipidemia, Stage II chronic kidney disease (CKD), benign prostatic hypertrophy (BPH), and a history of treated latent tuberculosis (TB) in the 1970s with baseline chest x-ray changes of apical scarring presented to the Emergency Department (ED) with a three day history of progressive dyspnea on exertion, exercise intolerance, and worsening bilateral lower extremity edema. The patient is a retired accountant. He was born in the Philippines and moved to Los Angeles in 1972 without a visit to the Philippines in over 10 years. The patient used to smoke 6 cigarettes daily for 20 years but quit about 10 years ago. There is no history of sick contacts, no recent travel outside of the Los Angeles area, and no animal or Eucalyptus tree exposures. The patient received the Bacillus Calmette-Guerin (BCG) vaccine in the Philippines with resultant positive tuberculin purified protein derivative (PPD) test in the 1980s and apical scarring noted on chest X-ray. Upon presentation to the ED, his oxygen saturation was 74% on room air. Labs showed a white count of 11.77, sodium of 131, brain natriuretic peptide (BNP) of 232, arterial blood gas (ABG) with pH 7.36, pCO2 41, and pO2 85% on 6 liters of supplemental oxygen. Troponins returned negative; electrocardiogram (EKG) showed no active ischemia. A chest x-ray (Figure 1) showed bilateral pulmonary vascular congestion with alveolar opacities throughout the right lung with central predominance, increased interstitial marking with hilar predominance in the left lung, and Kerley B lines. The patient was started on furosemide given concern for congestive heart failure as well as ceftriaxone and azithromycin for possible community acquired pneumonia.

The patient's hypoxia had improved but persisted after two days of intravenous furosemide and antibiotic therapy. A transthoracic echocardiogram showed normal systolic function, mild aortic stenosis, and an estimated ejection fraction of 60-65%. A chest x-ray (Figure 2) repeated at that time showed a dense central airspace consolidation within the right lung field and a lesser consolidation in the left lower lung field with resolution of pulmonary edema. A chest computed tomography (CT) (Figure 3) scan obtained for further evaluation showed patchy and confluent dense airspace opacities involving all lobes of the lungs, most notably in the right upper lobe favoring a multifocal pneumonia. The patient was ruled out for active tuberculosis with three negative acid-fast bacilli (AFB) stains. Bacterial and fungal sputum cultures returned negative. Additionally, the following serologic tests returned negative: HIV, MTB-Quantiferon-Gold, Aspergillus, Coccidiodes, Legionella, and Histoplasma. However, the cryptococcal serum antigen returned positive at a titer of 1:2. Pulmonary and Infectious Disease were consulted for further assistance. The patient's furosemide, ceftriaxone, and azithromycin were discontinued. The patient underwent diagnostic bronchoscopy with bronchoalveolar lavage (BAL) by Pulmonary with negative cultures and negative cytology. He was started on fluconazole 400mg po daily for pulmonary cryptococcosis.

The patient was able to be weaned down to 2 liters of supplemental oxygen via nasal cannula with improvements in his dyspnea on exertion and resolution of bilateral peripheral edema. The patient was then discharged to home to continue treatment with fluconazole. A Chest CT (Figure 4) was performed one month after treatment with fluconazole, showing near complete interval resolution of the previously seen patchy and confluent airspace consolidations involving

both lung fields and faint residual groundglass post-inflammatory scarring and fibrosis.

The patient was subsequently weaned off of supplemental oxygen completely. One month after treatment with fluconazole, the patient's serum cryptococcal antigen remained positive at a titer of 1:2 despite near radiographic resolution of the pneumonia. Currently, the patient remains on fluconazole with a planned duration of treatment of at least 6 months and close follow up with Infectious Disease.

***Discussion***

Infection with *Cryptococcus neoformans* occurs through inhalation of the yeast, which can be found in soil and pigeon and chicken droppings. *Cryptococcus gattii* occurs typically in tropical and subtropical regions, thought to be due to its association with the Eucalyptus tree. Goldman et al[5] suggest that a large portion of the population has been exposed to and infected by the yeast during childhood, specifically those living in more urban settings. Primary pulmonary cryptococcosis in the immunocompetent patient may be asymptomatic or produce symptoms that may mimic viral infections and, therefore, not be recognized as a fungal infection. A major factor of whether or not a patient develops symptomatic pulmonary cryptococcosis or disseminated disease is his or her immune status. Although is it less common for the immunocompetent patient to become symptomatic or have disseminated disease, it can still occur. Campbell reported 32% of the patients with pulmonary cryptococcosis were asymptomatic and the cases of pulmonary infection were incidental findings.[6] In immunocompetent patients, the clinical manifestations of pulmonary crypotococcosis can range from being completely asymptomatic to rarely acute respiratory failure. Common symptoms include fever, chest pain, dyspnea, cough, and hemoptysis.[3,4] Disseminated disease involving the skin, bone, or central nervous system (CNS) is more uncommon. [4] This can be contrasted with immunocompromised patients where the central nervous system is more commonly affected.

Diagnosis of pulmonary cryptococcosis involves chest radiography, fungal cultures, serum cryptococcal antigen, and histology, if available. Fungal cultures can be obtained from expectorated sputum samples or from bronchoalveolar lavage. If thoracentesis is performed for associated pleural effusions, encapsulated yeast forms may also be visualized in the pleural fluid. Serum cryptococcal antigen should also be obtained. It should be noted that antigen testing is less reliable for non-HIV infected patients than for HIV-positive patients with cryptococcosis. Pappas et al[7] noted that among the patients in their study, cryptococcal antigen testing was positive for only 56% and 86% of those non-HIV infected patients with pulmonary and CNS disease, respectively, whereas almost all HIV-positive patients with cryptococcosis had positive serum cryptococcal antigen titers.[7] Given that many HIV-negative patients with cryptococcosis may present with few signs and symptoms, serologic testing can be insensitive in this group and could potentially lead to delays in diagnosis and institution of therapy. The radiographic manifestations in immunocompetent patients can be variable. The imaging manifestations of pulmonary cryptococcosis can include pulmonary nodules or masses, reticulonodular opacities, and segmental or lobar consolidation. Cavitation of nodules or consolidation is considered rare for the immunocompetent patient.[8] Since dissemination of cryptococcosis to the CNS in immunocompetent patients is rare, a lumbar puncture is not always warranted. However, if the immunocompetent patient has CNS symptoms or a very high cryptococcal antigen titer (>1:512) even without any CNS symptoms, a lumbar puncture should be performed to evaluate for CNS involvement.[9]

The goal of treatment of pulmonary cryptococcosis is to prevent dissemination of the disease. The Infectious Diseases of America Society (IDSA) guidelines recommend administering fluconazole (400mg per daily orally) for 6-12 months for the treatment of mild-to-moderate symptoms in immunocompetent patients.[9] Itraconazole, voriconazole, and posaconazole are considered acceptable alternatives if fluconazole is not available or not tolerated by the patient. Persistently positive serum cryptococcal antigen titers should not be used as criteria to continue therapy beyond the recommended duration. Severe pulmonary cryptococcosis should be treated similarly to CNS disease, which includes treatment with amphotericin and flucytosine. Interestingly, there are several case reports of immunocompetent, asymptomatic patients with pulmonary cryptococcosis who received no antifungal treatment and still improved radiographically with observation alone.[3,4] Surgery can be considered if there is no response to antifungal therapy or if radiographic abnormalities persist.[9]

Pulmonary cryptococcosis in immunocompetent patients is uncommon. Our patient presented with progressive symptoms of dyspnea on exertion and was found to be hypoxemic with radiographic findings of a multifocal pneumonia. More often than not, patients are started on an empiric course of antibiotics, depending on their immune status and risk factors for healthcare associated pneumonia. Typically, sputum and blood cultures are obtained. Also, given the radiographic extent of the patient's pneumonia, serologic investigations including atypical causes of pneumonia including legionella, histoplasmosis, coccidioidomycosis, Cryptococcus, and aspergillus were obtained. It was unexpected that the patient's serum cryptococcal antigen would return positive. However, given that it returned at a low titer and there were no CNS symptoms, lumbar puncture was not performed. Sputum cultures and bronchoalveolar lavage cultures surprisingly returned negative. The patient had near radiographic resolution of the pneumonia after 4 weeks of treatment with fluconazole. Had the serum cryptococcal antigen not been checked, there ultimately would have been a significant delay

in the patient's diagnosis and institution of therapy. Therefore, in patients presenting with extensive or atypical radiographic findings of pneumonia, atypical causes of pneumonia should be further investigated.

**Figure 1**: Admission chest x-ray showing asymmetric pulmonary edema with alveolar opacities throughout the right lung and increased interstitial markings with hilar predominance in the left lung.

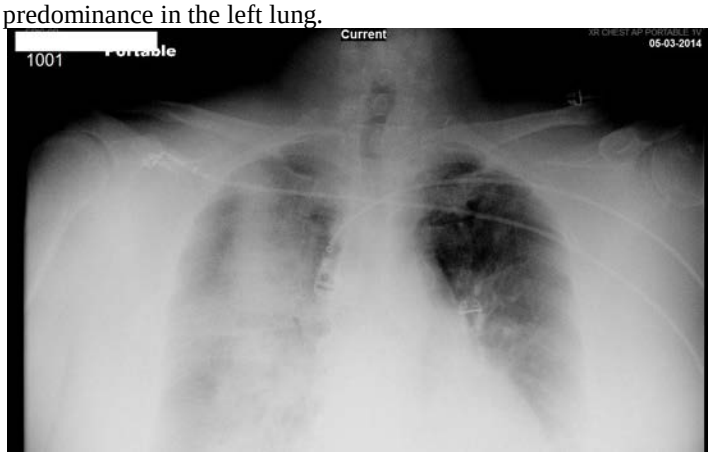



**Figure 2**: Chest x-ray after two days of intravenous furosemide with a dense central airspace consolidation within the right lung field and a lesser consolidation in the left lower lung field and resolution of pulmonary edema.

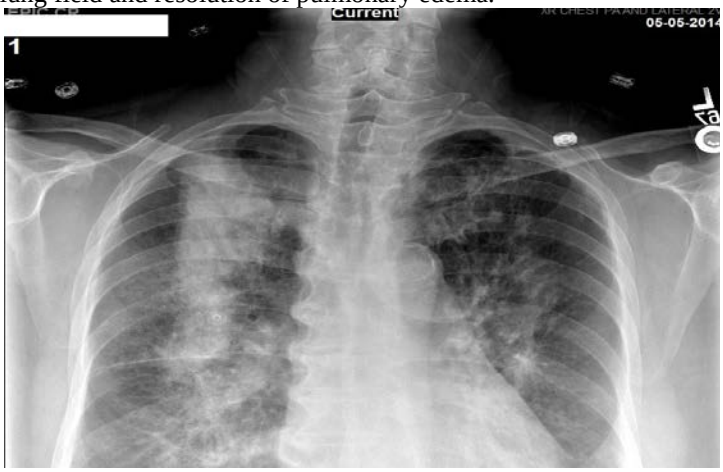



**Figure 3**: Chest CT with patchy and confluent dense airspace opacities involving all lobes of the lungs, most notably in the right upper lobe, favoring a multifocal pneumonia.

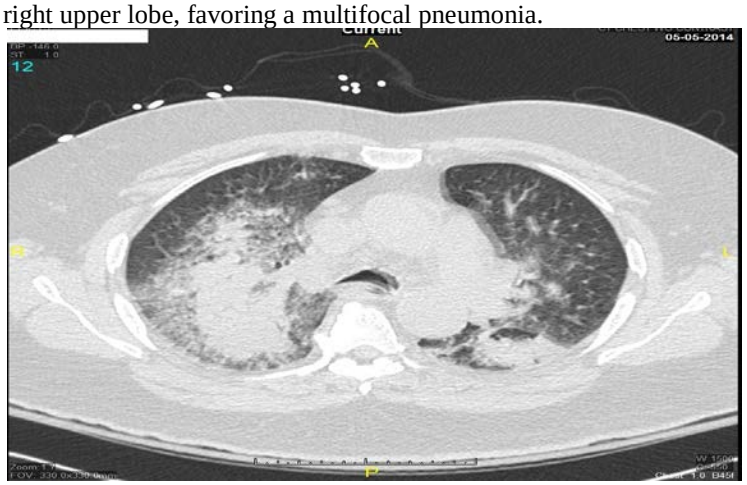
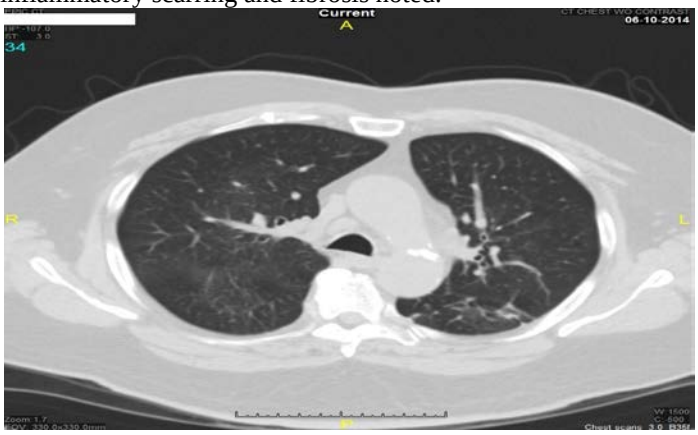



**Figure 4**: Chest CT one month after treatment with fluconazole showing near complete interval resolution of the previously seen patchy and confluent airspace consolidations involving both lung fields. Faint residual groundglass post-inflammatory scarring and fibrosis noted.

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