Pulmonary Cryptococcosis in Pregnancy: 2 Cases Report and Review of the Literature

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Abstract

Cryptococcosis is an important opportunistic fungal infection. Pulmonary disease is the second most common manifestation of cryptococcosis next to meningitis. Despite extensive literature addressing the general topic of pulmonary cryptococcosis, there is little specific information about its occurrence during pregnancy. Here we report 2 previously healthy women who develop pulmonary cryptococcosis during pregnancy and postpartum period. We also reviewed literature about the general topic of pulmonary cryptococcosis, the characteristics of previously reported cases with pulmonary cryptococcosis during pregnancy, the physiological effect of pregnancy on immune function and the therapeutic approach for the management of cryptococcosis during pregnancy. (J Intern Med Taiwan 2013; 24: 212-219)

Key Words: Pulmonary cryptococcosis, Pneumonia, Pregnancy, Postpartum

Introduction

Cryptococcosis is an important opportunistic fungal infection, especially in AIDS patients¹-³. In immunocompetent host, it causes clinical disease infrequently¹-³. Due to naturally occurring maternal immunosuppression, pregnancy represents a vulnerable period to mother and fetus, with increased risk of infection by a variety of pathogen including Cryptococcus neoformans⁴,⁵. Pulmonary cryptococcosis during pregnancy is rare. Here we report 2 cases of previously healthy women with pulmonary cryptococcosis during pregnancy and postpartum period.

Case Report

Case 1

A 28 y/o woman was previously healthy. She suffered from intermittent dry cough for 1 month in the third trimester. Afternoon low grade fever developed 5 days after delivery of a healthy baby in Nov, 2004. On physical examination, body temperature was 37.2°C, heart rate was 110 beats/ minutes, respiratory rate was 24/ minutes, and blood pressure was 110/80 mmHg. Respiratory sounds were coarse bronchial sound in right lower lung field. The peripheral white blood cell count was 14000/ul with a differential count of 83.8% neutrophils. A chest
radiograph (CXR) revealed dense consolidation in the right upper lobe (RUL) and right lower lobe (RLL) (Figure 1).

Penicillin G plus clarithromycin were administered for treatment of pneumonia. Microbiological studies including blood culture, sputum smears and cultures for bacteria, fungi and mycobacteria were performed, but only few Hemophilus parainfluenzae was isolated from sputum. Poor treatment response of RUL and RLL lobar consolidation was noted on follow-up CXR after one week of antibiotics therapy. Bronchoscopy was performed, which revealed normal tracheobronchial trees with no evidence of endobronchial lesion. C. neofor- mans was isolated from bronchoalveolar lavage fluid and serum cryptococcal antigen test was positive (1:32). The diagnosis of pulmonary cryptococcosis was confirmed. The serum human immunodeficiency virus (HIV) antibody test was negative. Lumbar puncture was unrevealing and blood fungus culture was negative. No evidence of extrapulmonary dissemination was found. A total of five months antifungal therapy with oral fluconazole 200 mg per day was completed. A series of CXR on follow-up revealed complete resolution of RUL and RLL consolidation. The serum cryptococcal antigen titer was decreased to 1:4 at the end of therapy. There was no relapse during follow up examination at six months after the discontinuation of antifungal therapy.

Case 2

A 30 y/o woman was in good health before. She experienced mild cough, chills and malaise in the 38th week of her first pregnancy. She delivered a healthy baby in the middle of Dec, 2008. She suffered from dry cough, fever, chills, left lower back pain and flank pain 2 weeks postpartum. She visited emergent department for help. On physical examination, body temperature was 38.5°C, heart rate was 111 beats/ minutes, respiratory rate was 18/ minutes, and blood pressure was 114/70 mmHg. Respiratory sounds were coarse bronchial sound in left lower lung field. The peripheral white blood cell count was 10970/uL with a differential count of 79.7% neutrophil. CXR revealed lobar consolidation in left lower lobe (Figure 2, A).

Empirical antibiotics with amoxicillin-clavulanate plus clarithromycin were prescribed. Microbiological studies including blood cultures, sputum smears and cultures for bacteria, fungi and mycobacteria, urine Legionella antigen and Streptococcus pneumoniae antigen were checked, but all tests were negative. Spiking high fever relapsed on the 4th admission day associated with persistent chest pain. Follow-up CXR revealed more dense large lobar consolidation in left lower lobe (LLL). Chest CT scan (Figure 2, B and C) revealed large lobar consolidation in LLL with small cavities. Necrotizing lobar pneumonia was suspected initially and parenteral antibiotics were switched to vancomycin, ceftriaxone, and clarithromycin in...
combination. On the 13th admission day, spiking high fever recurred again and follow-up CXR showed unresolution of LLL lobar consolidation. Echo-guide aspiration and biopsy of LLL subpleural consolidation was performed but no conclusive result was obtained. Serum cryptococcal antigen was positive at a titer of 1: 256. The serum HIV antibody test was negative. Lumbar puncture was performed with negative findings. Blood and urine fungus cultures were also negative. No evidence of extrapulmonary dissemination was found. Oral fluconazole 400 mg per day was prescribed and a total of 6 months antifungal therapy was completed. Followed up CXR revealed gradual resolution of LLL lobar consolidation and the serum cryptococcal antigen titer declined to 1:8 at the end of therapy and became negative 5 months after the discontinuation of antifungal therapy. There was no relapse during follow-up examination at 5 months after the discontinuation of antifungal therapy.

Discussion

Cryptococcosis is an important opportunistic infection that describes infection by the encapsulated...
nonmycelial budding yeasts *C. neoformans*. These saprophytic fungi are distributed worldwide and are particularly abundant in soil contaminated by pigeon dropping. The primary portal of entry for *Cryptococcus* is through the inhalation of the encapsulated yeast, and because the organism has a propensity to metastasize to the central nervous system, meningitis or meningoencephalitis is the most common recognized disease manifestation. Pulmonary disease is less common but is probably underdiagnosed. An identifiable environmental exposure is not typically apparent, and human-to-human transmission does not occur.

*Cryptococcus* species have long been known to cause disease in normal host, but the majority of patients have significant underlying immune defects. Important predisposing conditions for cryptococcosis include HIV infection, diabetes mellitus, hepatic cirrhosis, hematological malignancies, solid organ, and to a lesser extent, stem cell transplantation, corticosteroid therapy, sarcoidosis, connective tissue disorders, and other immunosuppressive medications.

Despite extensive literature addressing the general topic of pulmonary cryptococcosis, there is little specific information about its occurrence during pregnancy. We reviewed previous literature, and 7 otherwise healthy women with pulmonary cryptococcosis during pregnancy and postpartum period had been reported. Characteristics and salient aspects of our 2 cases plus the 7 previously reported cases are summarized in Table 1.

Pregnancy is considered a time of relative immunosuppression, designed to prevent fetal rejection by downregulating the maternal immune system. A host of different paternally derived antigen are expressed by the fetus and render the situation analogous to a transplanted allograft. The maternal immunosuppression persisted throughout pregnancy, peaking during the third trimester and returning to baseline by 3-5 months postpartum.

Cryptococcal pulmonary involvement range from asymptomatic infection to severe pneumonia with acute respiratory failure. Clinical presentation of pulmonary cryptococcosis is highly variable and often is related to the immune status of the patient. In the immunocompetent patient, clinical symptoms are present weeks to months before diagnosis; however, patients may be totally asymptomatic.

The onset of symptoms in immunocompromised patients is generally subacute, but rapidly progressive pulmonary disease in this population may occur. The natural history of pulmonary cryptococcosis is also highly dependant on the degree of immunosuppression, as isolated pulmonary disease in the immunocompromised host is more likely to disseminate, suggesting the need for early antifungal therapy.

A unique clinical circumstance is encountered in profoundly immunosuppressed HIV patients as they initiate highly active antiretroviral therapy and begin the process of immune reconstitution, or in solid organ transplant patients who withdraw or reduce immunosuppression. As cell-mediated immune responses are restored, there is the potential of a directed immune response to an underlying antigen. This results in clinical deterioration known as immune reconstitution inflammatory syndrome (IRIS). Our two pregnant patients both have respiratory symptoms in the late stage of pregnancy and exacerbated in the postpartum period. Besides, they both have good treatment response and outcome. Their illness may probably represent another form of IRIS.

The radiographic features of pulmonary cryptococcosis are varied and are influenced by the degree of immunosuppression of the patient. In HIV-negative patients, solitary or multiple pulmonary nodules are seen on approximately 60-80% of chest radiographs and focal or multifocal airspace consolidation is present in 10-30%. In patient with AIDS, the most
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Author (Ref.)</th>
<th>Year</th>
<th>Age (yr)</th>
<th>Onset (trimester)</th>
<th>Clinical features</th>
<th>Diagnostic tests</th>
<th>Radiographic features</th>
<th>Treatment (trimester)</th>
<th>Drug</th>
<th>Outcome Mother</th>
<th>Outcome Fetus</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ely (5)</td>
<td>1998</td>
<td>32</td>
<td>3rd</td>
<td>Chest pain, fever, SOB</td>
<td>TBBx + stain; serum Crypto Ag 1:64; CSF -; HIV -</td>
<td>Multilobar air-space consolidation and slight blunting of costophrenic angles</td>
<td>Postpartum</td>
<td>AmphoB 500 mg, fluconazole 2 mo</td>
<td>Well</td>
<td>Well</td>
</tr>
<tr>
<td>2</td>
<td>Ely (5)</td>
<td>1998</td>
<td>28</td>
<td>2nd</td>
<td>Pleuritic chest pain</td>
<td>Broncho x 1; FNA + stain; serum Crypto Ag -; CSF -; HIV -</td>
<td>Left apical focal lung nodule</td>
<td>None</td>
<td>None</td>
<td>Well</td>
<td>Well</td>
</tr>
<tr>
<td>3</td>
<td>Ely (5)</td>
<td>1998</td>
<td>30</td>
<td>3rd</td>
<td>Pleuritic chest pain</td>
<td>TBBx + stain; serum Crypto Ag 1:32; CSF -; HIV -</td>
<td>Right lower lobe numerous nodules</td>
<td>Postpartum</td>
<td>AmphoB 1000 mg, fluconazole 6 mo, itraconazole 2 mo</td>
<td>Well</td>
<td>Well</td>
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<tr>
<td>4</td>
<td>Ely (5)</td>
<td>1998</td>
<td>35</td>
<td>1st</td>
<td>SOB, cough</td>
<td>Bronchoscopy x 2; OLBx + stain/culture; serum Crypto Ag 1:8</td>
<td>Lingula and right lower lobe air-space consolidation</td>
<td>1st</td>
<td>AmphoB 2093 mg</td>
<td>Well</td>
<td>Well</td>
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<tr>
<td>5</td>
<td>LaGatta (18)</td>
<td>1998</td>
<td>28</td>
<td>Postpartum</td>
<td>Headache, generalized myalgia, fever, dry cough</td>
<td>TBBx + stain; serum Crypto Ag 1:512; CSF -; Bone marrow -; HIV -</td>
<td>Multilobar air-space consolidation</td>
<td>Postpartum</td>
<td>Fluconazole 200 mg/day x 2 wk, DC due to drug allergy</td>
<td>Well</td>
<td>Well</td>
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<tr>
<td>6</td>
<td>Current report Patient #1</td>
<td>2004</td>
<td>28</td>
<td>3rd</td>
<td>Progressive cough, low grade fever</td>
<td>BAL + culture; serum Crypto Ag 1:32; CSF -; HIV -</td>
<td>Right upper lobe and right lower lobe air-space consolidation</td>
<td>Postpartum</td>
<td>Fluconazole 200 mg/day x 5 mo</td>
<td>Well</td>
<td>Well</td>
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<td>7</td>
<td>Current report Patient #2</td>
<td>2008</td>
<td>30</td>
<td>3rd</td>
<td>Fever, chills, pleuritic chest pain, cough</td>
<td>FNA - stain; serum Crypto Ag 1:256; CSF -; HIV -</td>
<td>Left lower lobe lobal consolidation</td>
<td>Postpartum</td>
<td>Fluconazole 400 mg/day x 6 mo</td>
<td>Well</td>
<td>Well</td>
</tr>
<tr>
<td>8</td>
<td>Nakamura (19)</td>
<td>2008</td>
<td>30</td>
<td>3rd</td>
<td>Hemosputum</td>
<td>Serum Crypto Ag 1:8; CSF -; HIV -</td>
<td>Right middle and right lower lobe nodules</td>
<td>Postpartum</td>
<td>Fluconazole 400 mg/day x 3 mo</td>
<td>Well</td>
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</tr>
<tr>
<td>9</td>
<td>Nakamura (19)</td>
<td>2008</td>
<td>29</td>
<td>3rd</td>
<td>Cough, no neurological symptoms or signs</td>
<td>Serum Crypto Ag 1:256; BAL fluid Crypto Ag 1:64 but culture -; CSF Crypto Ag 1:8 but culture -</td>
<td>Multiple nodule lesions in both lungs</td>
<td>Postpartum</td>
<td>Fluconazole 400 mg/day x 6 months + 5-FC 1.5 g/day x 3 mo</td>
<td>Well</td>
<td>Well</td>
</tr>
</tbody>
</table>

Abbreviation: AmphoB= amphotericin B; BAL= bronchoalveolar lavage; Crypto Ag= cryptococcal antigen; DC= discontinue; FNA= fine needle aspiration; CSF= cerebrospinal fluid; HIV= human immunodeficiency virus; OLBx= open lung biopsy; SOB= shortness of breath; TBBx= transbronchial biopsy.
common radiographic abnormalities are diffuse interstitial and lobar, often mass-like, infiltrates occurring in 70-75% of infections. Pulmonary nodules are expected in 30%, but are more likely to cavitate than nodules in patients without immune compromise. In this report, our two pregnant patients both have large air-space consolidation rather than pulmonary nodules.

In addition to consistent clinical history and radiographic features, a definitive diagnosis of cryptococcosis is made by culture and identification of the organism from a nonsterile site. Sputum samples are easily obtained for testing, but are limited by low sensitivity of diagnosis. Better yields will occur if more invasive procedures such as bronchoscopy with bronchoalveolar lavage, transbronchial biopsy, or open lung biopsy are performed. Presumptive diagnosis of cryptococcosis can also be made by examination of preparations from clinical samples or tissues. Gomori methenamine silver or periodic acid-Schiff staining allows for identification of the organism.

Serum cryptococcal antigen (CrAg) detection is highly accurate for the diagnosis of disseminated cryptococcosis. CrAg is found in cerebrospinal fluid in more than 90% and in serum in more than 80% of patients with cryptococcal meningitis. However, the utility of this test is much more limited in patient with only cryptococcal lung disease. In HIV-negative patients with isolated pulmonary cryptococcosis, serum CrAg is positive in 25-56% of patients. Our 2 patients reported here both have isolated pulmonary cryptococcosis and positive serum CrAg. In addition to the utility of diagnosis, some authors advocate that serum CrAg may serve as a marker of disease activity or overall organism burden in the patients with isolated pulmonary cryptococcosis (IPC) and that a positive serum CrAg in patients with IPC might reflect an increased risk for more severe local disease or for dissemination.

The goals and expectations of the treatment of cryptococcal lung disease are to control the signs and symptoms of pneumonia, prevent dissemination, sterilize infected tissue, and prevent recurrence. Because the risks of dissemination and recurrence are related to host immunity, treatment approach for pulmonary cryptococcosis should be categorized on the basis of patient immune function.

The pregnant women with disseminated disease and moderate to severe pulmonary cryptococcosis should receive amphotericin B with or without flucytosine and after delivery, a change from amphotericin B to fluconazole is probably warranted in most cases to avoid amphotericin B toxicity to the mother. No data are available to guide optimal duration of antifungal therapy for cryptococcosis during pregnancy, but non-pregnant patients without AIDS are treated for 6-12 months based on controlled trials. In pregnant patient who has very mild and stable pulmonary cryptococcosis manifested with limited nodular pulmonary disease, and no evidence of dissemination, treatment may be withheld safely until after delivery. However, closely clinical observation is necessary. Serial examinations of the serum cryptococcal antigen titer may provide a useful method for monitoring the status of the infection. Our two patients reported here both have moderate pulmonary cryptococcosis and are diagnosed after delivery. They are treated successfully with fluconazole and have an excellent maternal and fetal outcome.

The use of fluconazole as primary therapy for pulmonary cryptococcosis during pregnancy should be avoided as possible, because of its class C status, and a single case report of fetal malformation, combined with the extensive experience with amphotericin B and its lack of associated teratogenicity.

In conclusion, pregnancy is considered a time of relative immunosuppression. Although at present, there are insufficient epidemiologic data...
to determine whether incidence of pulmonary or disseminated cryptococcosis actually increase during pregnancy, this report emphasizes the need for heightened awareness of pulmonary cryptococcosis in the differential diagnosis of pulmonary disease in the pregnant patient.

References
懷孕期併發肺部隱球菌感染症：兩病例報告及文獻回顧

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摘 要

隱球菌感染症是一種重要之伺機性黴菌感染症。肺部疾病是僅次於腦膜炎第二常見之隱球菌感染症臨床表現。雖然有極多且廣泛之文獻描述肺部隱球菌感染症之一般主題，就我們所知卻只有極少有關於肺部隱球菌感染症發生於懷孕期之相關資訊。在這篇文章中我們描述二位平時健康之婦女於懷孕期及產後期發生了肺部隱球菌感染症。同時我們也針對肺部隱球菌感染症之相關主題、先前文獻已報告過之懷孕婦女肺部隱球菌感染症患者的臨床特徵、因懷孕對免疫功能之生理影響、以及懷孕中發生隱球菌感染症之治療方針做了一些文獻回顧。