

# Pulmonary Cryptococcosis in an HIV-infected Patient

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## ABSTRACT

The authors report a case of HIV infection presented with fatigue and weight lost for six weeks. Female patient had developed pleuritic chest pain and non-productive cough after starting antiretroviral treatment for a week. Chest X-ray showed ill-defined mass at left lower lung. Computerized tomography showed a wedge-shaped consolidation and cavitory lesion in left lower lobe. Bronchoalveolar lavage and transbronchial biopsy was performed. The encapsulated yeast was identified from pathologic section, and pulmonary cryptococcosis was diagnosed. Fluconazole 400 mg/day was started and her symptoms gradually improved. (*J Infect Dis Antimicrob Agents* 2011;28:203-7.)

**Note:** This case had been presented and discussed in the Interhospital Case Conference on Infectious Disease (ICCID), 19 May 2011, Bangkok, Thailand.

## INTRODUCTION

Pulmonary cryptococcosis is relatively uncommon, even though the lung is the portal route of entry. Most patients have no chest symptoms and are detected by routine chest X-ray in patients with other presentations e.g. meningitis. The spectrum of clinical manifestation varies depends on the host immunity. The number of cases of pulmonary cryptococcosis increases as the prevalence of HIV infection increases. The clinical presentations, severity of diseases, radiologic findings

and treatment are different between patients who have and who do not have HIV infection. We reported an AIDS patient with pulmonary symptoms, and was finally diagnosed as pulmonary cryptococcosis.

## CASE REPORT

A 17-year-old female was diagnosed as HIV infection for 6 months, when she sought for medical care because of pruritic papular eruption. Antiretroviral

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therapy was not started. She felt fatigue for 6 weeks and lost 5 kilograms in 1 month before this admission.

Two weeks later, she went to a district hospital. The chest X-ray was performed as shown in Figure 1. Her CD4 cell count was 6 cells/mm<sup>3</sup>, sputum examination including Gram, AFB, MAFB, and Wright's stains were negative for microorganisms. Combination antiretroviral therapy (stavudine 30 mg, lamivudine 150 mg, and nevirapine 200 mg twice a day) was started.

One week later, she had chest tightness, and pleuritic chest pain, the pain radiated to left chest wall. She had neither fever nor night sweat. She returned to the district hospital. However, no specific treatment for her chest symptoms was prescribed.

Two weeks later or 1 week before this admission, she complained of dry cough, in addition to pleuritic chest pain and fatigue. She returned to the district hospital and chest computerized tomography was performed and showed a wedge-shaped consolidation, and a thick-smooth wall cavitary lesion in left lower lobe as shown in Figure 2. Multiple mediastinal nodes were noted. She was then referred to our hospital for further investigations.

On admission, her body temperature was 37.3°C, blood pressure 130/70 mmHg, respiratory rate 16/minute, and pulse rate 90 beats/minute. Mild pale conjunctivae and oral thrush were observed. Two palpable left cervical lymph nodes were 0.5 cm and 1.0 cm in size, no tenderness, firm consistency, and movable. Chest examinations were normal. No stiffness of neck and normal neurological examinations were noted.

Laboratory showed hemoglobin 10.4 g/dL, white blood cell 4,100 cells/mm<sup>3</sup> (N 61%, E 5%, L 23%, M 11%), platelet 524,000/mm<sup>3</sup>. Liver function test was as follows: albumin/globulin 2.8/6.5 g/dl, AST/ALT 79/52 U/L, and alkaline phosphatase 204 U/L, total bilirubin/direct bilirubin 0.31/0.07 mg/dl. Oxygen saturation was 99% at room air. The chest X-ray showed patchy infiltration and cavitation at left lower lobe as previously described. Adequate sputum revealed no pathogens on Gram, AFB, MAFB, and Wright's stains. No bacterial and mycobacterial growth from cultures. Serum cryptococcal antigen was negative. The cervical lymph nodes biopsy showed no organisms. Lymph nodes cultured for bacteria, mycobacteria, and fungus

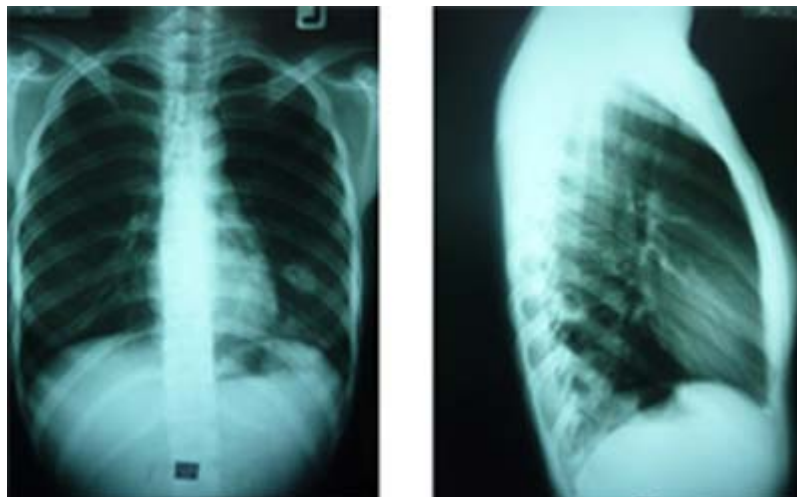
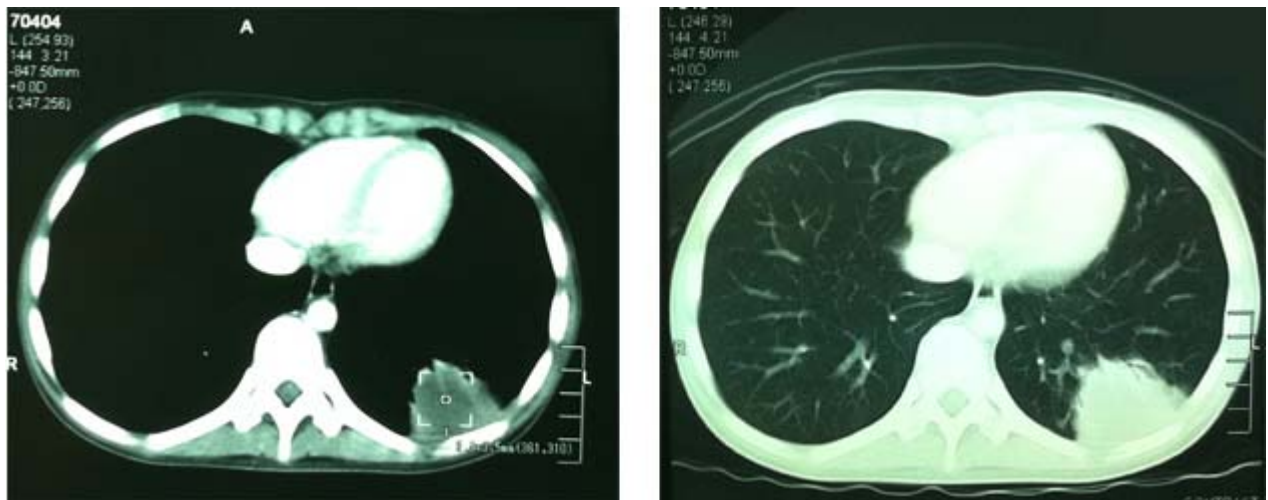
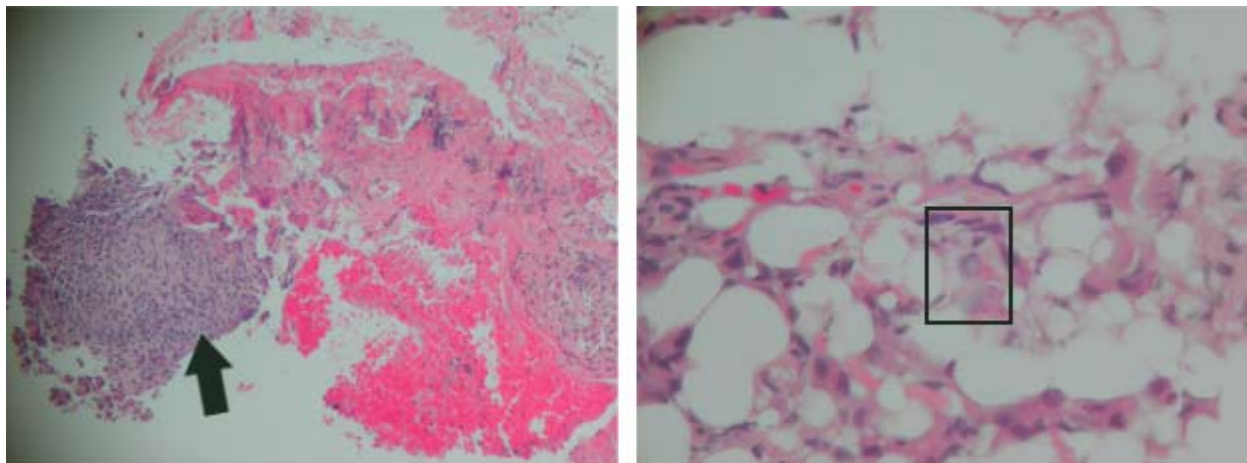


Figure 1. Chest X-ray PA and lateral view three weeks before the admission.



**Figure 2. Computerized tomography 1 week before the admission.**

**Right: non-contrast mediastinal window, Left: contrast lung window**



**Figure 3. Transbronchial biopsy. Right: poorly-formed granuloma (arrow).**

**Left: large encapsulated yeast.**

were all negative. Bronchoscopy was performed. Bronchoalveolar lavage and transbronchial biopsy were done. No organism was found from Gram, AFB, MAFB, and Wright's stains of BAL. Culture of BAL for mycobacteria was no growth, however cultures for bacteria and fungus were not performed. Transbronchial biopsy pathology revealed large budding yeasts with thick capsules. (Figure 3) The pulmonary cryptococcosis was diagnosed. The lumbar puncture was performed to exclude cryptococcal meningitis. Cerebrospinal fluid

analysis was normal. CSF cryptococcal antigen, and fungus culture were negative. Fluconazole 400 mg/day was started. Two months after treatment, at last follow-up, her symptoms including chest symptoms improved, and returned to normal activity.

### DISCUSSION

We presented a possible case of symptomatic isolated pulmonary cryptococcosis in HIV-infected patients. Symptomatic cryptococcosis is uncommon,

although the lung is the portal route of entry. The prevalence of symptomatic cryptococcosis in HIV-infected patients presented with meningitis was around 2%.<sup>1-2</sup> The patients usually had abnormal chest X-ray.<sup>1-2</sup> In addition, only 8.3% of serum cryptococcal antigenemic patients have isolated pulmonary cryptococcosis.<sup>3</sup> The clinical spectrum of pulmonary cryptococcosis depends on host's immune defense, and varies from localized infection to acute respiratory failure.<sup>2</sup>

Pulmonary cryptococcosis is caused by *Cryptococcus neoformans*. More than 30 species are identified, but only 2 species are document as pathogenic yeast, *C. neoformans* and *Cryptococcus gatii*.<sup>1</sup> *C. neoformans* can be found worldwide in the excreta of certain birds, e.g pigeons and tree hollows. *C. gatii* is found mainly in tropical, subtropical area, and reported outbreak in Vancouver, Canada.<sup>4</sup> The yeast form of *C. gatii* is in eucalyptus trees, firs, and oaks. The molecular analysis of capsule is used to divide the *C. neoformans* into 2 varieties (grubii, neoformans) and 3 serotypes (A, D, AD), and to divide the *C. gatii* into 2 serotypes (B, C).<sup>1</sup> In Thailand, serotype A belonging to *C. neoformans* is mostly found, and only 4.3% is serotype B.<sup>5</sup>

Yeast, asexual form, is the natural infected stage to humans by inhalation.<sup>6</sup> The pathogenicity of cryptococcus are polysaccharide capsule, melanin, the capability of fungus growing in the body temperature, and extracellular enzymes e.g lactase, phospholipase B, and urease.<sup>6</sup> The defect of the host defenses also plays an important role in disease development, e.g. HIV infection, use of corticosteroid > 20 mg/days, solid organ transplant, malignancy, connective tissue disease, receiving monoclonal antibodies, diabetes mellitus, chronic pulmonary disease, renal failure, cirrhosis and pregnancy.<sup>1</sup>

In HIV-infected patients, they usually present

with fever, malaise, chest pain, cough (often dry cough), and pleuritic chest pain. Acute respiratory failure is a rare complication.<sup>7-8</sup> Diffuse bilateral interstitial infiltration is the most common radiologic findings. Hilar adenopathy, focal consolidation, and nodular opacity are also frequently found in chest X-rays.<sup>8</sup> In Thailand, reticulonodular infiltration, air-filled in cystic space, and pleural effusion are common.<sup>9</sup>

Serum cryptococcal antigen test is both sensitive and specific to cryptogenemia. The negative serum cryptococcal antigen test virtually rules out cryptococcal meningitis, but could be seen in isolate pulmonary cryptococcosis.<sup>8</sup> Positive serum cryptococcal antigen test needs future evaluation for other organ involvement. Broncho-alveolar lavage fluid, or pleural fluid cryptococcal antigen might be useful for diagnosis.<sup>8</sup>

Identification of yeast in organ or culture is the confirmatory method. Sputum or BAL culture usually establishes the diagnosis. Bronchoalveolar lavage culture is positive in 82% of the cases and more sensitive than transbronchial biopsy (48%).<sup>8</sup> Varying size of encapsulated yeast from 4-8  $\mu$ m in hematoxylin and eosin stain is characteristic findings.<sup>2</sup> In addition, Gomori's methenamine silver is used to identify yeast, whereas mucicarmine/alcian blue is used to identify the capsule of the yeast.<sup>10</sup>

Pulmonary cavitation in HIV-infected patients particularly with low CD4 cell count can be caused by other opportunistic pathogens, e.g. mycobacterial infection, histoplasmosis, penicilliosis, rhodococcosis, nocardiosis, and neoplasms.<sup>11</sup> The organism identification is crucial for making the diagnosis. Due to the lack of culture proven in our case, the definite diagnosis cannot be ensured. However, the pathognomonic feature of encapsulated yeast in H&E stain of transbronchial biopsy as shown in Figure 3 is helpful in making diagnosis in our patient.

Treatment modalities depend on the patient's immunity (compromised, non-compromised) and the extension of disease (disseminated, non-disseminated). Treatment outcome depends on antifungal regimens and duration of treatment.<sup>12-13</sup> Antifungal agents, duration of treatment, and secondary prophylaxis are also different in each group.<sup>12-13</sup> Corticosteroids might be useful in acute respiratory distress syndrome.<sup>12-13</sup> In our case, hemocultures for fungus were negative. Cerebrospinal fluid cultures and cryptococcal antigen titer were negative. Fluconazole 400 mg/day was prescribed and planned to continue for 6-12 months, followed by 200 mg/day for secondary prophylaxis until CD4 is > 100 cell/mm<sup>3</sup> after 1 year of treatment.<sup>13</sup> The patient's symptoms were gradually improved and they returned to normal daily activity at last follow-up (2 months after treatment).

In summary, we reported a case of symptomatic isolated pulmonary cryptococcosis in HIV-infected patient, who presented with lung cavitary lesion. The pulmonary cryptococcosis should be considered in HIV-infected patients, and there also are needs for further identification of other sites of infection. Combination antiretroviral therapy is crucial to raise the CD4 cell count, which enables discontinued antifungal suppressive treatment.

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