Pulmonary cryptococcoma with CD4 lymphocytopenia and meningitis in an HIV-negative patient

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Introduction

Cryptococcus neoformans is a ubiquitous yeast which is usually found in pigeon and chicken excreta. With the increased use of steroid and immunosuppressive agents and the increasing incidence of acquired immunodeficiency syndrome (AIDS), the incidence of cryptococcal disease seems to be increasing (1). Clinically, the most commonly recognized form of cryptococcal disease is chronic meningitis (2). In some post mortem studies, C. neoformans has presented in the lung and the central nervous system with equal frequency (3,4).

The present case report describes a case of pulmonary cryptococcoma with CD4 lymphocytopenia and meningitis, but without HIV infection. Routine cytological examination of sputum and transcutaneous fine needle biopsy provide a judicious assessment to approach this disease. The clinicopathologic features, radiological findings and treatment are discussed.

Case Report

A 74-year-old Chinese male was hospitalized with a history of productive cough with whitish sputum, malaise, mild fever and headache for 2 months. Pulmonary tuberculosis had been diagnosed at a district hospital with adequate treatment 10 years earlier, otherwise there was no significant past medical history.

On admission, temperature was 37.6°C, blood pressure was 120/80 mmHg, pulse rate was 88 beats min⁻¹ and respiration rate was 23 breaths min⁻¹. Physical examination disclosed bibasal expiratory rales; others were unremarkable, including neurological examination. Laboratory data showed Hgb, 10.7 g dl⁻¹; WBC, 4300 cumm⁻¹ with 74% neutrophils, 5% lymphocytes and 9% monocytes; and platelets, 228 000 cumm⁻¹. The serum biochemistry showed sodium, 124 meq l⁻¹; urea nitrogen, 22 mg dl⁻¹; and albumin, 2.7 mg dl⁻¹. The carcinoembryonic antigen (CEA) was 1.9 ng dl⁻¹. The chest roentgenogram (Plate 1) showed nearly total opacification of the right hemithorax and patchy infiltration in the left mid zone.

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Microbiological examinations of the sputum, including TB, bacterial, fungal culture and acid-fast stain, were all negative. A routine cytological examination of the sputum...
PLATE 2. Computed tomographic scanning of the thorax demonstrating a huge mass with extensive necrosis in the right lower hemithorax.

PLATE 3. Cytological examination of sputum showing numerous fungi with ovoid to spherical and focal teardrop shape budding (arrow). (Papanicolaou stain, original magnification × 400).

PLATE 4. Transthoracic fine needle biopsy of the mass showing a few cryptococcal neoformans with a thick and clear capsule (PAS stain, original magnification × 800).

showed no evidence of malignancy, but incidentally found numerous ovoid to spherical, and yeast-like fungal balls with a thick capsule (Plate 3). A transcutaneous fine needle biopsy through different sites of the mass was performed twice and revealed only C. neoformans without any evidence of malignancy (Plate 4).

The serum and cerebrospinal fluid (CSF) cryptococcal antigens were 1:1024 and 1:64, respectively. The lumbar puncture showed normal opening pressure, and examination of CSF revealed no leukocytes and a glucose of 48 mg dl⁻¹. His serum CD4 lymphocyte count was 163 cumm⁻¹ (normal value >400 cumm⁻¹) and human immunodeficiency virus (HIV) was negative. The immunoglobulins were all within normal limits.

After initial diagnostic tests, the patient was started on a regimen of amphotericin B intravenously to a total dose of 7 g which was then discontinued because of azotaemia and vomiting. Subsequently, oral fluconazole 200 mg day⁻¹ was prescribed and the symptoms improved. He was discharged with a prescription for 1 month of fluconazole.

On follow-up 4 months later, there was no relapse and the repeat HIV was negative. His CD4 lymphocyte count recovered to 250 cumm⁻¹. Follow-up chest roentgenogram and chest CT scanning showed that cryptococcoma signs were decreasing.

Discussion

Cryptococcus neoformans is a very common opportunistic fungal infection in immunocompromised patients (5). Especially in AIDS, the gradual deterioration of CD4
lymphocytes seriously impairs the ability to respond to this pathogen. There are many factors other than HIV infection that can influence the CD4 lymphocyte count, including age, infection and chemotherapeutic agents (6). In this HIV-negative patient, the CD4 cell counts were recovered from 163 and 250 cumm \(^{-1}\) after antifungal treatment. However, the CD4 cell count did not return to normal levels. It is, therefore, uncertain whether the low CD4 cell count was secondary to the infection. Patients with idiopathic CD4 lymphocytopenia have been described previously in several studies (7,8), and it is likely that the present patient also belongs to this group.

Although the definite diagnosis of cryptococcal infection depends on the demonstration of a yeast-like organism in pathological or culture findings, the cytological examination may be a better tool to obtain early diagnosis (9). The cytological findings of sputum in an unsuspected case, as reported here, provide a judicious assessment to approach the disease. Transcutaneous fine needle biopsy and transbronchoscopic brushing and biopsy are less invasive diagnostic techniques in the establishment of a definite diagnosis, and help to avoid an unnecessary thoracotomy.

Pulmonary cryptococcoses in radiological findings may be varied widely. Khoury et al. reported that cryptococcal pulmonary disease in immunocompetent patients is predominantly characterized by nodular opacity, whereas the disease in immunocomprised hosts tends to be diffuse infiltration (10). The unusual finding in the present patient was the presence of a huge mass involving the right lower hemithorax. These are virtually adequate to establish the diagnosis of pulmonary cryptococcoma.

Incidences of pulmonary cryptococcoses combined with lung carcinoma have been reported (1). As no malignant cells were found in the sputum, the biopsy or the transbronchoscopic brushing, the certainty of malignancy could be excluded completely. However, this particular clinical manifestation warrants close follow-up.

Pulmonary cryptococcoses is usually accompanied by subclinical or disseminated life-threatening meningitis (5). Headache is an almost universal complaint and the diagnosis is usually made by a culture of the CSF (11). Immunological detection of cryptococcal antigen in the CSF provides an alternative means to establish the diagnosis of cryptococcal meningitis. Saag et al. reported abnormal mental status, a CSF cryptococcal antigen titre of more than 1:1024, and a blood culture positive for C. neoformans as predictive of early death (12). In the present patient, the evidence of cryptococcal meningitis was headache and mild elevated cryptococcal antigens in the CSF. Nevertheless, this did not seem to influence the clinical outcome.

The treatment of pulmonary cryptococcosis with meningitis remains a difficult problem and is discussed in many clinical reports (12,13). Amphotericin B and fluconazole are two well-documented effective primary antifungal drugs used in treating serious cryptococcal meningitis in AIDS (12,13). Although this HIV-negative patient was immunocompromised, the treatment was not complicated. Amphotericin B was used initially, and then fluconazole was used to treat him successfully. After he recovered his immune response, the disease activity decreased, even without further antifungal treatment.

References