Cryptococose Pulmonar num doente imunocompetente.
Revisão do tema a propósito de um caso clínico

Pulmonary cryptococcosis in a immunocompetent patient.
A case report and a review

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RESUMO

A Criptococose é uma infecção relativamente rara causada por um fungo, o Cryptococcus neoformans, que se encontra largamente distribuído por todo o mundo. Após a sua inalação as manifestações clínicas variam desde uma simples colonização pulmonar até uma infecção disseminada e invasiva. A maioria dos casos ocorre em doentes imunodeprimidos sendo a meningoencefalite a principal manifestação da criptococose.

ABSTRACT

Cryptococcosis is a relatively rare infection, caused by the yeast-like fungus Cryptococcus neoformans, an organism with a worldwide distribution. After the inhalation of Cryptococcus neoformans the clinical manifestations range from pulmonary colonization to disseminated invasive fungal infection. Most cases occur in immunocompromised patients and meningoencephalitis is the most common manifestation of cryptococcosis.
INTRODUCTION

Cryptococcosis is a rare chronic, subacute to acute infection that causes three major forms of disease: central nervous system (CNS), pulmonary, and disseminated infection. A truly cosmopolitan fungus, *Cryptococcus neoformans*, recognized to cause human infection on all five continents causes this disease. In contrast to other fungal diseases such as histoplasmosis and coccidioidomycosis, which are endemic in well-defined regions, cryptococcosis is ubiquitous.

*Cryptococcus neoformans*, an encapsulated yeast, with variable size and shape (round to oval) (1) was originally described as a human pathogen in 1894, as cited by Cameron and Perfect (2) and is classically associated with desiccated pigeon feces, although the organism can be found in the feces (3) of other birds including turkeys and starlings as well as in bat feces. Soil often contains *Cryptococcus*, especially if it is contaminated with bird droppings.

Cryptococcosis is acquired by inhaling aerosols containing the yeast; it rarely occurs as a consequence of direct inoculation. *Cryptococcus* does not appear to spread directly from person to person (4). Once in the alveoli, propagation of the yeast begins by binary fission, and the organism reacquires its characteristically large polysaccharide capsule. *Cryptococcus* is unique among the pathogenic fungi in expressing an extensive polysaccharide capsule, which is primary determinant of virulence in vivo (5). This capsule is strongly antiphagocytic, and its presence inhibits chemotaxis. In many healthy individuals, there is a little cellular response, and the organism grows as a mass of gelatinous material; in others, abundant granuloma formation occurs, and the number of organism is small. The fungus produces no toxins, and there is very little tissue destruction.

Although yeast can be isolated from the respiratory tract of immunocompetent hosts, *C. neoformans* is not considered normal respiratory flora in either humans or animals (6).

Primary infection with *Cryptococcus neoformans* usually follows inhalation of the fungus with infection of the lungs. A transient colonization of the tracheobronchial tree may result, or more extensive pulmonary involvement may develop. Cryptococcal infection results in self-limited pulmonary disease in most healthy persons. Occasionally, isolated pulmonary cryptococcosis is diagnosed (7). The final result of pulmonary cryptococcal infection may be a cryptococcoma or a residual pulmonary nodule (8).

After some time in the lungs, the organism hematogenously spreads to extrapulmonary tissues; since it has a predilection for the CNS, infected persons usually contract meningencephalitis (9), which is the most commonly recognized manifestation of cryptococcosis and the most common cause of death from cryptococcal infection (10). The prostate, kidneys, lymph nodes, bone and skin may be involved in disseminated cryptococcosis, in fewer than 25% of cases.

This article reports the case of an immunocompetent patient that presented a mass on chest radiograph, strongly suspicious to be malignant.
CASE REPORT

A 38 year-old Chinese smoker (20 pack-years) male was sent in June 1996 to the outpatient Department of Pulmonology of Centro Hospitalar Conde S. Januário because had an abnormal chest radiograph. He had experienced dry cough and recurrent frontal pulse-like headache with dizziness since March 1996. He also reported a right chest pain for few days and a 3-4 kg weight loss. He denied dyspnea, hemoptysis, fever, chills and night sweats. He had no history of alcohol or drug use, HIV risk factors and had no known contact with an active tuberculosis patient. Social history was noncontributory.

Several practitioners prescribed him a non-steroid anti-inflammatory that relieved the headache. After a chest radiograph, that showed an abnormal image, he was referred to our hospital.

He had been employed as a blacksmith during several years.

On physical examination his temperature, pulse, and respiratory rate were within normal ranges. Lung auscultation revealed slight decrease of breath sounds at the right posterior lower lung field. No lymphadenopathy was palpatble and the neurologic examination showed no alterations.

Laboratory studies were normal, except mild leukocytosis (13.300 cells/mm3 with 72% neutrophils), and increased erythrocyte sedimentation rate (81 mm/h). The HIV1 and 2 serologic tests were negatives.

The chest radiograph showed a well-demarcated mass in the right lower lobe with occlusion of the right costo-diaphragmatic angle. There was no hilar or mediastinal adenopathy (Fig.1).

Computed tomography (CT) of the chest (Fig.2) showed a 5x 6-cm mass of heterogeneous density in the right lower lobe. A CT scan of abdomen and brain did not disclose any abnormalities.

The examination with a bronchofiberscope revealed slight redness of the mucous on posterior basal segment of right lower lobe bronchus. The biopsy specimen of the mucous demonstrated inflammatory signs. All cultures of the lavage fluid were negative and cytological examination of the lavage cell showed no evidence of malignancy.

A percutaneous fine-needle aspiration was performed under fluoroscopic, and three specimens were obtained which showed an oval-shaped yeast, with
50µm diameter, that was uniformly positive with the Grocott methenamine silver (GMS) method (Fig. 3) and strongly positive with mucicarmine (Fig. 4) suggestive of *Cryptococcus neoformans*.

The patient was treated with amphotericin B (0.3 mg/kg/day), and 5-flucytosine (100mg/kg/day) over 6 weeks. He was switched to oral fluconazol (400mg daily) for three more weeks. The dimensions of the

![Fig. 3](image-url) - Fine-needle aspiration showing an oval-shaped yeast, that was uniformly positive with Grocott's methenamine silver nitrates (GMS) method staining

![Fig. 4](image-url) - Mucicarmine stain showing densely staining cell wall and almost perfectly round shape, characteristic of *Cryptococcus neoformans*
mass markedly decreased (Fig. 5) but the patient underwent excision of the mass because medical treatment could not completely eradicate the infection.

**DISCUSSION**

A rare disease before the HIV epidemic, cryptococcosis was identified very early in the epidemic as one of the most common life-threatening infections in AIDS patient's (11).

Although the prevalence of *C. neoformans* in pulmonary specimens is rare, the significance will depend mostly on the immune status of the host, the virulence of the *C. neoformans*, and the size of the inoculum (12). The main morbidity in cryptococcal infection comes from the dissemination of the fungus beyond the confines of the lung.

*C. neoformans* is strongly tropic for the CNS, and the vast majority of clinically recognized infections involve the meninges.

Cryptococcal infection can affect people with intact immune system, although it is diagnosed most often in persons with underlying immune defect (13). *Cryptococcus* causes disease in immunocompromised hosts as well in apparently immunocompetent (14,15) like this case illustrates.

The predisposing conditions reflect the fact that T-cell-mediated immunity is the most important mechanism of defense against *Cryptococcus* (16). Once a certain amount of *Cryptococcus neoformans* is inhaled it will form a polysaccharide capsule. The capsular polysaccharide has been shown to interfere with the attachment of phagocytic cells to cryptococci and will induce T-cell suppression of both the cell-mediated and antibody response to the organism. In most individuals, the symptoms are self-limited as polymorphonuclear leukocytes can kill the cryptococci before they capsule. In the immunocompromised individuals, the organism in the lung will cause a mild inflammatory response. In this patient we do not found any predisposing factors to the cryptococcal infection.

Approximately 80 to 90% of cases of cryptococcosis are identified in hosts with advanced HIV infection (17,18).

Other well-described causes of immunosuppression include long-standing immunosuppressive treatment regimens, organ transplantation, Hodgkin’s and non-Hodgkin’s lymphoma, leukemia, diabetes mellitus, and liver disease such as cirrhosis (12). The infection there appears to be no race-related predilection but has been diagnosed in two to three times as many males as females and typically occurs in adults (4). The fungus demonstrates no endemic pattern of distribution (19).

Temperate climates are the primary location for this encapsulates fungus that is believed to lead to cryptococcosis following inhalation of the organism (20). Pulmonary infection can be asymptomatic and subclinical, mild and self-limited, or severe and progressive (4). The majority of patients with clinical symptoms are immunocompromised (2,4). In immunocompetent patients, cryptococcal infections usually are limited to the lung; disseminated disease is rare (2,4). Primary pulmonary cryptococcosis was first reviewed by Campbell in 1996 (21). In this case series, only 20% had positive sputum culture. Approximately one-third of hosts are asymptomatic, while the other two thirds present with symptoms such as
cough, chest pain, sputum production, fever, weight loss, and hemoptysis.

In another series (22) individuals nonimmunocompromised with the pulmonary form developed symptoms in about one-half of the cases while the remaining patients were discovered to have cryptococcosis only after evaluation of an abnormality discovered on routine chest radiographic examination. Cough, mild sputum production, and low-grade fever may be the only manifestation of initial exposure to \textit{C. neoformans}.

In contrast to nonimmunocompromised patients, most patients with AIDS and pulmonary cryptococcosis have symptoms of fever and cough (23). Immunosuppressed patients with pulmonary cryptococcosis commonly (in about 80\% of cases) develop meningoencephalitis (7).

Radiographic manifestations of pulmonary infection ranges widely and depend on both the immune status and type of \textit{C. neoformans}. Well-defined nodular (single or multiple) infiltrates or well-defined patchy infiltrates are commonly seen in the normal host (22). Diffuse pulmonary disease associated with diffuse interstitial infiltrates, or widespread alveolar consolidation is more commonly seen in AIDS patients or in those who are severely immunodeficient (24,25). Mass lesions, as seen in our patient, are not uncommon and may resemble malignancy. Pleural effusion is rare. Cavitation is uncommon, and mediastinal adenopathy, pleural effusion, and calcification are rare. Empyema, pneumothorax and pleural involvement suggesting a Pancoast’s tumor have been reported (26,27,28). Miliary pattern in a patient with the AIDS was described by Douketis (29).

Diagnosis of cryptococcal pulmonary infection requires isolation of the organism from pulmonary secretions or tissues or visualization in histopathologic specimen (30). Sputum cultures are unreliable for establishing the diagnosis because \textit{C. neoformans} can colonize the upper airway of uninfected patients, and cultures may be negative even with an active infection (3). The diagnosis by fine needle aspiration, has been previously described (31), may be necessary to confirm the diagnosis of pulmonary infection. The diagnostic yield of fine needle aspiration, in cases like our patient, has been shown to be higher than that of bronchoscope with biopsy (32).

Cryptococci may be difficult to visualize on routine hematoxylin-and-eosin-stained sections, although identification of the organism can be enhanced by use of appropriate special stain (30). The diagnosis is based on the strongly positive Mayer’s mucicarmine, Grocott’s Methenamine Silver or Perodic acid-Schiff staining of the organism in the tissue (33). Increased cryptococcal antigen titers (1:8 or more) are indicative of high burden of organism in the lung or of disseminated infection or both (2). Direct cryptococcal antigen determinations on lung aspirates (34), brochoalveolar fluid (35), pleural effusion (36), serum (37), have also previously been utilized in the diagnosis of pulmonary cryptococcosis. In a recent review (38) Aberg and colleagues concluded that in the majority of the patients with pulmonary cryptococcosis who are not HIV-infected, the lung appeared to be the sole organ involved, and a workup for systemic infection was rarely helpful.

As the treatment of pulmonary cryptococcosis has not been the subject of extensive study, recommendations regarding therapy for this form of cryptococcal infection must be inferred from treatment regimens used for meningitis (30). Patz et al (39) and Kerkring (40) suggest that isolated pulmonary infections in immunocompetent patients does not require antifungal therapy. Amphotericin B and Fluycytosine for at least 6 weeks have been considered standard for patients without HIV infection. Beyond medical management surgical treatment is considered in those patients with localized disease (41) and/or has no response to medical treatment.

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