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Intra-cavitary pulmonary cryptococcoma in poorly controlled diabetes mellitus

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ABSTRACT

A 59-year-old HIV-negative Ugandan man presented with a long-standing history of respiratory symptoms and was found to have an intra-cavitary pulmonary cryptococoma by chest imaging and sputum culture. The serum cryptococcal antigen was negative. The sputum Xpert® MTB RIF Ultra assay was negative. He was previously treated for cavitary pulmonary tuberculosis. The patient had poorly controlled diabetes (HbA1c, 9.3%). The patient was successfully treated with oral fluconazole.

1. Introduction

Cryptococcal infections (cryptococcosis) refers to a spectrum of clinical syndromes caused by the opportunistic yeasts, *Cryptococcus neoformans* and *Cryptococcus gattii* [1,2]. These syndromes include but are not limited to cryptococcal meningitis, pulmonary cryptococcosis, cutaneous cryptococcosis and asymptomatic cryptococcaemia [3]. Meningitis is the commonest and most lethal form of cryptococcosis worldwide with HIV/AIDS as the most important risk factor [4]. However, isolated pulmonary cryptococcal disease commonly occurs in apparently immunocompetent individuals and is often non-specific in its clinical and radiological picture, thus its diagnosis is not straightforward. Patients frequently have subclinical features or may present with non-specific symptoms such as productive cough, chest pain, hemoptysis, fever, fatigue and chest discomfort [5–10].

Radiological findings of pulmonary cryptococcosis are often non-specific and may include, single or multiple nodules, masses, cavities, effusions or diffuse parenchymal infiltrates [6,11]. Cavitary pulmonary cryptococcosis often mimics other infectious and non-infectious cavitary pulmonary diseases such as lung abscesses, lung cancer, cavitary pulmonary aspergillosis, and pulmonary tuberculosis (PTB), creating a diagnostic dilemma [6,12,13].

Herein, we present a case of intra-cavitary pulmonary cryptococcoma occurring in a poorly controlled diabetes mellitus patient initially misdiagnosed as smear negative PTB.

2. Case

We admitted a 59-year-old Ugandan man in the pulmonology unit of Mulago National Referral Hospital, Kampala, Uganda presenting with a 2-year history of intermittent productive cough associated with occasional hemoptysis, left-sided chest pain and constitutional symptoms of low-grade fevers and weight loss. There was no history of drenching night sweats. Three months prior to admission, he started having frank hemoptysis associated with easy fatigability, exertional dyspnea, palpitations and generalized body weakness. There was no history of orthopnea, paroxysmal nocturnal dyspnea or lower limb swelling. Because of his worsening respiratory symptoms and despite a negative microbiologic work up for PTB (i.e. negative sputum microscopy and a negative Xpert® MTB RIF Ultra), he was empirically started on *anti*-TB medications from a regional referral hospital on a “clinical” basis. However, he progressively worsened while on *anti*-TB treatment leading to a decision to withhold his PTB treatment and prompting a referral to our centre, a national referral hospital for further evaluation and management. His past medical history was significant for diabetes mellitus diagnosed at the age of 56 (3 years prior to current admission). His high blood sugar was initially managed on metformin for 2 years and later switched to subcutaneous insulin due to poor glucose control. At the time of diabetes diagnosis, he was diagnosed and treated for bacteriologically confirmed PTB. He completed his TB treatment and was declared cured.

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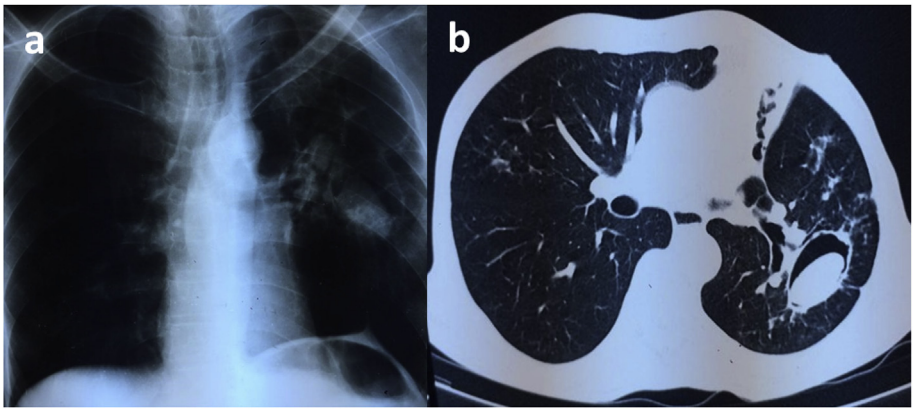

Fig. 1. a) Chest xray showing left apical cavitation and features of pulmonary fibrosis. **b)** Chest CT scan showing a cavity on the left upper lobe containing an ovoid soft tissue density mass with a crescenteric lucency superior to the mass. There appears to be a volume loss on the ipsilateral lung with a compensatory hyperinflation on the right seen crossing the midline anteriorly. The bronchial walls of the bronchi arising from the left hilum are dilated.

On examination (day 0), he was moderately wasted, had mild pallor of mucous membranes and grade 4 digital clubbing. He was afebrile – axillary temperature of 36.7° Celsius (normal), blood pressure 128/87 mmHg (normal), pulse rate 93 beats per minute (normal) and respiratory rate of 22 breaths per minute (tachypnea). Chest examination revealed mild respiratory distress, dull percussion note and amphoric breath sounds in the left infra-mammary regions.

At the bedside (day 0), his fasting blood sugar was 15.0 mmol/l (high) and a random sugar later in the day was 22.3 mmol/l (high). His hemoglobin was 10.0g/dl (low) with a mean corpuscular volume of 69 fL (low, microcytic anemia). The platelets and total white cell counts and differentials were within normal limits. Liver and renal function tests were normal. On day 2, repeat sputum Xpert® MTB RIF Ultra assay was negative and he was also found to be HIV negative using antibody tests. However, his Chest x-ray showed left apical cavitation and features of pulmonary fibrosis (Fig. 1a). A day later (day 3), we performed a contrasted chest CT-scan that showed a fungal ball with positive crescent sign (Fig. 1b).

Our differential diagnoses were chronic cavitary pulmonary aspergillosis with a fungal ball, pulmonary mucormycosis and a pulmonary cryptococoma. Both serum *Aspergillus*-specific IgG/IgM (LD Bio, Lyon, France) and cryptococcal antigen (CrAg) (IMMY, Oklahoma, USA) point-of-care tests were negative (day 3). High volume culture of spontaneously expectorated sputum on Sabouraud dextrose agar yielded creamy, moist colonies (day 6) (Fig. 2a). Light microscopy of the isolates demonstrated encapsulated budding yeasts positive with India ink and consistent with the morphological identification of *Cryptococcus* species (Fig. 2b).

We were unable to perform molecular assays and serum beta-d glucan since they are not available in our settings. On day 9, his glycosylated hemoglobin (HbA1c) came out as 9.3%. We diagnosed intracavitary cryptococcoma complicating previously treated cavitary PTB in poorly controlled diabetes mellitus.

For his treatment, we optimized his glucose lowering agents and also commenced ferrous sulphate and folic acid for the mild anemia. We commenced him on oral fluconazole 400mg once daily for a period of 6 months with excellent clinical and radiological responses.

3. Discussion

Cryptococcosis is primarily a pulmonary disease acquired through inhalation of desiccated yeasts of *Cryptococcus* species [2]. Systemic disease results from reactivation of latent pulmonary disease in severely immunocompromised patients [5]. However, isolated pulmonary cryptococcal disease can also occur in immunocompetent or subtly immunocompromised states, especially those with poorly controlled diabetes mellitus, alcoholism, or patients on immunosuppressive agents such as chronic corticosteroid therapy [6,12,13]. We demonstrate the use of high volume sputum culture in the diagnosis of pulmonary cryptococcosis in a patient with a negative serum CrAg. This has not been described before.

Primary pulmonary cryptococcosis is diagnosed based on clinical presentation, radiographic findings, sputum culture and antigen testing [2]. Clinically, it may be totally asymptomatic or may present with non-specific symptoms such as cough, hemoptysis, chest pain, dyspnea and fever [6]. As seen in the present case, physical examination may be unremarkable or may reveal evidence of consolidation, or pleural effusion [14,15].

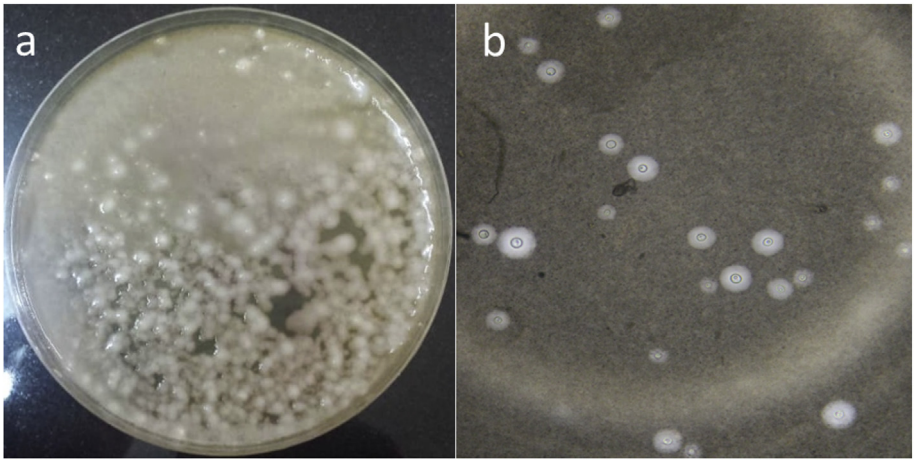

Fig. 2. a) High volume sputum culture plate with Sabouraud dextrose agar showing creamy, moist colonies. **b)** Image of a positive India ink preparation showing encapsulated budding yeasts of *Cryptococcus* species.

Radiologically, pulmonary cryptococcosis may mimic other infectious and non-infectious pulmonary disease presenting as nodules, cavities, pleural effusions, consolidations and pulmonary infiltrates on chest x-ray and/or CT scan [6,11]. Diagnosis is usually confirmed by cultures obtained from sputum, bronchial lavage, pleural effusion or tissue biopsy in patients with clinical or radiographic suspicion [1,2]. CrAg test on an appropriate specimen is a highly sensitive and specific microbiological tool, so is used to establish diagnosis of cryptococcaemia and cryptococcal meningitis [14]. However, as observed in the present case, serum CrAg test is often negative in patients with isolated pulmonary cryptococcosis [14]. Histopathological examination of stained tissue biopsy specimens from CT guided transthoracic fine needle aspiration biopsy, *trans*-bronchial biopsy, surgical lung biopsy and pleural biopsy reveals encapsulated budding yeasts on light microscopy which is also diagnostic [1,2].

Treatment of cryptococcosis varies based on disease involvement and host factors. For primary pulmonary cryptococcosis, oral fluconazole 400mg daily for 6–12 months is the recommended first-line of therapy for symptomatic patients [1]. Itraconazole (200mg twice per day, orally), voriconazole (200mg twice per day, orally) or posaconazole (400mg twice per day, orally) are acceptable alternatives if fluconazole is not available or contraindicated [1,16]. Intravenous amphotericin B is reserved for those with very large and multiple cryptococcomas [1,16]. Within six months of treatment with oral fluconazole, our patient improved clinically and the intra-cavitary mass reduced in size. This is consistent with previously reported cases of pulmonary cryptoccosis in patients with diabetes [12,13].

In immunocompromised patients with a positive serum CrAg, meningitis should be ruled out by performing a lumbar puncture [1]. Surgery should be considered for cases with persistent radiographic abnormalities, obstruction of vital organs and in those with refractory symptoms or non-reducing fungal ball size despite at least 1 month of anti-fungal therapy [1,16]. Patients with isolated pulmonary cryptococcosis generally have a good prognosis. In a cohort study, none of the pulmonary cryptococcosis patients had relapses, developed a disseminated disease or died [17]. However, patients with extrapulmonary involvement tend to have a poorer prognosis. In one study, about one-third of patients with pulmonary cryptococoma who had concomitant meningitis or peritonitis developed respiratory failure which lead to death in about 55% of the patients [18].

In conclusion, pulmonary cryptococcosis clinically and radiologically mimics a number of benign and malignant lung conditions. Pulmonary nodules are the most common forms of pulmonary cryptococosis and patients are often asymptomatic. Serological tests and culture of respiratory samples have low sensitivities for pulmonary cryptococcosis, leading to under diagnosis. The absence of a validated point of care diagnostic tools that can detect CrAg in respiratory samples is a substantial gap in the management of pulmonary cryptococcosis in resource-limited settings where advanced molecular assays are not available.

Declaration of competing interest

There are none.

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