Case Report

Invasive Pulmonary Cryptococcal Infection Masquerading as Lung Cancer with Brain Metastases: A Case Report

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Abstract

Cryptococcosis, a global disease problem, seen frequently in the immuno-suppressed, also affects patients without apparent immuno-suppression. Pulmonary cryptococcosis patients often present as cryptococcal pneumonia, whereas intracranial cryptococcosis presents with meningitis. We present a 33-year-old immunocompetent man, diagnosed with invasive pulmonary cryptococcal disease with spread to the brain. This case is unique because the patient was previously treated for tuberculosis and presented with typical bronchopulmonary thoracic, extra-thoracic as well as computed tomography (CT) scan features suggestive of lung cancer. Cryptococcosis was diagnosed by identification of oval thick-walled yeast on histology of lung biopsy specimen. The patient was treated with flucytosine and fluconazole initially and subsequently with Amphotericin B and fluconazole. He made clinical improvement with the resolution of symptoms but had residual radiological features. Invasive cryptococcosis affecting the lung and brain may present with a clinical picture similar to metastatic lung cancer. We recommend routine fungal stains and fungal culture in suspected cases.

Keywords: *Bronchogenic cancer, case report, cryptococcoma, invasive cryptococcal disease*

Résumé

La cryptococcose, une maladie mondiale, fréquemment observée chez les sujets immunodéprimés, affecte également les patients sans immunodépression apparente. Les patients atteints de cryptococcose pulmonaire se présentent souvent comme une pneumonie cryptococcique tandis que la cryptococcose intracrânienne se présente avec une méningite. Nous présentons un homme immunocompétent de 33 ans, diagnostiqué avec une maladie pulmonaire invasive cryptococcique avec propagation au cerveau. Ce cas est unique car le patient a déjà été traité pour tuberculose et s'est présenté avec des caractéristiques bronchopulmonaires thoraciques, extra-thoraciques ainsi qu'une tomodensitométrie (TDM) typiques suggérant un cancer du poumon. La cryptococcose a été diagnostiquée par l'identification d'une levure ovale à paroi épaisse sur l'histologie d'un échantillon de biopsie pulmonaire. Le patient a été traité initialement par Flucytosine et Fluconazole, puis par Amphotéricine B et Fluconazole. Il a fait une amélioration clinique avec la résolution des symptômes mais avait des caractéristiques radiologiques résiduelles. La cryptococcose invasive affectant le poumon et le cerveau peut présenter un tableau clinique similaire au cancer du poumon métastatique. Nous recommandons des colorations fongiques de routine et une culture fongique dans les cas suspects.

Introduction

Cryptococcus neoformans and *Cryptococcus gattii* are the two pathologic species responsible for cryptococcosis. The most common risk for cryptococcosis caused by *C. neoformans* is acquired immune deficiency syndrome (AIDS), whereas infections caused by *C. gattii* are more often reported in immunocompetent patients. The environmental source of *C. neoformans* is exposure to pigeon nests and droppings, whereas the environmental source of *C. gattii* is exposure to Eucalyptus camaldulensis trees.

It is the third most common invasive fungal infection in transplant recipients and accounts for 8% of invasive fungal infections.[1,2] About 1 million cases of Cryptococcosis occur throughout the world and an estimated 650,000 associated deaths occur annually.[3] Most of these cases occur in patients with advanced HIV. *Cryptococcus neoformans* causes a high proportion of cases of meningitis among HIV-1-infected patients in sub-Saharan Africa; the associated high case-fatality rate reflects the absence of affordable treatment

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as well as possible diagnostic index. The greatest burden of cryptococcosis occurs in sub-Saharan Africa, where mortality is estimated to be 50% to 70%.[4]

Systemic disease is contracted by inhalation of the desiccated yeast which leads to a primary pulmonary infection.[5] This can remain latent for extended periods of time, but can re-emerge and disseminate if the host becomes immunocompromised. Upon dissemination the organism shows particular tropism for the central nervous system (CNS), frequently causing fatal meningitis.[6]

We report the case of an immunocompetent young man who presented with features of a right lung mass and CNS manifestations that mimicked a metastatic lung cancer with intra-cranial space-occupying lesion. These features contrasted with the typical presentation of *Cryptococcal pnemonias* and *Cryptococcal meningitis*.

Case Report

A 30-year-old male presented to us in March 2017 with complaints of recurrent headache of a year's duration, progressive weight loss of about 3 months duration, persistent difficulty in breathing and cough of two months, and dizziness of a month's duration.

He described the headache as recurrent, initially frontal but later occipital, throbbing, with radiation to the neck, and associated blurred vision, dizziness, weakness of the left limbs, and seizures. The seizures were generalized tonic-clonic and he had had four episodes prior to presentation, with each episode lasting less than five minutes.

He complained of intermittent fever, cough which was associated with hemoptysis and he had dyspnea on exertion. He did not have any clinical evidence suggestive of congenital or acquired immunodeficiency. He had a history of two pack-years of tobacco use but had stopped smoking about 10 years earlier. He was treated for pulmonary tuberculosis about 2 years prior to presentation.

On examination, he was conscious, ill-looking, and cachectic. He was febrile with a body temperature of 38.5°C. His pulse rate was 130 beats per minute, regular and of good volume; and the blood pressure 164/126 mm of mercury. There was dullness to percussion in the right middle lung zones, with diminished breath sounds over the same areas. He also had left-sided hemiparesis and ataxia. Power on the left side was 3/5.

His full blood count (FBC); electrolytes, urea, and creatinine (EUCr); and liver function tests (LFTs) were normal. He had negative ELISA HIV tests and hence, HIV viral load and CD4 count were not done. A chest X-ray showed a large mass in the right middle lung zone extending to the hilum. Further evaluation with chest CT [Figure 1] scan confirmed the presence of a mass infiltrating the right upper and middle lung lobes. The mass measured 10 cm × 10 cm in its widest diameter.

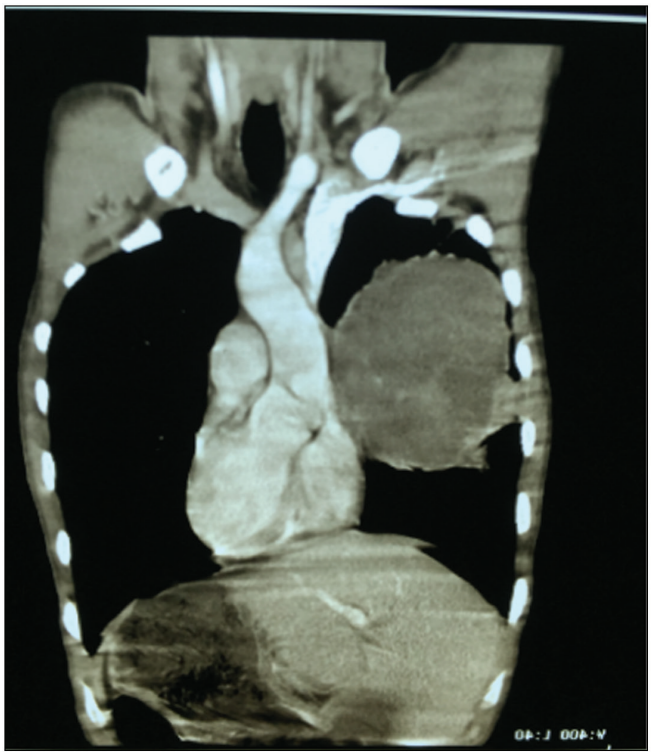

Figure 1: Chest CT: Reconstructed view showing mass in the right upper lung with attachment to the mediastinum and chest wall (original)

In view of his neurological presentation, he had brain CT [Figure 2] which revealed a 5 cm × 4 cm intracranial mass in the posterior cranial fossa with perilesional edema.

Provisional diagnosis at this time was metastatic lung cancer with intracerebral metastases. Due to the lack of less invasive means, open surgical lung biopsy was done to obtain tissue for histological characterization of the tumor. Histology of the specimen obtained revealed the presence of interstitial mononuclear infiltrate, numerous foamy macrophages, and granuloma formation with congested capillaries, focal fibrosis, and thickening of the interstitial alveolar septa. Lying freely within the tissue were numerous oval-shaped, thick-walled yeast cells compatible with *Cryptococcus* spp. [Figures 3 and 4].

Fungal culture of pulmonary masses was not routine in our practice at the time of management of this patient and hence it was not done. Moreover, the lung biopsy specimen had been fixed in formalin and thus was not suitable for fungal culture. We opted for special histochemical staining. Periodic Acid Schiff (PAS) staining was strongly positive for fungal cell walls, further supporting our diagnosis. Immunohistochemical stains for cytokeratin 5/6, thyroid transcription factor 1, and lymphoma markers were negative.

He was treated with oral flucytosine 1500 mg 6 hourly and intravenous fluconazole 800 mg once daily initially, as Amphotericin B was not readily available. He had this regimen for 7 days. When it became available, he was treated with 14 days of intravenous Amphotericin B 50 mg daily before he

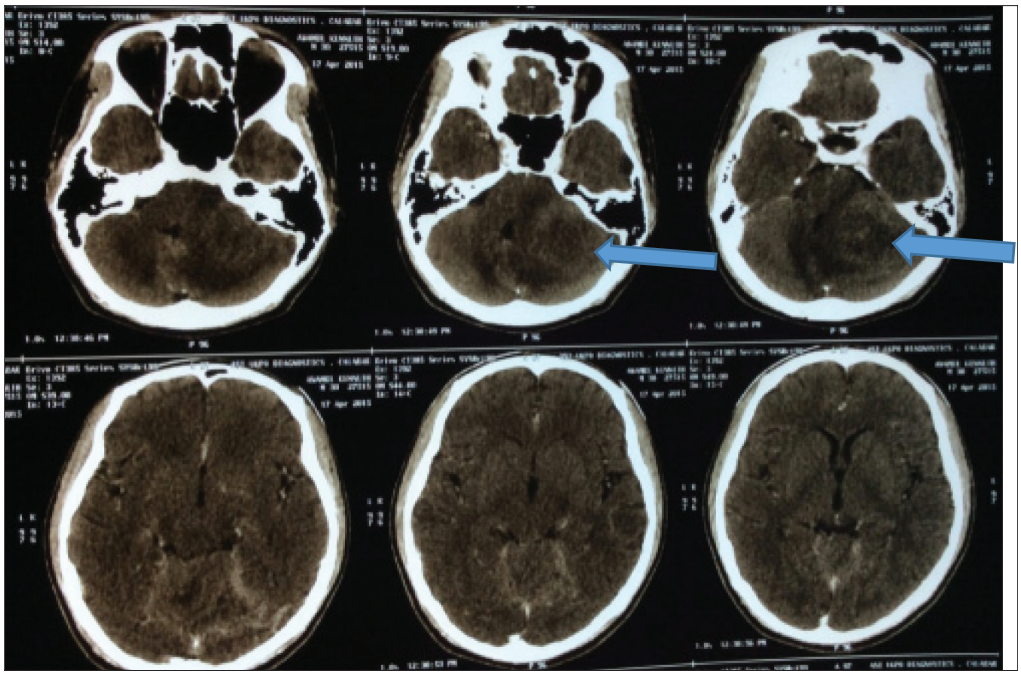

Figure 2: Brain computerized tomography scan showing intracranial mass (arrowheads) (original)

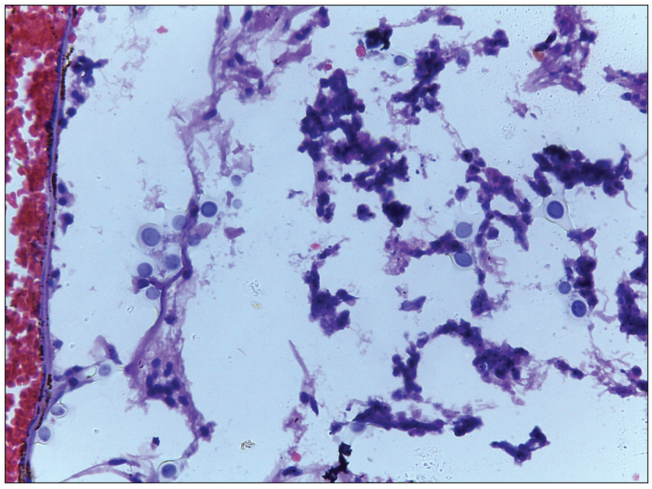

Figure 3: Photomicrograph showing thick-walled fungal organisms lying freely with little inflammatory background (original)

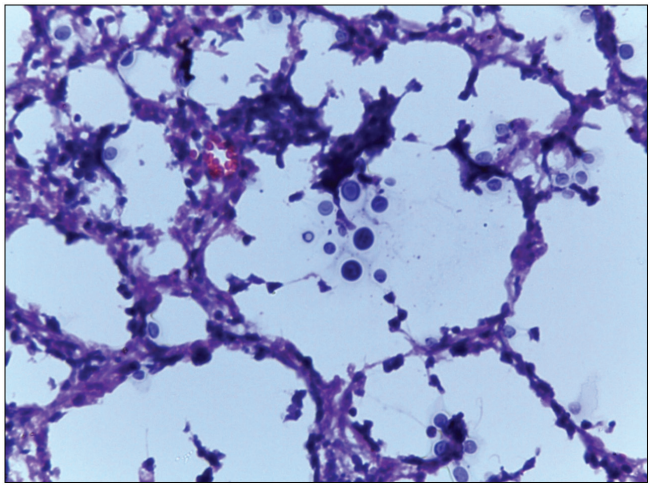

Figure 4: Showing relationship of yeast with alveoli (original)

was transitioned again to oral flucytosine 1500 mg 6 hourly and oral fluconazole 400 mg daily for 8 weeks, then fluconazole 200 mg daily for 6 months. On completion of this treatment, both pulmonary aspirate and cerebrospinal fluid (CSF) cultures were negative for fungal growth; however, there was residual radio-opacity in the lung. His renal and LFTs were monitored during the 8 weeks of induction and treatment. His LFT and EUCr results remained normal during this time.

He made significant clinical progress with the resolution of hemiparesis and cerebellar ataxia. He had an ipsilateral empyema thoracis with empyema necessitans and spontaneous bronchopleural fistula 18 months after antifungal treatment. This was managed using a chest tube. Culture of the pleural aspirate yielded growth of multi-drug resistant Klebsiella sensitive to Amikacin but there was no fungal growth. His general condition improved evidenced by weight gain. He has been followed up for 3 years with no recurrence of symptoms.

Discussion

Infection with *Cryptococcus neoformans* generally affects immunocompromised individuals, although cases have been reported in individuals with no apparent underlying immunodeficiency. Most of the cases occur amongst patients with advanced HIV disease, solid organ transplant recipients, patients receiving large doses of exogenous glucocorticoids, cytotoxic chemotherapy or biologic immunomodulating therapies and patients with primary and secondarily acquired immunodeficiency states. A high index of clinical suspicion is necessary in the appropriate clinical setting to facilitate targeted

investigation and timely diagnosis. Fungal cultures of lung biopsy specimen should be routine in patients who are at risk.

The case presented is that of a young, HIV-negative male who presented with disseminated cryptococcosis confirmed on lung tissue biopsy. He presented with bronchopulmonary symptoms which could be ascribed to lung cancer. His additional symptoms of dizziness and ataxia were attributable to intracranial metastases. The finding of intrapulmonary and intracranial masses masqueraded as lung cancer with brain metastases. The clinical presentation of this patient is unusual. He had features of pulmonary mass and intra-cranial space-occupying lesion in the absence of overt pneumonia and meningitis which are typical features of pulmonary and CNS cryptococcosis, respectively. Management was hampered by a lack of bronchoscopy and video-assisted thoracoscopic surgery (VATS) which necessitated open biopsy procedure in an effort to establish a histological diagnosis. Minimally invasive procedures such as bronchoscopy and VATS could have prevented open thoracotomy for biopsy which is a major surgery. This practice of open thoracotomy for biopsy of lung masses is not unusual in many health facilities in low- and middle-income countries.

The virulence of *Cryptococcus* is attributed to the polysaccharide capsule, the presence of lactase, phospholipase B, and inositol phosphosphingolipid-phospholipase enzymes. The presence of melanin and mannitol directly correlates with resistance to osmotic, heat, and oxidative stress.[6]

In the immunocompetent host, acute infection may present as a pneumonia manifesting with fever, fatigue, cough, and sputum production. In immunocompromised patients, severe symptoms including fever, cough, and shortness of breath are key manifestations.

In humans, *C. gattii* infection occurs dominantly in immunocompetent patients in whom the most common clinical presentation was meningoencephalitis followed by pulmonary infection. Compared to patients with *C. neoformans* infections, patients with *C. gattii* infections were more likely to have a CNS or pulmonary cryptococcoma and to undergo surgical procedures to treat this complication. *Cryptococcus gattii*, an emerging agent of cryptococcosis, was initially reported only in tropical and subtropical zones, but has subsequently been reported in a much less restrictive geographical region of China.[7]

A multicenter retrospective study of pulmonary cryptococcosis from China reported pulmonary cryptococcosis as the third most prevalent fungal lung infection in their series.[8] Interestingly most of their patients had no apparent underlying disease much like our index patient. Our patient also had a history of previous treatment for pulmonary tuberculosis. This calls to question if the pulmonary cryptococcal and tuberculous infections were a coinfection or a sequential infection. Pulmonary cryptococcal and tuberculous coinfection in a patient on antiretroviral therapy has been reported in a Nigerian patient.[9] It would appear that our patient presented at a very late stage of his illness with a large mass causing respiratory distress alongside neurological features most likely due to the space-occupying cryptococcoma noted on brain computerized tomography scan.

Pulmonary cryptococcosis may show as a variety of radiological features. Chest CT features may report solitary or multiple pulmonary nodules which could be smooth or speculated. It could also present as focal or multifocal airspace consolidation[10] in the immunocompetent, whereas cavitation and the presence of the halo sign are more commonly seen in immunocompromised hosts. Our patient did not have these typical CT features. Liu *et al.*[8] had noted that pulmonary lesions were mainly seen in the peripheral lung fields, we had a lesion that spanned the breath of the hemithorax with infiltration of the chest wall.

Routine fungal cultures in patients at risk is the take-home lesson from this case. Based on the clinical picture and radiological findings, we were almost convinced that this patient had a malignancy. However, the histology, histochemical staining, and response to antifungals have taught us to routinely include fungal cultures in the panel for lung biopsy investigations. This is particularly true as the specimen is not readily accessible for further investigations afterward.

Regarding treatment, the choice of therapy depends on the immune status of the host and the presence of extrapulmonary infection. In severe cases with dissemination the treatment is divided into three phases namely induction, consolidation and maintenance regimens.[11] Induction is commonly achieved with intravenous amphotericin B deoxycholate 0.7–1 mg/kg/day and flucytosine 100 mg/kg/day. The consolidation and maintenance phases are achieved with oral fluconazole 400–800 mg/day and 200–400 mg/day, respectively. The patient received flucytosine and fluconazole and then Amphotericin B as this was not readily available initially.

John F. Fisher raised a number of pertinent questions about cryptococcosis in the immunocompetent patient.[12] It may not be possible to answer all the questions based on the experience with this patient; however, it is noted that discontinuation of antifungal treatment with negative culture despite residual radiographic abnormalities did not result in recurrence of fungal disease during the 3-year follow-up of this patient. Following the experience gained from the management of this patient, consideration should be given to lowering the threshold for fungal studies on lung biopsy specimens.

Conclusion

Pulmonary cryptococcosis may have intracranial dissemination. This may give rise to radiological findings in the lung and brain masquerading as a metastatic lung cancer. A high index of suspicion is necessary and, when applicable, fungal panel should be included among special stains in the processing of lung biopsy specimens.

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Conflicts of interest

There are no conflicts of interest.

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