CASE REPORT

Uncommon mycosis in a patient with diabetes

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SUMMARY

Cryptococcosis is a fungal infection that usually occurs in immunocompromised individuals. Meningitis is the most frequent presentation; uncommonly, a disseminated form occurs. Cryptococcosis can sometimes occur in immunocompetent individuals with certain predisposing conditions such as diabetes mellitus. However, disseminated cryptococcosis is exceedingly rare in these individuals. A 48-year-old man presented with a lung mass and was initially suspected to have bronchogenic carcinoma. However, on further evaluation, it turned out to be disseminated cryptococcosis due to *Cryptococcus gattii*, with pulmonary, pleural and meningeal involvement.

BACKGROUND

Cryptococcus is a pathogenic yeast characterised by its large polysaccharide capsule. It most commonly involves the central nervous system (CNS), causing cryptococcal meningitis. Lung involvement due to cryptococcosis is rare.¹ Pulmonary cryptococcosis can present as nodules or mass-like lesions. There have been few reports of cryptococcal lung abscess.^{2 3} We describe an apparently immunocompetent patient who presented to us initially with a lung mass that progressed to lung abscess and empyema, and was diagnosed as disseminated cryptococcal disease.

CASE PRESENTATION

A 48-year-old man was admitted to our hospital with fever, cough and purulent expectoration. The patient had felt well until 8 months before admission, when he started having dull aching pain in the right side of his chest. He took over-the-counter analgesics, which relieved the pain temporarily. Six months prior to presentation, he had started having low-grade intermittent fever and cough with minimal expectoration. For these symptoms, he entered another hospital, where chest radiography showed a mass-like lesion in the right middle zone (figure 1A). Ziehl-Neelsen staining of his sputum did not show any acid-fast bacilli. The patient was treated with multiple courses of oral antibiotics, but fever and cough persisted. Subsequent chest radiographs showed enlargement of the lesion. A contrast-enhanced CT of the chest was performed, which showed a well-circumscribed mass in the right upper lobe with distal collapse (figure 1B). Two months before admission, the patient had been subjected to bronchoscopy on an outpatient basis, which revealed a mucus plug involving the anterior segment of the right upper lobe. Bronchoalveolar lavage showed neutrophil-rich fluid without any malignant cells. It was sterile

on bacterial culture and did not show any acid-fast bacilli. The patient did not present for a follow-up visit, even as his cough continued to worsen with copious, foul-smelling, purulent expectoration of about 200 mL/day. One month prior to admission, the patient also started having breathlessness while walking briskly on level ground. He also had significant reduction in appetite and had lost 6 kg of weight over the preceding 6 months. The patient was then admitted to this hospital.

The patient had smoked 20 bidis daily for the past 20 years (smoking index 400).⁴ He had also consumed 100 g of alcohol daily for 4 years. He suffered from hypertension and was on treatment with amlodipine 5 mg/day for the past 2 years. He was treated successfully for abdominal tuberculosis 5 years prior, with antituberculosis drugs for 6 months. He denied any history of high-risk sexual behaviour or drug abuse. He did not have any significant exposure to pigeon excreta or eucalyptus trees. He did not report any visit to farms, or rural or forest areas.

On physical examination, the patient was alert. Pulse rate was 120/min, respiratory rate 28 breaths/min and temperature 101°F. Blood pressure was 130/84 mm Hg and oxygen saturation was 92% by pulse oximetry on breathing ambient air. Pallor was present. There was no icterus, no cyanosis and no clubbing. Funduscopy did not reveal any abnormality. There was no peripheral lymph node enlargement and the jugular venous pressure was not elevated. There was evidence of volume loss of the right hemithorax and reduced respiratory movements were observed on that side. A dull note on percussion was observed over the right mammary, infra-axillary and infra-scapular areas. Shifting dullness was absent. Coarse inspiratory crackles were heard over the right mammary area. The abdomen was soft and non-tender without a palpable liver or spleen. There was no peripheral oedema.

INVESTIGATIONS

Laboratory investigations revealed anaemia (haemoglobin 9.0 g/dL) with normal leucocyte and platelet counts (table 1). Renal and liver function tests were normal except for mildly elevated alkaline phosphatase levels (167 IU/L). Arterial blood gases revealed mild respiratory alkalosis with metabolic compensation. During his hospital admission, the patient was found to have high blood glucose levels (fasting 152 mg/dL and postprandial 230 mg/dL) and a raised glycated haemoglobin level (8.7 g/dL).

Chest radiography showed consolidation with breakdown in the right middle and lower zones along with a right-sided pleural effusion (figure 2A).

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Figure 1 (A) Chest radiograph showing a homogeneous opacity in the right middle zone. (B) Contrast-enhanced CT of the chest showing a well-circumscribed mass with low attenuation areas in the right upper lobe with distal collapsed lung.

Contrast-enhanced CT scan of the chest was performed, which revealed multiple abscesses in the right lung and a loculated right hydropneumothorax (figure 2B).

DIFFERENTIAL DIAGNOSIS

- ▶ Pyogenic lung abscess
- ▶ Pulmonary tuberculosis
- ▶ Nocardiosis
- ▶ Mucormycosis
- ▶ Lung cancer

Both sputum and CT-guided fine-needle aspirate from the mass lesion revealed numerous Gram-positive cocci, which on India ink staining conformed to the morphology of *Cryptococcus* spp. Pleural fluid aspiration showed gross pus, which also showed cryptococci on India ink and calcofluor-white staining (figure 3). Bacterial culture of pus from the pleural cavity showed growth of *Pseudomonas aeruginosa*. Serum latex agglutination test for cryptococcal antigen was positive. Fungal cultures of both sputum and pus later showed growth of fungal colonies—the species was identified as *Cryptococcus gattii*. Although the patient did not have any neurological symptoms, a cerebrospinal fluid (CSF) examination was performed. It showed a total leucocyte count of 400 cells/ μ L with 90% polymorphs, protein

Figure 2 (A) Chest radiograph showing multiple lung abscesses and a right-sided pleural effusion. (B) Contrast-enhanced CT of the chest showing right hydropneumothorax and pulmonary nodules.

246 mg/dL and sugar 2 mg/dL. CSF India ink staining showed cryptococci. Serology for HIV was negative. CD4 cell count was 451 cells/ μ L. Serum immunoglobulin levels and tests of neutrophil function were normal.

TREATMENT

A diagnosis of disseminated cryptococcal disease was made (cryptococcal meningitis, lung abscess and empyema). The empyema was drained with a pig-tail catheter. The patient was started on intravenous cefoperazone-sulbactam (2 g two times a day). He was offered liposomal amphotericin B and flucytosine, which he refused as he could not afford the cost of the treatment. Therefore, intravenous amphotericin B deoxycholate 1 mg/kg/day was administered. Euglycaemia was achieved with subcutaneous insulin. The patient was also administered subcutaneous unfractionated heparin (5000 units three times a day) and intravenous pantoprazole (40 mg once daily). The fever abated in 5 days and cough was minimal by the end of 2 weeks. Amphotericin was continued for another 4 weeks (cumulative dose 25 mg/kg) following which the patient was started on oral fluconazole (400 mg/day for 8 weeks as consolidation phase followed by 200 mg/day as maintenance phase), which is planned to be continued for another 6–12 months.

OUTCOME AND FOLLOW-UP

The patient was well at the 3-month follow-up visit. Chest radiograph showed decrease in the size of the right upper lobe mass and residual right-sided pleural thickening. A repeat testing for HIV with ELISA was negative.

Figure 3 Pus from the pleural cavity, stained with calcofluor white, showing round budding yeast cells under fluorescent microscopy.

Table 1 Laboratory findings of the patient

Parameter	Value
Haemoglobin (g/dL)	9.0
Total leucocyte count (cells/mm ³)	10 700
Platelet count ($\times 10^3$ /mm ³)	464
Blood urea (mg/dL)	23
Serum creatinine (mg/dL)	1.0
Serum albumin (g/dL)	3.1
Serum bilirubin (mg/dL)	0.5
Alanine transaminase (U/L)	30
Aspartate transaminase (U/L)	39
Alkaline phosphatase (U/L)	167
Serum calcium (mg/dL)	8.0
Serum sodium (mEq/L)	136
Serum potassium (mEq/L)	4.1
pH	7.46
PaO ₂ (mm Hg)	82
PaCO ₂ (mm Hg)	30
HCO ₃ ⁻ (mmol/L)	20.9
FiO ₂	0.21

FiO₂, fractional inspired oxygen; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen.

DISCUSSION

Cryptococcosis is a rare form of systemic mycosis. Cryptococci and their spores are found in the soil and are primarily acquired by inhalation. Once acquired, further dissemination occurs by the haematogenous route, especially in the immunocompromised. Reactivation of latent subclinical infection has also been suggested.⁵

Cryptococcosis in humans is usually caused by two species, namely *C. neoformans* and *C. gattii*. While the former has been associated with bird droppings and rotten vegetation,⁶ the latter has been associated with eucalyptus trees.^{7–8} In our patient, *C. gattii* was isolated, although he did not have any known exposure to the natural habitats of cryptococci.

C. neoformans is predominantly an opportunistic pathogen infecting immunocompromised individuals, especially patients with HIV-infection and transplant recipients on immunosuppressive medications.⁹ It rarely causes disease in immunocompetent individuals. In contrast to *C. neoformans*, *C. gattii* is more likely to infect immunocompetent individuals. Conversely, a majority of cryptococcal infections in immunocompetent hosts are caused by *C. gattii*.^{9–10} Many of these apparently immunocompetent individuals have one of the following predisposing factors: diabetes, chronic liver disease, chronic kidney disease, underlying malignancy or autoimmune disease.¹¹ Our patient was HIV negative but had a predisposing factor in the form of diabetes mellitus, which was detected in the current episode. He was also a chronic alcohol consumer, which might have also contributed to the immune dysfunction.

Pulmonary cryptococcosis is the second most common manifestation of cryptococcal disease, after meningitis, in immunocompetent patients.^{11–13} The most common radiological appearance in non-HIV-infected patients is that of a single or multiple pulmonary nodules/masses in the subpleural location.^{14–15} Cavitation is more common in patients with HIV infection or other conditions causing an immunocompromised state.^{14–16} Interstitial opacities and mediastinal lymphadenopathy are also more common in patients infected with HIV.^{17–18} Cryptococcomas occurring in the brain and lungs are larger and more numerous with *C. gattii* infection than in infection with *C. neoformans*.¹⁹

Pulmonary cryptococcosis is known to mimic other conditions clinically and radiologically. Pulmonary cryptococcosis presenting as a mass-like lesion has been previously reported.^{20–21} Our patient initially presented with a mass-like lesion, which initially led to the clinical suspicion of a lung carcinoma. His later presentation with multiple lung abscesses and empyema suggested an infectious aetiology. Finally, he was found to have cryptococcal lung abscess and empyema along with asymptomatic involvement of the meninges. Although cavitating lung nodules have been described in pulmonary cryptococcosis, presentation with lung abscesses due to *Cryptococcus* is extremely rare. We came across only four cases of cryptococcal lung abscess reported in the published literature.^{2–3 22–23} Empyema due to *Cryptococcus* infection is also rare, with only a few reports both in HIV-infected and non-HIV-infected patients with other immunocompromising conditions.^{24–25} Our patient had empyema; both *P. aeruginosa* and *C. gattii* were isolated from the pus, thus implicating both the pathogens for this complication.

Our patient had evidence of cryptococcal meningitis in CSF examination although he did not have any symptoms. Asymptomatic cryptococcal meningitis has been described in HIV-positive and HIV-negative individuals.^{26–27} In a study of HIV-negative adult patients, 43% of patients with culture-positive cryptococcal meningitis were asymptomatic.²⁷ The Infectious

Diseases Society of America (IDSA) guidelines²⁸ recommend CSF examination for all non-immunocompromised patients with pulmonary cryptococcosis, to rule out asymptomatic CNS involvement. Further, patients with cryptococcomas due to *C. gattii* may also not have any neurological symptoms. In one study, 7% of patients with *C. gattii* infection but without any neurological manifestations had a single large cryptococcoma.²⁹ Thus, CNS imaging may be warranted in such individuals to diagnose occult CNS disease, even when CSF examination is normal.

Disseminated cryptococcosis has been defined by various studies as the presence of one of the following: a single-positive blood culture, or positive cultures from two or more different sites or a single-positive culture from a site (other than blood) along with a positive serum cryptococcal antigen test.^{27–30} Our patient clearly had disseminated cryptococcosis with cryptococci being isolated from the lung, pleural cavity and CSF along with an evidence of cryptococcal antigenaemia. In immunocompetent patients developing pulmonary cryptococcosis, the lung is usually the only organ involved and dissemination is uncommon,^{14–31} although it has been described occasionally.^{20–27 30}

There is adequate evidence to suggest that the combination of amphotericin B and flucytosine, followed by fluconazole, is the best available therapy for cryptococcal meningitis.³² There are no prospective randomised controlled trials to guide treatment decisions in pulmonary cryptococcosis. Treatment recommendations for pulmonary cryptococcosis have been extrapolated from these studies that were performed on patients with cryptococcal meningitis who were HIV infected or had other forms of immunosuppression. For pulmonary cryptococcal disease in non-immunosuppressed individuals (non-HIV, non-transplant), the IDSA guidelines²⁸ recommend treatment with oral fluconazole 200–400 mg/day for 6–12 months for patients with mild-to-moderate disease. For patients with more severe disease, the treatment recommendation is similar to that for CNS disease. This consists of an induction phase with intravenous amphotericin B deoxycholate 0.7–1.0 mg/kg/day along with oral flucytosine 100 mg/kg/day (in 4 divided doses) for 4 weeks followed by a consolidation phase with oral fluconazole 400 mg (6 mg/kg/day) for 8 weeks. After induction and consolidation, maintenance therapy with fluconazole 200 mg (3 mg/kg/day) should be continued for 6–12 months. Our patient responded well to intravenous amphotericin without flucytosine followed by oral fluconazole treatment.

In conclusion, disseminated cryptococcosis can, rarely, present in immunocompetent individuals. Appropriate treatment results in complete recovery with a good prognosis.

Learning points

- ▶ Pulmonary cryptococcosis can, rarely, present in immunocompetent adults.
- ▶ It can mimic common conditions such as lung cancer, tuberculosis and bacterial lung abscess.
- ▶ Prompt evaluation and careful microbiological and histopathological confirmation of clinical diagnosis could avoid misdiagnosis and diagnostic delays in these patients.
- ▶ Extensive dissemination including central nervous system disease can occur in asymptomatic, apparently immunocompetent adults with cryptococcal disease, hence a careful systemic evaluation including cerebrospinal fluid examination is warranted in such patients.

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