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Case report

Cryptococcus neoformans presenting as a large pulmonary cavitary lesion in an immunocompetent female

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ABSTRACT

Pulmonary cryptococcus is a rare but fatal fungal infection historically associated with Human Immunodeficiency Virus (HIV) and immunosuppression, yet increasingly also being recognized in immunocompetent patients as a result of antiretroviral therapy and improved HIV control reducing HIV-associated cryptococcus in advanced countries. Appropriate management may be delayed if left unrecognized. We present the case of an immunocompetent middle-aged female with nonspecific respiratory symptoms who was found to have a large cavitary lung mass resulting in external compression of the pulmonary vein, ultimately leading to a diagnosis of pulmonary *Cryptococcus neoformans*. By presenting this case, we hope to elucidate the challenges in diagnosing and managing this fatal disease in timely fashion.

Introduction

Cryptococcus is an encapsulated yeast with narrow-based budding that primarily manifests in immunocompromised individuals [1–3,5] and causes aggressive fungal infections. Patients with Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), solid organ transplant, chronic renal disease, decompensated cirrhosis, diabetes, prolonged use of steroids, and other forms of immunocompromise are especially vulnerable to this infection [1,3,4]. Risk factors for infection include exposure to bird feces, hollows in trees, rotting dairy products, and soil [3,4]. Nonetheless, reports of pulmonary cryptococcus manifesting in immunocompetent patients are also increasing [4].

Diagnosing systemic fungal infections in a timely fashion can be very challenging as symptoms are generally nonspecific or even silent until well advanced in the disease process. Chest imaging with radiography or high-resolution computed tomography (CT) may identify incidental findings in asymptomatic patients which can guide the clinician into a proper workup but even still, proper fungal workup is frequently disregarded. A diagnosis of any systemic fungal infection warrants a proper workup to evaluate for any sort of underlying malignancy or immune deficiency. We present the case of a middle-aged previously immunocompetent female who presented with subacute dyspnea and dry hacking cough which progressed to hemoptysis. Initial studies revealed a large cavitary lung mass resulting in external compression of the pulmonary vein which ultimately led to a diagnosis of pulmonary *Cryptococcus neoformans*. Our case elucidates the challenges in promptly managing such diseases processes and prompts clinicians to recognize such diagnoses even amongst immunocompetent individuals.

Case presentation

A 64-year-old female with a past medical history of hypertension, multinodular goiter, and recent SARS-CoV-2 (COVID-19) respiratory infection three months prior presented with chest pain and shortness of breath. The chest pain was described as dull, non-radiating, and diffuse across the anterior chest wall. She also reported progressively worsening dyspnea on exertion and dry hacking cough that had an onset shortly after her COVID-19 infection. She felt as though her chest pain was due to persistent coughing, however it continued to progressively worsen. Her vital signs on presentation were as follows: temperature 100.1 F, blood pressure 110/74, pulse 59, respiratory rate 16, O2 saturation 100% on room air. Physical exam was significant for diffuse anterior ribcage pain that was tender to palpation. She denied any hemoptysis,

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weight loss, fever, chills, nausea, vomiting, and headache at this time.

Computed tomography angiography (CTA) of the chest revealed a right upper lung mass, 5.1 cm × 3.2 cm, which was new compared to a CT of the chest obtained one year prior. Concomitant mediastinal and right hilar lymphadenopathy was also visualized. Cardiac workup was unremarkable, and she was provided with supportive care. She underwent bronchoscopy with lavage and brush samples were obtained for cultures and cytology. Unfortunately, a biopsy could not be read due to inadequate tissue sample size. She then underwent CT-guided biopsy which only revealed necrosis and acute inflammatory changes with rare atypical cells, but was negative for definitive malignancy. Preliminary analysis of bronchial washings identified normal flora on respiratory bacterial stain and culture. No growth to date was initially identified for 14 days on either preliminary fungal stain & culture or on bacterial gram stain & culture of the biopsied tissue. She also had fungal antibody serology performed for endemic mycoses including *Aspergillus, Histoplasma, Coccidioides,* and *Blastomyces*, all of which were negative. Additional analysis of bronchial washings included HSV PCR and Acid-Fast Bacillus culture & smear, the former of which was negative and the latter demonstrated no growth after 7 days. Blood cultures demonstrated no growth for 6 days and remained negative. She completed 3 days of azithromycin and piperacillin-tazobactam was discharged home with a 14-day course of amoxicillin-clavulanate.

Unfortunately, she presented again 15 days later with similar complaints accompanied by mild hemoptysis. It was uncertain whether the hemoptysis was pathologic or due to recent biopsy. A lab workup consisting of complete blood count, complete metabolic panel, serum troponin, electrocardiography, QuantiFERON gold, antinuclear antibodies, antineutrophilic cytoplasmic antibody, rheumatoid factor, C-reactive protein was again unremarkable. However, a repeated computed topographical angiography of the chest revealed an increase in size of the right upper lung mass, now measuring 5.4 cm × 4.0 cm and with new crescenteric cavitation (Fig. 1A, D). A new pulmonary vein thrombus involving the anterior branch of the right pulmonary vein with partial extension to the left atrium could also be visualized, which was initially felt to be due to hypercoagulable state in setting of recent COVID-19 infection, but it was subsequently posited that the cavitary lesion played a greater role in the formation of the thrombus due to its proximity to the pulmonary vein resulting in external compression of the vessel (Fig. 1A). Intravenous heparin guttae was initiated and she was admitted for further evaluation with repeat bronchoscopy.

Her IgG levels and CD4 cell counts were within normal limits. As we scheduled the patient to undergo a repeat computed tomography-guided biopsy of the mass, we received correspondence from the laboratory department regarding the finalized results of her fungal cultures from bronchial washings and bronchiolar lavage during her prior hospitalization. Although no fungus had been observed on initial smear, and "yeast" was first observed at 14 days, *Cryptococcus neoformans* (Fig. 1B, C) was only definitively identified on fungal culture from bronchial washings 17 days after collection. Culture from her bronchoalveolar lavage (BAL) during the initial hospitalization was now also definitively identified as *Cryptococcus neoformans*. Just as with the bronchial washings, "yeast" was observed at 14 days after collection, but *Cryptococcus neoformans* was only identified on day 17. Her planned biopsy was canceled, and she was empirically treated with intravenous amphotericin B with standard dose of 3 mg/kg and oral flucytosine 25 mg/kg for a

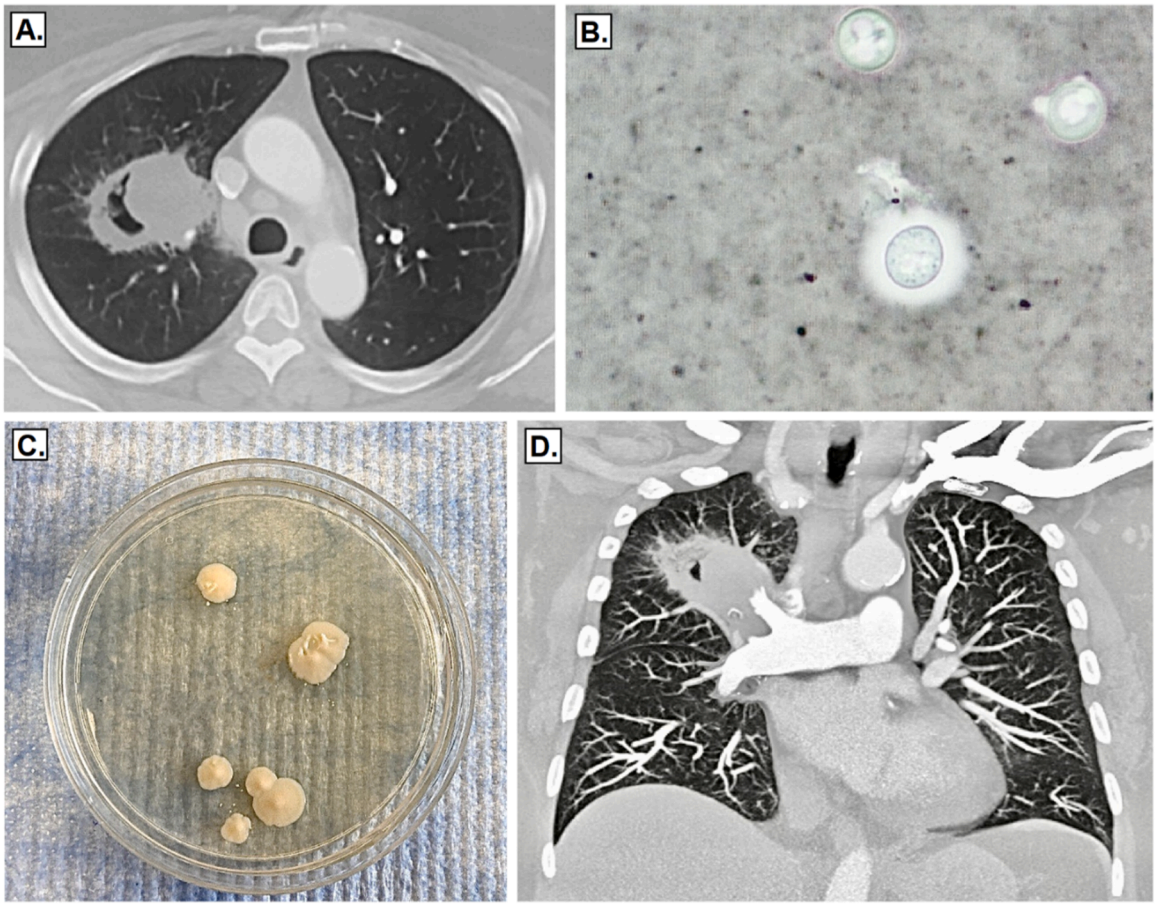

Fig. 1. Panel A demonstrating CTA Chest performed during patient's second hospitalization demonstrating a large crescenteric mass, axial view. Panel B revealing cytology globular, encapsulated yeast, in this case without budding, typical of *Cryptococcus neoformans;* Panel C fungal cultures productive of white, mucoid colonies, typical of *Cryptococcus neoformans;* Panel D with CTA Chest performed during patient's second hospitalization demonstrating a large crescenteric mass, frontal view.

total of 4 days. Serum cryptococcal antigen was analyzed and found negative 3 days into her second hospitalization. Since serum cryptococcal antigen was negative and she had clinically stabilized, she was therefore discharged home on oral fluconazole 400 mg daily for 6 months with the expectation of repeat imaging in 1 month to evaluate response.

Unfortunately, upon follow-up at an outside institution the patient was found to have metastatic non-small cell lung cancer with giant cell and spindle features and rapidly deteriorated. She underwent palliative radiation and started chemotherapy with carboplatin and etoposide while subsequently continuing treatment for *Cryptococcus neoformans* for a total of 92 days. She was admitted to hospice and died 4 months after her initial presentation.

Discussion

Cavitary pulmonary cryptococcosis is a rare manifestation of *Cryptococcus neoformans*. Diagnosis of pulmonary cryptococcosis is primarily done through a combination of histopathology, culture, and cryptococcal antigen testing [1]. Radiological studies such as chest radiography and computed tomography are also important for both diagnosis and analyzing the progression of disease, especially as patients can present as asymptomatic with incidental imaging findings [1,6].

Radiological studies are often the first step in the diagnosis of pulmonary cryptococcosis, often revealing either solitary or multiple pulmonary nodules measuring less than 10 mm in diameter and rarely ever cavitate [6]. Our case critically elucidates the potential unpredictability of this disease as it can even affect individuals presumed to be immunocompetent. One could argue our patient's true state of immunocompetence to be questionable given her state of recent SARS-CoV-2 respiratory infection 3 months prior and the later discovery of underlying pulmonary malignancy. However, biopsy was unrevealing with negative stains for AFB and fungus and a complete autoimmune and immune workup, including serum IgG levels and CD4 count, were well within reference ranges. This patient also had no known history of administration of immunosuppressive agents.

Following identification of abnormal imaging findings consistent with pulmonary cryptococcosis, diagnosis is primarily made through histopathology, culture, and/or cryptococcal antigen testing [1]. India Ink stain can be used as part of the diagnostic process, with India Ink uniquely giving the appearance of a refractile unstained capsule against a darkly staining background [1,7]. However, it should be noted that these tests were done in the context of meningitis and India Ink was noted to have a significantly lower positive rate in patients without AIDS, suggesting that India Ink stain may not be most reliable test for pulmonary cryptococcosis in immunocompetent patients [7]. A more reliable diagnostic test is identification of *cryptococcosis* on lung tissue or bronchoalveolar lavage (BAL), which provides optimal sensitivity and specificity and is the gold standard for diagnosis. (Figure B, C) [1,2]. Expectorated sputum culture is unreliable as there is an increased possibility of contamination [1]. Routine susceptibility testing is not typically required or recommended since there is no direct correlation between minimum inhibitory concentration (MIC) and outcomes [8]. Another test that can significantly contribute to diagnosis is a cryptococcal antigen testing, commonly performed with a lateral flow assay [9]. This test provides high sensitivity and specificity in both serum and cerebrospinal fluid, and has the advantages of low cost and ease of use, making this a feasible option for most [10]. Ultimately, our patient's fungal cultures from her bronchoalveolar lavage were positive for *Cryptococcus neoformans*; however, her serum cryptococcal antigen test was consistently negative despite testing being repeated several times over the course of 2 months. It is possible that if the serum cryptococcal antigen test had been performed as part of the initial workup back when the CT-guided biopsy was first performed instead of during her second hospitalization, it would have been positive earlier and led to earlier identification and diagnosis of the disease.

With regards to our patient's clinical presentation, it remained unchanging with symptoms of chest pain, intermittent cough worse in the mornings, and scant, infrequent hemoptysis. Her vitals also remained stable, and she never required supplemental oxygen during her hospitalization. Her clinical presentation is consistent with the tendency for pulmonary cryptococcosis in immunocompetent patients to present with less severe and more nonspecific symptoms [2]. However, her seemingly stable clinical presentation belied a severe manifestation of pulmonary cryptococcosis, due to the presence of a large cavitating mass in her lung likely causing external compression of the pulmonary vein that led to a subsequent acute pulmonary thrombus. She underwent extensive workup to assess for immunodeficiency, including HIV antigen/antibody testing, IgG levels, and CD4 count, which were all unremarkable. She was not known to be on any steroids or had any history of diabetes or solid organ transplant. There were no definite underlying factors identified in this patient that would cause immunodeficiency. Further workup including galactomannan antigen and lumbar puncture were eventually performed at an outside facility after discharge, both of which were unremarkable. Although our patient presented without neurological complaints or an abnormal neurologic exam, given the severity of her radiologic pulmonary findings and ongoing symptoms, a lumbar puncture would have been warranted to rule out cryptococcal meningitis.

The first-line treatment of systemic pulmonary cryptococcosis is intravenous amphotericin B deoxycholate (AmBD) and oral flucytosine, followed by oral fluconazole divided into induction, consolidation, and maintenance phases for therapy [8,11]. For patients who are not HIV infected and do not have a history of transplant, it is recommended that patients receive IV AmBD 0.75–1.0 mg/kg daily or liposomal amphotericin B (LAmB) 3–4 mg/kg daily and oral flucytosine 25 mg/kg 4 times a day [11]. Induction therapy is recommended to be given for 4 weeks in patients with meningoencephalitis followed by 8 weeks of oral fluconazole 400 mg daily for consolidation therapy [11]. However, for lower risk immunocompetent patients, an altered course of IV amphotericin B plus oral flucytosine for 2 weeks only, followed by consolidation therapy with oral fluconazole 800 mg daily for 8 weeks may be administered [11]. Although 2 weeks of induction therapy is a recommended value, the actual duration of induction therapy varies in the clinical setting and is often based on clinical response rather than a set value [8]. Some sources suggest that for mild or moderate pulmonary cryptococcosis, oral fluconazole directly without IV amphotericin B or flucytosine is adequate if immunocompetent [8]. Regardless of the duration of induction and consolidation therapy, patients are typically given maintenance therapy with oral fluconazole 200 mg daily for 6–12 months afterwards [8,11].

Our patient was initiated on IV LAmB 3 mg/kg daily and oral flucytosine 25 mg/kg 4 times a day per guideline-directed medical therapy. However, she was then transitioned to oral fluconazole 800 mg daily after only 4 days due to continued stability of the patient's clinical presentation and negative serum cryptococcus antigen testing. The patient continued oral fluconazole 400 mg daily on discharge, with a follow-up plan of remaining on oral fluconazole for 6–12 months. Although oral fluconazole without induction therapy may have been adequate for a patient with a mild to moderate presentation of pulmonary cryptococcosis, serum cryptococcal antigen does not appear to be a criterion for which a patient can be transitioned from induction to consolidation therapy [8]. The ambiguity on proper induction dose duration for patients with mild to moderate symptoms in the setting of pulmonary cryptococcosis could benefit from greater scrutiny and attention to radiologic findings.

Our patient did however have pulmonary findings consistent with a severe manifestation of pulmonary cryptococcosis including a cavitary mass and compression of the greater vessels. The severity of her pulmonary findings should have resulted in at least a standard induction duration of 2 weeks prior to transitioning to oral therapy, if not a longer duration of induction therapy until radiologic improvement was noted.

It is unclear whether the transition to oral fluconazole in our patient was influenced by patient preference. The patient could have potentially benefitted from a longer dose of induction therapy with IV LAmB and flucytosine despite stability, considering the severity of a large and cavitary lesion present in her right upper lung. On the other hand, the patient was placed on appropriate consolidation and maintenance therapy, provided that on follow-up her fluconazole was reduced to 200 mg after 8 weeks for her extended maintenance therapy dose. Unfortunately, the patient rapidly deteriorated after discovery of non-small cell lung cancer despite continuous treatment of both the underlying malignancy and pulmonary cryptococcosis.

Pulmonary cryptococcosis is a rare lung infection in immunocompetent individuals that can manifest with nonspecific symptoms and is often be misdiagnosed or missed due to overlap with other pulmonary diagnoses. This can lead to a delay in diagnosis and management, which may be confounded by ambiguity over how long appropriate induction therapy with IV amphotericin B and flucytosine should be given prior to transitioning to oral fluconazole in an immunocompetent individual. Unfortunately, data has shown higher mortality associated with cryptococcal infections in non-HIV, non-transplant individuals making early recognition and treatment essential [12]. A prompter and more extensive laboratory workup in patients who are suspected to have pulmonary cryptococcosis, including serology and antigen testing for *Cryptococcus* and endemic mycoses and galactomannan antigen for invasive molds, should be considered in order to facilitate early identification, diagnosis, and management of both this disease and other fungal infections. This case highlights a severe manifestation of pulmonary cryptococcosis with a large cavitary mass compressing the pulmonary vein leading to pulmonary vein thrombosis. Through this case, we hope to raise awareness of pulmonary cryptococcosis in immunocompetent patients, so that more clinicians will give serious consideration to this diagnosis in their differential and therefore increase timely recognition and appropriate management of this disease.

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Ethical approval

Not required.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRediT authorship contribution statement

Jason Kim: Writing – original draft, Conceptualization, Illustration. **Katherine Graebel:** Writing – review & editing. **Aakash Kumar:** Validation, Supervision. **Fnu Sandesh:** Data curation. **Shivangi Patel:** Writing – review & editing. **Hafez Golzarian:** Supervision, Project administration.

Declaration of Competing Interest

The authors have no financial or personal relationships to disclose.

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