Pulmonary Cryptococcosis with Trachea Wall Invasion in an Immunocompetent Patient: A Case Report and Literature Review

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Abstract
Cryptococcosis causes significant morbidity and mortality in the world. Pulmonary cryptococcosis is a kind of subacute or chronic pulmonary fungal disease. We present a case of pulmonary cryptococcosis with a trachea wall invasion-like malignant tumor in an immunocompetent patient and a literature review. The 44-year-old man, a nonsmoker, suffered from mild dyspnea and white sputum with intermittent blood streaks. A computed tomography (CT) scan of his chest showed two possibly malignant lesions in the right hilum and upper-right field of his lung, which have higher uptake values of fluorodeoxyglucose on positron emission tomography (PET)/CT. Lung biopsy pathology showed scattered fungal spores and positive periodic acid-Schiff (PAS) staining. The immune status and blood tumor markers were all normal in this patient. The titer of \textit{Cryptococcus} antigen latex agglutination test was 1:1,280. Under fiberoptic bronchoscopy, a prominent new mass on the right wall of the trachea blocked most of the right main bronchus. To reduce the symptoms of airway obstruction, treatment by bronchoscopy, i.e., ablation and endotracheal stent, was used. As his symptoms were aggravated by the use of itraconazole, amphotericin B liposome was used as antifungal treatment.

Key Words
Pulmonary cryptococcosis · Immunocompetent patient · Trachea wall invasion

Established Facts
- Pulmonary cryptococcosis commonly occurs in immunocompromised patients with the clinical manifestations of localized nodular lesions, segmental pneumonic, patchy interstitial or alveolar infiltrates.

Novel Insights
- Pulmonary cryptococcosis sometimes mimics a lung neoplasm radiologically and bronchoscopically, even in immunocompetent patients. Treatment with antifungal drugs and bronchoscopy, such as ablation and endotracheal stent, is a good choice.
All these methods led to a better prognosis. We conclude that pulmonary cryptococcosis may mimic lung neoplasms radiologically and bronchoscopically, even in immunocompetent patients.

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Introduction

*Cryptococcus neoformans* is an opportunistic yeast commonly found in soil contaminated by bird feces throughout the world [1]. Cryptococci have a tropism for the central nervous system (CNS). After the CNS, the respiratory system is most commonly affected. Cryptococcosis continues to cause significant morbidity and mortality in immunocompromised and immunocompetent patients [2]. Pulmonary cryptococcosis with trachea wall invasion-like malignant tumor is exceedingly rare in immunocompetent patients, and it is often easily misdiagnosed.

Case Report

As we described in a previous report [3], a 44-year-old man presented with mild dyspnea on exertion and a progressive worsening of cough and white sputum with intermittent streaks over 3 months, with no significant cause evident and no chest pain, chills or fever. Computed tomography (CT) scan of his chest showed two possible malignant lesions in the right hilum and upper-right field of his lung (fig. 1a, b). After 4 days of antibiotic treatment, his symptoms had not improved. Percutaneous lung biopsy pathology showed scattered spores without malignant tumor cells, indicating a fungal infection. Ten days later, percutaneous lung puncture biopsy guided by color Doppler ultrasound was performed, and the pathology revealed interstitial tissue hyperplasia and scattered cryptococcosis. Moreover, periodic acid-Schiff (PAS) staining was positive and acid-fast staining was negative. Before this, the patient had been healthy. He told us that one of his neighbors had been feeding pigeons for a long time. At a physical examination upon admission, his temperature was 36.5°C, his breathing was smooth and auscultation showed that his bilateral lungs were clear with no wheezing, rales or rhonchi. His whole blood count was 10.56 × 10⁹/liter and nitrogen 76.4%. Tumor markers of blood including carcinoembryonic antigen, cancer antigen 125 (CA125), CA19–9, neuron-specific enolase, squamous cell carcinoma and cytokeratin 19 were all normal. The patient was then evaluated for an underlying immunosuppressive state. An enzyme-linked immunosorbent assay test for HIV was negative. Total lymphocyte, CD4 and CD8 counts, serum complement and immunoglobulin levels were normal. Triple sputum smears for acid-fast bacilli test and fungus were all negative. The titer of *Cryptococcus* antigen determined by a *Cryptococcus* antigen latex agglutination test was 1:1,280. Positron emission tomography (PET)/CT scan revealed FDG-PET-positive multiple lung masses with a maximum standardized uptake value of 9.41 in the upper-right lobe of the lung and 9.86 in the right hilum and mediastinal enlarged lymph node (fig. 1c). Under fiberoptic bronchoscopy, a prominent new mass was found on the lower trachea right wall; it blocked most of the right main bronchus, leaving only a gap and bleeding easily when touched (fig. 2). This appearance indicated malignancy. With the bronchoscope, we saw that the right intermediate bronchus was unobstructed, with light-yellow, extremely viscous secretions completely blocking the nozzles of the lower lobe. A *C. neoformans* growth was observed in the neoplasm biopsy tissue culture 4 days later; it was moderately sensitive to fluconazole and sensitive to amphotericin, itraconazole and voriconazole. So the patient took itraconazole (400 mg daily) as an antifungal therapy.

During 2 weeks of antifungal therapy, the patient felt that his cough and shortness of breath progressively worsened. Another chest CT scan was taken, which indicated that the right hiliar mass had increased, the mediastinal lymph node had enlarged and the right main bronchus had been invaded. A possible diagnosis of pulmonary malignant tumor accompanied by *Cryptococcus* infection was made based on the symptoms and the image report. In order to improve airway stenosis, stent implanting was performed via bronchoscopy. Under bronchoscopy, severe stenosis of the lower trachea was observed, with about 70–80% of lumen being obstructed. The right main bronchus was completely occluded by a neoplasm, which projected to the nozzle of the left main bronchus. First, we removed the neoplasm in the lower trachea with high-frequency electric ablation. Second, the neoplasm of the right main bronchus was also removed by repeated argon plasma coagulation ablation and cryoaublation until this bronchus gradually cleared. During the process of ablation surgery, a small amount of bleeding occurred, but soon stopped after suction and local spraying of a small amount of epinephrine via the bronchoscopy. Finally, a mesh nitinol alloy endotracheal stent was implanted at the lower trachea. Pathology of the neoplasm showed a lot of round and translucent tissues scattered, which were positive for Grocott’s methenamine silver stain and PAS and negative for acid-fast staining (fig. 3). This indicated the diagnosis of *Cryptococcus* infection instead of a malignant tumor. As amphotericin had severe side effects, only the itraconazole therapy was continued.

One month later, chest CT scan determined that the masses in the lung had not reduced in size. Amphotericin B liposome instead of itraconazole was given to the patient. After 45 days treatment, the masses in the upper-right lung, right hilum and mediastinum were slightly reduced in size. Unfortunately, severe gastrointestinal reaction and hypokalemia, the common side effects of amphotericin B liposome were observed, so voriconazole was used as an antifungal therapy. Two months later, the symptoms of cough and shortness of breath were aggravated and a chest CT scan showed the masses in the lung to have grown again. Bronchoscopy revealed granuloma-like new protrusions in the tracheal cavity and at both ends of the stent; these covered most of the right main bronchus. Ablation was repeated to remove the neoplasm, and amphotericin B liposome was used again instead of voriconazole. Scattered *Cryptococcus* in the neoplasm was also found upon examination of the pathology. After 1 month of treatment, the bronchial tumor disappeared and the mucous membrane became smooth. Another month on, the neoplasmic mass in the right hilum and lung was markedly reduced in size on chest CT scan (fig. 1d). After another 3 months treatment with amphotericin B liposome, the patient was discharged with an occasional mild cough as the only symptom.
Discussion

*C. neoformans* is the main clinical cryptococcal pathogen. It is widespread, especially in pigeon droppings or in soil contaminated with these droppings. Cryptococci have a tropism for the CNS; after the CNS, the respiratory system is the most commonly affected. Pulmonary cryptococcosis is a kind of subacute or chronic pulmonary fungal disease mainly caused by *C. neoformans* infection, which constitutes about 20% of fungal disease in the lungs, secondary to *Aspergillus* infection. It commonly occurs as an opportunistic infection in immunocompromised patients, but rarely in individuals with normal immunity. The clinical manifestations include localized nodular lesions with or without cavitations, segmental pneumonic, patchy interstitial or alveolar infiltrates, pleural effusions, hilar masses and thoracic lymphadenopathy [4]. Patients who are symptomatic with cryptococcal pneumonia can present with cough, chest pain, increased sputum production, fever, weight loss and hemoptysis. Campbell [5] reported 32% of the patients with pulmonary cryptococcosis to be asymptomatic. In these cases, pulmonary infection was discovered as an incidental finding. According to the literature [6], the imaging manifestations of pulmonary cryptococcosis have the following features: isolated mass, single or multiple nodules, single or multiple patchy infiltrates, diffuse miliary shadow and interstitial pneumonia. Diffuse miliary shadow and interstitial pneumonia are not common.

In our case, the immunocompetent patient had a history of exposure to pigeon droppings and a progressive localized disease without any systemic inflammatory re-
sponse. His radiograph showed many masses and multiple nodules in the right upper-lobe posterior segment and the right hilum, some with an unclear boundary and some with the halo sign. The right upper lung mass had invaded the right bronchus. PET/CT showed a soft-tissue mass with abnormally increased glucose metabolism. These findings simulated the presentation of a malignant lung disease. As reported in the literature [7, 8], pulmonary cryptococcosis often mimics primary or metastatic lung cancer on (18)F-FDG PET/CT scan. Tissue confirmation should be considered for any suspicious pulmonary nodules showing high FDG uptake.

We initially employed the usual diagnostic tools for pulmonary cryptococcosis which include histology, fungal culture, serum cryptococcal antigen and radiography. However, if the results are inconclusive, biopsy is recommended. The yeast form of Cryptococcus can be identified in histopathological specimens using the GMS or PAS stain. In our case, the yeast form was identified. Vacuoles in the tissue were also seen, likely representing lipid or fat. The identification of C. neoformans is supported by the presence of a urease-positive, encapsulated yeast. Further confirmation can be achieved with biochemical tests contained in commercial kits and by detection of the enzyme phenol oxidase, which is solely produced by C. neoformans. However, most clinical microbiology laboratories do not stock the expensive agars required for detecting this enzyme. Invasion of the trachea or bronchus, projecting into the lumen of the trachea and resulting in stenosis are very rare in pulmonary cryptococcosis. Physicians should pay attention to the differential diagnosis.

Candidates for treatment are clearly patients with persistent and/or disabling symptoms, multiple nodules or extensive infiltrates on chest X-ray and/or positive serum cryptococcal antigen test results. Fluconazole is active against C. neoformans, is easily administered and has an excellent safety profile. If the patient has an intolerance or resistance to fluconazole, and if there are symptoms and signs of disease progression, amphotericin B is recommended for use [9]. Despite an extensive evaluation, we found no evidence of immune deficiency in our patient. Cryptococcus was not sensitive to fluconazole and the symptoms were aggravated by the use of itraconazole and voriconazole. To reduce the drug side effects, we preferred amphotericin B liposome to amphotericin B. This led to a better prognosis. As the patient had multiple lesions and the trachea, right main bronchus as well as some blood vessels had been invaded by the infection, he was not able to undergo surgery. For such patients, in particular those with endobronchial pulmonary cryptococcosis, treatments via bronchoscopy are a good choice, such as bronchoscopic resection, ablation and endotracheal stent [10, 11], effectively relieving shortness of breath, hypoxia, cough and other symptoms.

This case report highlights the fact that pulmonary cryptococcosis can sometimes mimic a lung neoplasm, radiologically and bronchoscopically, even in immunocompetent patients. This must be taken into consideration in the differential diagnosis of mass lesions with airway wall invasion that have a high standardized uptake value score on (18)F-FDG PET/CT scan.

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