A unique case report of endobronchial cryptococcosis and review of the literature

Shi-Yuan Shuai¹, Liang Xiong¹, Xin-Liang He¹, Fan Yu¹, Qin Xia², Qiong Zhou³,∗

¹ Department of Respiratory and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
² Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

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ABSTRACT

Cryptococcosis is an infection caused by the yeast-like fungus Cryptococcus neoformans. Pulmonary cryptococcosis is typically identified as a single mass or as multiple nodules, while endobronchial lesions are quite rare. Here we report an uncommon case of pulmonary cryptococcosis presenting as endobronchial lesion in an immunocompetent patient. A 49-year-old male patient complained of intermittent cough with hemoptysis for two years. Computerized tomography of the chest showed a filling defect in the basal segment of the right lower lobe bronchus. A flexible bronchoscopic examination revealed a white smooth-surfaced polypoid lesion completely occluding the medial basal segment of the right lower lobe bronchus. The diagnosis was confirmed by bronchial biopsy under bronchoscopy, and the histopathologic findings showed the organisms were Cryptococcal neoformans. The patient was treated with fluconazole at a dose of 400 mg daily. The endobronchial lesion was found rapidly diminished after 18 days of therapy, and disappeared after 6.5 months of therapy by repeated fiberoptic bronchoscopy. Then the patient continued fluconazole for another 2.5 months. During the total 16 months' follow-up visits, the patient repeated CT scanning for five times, the results of which were all normal. The patient's symptoms disappeared as well, and now he is still under follow-up. This case highlights the fact that pulmonary cryptococcosis can present as endobronchial lesions even in immunocompetent subjects, mimicking lung tumor. Pathological confirmation is important to establish the definite diagnosis.

1. Introduction

Cryptococcosis is an infection caused by the yeast-like fungus Cryptococcus neoformans. The infection is thought to be acquired by inhalation of spores into the airway, and is mostly common in immunocompromized patients. The clinical manifestations of cryptococcosis are protean, and the radiological findings are also nonspecific, so the diagnose is often a challenge. Pulmonary cryptococcosis is typically identified as a single mass or as multiple nodules infiltrates, while endobronchial lesions are quite rare. There are only a few case reports of pulmonary cryptococcosis presenting as endobronchial lesions. Here, we report such a rare case, and a systematic literature review was performed for similar published cases of endobronchial cryptococcal infection in immunocompetent and immunocompromised patients.

2. Case report

A 49-year-old Chinese man complained of intermittent cough with hemoptysis for two years, sometimes with a slight fever. He denied having any chest pain, dyspnea, night sweats, weakness, headache, or weight loss. The patient had been intermittently treated by his local physician with antibiotics, but his symptoms persisted, and also developed productive cough with green or black sputum. There was no history of allergies, smoking or using illicit drugs. He took no medications and did not own any pets. A chest CT scan showed a lesion in the basal segment of the right lower lobe bronchus, which was initially considered as secretion or space occupying lesion by radiologist (Fig. 1). So he was admitted to our hospital for further evaluation.

On physical examination, he appeared anxious. His temperature was 36.6°C and pulse rate was 103 bpm. Systemic examination was normal.
The blood assay showed white cell count 4640/mm³ (3500–9500; neutrophils, 55.10%, lymphocytes, 32.80%), hemoglobin 14.5 g/dl (13.0–17.5) and platelet 242,000/mm³ (125,000–350,000). Tests of renal function, liver function, blood sugar, coagulation function and tumor markers were all normal. Sputum smear for fungi or acid-fast bacillus was negative. Sputum and blood samples grew no pathogens. Cryptococcus neoformans capsular polysaccharide antigen was absent in the serum.

The patient underwent a fiberoptic bronchoscopic examination. It showed a white polypoid lesion completely occluding the medial basal segment of the right lower lobe bronchus. (Fig. 2A). Then biopsies of the endobronchial lesion under bronchoscopy were performed. Histological examination of the samples revealed dense accumulation of the histiocytes and yeast-form fungi that did not uptake the Hematoxylin and Eosin (H&E) staining. Notably, these organisms were positive for Periodic Acid-Schiff staining, that was consistent with cryptococcosis (Fig. 3). Fungal culture of the sample was not performed for this patient.

The patient was then evaluated for his immune status. Test for human immunodeficiency virus (HIV) was negative. Total lymphocyte count, CD4 and CD8 count, and immunoglobulin levels were normal. The patient had no evidence of disseminated cryptococcal infection and his neurological examination through MRI was normal. On the basis of these findings, the diagnosis of primary endobronchial cryptococcosis was established.

The patient was initiated on intravenous fluconazole at a dose of 400 mg per day. After 18 days, a repeated fiberoptic bronchoscopy demonstrated that the endobronchial lesion in the basal segment of right lower lobe bronchus had diminished significantly (Fig. 2C). Afterwards, the patient was treated with fluconazole for another 2.5 months. So the duration of treatment for fluconazole was 9 months totally. During the 16 months’ follow-up visits, the patient underwent repeated CT scanning for five times, respectively after 3, 6, 9, 12 and 14 months of therapy, and all the results were normal without any lesion in the previous lesion site (Fig. 4). The patient’s symptoms disappeared as well. Now the patient is still under follow-up.

3. Discussion

Cryptococcosis is caused by Cryptococcus neoformans, a ubiquitous budding yeast-like basidiomycete that is endemic in many countries. Cryptococcosis is most often associated with human immunodeficiency virus (HIV) infection. Patients with other immunodeficiency states including organ transplantation, and the use of corticosteroid and other immunosuppressive therapies, are also at increased risk of infection. However, cryptococcosis is also well described in apparently healthy hosts. The clinical manifestations of cryptococcosis are protean. Cryptococcal meningoencephalitis is the most frequent and most severe form in both immunocompromised and immunocompetent patients. Pulmonary disease is the next most common presentation. Besides, skin/subcutaneous, ophthalmic, bone, and prostatic disease also occur [1].

Generally, pulmonary cryptococcosis is difficult to diagnose because the symptoms and radiological findings are nonspecific, and are variable depending on the immune status of the patient [2]. The most common radiologic manifestations of cryptococcal lung lesions include a single well-defined mass (often based in the pleura), multiple nodules or a well-defined consolidation [3,4]. Some unusual features such as cavitations, pleural effusion, and lymphadenopathy may be present in immunocompromised patients [3]. Development of an endobronchial lesion is a rare manifestation of pulmonary fungal infection. Review of the literature done by Karnak et al. [5] found that the majority of these cases were related to infections with Aspergillus species. Endobronchial infections with Cryptococcus neoformans were found to be less...
Fig. 3. Histopathological examination of the endobronchial biopsy after fiberoptic bronchoscopy. A: Histopathological examination of the endobronchial biopsy specimen showed dense accumulation of the histiocytes and yeast-form fungi that did not uptake the Hematoxylin and Eosin (H&E) staining (H&E staining, 400×). B: These organisms were positive for Periodic Acid-Schiff stain (PAS, 400×) consistent with cryptococcosis (arrows).

Fig. 4. Repeated thoracic computed tomography respectively after 3, 6, 9, 12 and 14 months of treatment, showing disappearance of the previous lesion in the basal segment bronchi of right lower lobe. A: CT scan after 3 month. B: CT scan after 6 months. C: CT scan after 9 months. D: CT scan after 12 months. E: CT scan after 14 months. a: Parenchymal window. b: Mediastinal window. c: Coronal section.
| Year | Age | Sex | Site                  | Chest X-ray or CT                                                                 | Symptoms                                                                 | History                                                                 | C.organism/antigen in CSF | Therapy                                                                 |
|-----|-----|-----|-----------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------|
| 1972 | 36  | M   | RUB                  | Consolidation of the RUL                                                        | Weakness, chest pain, productive cough, weight loss                       | NA                                                                         | (−)                        | AMPH-B, resection                                                      |
| 1985 | 26  | M   | RMB                  | Large hemorrhagic lesion                                                        | NA                                                                        | NA                                                                         | (−)                        | AMPH-B, 5-FC                                                           |
| 1992 | 65  | M   | LL&B&LUB             | Mass lesion                                                                       | Dyspnea, cough, weight loss                                              | NA                                                                         | (−)                        | AMPH-B, 5-FC                                                           |
| 1995 | 46  | M   | TB                   | Soft, reddish broad-based lesion                                                 | Productive cough, fever, hemoptysis                                       | GOG, chest discomfort                                                     | (−)                        | FLCZ, ITCZ                                                             |
| 2000 | 19  | M   | TL                    | White, subtly elevated lesion                                                    | Restriction of the bronchus                                               | NA                                                                         | (−)                        | NA                                                                     |
| 2003 | 45  | M   | T&L&LL               | White slightly raised plaque-like lesions                                        | Mass in the left hilar region                                              | NA                                                                         | (−)                        | FLCZ                                                                   |
| 2005 | 33  | M   | LUB                  | Reddish elevated lesion                                                         | HA                                                                         | NA                                                                         | (−)                        | FLCZ                                                                   |
| 2010 | 46  | M   | RUB                  | Large smooth-surfaced mass                                                       | Dyspnea, chest tightness, wheezing                                         | NA                                                                         | (−)                        | FLCZ                                                                   |

**Table 1**

Reported cases of endobronchial cryptococcosis.

| Year | Age | Sex | Site                  | Chest X-ray or CT                                                                 | Symptoms                                                                 | History                                                                 | C.organism/antigen in CSF | Therapy                                                                 |
|-----|-----|-----|-----------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------|
| 1972 | 36  | M   | RUB                  | Consolidation of the RUL                                                        | Weakness, chest pain, productive cough, weight loss                       | NA                                                                         | (−)                        | AMPH-B, resection                                                      |
| 1985 | 26  | M   | RMB                  | Large hemorrhagic lesion                                                        | NA                                                                        | NA                                                                         | (−)                        | AMPH-B, 5-FC                                                           |
| 1992 | 65  | M   | LL&B&LUB             | Mass lesion                                                                       | Dyspnea, cough, weight loss                                              | NA                                                                         | (−)                        | AMPH-B, 5-FC                                                           |
| 1995 | 46  | M   | TB                   | Soft, reddish broad-based lesion                                                 | Productive cough, fever, hemoptysis                                       | GOG, chest discomfort                                                     | (−)                        | FLCZ, ITCZ                                                             |
| 2000 | 19  | M   | TL                    | White, subtly elevated lesion                                                    | Restriction of the bronchus                                               | NA                                                                         | (−)                        | NA                                                                     |
| 2003 | 45  | M   | T&L&LL               | White slightly raised plaque-like lesions                                        | Mass in the left hilar region                                              | NA                                                                         | (−)                        | FLCZ                                                                   |
| 2005 | 33  | M   | LUB                  | Reddish elevated lesion                                                         | HA                                                                         | NA                                                                         | (−)                        | FLCZ                                                                   |
| 2010 | 46  | M   | RUB                  | Large smooth-surfaced mass                                                       | Dyspnea, chest tightness, wheezing                                         | NA                                                                         | (−)                        | FLCZ                                                                   |

**Table 1**

Reported cases of endobronchial cryptococcosis.

| Year | Age | Sex | Site                  | Chest X-ray or CT                                                                 | Symptoms                                                                 | History                                                                 | C.organism/antigen in CSF | Therapy                                                                 |
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| 1972 | 36  | M   | RUB                  | Consolidation of the RUL                                                        | Weakness, chest pain, productive cough, weight loss                       | NA                                                                         | (−)                        | AMPH-B, resection                                                      |
| 1985 | 26  | M   | RMB                  | Large hemorrhagic lesion                                                        | NA                                                                        | NA                                                                         | (−)                        | AMPH-B, 5-FC                                                           |
| 1992 | 65  | M   | LL&B&LUB             | Mass lesion                                                                       | Dyspnea, cough, weight loss                                              | NA                                                                         | (−)                        | AMPH-B, 5-FC                                                           |
| 1995 | 46  | M   | TB                   | Soft, reddish broad-based lesion                                                 | Productive cough, fever, hemoptysis                                       | GOG, chest discomfort                                                     | (−)                        | FLCZ, ITCZ                                                             |
| 2000 | 19  | M   | TL                    | White, subtly elevated lesion                                                    | Restriction of the bronchus                                               | NA                                                                         | (−)                        | NA                                                                     |
| 2003 | 45  | M   | T&L&LL               | White slightly raised plaque-like lesions                                        | Mass in the left hilar region                                              | NA                                                                         | (−)                        | FLCZ                                                                   |
| 2005 | 33  | M   | LUB                  | Reddish elevated lesion                                                         | HA                                                                         | NA                                                                         | (−)                        | FLCZ                                                                   |
| 2010 | 46  | M   | RUB                  | Large smooth-surfaced mass                                                       | Dyspnea, chest tightness, wheezing                                         | NA                                                                         | (−)                        | FLCZ                                                                   |

**Table 1**

Reported cases of endobronchial cryptococcosis.
common.

Including the present case, only 21 cases of pulmonary cryptococcosis presenting as endobronchial lesions have been reported [6–25] (Table 1). Radiological features of all the 21 cases were lung processes (mass, consolidation or atelectasis) with or without apparent endobronchial lesions, except for two cases. One of which is the present case, presenting only a polypoid endobronchial lesion in the opening of basal segment bronchi of right lower lobe without any process in lung lobe or mediastinum. The other case [21] presented as a white patchy ulcerated lesion in posterior wall of the trachea just above the carina causing narrowed bronchus intermedius, also with none process in lung lobe or mediastinum. Of the 21 cases, 6 patients [12,14–16,18,21] were immunocompromised, suffering from AIDS or other diseases maintaining a prednisolone therapy. Within the 15 immunocompetent patients [6–11,13,17,19,20,22–25], 2 patients [22,24] admitted the exposure to pigeons and 1 patient [14] suffered from DM. It’s worth mentioned that there is another interesting case [26] of pulmonary cryptococcosis in a diabetic, presenting as lung abscesses and hydro pneumothorax without endobronchial lesions, for which it wasn’t included in the 21 cases. Whether there is a connection between cryptococcosis and DM is not yet known, which should be further explored. Imaging findings of the immunocompetent patients consisted of lung mass (5/15), consolidation (3/15), nodules (1/15), endobronchial mass (2/15), endobronchial polypoid lesion (1/15), lung lobe collapse (6/15), narrowed bronchus (2/15) and lymphadenopathy (2/15). Radiological manifestations of the patients with HIV [12,18] seem to be more aggressive which presented as cavitation or fistula formation in addition to the ordinary lesions. In contrast, the difference of imaging findings between those who maintained a prednisolone therapy [14–16,21] and the immunocompetent individuals is unremarkable.

In the 20 reported cases, the location of the endobronchial lesions ranged from the trachea to the subsegmental bronchi. The bronchoscopic characteristics of these cases included white or red plaque-like, ulcerated, polypoid, nodule, lobulated, hemorrhagic, elevated, or mass lesions. In the present case, the bronchoscopy examination revealed a white smooth-surfaced polypoid lesion in the basal segment of right lower lobe causing occlusion of medial basal segment bronchus. Diagnosing pulmonary cryptococcosis may be problematic owing to lack of specificity of symptoms. A majority of patients with pulmonary cryptococcosis are asymptomatic or simply reported cough, productive sputum, fever, dyspnea, or chest pain [27–30], which were indistinguishable from other causes of pneumonia. In the 20 reported cases of endobronchial cryptococcosis, clinical presentations included cough, sputum production, chest pain, dyspnea, hemoptysis, wheezing and fever. Only one patient was asymptomatic. Apart from these, neurological syndromes such as headache, nausea, anorexia, vomiting or blurred vision were observed in 6 patients [8,12,17,18,24,25]. All of them underwent a lumber puncture and 5 of them were diagnosed as cryptococcal meningitis with cryptococcal organism or antigen positive in CSF. The left one [25] was suspected cryptococcal meningitis for his brain magnetic resonance imaging with gadolium enhancement showed many small enhancing lesions, although his cerebrospinal fluid culture was negative. In the present case, the patient complained of intermittent cough and hemoptysis with occasional low grade fever. This case could possibly be mistaken for tumor disease for the symptoms and radiological findings mimicking lung malignancy, which highlighted the importance of bronchoscopy examination and tissue biopsy in diagnosis of this sort of disease. We didn’t arrange a lumber puncture because the patient had no neurological signs at all.

Among the 20 reported cases, 3 patients [6,13,19] were treated with surgical or endoscopic resection after ineffective drug therapy. The remaining patients were treated with antifungal drugs. The antifungal drugs consisted of amphotericin-B, flucytosine, fluconazole, itraconazole and voriconazole. In the established guidelines [31], the administration of 400mg fluconazole daily (then taper to 200mg) for 6 months or itraconazole for 6 months are recommended for mild to moderate symptoms and focal pulmonary cryptococcosis. In the present case, the patient insisted on oral fluconazole 400mg daily for 9 months, which results in good clinical and radiological improvement. Now, the patient is still under follow-up.

Overall, our case is unique, as the patient had an endobronchial polypoid lesion without any process in lung lobe or mediastinum. However, our case report has limitations. First, fungal culture of the biopsy samples was not performed. As we all know, fungal culture is the most important criteria for establishing the diagnosis of fungal infection diseases. Second, we didn’t arrange lumber puncture for this patient, considering he had no neurological signs at all and the blood test of cryptococcus neoformans capsular polysaccharide antigen revealed negative.

4. Conclusion

This case highlights the fact that pulmonary cryptococcosis can present as endobronchial lesion even in immunocompetent subjects, mimicking lung tumor. Therefore it needs to be considered in the differential diagnosis of such lesions, and pathological confirmation is important in the management of primary pulmonary cryptococcosis.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All material and data described in the manuscript are available upon request to the corresponding author of the present article.

Conflicts of interest

The authors declare that they have no competing interests.

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Authors’ contributions

QZ, SYS and LX collected the data from the patient’s medical records and wrote the manuscript. QX performed pathological examination of the patient’s biopsy tissue. XLY and FY followed the patient and prospectively recorded the patient’s clinical data. SYS and LX searched PubMed and Web of Science databases for similar published cases of endobronchial cryptococcosis. All authors participated in the drafting of the manuscript and approved the final manuscript.

Author details

Department of Respiratory and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2018.09.014.

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