Respiratory Medicine Case Reports 25 (2018) 247–252

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

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

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ARTICLE INFO

Keywords:
Case report
Cryptococcosis
Endobronchial mass
Pulmonary cryptococcosis

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 gradually 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.

Abbreviations: H&E, Hematoxylin and Eosin; HIV, human immunodeficiency virus

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https://doi.org/10.1016/j.rmcr.2018.09.014
Received 26 March 2018; Received in revised form 22 September 2018; Accepted 22 September 2018

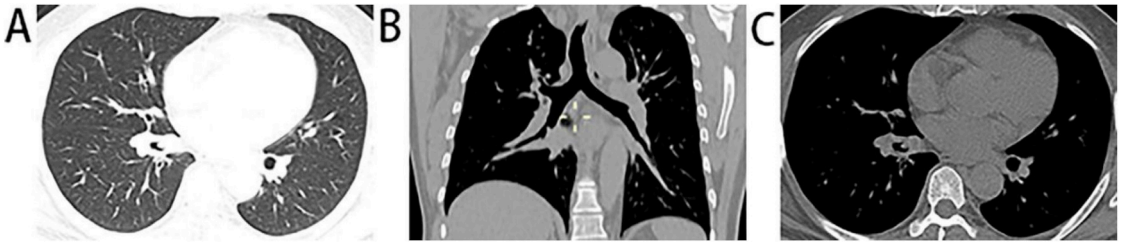

Fig. 1. Thoracic computed tomography showed a neoplasm in the basal segment bronchi of right lower lobe. A: Parenchymal window. B: Mediastinal window. C: Coronal section.

The blood assay showed white cell count 4640/mm^3 (3500–9500; neutrophils, 55.10%, lymphocytes, 32.80%), hemoglobin 14.5 g/dl (13.0–17.5) and platelet 242,000/mm^3 (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. 2B). Meanwhile, another biopsy was performed and the histological examination revealed chronic inflammation with necrosis of the superficial epithelium, but negative outcome of PAS staining. The patient was then discharged home on oral fluconazole 400 mg per day, continued fluconazole for another 6.5 months and underwent bronchoscopy examination once again. The endobronchial lesion was found disappeared completely remaining a narrow medial basal segment bronchus (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 *Cryptococcosis neoformans* were found to be less

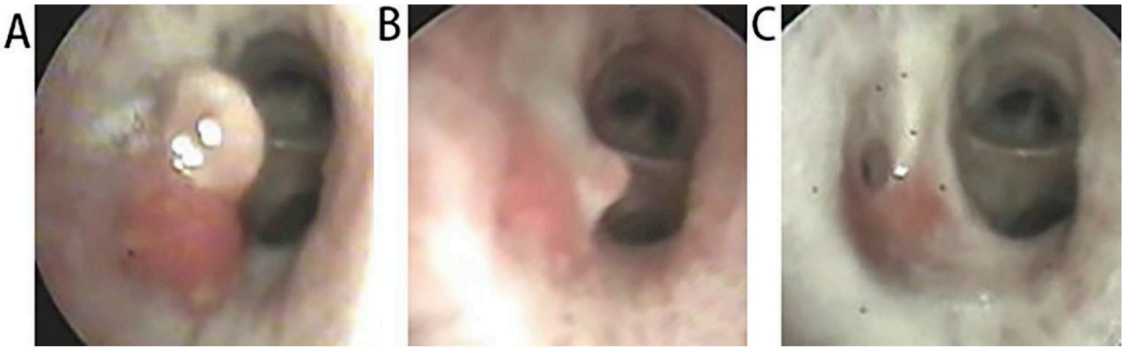

Fig. 2. Bronchoscopic examination. A: Bronchoscopic examination revealed a white smooth-surfaced polypoid lesion completely occluding the medial basal segment of the right lower lobe bronchus. B: The endobronchial lesion diminished after 18 days of treatment with oral fluconazole. C: The endobronchial lesion disappeared after 6.5 months of treatment with oral fluconazole.

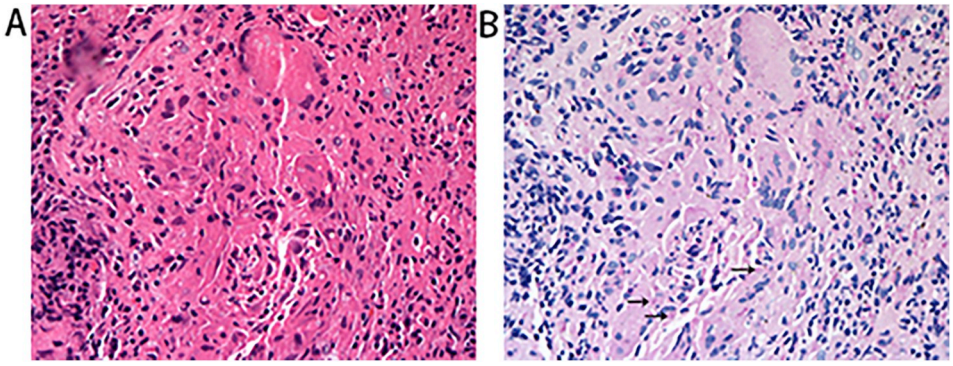

Fig. 3. Histopathological examination of the endobronchial biopsy after fiberoptic bronchoscopy. A: Histopathological examination of the endobronchial biopsy specimen showed dense accumulation of the histiocytes and yeast-form fungi that did not uptake the Hematoxylin and Eosin(H&E) staining (H&E staining, 400×). B: These organisms were positive for Periodic Acid-Schiff stain (PAS, 400×) consistent with cryptococcosis (arrows).

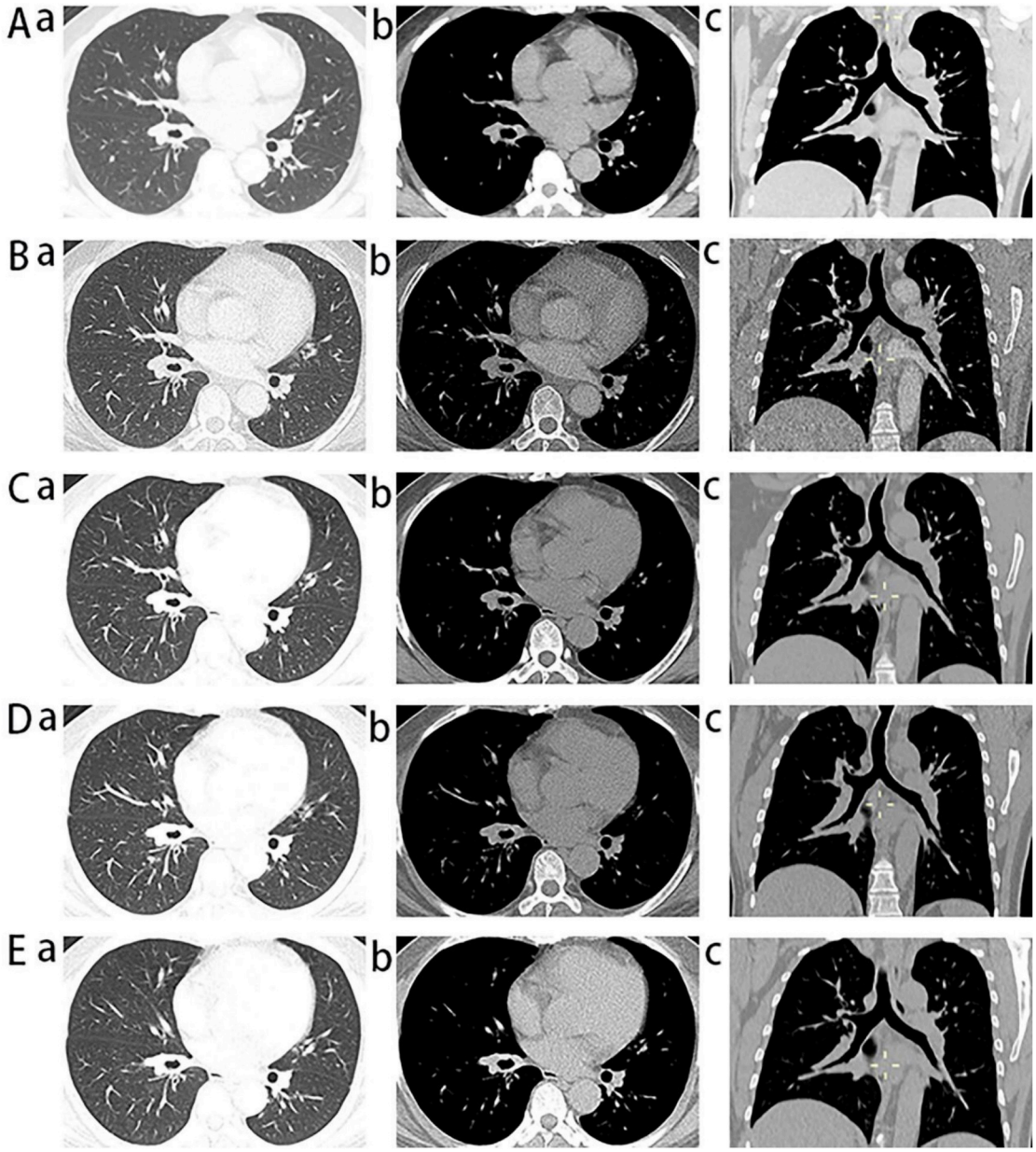

Fig. 4. Repeated thoracic computed tomography respectively after 3, 6, 9, 12 and 14 months of treatment, showing disappearance of the previous lesion in the basal segment bronchi of right lower lobe. A: CT scan after 3 month. B: CT scan after 6 months. C: CT scan after 9 months. D: CT scan after 12 months. E: CT scan after 14 months. a: Parenchymal window. b: Mediastinal window. c: Coronal section.

Table 1
Reported cases of endobronchial cryptococcosis.

Year	Age	Sex	Site	Endobronchial lesion	Chest X-ray or CT	Symptoms	History	C.organism/ antigen in CSF	Therapy	Ref
1972	36	M	RUB	Gelatinous mass	Consolidation of the RUL	Weakness, chest pain, productive cough, weight loss	(−)	NA	AMPH-B, resection	[6]
1985	26	M	RMB	Large hemorrhagic lesion	Consolidation in the RML	NA	(−)	NA	AMPH-B,5-FC	[7]
1992	65	M	LLB&LUB	Mass lesion	Left lung collapse	Dyspnea, cough, hemoptysis, weight loss, headache	(−)	(+)	AMPH-B,5-FC	[8]
1995	46	M	LMB	Soft, reddish broad-based lesion	Lingular mass, subcarinal mass	Cough	(−)	(−)	AMPH-B,5-FC, FLCZ	[9]
1996	43	M	Origin of BI	White lobulated endobronchial lesion	RML&RLL collapse	Cough, sputum, dyspnea, weight loss	(−)	NA	AMPH-B,5-FC, ITCZ	[10]
2000	19	M	TI	Reddish elevated lesion	Multiple nodular shadows	Fever, productive cough	(−)	NA	FLCZ	[11]
2003	45	M	Trachea and left bronchi	White slightly raised plaque-like lesions	Consolidation including a cavity in the LLL	Productive cough, fever, headache	AIDS	(+)	AMPH-B	[12]
2005	33	M	LUB	White polypoid lesion	Mass in the LUL bronchus, LUL collapse	Cough, chest discomfort	Type B viral hepatitis	NA	FLCZ, Resection	[13]
2005	66	F	carina	Flat ulcerated lesion	NA	Shortness of breath, noisy breathing	DM, hypertension, suspected WG, PSL 50mg/d	(−)	FLCZ	[14]
2007	54	F	LUB	Three white elevated lesion	Mass in the LUL, left hilar and mediastinal lymphadenopathy	Productive cough	Sjogren syndrome, Sweet syndrome, PSL 7.5mg/d	NA	FLCZ	[15]
2008	64	F	LPBB	White polypoid lesion	Bilateral airspace consolidation and multiple nodules	Asymptomatic	RA, PSL 10mg/d	NA	FLCZ	[16]
2008	30	M	Posterior segment of LLB	Mass lesion	Consolidation in the LLL	Hemoptysis, headache, blurred vision	(−)	(+)	AMPH-B, FLCZ	[17]
2009	35	M	Upper third of the trachea	Diffuse and irregular process affecting the tracheal wall and fistulization to the mediastinum	Tracheal wall thickening forming fistula to the mediastinum, RLL opacity	Headache, productive cough, nausea, vomiting	AIDS	(+)	AMPH-B, FLCZ, Bactrim, antiretroviral	[18]
2010	46	M	RUB	Large smooth-surfaced mass	Mass in the right hilar region, RUL atelectasis	Dyspnea, chest tightness, wheezing, cough	(−)	(−)	FLCZ, bronchoscopic resection	[19]
2012	65	M	RUB	Tumor-like growth	Mass in the RUL, the RUB narrowed	Productive cough, chest pain	(−)	NA	AMPH-B, ITCZ, anti-tuberculosis	[20]
2013	73	F	Posterior wall of the trachea just above the carina	White patchy ulcerated lesion	Narrowed BI	Dyspnea on exertion, productive cough	Bronchial asthma, PSL 5–10mg/d	(−)	FLCZ	[21]
2013	33	M	LMB	White polypoid mass lesion	Mass in the left main bronchus, LUL complete collapse and LLL partial collapse	Dry cough, breathlessness on exertion, wheezing	Exposure to pigeons	NA	AMPH-B, FLCZ,	[22]
2013	44	M	RMB orifice	Mass lesion	Mass in the RUL and right hilar, RUL bronchus narrowed (P)	Cough, hemoptysis, weight loss	(−)	NA	ITCZ, VRCZ, tracheal endoscopic ablation, AMPH-B,	[23]
2014	58	M	Each bronchial lumen of the RML	Polypoid lesions with red smooth surface	RML atelectasis, right hilar lymphadenopathy	Right chest pain, fever, anorexia, general malaise	Exposure to pigeons	(+)	FLCZ, L-AMB, 5-FC, VRCZ	[24]
2014	41	M	LMB	Aggregated white nodes	Mass in the LLL with mediastinal lymphadenopathy	Cough, wheezing, febricula, headache	(−)	(−)	L-AMB, 5-FC, FLCZ	[25]
Present case	49	M	Opening of basal segment bronchi of RLL	White polypoid lesion	Filling defect in the basal segment bronchi of RLL	Intermittent cough with hemoptysis	(−)	Not done	FLCZ	

M, male; F, female; RUB, right upper bronchus; RMB, right middle bronchus; LLB, left lower bronchus; LUB, left upper bronchus; LMB, left middle bronchus; LPBB, left posterior basal bronchus; BI, bronchus intermedius; TI, Truncus intermedius; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe; LLL, left lower lobe; LUL, left upper lobe; NA, not available; AIDS, acquired immune deficiency syndrome; DM, diabetes mellitus; WG, Wegener's granulomatosis; RA, rheumatoid arthritis; PSL, prednisolone; C.organism, cryptococcal organism; CSF, cerebrospinal fluid; AMPH-B, amphotericin B; 5-FC, 5-fluorocytosine; FLCZ, fluconazole; ITCZ, itraconazole; VRCZ, voriconazole; L-AMB, liposomal amphotericin B.

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 hydropneumothorax 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 gadolinium 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.

Funding

This work was supported by grants from National Natural Science Foundation of China (No. 81470274 and 81770090).

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. XLH 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.

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Acknowledgements

None.

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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