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MAJOR ARTICLE

Postoperative Antifungal Treatment of Pulmonary Cryptococcosis in Non-HIV-Infected and Non-Transplant-Recipient Patients: A Report of 110 Cases and Literature Review

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Background. To explore the efficacy of postoperative antifungal treatment for preventing the recurrence of pulmonary cryptococcosis (PC) and occurrence of cryptococcal meningitis (CM), a retrospective study was conducted in 112 hospitalized PC patients with or without antifungal treatment following surgery.

Methods. The treatment failure rate, PC recurrence rate, and CM incidence were compared. Additionally, the effectiveness of postoperative antifungal therapy was assessed by gathering and analyzing the published literature.

Results. The failure rate ($P = .054$) and recurrence rate ($P = .178$) were similar in the 2 groups, but the incidence of CM was lower in the group that received postoperative antifungal treatment ($P = .039$).

Conclusions. This study did not show any difference in the PC recurrence rate or failure rate in the different treatment duration groups. Thus, a shorter antifungal treatment course of 2 months may be an optional treatment. In addition, upon review of the literature, no case of CM occurrence was reported among the 169 cases given postoperative antifungal treatment.

Keywords. antifungal therapy; cryptococcal meningitis; pulmonary cryptococcosis; surgery.

Pulmonary cryptococcosis (PC) is an opportunistic infection resulting from the inhalation of contaminated fungal organisms. Although most PC studies have focused on immunocompromised hosts, such as HIV-infected patients and transplant recipients, interest in the occurrence of PC in other patients has increased recently [1]. The Infectious Diseases Society of America's (IDSA's) 2010 Clinical Practice Guidelines for the management of cryptococcosis outlined 3 key populations at risk for the disease: (1) HIV-infected individuals, (2) transplant recipients, and (3) HIV-negative/non-transplant-recipients [1]. Because there are no typical symptoms in non-HIV-infected and non-transplant-recipient PC patients and the most common imaging abnormality is a lung mass, it is difficult to differentiate PC from lung cancer, tuberculosis, or pneumonia by chest x-ray and computed tomography (CT). False-positive 18FDG-PET examinations often lead to initial clinical misdiagnosis of cancer [2].Thus, these patients often undergo segment resection and are diagnosed with PC by histopathological examination [3–5].

At present, there are no specific recommendations for additional antifungal treatment for postoperative PC patients. Revised guidelines for cryptococcal infection were developed by the IDSA in 2010, but the need for postoperative antifungal therapy has not been confirmed [1, 6–10]. Some investigators believe that non-HIV-infected and non-transplant-recipient PC patients may not need postoperative antifungal therapy if they are asymptomatic after resection of the lesion and have no clinical, serological, or radiographic evidence of extrapulmonary disease [11, 12]. For example, Kishi et al. reported no reoccurrence of PC in 8 immunocompetent patients treated only by surgical resection, implying that additional antifungal treatment might not be essential [3]. Nevertheless, the evidence is scarce and remains controversial [3, 5–7].

In addition, surgical resection can only remove PC lesions and cannot treat dormant infections outside lesions. In most cases, cryptococcal lung disease is thought to be caused by reactivation of dormant infections, and infectious vegetative bodies have been acquired long before the diagnosis of cryptococcosis [1]. Recurrence of PC and occurrence of CM may

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be caused by incomplete treatment of dormant infections outside lesions. And the central nervous system (CNS) is easily infected through the spread of the residual pathogens from the lung. Although the incidence of postoperative cryptococcal meningitis (CM) is rare, the mortality rate is as high as 20% [1] and even 30% in some studies [13, 14]. However, few efforts have been made by early studies to investigate the occurrence of postoperative CM. In the present study, we attempted to answer the urgent questions of whether postoperative antifungal treatment is indispensable for preventing PC recurrence as well as the occurrence of CM.

METHODS

Patients and Data Collection

The clinical data of 112 PC patients hospitalized in Fuzhou City of Fujian province of China from January 2008 to December 2017 were retrospectively analyzed. The inclusion criterion was PC diagnosed by surgical biopsy and histopathological examination. Cryptococcal granulomas were found in all cases based on the positive results of periodic acid Schiff (PAS) and periodic acid-silver methenamine (PASM) staining. The PC lesions and all nodules were surgically removed completely, and the clean margins were verified by a pathologist. In immunocompetent patients, the host response to *Cryptococcus* is predominantly granulomatous inflammation or granuloma, which is accompanied by various degrees of fibrosis and necrosis. The histologic diagnosis of *Cryptococcus* was based on its typical morphology of narrow-based budding yeasts (4–10 μm in size) with a thick mucicarmine-positive capsule. All the cases in our study were performed using Gomori methenamine-silver (GMS), PAS, and mucicarmine staining. Fontana Masson stain was performed in cases with fewer characteristic capsules to discriminate yeasts of similar size, such as *candida* or histoplasma. This staining works such that only cryptococci, which contain melanin, are positive, so we were able to distinguish cryptococci from other yeasts. According to the 2010 consensus reached by the IDSA and Chinese experts on the diagnosis and treatment of PC, postoperative patients did or did not receive 400 mg of fluconazole orally daily [1]. This study was approved by the Institutional Review Board (IRB) and Regional Ethics Committee of Fujian Provincial Hospital. The ethics committee waived the requirement for written informed patient consent, because this was a retrospective study based on the assessment of medical records.

Follow-up

The follow-up procedures included chest CT examination at 3–6 months postsurgery, followed by annual CT examinations for 5 years. Liver function, renal function, and electrolyte laboratory tests were conducted once a month to monitor the occurrence of adverse effects related to fluconazole. The duration of follow-up was at least 6 months after surgery and antifungal therapy. All included postoperative patients were divided into antifungal treatment and non–antifungal treatment groups. Depending on the duration of the postoperative treatment courses, the antifungal treatment patients were further divided into 2 groups: 2 months and > 2 months. These treatment course cutoffs were established according to the 2010 consensus reached by Chinese experts, which recommends at least 2 months' treatment after surgery [15]. Treatment failure was defined as postoperative recurrence of PC and/or CM occurrence. CT detection of relapse of a lung mass was regarded as a postoperative recurrence, confirmed by a transbronchial lung biopsy and absorption of the lesions after antifungal treatment. The treatment failure rate, PC recurrence rate, and CM incidence after surgery were compared between the antifungal therapy group and the non–antifungal treatment control group. In addition, the treatment failure rate and PC recurrence rate after surgery were compared among the 3 groups that received antifungal treatment for different durations.

Statistical Analysis

IBM SPSS Statistics (version 23.0) was used to analyze the patient data, including gender, age, lifestyle, clinical manifestations, immunocompromising diseases, lesion locations and sizes, presence of single or multiple nodules, types of surgery, and administration of antifungal treatment and the corresponding regimen. Continuous variables with a normal distribution were presented as mean ± standard deviation and compared by the Student *t* test or variance analysis. Proportional variables were analyzed by the Fisher exact test. *P* values <.05 were considered significant.

Literature Review

Our literature review scope included literature published in the PubMed, CENTRAL, and Embase databases before December 19, 2018, identified by searching titles and abstracts with the following keywords: "surgical treatment," "sublobar resection," "lobectomy," "segmentectomy," "wedge resection," "pulmonary cryptococcosis." The effects of postoperative antifungal treatment, including the treatment failure rate, PC recurrence rate, and CM incidence, were evaluated by collecting and analyzing the published data from the relevant literature.

RESULTS

Effects of Postoperative Antifungal Treatment

During the follow-up, 2 of the 112 patients were lost to follow-up, leaving 110 patients who were successfully followed-up with a median duration (range) of 47.70 (14–116) months by December 2018. These cases included 22 cases not given antifungal treatment, 30 cases who received 2 months of antifungal treatment, 60 cases who received >2 months of treatment. None of these 110 patients had CNS symptoms. According to the cryptococcal infection guidelines [1], routine lumbar puncture is usually unnecessary for patients without CNS symptoms to assess the

pulmonary nodule or infiltrate for normal hosts. Among the 22 patients not given antifungal treatment, 3 suffered therapy failure with 1 case of PC recurrence, 1 case of CM, and 1 case with both PC recurrence and CM occurrence. Of the 90 cases who received postoperative antifungal treatment, 2 cases were lost during follow-up, leaving 88 patients who all received oral fluconazole at a dose of 400 mg per day. Of these, there were 2 cases of relapse but no cases of CM. These patients were diagnosed with PC recurrence by surgical biopsy and histopathological examination. The failure rate did not differ significantly between the antifungal and non–antifungal treatment groups (2 of 88 vs 3 of 22; $P = .054$), nor did the PC recurrence rate (2 of 88 vs 2 of 22; $P = .178$) (Figure 1). However, the incidence of CM in the postoperative antifungal treatment group was significantly lower than in the non–antifungal treatment group (0 of 88 vs 2 of 22; $P = .039$) (Figure 1). Furthermore, statistical comparisons between the groups for all other clinical characteristics revealed a significant difference only in nodule location (Table 1), which was excluded by the subsequent risk factor analysis (Table 3). The failure rate did not differ significantly between the patients who underwent local excision and those who underwent standard lobectomy (3 of 86 vs 2 of 24; $P = .316$).

Effects of Different Antifungal Treatment Durations

As shown in Table 2, there was 1 case of PC recurrence in the group who received 2 months of antifungal treatment and 1 case in the group who received >2 months of treatment. The PC recurrence rate and failure rate did not differ significantly between the 2 groups, with differing durations of antifungal treatment ($P = 1.000$). Additionally, there was no difference in the incidence of liver dysfunction between the 2 groups ($P = 1.000$), and the liver damage rates were 2 of 30 and 4 of 58, respectively. No other adverse effects of fluconazole were observed between the 2 groups. Except for the expected differences in the medication cost ($266 ± $112, and $518 ± $188, respectively; $P < .05$), no other significant differences were found between the 2 groups with differing antifungal treatment durations (Table 2). Taken together, these results indicated that there were no differences in the clinical characteristics of patients between the 2 groups.

Review of the Literature on Postoperative Antifungal Treatment of PC

Our literature search identified 18 articles [2, 5, 6, 9, 16–29] containing 286 cases who met our search criteria (Figure 2; Table 3). Studies were rated according to the level of evidence provided according to the criteria of the Centre for Evidence-Based Medicine in Oxford, UK [30]. The methodological quality of retrospective studies was assessed by the modified Newcastle-Ottawa scale [31], which consists of 3 factors: patient selection, comparability of the study groups, and assessment of outcome. A score of 0–9 (allocated as stars) was allocated to each study. Observational studies achieving ≥6 stars were considered to be of high quality. Agreement between the 2 reviewers was 96% in study selection and 93% in quality assessment. The characteristics of the included studies, which ranged from 6 to 7 stars by the grading systems, are summarized in Table 3, and the effectiveness of postoperative antifungal treatment was evaluated. However, the quality of the literature evidence was generally

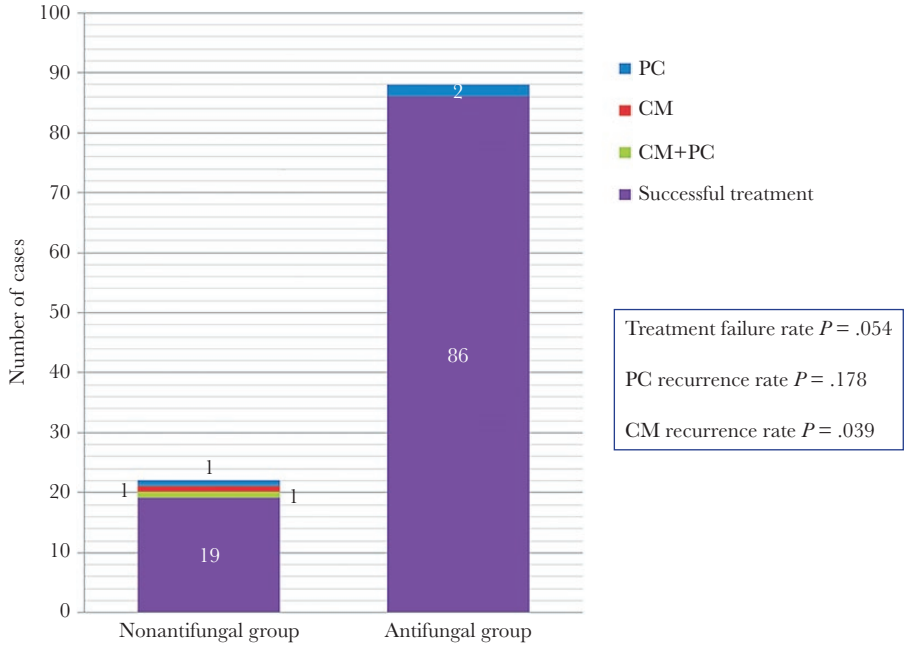

Figure 1. Comparison of the treatment failure rate, pulmonary cryptococcosis recurrence rate, and cryptococcal meningitis incidence after surgery between the antifungal therapy group and the non–antifungal treatment control group. Abbreviations: CM, cryptococcal meningitis; PC, pulmonary cryptococcosis.

Table 1. Baseline Characteristics of Patients

Factors	Nonantifungal Treatment	Antifungal Treatment	*P*
No.	22	90 (88)[a]	
Age, mean ± SD, y	49.90 ± 10.69	49.47 ± 9.16	.371
Gender			.249
Male	10 (45)	52 (59)	
Female	12 (55)	36 (41)	
Location			.008
Left lung	18 (82)	42 (48)	
Right lung	4 (18)	46 (52)	
Diameter of nodules[b] nodu^			.070
≤3 cm	12 (55)	66 (75)	
>3 cm	10 (45)	22 (25)	
Nodule types			.442
Single	14 (64)	48 (55)	
Multiple nodules in a single lobe	8 (36)	40 (45)	
Type of surgery			.778
Wedge resection	18 (82)	68 (77)	
Lobectomy	4 (18)	20 (23)	
Lifestyles[c]			.367
None	17 (77)	75 (85)	
Yes	5 (23)	13 (15)	
Clinical symptoms			.609
With	16 (73)	59 (67)	
Without	6 (27)	29 (33)	
Immunocompromising disease			.193
Without	16 (73)	76 (86)	
With	6 (27)	12 (14)	
Median duration of follow-up, mean ± SD, wk	48.91 ± 5.01	47.40 ± 1.96	.087
Failure rate	3[d] (13.636)	2 (2.273)	.054
Recurrence of PC	2 (9.091)	2 (2.273)	.178
Occurrence of CM	2 (9.091)	0 (0)	.039

Data are presented as No. (%), unless otherwise specified.

[a]Two cases were lost to follow-up.

[b]The longest lesion dimension was measured with a cutoff of 3 cm. According to the consensus of Chinese experts in lung nodules, ≤3 cm was defined as a placeholder and > 3 cm as a mass [34].

[c]Damp conditions or a history of contact with pigeons or other birds.

[d]One case of PC recurrence, 1 case of CM, and 1 case of both.

low. Matching of criteria such as underlying diseases, lifestyles, symptoms, nodule sizes, imaging characteristics, lesion locations, and types of surgery was not possible, because this information was not clearly described in all studies. Among them, treatment failure events occurred in both the antifungal (1/169) and non–antifungal treatment (4/117) groups. However, no CM incidence was reported among patients given postoperative antifungal treatment. In contrast, 3 CM cases were reported among patients without postoperative antifungal treatment. Nevertheless, because postoperative treatment failure is rare and the number of related articles was limited, a meta-analysis was almost impossible.

Case 1

The patient had an immunocompromising disease, and the PC was diagnosed by surgical biopsy and histopathological examination. Both smear and culture test of sputum and alveolar lavage fluid were negative. No postoperative treatment was administered, and PC relapse and CM occurred 1 year after surgery. The complications of type I respiratory failure and cerebrospinal fluid abnormalities were cured after treatment. This case was reported by Lan et al. in 2016 with 3 years of follow-up [27].

Case 2

A patient with an APACHE II score of 0–9 was diagnosed with mild PC by surgical biopsy and histopathological examination. Immunoassay showed that the *cryptococcus* capsular polysaccharide antigen titer was negative (≤1:4). After surgery, this patient did not receive any treatment until the PC relapsed, and the conditions were improved by further therapy. This case was reported by Wang et al. in 2014 with continued follow-up [25].

Case 3

A patient with an APACHE II score of 10–20 was also reported by Wang et al. in 2014; this individual was diagnosed with

Table 2. Baseline Characteristics of Patient Groups According to the Duration of Postoperative Antifungal Treatment

Factors	2 mo	>2 mo	*P*
No.	30	60 (58)[a]	.426
Age, mean ± SD, y	50.57 ± 9.354	48.91 ± 9.097	
Gender, No. (%)			.820
Male	17 (57)	35 (60)	
Female	13 (43)	23 (40)	
Location			.265
Left lung	13 (43)	33 (57)	
Right lung	17 (57)	25 (43)	
Nodule size			1.000
≤3 cm	23 (77)	43 (74)	
>3 cm	7 (23)	15 (26)	
Nodule type			.824
Single	17 (57)	31 (53)	
Multiple nodules in a single lobe	13 (43)	27 (47)	
Type of surgery			1.000
Wedge resection	24 (80)	44 (76)	
Lobectomy	6 (20)	14 (24)	
Lifestyles[b]			1.000
Without	26 (87)	49 (84)	
With	4 (13)	9 (16)	
Clinical symptoms			.157
With	17 (57)	42 (72)	
Without	13 (43)	16 (28)	
Immunocompromising disease			.744
Without	27 (90)	49 (84)	
With	3 (10)	9 (16)	
Recurrence	1 (3.333)	1 (1.724)	1.00
Occurrence of CM	0	0	
Cost, mean ± SD, $	266 ± 112	518 ± 188	<.05
Liver dysfunction	2 (6.667)	4 (6.897)	1.000

Data are presented as No. (%), unless otherwise specified.

Abbreviation: CM, cryptococcal meningitis.

[a]Two cases were lost to follow-up.

[b]Damp conditions or a history of contact with pigeons or other birds.

severe PC by surgical biopsy and histopathological examination. After postoperative antifungal treatment for 3–12 months, PC relapsed, although the conditions were finally improved by further therapy. This case was still in further follow-up when the article was published [25].

Case 4

A 63-year-old immunocompetent male was admitted with a right lung mass accidentally found after trauma. PC was diagnosed by surgical biopsy and histopathological examination. He did not receive any postoperative treatment, and the CM developed 5 months after surgery and was cured by further therapy. This case was reported by Hu et al. in 2006 with 30 months of follow-up [18].

Case 5

This immunocompetent patient was diagnosed with PC by surgical biopsy and histopathological examination. No cryptococcosis was detected by bronchoscopic examination. The patient did not receive any postoperative treatment, and PC relapse and CM development occurred after surgery. The conditions were improved by further therapy. The case was reported by Liu et al. in 2006 with continued follow-up until the article was published [17].

DISCUSSION

In this report, our retrospective review of 110 cases revealed no significant differences in the PC recurrence rate between groups with and without antifungal treatment. Therefore, in consideration of the limited sample size in the present study, we cannot definitively conclude that postoperative antifungal treatment is dispensable. On the other hand, the postoperative CM incidence among 88 cases in the antifungal treatment group was significantly lower than that in the non–antifungal treatment group. In addition, no CM incidence has been reported in 169 postoperative antifungal treatment cases described in the published literature. Taken together, these results strongly support

Table 3. Summary of Literature Review

Study	Year	Design	Nation	Level of Evidence	Antifungal Treatment Length, mo	Patients, No.	Event	Follow-up Period, y	Quality Score
Nadrous et al. [6]	2003	R		4	0	6	0	1.6	★★★★★★★
Wang et al. [16]	2005	R	China	4	0	10	0		
Liu et al. [17]	2006	R	China	4	6–12	19	0	2–5	★★★★★★★
	2006				0	6	1 case PC and CM		
Igai et al. [5]	2006	R	Japan	4	1–2	6	0	2	★★★★★★★
Hu et al. [18]	2006	R	China	4	0.5–6	2	0	2.5–6	★★★★★★★
	2006				0	5	1 case CM		
Kishi et al. [2]	2006	R	Japan	4	0	8	0	3.5	★★★★★★★
Dewar et al. [9]	2008	R	Canada	4	0	2	0		★★★★★★
Sakurai et al. [19]	2009	R	Japan	4	NA	4	0	NA	★★★★★★
	2009				0	4	0		
Ito et al. [20]	2011	R	Japan	4	NA	1	0	NA	★★★★★★
	2011				0	16	0		
Ye et al. [21]	2012	R	China	4	NA	26	0	NA	★★★★★★
	2012				0	9	0		
Xie et al. [22]	2012	R	China	4	1–1.5	51	0	3.5	★★★★★★★
	2012				0	18	0		
Yu et al. [23]	2012	R	China	4	1–2	5	0	3–11	★★★★★★★
	2012				0	4	0		
Peng et al. [24]	2014	R	China	4	0.67–4	14	0	0.1–3.6	★★★★★★
	2014				0	4	0		
Wang et al. [25]	2014	R	China	4	6–12	8	1 case PC	NA	★★★★★★
	2014				0	15	1 case PC		
Hayakawa et al. [26]	2015	R	Japan	4	3	2	0		★★★★★★
Lan et al. [27]	2016	R	China	4	3–6	26	0	0.3–3	★★★★★★★
	2016				0	5	1 case PC and CM		
Kanjanapradit et al. [28]	2017	R	Thailand	4	6	3	0	0.5	★★★★★★
Wang et al. [29]	2018	R		4	3	2	0		
					0	5	0		

Treatment length 0 = no antifungal treatment after surgery (total of 117 cases).

Abbreviations: NA, treated with antifungal treatment but the duration was not available; R, retrospective analysis.

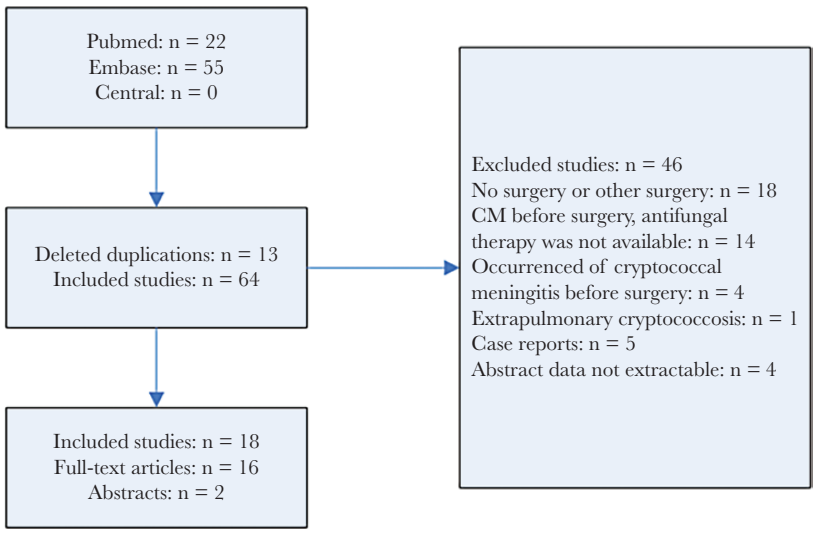

Figure 2. Flow diagram of identification of relevant literature reports. Abbreviation: CM, cryptococcal meningitis

the idea that the hematogenous spread of cryptococci to the CNS after surgery can be prevented by early vigorous antifungal treatment [7].

For PC patients with mild to moderate symptoms, the present antifungal treatment scheme includes oral fluconazole (400 mg per day orally) for 6–12 months [1]. However, the specific postoperative treatment and optimal duration of therapy have not been precisely elucidated. In our retrospective study, the PC recurrence rate and failure rate did not differ significantly between the 2 groups with different antifungal treatment durations. There also was no difference in the incidence of liver dysfunction among the 2 groups. Therefore, in consideration of the high cost, the effect of extended antifungal treatment after surgery is limited, and a shorter treatment course of 2 months may be an optional treatment. At the same time, similar PC recurrence and CM occurrence rates were found between the groups that underwent 2 types of surgery ($P = .316$), indicating that standard lobectomy may not be needed if local excision can remove lesions completely. Considering these findings together, we propose that a regimen of 2 months of oral fluconazole treatment following lung local wedge resection is economical and optional for preventing PC recurrence and CM occurrence.

There were some limitations in the current study. For example, in our study, lumbar puncture was not performed to rule out asymptomatic CNS involvement, although according to the cryptococcal infection guidelines [1], routine lumbar puncture is usually unnecessary for patients without CNS symptoms to assess the pulmonary nodule or infiltrate for normal hosts. The PC diagnosis tests also include pathogen culture, smear slides, and cryptococcal latex agglutination test, but the results of these laboratory tests were not fully available for this retrospective study. Whether fluconazole was given was based on the experience of the governing physician, which may have led to selection bias. The canavanine-glycine-bromothymol blue assay and genome sequencing were not applied, making it difficult to distinguish cases of infection by *C. neoformans* from *C. gattii* [32, 33]. Moreover, antibiotic resistance can reduce the effectiveness of antifungal therapy. Nevertheless, in our clinical laboratory, cryptococcosis pathogen identification (ID) and antibiotic susceptibility test (AST) are not available. Therefore, we cannot exclude the possibility that the presence of resistant strains may have contributed to the postoperative therapy failure. If the antifungal drug can be selected based on a drug susceptibility test, the postoperative treatment failure rate will be further reduced. Second, this retrospective study had a follow-up length of <9 years, whereas cryptococcosis may recur decades later when triggered by other conditions. Furthermore, the sample size was relatively small, and the treatment sites were limited to 3 hospitals in a local region of China. In summary, a prospective, large-sample case–control study is needed to validate and reinforce our conclusions.

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Compliance with ethical standards. All authors confirm compliance with ethical standards.

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Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis **2010**; 50:291–322.
2. Zhang Y, Li N, Zhang Y, et al. Clinical analysis of 76 patients pathologically diagnosed with pulmonary cryptococcosis. Eur Respir J **2012**; 40:1191–1200.
3. Kishi K, Homma S, Kurosaki A, et al. Clinical features and high-resolution CT findings of pulmonary cryptococcosis in non-AIDS patients. Respir Med **2006**; 100:807–12.
4. Doo SK, Soo LK, Pyo CM, et al. Pulmonary cryptococcosis: imaging findings in 23 non-AIDS patients. Korean J Radiol **2010**; 11:407–16.
5. Igai H, Gotoh M, Yokomise H. Computed tomography (CT) and positron emission tomography with [18F]fluoro-2-deoxy-d-glucose (FDG-PET) images of pulmonary cryptococcosis mimicking lung cancer. Eur J Cardio-Thorac Surg **2006**; 30:837–9.
6. Nadrous HF, Antonios VS, Terrell CL, Ryu JH. Pulmonary cryptococcosis in nonimmunocompromised patients. Chest **2003**; 124:2143–7.
7. Wu B, Liu H, Huang J, et al. Pulmonary cryptococcosis in non-AIDS patients. Clin Invest Med **2009**; 32:E70–7.
8. Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryptococcosis: clinical implications from a study of 41 patients with and without compromising host factors. Ann Intern Med **1981**; 94:611–6.
9. Dewar GJ, Kelly JK. *Cryptococcus gattii*: an emerging cause of pulmonary nodules. Can Respir J **2008**; 15:153–7.
10. Perfect JR, Cloud GA, Henderson H, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis **2001**; 33:690–9.
11. Aberg JA. Pulmonary cryptococcosis in normal hosts. Chest **2003**; 124:2049–51.
12. Aberg JA, Mundy LM, Powderly WG. Pulmonary cryptococcosis in patients without HIV infection. Chest **1999**; 115:734–40.
13. Brizendine KD, Baddley JW, Pappas PG. Predictors of mortality and differences in clinical features among patients with cryptococcosis according to immune status. PLoS One **2013**; 8:e60431.
14. Bratton EW, El Husseini N, Chastain CA, et al. Comparison and temporal trends of three groups with cryptococcosis: HIV-infected, solid organ transplant, and HIV-negative/non-transplant. PLoS One **2012**; 7:e43582.
15. Wen M, et al. Chinese expert consensus statement on management of cryptococcal infection. Chinese J Mycol **2010**; 5:65–8.
16. Wang T, Sun YE, Yu CH, et al. Surgical treatment of primary pulmonary cryptococcosis. J Clin Pulm Med **2005**; 43:1447–1449.
17. Liu M, Jiang GN. Surgical treatment of pulmonary cryptococcosis. Chinese J Tuberc Respir Dis **2006**; 29:307–309.
18. Hu HJ, Zhou P, Hu JB, et al. A report of 12 cases of primary pulmonary cryptococcosis. Chinese J Inter Med **2006**; 45:721–4.
19. Sakurai H, Kaji M, Seumasu K. Clinicopathological characteristics of pulmonary cryptococcosis. Kyobu Geka **2009**; 62:863–7.
20. Ito A, Tachibana H, Ishida T. Clinical characteristics of surgically-diagnosed pulmonary cryptococcosis. Eur Respir J **2011**; 38:SUPPL.55.
21. Ye F, Xie JX, Zeng QS, et al. Retrospective analysis of 76 immunocompetent patients with primary pulmonary cryptococcosis. Lung **2012**; 190:339–46.
22. Xie D, Chen XF, Jiang GN, et al. Clinical analysis of 81 cases of pulmonary cryptococcosis. Chin J Surg **2012**; 50:430–3.
23. Yu JQ, Tang KJ, Xu BL, et al. Pulmonary cryptococcosis in non-AIDS patients. Braz J Infect Dis **2012**; 16:531–9.

24. Peng YT, Ouyang RY, Jiang Y. Clinical characteristics of primary pulmonary cryptococcosis in 28 patients. J Cent South Univ **2014**; 39:49–55.
25. Wang L, Shi Y, Ding Y, et al. Pulmonary cryptococcosis: a retrospective analysis of 65 cases. Chinese J Tuberc Respir Dis **2014**; 37:764–768.
26. Hayakawa M, Oda K, Uda H. Two cases of pulmonary cryptococcosis mimicking lung cancer. Haigan **2015**; 55:1075–9.
27. Lan CQ, Weng H, Li HY, Chen L, Huang JB. Retrospective analysis of 117 cases of pulmonary cryptococcosis. Chinese J Tuberc Respir Dis **2016**; 39:862–5.
28. Kanjanapradit K, Kosjerina Z, Tanomkiat W, et al. Pulmonary cryptococcosis presenting with lung mass: report of 7 cases and review of literature. Clin Med Insights Pathol **2017**; 10:1179555717722962.
29. Wang D, Wu C, Gao J, et al. Comparative study of primary pulmonary cryptococcosis with multiple nodules or masses by CT and pathology. Exp Ther Med **2018**; 16:4437–44.
30. Phillips B, Ball C, Sackett D, et al. Levels of evidence and grades of recommendation. Oxford Centre for Evidence-based Medicine Website. Available at: http://www.cebm.net/index.aspx?o=1025. Accessed 26 April 2012.
31. Wells G, Shea B, O`Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute Website. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 15 March 2012.
32. Dixit A, Carroll SF, Qureshi ST. *Cryptococcus gattii*: an emerging cause of fungal disease in North America. Interdiscip Perspect Infect Dis **2009**; 2009:1–13.
33. Diaz M, Fell JW, Boekhout T, et al. Proposal to conserve the name *Cryptococcus gattii* against *C. hondurianus* and *C. bacillisporus* (*Basidiomycota, Hymenomycetes, Tremellomycetidae*). Taxon **2002**; 51:804–6.
34. Wang L, Hong QY, et al. Interpretation of Chinese expert consensus on the diagnosis and treatment of pulmonary nodules (2018 version). Chinese J Pract Inter Med **2018**; 41:763–71.