Original Article

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Imaging of pulmonary cryptococcosis with consolidations or diffuse infiltrates suggests longer clinical treatment in non-HIV patients

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SUMMARY This article was to summarize the clinical features and treatment course in patients with pulmonary cryptococcal infections with different imaging manifestations and to analyse the relevant factors. Categorical variables are described in this paper as percentages, and continuous variables are expressed as medians and quartiles or means and standard deviations. Factors associated with prolonged treatment of pulmonary cryptococcosis with different imaging manifestations were estimated via multivariable analyses with the Cox proportional hazards model. A total of 238 patients were analysed. A significant proportion of patients with diabetes mellitus constituted 18% to 25% of patients with multiple nodules and diffuse infiltrates ($p = 0.026$). The serum antigen level was markedly elevated in patients with diffuse infiltrates and consolidation ($p < 0.001$). A significant proportion of patients who presented with solitary nodules were initially diagnosed through thoracic surgery conducted to remove the lesion ($p < 0.001$). The treatment duration for patients with pulmonary cryptococcosis presenting as single or multiple nodules on imaging was shorter than the traditionally considered 6 months ($p < 0.001$). Imaging revealed that pulmonary cryptococcosis most commonly involved the right lower lung. Serum antigen assays, the number of infectious lobes, the presence of extrapulmonary lesions and the presence of lesions in the lower right lobe were suggested to be predictive indicators for a longer treatment duration. There was no significant difference in the percentage of patients who used amphotericin B or amphotericin B liposomes among patients with the four different types of imaging presentations.

Keywords pulmonary cryptococcosis, imaging characteristics, treatment, prognosis

1. Introduction

Cryptococcus can infect any tissue or organ of the human body. The respiratory system is the most common site of infection, followed by the central nervous system and skin (*1,2*). Chest imaging, which uses high-resolution computed tomography (HRCT), forms a cornerstone of the diagnostic toolkit for pulmonary cryptococcosis. Patients may have single or multiple parenchymal nodules, which are often subpleural (*3*); moreover, cavitation may be observed, particularly in immunocompromised patients (*4*).

Although the imaging features of pulmonary cryptococcosis have been previously reported in the literature, there are few studies on the relationship between imaging and clinical manifestations of pulmonary cryptococcosis (*5-7*). In this investigation, we analysed the pulmonary imaging characteristics of 216 patients with cryptococcosis. This is the first study to evaluate the different clinical features presented by different imaging manifestations, and it is also the first to investigate the response of different imaging manifestations to therapeutic drugs and the role of imaging manifestations in determining patient prognosis.

2. Patients and Methods

2.1. Case series

Patients were deemed eligible if they were admitted to the Infectious Diseases Department at Zhongshan Hospital, Fudan University, between January 1, 2012, and December 31, 2021. Data regarding patient demographics, clinical features, laboratory results, pathogenic findings, treatments, and outcomes were obtained from the Zhongshan Hospital Information System. This project received approval from the Ethics

Committee of Zhongshan Hospital (Ethics approval number B2024-276), and informed consent was obtained from all the subjects or their legal guardians. All research was performed in accordance with relevant guidelines and the Declaration of Helsinki. All the data were reviewed by two physicians (QQW and YS), and any discrepancies in interpretation between the primary reviewers were resolved by a third researcher (JP and BJH). The data that support the findings of this study are available from the corresponding author.

2.2. Case definition

Cryptococcosis patients include confirmed and clinical patients. Confirmed cryptococcosis was identified as a positive result of Cryptococcus culture from any site. Clinical cryptococcosis can be identified by positive histopathology or cryptococcal antigen results, together with clinical or radiographic evidence of disease (*8*). The treatment duration refers to the period between starting the medication and discontinuing it. Improvement days denote the period between the initiation of medication and the improvements seen on chest imaging. The morphological features on CT scans can be categorized as solitary nodules/masses, multiple nodules/masses, consolidation, or diffuse infiltrates (nodules/masses with consolidation) (*3*) (Figure 1).

2.3. Statistical analysis of data

Depending on the data distribution, categorical variables are described herein as percentages, and continuous variables, including age, serum antigen assay, improvement days and treatment days, are described as medians and quartiles. Continuous variables, including laboratory results, are described as the means and standard deviations. The chi-square test was used to screen for differences in sex, immune status, chronic disease, clinical symptoms at onset, medical or surgical treatment, extrapulmonary involvement, lesions that improved but remained nonresorbed, CT characteristics, the number of involved lung lobes and treatment. A median comparison of nonparametric tests was used to compare age, serum antigen assay, improvement days and treatment days. Independent sample Kruskal–Wallis tests of nonparametric tests were used to compare laboratory results. Factors associated with prolonged treatment of pulmonary cryptococcosis with different imaging manifestations were estimated *via* multivariable analyses with the Cox proportional hazards model. A probability (P) value < 0.05 indicated a statistically significant difference. Statistical analyses were performed *via* SPSS software (version 23). The figures were created through GRAPHPAD PRISM 8.0.

3. Results

3.1. Patient selection and classification

A total of 238 patients were included in this analysis. Of these, 216 patients with pulmonary Cryptococcus infection (15 cases with positive culture) and other site infections in combination with pulmonary infection were subjected to further analysis (Figure 2).

3.2. Clinical manifestations and laboratory results

A significant proportion of patients with diabetes mellitus constituted 18% to 25% of patients with multiple nodules and diffuse infiltrates ($p = 0.026$). As seen in Table 1, over half of the patients with solitary nodules and diffuse infiltrates presented with clinical manifestations, the most prevalent of which was cough ($p < 0.001$). Compared with that in patients with solitary nodules and multiple nodules, the serum antigen level was markedly elevated in patients with diffuse infiltrates and consolidation ($p < 0.001$). A significant proportion of patients who presented with solitary nodules were initially diagnosed with thoracic surgery to remove the lesion ($p < 0.001$). The treatment duration for patients with pulmonary cryptococcosis presenting as single or multiple nodules on imaging was shorter than the traditionally considered 6 months ($p < 0.001$). The proportion of patients who exhibited lesion improvement but persistent lesion nonresorption was significantly greater in patients who presented with consolidation and diffuse pulmonary infiltrates ($p < 0.001$).

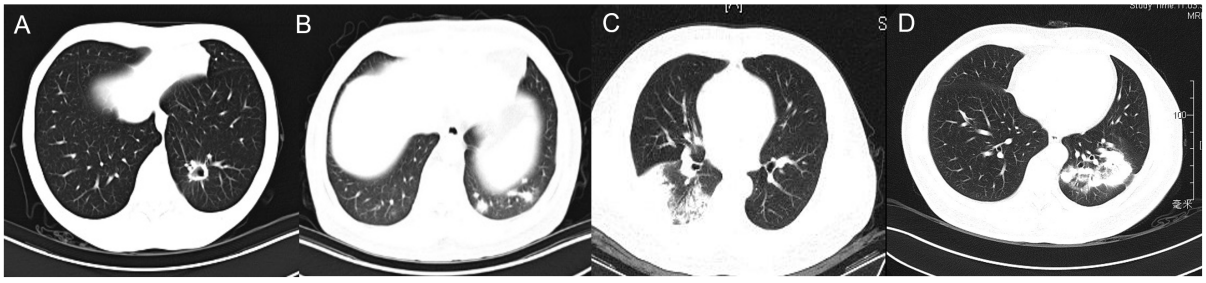

Figure 1. Classification of the imaging manifestations of Cryptococcus pneumoniae. A: Solitary nodule. **B:** Multiple nodules. **C:** Consolidation. **D.** Diffuse infiltrates (nodules/mass with consolidation).

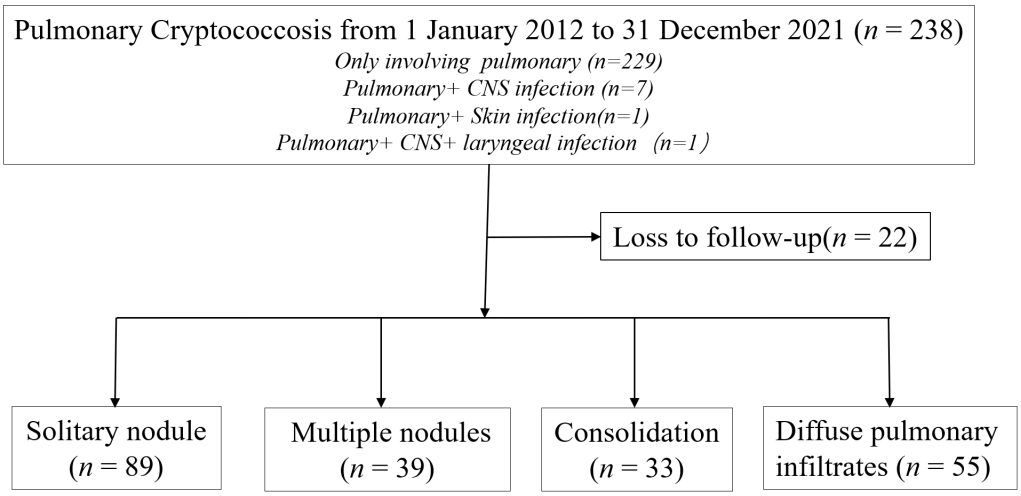

Figure 2. Flow chart of case selection and chest imaging classification. CNS: central nervous system.

Table 1. Clinical manifestations and laboratory resultsalue

Items	Solitary nodule (*n* = 89)	Multiple nodules (*n* = 39)	Consolidation (*n* = 33)	Diffuse pulmonary infiltrates (*n* = 55)	Chi-square Value	*p*
Male/female	50 (56.18)	27 (69.23)	20 (60.61)	32 (58.18)	1.995	0.573
Age, years	49 (42,59)	52 (44,64)	48 (39.64)	52 (42,63)	/	0.376
Immunocompetent/ Immunocompromised	70 (78.65)	31 (79.49)	26 (78.79)	40 (72.73)	0.896	0.826
Chronic disease						
Diabetes	6 (6.74)	10 (25.64)	4 (12.12)	10 (18.18)	9.239	0.026*
Chronic kidney disease	0 (0.00)	1 (2.56)	0 (0.00)	0 (0.00)	4.560	0.207
Solid organ transplantation	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1.434	0.698
Rheumatologic disease	1 (1.12)	0 (0.00)	0 (0.00)	1 (1.82)	1.188	0.756
Solid tumours	8 (8.99)	2 (5.13)	2 (6.06)	1 (1.82)	3.158	0.368
Haematologic malignancy	0 (0.00)	1 (2.56)	2 (6.06)	3 (5.45)	5.326	0.149
Chronic steroid or immunosuppressive drug use	7 (7.87)	6 (15.38)	3 (9.09)	8 (14.55)	2.464	0.482
Chronic liver disease	2 (2.25)	1 (2.56)	2 (6.06)	4 (7.27)	2.697	0.441
Clinical symptoms at onset	20 (22.47)	14 (35.90)	19 (57.58)	30 (54.55)	20.835	< 0.001*
Fever	7 (7.87)	4 (4.49)	8 (24.24)	11 (20.00)	7.806	0.050
Cough	13 (14.61)	10 (11.24)	14 (42.42)	26 (47.27)	20.902	< 0.001*
Expectoration	10 (11.24)	10 (11.24)	9 (27.27)	20 (36.36)	13.109	0.004*
Shortness of breath	2 (2.25)	0 (0.00)	1 (3.03)	2 (3.64)	1.455	0.693
Chest pain	3 (3.37)	1 (2.56)	4 (12.12)	5 (20.00)	5.017	0.171
Serum antigen assay	7.5 (0,20)	20 (15,40)	40 (10,320)	80 (20,320)	/	< 0.001*
Leukocytes $*10^9$/L	6.66 ± 1.89	6.70 ± 2.74	7.30 ± 3.81	6.87 ± 2.52	/	0.781
Neutrophils $*10^9$/L	4.43 ± 1.74	4.50 ± 2.70	4.91 ± 3.55	4.73 ± 2.40	/	0.700
Lymphocytes $*10^9$/L	1.34 ± 0.71	1.60 ± 0.74	1.58 ± 0.57	1.41 ± 0.61	/	0.357
CD4 (cells/μL)	462.28 ± 369.48	479.88 ± 365.03	435.04 ± 416.97	496.41 ± 311.28	/	0.838
ESR (mm/H)	14.69 ± 12.99	17.36 ± 18.30	28.12 ± 30.89	21.27 ± 19.95	/	0.239
CRP (mg/L)	4.88 ± 7.40	8.08 ± 16.48	13.71 ± 29.63	10.48 ± 20.10	/	0.534
IL-2 (U/mL)	204.54 ± 251.84	369.57 ± 231.64	378.45 ± 160.56	659.20 ± 663.65	/	0.062
IL-6 (pg/mL)	2.26 ± 3.30	4.02 ± 3.79	3.29 ± 2.56	5.06 ± 5.78	/	0.022
INF-γ (pg/mL)	6.63 ± 7.32	8.52 ± 7.97	32.49 ± 96.91	11.26 ± 9.20	/	0.106
Initial treatment: Medication/ surgery	47 (52.81)	29 (74.36)	33 (100.00)	54 (98.18)	50.754	< 0.001*
Involvement of other sites	3 (3.37)	2 (5.13)	1 (3.03)	2 (3.64)	0.292	0.961
Improvement days	33 (27,58)	40 (33,58)	32 (16,62)	30 (14,45)	/	0.149
Treatment days	111 (31,199)	150 (90,307)	207 (134,323)	280 (163,364)	/	< 0.001*
Improved but nonresorbed lesions	40 (44.94)	24 (61.54)	29 (87.88)	47 (85.45)	60.076	< 0.001*

The values in brackets for chronic disease, clinical symptoms at onset, medication, other parts involved and lesions that improved but remained nonresorbed are percentages, and the values in brackets for age, serum antigen assay, improvement days and treatment days are quartiles. Bolded text and asterisks (*) indicate significant differences. ESR: erythrocyte sedimentation rate, CRP: high-sensitivity C-reactive protein, IL-2: interleukin-2, IL-6: interleukin-6, INF-γ: interferon-gamma. Involvement of other sites: 9 cases are shown in Figure 2.

3.3. Imaging manifestations

Burrs were most commonly observed in solitary nodules or multiple nodules, followed by lobulation ($p = 0.031$*) and cavitation. The air bronchial sign was the predominant manifestation on imaging of consolidation and diffuse pulmonary infiltrates ($p < 0.001$*). Imaging of single nodules, multiple nodules, and consolidation of pulmonary cryptococcosis most commonly involved the right lower lung, followed by the left lower lung in Table 2.

3.4. Factors related to the treatment course

It was proposed that the serum antigen assay, the number of infectious lobes, and the involvement of extrapulmonary lesions and lower right lobes be employed as predictive indicators for a longer treatment duration than the median treatment duration for patients with different imaging manifestations (Figure 3).

3.5. Treatment for different imaging manifestations and prognoses

There was no significant difference in the percentage of patients who used amphotericin B or amphotericin B liposomes among patients with four different types of imaging presentations. Only one patient who underwent imaging for consolidation died because of

Table 2. Imaging manifestations

Items	Solitary nodule ($n = 89$)	Multiple nodules ($n = 39$)	Consolidation ($n = 33$)	Diffuse pulmonary infiltrates ($n = 55$)	Chi-square Value	p
CT characteristic						
lobulation	13 (14.61)	4 (10.27)	0 (0.00)	2 (3.64)	8.857	0.031*
burr	17 (19.10)	9 (23.08)	2 (6.06)	5 (9.09)	6.630	0.085
cavitation	11 (12.36)	5 (12.82)	3 (9.09)	10 (1.82)	1.703	0.636
halo sign	1 (1.12)	2 (5.13)	1 (3.03)	5 (9.09)	5.601	0.133
air bronchial sign	1 (1.12)	4 (10.26)	8 (24.24)	17 (30.91)	28.836	< 0.001*
mediastinal lymph nodes	2 (2.24)	4 (10.26)	1 (3.03)	2 (3.64)	4.589	0.205
pleural effusion	0 (0.00)	0 (0.00)	1 (3.03)	0 (0.00)	5.571	0.135
Involvement of lung lobes						
upper left lobe	10 (11.24)	14 (35.90)	6 (18.18)	22 (40.00)	106.481	< 0.001*
lower left lobe	24 (26.97)	18 (46.15)	10 (30.30)	10 (18.18)	160.782	0.005*
upper right lobe	17 (19.10)	16 (41.02)	5 (15.15)	19 (34.55)	119.555	0.013*
middle right lobe	4 (4.49)	17 (43.59)	7 (21.21)	10 (18.18)	69.319	< 0.001*
lower right lobe	34 (38.20)	25 (64.10)	17 (51.52)	31 (56.36)	208.152	0.030*

The values in brackets are percentages, and the values in bold and * indicate significant differences.

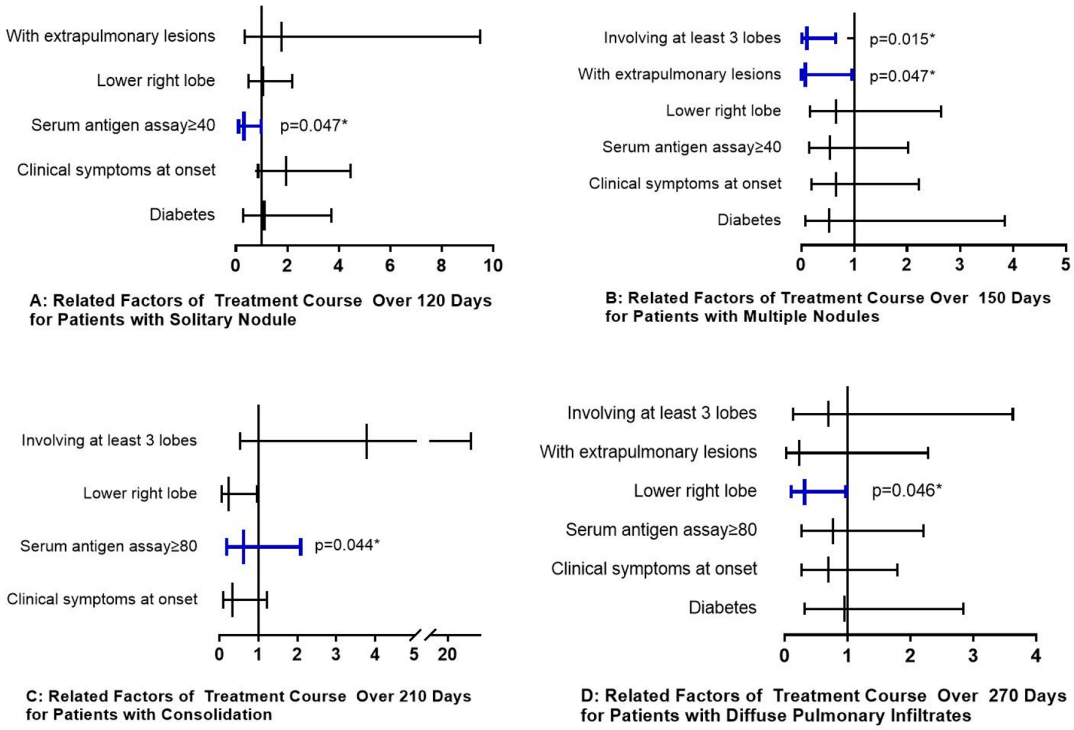

Figure 3. Factors associated with prolonged treatment of pulmonary cryptococcosis with different imaging manifestations.

Table 3. Treatments for the different imaging manifestations

Treatment	Solitary nodule (*n* = 89)	Multiple nodules (*n* = 39)	Consolidation (*n* = 33)	Diffuse pulmonary infiltrates (*n* = 55)	Chi-square Value	*p*
No medicine	23 (25.84)	6 (15.38)	0 (0.00)	0 (0.00)	25.581	< 0.001*
Triazoles ± Fluorocytosine	54 (60.67)	27 (69.23)	28 (84.85)	50 (90.91)	18.671	< 0.001*
Amphotericin B/ Amphotericin B Liposome after Fluconazole	6 (6.90)	5 (12.82)	5 (15.15)	4 (7.27)	2.882	0.410
Amphotericin B/ Amphotericin B Liposome ± Fluorocytosine	4 (4.49)	1 (2.56)	0 (0.00)	1 (1.82)	2.108	0.550
Surgery after medication	2 (2.25)	0 (0.00)	0 (0.00)	0 (0.00)	2.881	0.410

The values in brackets are percentages. Bold and * indicate significant differences. Triazoles include fluconazole, voriconazole and itraconazole. Amphotericin B/amphotericin B Liposome after fluconazole: Fluconazole was ineffective at treating this condition; thus, the treatment was switched to amphotericin B/amphotericin B Liposome.

myelodysplastic syndrome in Table 3.

4. Discussion

Consideration of imaging changes is highly important when evaluating the efficacy of pulmonary cryptococcosis treatment. This paper presents an inaugural examination of the time to improvement in patients exhibiting pulmonary cryptococcosis with varying imaging manifestations. Our findings contrast with our initial hypothesis that the time to improvement on imaging would be dependent on the lesion size. However, the time to improvement was approximately four weeks for both the nodular and diffuse lesions. These results suggest that a period of approximately four weeks should be allowed for follow-up imaging to assess improvement following the use of antifungal drugs.

The global guidelines for diagnosing and managing cryptococcosis indicate that the recommended course of treatment for pulmonary cryptococcosis is 6–12 months, with the possibility of a shorter duration (*e.g.*, 3 months) in immunocompetent individuals with mild isolated pulmonary cryptococcosis (*9*). This conclusion is generally consistent with the findings of our study. We aimied to further prognosticate the treatment time that may be required for different imaging presentations. Our findings indicate that the treatment of a single nodule or multiple nodules may take less than six months, whereas the treatment of patients showing consolidation and diffuse pulmonary infiltrates upon imaging may require six to twelve months.

The question of when treatment for pulmonary cryptococcosis can be discontinued has always been of great interest to clinicians. Only 12–55% of patients with pulmonary cryptococcosis achieve complete resolution of their intrapulmonary lesions, and the majority of patients will have long-term residual intrapulmonary lesions. In our study, lesions extending to a single nodule stabilized after approximately four months of treatment, whereas other imaging manifestations of pulmonary cryptococcosis stabilized with no lesion resorption after seven to nine months of treatment. Therefore, the persistence of nonresorption assessed by imaging does not constitute an indication for the long-term use of drugs.

Recent studies have reported a 10%-30% incidence of fluconazole-resistant Cryptococcus isolates in patients (*10,11*); moreover, Cryptococcus has the potential to acquire fluconazole resistance during long-term treatment with this drug (*12-14*). The finding that the proportion of pathologies requiring amphotericin B or amphotericin B liposome therapy after ineffective fluconazole treatment did not increase with consolidation or diffuse pulmonary infiltrates in patients with cryptococcosis compared with those with nodular forms of cryptococcosis is not entirely consistent with our conventional knowledge (*9,15*). These results indicate that imaging findings are not indicative of the therapeutic efficacy of fluconazole in patients. Consequently, active drug sensitivity testing is essential in diagnostic and therapeutic processes.

The detection of cryptococcal antigen (CrAg) may prove to be an efficacious diagnostic tool for pulmonary cryptococcosis that facilitates the prompt commencement of antifungal therapy (*16,17*). The patient's immune status and imaging modality affect the detection of cryptococcal antigens (*18,19*). In our study, cryptococcal antigen titres were found to be significantly greater in patients with imaging manifestations of consolidation and diffuse infiltrates than in those with nodular phenotypes. Additionally, elevated antigen titres were observed to predict higher fungal loads and longer treatment times.

Because of the retrospective study design, certain preliminary laboratory data were absent for the evaluation of cellular immunity (CD4) and cytokines (IL-2, IL-6, INF-γ). Additionally, the comparison of follow-up chest imaging intervals and discontinuation times

among various physicians was subjective and lacked a standardized and rigorous definition were the limitations.

In conclusion, the duration of the treatment regimen for pulmonary cryptococcosis is contingent upon the imaging presentation. The serum antigen level, number of infectious lung lobes, presence of extrapulmonary lesions and presence of lesions in the lower right lobe are predictive indicators for a longer treatment duration. Antifungal treatment is recommended for approximately one month. Follow-up imaging should also be performed.

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