Letter to the Editor

DOI: 10.5582/ddt.2024.01081

Clinical characteristics and aetiological analysis of combined central and pulmonary cryptococcal infection: Clinical cases

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SUMMARY This paper presents a summary of seven cases of combined pulmonary and central cryptococcal infection and analyses of their clinical features, treatment and prognosis. No clear correlation was identified between the intracranial cryptococcal capsular antigen titre and either the intracranial pressure or the amount of protein in the cerebrospinal fluid. Pulmonary lesions may develop in any of the lung lobes and manifest in multiple forms. Infection at the central level is predominantly meningitis. As the central cerebrospinal fluid (CSF) capsular antigen titre can be considerably elevated even when serum capsular antigen titres are markedly low, lumbar puncture and subsequent analysis are essential for every case of pulmonary cryptococcal infection. Patients with renal insufficiency or who refused intravenous treatment opted for oral fluconazole therapy, and their prognoses were favourable.

Keywords Pulmonary cryptococcosis, cryptococcal meningitis, imaging characteristics, treatment, prognosis

Letter to the Editor:

Cryptococcosis is a major cause of morbidity and mortality worldwide. *Cryptococcus neoformans* was listed at the top of the WHO fungal pathogens priority list in 2022 (*1*). Cryptococcosis often involves the central nervous system (CNS) or the lungs and can disseminate to any organ.

While numerous studies have examined the clinical characteristics of pulmonary cryptococcosis and central cryptococcosis (*2-5*), cases involving the coexistence of pulmonary and central cryptococcosis warrant further investigation. This paper presents a summary of seven cases of combined pulmonary and central cryptococcosis, allowing an analysis of their clinical features.

Patients were deemed eligible if they were admitted to the Infectious Diseases Department at Zhongshan Hospital, Fudan University, between January 1, 2012, and September 30, 2024. Data regarding patient demographics, clinical features, laboratory results, pathogenic findings, treatments, and outcomes were obtained from the Zhongshan Hospital Information System. This project was approved by 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.

Patients with confirmed and clinical cases of cryptococcosis were included. Confirmed cryptococcosis was identified as a positive *Cryptococcus* culture from any site. Clinical cryptococcosis was identified as positive histopathology or cryptococcal antigen results and clinical or radiographic evidence of disease (*6*). The treatment duration refers to the period between medication initiation to medication discontinuation. Improvement days denote the period between medication initiation and improvements observed on chest imaging and review of lumbar puncture results. The morphological features on CT scans can be categorized as solitary nodules/masses, multiple nodules/masses, consolidation, or diffuse infiltrates (nodules/masses with consolidation) (*5*).

C. neoformans spores or yeast cells are ubiquitous in the environment and are inhaled by immunosuppressed or immunocompromised individuals. The yeast cells become dehydrated and cause respiratory system infections. In the event of a defective immune response, *C. neoformans* can disseminate to various parts of the body, such as the brain, kidney, and bone marrow. Various studies on cryptococcal infection and dissemination indicate that after pulmonary infection, it disseminates to the brain and

can cross the blood-brain barrier (BBB) *via* paracytosis, transcytosis and the Trojan horse strategy (*7,8*).

During our investigation, we identified a single female patient with positive cultures for both pulmonary and intracranial cryptococcal infections. Furthermore, the presence of a *Cryptococcus* infection at multiple sites in two patients without an underlying disease was a cause for concern. No clear correlation was identified between the intracranial cryptococcal capsular antigen titre and either intracranial pressure or amount of protein in the cerebrospinal fluid in this study (Table 1).

The relationship between the *Cryptococcus* capsular antigen assay and intracranial infection has always been worthy of further exploration. According to recent guidelines for managing a *Cryptococcus* infection, lumbar puncture examination for every patient with pulmonary cryptococcosis (*9*). However, in the past 10 years in our Infectious Diseases Department, according to the literature we reviewed, lumbar puncture has not been routinely performed for patients without central nervous system symptoms, with lesions relatively limited to the lung, and with a serum *Cryptococcus* capsular antigen titre ≤ 1:160 (*10*). In the seven patients included in this study, no correlation was detected between the serum and cerebrospinal fluid (CSF) capsular antigen levels. Notably, the central CSF capsular antigen titre can be elevated even when the serum capsular antigen titre is markedly low. Consequently, lumbar puncture and subsequent analysis are necessary for every case of pulmonary cryptococcal infection.

The morphological features on CT scans can be categorized as solitary nodules/masses, multiple nodules/masses, consolidation, or diffuse infiltrates (nodules/masses with consolidation) (*11*). Immunocompetent patients mainly present solitary nodules, whereas immunocompromised patients present multiple nodules/masses, consolidation, or diffuse infiltrates (*12*). In our 7 patients with pulmonary and central cryptococcal infections, lung imaging revealed any of the four forms described above. The main cranial MRI findings were basal meningeal enhancement (44.6%), dilated Virchow–Robin space/pseudocyst, "dirty" cerebrospinal fluid sign, hydrocephalus, acute/subacute cerebral infarct, cryptococcoma, and hazy brain base in HIV-negative adults (*13,14*). Among our 7 patients, one presented with white matter lesions, which are rarely reported in HIV-negative patients, and 5 patients had no brain parenchymal involvement (*15*) (Figure 1).

Compared with CSF samples, lower respiratory tract samples presented less microorganisms. The mNGS positivity rate was higher in lower respiratory tract specimens than in conventional cultures. Conversely, the culture results were more positive in the CSF samples than in the mNGS samples. The sensitivity structure exhibited sensitivity to triazoles and amphotericin B (Figure 2).

Patients 1 and Patient 4 were eventually cured. In

Table 1. Patient characteristics and laboratory indicators

No.	Sex	Age	Underlying disease	WBC (*10^9)	Lymphocytes (*10^9)	CRP (mg/L)	IL_2 (U/mL)	IL_6 (pg/mL)	CD4 (cell/uL)	Serum capsular antigen titre	Titer	Pressure (mmH_2O)	WBC ($/mm^3$)	Sugar (mmol/L)	Chloride (mmol/L)	Protein (g/L)	Other Infections
1	M	67	DM+IgG4+ Autoimmune Pancreatitis	5.26	0.4	18.4	1341	7	385	1:2560	1:2	60	1	10.9	125	0.53	
2	M	33	Kidney Transplant +Hepatitis B	7.73	0.75	17.2	1086	15.4	258	1:80	1:10	130	125	1.7	123	0.51	Cryptococcus Laryngeal Infection
3	M	65	MDS	2.4	1.5	4.8	386	4.8	/	1:320	1:320	300	72	2.9	126	1.7	Pulmonary Acinetobacter Baumannii Infection
4	M	45	DM	6	1	1.5	292	2.8	354	1:1280	1:40	>400	23	3.8	119	0.49	
5	M	47	None	5.13	0.3	5.7	/	/	/	1:2560	1:2560	170	120	2.7	117	3.53	
6	M	47	Antiphospholipid Syndrome	12.38	0.5	8.2	933	5	43	1:10	1:640	190	51	3	121	0.59	Pulmonary Nocardia Infection
7	F	26	None	9.23	2.5	2.7	432	4.3	1066	>1:2560	1:2	170	0	3.8	125	0.18	

WBC: White blood cell count. CRP: highly sensitive C-reactive protein. DM: Diabetes mellitus. MDS: Myelodysplastic Syndrome.

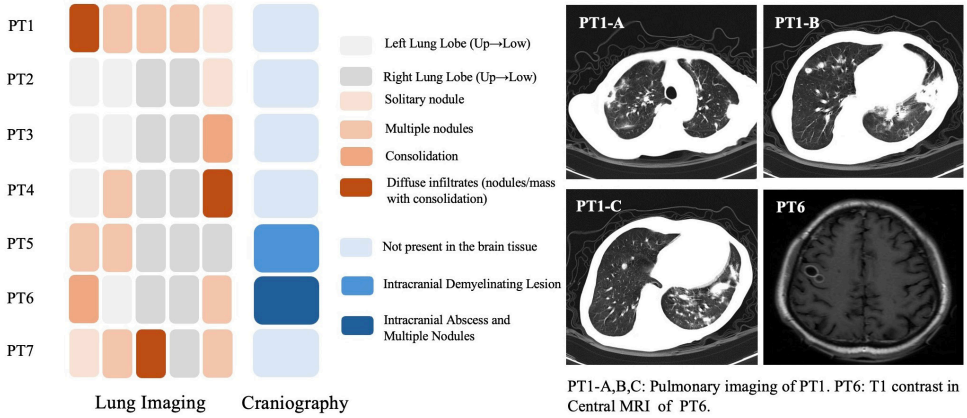
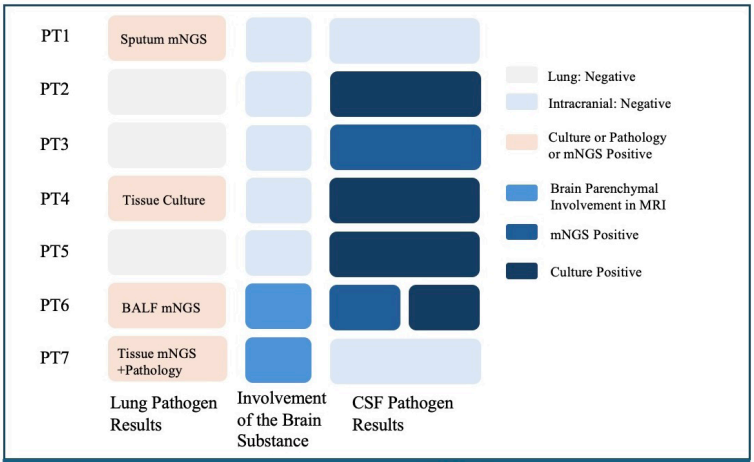


Figure 1. Imaging of pulmonary lesions and intracranial lesions in 7 patients with cryptococcal disease.



No.	Source of Strain	MIC/RAD				
		Fluconazole	Voriconazole	Itraconazole	Flucytosine	Amphotericin B
2	CSF	4	≤0.125	0.125	≤0.5	≤4
4-1	Lung Tissue	4	≤0.125	0.125	≤0.5	≤4
4-2	CSF	4	≤0.125	0.125	≤0.5	≤4
5	CSF	≤1	≤0.125	≤0.06	≤0.5	≤4
6	CSF	4	≤0.125	≤0.06	≤0.5	≤4

CSF: Cerebrospinal Fluid. MIC: Minimum Inhibitory Concentration.

Figure 2. Microbiological findings and antifungal drug sensitivity results.

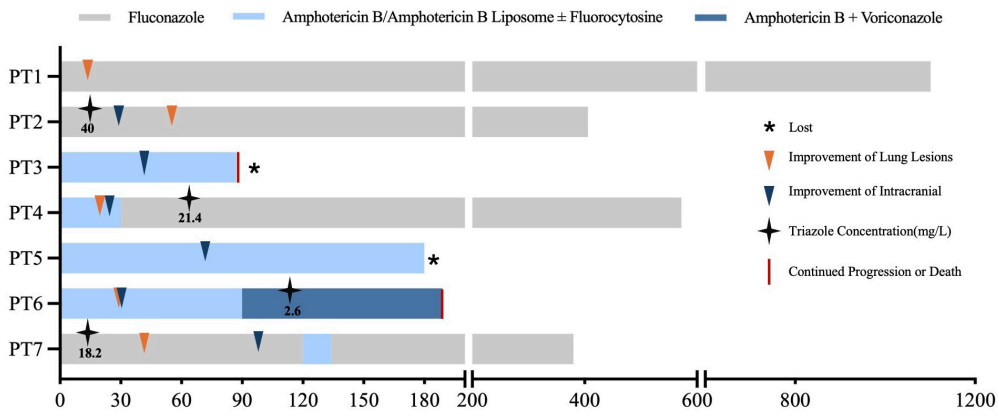


Figure 3. Treatment regimen and duration, time to signs of improvement, drug concentration detection and prognoses.

Patient 2, the fluconazole dosage was adjusted to 0.3 g per day due to the presence of his renal insufficiency, which was administered continuously. Patient 3 was automatically discharged from the hospital because of haematological disorders, a progressive decline in their general condition, and continued progression of lung lesions during the course of the disease. Patient 5 was stable after a six-month period of hospitalization with amphotericin B. He was discharged on oral fluconazole therapy and subsequently lost to follow-up. Patient 6 was successfully treated for cryptococcosis but ultimately died of COVID-19 pneumonia. At the time of this report, Patient 7 has been on medication for 380 days (Figure 3).

According to the guidelines, an intravenous regimen of amphotericin B or liposomal formulations is recommended as the first-line treatment, and oral fluconazole is used as a secondary option (*9,16*). Oral fluconazole may be considered for patients in better overall health because of the prolonged duration of intravenous amphotericin B administration. Three patients with renal insufficiency and who refused intravenous treatment opted for oral fluconazole therapy, and their prognoses were favourable.

Acknowledgements

We would like to thank all the study participants whose data were used in this study. Furthermore, we are most grateful for the assistance and support of clinicians, laboratory technicians and radiologists at Zhongshan Hospital, Fudan University.

Funding: This work was supported by grants from the National Key Research and Development Program of China (2021YFC 2300400) and the Fund of Zhongshan Hospital Fudan University (2021ZSFZ15).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received November 10, 2024; Revised December 2, 2024; Accepted December 8, 2024.

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Released online in J-STAGE as advance publication December 11, 2024.