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ORIGINAL RESEARCH

# Clinicopathological Analysis of 60 Cases of Pulmonary Cryptococcosis

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**Introduction:** Pulmonary Cryptococcosis (PC) is an invasive pulmonary fungal disease caused by cryptococcal infection, with diagnosis being challenging and prone to misdiagnosis. This research comprehensively analyzes the clinical, imaging, and pathological characteristics of PC, aiming to enhance diagnostic and therapeutic proficiency for PC.

**Methods:** Clinical data of 60 PC patients diagnosed in our hospital from January 2019 to June 2024 were retrospectively scrutinized.

**Results:** 60 patients were enrolled (40 males, 20 females), with an average age of 49.1±13.3 years. Notably, 47 patients (78.3%) were 40 years old or older. 47 cases had chronic underlying diseases, including 2 AIDS patients. Respiratory symptoms were observed in 33 patients, with cough being the most common. Serum cryptococcal capsular antigen testing was conducted on 52 patients, revealing a diagnostic sensitivity of 44.2% (23/52). Imaging revealed predominant involvement of the right lower lung. A peripheral subpleural distribution pattern was observed in 28 cases (46.7%). Lesions exhibited diverse morphologies: solitary, multiple nodules/masses, patchy/consolidation shadows, and a mixed form of these. The mixed type was most prevalent, with 30 cases. Initially, 56 cases were misdiagnosed as tuberculosis, lung cancer or others prior to pathological confirmation. Histopathology showed granulomas and/or multinucleated giant cells in 57 cases. Cryptococcal yeast cells phagocytosed within these cells appeared as colorless, transparent, round or oval structures (4–15 um in diameter) with a refractile clear halo on HE staining, while methenamine silver and PAS staining highlighted them as black or bright-red, facilitating diagnosis. Eleven patients underwent surgical resection followed by fluconazole therapy, and 45 received fluconazole or itraconazole therapy, with most achieving stable outcomes.

**Conclusion:** PC predominantly impacts men over 40 with chronic comorbidities. Serological tests and imaging may indicate PC, yet a definitive diagnosis necessitates lung biopsy or surgical pathology. Antifungal drugs and/or surgery typically resulted in a favorable prognosis.

**Keywords:** pulmonary cryptococcosis, pathology, diagnosis, tuberculosis

## Introduction

Cryptococcus is a genus of basidiomycetous fungi ubiquitously distributed in the environment. Pulmonary Cryptococcosis (PC) is a globally invasive fungal disease caused by Cryptococcus infection. Cryptococcus typically enter the body via the respiratory tract or skin, leading to a spectrum of infections ranging from localized pulmonary disease to severe disseminated or central nervous system infections.[1] PC was previously believed to occur in immunocompromised individuals such as acquired immune deficiency syndrome (AIDS), malignancies, diabetes, long-term immunosuppressive therapy, or organ transplantation. However, with the advancement of imaging techniques and enhanced clinical awareness, cases among immunocompetent individuals have also been reported in recent years.[2,3] Early diagnosis of PC poses significant challenges due to the lack of specific clinical manifestations and characteristic imaging findings, along with the low positivity rate and time-consuming nature of blood cultures. Before definitive diagnosis, patients are often misdiagnosed with conditions such as community-acquired pneumonia, tuberculosis, or lung cancer, leading to delays in appropriate treatment.[2,4] Delayed treatment of Pulmonary Cryptococcosis can precipitate severe complications like cryptococcal meningitis and disseminated infection, thereby yielding a poor prognosis. This

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retrospective study evaluated 60 histologically proven PC cases, systematically assessing their clinical presentation, imaging findings, and pathological features to improve diagnostic accuracy and facilitate early detection.

# Methods

## Study Design

This is a retrospective observational study on the visits of patients with PC in Wuhan Pulmonary Hospital. Informed consent was waived due to the retrospective nature of the study and all data were anonymous. This study was approved by the Medical Ethics Committee of Wuhan Pulmonary Hospital, and the approval number was Wuhan Pulmonary Hospital Ethics (2024) No. 045.

## Participant and Data Collection

A total of 60 cases of PC diagnosed by histopathology in hospitalized patients from January 2019 to June 2024 were included in this study. The diagnosis of PC in 60 patients was made by two pathologists with more than 10 years of experience in diagnostic pathology. Medical records of these patients including demographic characteristics (age, sex, clinical symptoms, underlying diseases, imaging results, serum cryptococcal antigen, and histopathological findings, treatments and prognosis were extracted from patient medical records held at Wuhan Pulmonary Hospital).

## Pathological Examination

Pathological specimens were fixed in 10% neutral formalin, routinely dehydrated, embedded in paraffin, and sectioned at 4 um thickness. Hematoxylin and Eosin (HE) staining was performed for light microscopy observation. Fungal staining with Periodic Acid-Schiff (PAS) and methenamine silver staining were conducted according to the manufacturer's instructions (BASO Co., Ltd).

## Statistical Analysis

Continuous variables were described as median with interquartile range (IQRs) and categorical variables were expressed as frequency (n) and percentage (%).

# Results

## Clinical General Information

Among the 60 PC patients, 40 were male and 20 were female, with a male-to-female ratio of 2:1. The age ranged from 27 to 81 years, with an average age of 49.1 ± 13.3 years and a median age of 49 years (IQR: 43, 60). A total of 47 patients (78.3%) were 40 years old or above. Underlying Diseases: Of the 60 patients, 13 (21.7%) had no underlying diseases, 2 had AIDS, and the remaining 45 suffered from one or more chronic underlying diseases. These included hypertension (14 cases), diabetes (11 cases), malignant tumors (10 cases), active pulmonary tuberculosis (7 cases), chronic hepatitis B (3 cases), autoimmune diseases (2 cases), coronary heart disease (2 cases), nephrotic syndrome (1 case), and uremia with renal transplantation (1 case). Clinical Symptoms:27 patients (45.0%) had no distinct respiratory symptoms and were diagnosed incidentally through chest imaging during routine check-ups. The remaining cases manifested one or more of the following symptoms: cough (21 cases), cough with sputum (7 cases), fever (7 cases), chest tightness (5 cases), chest pain (5 cases), and hemoptysis (4 cases). One patient had central nervous system involvement and was diagnosed with cryptococcal meningitis. Serum Cryptococcal Antigen Testing: A qualitative serum cryptococcal capsular antigen test (colloidal gold immunochromatography) was conducted in 52 patients, with 23 testing positive. Using histopathology as the gold standard, the sensitivity of the test was 44.2%. Exposure History: Only 2 patients reported a clear history of exposure to birds droppings or jungle environments. Disease Course and Misdiagnosis: The disease duration ranged from 1 day to 1 year. Prior to diagnosis, 18 patients were misdiagnosed with pulmonary tuberculosis at other hospitals and received anti-tuberculosis treatment for 1 week to over 3 months. 9 patients were admitted with a suspected diagnosis of lung cancer, 4 with PC, and the rest with pulmonary shadows (Table 1).

**Table 1** Baseline Clinical Characteristics of 60 Patients

| Variables | No.(%) |
|---|---|
| Sex, n (%) | |
| Male | 40(66.7) |
| Female | 20(33.3) |
| Age, n (%) | |
| ≥40 | 47(78.3) |
| <40 | 13(21.7) |
| Underlying diseases, n (%) | |
| Yes | 47 |
| No | 13 |
| Signs and symptoms, n (%) | |
| Cough | 21(35.0) |
| Cough with sputum | 7(11.7) |
| Fever | 7(11.7) |
| Chest tightness | 5(8.3) |
| Chest pain | 5(8.3) |
| Hemoptysis | 4(6.7) |
| Positive serum cryptococcal antigen testing, n (%) | 23(44.2) |
| Preliminary diagnosis, n (%) | |
| Pulmonary tuberculosis | 18(30.0) |
| Lung cancer | 9(15.0) |
| PC | 4(6.7) |
| Pulmonary shadows | 29(48.3) |

## Chest CT Findings

All 60 patients underwent routine chest CT scans, which disclosed pulmonary shadows. Lesion Location: The right lung was involved in 34 cases (56.7%), the left lung in 12 cases (20%), and both lungs in 14 cases (23.3%). Lesions affected the upper lobes (25 cases), middle lobes (4 cases), and lower lobes (43 cases). The peripheral subpleural distribution pattern was the most prevalent, witnessed in 28 cases (46.7%). Lesion Morphology: The imaging manifestations encompassed solitary solid nodules/masses (15 cases, 25.0%) (Figure 1A), solitary mixed ground-glass nodules (2 cases, 3.3%) (Figure 1B), multiple nodules/masses (11 cases, 18.4%) (Figure 1C), patchy/consolidation shadows (2 cases, 3.3%) (Figure 1D), and a combination of these patterns (30 cases, 50.0%) (Figure 1E and F). Associated Imaging Signs: Halo signs were noticed in 10 cases (16.7%) (Figure 1F), cavities/bullae in 17 cases (28.3%) (Figure 1E), and air bronchograms in 6 cases (10%). Other less common signs included lobulation, spiculation sign, and tree-in-bud patterns.

## Pathological Characteristics

Diagnosis was affirmed by lung biopsy in 47 cases, surgical resection in 11 cases, and transbronchial lung biopsy (TBLB) in 2 cases. Gross Examination:The lesions appeared solid, homogeneous, and grayish-yellow on cut sections, sometimes with a gelatinous appearance and moderate consistency. Microscopic Examination (HE Staining):The pathological morphology of PC was diverse, but the most significant features were the formation of granulomas and/or multinucleated giant cells. Granulomas and/or multinucleated giant cells were witnessed in 57 cases, while the remaining 3 cases demonstrated extensive Cryptococcus yeast cells destroying lung tissue without clear granuloma formation (Figure 2A and B). Forty-six cases exhibited granulomatous inflammation without necrosis. The granulomas were composed of epithelioid histiocytes and multinucleated giant cells, which could be well-formed (resembling tuberculous granulomas) or poorly formed, sometimes appearing as scattered multinucleated giant cells. The background lung tissue showed mucoid changes, chronic inflammatory fibrosis (Figure 2C and D), and organizing pneumonia (Figure 2E), which served as diagnostic clues. Eleven cases showed granulomatous inflammation with necrosis (Figure 2F), characterized by coagulative or caseous necrosis containing Cryptococcus yeast cells, often leading to misdiagnosis as tuberculosis.

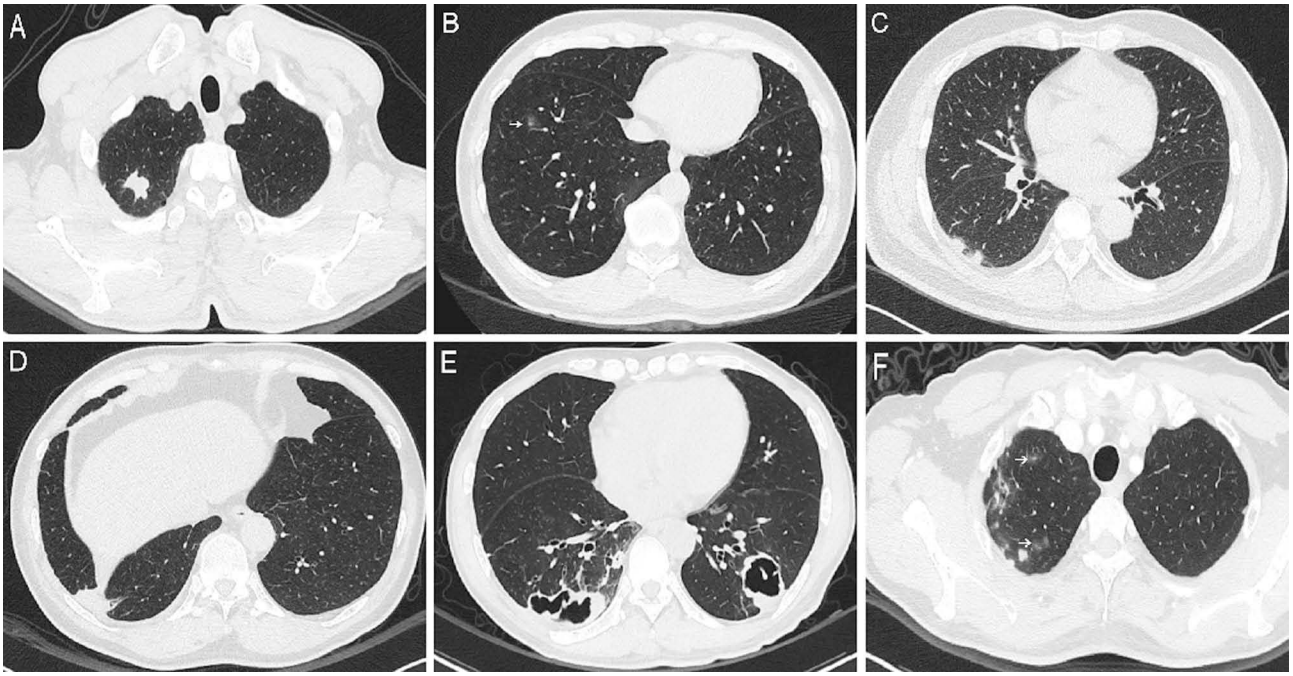


**Figure 1** (**A**) A 66-year-old male with a solitary solid nodule in the right upper lobe, exhibiting lobulation and spiculation sign, initially misdiagnosed as a tumor. (**B**) A 46-year-old male with a solitary mixed ground-glass nodule in the right lower lobe (white arrow), initially misdiagnosed as a tumor. (**C**) A 71-year-old male with multiple small solid nodules in the subpleural region of the right lower lobe. (**D**) A 54-year-old male with a solid patchy shadow in the subpleural region of the right lower lobe. (**E**) A 71-year-old male with mixed patchy and nodular shadows in the subpleural regions of both lower lobes, accompanied by irregular cavitation. (**F**) A 50-year-old male with mixed patchy and nodular shadows in both upper lobes, showing a halo sign (white arrow).

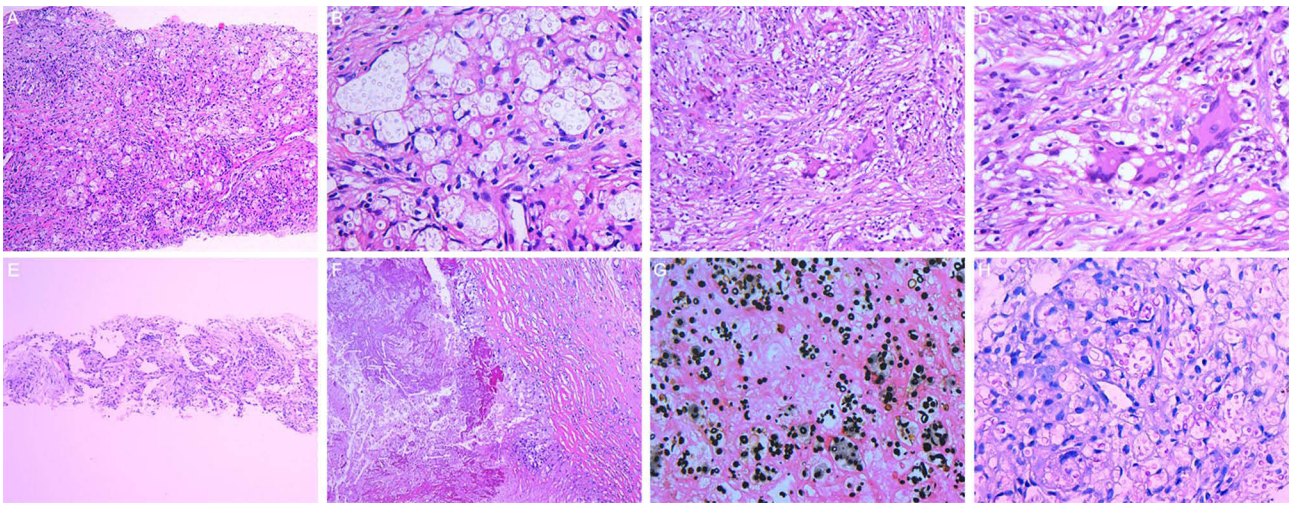


**Figure 2** (**A**) Destruction of lung tissue architecture with numerous colorless, transparent Cryptococcus yeast cells and no granuloma formation (HE, ×100). (**B**) Magnified view of (**A**), showing abundant colorless, transparent, oval Cryptococcus yeast cells (HE, ×400). (**C**) Chronic inflammatory fibrosis in the lung background with scattered multinucleated giant cells, containing transparent Cryptococcus yeast cells within their cytoplasm (HE, ×200). (**D**) Magnified view of Figure 2C, demonstrating multinucleated giant cells engulfing colorless, transparent, round to oval Cryptococcus yeast cells, surrounded by clear spaces (HE, ×400). (**E**) Mucoid organizing pneumonia background with multinucleated giant cells (HE, ×100). (**F**) Granulomatous inflammation with necrosis in lung tissue, showing Cryptococcus yeast cells within the necrotic area (HE, ×100). (**G**) Methenamine silver staining highlighting Cryptococcus yeast cells in black (Methenamine silver, ×400). (**H**) PAS staining highlighting Cryptococcus yeast cells in bright red (PAS, ×400).

The Cryptococcus yeast cells were mainly located within the cytoplasm of multinucleated giant cells and epithelioid histiocytes in granulomas. In some cases, the Cryptococcus yeast cells were diffusely distributed throughout the lung tissue. The Cryptococcus yeast cells measured approximately 4–15 μm in diameter, with significant size variation even within the same case. They appeared colorless, transparent, round to oval, and refractile, often surrounded by clear

spaces, particularly within multinucleated giant cells. All pathological specimens were further confirmed with methenamine silver and PAS staining. Methenamine silver stained the cryptococci black (Figure 2G), while PAS stained them bright red (Figure 2H).

## Treatment and Prognosis

Eleven patients underwent surgical resection followed by antifungal therapy, receiving oral fluconazole at 400 mg once daily or 200 mg twice daily for 3–6 months. Among the remaining cases, 45 received antifungal treatment after diagnosis, including 41 treated with fluconazole (400 mg once daily or 200 mg twice daily) and 4 treated with itraconazole (200 mg once daily). Outcomes: One patient with concurrent cryptococcal meningitis passed away one year later, and another died of hemorrhagic shock following percutaneous lung biopsy. The majority of patients remained stable with no recurrence.

# Discussion

Cryptococcus is a genus of yeast-like fungi widely distributed in the environment, comprising over 30 subspecies, of which only Cryptococcus neoformans and Cryptococcus gattii are pathogenic to humans.[2] Cryptococcus is ubiquitous and can be found in bird droppings (eg, pigeons), decaying wood, soil, vegetables, and fruits.[1,5] The life cycle of Cryptococcus includes both asexual reproduction (yeast phase) and sexual reproduction (basidiospore phase), with the former being predominant. In environments such as bird droppings and soil, or within a host, Cryptococcus primarily exists as a single-celled yeast, reproducing asexually through budding. Under specific conditions, it can undergo sexual reproduction, forming basidiospores. Humans are typically infected by inhaling aerosolized Cryptococcus spores or desiccated yeast cells from the environment, which initially colonize the lungs. The pathogen can subsequently disseminate to multiple organs, including the lungs, central nervous system (CNS), skin, and bones, with the highest affinity for the CNS.[6] Close contact with bird droppings, especially from pigeons, is often regarded as a significant risk factor for PC. In this study, only two patients reported a history of exposure to bird or jungle environments, consistent with previous literature.[1,7] Possible reasons for this include: (1) environmental exposure may not be a necessary factor for PC onset; (2) patients may not recall or consider such exposures significant, such as farmers working in fields or forests who are inevitably exposed to these risk factors; and (3) initial physicians may not thoroughly inquire about environmental exposure history. Nevertheless, improving living and working conditions, properly managing bird breeding, and disinfecting contaminated environments are meaningful measures to reduce the incidence of PC.

Cryptococcus is often regarded as an opportunistic pathogen, typically affecting immunocompromised individuals, such as those with AIDS, diabetes, malignancies, long-term steroid therapy, organ transplantation, or liver cirrhosis.[1,8] This study also found that 47 patients (78.3%) had one or more chronic diseases, primarily hypertension, diabetes, malignancies, and pulmonary tuberculosis. However, some studies[3,9] report a higher incidence of PC in immunocompetent individuals, possibly due to regional factors or an actual increase in PC incidence in this population, coupled with enhanced health awareness and widespread use of CT imaging, leading to higher detection rates. In terms of demographic distribution, the incidence of PC in males was twice that in females in this study, likely due to greater environmental exposure among males. Estrogen has been shown to modulate host immune responses against Cryptococcus and attenuate fungal virulence, potentially accounting for sex-based disparities in cryptococcosis.[10] Additionally, 47 patients (78.3%) were aged 40 or older, consistent with some literature reports.[11] Progressive immune dysfunction with aging may account for this.

PC lacks specific clinical symptoms and signs. In this study, 27 patients (45%) were diagnosed incidentally through imaging without obvious symptoms, similar to the 42% reported in the literature.[4] The remaining 33 patients presented with respiratory symptoms, predominantly cough and sputum production, consistent with previous reports.[2] Other symptoms included fever, chest tightness, chest pain, and hemoptysis, which overlap with those of lung cancer, tuberculosis, and pneumonia. In this study, 56 cases were initially misdiagnosed as other conditions, including tuberculosis and pulmonary neoplasms, instead of PC. This finding highlights the significant likelihood of diagnostic oversights or errors when dealing with PC.

Serum cryptococcal capsular antigen testing is a crucial non-invasive diagnostic tool for PC. Compared to traditional fungal cultures and pathological examinations, it offers simplicity and rapidity. For patients presenting with characteristic clinical features and imaging findings alongside positive serum cryptococcal capsular antigen results, a clinical diagnosis of PC may be established. However, during treatment, regular reevaluation through pulmonary imaging and pathogen detection tests should be emphasized.[12] With high sensitivity and specificity,[11,13,14] ranging from 65.9% to 97%,[4] it shows promise as a key diagnostic tool. In this study, only 23 of 52 tested patients were positive, yielding a sensitivity of 44.2%, lower than reported in the literature. Possible reasons include: (1) variability in operator proficiency; (2) differences in lesion quantity and distribution, as nodular/mass lesions may have lower positivity rates compared to pneumonia-like or mixed patterns; (3) potential cross-reactivity with other antigens, bacteria, or unknown proteins;[15] and (4) the test only targets Cryptococcus neoformans and not Cryptococcus gattii.

PC imaging findings vary, including solitary nodules/masses, multiple nodules/masses, pneumonia-like patterns, and mixed patterns. Different studies suggest that PC may predominantly present as nodular/mass, pneumonia-like, or mixed patterns.[3,4,16] Additionally, immune status may influence imaging patterns, with immunocompromised individuals more likely to exhibit pneumonia-like or mixed patterns, while immunocompetent individuals often present with nodular/mass patterns.[3] In this study, mixed patterns were most common, accounting for 50% of cases. This may be due to the hospital's role as a tuberculosis referral center, where mixed and multifocal lesions are more commonly associated with tuberculosis, leading to potential diagnostic bias. Lesion distribution patterns: in the literature generally describe PC as predominantly affecting the right lower lung.[3,17,18] This study also found the right lung to be the most frequently involved (34 cases, 56.7%), with the lower lobes being the most common site (43 lesions), consistent with the literature. This distribution aids in differentiating PC from tuberculosis, which typically affects the upper lobes and lower lobe dorsal segments. Notably, while literature often describes PC lesions as predominantly distributed in the peripheral subpleural regions, with rates as high as 84.5%,[11] this study observed this pattern in only 28 cases (46.7%). Key internal imaging features included cavities/bullae (17 cases, 28.3%) and air bronchograms (6 cases, 10%), which can also occur in lung cancer, tuberculosis, and pneumonia. Edge features such as spiculation sign and lobulation may mimic malignancy, while the halo sign, caused by fungal invasion of pulmonary vessels leading to thrombosis, necrosis, and surrounding hemorrhage, is a significant feature of PC.[17,18] However, this study observed the halo sign in only 10 cases (16.7%). One case also exhibited tree-in-bud signs around the lesion, which can be mistaken for tuberculosis or pneumonia.

The diagnosis of PC predominantly hinges upon mycological culture and histopathological examination, both of which hold equivalent diagnostic significance.[19] Histopathological examination serves a dual purpose. It not only validates the existence and type of infection, simultaneously ruling out fungal contamination, but when complemented by fungal staining, it also enables the in-situ detection of fungal pathogens within the lesional tissues. Regarding culture, specimens like bronchoalveolar lavage fluid (BALF), sputum, or biopsy tissue can be utilized. Nevertheless, this approach generally demands around one week, and its positivity rates are relatively low. Consequently, histopathology continues to be the gold standard for the conclusive diagnosis of PC.[1,4,12,19,20] Pathologically, PC exhibits diverse morphological features, but the most critical are the formation of granulomas and/or multinucleated giant cells.[1,20] The granulomatous structures may be well-developed, bearing resemblance to tuberculoid granulomas, or poorly developed, sometimes manifesting merely as scattered multinucleated giant cells. Inside these granulomatous structures and within the cytoplasm of multinucleated giant cells, phagocytosed Cryptococcus yeast cells can be discerned, with no hyphae in sight. The yeast cells are round or oval, having an average diameter of around 4–15μm. They are encircled by a thick layer of mucopolysaccharide capsule that is recalcitrant to staining with ordinary dyes and demonstrates high refractivity. Consequently, when stained with HE, the yeast cells present as colorless, transparent, round or oval entities, encircled by a distinct halo. This transparent halo is more prominent within multinucleated giant cells, and fine-tuning the microscope reveals their strong refractivity. These characteristics serve as the most crucial foundation for pathologists to identify Cryptococcus and diagnose PC. Employing PAS and Grocott's methenamine silver stains enables more straightforward identification of Cryptococcus yeast cells, thus decreasing the probability of missed diagnoses.In this study, 57 cases showed granulomas and/or multinucleated giant cells, while the remaining 3 cases lacked clear granuloma formation, instead displaying extensive Cryptococcus yeast cells destroying lung tissue. These three cases included two AIDS patients and one with chronic hepatitis B-related cirrhosis, suggesting that a robust immune response facilitates granuloma formation, whereas immunocompromised states may lead to

disseminated infection.[21] The background tissue often shows mucoid changes and chronic inflammatory fibrosis. Notably, drawing upon the author's experience spanning over a decade in pathological diagnosis, organizing pneumonia is a common finding in biopsy specimens of PC, necessitating high-magnification examination to identify Cryptococcus yeast cells and avoid misdiagnosis. When Cryptococcus yeast cells are sparse or granulomas exhibit caseous necrosis, as seen in 11 cases in this study, PC can be easily missed or misdiagnosed as tuberculosis. Therefore, acid-fast staining, mycobacterial nucleic acid testing, and fungal staining (eg, PAS and methenamine silver) are essential for accurate diagnosis.

Differential Diagnosis: 1. Tuberculosis: Presents as granulomatous inflammation with or without caseous necrosis. PC can also exhibit similar necrosis, necessitating careful examination for Cryptococcus yeast cells. In clinical practice, we found pulmonary tuberculosis and PC can co-occur, highlighting acid-fast staining, mycobacterial nucleic acid testing, and fungal staining for differential diagnosis. 2. Histoplasmosis: A dimorphic fungus that can cause granulomatous inflammation with or without necrosis. Yeast forms are 2–5 μm in diameter, uniform in size, and located within foamy macrophages. Budding yeast forms with narrow-based buds are characteristic on methenamine silver staining. 3. Talaromyces marneffei: Another dimorphic fungus that can cause granulomatous or suppurative inflammation. Yeast forms are 2.5–4.5 μm, with distinctive sausage-shaped, septate structures located within histiocytes.[22]

Treatment of PC: The goal of treatment is to control and prevent the spread of infection, typically involving antifungal therapy and, in some cases, surgery. Treatment regimens depend on the patient's immune status and disease severity. According to expert consensus on cryptococcal infection management,[12] immunocompetent asymptomatic patients may be closely monitored or treated with fluconazole 200–400 mg/day for 3–6 months. Immunocompetent patients with mild to moderate symptoms, non-severely immunocompromised patients, or those with diffuse lung lesions should receive fluconazole 200–400 mg/day for 6–12 months. For patients intolerant to fluconazole, itraconazole is an alternative. Patients who undergo surgical resection due to misdiagnosis as tumors or other conditions should receive at least 2 months of antifungal therapy postoperatively.[23] In this study, all 11 patients who underwent surgical resection received antifungal therapy, and non-surgical patients were treated according to guidelines with fluconazole or itraconazole. Most patients remained stable without recurrence or dissemination. One patient with concurrent cryptococcal meningitis died one year later, and another died of hemorrhagic shock following percutaneous lung biopsy.

## Conclusions

This research indicates that PC predominantly affects males aged 40 years or above who have chronic underlying diseases. Owing to its non-specific clinical symptoms and imaging manifestations, it is often misdiagnosed as tuberculosis or other pulmonary disorders. Considering the relatively low sensitivity of serum cryptococcal antigen testing, we suggest that histopathological examination remains the gold standard for a definitive diagnosis. The characteristic histopathological features include granulomatous inflammation, and the precise identification of characteristic Cryptococcus yeast cells is crucial for diagnosis. Antifungal therapy is the cornerstone of the treatment for pulmonary cryptococcosis. These findings could potentially enhance the understanding and diagnostic competence of clinicians, radiologists, and pathologists with respect to PC, thus reducing misdiagnosis and the grave consequences of delayed treatment. Despite the limitations of this study, such as its single-center design and limited sample size, further in-depth and meticulous research is likely to improve early diagnosis and therapeutic outcomes for patients with PC.

## Ethical Statement

The study was approved by the medical ethics committee of Wuhan Pulmonary Hospital, and the approval number was Wuhan Pulmonary Hospital Ethics (2024) No. 045. Informed consent was waived because the study was retrospective in nature and all data were anonymous. This study complied with the Declaration of Helsinki.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors have no conflicts of interest to declare for this work.

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