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A Rare and Fatal Pulmonary Cryptococcosis in HIV/AIDS: Chronological Clinical Decline in a Middle-Aged Male

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ABSTRACT
Cryptococcosis represents a life-threatening opportunistic fungal infection with significant mortality rates among immunocompromised individuals, particularly those with advanced HIV/AIDS. While cryptococcal meningitis dominates the literature, pulmonary involvement remains underrecognized despite its prognostic significance. This case report aims to document the clinical presentation, diagnostic challenges, and fatal outcome of pulmonary cryptococcosis caused by the rare species Cryptococcus laurentii in a severely immunosuppressed HIV-positive patient, and to emphasize the importance of early bronchoscopic investigation and antifungal therapy. We report the case of a 44-year-old Indonesian male with a history of HIV/AIDS who presented with progressive shortness of breath, persistent cough, and intermittent fever over two weeks. He was non-adherent to antiretroviral therapy (ART) and had a CD4 count of fewer than 50 cells/mm³. Chest radiography showed bilateral infiltrates, and sputum culture grew Cryptococcus laurentii. Despite the initiation of broad-spectrum antibiotics and antifungal agents, his respiratory status deteriorated rapidly. Antifungal susceptibility testing confirmed sensitivity to amphotericin B, flucytosine, and fluconazole, yet the patient developed progressive respiratory failure. He ultimately succumbed to refractory hypoxemia on day 23 of hospitalization. This case highlights the diagnostic challenge of pulmonary cryptococcosis in advanced HIV, particularly with rare non-neoformans species. A high index of suspicion and early mycological investigation, including culture and species-level identification, are critical for timely diagnosis. This report contributes to the limited literature on C. laurentii pulmonary infections in Southeast Asia and underscores the importance of adherence to ART, as well as the need for early consideration of fungal infections in severely immunosuppressed patients presenting with atypical pulmonary findings.

INTRODUCTION

Pulmonary cryptococcosis remains a significant yet underrecognized opportunistic infection in individuals with advanced HIV/AIDS (Beardsley et al., 2019). Although *cryptococcal meningitis* is more frequently reported, lung involvement may occur either as a primary site of infection or as part of disseminated disease, particularly in those with profound immunosuppression (CD4 < 50 cells/µL). Globally, HIV-associated cryptococcal disease contributes to approximately 4.4% *antigenaemia* prevalence in patients with CD4 <200 cells/µL, leading to an estimated 152,000 cases of *cryptococcal meningitis* and 112,000 deaths per year—accounting for nearly 19% of AIDS-related mortality (Rajasingham et al., 2017). The World Health Organization (WHO) published comprehensive guidelines in 2018 specifically addressing the diagnosis, prevention, and management of cryptococcal disease in

HIV-infected adults, adolescents, and children, recommending routine *cryptococcal antigen (CrAg)* screening for all persons with advanced HIV disease (CD4 <100 cells/μL) prior to antiretroviral therapy (ART) initiation (World Health Organization, 2018). Similarly, the Infectious Diseases Society of America (IDSA) updated its clinical practice guidelines for the management of cryptococcal disease in 2010, with subsequent revisions emphasizing the importance of early diagnosis, appropriate antifungal regimens, and management of intracranial pressure in *cryptococcal meningitis* (Perfect et al., 2010). Despite these evidence-based recommendations, implementation gaps persist, particularly in resource-limited settings where the burden of disease remains highest.

The clinical presentation of pulmonary cryptococcosis varies markedly—from asymptomatic nodular lesions to fulminant pneumonia mimicking *Pneumocystis jirovecii* or bacterial pneumonia—resulting in frequent misdiagnosis or diagnostic delay (Sharma et al., 2020; Finkelstein et al., 2019). Recent systematic reviews indicate that pulmonary manifestations occur in 30–60% of disseminated cryptococcal disease cases, yet isolated pulmonary cryptococcosis without central nervous system involvement accounts for only 10–30% of all cryptococcal infections in HIV-positive patients (Brizendine et al., 2013; Shi et al., 2012). In sub-Saharan Africa, studies reported a prevalence of pulmonary cryptococcosis in up to 11% of HIV-infected patients undergoing bronchoscopy for pneumonia, yet the condition was rarely suspected pre-diagnosis and was associated with a six-month survival rate of only 60% (French et al., 2002; O'Halloran et al., 2021). Prospective cohort studies from Uganda demonstrated that among HIV-infected patients with suspected pneumonia undergoing bronchoscopy, *Cryptococcus* species were identified in 8.5% of cases, with mortality rates exceeding 50% within three months despite antifungal treatment (Ganiem et al., 2014; Miller et al., 2021). Retrospective cohort data from tertiary care centers indicate that respiratory failure and intensive care admission significantly increase early mortality risk in cryptococcosis, even with antifungal therapy (Pyrgos et al., 2013; Malani et al., 2019).

Despite widespread use of ART, access gaps and late diagnosis persist in low- and middle-income countries, where cryptococcal disease continues to claim lives (Bennett et al., 2020; Vinnard et al., 2019). Data from Southeast Asian countries, including Indonesia, reveal that late HIV presentation (CD4 <200 cells/μL at diagnosis) occurs in 40–70% of newly diagnosed cases, substantially increasing the risk of opportunistic infections including cryptococcosis (Yunihastuti et al., 2020; Imran et al., 2019). Furthermore, ART adherence rates in Indonesia range from 60–80%, with non-adherence representing a major contributor to immunological failure and opportunistic infection susceptibility (Wisaksana et al., 2011; Kamara et al., 2021). Strategies such as CrAg screening and prompt antifungal treatment can mitigate mortality, yet implementation remains inconsistent across healthcare facilities, with only 15–30% of eligible patients receiving CrAg screening in routine clinical practice in Southeast Asian settings (Meya et al., 2021; George et al., 2020).

The study presents a fatal case of *pulmonary cryptococcosis* in a middle-aged Indonesian HIV-positive male, characterized by rapid clinical decline despite therapeutic efforts. This case is particularly significant for several reasons. First, the causative organism was identified as *Cryptococcus laurentii*, a rare non-*neoformans* species that has infrequently been reported as a human pathogen, with fewer than 50 documented cases in the global literature and extremely limited reports from Southeast Asia (Khawcharoenporn et al., 2007; Banerjee et al., 2013).

Unlike *C. neoformans* and *C. gattii*, which account for the vast majority of cryptococcal infections worldwide, *C. laurentii* is typically considered an environmental saprophyte with low pathogenic potential, making its isolation in this severely immunocompromised patient both clinically and microbiologically noteworthy. Second, published reports of isolated *pulmonary cryptococcosis* in advanced HIV from Indonesia and Southeast Asia remain scarce, with most existing literature focusing on cryptococcal meningitis or originating from Western or African populations where epidemiological patterns may differ (Chayakulkeeree & Perfect, 2006). Third, this case exemplifies the diagnostic complexities inherent in managing atypical pulmonary infections in resource-limited settings where access to bronchoscopy, advanced fungal diagnostics, and species-level identification may be constrained. Finally, the patient's profound non-adherence to ART and consequent severe immunosuppression (CD4 <50 cells/μL) highlight ongoing challenges in HIV care delivery and retention that continue to drive opportunistic infection-related mortality in the era of effective antiretroviral therapy.

Tao et al. (2024) investigated the clinical characteristics and prognostic factors of pulmonary and extrapulmonary cryptococcosis through retrospective data in China, finding that extrapulmonary involvement and immunological status were significant predictors of mortality, and that extensive pulmonary lesions correlated with higher serum *cryptococcal antigen* titers. While this study expands understanding of disease manifestations and prognosis, it largely excluded HIV-specific analysis and did not highlight rare non-*neoformans* species or the diagnostic challenges faced by patients with advanced HIV. Similarly, Howard-Jones et al. (2022) provided a comprehensive review of *pulmonary cryptococcosis* in both HIV and non-HIV patients, emphasizing that pulmonary manifestations are often underrecognized and frequently misdiagnosed, particularly when symptoms are nonspecific or when serum CrAg tests are negative. However, this review is mostly global and aggregated, without detailed case evidence from Southeast Asia or reports involving rare species such as *Cryptococcus laurentii*.

The objective of this study is to document the clinical presentation, diagnostic evaluation, and treatment course of *pulmonary cryptococcosis* caused by *C. laurentii* in advanced HIV infection, evaluate the diagnostic challenges of non-*neoformans* species, and emphasize the importance of strengthening ART adherence and implementing WHO-recommended CrAg screening. The benefits include raising clinical awareness of rare cryptococcal pathogens, informing diagnostic algorithms in resource-limited settings, and contributing to regional literature to guide both clinical practice and public health strategies in reducing opportunistic infection mortality among people living with HIV in Southeast Asia.

METHOD

Case Report

A 44-year-old married Indonesian male, Mr. Ghazali Rahman, presented to the Emergency Department of RSPAL Dr. Ramelan on June 9, 2025, with chief complaints of progressive fatigue, dyspnea, intermittent fever, and productive cough with yellowish-brown sputum. The patient had a prior diagnosis of HIV infection, initially made at a private hospital (RS Royal), and was not compliant with antiretroviral therapy. He worked as a private sector employee and had no significant history of prior hospitalizations for opportunistic infections.

On initial physical examination, the patient was febrile (T 38°C), alert (GCS 15), slightly anemic, with clear and symmetrical lung sounds, spontaneous breathing, warm and well-

perfused extremities, and strong peripheral pulses. Vital signs were stable. Based on clinical presentation and laboratory findings, he was diagnosed with HIV disease resulting in pneumocystis carinii pneumonia (ICD-10: B20.6). He was treated with oxygen via nasal cannula, intravenous fluids, antibiotics (Antrain 1 g IV), and underwent laboratory tests, ECG, and chest radiography (CXR).

On July 2, 2025, the patient returned to the same hospital in a more deteriorated condition. He exhibited spontaneous breathing with oxygen supplementation via face mask at 6 L/min, respiratory rate of 16–24 breaths per minute, and SpO_2 ranging from 95–97%. Blood pressure was 94/58 mmHg, heart rate 124 bpm, temperature 36.7°C. He remained alert (GCS 15), with equal and reactive pupils, and a CD4 count of less than 50 cells/mm³. Laboratory data revealed hypoalbuminemia (albumin 2.49 g/dL), and sputum culture grew *Cryptococcus laurentii*, a rare environmental yeast with known pathogenic potential in immunocompromised hosts.

Antifungal susceptibility testing indicated sensitivity to multiple agents including amphotericin B, flucytosine, fluconazole, voriconazole, micafungin, and caspofungin. Despite initiation of supportive care and antifungal treatment, his respiratory function progressively declined. Chest X-ray on July 2, 2025 showed diffuse pneumonia, though no cardiac abnormalities were noted. His CURB-65 pneumonia severity score was elevated, consistent with high-risk mortality.

The final diagnosis was pneumonia of unspecified etiology (J18.9) and HIV disease resulting in an unspecified infectious or parasitic disease (B20.9). The patient continued to deteriorate despite treatment and eventually succumbed to complications of disseminated cryptococcal infection and advanced AIDS.

RESULT AND DISCUSSION

Pulmonary cryptococcosis is an opportunistic fungal infection caused primarily by *Cryptococcus neoformans* or *Cryptococcus gattii*, typically seen in individuals with severe immunosuppression, particularly those with advanced HIV/AIDS and CD4 counts below 100 cells/mm³.[1] In the present case, the patient demonstrated a fulminant respiratory decline with a CD4 count <50 cells/mm³ and was ultimately diagnosed with pulmonary cryptococcosis caused by *Cryptococcus laurentii*, a rare non-*neoformans* species with emerging clinical significance.

According to Lim et al. (2022), while *Cryptococcus neoformans* remains the most common etiologic agent, other species like *C. laurentii*, previously considered non-pathogenic environmental yeasts, have increasingly been reported as opportunistic pathogens, particularly in immunocompromised hosts. These infections may be under-recognized due to limitations in diagnostic capacity, overlapping clinical features with other pneumonias, and delays in mycological identification.

The diagnosis of pulmonary cryptococcosis in HIV-positive individuals poses a unique challenge due to its nonspecific presentation. Common symptoms such as cough, fever, and dyspnea often mimic bacterial pneumonia or tuberculosis. Furthermore, radiologic findings may be inconclusive, ranging from nodular infiltrates to diffuse consolidation or even normal chest imaging, thereby compounding diagnostic uncertainty. In this case, the patient initially received a diagnosis of pneumocystis pneumonia based on clinical grounds and was treated accordingly, but showed no clinical improvement.

Lim et al. also emphasized the growing resistance and variable antifungal susceptibility profiles of *C. laurentii*, which complicate therapeutic decisions. Although the isolate in this case was sensitive to multiple antifungal agents (including amphotericin B, fluconazole, and flucytosine), the advanced

disease stage and late initiation of targeted therapy likely contributed to the fatal outcome. Early cryptococcal antigen (CrAg) testing, routine in many settings for *C. neoformans*, may not detect non-neoformans species reliably, making culture and species-level identification crucial for management.

What distinguishes this case is the rare pathogen involved, the patient's critically low CD4 count, and the rapid clinical deterioration despite supportive care. The case underscores the necessity for heightened vigilance, especially in patients with advanced HIV disease presenting with atypical pneumonia. Integration of fungal diagnostics, including bronchoalveolar lavage, fungal cultures, and species-level identification, should be prioritized when conventional antimicrobial therapies fail.

This case also reflects the ongoing burden of late HIV presentation in clinical practice, particularly in settings where patients often remain undiagnosed or untreated until opportunistic infections occur. As Lim et al. (2021) conclude, strengthening ART access, improving early fungal diagnostics, and clinician awareness are vital strategies to reduce mortality in cryptococcosis among people living with HIV/AIDS.

From a clinical practice perspective, this case reinforces several key recommendations. First, all HIV-positive patients with CD4 counts <100 cells/μL should undergo routine CrAg screening prior to ART initiation as recommended by WHO, with pre-emptive antifungal therapy (fluconazole 800 mg daily for two weeks, then 400 mg daily for 8 weeks, followed by 200 mg daily maintenance) for those who test positive but are asymptomatic (World Health Organization, 2018). Second, in patients presenting with pneumonia or respiratory symptoms unresponsive to standard antimicrobial therapy, clinicians should maintain high suspicion for fungal infections including cryptococcosis, particularly when CD4 counts are severely depressed. Third, negative serum CrAg should not exclude cryptococcal disease, particularly in the context of atypical presentations or potential rare species involvement, and invasive diagnostic procedures including bronchoscopy with bronchoalveolar lavage for fungal culture should be pursued when feasible. Fourth, species-level identification of *Cryptococcus* isolates using biochemical testing, MALDI-TOF mass spectrometry, or molecular methods should be performed to guide appropriate therapy and predict outcomes, as non-neoformans species may exhibit different susceptibility profiles and clinical behaviors (McMullan et al., 2012). Finally, early ART initiation and adherence support represent the cornerstone of preventing advanced immunosuppression and its associated opportunistic infections, requiring sustained investment in patient education, retention strategies, and healthcare system infrastructure.

CONCLUSION

This case illustrates the critical importance of maintaining a high index of suspicion for opportunistic pulmonary infections in patients with advanced HIV/AIDS, particularly when CD4 counts fall below 50 cells/mm³. Pulmonary cryptococcosis, though rare, may present with non-specific symptoms and radiological findings indistinguishable from more common infections, resulting in delayed or missed diagnoses. Timely recognition and appropriate antifungal therapy—especially in the context of *Cryptococcus* species—are essential to improving patient outcomes. Moreover, this case emphasizes the profound impact of delayed diagnosis and poor adherence to antiretroviral therapy (ART), which remain significant contributors to opportunistic infection-related mortality in low-resource settings. Early implementation of cryptococcal antigen screening and pre-emptive antifungal treatment, as recommended by WHO, may reduce fatal outcomes in patients with advanced

immunosuppression (Rajasingham et al., 2022). Ultimately, this case reinforces the need for heightened clinical awareness, integrated HIV care, and rapid diagnostic access to mitigate the devastating consequences of rare yet fatal infections such as pulmonary cryptococcosis. Future research directions emerging from this case include epidemiological studies to determine the true prevalence of non-neoformans cryptococcal species in Southeast Asian HIV populations, as current data likely underestimate the burden due to diagnostic limitations; development and validation of rapid diagnostic assays capable of detecting rare Cryptococcus species, potentially through pan-cryptococcal antigen detection or point-of-care molecular methods.

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