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Perspectives on non-*neoformans* cryptococcal opportunistic infections

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ABSTRACT

Non-*neoformans Cryptococcus* species, including C. *laurentii* and C. *albidus*, have historically been classified as exclusively saprophytic. However, recent studies have increasingly implicated these organisms as the causative agent of opportunistic infections in humans. Herein, the case is presented of *C. laurentii* meningitis in a critically ill patient receiving corticosteroids. *C. laurentii* has been implicated in an additional 18 cases of opportunistic infection, predominantly of the skin, bloodstream, and central nervous system. The most clinically significant risk factors for non-*neoformans* cryptococcal infections include: impaired cell-mediated immunity, recent corticosteroid use, and invasive catheter placement. This article provides a comprehensive review of the clinical relevance, pathogenesis, risk factors, and treatment of non-*neoformans Cryptococcus* species.

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1. Introduction

Non-*neoformans Cryptococcus* species, including *C. laurentii* and *C. albidus*, have historically been considered saprophytic and non-pathogenic. However, a literature review demonstrates an increasing prevalence in opportunistic infections [1–3]. The *Cryptococcus* genus consists of >70 species of anamorphic, basidiomycetous, encapsulated yeast [4]. *C. neoformans*, which includes the *C. gattii* and *C. neoformans* varieties, remains a common cause of opportunistic infections in immunocompromised states and is classified as an AIDs-defining illness [1]. Non-*neoformans Cryptococcus* species include *C. laurentii*, *C. albidus*, *C. curvatus*, *C. humicolus*, and *C. uniguttulantus*. These species were traditionally believed to be non-virulent to humans. However, there has been an increased incidence in recent decades of opportunistic infections involving the skin, lungs, bloodstream, and central nervous system (CNS). It has been theorized that this increasing incidence may be secondary to a growing number of at-risk or immunocompromised patients, improved awareness, or advancements in laboratory technology [3]. Within the non-*neoformans* cryptococcal species, *C. laurentii* and *C. albidus* account for 80% of pathogenic infections [1–5]. Understanding of the epidemiology and pathogenesis of these species will allow for prompt recognition of non-*neoformans* cryptococcal infections and improved patient outcomes. Additionally, understanding the common patterns of resistance will prevent further treatment failure.

2. Case description

A 48-year-old male with no significant past medical history presented with non-productive cough, fevers, chills, abdominal pain, and diarrhea. He was initially diagnosed with H1N1 Influenza A (2009 pandemic strain) and was started on oseltamivir, as well as empiric community acquired pneumonia coverage (ceftriaxone and azithromycin). The patient developed worsening respiratory status secondary to acute respiratory distress syndrome (ARDS), requiring intubation on day 2. Intravenous methylprednisolone was started at an initial dose of 60 mg intravenously (IV) q6h, per the ARDs Network Late Steroid Rescue Study (LaSRS) Steinberg. The patient underwent a prolonged 3-week steroid taper. Despite appropriate ARDs management, he was unable to be weaned from the ventilator and required tracheostomy placement. His hospital course was further complicated by atrial fibrillation with rapid ventricular rate and acute renal failure, which required continuous renal replacement therapy.

A notable mental decline was noted over the next 21 days. Although the patient opened eyes to commands, he did not withdraw when noxious stimuli

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were applied to the extremities, and he had marked hyporeflexia. Neurology was consulted, and an electroencephalogram demonstrated diffuse background slowing without epileptiform discharges. Magnetic resonance imaging (MRI) of the brain demonstrated multiple abnormalities, most significantly increased Fluid-Attenuated Inversion Recovery signal of the subcortical white matter, suggestive of acute hemorrhagic leukoencephalopathy (AHL). Given the H1N1-related AHL, the patient's prognosis was considered poor. The initial differential diagnosis included cerebritis and acute disseminated encephalomyelitis (ADEM). Steroid dosing was increased to 500 mg of methylprednisolone twice a day for 5 days and was eventually decreased to 250 mg twice a day. After a few days of high-dose steroids, he demonstrated mild neurologic improvement, with the ability to maintain intermittent basic communication through blinking.

The patient developed a gastric perforation and displaced gastrostomy tube requiring exploratory laparoscopy. Further antibiotic coverage was provided with cefepime and metronidazole for the intra-abdominal infection. He developed worsening pneumoperitoneum with complex free fluid, and consideration was given for a repeat exploratory laparoscopy/laparotomy.

Blood cultures became positive for *Candida tropicalis* on day 8 of hospitalization, which was treated successfully with micafungin. All invasive lines, including central venous access and hemodialysis catheters, were removed to prevent colonization or further infection. Blood cultures from the central venous catheter grew *Staphylococcus aureus* on subsequent days, and the patient received a course of vancomycin for 3 weeks. Subsequent blood cultures showed resolution of *Candida* fungemia. Repeat blood cultures performed on day 19 for persistent fevers and leukocytosis demonstrated *C. laurentii*, despite concurrent micafungin therapy. After speciation was notable for *Cryptococcus*, the patient was started on IV amphotericin B and flucytosine.

The patient's new diagnosis of *C. laurentii* fungemia and MRI findings were felt to represent a CNS infection. However, he remained too unstable to perform further evaluation with lumbar puncture. Although human immunodeficiency virus (HIV) antibody and antigen testing was negative, T- and B-cell enumeration demonstrated impaired cell-mediated immunity, with a CD4 count of 187. This was felt to be secondary to high-dose intravenous corticosteroid use as treatment of ARDs and ADEM. No abnormalities were noted on bronchoscopy, and no new infiltrate on chest imaging were noted to suggest a pulmonary source. As the patient showed no neurologic improvement, his family elected to pursue comfort measures, and he succumbed to his illness.

3. Discussion

A literature review identified 44 cases of non-*neoformans* species causing infections in humans, with approximately 18 cases due to *C. laurentii*. *C. laurentii* is found worldwide, although its natural habitat remains largely unknown [2,3]. It is the most common yeast inhabiting the soil of traditionally hostile environments, including tundra, the Antarctic, the Himalayas, the Caribbean, and the prairies. This survivability may be attributed to its psychrophilic abilities, with an optimal culture temperature of 15.0°C, and poor growth at temperatures >30.0°C [3,6]. Historically, it has been used as a biological pesticide to prevent the decay of fruits and has been demonstrated as a contaminant in the fermentation process of wines and beer [1,7]. Additionally, *C. laurentii* has been isolated in cases of bovine mastitis [5]. There have been approximately 18 reported cases of *C. laurentii* infections in the literature, most commonly disseminated, pulmonary, and cutaneous forms [3].

In a systematic review of 38 articles by Khawcharoenporn et al., non-*neoformans* cryptococcal infections typically presented as fungemia (39%) or CNS infection (32%), as well as pulmonary, gastrointestinal, ocular, or dermatological infections. HIV is associated with a higher risk of CNS infections (57% vs. 27%; $p = 0.05$). CNS infections most likely present with meningeal signs (50%), but may also present with encephalopathy, gait instability, nausea, vomiting, paresthesia, or flaccid/spastic paralysis. Pulmonary non-*neoformans* infections predominantly follow a course of chronic, indolent disease [3].

Transmission of *C. laurentii* is primarily through inhalation of infective particles by close contact with pigeons or contaminated soil [1–3,6]. In 1998, Johnson et al. initially proposed that nosocomial spread was the primary means of transmission. However nosocomial transmission appears to be a rare cause of disease spread. In a systematic review by Khawcharoenporn et al., only two cases of such transmission were reported, and it was theorized that disease spread in the hospital setting was perpetuated through infected respiratory supplies or via direct inhalation from airborne yeast. Disseminated infections are thought to be the result of hematogenous spread from pulmonary infections or via indwelling catheters. Even purely asymptomatic pulmonary infections can progress to widespread disseminated disease. A number of unique virulence factors expressed by cryptococcal species aid in dissemination, including melanin deposition, use of laccase enzyme, and outer capsule. Melanin deposition alters cell-wall integrity, allowing for evasion of the host immune system, and reduces the sensitivity to antifungal therapies. The capsule is composed of polysaccharides and participates in the evasion of phagocytosis [3].

The primary risk factor for development of non-*neoformans* cryptococcal infections is impaired cell-mediated immunity, which is implicated in 48% of such infections. Impaired immunity is often secondary to neutropenia, malignancy, lymphoproliferative disorders, immunosuppressant use, or prior organ transplant. Other common risk factors include HIV infection with a CD4 count of <100 (associated with 16% of non-*neoformans* infections), exposure to azoles, and the use of an invasive catheter device (specifically in *C. laurentii* infections; see Table 1). Khawcharoenporn et al. highlighted the significant differences between cases of *C. laurentii* and *C. albidus* infections, including the fact that *C. laurentii* infections tend to involve younger patients ($p = 0.01$) and carry a higher likelihood of survival ($p = 0.01$). Prior research into the predictors of mortality in non-*neoformans* infections have lacked statistical power to make conclusions due to the low prevalence of disease. However, prior research has suggested an association between age >45 years, CNS infection, and mortality [3,7].

Standard cryptococcal antigen testing demonstrates reduced sensitivities to the non-*neoformans* species compared to *C. neoformans* (25% vs. 99%). It is proposed that structural differences in the yeast antigen, lower disease burden in non-*neoformans* infections, or inherent limitations of the assay are likely contributors [3,4]. Further differentiation can be assisted with the use of birdseed agar, in which non-*neoformans* species do not form the typical brown/black colonies of *neoformans* species [4]. Additionally, traditional fungal testing using β-1–3-D-glucan assays are insufficient due to low levels of β-1–3-D-glucan in the cell wall in comparison to other fungal species (e.g. *Candida*). Although all cryptococcal species contain laccase, non-*neoformans* typically exhibit a lower level of laccase activity, which may aid in differentiation [3]. Speciation of *Cryptococcus* colonies requires genomic/DNA sequencing of non-coding DNA regions known as Internal Transcribed Spacer (ITS), specifically regions D1 and D2 of the 26S rDNA. Matrix-assisted laser desorption/ionization is a new diagnostic test that uses mass spectroscopy to analyze biopolymers that shows promising utility in the speciation of *Cryptococcus* [4,7].

Although echinocandins are commonly used in the treatment of fungal infections due to their activity against the β-1–3-D-glucan cell wall, *Cryptococcus* species are intrinsically resistant to this class of medications without a known etiology [4,8]. *C. laurentii* has added resistance due to biofilm formation, which prevents adequate antibiotic penetration [9]. Despite the lack of validated standardized treatment for non-*neoformans* cryptococcal infections, case reports have shown adequate treatment with the traditional *neoformans* treatment regimens, amphotericin B and flucytosine [2,3]. Prior in vitro studies indicated poor activity of fluconazole and flucytosine for non-*neoformans Cryptococcus*. However, more recent in vivo data demonstrate adequate susceptibilities. Nevertheless, there has been documented resistance to fluconazole and flucytosine in some cases, which warrants the need for susceptibility testing. Increased risk for fluconazole resistance is conferred with prior azole exposure (83% vs. 50%) [4]. Per the 2014 European Congress of Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology guidelines on management of rare invasive yeast infections, amphotericin B with or without flucytosine is recommended as induction therapy, followed by fluconazole as maintenance in severe *C. laurentii* infections or CNS infections; Level of Evidence Class C-III [4]. Non-*neoformans* may also demonstrate higher intrinsic minimum inhibitory concentration than traditional *neoformans* infections [1,3,10]. Duration of therapy depends on the clinical scenario, but most commonly an induction therapy of 14 days followed by approximately 28 days for the maintenance regimen is sufficient for treatment [3]. Additionally, Khawcharoenporn et al. suggest that preventative measures for *C. laurentii* infection are similar to typical cryptococcal infections, including avoiding exposure to contaminated environments, the use of antifungal prophylaxis in appropriate immunocompromised patient, and implementing measures to improve native host defenses (including the use of antiretroviral therapy in HIV patients). There have been no guidelines for prophylaxis of non-*neoformans* species in immunocompromised patients, but it has been suggested to follow the guidelines for *Cryptococcus neoformans* prophylaxis. Per the IDSA 2010 guidelines, primary prophylaxis is not routinely recommended for immunocompromised patients in the USA or the UK (Table 2). Although azole therapy has been shown to reduce the frequency of cryptococcal disease in patients with a CD4 count of <50, prophylaxis has not been shown to improve survival and may increases drug resistance as well as risk drug–drug interaction. The exception to this would be areas with

Table 1. Risk factors for *Cryptococcus laurentii* infection

C. laurentii risk factors
Impaired cell-mediated Immunity
1.. Malignancy
2. Neutropenia
3. Lymphoproliferative disorder
4. Immunosuppressant use
5. Prior organ transplant
6. HIV infection (CD4 count <100)
Prior exposure to azoles
Invasive catheter device

HIV = human immunodeficiency virus.

Table 2. Antifungal treatment regimens for non-*neoformans* cryptococcal infections

Infection, severity	Treatment	Level of recommendation
CNS/severe induction therapy	Induction: amphotericin ± flucytosine Consolidation: fluconazole ≥400 mg/day (if susceptible in vitro)	B-III
Non-CNS/mild to moderate	Preferred therapy: amphotericin B Other therapy: fluconazole >400 mg/day (if susceptible in vitro)	B-III C-III
Prophylaxis	Primary: none Select high-risk populations may be treated with azole therapy per clinical judgment[a]	B- I

[a]Areas of high prevalence, increased antiretroviral resistance, or lack of access to antiretroviral therapy.
CNS = central nervous system.

high prevalence of cryptococcal infections, increased antiretroviral drug resistance, and lack of access to antiretroviral therapy. In such scenarios, medication prophylaxis against *Cryptococcus* may be appropriate and should be considered on an individual basis [11].

This case illustrates a rare opportunistic infection in a critically ill patient. The patient underwent an extended hospital course during which he required high-dose steroids, likely contributing to the development of fungemia due to *C. laurentii*. Other risk factors in this patient included immunocompromised state (low CD4 count), prior exposure to azoles, and invasive central catheter placement. He was treated with amphotericin B and flucytosine, but due to the severity of his illness and multiple comorbid conditions, the patient succumbed to his illness.

Disclosure statement

No potential conflict of interest was reported by the authors.

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