Cryptococcal Lung Infections

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KEYWORDS

• Cryptococcus • Cryptococcosis • Fungal lung infection • Endemic mycoses • Treatment

KEY POINTS

- *Cryptococcus* infections have high morbidity and mortality rates worldwide, particularly in the context of immune suppression and central nervous system involvement.
- *Cryptococcus neoformans* can be found globally and predominantly affects the immune-suppressed individual, whereas *Cryptococcus gattii* is endemic to certain regions and often affects immune-competent individuals.
- Most individuals with cryptococcal pulmonary infection present with symptoms; however, they may be mild and nonspecific, making timely diagnosis challenging.
- Pulmonary nodules or focal consolidation is the most common radiographic finding with *Cryptococcus*.
- Azoles (specifically fluconazole) and amphotericin B (in severe disease) are key cryptococcal therapies. There is no role for echinocandins.

INTRODUCTION

Cryptococcus remains one of the leading causes of acquired immunodeficiency syndrome (AIDS)-related deaths, and is among the most common fungal pathogens worldwide.[1] *Cryptococcus* demands global attention because of the high mortality, unique geographic distribution, and its propensity to cause severe and rapidly progressive disease in both healthy and immunosuppressed individuals.[1,2] *Cryptococcus neoformans*, which mainly infects immunosuppressed individuals, and *Cryptococcus gattii*, which has a high propensity to infect healthy individuals, are the 2 major species of *Cryptococcus* that are associated with mortality.[1] Arguably, the greatest virulence factor for both species is the cryptococcal polysaccharide capsule, which helps evade immune detection.[3] The organism often leads to respiratory infection but can also disseminate to other organs, in particular to the meninges causing meningoencephalitis, which is associated with poor clinical outcomes.[2,4] Current diagnostics are based on detection of antigen and culture techniques, and treatment recommendations are tailored based on fungal susceptibility, location, and severity of disease. Research is advancing technologies to enable more effective and efficient diagnostics for early detection along with improved prophylactic and therapeutic regimes.

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EPIDEMIOLOGY

General Cryptococcal Epidemiology

Among the 37 species of *Cryptococcus*, only a few are human pathogens.[5] *C neoformans* is characterized as an opportunistic pathogen because it commonly causes infections in individuals with impaired immunity. *C neoformans* causes more than 1 million infections in AIDS patients annually, and, unfortunately, most of these patients will die within a few months of diagnosis.[2] By contrast, *C gattii* has a more distinct geographic range and is more likely to affect healthy individuals leading to its characterization as an endemic mycosis.[6,7] *C gattii* is classically located in tropical and subtropical areas of the world such as Australia and Papua New Guinea, but more recently it has emerged as an endemic mycosis on the west coast of Canada and the United States.[7] Rarely, *Cryptococcus laurentii* causes infection in individuals with compromised immunity[8–10] and even less often in patients who are immune competent.[11,12] Immunosuppression is a significant risk factor, and the prevalence of cryptococcal infection significantly increased during the emergence of AIDS.[13] Currently, in developed countries with effective antiretroviral therapies, the prevalence of opportunistic cryptococcal infections has decreased, but *Cryptococcus* continues to affect those with other defects in cell-mediated immunity. Infections also occur in healthy individuals, especially if exposed in endemic areas.[14,15]

Although *Cryptococcus* causes both endemic and opportunistic mycosis, transmission of *Cryptococcus* occurs directly from the environment rather than from human to human.[16–18] Although *Cryptococcus* can cause infection in animals such as cats, dogs, ferrets, cockatiels, parrots, llamas, horses, and marine mammals,[19,20] direct transmission from these species is exceptionally rare. The primary environmental sources of *C gattii* are trees, such as eucalyptus, Douglas-fir, red cedar, and Garry oak, among others,[16,17,21] but it can also be found in the soil, water, and air in endemic regions.[22] *C gattii* has been isolated from the environment mainly in Australia, New Zealand, Papa New Guinea, Central America, parts of South America, and the Pacific Northwest of North America including Vancouver Island.[18,21,23–25] Interestingly, *C gattii* has also been identified in the Mediterranean basin on various trees, including olive and eucalyptus, which marks the first detection of the species in Europe.[26] In contrast, *C neoformans* is found worldwide, with the primary source being pigeon excrement, although certain subtypes are more common in particular regions of the world.[16,18] *C neoformans* has also been linked to other bird species such as magpies and cockatiels.[27,28] Additionally, there seems to be a seasonality to *C gattii* infections in some regions, which has not been noted with *C neoformans*.[29]

Cryptococcal Subtypes

It is important to differentiate between subtypes of *C neoformans* and *C gattii* for clinical purposes. *C neoformans* is divided into 2 major groups known as *C neoformans* var *grubii* (serotype A) and *C neoformans* var *neoformans* (serotype D).[30] Additionally, a hybrid serotype, AD, has also been identified as a clinically significant subtype.[30] *C neoformans* and *C gattii* have also more recently been subdivided into 4 molecular types, termed *VNI*, *VNII*, *VNIII*, *VNIV* and *VGI*, *VGII*, *VGIII*, *VGIV*, respectively, which may lead to further species distinctions.[30,31] *C neoformans* var *grubii* and *C neoformans* var *neoformans* have important differences in their genomes and replication methods,[30] which have clinical implications, as certain serotypes and molecular types may be more likely to respond to treatment.[31]

STRUCTURE AND LIFE CYCLE

Cryptococci are eukaryotic organisms that belong to the phylum Basidiomycota of filamentous fungi.[32] The cryptococcal cell is enveloped by a cell membrane, cell wall, and a characteristic polysaccharide capsule.[4] The capsule is unique to *Cryptococcus* and sets it apart from other pathogenic fungi.[33] It is composed of glucuronoxylomannan (GXM), which is the predominant polysaccharide, GalXM (galactoxylomannan), and mannoproteins.[34,35] Structural differences in GXM allow for the identification of *Cryptococcus* based on serotype.[36] The fungal cell wall consists of chitin and β-glucans (which provide structural integrity), pores (which allow for the movement of important molecules and transport vesicles), melanin (which protects the cell from oxidative stress), and proteins that serve a variety of cellular functions.[37–39] Cryptococcal cells can be identified by light microscopy but require special stains such as mucicarmine or Periodic-acid Schiff to identify the capsule or silver stains to identify the cell wall.[40] *Cryptococcus* is also readily identified with India ink staining, in which exclusion of the stain in the perimeter of the fungal cell is indicative of the fungal capsule (**Fig. 1**).[41,42]

Cryptococcus species are able to reproduce asexually through simple budding, and sexually, through the mating of α- and a-mating types.[43,44] Asexual reproduction is more common and occurs in the human host.[43,45] Sexual reproduction

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