Cryptococcosis due to Cryptococcus gattii

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Cryptococcosis is caused primarily by 2 sibling species, Cryptococcus neoformans and Cryptococcus gattii [1, 2]. The primary site of infection is the lung, following the inhalation of cryptococcal spores. Dissemination usually involving the central nervous system (CNS) occurs in severe cases. Cryptococcus neoformans is global in distribution and is considered an opportunistic pathogen, causing disease predominantly in individuals with impaired cell-mediated immunity, although some recent studies have challenged this notion [3, 4]. In contrast, Cryptococcus gattii was thought to be confined to tropical and subtropical regions of the globe, as the organism is isolated from various species of eucalyptus trees [5]. Endemic C. gattii cryptococcosis is more common in immunocompetent individuals and has a greater propensity to cause CNS disease. Since 1999, C. gattii has been recognized as a primary pathogen in an ongoing outbreak in British Columbia, Canada, and the Pacific Northwest region of the United States. Several aspects of infections caused by outbreak and nonoutbreak strains of C. gattii appear to be different from infections caused by C. neoformans [6]. Nevertheless, the most recent version of the Infectious Diseases Society of America guidelines for the management of cryptococcal disease suggest that the principles for induction, consolidation, and suppressive/maintenance treatment are the same for infections caused by either species [7]. More diagnostic focus by radiology and follow-up examination is recommended for C. gattii, and surgical intervention is presented as an option if there is compression of vital structures by cryptococcomas and/or failure to reduce their size after 4 weeks of therapy. The same document, however, states that “the management of C. gattii infection in immunocompetent hosts needs to be specifically addressed.”

In a previous report, investigators from the Australia and New Zealand Mycoses Interest Group (ANZMIG) described the salient clinical features of endemic C. gattii cryptococcosis including prognostic factors and determinants of neurologic sequelae and deaths, in a cohort of 86 patients treated between 2000 and 2007 [8]. Most patients (72%) were not immunosuppressed, and neurologic disease (85%), with or without pulmonary involvement, was predominant. Serum cryptococcal antigen titers of ≥256 predicted death and/or neurologic sequelae, and there were significantly more C. gattii–associated deaths in immunocompromised individuals. The current ANZMIG report, in this issue of Clinical Infectious Diseases, presents details of antifungal therapy and the management of complications of C. gattii infections in the same cohort of patients. Induction with amphotericin B (or its lipid formulations) plus 5-fluorocytosine (5-FC) for 6 weeks in CNS disease and 2 weeks in isolated pulmonary disease was effective. Fluconazole appears not to have a role in induction therapy. Eradication therapy with fluconazole was adequate. The total duration of therapy (18 months in CNS disease, and 12 months in isolated pulmonary disease) was longer than current recommendations for C. neoformans cryptococcosis. The authors recommend routine identification of isolates to species level and performance of antifungal susceptibility testing in patients not responding to therapy. Elevated CSF pressure was not uncommon (66% among the 48 patients in whom it was measured), and surgical intervention to relieve elevated CSF pressure is recommended as it has prognostic implications. Despite these measures, the mortality was 13.6% in patients with CNS disease and 11% in patients with isolated pulmonary disease.

Where does all of this information leave us from a clinical standpoint? Although there are some differences in the ecology, epidemiology, pathobiology, clinical manifestations, and treatment between the 2 sibling species (and to some extent between endemic and outbreak strains of C. gattii), there is also considerable...
overlapping. Both cause infection, albeit to a varying degree of frequency, in immunocompetent and immunosuppressed hosts. Primary pulmonary infection is acquired by inhalation of organisms in both. The CNS is the most common site of dissemination in both. Cryptococcus gattii tends to produce larger and more numerous cryptococcomas in the lung and CNS (perhaps the result of a more robust inflammatory response?). Nevertheless, although the duration of therapy may vary, the agents used for therapy, and the general principles of management, are similar [7].

Some issues merit further scrutiny, such as the recommendation to identify all clinical isolates to species level. Currently, most laboratories do not do so. Does the clinician managing an individual case of cryptococcosis really need to know the species causing the infection, especially in resource-limited settings where C. gattii is known to be endemic? Although an argument can be made in favor of this recommendation for epidemiologic investigations and for tracking outbreaks and disease in nonendemic regions, I believe, as do others, that this information is not essential in routine clinical practice [9, 10]. The widespread availability of newer, rapid methods for identification and differentiation of Cryptococcus species might make this more feasible in the future [11].

One question raised but not answered by the current study is the potential role of newer antifungal agents in the treatment of C. gattii infection in light of the variable susceptibility of these organisms to fluconazole [12]. In one study, voriconazole was shown to be 10-fold more inhibitory than fluconazole against C. gattii and C. neoformans. There was no serum-enhancing activity for either agent against C. gattii, whereas activity was significantly increased against C. neoformans in the presence of serum [13]. In another study evaluating the in vitro activity of currently available and novel agents, isavuconazole had the lowest minimum inhibitory concentrations (MICs), followed by itraconazole, voriconazole, and posaconazole [14]. Amphotericin B had acceptable activity, whereas the MICs for fluconazole and 5-FC were relatively high. Although the clinical significance of elevated MICs is unclear, these data suggest that voriconazole, posaconazole, and isavuconazole may be superior to fluconazole and need to be evaluated for induction, consolidation, and suppressive treatment of cryptococcosis, individually and/or in combination regimens. There is some controversy regarding the use of combinations of amphotericin B and fluconazole as dynamic interactions ranging from synergism to antagonism do occur [15]. Whether these interactions will occur if amphotericin B is combined with other azoles, and whether they are of clinical importance, remains to be seen. Additionally, newer compounds (hydroxyaldimines) with potent antycryptococcal activity have been identified and are under development [16].

Why is cryptococcosis caused by C. gattii more common in immunocompetent individuals, and is the frequent occurrence of the immune reconstitution inflammatory syndrome the result of a more robust inflammatory response in such individuals? There is evidence to suggest that C. gattii induces higher amounts of proinflammatory cytokines (interleukin-1β, tumor necrosis factor α, interleukin 6, interleukin 17, and interleukin 22) compared to C. neoformans, suggesting a more powerful defense against these organisms [17]. Other investigators have demonstrated the role of complement in protection against C. gattii infection [18]. The ability of C. gattii to cause disease in immunocompetent hosts, despite a robust cytokine response, has led some investigators to hypothesize that certain as-yet unrecognized defects in the innate immune system of affected hosts might account for a predisposition to infection [17]. Others have hypothesized that subclinical antibody deficiencies may exist in a subset of immunologically healthy hosts, predisposing them to C. gattii infection [19]. Although these findings are of considerable interest and contribute toward the understanding of the pathobiology of C. gattii, no specific factors or immunologic deficits predisposing to C. gattii infection have yet been identified, and there appears to be no therapeutic role for agents such as the immunoglobulins or recombinant interferon γ. Efforts are under way to more fully understand these and other aspects of infections caused by C. gattii as outlined in a recent National Institutes of Health/National Institute of Allergy and Infectious Diseases white paper [20]. Will cryptococcosis caused by C. gattii continue to evolve, and will outbreaks appear in newer geographic areas? Studies describing dispersal mechanisms of C. gattii suggest that this is more than likely [21]. Will newer therapeutic agents/regimens have a significant impact on the morbidity and mortality currently associated with C. gattii infection? Will newer diagnostic/screening tools make it easier to identify individuals at risk for infection, and, if so, will it be possible to develop preventive or preemptive strategies for such individuals? The short answer to most of these questions probably is “yes.” However, as Yogi Berra stated, in his inimitable style, “Predictions are difficult, especially when they are about the future.” Only time will tell.

Note

Potential conflicts of interest. Author certifies no potential conflicts.

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