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Rachel Wake & Nelesh P Govender

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EDITORIAL

Cryptococcosis in apparently immune-competent patients: taxonomy, epidemiology, pathophysiology and treatment

Rachel Wake[a,b] and Nelesh P Govender[a,c]*

[a]*National Institute for Communicable Diseases [Centre for Opportunistic, Tropical and Hospital Infections], Johannesburg, South Africa*
[b]*Institute for Infection and Immunity, St. George's University of London, London, UK*
[c]*Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*
Corresponding author, email: Neleshg@nicd.ac.za

Taxonomy

Cryptococcosis, a systemic mycosis with a worldwide distribution, is caused by fungi within the pathogenic *Cryptococcus neoformans-Cryptococcus gattii* species complex. Until recently, this species complex simply included two species, namely *C. neoformans* (containing serotypes A [*C. neoformans* var. *grubii*], D [*C. neoformans* var. *neoformans*], and an AD hybrid) and *C. gattii* (containing serotypes B and C). In 2015, the current *C. neoformans* var. *grubii* and *C. neoformans* var. *neoformans* were proposed to be recognised as separate species, and five separate species were proposed within *C. gattii*, in addition to several hybrid species.[1] While this revised nomenclature has taxonomic relevance, it is unlikely to filter down to the clinic, not least because the molecular tools to separate these cryptic species are rarely available at diagnostic laboratories.

Epidemiology

Largely fuelled by the AIDS pandemic, the global burden of cryptococcosis is enormous, with a recent estimate of 221 400 (95% CI 180 640 to 267 600) cases per annum, 70% of which occur in sub-Saharan Africa (155 030 cases, 95% CI 126 950 to 186 240).[2] By country, Nigeria, India and South Africa are estimated to have the highest number of cases. *Cryptococcus neoformans* var. *grubii* [proposed name: *C. neoformans*] is the most common cause of meningitis among HIV-seropositive adults in southern and eastern Africa.[3,4] Cryptococcosis rarely occurs in HIV-seronegative individuals (around 1% of cases in South Africa).[5] Although most patients have a known risk factor, such as solid organ transplant or cell-mediated immunodeficiency, around 10%-40% are apparently immune-competent.[6,7] Disease in immune-competent patients is commonly caused by *C. gattii* species-complex; is more likely to have extra-neural and extra-pulmonary manifestations; and, is associated with a higher risk of mortality.[6–9]

Paediatric cryptococcosis is relatively less common than adult disease: 1 case per 100 000 people vs 19 cases per 100 000 people in the general population.[10]

The case reported in this edition of the Journal is, therefore, unusual in several respects: disseminated disease (involving the lungs, blood, bone marrow, skin, meninges, urinary tract, liver and lymph nodes) caused by *C. neoformans* var. *neoformans* [proposed name: *C. deneoformans*], which occurred in a young child who was considered to be immune-competent.

Pathophysiology

Since *Cryptococcus* is a ubiquitous fungus, it is unsurprising that exposure, through inhalation of spores or desiccated yeast cells is likely to be almost universal during early childhood. Serological studies reveal that children acquire antibodies to *C. neoformans* from the age of two years,[11] and that infection is usually asymptomatic in both immune-compromised and immune–competent individuals.[11–13]

Following inhalation, *Cryptococcus* is thought to remain dormant in the body. Evidence of latency exists in the finding of continuous antibody production,[11–14] molecular studies indicating that cryptococcosis presenting in Africans living in Europe was acquired many years earlier,[15,16] and in autopsy studies from patients without a history of cryptococcal disease or exposure describing pulmonary granulomas containing *C. neoformans*.[17,18] The ability of the fungus to persist in humans without triggering a successful immune reaction has likely evolved due to its saprophytic nature (reviewed in [7–9]). For example, *C. neoformans* is able to survive and replicate within macrophages in a similar way to which it exists as an intracellular parasite of amoebae in the environment.[19,20] Furthermore, its polysaccharide capsule which protects it from harsh conditions, including UV light and extremes of temperature in the environment, exhibits antiphagocytic mechanisms, causing macrophage dysfunction and lysis, and allowing resistance to phagosomal digestion.[21] These, along with many other 'ready-made' virulence factors (production of melanin, degradative enzymes and an ability to grow at physiological temperatures),[22] allow *Cryptococcus* to remain in dormant until host immune-compromise allows dissemination and disease, most commonly meningo-encephalitis in HIV-infected individuals.

Although disease usually represents reactivation of latent infection in immune-compromised hosts, primary acquisition can also be associated with clinical symptoms.[23] Acute infection may be more likely following exposure to a greater number of *Cryptococcus* cells.[24] This may be the mechanism of cryptococcal disease described in this case.

The rare occurrence of cryptococcosis in apparently-immunocompetent hosts highlights the multiplicity of innate and acquired immune factors, and complex immune interactions, required for successful defence against *C. neoformans*. Although CD4^{+} T-cell function is clearly of key importance (as demonstrated by the emergence of cryptococcosis alongside the HIV/AIDS epidemic), only 4%-11% of patients with CD4^{+} T-cell counts of less than 100 cells/μl in sub-Saharan Africa have cryptococcal antigen detectable in blood.[25–34] This indicates that additional or underlying factors, in addition to CD4^{+} T-cell deficiency, may lead to increased susceptibility in a subset of individuals. A greater understanding of host immunity to cryptococcosis has been achieved though recent studies in animal models as well as

humans, both with and without immune-compromise. Research findings have established innate and acquired immune factors and genetic polymorphisms that influence an individual's ability to resist or survive infection with *C. neoformans* (reviewed in [11,12]). Cryptococcosis in patients in which no immune deficiency has been identified, such as in this case, may represent the existence of an underlying immunological or genetic predisposition.

Treatment

The Infectious Diseases Society of America (IDSA) recommends that apparently-immunocompetent patients (i.e. non-HIV and non-transplant recipients) with disseminated cryptococcosis are treated with high-dose amphotericin B (0.7–1.0 mg/kg per day) and flucytosine (100 mg/kg per day in 4 divided doses) for up to 6 weeks followed by consolidation treatment with fluconazole (400 mg per day) for 8 weeks and maintenance low-dose fluconazole (200 mg [3 mg/kg] per day) for 6-12 months.[35] This approach to treatment is based on two early clinical trials in a heterogeneous group of patients with meningitis who were neither HIV-infected nor transplant recipients: the first trial documented the superiority of a combination low-dose amphotericin B and high-dose flucytosine regimen vs low-dose amphotericin B alone; and, the second, the superiority of a 6-week vs 4-week combination regimen.[36,37] These trials were published prior to the availability of triazole agents and adoption of the standard 3-phase regimen with a high-dose amphotericin B and flucytosine backbone. Thus, the IDSA recommendations have been modified to include currently-accepted doses of amphotericin B deoxycholate and flucytosine and consolidation/maintenance phases of treatment to reduce the risk of relapse. If flucytosine is not given or is unavailable, lengthening the duration of amphotericin B treatment by two weeks is recommended.[35]

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