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

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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.14 Cryptococcus 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.6-9 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 2-4). 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.21,22 These, along with many other ‘ready-made’ virulence factors (production of melanin, degradative enzymes and an ability to grow at physiological temperatures),23 allow Cryptococcus to remain in dormant until host immune-compromise allows dissemination and disease, most commonly meningocerebralitis 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.24 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 1). 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 fluconazole (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. 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 fluconazole regimen vs low-dose amphotericin B alone; and, the second, the superiority of a 6-week vs 4-week combination regimen. 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 fluconazole backbone. Thus, the IDSA recommendations have been modified to include currently-accepted doses of amphotericin B deoxycholate and fluconazole and consolidation/maintenance phases of treatment to reduce the risk of relapse. If fluconazole is not given or is unavailable, lengthening the duration of amphotericin B treatment by two weeks is recommended.

**References**

1. Hagen F, Khayhan K, Theelen B, et al. Recognition of seven species in the Cryptococcus gattii/Cryptococcus neoformans species complex. Fungal Genet Biol. 2015 May;78:16–48.
2. Park BJ, Rajasingham R, Smith R, et al. Update on the global burden of cryptococcosis. Oral Abstract presented at: ICCC; Amsterdam; 2014.
3. Jarvis JN, Meintjes G, Williams A, et al. Adult meningitis in a setting of an underlying immunological or genetic predisposition. Lancet. 2009;373(9668):1171–6.
4. Britz E, Mollendorf C, von Gottberg A, et al. The epidemiology of paediatric-onset and adult-onset cryptococcosis detected through population-based surveillance, 2005–2007. AIDS. 2012 Nov;26(18):2307–14.
5. Goldman DL, Khine H, Abadi J, et al. Serologic evidence for Cryptococcus neoformans infection in early childhood. Pediatrics. 2001 May;107(5):e66.
6. Deshaw M, Pirofski LA. Antibodies to the Cryptococcus neoformans capsular glucuronoxylomannan are ubiquitous in serum from HIV+ and HIV– individuals. Clin Exp Immunol. 1995 Mar;99(3):425–32.
7. Fleuridor R, Lyles RH, Pirofski L. Quantitative and qualitative differences in the serum antibody profiles of human immunodeficiency virus–infected persons with and without Cryptococcus neoformans meningitis. J Infect Dis. 1999 Nov;179(5):1526–35.
8. Abadi J, Pirofski L. Antibodies reactive with the cryptococcal capsular polysaccharide glucuronoxylomannan are present in sera from children with and without human immunodeficiency virus infection. J Infect Dis. 1999 Sep;180(3):915–9.
9. García-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. J Clin Microbiol. 1999 Oct;37(10):3204–9.
10. Ma H, May R. Virulence in Cryptococcus species. In: Advances in applied microbiology, Burlington, VT: Academic Press; 2009. p. 131–90.
11. May RC, Stone NRH, Wiesner DL, et al. Cryptococcus: from environmental saprophyte to global pathogen. Nat Rev Microbiol. 2015 Dec 21;14(2):106–17.
12. Rohatgi S, Pirofski L. Host immunity to Cryptococcus neoformans. Future Microbiol. 2015 Apr;10(4):565–81.
13. Coelho C, Bocca AL, Casadevall A. The intracellular life of Cryptococcus neoformans. Annu Rev Pathol Mech Dis. 2014 Jan 24;9(1):219–38.
14. Zuberbier BN, Shuman HA, Casadevall A. Cryptococcus neoformans interactions with amoebae suggest an explanation for its virulence and intracellular pathogenic strategy in macrophages. Proc Natl Acad Sci USA. 2001 Dec 18;98(26):15245–50.
15. Tucker SC, Casadevall A. Replication of Cryptococcus neoformans in macrophages is accompanied by phagosomal permeabilization and accumulation of vesicles containing polysaccharide in the cytoplasm. Proc Natl Acad Sci USA. 2002 Mar 5;99(5):3165–70.
16. Casadevall A, Steenbergen JN, Nosanchuk JD. ‘Ready made’ virulence and ‘dual use’ virulence factors in pathogenic environmental fungi — the Cryptococcus neoformans paradigm. Curr Opin Microbiol. 2003 Aug;6(4):332–7.
17. Kapoor A, Flechner SM, O’Malley K, et al. Cryptococcal meningitis in renal transplant patients associated with environmental exposure. Transpl Infect Dis. 1999 Sep;1(3):213–7.
18. Nosanchuk JD, Shoham S, Fries BC, et al. Evidence of zoonotic transmission of Cryptococcus neoformans from a pet cockatoo to an immunocompromised patient. Ann Intern Med. 2000 Feb 1;132(3):205–8.
19. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
20. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
21. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
22. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
23. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
24. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
25. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
26. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
27. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
28. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
29. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
30. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
31. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
32. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
33. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
34. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
35. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
36. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
37. Desmet P, kayembe K, Vroey C. The value of cryptococcal serum antigenemia in anti-retroviral naïve AIDS patients in Benin City, Nigeria. Microb Med. 2003;5:1993–2000.
34. Rugemalila J, Maro VP, Kapanda G, et al. Cryptococcal antigen prevalence in HIV-infected Tanzanians: a cross-sectional study and evaluation of a point-of-care lateral flow assay. Trop Med Int Health. 2013 Sep;18(9):1075–9.
35. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010 Feb;50(3):291–322.
36. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. N Engl J Med. 1979 Jul 19;301(3):126–31.
37. Dismukes WE, Cloud G, Gallis HA, et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. N Engl J Med. 1987 Aug 6;317(6):334–41.

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