Cryptococciosis: The Ubiquitous Yeast

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A lthough the pathogenic fungus Cryptococcus was identified and described way back in 1894, cases of cryptococcal infection and disease manifestations were practically unheard of for almost a century. However, with the emergence of HIV/AIDS in 1984, many cases of cryptococcal infection were detected and this fungus has emerged to be a major cause of life-threatening opportunistic infection in HIV-affected individuals. In most cases, cryptococci form a harmless colonization of the airways and prevail as asymptomatic infection in laboratory workers; but few cases may manifest as systemic disease. The crucial factor determining disease manifestation and outcome is not the virulence of the affecting organism but the immune status of the host. Most forms of this infection usually develop in patients with defective cell-mediated immunity e.g. patients with HIV/AIDS, organ transplantation, malignancy and corticosteroid therapy.

In 1894, Busse and Buschke isolated this yeast from the tibia of a 31-year-old woman and published a report describing cryptococci as a human pathogen for the first time. These fungi are ubiquitous, mainly found in soil and fowl manure, especially in pigeon droppings. Transmission occurs by inhalation of spores or contamination of wounds. Cryptococcosis is most common in cats but is also seen in dogs, cattle, horses, sheep, goats, birds and wild animals. Organs afflicted in decreasing order of frequency are kidneys, lymph nodes, spleen, liver, thyroid, adrenals, pancreas, bone, GI tract, muscle, myocardium, prostate, heart valves and tonsils.

A lthough the genus Cryptococcus contains more than 50 species, only Cryptococcus neoformans and Cryptococcus gattii are considered principal pathogens in humans and they are most commonly found in pigeon droppings. C. neoformans is found worldwide and C. gattii is found in Australia, South America, Southeast Asia, Central and sub-Saharan Africa, Southern California states of Washington and Oregon and Vancouver Island, British Columbia, Canada.

C. neoformans meningitis is responsible for more than 600,000 deaths per year worldwide. In sub-Saharan Africa, 15% - 30% of all patients with HIV/AIDS develop cryptococcal disease. However, in some areas, such as Zimbabwe, 88% of patients with HIV/AIDS have cryptococcal infection as their AIDS-defining illness.

Studies done at San Francisco General Hospital proved that 45% of AIDS patients had cryptococcosis as the first manifestation of HIV/AIDS. Early in the AIDS epidemic, approximately 5-8% of patients developed cryptococcal infection. The incidence of cryptococcosis started decreasing with availability of effective antiretroviral treatment (ART). Lesions associated with cryptococcosis vary from a gelatinous mass (consisting of numerous organisms with minimal inflammation) to granuloma formation. The lesion is usually composed of aggregates of encapsulated organisms within a connective tissue reticulum. The cellular response is primarily macrophages and giant cells with a few plasma cells and lymphocytes. Epithelioid giant cells and areas of caseous necrosis are less common than with other systemic mycoses.

The clinical presentation of cryptococcal disease in HIV infection can vary significantly from that in immunocompetent individuals and those with other causes of immunosuppression. Most common systems involved are respiratory and central nervous system.

A lthough pulmonary cryptococcosis is diagnosed less frequently than meningitis in patients with AIDS, the lung is most likely the portal of entry. Cryptococcal pneumonia may be either asymptomatic or symptomatic, with or without evidence of dissemination. It is unclear if disseminated disease represents a progression or reactivation of pulmonary disease because many patients have no evidence of pulmonary involvement at the time of diagnosis of disseminated disease. Due to factors such as nonspecific clinical features, variable radiographic signs, and increased frequency of other pulmonary opportunistic infections, it is likely that cryptococcal pneumonia is underdiagnosed and not recognized until dissemination. Driver et al discovered that 78% of patients with cryptococcal meningitis had evidence of pulmonary disease in the preceding 4 months. In a review by Cameron et al, 11 of 12
Many cases of cryptococcal lymphadenitis, meningitis, pulmonary cavitative lesions have been reported as an IRIS, although it is less common compared to tuberculosis and Pneumocystis jiroveci pneumonia. Symptoms and management remain the same in cases of IRIS.13

Present study published in this issue shows eight (20%) patients were apparently immunocompetent, 10 (25%) had predisposing factors other than HIV and 22 (55%) had HIV infection in a study of 40 consecutive patients of cryptococcal meningitis. Initial presentation was cryptococcal meningitis in 59% of the HIV positive patients. The presentation was variable ranging from headache, altered sensorium, motor deficits, cranial neuropathies, cerebellitis and transverse myelitis.14

The most rapid method of diagnosis is cytologic evaluation of nasal exudate, skin exudate, cerebrospinal fluid (CSF) or samples obtained by paracentesis of the aqueous or vitreous chambers of the eye or by impression smears of nasal or cutaneous masses. India ink is used to visualize the organism, which appears unstained and silhouetted against a black background. Detection of cryptococcal capsular antigen in serum, urine, or CSF is a useful and it is a rapid method of diagnosis in suspected cases in whom the organism is not detected on microscopy. This is a latex agglutination test, commercially available in kit form. The antigen titer can also be used to guide response to therapy. The organism can be cultured from exudates (nasal, skin), CSF, urine, joint fluid, and tissue samples if adequate sample volume is available.

As per ACTG clinical trial, amphotericin B (0.7 mg/kg intravenously per day) plus flucytosine (100 mg/kg/day) for 2 weeks, followed by flucytosine (400 mg daily) for 8 weeks of consolidation therapy and 200 mg daily for maintenance therapy, is recommended as first-line therapy. Strict monitoring is necessary for toxic effect of Amphotericin in the form of bone marrow depression and nephrotoxicity. Other alternative therapy is Fluconazole (2.5–10 mg/kg/day) or itraconazole (10 mg/kg/day) especially when patient is intolerant to Amphotericin B. Flucytosine can be used alone; however, drug resistance may develop, so combination therapy is recommended. CSF paracentesis is recommended for raised intracranial pressure. It may result in relieving symptoms like headache and altered sensorium.15

Primary prophylaxis is not advised for prevention of cryptococcosis. Even though patient of cryptococcal meningitis improve on complete therapy, cryptococcal antigen persists in CSF. USPHS/IDSA guidelines recommends discontinuation of secondary prophylaxis if patients have completed a course of therapy for cryptococcosis and remain asymptomatic with increase of CD4 counts to >200 cells/µL on ART. Prophylaxis should be restarted if the CD4 count declines to <200 cells/µL.16

References
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