Overview: Cryptococcosis in the patient with AIDS

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Abstract

Cryptococcosis is currently the most common life threatening mycoses found in patients with the acquired immunodeficiency syndrome (AIDS). Extrapulmonary involvement is most frequently seen, especially in the central nervous system and skin. Clinical findings are non-specific, even in patients with meningitis. Threshold for diagnosis of this infection should be low, with serum cryptococcal antigens, blood, urine and sputum cultures for Cryptococcus neoformans performed in febrile AIDS patients. Lumbar puncture should also be performed if unexplained headaches are included in a patient's complaints. There is currently no consensus for the most appropriate treatment strategy and the role of oral azoles versus amphotericin B or amphotericin B with flucytosine remains a serious question in need of further controlled studies. Patients eligible for multicentered trials should be encouraged to participate. Therapy for others should be individualized. This review will address some of these issues.

Infection caused by Cryptococcus neoformans has been recognized for many years, but only since its appearance as the most common life threatening mycosis found in patients with the acquired immunodeficiency syndrome (AIDS) has it generated much interest in the general medical community. In the United States, 5–10% of AIDS patients will develop cryptococcal meningitis during the course of their HIV infection. Currently, while AIDS patients represent the largest single patient group who develop cryptococcal disease, other patients with cell mediated immune deficits and the occasional patient with no known immunological abnormality still are being infected with C. neoformans. The purpose of this brief overview is to summarize clinically important information about cryptococcosis as it occurs in patients with AIDS. Many other reviews of the subject are available to supplement the information contained in this paper [1–6] and the reader is encouraged to consult these additional resources. A major theme of this review is that there are still many unanswered questions concerning management of AIDS patients with cryptococcosis.

Organism and epidemiology

C. neoformans is an ubiquitous yeast-like organism growing in soil, especially that enriched with pigeon excreta. Four different serotypes are recognized: A, B, C, and D. Serotypes A and D are known as C. neoformans var neoformans and B and C are classified as C. neoformans var gatti. While serotypes A and D have been isolated from
all areas of the world, B and C apparently have a more restricted geographic distribution and can be found especially in the southern California and in Australia. In the latter country, an association of serotypes B and C with eucalyptus trees has recently been reported [7]. Still an unexplained observation, almost all of the reported cases of cryptococcosis in AIDS patients have been with serotypes A and D, even in areas where serotypes B and C predominate [8]. No such relationship has been found in patients without HIV infection.

The unencapsulated spore is presumably the infectious propagule and once deposited into the lungs, infection can ensue. Cryptococci recovered from patient samples typically have capsules of varying size and these are usually easily visible under the microscope. In contrast to strains isolated from non-AIDS patients, unencapsulated strains have been cultured from AIDS patients [9]. The significance of this observation is not clear, but suggests that visualization of a capsule is not mandatory for the diagnosis of cryptococcosis to be entertained.

Clinical manifestations

The hallmark of the clinical presentation of cryptococcal meningitis in AIDS patients is its non-specificity. Typically, patients have fever (65%), malaise (75%), nausea/vomiting (40%) and headache (75%). However, these same symptoms are often present in these patients even when cryptococcosis is not present. Symptoms and signs of meningitis, e.g., stiff neck, altered mentation, and Kernig and Brudzinski signs occur, but are found in less than 50% of patients. Thus, the diagnosis must be suspected in any patient with unexplained fever, headache or malaise.

It is well documented that *C. neoformans* enters the body through the lungs and later disseminates to extrapulmonary sites. Most commonly involved are the brain and meninges, skin, bone, and prostate. One hypothesis, as yet untested, is that a spontaneously resolving pneumonia in AIDS patients may be due to infection with *C. neoformans* and subsequently meningitis develops. Indeed, in a series of 19 of our patients, in the 2 months prior to the diagnosis of cryptococcal meningitis, pneumonia (due to *Pneumocystis* or other pathogens) was found in 11 patients. In contrast, in the 2 months following the diagnosis of cryptococcal meningitis, when patients were typically under more intensive medical observation, only 2 cases of clinically apparent pneumonia was documented. This information suggests that pneumonia preceding the development of cryptococcal meningitis may be due to infection with *C. neoformans* and that appropriate diagnostic evaluation (e.g., serum cryptococcal antigen, culture of sputum or bronchoalveolar lavage fluid for *C. neoformans*) might identify these patients.

Diagnosis

The diagnosis of cryptococcosis is not very difficult once the diagnosis is entertained. The organism grows readily on routine media and can easily be presumptively identified by its brown color when grown on bird seed agar.

Since most patients with AIDS and cryptococcosis present with meningitis, most of the experience in diagnosis is with this presentation of cryptococcal disease. Serum and cerebrospinal fluid should be tested for the presence of cryptococcal antigen using one of the commercially available latex agglutination tests. Over 90% of patients with cryptococcal meningitis will have positive tests on either of these patient specimens [5]. Moreover, positive titers may be extraordinarily high, often in the 1000 s. In contrast, routine studies of CSF, such as white blood cell count, glucose, and protein, are not very helpful since abnormalities in these parameters are often not present and when they are, there are usually minimal derangements. India ink examinations of CSF may be positive in about 75% of patients, reflecting the high organism load.

Other studies which may be provide useful information include: blood cultures, urine cultures,