8.7.2 Cryptococcosis 1359

8.7.2 Cryptococcosis 1359

8.7.2 Cryptococcosis 1359 8.7.2 Cryptococcosis William G. Powderly, J. William Campbell, and Larry J. Shapiro ESSENTIALS Cryptococcus neoformans, which is found worldwide as a soil organism and thought to be transmitted by inhalation, most often causes disease in patients with abnormal cell-mediated immunity, notably patients with HIV infection and solid-organ transplant recipients, but the in- fection also occurs rarely in apparently immunocompetent people in restricted geographical areas, especially involving C. neoformans var. gattii. The most common presentation is with subacute meningo- encephalitis, but other manifestations (e.g. isolated pulmonary disease or disseminated infection, are well described). Diagnosis is usually by culture or serology. Untreated cryptococcal meningitis is fatal: aside from supportive care (including monitoring for raised intracranial pres- sure), the therapy of choice is an initial period (at least two weeks) of amphotericin B (ideally with flucytosine), followed by at least 3 months of fluconazole. Most immunocompromised patients subsequently re- quire maintenance suppressive therapy, usually with fluconazole. Aetiology and epidemiology Infection with the fungus Cryptococcus neoformans occurs mainly in patients with impaired cell-mediated immunity. It is the most common systemic fungal infection in patients infected with HIV and is also seen as a complication of solid-organ transplantation, lymphoma, and corticosteroid therapy. C. neoformans is found worldwide as a soil organism; it is an encapsulated yeast measuring from 4 to 6 µm with a surrounding polysaccharide capsule ranging in size from 1 to over 30 µm. Two varieties exist, distinguishable by serology: C. neoformans var. neoformans (serotypes A and D) and C. neoformans var. gattii (serotypes B and C). Virtually all HIV- associated infection is caused by C. neoformans var. neoformans. About 5% of HIV-infected patients in the Western world develop disseminated cryptococcosis; the disease is much more prevalent in sub-Saharan Africa and South-East Asia, with estimates of 750 000– 1 million cases annually. C. neoformans var. gattii infection is more common in tropical and subtropical areas (Australia, New Guinea, and the Philippines) in apparently immunocompetent people. Cases of Cryptococcus gattii were described on Vancouver Island, British Columbia, Canada, in 1999. The Pacific Northwest of North America (British Columbia in Canada, and Washington and Oregon in the United States) now has one of the highest incidences of this infection worldwide, and cases of C. neoformans var. gattii infection have occurred throughout North America. It has only rarely been reported in HIV-immunosuppressed patients. The exact mechanism of infection is unknown. It is assumed that transmission occurs via inhalation of the organism leading to colonization of the airways and subsequent respiratory infection. Throughout the world, the excreta of birds such as pigeons are the richest environmental source of C. neoformans var. neoformans. The ecological association of C. neoformans var. gattii is with river red and forest river gum trees (Eucalyptus camaldulensis and E. tereti cornis) and with mammals

such as koalas. It has been suggested that infective basidiospores are released at flowering. In the case of C. neoformans var. neoformans, the absence of an intact cell-mediated response results in ineffective clearance with subsequent dissemination. The polysaccharide capsule, composed mainly of glucuronoxylomannan, is thought to be its primary viru- lence factor. It is not clear whether cryptococcal infection in im- munocompromised patients represents acute primary infection or reactivation of previously dormant disease. Clinical features The most common presentation of cryptococcosis is a subacute meningitis or meningoencephalitis with fever, malaise, headache, and altered behaviour and level of consciousness. Symptoms are usually present for 2 to 4 weeks before diagnosis. Classic menin- geal symptoms and signs (such as neck stiffness or photophobia) (Fig. 8.7.2.1) occur in only about a quarter to a third of patients. Papilloedema and cranial nerve palsies (especially VI and VII) are common (Fig. 8.7.2.2). Patients might present with encephalopathic symptoms such as lethargy, altered mentation, personality changes, and memory loss. Analysis of the cerebrospinal fluid usually shows a mildly elevated serum protein, normal or slightly low glucose, and a lymphocytic pleocytosis. India ink staining of the cerebrospinal fluid will usually reveal the yeast. Cryptococcal antigen is almost in- variably detectable in the cerebrospinal fluid. The opening pressure in the cerebrospinal fluid is elevated in most patients. Infection with C. neoformans can involve sites other than the men- inges. Isolated pulmonary disease has been well described and usu- ally presents as a solitary nodule in the absence of other symptoms. Cryptococcal pneumonia also occurs. In immunocompromised Fig. 8.7.2.1 Neck stiffness in a Papua New Guinean patient with Cryptococcus neoformans var. gattii meningitis. Copyright D. A. Warrell.

 patients, especially those with AIDS, subsequent dissemination is common but presentations such as cough or dyspnoea, and abnormal chest radiographs can be the initial findings. Many patients have posi- tive blood cultures. Skin involvement is common; several types of skin lesion have been described (Fig. 8.7.2.3) but the most common form is that resembling molluscum contagiosum. Osteolytic bone le- sions and prostatic involvement have also been described. Infection with C. neoformans var. gattii is more likely to occur in older patients with other comorbid conditions. Infection with C. neoformans var. gattii appears to cause cryptococcomas in the lung and brain (often large, multifocal lesions) more commonly than C. neoformans var. neoformans, and patients with C. neofor mans var. gattii appear to have more aggressive retinal involvement with papilloedema and haemorrhagic papillitis in more than a half of patients, leading to blindness in one-third of survivors. Diagnosis Cryptococcal disease can be diagnosed through culture, by visual- ization of the organism in microscopy or tissue, or by detection of cryptococcal polysaccharide antigen (CrAg) in blood or cerebro- spinal fluid. CrAg testing is highly sensitive and specific in the diag- nosis of infection with C. neoformans. Three methods currently exist for antigen detection: latex agglutination, enzyme immunoassays, and lateral flow assay (a newly developed dipstick test that can be used as a point-of-care test). Cerebrospinal fluid CrAg is usually posi- tive in patients with cryptococcal meningoencephalitis. Serum CrAg is usually positive in both meningeal and nonmeningeal infection and might be detectable before symptoms are evident. Such patients should be evaluated for possible meningeal involvement. Culture of C. neoformans from any site should also be regarded as significant and is an indication for further evaluation and initiation of therapy. Treatment Management of patients with cryptococcal infection depends on the extent of the disease and the immune status of the patient. The finding of a solitary pulmonary nodule in a normal host might not need treatment, provided patients have careful follow up. Fluconazole (200–400 mg/day) can be given for 3 to 6 months in most patients with localized pulmonary disease. Extrapulmonary disease is gener- ally managed in the same way as meningitis. In patients who are not known to be immunosuppressed,

a search for underlying problems should be initiated. An HIV antibody test should be performed, as cryptococcal meningitis can be the initial AIDS-defining event. Additionally, a CD4+ lymphocyte count should be considered, as cryptococcal infection has been described as one of the manifest- ations of so-called ‘isolated CD4 T lymphocytopenia’. Untreated, cryptococcal meningitis is fatal. In patients with AIDS, the combination of amphotericin B and flucytosine (100 mg/kg per day in three or four divided doses) given for 2 weeks followed by fluconazole (400 mg orally) for a further 8 weeks is associated with the best outcome to date in prospective trials, with a mortality of 10–15% and a mycological response of approximately 70%. This regimen is also reasonable for treatment of meningitis in other circumstances. In the Western world, the liposomal formulation of amphotericin B is pre- ferred and dosed at 5 mg/kg/day. In resource-poor settings, the more nephrotoxic deoxycholate formulation of amphotericin is usually the only available formulation; its dosage for cryptococcal meningitis in 0.7–1.0 mg/kg/day. A recent study in Africa found that one week of amphotericin B with flucytosine was adequate as induction therapy. Clinical deterioration in patients with meningitis might be due to cerebral oedema, which can be diagnosed by a raised opening pres- sure of the cerebrospinal fluid. All patients with cryptococcal men- ingitis should have the opening pressure measured when a lumbar puncture is performed; if the opening pressure is high (>25 cmH2O), pressure should be reduced by repeated lumbar punctures, a lumbar drain, or a shunt. The use of adjunctive corticosteroids has been shown to be deleterious in the setting of HIV infection. Provided HIV infection and isolated CD4 lymphopenia have been excluded, immunocompetent patients with cryptococcal meningitis can be generally managed with a shorter (3–4 months) course of Fig. 8.7.2.2 Right cranial VI (abducens) nerve paralysis in an African HIV-seropositive patient with Cryptococcus neoformans var. neoformans meningitis. Copyright D. A. Warrell. Fig. 8.7.2.3 Cryptococcal cutaneous ulcer. Courtesy of Professor R. Hay.

Revision #1
Created 2026-01-22 16:46:01 UTC by Omar Ayman
Updated 2026-01-22 16:46:01 UTC by Omar Ayman