Cryptococcosis in Asia

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18.1 Introduction

Human cryptococcosis is caused by encapsulated basidiomycetous yeast *Cryptococcus neoformans*, and less frequently by *C. gatti*. Both species are ubiquitously distributed in the environment, and can be isolated from the bark of a wide variety of tree species; and from other organic matter, notably, bird feces. They are typically opportunistic pathogens. Primary infection, acquired by inhalation, is most often asymptomatic. This is followed by hematogenous dissemination, which occurs primarily in hosts with defective cell-mediated immune responses (e.g., HIV infection, solid organ and stem cell transplant recipients, etc.). Cryptococcal meningitis (CM), the commonest clinical manifestation of cryptococcosis, is potentially fatal, accounting for 15% of AIDS-associated deaths.

18.2 Epidemiology: Global and Asian

Rajasingham et al. estimated that there were 223,100 (95% CI 150,600–282,400) incident cases, and 181,000 (95% CI 119,400–234,300) deaths due to CM globally in 2014 [1]. Sub-Saharan Africa had the highest burden, accounting for 73% of these cases and 75% of the deaths.

An earlier study had estimated an yearly incidence of 120,000 cases and 66,000 deaths due to CM in South and Southeast Asia [2].

The average global cryptococcal antigenemia prevalence is estimated to be 6.0% (95% CI 5.8–6.2) among PLHIV with CD4+ T-lymphocyte counts <100 cells/mm^3.

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A. Chakrabarti (ed.), *Clinical Practice of Medical Mycology in Asia*,
https://doi.org/10.1007/978-981-13-9459-1_18

Table 18.1 Prevalence of cryptococcal antigenemia in Asian PLHIV

Country	Prevalence (95% CI) (%)	Population	Reference
India	8 (4–12)	Age > 18 years CD4 < 100	Kadam, Indian J Med Microbiol 2017 [3]
India	3 (NA)	ART naïve adults CD4 < 100	Anuradha, J Assoc Physicians India 2017 [4]
Vietnam	6 (3–11)	ART naïve CD4 < 100	Smith, PLoS ONE 2013 [5]
Thailand	11 (NA)	Women initiating ART CD4 < 100	Kwan, J Int Assoc Provid AIDS Care 2014 [6]
Thailand	13 (NA)	PLHIV with ARI	Harris, Clin Infect Dis 2012 [7]
Thailand	13 (NA)	PLHIV with ARI	Lindsley, Clin Infect Dis 2011
Thailand	9.2 (NA)	ART naïve	Pongsai, J Infect 2010 [8]

NA not available

The above table summarizes the reported CrAg prevalence among PLHIV in various Asian countries, which is above the global average (Table 18.1).

18.3 Clinical Features

The vast majority of patients with cryptococcosis and CM are immunocompromised due to AIDS, solid organ or stem cell transplantation, long-term steroid use, cirrhosis liver, etc. [9]. Neutralizing anti-interferon-γ autoantibody (nAIGA) associated immunodeficiency is emerging as an important predisposing condition for cryptococcosis in Southeast Asia [10]. CM can also occur in patients with no known causes for immunodeficiency. CM presents as subacute meningo-encephalitis. Common presenting symptoms include headache, fever, and malaise with duration of 7–14 days. Signs of meningeal irritation like neck stiffness and Kernig's sign are uncommonly present among PLHIV with CM. Severe manifestations include coma, which can end fatally. The case fatality rate can be as high as 40–60% despite antifungal treatment in resource-limited settings. Disseminated cryptococcosis can involve virtually any organ system—skin, reticulo-endothelial system, lungs, bones, prostate in men, fungemia, etc. Of these skin manifestations are the most common. Skin involvement (Fig. 18.1) can present as umbilicated papules, nodules, ulcers, and cellulitis (particularly among transplant recipients.)

18.4 Laboratory Diagnosis [9, 11, 12]

Mycological evidence of infection is essential for planning antifungal treatment. Laboratory methods include direct smear, antigen detection, and culture of CSF, blood, bone marrow, biopsy specimens, etc.

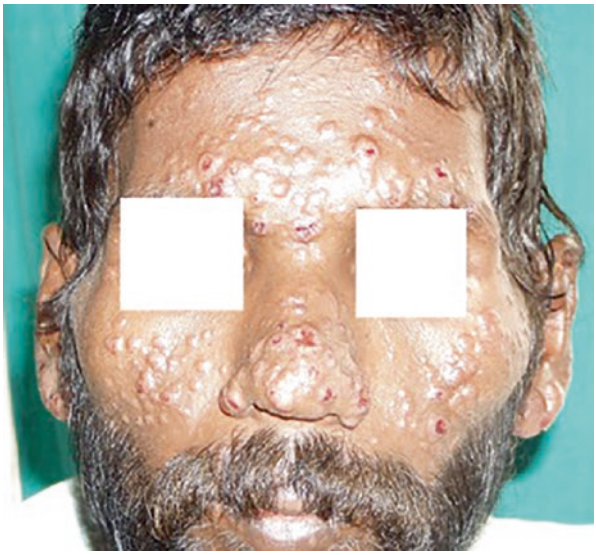

Fig. 18.1 Typical skin lesions in disseminated cryptococcosis among PLHIV - umbilicated papules, some with ulceration

Table 18.2 Comparison of diagnostic tests for CM

Test	Sensitivity	Specificity	Turnaround time	Cost
Culture	Gold standard	Gold standard	Slow	++
India ink smear	86%	100%	Rapid	+
CrAg LFA	99%	99%	Rapid	++

1. Culture is considered the "gold standard" for the diagnosis of CM. The major drawbacks of culture include the need for laboratory infrastructure, skilled personnel, and the turnaround time of up to 4 weeks.
2. India ink smear is quick, easy to perform, inexpensive, and is fairly accurate (sensitivity 86%). However, it may be falsely negative, especially in early stages of CM, when the fungal burden in the CSF is low.
3. Cryptococcal antigen (CrAg): The availability of CrAg lateral flow assay (LFA) has revolutionized the diagnosis of CM in resource-limited setting. This is an immunochromatographic dipstick test, which detects the presence of cryptococcal polysaccharide capsular antigen in serum, plasma, or CSF. This test is very accurate (high sensitivity and specificity), inexpensive, easy to perform, does not need sophisticated laboratory, and has a rapid turnaround time. All these advantages make this test ideal for use as a point-of-care test in resource-limited settings (Table 18.2) [12].

18.5 Treatment

Antifungal treatment: Antifungal treatment in HIV-associated CM is divided into three phases—induction, consolidation, and maintenance [13].

1. Induction: Combination of amphotericin B deoxycholate (1 mg/kg/day i.v.) with flucytosine (25 mg/kg Q6H p.o.) for 7 days (both potent fungicidal drugs), followed by fluconazole (1200 mg/day p.o.) for 7 more days has been shown to have the lowest mortality rate in comparison to amphotericin B with fluconazole and flucytosine with fluconazole in the recently published ACTA trial [14]. This regimen is the preferred treatment option recommended by WHO. The beneficial effect of this regimen is correlated with better clearance of the cryptococcal burden when compared to the other regimes. If flucytosine is not available, amphotericin B with fluconazole for 14 days can be used.

   Both amphotericin B (thrombophlebits, infusion-related toxicities like fever and rigors, hypokalemia, nephrotoxicity, anemia) and flucytosine (bone marrow suppression) are associated with significant toxicity. Using a central venous catheter or rotating the peripheral venous access site every 3 days can reduce thrombophlebitis. Pre-hydration (1 L 0.9% NaCl), potassium supplementation, and frequent monitoring of potassium, creatinine, and hemoglobin are recommended to reduce the incidence of toxicity [13].
2. Consolidation: Fluconazole 800 mg/day p.o. for 8 weeks is recommended [13].
3. Maintenance phase (secondary prophylaxis) of antifungal treatment (fluconazole 200 mg/day p.o.) is continued for at least 1 year on antifungals and antiretroviral treatment (ART), and there is evidence of sustained immunological recovery (CD4+ T-lymphocyte count >200 cells/mm^3 for 12 months) (Table 18.3) [13].

Management of raised intracranial pressure (ICP) [13, 15]: Raised ICP is a common complication, occurring in up to 80% of patients with HIV-associated CM. Raised ICP contributes to increased morbidity and mortality. Elevated ICP is most often characterized by headaches, vomiting, papilledema, reduction of visual acuity, cranial nerve palsy (most commonly cranial nerve VI), confusion, altered mental status, and coma. ICP may be elevated even in the absence of symptoms. Studies have shown that reduction of ICP is associated with improved survival. Therefore, measurement of ICP at the time of initial lumbar puncture (LP) is an

Table 18.3 Antifungal treatment of HIV-associated CM

Phase	Drugs	Duration	Comments
Induction	Ampho B 1 mg/kg/day i.v. + FC 25 mg/kg Q6H p.o. × 7 days, followed by FLU 1200 mg/day p.o. × 7 days	14 days	• Use central venous catheter or rotate infusion site • Monitor Hb, creat, K+ • Pre-hydration: 1 L 0.9% NaCl with 20 mEq KCl daily
Consolidation	FLU 800 mg/day p.o.	8 weeks	
Maintenance	FLU 200 mg/day p.o.	Till immunological recovery	

Ampho B amphotericin B, *FC* flucytosine, *FLU* fluconazole, *Hb* hemoglobin, *creat* creatinine

essential part of management of patients with CM. Aggressive reduction of ICP should be done by draining adequate amount of CSF (approximately 20 mL) to lower the pressure to <20 cm CSF (therapeutic LP). Persistent or recurrent symptoms of raised ICP during the initial induction phase of antifungal treatment require daily therapeutic LPs till resolution of symptoms. There are no published studies evaluating the optimal frequency of therapeutic LPs or volume CSF to be drained. Hence, the decision has to be guided by clinical features.

There is no role for drugs like frusemide, acetazolamide, mannitol, or dexamethasone in the management of raised ICP in patients with CM. A randomized trial (which included patients from Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi) evaluating the role of adjunctive dexamethasone in management of HIV-associated CM showed no benefit, but increased harm in dexamethasone treated patients [16].

Assessing treatment response is by clinical criteria. Adequate response is indicated by resolution of headache, altered mental status, other neurological symptoms, and fever. There is no role for routine LP at the end of induction phase of antifungals to document CSF sterilization in patients who have substantial clinical improvement. Randomized trials have shown that only about 60% of patients have negative cultures at the end of induction therapy. Serial estimation CrAg has also no role in assessment of therapeutic response [13].

Antiretroviral treatment: ART dramatically reduces morbidity and mortality due to HIV infection, and should be started in all ART naïve PLHIV presenting with CM. The COAT trial [17] done in Uganda showed that early ART (started within 2 weeks of the diagnosis of CM) was associated with higher mortality when compared to deferred (5 weeks) ART. A subsequent Cochrane review also concluded that early ART initiation increased mortality compared to delayed ART (RR 1.42, 95% CI 1.02–1.97) [18]. Based on these, WHO recommends initiating ART 4–6 weeks after starting the induction regimen of antifungals.

Cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) can occur in up to 50% patients [19] and typically occurs within 12 weeks of ART initiation, but may occur as late as 1 year following the initial diagnosis. The paradoxical form of C-IRIS presents as a worsening or recurrent meningeal or CNS disease, or at a new anatomic site (e.g., lymph node, lung). Patients present with fever and headache. CSF analysis typically reveals elevated WBC counts, low titers of CrAg and negative culture. Risk factors for C-IRIS include low CD4+ T-lymphocyte counts, very high plasma HIV load, and early initiation of ART. Management of C-IRIS includes continuation of ART and antifungals (consider restarting induction treatment) and a short course of steroids [13].

18.6 Prevention [13]

The best way to prevent CM in PLHIV is early initiation of ART. In patients presenting late (CD4+ T-lymphocyte count <100 cells/mm^3), screening for CrAg and preemptive fluconazole treatment (similar to the induction, consolidation, and

maintenance phase of definitive treatment) is recommended for those who test positive. Patients should also be carefully evaluated for clinical features suggestive of CM if the CrAg is positive, and if LP confirms the diagnosis, they should be managed as CM. ART can be initiated after 2 weeks of preemptive antifungal treatment if there is no evidence of CM.

18.7 Conclusions

South and Southeast Asian countries have substantial burden of morbidity and mortality due to HIV-associated CM. The availability of CrAg LFA has been a major advance in the diagnosis of CM. Combination of amphotericin B with flucytosine is the preferred initial treatment due to its ability to sterilize the CSF faster and survival benefit. Screening using CrAg LFA followed by preemptive antifungal treatment is now recommended for all PLHIV with CD4 cell counts below 100 cells/mm^3 at presentation.

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