Disseminated cryptococcosis in a patient with HIV/AIDS at a teaching hospital in Ghana

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Abstract
Objective: To raise awareness of the existence of cryptococcal infections in HIV/AIDS patients in Ghana.
Method: Detailed postmortem gross and histopathological analysis of an HIV/AIDS patient suspected to have cryptococcal meningitis was carried out and histopathological findings correlated with clinical findings.
Results: Showed disseminated Cryptococcosis in an HIV/AIDS patient which was confirmed with special stains.
Conclusion: Cryptococcal infection occurs in HIV/AIDS patients in Ghana and when clinically suspected the diagnosis should be pursued vigorously.

Keywords
Cryptococcosis, AIDS, Ghana

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Introduction
Cryptococcosis is a leading mycological cause of morbidity and mortality among patients with AIDS. About 5%–10% of AIDS patients develop cryptococcosis in the United States, Europe and Australia, compared to 15%–30% of patients in sub-Saharan Africa. It is estimated that 10%–25% of AIDS patients with cryptococcosis die despite antifungal therapy and 30%–60% succumb within the first year of onset of the infection. Some studies suggest that cryptococcal disease may be more common in Southern and East Africa than in West Africa. In a study conducted at the Komfo Anokye Teaching Hospital (KATH) Kumasi, Ghana, while admitting the possibility of bias, the investigators found that the prevalence of cryptococcal antigenemia in patients with advanced HIV infection enrolling in an antiretroviral programme appeared to be low in Kumasi, suggesting that the value of routine testing of outpatients diagnosed with advanced HIV infection may be limited in this population. The risk of infection with the fungus is strongly associated with CD4 T-cell counts of < 200 cells/mm3 and World Health Organization (WHO) clinical stages 3 and 4 of AIDS. In one study, CD4 count of < 100 cells/mm3 provided the highest sensitivity for the diagnosis (93%), Glasgow Coma Scale ≤ 8 provided the highest specificity (84%), and the combination provided the highest positive likelihood ratio.

A case of disseminated cryptococcosis in an HIV patient is presented, correlating with histopathological findings and existing literature and confirming the existence or presence of the condition.

Case report
In accordance with current requirements and practice at the Korle Bu Teaching Hospital, Ghana, regarding case reports, in general, and reports on deceased patients, in particular, we ensured that no identifying clinical and demographic data were used in this report, obviating the need for written consent and ethical approval.

A 36-year-old woman living with HIV 1 presented to the hospital 4 months after diagnosis with recurrent headache...
a year’s duration and diarrhoea of 2-weeks duration. She was cachectic, dehydrated and pale with mouth ulcers. She had no lymphadenopathy. Her neck was stiff, and Kernig’s sign was positive. She had no lateralizing signs, and her cardiovascular and respiratory systems were unremarkable.

Relevant investigations showed anaemia (Hb: 8.4 g/dL), normal white blood cell and platelet counts. Her CD4+ count was 18 cells/mm³. Cerebrospinal fluid (CSF) examination was normal. Indian ink staining was not done. A diagnosis of gastroenteritis and bacterial meningitis to rule out tuberculous or cryptococcal meningitis and cerebral toxoplasmosis was made, and she was started on antibiotics, antifungal medications and anti-tuberculous medications per the national protocols of Ghana in preparation for antiretroviral therapy (ART). She died 10 days after admission.

At autopsy, the external and internal examinations were consistent with the initial findings of cachexia, anaemia and dehydration. Both lungs were heavy and mildly oedematous, with patchy bronchocentric non-confluent consolidation. The mesenteric lymph nodes were enlarged but not matted together with the largest node being 40 mm across. The lymph nodes had homogenous tan cut surfaces. There was an isolated 30-mm nodule on the right ovary.

At examination of the central nervous system (CNS), the brain weighed 1150 g with hazy leptomeninges (Figure 1). The base of the brain was, however, devoid of opacification and of exudates. Sectioning the brain after 2-weeks fixation in 10% buffered formalin showed scattered 5- to 10-mm-sized irregular, shallow cystic cavities within the white matter of the brain in the region of the basal ganglia along the distribution of the lenticulostriate arteries. Most of the lesions were found in the cerebral hemispheres and a few in the cerebellum. No abscesses were seen. There were no other significant findings in any other organ system.

An air dried touch preparation was done of the leptomeningeal covering of the brain prior to fixation. This showed numerous cryptococci (Figure 2). The histological sections of the brain, mesenteric lymph node and ovarian nodule showed infiltration of their stroma by Periodic acid-Schiff (PAS) and Grocott positive fungi, consistent with cryptococcus infection (Figure 3).

The final autopsy diagnoses were as follows:

1. Disseminated cryptococcosis with moderate anaemia
2. HIV 1/AIDS.

Discussion

While the incidence of cryptococcal meningitis in the developed world has declined with widespread, early ART, cryptococcal disease remains a major opportunistic infection and a leading cause of mortality in patients infected with HIV in
much of the developing world.3 Cryptococcus neoformans is the leading cause of meningitis in HIV patients in central and southern Africa, accounting for 26.5%–45% of cases in studies conducted in Malawi, Central African Republic and Zimbabwe.3,8 In these areas, it is a main cause of mortality in HIV-infected individuals and is responsible for 13%–44% of all deaths, compared with tuberculosis which accounts for 5%–13% of deaths.3,8 The frequency of cryptococcosis in Ghanaian HIV patients is not documented, although some studies suggest a low prevalence in parts of the country.5

In HIV patients, dissemination as in this patient is due to defects in T-cell function and may represent a primary infection or reactivation of latent infection acquired many years earlier.1,3 With a CD4 count of 18 cells/mm³, this patient presented with signs and symptoms identical to those of the 75%–90% of patients who present with features of a subacute meningitis or meningoencephalitis with fever, malaise and headache and are generally symptomatic for 2–4 weeks prior to presentation, especially in profoundly immunosuppressed patients with CD4 counts of <100 cells/mm³.1,9–15 However, overt meningeal symptoms and signs as in this patient are unusual, occurring in about one-fourth to one-third of patients.13,15,16 Nausea and vomiting occurs in about 40% of patients, and 30% of patients have symptoms compatible with encephalopathy such as lethargy, altered mentation, personality changes and memory loss.1 Cryptococcomas, present in this patient, are rare in patients with AIDS.1

Although abnormalities on brain imaging are seen in up to 20% of patients, focal neurological signs or seizures are unusual and occur in only about 10% of patients.1,9 In the brain, three patterns of infection may be found; chronic meningitis, vasculitis and parenchymal invasion. Parenchymal invasion coexisting with chronic meningitis predominates, a combination found in this patient, was evidenced by the hazy meninges and the cryptococcomas. This may explain the profound neurological symptoms and signs in this patient. Although indolent in this patient, meningitis may be fulminant.17

Although seen in this patient, clinical findings have limited discriminatory diagnostic value.6,7 Histopathologically, the lack of protective granulomatous response and the extensive involvement of the brain parenchyma in addition to meningitis found in this patient are consistent with pathologic findings in autopsy series in HIV patients with cryptococcosis.17

Lumbar puncture often reveals markedly elevated opening pressures, >200 mm H₂O in up to two-thirds of patients, an important complicating factor.18 Like the index patient, CSF white cell counts, usually lymphocytes, are modestly elevated with mononuclear pleocytosis (>20 cells/mm³) occurring in 13%–31% of patients.18 Elevated protein levels exceeding 45 mg/dL are seen in one-third to two-thirds of cases.18 Glucose levels range from normal (as in this patient) to 300 mg/100 dL and are usually less than 60% of serum level in 17%–65%.18 Indian ink stain is positive in 74%–88% of infected patients.18 Although not done in our case, the high organism load may further increase the sensitivity of the stain. Serum cryptococcal antigen (SCA) testing is, however, the most sensitive and robust diagnostic test and may be supported with culture.18

Cryptococcal antigenaemia preceded symptoms by a median of 22 days (>100 days in 11% of patients) in one study.6 Cryptococcal antigen screening before initiation of ART in patients with a CD4 cell count of ≤100 cells/µL is believed to be highly effective for identifying patients at risk of cryptococcal meningitis and death and might be the basis for a targeted pre-emptive treatment strategy,19 approach which may be beneficial in our case. In addition, SCA screening has a substantial role for the early detection of cryptococcal infection in HIV-infected patients with low CD4 cell counts culminating in the suggestion that routine screening with SCA should be performed in patients with CD4 <100 cells/µL.20 The CrAg test was not available in the country at the time of our patient’s admission.

Acute mortality during initial therapy due to AIDS-associated cryptococcosis is high, 10%–25%,13–15 although patients without meningeal involvement do not seem to fare any better than those with meningitis.21 In patients with meningitis, early mortality correlated most with the mental status of the patient at presentation.21 One study showed that patients with any altered mentation as in this patient were far more likely to die than were patients with normal mentation.22

Other factors that appear predictive of mortality, some of which were present in this patient, during treatment include a high organism burden at baseline, poor inflammatory response in the CSF and an age of <35 years. High organism burden at baseline and abnormal mental status are, however, the most important predictors of death.13,22–24 Once over the acute cryptococcal infection and established on ART, the long-term outlook is good.3 Therefore, in the setting of expanding access to ART in Ghana, the challenge is to improve diagnosis and acute management and thereby increase the proportion of patients surviving the critical initial months.

The high mortality of HIV-related cryptococcal disease is due to the inadequacy of current antifungal therapy, restricted access to drugs in many areas including Ghana,25 antifungal therapy–related adverse effects and the problem of raised CSF pressure. In Ghana, this is coupled with diagnostic difficulties. Challenging areas in the fight against cryptococcal infection in HIV patients in Ghana include prevention and screening, clinical diagnosis once the infection is suspected, efficacious antifungal therapy with management of adverse effects, dealing with immune reconstitution in patients started on ART and dealing with raised CSF opening pressures.25

In conclusion, although cryptococcal infection has been sparsely reported in Ghanaian medical literature, factors for its existence are present, and the infection not only occurs
in the CNS but can also be disseminated and with a high mortality as demonstrated in our reported case. Thus, not only should the differential diagnosis of cryptococcal meningitis be pursued vigorously when investigating HIV-infected individuals but efforts should also be made to improve diagnosis using both the CrAg tests and culture and sensitivity of CSF. In addition, appropriate drug therapy should be made available for use with training of the health workers on the management of adverse effects.

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Declaration of conflicting interests
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References
1. Powderly WG. Cryptococcal meningitis and AIDS. Clin Infect Dis 1993; 17: 837–842.
2. Mitchell TG and Perfect JR. Cryptococcosis in the era of AIDS – 100 years after the discovery of Cryptococcus neoformans. Clin Microbiol Rev 1995; 8: 515–548.
3. Jarvis JN and Harrison TS. HIV-associated cryptococcal meningitis. AIDS 2007; 16: 2119–2129.
4. Lucas SB, Hounnou A, Peacock C, et al. The mortality and pathology of HIV infection in a West African city. AIDS 1993; 7: 1569–1579.
5. Mamoojee Y, Shakoor S, Gorton LR, et al. Low seroprevalence of cryptococcal antigenaemia in patients with advanced HIV infection enrolling in an antiretroviral programme in Ghana. Trop Med Int Health 2011; 16: 39–46.
6. French N, Gray K, Wateria C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS 2002; 7: 1031–1038.
7. Kisenge PR, Hawkins AT, Maro VP, et al. Low CD4 count plus coma predicts cryptococcal meningitis in Tanzania. BMC Infect Dis 2007; 7: 39.
8. Okongo M, Morgan D, Mayanja B, et al. Causes of death in a rural, population-based human immunodeficiency virus type 1 (HIV-1) natural history cohort in Uganda. Int J Epidemiol 1998; 27: 698–702.
9. Dismukes WE. Cryptococcal meningitis in patients with AIDS. J Infect Dis 1988; 157: 624–628.
10. Zuger A, Louie E, Holzman RS, et al. Cryptococcal disease in patients with the acquired immunodeficiency syndrome. Diagnostic features and outcome of treatment. Ann Intern Med 1986; 104: 234–240.
11. Kovacs JA, Kovacs AA, Polis M, et al. Cryptococcosis in the acquired immunodeficiency syndrome. Ann Intern Med 1985; 103: 533–538.
12. Eng RH, Bishburg E, Smith SM, et al. Cryptococcal infections in patients with acquired immune deficiency syndrome. Am J Med 1986; 81: 19–23.
13. Chuck SL and Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. N Engl J Med 1989; 321: 794–799.
14. Clark RA, Greer D, Atkinson W, et al. Spectrum of Cryptococcus neoformans infection in 68 patients infected with human immunodeficiency virus. Rev Infect Dis 1990; 12: 768–777.
15. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. N Engl J Med 1992; 326: 83–89.
16. Aberg JA and Powderly WG. Cryptococcosis and HIV, http://hivsite.ucsf.edu/InSite?page=kb-05-02-05
17. Lee SC, Dickson DW and Casadavall A. Pathology of cryptococcal meningoencephalitis: analysis of 27 patients with pathogenetic implications. Hum Pathol 1996; 27: 839–847.
18. Singh NN. HIV-1 associated opportunistic infections – CNS Cryptococcosis: differential diagnoses and workup, http://emedicine.medscape.com/article/1167389-diagnosis.
19. Jarvis JN, Lawn SD, Vogt M, et al. Screening for cryptococcal antigenemia in patients accessing an antiretroviral treatment program in South Africa. Clin Infect Dis 2009; 48(7): 856–862.
20. Pongsai P, Atamasirikul K and Sunghanuparp S. The role of serum cryptococcal antigen screening for the early diagnosis of cryptococcosis in HIV-infected patients with different ranges of CD4 cell counts. J Infect 2010; 60(6): 474–477.
21. Larsen RA, Bozzette S, McCutchan JA, et al. Persistent Cryptococcus neoformans infection of the prostate after successful treatment of meningitis. Ann Intern Med 1989; 111: 125–128.
22. McManus EJ and Jones JM. Detection of a Trichosporon beigelii antigen cross-reactive with Cryptococcus neoformans capsular polysaccharide in serum from a patient with disseminated Trichosporon infection. J Clin Microbiol 1985; 21: 681–685.
23. Clark RA, Greer DL, Valainis GT, et al. Cryptococcus neoformans pulmonary infection in HIV-1-infected patients. J Acquir Immune Defic Syndr 1990; 3: 480–484.
24. Larsen RA, Leal MAE and Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. A randomized trial. Ann Intern Med 1990; 113: 183–187.
25. Bicanic T, Wood R, Bekker LG, et al. Antiretroviral roll-out, antifungal roll-back: access to treatment for cryptococcal meningitis. Lancet Infect Dis 2005; 5: 530–531.