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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 Ghanaian 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.[1] 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.[2] 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.[3] Some studies suggest that cryptococcal disease may be more common in Southern and East Africa than in West Africa.[4] 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 antigenaemia 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.[5] The risk of infection with the fungus is strongly associated with CD4 T-cell counts of < 200 cells/mm^3 and World Health Organization (WHO) clinical stages 3 and 4 of AIDS.[6] In one study, CD4 count of < 100 cells/mm^3 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.[3,7]

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 of

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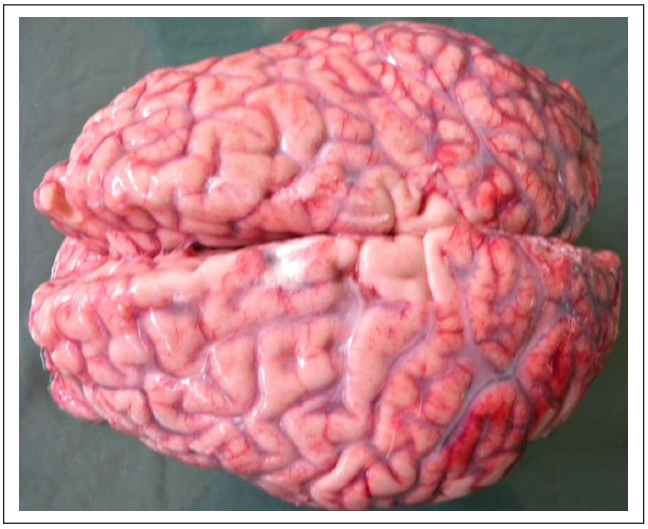

Figure 1. Showing the hazy appearance of the leptomeninges.

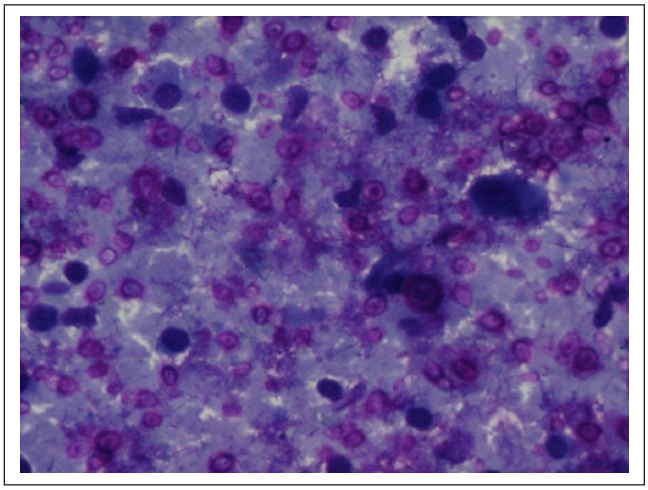

Figure 2. Giemsa-stained touch preparation of the brain showing numerous cryptococcal organisms with little inflammatory response (400×).

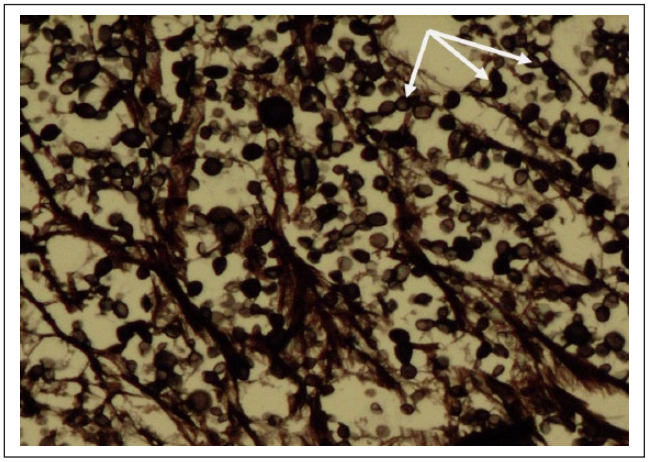

Figure 3. Grocott-stained histological section of mesenteric lymph node showing numerous cryptococcal organisms with no inflammatory response (400×).

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/mm^3. 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/mm^3, 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/mm^3.[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 H_2O 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/mm^3) 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.[1,3,22–24] 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

The authors declare that there is no conflict of interest.

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