

A Case of Systemic Cryptococcal Disease in HIV Infection

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INTRODUCTION

Globally, Cryptococcosis is the most common invasive mycosis in HIV disease. Incidence rates vary widely by geographical region and resource availability and reportedly range from 0.04 to 12% per year (1). Sub-Saharan Africa accounts for the greatest burden with a median incidence of 3.2% per year (1). Since the advent of widespread use of antiretroviral therapy (ART), incidence rates of opportunistic infections have been significantly declining (2). However, central nervous system (CNS) opportunistic infections (OI) continue to have significant effects worldwide (3) and mortality remains high (2). In Jamaica, OI remain a significant cause of death (4) and a single site review of all patients being diagnosed with an opportunistic infection in 2007, described cryptococcal meningitis in 10% of cases (5). Mucocutaneous disorders in the HIV population have also been commonly recognized and were identified in 74% of patients in the same population (6).

CASE REPORT

This is the case of a 41-year old male who presented to the University of the West Indies' Accident and Emergency Department in September 2011, with an eight-day history of what was described as "itchy water bumps" that ruptured upon scratching and subsequently crusted over.

This was associated with a two-day history of fever, headache and vomiting. He had no previous history of any chronic medical conditions or any known drug allergies and he claims to have been in perfect health prior to the onset of these symptoms. Physical examination revealed a reasonably well nourished male who was noted to be febrile at 38 °C, with reduced consciousness and signs of meningism. Upon inspection of the skin, numerous skin-coloured vesicles to the face (Fig. 1) and upper limbs primarily were noted, with only a few scattered lesions to the lower limbs. Also present were

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Fig. 1: Multiple papules noted to the forehead, some having a central umbilicated area. Note the bases do not appear necrotic.

crusted lesions to the face, neck and both upper and lower limbs along with excoriations. Target-like lesions were noted in the palms (Fig. 2). The scalp was free of any lesions.



Fig. 2: Target-like lesions noted in the palms.

Initial laboratory investigations included a complete blood count which showed a haemoglobin and platelet count of 12.8 g/dL and 177 x 10⁹/L, respectively and a white blood cell (WBC) count of 2.2 x 10⁹. Hepatic and renal function

along with an initial computed tomography brain scan, were all normal. An examination of the cerebrospinal fluid (CSF) revealed an elevated opening pressure with a positive India Ink stain showing the typical “halo” appearance. Cerebrospinal fluid culture was also positive for *C. neoformans*. The histology from a skin biopsy showed that the upper dermis was profusely infiltrated by sheets and aggregates of encapsulated spores that could also be seen erupting through the ulcerated areas. No granulomas or histiocytic giant cells were seen. The conclusion was that of cryptococcosis, gelatinous type.

A rapid HIV screening test, utilizing a 4th generation HIV Ag/Ab test, was performed and reported as positive, chronic infection. Other investigation findings included Hepatitis BsAg, anti-Hepatitis C, Mantoux and VDRL tests which were all negative. His initial CD4 cell count was less than 100 cells/mm³.

The patient was commenced on amphotericin B and fluconazole with a view to starting highly active antiretroviral therapy (HAART) therapy after completion of the maintenance phase of his cryptococcal therapy. His response to therapy was excellent and he was alert, conscious and oriented by day five of therapy. His course was, however, complicated by anaemia and after investigation, including upper gastrointestinal (GI) endoscopy, a diagnosis of cryptococcal gastritis was entertained. Subsequent to discharge, the patient was linked to an HIV treatment site where his follow-up included commencement of antiretroviral therapy. On review of the patient one week following discharge, the lesions to the face were not only less in number, but those with a central umbilicated area appeared to have a necrotic base (Fig. 3).



Fig. 3: Patient's face one week following discharge. The papules with central umbilication now appear to have a necrotic base.

DISCUSSION

Cryptococcosis is a systemic disease caused by *Cryptococcus neoformans*, a ubiquitous encapsulated yeast, that in its perfect form – *Filobasidiella neoformans* – is included in the Basidiomycetes class. It has four serotypes: A, B, C, D. It reproduces by budding and grows at 25 °C and 37 °C in

Sabouraud agar and blood agar within 24–48 hours (7). It is a saprophytic organism and can be found worldwide. Several strains are associated with pigeon and other avian excreta (8).

The organism is oval shaped, measures 4–12 µm in diameter and enclosed in a gelatinous capsule. The capsule contains abundant acid mucopolysaccharides and stains with India Ink, Gomorimethenamine silver, methylene blue, alcian blue, or mucicarmine stains (9). There are two histological types: granulomatous and gelatinous. The former is characterized by few organisms and scant necrosis, whilst the latter by numerous budding yeast cells in a gelatinous stroma resembling a “shotgun blast” associated with little or no inflammation (6), as was evident in this case.

Cryptococcal infection is associated with an immunocompromised state, the underlying aetiology of which may be due to immunosuppressive or glucocorticoid therapy, diabetes mellitus, malignancy, or as in this case, AIDS. Primary mode of transmission is *via* inhalation and as such causes a pulmonary focus of infection in the lungs. This tends to resolve spontaneously in the immunocompetent host. However, in HIV positive individuals, reactivation of latent infection may result in haematogenous dissemination to the meninges resulting in life threatening meningitis. Other commonly affected areas are: kidneys, prostate, bone, pericardium, peritoneum and skin. The gastrointestinal tract can also be affected in the stomach, as in this case, and the oral mucosa may also be involved in less than 5% of cases, manifesting as nodules or ulcers evident in the oral mucosa (10).

Cutaneous involvement is normally secondary to the systemic disease, occurring in 10–15% of cases and should therefore prompt screening of the other areas of possible infection to determine the extent of disease. These should include chest radiography, lumbar puncture and CSF, sputum, blood and urine cultures (11). Reported cutaneous findings include subcutaneous nodules, ulcers, cellulitis, palpable purpura, pyoderma gangrenosum-like ulcers, herpetiform lesions, Kaposi's sarcoma-like lesions, and Molluscum contagiosum-like lesions (10). Other cutaneous manifestations include papules, nodules and acneiform lesions. In HIV disease, lesions occur most commonly on the face and/or scalp.

Cryptococcosis has been described as affecting 5–10% of patients with AIDS, most commonly as a meningitis or meningoencephalitis (11). Fever and headache are the most prevalent initial symptoms to be described (9). However, altered mental status, associated with encephalitis, and focal neurological deficits or seizures, associated with cryptococcomas, may also be presenting features. It is therefore recommended that all HIV positive patients, especially those with late stage disease or AIDS, presenting with headache with or without fever, signs of meningism, altered mentation and focal neurological deficits or seizures be investigated for cryptococcal disease (11). In addition, any suspicious dermatological lesions, particularly umbilicated lesions,

should be biopsied (2), as such lesions can be the only symptom and early marker of disseminated cryptococcal disease (8).

Early diagnosis is an important aspect to the management of these cases as there is a high mortality rate associated with untreated disease of between 70 and 80%. Mortality can remain high at 56% even with appropriate therapy (2). Blood testing can be useful in making the diagnosis with serum cryptococcal antigen (CrAg) being almost universally positive, and blood cultures positive in 75% of cases (12). However, CrAg qualification is not useful in disease management while sterilization of the CSF has been a useful marker for appropriate response to therapy. Cerebrospinal fluid examination usually reveals elevated CSF pressures, a poor prognostic factor, and demonstrates few lymphocytes, mildly elevated protein and normal or mildly decreased glucose. Cerebrospinal fluid CrAg and culture are also almost universally positive (12).

The management of the HIV-infected individual with cryptococcal CNS involvement centres around the provision of antifungal agents, the management of raised intracranial pressures associated with this disease and the appropriate timing of ART. Treatment of cryptococcal meningitis involves three phases of therapy beginning with a consolidation phase of two weeks of amphotericin B (0.7–1.0 mg/kg/day) followed by a maintenance phase of eight weeks of fluconazole (400 mg) and a suppressive phase with fluconazole (200 mg) until immune reconstitution with ART has been achieved and maintained [CD4 counts greater than 100 cells/mm³ for at least six months] (11). Elevated CSF pressures must be actively managed with repeated lumbar puncture or ventriculo-peritoneal shunt placement as required (13). The timing of the initiation of ART remains controversial as the risk of immune reconstitution inflammatory syndrome must be balanced with the benefits of ART. Current recommendations are to consider ART after at least the initial two-week consolidation phase and within the next

eight weeks of the maintenance phase of cryptococcal therapy (11).

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