Cutaneous cryptococcosis in two patients with acquired immunodeficiency syndrome

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Summary: We present 2 cases of systemic cryptococcosis with cutaneous involvement in patients with acquired immunodeficiency syndrome (AIDS). Both patients were male, intravenous drug abusers, 31 and 35 years old, with severe immunodepression and a CD4+ lymphocyte count of 10/μl and 1/μl, respectively. They both had papular lesions reminiscent of molluscum contagiosum and in one patient with concomitant systemic leishmaniasis, there were spores of Cryptococcus neoformans coexisting with the leishmanias in the cutaneous lesions, constituting the first reported case of this particular association. Both patients responded well to amphotericin B followed by fluconazole.

Keywords: Cutaneous cryptococcosis, acquired immunodeficiency syndrome

INTRODUCTION

Cryptococcosis is a systemic disease caused by the yeast-like fungus C. neoformans. It is an encapsulated yeast whose perfect form, Filobasidiella neoformans, is included in the Basidiomycetes class, and it has 4 serotypes: A, B, C and D. It reproduces by budding and grows at 25°C and 37°C in Sabouraud agar and blood agar in 24–48h. It has a worldwide distribution, is found on the ground and in pigeon fæces, and is usually portal of entry is the airway, with the lungs being the primary site of infection.

In immunocompetent patients cryptococcus usually causes a subclinical or barely symptomatic infection. In immunodepressed patients, however, it is commonly disseminated via the blood-stream giving rise to systemic infection, with special predilection for the central nervous system, leading to meningitis or meningoencephalitis. Cutaneous involvement is normally secondary to the systemic disease, occurring in just 10–15% of cases, although the cutaneous lesions may sometimes precede the neurological manifestations.

The fundamental role played by cellular immunity in the defence against infection and subsequent dissemination explains the greater incidence of cryptococcosis in immunodepressed patients, especially those receiving immunosuppressive therapy and in those with lymphoproliferative disorders or AIDS, as in the 2 cases reported here.

CLINICAL CASES

Case 1

A 35-year-old male parenteral drug abuser, who had tested positive for anti-HIV antibodies 4 years previously, had developed papulonodular lesions, mainly on the head but also on the posterior surface of the upper limbs, over the 2 weeks prior to the visit. Their size varied from 3 mm to 3 cm in diameter, some of them showing ulceration, depression or a central scab (Figure 1). There was no change in his general state, nor were there any respiratory or neurological symptoms. The viral load at this time was 201,734 copies/ml and he had 2700 leukocytes/ml (1 CD4+ lymphocyte/ml). Both cutaneous biopsy and culture from a skin lesion showed the presence of spores of C. neoformans (Figure 2), which were later also detected in cerebrospinal fluid (CSF), sputum, and blood culture. The same skin biopsy also showed

Figure 1. Papulonodular lesions of varying sizes, some with a central crust, on the forehead

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leishmanias both within and outside the dermal histiocytes (Figure 3) and, likewise, bone marrow study showed the presence of leishmanias, confirming the existence of systemic leishmaniasis. Treatment with the lipid formulation of amphotericin B at 0.5 mg/kg/day followed by fluconazole achieved remission of the lesions.

**Case 2**

A 31-year-old male parenteral drug abuser who had recently tested positive for HIV and who was severely immunodepressed (viral load: 341,455, CD4: 10). Of note in the history were: prior alcoholism, hepatitis C, oesophageal candidiasis and labial herpes. He was admitted with fever and chills, profuse sweating, a highly productive cough, cephalgia unrelieved by analgesics, and raised 2–8 mm cutaneous lesions, some umbilicated, on the back and forearms (Figure 4). Skin biopsy revealed the presence of encapsulated spores typical of cryptococcus (Figure 5). The CSF also showed the presence of encapsulated yeast. Response to a 2-week course of lipid formulation of amphotericin B and fluconazole was good. Fluconazole was later continued at 200 mg/12 h for 6 weeks and 200 mg/24 h indefinitely.

**DISCUSSION**

The relatively rapid appearance of papulonodular and ulcerated lesions in HIV+ patients should suggest the possibility of cutaneous cryptococcosis, even, as in the case of our first patient, in the absence of typical respiratory and neurological symptoms. The primary cutaneous form is rare, and even more so an exclusively cutaneous presentation in patients with HIV infection. Cutaneous involvement generally indicates a systemic disease. Its diagnosis is important, especially if we bear in mind the high rate of mortality of the disease if left untreated (70–80%), and which is greatly reduced after adequate therapy (56%).

The cutaneous findings are not specific for a diagnosis of cryptococcosis, since its most common presentation is similar to that of molluscum contagiosum, followed in frequency by the
presentation of ulcerated lesions\textsuperscript{17,24}. Other possible presentations include herpetiform\textsuperscript{19,25}, aciform\textsuperscript{26}, varicelliform\textsuperscript{27}, or nodular lesions\textsuperscript{20,29}, or lesions similar to Kaposi’s sarcoma\textsuperscript{30}. In our cases, given the umbilicated papulae appear mainly on the upper part of the body, the differential diagnosis included molluscum contagiosum or a varicelliform infection. However, the rapid appearance of the lesions and their predominance on the face were of great value for their differentiation. A biopsy should be made of any suspicious lesion, and the presence of spherical spores of 4–12 mm diameter with a characteristic mucinous capsule, apparent with routine haematoxylin and eosin stains, enable diagnosis. Other stains, such as periodic acid-Schiff (PAS), mucicarmine, methenamine silver, toluidine blue or methylene blue facilitate visualization of the yeast\textsuperscript{31}.

Of interest in our first patient was the coexistence of leishmanias with cryptococci in the cutaneous lesion during the course of systemic leishmaniasis. Although there are reports of the coexistence of cryptococcosis with molluscum contagiosum\textsuperscript{32}, angiomatosis bacular\textsuperscript{33}, Kaposi’s sarcoma\textsuperscript{24,35} and histoplasmosis\textsuperscript{36}, we have been unable to find any report of co-infection in the same lesion of the 2 agents cryptococcosis and leishmaniasis. In an HIV+ patient with cryptococcosis the following complementary studies should be made to determine the extension of the disease: chest radiography, lumbar puncture, CSF culture, sputum, blood, and urine\textsuperscript{24,37}.

The classical treatment for disseminated cryptococcosis is a combination of intravenous amphotericin B and fluconazole, which enables the dose of both to be reduced, thereby decreasing their side effects\textsuperscript{38}. Some authors consider it inconvenient to start treatment with fluconazole in patients receiving zidovudine as it increases haematological toxicity\textsuperscript{2}. If it is used, though, renal function and fluconazole levels should be controlled, since alteration of renal function would mean accumulation, necessitating dose adjustment to avoid toxicity manifested by severe diarrhoea, leukopenia and low platelet levels. If treatment with fluconazole is impossible, amphotericin B at 0.4–0.6 mg/kg/day should be started, its side effects being reduced by means of the administration of low dose corticosteroids. The efficacy of fluconazole as an alternative treatment has been evaluated as it is better tolerated, and can be used in low-risk patients, i.e. those with a serum cryptococcus antigen titre in CSF lower than 1:64, with no neurological deficit or changes in mental state and with a leucocyte count in CSF of less than 20 cells/μl\textsuperscript{39,42}. Patients with AIDS, who have a high relapse rate, require maintenance therapy, with the drug of choice being fluconazole because of its lower toxicity\textsuperscript{40}. The response of both our patients to treatment with amphotericin B initially followed by fluconazole was good, despite their severe state of immunodeficiency.

The severity and diagnostic difficulty of deep mycosis in patients with HIV, coupled with the improved prognosis resulting from early treatment, mean that awareness and knowledge of these clinical pictures is important, so that histological and mycological studies can be performed as soon as possible.

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References


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