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Case Report

Disseminated Cryptococcosis Caused by Cryptococcus albidus during HIV-AIDS and Literature Review

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Abstract

The aim of our study is to report at first the only case of disseminated cryptococcosis caused by *Cryptococcus albidus* during AIDS revealed by a skin involvement in Bouaké and then to present an exhaustive review of the literature making the inventory of the infection with *Cryptococcus albidus* in immunocompromised HIV subjects.

A 44-year-old HIV-positive patient consults for skin involvement suspected of skin cryptococcosis. Mycological examinations of skin biopsy fragments and the cerebro-spinal fluid extension assessment revealed disseminated cryptococcosis due to *Cryptococcus albidus* in a patient with deep cell immunosuppression with TCD4 lymphocytes at 21 cells/mm3. The patient died after 7 days of monotherapy with fluconazole.

From 1996 to 2020 only four cases of *Cryptococcus albidus* infections during AIDS were published. There are 3 cases of invasive infections including two fungemias, one meningitis and one case of localized eye infection. Our case occurred in 2019, 5 years after the last publication. All organs can be affected with a predilection for the central nervous system and blood. The treatment is identical to that of forms due to *Cryptococcus neoformans.*

Keywords: *Disseminated Cryptococcosis; Skin Involvement; HIV-AIDS; Cryptococcus albidus; Fluconazole; Bouaké-Côte d'Ivoire*

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; CD4: Cluster of Differentiation 4; CSF: Cerebrospinal Fluid; *C. albidus*: *Cryptococcus albidus; C. neoformans: Cryptococcus neoformans;* HIV: Human Immunodeficiency Virus; MALDI-TOF MS: Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry; PCR: Polymerase Chain Reaction

Introduction

The incidence of cryptococcosis due to non-neoforman cryptococci is increasing with 80% of cases involving *Cryptococcus albidus* and *Cryptococcus laurentii* [1]. This mycosis can be encountered in the immunocompetent subject as well as in immunocompromised persons: HIV, hematological malignancies, corticosteroids, immunosuppressive therapy, organ transplant, kidney failure. It preferentially affects immunocompromised individuals, primarily HIV-positive patients [2].

In this study, we present the first case of dissaminated cryptococcosis caused by *C. albidus* in an HIV-positive patient as well as a review of the literature on the types of infections; biological aspects, therapeutic and evolutionary of cryptococcosis caused by *C. albidus* during AIDS.

Case Report

A 44-year-old patient, Ivorian, immunocompromised by HIV 1 screened and treated since 2010 consults at the dermatology department of the Teaching Hospital of Bouaké on 14 November 2019 for papular, itchy lesions with necrotic centre in places and scattered all over the body evolving for 3 weeks. A skin biopsy is performed on the same day for mycological and anatomopathological examination.

Direct examination of the skin biopsy fragments is inconclusive, but culture on Sabouraud-chloramphenicol medium without cycloheximide is positive at three days of culture with evidence of creamy colonies, of beige colour, grouped on the fragments giving an appearance of cauliflower. Identification using gallery ID 32 C (BioMérieux®: France 5, rue des Aqueducs 69290 Craponne) highlights *C. albidus* after 48 hours of incubation at 30°C.

Additional examinations are requested 5 days after the consultation for an extension assessment despite the absence of clinical signs of systemic cryptococcosis. The lumbar puncture performed revealed a clear cerebrospinal fluid (CSF) that looked like rock water. Direct examination with India ink of the CSF revealed fine refractive capsule yeasts. The diagnosis of disseminated cryptococcosis caused by *C. albidus* is retained and antifungal treatment is undertaken urgently with fluconazole in monotherapy at high doses (1200 mg per day at a rate of 600 mg morning and evening) orally, but on an outpatient basis at the insistence of the parents for lack of financial resources. *C. albidus* is also isolated from the CSF. The antifongigram produced with ATBFUNGUS® 3 (BioMérieux®: France 5, rue des Aqueducs 69290 Craponne) reveals a strain of *C. albidus* sensitive to all the antifungals tested, in particular amphotericin B, 5 fluorocytosine, fluconazole, itraconazole and voriconazole.

Pathological examination of biopsy fragments, cerebral CT scan and chest x-ray are not carried out due to lack of financial resources.

The blood count notes 5070 leukocytes/mm^3 with neutrophils at 3690/mm^3 and lymphocytes at 1150/mm^3; a hemoglobin level of 7.5 g/dl; bicytopenia with 2980 red blood cells/mm^3 and 52,000 platelets/mm^3. The rest of the results reveal a blood sugar level of 1.06 g/l; a creatinine level of 16.8 mg/l; uraemia at 0.33 g/l, transaminasemias at 62 IU/l (Alanine Amino-Transferase or ALAT) and 65 IU/l (Aspartate Amino-Transferase or ASAT). The patient also presents a profound immunosuppression with TCD4 lymphocytes at 21 cells/mm^3, i.e. 1.82% of all lymphocytes.

The viral load is 86,600 copies/ml. The post-treatment course is marked 2 days later by the appearance of neuromeningeal signs with left facial paralysis, justifying his hospitalization. The patient died 7 days after the start of treatment.

Discussion

Cryptococcosis is an infection caused by a fungus of the genus *Cryptococcus* classically divided into two categories: *Cryptococcus neoformans* and non-*neoformans* species [3]. While *C. neoformans* is a well-known human pathogen, non-*neoformans* species are generally saprophytic and rarely cause infection in humans [4]. In the present study, we report the first case of disseminated cryptococcosis caused by *C. albidus* revealed by skin involvement in an HIV-positive patient. We also present an exhaustive review of the literature exposing the various types of infection, the methods of identification of *C. albidus*, the treatment regimens and the course of *C. albidus* infection in subjects living with HIV.

From 1996 to 2020 only four cases of *C. albidus* infections during AIDS have been published (Table 1) [5-8]. These are 3 invasive infections including two fungemias [5,6], one meningitis [8] and one infection localized to the eye [7]. Our case arose in 2019, 5 years after the last published case highlighting the rare nature of *C. albidus* infection in AIDS.

Country YP* Reference	Age Gender	Type of infection	Identification methods	CD4/mm^3	Treatment	Course
France 1996 [5]	38 M	Invasive: fungemia	Unavailable	135	Itraconazole	Deceased
Greece 1998 [6]	47 F	Invasive: fungemia	API ID 32 C	5	Amphotericin B + Flucytosine	Deceased
USA 2004 [7]	16 F	Non-invasive: scleral ulceration	unavailable	42	Amphotericin B + Itraconazole	Healed
China 2013 [8]	28 M	Invasive: neuromeningeal cryptococcosis	unavailable	7,1	Fluconazole	Deceased
Our case 2021	44 F	Invasive: disseminated cryptococcosis	API ID 32 C	21	Fluconazole	Deceased

Table 1: *Summary of published cases of Cryptococcus albidus infection in AIDS.*

YP: Year of Publication; M: Male; F: Female; CD4: TCD4 Lymphocyte.*

No infection with *C. albidus,* to our knowledge, has been reported in Côte d'Ivoire; the reported cases, meningeal or cutaneous, having been presumed to be due to *C. neoformans* [9-11]. Skin lesions manifest in a context of disseminated infection or sometimes as a "sentinel" and allow early treatment if correctly diagnosed [12]. This study illustrates that culture of any atypical lesion is important in the diagnosis of this opportunistic condition. In fact, the patient presented skin signs without other signs of call for dissemination but the extension assessment found neuromeningeal involvement with a direct examination and a culture of the CSF in search of positive cryptococci.

C. albidus is morphologically similar to *C. neoformans* but different techniques allow their differentiation: culture on *Guizotia abyssinica* creatinine agar medium, assimilation of sugars, assimilation of esculin, assimilation of inositol, mass spectrophotometry (MALDI-TOF-MS), PCR or sequencing [13]. In the present study, the identification is made using the API 32C gallery. The same is true for the study carried out in Greece [6]. As for the studies carried out in France, the United States and China, the method of identifying the cryptococcal species in question was not notified [5,7,8].

This opportunistic infection often occurs at the late stage of immunosuppression with CD4 counts generally below 100 cells/mm^3, where the risk of infection is multiplied by 8 [14]. This is the case in almost all of the studies reported (4 cases including ours) [5,6,8]. The 16-year-old patient is on corticosteroid therapy combined with ritonavir, which is another associated risk factor. The recommendations are clear when prescribing ritonavir: concomitant prescription of fluticasone should be avoided [15]. This is because fluticasone is metabolized by the cytochrome P450 enzyme CYP3A4, which is itself inhibited by ritonavir. This combination leads to an accumulation of fluticasone with the corollary of a potentiation of its effects (immunosuppressant, reduction of the effect of anti-infectives, etc.). The combination of fluticasone and ritonavir could justify this opportunistic infection since corticosteroids suppress cell-mediated immunity and may increase the likelihood of developing opportunistic infections in HIV-positive patients [16].

Based on imidazole [5,8] and the 2 others of a bitherapy combining amphotericin B with flucytosine for one [6] and with itraconazole for the other [7].

For disseminated infection in the immunocompromised, the recommended treatment strategy is the combination of intravenous amphotericin B followed or not by flucytosine [12]. Molloy and colleagues during their work suggest that in the event of the unavailability of amphotericin B or in the event of a contraindication, in countries with limited resources, the oral fluconazole-flucytosine combination constitutes a lasting alternative [17]. In our case, the unavailability of amphotericin B and flucytosine in Bouaké, their high cost, constitute limits in the treatment.

Regarding the therapeutic aspect, 3 patients including ours received monotherapy. The patient died despite the antifungal treatment. In our review, the outcome was fatal for three patients and favorable for one. In total, the lethality was high, i.e. 80% of deaths represented only by invasive infections. According to Dromer, the existence of extra-meningeal localizations, dissemination, signs of intracranial hypertension (papillary edema, neurological deficit, disorder of consciousness, hypertension of the CSF) are elements of a poor prognosis whatever the HIV status [18]. The inappropriate treatment regimens and the presence of the aforementioned elements could justify the high number of deaths in this series of cases.

Conclusion

C. albidus infection in AIDS is rare. The data can be superimposed on those for *C. neoformans* infection. All organs can be affected with a predilection for the central nervous system and the blood. Treatment of *C. albidus* infection is not codified, it is based on the treatment regimen for forms caused by *C. neoformans*. The clinical picture is varied mainly represented by the invasive forms whose prognosis is appalling.

Conflict of Interest

There are none.

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