Medical Mycology Case Reports 38 (2022) 30–32

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Chronic disseminated cryptococcosis without meningeal involvement in a severely immunosuppressed HIV-infected patient successfully treated with fluconazole

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ARTICLE INFO

Keywords:
Cryptococcosis
Diagnosis
AIDS
Brazil

ABSTRACT

A 43-year-old female with advanced HIV infection presented with two chronic skin lesions. Cutaneous cryptococcosis was confirmed and pulmonary cryptococcosis was suspected. The patient was neurologically asymptomatic and the cerebrospinal fluid cryptococcal antigen lateral flow assay was negative. She received oral fluconazole and had resolution of the skin lesions and significant improvement of the lung lesions. We report a person with AIDS with chronic disseminated cryptococcosis without meningeal involvement successfully treated with oral fluconazole.

1. Introduction

Acquired immunodeficiency syndrome (AIDS)-associated cryptococcal meningitis has decreased in countries with access to combined antiretroviral therapy (ART), including Brazil[(1)]. However, cryptococcal meningitis continues to cause high mortality and morbidity, particularly in low- and middle-income countries, for several reasons: (i) late HIV diagnosis; (ii) barriers to initiate ART; non-compliance with ART; and (iii) virological and immunological failure to ART [1,2].

Cryptococcus spp. have a major predilection for establishing clinical disease in the central nervous system and lungs, and meningitis is the most frequent and lethal manifestation of cryptococcosis in people living with HIV (PLWHIV). About 70–90% of PLWHIV with cryptococcal meningitis have a subacute course [3]. Pulmonary involvement ranges from 10% to 55% of PLWHIV-associated cryptococcal meningitis [4]. Cutaneous involvement is the third most common clinical manifestation of cryptococcosis in PLWHIV and is observed in approximately 6% of these cases [5].

Disseminated cryptococcosis in PLWHIV, defined as the involvement of ≥2 non-contiguous sites, is common in clinical studies (~50%) [6], but particularly in necropsy studies (~70%) [7]. Central nervous system (CNS) and pulmonary involvement were identified in ~85% and ~78% of disseminated cryptococcosis cases, respectively, in a necropsy study [7], but practically any organ can be invaded by cryptococcosis. Despite this, meningitis usually predominates in the clinical picture and is the management priority. Cutaneous cryptococcosis in PLWHIV normally reflects the presence of disseminated disease and is uncommonly described in the absence of cryptococcal meningitis.

Here, we present a severely immunosuppressed HIV-infected patient with disseminated cryptococcosis characterized by cutaneous and pulmonary involvement, but without cryptococcal meningitis. Interestingly, cutaneous cryptococcosis was characterized by the presence of only two ulcerated lesions of chronic evolution.

2. Case

A 43-year-old female patient, diagnosed with HIV infection eleven years ago, was referred to our hospital from an outpatient medical service with diagnosis of cutaneous cryptococcosis. The patient reported that a lesion started as a small papule in the right frontal region, at day −150, accompanied by transient fever, non-productive cough and weight loss. Over the next few weeks, this lesion grew and ulcerated, and

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https://doi.org/10.1016/j.mmcr.2022.10.001
Received 31 August 2022; Received in revised form 15 October 2022; Accepted 23 October 2022
Available online 28 October 2022

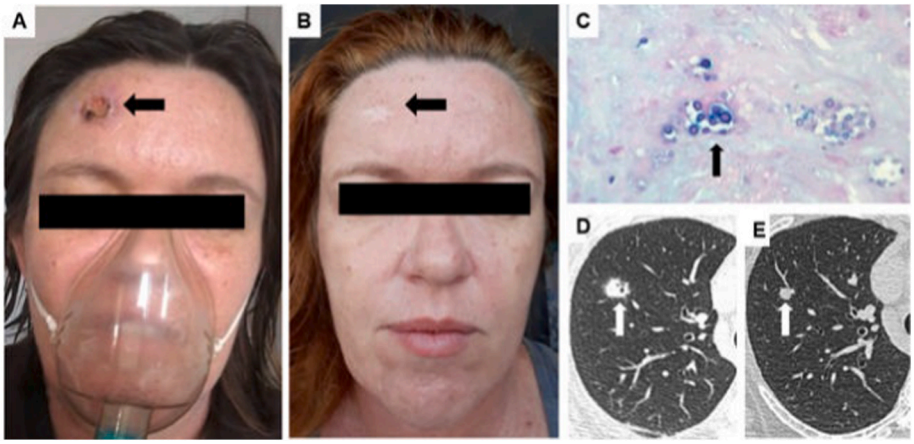

Fig. 1. Images of a HIV-infected individual with cutaneous and pulmonary cryptococcosis. Cutaneous lesion before (A) and during the use of fluconazole with complete healing (B). Histopathological study of the cutaneous lesion in (C) showing lymphohistiocytic infiltrate and formation of granulomas in the dermis associated with yeast-like structures with the presence of mucins compatible with Cryptococcus (arrow) (Alcian Blue stain, 400X). Chest computed tomography showing a nodular opacity with small cavitations before the use of fluconazole (D) and the control image showing unequivocal improvement during antifungal therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

another similar lesion appeared on her scalp. These lesions continued to grow, and the patient received two empiric courses of antibiotics with no improvement. Antiretroviral therapy (tenofovir disoproxil fumarate, lamivudine, and dolutegravir) was started at day -90, when the patient had a CD4 cell count of 19 cells/mm^3 and an HIV-1 viral load of 46,483 copies/mL. At day −7, the histopathology study of a punch biopsy of the frontal lesion revealed epithelial granulomas with Langerhans cells containing numerous yeast-like fungal structures, best visualized by PAS (periodic acid-Schiff) staining, with mucopolysaccharide capsules demonstrated by Alcian Blue staining, with scarce inflammatory infiltrate, compatible with cutaneous cryptococcosis (Fig. 1C), and fluconazole 750 mg/day was started. Culture of the biopsy specimen was not available. At day of hospital admission (day 0), the patient was able to care for self, but unable to do normal activities. She was thin, afebrile, with a normal respiratory rate, and without neurological abnormalities. An ulcerated nodule with a partial blood crust of 2.5 cm in length was observed on the right side of the forehead (Fig. 1A). Another ulcerated nodule with complete blood crust of 3 cm in length was observed on the scalp, in the right fronto-parietal region. Laboratory tests at admission showed hemoglobin 13.1 mg/dL, WBC 5100 cells/mm^3, platelets 327,000/μL, C-reactive protein 47 mg/dL, and normal kidney and liver parameters. Brain computed tomography (CT) showed mild cortico-subcortical atrophy. Chest CT showed peripheral nodular opacities in both lungs, some with a slight ground-glass halo and small cavitations (Fig. 1D), compatible with pulmonary cryptococcosis. Serum cryptococcal antigen (CrAg) latex agglutination was positive, and fingerprick CrAg lateral flow assay (LFA) was negative. Cerebrospinal fluid (CSF) study showed WBC = 0 cell/mm^3, proteins = 36 mg/dL, and glucose = 56 mg/dL; and the results of India Ink staining, fungal culture and CrAg LFA were all negative. CSF sample was not diluted to exclude a postzone phenomenon. At day +1, it was decided to introduce fluconazole 1200 mg/day and was indicated hospital discharge for outpatient follow-up. At day +28, skin lesions were completely healed (Fig. 1B). At day +90, the patient was asymptomatic with CD4 = 63 (7%) cells/mm^3 and HIV-1 viral load <40 copies/mL on regular use of fluconazole 900 mg/day, trimethoprim-sulfamethoxazole 160–800 mg/day and ART. In the last outpatient evaluation, at day +540, the patient remained asymptomatic on regular use of fluconazole 450 mg/day and the other medications. A new chest CT showed significant improvement of lung lesions (Fig. 1E). At this moment, the result of the CD4 cell count was 166 cells/mm^3 and the HIV-1 viral load was <40 copies/mL.

3. Discussion

We present an atypical case of disseminated cryptococcosis for several reasons: (i) there was no CNS involvement; (ii) the clinical course of pulmonary and cutaneous disease was chronic, mild and not progressive; and (iii) the presence of only two ulcerated nodules in the skin and peripheral nodules in the lung.

Classically, cryptococcal disease in PLWHIV presents as a subacute disease with disseminated involvement including meningitis with progressive clinical deterioration. In advanced HIV disease, pulmonary cryptococcosis usually also has cryptococcal meningitis and isolated pulmonary cryptococcosis is uncommon as reported in 7% of cases in a necropsy study [7]. In clinical studies, this proportion is lower. For example, *Cryptococcus* spp. was detected from induced sputum in 2.7% pneumonia patients (81% HIV-infected) in Botswana [8] and in 0.4% pneumonia HIV-infected patients (CD4 cell count <200 cells/mm^3 in 73% of cases) in Brazil [9]. Despite these results, it is likely that pulmonary cryptococcosis is underdiagnosed or misdiagnosed, mainly as pulmonary tuberculosis.

In PLWHIV, pulmonary cryptococcosis is usually symptomatic and in some cases can progress rapidly to acute respiratory distress syndrome, even in the absence of meningitis. In contrast, immunocompetent hosts usually present localized cryptococcosis, and most patients are asymptomatic or only have cough or unspecific chest pain [10]. In immunosuppressed patients, a broad spectrum of tomographic findings has been described, including single or multiple nodules, air bronchogram, cavitation and halo sign. In contrast, in immunocompetent host, single (more frequent) or multiple well-defined nodules, especially located in the peripheral area of the lung, are the most common tomographic finding of cryptococcosis [8]. Our patient had only mild and protracted respiratory complaints more compatible with the presentation of an immunocompetent host, but the images showed bilateral peripheral nodules with halo sign and cavitations more compatible with the profile of immunosuppressed hosts.

PLWHIV with severe immunosuppression can present a variety of cryptococcal skin lesions, but the most frequent appear as disseminated umbilicated papules and/or nodules mimicking molluscum contagiosum. In contrast, immunocompetent hosts usually present localized cutaneous cryptococcosis as primary disease and not secondary to disseminated disease. In this setting, solitary lesions are more frequent than multiple lesions [5]. Our patient had only two chronic ulcerated nodules. However, the presence of more than one lesion suggests hematogenic dissemination in contrast to classic single lesion observed in immunocompetent host.

Our patient presented disseminated cryptococcosis without CNS involvement and this pattern was described in 15% of cryptococcosis cases in a necropsy study, however, the frequency of concomitant cutaneous and pulmonary cryptococcosis was not reported [7].

Cerebrospinal fluid CrAg LFA showed better performance when compared with CrAg LA for the diagnosis of cryptococcal meningitis in PLWHIV [11]. However, there is scarce information about serum or whole blood CrAg LFA in PLWHIV with disseminated cryptococcosis

without meningitis or localized pulmonary cryptococcosis. Whole blood CrAg LFA showed very high agreement when compared with serum and plasma CrAg LFA results in PLWHIV with cryptococcal meningitis [12, 13]. Our patient had negative whole blood CrAg LFA and positive serum CrAg LA, suggesting that the use of both tests can be useful in selected cases. Several skin infections can present similar characteristics, therefore, the biopsy of the skin lesion with histopathology and culture is essential for the definitive diagnosis, as demonstrated in the present case, despite having been performed late.

The Guidelines for the Management of Cryptococcal Disease of the Infectious Diseases Society of America recommend treating disseminated disease as cryptococcal meningitis [14]. In addition, this document suggests use fluconazole to treat pneumonia with mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, and absence of severe immunosuppression [14]. The decision of the antifungal scheme was challenging in our patient, and amphotericin-based therapy was initially considered. However, due to the functional status, clinical stability, extension of lung and skin involvement, and the exclusion of meningitis, it was decided to introduce oral fluconazole. High doses of fluconazole were empirically chosen due to the presence of disseminated disease. In addition, we considered that when the patient was admitted to our hospital, she had been on ART for three months, had no evidence of worsening cryptococcal disease, did not have anemia, and showed a reasonable general clinical status, probably secondary to better control of the HIV infection. Fortunately, despite the initiation of ART, in the period of untreated disseminated cryptococcosis, the patient did not present any manifestation of the immune reconstitution inflammatory syndrome.

In conclusion, this case report highlights a very uncommon case of chronic disseminated cryptococcosis without meningeal involvement in a severely immunosuppressed HIV-infected patient successfully treated with oral fluconazole.

Conflict of interest

The authors have no conflicts of interest to declare. The authors are responsible for the content and the writing of the paper.

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