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CASE REPORT/CAS CLINIQUE

First report of two cases of cryptococcosis in Tripoli, Libya, infected with *Cryptococcus neoformans* isolates present in the urban area

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Summary Cryptococcosis is a potentially fatal fungal disease caused by the basidiomycetes yeasts *Cryptococcus neoformans* and *C. gattii* with high predilection to invade the central nervous system mainly in immunocompromised hosts. Skin can be secondarily involved in disseminated infection or be exceptionally involved as primary cutaneous infection by inoculation with contaminated materials. We report the first two Libyan cases of cryptococcal meningitis in HIV patients, in which one of them presented a secondary cutaneous involvement due to systemic dissemination. The first patient was a 17-year-old female, had fever, cough, headache and intractable vomiting as well as itchy water bumps on her skin and upper limbs. The cutaneous eruption prompted the accurate diagnosis. Cultures were positive for *C. neoformans* in both cerebrospinal fluid and skin specimens, as well as cryptococcal antigen was detected in serum. The isolate was identified, by molecular analysis, as *C. neoformans* AD-hybrid belonging to molecular type VNIII and mating type αAAα, the same genotype found for some environmental isolates recovered from olive trees in Tripoli. The second patient was a 36-years-old male with a long history of HIV on irregular treatment. Cryptococcal antigen in serum was positive and cultures yielded the growth of *C. neoformans var. grubii*, molecular type VNI and mating type αA. Both patients did not respond adequately to treatment and died of impaired central nervous system function and respiratory failure, respectively.

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Introduction

Cryptococcosis is caused by two yeast species, *Cryptococcus neoformans* and *C. gattii*, which are now considered two species complex including several cryptic species [1,2]. *Cryptococcus neoformans* comprises molecular types VNI, VNII, VNB, VNIII and VNIV, is found worldwide and causes cryptococcosis primarily in AIDS patients [3]. *Cryptococcus gattii*, including molecular types VGI, VGII, VGIII and VGIV, has an endemic distribution and often infects immunocompetent hosts [4].

Cryptococcus neoformans is the most frequent cause of meningitis in HIV-infected patients and can infect any organ in the human body. Central nervous system is commonly involved, and is mostly associated with VNI molecular type, which has the most widespread distribution worldwide accounting more than 90% of the cases in immunocompromised patients [3]. Skin is the most common external site of infection, affecting 10—20% of those with systemic involvement [5]. *Cryptococcus neoformans* var. *neoformans* (molecular type VNIV) has been more commonly isolated from these skin lesions, which could be related to dermotropism [5,6]. Cutaneous cryptococcosis lesions vary greatly in morphology and mimic other dermatological entities and are often the first presenting symptom of systemic disease [7]. In this study, we report for the first time two cases of cryptococcosis in HIV patients living in Tripoli, Libya.

Case 1

The patient was a 17-year-old Libyan female HIV infected since birth. Antiretroviral treatment was discontinuous depending on the availability of the drugs in the department. She presented to Tripoli Medical Center, in August 2016, with a three-week history of itchy water bumps that ruptured upon scratching and subsequently crusted over. This was also associated few days later with fever, headache and vomiting. No previous chronic medical condition or drug allergy was reported. Physical examination revealed that patient was malnourished with fever at 38.3 °C, good conscious level and no sign of meningitis. Upon inspection of skin, numerous skin-colored vesicles and crusted lesions were seen on the upper limbs (Fig. 1), on the face (Fig. 2), lower limbs and trunk. Laboratory tests as well as renal and hepatic function were within normal ranges. Direct microscopic examination of cerebrospinal fluid (CSF) and scraped crusts using India ink test revealed encapsulated yeast resembling *Cryptococcus*. The serum tested for cryptococcal antigen by lateral flow assay (CrAg LFA, IMMY, Norman, OK, USA) was positive. Culture of both CSF and skin lesions on sunflower seed agar yielded brown yeast colonies suggesting the presence of *C. neoformans*. Capsule observed in India ink preparation, urease production and ability to grow at 37 °C as well as Vitek2 compact system (bioMerieux, Firenze, Italy) confirmed *C. neoformans* identification. Molecular type and mating type allelic pattern were determined performing two specific multiplex PCRs as described elsewhere [8,9], which revealed that the isolate was a *C. neoformans* AD-hybrid belonging to molecular type VNIII and with mating type αAAα [10]. Disseminated tuberculosis was also diagnosed by tuberculosis lipoarabinomannan (TB-LAM) test, which was positive in urine, whereas other investigations including venereal disease research laboratory tests, hepatitis B surface antigens and anti-hepatitis core, were all negative. The initial $CD4^+$ count was 17 cells/mm^3, significantly lower than the patient $CD4^+$ baseline (350 cells/mm^3) detected six months before. The patient started an antifungal therapy with amphotericin B (50 mg/d) and fluconazole (750 mg/d), and two weeks later, an anti-tuberculosis therapy with isoniazid, rifampicin, ethambutol and pyrazinamide. After 25 days from admission, the patient vision decreased. Fundoscopic examination and serology by detection of IgM antibodies allowed diagnosing cytomegalovirus retinitis. Septrin, dexamethasone and ganciclovir were then administered. The patient response to therapy was very poor and she became unresponsive after 35 days from admission. Later, she was transferred to the intensive care unit where she died after one day with suspected severely impaired central nervous system function.

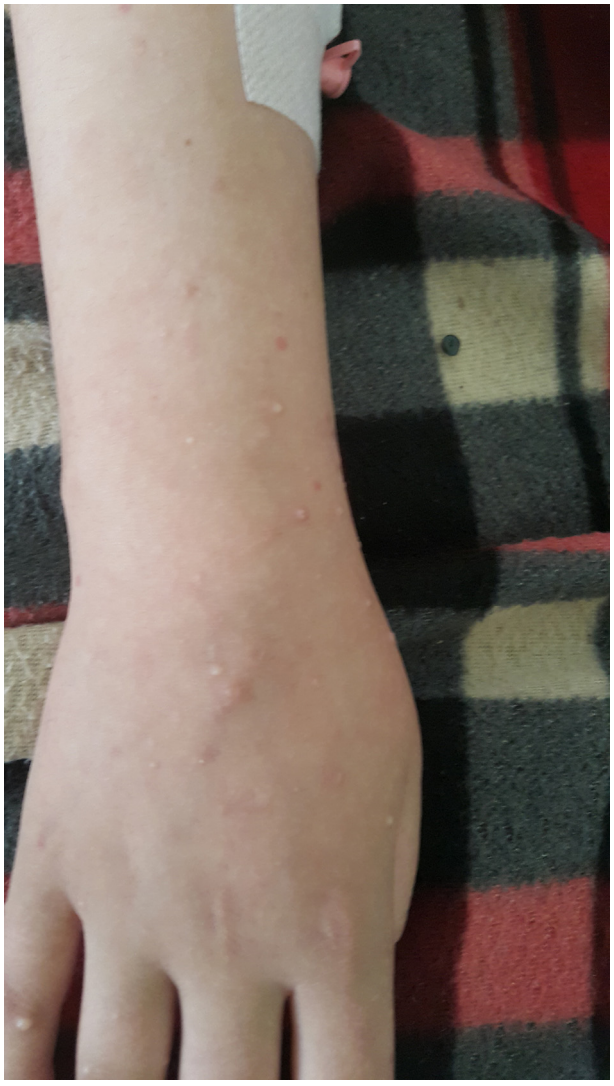

Figure 1 *Cryptococcus* skin-colored vesicles on the upper limbs.

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