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LETTER TO THE EDITOR

CUTANEOUS CRYPTOCOCCOSIS IN A PATIENT AFFECTED BY CHRONIC LYMPHOCYTIC LEUKAEMIA: A CASE REPORT

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Cryptococcosis is an opportunistic infection, the incidence of which is increased in the immunocompromised patients. *Cryptococcus neoformans* is an encapsulated fungus that mainly infects the lungs and the central nervous system, possibly involving different organs. Cutaneous cryptococcosis is classified into localized infection, usually occurring after traumatic inoculation (primary cutaneous cryptococcosis) and cutaneous manifestation due to hematogenous dissemination (secondary cutaneous cryptococcosis), mostly in patients with underlying immunosuppression. We report a case of cutaneous cryptococcosis in a patient affected by chronic lymphocytic leukaemia.

Cryptococcosis is an opportunistic infection which incidence is increased in immunocompromised patients (AIDS-stage HIV patients, organ transplant recipients, patients affected by hematologic malignancies, especially during the treatment with corticosteroids and polychemotherapy) (1).

Cryptococcus neoformans is an encapsulated fungus that mainly infects the lungs, the most common point of entry, and the central nervous system, possibly involving different organs (2). However, there is evidence obtained both in experimental models (3) and in humans (4) that the digestive tract and the skin were potential sites of contamination.

Cutaneous cryptococcosis is classified into localized infection, usually occurring after traumatic inoculation (primary cutaneous cryptococcosis, PCC) and cutaneous manifestation due to hematogenous dissemination (secondary cutaneous cryptococcosis), mostly in patients with underlying immunosuppression. Primary cutaneous cryptococcosis (PCC) has been reported in immunocompetent, as well as immunocompromised individuals (5-7).

We report a case of cutaneous cryptococcosis in a patient affected by chronic lymphocytic leukaemia.

MATERIALS AND METHODS

In April 2005, a 78-year-old man was referred to the Department of Dermatology for an erythematosus patch on the extensor surface of his right forearm. His history included: chronic lymphocytic leukaemia (CLL), diagnosed 9 years earlier at 69 years of age, for which he was receiving prednisone 15 mg/day and endoxan 100 mg/day; benign prostatic hypertrophy since 1985 for which he was treated with terazosin 5 mg/day; and

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atrial fibrillation since 1987 in treatment with carvedilol 12.5 mg/day, digoxin 0.125 mg/day and spironolactone 50 mg/day.

The cutaneous lesion, measuring approximately 5 cm in diameter at its widest point, was pruritic and was initially treated with an emollient cream. Two weeks later, the patient came again because of the worsening of the lesion, which had enlarged and was ulcerated. Only the right forearm was affected by the ulcers, and no lesions were observed on his skin elsewhere. The patient did not recall any local trauma. Locoregional lymph nodes were not palpable. On physical examination, multiple ulcers, some of them covered by purulent crusts, were present on the dorsal aspect of his right forearm. After removal of the crusts, several ovalar, confluent, shallow ulcers were evident on his right forearm, the largest measuring approximately 8 × 5 cm in diameter; the lesions were characterized by a red base covered by yellowish discharge. The lesions were painful. He had fever (37.5°C), abdominal pain, nausea and anorexia, and was therefore hospitalized. Laboratory findings revealed haemoglobin 10.3 g/dl, haematocrit 30.9%, RBC $3.17\times10^6/mm^3$, WBC $26.3\times10^3/mm^3$, platelets $61,000/mm^3$, neutrophils 8.9%, lymphocytes 89.8%, and monocytes 1.1%; gamma globulins were 0.22 g/dl. He did not present neuro-meningeal functional signs. A biopsy of the ulcer border revealed a diffuse infiltration of histiocytes and lymphocytes throughout the entire dermis. Numerous round yeasts were evident in the cytoplasm of histiocytes, and were demonstrated by positive diastase-periodic acid-Schiff staining of the capsule (Fig. 1).

Cultural examination of the secretion taken from an ulcer was performed.

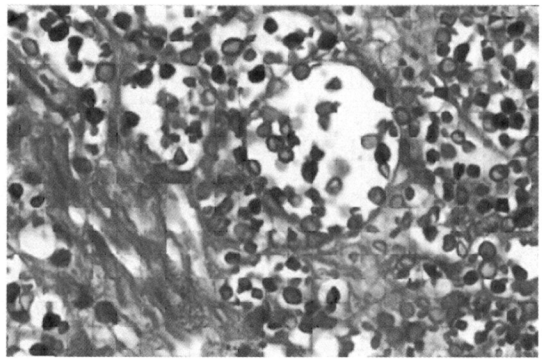

Fig. 1. *Numerous round yeasts in the cytoplasm of histiocytes evidenced by positive diastase-periodic acid-Schiff staining.*

RESULTS

A case report of cutaneous cryptococcosis in a patient affected by chronic lymphocytic leukaemia was examined in this study. The secretion taken from an ulcer of the patient was analysed. The cultural examination of this secretion was performed on Sabouraud glucose agar medium, with the addition of chloramphenicol at 37°C, for 72 hours. This cultural examination yielded colonies characterized by a creamy surface. Urease testing of the organism was positive. The isolate was identified as *Cryptococcus neoformans* var. *neoformans* by the API 20C AUX (bioMérieux, Marcy l'Etoile, France).

Susceptibility determination by means of ATB Fungus (bioMérieux, Marcy l'Etoile, France) showed that the isolate was susceptible to amphotericin B (minimal inhibiting concentration, MIC 0.5 μg/ml), itraconazole (MIC 0.25 μg/ml), 5-fluorocytosine (MIC 16 μg/ml) but resistant to fluconazole (MIC 32 μg/ml). Therefore, a therapy with liposomal amphotericin B 240 mg/die was started. In the meantime, the patient developed dyspnoea and a cough. CT scan showed interstitial thickening with slight thickening also in the inferior lobes of the lungs bilaterally, sub-centimetric lymphadenopaties in the left paratracheal region and bilateral pleural effusion with concurrent right atelectasia.

Unfortunately, after 6 days of treatment, despite slight improvement of the ulcerative lesion the patient died for worsening of his general condition.

DISCUSSION

Cryptococcosis is an important cause of morbidity and death in immunocompromised patients, even if in hematologic patients it is rarely reported, probably because of the low frequency of this complication or for diagnostic difficulties (8-12). In fact the diagnosis of cutaneous criptococcosis is often very difficult because of its non-specific and variable clinical appearance (13-20).

In patients with hematologic malignancies there is a severe defect of T-cell-mediate immunity; moreover, the degree and duration of granulocytopenia are the greatest risk factors for fungal infections. Another key risk factor is steroid use because it suppresses phagocyte migration, decreases the antifungal activity of monocytes and

alveolar macrophages, and reduces the cell-mediated immune response already compromised by bone marrow infiltration (21).

The most frequent form of cutaneous cryptococcosis is caused by haematogenous dissemination of the *Cryptococcus neoformans*, after pulmonary inoculation; the skin is involved in about 10 to 20% of these cases (22-23).

PCC was firstly described by Buschke and Joseph in 1928 (24), who hypothesized that the skin would be the site of inoculation in patients with a history of trauma or exposure to soil or birds.

The criteria for diagnosis of PCC are a matter of debate (25). Recently, a study proposed that the diagnosis of PCC must be supported by the identification of *C. neoformans* in the skin lesion biopsy specimen or by culture and either clinical criteria (presence of a chancriform syndrome) or histological criteria (lesion confined to the skin and subcutis), together with the absence of dissemination (6).

In our patient we were not able to distinguish between primary cutaneous and secondary cryptococcosis. In fact, according to the algorithm proposed by Ng et al (25) an important criteria for the diagnosis of primary cutaneous cryptococcosis is the absence of concurrent systemic involvement. Although the CT scan of the chest was suggestive for an infectious process, unfortunately we were not able to demonstrate the etiological agent responsible for it. We did not find any regional lymphadenopathy, which is another criterion for the diagnosis of primary cutaneous cryptococcosis. However, the localization of the skin lesions on an exposed area of the body, namely the dorsal surface of the forearm, the ulcerated appearance of the lesions and the rural area of origin of our patient all suggested the skin as the first portal of inoculation of *C. neoformans*.

Another important point of discussion in this case is the fluconazole-resistance of the *C. neoformans* isolated. In fact, even if fluconazole susceptibility has decreased in recent years in HIV-positive patients (26), this is unusual in HIV-negative patients (27-28). To our knowledge ours is the fourth case of fluconazole-resistant *C. neoformans* in HIV-negative patients with no previous fluconazole exposure (29-31).

In conclusion, we suggest that in patients with hematologic malignancies cutaneous cryptococcal infections must be suspected and diagnosed as early as possible to avoid dissemination of the disease which is usually fatal if untreated (32).

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