Atypical presentation of histoplasmosis in an immunocompromised patient*

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Abstract: We present a case of disseminated cutaneous histoplasmosis in a male patient, rural worker, HIV positive for 20 years, with a history of irregular use of antiretroviral therapy, T cell counts below 50 cells/mm3 and with good response to treatment with Itraconazole. We highlight importance of skin lesions in clarifying early diagnosis, since this co-infection often leads patients to death.
Keywords: HIV; HIV infections; Histoplasmosis

INTRODUCTION

Histoplasmosis is a systemic mycosis caused by a dimorphic fungus, *Histoplasma capsulatum var capsulatum*, which is endemic in Latin America and other tropical countries.[1] It is a saprophytic fungus found in soil contaminated by birds feces. Primary infection is acquired through inhalation of conidia present in nature (caves with bats, chicken coops, etc.). It is a self-limited disease with clinical signs absent in healthy individuals.[2] In individuals exposed to large numbers of spores, late cavitary pulmonary histoplasmosis, granulomatous mediastinitis or mediastinal fibrosis may occur. [3]

Clinical presentations are: acute and chronic pulmonary histoplasmosis, disseminated and primary cutaneous [2]. Infection is limited and restricted to the lungs in 99% of cases; the rest progresses to disseminated or chronic form. Advanced disease may occur as a progression of acute infection or late reactivation of focus with viable fungi. [4] In the disseminated form, the main findings are weight loss, fever, hepatosplenomegaly, generalized lymphadenopathy, and involvement of bone marrow, CNS, skin and mucous membranes. Regarding skin lesions, they are generally nonspecific, manifesting as macules, papules, pustules, verrucous plaques and ulcers.[2] Ulcers may also be found on oral and labial mucosa. [5]

In immunocompromised subjects, particularly in AIDS patients when their CD4 T-lymphocyte count is less than 50 cells/mm3, histoplasmosis may be presented in the form of a severe and widespread infection. [5] Skin lesions occur in 4-11% of patients and result from secondary invasion of skin in widespread form of infection, and it may be the first sign of the disease in immunocompromised individuals.[6]

The gold standard for diagnosis is the anatomopathological examination and culture for fungi of the involved skin tissues.[2] Fungus may also be evidenced in the sputum, blood, bone marrow and urine sediment.[2] Histopathological examination can detect the fungus through PAS and Grocott stains. The material for culture can be obtained by biopsy, aspiration, bronchial lavage and blood or marrow punction.[2] Detection of polysaccharide antigens in fluids such as urine or serum are also helpful, but there may be false-positive results, especially in patients with paracoccidioidomycosis.[3]

Complement fixation and immunodiffusion tests are usually negative in patients with HIV. [3] PCR on samples of blood and tissue is highly sensitive and specific. Histoplasmin skin test is indicated for non-endemic areas.[2]

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The objective of this study is to report the case of a subject with large skin and mucosa lesions, which allowed the diagnosis and early treatment of the disease. The patient was infected with HIV for 20 years and had severe immunosuppression, with disseminated fungal disease and satisfactory clinical outcome despite the severity of co-infection.

CASE REPORT

Man, 52 years old, rural worker, infected with HIV, with severe immunosuppression due to the irregular treatment with antiretroviral drugs. He has presented for 2 months poor general condition and verrucous lesions throughout integument, predominantly in the face and trunk (Figure 1). Examination showed pancytopenia and renal dysfunction (creatinine clearance 27 ml/min). Chest tomography revealed diffuse accentuation of the lung interstitium. Pathological examination (HE) showed epidermis with central ulceration, necrosis and numerous macrophages with clear cytoplasm and oval structures (Figure 2). Grocott stain was positive for *Histoplasma* (Figure 3). Direct mycological examination revealed fungal structures compatible with *Histoplasma*. Culture was performed from skin biopsy sample in Sabouraud-dextrose agar, at room temperature. On macroscopic examination white cotton-wool spots colonies were observed and, on microscopic examination, presence of hyphae, with rounded microconidia and macroconidia, was noted (Figure 4 and 5). Myeloculture and blood culture for fungus also showed the presence of *Histoplasma capsulatum var capsulatum*. Serology for specific antibodies was negative for the fungus. During hospitalization, the patient developed febrile neutropenia and therapy with Cefepime, Granulokine and reintroduction of antiretrovirals was started. CD4 was 7 cel/m^3 and viral load was 598,342 copies. A chemoprophylaxis with trimethoprim-sulfamethoxazole and azithromycin was performed. Therapy adopted was Itraconazole - 200 mg 3 times daily for 3 days in a row followed by 400 mg/day. It was of utmost importance the reintroduction of antiretrovirals, which led to an CD4 increase.

The evolution of the case was satisfactory, with progressive improvement soon after the institution of specific antifungal treatment. After monitoring for 11 months, the patient had a weight gain of 20 kilos, clinical resolution of all lesions and improvement in general condition (Figure 6).

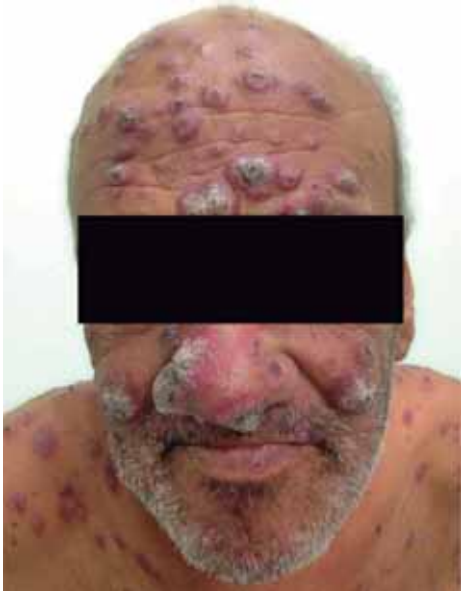

Figure 1: Pili torti. Polarized light microscopy, 10x magnification: Hair twisted about its longitudinal axis

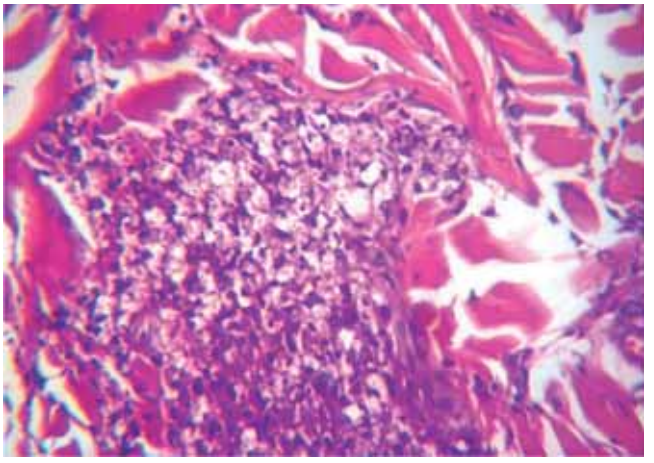

Figure 2: 100X HE: Skin sample containing histiocytic infiltration in the dermis, which show punctate structures in the cytoplasm

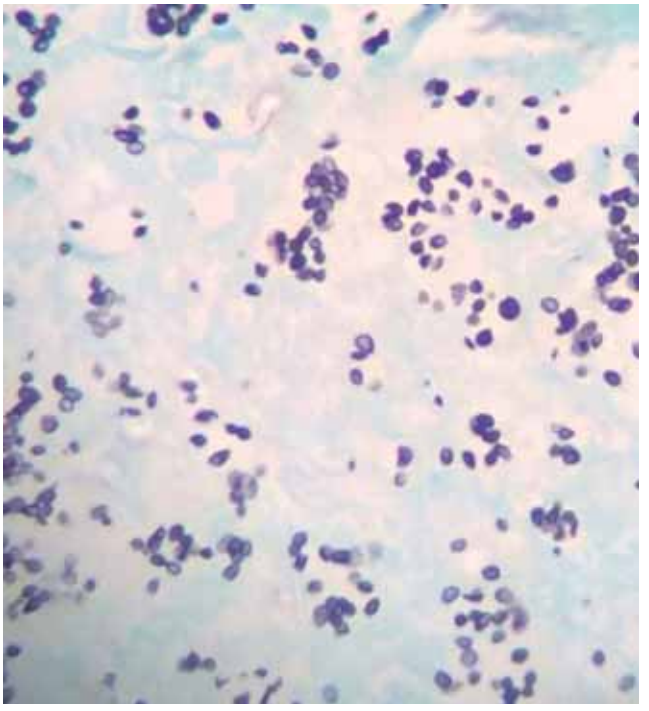

Figure 3: Groccot 400X: In the silver staining it's possible to note oval and uniform intracellular and grouped structures compatible with *Histoplasma*

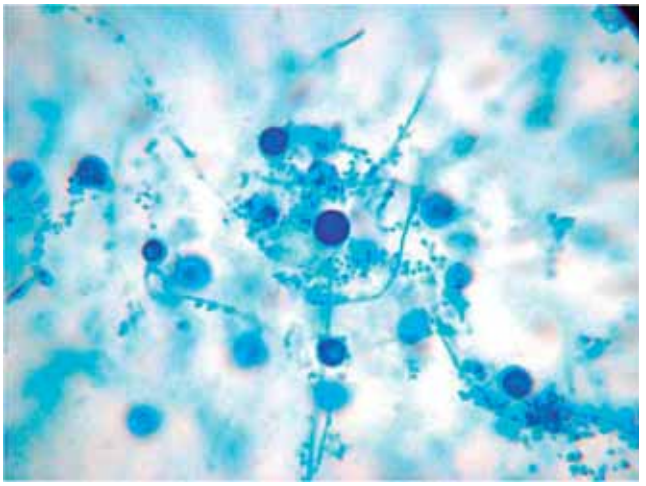

Figure 4: Culture - Microscopic examination: presence of tuberculate microconidia and macroconidia

DISCUSSION

The most important risk factor for reactivation of infection and progression to disease is HIV-induced immunosuppression.[3]

Co-infection of histoplasmosis and AIDS, particularly when CD4 T-lymphocytes count is less than 50 cells/mm3, leads to a severe and disseminated infection.[5] In our case, the importance of skin lesions as a sign of systemic disease was evident, and it also may assist in the early diagnosis of histoplasmosis. This allowed the immediate start of specific treatment, thus reducing the risk of disease progression, which has a high mortality rate in immunocompromised patients.[3]

Skin lesions are present in most Brazilian cases (38-85%) and they are often more extensive compared

Figure 5: Culture - macroscopic examination: presence of white cotton-wool spots nies

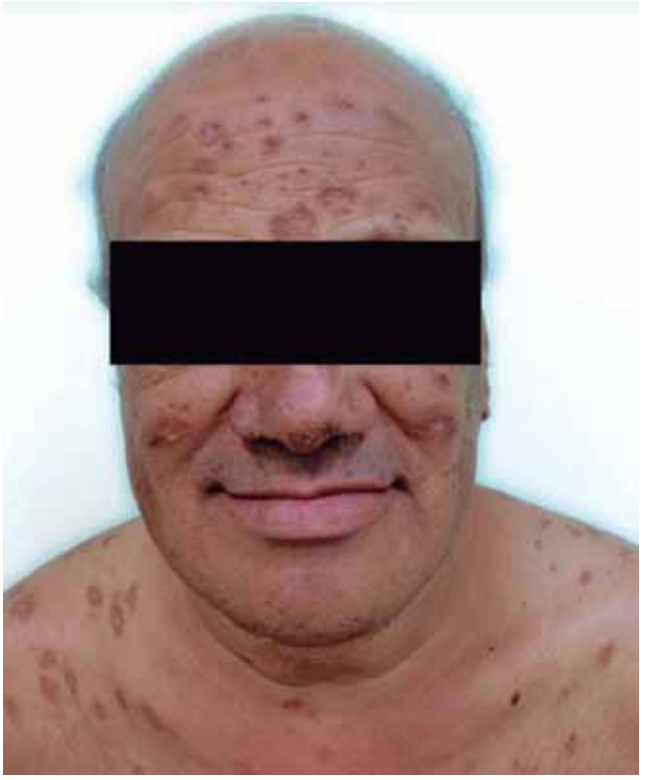

Figure 6: Culture - macroscopic examination: presence of white cotton-wool spots colonies

with those reported in the USA, thus justifying the tropism for skin of strains diagnosed in South America.[3] Skin lesions predominate when *H. duboisii* is the etiologic agent.[7] Histoplasmosis mortality in immunosuppressed patients is greater than 33%, while in immunocompetent individuals is approximately 17%. [3]

In the literature, the drug of choice for disseminated histoplasmosis is Amphotericin B, 0.5-0.7 mg/kg/day for 10 weeks, followed by Itraconazole, 200 mg 3 times a day and maintenance dose of 400 mg/day for 12 weeks. [8-9]

For our patient, the treatment of choice was Itraconazole, due to the associated comorbidities. The patient presented excellent therapeutic response, and the drug was kept at a dose of 400 mg/day until reversal of immunosuppression state. The patient remains well during outpatient follow up, already for 11 months. In conclusion, it should be emphasized that histoplasmosis, particularly in HIV-infected patients, needs early diagnostic clarification, seeking immediate specific therapy, which will surely bring better progress.❑

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