# Discrete cutaneous lesions in a critically ill patient treated only for AIDS and miliary tuberculosis: a case report of disseminated histoplasmosis

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## Abstract

Histoplasmosis is a systemic mycosis caused by the dimorphic fungus *Histoplasma capsulatum*, with disseminated histoplasmosis (HD) being one of its clinical forms. As a consequence of the HIV-AIDS pandemic, HD has become prevalent not only in regions that are recognized as endemic but also in areas not considered endemic, such as Europe and Asia. Its clinical manifestations are varied and mimic several infectious diseases, mainly tuberculosis. In endemic areas, it is the first manifestation of AIDS in 50 to 70% of patients. The diagnosis of histoplasmosis is difficult and HD can lead to death if not diagnosed early and if proper treatment is not instituted. The present report presents a patient with a recent diagnosis of HIV-AIDS, in treatment for miliary tuberculosis, who was diagnosed with disseminated histoplasmosis because of his dermatological manifestations.

*Keywords: disseminated histoplasmosis, HIV/AIDS, miliar tuberculosis, systemic mycosis*

## Introduction

Histoplasmosis (HP) is a systemic mycosis caused by the dimorphic fungus *Histoplasma capsulatum*, which has two variants: *Histoplasma capsulatum var. capsulatum*, prevalent in the Americas, and *Histoplasma capsulatum var. dubuosii*, most common in regions of Africa [1, 2]. Environmental sources of *H. capsulatum* include bat, chickens and birds, soil, and other organic substrates [3, 4]. The recognition of the worldwide presence of *Histoplasma capsulatum* has been modifying the epidemiology of systemic mycoses in the Americas, where for many years paracoccidioidomycosis was considered the most prevalent [3].

Histoplasmosis is widely distributed in the Americas and is very prevalent in certain areas of the United States, Mexico, Panama, the Caribbean, and several South American countries, including Brazil [4]. Northern Brazilian states, such as Amazonas, are considered endemic for histoplasmosis [5].

Fungal diseases kill more than 1.5 million people and affect more than 1 billion, but they are still neglected by the world's health authorities, including Brazilian authorities [6, 7]. Only last year, systemic mycoses were included in the group of tropical neglected diseases of the World Health Organization [8]. Recent global estimates have found more than 100,000 cases of disseminated histoplasmosis, a serious fungal infection that occurs as a consequence of certain health problems, such as HIV-AIDS [6].

As a consequence of the HIV-AIDS pandemic, disseminated histoplasmosis has become prevalent not only in regions that are recognized as endemic, but also in areas not considered endemic [9], such as

Europe and Asia [5]. Its clinical manifestations are so varied that this systemic mycosis is referred to as syphilis of the fungal world or the great imitator, because the disease mimics several non-infectious and infectious diseases, especially tuberculosis [3]. Underdiagnosis usually occurs owing to the relative lack of specific laboratory and radiological tests [7]. In endemic areas, such as Latin America, it is the first manifestation of AIDS in 50 to 70% of patients [10] and may lead to death if it is not recognized early and treated [3].

The present report is the case of a patient with a recent diagnosis of retrovirosis, already in treatment for miliary tuberculosis, who was diagnosed with disseminated histoplasmosis during his hospitalization through dermatological manifestations.

## Case Synopsis

A 22-year-old man was transferred, to Manaus in December 2017 because of co-infection of HIV and miliary tuberculosis (TBM). At admission, the patient reported asthenia and weight loss of 10kg for two months. He noted worsening dyspnea, productive cough of whitish discharge, intermittent fever, odynophagia, and xerostomia in the last month.

On physical examination, the patient was emaciated and dehydrated and exhibited, whitish plaques in the oral cavity suggestive of moniliasis. Pulmonary auscultation revealed murmur and diffuse wheezing and crepitations. Hepatosplenomegaly was found on abdominal palpation. Antiretroviral therapy (ART) was instituted with tenofovir 300mg, lamivudine 300mg (2-in-1), and raltegravir 400mg orally. In addition he was given treatment for oral moniliasis and continued treatment of tuberculosis with the regimen rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, and ethambutol 275mg (COXIP) orally.

Laboratory tests collected at the patient's admission showed pancytopenia (erythrocytes 3.16 million/mm$^3$ (reference value [RV] 4.2-5.5 million/mm$^3$), hemoglobin 9.38 g/dl (RV 12.5-15.5 g/dl ), hematocrit 27.97% (RV 36-47%), leukocytes 3.290/mm$^3$ (RV 4.000-10.000/mm$^3$, lymphocytes 14% (RV 25-40%), platelets 44.000/mm$^3$ (RV 150.000-450.000/mm$^3$)), hypoalbuminemia 2.9 (RV 3.5-4.5g/dl ), hyperbilirubinemia (total bilirubin 2.46mg/dl (RV 0.01-1.3 mg/dl), direct bilirubin 1.2mg/dl (RV 0.01-0.3mg/dl), indirect bilirubin 1.26mg/dl (RV 0.01-0.7mg/dl)).

The CD4 count on the third day of hospitalization was 37 cells/µl (17.14%), CD8 135 cells/µl (61.89%), viral load 3,000,000 copies and reticulocyte count 15.0% (RV 0.56-2.72%).

Chest X-ray on admission showed diffuse micronodular infiltrate in both lungs. Computed tomography of the chest showed diffuse reticular opacities in both hemithorax, tending to consolidation in lower lobes, and a small bilateral pleural effusion.

Patient progressed with intermittent abdominal pain, bloody diarrhea, vomiting, genital ulcers, inguinal lymphadenopathy, and left visual field dimming. There were persistent respiratory complaints, odynophagia, fever, and pancytopenia. After 18 days of hospitalization, the patient developed an erythematous-violet nodule, with ulcer and crust in the center, located in the right malar region. In addition, erythematous papules with

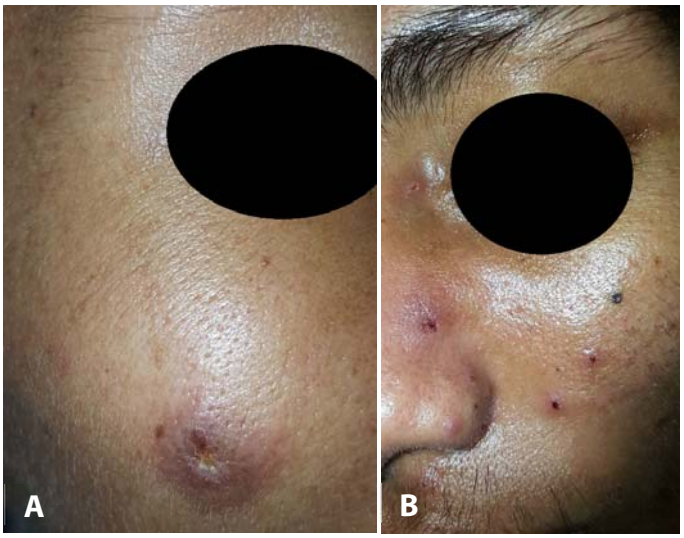


**Figure 1**. ***A)*** *Erythematous-violet nodule, infiltrated aspect, with central ulceration located in the right malar region.* ***B)*** *Erythematous-violet papules, with infiltrated base, containing central ulceration topped by hematic crostulas, located in the left malar region, with mollusc-like characteristics. There are also small papules and ulcerations in the left nasal region.*

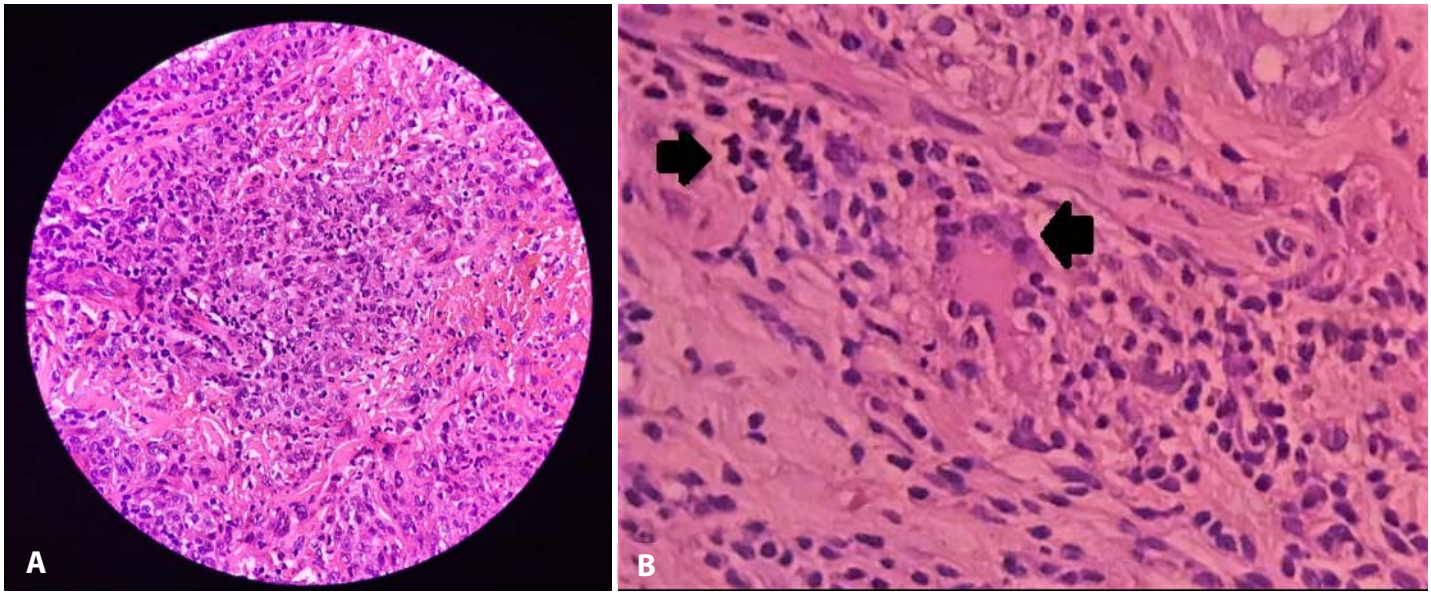


**Figure 2**. ***A)*** *Histopathological slide stained by hematoxylin and eosin (40×), showing skin fragment containing dense and diffuse inflammatory infiltrate involving superficial and deep dermis composed of lymphocytes, epithelioid cells and small structures inside and outside histiocytes in the dermis.* ***B)*** *Histopathological lamina stained with hematoxylin and eosin (400×), showing skin fragment with central epithelioid cell and small structures inside and outside histiocytes in the dermis (arrows).*

central crusts were distributed in the left malar region (**Figure 1**). In view of the above, the differential diagnosis included disseminated histoplasmosis, disseminated cryptococcosis, and paracoccidioidomycosis.

A biopsy of the cutaneous lesions was performed on the nineteenth day of hospitalization. Histopathological analysis revealed granulomatous inflammatory infiltrate consisting of lymphocytes, epithelioid cells, and small structures inside and outside histiocytes in the dermis [11], (**Figure 2**). Special staining by the Grocott method [11] demonstrated immune fungal structures (**Figure 3**), confirming the hypothesis of disseminated histoplasmosis. Intravenous amphotericin B therapy was instituted at a dose of 50mg per day for 14 days. After the end of this period, the patient started itraconazole 100mg orally, with a dose of 200mg per day. The patient was discharged on the thirty-fourth day of hospitalization on ART, COXIP, and itraconazole with clinical and laboratory improvement.

## Case Discussion

Histoplasmosis caused by *Histoplasma capsulatum var. capsulatum* typically presents as an acute or febrile respiratory condition, but the literature states that the manifestations vary according to the individual's immune status and the number of inhaled fungal particles [2]. Epidemics of acute histoplasmosis have occurred in endemic and non-

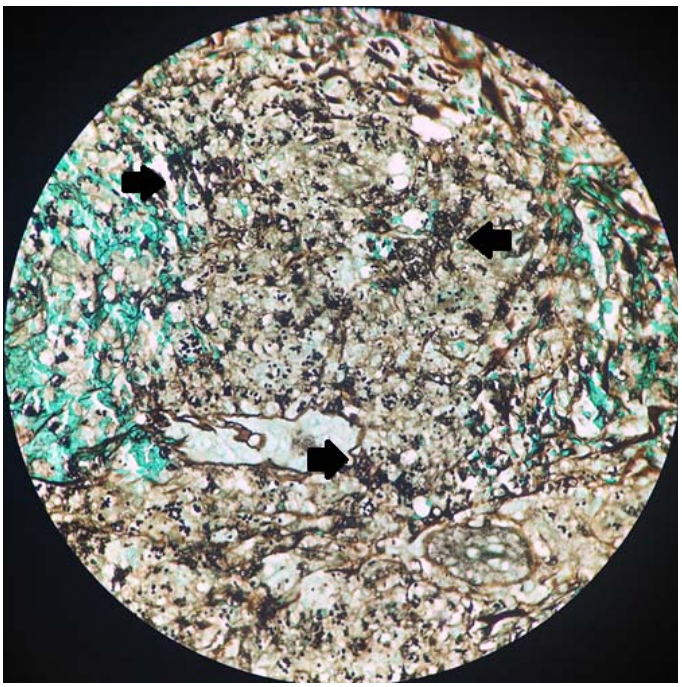

**Figure 3**. *Histopathological slide with special staining by the Grocott method (40×, arrows point to pathogens), evidencing immune fungal structures inside and outside histiocytes in the dermis.*

endemic areas after exposure to environments contaminated with fungus, particularly caves and other environments inhabited by bats or fowl, [4]. After being questioned, the patient reported having a fowl run in his residence and noted prolonged contact with the chickens.

Clinically, there are three forms: acute pulmonary, chronic, and disseminated pulmonary histoplasmosis (HD), the last appearing in 95% of HIV-positive patients who are at higher risk when the CD4 The lymphocyte count is <50 cells/µl [15]. The involvement of HIV-negative individuals is rare [14]. The patient's cell count in this report was 37 cells/µl with a viral load of 3,000,000 copies.

Studies indicate that the main symptoms of disseminated histoplasmosis include fever, general malaise, weight loss, cough, anorexia, diarrhea, and intermittent abdominal pain. Physical examination often shows hepatosplenomegaly, lymphadenopathy, pallor, and petechiae if pancytopenia is present. The involvement of pulmonary, ocular, gastrointestinal, and genitourinary tracts observed in the patient's clinical history is already described in the literature. Other systems often involved include cardiac, osteoarticular, and central nervous system in patients with HD [13, 16, 17]. Brazilian research that analyzed clinical and epidemiological characteristics of HIV-positive patients with disseminated histoplasmosis at the hospital of infectious diseases in the state of Goiânia showed that the most common affected organ was the lung, followed by liver, and cutaneous involvement [7].

Cutaneous lesions of histoplasmosis occur in less than 10% of patients in the USA, but are present in 38 to 85% of the cases reported in Latin America [12]. In Brazil, cutaneous lesions as the first clinical manifestation of opportunistic diseases in patients living with HIV are not uncommon and in the case of histoplasmosis, they are particularly evident [18]. They vary from macular, violaceous, papular, sometimes acneiform or mimicking contagious molluscum, plaques, and ulcerations, which may appear isolated or associated [15]. The discrete dermatological manifestations described in the literature are in agreement with lesions in our patient.

There are no laboratory-specific changes in the disease, and suggestive alterations include pancytopenia, elevated liver enzymes, elevated Westergren sedimentation rate, elevated C-reactive protein, and increased serum ferritin [4, 13]. Chest imaging examinations, such as radiography and computed tomography, may reveal normality [3] or diffuse pulmonary infiltrates [16]. Interstitial [4] or miliary patterns that are seen in patients with tuberculosis [19]. In the present report, a miliary pattern was observed.

The diagnosis of HIV-associated histoplasmosis is confounded with tuberculosis [9] because of the similarity of symptoms and changes in imaging tests [2]. In cases of HIV-positive patients who do not respond well to therapy against tuberculosis, co-infection with histoplasmosis should be considered [19]. It is worth noting that, in the present case, therapy for miliary tuberculosis was not discontinued.

The diagnosis of histoplasmosis is often difficult. A careful clinical history of possible exposure to *H. capsulatum* in daily activities or during a recent trip is crucial to arrive at the correct diagnosis [13]. Biopsy of skin [4], gastrointestinal tract, or aspirate of the bone marrow are necessary to obtain tissues or fluids for culture and histopathology [3]. In the histopathological analysis of material collected through skin biopsy, we observed the presence of sarcoid-like epithelioid granulomas, with microorganisms inside the phagocytic cells. Special stains, such as Gomori-Grocott and periodic acid Schiff, are required for proper visualization of the fungus. Cultures are very useful for diagnosis in individuals with the disseminated form, but they rarely show positivity in the acute forms, delaying the start of treatment [4].

The detection of antibodies may be useful but is not as sensitive, since false positives may occur [3, 9]. *Histoplasma capsulatum* antigen can be detected in many patients with HD, allowing the early diagnosis of the disease. However, in endemic countries, access to this diagnostic test is restricted [3]. The

literature indicates that the sensitivity of the diagnostic methods for disseminated histoplasmosis is 76% for histopathology, 74% culture, 75% antibodies, and 92% antigens [3].

In patients with AIDS, disseminated histoplasmosis shows signs and symptoms commonly seen in other diseases that affect these individuals, such as miliary tuberculosis, disseminated cryptococcosis, paracoccidioidomycosis, and lymphomas with extensive intra-abdominal involvement [4].

For treatment of disseminated histoplasmosis in HIV-positive patients, liposomal amphotericin B at the dose of 3mg/kg/day is the drug of choice. If not available, amphotericin B deoxycholate should be used at a dose of 1mg/kg/day. Both should be followed by itraconazole for at least one year [3]. A study looking at eradication of these fungi from HIV-positive patients diagnosed with disseminated histoplasmosis compared liposomal amphotericin B versus intraconazole and showed that faster elimination of fungemia occurred in patients who were given liposomal amphotericin B than those who were administered itraconazole for moderate and severe forms of histoplasmosis [20]. In Brazil, access to liposomal amphotericin B is restricted to the public health system owing to its high cost. Often then, initial treatment is with amphotericin B deoxycholate for 2 weeks followed by itraconazole.

## Conclusion

The present case shows the importance of the recognition of skin lesions by health professionals as indicators of histoplasmosis, a serious and potentially fatal systemic disease, allowing the early diagnosis and treatment. In addition, global health authorities should pay special attention to histoplasmosis and develop public policies for the prevention and control of this disease.

## Potential conflicts of interest

The authors declare no conflicts of interests.

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