J. Oral Diagn 2025;10:e265

CASE REPORT

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Oral ulcers as an early manifestation of histoplasmosis

Abstract:

Histoplasma capsulatum, the causative agent of histoplasmosis, is an uncommon systemic fungal illness that represents significant health risks to people living with HIV/AIDS (PLHV), especially those who are residents in endemic regions like Brazil. While oral histoplasmosis is rare, this observation can serve as a significant indicator of compromised immunological state, particularly in those with low numbers of TCD4+ cells. This study intends to examine recent literature on oral histoplasmosis and to provide a case of oral manifestations as the first indication of disseminated histoplasmosis in a young woman recently diagnosed with HIV.

Keywords: Histoplasmosis; Fungal infections; Opportunistic infections; HIV-Aids.

INTRODUCTION

Histoplasmosis is a fungal infection mostly caused by *Histoplasma capsulatum*; a dimorphic fungus found in the environment. Histoplasmosis was initially characterized by Dr. Samuel Taylor Darling in 1906, primarily impacting immunosuppressed individuals and, to a lesser extent, immunocompetent individuals. The first case of disseminated histoplasmosis associated to AIDS was reported in 1980, when a man first exhibited peripheral lymphadenopathy, and subsequent autopsy findings post-mortem indicated invasive pulmonary aspergillosis, mycobacterium avium-intracellular infection, and disseminated histoplasmosis[1,2].

Statement of Clinical Significance
Oral histoplasmosis serves as a important clinical marker for underlying HIV infection and requires immediate attention to prevent severe complications. Early diagnosis, appropriate treatment, and multidisciplinary care are essential components in managing this condition effectively.

In patients living with HIV/AIDS (PLHA), histoplasmosis presents as a widespread and symptomatic infection, with rapid evolution with the decline of lymphocytes TCD4+ and fatal in the absence of treatment[1,2].

Human histoplasmosis is induced by two separate organisms: *Histoplasma capsulatum var. capsulatum* and *Histoplasma capsulatum var. duboisii*. H. capsulatum var. duboisii is found solely in Africa, but H. capsulatum var. capsulatum has been detected on almost all continents, except Antarctica[3].

Histoplasmosis transmission comprises a complex interplay between the yeast infection and the host immune system. The infection begins with the inhalation of spores (*microconidia*) the lungs, which may get aerosolized during soil-disturbing actions such as construction, demolition, agriculture, or cleaning areas contaminated with bird or bat excrements. Upon entering the host, a rise in temperature (to roughly 37°C) initiates the conversion of microconidia into the more virulent yeast form of the fungus. The immune system of the host reacts to the infection. The interaction between the fungus and host immune cells, particularly macrophages, is crucial at this phase[3,4].

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Received on September 13, 2024. Accepted on November 26, 2024
https://doi.org/10.5327/2525-5711.265

After inhalation of the microconidia, most exposed individuals remain asymptomatic or develop self-limiting symptoms, with an incubation period of 3 to 17 days for acute disease[2]. Histoplasmosis typically manifests in acute, chronic, and disseminated forms, with nonspecific clinical findings like fever, fatigue, and weight loss. Patients may also present with respiratory symptoms like cough and dyspnea, dysphagia, and asthenia, as well as less frequent symptoms like digestive, neurological, mucocutaneous, polymorphic, and oral manifestations[5].

Acute pulmonary manifestations manifest after an average incubation period of 14 days, characterized by fever, chills, dyspnea, and cough. They may also be accompanied by chest pain and lymph node enlargement, and typically resolve within 1 to 2 weeks. Chronic pulmonary histoplasmosis classically occurs in middle-aged male patients, often associated with smoking. While symptoms such as productive cough, dyspnea, fever, chest pain, night sweats, and weight loss may persist, the condition is generally associated with exacerbation crises and radiographic worsening[6]. In the disseminated type of the disease, hematogenous dissemination develops beyond the lungs[5].

Although histoplasmosis is not exclusively seen in PLHA, the emergence of the HIV pandemic highlighted the epidemiology of Histoplasmosis, as individuals with HIV face higher risk of developing symptomatic disease and oral mucosa involvement is not uncommon. The clinical presentation in the oropharyngeal region may include ulcerations, nodular-ulcerative lesions, granulomas, verrucous and plaque-like lesions[5,7].

This study aims to present a case of oral ulcers as an early manifestation of histoplasmosis in a 33-year-old HIV-positive woman.

CASE REPORT

A 33-year-old woman, recently diagnosed with HIV, appeared at the oral medicine clinic with complaints of intense oral discomfort, dysphagia, and significant weight loss during the past 15 days.

During the extraoral examination, it was noted that the patient exhibited a low body mass index and a compromised overall health status. In the conversation, she disclosed her HIV diagnosis obtained from routine prenatal tests and indicated that she resides in severe poverty. Furthermore, she expressed challenges in maintaining consistent adherence to antiretroviral medication. The recent exams revealed low TCD4+ cell count of 206 cells/mm^3 and a viral load of 28.861 viral copies/mL.

She has been wearing a maxillary full denture for almost ten years. Following the removal of the prosthesis, we notice numerous shallow, widespread ulcers, accompanied by a pseudomembrane and hemorrhagic petechiae (Figures 1A, 1B and 1C). Additionally, we noted tongue coating and bilateral angular cheilitis.

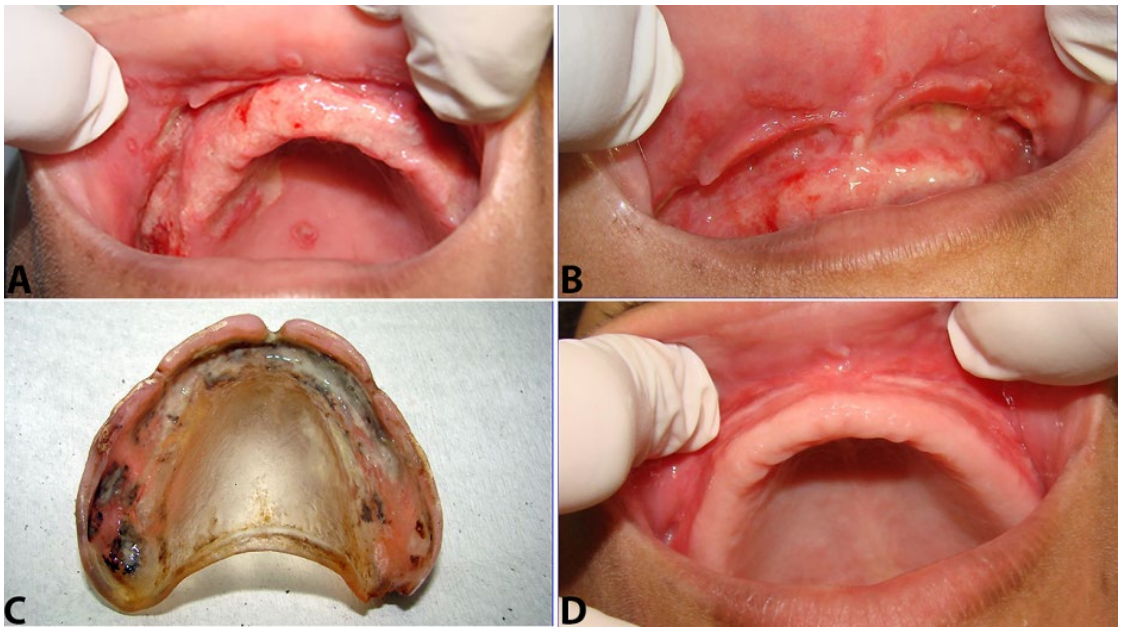

Figure 1. Multiple ulcerated lesions located in the alveolar ridge and hard, presenting with an irregular pattern, a granular surface, and painful during palpation (A). Extensive ulcers, covered by pseudomembrane and denture-associated hyperplasia were noticed (B). Dental prosthesis displaying biofilm formation, indicating insufficient self-care (C). Complete resolution of all lesions after two weeks of treatment (D).

An incisional biopsy was performed in the palate and posterior region of the maxilla, differential diagnosis included oral manifestations of tuberculosis, syphilis or other deep fungal infections as paracoccidioidomycosis.

The histopathological examination showed pseudoepitheliomatous hyperplasia, with a chronic granulomatous inflammatory process, where collections of macrophages organized in granulomas were observed, with small intracellular inclusions suggestive of *H capsulatum* infection. Grocott-Gomori stain confirmed the diagnostic hypothesis (Figure 2A and 2B).

The patient was referred for medical evaluation and treatment. Chest radiography showed no pulmonary changes. After administering amphotericin B intravenously (total dose=440 mg), the patient developed anemia and renal failure. Liposomal amphotericin B was prescribed and discontinued after two weeks due to altered renal function test values; prompt therapy modification to 200 mg of oral itraconazole twice daily was made. Simultaneously, she started over antiretroviral medication, which comprised Stavudine (30 mg, 2 tablets every 12 hours), Lamivudine (150 mg, 2 tablets every 12 hours), and Atazanavir (150 mg, 2 tablets every 12 hours). Complete remission of all lesions was observed after two weeks of treatment (Figure 1D). The patient was followed for 12 months with no recurrences.

DISCUSSION

Histoplasmosis is a soil fungal infection endemic in Latin America, India, Africa, East Asia, Australia, and Northeast and Central United States. Histoplasmosis in PLHA is generally present in a disseminated form, characterized by being strongly associated with low CD4+ counts and mainly with respiratory complications[2]. The clinical presentation of histoplasmosis is usually subacute, exhibiting nonspecific symptoms, such as fever, fatigue, and weight loss, since neurological, oral, and skin involvement are less frequent[6].

Mucocutaneous manifestations are uncommon, appearing in almost 20% of cases[2]. The literature provides a thorough description of localized primary mucocutaneous histoplasmosis. However, the rarity of this manifestation leads some authors to believe that the presence of oral manifestations in the absence of other clinical manifestations may represent the first clinical sign of the disseminated disease[6,8]. Several studies state that oral involvement in HIV-infected patients is considered a late manifestation of the infection's progressive dissemination through the reticuloendothelial system[6].

Interferon gamma (IFN-γ), interleukin 12 (IL-12), tumor necrosis factor (TNF)-α, macrophages, and CD4 T cells constitute the primary components of the immune system that respond to H. capsulatum. Four Reduced CD4 counts in individuals with HIV/AIDS can progressively diminish their cellular immunity, resulting in widespread severe infections caused by H. capsulatum[2].

Histoplasmosis is one of the most frequent opportunistic fungal infections among people living with HIV in the Americas and may account for 5–15% of AIDS-related deaths annually in this region. Prior to the highly active antiretroviral therapy (HAART) era, PLHA from endemic areas had an incidence of 2–55% and up to 25% in select cities. Disseminated infection occurred in 95% of infections, with oral manifestations present in 25-45% of cases[5,6,9].

In PLHA, there are two main clinical manifestations: a subacute wasting syndrome associated with fever, chills, and profound weakness, often accompanied by pulmonary infiltrates and diarrhea, and a fulminant

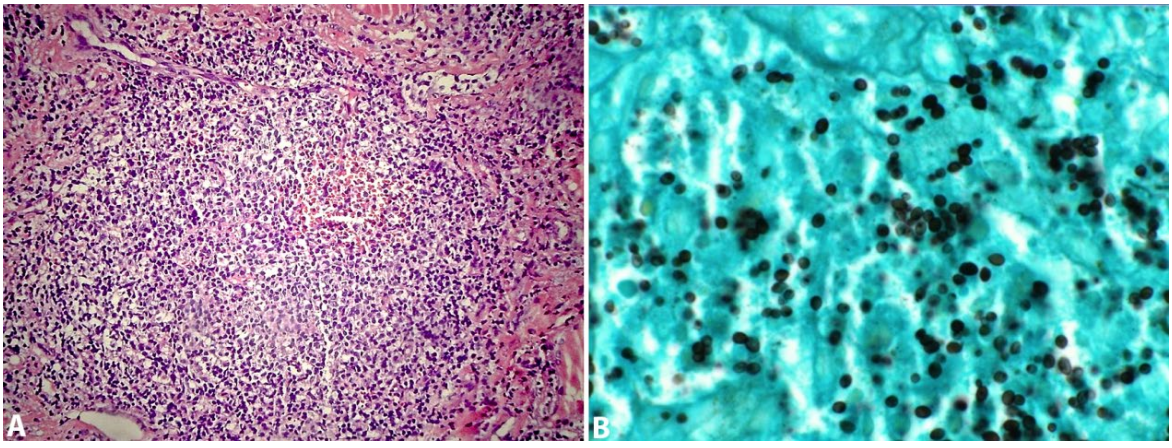

Figure 2. H&E stain presenting granulomas and sparse multinucleated giant cells (A) Identification of *Histoplasma capsulatum* yeasts using Grocott-Gomori stain (B).

presentation associated with multiple organ failure, which is fatal in the absence of treatment[6,9].

The diagnosis of histoplasmosis requires pathological investigations that are usually invasive[6]. In the presented case, we performed a tissue biopsy and, following a histopathological result suggestive of H. capsulatum, the special Grocott-Gomori stain confirmed the diagnostic hypothesis.

The Pan American Health Organization (PAHO) recommended the most recent treatment guidelines for PLHA, which advocate for the use of amphotericin B 3.0 mg/kg for two weeks as the treatment of choice. Due to its correlation with renal toxicity, there is a medical recommendation for dose adjustment or medication changes depending on the clinical evaluation of the individual's response to treatment. Given the patient's reduced renal function, the current scenario recommends administering Itraconazole at a dosage of 200 mg twice daily[5,9].

Pulmonary histoplasmosis can present as a subacute or chronic illness, with symptoms such as fevers, night sweats, weight loss, dyspnea, and pulmonary cavitary lesions. Extrapulmonary disease indicates disseminated infection, with symptoms like diarrhea, mucosal ulcers, skin lesions, hepatosplenomegaly, and lymphadenopathy. Laboratory studies may show transaminitis, pancytopenia, and significant elevations in serum lactate dehydrogenase and ferritin. Conversion from acute focal to progressive disseminated histoplasmosis occurs in 0.05% of cases[5].

The presence of extreme pain in the oral cavity and dysphagia led our patient to seek the oral medicine clinic, which allowed the early diagnosis of histoplasmosis and prompt referral to appropriate medical treatment.

A recent publication from our group emphasized the necessity of monitoring and following up with individuals who have PLHA and opportunistic infections, as well as the risk of disseminated histoplasmosis in those with compromised immune systems and CD4 counts below 200 cells/mm[6].

CONCLUSION

Although its widespread occurrence in Latin America, precise documentation of disseminated histoplasmosis is often insufficient. Recognizing extrapulmonary symptoms is essential for the early diagnosis of patients with HIV/AIDS, particularly those with poor treatment adherence.

AUTHORS' CONTRIBUTIONS

BR: data curation, writing – original draft. DSM: writing – original draft. KLO: conceptualization, investigation, supervision. CL: investigation, resources. MG: supervision. FM: conceptualization, supervision, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: Not applicable.

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