Disseminated histoplasmosis with oral and cutaneous manifestation in an immunosuppressed patient – A case report

Antonio Adilson Soares de Lima 1,*, Lorena Hauer Reichert Marcondes Ferraz 2, Vinicius Villas Boas Petroni 1, Cassiano Lima Chaiben 1, Francisca Berenice Dias Gil 2

1 Department of Stomatology, School of Dentistry, Universidade Federal do Paraná – UFPR, Curitiba, PR, Brazil
2 Hospital Oswaldo Cruz, Curitiba, PR, Brazil

Introduction

Histoplasmosis is a chronic granulomatous infectious disease caused by Histoplasma capsulatum, a thermally dimorphic fungus. This fungus has been found in soils with high nitrogen concentrations, especially those associated with bats and birds feces [1]. H. capsulatum reaches the human host by the inhalation of mycelial fragments of the fungus. Infection typically occurs after inhalation of these structures, which settle in airways followed by the thermally regulated transition to the parasitic yeast phase [2].

From the lungs, it can disseminate to several organs, giving rise to different clinical signs. Most infections caused...
by *H. capsulatum* are asymptomatic or subclinical. Sympto-
matic cases usually manifest as self-limiting respiratory
tract infections [3]. However, the severity of the illness
depends on the intensity of exposure and the immunity of
the host [4]. One of the early and more evident manifes-
tations of the disease is the presence of ulcers with irregular
margins on the oral mucous membranes, especially on the
tongue, palate and buccal mucosa. Histoplasmosis is one of
the most important systemic mycosis in United States, and
has also been reported in Latin America, Africa, Asia, India,
and Australia [6–9]. In Europe, most cases of HIV-associated
histoplasmosis occur in residents or travelers from South
America. Several cases of histoplasmosis have been notably
diagnosed in France, Spain, and Italy. Many cases are
diagnosed late because clinicians are not familiar with this
“endemic” disease [10–12].

In general, disseminated histoplasmosis occurs in debili-
tated patients with advanced age or immunosuppressed
[13]. Histoplasmosis is controlled effectively by antifungal
therapy, but recurrences are frequent and may cause
sequels or death. This manuscript describes a case of
disseminated histoplasmosis in a HIV-positive patient.

**Report of case**

A 39-year-old white male was admitted to the Hospital
Oswaldo Cruz (Curitiba, PR, Brazil) complaining of bleeding
and oral soreness. During the anamnesis, the patient related
that oral lesions initially appeared on inferior lip. Three
days before, he had tried to stop the bleeding by using
a topical medication. However, no improvement in oral
bleeding was observed and the patient decided to look for
medical attention.

Chronic cough, weight loss, appetite loss, fever, and
spontaneous oral and nasal bleeding were reported during
clinical examination. Three months ago, he had been tested
for tuberculosis(C0) and HIV(+ quick test). The patient was
initially treated with sulfamethoxazole 400 mg and trime-
throprim 80 mg.

Oral examination revealed ulcers covered with crusts on
the vermilion of the upper and lower lip (Fig. 1) and blood
clots on the tongue. However, it was not possible to perform
a complete oral examination due to bleeding of the lips.
According to these findings, two hypotheses of diagnosis
were issued: erythema multiforme and HSV infection. Thus,
acyclovir (500 mg, 8/8 h) was prescribed.

Hemogram, blood platelets counting, hemossedimentation
rate, serology (HIV, HCV, HBV, CMV, HSV, cutaneous leishma-
niosis, and mononucleosis), VDRL, viral load, and CD4 coun-
ting were performed. These laboratory exams showed the
following changes: anemia, leukopenia, thrombocytopenia,
liver dysfunction, renal failure, and an elevated hemossedi-
mentation rate (110 mm/h). The patient presented with fever
(37.8 °C) and continued with pallor and prostration. However,
all serological tests were negative, except for HIV.

Two weeks later, one of the crusts came loose and was
submitted to histopathological examination. This examina-
tion revealed a crust of fibrin associated with colonies of
bacteria and some fungi. Thus, the lip lesions were associat-
ed with thrombocytopenia. The patient received Kanakion®
(phytomenadione 10 mg EV), blood and platelet transfusion.
The lesions on the lip had completely repaired and there
was no bleeding seven days later. This fact allowed a more
detailed examination of the mouth after removal of the
dentures. A nodular reddish lesion, suggestive of Kaposi’s
sarcoma, was observed on the hard palate. Thus, an
incisional biopsy was scheduled. However, the lesion had
completely disappeared after one week and the biopsy was
canceled. Then, the diagnosis of nodular lesions in the
 palate was also associated with thrombocytopenia.

PCR for *Mycobacterium tuberculosis*, MAC and Cytomegalo-
virus were made. All results were negative. A chest CT scan
was performed and showed scattered nodular opacities.

Ulcerative lesions appeared covered by crusts on the skin
of the face and lip forty-five days after hospitalization
(Fig. 2). In this same period, ulcerated and nodular lesions
also appeared on the dorsum of the tongue (Fig. 3). Simulta-
neously, the ulcerated lesions showed granulomatous areas

![Fig. 1 – Ulcerated lesions covered with hemorrhagic crusts on the lower lip vermilion and the skin](image1)

![Fig. 2 – Aspect of the lesions at the skin](image2)
in the soft palate (Fig. 4). A new biopsy was performed in this region. The histopathology revealed the presence of a dense acute inflammatory infiltrate in the connective tissue. Small oval structures similar to spores of the fungus were observed associated to macrophages (Fig. 5). The histology of the structures found in the slides (HE and PAS staining) was definitive for the final diagnosis of disseminated histoplasmosis. Furthermore, bronchoscopy revealed the presence of an ulcerated lesion on the right arytenoid cartilage that was submitted to biopsy. Histopathology also confirmed the presence of ulcerated lesion with structures similar to the \( H. \ capsulatum \).

Initially, the patient was treated with IV amphotericin B (3.0 mg/kg daily) for ten days. Then, he was treated with Itraconazole 200 mg (8/8 h for 3 days and, then 12/12 h for 12 months). The patient had satisfactory clinic evolution becoming asymptomatic one month after the introduction of the therapy.

**Discussion**

Histoplasmosis is clinically classified as a primary acute pulmonary form that is usually asymptomatic; a chronic pulmonary form that occurs in the presence of underlying pulmonary disease; and a disseminated form, which occurs almost exclusively in infants, the elderly, and in debilitated or immunocompromised patients [3].

In this case report, an adult male patient developed disseminated histoplasmosis due to HIV/AIDS infection. The majority of case reports of histoplasmosis affect males and there are some case reports on literature about this disease in immunocompromised patients [14]. Besides the immunosuppression associating with HIV, the profession of the patient may have contributed to the establishment of the infection. He worked daily delivering documents throughout the city using a motorcycle. This kind of work exposes the patient directly to different locations in the city. Thus, he may possibly have transited by a region with pigeons infected by \( H. \ capsulatum \). In addition, the patient lived in a city that had caves and that is considered a region endemic for histoplasmosis, although he has stated that he had never visited a cave.

The patient developed oral ulcerations on the arytenoid cartilage, tongue, lips, and soft palate. According to the literature, oral lesions of histoplasmosis frequently are granulomatous and appear as nodular ulcerative or vegetative lesions that may be painful, localized on the oral mucosa, tongue, hard and/or soft palate, and lips. The ulcers have raised and rolled borders commonly covered by a yellow or grayish membrane, resembling carcinoma or tuberculosis [3].

Disseminated histoplasmosis presents with variable clinical appearance that depends on the degree of infection by
fungi. Cases with severe degrees of infection (acute disseminated disease) occur principally in infants and immunosuppressed patients, and may be fatal. There is often high, persistent fever and extensive involvement of the reticuloendothelial system with hepatosplenomegaly; anemia, leukocytopenia, and thrombocytopenia may also be seen [15]. Clinically, the patient presented fever, disseminated lesions on the body, hematological alterations, and hepatosplenomegaly.

Cutaneous lesions occur in only 6% of patients with disseminated histoplasmosis, but may rarely be the presenting sign [16, 17, 5]. Cutaneous lesions occur in a wide variety of forms, none of which can be said to be characteristic. Most commonly they consist of primary ulcers, often with annular, heaped-up borders [17, 18]. They may also consist of papules, nodules, or large plaque-like lesions [5, 19]. Papules may umbilicate, causing a resemblance to lesions of molluscum contagiosum [20]. Lesions may be purpuric or crusted, or may develop pustular caps and ulcerate. There may be tender, red nodules due to panniculitis [21].

In contrast to the rarity of cutaneous lesions, lesions of the oral mucosa occur in about half of all cases of disseminated histoplasmosis [5]. Lesions of the oral mucosa often start as painless papular swellings and usually ulcerate. Cutaneous lesions vary and described aspects include crusted or noncrusted papules, aceneiform pustules, nodules, widespread erythematous lesions, and ulcers [22]. The present case presented with multiple crusted papules and ulcers on the face, a nondiagnostic but characteristic aspect in patients with AIDS.

Histoplasmosis is usually diagnosed on the basis of clinical examination, roentgenograms to detect pulmonary lesions, and lesional biopsy or exfoliative cytology. The best and speediest way to establish the diagnosis of this fungal disorder is by direct examination of clinical specimens, which allow detection of the H. capsulatum cells. The identification of the fungus in histological sections can be performed by hematoxilin–eosin. However, the most useful methods include Grocott’s silver-methenamin, and Schiff’s periodic acid [15]. The biopsy was essential for the diagnosis of this case. The slides stained with HE showed a chronic inflammatory reaction. H. capsulatum cells appear as round or oval bodies surrounded by a clear space in Schiff’s periodic acid. Clinic data and microscopy examination were decisive to the diagnosis of this case.

Triazoles (particularly itraconazole) have been extensively used for the treatment of histoplasmosis. The treatment of histoplasmosis is lengthy, starting with an aggressive dosage of antifungal agents, to which a maintenance treatment follows for months. According to Wheat et al. [4], amphotericin B (3.0 mg/kg daily) is recommended for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months). When amphotericin B is used, the patient’s electrolyte level, renal function, and blood cell count should be monitored several times per week and documented in the medical record.

Finally, histoplasmosis should be suspected in patients with an appropriate travel history who experience weight loss and have pulmonary, mucosal, and cutaneous lesions. Furthermore, the examination of the mouth and oropharynx should be performed in patients suspected of histoplasmosis.

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