



## Case report

## Uncommon case of histoplasmosis with oral manifestation: A case report of diagnosis in a South American patient

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## ABSTRACT

**Introduction:** Histoplasmosis is a systemic fungal disease caused by the *H. capsulatum* fungus, which is mainly present in feces and guano of birds and bats. This condition manifests in several ways and it is more severe in its disseminated form and in immunosuppressed patients, putting the patient at risk of death if not diagnosed in time.

**Case presentation:** This report presents the case of a 39-year-old white female patient, a seller of agricultural machinery, with a history of lupus erythematosus, who attended a private dental office complaining of a tongue lesion. The patient reported having been subjected to an incisional biopsy of this lesion and the histopathological examination identified an inflammatory process. Considering the inefficient management of the lesion with intralesional application of corticosteroids, squamous cell carcinoma or granulomatous fungal infection was suspected, and a new biopsy was performed allowing the diagnosis of histoplasmosis already spread to the liver, intestines, and bone marrow. The diagnosed disease led the patient to undergo extensive antifungal treatment, including a period of hospitalization.

**Discussion:** The diagnosis of histoplasmosis can be delayed due to several factors, mainly due to its diverse clinical presentation between acute, chronic and disseminated forms. However, achieving an early diagnosis for histoplasmosis is very important to maintain the patient's quality of life.

**Conclusion:** Greater education, information, and awareness about histoplasmosis among health professionals are required for managing these cases, especially in endemic areas to *H. capsulatum*.

### 1. Introduction

Fungi can infect humans and cause various diseases [1]. Some of these fungi inhabit the soil or grow in the presence of animal feces, such as *Histoplasma capsulatum*, which is the most common cause of fungal respiratory infections in immunocompetent hosts [2,3]. Several environmental, occupational, and exposure risk factors in wild areas may predispose residents and visitors to histoplasmosis, both in endemic and non-endemic regions [4]. In Brazil, cases of histoplasmosis have been described across the country, mainly in the Midwest, Northeast, and Southeast regions [5] and, in some areas, the positivity for histoplasmin

can reach approximately 90% [6].

The human infection occurs after the fungus is inhaled, travels through the respiratory system, and reaches the alveoli, where it expresses virulence genes and causes disease [3,7]. The severity of the disease may be related to both the spore load inhaled and the host's immune status [7,8]. Once contamination has occurred, histoplasmosis may settle in an acute, chronic, or disseminated form. The acute form is characterized by self-limited lung infection with flu-like symptoms not easily distinguishable from other more common causes of viral or bacterial pneumonia but whose negative response to antibiotics or antivirals is suggestive. Chronic histoplasmosis, in turn, may seem clinically

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similar to tuberculosis, with productive cough, dyspnea, fever, chest pain, night sweats, and weight loss, mainly affecting the lungs of immunosuppressed patients [8,9].

The disseminated form also disproportionately affects immunocompromised individuals, reaching multiple organs such as the spleen, adrenal glands, liver, lymph nodes, gastrointestinal tract, central nervous system, kidneys, and oral mucosa [8]. Although oral involvement is very rare in histoplasmosis, being associated only with this disseminated form [10], oral lesions may occur anywhere in the mouth and are more commonly found on the tongue, palate, and cheek mucosa as painful ulcers that persist for several weeks [8]. Although histoplasmosis does not usually cause a high degree of mortality or morbidity and much of the disease is self-limiting [11], immunocompromised individuals may develop more severe forms of the disease due to fungal spread to various organs [5].

Based on the above, the present report aims to describe the approach to an oral lesion from a disseminated histoplasmosis infection in a patient with lupus erythematosus. This study was reported following the SCARE criteria [12].

## 2. Presentation of case

Female patient, 39 years old, white, single, a seller of agricultural machinery in the state of Bahia, BA, Brazil, with a history of lupus erythematosus, attended a private dental office in the city of Passo Fundo, RS, Brazil complaining of an ulcerated lesion in dorsal and ventral regions of the tongue, on the right side (Fig. 1). The patient's family history did not indicate any hereditary condition and the social history did not indicate the use of tobacco, alcohol or recreational chemical substances. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

The patient reported having been subjected to an incisional biopsy of this lesion and the histopathological examination identified only an inflammatory process, probably related to lupus erythematosus. In possession of this report and based on the patient's medical history, 1 mL of the Betamethasone corticosteroid (Celestone™ soluspan) was injected directly in the lesion, which showed some improvement in the first days with a reduction of the ulcerated aspect. In the return visit about two weeks later, the patient reported worsening of the aspect of this tongue

lesion. Therefore, a new incisional biopsy was performed, with the diagnostic hypotheses of squamous cell carcinoma or granulomatous fungal infection. All procedures were performed in a private office by a dentist, specialist in Stomatology, with eighteen years of experience (Fig. 2).

The histopathological examination revealed the presence of non-caseating granulomas within the connective tissue, with giant multinucleated cells similar to Langhans cells and foreign bodies (gigantocytes) containing multiple grains of yeast spores in their cytoplasm. There was an intense chronic inflammatory infiltrate in these granulomas, with a predominance of epithelioid cells. There was also the presence of endospores inside intracellular phagosomes in macrophages and disseminated in the chorion underlying the squamous epithelium of the mucosa (Fig. 3), justifying the report of specific chronic inflammation compatible with histoplasmosis.

The patient was referred to an appointment with a pulmonologist, who administered oral treatment with the Ketoconazole antifungal, after diagnostic confirmation of histoplasmosis by serological examination. As there was no effective improvement in the condition with this treatment, the patient was admitted for tests at the Moinhos de Vento Hospital in Porto Alegre, RS, Brazil, where it was found that the fungal infection had spread to the liver, intestines, and possibly the bone marrow. Hence, intravenous treatment with the Amphotericin B antifungal was administered, from which the systemic infection could be controlled and the tongue lesion regressed (Fig. 4). Subsequently, the patient used Itraconazole orally, twice a day, for another six months. The case is currently under follow-up for two years and the patient reports feeling substantially better after the diagnostic protocol and therapy performed.

## 3. Discussion

The present report described the case of a patient with lupus erythematosus affected by histoplasmosis. The patient was probably contaminated during her job activities as a machinery seller, as she frequently visited inland areas where the conditions for the presence and contamination by *H. capsulatum* and its routes of transmission may be typical. The diagnostic process was challenging, since initially the lesion was diagnosed as an ulcer related to lupus erythematosus and, given its persistence after application of corticosteroids, it could be a squamous cell carcinoma or a fungal granulomatous infection. Finally, the biopsy

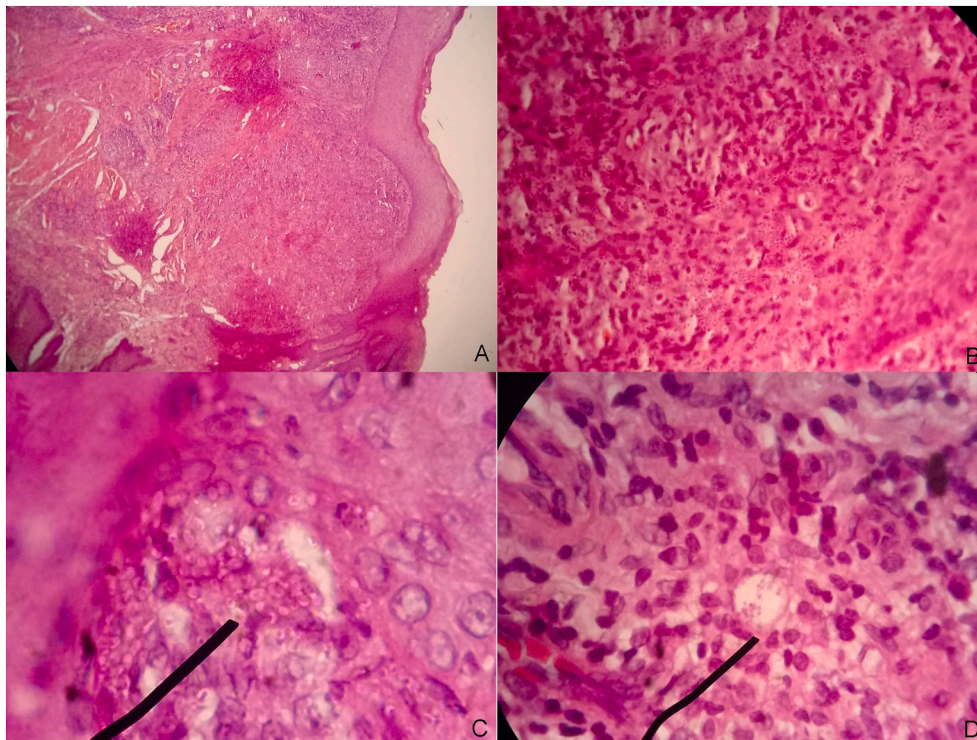


Fig. 1. Initial aspect of the lesion affecting the dorsal and ventral right regions of the tongue.





**Fig. 2.** Incisional biopsy of the tongue lesion. The procedure was performed in a dental chair, under anesthesia with 2% lidocaine and suture with 4-0 nylon thread, using simple stitches.



**Fig. 3.** (A) presence of non-caseating granulomas inside the connective tissue (100×); (B) intense chronic inflammatory infiltrate in these granulomas (400×); (C) multiple grains of yeast spores in the cytoplasm of multinucleated giant cells (1000×); (D) endospores within intracellular phagosomes in macrophages (1000×). All microphotographs were obtained from slides stained by the H.E. technique - hematoxylin-eosin.

of the oral lesion confirmed the diagnosis of histoplasmosis, which allowed the initiation of appropriate treatment.

Histoplasmosis is increasingly imported from endemic areas to non-endemic areas worldwide and climate change is likely to provide a warming ecosystem that favors the growth of fungi, and some comorbidities may provide more susceptible human hosts [4]. Histoplasmosis may also affect patients with lupus erythematosus because this condition is a risk factor in the development of disseminated histoplasmosis

due to its inherent defects in humoral and cellular immunity in this population [13]. The patient in this report has lupus erythematosus, which at first and based on the previous histopathological report was considered the potential etiology of the tongue lesion examined.

Systemic lupus erythematosus is an autoimmune disease not commonly associated with fungal infections [14] such as progressive disseminated histoplasmosis, which reported incidence ranging from 0.64 to 1.04% in patients with this condition, approximately one case



Fig. 4. Aspect of the lesion after treatment with Amphotericin B.

per year [15]. However, both chronic immunosuppression therapy and immunity defects may put patients with lupus erythematosus at risk of acquiring severe forms of histoplasmosis [13], as found by the clinician in the present study.

The early diagnosis of histoplasmosis is important to improve the quality of life of patients [10] but it may be delayed in many cases, especially in patients with another concomitant condition [13]. In this case, the previous histopathological report, the aspect of the tongue lesion, and the positive response to the first administration of Betamethasone were the reasons that may have contributed to a delay in diagnosis and, consequently, in the treatment of the condition. In this case, the attention given to the tongue lesion, the incisional biopsy, the identification of histoplasmosis through the histopathological examination, and the subsequent referral of the patient to a competent physician who could proceed with the systemic treatment of the condition were decisive for the appropriate management of the case.

The treatment of histoplasmosis depends on the severity of the infection and its specific manifestation but the underlying health problems of the patient often guide the treatment. Immunocompromised patients and cases of disseminated disease should always be treated [8,16]. Antimycotic medications are usually indicated. In the present case, considering it was the second histopathological report indicating a potential infection by histoplasmosis, the patient received oral antifungal drug treatment for the tongue lesion. These drugs often result in numerous and serious side effects, aggravating the difficulty in treating these patients [8].

The patient's already delicate health condition facilitating the spread of the histoplasmosis infection justifies the recommendation to use Amphotericin B in a hospital with subsequent use of Itraconazole orally for six more months. The prognosis, however, is directly related to the severity and health status of the patient and it may vary [8]. In the present case, the infection could be managed using this protocol, with a noticeable improvement in the general condition of the patient and the regression of the oral lesion.

#### 4. Conclusion

Greater attention should be paid to the association of histoplasmosis with other potentially serious systemic diseases such as lupus erythematosus, which facilitates the diagnostic process and treatment of affected patients. More education, information, and awareness about histoplasmosis among health professionals are required to manage these cases, especially in endemic areas to *H. capsulatum*, as in the case of Brazil, considering that early treatment with an appropriate antifungal may reduce morbidity and mortality. Due to the increase in outdoor recreational tourism, the interest in histoplasmosis should not come only

from professionals and workers of endemic areas but treated as a public health problem in these locations.

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#### Ethical approval

The present clinical case was approved by the Ethics Committee of the University of Passo Fundo/RS/Brazil, under opinion 4,675,949.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

#### Author contribution

Leticia Copatti Dogenski – Literature review, translation and spelling revision; conception and design of the study.

Eduarda Mafacioli Pasqualotto – Execution of the surgical step; acquisition of data.

Mateus José Dutra – Literature review, translation and spelling revision; conception and design of the study.

Gisele Rovani - Microscopic analysis and image acquisition.

Micheline Sandini Trentin – Writing work, discussion and final approval; conception and design of the study.

João Paulo De Carli – Execution of the surgical step; writing work, discussion and final approval; conception and design of the study.

#### Registration of research studies

Not applicable.

#### Guarantor

João Paulo De Carli.

**Declaration of competing interest**

None of the authors has any conflict of interest.

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