

# Oral histoplasmosis in an HIV-negative patient

Mônica Leal Alcure, DDS, MSc,<sup>a</sup> Oswaldo Di Hipólito Júnior, DDS, PhD,<sup>b</sup>  
Oslei Paes de Almeida, DDS, PhD,<sup>b</sup> Hamilton Bonilha, MD,<sup>c</sup>  
and Márcio Ajudarte Lopes, DDS, PhD,<sup>b</sup> Sao Paulo, Brazil  
UNIVERSITY OF CAMPINAS AND PRIVATE PRACTICE

Histoplasmosis is a deep mycosis caused by *Histoplasma capsulatum*, which has been found in soil with accumulated excreta of bats and birds. This disease has variable clinical findings with only pulmonary or systemic involvement. Upper aerodigestive lesions are found mainly associated with systemic disease, affecting particularly patients with immunosuppression conditions mainly caused by HIV. However, it is uncommon in immunocompetent patients. This report describes a case of oro-laryngeal-esophageal histoplasmosis in a HIV-seronegative patient without detectable systemic involvement. (**Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:E33-6**)

Histoplasmosis is a systemic mycosis caused by *Histoplasma capsulatum*, a saprophytic and dimorphic fungus found globally in soil. At room temperature in the soil, it presents as mycelial form, characterized by septate hyphae that produces microconidia. Human contamination occurs by inhalation of the airborne spores, which are phagocytized by pulmonary macrophages and reside within a membrane-bound vacuole. At body temperature, *Histoplasma capsulatum* converts to yeast and is able to replicate in the host.<sup>1,2</sup>

Some areas are endemic, including the Ohio and Mississippi River valley regions of the United States and scattered areas of Central and South America, Africa, Asia, the Far East, and Australia.<sup>1,3</sup> In Brazil, histoplasmosis has been found in the whole country, with some well-delimited areas presenting high endemicity with positivity to histoplasmin skin test reaching up to 93.5%.<sup>4,5</sup>

The clinical findings of histoplasmosis depends on the inoculum exposure and immunity of the patients. The disease may affect only the lung or involve extrapulmonary sites when the fungi spread through the reticuloendothelial system.<sup>2,6</sup> Upper aerodigestive histoplasmosis has been recorded in immunocompromised patients, mainly in human immunodeficiency virus



Fig. 1. Clinical aspects of the oral lesions.

(HIV)-seropositive patients, and may be the first manifestation of acquired immunodeficiency syndrome (AIDS).<sup>7-12</sup> In immunocompetent patients these lesions have been rarely described.<sup>9,12-15</sup> We describe an additional case of oro-laryngeal-esophageal histoplasmosis without detectable systemic involvement in an HIV-seronegative patient.

## CASE REPORT

A 61-year-old Caucasian man was referred by his general dentist to the Oral Diagnosis Clinic (Orocentro) at the School of Dentistry, University of Campinas, for evaluation of painful oral lesions. The lesions had been present for about 1 month, and were associated with hoarseness, dysphagia, and odynophagia. The patient reported progressing anorexia in the previous 2 months with weight loss. He had been a heavy smoker for about 50 years and quit this habit recently.

Clinical oral examination revealed ulcerated red lesions covered by pseudo-membrane located in the hard and soft palate, upper right buccogingival sulcus, and alveolar ridge (Fig. 1). Panoramic radiographs showed no bone alterations. No cervical lymphadenopathy was noted.

An incisional biopsy of the soft palate was performed and microscopic analysis displayed acanthomatous epithelium

<sup>a</sup>PhD Student, Oral Semiology and Oral Pathology, Department of Oral Diagnosis, Dental School, University of Campinas (UNICAMP), Piracicaba, Sao Paulo, Brazil.

<sup>b</sup>Professor, Oral Semiology and Oral Pathology, Department of Oral Diagnosis, Dental School, University of Campinas (UNICAMP), Piracicaba, Sao Paulo, Brazil.

<sup>c</sup>In private practice of Medicine (Infectious Diseases), Piracicaba, Sao Paulo, Brazil.

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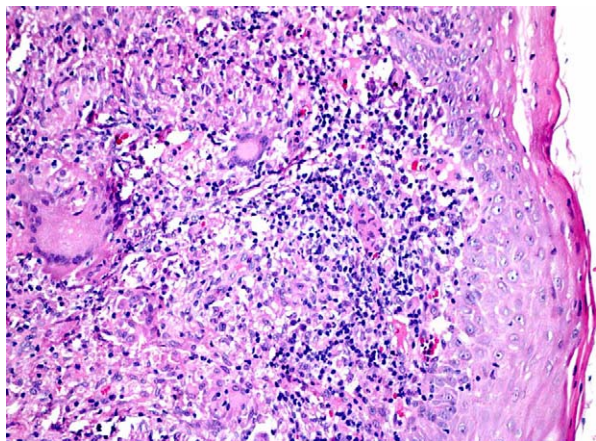


Fig. 2. Low-power photomicrograph of specimen shows noncaseating granulomatous inflammation with giant cells (hematoxylin and eosin stain, original magnification  $\times 200$ ).

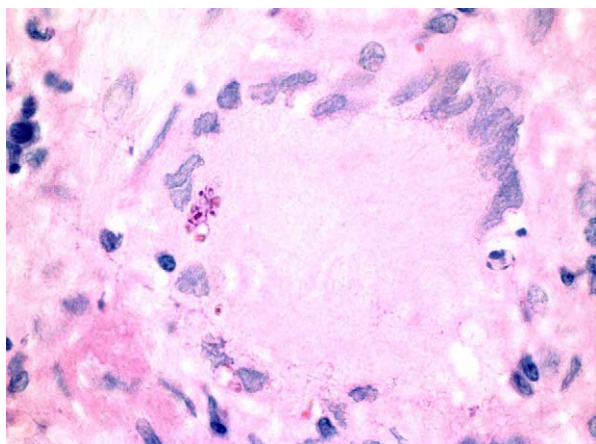


Fig. 3. Multinucleated giant cell containing numerous small yeast-like bodies (periodic acid-Schiff stain, original magnification  $\times 1000$ ).

with areas of ulceration. The subepithelial connective tissue was infiltrated by histiocytes with granulomatous arrangement and giant cells, surrounding by a chronic inflammatory cell infiltrate (Fig. 2). Small intracellular inclusions, 1 to 4  $\mu\text{m}$  in diameter, were observed in the phagocyte cytoplasm, which were periodic-acid Schiff (PAS) and Gomori-Grocott's stained and were consistent with *Histoplasma capsulatum* (Fig. 3 and Fig. 4). No fresh tissue was submitted for microbiologic examination.

The patient was referred to a physician for medical evaluation. Laboratory data were as follows: hemoglobin 12.7g/dL, hematocrit 39.6%, platelets  $293 \times 10^3/\text{mm}^3$ , white blood cell count  $8.7 \times 10^3/\text{mm}^3$  with 18.6% eosinophils and 1.6% basophils. Laryngoscopy and esophageal endoscopy revealed multiple areas of erosion and ulceration mainly in the glottic region and the esophagus. Incisional biopsy of these regions had the same diagnosis of histoplasmosis (Fig. 5 and Fig. 6).

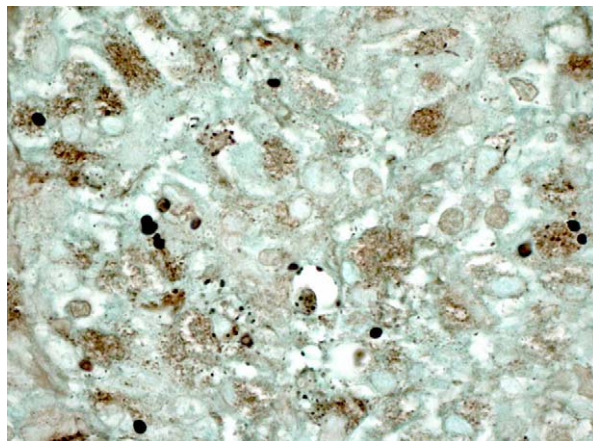


Fig. 4. Numerous circular yeast-like cells scattered throughout the tissue (Gomori-Grocott's stain, original magnification  $\times 1000$ ).

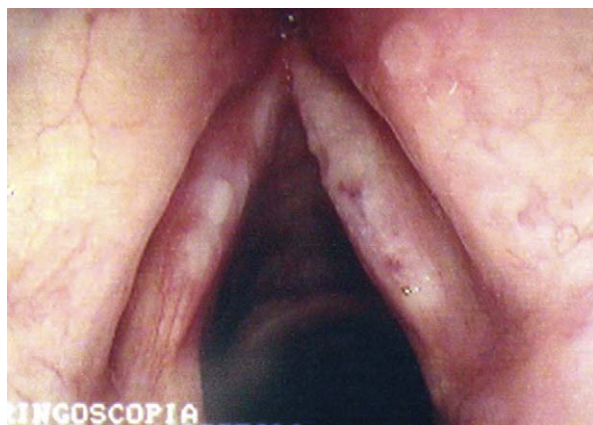


Fig. 5. Laryngoscope view shows ulcers in both sides of the vocal cords.

Chest x-ray showed no lung alteration and abdomen computed tomography (CT) scan showed no evidence of hepatosplenomegaly or lymphadenopathy. Serological tests were positive for anti-histoplasma at titer of 1:64 and negative for anti-HIV1-2.

Treatment with itraconazole 200 mg per day orally was started with complete remission of the oro-pharyngeal-esophageal lesions after 2 months. At recent follow-up 14 months later, no upper aerodigestive tract lesions were found and the patient gained weight. At that time, hematological tests were normal, and the serological test for antihistoplasma was negative.

The patient was further questioned regarding his travel history and contact with bats and birds. He related that he had had direct contact with dried excreta of bats during cleaning his recreation place in the central region of Brazil 10 years ago. He also related to have visited other recreation areas twice a month for the past 7 years where bats were living in the ceiling.



## DISCUSSION

*Histoplasma capsulatum* has been found in areas contaminated with excreta of bats and birds, such as chicken coops, attics, caves, abandoned buildings, trees, and roosting areas. Therefore, the fungi may be disturbed by exploring of caves, demolishing old buildings, excavation of soil, spelunking, and farm work.<sup>1,2</sup>

After inhalation, the fungi are phagocytized by pulmonary macrophages. Immunocompetent persons exposed to a low inoculum develop antigen-specific CD4+ T lymphocyte-mediated cellular immune responses with activation of macrophages and the disease is controlled.<sup>2</sup> When the cell-mediated immunity of the host is impaired, *Histoplasma capsulatum* can produce progressive systemic and potentially lethal disease with the spread of the fungi through the reticuloendothelial system. In these cases, the fungi act as an opportunistic agent.<sup>1,2,6</sup>

This severe form of histoplasmosis more commonly affects infants younger than 2 years of age with known immaturity of immune mechanisms and the elderly because of a decrease in cell-mediated immunity.<sup>1,13,16</sup> Patients with serious systemic illness, undergoing chemotherapy, or taking corticosteroids may also be affected.<sup>1,17-20</sup> Histoplasmosis is also associated with AIDS, a fact that led the Centers for Disease Control and Prevention (CDC) to include extrapulmonary histoplasmosis as an AIDS-defining illness in HIV-seropositive patients.<sup>1,8,12,13</sup> Although our patient lives in a nonendemic area, he related frequent contact with dried excreta of bats, which may be the cause of his infection.

Upper aerodigestive involvement has been reported in patients with chronic pulmonary and chronic disseminated forms of histoplasmosis and may be the initial or only manifestation of the disease.<sup>10,18</sup> Lesions in this location are particularly found in HIV-seropositive individuals.<sup>7-12</sup> On the other hand, it is very unusual in immunocompetent patients.<sup>9,12-15</sup> Accordingly, concurrent HIV infection should be investigated when upper aerodigestive histoplasmosis is found.<sup>8,12</sup> In our patient, the lesions were observed in the oral cavity, larynx, and esophagus without pulmonary or other systemic manifestations. The patient was HIV-seronegative and no reason for immunosuppression was identified.

The upper aerodigestive lesions frequently present as ulcers covered by pseudomembrane, nodules, or vegetations; are often painful, and the patients may present with hoarseness, odynophagia, and dysphagia. Oral lesions associated with *H capsulatum* may occur in isolation or associated with pharyngeal and laryngeal lesions.<sup>3,8-15,18,19,21-23</sup>

These lesions may mimic other ulcerated lesions, such as squamous cell carcinoma, tuberculosis, and other deep mycoses. However, the presence of multiple

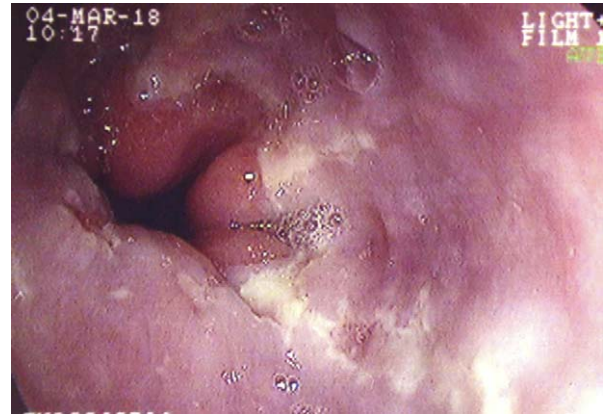


Fig. 6. Endoscopic view of the esophagus with multiple ulcerated lesions covered by fibrin exsudate.

lesions is more suggestive of infectious etiology, and histoplasmosis should be suspected mainly when it occurs in immunosuppressed patients.<sup>3,12,18,19,21-24</sup>

The laboratory methods available for histoplasmosis diagnosis include biopsy and culture of tissue, body fluids, and secretions, as well as tests for antigens and serum antibodies. The different diagnosis modalities are useful when the clinical form of histoplasmosis and the immune status of the host are considered.<sup>6,7</sup> The biopsy is indicated mainly for mucocutaneous lesions and special stains such as periodic acid-Schiff and Gomori-Grocott's methenamine silver nitrate are very useful.<sup>3,6,12,21,25</sup> In our patient there was a granulomatous pattern of inflammation and scarce fungi. These features may indicate good response of the host and better prognosis.<sup>21</sup>

The treatment varies according to severity of the disease and immune status of the host. The dosage and drug combinations as well as suppressive maintenance therapy to prevent relapse are variable and must be determined for each case.<sup>7,16,26</sup> In our patient, neither pulmonary nor other extrapulmonary sites of involvement were identified and after 2 months of itraconazole use the lesions disappeared and the response to *H capsulatum* was negative.

In conclusion, although the oral lesion of histoplasmosis is more common in HIV-positive patients, it may also affect immunocompromised persons and may be the first manifestation of the disease. Therefore, early diagnosis is important for decreasing the morbidity and mortality of these patients.

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*Reprint requests:*

Márcio Ajudarte Lopes, DDS, PhD  
 Faculdade de Odontologia de Piracicaba-UNICAMP  
 Semiologia - Diagnóstico Oral  
 Av. Limeira, 901 - Caixa Postal 52 - CEP: 13414-903  
 Piracicaba/SP, Brazil  
[malopes@fop.unicamp.br](mailto:malopes@fop.unicamp.br)