Treating Oral Histoplasmosis in an Immunocompetent Patient
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Histoplasmosis is a systemic mycosis caused by *Histoplasma capsulatum*, a dimorphic pathogenic fungus that develops a branching hyphal form in soil and a yeast form in the host tissue. Infection by this organism is endemic in North America, Central America and South America, but it also has been reported in Africa, Asia, India and Australia. The inhalation of spores, which are present in chicken, pigeon and bat excrement, by immunocompetent hosts usually results in an asymptomatic pulmonary infection. Immunocompromised hosts may develop a generalized infection that involves several organs. The clinical manifestations include fever, weakness, weight loss, hepatosplenomegaly and mucocutaneous lesions.

Clinically, histoplasmosis is classified into three forms: primary acute, pulmonary and chronic disseminated. The course of this disease can be affected by the immune status of the host and by the degree of exposure to infective propagules. Oral lesions have been reported in 25 to 45 percent of patients with documented cases of progressive disseminated histoplasmosis and in several case reports.

In endemic areas, *H. capsulatum* is a major opportunistic pathogen in the oral cavity. In endemic areas, *H. capsulatum* is a major opportunistic pathogen in the oral cavity. Dr. Muñante-Cárdenas is a master’s degree student, Division of Oral and Maxillofacial Surgery, Piracicaba Dental School, State University of Campinas, São Paulo, Brazil. Dr. Assis is a doctoral student, Division of Oral and Maxillofacial Surgery, Piracicaba Dental School, CP 52, State University of Campinas, 13414-903, Piracicaba, São Paulo, Brazil, e-mail “adiroassis@yahoo.com.br”. Address reprint requests to Dr. Assis. Dr. Olate is a doctoral student, Division of Oral and Maxillofacial Surgery, Piracicaba Dental School, State University of Campinas, São Paulo, Brazil. Dr. Lyrio is a doctoral student, Division of Oral and Maxillofacial Surgery, Piracicaba Dental School, State University of Campinas, São Paulo, Brazil. Dr. Moraes is a professor, Division of Oral and Maxillofacial Surgery, Piracicaba Dental School, State University of Campinas, São Paulo, Brazil.
patients infected with the human immunodeficiency virus (HIV); approximately 5 percent of patients with AIDS in these areas develop disseminated histoplasmosis. In immunocompetent hosts, few cases of oral histoplasmosis without detectable systemic involvement have been described. Oral histoplasmosis may manifest at any region of the mouth as nodules, deep ulcerative or vegetative lesions or painful shallow lesions. The clinician usually makes a definitive diagnosis by using a combination of methods, including culture, detection of \textit{H. capsulatum} in tissues, quantification of antibodies and/or detection of antigens.

We report a case of localized histoplasmosis that consisted of oral lesions only in an HIV-negative immunocompetent patient.

**CASE REPORT**

A 60-year-old man was referred by his general physician to the oral and maxillofacial surgery division of Piracicaba Dental School, State University of Campinas, São Paulo, Brazil, for evaluation of painful oral lesions. The lesions had been present for three months and were associated with pain, dysphagia and weight loss (approximately 11 pounds). The patient reported a 12-year history of systemic hypertension, for which he took 50 milligrams of captopril daily.

One of us (A.F.A.) conducted a clinical oral examination, which revealed two ulcerated lesions: a 3.0 × 1.5-centimeter well-demarcated lesion with an elevated border and a granular surface in the anterior maxillary vestibule, as well as a smaller lesion with the same characteristics in the hard palate (Figures 1 and 2). The clinician did not observe any cervical lymphadenopathy or extraoral lesions.

The results of radiographic tests did not reveal any alteration in the bone architecture or invasion of the maxillary sinus or nasal cavity. The clinician considered squamous cell carcinoma and systemic mycosis in the differential diagnosis.

One of us (J.L.M.-C.) performed an exfoliative cytologic evaluation and obtained tissue biopsy samples from the maxillary vestibule and hard palate lesions. Both of the tissue fragments were submitted for histopathologic examination with hematoxylin-eosin, periodic acid-Schiff (PAS) and Grocott-Gomori staining. Microscopic examination showed the presence of vacuolated macrophages containing numerous small yeast cells (2 to 5 micrometers in diameter), some of which were replicating by budding (Figures 3 and 4). The results were consistent with histoplasmosis, and we immediately contacted the patient’s physician for a medical evaluation and initiation of systemic treatment.

Laboratory data within the normal range of values included the following: hemoglobin, 15.8 grams/deciliter (normal, 13.5 to 18 g/dL), hematocrit, 47.4 percent (normal, 40 to 54 percent) and a white blood cell count of 8,300/cubic millimeters (normal, 5,000 to 10,000/mm$^3$). The patient’s platelet count was slightly below normal at 141,200/mm$^3$ (normal, 150,000 to 300,000/mm$^3$). Chest radiographs showed no evidence of lung alterations.

The patient initially received itraconazole treatment (200 mg per day for one month), accompanied by a clinical evaluation every two weeks. His physician also initiated treatment with nystatin and chlorhexidine mouthrinse (0.12 percent).
cent, 10 milliliters, two times a day). After one month, the physician reduced the itraconazole dosage to 100 mg daily, and the treatment continued for three more months until the lesions had resolved completely.

**DISCUSSION**

Histoplasmosis is a fungal infection caused by *H. capsulatum*. Oral manifestations, usually associated with the chronic disseminated form of the disease, constitute a rare event in immunocompetent patients. Most primary infections caused by *H. capsulatum* are asymptomatic, or the symptoms are acute and affect only the lungs. Oral lesions exhibit a varied clinical appearance and rarely are painful. The most common presentation is an ulcerative lesion with an elevated border, located mainly on the gingiva, palate and tongue.

Miller and colleagues reported that oral lesions of histoplasmosis occurred only as secondary local manifestations of pulmonary or disseminated disease. Some investigators have questioned this, claiming that primary oral histoplasmosis is possible and may develop as a result of direct inoculation of the fungus into the mucosa.

Clinicians usually diagnose primary oral histoplasmosis after discovering the lesions in the upper digestive tract in the absence of pulmonary signs, and the diagnosis is based on identification of the fungus. For superficial and accessible oral lesions, cytologic evaluation and a biopsy are recommended. However, in cases in which the lesions are not accessible, serologic examination to detect antibodies or antigens may be a complementary diagnostic tool. The differential diagnosis should include traumatic ulcers, necrotizing ulcerative gingivitis or stomatitis, tuberculosis, syphilis, squamous cell carcinoma and other mycoses, such as paracoccidioidomycosis.

Pisanty reported a case of spontaneous remission of oral histoplasmosis. However, failure to treat the infection in patients with AIDS may result in death. Practitioners should consider the possibility of a hidden immunosuppression, especially HIV infection. General practitioners must exercise caution when examining patients, because oral lesions of histoplasmosis may be the only sign of AIDS. The basic inflammatory response in a deep fungal infection is granulomatous, with macrophages and multinucleated giant cells dominating the histologic picture. Diffuse, small granulomas contain a variable number of yeastlike *H. capsulatum* cells, which are highlighted by PAS and methenamine silver staining.

Traditionally, treatment of this systemic disease has consisted of intravenous amphotericin B, which should be administered in a hospital because of its varied adverse effects, such as nausea, chills, fever, vomiting and renal complications. On the other hand, new and less toxic antifungal agents are available, such as the oral azoles, which are the drugs of choice for long-term maintenance therapy. Negroni and colleagues reported that treatment with itraconazole was favorable for localized oral lesions, when no systemic signs or symptoms could be detected. This drug appears to be safe and effective for both induction and maintenance therapies, with less toxicity than that of amphotericin B.
CONCLUSION

Although histoplasmosis rarely affects the immunocompetent patient, knowledge of the oral manifestations of histoplasmosis might enable clinicians to make earlier diagnoses and initiate therapy more quickly. Therefore, it is important for practitioners to perform thorough clinical examinations and include histoplasmosis in the differential diagnosis of ulcerated oral lesions, in both endemic and nonendemic areas.

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