ORAL HISTOPLASMOSIS: AN UNUSUAL PRESENTATION

Nagamani Narayana, MS, DMD,1 Ryan Gifford, DDS,2 Peter Giannini, DDS, MS,1 John Casey, MD1

1 Department of Oral Biology, UNMC College of Dentistry, 40th and Holdrege streets, Lincoln, Nebraska 68583. E-mail: nnarayana@unmc.edu
2 Private Practice, 3811 W. Charleston Blvd. Suite 201, Las Vegas, Nevada 89102

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Abstract: Background. Histoplasmosis is a localized or systemic fungal infection which may present as an acute primary or “reactivation” infection in the setting of immunosuppression. Tumor necrosis factor alpha (TNF-α) antagonists, used in the management of rheumatoid arthritis and Crohn disease, have been linked to reactivation of quiescent histoplasmosis. Microscopically, granulomas are either not evident or are infrequent in histoplasmosis when associated with TNF antagonist therapy presumably due to the suppression of macrophage activity.

Methods and Results. This article describes an unusual presentation of oral histoplasmosis in a 75-year-old woman patient on TNF-α antagonist, namely infliximab. Microscopically, cellular atypia resulted in a work-up to rule out lymphoma. Gomori’s methenamine silver stain demonstrated Histoplasma capsulatum leading to a diagnosis of histoplasmosis. She was treated successfully with itraconazole.

Conclusion. This is the first reported case, insofar as the authors are able to determine, of oral histoplasmosis, in a patient undergoing treatment with infliximab.

Keywords: oral histoplasmosis; atypical lymphocytic proliferation; immunosuppressive medications; TNF-alpha antagonists; infliximab

Histoplasmosis is a localized or systemic deep fungal infection that may present itself as an acute primary infection or “reactivation” infection during immunosuppression as seen with tuberculosis. Microscopically, the infection usually appears as granulomas providing a clue to the nature of the process.1,2 This article describes an unusual clinical and microscopic presentation of histoplasmosis in a patient taking infliximab.

CASE REPORT

A 75-year-old woman was seen at the University of Nebraska College of Dentistry for routine evaluation. Her medical history was significant for type 2 diabetes mellitus, bilateral knee replacements, cholecystectomy, hypercholesterolemia, hypertension, and rheumatoid arthritis. Medications included prednisone, atenolol, hydrochlorothiazide and triamterine, clonazepam, pioglitazone, amlodipine, ezetimibe and simvastatin, glipizide, hydrocodone plus acetaminophen, and infliximab. All systemic diseases were under control. The patient described the gingiva adjacent to tooth no. 24 as “sensitive.” An intraoral examination revealed a 3-mm recession along the facial aspect of tooth no. 24, with no keratinized or
attached gingiva. A connective tissue graft was recommended to alleviate sensitivity. The patient was subsequently scheduled for treatment.

The patient presented in the emergency clinic 1 month later for evaluation of swollen anterior facial mandibular gingiva. Pulp testing was performed on teeth 23 to 25 with all teeth testing vital. Periapical radiographs were within normal limits. The patient was given a prescription for amoxicillin and scheduled for a follow-up evaluation with a periodontist. The differential diagnosis included an abscess of either periodontal or endodontic origin.

Two weeks later, the patient returned with a chief complaint of an ill-fitting mandibular partial denture. The patient had recently been placed on cephalixin, amoxicillin, and clindamycin for a persistent cough treated as bronchitis. A chest radiograph was reported as normal. Intraoral examination revealed ulceration of the gingiva and mucosa extending from teeth 22 to 27 (Figures 1 and 2). The tissue had a rubbery consistency interspersed with areas of white, thickened mucosa. Both the facial and lingual tissues were indurated. Palpation of the submental region revealed movable submental lymph nodes. A radiograph failed to reveal periapical pathology, expansion, or osseous change in the region. Probing depths were within normal limits. An incisional biopsy was performed since the lesion did not resemble any known pathologic entity.

**Biopsy Results.** Microscopically, the lesional biopsy consisted of focally ulcerated mucosa overlying fibroconnective tissue containing numerous atypical histiocytes. Atypical small lymphocytes were admixed with few multinucleated giant
cells (Figure 3). The initial impression of multiple pathologists, including a hematopathologist, was that the lesion represented a lymphoproliferative process, possibly lymphoma. Immunohistochemical and molecular studies for lymphoma were negative. As part of the microscopic evaluation, Gomori’s methenamine silver stain was performed and the lesion was positive for fungus morphologically characteristic of *Histoplasma capsulatum* (Figure 4). The Fite stain was negative for acid-fast organisms.

**Treatment.** The patient was treated with itraconazole intravenously for 4 days followed by oral medication. The oral lesions regressed, and the patient is doing well 4 months following diagnosis (Figures 5 and 6).

**DISCUSSION**

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine playing an essential role in host defenses against intracellular pathogens such as fungal and mycobacterial organisms. TNF-α plays a major role in activating the inflammatory pathways in diseases such as ulcerative colitis, Crohn disease, psoriatic arthritis, and rheumatoid arthritis. These conditions may be managed by TNF-α antagonists. TNF-α antagonists can be of 2 types: monoclonal antibodies and soluble receptors. Infliximab and adalimumab are monoclonal antibodies that block the binding of TNF-α with its receptor on the cell surface. Etanercept is a soluble receptor acting as a “decoy” TNF-α receptor. Both types reduce inflammation and relieve symptoms associated with ulcerative colitis, Crohn disease, and rheumatoid arthritis.3–7

TNF-α antagonists, when used in disease management, have been linked to primary or reactivation of quiescent tuberculosis and histoplasmosis. The majority of such cases have been reported with patients taking infliximab.3 Microscopically, granulomas are either not evident or are infrequent in tuberculosis and histoplasmosis when associated with TNF antagonist therapy presumably due to the suppression of macrophage activity. The majority of the reported cases of TNF-α-therapy-associated histoplasmosis is pulmonary and has been diagnosed by bronchoalveolar lavage or lung biopsy. The case presented here represents the rare event of a diagnosis of histoplasmosis as a gingival presentation and biopsy. A review of 39 cases of infliximab-associated histoplasmosis reported in the literature did not reveal any description of a primary presentation of oral histoplasmosis.5 Our patient was concurrently taking prednisone (5 mg) and infliximab in addition to being diabetic. These factors may have been synergistic in contributing to the development of oral histoplasmosis. The present lesion could represent either a primary oral infection or a reactivation of a quiescent infection. The inhibition of macrophage function in patients taking TNF-α antagonists further contributed to the histopathological dilemma by preventing the formation of granulomas characteristic of the infections discussed above. The combination of rapid disease onset with signs of inflammation and atypical histopathology due to infliximab made this case difficult to diagnose. The patient responded to a course of itraconazole.

**CONCLUSION**

The purpose of this report is to describe a case of oral histoplasmosis with an unusual presentation.
in an immunosuppressed patient and to illustrate the diagnostic difficulty in histopathologic diagnosis associated with immunosuppression. This patient had diabetes, rheumatoid arthritis, and hypertension, treated with numerous medications including prednisone and infliximab. To our knowledge, this case represents the first case of histoplasmosis localized to the oral cavity in a patient undergoing treatment with infliximab, reported in the literature. Since TNF-alpha antagonists are being used with increasing frequency, the possibility of tuberculosis or histoplasmosis needs to be included in the differential diagnosis of atypical gingival or other intra-oral lesions. Likewise, if an atypical lymphocytic infiltrate is observed on biopsy, a review of the patient’s medical history is mandatory as well as special stains for fungi and mycobacteria. A silver stain such as Gomori’s methenamine silver should be examined along with the more commonly performed periodic acid–Schiff stain since *Histoplasma capsulatum* stains very weakly, if at all, with the periodic acid–Schiff stain. If these special stains are negative or if the cellular atypia is significant, immunohistochemical staining and molecular studies to exclude lymphoma are warranted. TNF antagonists have been reported to predispose the patient to the development of lymphoma, although this concern has been challenged in a recent study.¹⁸

**REFERENCES**