Oral ulcerative lesions in a post-liver-transplantation patient

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Abstract

Oral involvement is rarely found in histoplasmosis, except in its disseminated form, which is mostly observed in the severely immunocompromised host. Herein, we presented the case of a 36-year-old female with a previous history of liver transplant, who was hospitalized due to fever, chills, night sweats, diarrhea, and painful oral lesions over the last 3 days. The oral examination revealed the presence of painful shallow ulcers lined by a pseudomembrane in the gingiva and the soft and hard palate. The initial working diagnosis comprised cytomegalovirus reactivation or herpes simplex virus infection. The diagnostic work-up included incisional biopsies of the gingiva and the sigmoid colon. Both biopsies confirmed the diagnosis of histoplasmosis. Intravenous itraconazole was administered with significant improvement after 7 days. Although oral involvement is rare, histoplasmosis should be included in the differential diagnosis of oral lesions, particularly when the patient is immunosuppressed. This study reports a rare presentation of histoplasmosis involving the mucosa of the oral cavity and the colon.

Keywords
Histoplasmosis; Liver Transplantation; Oral ulcer; Immunosuppression

INTRODUCTION

Histoplasmosis is an opportunistic fungal infection caused by \textit{Histoplasma capsulatum}, a dimorphic fungus that lives in soil that is rich in birds and bats droppings.\textsuperscript{1} It is more prevalent in some regions in North, Central, and Latin America, as well as in Africa, and is typically found in tropical and temperate rural areas. The disease mostly occurs in the lungs and is acquired through the inhalation of dust particles from the soil contaminated with bat or bird excrement, which contains fungal spores—the infectious form of the microorganism.\textsuperscript{1}

After reaching the airways, the microconidia are phagocytosed by the macrophages where they start to replicate. Hematogenous spread occurs within 2 weeks after infection. In immunocompetent patients, the macrophages have a fungicidal role by phagocytizing \textit{H. capsulatum}, and therefore hamper the disease progression.\textsuperscript{1} However, in immunocompromised patients, such as those who are HIV-positive, transplant recipients, and patients with hematological neoplasm, the clinical course is more aggressive, with disseminated disease involving the lungs, skin, intestines, and oral mucosa.\textsuperscript{2} Here, we present an uncommon case of oral histoplasmosis, which was clinically misconceived as a viral infection.

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CASE REPORT

A 36-year-old woman presented to the Emergency Department of the Cancer Center, complaining of fever, chills, night sweats, diarrhea, and painful oral lesions, over the past 3 days. The patient had a medical history of liver transplantation 8 years before, due to biliary cirrhosis, and was taking prednisone 5mg/day and mycophenolate sodium 360 mg. She also reported cytomegalovirus (CMV) infection 3 months after the transplantation, which was successfully treated with ganciclovir. The oral examination showed three well-defined shallow ulcerative lesions covered by fibrin with regular erythematous borders on the hard palate, measuring 1 cm (Figure 1A); on the vestibular and palatal gingiva between the 16 and 17 teeth measuring 0.5 cm (Figure 1B); and on the left soft palate near the uvula measuring 1.0 cm (Figure 1C).

According to the clinical findings and the previous history of CMV, the main diagnostic hypotheses were CMV reactivation or herpes simplex virus (HSV) infection. Exfoliative cytology of oral lesions was performed and an anti-CMV immunoglobulin (Ig)G test was requested. Because of the immunosuppression, ganciclovir 300mg tid was prescribed, but no improvement was observed within 7 days. Since the exfoliative cytology and the anti-CMV IgG tests were negative, the hypothesis of viral infection became less probable. A chest x-ray was normal, which ruled out lung involvement. Due to the worsening of oral lesions and the presence of gastrointestinal tract symptoms, two oral incisional biopsies—in the gingival and the palate—were taken, and a colonoscopy was performed with biopsy of a rectal lesion. The colonoscopy image showed areas with inflammatory process and eroded mucosa with an extensive ulcer measuring 2 cm on the descending colon extending to the rectum (Figure 2).

Histological sections of oral cavity biopsies revealed fragments of squamous mucosa with intense histiocytic inflammatory infiltrate associated with rounded fungal structures, which were consistent with H. capsulatum, and were confirmed by Gomori–Grocott’s staining in the gum and the palate (Figure 3). Similar findings were observed in the rectal biopsy. Based on the clinical and histopathologic findings, the final diagnosis was histoplasmosis (Figure 4).

The treatment consisted of itraconazole 300 mg/day with significant improvement of local and systemic symptoms after 7 days (Figure 5). The patient was followed up for 12 months with no further lesions.

DISCUSSION

Clinical presentation of oral histoplasmosis is rare and the diagnosis is challenging. However, when present in the oral cavity, the involved sites include the tongue, the palate, the oral mucosa, the gingivae, and the pharynx. The mucosal involvement may occur as granular ulcerations, multiple painful ulcers and verrucous growths, as a deep ulcer surrounded by infiltrative edges with erythematous...
or white areas with irregular surfaces, as hardened and irregular nodular lesions accompanied by local lymphadenopathy, all of which mimic other infectious diseases or malignant tumors. This case report shows a case of histoplasmosis, which was initially misconceived as a viral infection.

The differential diagnoses of oral histoplasmosis include viral infections such as CMV and HSV. CMV is a ubiquitous herpes virus, which, depending on the studied population, infects 50%-100% of humans. Primary CMV infection in immune competent individuals presents most commonly without symptoms. However, in individuals with compromised immunity (e.g. liver transplant recipients) clinical disease may be fatal.

**Figure 2.** Colonoscopy image depicting area of inflammatory process with mucosal erosion and ulceration in the descending colon.

**Figure 3.** Photomicrograph of the oral biopsy. **A** – Areas of squamous mucosa with intense histiocytic inflammatory infiltrate associated with rounded fungal structures consistent with *Histoplasma* spp. (H&E 200X); **B** – Gomori–Grocott’s staining showing positivity for fungi (H&E 200X).

**Figure 4.** Photomicrograph of the rectal biopsy. **A** – Areas with intense histiocytic inflammatory infiltrate associated with rounded fungal structures consistent with *Histoplasma* spp. (H&E 400X); **B** – Gomori–Grocott staining showing positivity for fungi (400X).
CMV infection is the most common viral infection after solid transplant and usually appears during the first year after transplantation as observed in our case. The incidence after liver transplantation varies between 22% and 29%. CMV causes febrile illness, which is often accompanied by bone marrow suppression, and in some cases, involves other tissues including the transplanted liver allograft and gastrointestinal tract, causing abdominal pain and diarrhea. The skin and oral lesions usually present as chronic ulcers. Our patient presented fever, diarrhea, cutaneous rash, and oral lesions—features that are consistent with the diagnosis of CMV infection.

In contrast, HSV infection is a double-stranded DNA virus, which is usually acquired during childhood via infected saliva or direct contact with mucocutaneous lesions. After primary infection, the virus remains dormant until reactivation. The recurrent herpetic stomatitis is less common than the herpes virus remains dormant until reactivation. The recurrent mucocutaneous lesions. After primary infection, the child infection: overview on relevant clinico-pathological features. J Oral Pathol Med. 2008;37(2):107-21.

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In conclusion, a case of histoplasmosis involving the oral cavity in an immunosuppressed patient is reported, which was initially misdiagnosed due to her previous medical history of CMV disseminated infection. The early and accurate diagnosis of histoplasmosis is essential for the correct treatment and cure.
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The patient signed an informed consent authorizing the publication of the report as well as the images. The manuscript is in accordance with the Institutional Ethics Committee rules.

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