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Abstract The clinicopathologic features of oral cryptococcosis manifested as multifocal tumor-like lesions located in the upper and lower gingival tissues of a 36-year-old male patient with AIDS are described. The gingival lesions were the initial manifestation of disseminated cryptococcosis from which central nervous system involvement was established. Clinical differential diagnosis and histopathologic features are discussed. Effect of treatment on the gingival lesions after 18 months follow-up is presented.

Keywords Cryptococcosis · Diagnosis · HIV · Acquired immunodeficiency syndrome · Gingiva

Clinical Presentation

A 36-year-old male patient with AIDS suffered with headaches for several months and was sent for consultation because he presented with mass lesions located in the gingivae of the anterior part of the maxilla, mandible, and left tuberosity. He was asymptomatic and mentioned that he had noticed the gingival enlargements for approximately 3 months. The upper and lower incisors presented moderate mobility. The patient had not received highly active antiretroviral therapy (HAART).

Clinically the lesions appeared as tumor-like masses, with erythematous color, granular texture and micro-ulcerations covered by serous secretions and some bleeding. Both buccal and lingual/palatal gingiva were involved. The lesion of the tuberosity involved part of the hard and soft palate (Figs. 1, 2).

Differential Diagnosis

The case can be defined as multifocal growths with granular texture developed in the gingivae mucosa of an AIDS patient. The differential diagnosis in this particular case should include firstly, fungal infections, then secondly, a malignant neoplasm, and more rarely, a bacterial infection.

Different species of fungus produce lesions in the oral mucosa of AIDS patients which can be primary infections or, more frequently, a result of pulmonary infection with subsequent dissemination. Considering the immunocompromised state of the patient, histoplasmosis, cryptococcosis, and paracoccidiodomycosis are the main mycotic infections that need to be ruled out. However, many other fungal organisms, could produce similar lesions [1, 2].

Among oral malignant neoplasms, non-Hodgkin’s lymphoma and Kaposi’s sarcoma should be considered in the differential diagnosis. Lymphoma is the most frequent non-epithelial malignant tumor in the oral cavity and maxillofacial region. Oral non-Hodgkin’s lymphoma can be a component of a disseminated disease process or it may represent a primary extranodal disease confined to the oral cavity or jaws. On the other hand, it is important to point out that extranodal lymphoma is increasing in the AIDS population and in the oral tissues; diffuse large B cell lymphoma, plasmablastic variant, has been reported. Also, an increase incidence of immunoblastic and undifferentiated lymphoma or Burkitt’s types has been seen in AIDS.
patients. A review of the literature indicates that intraoral lymphoma may present as the initial feature of HIV infection [3].

Although the clinical appearance of the gingival lesions is not typical of Kaposi’s sarcoma, the fact that the patient has AIDS must lead to the clinician considering this tumor in the differential diagnosis.

Regarding bacterial infection as the etiologic cause of this case, it is important to mention that lung infections by *Mycobacterium tuberculosis* and *M. avium intracellulare* are relatively common complications found in HIV-affected individuals. Therefore, there is a possibility that dissemination of these bacterial pathogens to the oral tissues can occur. Oral tuberculosis may be either primary or secondary, with the latter associated with pulmonary disease. Secondary oral tuberculosis usually presents as a painful ulcer most commonly on the dorsum of the tongue [4]. Although tuberculosis of the oral tissues is rare and has not been described as a common finding in AIDS patients, this disease must be considered.

### Diagnosis and Treatment

Under local anesthesia, incisional biopsies were taken from the maxillary and mandibular gingiva. The microscopic study of H&E-stained sections obtained from the biopsies showed a marked hyperplastic oral epithelium, chronic inflammation with few neutrophil leucocytes, histiocytes, and abundant encapsulated yeast-like organisms, ranging in size from 4 to 15 μm (Fig. 3). The organisms were morphologically consistent with *Cryptococcus neoformans*. The definitive diagnosis of cryptococcosis was established with periodic acid schiff (PAS) and mucicarmine-stained preparations. The fungal cytoplasm appeared bright red by PAS stain, and the fungal capsule by mucicarmine (Figs. 4, 5).

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**Fig. 1** Gingival enlargements with erythematous color, granular texture, and micro-ulcerations covered by serous secretions and some bleeding.

**Fig. 2** Tumor-like mass with ulceration involving the tuberosity and part of the hard and soft palates.

**Fig. 3** Proliferating cryptococci (arrows) presents as extra-and intracellular yeast cell with some budding forms with reactive macrophages, minor lymphocytic infiltrate, and few neutrophils. The epithelium (E) appears hyperplastic. H&E stain (×200).

**Fig. 4** Massive proliferation of cryptococci including budding forms depicted with PAS stain. The fungal cytoplasm appears red (arrows) (×200).
Analysis of the peripheral blood showed a white blood cell count of 4,500/mm², 30% which were lymphocytes, and CD4+ lymphocyte cell count of 130/mm². Cerebrospinal fluid (CSF) tested positive for cryptococcal antigen with a titer 1:470. The chest X-ray was unremarkable.

Based on the histopathologic findings of the gingival biopsies and the positive test for cryptococcal antigen found in the cerebrospinal fluid, the final diagnosis of the case was gingival cryptococcosis and cryptococcal meningoencephalitis.

Treatment consisted of the administration of 200 mg of fluconazole 2 times/day for 8 weeks followed by 200 mg of fluconazole once/day permanently. The headache disappeared at the 7th day of treatment. Results of treatment on the gingival lesions after 18 months are shown in Fig. 6. Gingival biopsies taken at this time showed fibrous connective tissue with diffuse moderate chronic inflammatory infiltration. Special stains were unable to demonstrate the presence of cryptococcus.

Discussion

Cryptococcus is a fungus found in the roosting sites of birds, especially pigeons. Of the 19 different species of the fungus, only Cryptococcus neoformans produces infection in humans. The primary site of C. neoformans infection is the lung. It occurs through aspiration of airborne spores that lodge in the lungs producing pulmonary cryptococcosis, and by hematogenous dissemination of cryptococcosis to the CNS. Cutaneous, mucocutaneous, osseous, and visceral forms of the disease may occur through dissemination from the primary pulmonary focus. The most common clinical presentation is meningoencephalitis. The infection affects mainly immunocompromised patients, but may also present in immunocompetent individuals. The incidence of cryptococcosis in AIDS patients in the era before HAART ranged from 6 to 12%. Recent studies estimate that cryptococcal infection is the AIDS-defining illness in 3% of HIV+ patients. The decrease in frequency of cryptococcosis in AIDS patients is attributed to HAART.

Cryptococcosis of the oral mucosa very rarely represents as a primary infection. The few oral cases reported in the literature are the result of hematogenous spread of the infection localized in the lungs of AIDS patients. However, oral cryptococcosis can be the first manifestation of a disseminated infection. The oral lesions have been described as ulcers on the tongue [5] and palate [6–8], and non-healing ulceration after tooth extraction [9]. Tzeros et al. [8] have reported one case with an exclusive oral presentation, and Dodson et al. [9], described one case where AIDS was diagnosed in a homosexual man after a diagnosis of oral cryptococcosis was established.

Regarding the histopathology of cryptococcosis, it is interesting to note that the tissue changes are closely related with the immunological status of the affected patient. In an immunocompetent individual, typical granulomas are usually encountered at the site of cryptococcal infection and are formed by a compact aggregate of macrophages with epithelioid features and multinucleated giant cells, of both foreign body and Langhans-type, containing numerous intracytoplasmic yeast cells with budding forms. Cryptococci are also seen as extracellular organisms. However, in AIDS patients, the histopathology of cryptococcosis is different. In individuals with impaired T-cell function, the cryptococcal lesion shows marked intracellular yeast-cell proliferation with a histiocytic response, and only minor lymphocytic and neutrophilic components. Giant cells, if present, are scarce, and well-defined granulomas are not found [10]. In the present case, the histopathology of gingival biopsies showed a massive proliferation of cryptococci and reactive macrophages with minor lymphocytic infiltrate accompanied by marked hyperplastic oral epithelium that surrounded the organisms.
A lack of granulomatous inflammation was noted, as well as an absence of neutrophils and giant cells.

After reviewing the literature and analyzing the clinical characteristics of the case, we can confirm that this is the first report of oral cryptococcosis manifested as tumor-like lesions located in the gingival tissues. Previous reported cases were described as ulcers. Chronic asymptomatic multifocal growths with granular texture developed in the oral cavity of an AIDS patient, particularly if not receiving HAART, should lead to the suspicion of fungus infection, and particularly cryptococcosis, since it constitutes one of the major opportunistic infections associated with immunosuppression. Clinical differential diagnosis of oral mucosal cryptococcosis may be difficult. This is because similar clinical appearance can be observed in histoplasmosis, paracoccidioidomycosis, tuberculosis, non-Hodgkin’s lymphoma, and squamous cell carcinoma. On the other hand, it is important to remember that persistent headache can be a symptom of brain cryptococcosis particularly when it occurs in AIDS patients.

In the present case, cryptococcal meningoencephalitis was established after the diagnosis of gingival cryptococcosis was made with the oral lesions being the first manifestation of disseminated cryptococcosis in a patient with acquired immunodeficiency syndrome. Finally, it is necessary to emphasize that biopsies and the use of appropriate laboratory techniques are fundamental for the correct diagnosis of hyperplastic tissue, tumor-like lesions, or persistent ulcerations detected in the oral mucosa of normal or immunosuppressed patients.

References