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EDITORIAL

Oral manifestations in AIDS☆

Manifestações orais na SIDA

Nowadays, patients with AIDS can live a life with considerable quality in relation to oral health, being healthy enough to tolerate most surgical and dental procedures. Furthermore, several studies have shown that patients with HIV disease are not more susceptible to complications, regardless of CD4-cell counts.

There are no oral lesions that are specific to HIV patients. All lesions found among HIV-positive patients also occur in other diseases associated with immunosuppression. Thus, we conclude that there is a clear correlation between the onset of oral lesions and decreases in the immune system. Several lesions, such as oral thrush, hairy leukoplakia, ulcerative necrotizing periodontal disease and Kaposi's sarcoma are strongly suggestive of impaired immune response, with CD4 counts below 200 cells/mm^3. If we consider oral lesions as markers of immunosuppression and progression of AIDS, it may play a role in intervention strategies and treatment.

We can cite as major oral lesions of patients with HIV:

Fungal infections

Candidiasis: Caused primarily by *Candida albicans*, it is the most frequent oral manifestation. Although not being, by itself, pathognomonic of AIDS, oral candidiasis may be an indication of immunosuppression and disease progression.

Angular cheilitis: Mixed infection involving *C. albicans* and *Staphylococcus aureus*, manifests itself as red cracks with origin from the labial commissure of the mouth, and may be present along with intraoral candidiasis. The concomitant occurrence of dry mouth is not an uncommon cofinding.

The treatment of oral candidiasis includes topical and systemic antifungal medication. Topical therapies include topical antifungal mouthwash, tablets and oral gel. These formulations should be used concomitantly with systemic drugs, especially in cases of esophageal candidiasis. Topical antifungal therapies are more effective in patients with CD4 counts over 150–200 cells/mm^3. Common topical treatments are nystatin oral suspension (100,000 units/mL), nystatin tablets, and oral gel, for example, miconazole and clotrimazole 1%. The most common systemic antifungal agents are fluconazole (150-mg tablets) and itraconazole 100 mg. Resistance to fluconazole was reported as occurring in patients with severe immune deficiency.

Treatments of fluconazole-resistant patients with a combination of fluconazole and terbinafine have been successful.

Deep infections

Intraoral manifestations caused by *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Geotrichum candidum* and *Aspergillus* spp. are uncommon and generally suggest a significant immunosuppression. Disseminated intraoral lesions associated with cryptococcosis, histoplasmosis and aspergillosis were described as ulcerative and nodular events, while geotrichosis lesions are described as pseudomembranous events. As the oral lesions in this category are non-specific, the definitive diagnosis requires histological verification. In general, the treatment of these lesions consists in intravenous amphotericin B.

Viral infections

Although there are no specific oral lesions caused by HIV infection, patients may exhibit oral manifestations as an early sign of HIV infection.[1] Such symptoms include non-specific oral ulcers, pharyngitis and oral candidiasis during the acute phase of infection.

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Herpes virus (HSV)

In general, the presence of intraoral lesions by HSV is the result of the reactivation of a latent virus, and among immunocompromised individuals, this condition can be more severe, with a diverse manifestation. Although ulcers caused by HSV-1 and HSV-2 are clinically indistinguishable, in the oral cavity HSV manifest in the form of vesicles with ulceration, with subsequent healing. These are small, shallow ulcers, and tend to be healed in 7–10 days, although this period may be extended in immunocompromised patients. Patients may present clinical signs and symptoms that resemble those of a primary HSV infection, such as malaise and an intensely painful cervical lymphadenopathy.

Differential diagnosis should include other viral infections, such as cytomegalovirus, varicella zoster, and aphthous ulcers. The diagnosis should be based on clinical history and laboratory tests (cytological staining for Tzanck cells, viral culture of the ulcer, biopsy, or presence of antibody). Treatment includes acyclovir and famciclovir (can cause side effects in immunocompromised patients). Foscarnet can be used for resistant infections.

Cytomegalovirus (CMV)

Oral manifestation of cytomegalovirus (CMV) is observed only in patients with CD4 counts below 100 cells/mm^3 in the disseminated form of the disease. The lesions associated with CMV are non-specific ulcerations in any area of the oral mucosa. The differential diagnosis should include recurrent aphthous ulcers and HSV. A definitive diagnosis should include a biopsy revealing intranuclear inclusions of CMV in basophils, or on the identification by monoclonal antibody assay. As a therapeutic regimen, acyclovir may be given in high doses (800 mg PO 5$\times$/day) for a minimum period of two weeks.

Epstein–Barr virus (EBV)

Various manifestations may be related to EBV, such as mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma and oral hairy leukoplakia. Oral hairy leukoplakia was initially described as a pathognomonic lesion of AIDS, but this condition has been diagnosed in many other diseases. Hairy leukoplakia may be present at all stages of HIV disease, but this condition is more commonly found in patients with CD4 counts below 200 cells/mm^3. Leukoplakia manifests as a white lesion in the form of hyperkeratotic vertical streaks on the side margins of the tongue.

Usually, there is no need to treat this injury, unless the patient complains of his/her injury, either esthetically or for some functional impairment. Antiviral therapy (acyclovir 800 mg PO 5$\times$/day) is effective in achieving resolution.

Varicella-Zoster virus

There are reports of increased incidence of human varicella-zoster virus (HZV) among HIV-infected patients. This occurrence is common and can be severe, especially for those individuals with CD4 counts below 200 cells/mm^3. Clinically, the oral lesion presents in the form of vesicles which rupture quickly, forming multiple shallow ulcerations with an erythematous base, distributed along a unilateral division of fifth cranial nerve. Patients often complain about severe pain. Laboratory tests: Histological staining for giant cells with intranuclear inclusions, direct immunofluorescence and cytology. Generally, the treatment consists in supporting and preventing from postherpetic neuralgia, consisting of high-dose acyclovir (800 mg PO 5$\times$/day), famciclovir (500 mg PO 3$\times$/day), or valacyclovir (500 mg PO 3$\times$/day).

Human papillomavirus (HPV)

Oral manifestations of papillomavirus may present different features, including: verruca vulgaris, focal epithelial hyperplasia and condyloma acuminatum. The presence of HPV lesions is not pathognomonic of HIV infection.[2]

Cosmetic treatments for HPV include surgical removal, laser ablation, cryotherapy, and topical application of keratinolytic agents. The use of intralesional injection of antiviral agents, for instance, injection (1,000,000 IU/cm^2, 1$\times$/week) and subcutaneous (3,000,000 IU/cm^2, 2$\times$/week) interferon-α, demonstrated efficacy in long-term resolution.

Kaposi's sarcoma (KS)

Kaposi's sarcoma lesions are found in the soft palate, in the form of red-blue or purple-blue color maculae, or in the form of nodules. Initially, the lesions are asymptomatic, but due to minor traumas and ulcerations, may become symptomatic for speaking and chewing. Lesions on the gums and tongue are also common. Extrapalatal lesions are associated with a quick progression of AIDS. These injuries usually occur in patients with CD4 counts below 200 cells/mm^3, but can be observed at all stages of disease. Differential diagnosis with physiologic pigmentation: bacillary angiomatosis, lymphoma and trauma. For the definitive diagnosis, a biopsy is required. Treatment for SK consists of radiation, surgical excision, and intralesional injections of an appropriate chemotherapeutic agent. It is important to realize that most of these treatments are not curative, but they are prescribed to reduce the size and number of lesions. Recent studies have shown some efficacy with antiangiogenesis agents, such as thalidomide and retinoic acid.

Bacterial infection: periodontal disease

Oral manifestations of bacterial origin are associated with periodontal conditions and can be classified as: linear gingival erythema (LGE), necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP).

It was also observed that HIV-seropositive patients and with prior periodontal disease may exhibit faster rates of periodontal deterioration.

The differential diagnosis should include erythema due to a dry mucosa in association with mouth breathing, lichen planus, mucosal pemphigoid, or an allergic reaction.

Such manifestations may be associated with subgingival candidiasis as a possible cause. The treatment consists in oral health care improvement and use of topical antifungals.

Manifestations of NUG and NUP are triggered by changes in the immune status, more likely aggravated by bacteria, stress, anxiety, malnutrition and smoking.

Definite diagnosis is based on a clinical workup and radiological evaluation, with panoramic or periapical radiographs. There may be need for specific laboratory tests for exclusion of the following conditions and injuries, among others: bullous lesions of benign mucosal pemphigoid, erythema multiforme, acute forms of leukemia and major-type aphthous ulcerations. The treatment for both conditions consists in debridement of necrotic soft and hard tissues and antibiotic therapy.

Tuberculosis (TB)

Intraoral lesions associated with TB may present as painful granulomatous ulcerations, mainly on the tongue and palate. The clinical diagnosis is difficult, and tubercle bacilli survey and an assessment of the airways (lung and larynx) are required.

Syphilis

The clinical presentation of syphilis includes cankers, ulcers and plates. Cankers are indurated ulcers which, in most cases, are asymptomatic and often seen on the lips, oral mucosa, tongue, palate and posterior pharyngeal wall. The secondary injury is characterized by mucosal ulcers or plaques with an opalescent white lesion aspect. The differential diagnosis should include cold sores, deep fungal infections, ulcers associated with mycobacteria, malignant ulcers and trauma. The definitive diagnosis is done by dark field microscopy, demonstrating *Treponema pallidum*. Treatment is with systemic antibiotics.

Nonspecific ulcers

Necrotizing stomatitis is an acute painful ulcerative lesion in mucosal surfaces, leading to tissue necrosis and subsequent bone exposure. No specific microbial agent or mechanism has been associated with its etiology. This condition is seen in patients with CD4 counts below 100 cells/mm^3. The differential diagnosis includes aphthous ulceration and NUP. Treatment involves a careful debridement and therapy with steroids and antibiotics.

Aphthous ulcerations

Recurrent aphthous ulcerations (RAUs) are idiopathic oral ulcerations. Clinical presentations: minor, major and herpetiformis RAU. This is a diagnosis of exclusion. Its duration is about 1–2 weeks, being healed without scarring. Minor aphthous ulcerations are also prevalent in HIV-infected and uninfected populations. Major aphthous ulcers can occur in any area of the oral mucosa and tend to persist for more than three weeks, being healed with scar formation. In HIV-infected patients, aphthous ulcerations have been associated with severe immunosuppression, with CD4 counts below 100 cells/mm^3, being markers of HIV disease progression. Treatment for major aphthous ulcerations includes systemic corticosteroids. Topical formulations of clobetasol or dexamethasone elixir (0.5 mg/5 mL) and the systemic administration of prednisone 60–80 mg/day for 10 days were used with success. For corticosteroid-resistant patients, an alternative therapy with thalidomide 100–200 mg may be effective. Colchicine or levamisole are alternatives.

Ulceration induced by medication

Several drugs frequently used for patients with HIV infection have been associated with the development of ulcerations: zidovudine, zalcitabine, foscarnet, interferon and ganciclovir. Certain antiretroviral therapies can induce neutropenia and subsequent occurrence of oral ulcerations.

Xerostomia

Xerostomia or dry mouth is a symptom frequently observed in HIV-infected patients. It has been reported that reduced salivary flow occurs in 2–30% of subjects. The most common cause of reduced salivary flow is due to the side effects of medication, for example, anti-retroviral agents (including nucleoside transcriptase inhibitors, protease inhibitors), as well as antihistamines, anticholinergics, antihypertensive agents, decongestants, narcotic analgesics, and tricyclic antidepressants. Furthermore, xerostomia can result from a salivary gland disease associated with HIV.

The parathyroid glands are more frequently affected; however, minor salivary glands may also be affected by a viral infection, for example, CMV.

The treatment for xerostomia focuses on symptomatic relief through hydration, minimizing the consumption of alcohol and caffeine, and using artificial saliva. The use of pilocarpine to stimulate saliva flow may be a useful option.

Final considerations

It is important to recognize the oral lesions of patients with HIV, both by otorhinolaryngologists and by our residents who had no contact with these patients in the years 80–90, when diagnosis was often obtained through these injuries. Even today, despite the effectiveness of therapeutic programs and of drug efficacy, a large number of individuals exist who are unaware that they are infected, and thereby the disease can develop at any particular time. In addition, at outpatient clinics we have seen patients who neglect or refuse treatment, and again show these lesions without revealing that they are carriers.

Conflicts of interest

The author declares no conflicts of interest.

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