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Oral diseases in patients infected with HIV

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Abstract

Introduction: In recent years, more and more people have become infected with Human Immunodeficiency Virus. Of great importance in the course of HIV infection are symptoms and diseases, which often occurs in the oral cavity with a corresponding decrease in lymphocytes.

Aim: The aim of the study was the study was to present the most common oral diseases in patients infected with Human Immunodeficiency Virus like hairy leukoplakia, Candidas, angular cheilitis, Linear Gingival Erythema, Herpesviridae virus infections, ulcerative lesions.

Description: Clinicians should pay attention to oral manifestation of HIV infections because it may speed up the diagnostics process and may allow better control of the course of the infection. Hairy leukoplakia related to EBV is a marker of HIV on the side border of the tongue and appears as a hyperkeratotic stripes. Candidiasis may occur in many forms as acute pseudomembranous candidiasis, acute erythematous candidiasis, hyperplastic candidiasis or Median Rhomboid Glossitis. The most common fungus is Candida albicans but there may also be Candida krusei, Candida glabrata or Candida tropicalis. Another disease is Angular Cheilitis which is an inflammatory process localized in the commissure of the labia and can be caused by vitamin B deficiency, Candida, Staphylococcus or Streptococcus infection. Linear Gingival Erythema is a red linear lesion on the gingival margin infiltrated by polynuclear leukocytes and plasma cells. Patients with HIV also present Herpesviridae infections symptoms, ulcerations and xerostomia.
Summary: This review shows that HIV/AIDS patients should be monitored for oral manifestation of the HIV infection and weakened immune system. Diseases described in this study are reliable markers of the HIV infection and clinicians should pay attention to them to monitor the course of primary infection.

Keywords: HIV, oral, diseases, leukoplakia, candida, herpes

Introduction

The population infected by Human Immunodeficiency Virus (HIV) continues to grow annually. According to UNAIDS in 2021, there were 38.4 million (33.9 million–43.8 million) people living with HIV and 1.5 million (1.1 million–2.0 million) people became recently infected with HIV.

The oral manifestations (OM) of HIV are well settled indicators of disease progression, and their inherence might be a determinant of a compromised immune status. They can increase rates of morbidity and significantly contribute to the deterioration of the quality of life of patients.[1] With the development of antiretroviral therapy (ART) the evidences found in the literature show decrease in the prevalence of the OM in HIV infected patients.[2,3] On the other hand, there are still some inequalities in accessibility to health care, especially in African countries where ART is limited, what makes OM in HIV-positive a crucial burden to these countries' health care systems.[4]

Our goal in this paper is to draw attention to the importance of changes in the oral cavity in the course of HIV infection and bring their figures closer to clinicians, thus enabling their more frequent diagnostics, which may contribute to the effectiveness of treatment of HIV-positive patients.

Hairy leukoplakia

This specific oral lesion has been shown to be a reliable marker of HIV disease progression.[5,6] Oral hairy leukoplakia (OHL) is related to Epstein-Barr virus (EBV,HHV-4). Symptoms are marked asymmetrically on the side border of the tongue as white, hyperkeratotic, upright stripes that cannot be removed mechanically.[7] OHL is more frequent in men compared to women.[8,9]

Hairy leukoplakia is mostly observed on the tongue. It can be exceptionally found on the mucosal surface of the throat, but is not located on the mucosal surface of the anus.[10,11] The diagnosis of OHL is sometimes difficult when only the clinical aspects of the disease remain to be confirmed. To obtain verification of hairy cell leukoplakia, it is necessary to perform in situ hybridization for HHV-4.[12]

There is a small amount of proof for the treatment on OHL. Acyclovir is one of the drugs administered systemically. After stopping treatment, lesions tend to reappear. Topically, podophyllin resin 25% and acyclovir 5% cream are used for local therapy.[8,13,14]

Candidiasis

Candida is an organism that is a component of the natural flora of humans. It inhabits the epithelium of the gastrointestinal tract and genitourinary tract. A weakened organism as a result of chronic diseases and in people with malfunctioning immune systems is vulnerable to fungal infections.[15] Although there are more than 17 Candida species that can cause infections in the oral cavity, only five of them are responsible for more over 90% of oral candidiasis infections. These include *C. glabrata* and *C. parapsilosis*, *C. tropicalis* and *C. krusei* and the most common *Candida albicans*.[16] It is possible to distinguish several clinical types of oral candida that are associated with HIV infection.[5]

Acute pseudomembranous candidiasis

Acute pseudomembranous candidiasis is seen in patients with malfunctioning immune systems and in children up to 4 weeks old. It is widely also known as thrush.[17] This fungal condition accounts for about 33% of cases, which classifies it as a major infection. It is characterized by the occurrence of whitish spots, which are easily removed mechanically. Beneath them is revealed a reddened, erythematous mucosa. Oral bleeding, burning, and taste disturbances are all common in patients with presenting symptoms.[18,19] Such white lesions are found on the hard and soft palate, tongue, mucous membrane of the lips and cheeks, and throat.[20] Clotrimazolum is the first choice treatment.[17]

Acute erythematous candidiasis

It reveals itself as reddish patches on the palate and the dorsum of the tongue. There are no papillae on the tongue at the site of the lesions.[5,7] The most common symptom is a burning feeling in the oral cavity and on the tongue. These symptoms are stimulated by salty food and acidic drinks.[8] Generally, a clinical diagnosis is sufficient to initiate treatment. The same treatment is provided as in the case of acute pseudomembranous candidiasis.[17]

Hyperplastic candidiasis

This condition causes whitish spots on the tongue, cheek mucosa and lips. They can remain for a period of years. They are a carcinogenic risk.[21] These lesions are rough and hard on clinical examination.[22] They are deeply ingrained and impossible to wipe off.[7] A connection exists with smoking, and a total solution seems to rely on quitting tobacco usage.[20] Fluconazole and ketoconazole are the drugs of first choice.[5]

Median Rhomboid Glossitis (MRG)

It manifests with atrophy of the papillae in the middle part of the tongue. Applies to 0.01 %-1.00% of the community. This lesion is symmetrical in a rhombus shape.[19] Taking inhaled steroids and smoking may be possible causative factors of MRG.[20] A concerning lesion may appear on the palate. It may be a sign of immunosuppression which is called a "kissing lesion" and could be a marker of HIV, so further diagnostics should be done in this direction.[18,23]

Angular cheilitis (AC)

Also known as angular cheilosis, angular stomatitis, commissural stomatitis, rhades or perleche. This disease is defined as an inflammatory process localized in the commissure of the labia (in the corner of the lips) and has a varied etiology. This location is a transition zone between the facial squamous epithelium and the oral mucosa. It is a place that is mechanically more resistant and more adapted to movement and tensile forces than the other structures that make up the lips.[24] They usually appear bilaterally at the corners of the mouth and cause painful discomfort.[25]

It can be caused by a deficiency of B vitamins. An inadequate supply of zinc and iron can also affect the appearance of this fungal infection. Moreover, poorly fitting dentures or too much saliva production could be a cause of angular cheilitis.[26,27] As a result, the angles of the lips are exposed to various types of stress as well as chemical, environmental or infectious exposure. They are one of the body's first lines of defense and can reflect the internal state of the body.[24].

The immune system with low level of CD4+ T-lymphocytes have reduced cell-mediated and humoral immunity, what in turn leads to clinical oral manifestations and lesions, those can be serve as early indicators of HIV infection.[28] AC might be also associated with Sjögren's syndrome or Crohn's syndrome.[24] Microorganisms such as *Candida albicans*, *Staphylococcus spp.*, *Beta-hemolytic Streptococci*, *C. albicans* and *S. aureus* co-infection are the most common causes of AC (60-75%).[24,29]

AC has been added as a one of the diagnostic criteria for oral lesions in HIV-positive patients and is not observed routinely, but may be one of the indicator diseases.[29] One of the studies found that angular cheilitis and papular pruritic eruptions were external predictors of a CD4 cell count of less than 250 cells/mm3. Angular cheilitis, along with upper respiratory tract infection, are sensitive indicators of AIDS and can appear at cell levels below

350 cells/mm3.[30] In a Tanzanian study, it was found that the three above-mentioned symptoms- angular cheilitis, papular pruritic eruption and upper respiratory tract infections can improve the WHO classification regarding the stages of HIV infection and choose the right time to start treatment.[30]

Lowe et al.[31] in their study on the prevalence of dermal manifestations in adolescents HIV-positive, in hospitals in Zimbabwe, recurrent skin rashes and angular cheilitis were associated with high levels of immunosuppression. There was no other single skin lesion associated with CD4 cell count <200cells/µl, suggesting that the CD4+ cell count in adolescents (10 – 19 years) survivors of vertically acquired HIV infection is less correlated with clinical manifestations associated with immunosuppression compared to other age groups. In the HIV-positive group of teenagers, the occurrence of AC reached 39%, and in the HIV- group: 4%.

Linear Gingival Erythema (LGE)

Linear gingival erythema was included in the ECClearinghouse classification as clinical oral manifestation of HIV infection and can show disease advancement. There are also some cases reported in HIV-negative kids.[18,19,32] HIV-related periodontal diseases also include linear gingival erythema. Some studies have shown that the presence of linear gingival erythema is the only significant difference compared to the HIV+ and HIV- groups in terms of periodontal parameters.[33,34]

LGE belongs to the group of gingivitis and it is characterized by the presence of a fiery red, linear lesion 2-3 mm from the gingival margin often associated with petechiae or diffuse red lesions on the attached or free gum.[35–37] It most often occurs in the area of the anterior teeth, sometimes it is characterized by bleeding and discomfort.[35] It can be located near one or two teeth, but more often it covers the entire gingival margin.[36]

LGE microflora is similar to other periodontal diseases.[37] The influence and role of the presence of *Candida spp.* with the etiopathogenesis of this process and other pathological processes occurring in the periodontium in the course of HIV infection are found.[35] However, its exact etiology and pathogenesis are under consideration.[32] Initially it was considered to be HIV-associated gingivitis, but a correlation was also noted between LGE and *Candida spp*. colonies in the subgingival plaque. Hence, some authors formulate the conclusion that LGE is one of the variants of candidiasis and not a separate disease entity.[38]

The incidence ranges from 5.5% in HIV-positive children to 16.6-29.5% in HIV-positive adults, and its severity increases with decreasing immunocompetence and CD4 cell count.[39]

Patients with oral candidiasis are more likely to develop LGE.[33,39–41]

Polynuclear leukocytes and plasma cells are revealed by histopathological examination of a LGE slice. It is different in the case of gingivitis or SLE, where the infiltration is dominated by T-lymphocytes, and B-lymphocytes and macrophages are less noticeable.[39]

A study performed by *Sharm et al.*[42] in a HIV-infected population in southern India showed a trend inversely related to the number of CD4 cells with the incidence of LGE. Accordingly, in the case of the CD4 cell count above 500 cells/mm3, the presence of LGE was not found, in the group of people with the number of cells in the range of 201-500cells/mm3, 11.1% of the respondents had LGE, and in the group of people with the number of CD4 cells in the range of 0-200cells/mm3 the number of people with LGE was 12.9% of the group.

***Herpesviridae* virus infections**

HHV-1 and HHV-2

Oral infections caused by HSV-1 and HSV-2 (mostly by HSV-1) with recurring character are also type of lesion associated with HIV infection, however to a lesser extent than Kaposis's sarcoma.[43] Most common form to observe are herpes labialis and primary herpetic gingivostomatitis, which often go in pair with extraoral symptoms such as fever or cervical lymphadenopathy.[8,44] Lesions are noticeable during standard oral examination and take form of small ulcerations which can connect with themselves. Mostly located in the lip area and gingiva, they can cause strong pain for patients. One of the first indications of immunosuppression are persisting ulcers for more than 1 month. Those long lasting lesions can be associated with weight loss which is an effect of reduced intake of food caused by pain during consumption.[45]

HHV-3

Infection of HHV-3, also called varicella-zoster virus (VZV) can occur as a primary infection, called chicken pox and as a herpes zoster infection, caused by latent reinfection in favorable conditions for virus (such as immunodeficiency), which goes latent in human host's cells (harbored in trigeminal nerve – CN V).[14] Because of wide innervation of trigeminal nerve, multiple dermatomes can present lesions and get involved in infection. One of common symptoms (10-15% and over 50% for affected persons older than 60 years) for VZV infection is postherpetic neuralgia, which occurs as strong, one-sided pain of dermatomes innervated by CN V.[46]

HHV-8

HIV-associated oral malignancy which occurs with highest frequency is Kaposis's sarcoma. Caused by HHV-8, which goes by the name Kaposi sarcoma-associated virus, disease can be noticed in several parts of the mouth such as the palate and gingiva. On cellular level, infection causes endothelial cells to create neoplastic hyperproliferation.[47,48] The resulting changes in oral cavity present themselves as lesions which can have wide color range, from purple to yellow-brown and depending on advancement of AIDS can be plural and ulcerate.

Most common complications for Kaposis's sarcoma are hemorrhages with risk growing in proportion to size of lesion. Other complications can be bone pathologies leading to destruction of bone and periodontium, causing troubles in functionality and aesthetics of

stomatognathic system.[8] The most recent data from USA present a decreasing trend for risk of Kaposi's Sarcoma.[49] Based on information from Globocan 2020, published in 2021 World's incidence rate for year 2020 was 34270 cases with 15086 mortality, with most cases occurring in Southern and Eastern African countries.[50]

Ulcerative lesions

In many cases, oral ulcerative lesions are common manifestations of symptomatic and asymptomatic medical conditions. They could be categorized into various groups, such as acute, chronic and recurrent.[51] It is known that HIV-associated oral conditions may develop as specific and also non specific ulcers.

Considering the first group of those lesions there is various number of diseases such as necrotizing gingivitis (NG).[52] This ailment is examined as one of acute, specific and typical necrotizing periodontal conditions.[53] Necrotizing gingivitis could progress into necrotizing periodontitis (NP) and at later stages into necrotizing stomatitis (NS) or even into noma (cancrum oris). They are considered as different stages of one condition according to their clinical manifestation and etiology.[54] Necrotizing gingivitis appears without clinical attachment loss but mosty with necrosis of interdental papilla – its progression with attachment loss is being considered as necrotizing periodontitis. Moreover, gingival necrosis which spreads onto bone tissue is referred to be as necrotizing stomatitis.[55] All of those conditions have common etiology and those microbiota includes *Fusobacterium* spp., *Treponema* spp., *Selenomonas* spp. and *Prevotella intermedia*.[54,56] Clinically those conditions might manifest with gingival bleeding (provoked or spontaneous), presence of pseudomembranes, metallic taste in mouth, unpleasant smell, malaise, intense pain, lymphadenopathy and fever.[51,52,57] There are various factors which may predispose those conditions to occur, such as psychological stress, poor oral hygiene, poor sleep habits, tobacco smoking [4], diabetes, autoimmune conditions.[57] The most important component appears to be an immunosuppression – necrotizing periodontal diseases are considered as an indication of severe immunosuppression. Correlation between those conditions and CD4+ cell counts of less than 200 cells/mm^3 is also known. According to this informations development of oral ulcerative lesions may lead to habituate blood investigations in order to find it's cause.[58]

One of the cases shows the 44-year-old female who was unable to brush her teeth properly due to the fact that she felt pain in the upper and lower gums, bleeding was also present. Clinically there were ulcerations covering interdental papilla and in addition, badly necrosed marginal and attached gingiva in both arches. Patient's medical history did not show any present illnesses. The woman was advised for a blood test which revealed absolute CD4+ cells count at the level of 75 cells/mm^3. Due to this result, an ELISA test was performed to confirm HIV infection – it was positive and the patient started an antiretroviral therapy. This case reports that unidentified systemic illness may be diagnosed by the presence of oral ulcerative lesions, such as necrotizing periodontal diseases.[58,59]

Another case shows the 41-year-old HIV-infected male whose blood tests revealed absolute CD4+ cells level above 500 cells/mm^3. Patient had been receiving an antiretroviral therapy for 10 years and his response to the treatment was satisfactory. During a visit in the

clinic, the man complained about pain in the oral area, which was becoming worse, which led to hospital admission. His medical history did not show any new conditions. Taking risk factors into consideration – he had smoked cigarettes for 28 years, 1 pack a day and started a low-calorie diet two months before admission. Clinically the serious intraoral inflammation was spread from the soft palate to the throat and numerous ulcers were present on upper and lower gingiva along with pseudomembranes. Final examination using Gram staining showed microbiota closely related to necrotizing periodontal diseases. Adequate treatment was habituated. This case reports that even if absolute CD4+ cells level is within permissible limits during HIV infection, necrotizing periodontal diseases may also be the cause of patient's intraoral problems, especially if risk factors are present.[60,61]

Next case shows the 46-year-old HIV-infected male with numerous and painful gingival lesions along with ulcers. They were located on the upper labial mucosa along with necrosed marginal gingiva of the lower arch. Patient had been on the antiretroviral therapy since HIV infection was confirmed - 8 years ago - but 1 year before visiting the clinic he had stopped it and resumed 3 weeks before visit. His blood sample revealed absolute CD4+ cells at the level of 5 cells/mm^3 and neutrophil cells at the level of $0.29x10^9$ cells/dm^3 that indicated severe neutropenia, which is common in HIV infection.[62]

Necrotizing periodontal diseases are rarely common in HIV-positive subjects along with severe neutropenia, despite necrotizing periodontal diseases being common in HIV-positive subjects. Isolated severe neutropenia is considered as a risk factor for nonspecific oral ulcers.[63] The final diagnosis was made by analyzing microbiological and histopathological features because the treatment of HIV-associated neutropenic ulcers and HIV-positive nonspecific ulcers are different. To sum up this case, nonspecific oral ulcers in HIV-positive subjects with neutropenia was considered and treated as neutropenic ulcers.[52]

Although necrotizing gingivitis and necrotizing periodontitis are included in „*Group 1.* Lesions strongly associated with HIV infection" according to the Classification and diagnostic criteria for oral lesions in HIV infection, there are also other common conditions in remaining groups. Recurrent aphthous stomatitis is measured as idiopathic oral ulcerations, multiple or single painful lesions with various shapes. [64–66]

There are major aphthous stomatitis which reach above 10 mm, minor aphthous stomatitis which reach below 10 mm and herpetiform aphthous stomatitis which reach between 2-3 mm. Lesions are commonly surrounded with erythematous halo and contain gray or white pseudomembranes. Time of healing is much longer for the first type – they may last more than three weeks, opposite to the second type – they usually heal within 1 – 2 weeks.[65,67] Ulcers are commonly localized in buccal mucosa, tongue, mouth floor and labial mucosa. Severe immunosuppression is known to manifest as aphthous ulcerations, especially with absolute CD4+ cells at the level below 100 cells/mm^3.[66] There are various factors which predispose to this condition to occur, such as trauma, nutritional deficiency, drugs, fever syndromes and hematologic induced.[67]

Recurrent aphthous ulcers are included in „*Group 1.* Conditions commonly associated with pediatric HIV infection", in opposite to adults' classification – recurrent aphthous

stomatitis is included in „*Group 3*. Lesions seen in HIV infection" because this condition occurs more often among children. Ulceration not otherwise specified is included in „*Group 2.* Lesions less commonly associated with HIV infection".[64,68] It's etiology or pathomechanism remain unknown, so diagnosing this condition is based on exclusion of another causes of lesions.[64] Absolute CD4+ cells at the level below 100 cells/mm^3 is being associated with this ailment.[65]

All of ulcerative lesions during HIV/AIDS are multifactorial conditions - for example they can be linked with antiretroviral therapy.[69] Study shows that group of patients who got antiretroviral therapy has increased frequency of oral ulcers compared to group of patients who did not get any therapy. Recurrent oral conditions during therapy may suggest it's failure and might require immediate change.[70]

Group 1: lesions strongly associated with HIV infection	***Group 2: lesions less strongly associated with HIV infection***	***Group 3: lesions seen in HIV infection***
❖ Hairy leukoplakia ❖ Kaposi's sarcoma ❖ Periodontal disease • Necrotising (ulcerative) gingivitis • Necrotising (ulcerative) periodontitis • Linear gingival erythema ❖ Non-Hodgkin's lymphoma ❖ Candidosis • Erythematous • Pseudomembranous	❖ Bacterial infections • Mycobacterium tuberculosis • Mycobacterium avium intracellulare ❖ Salivary gland disease ❖ Ulceration not otherwise specified ❖ Thrombocytopenia purpura ❖ Melanotic hyperpigmentation ❖ Unilateral or bilateral swelling of major salivary glands ❖ Necrotising (ulcerative) stomatitis ❖ Dry mouth caused by decreased salivary flow rate ❖ Viral infections • Human papillomavirus (wart-like) lesions • Verruca vulgaris • Herpes zoster • Condyloma acuminatum • Varicella • Herpes simplex • Focal epithelial hyperplasia • Varicella zoster wirus	❖ Bacterial infections • Escherichia coli • Cat-scratch disease and epithelioid (bacillary) angiomatosis • Klebsiella pneumonia • Actinomyces israelii • Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis) ❖ Fungal infection other than candidiasis • Geotrichum candidum • Mucoraceae (mucormycosis zygomycocis) • Aspergillus flavus • Cryptococcus neoformans • Histoplasma capsulatum

Tab. 1 Consensus on classification of oral lesions associated with HIV.[43]

Xerostomia

In the course of HIV and other diseases related to the immune system (Sjorgen syndrome, rheumatoid arthritis, sarcoidosis), xerostomia can be observed in patients' oral cavity.[71] It is described as dry mouth or dryness of oral cavity and is caused by minimize saliva secretion or even complete deficiency of saliva.[72] Xerostomia can be divided into 2 types: true xerostomia *(xerostomia vera, primaria)*, based on malfunction on salivary glands which results in deteriorated secretion of saliva and pseudo xerostomia *(xerostomia spuria, symptomatica)*, which is based on subjective impression of oral dryness by patient and normal secretory function of salivary gland. Besides of discomfort associated with mouth dryness, xerostomia can be manifested by:

- problems with food ingestion, frequent consumption of fluids during meals
- *fetor ex ore,* [73]
- burning mouth syndrome (BMS), [74,75]
- the presence of “milky” saliva, [76]
- oral caries located at normally non-predisposed sites.

Exact etiopathogenesis of xerostomia in HIV-infected patients isn’t known, but there are mainly two theories, which are trying to explain impression of oral dryness.[77] First one tells that high level of HIV RNA contain in lymph nodes which are located directly in parotid glands during embryonic development and infection of HIV can spread into pulp gland and cause inflammation.[78–82] The other theory is based on increased infiltration of CD8+ lymphocyte into enclosed lymph nodes which can cause hyperplasia in parotid gland and will manifest as hypofunction or enlargement of parotid region.[83–86]

Human immunodeficiency virus is associated with inflammation and enlargement of the salivary gland which results in decreasing saliva secretion. During assessment of submandibular/sublingual saliva (SMSL) decreased level of unstimulated and citric acid-stimulated saliva secretion was observed.[87] Worth adding is that, both HAART (Highly active antiretroviral therapy) and non-HAART patients was examined with decreased level of saliva, which shows that antiretroviral therapy doesn’t cure symptoms of xerostomia and it should be specifically cured.[88]

Summary

Increase of HIV infection is observed for years, which may lead to increase in the number of immunocompromised patients and occuring specifical lesions in the oral cavity. Clinicians should keep in mind the oral manifestation of HIV infection, as they may diagnose patients with HIV infection. Moreover, diagnosed patients should be under the care of a doctor to control lesions in the oral cavity and treat them. Oral lesions may also be indicators of HIV infection. The most common oral diseases in HIV patients are hairy leukoplakia, Candida infections, Angular Cheilitis (AC), Linear Gingival Erythema (LGE), Herpesviridae virus infections (HHV-1, HHV-2, HHV-3, HHV-8), ulcerative lesions or xerostomia. All of them have specific clinical courses, described in this article and may be diagnosed in the doctor's office.

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