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Oral cavity diseases in HIV infected patients

Patrycja Łanowy*, Miłosz Bichalski, Jakub Dzindzio, Maria Blaszkowska, Jerzy Jaroszewicz

Department of Infectious Diseases and Hepatology in Bytom,
Medical University of Silesia in Katowice, Poland

*E-mail address: patrycjalanowy@gmail.com

ABSTRACT

Oral cavity lesions are amongst the earliest manifestations of HIV-infection. Thorough examination of oral cavity as well as awareness of associations between specific symptoms and HIV-infection can lead to early diagnosis of this life-long disease. Consequently, early diagnosis of HIV infection allows for prompt introduction of antiretroviral therapy allowing to improve patients' quality of life, their life expectancy but also reducing the risk of transmission. Therefore, raising awareness on oral cavity disorders suggestive of HIV-infection among general physicians and dentists is of a great importance. In this article we described the most common oral cavity manifestations associated with HIV infection including: oral candidiasis, hairy leukoplakia and Kaposi's sarcoma in detail.

***Keywords*:** HIV infection, oral lesions, HIV manifestation, AIDS, candidiasis, Kaposi's sarcoma, hairy leukoplakia

1. INTRODUCTION

It is estimated that over 35 million people all over the world are infected with HIV (Humman Immunodeficeincy Virus). Almost 1/3 of infected is not receiving antiretroviral treatment. Antiretroviral therapy is not only increasing life expectancy of HIV-infected but also reducing the risk of virus transmission. What is alarming – an estimated number of approximately 25% HIV-positive people are unaware of their infection [1-4]. HIV attacks the

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immune system - precisely cells with CD4 glycoprotein and chemokine CCR5 and CXCR receptors - lymphocytes T CD4+, monocytes, macrophages or dendritic cells in lymphoid germinal centers. Infection with HIV leads to apoptosis of the infected CD4+ cells. In the first stage of infection, it result in the decreasing number of those cells and most typical symptoms include lymphadenopathy, fever, diarrhea, pharyngitis and other illnesses (stage 1 of HIV infection). After that stage neutralizing antibodies appear - but due to the high number of somatic mutations of the virus they cannot completely eliminate it. Thanks to this process the number of T CD4+ cells partially recovers and the infection becomes latent and asymptomatic (stage 2). Unfortunately, the amount of T-cells CD4+ is gradually decreasing and as a consequence the immunodeficiency of the patient intensifies. Symptoms of immunodeficiency may be observed before the infection is diagnosed, so a manifestation of decreasing immunity can suggest urgent diagnostics. As the infection proceeds, due to the progressive impairment of the cellular response - many opportunistic infections and neoplasms appear (stage 3) [5,6].

Five clinical stages of HIV infection can be distinguished. Stage 0 is described as very early infection with HIV (indeterminate antibody, antigen/antibody, or nucleic acid test) with following seroconversion to anti-HIV positivity. Stages 1,2,3 are based on results of lymphocyte T CD4+ counts or diagnosis of opportunistic diseases. If the number of lymphocytes is not established an unknown stage is identified.

As it comes to the clinical characteristics of the above mentioned stages of the infection:

Stage 1 is acute HIV infection and may be manifested unspecific by flu-like symptoms and lymphadenopathy (acute retroviral diseases) appearing after about 2-4 weeks after infection.

Stage 2 appears as clinical latency also called chronic HIV infection – the infection is very often asymptomatic or some diseases may occur not necessarily typical for HIV.

Stage 3 is acquired immunodeficiency syndrome (AIDS). AIDS can be diagnosed when CD4+ T-lymphocyte number is below 200 cells/μL or when opportunistic HIV-associated illness appear [7,8].

Table 1. The most typical opportunistic illness [7].

Opportunistic diseases in AIDS
Candidiasis of bronchi and esophagus
Cryptococcosis, extrapulmonary
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV
Histoplasmosis
Kaposi's sarcoma
Lymphoma - Burkitt's
Lymphoma –immunoblastic
Lymphoma - primary of brain
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii pneumonia

2. ORAL LESIONS IN HIV INFECTION

One of the earliest and the most significant indicators of HIV infection are oral lesions [9]. According to *Mocoroft et al.* almost 40-60% patients in developed countries are diagnosed in late period of infection (so-called LP - late presentation). This patients are diagnosed with CD4+ lymphocytes <350 / mm^3 or diagnosed with AIDS within 6 months of HIV diagnosis. Treatment of LP is demanding – an anti-retroviral therapy (ART) commanded without delay may indicate severe intoxication or an immune reconstitution inflammatory syndrome. However, the patient may also benefit from the early beginning of therapy as faster recovery. Moreover, treatment of opportunistic diseases diagnosed in those patient is necessary. The LP is associated with high AIDS rate and mortality, during 2 years after diagnosis, in Europe. What is more – treatment costs of patients and risk of virus transmission are higher [10-12].

Early diagnostic of HIV infection is important to extend the life of the infected. Through the improvement of medical strategies in this area it is possible to detect the virus earlier, which results in prompt implementation of treatment, reduction of treatment costs, increasing of the safety of medical personnel or people in close contact with the patient [10,11,13,14].

Moreover, this process plays an essential role for physicians who if necessary should encourage patients to make appropriate tests. Therefore, medical professionals should be well aware of the early indicators of immunodeficiency or an HIV infection.

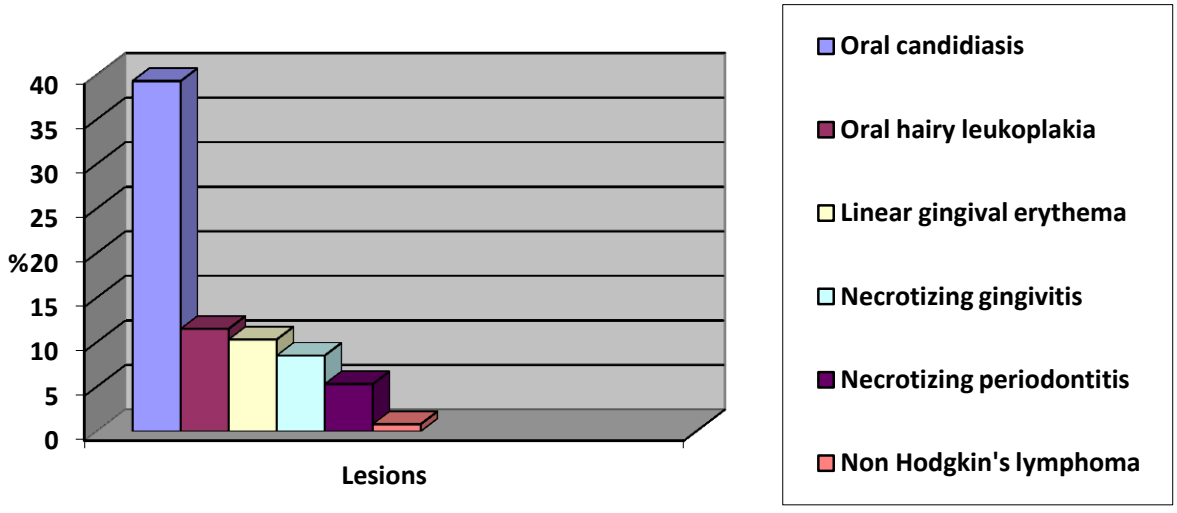

Figure 1. Prevalence of oral lesions in HIV-positive patients (n = 399) [15].

Manifestations in the oral cavity may be among the first sign of infection with HIV. Oral lesions related with the HIV infection can be important indicators of progression of the disease and are associated with decreasing number of CD4+ lymphocytes. The prevalence of oral lesions in the oral cavity increases as the number of CD4 + lymphocytes decreases. Frequency of the oral manifestations of HIV infection significantly increases, when CD4+ number is <200 cells/mm^3 and HIV-RNA >3000 copies/mL [16-18].

Table 2. Modified table presenting HIV-associated oral lesions divided into three groups (EEC Clearinghouse Criteria) created by *Bodhade et al.*, [15].

Group I: Lesions most commonly associated with HIV infections	Group II: Lesion less commonly associated with HIV infection	Group III: Lesions not associated with HIV infection
Oral candidiasis **Hairy leukoplakia** **Kaposi's sarcoma** **Linear gingival erythema** **Necrotizing ulcerative gingivitis/periodontitis** Non-Hodgkin lymphoma	Melanotic hyper pigmentation Ulcers not otherwise specified Herpes simplex virus infection Decreased salivary flow rate	Recurrent apthous ulcers Lichenoid reaction Facial palsy

In the following parts of the article some of the most prevalent oral cavity diseases in relation to the duration of the HIV-infection (also the decreasing count of lymphocytes CD4) will be described [15].

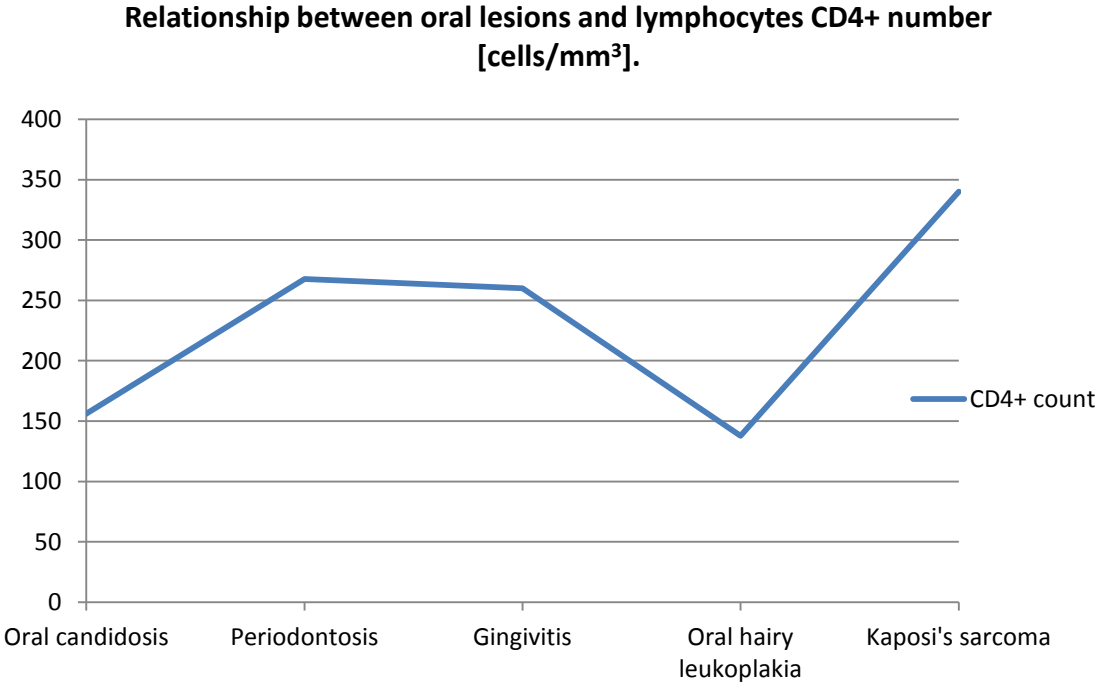

Figure 2. The association between CD4 T-cell count and oral lesions. Modified from *Frimpong et al.* [19, 20].

Table 3. Average count of CD4+ lymphocytes at the diagnosis of oral cavity disease [Modified form 19].

Oral lesion	Mean baseline of CD4+ (cells/mm^3) upon oral lesion presentation
Oral candidiasis	156.00
Periodontitis	267.71
Gingivitis	259.96
Oral hairy leukoplakia	137.80
Kaposi's sarcoma	340.00

2. 1. Periodontal diseases

HIV contributes to an increased incidence of periodontal diseases such as necrotizing ulcerative gingivitis and periodontitis, and linear erythema of the gums. Periodontal diseases usually appear when CD4+ count ranges from 200 to 500 cells/mm^3, on average when CD4+ count is 267.71 cells/mm^3 [19].

Jagganatha and *colleagues* show that over 36% of HIV-infected patients suffer from periodontal diseases. Many factors contribute to its occurrence, including immunological reactions towards plaque, but also poor hygiene, smoking, age and stage of the HIV infection [21-24]. It is suggested, that reduction of IL-17 and IL-22 production, as a result of the decreased number of lymphocytes caused by HIV infection, is responsible for an increase in the translocation of microorganisms in digestive system leading to exacerbate the inflammatory process. Gut-associated lymphoid tissue (GALT) is similar to the lymphoid tissue of the oral mucosa, so this can cause alike process in this tissue [54,26]. There is an increased oral colonization by Micrococcus sp. or Entameba gingivalis in HIV-infected patients. In contrast to healthy subjects in whom these species present commensalism in HIV-seropositive individuals they yield a pathogenic potential. The invasion of pathogenic bacteria and the periodontal disease itself manifests in deepening of the periodontal pocket, then loss of attachment which is a gateway to systemic infection [22,25,27]. This may consequently lead to bleeding or loosing teeth. What is more, necrotizing ulclerative periodontitis is indicative of severe immunodeficiency. In this illness gingival papillae may be ulcerated and there is a loss of soft and hard tissues. Treatment includes removing of necrotized tissues, rinses with 0.12% chlorhexidine gluconate, professional deliberating of tooth surfaces from calculus and appropriate antibiotic therapy. In HIV-positive cases ART is indispensable. If the patient feels pain, adequate analgesia is necessary [27].

2. 2. Candidiasis

Oral candidiasis usually appears when CD4+ count drops below 500cells/mm^3, however it is significantly more frequent with the decreased CD4+ count below 200 cells/mm^3. Statistically mean CD4+ count in patients in which it occurs is 156 cells/mm^3 [15,20].

Due to the increase of HIV infections the number of diagnosed oral candidiasis has grown. In the oral cavity Candida spp. occurs as a commensal, with most typical C. albicans and C. glabrata [28]. Those species of fungi cause infection, when their environmental conditions change for supporting their expansion. Immunodeficiency is one of those states [28,29]. *Mezenes and colleagues.*, showed that, except caries (which is also a common disease in healthy population), the most common lesion in the oral cavity during HIV infection is candidiasis, which affects 32% of the infected [16,28]. Candidiasis caused by C. albicans and C. glabrata may be among the first symptom of immunodeficiency [29,30]. Candidiasis development is enhanced by wearing a denture, smoking, endocrine disruptions, patients' age or cancer. What is more, risk factors for developing candidiasis also include: using drugs like antibiotics, corticosteroids, antidepressants or diet with a high carbohydrate content [31,32,33]. Furthermore, HIV infection may as well cause a dysfunction of salivary glandes which results in a reduction of the amount of secreted saliva. A great deal of HIV positive patients suffer from HIV-associated salivary gland disease (HIV-SGD) [34,35].

The composition of saliva also changes adversely - the secretion of lactoferrin and IgA decreases. These conditions combined with the overall immunodeficiency may promote the development of fungal infections such as candidiasis. Concerning further pathomechanisms of candidiasis progression in HIV-infected, *Mukerjee* and *colleagues.*, show that in the oral cavity of HIV infected patients the ratio of Candida spp. to Pichia spp. Increases. It is of importance since Pichia inhibits growth and reduces the virulence of Candida [36].

Oral candidiasis could be divided into four oral forms:

Pseudomembranous candidiasis appears on the mucosa, lesions are creamy, white and look like cottage cheese. After scraping erythematous surface shows up with sporadic bleeding. Lesions occur on the side parts of the tongue or palate, in the throat area, symptoms such as itching or burning are rare. This form of candidiasis often occurs in case of immunosuppression, especially in extreme cases. According to *Spalanzani et al.* as many as 50% of HIV infected patients, who suffer from candidiasis, manifest this form [28,31,37].

Acute erythematous candidiasis is usually linked with using broad-spectrum antibiotics. It presents as areas of erythema, mainly located on the palate and on the tongue. Chronic erythematous candidiasis commonly appears in HIV-positive patients, it includes atrophic lesions and often accompanies angular cheilitis. Erythematous form is usually associated with pain [28,38].

Occasionally, the linear gingival erythema appears (known as HIV-gingivitis). This disorder manifest as linear erythematous rim located on the marginal gingiva erythematous lesions. In this case typical antifugal treatment is not required, but therapy consists of mouthwash with 0.12% chlorchexidine solution (twice-daily) and professional tooth deliberating. [31,27].

The diagnosis of candidiasis can be confirmed by using microbiological methods - cultures and smears [33]. Microbiologists can identify the fungus species with appropriate tests which is of a great importance since recently much attention also has been driven to non-candida species that may cause oral candidiasis in HIV positive patients. [37].

In the case of HIV-infection the priority in curing of candidiasis is antiretroviral therapy Appropriately personalized anti-retroviral therapy (ART) is used in each case - independently of the stage of the disease and the amount of CD4+ lymphocytes. In this therapy seceral classes of anti-HIV drugs can be used, which include Nucleoside Reverse Transcriptase Inhibitors (NRTI), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI), Protease

Inhibitors (PI), Integrase Inhibitors (InI) and Entery/Fusion Inhibitors (FI) and Coreceptor CCR-5 Inhibitors. Recommended first-time treatment regimens contain two NRTIs in combination with: integrase inhibitor or NNRTI or PI boosted (bustated) ritonavir (RTV) / cobicistat (COBI). Aim of this treatment is to effectively inhibit the replication of the virus. ART treatment extends life expectancy and reduces risk of the virus transmission. Unfortunately Candidas' infection can occur in up to 1/3 of patients with advanced AIDS - even though they are ART treated - candidiasis remains a significant problem [34,36,39-41]

Due to etiology of infection using anti-fungal agents is also useful. The antifungal agents used in the treatment of candidiasis include polyethylenes and azoles. Polyethylenes, despite of their toxicity, are used in the treatment of chronic erythematous candidiasis. Preferred schedule of treatment of a oropharyngeal candidiasis is therapy lasting 7-14 days with Fluconazole 100 mg p.o once daily. Alternatively, with Ketoconazole troches 200 mg dosed p.o 2 times daily or with Itraconazole oral solution 200 mg dosed p.o daily. In HIV-positive patients with AIDS a suspension of amoftericin B is used in cases of resistant candidiasis. The azole agent, fluconazole is bacteriostatic and secreted in large quantities into the saliva, but in recent years Candida has been resistant to azoles [28,39,42-44]. In order to assist physicians, clinical microbiologists should identify the given species and their profile of resistance since more and more attention is paid on non-candida species which also cause oral candidiasis in HIV positive people [36]. Reduction of C. albicans prevalence can be achieved by simple methods such as improving oral hygiene, removing the prosthesis overnight, using appropriate mouthwashes containing triclosan, chlorhexidine or oil tetracycals such as eucalyptol or thymol [28,43].

2. 3. Hairy leukoplakia

Hairy leukoplakia (HL) is regarded as a lesion strongly associated with the HIV infection. It is a symptom of Epstein-Barr virus infection - almost exclusively in HIV positive people in advanced stage of the HIV-infection. Hairy leukoplakia is usually observed when CD4+ count drops below 500 cells/mm^3, the median count is 137,80 cells/mm^3 [19].

It is observed in maximally 50% of HIV-infected untreated people [45-47]. HL can also appear in other diseases connected with immunodeficiency such as: leukemia, multiple myeloma or other states of immunosuppression as a result of chemotherapy or intake of chronic systemic steroids [47,48].

HL lesions are usually asymptomatic, located bilaterally at the lateral parts of tongue, in the form of white, corrugated, flat or hairy patches that cannot be scratched [45,47,49,50]. Histology specimens show hyperkeratosis, acanthosis and intracellular edema, without inflammatory marks. The results of the clinical and histological examination were once sufficient to provide a diagnosis, but a similar histological picture may also occur in other lesions, therefore the diagnosis was extended with the detection of the EBV genetic material in epithelial cells. Nowadays, we determine hairy leukoplakia by detecting EBV in connective tissue [49-52]. The golden standard for the diagnosis of the EBV virus is nucleic acid hybridization (ISH), techniques such as electron microscopy, immunohistochemistry and polymerase chain reaction can also be used [49,53].

Hairy leukoplakia treatment is rarely necessary because it is often asymptomatic and there is a lack of malicious changes. Moreover, HL often vanishes during the antiretroviral treatment. In onerous hairy leukoplakia cases acyclovire and recently valacyclovir are used. [45,46,48].

2. 4. Kaposi's sarcoma

Kaposi's sarcoma (KS) is classified as a malignant neoplasm, it is caused by a herpesvirus - human herpes virus type 8 (HHV-8) also known as Kaposi's Sarcoma Herpesvirus (KSHV). Mean CD4+count for the development of Kaposi's sarcoma is 340 cells/mm^3. The range in which it appears is 90-455 cells/mm^3 [20].

The vast majority of people infected with HHV-8 do not develop KS - however, it may affect people infected with HIV. Co-infection with the cytomegalovirus (CMV), herpes simplex virus (HSV) or herpesvirus 6 (HHV-6) can lead to the reactivation of HHV-8. Aggression of variant of Kaposi's sarcoma associated with HIV (HIV-KS) is much higher than other types (other types: iatrogenic, endemic, classic) [54-56]. Kaposi's sarcoma occurs in the oral cavity in 22% of HIV-positive (HIV+) patients. In 71% HIV-infected with KS affecting different location, sooner or later it appears in the oral cavity [57,58]. Occupation of the mouth is associated with poor prognosis and unfortunately is quite common [54-56]. KS can occur at any stage of HIV infection, more often affects males than females, and its prevalence increases with decreasing number of CD4 + lymphocytes [59].

In the oral cavity this neoplasm usually affects the gingiva, the oropharynx, the hard palate, the dorsum of the tongue and the alveolar mucosa [54,59]. It appears as spots, plaques or tumors, and its color ranges from brown to red and purple. Moreover, patients are more often diagnosed with multifocal lesions than single ones. Diagnosis can by confirmed by performing a biopsy, which allows differentiate KS from other skin diseases like non-Hodgkin's lymphoma or angiomatosis [54,55,60].

Thanks to antiretroviral therapy, the risk of development KS during the patient's life, has significantly decreased, especially in countries where this therapy is easily available. It should be pointed out that HAART therapy does not directly affect the replication of the HHV-8 virus. The use of radio- and chemotherapy for HIV-related KS without antiretroviral treatment is associated with low survival, however, results of a number of studies show that chemotherapy with antiretroviral therapy gives favorable results in patients with Kaposi's sarcoma [61].

Gbabe and colleagues., studied the influence of various treatment regimens of KS, however, they did not prove any significant differences in the effects of treatment with different treatment regimens with chemotherapeutic agents such as liposomal doxorubicin, liposomal daunorubicin and paclitaxel. Cyclophosphamide, vincristine, doxorubicin or prednisolone are used in 4-6 cycles. [53,60].

3. CONCLUSIONS

Due to high prevalence of HIV worldwide and especially relatively low rate of diagnosis of this disease it is necessary to raise awareness of physicians on oral cavity lesions as potential first manifestation of HIV-infection. HIV infection has its natural course, lesions in the oral cavity occurring during the gradual destruction of the immune system, are its natural part. Due to the location, they may be quickly noticed and due the of unpleasant symptoms are quickly reported by patients.

Those lesions are easy available to examine during physical examination. It is of a great importance to suggest HIV-testing to all subjects presenting oral cavity diseases including oral candidiasis, Kaposi's sarcoma, hairy leukoplakia and other described in the manuscript.

Furthermore, prompt introduction of antiretroviral treatment and regular monitoring of oral cavity in HIV-subjects should significantly decrease the burden of oral cavity diseases in this population.

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