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Chapter 9

Oral Neoplasms in HIV Positive Patient

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Abstract

Acquired immune deficiency syndrome (AIDS) is a disease that manifests itself after the human body is infected with human immunodeficiency virus (HIV). The virus destroys defense cells (T-CD4 lymphocytes) and an important increase identifier of immunosuppression and/or failure to an immune response, the early signs often appear in the oral cavity in the form of various lesions. With the advent of HAART, it was also observed that it is accompanied by medium- and long-term side effects, mainly metabolic and bone changes. Other clinical manifestations that may occur are the human papillomavirus (HPV) infections in the oral cavity; HPV infections show exophytic growth and are often confluent, showing a "cauliflower" appearance and may or may not correspond to keratinized or non-keratinized tissues. In recent studies on papillomavirus, the literature indicates that HPV 16 and 18 are considered risk factors in the etiology of oral cancer development. Several neoplasias can occur in the oral cavity of patients with AIDS or HIV, and often the oral cavity is the place where we have the first manifestation of the disease, but multidisciplinary follow-up is necessary, so that the patient has care and a better quality of life.

Keywords: neoplasm, HIV positive, oral

1. Introduction

Acquired immunodeficiency syndrome (AIDS) was recognized in 1981 by the Centers for Disease Control (CDC) in Atlanta, USA because of an explosion of unexplained cases of Kaposi Sarcoma and Pneumonia by *Pneumocystis carinii*, which is currently called as *Pneumocystis jirovecii*, in men who have sex with men (MSM), mainly in two major centers,

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New York on the east coast and Los Angeles on the west coast of the USA. The first description of the clinical picture of AIDS was made by Gottlieb in Los Angeles and by Mansur in New York in 1981. In 1983 the HIV type 1 virus was discovered by Luc Montagnier at the Pasteur Institute in Paris and was identified later in 1984, as the etiological agent causing the disease, and in the same year, Robert Gallo in Bethesda (USA) established a cell culture system for the development and multiplication of HIV 1. In 1985, the laboratory test was started to prove the infection [1].

AIDS is a disease with a tendency to chronify, requiring follow-up, treatment and control. Acquired immunodeficiency syndrome (AIDS) is a disease that manifests itself after the human body is infected with the human immunodeficiency virus (HIV). This has received increased attention from researchers and health agencies because of its severity and seriousness. This is due to not only the mortality rate, but also the various economic, social and public health aspects associated with it. In order for the virus to reproduce, it must infect a cell, because viruses are not technically alive. As the human body is constantly producing new cells, each of them often makes new proteins to stay alive and reproduce [2, 3].

Since its clinical recognition in 1981, the human immunodeficiency virus and acquired immunodeficiency syndrome have been fatal even for people who administer highly potent antiretroviral therapy (HAART). In 1996, the "cocktail of drugs" = HAART was created. Currently, there are six groups of drugs that can be used in the treatment of HIV in individuals at the beginning of treatment or for those who have already started therapy, which is done by combining several drugs approved by the Brazilian Ministry of Health—Anvisa, belonging to six different classes, namely protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), fusion inhibitors (IF), integrase inhibitors (II), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and CCR5 antagonist [4–6].

1. Protease inhibitors
2. Nucleoside reverse transcriptase inhibitors (NRTIs)
3. Fusion inhibitors (IF)
4. Integrase inhibitors (II)
5. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
6. CCR5 antagonist

1. Protease inhibitors. Protease inhibitors prevent new HIV from maturing and infecting other cells. Protease is essential for the production of infectious and mature viral particles. It breaks new viral multi-proteins into individual (central) internal structural proteins, and the action of protease is a key step in structuring these proteins, which occurs for the virus to become infectious.

2. Nucleoside reverse transcriptase inhibitors (NRTIs). NRTIs called "nucleoside analogs" or "nuclear weapons" contain defective versions of the building blocks (nucleotides) used by

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reverse transcriptase to convert RNA to DNA. When reverse transcriptase uses these defective blocks, the new DNA cannot be properly constructed and the HIV genetic material cannot be incorporated into the healthy genetic material of the cell and prevents it from producing new viruses.

3. Fusion inhibitors (IF). Fusion inhibitors are a new type of compound that prevents the virus from binding to and entering human CD4 cells. They act at a stage in the life cycle of HIV, before the virus enters the cell, preventing the infection of new cells.

4. Integrase inhibitors (II). They prevent the insertion of HIV viral DNA into human DNA. It is a new mechanism of action, which inhibits the replication of the virus and its ability to infect new cells.

5. Non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs bind to the reverse transcriptase at a specific site; after being bound to the enzyme, NNRTIs affect the activity of the enzyme, restricting its mobility at a critical point and rendering it incapable of functioning. The enzyme is now unable to interact properly with the viral RNA to produce the viral DNA. The production of the latter is discontinued, although the virus is not killed.

6. CCR5 antagonist. CCR5 is a co-receptor of the HIV virus. In other words, is, the virus needs beyond the CD4 receptor, this co-receptor, or some other, to penetrate the cell. CCR5 means chemokine (C-C motif) receptor 5.

People live longer because of the beneficial effects of antiretroviral treatment, which most of the time interferes positively in people's lives, improving the quality of life of this population. However, the number of AIDS-related deaths has fallen by more than 10% in the last 5 years, as more people have gained access to treatment, saving many lives. The UNAIDS and the WHO estimate that since 1996, when antiretroviral treatment became available, about 2.9 million lives were saved. As the progression of the disease is evidenced by association with high levels of HIV'S RNA in the blood (viral load), one of the important goals of antiretroviral therapy is to reduce viral load. Opportunistic diseases in HIV patients and quality of life have changed since the introduction of HAART, resulting in a significant reduction in viral load (VL) and an increase in T-CD4 lymphocyte count. However, access to HAART is still uneven and may vary depending on the public interest policies of each country [7, 8].

According to the WHO, there are currently more than 42 million infected 20–60% of those infected may present oral manifestations. Epidemiology has been delineated since the onset of the syndrome, predominantly in MSM (men who have sex with men), later in HET (heterosexual), followed by female partners of these HET/MSM, and consequently covered women of childbearing age, with vertical transmission occurring to children infected with HIV and older people. There is currently a stabilization in cases of women of childbearing age, but there is a marked increase in cases of young people starting sexually (12–16 years) and an increase in cases in the elderly, who are over 60 years of age.

The risk of vertical transmission is 25–30%, depending on CD4, viral load, STDs, nutritional status and previous pregnancies. With the use of zidovudine (AZT) medication, the risk of vertical transmission dropped to 8%.

The risk of infection of the fetus is greater when, during pregnancy, the woman shows signs of AIDS or has recently been infected. The baby is born with the antibodies of the mother, and every child born to women with AIDS has tested positive for HIV, and only 18 months after birth, the child begins to produce its own antibodies. Subsequently, the serological test with positive result indicates that the child is HIV positive.

There are several symptoms related to HIV infection. Depending on the stage of infection, such as an acute infection, occurs approximately 2-6 weeks after exposure to the virus.

In general, the most common constitutional signs and symptoms are fever, lymphadenopathy, pharyngitis, exanthema (= Rash), papular papular erythema and mucocutaneous ulcers (mouth, esophagus and genital organs).

In acute infection, there is a violent replication of HIV in the body, and only when a viral load (quantity of virus per ml in the blood) is reached, the body reacts, causing that viral load to decrease to a certain level, thus generally remaining from 8 to 10 years, when the body start to lose their ability to respond. The immune window is the space where the body cannot identify HIV. Only after severe infection by HIV, the virus can be identified, thus forming antibodies that, even so, are unable to contain the advancement of infection. For a period between 3 weeks to 6 months, the blood does not have antibodies to HIV; this means that an anti-HIV serological test can give a false-negative result.

The objective of this review is to guide the dental surgeon in the diagnosis and treatment of oral neoplasms that are common in patients with HIV/AIDS.

2. Oral neoplasms

Oral alterations in HIV patients are vast, comprising more than 40 manifestations, which many times appear as the first manifestations of the disease, or even today, as an important identifier of therapeutic failure. Early diagnosis of oral lesions due to HIV infection is important to define the stage of the disease or indicate the possibility of HIV infection in undiagnosed individuals, since oral manifestations are usually the first signs of infection. Oral exams are an essential component for the early recognition of disease progression and overall assessment of HIV-infected patients [9, 10].

The evaluation by the dental professional should include resolution of emergency problems such as pain, abscesses, ulcerated lesions and other acute infections, guidance on local procedures, resolution of chronic problems and resolution of traditional treatment. HIV patients are afflicted with multiple diseases and are medicated with several different drugs. The patient's medical history should be carefully considered, and important aspects should be noted [11, 12].

3. Human papillomavirus

The human papillomavirus appears in the oral mucosa of the white, vegetative, proliferative lesion, a wartlike appearance, similar to cauliflower. And its etiology is by Human papillomavirus (HPV) infection. It is presented as synonymy: cock crest, crested alligator, venereal wart, vulgar verruca, genital wart, and condyloma acuminata. HPV has more than 200 subtypes: pairs 6, 7, 11, 13, 16, 18, 32 are responsible for vegetative lesions in the oral cavity. Subtypes 16 and 18 are most related to induction for the development of malignant neoplasms [13].

Viruses belong to the papoviridase family that penetrates by absorption into microtraumatized regions, being highly infective. They present a high recurrence rate, with a tendency to reinfection. Incubation is generally 1–8 months for the onset of the first lesion, the active phase depends on the immune response. In the late phase, it is 9 months/years [14].

The main co-factors for HPV are smoking, alcohol, stress, low immunity (HIV/AIDS), sexual promiscuity and hygiene.

Diagnosis may be clinical (noting formations known as condyloma and/or papilloma), or subclinical by histopathological study, and latent biomolecular analyzes by in situ hybridization or PCR techniques [15].

The incidence in general is usually from 10 to 25% in the oral cavity [16].

4. Kaposi's sarcoma

Kaposi's sarcoma (KS) was first described in 1872 by Moritz Kaposi as "pigmented idiopathic sarcoma of the skin" before the advent of the AIDS epidemic. Kaposi's sarcoma was classified as: classic KS, involving men of European origin, mainly residents of eastern Europe and the Mediterranean Sea, with a preferential location in the lower limbs; African endemic KS occurring in black and young men in equatorial Africa; SK iatrogenic, related to immunosuppressive therapy in transplanted patients. But this epidemiological profile is altered with the first reports of AIDS, because there was an explosion of cases of KS, which was then called epidemic KS [17].

SK is the most common neoplasm in patients with AIDS. The incidence has been declining from 40% at the beginning of the epidemic to less than 15% today. The reason for this is not fully known, but it may be related to the greater preventive care, effectiveness of highly potent antiretroviral therapies and earlier diagnoses, as well as safer sexual practices in the community of men who have sex with men [18].

In some regions of Africa, the incidence of KS in women is much higher, occurring in 40% of all KS cases related to HIV infection. In these patients, SK tends to be more indolent, with

a course similar to that observed in classic KS. The pathogenesis of KS is related to human herpes virus type 8 (HHV-8) or herpes virus associated with Kaposi's sarcoma (SK-HV). This virus is transmitted through sexual contact, which explains the prevalence in men who have sex with men in the US and in heterosexual women in Africa. The clinical characteristics are variable, usually beginning as erythematous, violet or brownish, asymptomatic macules that develop into papules, plaques, nodules or tumor lesions.

The manifestations of KS can compromise mucous membranes, such as the oral cavity and viscera, gastrointestinal tract, lungs and lymph nodes. Lesions in their evolution may grow, coalesce, form large plaques and envelop lymphatic vessels, leading to lymphoedema in the affected limb. KS can occur as the first manifestation of AIDS, concomitant with other manifestations or late in the course of the disease.

Initially they manifest themselves with enlarged and enlarged blood vessels in the dermis, with large endothelial cells, protruding into the lumen. There is perivascular infiltrate composed of lymphocytes, plasma cells and some macrophages, and groups of extravagant erythrocytes and hemosiderin deposits can be visualized. Several skin lesions, both inflammatory and neoplastic, should be included in the differential diagnosis: purpura, hemangiomas, bacillary angiomatosis, lichen planar dermatofibroma, pink pityriasis, fungal mycosis, nevi, malignant melanoma, cutaneous lymphoma and secondary syphilis were reported as SK simulators [19].

5. Non-Hodgkin lymphoma

Its etiology comes from the chronic stimulation of B cells and its incidence occurs with late manifestations, mainly located in the gingiva. For more than 30 years the relationship between immunodeficiency and non-Hodgkin's lymphoma is known, relating to AIDS. Non-Hodgkin's lymphoma is evidenced by polygamous hypergammaglobulinemia, cytokines, and growth factors: 11–6; 11–10. Since the beginning of the epidemic the CDC defines HIV+ patients with a diagnosis of non-Hodgkin's lymphoma as AIDS [17].

The diagnosis may be clinical, associated with biopsy, radiographs, CT scans, MRI [17].

6. Epidermal carcinoma

It is the most common malignant neoplasm of the oral cavity, corresponding to 95% of the tumors of the patients, of form. We highlight the growing prevalence of HIV/AIDS patients. According to the National Institute of Cancer (INCA)/Ministry of Health (MS), the estimate for 2018, regarding the number of cases of oral cancer in general in Brazil, is 14,700 new cases, considering the region as the seventh most frequently affected by malignant tumors in the Brazilian population.

Clinical features include ulcerated superficial, endophytic lesions (infiltrative ulcer and destructive ulcer), exophytic lesions (moriform vegetative, papilliferous vegetative and cauliflower vegetation), nodular (sub mucosa and deep) lesions. The most common clinical feature of squamous cell carcinoma is chronic ulcer. Due to this ulcerated clinical aspect, often granulomatous, we

must associate in the differential diagnosis ulcerated lesions of long duration of infectious diseases such as tuberculosis, syphilis, histoplasmosis and paracoccidioidomycosis [20, 21].

Its prevalence and incidence is greatest in individuals over 40 years of age, smokers and alcoholics. The male gender is more affected than the female in the proportion of 3:1.

7. Discussion and recommendations

The relationship of the dentist to the patient's physician should result in knowledge of modifying factors that may interfere with dental treatment. See **Table 1**, which highlights these factors.

7.1. Evaluation of medical factors modifying the dental treatment

Treatment of human papilloma virus can be surgical (incisional biopsy) or cryotherapy, high-power laser therapy (CO^2), topical application of 25% podophylline alcoholic solution, topical application of 90% trichloroacetic acid (ATA) or medications such as Wartec®-Podofilotoxin and Aldara® Cream-Imiquimod Gel [8, 13–15, 22].

In relation to Kaposi's sarcoma, the biopsy is predominant to establish the diagnosis. Treatment of KS includes antiretroviral drugs, since the lesions usually regress with improved immune compromise. Localized destructive treatments may be indicated for isolated or sporadic injuries, such as cryotherapy with liquid nitrogen. Radiation therapy is effective for painful lesions of palms and plants and when there is edema. Intralesional injection of vinblastine may be effective if the patient has few lesions, but the method is associated with pain caused by the injection. The combination of traditional chemotherapeutic agents, such as vinblastine, etoposide (VP-16) and adriamycin, produces regression of SK lesions, but these drugs are myelosuppressive and potentially immunosuppressive. Vincristine and bleomycin, non-myelotoxic drugs, can be used with good results. Interferon can be used both intralesional and systemically. Doxorubicin and liposomal daunorubicin are also effective [17–19].

Treatment of Non-Hodgkin lymphoma may be via prophylaxis with infiltration into the central nervous system of cytarabine or methotrexate medications. Also noteworthy is the study of the use of antiviral, and growth factors should be observed, and the administration of prophylaxis for the treatment of *Pneumocystis carinii* (*jirovecii*) should be considered [17].

Epidermal carcinoma shows the main locations are the lower lip, tongue border, floor of mouth and gum. There are important factors and determinants of risks such as: heredity, sex,

Hematological status	Neutrophils and granulocytes (<300 mm^3)
Coagulation—platelets	(Thrombocytopenia <15,000 mm^3)
Drug interactions	Adverse effects of HAART
Opportunistic diseases	Related to immunosuppression

Table 1. Medical factors modifying dental treatment.

age and race. The treatment protocols and procedures go through surgical removal, chemotherapy and radiotherapy [20, 21].

8. Conclusion

This study evidences the early diagnosis, aiming mainly to guide the dental surgeon, regarding the evaluation and conduct of oral neoplasias that commonly affect patients with alterations in the immune system by HIV/AIDS, seeking to improve the quality of life of immunocompromised patients. It indicates the continuous study and deepening of the knowledge of the etiology, diagnosis and new treatments for oral neoplastic changes.

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