

HIV: A Global Challenge and its Oral Manifestations: Review Article

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ABSTRACT

HIV is a devastating global challenge to the mankind. This paper discusses the importance of oral lesions as indicators of infection with human immune deficiency virus and as predictors of progression of HIV disease to Acquired Immuno Deficiency Syndrome (AIDS). Oral manifestations are the earliest and most important indicators of infection with HIV. The presence of oral lesions can have a significant impact on health related quality of life. It is important that all health care workers receive education and training on the importance of oral lesions in HIV and the use of oral lesions as surrogate markers of progression of the disease.

Key words: Global health issue, anti retroviral, opportunistic.

INTRODUCTION

The status of the Global HIV Epidemic

HIV remains a global health issue of unprecedented dimensions. Unknown 30 years ago, HIV has already caused an estimated 25 million deaths worldwide. The most recent international epidemiological data reveal some good news. In some countries in Asia, Latin America and sub – Saharan Africa, the annual number of new HIV infections is falling. The estimated rate of AIDS deaths has also declined, in part as a result of success in expanding access to antiretroviral drugs in resource-limited settings. Yet these favourable trends are not uniformly evident, either within or between regions, underscoring the need for more comprehensive progress in implementing effective policies and programmes(1).

Current Epidemiological Situation of HIV/AIDS in India

India had an estimated 1.9 – 2.9 million HIV positive persons in 2007, with an estimated adult HIV prevalence of 0.34% (0.25%-0.43%). As

the HIV prevalence among the high risk groups (HRG) is very high compared to that among the general population, India continues to be in the category of concentrated epidemic.

Acquired Immuno Deficiency Syndrome is a deadly disease caused by a Retro virus called Human Immuno Deficiency Virus which is a RNA virus and is characterized by chronic Immunosuppression along with development of opportunistic infections, secondary neoplasms and neurologic manifestations.

Oral Manifestations

HIV infected individuals constitute a special group of patients in dental and other professional hospitals. Many times, the patients are not aware of their HIV status, the oral cavity is an important source of diagnostic and prognostic information in patients with HIV/AIDS diseases. Therefore knowledge of HIV infection and its oral manifestation have become a critically important requirement for professionals responsible for oral health care delivery.

The oral lesion in HIV infection is of great significance because, they indicate HIV infection in previously undiagnosed cases, predict HIV disease progression, represent early clinical features of clinical AIDS, form determinants for anti retroviral therapy and opportunistic infection therapy. The presence of these lesions may be an early diagnostic indicator of immunodeficiency and HIV Infection, may change the classification of the stage of HIV infection, and is a predictor of the progression of the disease(2,3)

According to EC Clearinghouse(4) on Oral Problems Related to HIV infection, September 1992, The oral lesions due to HIV are grouped as below:

Group I Lesions strongly associated with HIV infection

1. Erythematous
2. Pseudomembranous
- Hairy leukoplakia
- Kaposi's sarcoma
- Non Hodgkin's lymphoma
- Periodontal diseases
 1. Linear gingival erythema
 2. Necrotizing (ulcerative) gingivitis
 3. Necrotizing (ulcerative) periodontitis

Group II Lesions less commonly associated with HIV infection

- Bacterial infections
1. Mycobacterium aviumintracellulare
 2. Mycobacterium tuberculosis
- Melanotic hyperpigmentation
- Necrotizing (ulcerative) stomatitis
- Salivary gland disease
1. Dry mouth due to decreased salivary flow rate
 2. Unilateral or bilateral swelling of major salivary gland
- Thrombocytopenic purpura
- Ulceration NOS (not otherwise specified)
- Viral infections
- Herpes simplex virus
- Human papilloma virus
1. Condylomaacuminatum
 2. Focal epithelial hyperplasia
 3. Verruca vulgaris
- Varicella zoster virus

Group III Lesions seen in HIV infection

- Bacterial infections
- Actinomycesisraelii
- Escherichia coli
- Klebsiellapneumoniae, Cat scratch disease
- Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis) Epitheloid (bacillary) angiomatosis, Fungal infections other than Candidiasis
- Cryptococcus neoformans
- Geotrichum
- Histoplasma capsulatum
- Mucormycosis
- Aspergillus flavus Neurologic disturbances
- Facial palsy
- Trigeminal neuralgia ,Recurrentaphthous stomatitis,
- Viral infections
- Cytomegalovirus
- Molluscum contagiosum

No particular oral lesion is distinctly associated with HIV infection. However, the presence of one or more lesions requires that HIV infection be considered as a possible underlying cause. oral lesions like such as oral candidiasis and oral hairy leukoplakia, are so strongly and prominently associated with HIV infection that they have been incorporated into the Centers for Disease Control and Prevention clinical classification of HIV disease (5).

Oral health is an important component of overall health status in HIV infection. Even common dental diseases such as caries and periodontal disease have greater impact on patients with HIV infection. Odontogenic pain and non-replacement of missing teeth may limit oral intake of food required for adequate nutrition. Many medications used to treat HIV infection and associated opportunistic infections contribute to increased numbers of caries as a result of decreased salivation and cariogenic fermentable carbohydrate substrates in the presence of several topical oral medications. Painful HIV-associated oral diseases such as necrotizing ulcerative periodontitis and stomatitis, major aphthous ulceration, candidiasis, and Kaposi's sarcoma impair ingestion of food and negatively impact on nutritional health. Therefore, it is essential that the physician and dentist, together, identify and

reduce risk factors for oral disease in the patient with HIV infection (6).

Fungal Infections

Candidiasis

The most common HIV-related oral lesion is candidiasis, predominantly due to *Candida albicans*. *Candida* is a normal commensal and can be isolated from 30–50% of the oral cavities of healthy adults, clinical oral candidiasis rarely occurs in healthy patients (7,8). The prominent finding is that, clinical oral candidiasis has been reported to occur in 17–43% of patients with HIV infection and in more than 90% of patients with AIDS (9,10). Based on clinical appearance, oral candidiasis can appear as one of four distinct clinical entities: erythematous or atrophic candidiasis, pseudomembranous candidiasis, hyperplastic or chronic candidiasis, and angular cheilitis. In all cases, the infection is superficial. While in most instances the clinical appearance is adequate to arrive at a diagnosis, simple exfoliative cytology will identify the characteristic budding yeast and hyphae.

Treatment of oral candidiasis is determined by the clinical type, distribution, and severity of infection (11). Topical treatment is effective for limited and accessible lesions. Clotrimazole troches, nystatin pastilles, and nystatin oral suspension are effective for mild-to-moderate erythematous and pseudomembranous candidiasis. Systemic treatment for oral candidiasis involves the use of imidazole (ketoconazole) and triazole (fluconazole and itraconazole) antifungal medications.

Deep Fungal Infections

Unlike the superficial infection of candidiasis, several systemic fungal infections can infrequently lead to single or multiple, deep oral lesions with the potential for considerable local tissue destruction. Cryptococcosis, histoplasmosis, aspergillosis, and mucormycosis are uncommon oral deep fungal infections which require histological diagnosis. Treatment typically requires the use of intravenous antifungal therapy with amphotericin B.

Viral Infections

Herpesvirus accounts for the majority of HIV-related oral viral infections, most frequently manifested either as recurrent oral herpes due to herpes simplex virus (HSV) or Epstein-Barr virus (EBV)-induced oral hairy leukoplakia (OHL) (12). Less commonly occurring viral infections involving the oral cavity include cytomegalovirus and human papilloma virus.

Herpes Simplex Virus

Intraoral herpes in healthy individuals results in multiple, small, shallow ulcers with irregular raised white borders. Small clusters and crops of lesions usually coalesce to form a larger ulcer, which heals uneventfully in 7–10 days. While the prevalence of seropositive HSV and the rate of reactivation is similar among both HIV-infected and non-infected populations, estimated to be 60% for those older than 30 years of age, recurrent intraoral HSV in patients with HIV infection often results in ulceration and pain of longer duration (13-16).

more common sites for the recurrent intraoral herpes are the poorly keratinized tissue like the buccal and labial mucosa. The pain associated with persistent herpetic ulceration can result in reduced oral intake of food and significant loss of body weight. Clinical diagnosis can be assisted by culture and examination of a cytologic smear for the virus. Culture results should be interpreted with caution due to the high HSV seropositivity and the potential for false negative results due to silent shedding of HSV(6).

Intraoral HSV infection responds well to systemic acyclovir, 2 grams given in divided doses daily. Recently, the incidence of acyclovir-resistant HSV has increased among patients with HIV infection. For most of these cases, oral famciclovir and valacyclovir and intravenous foscarnet alone or in combination are effective. Topical acyclovir is approved for genital HSV infections, but has been found to have little therapeutic effect for oral HSV (17,18).

Oral Hairy Leukoplakia (OHL)

Oral Hairy leukoplakia appears as an asymptomatic adherent white patch with vertical

corrugations, most commonly on the lateral borders of the tongue. This lesion has been observed in other immune deficiency states as well as in immunocompetent individuals (19,20). Oral hairy leukoplakia has been shown to be associated with a localized Epstein-Barr virus (EBV) infection and occurs most commonly in individuals whose CD4 lymphocyte count is less than 200/mm³ (21). While the diagnosis is most often clinical, histological inspection will reveal typical epithelial hyperplasia suggestive of EBV infection. Oral acyclovir (3,200 mg daily in divided doses), retinoids, topical podophyllum resin, and surgical excision are advocated in its management. In most cases, the lesion returns after initial therapy, thus requiring prophylactic treatment with acyclovir 200 mg daily (22-24).

Human Papilloma Virus (HPV)

Oral wart, is a focal epithelial and connective tissue hyperplasia, seen in some patients with HIV infection, caused by HPV. More than 50 strains of HPV are noted. The most common genotypes found in the mouth of patients with HIV infection are 2, 6, 11, 13, 16 and 32. Surgical removal, with or without intraoperative irrigation with podophyllum resin, is the treatment of choice.

Cytomegalovirus (CMV)

An uncommon cause of intraoral ulceration in patients with HIV disease, is the Cytomegalovirus. Such a lesion, in a HIV infected person, may represent an early sign of disseminated CMV infection (25). Disseminated CMV infection must be diagnosed as early as possible because of the serious nature of its sequelae, including retinitis and meningitis. A solitary, deep, chronic ulceration of the labial and buccal mucosa are its manifestation. Clinically, it is indistinguishable from other nonspecific ulcerations such as chronic HSV and major aphthous ulceration. Thus, biopsy and histological inspections are essential for definitive diagnosis. Ganciclovir is the drug of choice, now available in a tablet formulation. Many patients with a history of CMV are placed on a prophylactic regimen (1.0 g ganciclovir, 3 times daily with food)(6).

Bacterial Infections

The most common bacterial infections

affecting the oral cavity in HIV infected are linear erythematous gingivitis, necrotizing ulcerative periodontitis, and, much less commonly, bacillary epithelioid angiomatosis and syphilis. In the case of the periodontal infections, the bacterial flora is similar to that of a healthy individual with periodontal disease. Isolated cases of oral infection with *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Actinomyces israelii*, *Escherichia coli*, and *Mycobacterium avium-intracellulare* have been reported in patients with HIV infection.

Linear Gingival erythema

Linear gingival erythema appears as a distinct fiery red band along the margin of the gingiva. The amount of erythema is disproportionately intense for the amount of plaque seen. No ulceration is present and no evidence of pocketing or attachment loss (26). A fiery red, linear band 2 to 3 mm wide on the marginal gingiva accompanied by petechiae-like or diffuse red lesions on the attached gingiva and oral mucosa. The amount of erythema is disproportionately intense given the amount of plaque present. The erythema may be accompanied by bleeding during brushing and, in severe cases, by spontaneous bleeding. It is most notable on the buccal surfaces from cuspid to cuspid. Pain is rarely associated with linear gingival erythema (27). Unlike conventional gingivitis, the erythema often persists following simple dental prophylaxis. Oral rinsing with chlorhexidine gluconate 0.12% often reduces or eliminates the erythema and typically requires prophylactic use to avoid recurrence.

Necrotizing Ulcerative Periodontitis (NUP)

This unique periodontal lesion is characterized by generalized deep bone pain, significant erythema that is often associated with spontaneous bleeding, and rapidly progressive destruction of the periodontal attachment and bone. This painful bone and periodontal lesion adversely affects oral intake of food, resulting in significant and rapid weight loss. Because the periodontal microflora is no different from that seen in healthy patients, the lesion probably results from the altered immune response in HIV infection. More than 95% of patients with NUP have a CD4 lymphocyte count of less than 200/mm³ (28,29). Treatment consists of rinsing twice daily with chlorhexidine gluconate

0.12%, metronidazole (250 mg orally four times daily for 10 days) and periodontal debridement, which is performed after antibiotic therapy has been initiated. Within 36–48 hours of antibiotic therapy, relief of pain associated with NUP is obtained.

Neoplasms

Kaposi sarcoma

Kaposi's sarcoma is the most common intraoral malignancy associated with HIV infection. Recognition of the lesion is essential, since oral KS is often the first manifestation of the disease and is a diagnostic criterion for AIDS (5). The lesion may appear as a red-purple macule, an ulcer, or as a nodule or mass. Intraoral KS occurs on the heavily keratinized mucosa, the palate being the site in more than 90% of reported cases. However, lesions have also been reported on the gingivae, tongue, and buccal mucosa. Prophylaxis with foscarnet and ganciclovir, but not acyclovir, has been shown to reduce the incidence of KS in a large at-risk cohort (30).

Definitive diagnosis of KS requires histological examination. There is no cure for KS. Therapy for intraoral KS should be instituted at the earliest sign of the lesion, the goal being local control of the size and number of lesions. When only one or a few lesions exist and the lesions are small (<1 cm), intralesional chemotherapy with vinblastine sulfate (0.2–0.4 mg/ml per cm² of lesion) or sclerotherapy with 3% sodium tetradecyl sulfate (0.1–0.2 ml per cm² of lesion) is effective. Radiation therapy (800–2,000 cGy) is effective for larger or multiple lesions.

Non-Hodgkin's Lymphoma (NHL)

NHL is the most common lymphoma associated with HIV infection and is usually seen in late stages with CD4 lymphocyte counts of less than 100/mm³. It appears as a rapidly enlarging mass, less commonly as an ulcer or plaque, and most commonly on the palate or gingivae. NHL may be indistinguishable from masses caused by KS or other diseases in HIV-infected patients. Histological examination is essential for diagnosis and staging. Prognosis is poor, with mean survival time of less than one year, despite treatment with multi-drug chemotherapy (31)

Immune-Mediated Oral Lesion

The most common immune-mediated HIV-related oral disorder, is the major aphthous ulceration, with a prevalence of approximately 2–3% (32,33). The large solitary or multiple, chronic, deep, painful ulcerations of major aphthae appear identical to those in non-infected patients, but they often last much longer and are less responsive to therapy. Treatment is by a potent topical steroid such as clobetasol (0.05% ointment applied for 45 seconds 3 times daily) when the lesion is accessible or dexamethasone oral rinse (0.5 mg/5 ml dexamethasone elixir 3 times daily, rinse for 45 seconds and expectorate) when inaccessible. When multiple ulcers are present or response to topical treatment is incomplete, systemic glucocorticosteroid therapy is required (prednisone 1 mg/kg). Major aphthae are associated with advanced HIV infection (typically with CD4 lymphocyte counts of less than 50/mm³). Long-term use of systemic prednisone may lead to complications such as oral candidiasis, reactivation of tuberculosis. Therapeutic modalities such as dapsone 50–100 mg daily (34) and thalidomide 200 mg daily for 4 weeks (35) should be considered. When immunosuppressant or modulating drugs are used, concurrent antifungal medications such as fluconazole 100 mg tablet 1–2 daily, itraconazole 100 mg tablet 1–2 times daily, and antibacterial medications such as chlorhexidine gluconate oral rinse 0.12% 3 times daily, may be required to prevent superinfection or opportunistic overgrowth.

Significance of oral manifestations

Clinicians easily examine the mouth and pharynx and oral lesions are often clearly visible. The significance of these oral manifestations are:

- Indicate HIV infection .
- Predict progression.
- Entry or endpoints in therapy and vaccine trials.
- Determinants of anti- opportunistic infection and anti- HIV therapy.
- Used in staging and classification systems .

CONCLUSION

Oral manifestations seen in association with HIV disease are still quite prevalent and clinically significant. A thorough examination of the

oral cavity can easily detect most of the common lesions. An understanding of the recognition, significance, and treatment of said lesions by

primary health care providers is essential for the health and well-being of people living with HIV disease, in the present Indian scenario.

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