REVIEW

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Oral manifestation of opportunistic infection and HIV associated malignancy

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ABSTRACT

Oral manifestations of HIV are common and have been important in identification of patients harbouring the HIV virus and in predicting suppression of their immune system. Careful history taking and detailed examination of the patient's oral cavity are important parts of the physical examination. Many HIV-associated oral disorders occur early in HIV infection, not infrequently as the presenting sign or symptom. Thus, early detection of associated oral disease should, in many cases, result in earlier diagnosis of HIV infection. Likewise, awareness of the variety of oral disorders which can develop throughout the course of HIV infection, and coordination of healthcare services between physician and dentist, should improve overall health and comfort of the patient. Present review discusses common oral disorders associated with HIV infection.

Keywords: AIDS, HIV, Oral disorders

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Introduction:

Acquired immunodeficiency syndrome (AIDS) is an infectious disease caused by the HIV, and is characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasm and neurologic manifestations. The magnitude of this modern plague is truly staggering. India is one of those countries where the HIV epidemic is growing rapidly.[1] The estimated number of persons living with HIV worldwide in 2007 is now assumed to be 33.2 million [30.6–36.1 million], a reduction of 16% compared with the estimate published in 2006 (39.5 million [34.7–47.1 million]. In developing countries in 2007, an estimated 330,000 children younger than the 15 years of age died of AIDS, and more children younger than the age of 5 years die from AIDS now than from any other cause. HIV infection leading to AIDS has been a major cause of illness and death among children, teens, and young adults worldwide. In 2007 alone, 420,000 infants and children were newly infected with HIV in developing countries, more than 1,150 every day. An estimated 330,000 children died from HIV and AIDS during 2007, joining more than 4 million children already claimed by the epidemic.[2]

Dental expertise is necessary for proper management of oral complications in HIV infection or AIDS. Medical clinicians should be able to recognize HIV-associated oral disease and to provide appropriate care and referral.[3]

In developed countries, HIV disease progression is monitored by two key laboratory markers: CD4+ lymphocyte count and HIV viral load. Unfortunately, these tests are not readily available in many developing countries.[4] Reduction of circulating CD4 count is the main criteria for assessing the immunosuppression status in HIV-positive patients. The number of circulating CD4 cells ranges from 600 to 1600 cells/mm, but the initial signs of immunosuppression occur when CD4 count is lower than 500 cells/mm.[5]

The oral cavity is easily accessible to clinical examination & orofacial lesions associated with HIV infection may be used as clinical markers of HIV disease progression.[3] Oral manifestations are often among the first symptoms of HIV/AIDS and thus can be useful in early detection of the disease. Based on standard classification and diagnostic criteria, common HIV-associated oral disorders can be broadly classified into four categories by pathophysiological process: infection, neoplasm, immune-mediated & others.[6]

Common HIV-Associated Oral Disorder[7]

Infection:

Fungal: Candidiasis; Cryptococcus; Histoplasmosis; Aspergillosis.

Viral: Herpes simplex virus; Oral hairy leukoplakia (Epstein-Barr); Human papilloma virus; Cytomegalovirus.

Bacterial: Bacillary Epithelioid Angiomatosis (BEA); linear erythematous gingivitis; Necrotizing ulcerative periodontitis.

Neoplasm:

Kaposi's sarcoma.

Non-Hodgkin's lymphoma.

Immune-Mediated:

Major aphthous.

Necrotizing stomatitis.

Other:

Fungal: Xerostomia; Parotid disease.

Viral: Pain syndromes.

Bacterial: Nutritional.

Group 1 Lesions strongly associated with HIV infection
Candidiasis
Erythematous
Pseudomembranous
Hairy leukoplakia
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Periodontal disease
Linear gingival erythema
Necrotizing (ulcerative) gingivitis
Necrotizing (ulcerative) periodontitis
Group 2 Lesions less commonly associated with HIV infection
Bacterial infection
Mycobacterium avium-intercellulare
Mycobacterium tuberculosis
Melanotic hyperpigmentation
Necrotizing (ulcerative) stomatitis
Salivary gland disease
Dry mouth due to decreased salivary flow rate
Unilateral or bilateral swelling of major salivary glands
Thrombocytopenic purpura
Ulceration NOS (not otherwise specified)
Viral infection
Herpes simplex virus
Human papillomavirus (wart-like lesions)
Verruca vulgaris
Group 3 Lesions seen in HIV infection
Bacterial infections
Actinomyces israelii
Escherichia coli
Klebsiella pneumoniae
Cat-scratch disease
Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis)
Epithelioid (bacillary) angiomatosis
Fungal infection other than candidiasis
Cryptococcus neoformans
Geotricum candidum
Histoplasma capsulatum
Aspergillus flavus
Neurologic disturbances
Facial palsy
Trigeminal neuralgia
Recurrent aphthous stomatitis
Viral infections
Cytomegalovirus
Molluscum contaginosum

Table 1.Revised classification of oral lesions associated with HIV infection[8]

Clinical presentation

Infection:

Fungal infections

Candidiasis:

The most common HIV-related oral lesion is candidiasis, predominantly due to *Candida albicans*. While *Candida* can be isolated from 30–50% of the oral cavities of healthy adults, making it a constituent of the normal oral flora, clinical oral candidiasis rarely occurs in healthy patients. 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.[6]

1. Erythematous (atrophic) candidiasis appears clinically as multiple small or large patches, most often localized on the tongue and/or palate.

2. Pseudomembranous candidiasis (oral thrush) is characterized by the presence of multiple superficial, creamy white plaques that can be easily wiped off, revealing an erythematous base. They are usually located on the buccal mucosa, oropharynx, and/or dorsal surface of the tongue.[4]

3. Hyperplastic candidiasis is otherwise known as Canadidal leukoplakia. Hyperplastic candidiasis will be present as a white plaque that cannot be wiped away by the clinician. However, lesions should completely resolve with routine antifungal therapy. This variant is also sometimes termed "plaque-like candidiasis" or "nodular candidiasis". The most common site of involvement is the commisural region of the buccal mucosa, usually on both sides of the mouth.[9]

4. Angular cheilitis is erythema and/or fissuring and cracks of the corners of the mouth. Angular cheilitis can occur with or without the presence of erythematous candidiasis or pseudomembranous candidiasis.

5. Hyperplastic or chronic candidiasis presents as white non removable plaques over the mucosal surface; hence they cannot be scraped off.[10]

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 & Mucormycosis are uncommon oral deep fungal infections which require histologic diagnosis.[11]

Viral infections

Herpes simplex virus:

HSV infection appears as a crop of vesicles usually localized on the keratinized mucosa (hard palate, gingiva) and/or vermillion borders of the lips and perioral skin. The vesicles rupture and form irregular painful ulcers. They may interfere with mastication and swallowing, resulting in decreased oral intake and dehydration.[4]

Herpes Zoster:

In HIV/AIDS herpes zoster develops both in skin and oral mucosa with or without prodromal symptoms. Vesicles appear along the course of the nerve unilaterally and these vesicles are large, thick and

persist for long-time and rupture forming ulcerations, which take long-time to heal. The peculiarity of herpes zoster in HIV/AIDS is that the disease repeatedly occurs with prominent vesicles and prominent scars.[12]

Oral squamous papilloma:

Oral squamous papillomas may be found on the vermilion portion of the lips and any intraoral mucosal site, with a predilection for the hard and soft palate and the uvula. The latter three sites account for approximately one third of all lesions. The lesions generally measure less than 1 cm in range and appear as pink-to-white exophytic granular or cauliflower-like surface alterations. Patients who are HIV-positive often have multiple oral lesions. Malignant transformation of a papilloma is more common in the multiple-recurring type.[13]

Oral hairy leukoplakia:

Although originally postulated to be pathognomonic for HIV infection, this lesion has subsequently been reported in other immune deficiency states as well as in immunocompetent individuals. It appears as an asymptomatic adherent white patch with vertical corrugations, most commonly on the lateral borders of the tongue. It may infrequently be confused with hypertrophic candidiasis and is predominantly found in homosexual males. Oral hairy leukoplakia has since 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/mm^3. While the diagnosis is most often clinical, histological inspection will reveal typical epithelial hyperplasia suggestive of EBV infection. This asymptomatic lesion does not require treatment. However, for cosmetic purposes, some patients may request treatment. Oral acyclovir (3,200 mg daily in divided doses), topical podophyllum resin, retinoids, and surgical removal have all been reported as successful treatments. In most cases, the lesion returns after initial therapy, thus requiring prophylactic treatment with acyclovir 200 mg daily.[7]

Bacterial infections

Bacillary Epithelioid Angiomatosis(BEA) : This lesion appears to be unique to HIV infection and is often clinically indistinguishable from oral Kaposi's sarcoma (KS). Since both may present as an erythematous, soft tissue mass which may bleed upon gentle manipulation, biopsy and histological examination are required to distinguish bacillary epithelioid angiomatosis (BEA) from KS. The presumed etiological pathogen, Rochalimaea henselae, can be identified using Warthin–Starry staining. Both KS

and BEA are histologically characterized by atypical vascular channels, extravasated red blood cells, and inflammatory cells. However, prominent spindle cells and mitotic figures occur only in KS. Erythromycin is the treatment of choice for BEA.[10]

Linear gingival erythema:

HIV-associated gingivitis which is now known as Linear gingival erythema (LGE) happened to be the most frequent presentation of periodontal disease(16.6%), it is more common than HIV-associated periodontitis(11.7%).

Linear gingival erythema presents as a bright red line characterised by intense, asymptomatic erythema of the marginal gingiva not proportional to accumulated plaque present. This may progress to HIV associated periodontitis if not vigorously treated.[14]

Necrotizing ulcerative periodontitis:

Necrotizing ulcerative periodontitis (NUP) is escorted by bleeding, sharp pain, ulcerated gingival papillae, rapid and extensive soft tissue necrosis and advanced loss of periodontal attachment, frequently leading to bone exposure. Risk factors for periodontal disease in HIV-infected individuals besides the general factors of age, smoking, preexisting gingivitis, poor oral hygiene and poor diet, include counts of CD4 + cells viral load and specific species of microbiota.[15]

Neoplasm:

Kaposi's sarcoma:

Oral lesions have been reported in 33% to 71% of patients with KS. Oral lesions are the initial presentation of KS in 15% of patients. Lesions range from flat, red to violet papules to exophytic, ulcerative nodules. Lesions most commonly occur on the palate (53%), oropharynx (15%), and gingiva (11%), but may involve any part of the mucosal surface including the tongue, tonsillar pillars, floor of the mouth, pharynx, or trachea. Trauma during normal chewing may cause pain, bleeding, ulceration, and secondary infection. Bulky lesions may interfere with nutrition and speech.[16]

Non Hodgkin's lymphoma:

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 gingiva.

NHL may be indistinguishable from masses caused by Kaposi's sarcoma 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.[11]

Immune-Mediated:

Major aphthous:

They are the most common immune-mediated HIV-related oral disorder, with a prevalence of approximately 2–3%. These ulcers are either large solitary or multiple, chronic, deep, and painful often lasting much longer in the seronegative population and are less responsive to therapy. Treatment requires the use of a potent topical steroid such as clobetesol when the lesions are accessible or dexamethasone oral rinse when not accessible. Systemic glucocorticosteroid therapy may be required (prednisone 1 mg/kg) in the case of large multiple ulcers and those not responding to topical preparations.[10]

Necrotizing stomatitis:

Necrotising Stomatitis (NS) is an inflammatory disease of the mouth characterised by the destruction of epithelium, connective tissue and papillae. The disease may cause a loss of periodontal attachment and the destruction of bone, in advanced stages it may lead to cancrum oris. Signs and symptoms include, painful ulcers with necrotic base,

foul smell, halitosis, fever, associated inflamed and painful gingivae/oral mucosa, sequestrum formation and cervical lymphadenopathy. Patient experiences difficulty in eating and swallowing.[17]

Other:

Xerostomia:

Xerostomia is a common symptom of HIV-infected individuals and has many potential causes. The causes of xerostomia include HIV infection itself, therapeutic antiviral and antimicrobial drugs, prophylactic medications, antiretrovirals (such as didanosine), gamma globulin, or lymphocytic infiltration of the major salivary glands. Clinical features include dry mouth and severely reduced salivary flow rates. Reduced salivary flow results in a mucosa that is desiccated and is at higher risk for opportunistic infections such as candidiasis and increased caries. Xerostomia may appear with or without parotid swelling.[18]

Parotid disease

Parotid enlargement is commonly associated with HIV infection in children (10-30%), and less commonly in adults. It has been shown to occur in the late course of HIV infection and to be associated with a slower rate of HIV disease progression. The median time from its diagnosis to death has been reported to be 5.4 years among HIV-infected children. Lymphocytic infiltration of the salivary glands may be an etiologic factor. Parotid enlargement occurs as unilateral or

bilateral swelling of the parotid glands. It is usually asymptomatic but may be accompanied by decreased salivary flow (xerostomia).[19]

Pain syndromes

Pain is a common symptom experienced by patients with HIV infection. Pain may result from a wide variety of disease processes, including direct effects of HIV on the central or peripheral nervous system, infection, malignancy, and antiretroviral therapy. Headache is a common symptom, occurring in approximately 46% of patients with HIV infection and accounting for approximately 17% of all pains in patients with HIV infection. Neuropathic pain is common among patients with HIV infection (19%), the most common diagnosis being painful peripheral sensory neuropathy.[11]

Laboratory diagnosis in HIV

It is well established now that 20-80% of the people in different parts of the world who have HIV infection do not know their HIV status. It is therefore important to make use of every opportunity to offer to test people who are unaware of their status.[20] Current routine laboratory diagnosis of HIV infection is mainly based on the detection of specific anti-HIV antibodies. Antibodies to HIV usually begin to be detectable 3 to 6 weeks (on average 22 days) after infection. The time from infection to first reactivity of screening tests (seroconversion) is called the "window period". During this period, the patient is highly infectious but the antibody test is negative.[21] Although many tests can be used to detect virus in general.[22] (Table 2.)

THE CDC RECOMMENDATIONS

The essential elements of the 2006 CDC Revised Recommendations for HIV Testing are:

1. All patients ages 13−64 years should be screened for HIV, in all medical settings, without regard to risk.
2. Separate written consent for HIV testing should not be required.
3. HIV prevention counseling should not be a prerequisite for HIV testing.

SEROLOGICAL TESTS (Indirect)	Alternative Antibody Testing Technologies	Viral Identification Assays (Direct)
1) HIV -1 antibody Screening assays **a) ELISA** **b) Home access (HIV -1 test system/ dried blood spot)** **c) Rapid tests** **d) Rapid latex agglutination assay** **e) Dot immunobinding and**	1. Oral fluid 2. Urine	1. DNA PCR 2. Plasma HIV RNA Assays 3. Viral culture 4. p24 antigen assay

other assays		
2) HIV-1 confirmatory Antibody assays a) Western blot b) Indirect immunofluorescence c) Radioimmunoprecipitation assay d) Line immunoassay		
HIV-2 Tests		
Monitoring tests		
Lymphocyte analysis	Viral load assay	Drug resistance tests
	1. Reverse transcriptase Polymerase Chain Reaction (RT-PCR) 2. Branched DNA assay (bDNA) 3. Nucleic acid sequence based assay – (NASBA)	1.Genotyping 2.Phenotyping

Table 2. Diagnostic and monitoring tests for HIV[22]

Treatment for HIV

All adults with HIV infection should be offered Antiretroviral treatment(ART) regardless of CD4 cell count. Based on recent observational cohort data all patients may benefit from Antiretroviral treatment and data from a randomized controlled trial showed that ART reduces the likelihood of HIV transmission while providing clinical benefit to treated individuals. When prescribing ART, the following should be considered: (1) a patient must be ready and willing to adhere to ART, and adherence education and support should be offered; (2) the benefit of ART is unknown in elite controllers (HIV-1 RNA below the level of quantification without ART) and long-term nonprogressors (those with stable CD4 cell counts >500/μL and HIV-1 RNA <1000 copies/mL while not taking ART); (3) the benefit of ART in asymptomatic acute HIV infection is not as well studied as in symptomatic acute HIV infection; and (4) there is no CD4 cell count threshold at which starting therapy is contraindicated, but the strength of the recommendation and the quality of the evidence supporting initiation of therapy increase as the CD4 cell count decreases and when certain concurrent conditions are present.[24]

Table 3. The Key Elements in Comprehensive HIV Prevention (WHO/UNAIDS, 2003)[25]

- **AIDS education and awareness**
- **Behavior change programs, particularly for young people and populations at higher risk of HIV exposure, as well as for people living with HIV**
- **Promoting male and female condoms as a protective option along with abstinence, fidelity, and reducing the number of sexual partners**
- **Voluntary counseling and testing**
- **Preventing and treating sexually**

transmitted infections

- Primary prevention among pregnant women, and prevention of mother-to-child transmission
- Harm-reduction programs for injecting drug users (AQ)
- Measures to protect blood supply safety
- Community education and changes in laws and policies to counter stigma and discrimination

Discussion

At least 90% of HIV-infected patients will have at least one oral manifestation at some time during the course of their disease. Oral lesions might herald underlying immunodeficiency.[12] Oral manifestations not only have a role as a diagnostic tool in newly infected cases, but may also play a part in monitoring disease progression.[8] Even in seropositive cases few patients have oral manifestations.[12] Candidiasis involving the oral cavity is rare in immunocompetent patients; however, it is a common feature of HIV infection and occurs in as many as 75% of infected patients.[6] Angular chelitis and hairy leukoplakia also occur more.[12] HIV-associated KS has an unpredictable course that ranges from a small number of stable lesions to explosive progression of disease activity.[16] Many studies have confirmed that the risk for oral complications increases as the level of immunodeficiency rises.[6]

Various confirmatory tests such as western blot test, indirect immunofluorescence assay, radio immunoprecipitation assay and assays using recombinant antigens are available. Among these supplemental tests, the western blot is the most informative and it is the current "gold standard" for confirmation of HIV serological assays. CD4 cell enumeration and HIV-1 antigen capture assay are useful in predicting the course of HIV-1 infection and in monitoring anti retroviral therapies.[22]

Antiretroviral therapy have resulted in dramatically reduced numbers of opportunistic diseases and deaths where ART is accessible. New data show that viral suppression due to ART results in decreased human immunodeficiency virus (HIV) transmission on individual and population levels and that, when used consistently by HIV-uninfected persons, ART also may provide protection against HIV infection.[24]

The WHO Global Oral Health Program, in collaboration with other WHO technical programs and WHO Collaborating Centres in Oral Health, will facilitate and coordinate the expansion of successful initiatives through technical and managerial support. Such activities may

focus on WHO technical support of meetings, at regional or interregional levels, aimed at sharing country experiences in monitoring HIV/AIDS prevention and lifestyle modification through campaigns and community programs assistance to countries in their efforts to develop oral health systems that incorporate oral health care, health promotion, and oral disease prevention aimed at disadvantaged people infected with HIV.[25]

Conclusion

Oral conditions seen in association with HIV disease are clinically significant and prevalent component of this disease complex. Each lesion has got its own characteristic as diagnostic features. Careful examination of oral cavity will help to detect these oral manifestations so as a clinician can diagnose HIV at an early stage. An understanding of the recognition, significance, and treatment of said lesions by primary healthcare providers is essential for the health and well-being of people living with HIV disease.

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