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HIV and It's Periodontal Sequele: Review

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Abstract
HIV (Human immunodeficiency virus) the virus that causes AIDS (acquired immunodeficiency syndrome), is one among the world's serious health problem. Human immunodeficiency virus (HIV) is a member of the lentivirus family, a subgroup of retroviruses. HIV encompasses a robust affinity for cells of the immune system. Patients with AIDS might develop serious oral and periodontal conditions, sometimes they are the primary symptoms to develop and different times they indicate a modification within the disease's progress, so it's vital for HIV-positive patients to take care of their oral hygiene and receive regular dental care. Dentists can play a significant role in diagnosing and management of oral conditions associated with AIDS. This review aims to supply insights relating to HIV associated periodontal lesions their prevalence, clinical features and management ways.

Keywords: HIV, AIDS, Periodontium, immune system

1. Introduction
HIV infection still remains a major global medical problem. It is estimated that approximately 37.9 million people are currently living with HIV, and tens of millions of people have died of AIDS-related causes since the beginning of the epidemic [1]. But the proportion of individuals living with HIV has stabilised since 2000, the range of individuals living with HIV has shown steady rise, as new infections occur annually. HIV management protocols have extended life and additionally, new infections still overcome total AIDS deaths [2].
The earliest case of HIV was from the Democratic Republic of Congo in 1931 transmitted from chimpanzee to humans. Robert Rayford, a 16 year-old was the earliest case in North America. It was initially believed certain people which included hemophiliacs, homosexual men, heroin users, haitians or people of Haitian origin were at high risk of getting infected HIV [3]. Nowadays sexual activity and drug abuse are considered to be common modes of transmission [4].
According to WHO statistics 0.8% of adults of age group of 15–49 years worldwide are living with HIV. African region has shown to have maximum population to be infected with HIV with nearly 1 in every 25 adults (3.9%) having HIV and it contributes for more than two-thirds of the people living with HIV worldwide [5]. India is considered third most country affected by HIV. In India as per 2017 statistics 2.1 million people are still living with HIV [6].
HIV-1 and HIV-2 are the two main types of HIV. HIV-1 contributes for around 95% of all infections worldwide. HIV-2 virus is generally present in West Africa. HIV-1 shows presence of four subgroups - M, N. O, P., M is the 'major' group and is responsible for the majority of the global HIV cases [7].
AIDS [acquired immunodeficiency syndrome]- is the final and most serious stage of HIV disease, which causes severe damage to the immune system. The Centers for Disease Control has defined AIDS as beginning when a person with HIV infection has a CD4 cell (also called "T-cell", a type of immune cell) count below 200 cells per cubic millimeter of blood. It is also defined by numerous opportunistic infections and cancers that occur in the presence of HIV infection [8].
Periodontal diseases are caused by specific groups of microflora and host immune response plays vital role in initiation of the disease [9]. As HIV directly affects the immune system the

periodontal lesions can manifests in the form of linear gingival erythema, necrotizing ulcerative gingivitis, and necrotizing ulcerative periodontitis and oral lesions include oral hairy leukoplakia, Kaposi's sarcoma, non-Hodgkin's lymphoma [10, 11].

2. Prevalence of Periodontal Diseases in HIV Patients

Introduction of HAART therapy has led to significant dip in the oral lesions. From 47-85% (pre HAART era) it has significantly decreased to 32-56% (post HAART era). HIV associated periodontal lesions showed prevalence rates of between 9 and 50% for linear gingival erythema, for necrotizing ulcerative gingivitis between 11 and 25% and for necrotizing ulcerative periodontitis between 1 and 18% in pre HAART era [2].

3. Pathogenicity of HIV in Periodontal Diseases

The mechanism by which HIV interacts with oral environment and how it alters the host immune response is still not clearly understood. But in general subgingival oral microflora plays an important role in activation of the inflammatory response which releases various inflammatory mediators like interleukin-1 – IL-1, tumour necrosis factor-α – TNF-α, nuclear factor-kappa B – NF-κB, interferon gamma which causes destruction of periodontal tissues [12]. Alpagot *et al.* (2003) showed presence of high levels of inflammatory cytokine interferon-gamma in GCF of HIV infected patients [13] and also significant levels of prostaglandin E2 (PGE2) transforming growth factor-beta (TGFb1), matrix metalloproteinase -1 (MMP-1)were also found in gingival crevicular fluid (GCF) of periodontitis sites in HIV/ AIDS [14]. This can serve as prognostic markers for periodontal destruction in HIV patients.

4. Bacteriology associated with periodontal diseases in HIV patients

Periodontal diseases are result of complex interaction between host immune response and the oral microbiota. In pre HAART period many microbiological studies have shown high levels of periodontal pathogens i.e Porphyromonas gingivalis, Aggregatibacter actinomycetemcommitans, Prevotella intermedia, and Eikenella corrodens in HIV infected individuals [15]. Certain opportunistic microorganisms like Candida spp,Enterobacter faecalis Clostridium clostridiiforme, Clostridium difficile, Klebsiella, Mycoplasma salivarium has showed high rates of prevalence due immunocompromised status of HIV individuals [16, 17, 18, 19]. Species like Veillonella parvula, Prevotella pallens, Campylobacter rectus, Campylobacter concisus and Megasphaera micronuciform were found in tongue biofilm, which may be associated in HIV infected subjects [20].

5. Periodontal Manifestations of HIV

The first link between periodontal diseases and HIV was established in 1985 by Dennison *et al.* [21].

In 1992 Winkler *et al* in their review reported clinical and microbiological features of forms of periodontal diseases associated with HIV [22].

A comprehensive classification of HIV related oral lesions was given in 1993 by EC-Clearinghouse in which periodontal diseases associated with HIV was classified as: [23]

1. Linear gingivitis erythema (LGE),
2. Necrotizing ulcerative gingivitis (NUG)
3. Necrotizing ulcerative periodontitis (NUP)

6. Linear Gingivitis Erythema

Linear gingivitis erythema was formerly termed as HIV associated gingivitis. The clinical presentation was described as erythema of the gingival margin with intensely red linear band that extends 2 to 3 mm apically from the gingival margin. It was also characterized by punctate or speckled areas of erythema may involving attached gingiva, gingival margin and alveolar mucosa which is associated with bleeding on probing [Fig:1]. Pain was present frequently but was not a consistent finding [23] According EC-Clearinghouse in 1991 there was no evidence of pocket formation and attachment loss [24].

An Immunohistochemical study carried out by R.S Gomez *et al* showed high percentage of neutrophils and IgG (plasma cell's secretors of IgG) in oral epithelium of the patients with HIV associated gingivitis suggestive of increased tissue inflammation [25].

One of the earliest study done by Murray *et al* showed that bacterial microbiota of LGE is similar to chronic periodontitis but candida albicans was found in higher proportion in almost 50% sites [15]. Later in 1994 LGE was classified under gingival disease of fungal origin [26]. Saccharomyces cerevisiae and C. dubliniensis are other fungal species strongly associated with LGE [27, 28].

Certain lesions can show similar clinical presentation as LGE i.e [29]:

1. Conventional chronic gingivitis
2. Oral lichen planus
3. Mucous membrane pemphigoid
4. Gingivitis like changes due to thrombocytopenia

6.1 Treatment for Linear Gingival Erythema

LGE may not respond to the conventional periodontal therapy as the primary etiological factor is of fungal origin [30]. Treatment protocol includes oral hygiene instructions and supragingival debridement with 0.12 chlorhexidine gluconate antimicrobial mouth rinse twice daily. If lesion doesn't subside topical anti-fungal medications can be given [31].

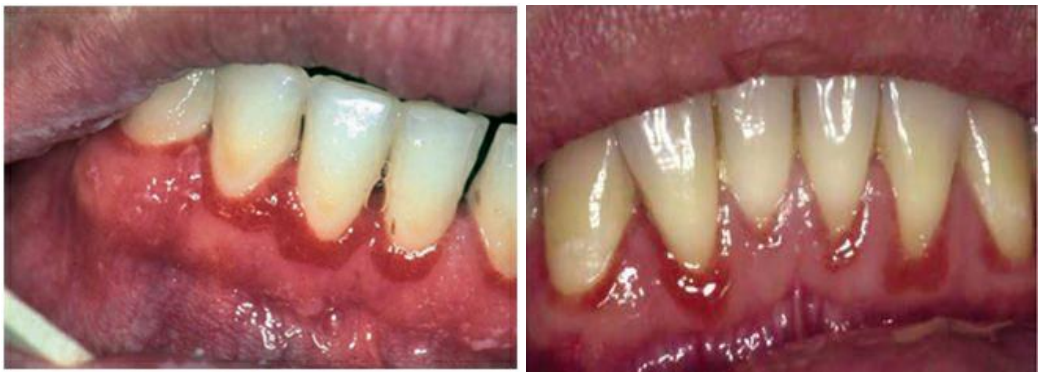

Fig 1: Linear gingival erythema

7. Necrotizing Ulcerative Gingivitis (NUG)

Necrotizing Ulcerative Gingivitis (NUG) is an infection characterized by gingival necrosis presenting as "punched out" papillae, with gingival bleeding and pain [32]. It is also called as Vincent's disease, fusospirochetal gingivitis and trench mouth [33]. It is also characterized by fetid breath, yellowish-white or greyish slough "pseudomembrane" covering ulcerated papilla which can be counted as secondary features. Rapid attachment loss and subsequent exposure of the bone have also been noticed. In some cases, the lesions are denuded of the surface pseudomembrane, thereby exposing the gingival margin, which is red, shiny, and haemorrhagic [Fig: 2]. Extra oral signs include lymphadenopathy, fever and malaise [34] HIV patients show peculiar ulcerated and necrotic interdental papillae with spontaneous haemorrhage and characteristic fetor accompanied by severe pain [35].

Bacteria involved in NUG include opportunistic bacteria like fusiform and spirochetes. Majority of Gram negative bacteria, including Bacteroides intermedius and Fusobacterium species are associated species with NUG [36]. Other microbiota are Treponema spp., Selenomonas spp., Fusobacterium spp., and Prevotella intermedia [37].

Histologically NUG shows presence of gingival ulcerous region with fibrin deposition and neutrophil infiltration on the surface. Congested blood vessels and neutrophil infiltration also were observed in the connective tissue beneath the ulcerous region. Many microorganisms, fibrin, cell debris, and enlarged intercellular spaces of the epithelium were seen on the surface on the ulcerous region [38].

Investigations to diagnose NUG should include thorough medical and dental history, nutritional regime. Extra oral examination should include examination of lymph nodes of the head and neck for lymphadenopathy and clinical features of NUG should be identified for intra-oral examination [34].

Differential Diagnosis Includes [34]:

1. Neutropenic mucositis
2. HSV gingivostomatitis
3. HIV-associated periodontitis and invasive fungal disease.
4. Desquamative gingivitis
5. Multiforme erythema
6. Pemphigus vulgaris

7.1 Treatment for necrotizing ulcerative gingivitis

Treatment of NUG is done in various phases. The first phase (acute phase) should include non-surgical therapy like thorough gentle debridement and ultrasonic scaling to remove plaque and calculus [37]. Mechanical oral hygiene care should be restricted for this phase, as tooth brushing would delay healing and cause pain. Instead, the use of chemical plaque-control formulations, for example 0.12% to 0.2% chlorhexidine-based mouth rinse or mouthwash such as warm water mixed with 3% hydrogen peroxide solution, is recommended [39]. Systemic antibiotics (like amoxicillin or metronidazole) are prescribed for patients with moderate to severe tissue destruction, localized lymphadenopathy or systemic or both. After the acute phase treatment the treatment for pre existing condition like chronic gingivitis and periodontitis should be initiated and if required gingivoplasty or gingivectomy procedures should be carried out for interdental craters [35].

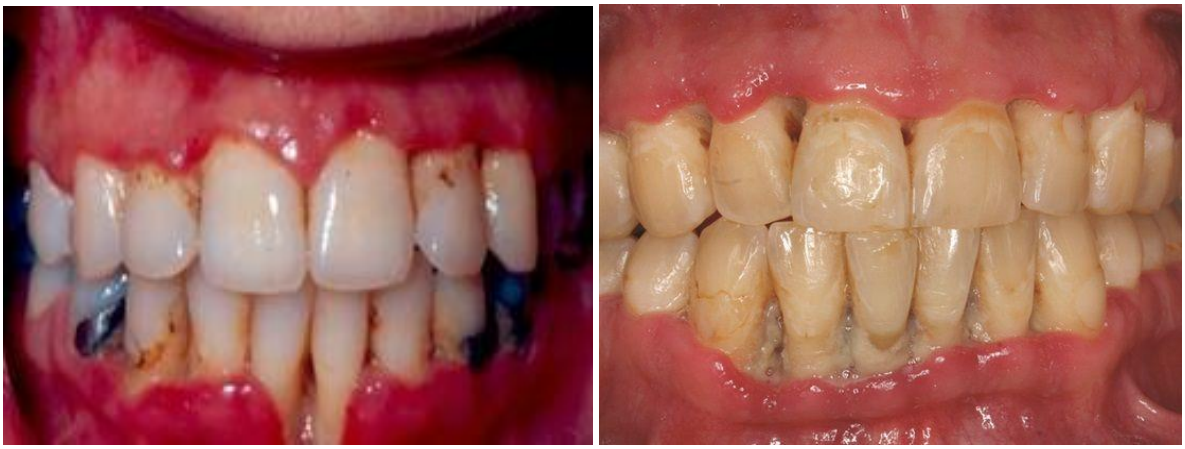

Fig 2: Necrotizing ulcerative gingivitis

8. Necrotizing Ulcerative Periodontitis (NUP)

Necrotizing ulcerative periodontitis is an acute infection that is defined by the presence of one or more interdental papillae and loss of clinical attachment and alveolar bone [40]. It was previously termed as necrotizing ulcerative gingivoperiodontitis in 1986 and later it was renamed as Necrotizing ulcerative periodontitis at the 1989 World Workshop in Clinical Periodontics. The adoption of NUP as a disease entity occurred in 1989 when there were an increase in the number of necrotizing periodontitis cases being diagnosed More cases of NUP were being described among immunocompromised patients, especially those who were human immunodeficiency virus (HIV)positive or who had acquired immunodeficiency syndrome (AIDS) [41].

NUP is characterized by ulceration and necrosis of interdental papilla with erythematous gingival margin which bleeds easily. Severe bone loss and deep osseous craters are the characteristic features of necrotizing periodontitis. Bone is exposed and becomes necrotic with sequestration [Fig:3]. Histologically destruction of epithelium as well as connective tissue takes place [42]. Severe pain, weight loss and difficulty in mastication are other features associated with NUP.[43]In 1994 Glick *et al* described strong link between CD4+ cells count and NUP in HIV patients. It is proposed that NUP is associated with below 200 cells/mm3 and might be a good marker of immune suppression [44]. Various predisposing factors are associated with NUP like smoking, stress, inadequate sleep, poor oral hygiene, poor diet, immunocompromised status, preexisting periodontal disease and malnutrition [45].

A fusiform-spirochete bacterial flora has been associated with pathogenesis for NUP [44]. Cobb and colleagues showed

histologic similarities between NUP in HIV-positive patients and previous descriptions of NUG in HIV-negative patients. Microscopically it revealed biofilm composed of a mixed microbial flora with different morphotypes and a subsurface flora with dense aggregations of spirochetes [i.e., the bacterial zone]. Below the bacterial layers were dense aggregations of polymorphonuclear leukocytes (PMNs)(i.e., the neutrophil-rich zone])and necrotic cells (the necrotic zone).[46] Murray *et al* in their study showed presence of significantly higher numbers of Candida albicans and a higher prevalence of Actinobacillus, Aggregatibacter actinomycetemcomitans, P. intermedia, Porphyromonas gingivalis, Fusobacterium nucleatum, and Campylobacter species. The study was conducted in cases of NUP in HIV- positive and AIDS patients [15]

Feller and Lemmer in their review article showed presence of that spirochetes, herpes viruses, candida and HIV in NUP lesions in the HIV seropositive individual. They demonstrated that spirochetes can modulate immune responses and activate host inflammatory reactions, which may lead to immunosuppression and facilitate development of necrotizing disease. The activation of herpes virus also can deregulate immune system. Candida albicans has been reported to produce eicosanoids leading to the release of proinflammatory mediators, which may facilitate spirochete colonization and invasion, promoting the development of necrotizing periodontal disease. Immunosuppression can lead to altered T-cell ratios which can contribute to NUP [44].

Differential Diagnosis Includes [47]

- Acute herpetic gingivostomatitis
- Desquamative gingivitis
- Agranulocytosis
- Leukemia
- Noma
- Necrotizing stomatitis
- Chronic periodontitis

8.1 Treatment for Necrotizing Ulcerative Periodontitis

The initial treatment includes debridement under local anesthesia and gentle scaling. The pseudomembrane should be removed using a cotton pellet dipped in 0.12% chlorhexidine. Patient's oral hygiene maintenance and other periodontal surgeries are done in successive appointments in the acute and healing stages of NUP. Pain management should include analgesics i.e ibuprofen 400–600 mg, t.i.d. or acetaminophen 750 mg, t.i.d [47]. Narrow spectrum antibiotics (metronidazole 500mg, dispensing 14-20 tablets, 1 tablet twice daily for 7 to 10 days or clindamycin or amoxicillin) along with nutritional supplementation or counselling if necessary should be included in initial visit. Follow up visits include periodontal care like scaling and root planning [48].

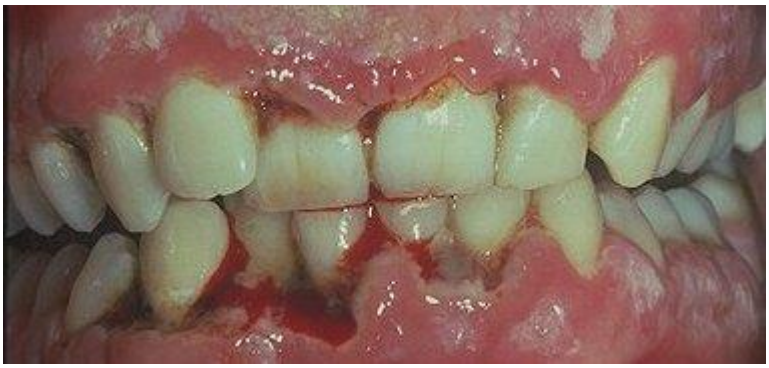

Fig 3: Necrotizing ulcerative periodontitis

9. Necrotizing Ulcerative Stomatitis (NUS)

Necrotizing ulcerative stomatitis (NUS) is an inflammatory disease of the oral cavity characterized by rapid destruction of epithelium, connective tissue, and dental papillae [49].

William defined necrotizing stomatitis as ulcero-necrotic infection of gingiva that extends into contiguous mucosal and palatal tissues, thus resulting in exposure of bone [50]. But it was later redefined by EC-Clearinghouse in 1993 as a painful ulcero-necrotic lesion of the oral mucosa that may expose underlying bone or extend into contiguous tissue as it extends to oral mucosa as well [23]. It is regarded as extension of the necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP) leading to gingival necrosis which extends beyond alveolar ridges causing destruction of oral cavity the necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), and necrotizing ulcerative stomatitis (NUS)together they are called as necrotizing gingivostomatitis [NG] [51].

Clinically necrotizing ulcerative stomatitis can be described as necrosis of gingival tissues, and loss of periodontal ligament and alveolar bone, if the necrotic process extends through the oral mucosa to the facial skin, it will result in cancrum oris (NOMA) [52]. Horning and Cohen described necrotizing gingivostomatitis in seven stages i.e [45]

Stage1- only the tip of the interdental papilla was affected (corresponds to NUG)

Stage 2- marginal gingiva was affected, with punched-out papilla (corresponds to NUG or NUP)

Stage 3 and 4 where attached gingiva was also affected and bone was exposed. (corresponds to NUP)

Stage 5 and 6 (corresponds to NUS)

Stage 7- perforation of skin (corresponds to NOMA)

The microbiota involved in pathogenesis of NUS include Fusobacterium necrophorum, Spirochetes (example Borrelia species) and Pseudomonas aeruginosa and herpes virus which altogether leads to suppression of the immune system [49].

The histopathologic features shows presence of deep ulcerations with fibrous connective tissue which exhibit areas of necrosis, leukocytoclasia, histiocytic vasculitis with luminal fibrin clots, and extensive inflammatory cell infiltrate [51].

9.1 Treatment of Necrotizing Ulcerative Stomatitis

The treatment modalities of NUS are similar to NUP which includes counselling and patient education, deep scaling and debridement, antibiotics like metronidazoles, analgesics [paracetamol] for pain management, mouth washes [chlorhexidine] and supportive therapy - folic acid, vitamin B-

complex, vitamin C. Removal of the necrosed bone if necessary.

10. Conclusion

HIV is one of the most noxious virus which causes destruction of periodontium. Early diagnosis, efficient periodontal management, proper oral hygiene maintenance are the key for the treatment of periodontal manifestation of HIV.

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