Periodontal Considerations in the HIV-Positive Patient

Committee on Research, Science and Therapy

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The American Academy of Periodontology
Scientific, Clinical and Educational Affairs Departmnet
737 North Michigan Avenue, Suite 800
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Fax: (312) 573-3234

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PREFACE

This paper was prepared by the Committee on Research, Science and Therapy of The American Academy of Periodontology for the information of the dental profession. It represents the position of The American Academy of Periodontology regarding periodontal considerations in the HIV-positive patient.

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INTRODUCTION

Infection with HIV-l virus continues to be a critical worldwide public health problem. In the United States, the predominant modes of transmission are still homosexual contact and intravenous drug users.[1] Worldwide, by contrast, the predominant mode of transmission is heterosexual contact.[2] The oral complications of HIV infection with its progression of impairment of the host response to combat infection present unique challenges to the periodontist, The appearance of oral soft tissue lesions as well as severe forms of gingivitis and periodontitis may be an indication that a patient is infected with HIV, In addition, these oral lesions may become more frequently encountered in HIV-infected patients as CD4 lymphocyte counts decrease during the natural history of this infection, The early detection of HIV infection may enable the practitioner to more closely monitor the progression of the disease, Preventive measures aimed towards reducing the intraoral microbial load through oral hygiene instruction, antimicrobial therapy, etc, may then be applied.

In order to understand the relationship of the progression of HIV infection to the occurrence of oral lesions including the HIV-related periodontal diseases, several staging systems have been employed, In the past, the two most widely used systems were: 1) the Centers for Disease Control and Prevention (CDCP) group classification based upon clinical symptoms[3] and 2) the more quantitative Walter Reed Staging Classification system based primarily upon CD4 (helper T-lymphocyte) cell counts, altered delayed hypersensitivity and the presence of intraoral candidiasis.[4] In January 1993, the CDC instituted a new classification system which combines the features of these older systems, The new system is based on three ranges of CD4 counts (< 200, 200-499, and ≥500) and three clinical categories combined into a matrix of nine separate categories, Clinical AIDS is now defined by a CD4 count < 200 and/or a CD4 percentage < 14.[5]

At the time of initial HIV infection, the patient may experience a mononucleosis-like syndrome with skin rash for two to four weeks, This is followed by an asymptomatic infection which may last from I to 20 years, At the time of initial acute infection, HIV- I antigens such as P24 free viral protein can be detected in the serum.[6] However, serum antibody titers to the virus (HIV-seroconversion) are usually not seen until 6 to 16 weeks after initial infection, Approximately 6 - 10% of this pool of asymptomatic HIV-infected patients per year will progress to later clinical stages.[7] The first of these later stages is a persistent generalized Iymphadenopathy with low grade fever characterized by the presence of Iymph nodes > 1 cm in diameter in two or more extrainguinal sites for more than three months.

Enlarged perioral lymph nodes that may be associated with the generalized persistent Iymphadenopathy may be first detected by the dental practitioner on routine examination. Patients with either the asymptomatic infection or persistent generalized Iymphadenopathy may demonstrate an increased prevalence of several intraoral lesions including hyperplastic and/or pseudomembranous candidiasis, herpetic stomatitis, exfoliative cheilitis, and depapillated tongue.[8-11] Several studies have reported an increase in the prevalence of acute necrotizing ulcerative gingivitis (ANUG) in HlV-infected individuals.[12-15] In the last stages of HIV disease, the patient can present with general constitutional disease of persistent fever, diarrhea, and/or weight loss, neurological disorders, a variety of secondary infectious diseases, and secondary cancers. Under the new CDCP classification system, irrespective of clinical symptoms, patients with CD4+ helper Iymphocyte counts below 200 or CD4 percentage below 14% are classified as having AIDS.[5] Of particular importance to the dental practitioner are observations from cross-sectional studies that unusual oral lesions such as hairy leukoplakia, Kaposi's sarcoma, ANUG, a form of gingivitis characterized by intense marginal erythema, and a form of periodontitis characterized by rapid gingival and bone necrosis are seen with increasing frequency as patient immunocompetence declines (decreased CD4 counts).[8-I2,I6]

PERIODONTAL DISEASES IN HIV POSITIVE PATIENTS

Diagnosis and Epidemiology

In the mid 1980s reports from Europe, Canada, and the United States described necrotic gingival lesions in HlV-infected male homosexuals characterized by localized soft tissue and bone destruction, and/or a generalized intense marginal to diffuse gingival erythema.[9,17-23] Some investigators referred to these gingival erythematous changes as HIV-associated gingivitis (HIV-G) and the destructive lesions as HIV associated periodontitis (HIV-P).[23] Several international consensus groups have suggested changing the names of these HlV-associated periodontal diseases to conform to a broader classification system which incorporates both HIV and non-HIV associated periodontal diseases. Since it is possible that similar clinical lesions may be encountered in non-HIV groups such as immunocompromised patients, the current terminology for HIV-G is "linear gingival erythema (LGE) seen in HlV-infected (HIV+) individuals," and for HIV-P, "necrotizing ulcerative periodontitis (NUP) seen in HIV+ individuals."[3]

The linear gingival erythema (LGE) reported in HIV-infected individuals is characterized by a 2 to 3 mm marginal band of intense gingival erythema with more apical focal and/or diffuse areas of erythema that may extend beyond the mucogingival line.[25] These erythematous changes are usually generalized but may be confined to one or two teeth. A major clinical hallmark of LGE is that this condition does not respond to conventional scaling, root planing and plaque control.[2l,24-26]

Necrotizing ulcerative periodontitis (NUP) seen in HIV+ individuals is characterized by marginal necrosis of the gingiva and rapid destruction of the underlying alveolar bone.[21,24-26] It is usually associated with severe pain and spontaneous gingival bleeding. Several case reports of NUP seen in HIV+ individuals have reported extensive destruction leading to exfoliation of affected teeth within 3 to 6 months from the onset of NUP.[25,27] In addition, several case reports have observed extension of the NUP lesion to sequestration of necrotic alveolar bone and necrotic involvement of the adjacent mandible and maxilla.[27] Following acute phases of HIV-periodontitis, the periodontium around remaining teeth presents with gingival blunting and marked reverse architecture.

The prevalence of LGE in HIV+ individuals has a reported range of 0 to 50%, and the prevalence of NUP in HIV+ individuals has a reported range of 0 to 5% among HlV-infected subjects.[9,13,14,16,28-33] These variations, particularly with LGE, may be due to such factors as the average staging level of the study population, geographic location of the study, whether the study subjects were referred for acute symptoms or were from a non-referred cohort, and the clinical criteria used to define HIV-G and HIV-P. By comparison, in one study, the prevalence of candidiasis, hairy leukoplakia and ANUG in similar groups has been reported to be 61%, 24%, and 11% respectively.[29] A higher incidence of periodontal diseases seen in HIV-infected individuals may also be dependent on other factors such as oral hygiene levels and tobacco consumption.[14] Several studies have compared the prevalence of LGE and NUP in HIV+ individuals in relation to HIV staging systems. In some studies LGE is commonly first seen earlier in the course of HIV infection where CD4 counts are in the low to normal range while NUP is usually detected at later stages where CD4 counts were markedly depressed.25 Other studies showed no clear correlation between CD4 and the incidence of HIV-associated lesions.[14]

The NUP seen in HIV+ individuals has several clinical similarities to previously described necrotic periodontal lesions in non HlV-infected individuals such as ANUG and necrotizing periodontitis (also termed necrotizing stomatitis or periodontitis ulcerosa). In addition, NUP in HlV-infected individuals has

a similar clinical appearance to Burkitt's Iymphoma, cytomegalovirus infection, or herpes zoster infection of the periodontal tissues.[34-36] These similarities can often make diagnosis confusing. The wide variations in epidemiological findings point to a need to develop a standard evaluation criteria to define periodontal diseases seen in HIV+ individuals. Currently such definitions are being developed based upon: 1) conventional criteria (gingival index, attachment loss, probing depth, etc.); 2) criteria specific for the severe forms of periodontal disease seen in HIV infection (tissue necrosis, marginal bands of erythema, etc.);[14,32] and 3) CD4 count groupings in accordance with the new CDC classification system.[5]

Microbiology and Pathogenesis

The microbiology of LGE and NUP in HIV+ individuals has been investigated through direct culture, microscopy, immunofluorescence, and DNA probe analysis.[37-43] From both LGE and NUP lesions in HIV+ subjects, there are high recovery rates of bacterial species as previously reported for adult periodontitis in HIV-negative patients such as of *P. gingivalis, P. intermedia, E nucleatum, E. corrodens*, and spirochetes. A striking feature of LGE versus NUP in HIV+ individuals is that both lesions have a similar microbiological profile. This contrasts with the markedly different microbiological profiles of chronic gingivitis versus adult periodontitis in HIV-negative patients. The similarity of flora between LGE and NUP lesions in HIV+ subjects, coupled with the observations that LGE generally occurs at earlier stages of HIV infection, has led some investigators to infer that the LGE lesion may be a precursor to the NUP lesion.[37,38,41]

In addition to microorganisms normally associated with adult periodontitis, high numbers of candida species, *Campylobacter rectus, Peptostreptococcus, Capnocytophaga*, and *A. actinomycetemcomitans* have also been recovered from LGE and NUP lesions in HIV+ subjects.[37-43] In addition to oral flora, there are unusually high recovery rates of opportunistic flora not normally associated with the oral cavity. These include *E. coli, Clostridium* species, mycoplasma, and *Klebsiella pneumoniae*.[39,40] Many of these enteric pathogens are associated with tissue destruction. For example *Clostridium difficile* is associated with pseudomembraneous ulcerative colitis.[44] Thus, it is possible that the flora associated with the LGE and NUP lesion in HIV+ subjects may play a direct role in the rapid tissue destruction.

Alterations in the host response during HIV infection may play a pivotal role in the pathogenesis of the LGE and NUP lesion. For example, peripheral neutrophil function in HIV+ subjects with the NUP lesion demonstrate a profile characteristic of a "primed" or toxic neutrophil associated with chronic infection. These alterations include elevated phagocytosis and oxidative burst,[45] but depressed chemotaxis[46] and intracellular killing of Candida albicans.[47] A heat-labile factor in the HIV+ serum appears in part to be responsible for these altered neutrophil functions.[47]

Preliminary studies of the crevicular fluid from HIV+ individuals show several alterations in inflammatory mediator levels including interleukin- 1 β[48] and tissue necrosis factor alpha (TNFα)[49] Future studies in this area may give new insights into the pathogenesis of periodontal diseases in HIV infection. The role of depressed serum and tissue[49] CD4 counts in HIV infection and periodontal diseases remains unclear. Although previous studies on HlV-negative subjects have shown a direct relationship between depressed CD4 levels and inflammation, there were no clear relationships with attachment loss or disease activity.[51]

A third area of inquiry into the pathogenesis of LGE and NUP in HIV infection is the cytotoxic role of the HIV virus itself. HIV virus has been recovered from the crevicular fluid at all stages of HIV infection.[52] Other viruses such as cytomegalovirus, herpes zoster, Epstein-Barr virus, and human papilloma virus have also been recovered from ulcerative periodontal lesions in HIV+ subjects.[34-36 53,54] A direct role,

however, for either the HIV virus or any other associated viruses in the progression of NUP or LGE has yet to be established. *Candida albicans* and other fungal infections may also play a direct role in the pathogenesis of HIV-associated periodontal lesions in HIV infection. How ever, at present, these mechanisms are unclear.

Management

A widely used treatment for the LGE and/or NUP lesion in HIV+ individuals involves gross scaling to remove visible plaque and calculus deposits and debridement of necrotic tissue when present.[17,20,26,27] Access for both debridement and for topical antimicrobial therapy is aided by the fact that pocket depths are often minimal in the NUP lesion. During debridement, povidone-iodine irrigation has been used for its antiseptic and anesthetic effects.[17,26]

Antibiotics should be used with caution due to the increased risk of overgrowth of *Candida albicans*,[17,26] and other microflora associated with HIV infection. To prevent overgrowth of opportunistic microorganisms the use of a concurrent antifungal agent has been recommended.[17,55] Narrow spectrum antibiotics such as metronidazole which leave much of the aerobic Gram positive flora unperturbed has also been recommended to prevent *Candida* overgrowth in the management of LGE and NUP lesions.[17]

Following initial debridement, follow-up visits are necessary in order to thoroughly remove plaque, calculus, and other deposits and to provide strict plaque control instruction. Home use of an antimicrobial mouthrinse such as chlorhexidine has been shown to be an effective therapeutic aid in reducing the acute symptoms of LGE and NUP in HIV+ patients and in preventing the recurrence of these lesions.[21,26] Clinical case reports and controlled studies have shown this therapy to be generally effective in reducing the acute symptoms of NUP and LGE and in halting the progression of the necrotic lesion. The response to therapeutic intervention may, however, depend upon the patient's current HIV stage, intake of systemic medication to treat the HIV infection itself (e.g., zidovudine [AZT]), intake of antibiotics, and oral habits (e.g., tobacco smoking).

OTHER PERIODONTAL CONSIDERATIONS

The NUP and LGE lesions seen in HIV+ subjects are often superimposed on conventional periodontitis. In previous studies, the relationship of HIV+ status and severity of periodontitis was unclear. For ex ample, some studies found no direct correlation between the relationship of pocket depth or plaque index with HIV staging.[28,42] In other studies, attachment loss was greater at later stages of HIV infection.[30,31] especially when CD4 counts fell below 200 [56] Several investigators have suggested using a CD4 count of <200 as a cutoff point for correlation studies between HIV-infection and conventional periodontal disease.[15] One recent longitudinal study has reported that HIV+ patients with pre-existing periodontitis have a greater rate of attachment loss over time when compared with matched HIV-negative controls.[57] In HIV+ subjects, the prevalence and severity of common forms of periodontal diseases such as chronic inflammatory periodontal disease (adult periodontitis) may vary between risk groups due to other factors such as oral hygiene levels, smoking habits, medications, etc.

With HIV+ patients, in addition to linear gingival erythema and necrotizing ulcerative periodontitis, several other lesions may localize in the periodontium. The gingiva is the second most common site for intraoral Kaposi's sarcoma.[58] A case of oral mucosal bacillary epithelial angiomatosis (which has a similar clinical appearance to Kaposi's sarcoma) has also been reported in an HIV+ subject.[59] Gingival papillary wart-like lesions similar in appearance to venereal warts (gingival condyloma accuminata) have also been reported.[10] Lymphomas and other tumors associated with HIV can appear as distinct gingivalmu-

cosal enlargements and on radiographs as discrete radiolucencies in the alveolar bone.[35,59,61]

There are several general considerations in the periodontal management of the HIV-infected patient with or without periodontal disease. To date there have been no reported clinical studies on alterations in healing following periodontal surgical procedures in HIV+ patients. In studies on other intraoral surgical procedures, there were no differences in the incidence of dry socket following extraction[62] or in the incidence of post scaling bacteremias between HIV-infected and non-infected individuals.[63] However, HIV-infected patients have shown delayed healing after other forms of surgery.[64] During any procedure, the current principles of strict infection control as recommended by OSHA[65] and the American Dental Association should be carefully followed, not only for patients with known HIV infection, but for all patients in order to insure the maximum safety for both health care provider and the patient.

CONCLUSIONS

Periodontal diseases in HIV-infected individuals present unique challenges in diagnosis, monitoring, treatment, and maintenance. The presence and severity of LGE, NUP, ANUG, and other oral lesions may indicate the presence of HIV infection.

In HIV+ subjects, the prevalence of these lesions may increase with progressive impairment of the immune system. The altered immunity and host response in patients with HIV infection may also affect the incidence and severity of other common forms of periodontal disease not associated with HIV infection. There is a wide variation in recent reports on the epidemiology of HIV-associated diseases. These variations point to the need for a standard definition for periodontal diseases seen in HIV+ patients using both conventional periodontal evaluation criteria and criteria designed specifically for the characteristics of the less common periodontal diseases seen in HIV+ patients. HIV staging, geographic location, antiviral and antimicrobial therapies, and oral habits should also be taken into consideration when treating HIV-infected patients. Both the LGE and NUP lesions in HIV+ subjects have similar microbiologic profiles to HIV- adult periodontitis lesions. In addition, periodontal lesions in HIV+ patients may have a unique opportunistic microflora. The pathogenesis periodontal diseases in HIV+ subjects may be due to the microflora, the effects of HIV and other viral agents, and/or alterations in the host response. These factors should be taken into consideration in the treatment and prevention of periodontal diseases in the HIV patient.

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