

# Necrotizing Gingivitis as it Relates to HIV Infection: A Review of the Literature

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Necrotizing gingivitis (NG) and necrotizing periodontitis (NP) are considered to be different clinical stages of the same disease process and may be the first clinical indicators of human immunodeficiency virus (HIV) infection. NG/NP is a disease with distinctive clinical manifestations that respond to an uncomplicated regime of treatment. The clinical signs and symptoms of NG in HIV-positive patients are identical to those in HIV-negative patients, and the microflora is the same in either case. In contrast to the reported important role of smoking in NG/NP and periodontal disease in general, smoking does not seem to play a contributory role in the pathogenesis of NG/NP in HIV-positive patients. The lesions of NG/NP tend to affect predominantly the upper and lower anterior periodontal segments, and recurrence after treatment is not common.

**Key words:** necrotizing ulcerative gingivitis, necrotizing gingivitis, human immunodeficiency virus

## INTRODUCTION

In this paper the terms necrotizing gingivitis (NG) and necrotizing periodontitis (NP) will be used in preference to the customary terms necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP) which in our opinion are inappropriate because in NG, ulceration is not a primary feature, but is secondary to necrosis of the gingival margins; and in NP, the necrotizing disease by definition is in the attachment apparatus where the term ulceration is not applicable.

NG is characterized by marginal gingival necrosis starting at the interdental papillae with gingival bleeding and pain. The breath may be foetid and there may be pseudomembrane formation and lymphadenopathy but these features are not invariable (American Academy of Periodontology, 1999; Barends et al, 1973; Falker et al, 1987; Horning and Cohen, 1995; Johnson and Engel, 1986; Kinane, 2001; Muryama et al 1994; Rowland, 1999).

Necrotizing periodontitis (NP) is an extension of NG into the periodontal attachment apparatus, being commonly observed in debilitated subjects with predisposing conditions including, but not

limited to severe malnutrition (Enwonwu, 1972; Jenkins and Papapanou, 2001; Novak, 1999; Osuji, 1990; Taiwo, 1993) and immuno-suppression (Cogen et al, 1983; Glick et al, 1994).

## NG/NP IN HEALTHY SUBJECTS

Although the aetiopathogenesis is not entirely clear (Darby and Curtis, 2001), NG/NP has been associated with virulent bacteria (Loesche et al, 1982) and impaired host defence mechanisms (Claffey et al, 1986; Cutler et al, 1994). Spirochaetes and fusiform bacilli are the most common causative agents of NG (Listgarten, 1965; Listgarten and Socransky, 1964) and can be found in dentogingival bacterial plaques and gingival connective tissues of subjects with NG (Listgarten and Lewis, 1967; Riviere et al, 1991). There is evidence to support the relationship between the development of NG/NP and dysfunction of the innate and adaptive immune responses towards bacterial challenge. Abnormalities in polymorphonuclear (PMN) leukocyte function as measured by chemotactic, phagocytic and bactericidal activities, depressed mitogenic response of lymphocytes, and

depressed IgG and IgM competence have been demonstrated to be associated with bacteria specific to NG/NP (Chung et al, 1983; Claffey et al, 1986; Cutler et al, 1994; Jakob et al, 1982; Kinane et al, 2001; Rowland, 1993; Rowland et al, 1993).

An ineffective innate immune response can be the primary feature preventing the host from containing the bacterial challenge, resulting in increased susceptibility to NG/NP. On the other hand an ineffective cellular and humoral immune response may be secondary to the challenge of virulent bacteria generally associated with NG/NP and may set the stage for the same virulent bacteria to cause the lesion of NG/NP (Claffey et al, 1986). Thus, although susceptibility to NG/NP is undoubtedly multifactorial, it is apparent that regardless of the specific mechanisms involved, suppression in the host immune response is an important factor associated with the development of NG/NP (Novak, 1999; Rowland, 1999).

With regard to the multifactorial nature of NG/NP, apart from the immune factors outlined above, predisposing factors may include stress (in the military, withdrawal of drugs from addicts, university examinations, etc.); tobacco smoking (gingival vasoconstriction, local hypoxia, oxidative burst products); malnutrition and states of general debilitation (American Academy of Periodontology, 1996; Davis and Baer, 1971; Giddon et al, 1964; Group and Wilder, 1956; Moulton et al, 1952; Shields, 1977; Stevens et al, 1984).

In the industrialized countries, NG is essentially a disease of young adults that rarely occurs before adolescence (Jenkins and Papapanou, 2001). During World War II it affected up to 14% of Danish military personnel (Pindborg, 1951). After the war it became less common, affecting 2.2% of individuals aged 17 to 21 years entering military training in the United States (Groupe and Wilder, 1956) and 2.5% of students entering a United States university (Giddon et al, 1964).

In recent times the prevalence of NG has dropped to 0.5% and 0.001% among American and Danish military personnel respectively (Horning et al, 1990; Holmstrup and Westergaard, 1998).

The prevalence of NP in otherwise healthy people in the industrialized countries is uncertain, since most studies of necrotic periodontal lesions have failed to differentiate NP from NG superimposed upon pre-existing periodontal attachment loss (Novak, 1999).

In the authors' experience, there are undoubtedly cases of gross NP with necrotic denudation of alveolar bone and loss of periodontal support that has progressed so rapidly, according to the subject's report, that no initial phase of NG has been observed. The connection between NG/NP can be concluded from the concurrent existence of areas of NG and NP in the same subject.

The frequently localized nature of NG is well established (Barnes et al, 1973; Robinson et al, 1998). It is thus entirely possible, and indeed probable that localized sites of the disease may pass unobserved through the phase of NG and be seen as established NP when the erroneous conclusion may be reached that the NP is a primary condition.

Until such time as reliable clinical and radiological documentation becomes available in prevalence studies, and indeed even in investigations of individual subjects, NG and NP should be grouped together, while recognizing that the former will be seen far more frequently than the latter.

The prevalence of NG/NP in some developing countries on the African continent is higher than in the industrialized countries, and the disease affects younger individuals who may be immunocompromised through malnutrition and/or systemic disease (Albandar and Tinoco, 2002).

NG/NP responds to conventional periodontal therapy of scaling, root planning and polishing of teeth, plaque control instruction, the use of chlorhexidine mouthwash and the administration of systemic antibiotic/antibacterial therapy, in particular metronidazole for the first 3-5 days (Clerehugh and Tagnait, 2001; Shangase et al, 2004), which will bring about dramatic diminution of signs and symptoms (Harnet and Shiloah, 1991; Johnson and Engel, 1986; Rowland, 1999).

Patients presenting with NG are often susceptible to recurrence of the disease (Goldhaber and Giddon, 1964; Johnson and Engel, 1986; Silver et al, 1974), unless the risk factors are eliminated (Clerehugh and Tagnait, 2001), and the NG may progress to NP, but in the authors' experience this progression is very uncommon.

## NG/NP AND HIV INFECTION

With the alarming increasing global experience of HIV infection since the first cases were identified in the early eighties, NG/NP has been increasingly

observed not only in confirmed HIV-positive subjects, but also in apparently healthy individuals who, when investigated proved to be HIV-positive (Shangase et al, 2004).

The natural history from initial HIV-infection to AIDS is the result of a dynamic interaction between the virus and the host's immune system, with a progressive decrease in number and reduction in functional competence of the CD4+ T-cell lymphocytes leading to immuno-deficiency (Sleasman and Goodenow, 1998). Abnormalities of the CD4+ T-cell lymphocytes have received most attention in connection with AIDS. However, there are other important contributing endogenous cofactors to HIV disease, including B lymphocytes and monocyte/macrophage abnormalities (Fauci and Clifford Lane, 1998; Mitchel and Kumar, 2003).

It is therefore not surprising that, in a population group with such immuno-deficiency, NG/NP in the HIV population will far outstrip its prevalence in the general population. This has been confirmed in several publications (Anil and Challacombe, 1977; Arendorf et al, 1997; Arendorf et al, 1998; Ceballos-Salobrena et al, 1996; Ficarra et al, 1994; Laskaris et al, 1992; Palmer et al, 1996; Patton et al, 2000; Patton, 2003; Ramirez-Amador et al, 1998).

The predictive value of certain oral lesions, singly or in combination, in tracing the chain of events from HIV sero-conversion to full-blown AIDS is well documented (Cobundlers et al, 1991; Greenspan and Greenspan, 2002; Hodgson and Rachanis, 2002; Matee et al, 1996; Piot et al, 2001).

Hairy leukoplakia and pseudomembranous candidosis have certainly been associated with immuno-deficiency states unrelated to HIV infection (American Academy of Periodontology, 1999; Kinane, 2001; Rowland, 1999). However, at present these oral conditions, together with Kaposi's sarcoma, are widely considered to be suggestive of HIV infection (Greenspan and Greenspan, 2002; Lasakaris, 1992). Hairy leukoplakia, oropharyngeal candidosis manifesting in more than one form at the same time and Kaposi's sarcoma in any combination on the other hand, are very likely to be indicative of the progression of the HIV-positive state to AIDS (Greenspan and Greenspan, 2002). Recently Shangase et al (2004) reported that about 70% of a group of black South Africans diagnosed with NG/NP who were unaware of their HIV status were found to be HIV-positive.

The authors' recommendation is that NG/NP should be added to the list of oral lesions that are strongly indicative of HIV infection. Although they do not specifically state it in their publication, Shangase et al were convinced that neither in terms of clinical presentation nor in response to treatment, could NG/NP in subjects with HIV disease be distinguished from NG/NP subjects without HIV-disease (personal observation).

The microflora found in NG/NP lesions of HIV-positive patients is similar to that in NG/NP lesions of HIV-negative patients, consisting mainly of fusiform bacilli and spirochetes (Robinson et al, 1998). However, elevated levels of opportunistic bacterial, fungal and viral species associated with tissue damage are additionally found within periodontal tissues of HIV-positive patients (Odden et al, 1994; Rams et al, 1991; Ryder, 2002).

Candida species have been found in the subgingival plaque of HIV-positive patients with NG/NP (Jabra-Rizk et al, 2001) and the herpes virus family including cytomegaloviruses (HHV5), Epstein-Barr viruses (HHV4), as well as HHV6, 7 and 8 may also play a role in the pathogenesis of periodontal diseases in HIV-positive patients (Contreras et al, 2001; Dodd et al, 1993; Mardirossian et al, 2000; Slots and Contreras, 2000).

Levels of serum antibody to oral micro-organisms in NG/NP of HIV-positive patients have not been well investigated (Kinane et al, 2001), although a recent study by Steinsvoll et al (1997) demonstrated reduced serum IgG reactivities with bacteria from dental plaque in HIV-infected persons with periodontitis.

There are reports in the literature that with each relapse of NG there is further loss of attachment and progression to NP (MacCarthy and Claffey, 1991; Robinson, 2002), and sometimes even to necrotizing stomatitis (Patton and McKair, 1998; Robinson et al, 1998; Williams et al, 1990). However, in the authors' experience, and supported by other reports (Scully et al, 1991; Robinson, 1997), the NG/NP lesions in HIV-positive subjects respond as readily to conventional treatment as do those of non-HIV infected subjects with NG. The treatment of NG/NP in HIV-positive patients is simple and as effective as in HIV-negative patients.

The literature recommends that gross scaling and removal of necrotic tissue in conjunction with povidone iodine irrigation for its anaesthetic and anti-septic effects, should be started immediately after

diagnosis, followed by administration of metronidazole and chlorhexidine mouthwash (Robinson et al, 1998; Robinson, 2002).

Our approach is the reverse. First pain, bleeding and the embarrassment of foetid breath should be relieved by the use of chlorhexidine mouthwash and metronidazole. There is no need to curette the necrotic marginal tissues. Once the acute pain has been reduced and the tissue quality somewhat improved, vigorous brushing, scaling and, if necessary, root planing should follow.

The clinical rationale for this less aggressive treatment is, first, that we are convinced that progression from NG to NP does not and will not occur once chemotherapy has been started and, secondly, that our routine gives excellent clinical results and reduces the risk of loss of attachment from curettage of highly inflamed and fragile gingival bordering on the necrotic tissues. Despite published reports to the contrary (Williams et al, 1990; Patton and McKaig, 1998; Robinson et al, 1998), NG/NP lesions in HIV-positive subjects do not have any greater tendency to rapid loss of attachment and progression to necrotizing stomatitis than do those of HIV-negative subjects. Indeed, in our experience – although without data to confirm it – the relapse of NG/NP lesions in HIV-positive patients is not common and is much the same as in HIV-negative patients.

NG/NP is more prevalent in subjects with early HIV infection than in those with long-standing infection or with AIDS (Robinson, 2002; personal information). One can perhaps postulate that the pathogenesis of NG/NP may not be as strongly influenced by the drop in the CD4+ T-cell count in HIV-positive individuals, as by local bacterial virulence factors and stress impacting on leukocyte function.

Systemic metronidazole is valuable for the treatment of NG/NP, and the fact that it is a narrow spectrum antimicrobial, specifically effective against a range of gram-negative anaerobic bacteria – such as are responsible for NG/NP, but sparing the proportion of gram-positive flora – might prevent the candidal overgrowth so very common in HIV-positive patients (Ryder, 2002).

The fact that a relapse of NG/NP is not common and that NP is in any case an entity of uncertain incidence is significant in the clinical management. Following initial conventional treatment as outlined above, there is therefore no further or pro-

longed need for either local or systemic chemotherapy to prevent recurrence of NG/NP or progressive loss of periodontal attachment.

Highly active anti-retroviral treatment (HAART) is a relatively new approach to the treatment of subjects with HIV/AIDS. The goal is to reduce the HIV load in the blood to undetectable levels by a combination of reverse transcriptase inhibitors and protease inhibitors (Paul et al, 1999; Richman, 2001; Ryder, 2002). This can result in great improvement in the immune systems of individuals infected with HIV (Powderly et al, 1998), and to a decrease in the prevalence of several oral HIV-related conditions including NG/NP (Greenwood et al, 2002; Patton et al, 2000; Schmidt-Westhausen et al, 2000). The decline in the prevalence of some HIV-related oral diseases following the introduction of HAART may, however, be short-lived (Ryder 2002). NG/NP and other oral diseases associated with HIV may show a resurgence if HAART loses its effectiveness, leading to re-elevated viral loads and renewed immuno-suppression (Ryder, 2002).

In both HIV-positive subjects (Robinson et al, 1998) and in HIV-negative subjects (Barnes et al, 1973) NG occurs mainly in the anterior gingivae, the lower being somewhat more frequently and extensively affected.

Shangase et al (2004) found that 46% of HIV-positive subjects with NG/NP were smokers. Glick et al (1994) reported that the prevalence of smoking in a group of HIV-positive patients with NP was lower than in the control group of HIV-positive subjects without NP lesions. These findings suggest that although smoking is a well-known risk factor for the development and progression of periodontal disease (Rivera-Hidalgo, 1986; Scot et al, 2001; Tomar and Asma, 2000), it probably does not influence the pathogenesis of NG/NP in HIV positive subjects (Glick et al, 1994; Shangase et al, 1994).

## DISCUSSION

One would think, by the nature of HIV infection, considering the risk factors for periodontitis – in particular smoking – that as the competence of the immune system declines with the progression from early HIV infection to AIDS there would be a progressive increase in the severity and in the frequency of recurrence of NG/NP in the HIV-posi-

tive population. This is not the case. NG occurs early in the natural history of HIV infection and appears to be minimally influenced, if at all, by tobacco smoking.

As HIV disease plays out its inevitable course, logic and clinical intuition would predict increasing difficulties in the treatment of associated NG/NP. However, treatment has presented no difficulties beyond those encountered in treating NG/NP in HIV-negative patients; and recurrence of NG/NP, rather than becoming an escalating clinical problem, poses little or no problem.

In this paper we have reviewed some of the literature on necrotizing gingivitis as it relates to HIV infection and have offered some views based on our substantial clinical experience. Certain clinical realities, which appear to fly in the face of clinical expectation, are as yet inexplicable and await fully documented confirmation and systemic research.

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