The Severity, Extent and Recurrence of Necrotizing Periodontal Disease in Relation to HIV Status and CD4+ T CELL Count

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Abstract

South Africa ranks among the three countries with the highest prevalence of HIV infection in sub-Saharan Africa, with an estimated 29.5% of women attending antenatal clinics being infected. Necrotizing periodontal disease is a well recognized HIV-associated oral condition. The objective of this investigation was to determine a possible correlation between the extent, severity and treatment outcome of necrotizing periodontal disease in relation to a person's HIV status and $CD4^+$ T cell count. Data from 105 consecutive patients presenting with necrotizing periodontal disease at an academic oral health centre in South Africa were analysed. All patients were provided with an opportunity to undergo voluntary counseling and testing for HIV infection, were treated for necrotizing periodontal disease and followed over a period of nine months. The mean age of the cohort was 28 years old (range 12 - 52). Of 98 (93.3%) patients unaware of their HIV serostatus at the initial visit, 59 (56.2%) consented to testing. In total 45 (42.9%) were HIV-seropositive with a mean CD4+ T cell count of 222.7 cells/μl and 14 (13.3%) were HIV-seronegative, with a significantly higher mean CD4+ T cell count of 830 cells/μl (Fisher's exact test, $p < 0.001$), while the status of 46 (43.8%) remained unknown. In 101 (96.2%) patients, ≥ 5 tooth sites were affected, and in 27 (26%) ≥ 4 mm of gingival tissue were affected. This study, which included HIV-seropositive, HIV-seronegative and persons of unknown HIV status, revealed no statistical evidence that HIV infection was associated with the extent, severity or relapse of necrotizing periodontal disease. No statistically significant association could be demonstrated between the extent, severity and recurrence of necrotizing periodontal disease and a $CD4^+$ T cell count ≤ 200 cells/μl among HIV-seropositive patients.

Key words: HIV, AIDS, necrotizing periodontal disease, $CD4^+$ T cell count, Africa

Introduction

While numbers fluctuate, South Africa remains one of three countries with the highest prevalence of HIV infection in the sub-Saharan region of Africa. Based on data gathered from a population survey and attendees at antenatal clinics it is estimated that 4.9 – 6.6 million South Africans are infected out of a total estimated population of 48 million (UNAIDS, 2009). In a World Health Organisation (WHO) report released in February 2009, only 460,000 people were estimated to be receiving highly active antiretroviral therapy (HAART) (WHO, 2009).

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Necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP), collectively termed necrotizing periodontal diseases (NPDs), have been found to be more prevalent in HIV-seropositive patients than in immunocompetent patients, and may be the first sign of HIV infection or an indicator of progression to full-blown AIDS (Glick *et al.*, 1994; Shangase *et al.*, 2004). NUG is characterized by marginal gingival necrosis, gingival bleeding and pain, while NUP is an extension of NUG into the periodontal attachment apparatus. Additional common features, but not pathognomonic, include pseudomembrane formation, cervical lymphadenopathy and fetid breath (American Academy of Periodontology, 1999).

The pathogenesis of NPDs is multifactorial and involves infection of the gingiva by periodontopathic bacteria, mainly spirochetes and fusiform bacilli, a compromised immune response in the host and other predisposing factors such as physical and emotional stress, malnutrition and other general debilitating states (Feller

and Lemmer, 2008; Listgarten and Socransky, 1964). If untreated, NUG may progress to NUP (MacCarthy and Claffey, 1991; Robinson *et al.*, 2002) and further to necrotizing stomatitis (NS) (Patton and McKaig, 1998; Williams *et al.*, 1990). NS might arise from NUG/NUP disease progressing beyond the mucogingival demarcation or may develop away from the periodontium, involving contiguous oral mucosa, and may result in bone exposure and necrosis (Barasch *et al.*, 2003; Chapple and Hamburger, 2000; Neville *et al.*, 2002). Thus NUG, NUP and NS may represent different clinical stages of a single infectious pathogenic mechanism (Feller and Lemmer, 2008; Robinson, 2002; Robinson *et al.*, 2002). Evidence is emerging that the clinical manifestation of HIV disease differs between patients in developing and developed countries (Arendorf and Holmes, 2000; Ranganathan and Hemalatha, 2006) but no published data could be found concerning the response to treatment of NPDs in relation to HIV status and immune status of patients from developing countries, where the majority of HIV/AIDS patients are still not receiving HAART. The objective of this study was therefore to investigate the extent and severity of NPDs and response to treatment by patients presenting with NPDs at a South African academic dental hospital in relation to their HIV status and $CD4^+$ T cell counts.

Patients and methods

All oral examinations and treatments were conducted by a single oral medicine-trained examiner who used established, presumptive, clinical diagnostic criteria for NPDs (American Academy of Periodontology, 1999; Shangase *et al.*, 2004).

The data gathered from 105 consecutive patients who were diagnosed with NPDs in the Department of Periodontology and Oral Medicine, MEDUNSA Oral Health Centre, and who were followed up over a 9-month period (2004 – 2005), were analysed. A diagnosis of NPDs was made when gingival necrosis, bleeding and pain were evident on examination. All the patients included in this study of unknown HIV status at the time of admission were advised to have an HIV test. Patients who agreed to be tested signed a consent form and received pre-test counseling. Post-test counseling was carried out when the results were available and the HIV-seropositive patients were subsequently referred to the regional HIV clinic for further evaluation and management of their HIV infection.

All patients were treated for NPDs with a 5-day course of metronidazole 400 mg three times a day, paracetamol 500 mg three times a day, and chlorhexidine digluconate 0.2% mouthwash daily. Plaque control instruction, scaling and root planing, when indicated, were carried out at the end of the five-day chemotherapeutic treatment phase.

Data recording was performed as described by Robinson *et al.* (1998), with NUG and NUP being combined into one category. In determining the extent of the NPDs lesions, data were categorized into ≤ 4 and ≥ 5 tooth sites involved, while severity was categorized according to tissue necrosis extending ≤ 3 mm or ≥ 4 mm from the gingival margin. Resolution following the prescribed treatment was defined as lack of pain and gingival bleeding, and the healing of the gingival ulcerations. Relapse was defined as lesions that did not respond to the initial treatment and required further treatment. Recurrence was considered as presentation with a second episode of NPDs within nine months after a successful initial treatment.

The project was approved by the Research Ethics Committee (DP 07/04), and informed consent was obtained from all patients to use the data for research and publication purposes, without breach of individual patient confidentiality. Data recording forms were labeled only with a study identification number in order to maintain this confidentiality.

Statistical analyses were conducted using SAS®, Release 9, and run under Microsoft® Windows® XP for a personal computer. Fisher's exact test and logistic regression analysis were performed and p values ≤ 0.05 were considered significant.

Results

The demographic data of the patients included in this study are summarized in Table 1. Of the 105 patients diagnosed with NPDs, seven (6.6%) reported that they were HIV-seropositive at the initial consultation. None of them were receiving HAART at the time of diagnosis of NPDs. Of the remaining 98 patients who were unaware of their HIV serostatus, 46 (43.8%) refused testing and their status remained unknown. In total, laboratory results confirmed that 45 (42.8%) patients were HIV-seropositive and 14 (13.3%) were HIV-seronegative. Forty-four (41.9%) patients were male and 61 (58.1%) were female, with equal numbers of male and female patients refusing testing. The mean age of the patients with NPDs at the time of initial presentation at the clinic was 28 years old (range 12-52 years). Only 21 (20.8%) patients smoked (data missing, n = 4), while 2 (2%) were using smokeless tobacco (snuff) that is usually placed in the mandibular labial sulcus. Forty-seven (46.1%) patients reported that they were consuming alcohol (data missing, n = 3). The mean age of HIV-seronegative patients (22 years) was lower than the mean age of HIV-seropositive patients (45 years) and the group with unknown HIV serostatus (29 years) (Fisher's exact test, $p \leq 0.01$). Of 105 patients, a total of 41 did not return for follow-up visits and could not be contacted by telephone to enquire about a possible recurrence of NPDs.

Table 1: Demographic data according to HIV status of 105 patients presenting with NPDs.

	HIV+ (n = 45)	HIV- (n = 14)	Unknown (n = 46)	Total (n = 105)
Gender				
Male	13	8	23	44 (41.9%)
Female	32	6	23	61 (58.1%)
Age (years)				
Mean	45	22	29	28 years
Range	12 - 52	14 – 31	19 - 51	12-52 years
		$p \leq 0.01$		
Tobacco usage				
Smoking	8	5	8	21 (20.8%)
Smokeless tobacco	1	-	1	2 (2%)
Non-smoking	35	8	35	78 (77.2%)
Data missing	1	1	2	4
Alcohol consumption				
Currently consuming	18	5	24	47 (46.1%)
Not consuming	26	8	21	55 (53.9%)
Data missing	1	1	1	3

Logistic regression analysis of severity and extent of NPDs with $CD4^+$ T cell count, gender, HIV status, age, tobacco usage and alcohol consumption as predictor variables did not indicate any of the variables to significantly contribute to either the severity or extent of NPDs.

Table 2. Extent, severity and response to treatment of NPDs in 59 patients of confirmed HIV status.

	HIV-positive (n = 45)	HIV-negative (n = 14)	*p* values*
Extent of NPDs			
≥ 5 tooth sites	42	14	
≤ 4 tooth sites	3	0	$p = 0.56$
Severity			
≥ 4 mm gingiva affected	12	2	
≤ 3 mm gingiva affected	32	12	$p = 0.48$
Data missing	1		
Relapse	-	-	
Recurrence after initial treatment	2	1	
No recurrence	24	13	$p = 0.53$
Lost to follow-up	19	-	

*Fisher's exact test

A summary of the extent and severity of NPDs, as well as the response to treatment in relation to the HIV serostatus of the patients is presented in Table 2. No statistically significant correlation could be found between HIV serostatus and the extent of NPDs (Fisher's exact test, $p = 0.56$), or the severity of NPDs (Fisher's exact test, $p = 0.48$). All patients responded to the initial treatment and of the 64 that were followed up, two HIV-seropositive and one confirmed HIV-seronegative patients experienced a recurrence of NPDs. There was no statistically significant correlation between recurrence of NPDs and HIV serostatus (Fisher's exact test, $p = 0.53$).

In Table 3 the extent and severity of NPDs and patients' response to treatment is presented in relation to the various categories of $CD4^+$ T cell counts. The $CD4^+$ T cell counts ranged between 21 and 693 cells/μl for the HIV-seropositive patients (mean 223 cells/μl), and between 475 and 1157 cells/μl for the HIV-seronegative patients (mean 830 cell/μl). A statistically significant difference was demonstrated, in terms of the mean $CD4^+$ T cell count, between HIV-seropositive and

Table 3. Extent, severity and response to treatment of NPDs in relation to $CD4^+$ T cell count among patients of confirmed HIV status.

	HIV-positive (n = 32) Mean $CD4^+$T cell count 222.7 cells/µl Range 21 - 693			HIV-negative (n = 11) Mean $CD4^+$ T cell count 830 cells/µl Range 475 - 1157	
	≤ 200 cells/µl	200-499 cells/µl	≥ 500 cells/µl	< 500 cells/µl	≥ 500 cells/µl
Number of patients	14 (43.8%)	17 (53.1%)	1 (3.1%)	1 (9%)	10 (91%)
Extent of NPDs					
≥ 5 tooth sites involved	14	17	1	1	10
≤ 4 tooth sites involved	-	-	-	-	-
Severity					
≥ 4 mm gingiva affected	4	6	-	-	1
≤ 3 mm gingiva affected	10	11	1	1	9
Relapse	-	-	-	-	-
Recurrence after initial treatment	1	1	-	1	-
No recurrence	8	7	1	1	9
Lost to follow-up	5	9	-	-	-

A statistically significant difference was demonstrated in the mean $CD4^+$ T cell count between HIV-seropositive and HIV-seronegative patients with NPDs (Fisher's exact test, $p < 0.001$). However, no statistically significant association was detected between the extent, severity and recurrence of NPDs among HIV-seropositive patients with either a $CD4^+$ T cell count ≤ 200 cells/µl or 201 – 499 cells/µl.

HIV-seronegative patients with NPDs (Fisher's exact test, $p < 0.001$). However, no statistically significant association was detected between the extent, severity and recurrence of NPDs among HIV-seropositive patients with either a $CD4^+$ T cell count ≤ 200 cells/µl or 201 – 499 cells/µl. Similarly, when logistic regression analyses were conducted of severity and extent of NPDs with $CD4^+$ T cell count, gender, HIV serostatus, age, smoking and alcohol consumption as predictor variables, none of the variables were found to significantly contribute to either the severity or extent of NPDs.

Discussion

While reference is made to an unpublished pilot study indicating an increase in the prevalence of NPDs in relation to the HIV epidemic in Africa (Reddy, 2007), no published data on NPDs and HIV status in patients in sub-Saharan Africa could be obtained. This study, which includes HIV-seropositive, HIV-seronegative and patients of unknown HIV status, is therefore the first to provide information regarding the extent, severity and response to treatment of NPDs in relation to HIV serostatus and $CD4^+$ T cell counts in a developing country. The findings differ from what has previously been described in the developed world (Glick, *et al.*, 1994) and reasons for this can only be speculated on.

In a previous study by our group it was established that patients who presented with NPDs and who were unaware of their HIV serostatus had a 70% probability of being HIV-seropositive. In the present study 59 patients had a confirmed HIV status, of whom 46 (76.3%) were HIV-seropositive. If the same percentage (70%) applied to the group of 46 patients who refused testing, an estimated 35 could possibly be HIV-seropositive. These 46 (43.8%) patients who refused testing represent an increase from the previous study in which 35% of patients presenting with NPDs refused testing (Shangase *et al.*, 2004).

The increase in individuals who refused testing in this study (46%) as opposed to a previous study (35%) is of great concern for a number of reasons. Until recently patients' HIV serostatus would only be determined when they were admitted to hospital with conditions suggestive of an underlying HIV infection. Females attending antenatal clinics normally consent to anonymous HIV testing. A voluntary counseling and testing (VCT) campaign was instituted which attempts to remove the stigma associated with HIV disease and identify individuals who qualify for the timely introduction of HAART. To what extent the fact that the majority of patients included in this study are predominantly from rural areas contributed to their refusal to undergo HIV testing is not known. It is possible that the VCT campaign had not reached them and the benefits of early diagnosis of HIV thus remain unknown to them. Those individuals who are unaware of their HIV serostatus not only pose serious social implications, since they will continue to constitute a potential source of transmission of a fatal disease (Shangase *et al.*, 2004), but they also forgo the possibility of receiving HAART. While all attempts are made to supply HAART to as many patients as possible, there could be a waiting period for some patients. The introduction of HAART in the early stages of HIV disease is known to result in reduced plasma viral loads,

substantial reconstitution of the immune system, and a better general prognosis of HIV disease compared to that of HIV-seropositive patients who are not receiving HAART (Patton *et al.*, 2000). Had the 14 patients with a $CD4^+$ T cell count below 200 cells/μl (Table 3) who were diagnosed as HIV-seropositive during this study responded to calls for VCT, they might have qualified to receive HAART at an earlier stage of their HIV disease, and the prognosis of their HIV disease could have been improved.

Twenty-one percent of the participants in this study were smokers (Table 1), comparable to the reported prevalence of smoking in the general black population in South Africa that ranges between 18% and 20.5% (Stein *et al.*, 2008). In establishing tobacco usage among patients, it was not attempted to determine how many cigarettes per day or for how many years patients had been smoking, but merely whether they smoked or used smokeless tobacco. Only 19% of patients presenting with NPDs and who tested positive for HIV were smokers. Of the HIV-seronegative patients with NPDs, 36% smoked. Logistic regression analysis with tobacco usage as one of the predictor variables failed to reveal any contribution of smoking to either the extent or severity of NPDs, confirming previous reports (Glick *et al.*, 1994; Shangase *et al.*, 2004). While a number of studies displayed a relationship between smoking and periodontal tissue breakdown, it would seem that it is dose- and duration-related, with heavy smokers displaying worse periodontal breakdown and less bleeding tendency (Moimaz *et al.*, 2009; Vourous *et al*, 2009). It would also suggest the relationship to be between smoking and chronic periodontitis rather than acute periodontitis such as in this case of NPDs. Determining the extent of alcohol consumption is a contentious matter and the information included in this study was a mere "yes" or "no" response to a question whether alcohol is consumed.

From the summary of results in Table 3 it is evident that NPDs are associated with all the immunological categories of HIV disease in this cohort of patients and are not limited mainly to individuals with a $CD4^+$ T cell count of < 200 cells/μl, as was the finding by Glick *et al.* (1994). It can only be speculated that other factors such as malnutrition, a difference in the composition and virulence of periodontopathic microflora or plaque control practices might account for the difference in findings of this study and others. Due to resource constraints it was not possible to determine what bacteria or viruses were present in the NPDs lesions of this particular cohort of patients.

Different approaches to the treatment of NPDs are in use. Some recommend that scaling and curettage of gingival necrotic tissue, together with povidone iodine irrigation should be initiated at the time of NPDs diagnosis, followed by the administration of metronidazole and chlorhexidine mouthwash (Robinson, 1998; Robinson, 2002). However curettage of the necrotic tissue and inflamed gingiva at the time of diagnosis could result in unnecessary gingival recession. Therefore, reducing the inflammatory process and controlling the acute pain by systemic metronidazole, chlorhexidine mouthwash and analgesics as an initial therapeutic step is recommended (Feller and Lemmer, 2008; Shangase *et al.*, 2004). The current study confirmed the effectiveness of this empirical approach (Tables 2 and 3), with only three patients (two HIV-seropositive and one HIV-seronegative) out of the 64 that were followed up experiencing an episode of recurrence. All three patients responded favorably to the repeat treatment.

In HIV-seropositive patients, as in immunocompetent patients, NPDs may involve a single tooth site or multiple tooth sites in different regions of the jaws (Holmstrup and Westergaard, 1994). The anterior mandibular and maxillary gingiva may be the most commonly affected sites (Robinson *et al.*, 1998). However, others did not find any oral site predilection in the distribution of NPDs (Smith *et al.*, 1995), as was the case in this study (results not shown). In addition, on average, more than five tooth sites were involved in each episode of NPDs. This result differs from that of Robinson *et al.* (1998), who reported that most episodes of NUG in HIV-seropositive patients involve fewer than five teeth. The most likely explanation for the higher number of affected sites per single episode of NPDs in this study may be attributed to patients who generally seek treatment at a very late stage of an illness (Hatchett *et al.*, 2004). Other possible factors include the fact that none of the patients included in this study were receiving HAART.

Twenty percent of patients with NPDs were diagnosed clinically with other oral lesions associated with HIV infection, such as candidiasis, oral leukoplakia and herpes simplex virus infection (results not shown). The diagnosis in these cases was presumptive, based on clinical observations. Therefore, no attempt was made to correlate these conditions with any of the parameters investigated in this study.

In this cohort of patients it would thus seem that the natural course of NPDs is similar in HIV-seropositive and -seronegative patients, and there is no correlation between the clinical signs and natural course of NPDs and the $CD4^+$ T cell counts. There was no statistically significant difference between HIV-seropositive and -seronegative patients in terms of response to conventional periodontal therapy, which encompasses the administration of systemic antimicrobial therapy and chlorhexidine mouthwash, followed by plaque control measures and removal of plaque and calculus. With a probability of 70 – 76% of being HIV-seropositive, it is strongly recommended that patients presenting with

NPDs who are of unknown HIV serostatus be encouraged to consent to HIV testing for early diagnosis and appropriate management.

Conclusion

The outcome of this study among HIV-seropositive, HIV-seronegative and persons of unknown HIV status conclusively demonstrates no statistically significant association between extent, severity or recurrence of NPDs and HIV-serostatus, gender, age, smoking or alcohol consumption. While the $CD4^+$ T cell count of the HIV-seropostive patients was significantly lower than that of HIV-seronegative patients, the extent and severity of NPDs was not associated more significantly with a $CD4^+$ T cell count below 200 cells/μl among HIV-seropositive patients.

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