Necrotising Stomatitis in a HIV-Seropositive Patient: Report of a Case and a Review of the Literature

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Necrotizing gingivitis (NG), necrotizing periodontitis (NP) and necrotizing stomatitis (NS) are well documented oral diseases associated with HIV infection, and might represent a spectrum of clinical manifestations of a single infectious process. While NG is a relatively common periodontal disease mainly observed in early HIV infection, NS is less common, and is usually associated with a well-established HIV infection and deterioration in the immune status. However, all three conditions may arise in non-HIV affected individuals.
A case is presented of NS occurring simultaneously with NG, but not on contiguous areas, leading to the diagnosis of HIV infection in a patient unaware of her HIV status, and the literature of NG and NS is reviewed.

Key words: necrotizing stomatitis, necrotizing gingivitis

INTRODUCTION

Necrotizing gingivitis (NG) and necrotizing periodontitis (NP) are collectively referred to as necrotizing periodontal diseases (NPD) (International Workshop for the Classification of Periodontal Diseases and Conditions. Consensus Report, 1999). NPDs are considered to be more common in HIV-seropositive subjects compared to immunocompetent individuals, and might be the first clinical manifestation of HIV infection or an indication of immune deterioration in these subjects (Shangase et al, 2004; Vastardis et al, 2003; Laskaris et al, 1992).
NG is characterised by gingival necrosis, bleeding and pain. Secondary clinical signs may include fetid breath, pseudomembrane formation, lymphadenopathy, fever and malaise (Horning and Cohen, 1995), and the main predisposing factors are poor oral hygiene, smoking, stress, poor nutrition and immunosuppression. NP is an extension of NG to include the periodontal attachment apparatus and is most commonly observed in HIV-seropositive subjects and other immunosuppression states (International Workshop for the Classification of Periodontal Diseases and Conditions. Consensus Report, 1999).
The prevalence of NP is uncertain, since most studies of necrotic periodontal lesions have failed to differentiate NP from current NG superimposed upon pre-existing periodontal attachment loss and therefore, in the majority of cases, NG and NP should be grouped together under the heading of NDP (Feller and Lemmer, 2005). Smoking is a well-established risk factor for the development and progression of periodontal disease. However, its role in the pathogenesis of NPD in HIV-seropositive subjects is less clear (Shangase et al, 2004; Glick et al, 1994).
The clinical signs and symptoms, as well as the microflora of NG in HIV-seropositive subjects are the same as those in HIV-seronegative subjects (Feller and Lemmer, 2005). Dramatic resolution of signs and symptoms occur following conventional periodontal therapy of plaque control instructions, mechanical debridement of plaque and calculus, the

use of chlorhexidine mouthwash and the administration of systemic antimicrobial therapy, in particular metronidazole for the first three to five days (Shangase et al, 2004; Clerehugh and Tagnait, 2001; Rowland, 1999; Feller and Lemmer 2005). NS can be defined as a localised, acute, painful ulceronecrotic lesion of the oral mucosa that exposes underlying bone, and may extend into contiguous tissues (Greenspan et al, 1992). NS might be the outcome of NG/NP disease progression beyond the mucogingival demarcation, or arise on the oral mucosa separately, away from the periodontium (Rees, 2002; Neville et al, 2002). NS involves mainly the soft tissues, but may extend into the underlying bone, causing massive tissue destruction and ultimately oro-anteral or oro-nasal fistulae may develop (Felix et al, 1991; Chapple and Hamburger 2000). If the necrotising process spreads through the oral mucosa to the facial skin, it will result in NOMA (cancrum oris) (Neville et al, 2002).

CASE REPORT

A 25-year-old black female presented to the Oral Medicine Clinic at the Medunsa Oral Health Centre, Faculty of Dentistry, University of Limpopo, with a chief complaint of a painful lesion in the back of her mouth and painful bleeding gums.

At the time of the initial examination, the patient was unaware of her HIV status, claimed to be in good health, and her medical history was unremarkable. The patient denied any smoking habits, fever, chills, sweats or having had such oral lesions previously, and reported that she became aware of the lesion on her palate a few days previously, and since then, it had been progressively enlarging and inflicting pain upon speaking, mastication and swallowing. The day following the appearance of the palatal lesion, her gums started to be painful and to bleed.

Head and neck examination revealed bilateral submandibular and cervical lymphadenopathy. Intra-oral examination showed a large necrotic lesion on the middle of the soft and hard palate measuring approximately 4 cm x 2 cm, without underlying bone exposure (Fig 1). In addition, the interdental papillae of the majority of the teeth exhibited spontaneous bleeding and ulcerations. Figs 2 and 3 demonstrate characteristic areas of NG lesions. There was only minimal plaque accumulation, the periodontal probing depths were 1 to 3 mm, the intra-oral periapical radiographs revealed normal alveolar bone height and architecture, and the patient had the oral malodour characteristic of NG.

The patient was advised to have a blood test to confirm the presence of HIV infection. Consent was obtained, and the patient received pre-HIV test counselling. Blood was drawn for HIV antibody ELISA test and CD4-positive T cell count.

The patient was prescribed a five-day course of metronidazole (400 mg three times per day), amoxicillin (500 mg three times per day), paracetamol (500 mg three times per day) and 0.2% Chlorhexidine mouthwash twice daily for seven days. HIV positivity was confirmed. The CD45-positive white cell and the differential counts were within normal range. The patient received post-HIV test counselling before the HIV test results were disclosed to her. At this stage the NG lesions had completely resolved, with no pain or gingival bleeding present. The palatal lesion had improved substantially, but a shallower ulcer was still present. Since there were no periodontal pockets present, there was no indication for root planing. However, scaling and polishing of all teeth was performed, and plaque control instructions given. The patient was instructed to continue with the chlorhexidine mouthwash, and was referred to the HIV-clinic at the regional referral hospital for systemic management. A week later (two weeks since her first visit to our clinic) the palatal lesions healed completely, and at present, six months later, there are no signs of recurrence of the gingival nor the palatal lesions (Figs 4, 5).

DISCUSSION

NG, NP and NS may be different clinical stages of the same disease process (Robinson 2002; Robinson et al, 2002) and may be referred to collectively as necrotizing gingivostomatitis (Horning and Cohen, 1995). Some suggest that noma (cancrum oris) also belongs to this spectrum of diseases (Falkler et al, 1999; Enwonwu et al, 1999), since it shares with NPD and NS similar histopathological and bacteriological features (Neville et al, 2002; Falkler et al, 1999).

If untreated, NG may progress to NP, and NG/NP may progress to NS (Williams et al, 1990; Patton

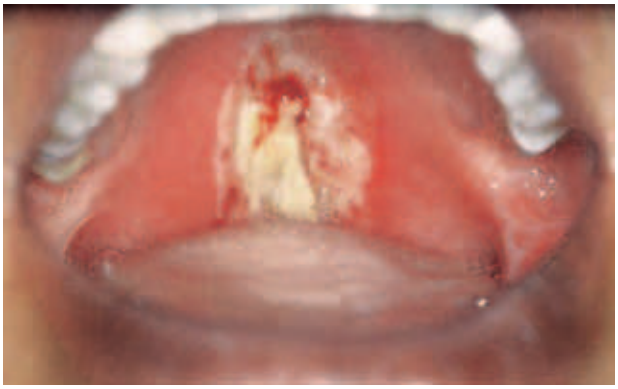

Fig 1 The necrotic lesion in the palate.

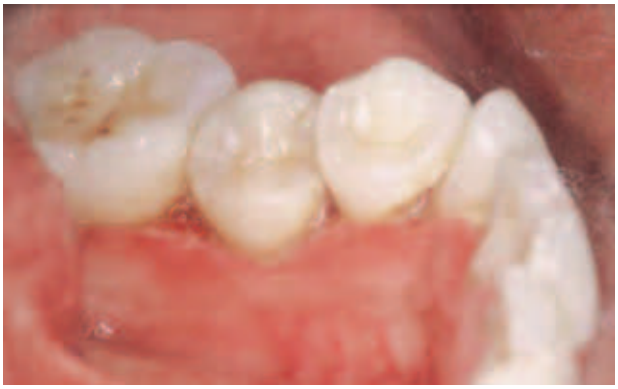

Fig 2 Necrotizing gingivitis, lingual aspect of lower left area.

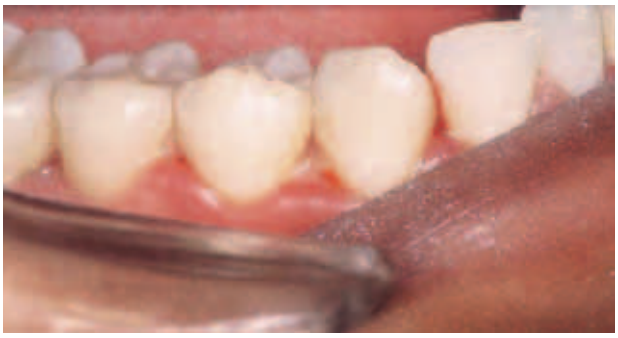

Fig 3 Necrotizing gingivitis, buccal aspect of lower right area.

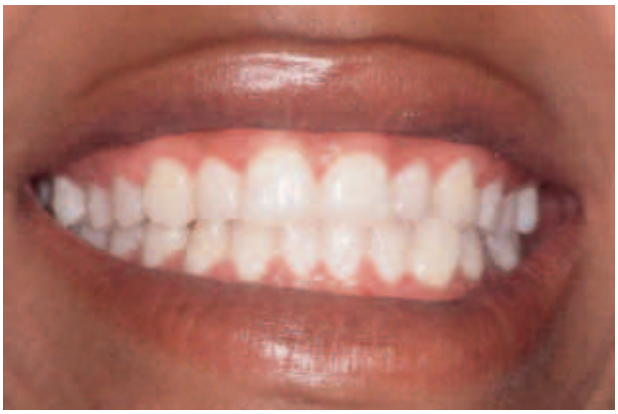

Fig 4 View of the gingiva one week after chemotherapy.

and McKaig 1998). In NS, the necrotizing process extends beyond the mucogingival margins into contiguous oral mucosa, and may result in bone exposure and necrosis. However there are reports in the literature of NS, which arose without apparent origin from NPD, in sites completely separated from the periodontium (Barasch et al, 2003; Salama et al, 2004). In the case presented here the NS lesion on the palate did not have any association with the extensive NG lesions. The palatal lesion developed separately, but occurred simultaneously with the NG, and this was the patient's first indication of her HIV positive status.

Noma occurs when the necrotizing process described above spreads further, and penetrates the external facial skin (Robinson et al, 2002; Falkler et al, 1999; Enwonwu et al, 1999). The histological features of NG, NP and NS are general-

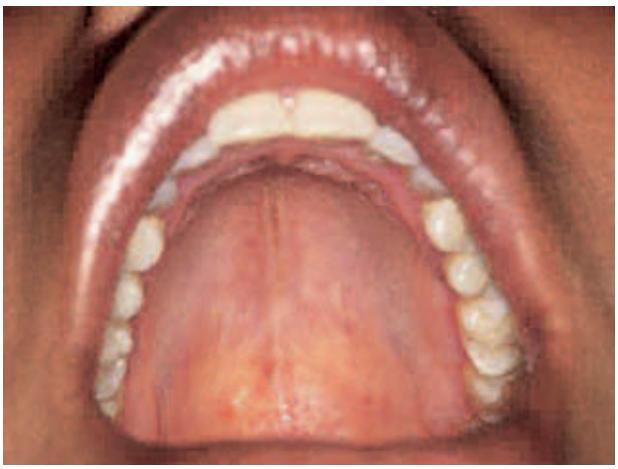

Fig 5 View of the healed palate two weeks after treatment.

ly reported to be not specific and usually include surface ulceration covered by a fibro-purulent membrane, with an acute or mixed inflammatory cell infiltrate and extensive hyperaemia of the underlying lamina propria (Neville et al, 2002). Since the histological features of NS are not pathognomonic, a biopsy is usually not indicated (Greenspan et al, 1992). However, some suggest that NS is a separate entity with a different aetiopathogenesis from NPD. Jones et al (2000) reported on 18 HIV-seropositive individuals with NS-like lesions in which the histopathological features were different and specific; the inflammatory infiltrate contained proliferation of large atypical histiocytes (CD68-positive cells) with amphophyllic cytoplasm, vesicular nuclei and prominent nucleoli interspersed with crescentic histiocytes, a histopathological picture described in necrotizing histiocytic lymphadenitis (Kikuchi's disease).

The pathogenesis of NPD is multifactorial, and includes in addition to specific virulent bacteria, impairment of the host immune response towards the bacterial challenge and predisposing factors such as physical and emotional stress, malnutrition and general debilitation (American Academy of Periodontology, 1999). However, it is not clear if the suppression of the immune response towards the bacterial insult is a primary event, permitting the bacterial infection, or secondary to the virulent activities of the bacteria generally associated with NPD which then may cause the lesions of NG/NP (Feller and Lemmer, 2005). The same pathogenesis most probably applies to NS as well.

Fusiform bacteria and spirochetes are the most common microorganisms involved in the causation of NPD (Listgarten, 1965; Listgarten and Socransky, 1964) and NS (Salama et al, 2004), and recently Pseudomonas aeruginosa was implicated with NS as well (Barasch et al, 2003). Fusiforms and spirochetes are part of the normal oral flora and are associated with NPD and other periodontal diseases in immunocompetent individuals. In HIV-seropositive subjects, there is an increase in the prevalence of NPD and NS, most probably due to profound impairment of the host immune response and the increase in fungal and viral presence in the oral cavity in these subjects, which might provide a favourable environment for bacterial overgrowth, causing oral necrotic lesions (Salama et al, 2004).

Members of the herpes virus family have been implicated in the pathogenesis of various periodontal diseases in immunocompetent subjects (Contreras and Slots, 2000; Slots, 2004). Herpes simplex virus (HSV), Epstein-Barr virus (EBV), human cytomegalo virus (HCMV), human herpes virus (HHV)-6, HHV-7 can be detected in subgingival plaque samples and gingival biopsies from periodontal pockets in higher frequency than healthy periodontal sites (Contreras et al, 1999; Kamma and Slots, 2003). HIV-seropositive subjects with periodontal disease have greater numbers of herpes viruses in the periodontal soft-tissues (including HHV-8 that is usually absent in periodontal pockets of immunocompetent individuals), than HIV-seronegative control subjects with periodontal disease (Mardirosian et al, 2000; Contreras et al, 2001). Active herpes viruses in the periodontal tissues may result in local immune suppression, facilitating overgrowth of periodontopathic bacteria, leading to periodontitis and NPD, and subsequently periodontal tissue destruction (Kamma and Slots, 2003; Slots, 2004). This mechanism may partly contribute to the increased prevalence of NPD and NS in HIV-seropositive subjects.

In addition, HIV-seropositive subjects demonstrate higher prevalence of Candida in their subgingival microbial flora obtained from periodontal pockets (Zambon et al, 1990; Jabra-Risik et al, 2001) and NPD (Odden et al, 1994). Candida albicans itself has the potential to produce eicosanoids (Noverr et al, 2001; Noverr et al, 2002; Noverr et al, 2003), and to induce host-derived release of arachidonic acid, eicosanoids and other pro-inflammatory mediators (Deva et al, 2000), that promote fungal colonization and invasiveness, by shifting the TH1/TH2 balance of cellular immunity towards a humoral TH2 type response that is less effective in combating fungus (Noverr et al, 2002). Such an interference with the local immune and inflammatory responses in the oral soft tissues has the potential to increase the destructive inflammatory process in periodontal disease, and contribute to the development of necrotic oral lesions (Odden et al, 1994).

In HIV-seropositive individuals there is a significant reduction in Langerhans cells (LC) in the oral epithelium, compared to HIV-seronegative subjects.(Myint et al, 2000). The oral mucosal LC are the target of HIV, and HIV p17 structural protein can be detected in oral LC of HIV-seropositive subjects, particularly in patients with high HIV viral load. Such HIV-infected dendritic cells could stim-

ulate a cytotoxic T-cell response, resulting in the depletion of LC in the HIV-affected areas of the oral epithelium (Chou et al, 2000). It is therefore possible that the localised depletion of LC in the oral epithelium of HIV-seropositive subjects will reduce the local host immune response towards micro-organisms, and increase the susceptibility of the HIV-seropositive patient to develop necrotic periodontal diseases (Myint et al, 2000; Chou et al, 2000) and necrotising stomatitis.

The treatment of NPD and NS is simple and effective. Resolution of NPD lesions occur following mechanical debridement of plaque and calculus, plaque control instructions, the use of chlorhexidine mouthwash and the administration of systemic antimicrobial therapy (Shangase et al, 2004; Feller and Lemmer, 2005). NS responds well to antibiotic therapy and complete resolution is observed following administration of oral penicillin alone (Salama et al, 2004).

We have decided to treat our patient empirically with broad spectrum systemic antimicrobial agents due to the worrying presentation of the palatal necrotic ulcer, that interfered with the normal functions of mastication and swallowing. The combination of amoxicillin and metronidazole was effective: resolution of the NG lesions occurred in less than one week and of NS less than fourteen days. This dramatic response to systemic antimicrobial therapy suggests that indeed the main causative agents in the development of NS and NPD are bacterial in origin, and HIV-seropositive subjects respond well to such a treatment.

Our diagnosis of the palatal lesion was NS, and it was made on clinical grounds. This was a presumptive diagnosis, and other possible diagnoses cannot be definitively ruled out, given the non-contiguous nature of the NG and the palatal erosion. The synchronous co-existing of typical NG lesions that share with NS the same aetiopathogenesis directed us to assume that it is not only likely, but also probable that the palatal lesion is NS, even though it was not contiguous with the NG.

The midline area of the palate can host a great variety of lesions which may have a similar clinical appearance as NS, and typically include: peripheral angiocentric T-cell lymphoma, Wegener's granulomatosis, nasopharyngeal carcinoma, tuberculosis and non-tuberculous mycobacteriosis, leprosy, syphilis, deep mycosis, cat scratch disease, toxoplasmosis and necrotizing sialometaplasia.

Another possible differential diagnosis could have included ulceration NOS (not otherwise specified) which is relatively common in HIV-seropositive patients and has a similar clinical appearance as this palatal NS case (Reichart, 1997). It is important to point out that we cannot eliminate syphilis or yaws as a cause of the palatal lesion, because these would also respond to systemic antimicrobial therapy. With hindsight, we would recommend microbiological investigation to help arrive at a definitive diagnosis for non-gingival lesions, where non-contiguous NS is suspected.

The excellent response to the systemic antimicrobial therapy confirms an infective aetiology in our case. Should resolution of the palatal lesion not have occurred in 14 days, a biopsy would have been taken to exclude the possibility of any of the above-mentioned conditions.

The introduction of highly active antiretroviral therapy (HAART) has reduced the occurrence of HIV associated oral lesions including NPD (Chapple and Hamburger 2000). HAART consists of a combination of at least 3 antiretroviral agents that target viral replication at more than one stage of the viral cycle, causing suppression of HIV replication. This results in the reduction of plasma HIV load and the improvement of the immune system of HIV-seropositive subjects (Patton 2003). Patton et al (2000) reported a decrease of about 35% in the prevalence of NPD following HAART. However, this decline may be short-lived. As HAART loses its effectiveness, re-elevated plasma viral load and renewed decline in CD4+ T cell counts may lead to resurgence in the prevalence of NPD (Ryder, 2002).

CONCLUSIONS

1. NS as well as NPD may be the initial signs for HIV-infection. It is therefore recommended to refer high-risk subjects with NS/NPD for HIV testing.
2. Appropriate oral antimicrobial therapy may lead to rapid resolution of NS in HIV-seropositive subjects who have high CD4 counts and low viral loads. Cases that do not respond to therapy should be biopsied to exclude other disease states and underlying bone necrosis.

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