Kaposi Sarcoma and Calcium Channel Blocker-Induced Gingival Enlargement Occurring Simultaneously: Review Of The Literature and Report of a Case

L. Feller[a], Y. Jadwat[a], E. J. Raubenheimer[b]

[a]*Department of Periodontology and Oral Medicine, Medunsa Oral Health Centre, Faculty of Dentistry, Medical University of Southern Africa, Mendunsa, South Africa.*
[b]*Department of Oral Pathology, Medunsa Oral Health Centre, Faculty of Dentistry, Medical University of Southern Africa, Mendunsa, South Africa.*

Summary: The gingiva is a site which hosts a great number of overgrowths; plaque induced and drug induced gingival enlargements, neoplastic lesions and gingival reactive overgrowths with or without calcification.
A case is presented in which Kaposi sarcoma (KS) and calcium channel blocker drug therapy simultaneously resulted in severe gingival overgrowth affecting the entire dentition. To the best of our knowledge it is the first time that such a combination of gingival overgrowth has been reported. The gingival overgrowths we report involved both the attached gingiva as well as the interdental papillae, clinically appearing as erythematous and lobulated, while some of the lesions were mulberry shaped. The lesions did not blanche upon pressure and readily bled on mechanical irritation. The overgrown gingiva was not painful or tender except for the areas traumatized upon mastication. The excessive growth of the gingival tissue gave rise to considerable speech, masticatory and aesthetic problems.
It is imperative to establish the HIV-status of the patient since early introduction of anti-retroviral drug therapy in HIV-seropostive individuals has been associated with regression in the size of existing oral KS lesions and a decrease in the development of new lesions.

Key words: Kaposi sarcoma, gingival overgrowth, calcium channel blocker

Oral Biosci Med 2004; 1: 291-297 *Submitted for publication 30 September 2004; accepted for publication 2 November 2004.*

INTRODUCTION

Calcium channel blocker agents are a class of drugs used in the management of hypertension and angina pectoris, and are associated with gingival enlargement in some cases (Ellis et al, 1999; Pilloni et al, 1998; Miranda et al, 2001). The pathogenesis of calcium channel blocker-induced gingival enlargement is not well understood but it has been suggested that the drugs cause alteration in fibroblast function, resulting in an increase in connective tissue extra-cellular matrix components, mainly collagen fibres and non-collagenous proteins (Seymour, 1991; Sooriyamoorthy and Gower, 1989; Henderson et al, 1997; Fujii et al, 1994).

Clinically, in the absence of inflammation, the gingival overgrowth is firm, normal in colour with the surface smooth or lobulated in texture. In the presence of plaque-induced inflammation the affected gingiva may be erythemathous and lobulated, with the surface becoming friable, occasionally ulcerated, bleeds readily upon mechanical irritation and resembles a pyogenic granuloma-like-overgrowth. The gingival enlargement usually starts in the interdental papillae and progresses to involve the masticatory mucosa around the dentition. Edentulous areas are usually not affected, but enlargements under dentures and around dental implants have been reported (Pilloni et al, 1998; Neville et al, 2002).

Kaposi sarcoma (KS), is a multi-focal angio-proliferative neoplasm, primarily affecting muco-cutanous tissues, but may affect visceral organs as well. Oral KS most frequently involves the palatal mucosa, the masticatory gingival mucosa and the dorsum of the tongue (Reichart et al, 1993; Lager et al, 2003; Hille et al, 2002). The lesions present as bluish-purple to red macules which progress to a papulo-nodular form and eventually to a large exophitic mass. They are either singular or multi-focal, and in advanced stages the tumour can cause resorption of the underlying alveolar bone and loss of teeth (Reichart, 2003; Lausten et al, 2003; Reichart et al, 1993; Ficarra et al, 1998; Krown, 1997).

The pathogenesis of KS is multi-factorial and includes infection by human herpesvirus-8 (HHV-8), altered cell receptor expression and response to cytokines and growth factors and HIV gene products that modulate cell growth (Lager et al, 2003; Lausten et al, 2003).

CASE REPORT

A 41-year-old Black male patient presented to the Oral Medicine Clinic, Faculty of Dentistry at the Medical University of Southern Africa, with a chief complaint of enlarged gingiva. The patient had been previously diagnosed and treated by gingivectomies for calcium channel blocker-induced gingival overgrowth. The clinical examination showed generalized severe gingival enlargement involving the entire dentition, but in particular around the upper anterior sextant and the upper left premolars (Figs. 1-4).

The gingival overgrowth appeared lobulated, nodular, erythematous and in areas mulberry-shaped. It readily bled on probing and did not blanch on pressure.

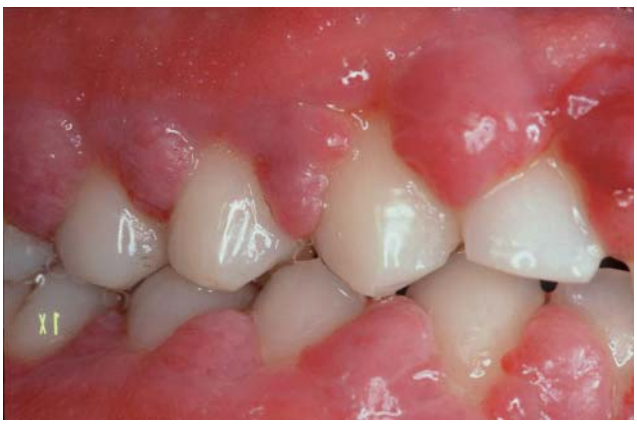

Fig. 1 Right side, buccal aspect of the masticatory gingiva.

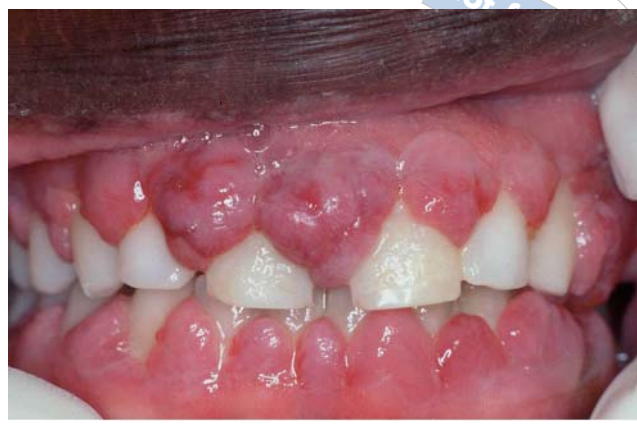

Fig. 2 Anterior segment buccal aspect of the masticatory gingiva.

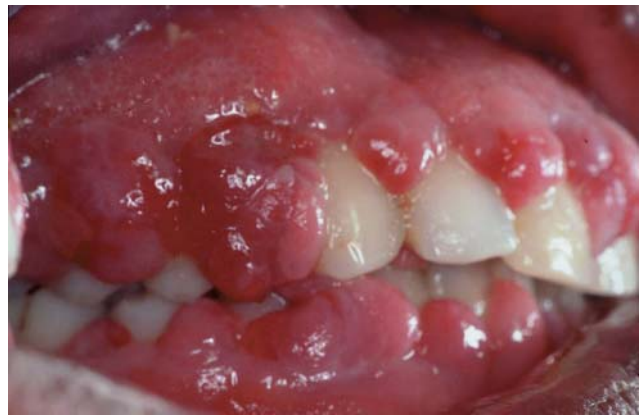

Fig. 3 Mirror image of left side, buccal aspect of the masticatory gingiva.

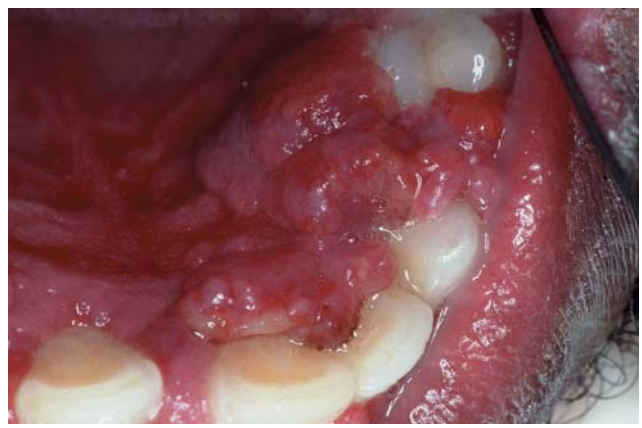

Fig. 4 Mirror image of occlusal plane. The gingival overgrowth completely covering the upper left premolar. Note the ulcerations secondary to trauma of mastication.

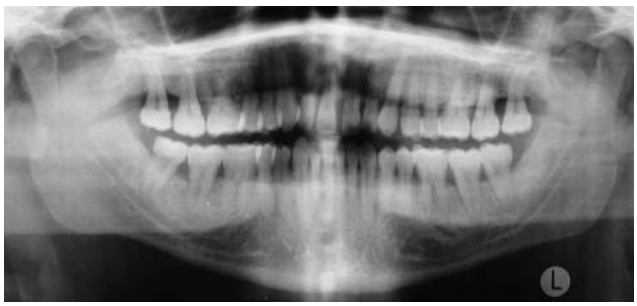

Fig. 5 Panoramic radiograph revealing moderate alveolar bone loss.

Some areas were firm while others were edematous. Panoramic radiographs showed moderate horizontal alveolar bone loss (Fig. 5), which was attributed to long-standing periodontal disease. The gingival overgrowth in the upper left first premolar area extended and covered the occlusal surfaces of the teeth. As seen in Fig. 4, the gingiva was secondarily ulcerated due to occlusal trauma, and was painful.

The patient reported having similar gingival lesions 4 years previously which were excised by gingivectomy at a different clinic. One year later the gingiva started to enlarge again and was excised for the second time 2 years ago. However, a histological diagnosis was not available.

The patient's medical history included chronic hypertension that was controlled by amilodipine, a calcium channel blocker agent, carvedilol, perindopril and aspirin. Previously, he was treated with nifedipine, however this agent was substituted by his physician on the request of the referring dentist who attributed the gingival enlargement to the nifedipine medication. The patient was unaware of his HIV-status, and did not have any suggestive findings in this respect. No skin lesions could be detected, and except for his chronic hypertension, the patient claimed to be healthy.

After the patient had given informed consent, an incisional biopsy was taken under local anaesthesia from the exophytic mass of the palatal soft tissue opposite the left upper canine area. The specimen was submitted for histopathological examination and diagnosed as Kaposi sarcoma. The growth was polypoid in nature and consisted of sub-acutely inflamed vascular tissue. Large capillary spaces as well as smaller capillaries were present. In areas solid proliferations of spindle-shaped cells with red blood cell extravasation were seen (Fig. 6), and the cells were positive for factor VIII (Fig. 7). Figure 8 shows the drug-induced gingival hyperplasia portion of the biopsy specimen demonstrating the connective tissue hyperplasia component.

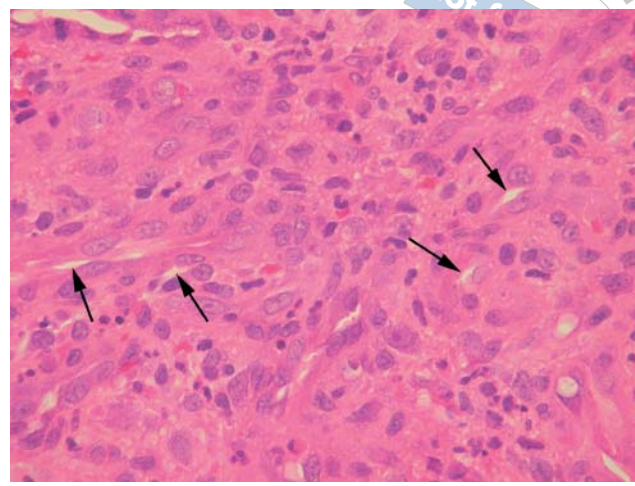

Fig. 6 Proliferation of plump spindle-shaped cells forming vascular slits (arrows). H&E stain ×150.

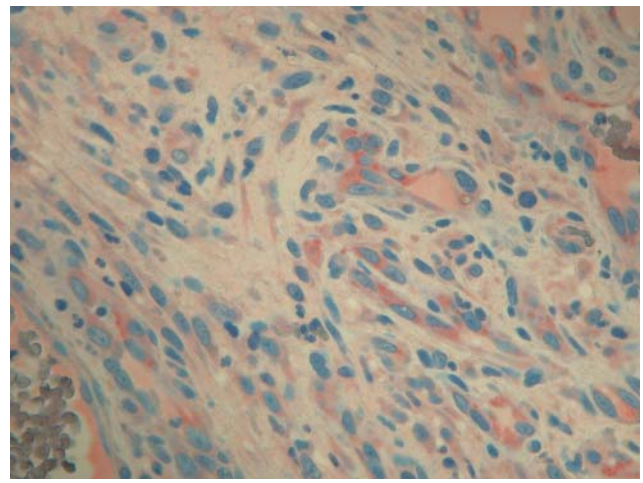

Fig. 7 Brick-red cytoplasmic positivity for Factor VIII of stromal spindle-shaped cells. (Immunoperoxidase stain, ×150).

After informing the patient the definite diagnosis of his oral condition, he was advised to have a blood test to establish his HIV-status. However, the patient firmly refused, and refrained from attending our clinic again. To the best of our knowledge the patient has not had any treatment until today, three months after the diagnosis of KS. The importance of having an HIV test was explained to him, as well as the benefits of early treatment for his oral condition, but in vain.

DISCUSSION

The gingiva may be the site of a great number of overgrowths: neoplastic lesions, gingival reactive over-

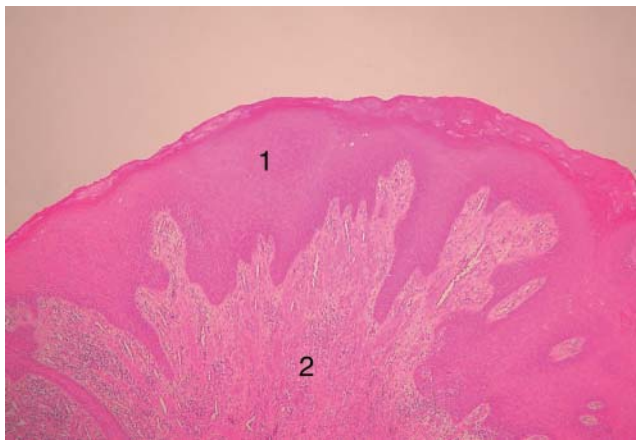

Fig. 8 Microscopic view of the reactive gingival hyperplasia portion of the biopsy. Note the acanthotic epithelium (1), and the chronic inflamed connective tissue core (2). (H&E stain ×100).

growths with or without calcification, plaque induced and drug induced gingival enlargements and gingival fibromatosis in association with one of several hereditary syndromes such as Zimmermann-Laband, Murray-Puretic-Drescher, Rutherfurd, Cross syndrome (Regezi and Sciubba, 1993; Feller et al, 2004).

There have been reports in the literature of KS in association with cyclosporin-induced gingival hyperplasia (Qunibi et al, 1988), and KS lesions which mimic in their clinical appearance gingival hyperplasia (Bowie and Back, 1999). However, to the best of our knowledge this is the first time that an association between calcium channel blocker induced gingival enlargement and KS has been reported.

Gingival overgrowth induced by calcium channel blockers is a well established phenomenon (Ellis et al, 1999; Miranda et al, 2001). It usually develops in 6 months following initiation of treatment and is a result of direct drug effect in the presence of plaque induced gingival inflammation (Bullon et al, 1994; Seymour, 1991). Histologically such overgrowths are characterized by changes in the gingival epithelium and the underlying connective tissue. The gingival epithelium is usually parakeratinized with elongated rete pegs. The underlying connective tissue contains dense collagen fibres with an inflammatory cell infiltrate composed mainly of plasma cells. In our case the histological findings are characteristic of a hyperplastic process (Fig. 8). However, there are cases where the histological examination exhibits redundant tissue of apparently normal composition (Neville et al, 2002).

It is not uncommon to experience recurrence of drug-induced gingival overgrowth in spite of repeated periodontal surgery, if the causative drug has not been discontinued, and if there is an inadequate plaque control. Plaque-induced gingival inflammation exacerbates the initial effects of the calcium channel blocker agents, and once the gingival enlargement is established, the further plaque accumulation might be the result of plaque control impairment posed by the gingival overgrowth (Pilloni et al, 1998; Ellis et al, 1999).

It is impossible to determine whether, in this case, the poor plaque control was a contributing factor to the development of the drug induced gingival overgrowth component or the consequence of it. At the examination, the enlarged gingiva was erythemathous, lobulated and in areas resembled a pyogenic granuloma. It was not tender, except for the traumatized occlusal and palatal soft tissue in the upper left anterior segment and premolars. However, it bled readily on probing. The plaque control was inadequate and the condition caused the patient a great deal of discomfort. The severity of the gingival overgrowth and the complete lack of response to periodontal therapy were worrisome indicators. We suspected the presence of a more severe underlying condition, in addition to the chronic medication and the inadequate plaque control, may have played a role in the pathogenesis of the dramatic signs and symptoms observed in this case.

The histopathologic examination of the incisional biopsy confirmed that the gingival overgrowth was KS. KS is the most common neoplasm seen in subjects with acquired immunodeficiency syndrome (AIDS), and in 22% the initial presentation is in the oral cavity. In 50-80% of HIV seropositive subjects with KS, the oral tissues are involved (Lager et al, 2003; Lausten et al, 2003; Antman and Chang, 2000; Rosenberg et al, 1984; Reichart et al, 1993; Ramirez-Amador et al, 1993; Ficarra et al, 1998).

The histological diagnosis of oral KS is relatively straightforward when the lesions are advanced. It is characterized by spindle cells forming a nodular tumour-like mass with poorly defined slit-like vascular spaces and the presence of extravasated erythrocytes. In the majority of cases the spindle cells express HHV-8 DNA sequences, CD34, CD31 and factor VIII antigens when immunohistochemical methods are applied (Neville et al, 2002; Jordan and Regezi, 2003; Lager et al, 2003). The spindle cells in KS originate from angiogenic mesenchymal cells which proliferate and differentiate in response to cytokines released by HHV-8 infected cells and HIV infected cells. The HHV-8 infected cells include peripheral blood mononuclear cells and B lymphocytes, and locally, tumour spindle cells, macrophages, endothelial cells, epithelial cells and lympho-

cytes (Lager et al, 2003; Cortan et al, 1999; Hille et al, 2002; Webster-Criaque, 2002; Cannon et al, 2003).

HIV infected cells include circulating T lymphocytes and monocytes and locally, Langerhans cells, macrophages and lymph node follicular cells (Cortan et al, 1999). The presence of HIV gene products are not mandatory for the development of KS, since KS can occur in HIV-seronegative patients as well (Lager et al, 2003; Cortan et al, 1999).

In addition, HHV-8 DNA may be found in semen, urine, rectal specimens and oral fluids. HHV-8 is frequently shed in saliva of HIV-seropositive subjects. The oral cavity may be a site of recurrent viral innoculation, and the oral epithelial cells may be the site of viral latency and replication (Webster-Criaque, 2002; Cannon et al, 2003; Beyari et al, 2003). These findings can explain the high prevalence rate of oral tissue involvement in subjects with KS. HHV-8 may be transmitted via sexual routes and via viral shedding in the oral cavity in a non-sexual manner within households (Cannon et al, 2002; Pauk et al, 2000; Beyari et al, 2003).

African endemic KS can be divided into 4 subtypes: nodular, infiltrative, florid and lymphadenopathic. The nodular type is a slowly progressive disease, which mimics the classic form of KS in its behaviour. Only 10-20% die of the disease after 8-10 years, but 25% might die of secondary malignancy. The infiltrative type is characterized by local invasion and involves underlying soft tissues and bone. Distinctive features of the florid type include a rapidly progressive lesion and frequent visceral involvement. The lymphadenopathic type, occurs primarily in Black children and typically involves lymph nodes and occasionally visceral organs without skin involvement. The prognosis of the infiltrative, florid and lymphadenopathic types of KS is overall poor and depends on the patient's immune status (Neville et al, 2002; Wang et al, 1997; Cottoni and Montesu, 1996; Iscovich et al, 2002).

The natural clinical course of epidemic HIV-associated KS in Africa is to some extent different from the endemic varieties of African KS. The lymphodenophatic type of endemic KS which affects children is not associated with HIV infection. The nodular type in HIV-associated KS is more aggressive than the chronic nodular type but less invasive than the locally infiltrative type seen in the endemic African KS. In general the epidemic African HIV-associated KS involves lymph nodes and visceral organs more frequently and is less responsive to treatment than the endemic African forms. In addition HIV-seropositive associated KS subjects with oral lesions have a higher death rate than those having exclusively cutaneous lesions, and the average survival of patients with oral KS is 21 months (range 3-45 months) (Reichart, 2003; Rohrmus et al, 2000).

On clinical and histological grounds we can assume that our case had a nodular type of oral KS. However not all the gingival lesions may have necessarily been KS, but rather some lesions were drug-induced gingival hyperplasia. The patient was in good physical state, the underlying alveolar bone was not affected by the lesions, and to the best of our knowledge no visceral organs or skin involvement were present.

The treatment of AIDS-associated KS is not generally effective. There is no cure for KS and the treatment is targeted to alleviate symptoms: reduce pain and bleeding, improve aesthetics and mastication and prevention of disease progression when possible (Lager et al, 2003; Lausten et al, 2003).

The patient in this case was advised to have a blood test in order to evaluate his HIV status, however he firmly declined on several occasions. We felt strongly that the establishment of the HIV-status of the patient is beneficial to the patient, and mandatory to determine the best treatment modality. The issue of refusing to have an HIV blood test in spite of the presence of suggestive oral lesions, as in this case, is an important public health concern in addition to the adverse personal consequences. The first line of management should be the introduction of anti-retroviral drug therapy to reduce the HIV-1 viral load and to restore the CD4+T cell counts. Such mode of therapy has been associated with regression in the size of existing KS lesions and the decrease in numbers of new lesions (Dezube, 2000; Ledergerber et al, 1999).

Asymptomatic macular oral lesions do not require active therapy and should be observed only. Large symptomatic nodular exophytic lesions can be treated by intralesional chemotherapeutic drugs such as sclerosing agents and vinblastine. Radiation therapy, cryosurgery, excisional surgery of large solitary lesions, photodynamic therapy, infrared coagulation and a variety of chemotherapeutic and immune modifier regimens are also recommended (Reichart, 2003; Lausten et al, 2003; Schwartz, 1996). Without treatment the lesions may regress, but tend to recur as the immune status of the AIDS patient deteriorates. However, no treatment modality can eradicate completely the oral lesions, and they tend to recur.

CONCLUSION

This case demonstrates that gingival overgrowths with a trivial history and apparently a clear causative factor,

may turn out to be a neoplasm. This bears significant clinical consequences. Attempting to remove such an extensive overgrowth, mistaken to be calcium channel blocker gingival enlargement, by external bevel gingivectomy, can be met with surgical complications of excessive intra-operative bleeding.

It is recommended, when there is any suggestive doubt in respect to the nature of the gingival overgrowth, to initially perform a small but adequate incisional biopsy to rule out neoplasms such as KS, leukaemia and lymphoma. Final diagnosis is ultimately made by microscopic examination which is essential for distinguishing between lesions with similar clinical appearances.

ACKNOWLEDGEMENT

The authors wish to thank Mrs. S. Revell for the typing and help in the composition of this manuscript.

REFERENCES

Antman K, Chang Y. Kaposi's sarcoma. N Engl J Med 2000;342: 1027-1038.

Beyari MM, Hodgson TA, Cook RD, Kondowe W, Molyneux EM, Scully CM, et al. Multiple Human herpesvirus-8 infection. J Infec Dis 2003;188:678-689.

Bowie SA Jr, Back D. Oral Kaposi's sarcoma in a non-AIDS patient. Gen Dent 1999;47:413-415.

Bullon P, Machuca G, Martinez-Sahuquillo A, Rios JV, Rojas J, Lacelle JR. Clinical assessment of gingival hyperplasia in patients treated with nifedipine. J Clin Periodontol 1994;21:256-259.

Cannon MJ, Dollard SC, Black JB, Edlin BR, Hannah C, Hogan SE, et al. Risk factors for Kaposi's sarcoma in man seropositive for both human herpes virus 8 and human immunodefiency virus. AIDS 2003;17:215-222.

Chou LL, Epstein J, Cassol SA, West DM, He W, Firth JD. Oral mucosal Langerhans' cells as target, effector and vector in HIV infection. J Oral Pathol Med 2000;29:394-402.

Cortan RS, Kumar V, Collins T, Robbins SL, editors. Diseases of immunity. In: Robbins Pathologic Basis of Disease. 6th ed. Philadelphia: W.B Saunders 1999:248-249.

Cottoni F, Montesu MA. Kaposi's sarcoma classification: A problem not yet defined. Int J Dermatol 1996;35:480-483.

Cutler CW, Jotwani R. Antigen presentation and the role of dendritic cells in periodontitis. Periodontol 2000 2004;35:135-157.

Dezube BJ. New therapies for the treatment of Aids-related Kaposi sarcoma. Curr Opin Oncol 2000;12:445-449.

Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ, Mark Thompson J. Prevalence of gingival overgrowth induced by calcium channel blockers: A community-based study. J Periodontol 1999;70:63-67.

Feller L, Buskin A, Raubenheimer EJ. Cemento-Ossifying Fibroma: Case report and review of the literature. Int J Acad Periodontol 2004;6:131-135.

Ficarra G, Berson AM, Silverman S Jr, Quivey JM, Lozada-Nur F, Sooy DD, et al. Kaposi's sarcoma of the oral cavity: A study of 134 patients with a review of the pathogenesis, epidemiology, clinical aspects and treatment. Oral Surg Oral Med Oral Pathol 1988;66:543-550.

Fuji A, Matsumoto H, Nakao S, Teshigawara H, Akimoto Y. Effect of calcium-channel blockers on cell proliferation, DNA synthesis and collagen synthesis of cultured gingival fibroblasts derived from human nifedipine responders and non-responders. Arch Oral Biol 1994;39:99-104.

Henderson JS, Flynn JC, Tucci MA, Tsao AK, Zebrowski EJ, Odlum O, et al. Site specific variation in metabolism by human fibroblasts exposed to nifedipine in vitro. J Oral Pathol Med 1997;26:6-10.

Hille JJ, Webster-Cyriaque J, Palefski JM, Raab-Traub N. Mechanism of expression of HHV-8,EBV and HPV in selected HIV-associated oral lesions. Oral Dis 2002;8:161-168.

Iscovich, J, Boffetta P, Franceschi S, Azzi E, Sarid R. Classic Kaposi sarcoma: Epidermiology and risk factors. Cancer 2000;88:500-517.

Jordan RCK, Regezi JA. Oral spindle cell neoplasms: A review of 307 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:717-724.

Krown SE. Acquired immunodefiency syndrome-associated Kaposi's sarcoma. Med Clin North Am 1997;81:471-494.

Lager I, Altini M, Coleman H, Ali H. Oral Kaposi's sarcoma: a clinicopathologic study from South Africa. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;96;701-710.

Lausten LL, Fergusen BL, Barker BF, Cobb CM. Oral Kaposi sarcoma associated with severe alveolar bone loss: Case report and review of the Literature. J Periodontol 2003;74:1668-1675.

Ledergerber B, Telenti A, Egger M. Risk of HIV-related Kaposi's sarcoma and non-Hodgkin's lymphoma with potent antiretroviral therapy: Prospective cohort study. Br Med J 1999;319:23-24.

Miranda J, Brunet L, Roset P, Berini L, Farre M, Mendieta C. Prevalence and risk of gingival enlargement in patients treated with nifedipine. J Periodontol 2001;72:605-611.

Myint M, Juan ZN, Schenck K. Reduced numbers of Langerhans cells and increased HLA-DR expression in keratinocytes in the oral gingival epithelium of HIV-infected patients with periodontitis. J Clin Periodontol 2000;27:513-519.

Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology, 2nd ed. Philadelphia: W.B. Saunders 2002;484-488.

Pauk J, Haung ML, Brodie SJ, Wald A, Koelle DM, Schcker T, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med 2000;343:1369-1377.

Pilloni A, Camarago PM, Carere M, Carranza Jr FA. Surgical treatment of cyclosporine A- and nifedipine- induced gingival enlargement :gingivectomy versus periodontal flap. J Periodontol 1998;69:791-797.

Qunibi WY, Akhtar M, Ginn E, Smith P. Kaposi's sarcoma in cyclosporine-induced gingival hyperplasia. Am J Kidney Dis 1988;11: 349-352.

Ramirez-Amador V, Gonzalez M, De la Rosa E, Esquivel L, Volkov P, Ochoa, FJ, et al. Oral findings in Mexican AIDS patients with cancer. J Oral Pathol Med 1993;22:87-91.

Regezi JA, Sciubba JJ. Oral Pathology. Clinical-pathologic correlations. 2nd ed. Philadelphia: W.B.Saunders 1993;194-238.

Reichart PA, Langford-Kuntz, Pohle HD. Epidemic orofacial Kaposi's sarcoma (EKS)-Report of 124 cases. Oral Oncol Eur J Cancer 1993;29B:187-189.
Reichart PA. Oral manifestations in HIV infection: fungal and bacterial infections, Kaposi's sarcoma. Med Microbiol Immunol 2003;192:165-169.
Rohrmus B, Thoma-Greber EM, Bonger JR, Rocken M. Outlook in oral and cutaneous Kaposi's sarcoma. Lancet 2000;356:2160.
Rosenberg RA, Schneider KL, Cohen NL. Head and neck presentations of acquired immunodeficiency syndrome. Laryngoscope 1984;94:401-405.
Schwartz R A. Kaposi's sarcoma: advances and perspectives. J Am Acad Dermatol 1996;34:804-814.
Seymour RA. Calcium channel blockers and gingival overgrowth. Br dent J 1991;170:376-379.
Silverstein LH, Koch JP, Lefkove MD, Garnick JJ, Singh B, Steflik A. Nifedipine-induced gingival enlargement around dental implants: a clinical report. J Oral Implantol 1995;21:116-120.
Sooriyamoorthy M, Gower DB. Drug induced gingival overgrowth: Clinical features and possible mechanisms. Med Sci Res 1989;17:881-884.
Wang CYE, Schroeder AL, Daniel WP. Acquired immunodeficiency syndrome-related Kaposi's sarcoma. Mayo Clin Proc 1995;70:869-879.
Webster-Cyriaque J. Development of Kaposi's sarcoma in a surgical wound. N Engl J Med 2002;346:1207-1210.

Reprint requests:
Professor L Feller
Department of Periodontology and Oral Medicine
Box D26, Faculty of Dentistry
Medunsa 0204
South Africa
E-mail: revell@medunsa.ac.za