Oral medicine case book 50:
HIV associated Kaposi sarcoma

SADJ June 2013, Vol 68 no 5 p232 - p235

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CASE REPORTS

Case no 1

A 33-year-old female of African descent was referred to the Oral Medicine Clinic from a neighbouring rural clinic. The patient presented with painful nodular lesions on her gingivae and hard palate, having noticed the enlarging lesions two months earlier when they started to impair her speech and mastication. She reported that she had been diagnosed with HIV infection two years earlier and had been on antiretroviral medication for the past eleven months. The patient had a recent history of pulmonary tuberculosis and cryptococcal meningitis. At the time of the initial examination, her CD4 count was 230/µl (normal levels in adults: ±1000 cells/µl) and the laboratory report indicated viral load failure, i.e. the patient was no longer responding satisfactorily to the HAART therapy.

Extra-oral examination revealed palpable cervical lymph nodes. Purple patches and nodules were present on her forearms and lower limbs. A nodular exophytic growth was present intra-orally and it covered the entire anterior part of the hard palate. Similar nodular growths were present on the buccal gingiva, in the upper left quadrant and on the lingual gingiva in the lower right quadrant. The lesions had a purple-to-red discolouration and were covered by atrophic mucosa, with areas of erosion covered by a yellow slough (Figures 1, 2). The remaining gingivae displayed areas of desquamation and the lower labial and buccal mucosa presented with several shallow ulcers, presumably as a result of an accompanying neutropenia. The patient reported that she neither smoked nor used any alcoholic beverages.

On the basis of the medical history and the clinical features, a clinical diagnosis of HIV associated Kaposi sarcoma was made. An incisional biopsy of the lesion in the upper left quadrant was performed and post-operative bleeding was

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ACRONYMS

AIDS:	Acquired Immune Deficiency Syndrome
HAART:	Highly Active Antiretroviral Therapy
HHV8:	Human Herpes Virus 8
HIV:	Human Immunodeficiency Virus
HIV-KS:	HIV associated Kaposi Sarcoma
KS:	Kaposi Sarcoma
KSHV:	Kaposi Sarcoma Herpes Virus

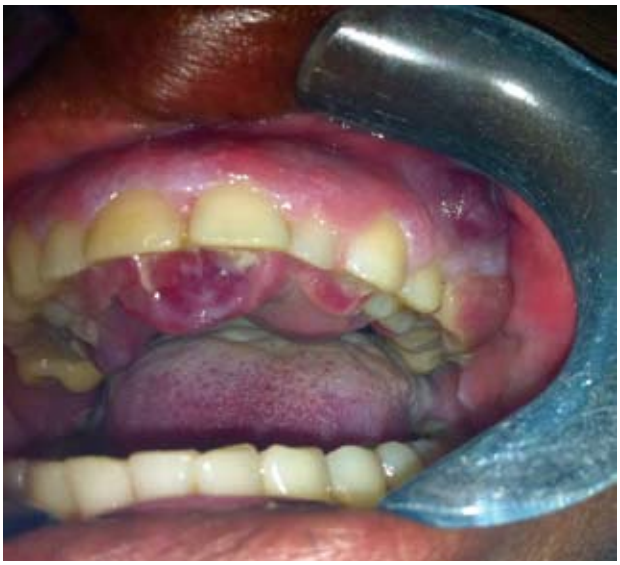

Figure 1: This photograph of Case No 1 shows multifocal exophytic soft tissue lesions on the hard palate and upper left buccal gingiva and buccal fold.

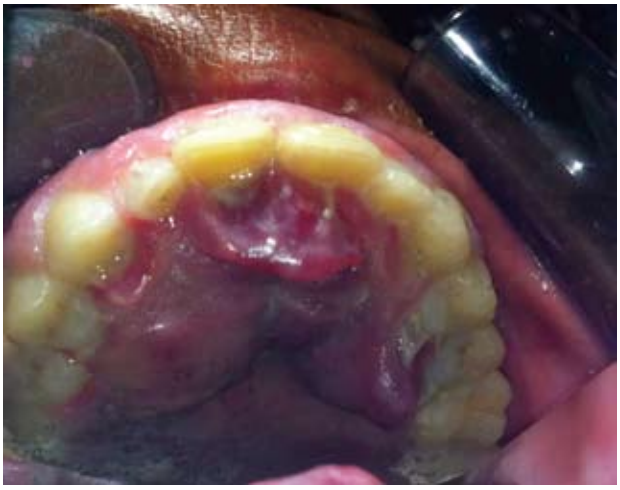

Figure 2: This occlusal view of Case 1 displays the extent of the soft tissue lesion on the hard palate and also shows the surface ulceration.

controlled by cauterising the biopsy site. The patient was provided with a 0.2% aqueous solution of chlorhexidine digluconate, as an antibacterial mouthwash, and instructed to return after two weeks for further management.

The histopathological report indicated that the surface epithelium exhibited acanthosis, parakeratosis and superficial degenerative cells. The connective tissue core of the lesion exhibited haemorrhage, granulation tissue and the presence of dilated small ectatic vascular channels, suggestive of a haemangioma. The cells also stained positive for Human Herpes Virus 8 (HHV-8).

Considering the clinical features, the medical history and histopathology, a clinical diagnosis of HIV associated Kaposi sarcoma was confirmed. At the follow-up appointment, the test results were discussed with the patient and she was referred for further management to the Kaposi Sarcoma Clinic at the nearby tertiary hospital. Subsequently, further contact with the patient could not be re-established and no follow-up information was available at the time of publication.

Case no 2

A 26-year-old African female presented at the Oral Medicine Clinic with a growth on her palate. The lesion had grown rapidly over the previous 3 weeks and bled on touch. The patient reported that she was anaemic and was taking folic acid and iron supplements for the condition. She admitted to smoking approximately 10 cigarettes per day. Extra-oral examination revealed bilateral cervical lymphadenopathy and on intra-oral examination the gingivae were seen to be extremely erythematous. In addition a sessile nodular soft tissue growth was present on the anterior part of the hard palate and on the palatal gingiva alongside the upper incisors and right canine. The lesion was firm in consistency, had a red-to-purplish appearance, with surface ulceration (Figure 3). A purplish plaque was present on the left side of the central hard palate, extending towards the midline (Figure 4). The general oral hygiene of the patient was poor, with abundant deposits of plaque and calculus throughout the oral cavity.

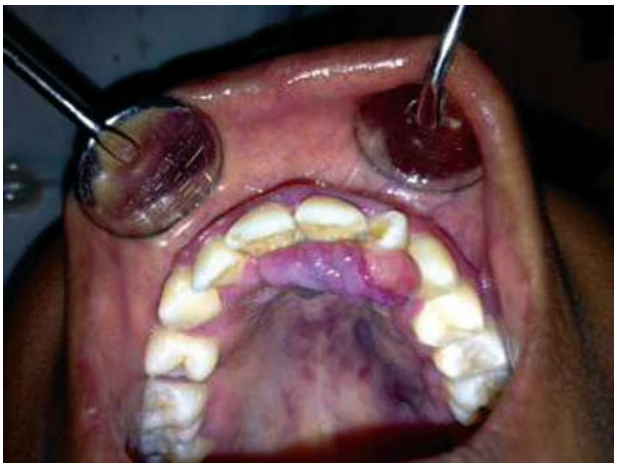

Figure 3: An exophytic soft tissue growth with a purple-to-red colouration is present on the anterior hard palate of the patient (Case No 2) and the lesion extends from the mesial aspect of tooth 12 to the distal aspect of tooth 23.

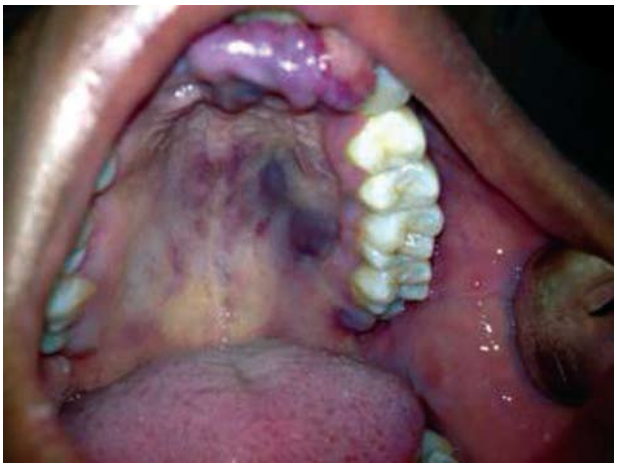

Figure 4: The left side of the hard palate in Case No 2 shows a slightly raised purple-red lesion that extends towards the midline.

The differential diagnosis of the lesion included multifocal Kaposi sarcoma, pyogenic granuloma, haemangioma and necrotising ulcerative gingivitis. The patient was placed on a five-day course of antibiotics and was instructed in the use of a 0.2% aqueous solution of chlorhexidine digluconate as an antibacterial mouthwash. She was referred for dental cleaning and plaque control and for HIV testing and blood studies that included a CD4 count, a full blood count, differential white cell count and iron levels. Her results revealed HIV infection with a low CD4 count and that the patient was anaemic, sideropaenic and neutropaenic.

These test results, taken together with the typical history and clinical appearance resulted in a final diagnosis of HIV associated Kaposi sarcoma, without recourse to a biopsy. She received further post-test counselling before being referred to the Kaposi Sarcoma Clinic at the local tertiary hospital for further management. At the time of publication, no further information regarding her progress was available.

Case no 3

A 30-year-old female of African origin presented at the Oral Medicine Clinic with a white lesion covering her palate and complaining that she suffered from a burning sensation in her mouth and dysgeusia. The patient reported that she had been diagnosed as HIV-positive five years earlier. However, as her CD4 levels were above the defined threshold of 200 cells/µl, she was ineligible to receive antiretroviral therapy.

Extra-oral examination revealed nothing of note. Intraorally, an extensive white pseudomembranous plaque was seen covering the left and right buccal mucosa, floor of mouth, tongue, attached gingivae and palate. The plaque could be wiped off, revealing a flat dark erythematous lesion on the palate (Figure 5). A provisional diagnosis of pseudomembranous oral candidiasis was made and a smear of the lesion was sent for Periodic-acid Schiff (PAS) staining. The patient was also referred to her local clinic to confirm her HIV-status and establish her CD4 levels. In the interim, the patient was put on a course of antifungal therapy consisting of a topical antifungal suspension (10 ml nystatin drops, 3 times per day), as well as systemic anti-fungal tablets (200mg fluconazole per day) for 14 days. On her return visit, a week later, the white pseudomembranous plaque-like lesion had resolved. This enabled better visibility of the underlying dark erythematous plaques. It became apparent that they were purplish-red in colour and involved both sides of the palate (Figure 6).

The laboratory results confirmed a diagnosis of oral candidiasis, HIV-positivity and a CD4 count of 248 cells/µl. Based on the medical history, test results and clinical features of the case, a clinical diagnosis of a HIV associated Kaposi sarcoma was made and therefore a biopsy was considered unnecessary. However, before a consultation at the Kaposi Sarcoma Clinic could be made, the patient was required to have been on antiretroviral therapy for at least a month to allow possible regression of the lesion. Consequently,

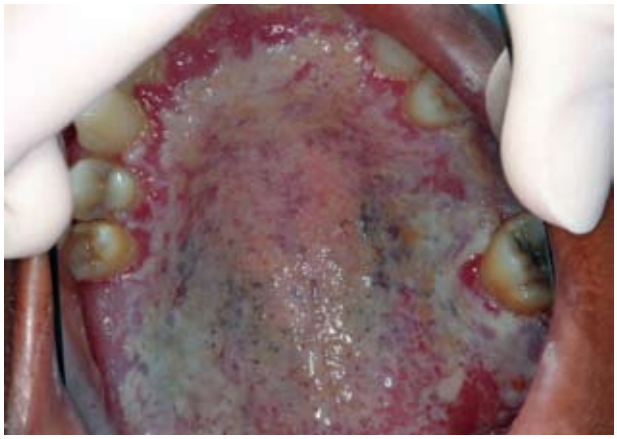

Figure 5: The entire palate is covered by a thick white pseudomembranous plaque overlying an erythematous lesion beneath.

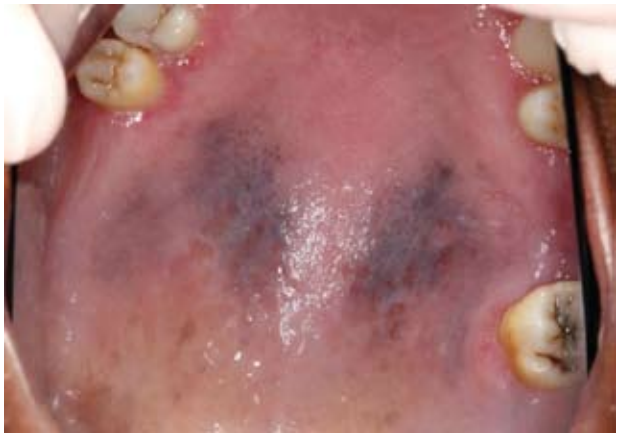

Figure 6: A week after anti-fungal therapy was initiated, the hard palate was clear and revealed the extent of the flat purplish-red lesions on either side of the mid-line on the central part of the palate.

the patient was referred for antiretroviral therapy which was commenced 3 weeks later and, as a consequence, the appointment at the Kaposi Sarcoma Clinic could be confirmed. Unfortunately, despite concerted efforts, further contact with the patient was lost and no further information regarding her progress was available at the time of publication.

DISCUSSION

The three cases presented above share a number of clinical features. All three are HIV-positive, young females who presented with multifocal Kaposi sarcoma of the oral cavity. In two cases, the patients had been diagnosed as HIV-positive prior to the appearance of the lesions. However, in one patient the diagnosis of Kaposi sarcoma had prompted the discovery of an underlying HIV infection. In two cases the lesions developed rapidly and grew to be quite extensive in size. The palate was the primary site in all three cases, whilst two had additional gingival and/or buccal lesions. In the one case, the patient presented with severe oral candidiasis, an AIDS-defining condition. Only one patient displayed extra-oral lesions reminiscent of KS. These features are all typical of HIV associated Kaposi sarcoma in South Africa.[1] Unfortunately, all three patients were lost to follow-up, an occurrence that is regretfully all too common in patients from severely disadvantaged backgrounds who get lost in an overstretched public health system.

CLINICAL PRESENTATION OF KS

Kaposi sarcoma (KS) was first described in 1872 by the Hungarian dermatologist, Moritz Kaposi and is categorised as a proliferating tumour of endothelial lineage involving blood and lymphatic vessels. It commonly affects the skin, mucosal surfaces of various anatomical sites, and lymph nodes as well as internal organs.[2,3,4] It is a low-grade neoplasm presenting as brown to red/blue cutaneous lesions or mucosal growths in the larynx, trachea, stomach, liver and colon. Prior to the onset of the HIV epidemic in the early 1980s, KS was considered to be a non-lethal condition found mostly on the extremities of elderly males of Mediterranean or Jewish descent. This classic type of KS mainly affects the skin and the mucosa of the oral cavity, genitalia and gastrointestinal tract and rarely metastasises to other organs and, at times, may even regress.[2,4,5]

Four clinical subtypes have been described: Classic KS, as described above; African endemic KS; KS in iatrogenically immunosuppressed patients (also known as transplant-associated KS); and HIV-related KS (HIV-KS). All these variants have similar histological features and start as purple to reddish macules that progress into plaques and ultimately become exophytic.[1, 3] African endemic KS is a common neoplasm found in sub-Saharan Africa and has four clinical variants that range from a mild condition similar to classic KS, to more aggressive forms affecting younger individuals and with a high mortality rate. Iatrogenic KS presents in immunodeficient individuals following organ transplantation or after continued exposure to immunosuppressive therapy for other reasons. Skin lesions are multifocal and oral and lymph node involvement is common.[2,5]

Presently, HIV-KS is considered to be the most prevalent malignancy in AIDS patients worldwide and is considered as one of the AIDS-defining conditions.[2,5] It is seen in patients who are not on highly active antiretroviral therapy (HAART) and it is an aggressive condition manifesting with disseminated involvement of the skin, mucosa and visceral organs.[2] In a first world setting, HIV-KS affects males more often than females, however, in sub-Saharan Africa with its high prevalence of HIV infection, especially in young females, the reverse trend is found with more females presenting with the condition.[1,6] HIV-KS typically presents on any area of the head and neck, trunk or extremities and the lesions are typically symmetrical and occur in skin lines and creases. The lesion has a pink to purple or brown to black discolouration and may be flat (macular), plaque-like (papular) or nodular. The individual lesions may coalesce to form large areas of tumour involvement.[5] The mouth is the most- frequently affected site and in approximately 20% of HIV positive individuals the oral cavity is the initial site of KS presentation. Oral lesions may develop at any stage of HIV infection but are frequently observed in individuals with low CD4 lymphocyte levels.[8, 3] Intra-orally, they may present as single or multiple lesions and tend to start out as single macules that progressively enlarge and coalesce to become nodular and ultimately exophytic lesions, the latter frequently presenting with superficial ulceration. The lesions are initially asymptomatic but may become painful as they enlarge and become secondarily infected. Necrotising periodontal disease may be superimposed on KS lesions when affecting the gingivae.[3] The prognosis of HIV-KS is extremely poor and if left untreated the anticipated survival is less than two years.[2,5]

AETIOLOGY AND PATHOGENESIS OF KS

All four subtypes of KS develop only after there is a preceding infection with the human herpes virus-8, also known as the Kaposi sarcoma herpes virus (KSHV). KSHV infection alone will, however, not result in the development of KS as other co-factors are needed before KS will manifest.[2,3,4,7] KSHV-antibodies and KSHV DNA are found in mononuclear cells in the peripheral blood of infected individuals and indicate an

increased risk of developing KS. In established KS lesions, of all four subtypes, KSHV DNA is found in most cells of the lesion.[6] The virus is also shed in body secretions, particularly saliva. It is known that saliva contains considerably higher levels of KSHV DNA than do other body secretions probably due to a high concentration of viral particles originating from the shed epithelial cells of the oral and oro-pharyngeal tissues.[3] The mode of transmission of KSHV is still controversial and include saliva, sexual contact, non-sexual horizontal transmission from mother to child and via blood transmission.[3,5] Current opinion favours saliva as the main mode of transmission, particularly in African countries where the prevalence rate of KSHV sero-conversion reach levels exceeding 50%.[7]

The pathogenesis of KS is dependent on several factors but there is a paucity of information regarding the complex interaction between these factors leading to the onset of the disease. The promotion of growth in malignant tissue is stimulated by numerous cytokines and growth factors, including vascular endothelial growth factor, tumour necrosis factor, interleukin 1, interleukin 6 and basic fibroblastic growth factor. Moreover, HIV infection enhances the effect of KSHV in as far as the HIV Tat gene (a viral protein that activates HIV transcription) seems to play a key role by inducing inflammatory cytokines and angiogenesis, and by enhancing endothelial cell infectivity for KSHV. Patients with the more aggressive form of HIV-KS have been shown to have the highest amounts of KSHV DNA in skin lesions, and the lowest CD4 lymphocyte levels (less than 200/µl). Patients who are on HAART show regression of the KS lesions with subsequently lower KSHV DNA loads and higher CD4 lymphocyte levels. However, a loss of HIV viral control (i.e. HIV RNA levels of exceeding 5000 copies/ml) is associated with an increased risk of developing KS.[5]

The characteristic histological features of KS lesions are the proliferating abnormal vascular structures causing slit-like vascular spaces lined by atypical endothelial cells and containing lympho-plasmacytic infiltrates. These vascular structures are surrounded by spindle cells and extravasated red blood cells and hemosiderin pigmentation. The spindle cells eventually become the dominant cell population and develop into fascicles that compress the vascular slits as the lesion gradually becomes more nodular in nature.[5] Most tumour cells within a KS lesion are spindle cells which express endothelial markers such as CD31 and CD34.[2,8] Spindle cells have a typical spindle-shaped morphology and originate from a lymphatic endothelium lineage. Most of the spindle cells are infected with KSHV and although KSHV latent genes are expressed in the spindle cells, lytic replication occurs in only a few. Advanced KS lesions appear to be due to an increase in the number of KSHV infected spindle cells.[8] In addition to spindle cells, KS lesions also contain other cell types including T-cell lymphocytes, monocytes, macrophages, erythrocytes and dendritic cells.[2]

TREATMENT

Currently, a variety of treatment modalities for the management of KS lesions are employed, however, none has been uniformly successful. Local therapy is normally the treatment of choice but has limited use in cases of multifocal HIV-KS. Local therapy includes surgical excision, intra-lesional chemotherapy, intra-lesional sclerosing agents, cryotherapy and laser therapy. The advantages of local therapy is that it has fewer side effects and offers a convenient route of administration. However, oral HIV-KS lesions are best managed by placing the patient on HAART and by instituting specific systemic therapy as soon as possible. Although KS tumour cells are radiosensitive, radiotherapy is not recommended for oral KS lesions as it may result in severe mucositis which, in itself, may become life-threatening in some cases. It has been suggested that oral HIV-KS lesions should be managed with systemic cytotoxic chemotherapy at an early stage when the CD4 lymphocyte levels are still relatively high. This will diminish the chances of progression to large exophytic lesions that have a distinctly poorer prognosis.[3,5]

CONCLUSION

In areas where highly active antiretroviral therapy (HAART) is readily available, such as industrialised countries, HIV-KS is relatively uncommon.[7] This may be attributed to the suppression of HIV replication associated with the improvement in the CD4 lymphocyte levels.[2,5] However, in sub-Saharan countries, HIV-KS is regularly seen largely due to the lack of access to HAART in resource-poor communities.[5] The South African National HIV Survey done in 2008 showed that the total prevalence of HIV-infected individuals, of two years and older in the whole South African population, to be roughly 11% with considerably higher levels, at 32.7% and 25.8% respectively for females and males, in the age cohort of 25-29 years.[9] Although the overall prevalence rate for HIV infection in the Western Cape is considerably lower than for the other provinces (estimated to be 6.27% for 2013[10]), the levels amongst young adults, especially young females, is still alarmingly high. Thus oral health care professionals in this area, as in all other parts of South Africa, should be on the alert to correctly diagnose AIDS-defining illnesses. Often patients are not aware of their HIV status and oral lesions may be the initial and frequently the sole presenting sign of HIV-infection. This provides the oral health care professional with an early opportunity to initiate the process leading to the diagnosis of retroviral disease with consequent benefits to the patient. Currently, when a patient is diagnosed with a suspected HIV-defining oral lesion, the patient needs to be sent to a local or regional clinic for HIV pretest counselling. This may result in a delay in diagnosis and unnecessary anxiety and emotional distress on the part of the patient. It is therefore suggested that oral health care professionals should be trained to do the appropriate pretest counselling themselves to ensure early diagnosis of HIV infection and prompt enrolment into a HAART programme.

Declaration: No conflict of interest declared.

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