Publication Types: Case Reports

Relationship between oral Kaposi 's sarcoma and HAART: Contribution of two case reports

Julián Campo Trapero [1], Jorge Del Romero Guerrero [2], Jorge Cano Sánchez [1], Carmen Rodríguez Martín [2], José Mª Martínez González [1], Antonio Bascones Martínez [1]

(1) Department of Medicine and Buccofacial Surgery, School of Dentistry, Complutense University of Madrid, Spain
(2) Sandoval Health Centre, Madrid Health Service, Madrid Regional Government, Spain

Correspondence:
Dr. Julián Campo
Departamento de Medicina y Cirugía Bucofacial
Facultad de Odontología
UCM. Avda Complutense s/n
28080 Madrid, Spain
E-mail: jcampo@odon.ucm.es

Received: 19/01/2008
Accepted: 27/04/2008

Indexed in:

- *Science Citation Index Expanded*
- *Journal Citation Reports*
- *Index Medicus, MEDLINE, PubMed*
- *Excerpta Medica, Embase, SCOPUS,*
- *Indice Médico Español*

Campo-Trapero J, Del Romero-Guerrero J, Cano-Sánchez J, Rodríguez-Martín C, Martínez-González JM, Bascones-Martínez A. Relationship between oral Kaposi 's sarcoma and HAART: Contribution of two case reports. Med Oral Patol Oral Cir Bucal. 2008 Nov 1;13(11):E709-13.

http://www.medicinaoral.com/medoralfree01/v13i11/medoralv13i11p709.pdf

Abstract

Two HIV infected patients not receiving Highly Active Antiretroviral Treatment (HAART) presented with epidemic Kaposi's sarcoma of the oral cavity. One patient initially refused HAART, but when the lesion became large enough to be noticeable he agreed to HAART associated with excision of the intraoral lesion by CO_2 laser. The other patient developed KS and progressed to AIDS at two years after ceasing HAART due to adverse effects; he was referred to hospital for renewed administration of HAART. In both cases, the lesions observed in the oral cavity were the first clinical manifestation of AIDS. These reports underline the close relationship between the use of HAART and the control of KS lesions, highlighting the important role of the dentist in the identification and early diagnosis of these oral lesions.

Key words: *AIDS, Kaposi's sarcoma, oral lesions, HAART, CO_2 laser.*

Introduction

In 1872, Moritz Kaposi described five patients with cutaneous-mucous red-violet lesions that he designated "multiple idiopathic hemorrhagic sarcomas". This condition later became known as Kaposi's sarcoma (KS), the name proposed by Sternberg in 1912 (1). KS is a malignant, multifocal systemic disease that originates in the vascular endothelium and follows a variable course. The most frequent localization is on the skin but it is also observed in mucous membranes, lymphatic system, and other organs (especially lung, liver, intestine, and stomach). Four clinical forms have been classified: classic KS, iatrogenic immunosuppression KS, Africa-endemic KS and epidemic KS (EKS), associated with HIV infection. EKS remains the most frequent malignant disease indicating AIDS. It was first reported in the 1980s and is more frequent in homosexual males (MSM, Men who have Sex with Men) or bisexual males with AIDS (around 25%) than in other risk groups (1-5%) (2). In the USA, there has been a reduction in EKS cases of more than 66% since the introduction of HAART (3). In Spain, 5.3% of patients diagnosed with AIDS between 2003 and 2006 had EKS (4).

All forms of KS are due to infection by human herpesvirus type 8 (HHV-8), also known as KS-associated herpesvirus (KSHV), which is transmitted via sexual route, blood, or saliva (5). In HIV-infected patients, presence of KS provides definitive diagnosis of AIDS. However, despite the therapeutic effect of HAART on KS, the disease continues to progress in some patients and specific treatment of the tumor with liposomal anthracyclines (daunorubicin and doxorubicin) is needed. The association of HAART with paclitaxel (Taxol®, Bristol-Myers Squibb Company,

NY, USA) is a third therapeutic option when the disease progresses despite HAART treatment and involves other organs (6).

Since the introduction of the above therapies, the proportion of AIDS patients with oral KS has fallen from around a third to less than 20% in developed countries, due to new therapies (7). We present two cases of EKS of oral cavity as the first clinical manifestation of AIDS in patients who were not receiving HAART at the time of their EKS diagnosis. Their subsequent clinical course is also reported.

Case reports

- Case report 1

A 34-year-old MSM, diagnosed with HIV infection in 1989 and with syphilis and hepatitis B in 1999. He reported that he did not consume tobacco or other drugs. In April 1999, he had undergone a fine needle aspiration (FNA) biopsy of the right submaxillary gland that revealed a mesenchymal tumor with no atypical mitosis. The histopathology report identified a major salivary gland with KS. In June 1999, he was found to have a TCD4+ lymphocyte count/% of 1.111 cells/mm^3/30%, CD4/CD8 ratio of 0.6, and HIV-1 RNA viral load of 10318 copies/ml (bDNA). The patient was diagnosed with stage C1 HIV infection (AIDS), and his physician at the Sexually Transmitted Disease Clinic recommended HAART treatment with ddI (didanosine), d4T(estavudine), and efavirenz. However, the patient refused this therapy, citing fear of adverse effects.

In July 1999, he returned to our Oral Medicine Clinic at the Dental School with a 4-month-old reddish-blue lesion, 1.5 x 1 cm in size, of soft consistency and mildly painful on palpation, on the marginal gingiva at teeth 1.4, 1.5, and 1.6 (Fig. 1a). Tooth 1.5 had a periodontal pocket of 8 mm but X-ray showed no bone loss (Fig. 1b). The patient was strongly recommended to commence HAART for suspicion of KS but again refused this therapy. He missed the appointment made for a biopsy, finally returning six months later in January 2000. Examination revealed an almost doubling in size of the intraoral lesion (2.5cm x 2cm) and multiple macular lesions on skin of abdomen, left groin, and sole of right foot, suggesting EKS (Figs. 2a-d). The count/percentage of TCD4+ lymphocyte count/percentage was 858 cells/ml/21.5%, the CD4/CD8 ratio was 0.4, and the HIV-1 RNA viral load was 14,919 copies/ml. He was told that although his immunological situation did not appear highly compromised, the HIV disease was progressing rapidly and he was again urged to start HAART. He returned to our clinic one month later, reporting that the lesion was larger and noticeable when he laughed or talked. For esthetic reasons, the patient agreed to surgical excision of the lesion with CO_2 laser (20W) to prevent bleeding. Tooth 1.5 was extracted in the same surgical procedure. The pathology report confirmed the lesion as KS and the patient finally agreed to receive HAART with ddI (didanosine), d4T (estavudine), and efavirenz. He was followed up at one month and at three months and no signs of recurrence were observed. At the three-month follow-up, the patient had non-detectable viral load and the TCD4+ lymphocyte count had risen to 954 cells/mm^3.

- Case Report 2

We present the case of a 23-year-old male diagnosed with HIV infection in 1986 and with a history of hepatitis B and oral candidiasis (February 2002). He reported being a regularly cannabis user, smoker of 10 cigs/day, and a non-drinker of alcohol. He received HAART with nelfinavir +d4T (stavudine) +3TC (lamivudine) from 1999 until October 2000, when he stopped this treatment because of adverse effects. When he first visited our Oral Medicine Clinic in March 2002, he was found to have a TCD4+ lymphocyte count/% of 8 cells/ml/0.4%, CD4/CD8 ratio of 0.0 and HIV-1 RNA viral load of 9308 copies/ml (bDNA). The intraoral examination revealed several purplish macular/nodular lesions in the upper palatal area (bilateral) at teeth 1.6-1.8 and 2.6-2.8; and in the lower buccal gingiva

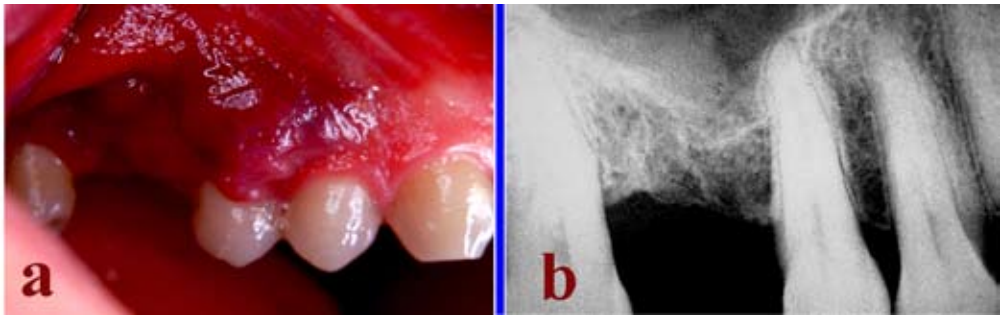

Fig. 1. CASE 1: (a.) Four-month-old reddish-bluish lesion on the marginal gingiva at teeth 1.4-1.5 and 1.6. (b) X-ray showed no bone loss at tooth 1.5.

.

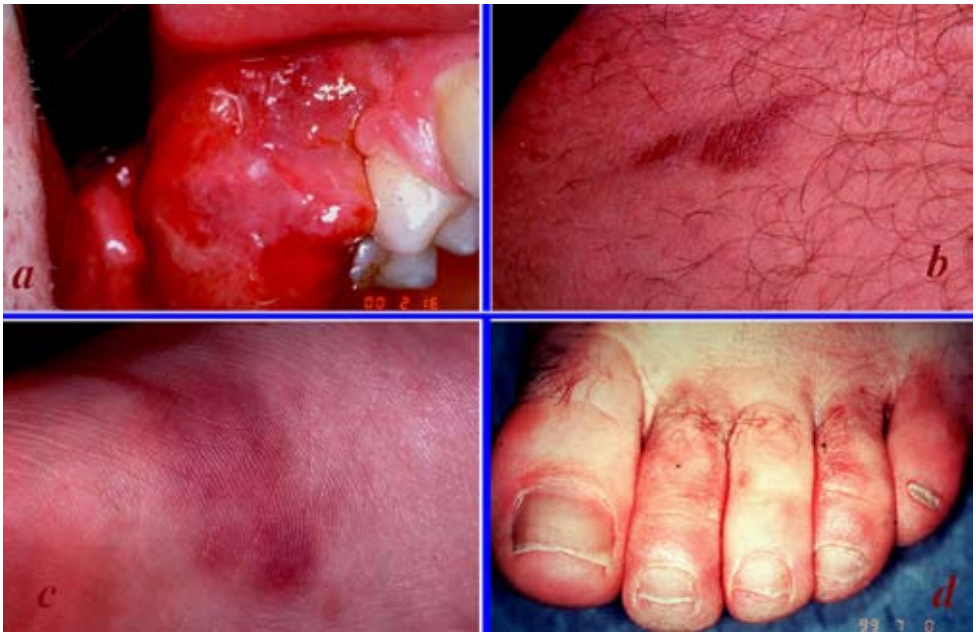

Fig. 2. CASE 1: (a)- Increase of tumor 6 months later (2.5cm x 2cm). (b,c,d) Multiple macular lesions on skin of abdomen and foot.

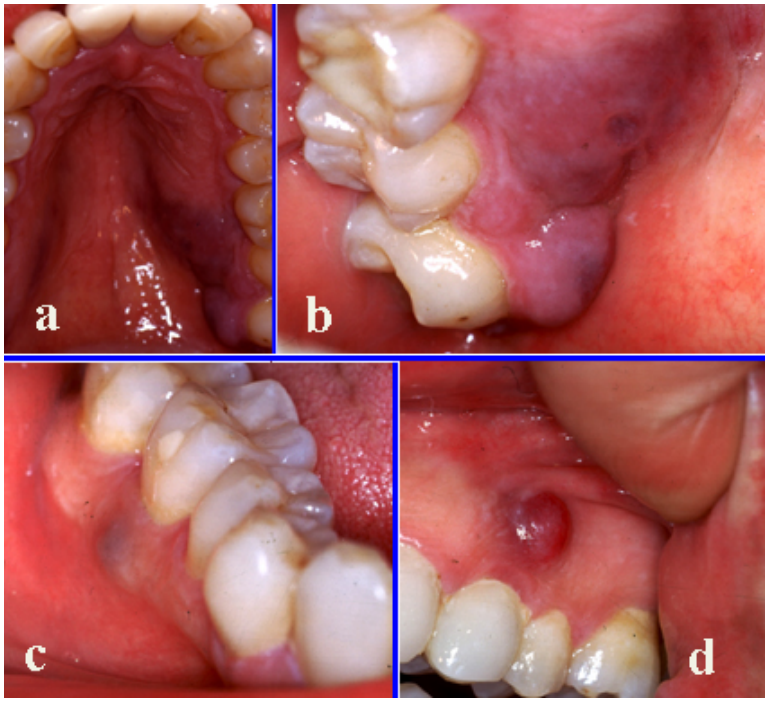

Fig. 3. CASE 2: (a,b). Several purplish macular/nodular lesions in upper palatal area. (c) Macular lesion on lower buccal gingiva at tooth 4.6. (d) Isolated nodule on buccal gingiva at tooth 2.4.

at tooth 4.6, with an isolated nodule on buccal gingiva at tooth 2.4 (Figs 3a-d). The lesions were clinically compatible with KS and this diagnosis was confirmed by the histopathological study. The patient reinitiated HAART with AZT (zidovudine), d4T (stavudine), and abacavir, which he has continued to receive to date with a good immunological and virological response. In December 2002, immune system recovery was observed, with TCD4+ and TCD8+ lymphocyte counts/% of 165 cells/ml/7% and 1538 cells/ml/63%, respectively, CD4/CD8 ratio of 0.1, and HIV-1 RNA viral load of <50 copies/ml (bDNA). The intraoral KS lesions had completely disappeared with no need for further treatment, despite the absence in his therapeutic regimen of any protease inhibitor (PI) to avoid the adverse effects, probably related to nelfinavir, which had led the patient to abandon HAART.

Discussion

KS is the malignant oral neoplasia most frequently associated with HIV-infection, although there has been a steep decline in its incidence since the introduction of HAART (8,9). It mainly affects MSM and is indicative of AIDS, with the highest incidence of KS lesions in the 30-38 year age group with 5 cases /100 people/yr (9).

HHV-8, immunosuppression, genetic predisposition, direct effect of HIV, coinfection of pathogens by sexual route, and production cell proliferation-inducing cytokines, among other factors, all play a role in the pathogeny of KS (10).

Oral cavity lesions appear as bluish-red or purple macular, papular, or nodular lesions that can ulcerate and cause local destruction, with the palate and gingiva as the most frequent oral sites (11). The ulceration and local destruction caused by KS lesions sometimes mandates the extraction of teeth that have lost support, as in our first case presented here. Some authors have reported the first clinical sign of KS to be in oral cavity in 20% of cases and simultaneously in oral cavity and skin or other sites in 70% of cases (11,12).

There is currently no curative therapy for AIDS-related EKS (9). The utilization of HAART, including at least one PI, not only stabilizes or slows the progression of lesions but can also reduce or eradicate them (7,13). More recent studies have postulated that the immune response may contribute to the reduction in the incidence of EKS during HAART, explaining the frequent and rapid resolution of EKS with initiation of this therapy (14,15). In the two present cases, the HAART did not include a PI, and there was even a total remission of symptoms in the second case with no need for any other therapeutic measure.

Interestingly, an HIV viral load of >5000 cop/cm3 was associated with an increased risk of EKS but there was no such association with a sudden fall in the TCD4+ lymphocyte count (9). Both of our patients had viral loads of more than 9,000 copies/ml but their CD4+ lymphocyte counts were very different, with a count above 1,000 cells/mm^3 in the first case.

In vivo and in vitro studies have demonstrated that the PIs indinavir and saquinavir have direct antiangiogenic activity (16) and that the PI ritonavir has anti-tumor and anti-KS activity at the blood concentrations in HAART-treated patients (9,17). HAART produces a fall in blood levels of HHV-8, presumably due to a reduction in HIV proliferation, HIV/HHV-8-mediated oncogenesis, and HIV-induced immunosuppression (13).

Numerous approaches have been adopted towards KS lesions in the oral cavity, including local radiation (16), intralesional injections of vinblastine or 3% sodium tetradecyl sulfate (18), laser therapy, surgical excision, cytotoxic alkaloids (vinblastine, vincristine, and vinorelbine), bleomycin, anthracyclines, paclitaxel (19), and liposomal anthracyclines (20). At the diagnosis of these patients, the decision was taken not to use surgical lesion with CO_2 laser. In the first patient this was because of the size and location of the tumor and to improve control of the hemorrhage, and in the second patient because lesions slowly reduced with the commencement and continuation of the HAART.

Only five agents are approved by the FDA for KS treatment: alitretinoin gel (topical administration), liposomal daunorubicin, liposomal doxorubicin, paclitaxel, and interferon-alpha (all four as systemic therapy) (21).

A series of drugs with high antiangiogenic effects are emerging that may be relevant in the short-term management of KS, such as thalidomide and matrix metalloproteinases. Other drugs under study include retinoids, cidofovir, and IM-862(dipeptide l-glutamine l-tryptophane with antiangiogenity activity) (9).

This paper confirms the importance of dentists being able to identify lesions associated with HIV infection. The onset of EKS lesions in the oral cavity can be the first clinical manifestation of AIDS, indicating the immediate initiation of HAART in these patients.

References

1. Geara F, Le Bourgeois JP, Piedbois P, Pavlovitch JM, Mazeron JJ. Radiotherapy in the management of cutaneous epidemic Kaposi's sarcoma. Int J Radiat Oncol Biol Phys. 1991 Nov;21(6):1517-22.

2. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet. 1990 Jan 20;335(8682):123-8.

3. Biggar RJ, Rabkin CS. The epidemiology of AIDS--related neoplasms. Hematol Oncol Clin North Am. 1996 Oct;10(5):997-1010.

4. Vigilancia Epidemiológica del SIDA en España. Registro Nacional de casos de SIDA. Actualización a 30 de Junio de 2005. Informe semestral nº1, Año 2007. Ministerio de Sanidad y Consumo. Disponible en: http://www.isciii.es/htdocs/centros/epidemiologia/pdf/SPNS_Informe_junio_2007.pdf.

5. Andreoni M, Goletti D, Pezzotti P, Pozzetto A, Monini P, Sarmati L, et al. Prevalence, incidence and correlates of HHV-8/KSHV infection and Kaposi's sarcoma in renal and liver transplant recipients. J Infect. 2001 Oct;43(3):195-9.

6. Podzamczer D, Miralles P, La Calle Md M, Zarco C, Berenguer J, López Aldeguer J, et al. Recommendations of GESIDA/Spanish Na-

tional Plan of AIDS on diagnosis and treatment of Kaposi's sarcoma and cervical cancer in HIV-infected patients. Med Clin (Barc). 2002 Jun 1;118(20):788-95.
7. Diz Dios P, Ocampo Hermida A, Miralles Alvarez C, Vázquez García E, Martínez Vázquez C. Regression of AIDS-related Kaposi's sarcoma following ritonavir therapy. Oral Oncol. 1998 May;34(3):236-8.
8. Ranganathan K, Reddy BV, Kumarasamy N, Solomon S, Viswanathan R, Johnson NW. Oral lesions and conditions associated with human immunodeficiency virus infection in 300 south Indian patients. Oral Dis. 2000 May;6(3):152-7.
9. Frezzini C, Leao JC, Porter S. Current trends of HIV disease of the mouth. J Oral Pathol Med. 2005 Oct;34(9):513-31.
10. Bascones A, Serrano C, Campo J. Oral manifestations of HIV infection. Med Clin (Barc). 2003 Mar 29;120(11):426-34.
11. Levine AM, Tulpule A. Clinical aspects and management of AIDS-related Kaposi's sarcoma. Eur J Cancer. 2001 Jul;37(10):1288-95.
12. Aguirre-Urízar JM, Echebarría-Goicouría MA, Eguía-del-Valle A. Acquired immunodeficiency syndrome: manifestations in the oral cavity. Med Oral Patol Oral Cir Bucal. 2004;9 Suppl:153-7, 148-53.
13. Bower M, Fox P, Fife K, Gill J, Nelson M, Gazzard B. Highly active anti-retroviral therapy (HAART) prolongs time to treatment failure in Kaposi's sarcoma. AIDS. 1999 Oct 22;13(15):2105-11.
14. Bourboulia D, Aldam D, Lagos D, Allen E, Williams I, Cornforth D, et al. Short- and long-term effects of highly active antiretroviral therapy on Kaposi sarcoma-associated herpesvirus immune responses and viraemia. AIDS. 2004 Feb 20;18(3):485-93.
15. Gaitan Cepeda LA, Ceballos Salobreña A, López Ortega K, Arzate Mora N, Jiménez Soriano Y. Oral lesions and immune reconstitution syndrome in HIV+/AIDS patients receiving highly active antiretroviral therapy. Epidemiological evidence. Med Oral Patol Oral Cir Bucal. 2008 Feb 1;13(2):E85-93.
16. Sgadari C, Monini P, Barillari G, Ensoli B. Use of HIV protease inhibitors to block Kaposi's sarcoma and tumour growth. Lancet Oncol. 2003 Sep;4(9):537-47.
17. Pati S, Pelser CB, Dufraine J, Bryant JL, Reitz MS Jr, Weichold FF. Antitumorigenic effects of HIV protease inhibitor ritonavir: inhibition of Kaposi sarcoma. Blood. 2002 May 15;99(10):3771-9.
18. Ramírez-Amador V, Esquivel-Pedraza L, Lozada-Nur F, De la Rosa-García E, Volkow-Fernández P, Súchil-Bernal L, et al. Intralesional vinblastine vs. 3% sodium tetradecyl sulfate for the treatment of oral Kaposi's sarcoma. A double blind, randomized clinical trial. Oral Oncol. 2002 Jul;38(5):460-7.
19. Stebbing J, Wildfire A, Portsmouth S, Powles T, Thirlwell C, Hewitt P, et al. Paclitaxel for anthracycline-resistant AIDS-related Kaposi's sarcoma: clinical and angiogenic correlations. Ann Oncol. 2003 Nov;14(11):1660-6.
20. Núñez M, Saballs P, Valencia ME, Santos J, Ferrer E, Santos I, et al. Response to liposomal doxorubicin and clinical outcome of HIV-1-infected patients with Kaposi's sarcoma receiving highly active antiretroviral therapy. HIV Clin Trials. 2001 Sep-Oct;2(5):429-37.
21. Dezube BJ, Pantanowitz L, Aboulafia DM. Management of AIDS-related Kaposi sarcoma: advances in target discovery and treatment. AIDS Read. 2004 May;14(5):236-8, 243-4, 251-3.