

Case Report Article

Oral Kaposi's sarcoma in immunosuppressed patients – report of cases

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Abstract

Introduction: Kaposi sarcoma is a vascular neoplasm composed of endothelium-lined vascular spaces and spindle-shaped cells. It often manifests with multiple vascular nodules on the skin and other organs. Kaposi sarcoma is rare in HIV negative patients and it is associated with HHV-8 infection. There are four types: classic, endemic, iatrogenic and HIV-associated. Patients with HIV/AIDS are also at increased risk of developing Kaposi sarcoma. **Objective:** The aim of this article is to present two cases of Kaposi sarcoma in the hard palate of HIV/AIDS male patients. **Case report and Conclusion:** Kaposi sarcoma should be considered in the differential diagnosis of any AIDS patient who presents with bluish, smooth, firm, nonpulsatile macule or nodule in the region of the hard palate. Development of Kaposi sarcoma in the oral cavity also has prognostic implications for untreated HIV patients, who are found to have higher death rates than patients affected only by cutaneous disease.

Introduction

Kaposi's sarcoma is a neoplasm of vascular endothelium that is characterized by proliferation of spindle cells, neoangiogenesis, inflammation

and edema [17]. Moritz Kaposi, a Hungarian dermatologist in 1872, first described it. Since then, this disease can be classified into four different clinical forms that have identical histological

features, but affecting specific populations. Lesions appear in different areas of the body and have a different clinical progression [18, 30].

In his original article entitled “Idiopathic multiple sarcoma of the skin”, Moritz Kaposi described the indolent and rare disease that is known as classic or sporadic Kaposi sarcoma. This clinical form is characterized by single or multiple lesions that are usually located in the lower extremities and affects elderly men [28]. The endemic form of Kaposi's sarcoma, present in Africa (mainly in the south of the Sahara Desert), is relatively rare, but more aggressive. It affects young adults and black children [7]. The iatrogenic form emerged with the advent of organ transplantation and immunosuppressive therapy, as well as the emergence of chemotherapy. Additionally, there is epidemic form that is associated with acquired immunodeficiency syndrome.

Epidemiological studies suggest that the disease is infectious, mainly associated with human herpes virus type 8 (HHV-8). In vitro studies show that the virus can infect various cell types such as endothelial cells and B-lymphocytes [15]. It is believed that HHV-8 is transmitted sexually. Most reports on the epidemic of Kaposi sarcoma has been described in homosexual men and very few cases have been reported among heterosexual men. The receptive anal sex is a significant risk factor [23].

Initially, the most common site of involvement is the skin [11]. However, in some cases, there is no cutaneous involvement or it is preceded by visceral, oral or ganglion lesions [21]. Skin lesions can be macular, plate-shaped, nodular or papules. Its length may vary from a few millimeters to large confluent plaques or nodules of ten centimeters or more [14, 21]. The color of the lesions can range from dark pink, red, purple or brown [15].

The average age of patients with Kaposi sarcoma/AIDS is 38 years-old; with 69% of cases occurring between the ages of 30 to 39 years. The ratio of affected men and women varies from 50 to 100:1. Six percent of children with HIV (+) develop the disease, and 8% of seropositive women. About 15% of all diagnosed cases of AIDS have associated Kaposi sarcoma [4].

Kaposi sarcoma is one of the first recognized opportunistic diseases in HIV infection and is still the most common malignancy associated with AIDS [32]. The purpose of this paper is to present two cases of Kaposi sarcoma in its epidemic form in HIV positive patients.

Report of cases

Case 1

A white, male patient, 24 years old, was referred by an ophthalmologist to the Oswaldo Cruz Hospital (Curitiba/PR/Brazil) with an indication of treatment for uveitis by cytomegalovirus. The main complaint of the patient was the loss of visual acuity with greater intensity in the left eye. The patient was HIV positive since 2008 and was initially diagnosed with tertiary syphilis. However, subsequently, the clinical and laboratory findings revealed that it was toxoplasmosis.

The dental examination revealed absence of some teeth and darkening of the clinical crown in the maxillary central incisors. According to the patient, the pigmentation of the tooth occurred after the endodontic treatment. The teeth #14, #24 and #25 had advanced caries and had an indication for endodontic treatment. Clinical examination also revealed the presence of erythematous candidiasis in the soft palate and purplish lesions suggestive of Kaposi's sarcoma in the hard palate (figure 1). Additionally, several telangiectasias were seen on the surface of the lesion.



Figure 1 - Extensive purplish macule and telangiectasias on the hard and soft palate

Laboratory tests revealed a CD4 count equal to $324/\text{mm}^3$ (18.39%) and an ESR of 15 mm. The renal function tests had the following results: GOT = 15, GPT = 40, creatinin = 1.0 mg/dL and urea = 22.2 mg/dL. The result of the blood count was as follows: erythrocytes = $4.77 \text{ M}/\mu\text{L}$, hemoglobin = 13.4 mg/dL, hematocrit = 41.2%, leukocytes = 5.400 and lymphocytes = 25. The platelet count was equal to 269.000 and the determination of glucose = 70 mg/dL. In

addition, patients had antibodies to type 1 and 2 herpes virus.

Oral candidiasis was initially treated successfully by Fluconazole (200 mg/day for 14 days). An incisional biopsy was performed in the palatal region close to the teeth #17 and #18. Then, tissue sample was sent for pathological examination at the Clinical Hospital of UFPR. The result showed a kaposiform vascular proliferation that confirmed the clinical hypothesis of Kaposi sarcoma (figure 2A and 2B). Then, the patient was submitted to upper endoscopy for staging of Kaposi's sarcoma and no lesion was found in the upper gastrointestinal tract. The patient was classified as poor risk according to the staging classification system for AIDS-related Kaposi proposed by the AIDS Clinical Trial Group. The patient received a referral for an infectious diseases consultation for the initiation of highly active antiretroviral treatment (HAART).

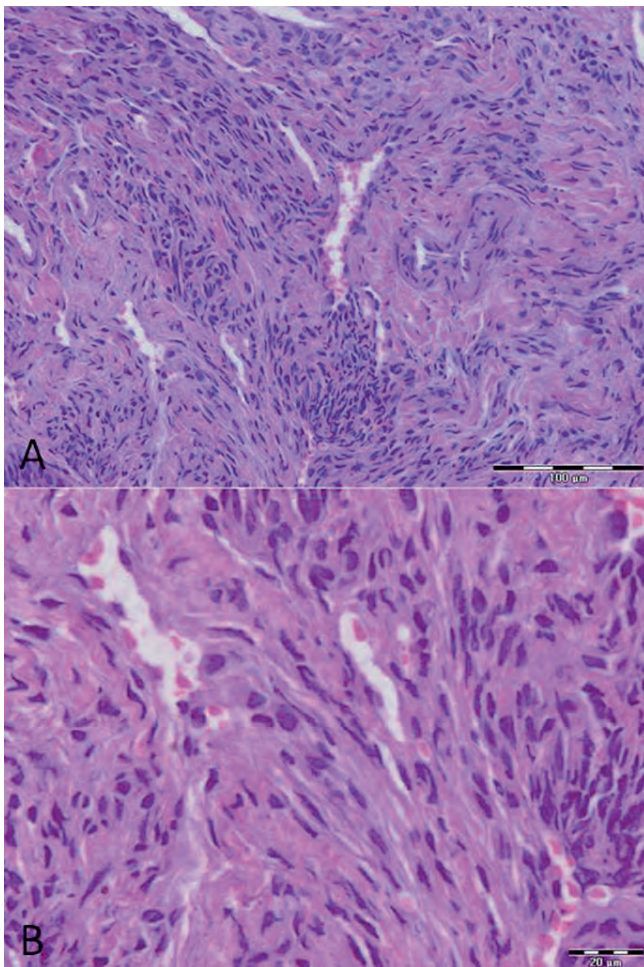


Figure 2 - A) Blood filled slits like spaces, spindle shaped cells with prominent pleomorphism (hematoxylin and eosin X200). B) Vascular spaces in the form of slits and proliferating pleomorphic spindle shaped cells (hematoxylin and eosin X400)

Case 2

A white male patient, 47 years old, was admitted to the Oswaldo Cruz Hospital (Curitiba / PR/Brazil) with fever, diarrhea, asthenia, anemia, thrombocytopenia, and edema of lower limbs. The patient was diagnosed with HIV infection and had a history of alcoholism and crack use.

Laboratory tests revealed a CD4 count equal to 324 (18.39%) and an ESR of 135 mm. The renal function tests had the following results: GOT = 19, GPT = 7, creatinin = 0.80 mg/dL and urea = 29 mg/dL. The result of the blood count was as follows: erythrocytes = 2.97 M/ μ L, hemoglobin = 9.0 mg/dL, hematocrit = 26.3%, leukocytes = 7.4 and lymphocytes = 25. The platelet count was equal to 64 k/ μ L and the determination of glucose = 70 mg/dL.

The physical examination revealed the presence of smoker's melanosis, cervical caries and wear of incisal and occlusal surfaces of teeth due to bruxism. Some purple, painless and slightly higher lesions were observed in the posterior region of the hard palate (figure 3). The patient was unaware of the presence of lesions. Thus, he could not specify the period of the appearance of them.



Figure 3 - Purplish nodules on the left side of the hard palate

The patient underwent an incisional biopsy. The fragment of the lesion was examined at the Clinical Hospital of UFPR. The histological sections showed an atypical spindle cell proliferation consistent with the clinical hypothesis of Kaposi sarcoma (figure 4A and 4B). The patient was classified as poor risk according to the staging classification system for AIDS-related Kaposi sarcoma because he exhibited the following changes: edema (swelling) due to the tumor, and extensive oral Kaposi sarcoma in other organs (lungs). The patient was referred for

treatment of Kaposi sarcoma at another hospital specializing in cancer treatment, but he died of respiratory complications.

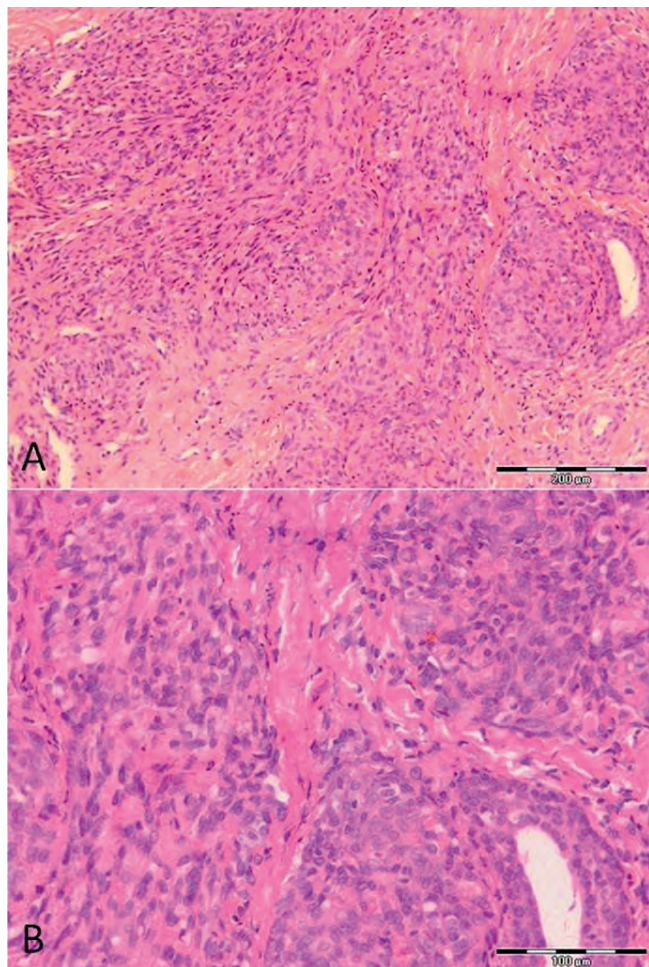


Figure 4 - A) Slit like vascular spaces and proliferation of pleomorphic spindle cells (hematoxylin and eosin X200). B) Pleomorphic spindle cells, hemosiderin and cellular infiltrate by lymphocytes and plasma cells (hematoxylin and eosin X400)

Discussion

The World Health Organization (WHO) identified HIV/AIDS as the world's most urgent public health challenge, because AIDS represents the greatest lethal epidemic in recent history. In HIV infected individuals, opportunistic viral infections are the major cause of morbidity and mortality. These agents cause infections which could be asymptomatic or mildly symptomatic in immunocompetent individuals, and it is often self-limiting. However, in immunosuppressed individuals and individuals with malignancy, infection with these agents leads to severe life-threatening diseases [25]. The increased

frequency and severity of diseases caused by these viruses in HIV-infected individuals is due mainly to dysfunction of both the adaptive and innate immune responses to viral pathogens [33].

One of the first HIV-related cases of Kaposi sarcoma was seen at San Francisco General Hospital in 1981. At this time, the Kaposi sarcoma tumor was rarely seen in the United States, and it was a complete surprise in young, previously healthy men. This was the beginning of the HIV/AIDS epidemic. This case was notable for multiple skin lesions and nearly confluent lesions on the inner thighs [22]. Kaposi sarcoma is one of the most common cancers caused by an infectious agent [13].

Four groups are at risk to develop Kaposi sarcoma: elderly males of Mediterranean and Eastern European lineage; children and adults from central Africa; persons who are iatrogenically immune compromised; and homosexual men infected with human immunodeficiency virus [1]. In both cases reported in this article, the Kaposi sarcoma was seen in patients with HIV-related immunosuppression. It seems that the route of HHV-8 transmission may be both sexual and nonsexual. Furthermore, the pathogenesis of Kaposi sarcoma is uncertain. Recent studies showed an association between all types of Kaposi sarcoma and infection with HHV-8, known as KS-associated herpes virus (KSHV) [12].

Kaposi sarcoma in HIV/AIDS patients, presents as purple macules or nodules. The lesions are painless and the hard palate is the most common location in the mouth [19]. The two patients described in this article have developed multiple purple lesions on the hard palate. Surprisingly, no lesions were observed in skin. However, the oral cavity is the first clinical site of disease in 22% of patients with Kaposi sarcoma, and up to 71% of HIV patients may develop oral Kaposi sarcoma concurrent with cutaneous and visceral involvement [25].

The clinical appearance of the oral Kaposi sarcoma may generate doubts about the diagnosis, because there are other lesions that are similar. The differential diagnoses for oral lesion include pyogenic granuloma, histiocytoma, hemangioma, angiosarcoma, bacillary angiomatosis, cutaneous lymphoma, lymphoendothelioma benign acroangiokeratitis, spindle cell hemangioendothelioma, angiolipoma and aneurysmal fibrous histiocytoma [5, 36]. Thus, oral biopsy and histopathological findings are essential for definitive diagnosis.

The following histopathological findings are observed in Kaposi sarcoma: blood filled slit like spaces, pleomorphic spindle cells with frequent mitoses, extravasated erythrocytes, hemosiderin laden macrophages and cellular infiltrate by lymphocytes and plasma cells [6]. In Kaposi sarcoma, cells that normally line small blood vessels proliferate in an abnormal way, extending outward from what would have been the lining of the vessel to penetrate between and partially surround nearby collagen bundles, thus creating “stellate” and “ecstatic” blood vessels that are not closed off but rather are open to surrounding tissue [31]. In addition, immunohistochemical staining (CD34 antibody) may be done for further diagnosis. It yields positive results for endothelial lining of slit like spaces and for spindle cells [2, 31]. The incisional biopsy was performed in two patients and histopathological examination confirmed the diagnosis of Kaposi sarcoma. The labeling immunohistochemistry was unnecessary, since the histopathology was evident.

Cancer staging is the process of using physical exams, imaging tests, and, in some cases, biopsy results to determine where and how much cancer is in the body. For many types of cancer, the stage is the most important factor in selecting treatment options and predicting a patient's outlook for recovery and survival. In 1988 a group of researchers known as the AIDS Clinical Trials Group (ACTG) proposed a staging classification system for AIDS-related Kaposi sarcoma [33]. The ACTG system considers three factors: i) The extent of the tumor, ii) The status of the immune system, as measured by the number of certain cells (CD4 cells) present in the blood, and iii) The extent of involvement within the body or systemic illness. In this context, the clinical findings revealed that both patients had poor risk.

There are multiple treatment modalities described in literature including, local surgical excision, cryotherapy, electrosurgery, chemotherapy, laser therapy and radiation therapy, HAART, besides adjuvant treatment with intralesional or systemic injections with cytostatic agents, alpha and beta-interferon, photodynamic therapy and topical therapy in form of nitrogen mustard or imiquimod [33]. For small and single lesions, surgical excision may be recommended [24]. Local recurrence is rare after complete excision of the primary lesion. When present, relapse occurs from six months to two years after the procedure [16, 24, 33]. Indications for systemic therapy include (i) Visceral involvement, (ii) Extensive Kaposi sarcoma

associated with lymph edema, (iii) Extensive and rapidly progressing Kaposi sarcoma and, (iv) Failure to respond to local therapy [35].

The neoplasms related to KSHV best illustrate the interplay between malignancy, infection and immunity [3]. Kaposi sarcoma is approximately 100 times more common during immunosuppression and can be resolved when iatrogenic immunosuppression is stopped and during HAART of HIV-1 infected individuals [3, 8]. However, the success of HAART in ameliorating Kaposi sarcoma likely is attributable not only to immune restoration, but also to the concomitant reduction in HIV-1 load [29, 37]. In case 1, the patient was treated with anti-retroviruses. The second patient died before receiving some kind of treatment for the Kaposi sarcoma.

The involvement of the oropharynx occurs in about one third of patients with Kaposi sarcoma and is most frequent lesion in the palate. Furthermore, this disease may also involve the gums, tongue, tonsils, pharynx and trachea [10]. Development of Kaposi sarcoma in the oral cavity may cause local tissue damage, pain, bleeding, or interference with oral functions and prosthesis wear, all of which may negatively affect a patient's nutritional status, adherence to medical therapy, and quality of life. Therefore, oral lesions clinically suggestive of Kaposi sarcoma should be biopsied and patients with biopsy-proven Kaposi sarcoma should be tested for HIV [9]. Thus, the dentist should be familiar with orofacial manifestations of Kaposi sarcoma, contribute to prevention of this disease by educating patients about risk factors, and question those engaged in risk behaviors about the presence of mucocutaneous lesions.

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