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KAPOSI SARCOMA IN PEOPLE LIVING WITH HIV/AIDS: CLINICAL AND HISTOPATHOLOGICAL ASPECTS OF CUTANEOUS LESIONS OF PATIENTS ATTENDED AT A REFERENCE UNIVERSITY HOSPITAL IN AMAZON REGION

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ABSTRACT

Kaposi's sarcoma (KS) corresponds to a systemic malignant and multifocal disease with a distinct clinical course, most commonly associated with Human immunodeficiency (HIV). Case series study to describe the clinical forms and histopathological changes of cutaneous lesions in patients with Kaposi's sarcoma and HIV coinfection at reference university hospital in Amazon region, from 2014-2017. From 20 individuals, 95% were male, mostly composed of young adults (35.1 years). Time of serological diagnosis: 11.67months and a skin lesion time: 11.47months. Cutaneous lesions were found in 3 forms: macule, infiltrated plaque and nodule located in different corporal segments. Immunological and virologic: 40% of individuals with <200 T-CD4 +cells/mm³ and 25% viral load above 10,000copies/ml. In all these forms: epidermis was found without alterations; with diffuse neoplastic distribution in papillary and reticular dermis, spindle cells, hemosiderin deposit, promontory sign, hyaline inclusions, extravasated red blood cells, anomalous capillaries and absence of desmoplasia. Infiltrate form red blood cells in subcutaneous. Nodular form: atypical endothelial cells and mitotic figures. Serological profile: 100% of HIV+ individuals were confirmed and the presence of KS confirms the prevalence of AIDS.

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INTRODUCTION

Kaposi's sarcoma (KS) corresponds to a systemic malignant and multifocal disease, caused by the involvement of the vascular endothelium and with a distinct clinical course. Initially and more frequently, skin lesions appear, followed by involvement of the mucous membranes, lymphatic system and viscera, such as the lung and the digestive tract (Tappero, 1993). It is worth mentioning that KS is the malignancy most commonly associated with Human immunodeficiency (HIV) - occurring in a range of 25 to 33% of patients - a fact that makes it difficult to distinguish the variant endemic from that associated with HIV (Bogaert, 2012). Pathologically, SK refers to a mesenchymal tumor caused by the herpes virus type 8 (HHV-8), besides being a definitive neoplasm of Acquired Immunodeficiency Syndrome - AIDS (Tancredi *et al*, 2017). The male sex is the most affected by the KS in people living with HIV / AIDS (PLHIV), possibly due to a protective effect of luteinizing hormone (LH) for females (Aboulafia, 2001; Tiussi *et al*, 2012). Regarding the classification of the 4 clinical types: 1) Classical - violet macules and papules with indolent course, which may progress to plaques / nodules, typically located in the distal extremities of the lower limbs of

caucasoid men older than 50 years; 2) African endemic - with predominance in adult men of Equatorial Africa and with nodular, infiltrative and lymphadenopathic subgroups; 3) Iatrogenic associated with immunodepression - similar to the clinical one of classic Kaposi's Sarcoma, occurring particularly in individuals submitted to organ transplantation; 4) Epidemic, associated with HIV infection - an aggressive and rapidly progressive form, often involving the trunk, midline of the face and oral mucosa, that is, closely related to the advanced stages of immunodepression (Fernandes *et al*, 2012). In relation to the clinical forms of presentation of KS, 1) macular KS, 2) non-destructive localized KS, 3) exophytic KS, 4) infiltrative KS, 5) generalized lymphadenoptic KS, 6) disseminated cutaneous KS and visceral, 7) KS telangiectatic, 8) Keloid KS, 9) Echimotic KS and 10) Cavernous KS or lymphangioma-like. Extracutaneous KS is more evident in the gastrointestinal tract, lymph nodes and lungs (Colferai *et al*, 2017). In terms of histopathology, there is a variation according to the development of the lesions: a) Macular lesions: there is proliferation of vascular spaces in the superficial dermis, lined by endothelial cells and discrete lymphocyte infiltrate and plasmocytes that separate the bundles of collagen. b) Plate lesions: vascular changes extend to the deep dermis and subcutaneous cellular tissue, where spindle cells appear that are positive for histochemical markers of vessels. c) Nodular lesions: predominance of fusiform cells with nuclear atypia and mitoses forming bundles, as well as bizarre vascular spaces in the periphery, which contain extravasated erythrocytes and macrophages with hemosiderin in the lymphocyte infiltrate, plasmacytes, histiocytes and, occasionally, neutrophils (Colferai, 2017).

In view of this, KS corresponds to the malignant neoplasm that became more important after the discovery of the epidemic type associated with AIDS. Its diagnosis is clinical and histopathological, usually of easy identification, due to its presentation in more advanced phases. However, the distinction between SK and a series of benign and malignant tumors, as well as inflammatory processes, may present some difficulties due to the overlap of histological changes in their initial forms, generating doubt as to the diagnosis. Thus, difficulties in the interpretation of the initial histopathological findings reveal the importance of deepening the studies of the microscopic characteristics and their standardization, being essential for the correct diagnosis and for the early initiation of the treatment. Based on the above, the present study aimed to describe the clinical aspects and the histopathological alterations of patients with Kaposi's sarcoma with cutaneous lesion treated at a reference university hospital in Amazon region.

METHODS

A case series study was conducted to describe the clinical forms and histopathological changes of cutaneous lesions in patients with clinical and histopathological diagnosis of Kaposi's sarcoma and with HIV coinfection at reference university hospital in Amazon region, in the period from 2014 to 2017. A convenience sample was used, where patients from a reference university hospital in Amazon region, inpatient and outpatient service were enrolled. All patients older than 18 years living with HIV who were diagnosed with Kaposi's sarcoma with cutaneous lesions in the established period were included in the sample. Epidemiological, clinical and histopathological variables, such as: sex, age, origin, race, profession, disease duration, lesion aspect, lesion location, comorbidities, immunosuppressive use, HIV infection, immunological status, microscopic aspects in medical records hospital In addition, a review of the slides with material from the biopsies, when available or in those without histopathological description in an attached report in medical records, was performed. This study was approved under opinion 787.848 of 08/26/2014, according to Resolution number 466/12 of the CNS/MS, which deals with research on human beings; and was only started after it was approved written. informed consent was obtained from all individual participants included in the study. All patients were screened for systemic lesions. The clinical diagnosis was based on the clinical aspect of the lesions observed under appropriate lighting. The evaluation was based on the division of skin and mucosal lesions into: macules, plaques, nodules, papules, vegetations and tumors (Mohanlal and Pather, 2015). For the histopathological examination, skin biopsies of each patient were performed, two samples were collected: one for histopathological analysis for diagnostic confirmation and observation of morphological aspects, and another for the isolation of the HHV8 virus for another work that was performed parallel to this. The collection was performed after antisepsis and anesthesia (lidocaine 2%) at the site, and the fragments were removed with punch number 4, which does not require the suture of the site. The material for morphological examination was stored in transparent glass vials with 10% buffered formalin and then embedded in paraffin. The analysis, organization and tabulation of the data were done in the program Microsoft Office Excel 2016, with elaboration of contingency tables and relevant descriptive statistics; for the writing of the study was used the program Microsoft Word 2016.

RESULTS

Epidemiological profile of the individuals under study: Of the 20 individuals that make up the study sample, 95% were male, mostly composed of young adults (70.00%), ranging in age from 25 to 54 years, with a mean of 35.1 years.

Table 1. Epidemiological profile of the population diagnosed with Kaposi's Sarcoma at the HUJBB, from 2014 to 2017

Epidemiological Profile		N	%
Sex		20	100,00
	Male	19	95,00
	Female	1	5,00
Age Group		20	100,00
	25 – 30 years	10	50,00
	31 – 35 years	4	20,00
	36 – 40 years	-	0,00
	41 – 45 years	1	5,00
	46 – 50 years	3	15,00
	More than 50 years	2	10,00
Color or Race		20	100,00
	Black	1	5,00
	White	1	5,00
	Brown	7	35,00
	Uninformed	11	55,00
Origin		20	100,00
	Belém and Metropolitan area	12	60,00
	Countryside	1	5,00
	Uninformed	7	35,00
Occupation		20	100,00
	Self-employed professional	6	30,00
	Liberal professional	4	20,00
	Others	3	15,00
	Uninformed	7	35,00

Source: Research protocol, 2018.

Table 2. Clinical aspects of the population diagnosed with Kaposi's sarcoma, at the University Hospital João de Barros Barreto, from 2014 to 2017

Individual	Age	Serological diagnosis time	Skin lesion time	Lymphocyte T-CD4$^+$ count	Viral charge	Antiretroviral Therapy (ART)	Associated opportunistic infection	Skin lesion location	Skin lesion clinical aspect	Visceral involvement
1	27	14 months	Uninformed	235 cells/mm^3	664 copies/ml	Yes	Pleural Tuberculosis	Thorax, Left Arm, Back of the left hand, Lower Members	Infiltrated Plates, Nodules	Yes
2	33	Uninformed	Uninformed	Uninformed	Uninformed	No	Uninformed	Thorax, Abdomen, Lower Members, Back and Sole of the right foot	Infiltrated Plates	Uninformed
3	54	15 months	Uninformed	14 cells/mm^3	767 copies/ml	Yes	Neurotoxoplasmosis	Lower Left Member	Infiltrated Plates, Nodules	Uninformed
4	26	Uninformed	6 months	278 cells/mm^3	Uninformed	Yes	Uninformed	Thorax	Infiltrated Plate	No
5	50	18 months	16 months	42 cells/mm^3	17.780 copies/ml	Yes	Uninformed	Lower Members	Infiltrated Plates, Nodules	No
6	33	17 months	14 months	57 cells/mm^3	551 copies/ml	Yes	HPV in mucosa	Back, Thorax, Oral Cavity (palate), Upper Members, Lower Members.	Infiltrated Plates, Nodules	Yes
7	31	18 months	18 months	27 cells/mm^3	Uninformed	Yes	Uninformed	Head, Torso	Infiltrated Plates, Nodules	No
8	50	Uninformed	30 months	Uninformed	Uninformed	No	Uninformed	Back of the left hand, Lower Members.	Infiltrated Plates, Nodules	Uninformed
9	52	Uninformed	2 months	66 cells/mm^3	17.063 copies/ml	Yes	Herpes Zoster	Abdomen	Macule	Yes
10	27	2 months	2 months	62 cells/mm^3	99.060 copies/ml	Yes	Oral Candidiasis Tuberculosis	Nose, Forehead, Right Side Face, Right Arm Thorax Abdomen	Macules	Yes
11	46	8 months	2 months	Uninformed	Uninformed	No	Oral Candidiasis, Pneumonia, Pneumocystose.	Pelvis, Glutes, Lower Members.	Macules, Infiltrated Plates, Nodules	No
12	44	Uninformed	84 months	60 cells/mm^3	7.468 copies/ml	Yes	Pneumocystose, Tuberculosis	Torso, 1st right foot pod, Sole of the right foot	Macules, Infiltrated Plates	No
13	30	1 month	1 month	Uninformed	Uninformed	Yes	Neurotoxoplasmose	Upper Members, Lower Left Member.	Macules, Infiltrated Plates	No
14	30	12 months	1 month	239 cells/mm^3	25.314 copies/ml	No	Uninformed	Upper Members	Infiltrated Plates	No
15	35	Uninformed	4 months	96 cells/mm^3	394.967 copies/ml	Yes	Uninformed	Face, Upper Members, Lower Members.	Macules, Infiltrated Plates	No
16	25	Uninformed	5 months	Uninformed	Uninformed	Yes	Uninformed	Face	Nodules	Yes
17	25	Uninformed	3 months	510 cells/mm^3	Undetectable	Yes	Uninformed	Torso, Upper Members, Lower Members, Sole of the right foot	Infiltrated Plate	No
18	29	Uninformed	1 month	469 cells/mm^3	Undetectable	Yes	Uninformed	Lower Members	Nodules	No
19	30	Uninformed	3 months	403 cells/mm^3	Undetectable	Yes	Uninformed	Face	Nodules	No
20	25	Uninformed	3 months	Uninformed	Uninformed	Yes	Uninformed	Face, Thorax, Upper Members.	Nodules	Yes

Source: Research protocol, 2018.

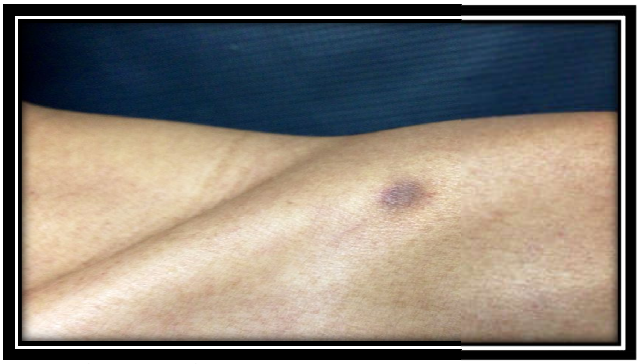
Regarding color or race, 35% of the individuals declared themselves to be brown, 5% black and 5% white. However, 55% do not have a color or race record in their records, as well as data on sexuality. The study group is mostly resident in XXX and metropolitan region (60%), however, 35% of the sample does not present a record of origin. In relation to the occupation, the majority of the patients are autonomous (30%), followed by professionals (20%), besides not having a record of salary income and schooling (Table 01).

Clinical aspects: The time of serological diagnosis ranged from 1 to 18 months, with an average of 11.67 months. The cutaneous lesion time ranged from 1 to 84 months, with an average of 11.47 months. In this context, the cutaneous lesions found in the study were presented in the three forms described in the literature: macula, infiltrated plaque and nodule - localized in different segments of the body, sometimes with visceral involvement (Table 02). Table 03 summarizes the immunological and virological profile of the study population, the stage of infection and laboratory indices of HIV-1 viremia, revealing 40% of individuals with a T-CD4 count of less than 200 cells / mm³.

Table 3. Antiretroviral Therapy (ART) and Immunological / virological profile of the population diagnosed with Kaposi's Sarcoma at HUJBB, from 2014 to 2017

TARV and Profile immunological/virological	N	%
Antiretroviral Therapy (TARV)	20	100,00
TARV in use	16	80,00
TARV absent	4	20,00
Lymphocyte T-CD4^{+} count	20	100,00
> 200 cel/mm^3	6	30,00
< 100 cel/mm^3	8	40,00
Uninformed	6	30,00
Viral Charge	20	100,00
Undetectable	3	15,00
< 1.000 copies/ml	3	15,00
≥ 5.000 copies/ml	6	30,00
Uninformed	8	40,00

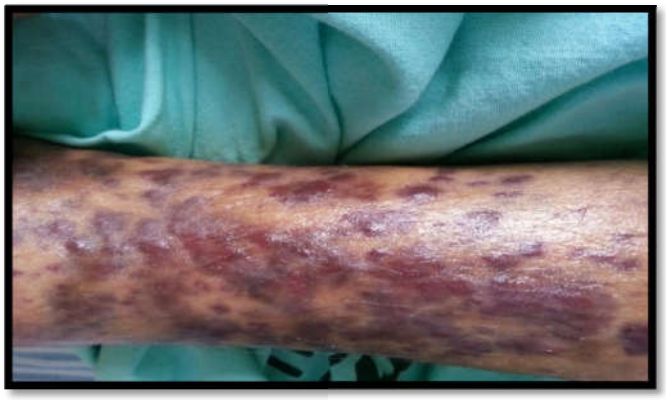
Source: Research protocol, 2018.



Source: Pires e Monteiro, 2014.

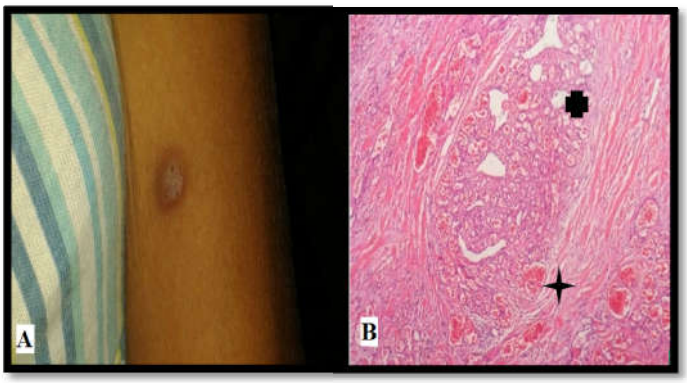
Figure 1. Violaceous macule with 1 cm in left infra-clavicular region

Histopathological aspects observed: Microscopic analysis of lesion biopsy correlated clinical lesion with histopathological changes. In the macular clinical form (Figure 01), the epidermis was unchanged, with diffuse and evident neoplastic distribution in the papillary and reticular dermis, presence of spindle cells, hemosiderin deposit, promontory deposit, hyaline inclusions, extravasated red blood cells, anomalous capillaries and absence of desmoplasia. In the clinical form of the infiltrated plaque (Figure 02), the epidermis was unchanged, with a diffuse neoplastic distribution involving papillary and reticular dermis, presence of spindle cells, hemosiderin deposits, anomalous vessels, extravasated red blood cells in the subcutaneous region, and absent desmoplasia. In the nodular clinical form (Figure 03A), no changes were found in the epidermis; a diffuse neoplastic distribution with a neoplastic level present in the papillary and reticular dermis, presence of proliferating spindle cells, atypical endothelial cells, hemosiderin deposit (Figure 04A), promontory sign (Figure 04B), hyaline inclusions, extravasated red blood cells figure 05A), enveloped vessels, mitotic figures, anomalous capillaries (Figure 05B) and presence of desmoplasia (Figure 03B).



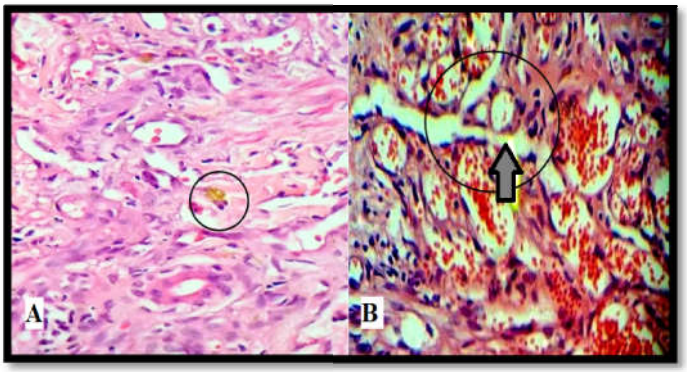
Source: Pires e Monteiro, 2014.

Figura 2. Erythematous lesions infiltrated plaques of various sizes with precise borders and irregular contours in the anterior aspect of the direct leg



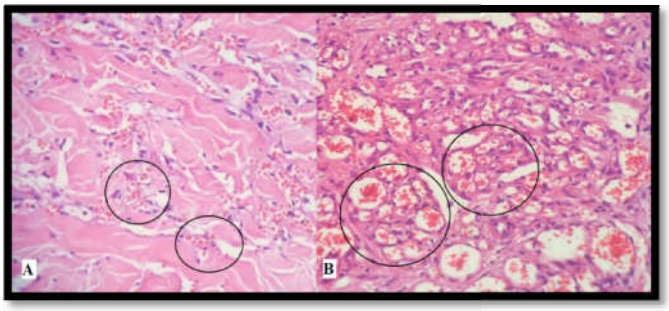
Source: Pires e Monteiro, 2014

Figure 3. A- Violet nodule with 2 cm on the left arm. B- Cut of the skin showing nodular area and desmoplasia to its surroundings, dermis (H & E, x40)



Source: Pires e Monteiro, 2014

Figure 4. A- Cut of skin showing deposit of hemosiderin in the dermis. (H & E x 40). B- Skin cut pointing the sign of the promontory in the dermis (H & E, x10)



Source: Pires e Monteiro, 2014.

Figure 5. A - Cut of the skin demonstrating extravasation of erythrocytes in the dermis. (H & E, x40). B- Cut of the skin showing diffuse anomalous capillary proliferation in the dermis (H & E, x40)

DISCUSSION

Kaposi's sarcoma refers to a malignant neoplasm originating from the endothelium, first described by Moritz Kaposi in 1872. In immunocompetent patients, the disease is typically limited to the extremities, whereas in immunocompromised patients - especially those with HIV / AIDS - is a systemic and multifocal disease (Tiussi, 2012; Santos *et al*, 2013). As for the epidemic variant associated with AIDS patients and coinfected with HIV and HHV8, Kaposi's sarcoma is quite aggressive and often lethal, occurring mainly in males and young adults (Resende *et al*, 2014). Consistent with several studies, it was found that male gender predominated (73.3%) among patients in the epidemic form (Tancredi *et al*, 2017), with 40 years for males, ranging from 24 to 67 years and 29.8 years in the female sex, ranging from 17 to 48 years (Souza *et al*, 2000); mean age around 38 years, with 69% of cases occurring in the age group of 30 to 39 years (Fonseca *et al*, 1999). Thus, it is suggested that the age group affected by this pathology has not altered despite the years following the publication of the cited works. It should also be noted that there is a discrepancy between the time of onset of cutaneous lesions between immunocompetent and immunosuppressed patients, indicating that KS can occur as the first manifestation of HIV / AIDS coinfection, concomitant with other manifestations, or late in the course of the disease. In addition, some lesions may remain unchanged for years, while others may arise in periods of immunosuppression, gradually and for weeks to months of disease (Fonseca *et al*, 1999; Aboulafia, 2001; Lima, 2015).

It has been found that the most common site of involvement is the skin, distributing to the head, neck and trunk, ranging from isolated lesions to disseminated lesions. Its distribution into the oral cavity is common and may be the first manifestation of the disease (Fonseca, 1999; Souza *et al*, 2000; Lima, 2015). This characteristic is present in the epidemic subtype - an aggressive and rapidly progressive form that frequently involves the trunk, midline of the face and oral mucosa, and is associated with the advanced stages of immunodepression (Fernandes *et al*, 2012). The laboratory characteristics of the individuals investigated are corroborated by several studies, pointing out that more than half of the patients (53.84%) had a CD4 + T cell count below 200 cells / mm³ (Lima, 2015); that SK can develop at any stage of infection, but the low count of these cells in People Living with HIV / AIDS (PLHA) may predict an increased risk of developing SK (Tancredi *et al*, 2017). Coinfection with HIV / AIDS contributes to the development and progression of KS, in view of the depletion of T-CD4 + lymphocytes leading to the depression of immunological mechanisms. Therefore, lymphocyte depletion symbolizes a poor prognosis, even with advances in diagnosis and continuous antiretroviral therapy (Fonseca *et al*, 1999).

In view of this, histopathology is the gold standard method for the diagnostic confirmation of Kaposi's sarcoma, presenting a large cytohistological variety, including: spindle cell proliferation; abnormal vascularization; promontory signal with collagen dissection; perineural infiltration; hemosiderin deposits; hemosiderin pigment; hyaline inclusions; extravasation of erythrocytes; vascular invasion; cellular atypia; desmoplasia and mitotic figures (Mohanlal and Pather, 2015; Speicher *et al*, 2015). It is worth noting that the histopathology does not vary with the type of Kaposi's sarcoma, but with the stage of the lesion. In addition to minimal cytological atypia in all grades, the most characteristic features are: a) macule - proliferation of angular vessels in the upper dermis, distributing parallel to the epidermis and coated by flattened endothelial cells, and may or may not have the signal of promontory (protrusion of preexisting vessels and vessels on newly formed vessels), associating with an inflammatory infiltrate of lymphocytes and plasma cells; b) plaque - compact angioproliferation involving the deep dermis and, sometimes, the subcutaneous cellular tissue; c) fusocellular and tumoriform nodule - proliferation that maintains angular vascular spaces along with solid areas; d) aggressive forms - infiltrative lesions with obvious sarcomatous character and reduction of the vascular component (Fernandes *et al*, 2012; Colferai *et al*, 2017).

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