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DOI: 10.1590/0103-6440201902599

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Distribution of Dendritic Cells in AIDS-Associated Oral Kaposi's Sarcoma

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The aim of this study was to determine if the distribution of Langerhans cells (LC) and interstitial dendritic cells (IDC) is altered in AIDS-associated oral Kaposi's sarcoma when compared to HIV-negative highly vascular oral lesions. Fifty-one cases of AIDS-associated oral Kaposi's sarcoma and 20 of highly vascular oral lesions were retrospectively retrieved. All cases of Kaposi's sarcoma were confirmed with immunoreactions against CD34 and HHV-8. Clinical data regarding sex, age and lesions location were obtained from pathology reports. Immunohistochemistry against CD207 (immature dendritic cells) and CD83 (mature dendritic cells) were done. LC were in the epithelium and IDC in the stroma. CD207+ cells predominated in the epithelium of the lesions, whereas CD83+ cells predominated in their stromal compartment. Kaposi's sarcoma had a lower CD207+ immature LC count ($p=0.02$) and an increased CD207+ IDC than highly vascular oral lesions ($p<0.001$). Moreover, Kaposi's sarcoma also showed an increased number of mature CD83+ IDC than highly vascular oral lesions ($p<0.001$). There were significant alterations in the distribution of LC and IDC in AIDS-associated Kaposi's sarcoma when compared to HIV-negative vascular oral lesions, suggesting that changes in their concentrations may play a role in the pathogenesis of Kaposi's sarcoma.

Key Words: Kaposi's sarcoma, AIDS, dendritic cells, Langerhans cells, CD207, CD83.

Introduction

Kaposi's sarcoma was first described by Dr. Moritz Kaposi and is defined as an intermediate-grade vascular malignancy always associated with HHV-8 infection (1). Incidence of Kaposi's sarcoma had a significant increase after the Acquired Immunodeficiency Syndrome (AIDS) burden early in the 1980's, followed by a decrease with HAART development. Kaposi's sarcoma is classified according to its epidemiological features as classic, endemic, immunodeficiency- and AIDS-associated disease, as well as according to its clinical stage of development as macule, patch or nodule Kaposi's sarcoma (2,3). In all these scenarios, the neoplasm is microscopically characterized by an intense vascular proliferation with a spindle cell component and chronic inflammatory infiltrate. However, microscopic findings may also give rise to different histological subtypes recognized in both cutaneous and oral mucosa presentations and include solid, lymphangioma-like, telangiectatic, desmoplastic, lymphangiectatic, ecchymotic, and anaplastic variants (4).

Kaposi's sarcoma is considered the most common neoplasm in the HIV infection context; nevertheless, in spite of the important improvements in the understanding of its pathogenesis, some authors still consider Kaposi's sarcoma as a reactive lesion, especially because of its potential to disappear after HAART. Although the complex inflammatory background of the disease is considered

a major component in its behavior, the importance of dendritic cells (DC) remains elusive and very few studies investigated the participation of these cells in Kaposi's sarcoma development.

In the skin and oral mucosa, Langerhans cell (LC) represents the most important antigen presenting cells (APC) located in the overlying epithelium, responsible to capture and exhibit foreign antigens to T-cells and, therefore, activating immune responses. When LC shifts to connective tissue during their movement to regional lymph nodes, they present morphological changes and are termed interstitial dendritic cells (IDC), which are also stromal resident cells (5). Our group has previously demonstrated that HIV-positive patients had a decreased concentration of LC and IDC in the mucosa of the oral tongue, predisposing these patients to a myriad of opportunistic infections (6,7). In addition, recent evidences pointed towards different DC subtypes as important agents for HHV-8 infection, which in turn would cause disturbances in the maturation, proliferation and function of these APC.

Current data on the importance of DC in the pathogenesis of KS are mostly derived from cutaneous lesions and from in vitro assays. In addition, plasmacytoid DC is the most investigated DC in the context of Kaposi's sarcoma and HHV-8 infection. Therefore, considering the previous reports observing DC disturbances in Kaposi's sarcoma and the lack of studies investigating this cellular

population in the oral manifestation of the neoplasm, the aim of this study was to determine if the distribution of LC and IDC is altered in AIDS-associated oral Kaposi's sarcoma when compared to HIV-negative highly vascular oral lesions.

Material and Methods

Samples

In a 30 year-period from 1985 to 2015, 51 formalin-fixed, paraffin-embedded cases of Kaposi's sarcoma were retrospectively retrieved from the files of the Oral Pathology Department of the School of Dentistry of the University of Pretoria (Pretoria/South Africa). New 5- μ m-thick histological sections stained with hematoxylin and eosin were jointly revised by two oral pathologists to confirm the original diagnoses that were further confirmed with positive immunohistochemical reactions for HHV-8 and CD34. Clinical data regarding age, sex and tumor location were retrieved from the patients' pathology reports. As a comparative group, 10 cases of oral pyogenic granuloma and 10 oral hemangiomas were retrieved from the files of the Oral Diagnosis Department (Pathology) of the Piracicaba Dental School of the University of Campinas (Piracicaba/Brazil). All cases presented the overlying epithelial tissue available to quantify the presence of Langerhans cells, although almost all cases also demonstrated focal areas of ulceration. Clinical data regarding age, sex and lesions location were also retrieved from the pathology reports.

Immunohistochemistry

Immunohistochemical reactions against HHV-8, CD34, CD83 and CD207 were done in 3 μ m histological sections of all cases. Samples were dewaxed with xylene and then hydrated in an ethanol series. For HHV-8 and CD34 the antigen retrieval was performed using EDTA /TRIS (pH 9.0), whereas for CD83 and 207 the antigen retrieval was done with citrate solution (pH 6.0). Endogenous peroxidase activity was blocked using 10% hydrogen peroxide and after PBS buffer wash (pH 7.4) slides were incubated overnight with primary antibodies against HHV-8 (Clone: 13B10, NOVACAstra, Nussloch, Germany, diluted 1:50), CD34 (Clone: QBEnd-10, DakoCytomation, Carpinteria, CA, USA, diluted 1:50), CD83 (Polyclonal, Santa Cruz Technology, California, USA, diluted 1:100) and CD207 (Polyclonal, Cell Marque, diluted 1:50). All slides were subsequently exposed to avidin-biotin complex, horseradish peroxidase reagents (LSAB Kit-DakoCytomation), and diaminobenzidine tetrahydrochloride (DAB, Sigma, St. Louis, MO, USA), and subsequently counter-stained with Carazzi hematoxylin. As positive controls, histological sections of intestine (blood vessel endothelium) were used for CD34, a previously diagnosed Kaposi's sarcoma was used for HHV-8, histological sections of normal skin were used for CD207

and normal lymph nodes were used for CD83. Negative controls were obtained by omitting the primary antibodies.

Immunohistochemical quantification

Quantification of LC was performed by a previously trained observer that counted the number positive cells in the surface epithelium and for IDC, positive cells were counted in the stroma of the lesions, far from the areas of ulcerations. In both counting, 10 sequential fields (40x) for each antibody were selected. Because of the ramified aspect of LC in the epithelium, morphological appearance of stained cells were also considered during the quantification process in order to avoid that one same cell was counted twice. The results were expressed as number of positive cells per case.

Statistical Analysis

The values were expressed as mean \pm standard deviation (SD) and as median (minimum and maximum values) for each group of lesions. Normality distribution of the results was investigated with Kolmogorov-Smirnov and Shapiro-Wilk tests, whereas Levene test was used to determine the homoscedasticity of the groups. The comparison of the cells distribution between Kaposi's sarcoma vs highly vascular oral lesions (hemangioma + pyogenic granuloma) was done using Student t-Test and Mann-Whitney test. A p-value < 0.05 was considered statistically significant. The software SPSS version 22.0 was used for the analyses. This study was approved by the Ethics Committee of the Piracicaba Dental School, University of Campinas (protocol 2.164.568/2017).

Results

In this study 51 cases of AIDS-associated oral Kaposi's sarcoma were used. Men and women were affected in the same proportion (M:F ratio 1:1) with a mean age of 31 years-old (range from 21 to 61 years-old) and a site predilection for the palate (21 cases), followed by the tongue (15 cases) and the gingiva (15 cases). Highly vascular oral lesions were retrieved to be used as a comparative group. Hemangioma comprised 10 cases, more commonly affecting females (M:F ratio 3:1) with a mean age of 57 years-old (range from 46 to 78 years-old) affecting the tongue (4 cases), lips (5 cases) and cheek mucosa (1 cases). Pyogenic granuloma accounted for 10 cases mostly affecting males (M:F ratio 2:1) with a mean age of 45.6 years-old (range from 18 to 87 years-old) always affecting the gingiva. There was no AIDS or HIV-positive patient in the highly vascular oral lesions group.

Microscopically, all 71 cases used in this study had the overlying epithelium present. Oral Kaposi's sarcoma was predominantly composed of proliferating spindle-cells with

the presence of variably sized blood vessels. Erythrocytes extravasation was commonly found, whereas mitosis figures were scarce. All cases were positive for CD34 and HHV-8 (Fig. 1). Hemangiomas exhibited blood vessels with different sizes being classified as either capillary or cavernous hemangioma. Pyogenic granulomas were characterized by the presence of the granulation tissue with intense chronic inflammatory infiltrate and a large number of blood vessels.

Immunohistochemically, both markers (CD207 and CD83) were predominantly found in the periphery of the lesions and more present in ulcerated areas, therefore, the cell counting was done distant from these regions. The expression of CD207 identified immature DC mostly in the overlying epithelium of all lesions, whereas only a few cells were found inside the lesions (Fig. 2). An opposite expression pattern was seen for CD83, which stained mature DC predominantly in the middle of the lesions, with only scattered cells in the epithelium (Fig. 3).

Immature CD207+ LC located in the epithelium presented their characteristic cytoplasm extensions and were found in all layers, whereas mature CD83+ LC in the epithelium, CD207+ immature IDC and CD83+ mature IDC in the middle of the lesions, lost their extensions and usually presented as round to oval cells.

Data on the mean (\pm standard deviation) and median (range) values obtained for CD207 in the epithelium and stroma of oral Kaposi's sarcoma and highly vascular oral lesions are summarized in (Table 1) In the epithelium, the number of immature CD207+ LC was significantly higher in highly vascular oral lesions than in Kaposi's sarcoma ($p=0.02$), whereas in the stroma of the lesions the number of immature IDC in Kaposi's sarcoma was higher than in benign lesions ($p<0.001$). Regarding the distribution of mature CD83+ LC and IDC, it was not observed any statistically significant difference between Kaposi's sarcoma and benign vascular lesions when the epithelium compartment was investigated ($p=0.373$), but the presence of mature CD83+ IDC in the stroma of the lesions was significantly higher in Kaposi's sarcoma than in vascular oral lesions ($p<0.001$).

Discussion

Kaposi's sarcoma is a low-grade vascular malignancy considered an AIDS-defining disease. Its incidence revealed a dramatic increase in the early 1980's following HIV-infection outburst worldwide and it is still overrepresented in this population, although the development of the highly active anti-retroviral therapy (HAART) usually lead to the involution of the neoplasm. Kaposi's sarcoma is also known to be tightly associated with HHV-8 infection, which is

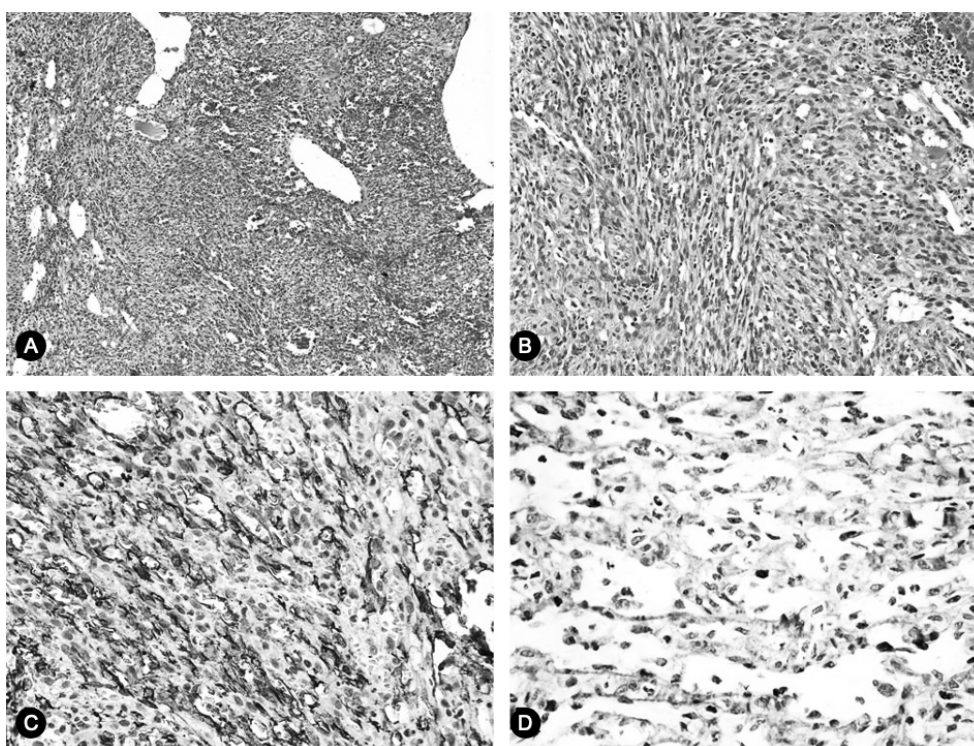


Figure 1. Microscopic and immunohistochemical aspects of oral Kaposi's sarcoma. A) All cases included in this study were categorized as solid Kaposi's sarcoma and exhibited a spindle cell component with irregular blood vessels with different shapes and sizes (H&E; 50X). B) Higher magnification demonstrating the spindle cell component of Kaposi's sarcomas (H&E; 100X). C) All cases were positive for the vascular marker CD34 (DAB; 200 \times) and D) were confirmed to be associated with HHV-8 infection, demonstrated as a nuclear staining in the neoplastic cells (DAB; 200 \times).

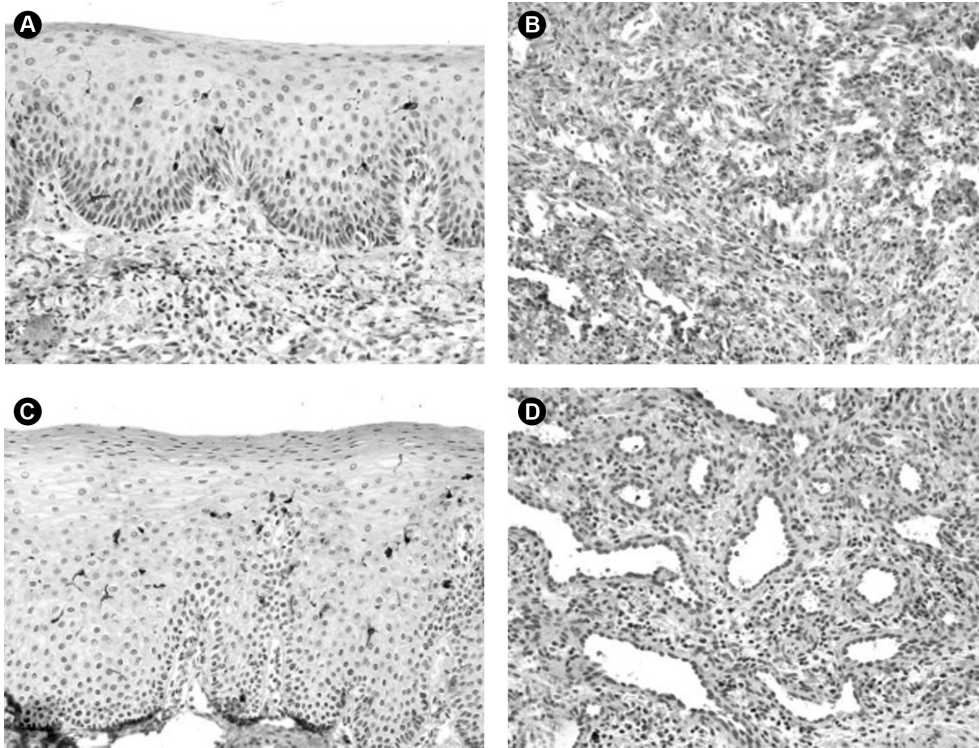


Figure 2. Immunohistochemical reactivity against CD207 in the epithelium and stroma of oral Kaposi's sarcoma and of highly vascular oral lesions A) CD207 stained immature LC in the overlying epithelium of oral Kaposi's sarcoma, revealing the dendritic characteristic of these cells (DAB; 200x). B) In the stroma of Kaposi's sarcomas, CD207+ IDC were very scarce and were observed as round cells without dendritic prolongations (DAB; 100x). C) A significantly higher count of CD207+ immature LC were observed in the epithelium of HIV-negative highly vascular oral lesions (DAB; 200x), D) whereas a lower count of CD207+ IDC was obtained inside the highly vascular oral lesions (DAB; 200x).

C. V. B. L. Cáceres et al.

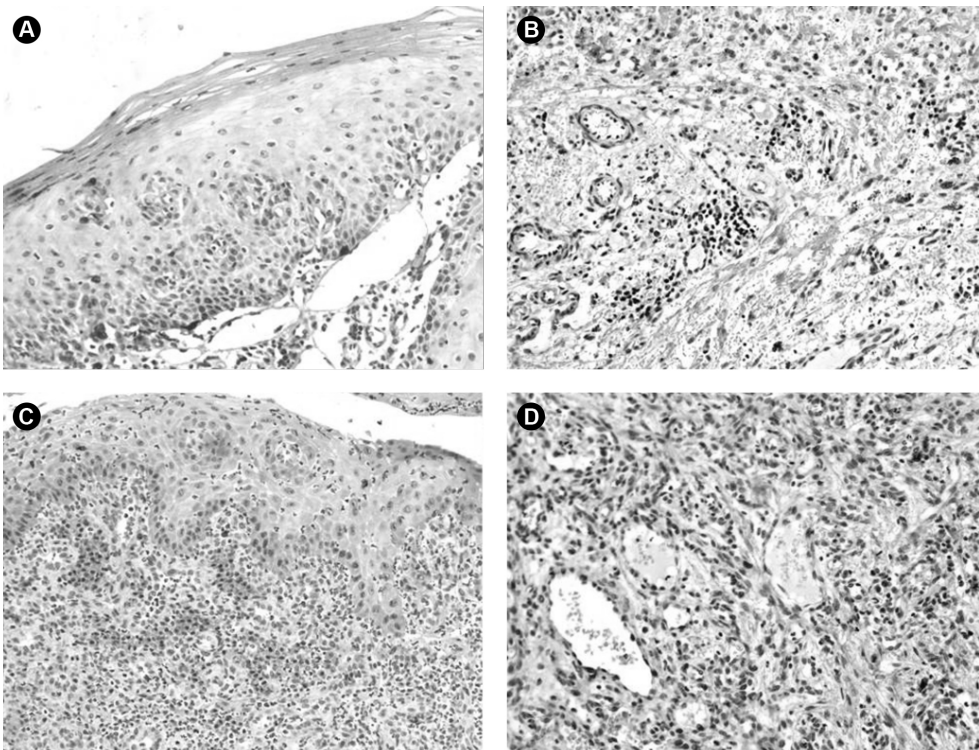


Figure 3. Immunohistochemical reactivity against CD207 and CD83 in the epithelium and stroma of oral Kaposi's sarcoma and of highly vascular oral lesions A) CD83 stained mature LC, few cells were observed in the epithelium of AIDS-associated oral Kaposi's sarcomas (DAB; 100X). B) In the stroma of Kaposi's sarcomas, whereas a higher number of CD83+ IDC (DAB; 100X). C) In highly vascular oral lesions, the number of CD83+ LC was lower than in Kaposi's sarcoma (DAB; 200x), and G) a significantly lower number of CD83+ IDC was observed in highly vascular oral lesions (DAB; 200x).

considered the main etiologic factor for the malignancy, despite the exact mechanisms that cause tumor growth remains to be fully established (1). Disruptions of systemic immunosurveillance are critical for Kaposi's sarcoma onset, but the importance of changes in the distribution and function of immune components in the local environment of the disease need to be more investigated. Therefore, in this study we demonstrated significant differences in the distribution of LC and IDC in AIDS-associated oral Kaposi's sarcoma when compared to HIV-negative highly vascular oral lesions, suggesting that alterations in the presence of these DC may play an important role in the pathogenesis of Kaposi's sarcoma.

LC are bone marrow derived DC found in the epithelium of normal skin and mucosae that encounter invading foreign pathogens in these surfaces, transfer to connective tissue where they are known as IDC and move toward regional lymph nodes where antigens are presented to naïve T lymphocytes (8). There is a growing number of evidences supporting the hypothesis that different subtypes of DC play important roles in the immunosurveillance against neoplastic cells and that the distribution and/or the regular function of these cellular populations are altered in many human tumors including oral cancer, lip cancer, mycosis fungoides, cutaneous squamous cell carcinomas, and others (8-11). Moreover, different authors have attributed a significant prognostic importance for DC in several of these malignant neoplasms (12,13), speculating that changes in these cells would not only predispose to neoplastic development, but it would also represent potential therapeutic targets for future chemotherapy schemes.

Our group has previously demonstrated that AIDS patients reveal important changes in the distribution of LC and IDC in the oral mucosa, predisposing these individuals to local opportunistic infections (6,7). Moreover, both cells are important for certain virus infections, including human immunodeficiency virus type 1, herpes simplex virus and cytomegalovirus (14). In addition, due to the strategic localization of these DC in the overlying oral mucosa and

the well known association of HHV-8 infection with the pathogenesis of Kaposi's sarcoma, we speculate that local alterations in the distribution of DC could be associated with the onset of this malignant vascular neoplasm. Further supporting this hypothesis, Rappocciolo et al. (14) recently showed that HHV-8 was capable of infecting three different DC types, monocyte-derived DC, LC and interstitial dermal dendritic cells, resulting in a reduced ability of these cells to stimulate allogeneic CD4+ T cells. The authors stated that HHV-8 caused DC infections by different receptors, ultimately altering their function. This same group previously demonstrated that the dendritic cell-specific ICAM-3 grabbing nonintegrin (DC-SIGN; CD209) would be one of the important receptors for HHV-8 infection of myeloid DCs and activated B lymphocyte (15,16). Therefore, the effects of HHV-8 on antigen presenting DC, may be the cause of the weak T cell responses against HHV-8 antigens (17).

In this study, we observed a significant decrease in the number of CD207+ LC in the epithelium of AIDS-associated oral Kaposi's sarcoma when compared to the epithelium of non-AIDS highly vascular oral lesions, suggesting that not only the function of these cells is altered by the viral infection, but also the concentration of this cellular population might be decreased. However, it is also possible to speculate that the number of these immature LC is not disrupted, but only its ability to express CD207, therefore, other LC immature- or pan-marker would be recommended to confirm these possibilities. Nevertheless, no matter what option is taking place, our result is per se important to demonstrate the loss of CD207 protein, given its known importance as a protective barrier against viral infections, like against HIV-1 (18,19); on the other hand, CD207 role in HHV-8 immune processing remains obscure and needs to be investigated since the effect of different viruses on LC may exhibit highly different results (20).

We have also observed that Kaposi's sarcoma patients exhibited a higher number of CD207+ and CD83+ IDC than benign lesions, we speculate that it possibly indicates a

Table 1. Distribution of LC and IDC in different compartments (epithelium and stroma of the lesions) of oral Kaposi's sarcoma and in highly vascular oral lesions (hemangioma and pyogenic granuloma)

Lesions	CD207				CD83			
	Epithelium		Stroma		Epithelium		Stroma	
	Mean (\pm SD)	Median (range)	Mean (\pm SD)	Median (range)	Mean (\pm SD)	Median (range)	Mean (\pm SD)	Median (range)
Kaposi's sarcoma	44.2 [†] (37.1)	35 (0 – 142)	17.9 (15.3) [†]	13 (0 – 62)	8.31 (8.0)	6 (0 – 37)	37.2 (20.9) [†]	35 (0 – 100)
Highly vascular oral lesions *	65.7 (26.4)	63 (18 – 109)	4.2 (2.4)	4 (1 – 11)	6.9 (6.9)	4 (0 – 21)	17.6 (11.0)	16.0 (4 – 46)

*Hemangioma and pyogenic granuloma. [†]Statistically significant differences.

host response against HIV and/or HHV-8 infections, with a higher concentration of immature and activated stromal DC being recruited, supposedly from circulating monocytes (5). IDC may complement the role of LC by adopting an immunostimulatory activity (20).

Although our study represents an original contribution

to the understanding of LC and IDC importance for Kaposi's sarcoma pathogenesis, several authors have previously attempted to investigate the role played by different DC subsets in the development of this lesion. We reviewed the available literature searching for studies dealing with DC and Kaposi's sarcoma, and Table 2 summarizes the

Table 2. Summary of the available studies that investigated the importance of different dendritic cells in the pathogenesis of Kaposi's sarcoma

Authors	Country	KS clinical subtype	Sample source	No. cases	KS location	HIV status	DC investigated	
Current study, 2017.	Brazil/South Africa	HIV-associated KS	Tissue	51 cases of KS ; 10 cases of pyogenic granuloma ; 10 cases of hemangioma	Oral mucosa	100% positive	Langerhans cells	
Rappocciolo et al., 2017	USA	NA	Neonatal cord blood	-	NA	NA	Langerhans cells, Interstitial Dermal Dendritic cell, monocyte-derived dendritic cells.	
C. V. B. L. Cáceres et al.	Jivan et al., 2016	South Africa	HIV-associated KS	Tissue	<i>Study groups:</i> 15 cases of KS without <i>Candida albicans</i> co-infection ; 17 cases of KS with <i>Candida albicans</i> co-infection; <i>Control groups:</i> 23 cases of non-candida and non-HIV infected mucosa overlying pleomorphic adenomas ; 19 cases of oral candidosis from healthy patients	Oral mucosa	100% positive	Langerhans cells
	Karouni et al., 2016	Lebanon	Classic KS	Tissue	20 cases of KS ; 20 cases of molluscum contagiosum	Cutaneous	100% negative	Plasmacytoid DC
	Ramdial et al., 2011	UK/South Africa	HIV-associated KS	Tissue	9 cases of anaplastic KS	Cutaneous	100% positive	Langerhans cells
	West et al., 2011	USA	NA	Peripheral blood	Health subjects ; Laboratorial HHV8 infected DC cells	NA	NA	Plasmacytoid DC
	Bella et al., 2006.	Italy	Classic KS	Peripheral blood	76 KS ; 72 controls	NA	100% negative	Myeloid cell ; Plasmacytoid cell ; Monocytes (DC precursor)
	Stebbing et al., 2003.	UK	HIV-associated KS	Peripheral blood	12 cases of HIV-positive ; KS patients; 6 cases of HIV-positive patients ; without KS	NA	100% positive	Myeloid cell ; Plasmacytoid cell ; Monocytes (DC precursor)
	Simonart et al., 2000	Belgium	Iatrogenic, sporadic and HIV-associated KS	Cell cultures derived from tissue	4 KS patients	Cutaneous	50% positive	Dendritic cell
	Tabata et al., 1993	Germany/ Japan	HIV-associated KS	Tissue	15 cases of HIV+ KS 19 cases of oral mucosa of HIV+ patients 22 cases of oral mucosa of HIV- patients	Oral mucosa	100% positive	Dendritic cells
	Kanitakis et al., 1992	France	Classic KS Immunosuppression-associated KS	Tissue	13 classic KS ;16 Immunes KS	Cutaneous	13 HIV+ patients	Dermal dendrocytes

NA: Not available.

investigations encountered. The diversity of molecules expressed by each DC not only makes their mechanisms more complex, but also impairs appropriate comparisons

among studies that used different markers to identify DC. The first investigations of DC in Kaposi's sarcomas used the unspecific proteins HLA-DR (21) and factor XIIIa to stain

Table 2. continuation

Authors	Country	Lab technique	Markers used	Main results
Current study, 2017.	Brazil/ South Africa	IHC	CD83 + ; CD207 +	KS revealed a significantly lower CD207+ immature LC count and an increased CD207+ IDC than benign vascular oral lesions. Moreover, KS also showed an increased number of mature CD83+ IDC than benign vascular lesions.
Rappocciolo et al., 2017	USA	Flow Cytometry; Cell culture; Immunofluorescence; PCR	HLA-DR CD1a CD11b CD14 CD91 CD80; CD86 CD83 ; CD209 CD207	HHV-8 can target both LC and iDDC for productive infection via different receptors and alter their function, supporting their potential role in HHV-8 pathogenesis and KS
Jivan et al., 2016.	South Africa	IHC	CD1a +	Significant lower count of LC in non-Candida infected KS than in uninfected normal mucosa.
Karouni et al., 2016.	Lebanon	IHC	BDCA-2 + ; MxA + (to evaluate interferon production)	pDCs are recruited into the skin lesions of classic KS, but there is a significantly lower plasmacytoid cells and lower interferon production in cKS than in molluscum cases.
Ramdial et al., 2011	UK/South Africa	IHC	S100+ ; CD1a+ ; CD207+	Presence of an extensive amount of intratumoral Langerhans cells.
West et al., 2011	USA	Flow cytometry; Cell culture	BCDA4+ ; BDCA2+ ; CD303+ ; CD123+ ; CD83-/+ ; CD86-/+	KSHV can infect and activate human pDCs, as measured by upregulation of CD83 and CD86, and by IFN- α secretion. Induction of IFN- α occurs through activation of TLR9 signaling.
Bella et al., 2006	Italy	Flow cytometry; Cell culture	HLA-DR + ; CD3 - ; CD19 - ; CD20 - ; CD16 - ; CD14 - ; CD11c + ; CD123 + ; CD80 -/+ ; CD83 -/+ ; CD86 -/+ ; CD49c -/+ ; CD91 -/+ ; CD34 -/+ ; CD14 -/+ ; CD1a + ; CD40+ ; ILT2, 3, 4 +	PBDC (both myeloid, plasmacytoid and monocytes) in cKS patients were significantly lower than controls, and was more severe in more advanced cases. PBDC expressing the HHV8 receptor CD49c was higher in cKS patients than in healthy control;
Stebbing et al., 2003	UK	Flow cytometry; Cell culture	CD3 - ; CD14 - ; CD16 - ; CD19 - ; HLA-DR + ; CD11c -/+ ; CD1a ; CD80 ; CD83 ; CD40 ; CD91	Despite the impaired functional capacity of DC in patients with KS, they retained the ability of activating and stimulating CD8 cytotoxic T cells. Plasmacytoid DCs were depleted in KS-positive compared with KS-negative HIV-1-infected patients.
Simonart et al., 2000.	Belgium	IHC ; Flow cytometry ; Cell culture	CD1a	Less than 1% of the spindle cells cultured were positive for CD1a. Spindle cell cultures have nearly always given rise to cells with fibroblastic and/or smooth muscle cell differentiation. KS spindle cells lack endothelial and/or leucocyte markers.
Tabata et al., 1993.	Germany/ Japan	IHC	HLA-DR +	The number of HLA-DR+ cells was increased in patch-like and nodular KS compared to HIV+ and HIV- normal mucosa.
Kanitakis et al., 1992	France	IHC	Factor XIIIa + ; Antigen H -	Dermal dendrocytes density tended to be decreased in immunosuppression-associated Kaposi's sarcoma when compared with classical form. The results do not support dermal dendrocytes as being the cells of origin of Kaposi's sarcoma. Decreased density of dermal dendrocytes could be related with a more aggressive clinical course.

NA: Not available.

dendrocytes, but CD1 (22,23) has been the most used DC marker, although it does not discriminate between mature and immature subpopulations. Using CD1a Jivan et al. (24) (2016) recently showed a lower count of LC in non-Candida infected oral kaposi's sarcoma than in uninfected normal mucosa. Interestingly, plasmacytoid DC (pDC) has been the most studied subpopulation in Kaposi's sarcoma given its ability to recognize single-stranded RNA and unmethylated CpG motifs associated with viral infection, inducing an antiviral response within the host and a high production of interferon (25–27). Similar to our study, Stebbing et al. (28) using HIV-1 infected patients, also showed a depletion of pDC in Kaposi's sarcoma patients compared with Kaposi's sarcoma-negative individuals, whereas Karouni et al. (29) observed a significantly lower pDC count and a lower interferon production in classic kaposi's sarcoma than in molluscum contagious cases.

Although we did not correlate the distribution of LC and IDC observed in Kaposi's sarcoma patients with their respective CD4 count since this data were unavailable for consultation, potentially representing a limitation of our study, Grulich et al. (30) stated that CD4 count could be an insensitive indicator of immune deficiency, because its count might not be an accurate or unbiased measure of immune function. It is also important to consider that the distribution of LC may vary according to different intraoral subsites, therefore, it remains to be determined if Kaposi's sarcomas biopsied in different oral locations could have interfered in our DC count.

In conclusion, we observed a reduction of CD207+ immature LC and an increase of CD207+ and CD83+ IDC in AIDS-associated Kaposi's sarcoma than in HIV-negative vascular oral lesions, suggesting that alterations in the distributions of these DC subsets, either because HIV and/or HHV-8 effect, may play a role in the pathogenesis of this malignant vascular neoplasm.

Resumo

O objetivo deste estudo foi determinar se a distribuição das células de Langerhans (CL) e das células dendríticas intersticiais (CDI) está alterada no sarcoma de Kaposi oral associado à AIDS quando comparado às lesões orais altamente vasculares HIV-negativas. 51 casos de sarcoma de Kaposi oral associado à AIDS e 20 de lesões orais altamente vasculares foram recuperados retrospectivamente. Todos os casos de sarcoma de Kaposi foram confirmados pela positividade para os anticorpos CD34 e HHV-8. Dados clínicos sobre sexo, idade e localização das lesões foram obtidos dos laudos histopatológicos. Foram realizadas imunohistoquímica contra CD207 (células dendríticas imaturas) e CD83 (células dendríticas maduras). As CL estavam presentes no epitélio enquanto as CDI estavam presentes no estroma. As células CD207+ predominaram no epitélio das lesões, enquanto as células CD83+ predominaram no estroma. O sarcoma de Kaposi teve uma contagem mais baixa de CD imaturas CD207+ ($p = 0,02$) e número aumentado de CDC CD207+ do que lesões orais altamente vasculares ($p < 0,001$). Além disso, o sarcoma de Kaposi também mostrou um número aumentado de CDI CD83+ maduras do que lesões orais altamente vasculares ($p < 0,001$). Houve alterações significativas na distribuição de

CL e CDI no sarcoma de Kaposi associado à AIDS quando comparado às lesões orais vasculares HIV-negativas, sugerindo que alterações na distribuição das mesmas podem desempenhar um papel na patogênese do sarcoma de Kaposi.

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Received January 5, 2019

Accepted May 13, 2019