Histopathological findings in the diagnosis of the stages of kaposi sarcoma; which are more valuable?

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Abstract

Background: Kaposi sarcoma (KS) is a local aggressive angioproliferative tumor with various stages having different histopathological findings. Histopathological findings have a diagnostic value depending on at what stage, how often, and with what findings they are observed. The study aimed to determine the finding or a group of findings which is prominent in different stages of KS and which can effectively identify that stage.

Methods: KS cases diagnosed were retrospectively reviewed. The relationship between morphological parameters and disease stages was investigated. In comparative analysis, Chi Square test and multivariate regression analysis were used. Statistical significance level was accepted as $p < 0.05$.

Results: When different stage groups and the frequency of parameters were compared, there was statistical significance; the multivariate regression analysis revealed that the presence of hemosiderin in the plaque stage was OR: 25.7 ($p: 0.02$; CI 95%: 1.6-398.2) times higher than that of patch stage, and the presence of mitosis in the nodule stage was OR: 3.7 ($p: 0.002$; CI 95%: 3.8 - 489.7) higher than that of plaque stage. It was statistically significant.

Conclusion: The diagnosis of KS will be safer if evaluated with the most valid and best-defining histopathological findings of the related stage.

Keywords: Kaposi sarcoma, histopathology, stage, frequency

Introduction

The human herpesvirus 8 (HHV-8) virus, a member of the gamma-herpesvirus subfamily, plays an important role in the pathogenesis of Kaposi sarcoma (KS), a type of tumor. The Hungarian dermatologist, Moritz Kaposi, first described it as an "idiopathic multiple pigmented sarcoma of the skin" in 1872 [1]. KS is a locally aggressive tumor with a low malignancy potential and is characterized by patch, plaque and nodular stages in its natural development [2]. Different histopathological features are prominent in each of the stages; hence, the stages present different difficulties in the histopathological diagnosis and the differential diagnosis. These difficulties in the differential diagnosis include benign or reactive lesions in the patch stage, or other vascular sarcomas or cutaneous spindle cell tumors

in the nodule stage [3,4]. Therefore, it is important to define valid and reliable histopathological diagnostic features for each stage of KS.

The histopathological features used in the diagnosis of KS were evaluated in our case series. The study aimed to determine the finding or a group of findings which is prominent in each stage of KS and which can effectively identify a specific stage of KS.

Methods

The histopathological details of 121 diagnosed Kaposi sarcoma cases were studied retrospectively and reevaluated. The histopathological sections were evaluated independently by two pathologists according to the presence, absence and frequency

of the following features: stage, hyperkeratosis, acanthosis, ulceration, presence of spindle cells, fascicle formation, cleft-like space, horizontally oriented vascular bundles, large vessels in the periphery, "promontory" sign, nodule formation, hyaline globules, extravasated erythrocytes, hemosiderin-laden macrophages, nuclear atypia, mitotic activity/10 high-power fields, necrosis and inflammatory cells and their type (lymphocyte, plasma cell or neutrophil). Moreover, the relationship between morphological characteristics and the disease stage was investigated. In the evaluation of the data, minimum, median and maximum values were used for qualitative evaluations, and figures and percentages (%) were used for quantitative evaluations. For comparative analyses, the Pearson Chi-square test and multivariate regression analysis were used. A statistical significance was considered to be $p < 0.05$.

Results

In the present study, the median age of the 121 cases at the time of diagnosis was 68.14 years (range: 26-93 years). KS was more common in males (62%) and most commonly present on the feet (53%). Most lesions were located in the lower limb (66%), followed by the upper limb (16.5%). In nine cases, the lesions were located on the head and neck regions, which is rare, and there was also one tumor found in the scrotum (Table 1).

Table 1. Distribution of Kaposi's sarcoma by location.

Location	n	%
Foot	53	43,8
Leg	35	28,9
Hand	10	8,3
Buttock	3	2,5
Arm	5	4,1
Ear	3	2,5
Others*	12	9,9
Total	121	100,0

* Others: Axilla, nose, tongue, abdomen, nasopharynx and scrotum

The incidences of the studied parameters according to the stages were as follows:

Vascular horizontal location, inflammation and erythrocyte extravasation (90%) in the patch stage; erythrocyte extravasation (100%), the "promontory" sign, presence of a hyaline globule and/or hemosiderin (96.6%) in the plaque stage; erythrocyte extravasation (98.8%) and the presence of globules (97.6%) in the nodule stage (Table 2, Figures 1-11).

The multivariate regression analysis, performed by selecting statistically significant parameters in stage groups, resulted in a hemosiderin OR: 25.7 (p : 0.02; CI 95%: 1.6-398.2) times higher in the plaque stage compared to the patch stage, and mitosis showed an OR: 3.7 (p : 0.002; CI 95%: 3.8-489.7) times

Table 2. Features present in >80% of patients with three stages of Kaposi's sarcoma.

Patch	Extravasated erythrocytes Promontory sign Horizontally orientated vascular bundles
Plaque	Extravasated erythrocytes Promontory sign Globules Inflammation Hemosiderin
Nodular	Hyperkeratosis Spindle cells Fascicles Clefts Large vessels in the periphery of the tumor Nodular development Globules Extravasated erythrocytes Hemosiderin

Figure 1. Hyperkeratosis (H&EX40).

Figure 2. Ulceration (H&EX40).

Figure 3. Spindle cells, fascicles (H&EX200).

Figure 6. Nodular development (H&EX40).

Figure 4. Horizontally orientated vascular bundles (H&EX200).

Figure 7. Hyalen globules, extravasated erythrocytes (H&EX1000).

Figure 5. Promontory sign (H&EX200).

Figure 8. Hemosiderin-laden macrophages (H&EX200).

Figure 9. Nuclear atypia, Mitotic activity/
10BBA(H&EX400).

Figure 10. Necrosis(H&EX200).

Figure 11. Inflammatory infiltration (presence of
lymphocytes, plasma cells and neutrophils) (H&EX200).

higher in the nodule stage compared to the plaque stage. Both were statistically significant (**Table 4**).

Discussion

Kaposi sarcoma, which originates from endothelial cells, is a multicentric angioproliferative spindle cell tumor with histopathological and clinical heterogeneity. It is encountered as multiple lesions in the lower extremity in men in their 6th-7th decades [5-8]. The demographic features of our case series were found to be compatible with the literature.

Previous studies have reported a nodular stage incidence of 36-87.5% [4-8]. In our study, the nodular stage (67,8 %) was the most commonly encountered. Alternatively, some studies have reported the plaque stage to be the most commonly observed stage in HIV positive KS patients [9]. The nodular stage was common in our HIV-positive patients, but the serological data of all patients could not be obtained.

Although not specific, hyaline globules, which are repositories for erythrocytic degradation products, are argued to have diagnostic significance in Kaposi sarcoma [5,10]. In this study, erythrocyte extravasation was the most commonly encountered histological feature (98.3%), and hyaline globules were observed in the cellular cytoplasm or extracellular matrix in 95% of cases. There were significant differences in the incidences of hyperkeratosis, acanthosis, ulceration, spindle cell presence, fascicles, cleft-like space, horizontally oriented vascular bundles, hemosiderin, large vessels at the periphery of the tumor, nodule, globule, atypia, mitosis and necrosis among the stages.

The initial or patch stage of KS is characterized by small, thin-walled, bulging, endothelium-lined vessels surrounded by large ectatic vessels and skin appendices. The opening of the small vascular structures to the lumens of the more ectatic neoplastic channels is called the 'promontory sign' and is a characteristic of KS. Mild inflammation characterized by plasma cells and lymphocytes, extravasated erythrocytes and hemosiderin-laden macrophages can be observed around the lesion. In the patch stage, the papillary dermis is generally intact [4-9]. In our study, horizontally oriented vascular bundles, erythrocyte extravasation and inflammation were the most common histological findings in this stage. In contrast, necrosis was not observed.

Among all the features we used to confidently identify the plaque stage, the presence of the promontory sign, erythrocyte extravasation, hemosiderin accumulation and inflammation have been indicated as helpful findings in the literature [8-11].

Our study suggests that horizontal placement of vascular structures, erythrocyte extravasation and the promontory findings are frequently observed and statistically significant in the patch stage, and that searching for their comorbidity may help support the diagnosis of that stage.

In the plaque stage, the proliferating vascular structures infiltrate the dermis and sometimes penetrate the subcutis.

Table 3. Frequency and statistical significance of histopathological features in Kaposi's sarcoma, according to the stages.

		Patchy(n: 10) (a)		Plaque (n: 29) (b)		Nodular (n: 82) (c)		P değeri
HIV (+)		0	(0,0%)	0	(0,0%)	4	(4,9%)	0,374*
Hyperkeratosis		6	60,0%	17	58,6%	73	89,0%	0,001* a-b>0,05 a-c: 0,04 b-c:0,001
Acanthosis		2	20,0%	10	34,5%	56	68,3%	<0,001* a-b>0,05 a-c: 0,008 b-c:0,003
Ulcer		0	0,0%	1	3,4%	33	40,2%	<0,001* a-b>0,05 a-c: 0,03 b-c:0,001
Spindle cell		3	30,0%	16	55,2%	75	91,5%	<0,001* a-b>0,05 a-c: 0,000 b-c:0,000
Fascicle		1	10,0%	7	24,1%	68	82,9%	<0,001* a-b>0,05 a-c: 0,000 b-c:0,000
Cleft		4	40,0%	17	58,6%	77	93,9%	<0,001* a-b>0,05 a-c: 0,000 b-c:0,000
Large vessels in the periphery		7	70,0%	22	75,9%	71	86,6%	0,056*
Horizontally orientated vascular bundles		9	90,0%	18	62,1%	16	19,5%	<0,001* a-b>0,05 a-c: 0,000 b-c:0,000
Nodule		1	10,0%	12	41,4%	69	84,1%	<0,001* a-b>0,05 a-c: 0,000 b-c:0,000
Promontory		8	80,0%	28	96,6%	72	87,8%	0,26*
Globule		7	70,0%	28	96,6%	80	97,6%	0,001* a-b: 0,004 a-c: 0,004 b-c >0,05
Extravasated erythrocyte		9	90,0%	29	100,0%	81	98,8%	0,08*
Atypia	1	2	20,0%	3	10,3%	27	32,9%	<0,0001* a-b>0,05 a-c: 0,000 b-c:0,000
	2	0	0,0%	3	10,3%	41	50,0%	
Mitosis		2	20,0%	3	10,3%	64	78,0%	<0,001* a-b>0,05 a-c: 0,001 b-c:0,000
Necrosis		0	0,0%	0	0,0%	29	35,4%	<0,001* a-c: 0,06 b-c:0,000
Inflammation	1	6	60,0%	26	89,7%	59	72,0%	0,06*
	2	3	30,0%	3	10,3%	22	26,8%	
Hemosiderin		6	60,0%	28	96,6%	76	92,7%	0,002* a-b: 0,015 a-c: 0,009 b-c >0,05

*Pearson Ki square test

L: Lymphocyte, N: Neutrophil, P: Plasma cell

Table 4. Multivariate analysis of the incidence of histological features in the three stages of Kaposi's sarcoma.

			OR	SE	CI 95%	p
Patch and plaque stages	Hemosiderin	present	1	--	--	0,02
		present	25,7	1,3	1,6 - 398,2	
	Globule	absent	1	--	--	0,09
		present	13,1	1,5	0,6 - 266,3	
Nodular and patch stages nodul compared to patch	Hyperkeratosis	absent	1	--	--	0,8
		present	1,3	1,3	0,1 - 19,6	
	Acanthosis	absent	1	--	--	0,3
		present	2,7	1,1	0,2 - 27,1	
	Spindle cell	absent	1	--	--	0,8
		present	1,2	1,6	0,04 - 33,2	
	Fasicle	absent	1	--	--	0,8
		present	1,6	2,1	0,02 - 113,3	
	Cleft	absent	1	--	--	0,5
		present	2,3	1,5	0,1 - 50,2	
	Nodule	absent	1	--	--	0,2
		present	9,5	2,08	0,1 - 562,05	
	Globule	absent	1	--	--	0,8
		present	0,7	1,8	0,02 - 28,6	
	Mitosis	absent	1	--	--	0,2
		present	3,7	1,1	0,3 - 37,6	
Nodular and plaque stages nodul compared to plaque	Hemosiderin	absent	1	--	--	0,1
		present	6,8	1,3	0,4 - 103,6	
	Hyperkeratosis	absent	1	--	--	0,02
		present	2,4	1,1	1,2 - 96,5	
	Acanthosis	absent	1	--	--	0,7
		present	0,2	0,7	0,2 - 5,9	
	Ulcer	absent	1	--	--	0,6
		present	0,6	1,4	0,1-32,7	
	Spindle cell	absent	1	--	--	0,3
		present	-0,8	1,0	0,05 - 3,1	
	Fasicle	absent	1	--	--	0,1
		present	1,6	1,2	0,4- 57,3	
	Cleft	absent	1	--	--	0,051
		present	2,3	1,1	0,9-101,3	
	Horizontally orientat- ed vascular bundles	absent	1	--	--	0,7
		present	-0,2	1,1	0,08 - 6,7	
	Nodule	yok	1	--	--	0,5
		present	-0,7	0,9	0,05 - 4,4	
	Atypia	absent ⁰	1	--	--	0,5 ⁰⁻¹
		mild ¹	-0,8	1,3	0,03-6,3	0,2 ⁰⁻²
		high ²	-1,8	1,6	0,007-3,4	
	Mitosis	absent	1	--	--	0,002
		present	3,7	1,2	3,8 - 489,7	
	Necrosis	absent	1	--	--	0,9
		present	19,5	6325,0	0,0	

Spindle cells begin to concentrate and form bundles around the proliferating vascular channels. Eosinophilic and hyaline globules can also be encountered [4-9]. In this study, the promontory sign, hyaline globules and hemosiderin were the most frequently observed features in the plaque stage. Necrosis was not observed. The promontory sign, which is a characteristic of the patch stage, was most frequently detected in the plaque stage. When compared to the patch stage, the most significant histomorphological finding was found to be the presence of hemosiderin in the plaque stage."

In the classical nodular stage of KS, intersecting, bundled spindle cells and erythrocyte-containing clefts that separate vascular structures are observed. The spindle cells have a honeycomb or sieve-like appearance in transverse sections. In the periphery of the nodular lesion, inflammatory cells (lymphocytes and plasma cells), hemosiderin accumulations and dilated vessels are observed. Another characteristic, but non-specific, feature of this stage's lesions is hyaline globules. Dilated vascular spaces similar to a cavernous hemangioma may be observed around some lesions. The large cutaneous nodules can ulcerate, and the tumor may exhibit cellular pleomorphism, necrosis and mitotic figures in this stage [2,3]. In our study, inflammation, globules, erythrocyte extravasation and spindle cells were the most common histological findings in cases diagnosed in the nodular stage.

Compared to the plaque stage, the most valuable differentiating feature in the nodular stage was the presence of mitosis. We believe that the combined detection of ulceration, necrosis, atypia and mitosis is useful in distinguishing the nodular stage from the other stages.

Conclusion

The concomitance of hemosiderin, the horizontal placement of vascular structures, erythrocyte extravasation and the promontory findings in the patch stage; of promontory, globule and hemosiderin in the plaque stage; and of an ulcer, necrosis, atypia and mitosis in the nodular stage are the most effective histopathological parameters.

In this retrospective study of KS, the demographic details and the distribution of histopathological features by stage were similar to those documented in the literature. The diagnosis of KS (which has different histopathological features at different stages) can be more definitively made when the histopathological finding that is most prominent at a given stage and best describes that stage is evaluated. Furthermore, the development of a scoring system alone with case series with higher numbers of cases would help facilitate the diagnosis of KS at different stages.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	SG	DB	OT	LY
Research concept and design	√	--	--	√
Collection and/or assembly of data	√	--	--	--
Data analysis and interpretation	√	√	--	--
Writing the article	√	--	--	--
Critical revision of the article	√	--	--	√
Final approval of article	√	--	--	--
Statistical analysis	--	--	√	--

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