Original Article

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Our Five Years of Kaposi's Sarcoma Experience: Which Histopathological Parameters are More Valuable in Diagnosis?

Beş Yıllık Kaposi Sarkomu Deneyimimiz: Hangi Histopatolojik Parametreler Tanıda Daha Değerlidir?

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ABSTRACT

Objective: Kaposi's sarcoma (KS) is a vascular proliferation associated with Human Herpes Virus 8. Typical histopathological findings of KS are characterized by vascular proliferation, inflammatory cell infiltration, extravasated erythrocytes and spindle cell proliferation, although it varies according to the stage. In this study, the clinical-histopathological features of patients with KS were examined. The value of histopathological parameters in the diagnosis was investigated.

Methods: Patients with KS diagnosed in University of Health Sciences Turkey, Samsun Training and Research Hospital Medical Pathology Department between 2016-2020 were retrospectively scanned. Clinical and tumor features and histopathological changes in the surrounding tissue were evaluated.

Results: The most common histopathological features belonging to tumor were extravasated erythrocytes, spindle cell changes, fascicle formation, slit-like space; the most common epidermal features were hyperkeratosis and acanthosis; the most common peritumoral features were the presence of large vessels and ectatic vessels in the periphery. There was a significant relationship between the promontory sign and the lymphangioma-like area and ulcer. Also there was a significant relationship between nuclear atypia and lymphangioma-like area.

ÖZ

Amaç: Kaposi sarkomu (KS), human herpes virüs 8 ilişkili vasküler bir proliferasyondur. Tipik histopatolojik bulguları, evreye göre değişmekle birlikte; vasküler proliferasyon, inflamatuvar hücre infiltrasyonu, ekstravaze eritrositler ve iğsi hücre proliferasyonu ile karakterizedir. Çalışmamızda KS olgularının klinik-histopatolojik özellikleri incelendi. Histopatolojik parametrelerin tanıdaki değeri araştırıldı.

Yöntemler: Sağlık Bilimleri Üniversitesi Samsun Eğitim ve Araştırma Hastanesi Tıbbi Patoloji Bölümü'nde 2016-2020 yılları arasında tanı alan KS olguları retrospektif olarak tarandı. Klinik, tümör özellikleri ve çevre dokudaki histopatolojik değişiklikler değerlendirildi.

Bulgular: En sık görülen tümöre ait histopatolojik özellikler ekstravaze eritrositler, iğsi hücre değişikliği, fasikül oluşumu, yarık benzeri boşluk; epidermise ait özellikler hiperkeratoz ve akantoz; peritümöral özellikler ise periferde büyük damar ve çevrede ektatik damar varlığıdır. Promontuvar belirti ile lenfanjiom benzeri alan ve ülser arasında; nükleer atipi ile lenfanjiyom benzeri alan arasında anlamlı ilişki saptanmıştır.

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ABSTRACT

Conclusion: While most of the histopathological features are characteristic for KS, none of them alone is specific. They should be evaluated together with all structural, tumoral and peritumoral features during the diagnostic approach.

Keywords: Kaposi's sarcoma, vascular tumor, histopathology, human herpes virus 8, HHV-8, promontory sign

ÖZ

Sonuç: Histopatolojik özelliklerin çoğu KS için karakteristik olmakla birlikte, hiçbiri tek başına spesifik değildir. Tanısal yaklaşım sırasında tüm yapısal, tümöral ve peritümöral özellikler birlikte değerlendirilmelidir.

Anahtar Sözcükler: Kaposi sarkomu, vasküler tümör, histopatoloji, human herpes virüs 8, HHV-8, promontuvar belirti

Introduction

Kaposi's sarcoma (KS) is a vascular proliferation associated with human herpes virus 8 (HHV-8), and is still contoversial whether it is a true sarcoma or not. It's worldwide estimated incidence is 0.6/100,000 person-year (1). Four different clinical/epidemiological subtypes of KS have been defined: classic, epidemic [acquired immunodeficiency syndrome associated], endemic (African type), and iatrogenic (transplantation-associated) KS (1-3). All these types show similar histomorphological spectrum. The histopathological development of the tumor occurs in clinically distinguishable patch, plaque and nodule stages. In addition to the usual type of KS, there are many histopathological subtypes defined in the literature such as anaplastic, lymphedematous, lymphangioma-like, lymphangiectatic, bullous, telangiectatic, hyperkeratotic, keloidal, micronodular, pyogenic granuloma-like, ecchymotic, intravascular, and regressed KS (2,4,5).

Typical histopathological findings of KS are characterized by vascular proliferation, inflammatory cell infiltration, extravasated erythrocytes and spindle cell proliferation, although it varies according to the stage. Apart from these well-known features, what other histological changes are observed in the tumor and surrounding tissue, and which ones are more valuable in making the diagnosis?

In our study, answers to these questions were sought, and detailed histopathological analysis of patients with KS diagnosed in the Medical Pathology Department of University of Health Sciences Turkey, Samsun Training and Research Hospital during the 5-year period covering the years 2016-2020 was carried out. Clinical and tumor features and histopathological changes in the surrounding tissue were evaluated. The value of histopathological parameters to making the diagnosis was investigated.

Methods

Case Selection

Patients with KS diagnosed in University of Health Sciences Turkey, Samsun Training and Research Hospital, Medical Pathology Department between 2016-2020 were retrospectively scanned from the hospital information management system (HIMS). Fourty three patients who had excisional or punch biopsies were detected. The slides of the patients were removed from the archive. Three patients were excluded because there was no slide or block in the archive. The clinical data of the patients (age, gender, localization of the lesions) were compiled from HIMS. Histopathological evaluation was performed using hematoxylin/eosin stained slides, immunohistochemical (HHV-8 in all patients) and histochemical (PAS in some patients) materials. One patient was not found to be compatible with KS after re-evaluation and was excluded from the study.

The study was approved by the Non-invasive Clinical Research Ethics Committee of University of Health Sciences Turkey, Samsun Training and Research Hospital (decision no: 2019/3/4) and performed in accordance with the Helsinki Declaration.

Histomorphological evaluation

The slides of the lesions included in the study were re-evaluated by double observers. Epidermal parameters (hyperkeratosis, acanthosis, papillomatosis, vesicle/bulla, ulcer), tumor features (vascular horizontal location, presence of miniature vessels in the center, lymphangioma-like area, hemangioma-like area, promontory sign, collagen fiber dissection, erythrocyte extravasation, hemosiderin/hemosiderin-laden macrophage, presence of spindle cell, slit-like space, fascicle formation, presence of hyaline globule, nuclear atypia, mitosis, necrosis, inflammatory infiltrate) and peritumoral features (large vessel in the periphery, ectatic vessel in the periphery) were evaluated. Mitosis was counted in 10 high power fields. Inflammatory infiltrate was graded as dense, moderate, mild, and the predominant cell component (lymphocyte, plasma, neutrophil) was determined. All other parameters were classified as present/absent.

Statistical Analysis

The SPSS 15.0 for Windows (SPSS Inc., Chiago, Illinois, USA) program was applied for statistical analysis. Descriptive statistics were given as numbers and percentages for categorical variables. Numerical variables were given as mean, standard deviation, minimum and maximum. Comparison of rates in independent groups was made with the chi-square test. Since the numeric variables showed normal distribution, comparisons of independent two groups were made with Student's t-test. Statistical alpha significance level was accepted as $p<0.05$.

Results

Of the 39 patients included in the study, 28 (71.8%) were male and 11 (28.2%) were female. The mean age ± standard deviation of the patients was 71.8±8.5, and the age range was between 49

and 92 years. Tumors were located in the lower extremity in 25 (65.8%) patients, in the upper extremity in 12 (31.6%) patients, and in the scrotum in 1 (2.6%) patient. Thirty two (82.1%) of the evaluated materials were excisional materials and 7 (17.9%) of them were punch biopsy materials. The stages of the patients were detected as "patch" in only 2 patients and as "nodul" in the others.

The histopathological parameters we evaluated and their incidence rates are shown in Table 1.

The most common finding we determined from the features of the tumor was the presence of extravasated erythrocytes (n=38), and the most common finding among the epidermis parameters was hyperkeratosis (n=34).

The rate of detection of spindle cell changes, fascicles, peripheral large vessels, slit-like spaces, and ulcers was statistically significantly lower in punch biopsies than excisional biopsies (Table 2).

Table 1. Results

	n	(%)
Features of tumor		
Erythrocyte extravasation	38	97.4%
Spindle cell change	36	92.3%
Fascicle	34	87.2%
Slit-like space	28	71.8%
Hemosiderin laden macrophages	21	53.8%
Nuclear atypia	12	30.8%
Promontory sign	11	28.2%
Collagen fiber dissection	10	25.6%
Hemangioma-like area	7	17.9%
Hyaline globule	6	15.4%
Vascular horizontal location	6	15.4%
Miniature vessels in the center	5	12.8%
Lenfangioma-like area	3	7.7%
Necrosis	1	2.6%
Parameters of epidermis		
Hyperkeratosis	34	87.2%
Acanthosis	25	64.1%
Papillomatosis	20	51.3%
Ulcer	19	48.7%
Vesicle/bulla	1	2.6%
Peritumoral features		
Large vessel in the periphery	29	74.4%
Ectatic vessel in the periphery	26	66.7%

When the findings were compared according to localization, no significant difference was found between the findings.

When the relationship between the parameters was examined;

- The rate of ulceration in sarcomas with promontory sign was statistically significantly higher than those without promontory sign (p=0.010) (Table 3).

- Presence of lymphangioma-like area in those without nuclear atypia was statistically significantly higher than those with nuclear atypia (p=0.024) (Table 4).

- The mean mitosis of patients with spindle cell changes, fascicles, peripheral great vessels, slit-like spaces, and ulcers were statistically significantly higher than those without them (Table 5).

- No significant difference was found in the findings of patients with or without hyaline globules.

A feature that caught our attention was the presence of moderate or intense mixed type lymphoplasmacytic inflammatory cell infiltration in each patient (Table 6).

Pictures of some of the histopathological parameters are given in Figure 1.

Discussion

Kaposi's sarcoma is an HHV-8-associated vascular proliferation primarily involving the skin, most commonly located in the lower extremities (1). Most of the studies which were reported until now on KS were related to demographic and clinical data, and studies examining histopathological features were in the minority. In our study, histopathological features as well as demographic data were discussed in detail.

When the demographic data of the patients included in our study were compared with the literature, no difference was found.

The mean age of onset of KS may differ according to the subtype (6-8). However, the mean age in classical KS has been reported to be between 65 and 75 in most studies (3,4,6,9). In our study, the mean age of the patients was 71.8 (age range between 49 and 92), which was similar to the literature.

The female/male ratio was reported at different rates between studies. While the M/F ratio was 2.36 in the study of Demirel et al., (4) 2.11 in the study of Kandemir et al., (5) 4.07 in the study of Errihani et al., (10) and this ratio was 6.5 in the study of Wu et al. (11). In our study, the male/female ratio was 2.54.

Typical histopathological findings of KS vary according to the stage. Patch-stage lesions are characterized by thin endothelial cell proliferation that breaks down collagen (1,2,4). The extension of small proliferating vascular structures towards to larger vessel lumens causes the appearance called "promontory sign" (2). Early stage lesions may be accompanied by promontory sign. Plaque stage lesions are more cellular and are characterized by dense dermal vascular infiltrate and spindle cell proliferation.

Table 2. Comparison of histopathological parameters according to biopsy type

	Biopsy type				
	Excision		Punch		
	n	%	n	%	p
Spindle cell change	32	100.0%	4	57.1%	**0.004**
Fascicle	30	93.8%	4	57.1%	**0.032**
Hyperkeratosis	28	87.5%	6	85.7%	1.000
Large vessel in the periphery	27	84.4%	2	28.6%	**0.007**
Slit-like space	26	81.3%	2	28.6%	**0.012**
Ectatic vessel in the periphery	22	68.8%	4	57.1%	0.566
Acanthosis	23	71.9%	2	28.6%	0.075
Papillomatosis	18	56.3%	2	28.6%	0.235
Ulcer	19	59.4%	0	0.0%	**0.008**
Collogen fiber dissection	8	25.0%	2	28.6%	1.000
Hemangioma-like area	7	21.9%	0	0.0%	0.313
Vascular horizontal localization	5	15.6%	1	14.3%	1.000
Miniature vessels in the center	3	9.4%	2	28.6%	0.213
Lenfangioma-like area	3	9.4%	0	0.0%	1.000
Vesicle/bulla	1	3.1%	0	0.0%	1.000

Table 3. Comparison of histopathological parameters according to promontory sign

	Promontory sign				
	Presence		Absent		
	n	%	n	%	p
Spindle cell change	11	100.0%	25	89.3%	0.545
Fascicle	10	90.9%	24	85.7%	1.000
Hyperkeratosis	11	100.0%	23	82.1%	0.296
Large vessel in the periphery	9	81.8%	20	71.4%	0.693
Slit-like space	10	90.9%	18	64.3%	0.130
Ectatic vessels in the periphery	9	81.8%	17	60.7%	0.276
Acanthosis	9	81.8%	16	57.1%	0.266
Papillomatosis	6	54.5%	14	50.0%	0.798
Ulcer	9	81.8%	10	35.7%	**0.010**
Kollogen fiber dissection	3	27.3%	7	25.0%	1.000
Hemangioma-like area	4	36.4%	3	10.7%	0.083
Vascular horizontal localization	3	27.3%	3	10.7%	0.323
Miniature vessels in the center	1	9.1%	4	14.3%	1.000
Lenfangioma-like area	3	27.3%	0	0.0%	**0.018**
Vesicle/bulla	1	9.1%	0	0.0%	0.282

Other expected findings are hyaline globules, siderophages, and slit-like spaces containing erythrocytes (1,2). Nodule stage lesions are much more cellular. The spindle cells form fascicles and slit-like spaces are common. Hyaline globules and mitoses can be seen (1,2).

Almost all of our patients were in the nodule stage, and in accordance with this, the most frequent tumor-related features we detected were extravasated erythrocytes, spindle cell changes, fascicles, slit-like space and hemosiderin-laden macrophages. Among the peritumoral features, the presence of large vessels in the periphery was a remarkable feature in KS with 74% of cases.

It has been reported in the literature that promontory sign is frequently seen in early-stage lesions (1,2). Since almost all of our patients were in the nodule stage in our study, we could not compare the relationship between the stage and the promontory sign. However, we observed that the promontory sign was not less in the nodule stage. In addition, we found that there was a statistically significant positive correlation between the

Table 4. Comparison of nuclear atypia and other histopathological parameters

	Nuclear atypia				
	Present		Absent		
	n	%	n	%	p
Spindle cell change	26	96.3%	10	83.3%	0.219
Fascicle	24	88.9%	10	83.3%	0.634
Hyperkeratosis	22	81.5%	12	100.0%	0.299
Large vessel in the periphery	21	77.8%	8	66.7%	0.693
Slit-like space	19	70.4%	9	75.0%	1.000
Ectatic vessels in the periphery	18	66.7%	8	66.7%	1.000
Acanthosis	16	59.3%	9	75.0%	0.477
Papillomatosis	15	55.6%	5	41.7%	0.423
Ulcer	12	44.4%	7	58.3%	0.423
Collogen fiber dissection	7	25.9%	3	25.0%	1.000
Hemangioma-like area	5	18.5%	2	16.7%	1.000
Vascular horizontal localization	2	7.4%	4	33.3%	0.060
Miniature vessels in the center	2	7.4%	3	25.0%	0.159
Lenfangioma-like area	0	0.0%	3	25.0%	**0.024**
Vesicle/bulla	1	3.7%	0	0.0%	1.000

Table 5. Comparison of the relationship between the number of mitosis and other histopathological parameters

		Mitosis … /10 HPF		
		Mean ± SD	Min-max	p
Spindle cell cgange	Positive	11.39±6.95	1-31	**0.012**
	Negative	0.67±1.15	0-2	
Fascicle	Positive	11.59±7.00	1-31	**0.020**
	Negative	3.60±5.41	0-13	
Hiperkeratosis	Positive	10.94±7.62	0-31	0.406
	Negative	8.00±3.87	3-12	
Large vessel in the periphery	Positive	11.97±7.14	1-31	**0.039**
	Negative	6.50±6.35	0-17	
Slit-like space	Positive	13.14±6.60	4-31	**<0.001**
	Negative	4.00±4.22	0-13	
Ectatic vessels in the periphery	Positive	11.04±6.71	1-31	0.572
	Negative	9.62±8.52	0-27	
Acanthosis	Positive	11.68±6.61	1-31	0.205
	Negative	8.57±8.22	0-27	
Papillomatosis	Positive	11.00±8.30	1-31	0.707
	Negative	10.11±6.23	0-23	
Ulcer	Positive	14.26±6.54	6-31	**0.001**
	Negative	7.05±6.23	0-23	
Collogen fiber dissection	Positive	8.00±6.09	0-17	0.200
	Negative	11.45±7.54	0-31	
Hemangioma-like area	Positive	10.57±4.04	3-15	0.998
	Negative	10.56±7.86	0-31	
Vascular horizontal localization	Positive	11.50±5.96	0-17	0.737
	Negative	10.39±7.56	0-31	

Table 5. Continued				
Miniature vessels in the center	Positive	5.80±5.26	0-13	0.118
	Negative	11.26±7.33	0-31	
Lenfangioma-like area	Positive	18.00±11.27	11-31	0.065
	Negative	9.94±6.72	0-27	
Vesicle/bulla	Positive	14.00	14-14	-
	Negative	10.47±7.35	0-31	

SD: Standart deviation, Min: Minimum, Max: Maximum

Table 6. Inflammatory infiltrate status in our patients

		n (%)
Inflammatory response	Severe lymphocyte predominant	24 (61.5%)
	Moderete lymphocyte predominant	12 (30.8%)
	Severe plasma cell predominant	2 (5.1%)
	Severe lymphocyte = plasma cell	1 (2.6%)

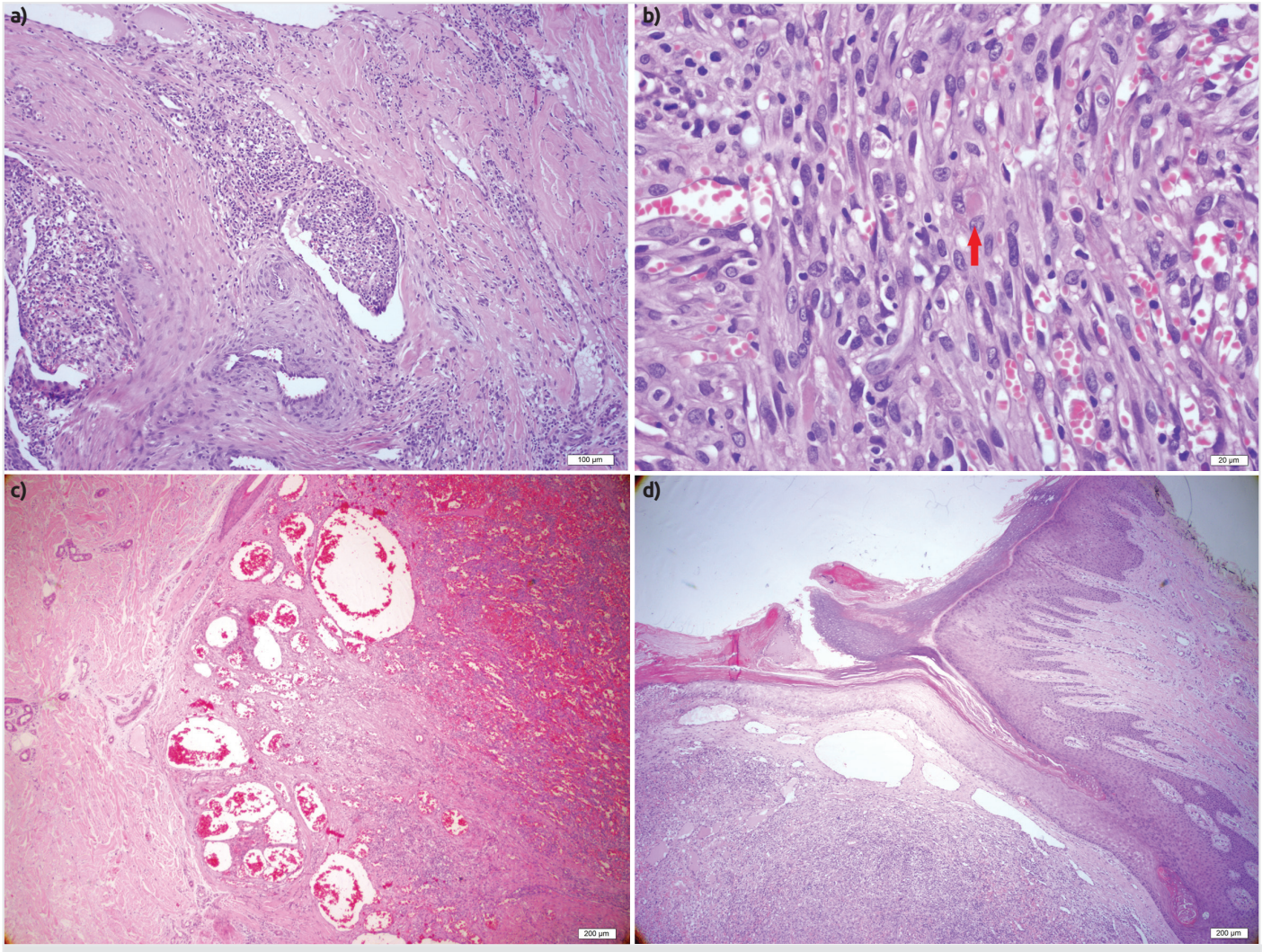

Figure 1. a) Promontory sign is seen. Its called for the extension of small proliferating vascular structures towards to larger vessel lumens (hematoxylin & eosin x100), b) Hiyalen globule is seen (hematoxylin & eosin, x400), c) Hemangioma-like area is seen (hematoxylin & eosin, x40), d) Ectatic vessel in the periphery (hematoxylin & eosin, x40)

promontory sign and the presence of ulcer. In the approach to an ulcerated skin lesion, the presence of promontory sign should raise suspicion in terms of KS. However, it should be noted that the promontory sign is not pathognomonic for KS. It has been emphasized that it is not an uncommon feature in patch or plaque stage of angiosarcomas (12), and it has been reported that it can also be seen in reactive benign vascular proliferations (13).

It has been reported that promontory sign is observed more frequently in lymphangioma-like subtype (2,5). Consistent with this, we also observed the presence of promontory sign in 3 of our 3 patients with lymphangioma-like areas.

In our study, some histopathological features such as spindle cell change and the presence of fascicles were found to be significantly lower in punch biopsies compared to excisional biopsies. These findings, which are strongly suggestive for diagnosis, may be observed less frequently in small biopsies, which may lead to missed diagnosis or delays in diagnosis.

Nuclear atypia and high mitosis are not common findings in KS. They can be observed more frequently in advanced lesions. In our study, we found a significant relationship between nuclear atypia and the presence of lymphangioma-like areas. Presence of lymphangioma-like area in those without nuclear atypia was statistically significantly higher than those with nuclear atypia. When we searched the literature, we did not find any study reporting a relationship between atypia and lymphangiomatous area. In this sense, our study presents a new finding.

When the relationship between the number of mitosis and histopathological changes was compared; we found a significant relationship between mitosis and spindle cell change, fascicle formation, large vessels in the periphery, slit-like space and ulcer. Considering that spindle cell changes, slit-like space and fascicle formation were more common findings in the nodule stage; it would not be wrong to say that the number of mitoses might be high in advanced lesions.

Conclusion

In this study, the clinical-histopathological features of patients with KS were examined. The most common histopathological features belong tumor were extravasated erythrocytes, spindle cell changes, fascicle formation, slit-like space; the most common epidermal features were hyperkeratosis and acanthosis; the most common peritumoral features were the presence of large vessels and ectatic vessels in the periphery. There was a significant relationship between the promontory sign and the lymphangioma-like area and ulcer. Also there was a significant relationship between nuclear atypia and lymphangioma-like area. Mitosis was found to be high in advanced lesions.

While most of the histopathological features were caracteristic for KS, none of them alone was specific. They should be evaluated together with all structural, tumoral and peritumoral features during the diagnostic approach. In addition, it should not be forgotten that the diagnosis could be missed, especially in punch biopsies; and small biopsies should be examined carefully.

Ethics

Ethics Committee Approval: The study was approved by the Non-invasive Clinical Research Ethics Committee of University of Health Sciences Turkey, Samsun Training and Research Hospital (decision no: 2019/3/4) and performed in accordance with the Helsinki Declaration.

Informed Consent: Since it was a retrospective study, patient consent was not obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: C.B.I., Concept: C.B.I., H.Ö.U., Design: C.B.I., Data Collection or Processing: C.B.I., Analysis or Interpretation: C.B.I., H.Ö.U., Literature Search: C.B.I., Writing: C.B.I.

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