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Evaluation of the relationship between c-Kit expression and mean platelet volume in classic Kaposi's sarcoma*

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Abstract: BACKGROUND: c-Kit is a proto-oncogene that encodes tyrosine kinase receptor (CD117). Mean platelet volume (MPV) is a useful marker, providing information on platelet function and diameter.
OBJECTIVE: To investigate c-Kit expression and intensity in patients with Kaposi's sarcoma (KS) and to investigate the relation between Ki-67 proliferation and MPV.
METHODS: A total of 32 patients, diagnosed with classic cutaneous KS, were included in this study. We reevaluated the histopathological reports with the preparations, confirmed the diagnosis and then determined the patients' histopathological stages. c-Kit expression and Ki-67 proliferation were investigated immunohistochemically in KS cases, while MPV in all cases was checked.
RESULTS: Although c-Kit expression was detected in 22 cases (68.8%), it was not expressed in 10 cases (31.2%). We detected 8 cases with + (25%), 6 with ++ (18.8%) and 8 with +++ (25%). Ki-67 expression was 5.0% (min-max 1.0-20.0). Relapse was observed in 5 cases (15.6%) out of 32. There was positive correlation between c-Kit expression and MPV (rs=0.598, p<0.001), and between c-Kit intensity and MPV (rs=0.588, p<0.001).
CONCLUSION: c-Kit is highly positive in KS. c-Kit positivity indicates a high risk of tumor growth, invasion and relapse. Furthermore, c-Kit expression stimulates megakaryocytes to release young and large thrombocytes into the periphery. Thus, high MPV, c-Kit expression and immunostaining intensity indicate high invasion and relapse in KS subjects.
Keywords: Proto-Oncogene proteins c-Kit; Sarcoma, Kaposi; Ki-67 antigen

INTRODUCTION

Kaposi sarcoma (KS) is a metacentric, low-grade vessel tumor of mesenchymal origin. Although it can be observed in all organs, it presents predominantly in mucocutaneous tissues.[1] There are 4 types with principally classified, defined according to histopathological characteristics (new vascular proliferation, erythrocyte extravasation, edema and mononuclear inflammatory cell infiltration): classic, African (endemic), iatrogenic and acquired immunodeficiency syndrome-related.[2] In practice, KS generally presents as one or multiple, asymptomatic, red-purple or brown patches, plaques or nodular skin lesions in the lower extremities.[3] C-Kit is involved in cell signal transduction in many different cell types and it encodes tyrosine kinase receptor (CD117). Furthermore, c-Kit is

a mutagenic effective proto-oncogene with a stem-cell factor (SCF) as a ligand, and it leads to tumor growth through impairment of cellular growth regulation.[4] In humans, it is localized in the q11-q22 region of the fourth chromosome. As a member of the platelet-derived growth factor (PDGF) family, c-Kit plays a key role in the tumorigenesis of KS.[5] In the literature c-Kit expression has been investigated but different results have been reported.[6-8]

Mean platelet volume (MPV) is a simple, inexpensive and easily applied test. Additionally, it provides information on thrombocyte functions and diameters, and is a good indicator for thrombocytes activation.[9] A high MPV indicates the presence of large and active thrombocytes in the periphery. These thrombocytes express

excessively PDGF, thromboxane A$_2$, glycoprotein Ib and IIb/IIIa receptors.[10] The production of these substances increases thrombosis in patients with cancer and especially, high level of PDGF may promote tumor growth and invasion in malignancies.[11] In the literature, MPV was reported as a prognostic factor for different cancers.[12,13]

In this study, we aimed to: investigate c-Kit expression and immunostaining intensity; explore whether there is a relationship between MPV and c-Kit expression; and determine whether MPV is a predictor for relapse risk in subjects with classic KS.

METHODS

The study was compiled following the principles outlined in the Declaration of Helsinki, and affirmed by the local ethics committee. A total of 32 patients (21 males, 11 females) were included in the study; they had been diagnosed with classic cutaneous KS in the pathology department between 2010 and 2014. The data obtained during recurrence in patients with relapse were only used their first data to the statistics. Histopathological reports with the preparations were reevaluated, the diagnosis was confirmed and the patients' histopathological stages were then determined. The subjects had no history of human immunodeficiency virus-1 infection, organ transplantation or immunosuppressive treatment.

Paraffin-embedded blocks of KS subjects were cut into 3 micrometer sections and put on positively charged slides for immunohistochemical study. CD117 (ready-to-use mouse monoclonal antibody, Biogenex, Fremont, CA, USA) and Ki-67 (ready-to-use mouse monoclonal antibody, Biogenex, Fremont, CA, USA) primary antibodies were applied to the sections for immunohistochemical study. The following were applied for the immunohistochemical staining system: biotin-free, HRP multimer-based, hydrogen peroxide substrate and 3,3'-diaminobenzidine tetrahydrochloride (DAB) chromogen containing ultraView™ Universal DAB Detection Kit (Catalog number 760-091, Ventana Medical Systems, Tucson, AZ,USA), and a fully automated immunohistochemistry staining device (Ventana Bench Mark XT, Ventana Medical Systems, Tucson, AZ, USA). Immunohistochemical staining included deparaffinization and antigen revealing procedures, which were carried out using Bench Mark XT fully automatic immunohistochemical staining devices. Primer antibodies CD117 and Ki-67 were only manually dripped at 37°C and incubated for 30 minutes. Mayer's hematoxylin was used as a contrast stain and the sections were evaluated blindly by 2 pathologists via Olympus BX51 light microscopy. Basal keratinocytes were used as a positive control for CD117 and Ki-67. Membranous or cytoplasmic staining of the tumor cells were positive > 1% for CD117. Moreover, CD117 staining and intensity were evaluated semi-quantitatively for all the subjects. The extent of CD117 staining was accepted as -, no positive or < 1% positive cells;+, (10% of cells), ++, (>10and <50% of cells), and +++ (>50% of cells).[8] CD117 intensity was scored as 0 (none), 1+ (weak), 2+ (moderate) and 3+ (strong).[14] Nuclear staining in tumor cells was considered positive for Ki-67. The hematologic parameters were studied using the Abbott Cell Dyn Ruby analyzer (Abbott Diagnostics, Abbott Park, IL, USA).

The results are expressed as a median (minimum- maximum) or a percentage where appropriate. Furthermore, the entire statistical analysis was performed using the statistical software SPSS for Windows (version 17; SPSS, Chicago, IL, USA) program. Non-numerical data such as gender, location and histologic stage were compared using the chi-square test or Fisher's exact test (when at least 25% of the cells had expected frequencies of under 5, Fisher's exact test was used). In this study, the Mann-Whitney U test or Kruskal–Wallis test (when the number of groups had frequencies of above 2, the Kruskal–Wallis test was performed) were used to compare numerical data because of their non-normal distribution and the small number of subjects. Spearman's formula was applied for correlation analysis. A P level of <0.05 was considered significant.

RESULTS

The lesions were localized as follows: 20 (62.5%) on the legs, 8 (25%) on the arms and 4 (12.5%) on the head and neck (H&N). While the vast majority of cases were at the nodular stage (53.1%), 31.3% of them were at the plaque stage, and the remaining 15.6% were at the patch stage. c-Kit expression was not detected in 10 cases (31.2%), 8 (25%) cases had +, 6 (18.8%) cases had ++ and 8 (25%) cases had +++. Furthermore, c-Kit immunostaining intensity was + for 7 cases (21.9%), ++ for 7 cases (21.9%) and +++ for 8 cases (25%) (Figure 1). Ki-67 expression was 5.0% (min-max 1.0-20.0) (Figure 1). Relapse was detected in 5 (15.6%) cases out of 32; c-Kit expression levels in relapse cases comprised 2 cases with +, 1 case with ++ and 2 cases with +++. All sociodemographic data are shown in table 1.

The cases (31.2%) with negative c-Kit expression (CN) were compared with those (68.8%) involving positive c-Kit expression (CP). The MPV level of the CN group was 7.0 (6.0-10.4) fL, whereas it
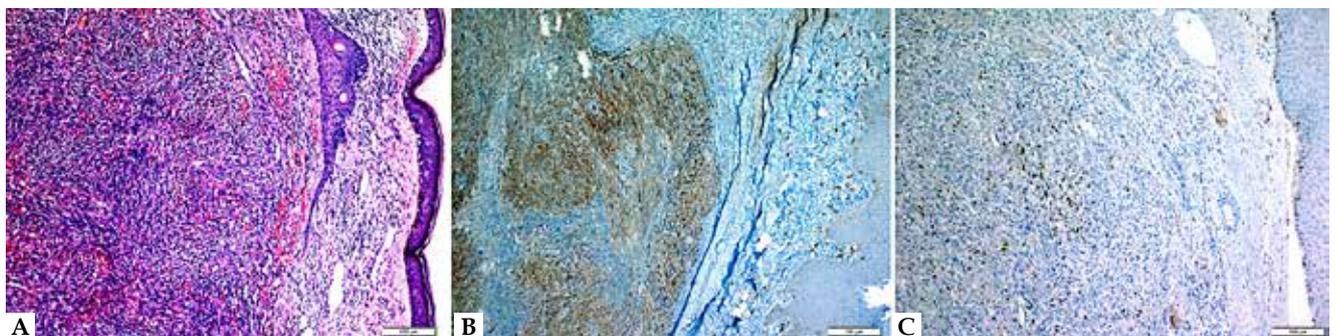
FIGURE 1: Classic Kaposi's sarcoma, nodular stage; (A) Hematoxylin and eosin staining, X100, (B) Neoplastic cells showing diffuse CD117 positivity, X100, (C) High Ki-67 proliferation in tumor cells, X100

was 8.4 (6.3-11.2) fL (p=0.007) in the CP group. While 5 cases showed relapse in the CP group, no relapses were noted in the CN group (p=0.155). However, there was no statistical significance. Other data revealed no significance. All the results are displayed in table 2.

Ki-67 expression in the plaque group was significantly higher than in the patch group (p=0.042). The white blood cell level of the plaque group was significantly lower than in the patch group (p=0.037). Interestingly, the Ki-67 level of the plaque group was higher than in the nodular group. Nevertheless, it was not statistically significant. The MPV levels of the patch and nodular groups correlated positively with increases in the disease stage. However, no statistical significance was noted. All the results are shown in table 3. Relapse was high in cases involving leg lesions. The MPV level and Ki-67 expression of subjects with relapse were higher than in subjects without relapse, although they were not significant. All the results are shown in table 4.

Comparison of Ki-67 according to gender revealed that while it was 10.0 (3.0-20.0)% in females, it was 4.0 (1.0-20.0)% in males (p=0.013). However, c-Kit expression, MPV and other parameters entailed no gender difference.

c-Kit expression correlated positively with both MPV (rs=0.602, p<0.001) and c-Kit intensity (rs=0.991, p<0.001). There were no positive or negative correlations between c-Kit expression and the other parameters (age, rs=0.102, p=0.547; stage rs=0.155, p=0.361; ki67 rs=0.300, p=0.072; white blood cell counts rs=0.146, p=0.388; hemoglobin rs=0.124, p=0.465; platelets rs=0.199, p=0.239, respectively). Further, c-Kit intensity correlated positively with MPV (rs=0.599, p<0.001). There were no positive or negative correlations between c-Kit intensity and the other parameters (age, rs=0.116, p=0.494; stage rs=0.137, p=0.418; ki67 rs=0.296, p=0.075; white blood cell counts rs=0.173, p=0.305; hemoglobin rs=0.142, p=0.401; platelets rs=0.226, p=0.179, respectively).

TABLE 1: Sociodemographical data, c-Kit staining and relapse in classic Kaposi's sarcoma cases

Patient	Age	Gender	Location	Histological stage	c-Kit expression	c-Kit intensity	Ki-67(%)	Relapse
1	55	M	LEG	NODULAR	+	+	5	+
2	88	M	LEG	NODULAR	0	0	2	
3	83	M	ARM	NODULAR	++	++	3	
4	67	F	LEG	PATCH	+++	+++	5	
5	62	M	ARM	PATCH	0	0	1	
6	71	M	ARM	PATCH	+	+	2	
7	84	F	ARM	PLAQUE	0	0	10	
8	59	M	H&N	PATCH	0	0	5	
9	81	F	H&N	NODULAR	+	+	3	
10	76	M	LEG	PLAQUE	+	+	7	
11	87	F	LEG	NODULAR	0	0	10	
12	80	M	ARM	PATCH	+	+	3	+
13	78	M	LEG	NODULAR	+++	+++	3	
14	85	F	LEG	NODULAR	+++	+++	8	+
15	95	M	LEG	NODULAR	+++	+++	20	
16	78	M	LEG	NODULAR	+	+	5	
17	61	M	LEG	NODULAR	0	0	7	
18	88	M	ARM	PLAQUE	0	0	15	
19	97	F	LEG	PLAQUE	+++	+++	20	+
20	68	F	LEG	PLAQUE	+++	+++	10	
21	64	M	LEG	PLAQUE	0	0	4	
22	51	F	ARM	PLAQUE	++	++	10	
23	65	M	H&N	NODULAR	+++	+++	15	
24	81	M	LEG	PLAQUE	+	+	1	
25	81	M	LEG	PLAQUE	+	++	4	
26	81	M	LEG	NODULAR	++	++	4	+
27	98	F	LEG	PLAQUE	++	++	20	
28	42	M	ARM	NODULAR	++	++	10	
29	84	F	LEG	NODULAR	0	0	10	
30	80	F	LEG	NODULAR	0	0	5	
31	59	M	LEG	NODULAR	++	++	3	
32	74	M	H&N	NODULAR	+++	+++	5	

Abbreviation: H&N, head and neck.

TABLE 2: Relationship between c-Kit expression and clinicopathological, hematologic parameters

	c-Kit negative (n=10)	c-Kit positive (n=22)	P value
Age (year) (median [min-max])	82.0 (59.0-88.0)	78.0 (42.0-98.0)	0.654***
Gender (n,%)			0.703**
Male	6 (60%)	15 (68.18%)	
Female	4 (40%)	7 (31.82%)	
Location (n,%)			0.639*
Arm	3 (30%)	5 (22.72%)	
Leg	6 (60%)	14 (63.64%)	
Head and neck	1 (10%)	3 (13.64%)	
Histological stage (n,%)			0.703*
Patch	2 (20%)	3 (13.64%)	
Plaque	3 (30%)	7 (31.82%)	
Nodular	5 (50%)	12 (54.54%)	
Relapse (n,%)			0.155**
Negative	10 (100%)	17 (77.28%)	
Positive	0 (0%)	5 (22.72%)	
Ki-67 (%) (median [min-max])	6.0 (1.0-15.0)	5.0 (1.0-20.0)	0.886***
Mean platelet volume(fL) (median [min-max])	7.0 (6.0-10.4)	8.4 (6.3-11.2)	0.007***
Platelets (×10^9/L) (median [min-max])	244.5 (171.0-341.0)	228.5 (132.0-420.0)	0.339***
White blood cell (×10^9/L) (median [min-max])	6.8 (3.5-10.6)	6.5 (4.2-11.3)	0.903***
Hemoglobin (g/dL) (median [min-max])	13.8 (11.0-16.8)	13.6 (9.8-16.2)	0.919***

*p value was calculated by Chi square test; **p value was calculated by Fisher's exact test; ***p value was calculated by Mann-Whitney test

TABLE 3: Relationship between histological stage and c-Kit intensity, clinicopathological and hematologic parameters

	Patch stage (n=5)	Plaque stage (n=10)	Nodular stage (n=17)	P value (¥ vs. patch group)
Age (year) (median [min-max])	67.0 (59.0-80.0)	81.0 (51.0-98.0)	80.0 (42.0-95.0)	0.212***
Gender (n,%)				
Male	4 (80%)	5 (50%)	12 (70.59%)	0.951**
Female	1 (20%)	5 (50%)	5 (29.41%)	
Location (n,%)				
Arm	3 (60%)	3 (30%)	2 (11.76%)	0.077*
Leg	1 (20%)	7 (70%)	12 (70.59%)	
Head and neck	1 (20%)	0 (0%)	3 (17.65%)	
C-Kit intensity (n,%)				0.364*
0	2 (40%)	3 (30%)	5 (29.41%)	
+	2 (40%)	3 (30%)	3 (17.65%)	
++	0 (0%)	2 (20%)	4 (23.53%)	
+++	1 (20%)	2 (20%)	5 (29.41%)	
Ki-67 (%) (median [min-max])	3.0 (1.0-5.0)	10.0 (1.0-20.0)¥	5.0 (2.0-20.0)	¥0.042***
Mean platelet volume (fL) (median [min-max])	7.1 (6.8-9.8)	8.0 (6.0-10.4)	8.3 (6.3-11.2)	0.371***
Platelets (×10^9/L) (median [min-max])	268.0 (146.0-322.0)	199.0 (171.0-251.0)	254.0 (132.0-420.0)	0.130***
White blood cell (×10^9/L) (median [min-max])	7.4 (6.5-10.6)	6.3 (4.2-9.4)¥	6.4 (3.5-11.3)	¥0.037***
Hemoglobin (g/dL) (median [min-max])	13.6 (11.5-16.8)	13.2 (9.8-16.1)	13.8 (12.0-16.2)	0.634***

*p value was calculated by Chi square test; **p value was calculated by Fisher's exact test; ***p value was calculated by Kruskal-Wallis test

Table 4: Relationship between histological stage and c-Kit expression, clinicopathological and hematologic parameters

	Relapse negative (n=27)	Relapse positive (n=5)	P value
Age (year) (median [min-max])	78.0 (42.0-98.0)	81.0 (55.0-97.0)	0.420***
Gender (n,%)			1.000**
Male	18 (66.66%)	3 (60%)	
Female	9 (33.34%)	2 (40%)	
Location (n,%)			0.764*
Arm	7 (25.93%)	1 (20%)	
Leg	16 (59.26%)	4 (80%)	
Head and neck	4 (14.81%)	0 (0%)	
Histological stage (n,%)			0.935*
Patch	4 (14.81%)	1 (20%)	
Plaque	9 (33.34%)	1 (20%)	
Nodular	14 (51.85%)	3 (60%)	
c-Kit expression (n,%)			0.199*
0	10 (37.04%)	0 (0%)	
+	6 (22.22%)	2 (40%)	
++	5 (18.52%)	1 (20%)	
+++	6 (22.22%)	2 (40%)	
Ki-67 (%) (median [min-max])	5.0 (1.0-20.0)	5.0 (3.0-20.0)	0.875***
Mean platelet volume (fL) (median [min-max])	7.9 (6.0-11.2)	8.2 (7.1-10.5)	0.337***
Platelets ($\times 10^9$/L) (median [min-max])	219.0 (146.0-341.0)	251.0 (132.0-420.0)	0.483***
White blood cell ($\times 10^9$/L) (median [min-max])	6.7 (3.5-11.3)	6.4 (6.0-8.4)	0.736***
Hemoglobin (g/dL) (median [min-max])	13.6 (9.8-16.8)	13.6 (11.7-14.4)	0.815***

*p value was calculated by Chi square test; **p value was calculated by Fisher's exact test; ***p value was calculated by Mann-Whitney test

DISCUSSION

As the results of our study demonstrate, c-Kit expression was observed in the vast majority of KS patients. c-Kit expression was positive in all patients with relapse. The MPV level of individuals with positive c-Kit expression was higher than in those with negative c-Kit expression. Ki-67 percentages were similar in both positive and negative groups. Whereas the Ki-67 percentage was significantly higher at the plaque stage than the patch stage, it was higher than at the nodular stage. However, it was not statistically significant. The MPV level was found to increase steadily with the stage, yet it was statistically insignificant. Ki-67 percentages and MPV levels in relapse patients were insignificantly higher than in those without relapse.

c-Kit expression in KS patients has been reported in different ranges by a limited number of studies. While Miettinen *et al.* reported a c-Kit expression rate of 15.3 % (13 cases) in KS, whereas Sarlomo-Rikala *et al.* reported no c-Kit expression in 7 cases.[6,15] However, both studies investigated a limited number of KS cases. Pantanowitz *et al.* also found that c-Kit expression was not linked to histopathological stage or tumor localization. However, they reported a c-Kit expression of 56% in classic KS cases.[7] Only 5 cases were investigated in the Pantanowitz *et al.* study. In a larger study, Kandemir *et al.* investigated 35 KS cases and uncovered a c-Kit expression of 62.8%. Reactivity was +1 (n=16), +2 (n=2), +3 (n=4). Additionally, they reported c-Kit immunostaining to be 60% at the patch stage, 66.6% at the plaque stage and 63% at the nodular stage. They found that both c-Kit expression and immunostaining intensity were unrelated to histopathological stage.[8] In our study, out of 32 cases, c-Kit

expression emerged in a range of 68.8%. In the three other studies, a low number of cases may lead to bias. However, the number of KS cases in our study is similar to the study of Kandemir *et al.* and both of the studies have got large population; therefore, both of the studies results' confirm each other.[8] Like Pantanowitz *et al.*, we found that c-Kit expression was not linked to histopathological stage or tumor localization.[7] Unlike the other studies, the relapse rate for KS in our study was 15.6%. Curiously, all patients with relapse had positive c-Kit expression, while cases with negative c-kit expression did not entail relapses. Nevertheless, there was no relationship between c-Kit intensity and relapse.

c-Kit is a member of the tyrosine kinase family and its positivity indicates indirectly the use of tyrosine kinase pathway in tumor growth and invasion.[16,17] Interestingly, although it was not statistically significant, MPV levels were higher in relapse cases. Furthermore, while MPV levels were low in cases with negative c-Kit, they were remarkably high in cases with c-Kit expression. The MPV level indicates young and large thrombocytes in the periphery. These thrombocytes release many aggregator substances that lead to arterial and venous thrombosis. c-Kit expression stimulates megakaryocytes, therefore we might have found high correlation between c-Kit expression and MPV.[18] Equally, PDGF is a factor released mostly from thrombocytes and it is a member of the tyrosine kinase family.[19] PDGF production contributes to both the development and invasion of the tumor.[20] We speculate that the presence of young and large thrombocytes in the periphery reflect indirectly the expression of both c-Kit and PDGF. This may be related to the strong

association between c-Kit expression and MPV level, a finding of our study. Rossi *et al.* have suggested the production of PDGF plays a role in KS etiology.[21] In a pilot study, Koon *et al.* found that imatinib, an inhibitor of tyrosine kinase, was an effective treatment in KS cases due to its inhibition of c-Kit and PDGF expression.[22]

Thus, the elevation of MPV level may be important not only in invasion and relapse but also in following the treatment response. The expression of a nuclear protein Ki-67 increases when cells start division. It is a good marker for cellular division[23] and was observed in 4.5-11.5% of KS cases.[24] In our study, it was expressed in 7.3±5.5% out of 32 KS patients. Interestingly, while Ki-67 proliferation was highest at the plaque stage, it was lowest at the patch stage. Lower Ki-67 at the nodular stage than the plaque stage does not indicate a relationship between the histopathological stage and Ki-67 expression. Similarly, Penin *et al.* reported that Ki-67 proliferation bore no relationship with the histological stage.[25] In this study, Ki-67 proliferation was higher in cases with relapse than in cases without relapse. However, it was not statistically significant. The percentage of Ki-67 in the cases with positive c-Kit was slightly higher than in those with negative c-Kit. But no relationship has been established between c-Kit expression and c-Kit immunostaining intensity. Compared with cases without relapse, those involving relapse entailed positive c-Kit, high MPV and high Ki-67 proliferation.

CONCLUSION

C-Kit positivity is extremely high in KS. The presence of c-Kit positivity increases the risk of tumor growth, invasion and relapse. As c-Kit is a member of the tyrosine kinase family, its expression simulates megakaryopoiesis, leading to the production of young and large thrombocytes in the periphery. Thus, a high MPV level, c-Kit expression and immunostaining intensity in KS cases may reflect invasion and relapse. Ki-67 indicates cell proliferation. According to our results, Ki-67 proliferation in KS was under 10% and it bore no relationship with the histopathological stage.❑

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