Original Article

C-Kit, CD34 & α-SMA Immunohistochemical Features in Classic Kaposi Sarcoma and Kaposiform Hemangioendothelioma

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A B S T R A C T

Purpose & Methods: The aim of this work was to study the clinicopathological features of Kaposi sarcoma (KS) & kaposiform hemangioendothelioma (KHE) and analyze their immunohistochemical expression of c-Kit, CD34, α-SMA. The study was performed on cutaneous 10 classic KS & 8 KHE.

Results: KHE shows several dilated lymphatic channels, focal capillary formation, lack of nuclear atypia and mitosis within tumor cells. These features help to exclude Kaposi sarcoma in spite of the kaposiform pattern of tumor cells. C-Kit was expressed by tumor cells in all KHE cases and in 60% only of KS. All elements within both tumor groups expressed CD34 antibody. α-SMA was expressed by tumor cells in 70% of KS cases and none of KHE.

Conclusion: C-Kit and CD34 seem to be reliable at labeling KS and KHE as they can help in diagnosis of these tumors in routinely processed tissue but they don't differentiate between them. If α-SMA also labeled the tumor, then KHE diagnosis can be ruled out. KS & KHE exemplify stem cell tumors that could give smooth muscle cell–like phenotype in KS. Anti C-kit therapy should be tested in KS & KHE to prevent recurrence.

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1. Introduction

Kaposi sarcoma (KS) has been first described as an idiopathic hemorrhagic-pigmented sarcoma of the skin ("sarcoma idiopathicum multiplex hemorrhagicum") affecting elderly male subjects by Moritz Kaposi in 1872 [1]. Histogenesis of these tumors is still controversial in spite of the authentic advancements that have been made for their understanding. Some authors still consider them as a low-grade vascular tumor associated either with HIV infection or immunosuppression [2,3].

Kaposiform hemangioendothelioma (KHE) is an intermediate/borderline vascular neoplasm between a hemangioma and a malignant angiosarcoma that was initially described by Zukerberg et al. [4]. It rarely metastasizes, but is a locally aggressive neoplasm, does not have a tendency for spontaneous regression and has characteristic histopathological features. Tumor cell architectural pattern resembles Kaposi sarcoma, along with lymphatic component, namely lymphangioma/lymphangiomatosis [5].

C-Kit is a protein that plays an important role in the development of hematopoietic stem cells, mast cells, germ cells, melanocytes, and interstitial cells of Cajal. It is

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encoded by the KIT gene located on chromosome 4q12 [6]. Through its interactions with its ligand; stem cell factor, c-KIT mediates crucial cellular functions as cell proliferation, intercellular adhesion and cellular spindling [7–9].

CD34 is a transmembrane phosphoglycoprotein, first identified in 1984 on hematopoietic stem and progenitor cells [10]. It is expressed by a wide range of cells as hematopoietic, stromal, epithelial, and endothelial cells. CD34 has a role in inhibition or facilitation of adhesion, cell proliferation, and regulation of differentiation but its function as a surface antigen is not known yet [11–14].

α-Smooth muscle actin (α-SMA) is a marker used for differential diagnosis of several tumors. It stains smooth muscle fibers, fibroblasts and myofibroblasts and is overexpressed in some mesenchymal tumors such as leiomyoma, leimyosarcoma, myofibroblastoma, inflammatory myofibroblastic tumor, and gastrointestinal stromal tumors with myogenic differentiation [15–17].

The immunohistochemical features of tumors could help in identification of their histogenesis and in discovering molecules that can be targeted as a new line in treatment. The aim of this work was to study the clinico-pathological features of Kaposi sarcoma (KS) & kaposiform hemangioendothelioma (KHE) and analyze their immunohistochemical expression of c- Kit, CD34, α-SMA.

2. Materials & Methods

This retrospective study was approved by the Ethical Committee of our Faculty. It consisted of 10 clinically and histologically proven cases of classic cutaneous Kaposi sarcoma & 8 KHE. Patients were diagnosed and treated at our University Hospital. All tissue samples were formalin-fixed and paraffin-embedded. Cases with history of immunosuppressive therapy, organ transplantation or HIV–1 infection were excluded.

The immunohistochemical staining was performed on paraffin-embedded tissues, using the UltraVision System (LabVision, Fremont, CA, USA). The antibodies c-Kit (polyclonal rabbit) ready-to-use (LabVision, Fremont, CA, USA), CD34 (QBend/10 clone), diluted at 1:100, and α-SMA (1A4 clone), diluted at 1:50 (LabVision, Fremont, CA, USA) were used. The heat-induced antigen retrieval was performed in high-retrieval solution (LabVision) for c-Kit. In case of CD34 and α-SMA, pepsin-enzymatic retrieval (LabVision) was used. The slides were developed using DAB (diaminobenzidine) solution. Counterstaining was performed using Mayer’s hematoxylin.

We assessed the cytoplasmic positivity of studied markers semiquantitatively in both tumor cells and vascular endothelial cells and expressed it as percentage. In case of positivity in more than 40% of tumor cells, we considered the cases with diffuse positivity. Cases that displayed positivity in 10–40% of tumor cells were considered to have focal positivity; the cut-off value of positivity was 10%. Besides, we assessed staining intensity for c-Kit and scored it as 1+ (weak), 2+ (moderate) and 3+ (strong) [3,18]. Positive control slides were sections from human tonsils for c-kit & CD34, and were sections from human intestine for α-SMA. Negative control slides consisted of sections to which no primary antibody was added.

2.1. Statistical analysis

Statistical analysis was performed using SPSS for Windows software (version 13.0; SPSS Inc. Chicago, IL, USA). The t-2 test, Spearman rank correlation coefficient, and one-way ANOVA were used for statistical analysis. P < 0.05 was considered significant.

3. Results

3.1. Clinico-paathological features

This study included 10 classic KS cases and 8 KHE cases. The median age of classic KS cases of this study was 62.5±2.983 years (58–67 years) and that of KHE cases was 2.5±17.64 years (1–45 years). The study included 11 male cases (8 had classic KS, 3 had KHE) and 7 female cases (2 had classic KS, 5 had KHE).

All KS cases and 4 KHE cases included in this study were located in the lower limbs, while the remaining 4 KHE presented as neck mass in 2 cases and as chest wall mass in the other 2 cases. All the tumors included in this study were manifested as dark violaceous skin lesions ranging from 1 to 3 cm in diameter (median=2±0.66) that formed palpable nodules in all KHE & in 7 cases of KS with top ulceration in 2 of them, and manifested as thick patch in the remaining 3 KS cases.

Microscopically, classic KS cases of the skin in this study consisted of dermal proliferation of irregular slit-like vascular channels with extravasated erythrocytes, hemosiderin, and plasma cells. The endothelial cells were plump or inconspicuous. In some areas, numerous small capillaries were cut in cross-sections giving a sieve-like appearance. Cellular atypia was seen in eight cases. Mitotic activity ranged from 3/50 HPF in 7 cases to 5/50 HPF in the remaining 3 cases. The vascular channels infiltrated between collagen bundles and surrounded existing blood vessels and appendages. The studied cases were classified into 2 types: Plaque stage (3 cases) that showed dermal proliferation of spindle cells with slit-like spaces in-between and nodular stage (7 cases) in which sarcomatous nodular proliferation of spindle cells totally replaced the dermis and showed hyaline globules, extravasated erythrocytes, and hemosiderin deposits (Fig. 1).

All KHE consisted of a well-circumscribed tumor with a lobular architecture. The individual tumor nodules were composed of subcutaneous and dermal proliferation of a mixture of small capillaries and solid lobules of cells arranged in a glomeruloid pattern. Proliferating cells are round or ovoid, some contain hyaline globules and others contain hemosiderin. Cytoplasmic vacuolization was a frequent sign of all cases. Areas of hemorrhage and hemosiderin deposits were seen but no cellular atypia or necrosis. Mitotic activity ranged from 1-3/50 HPFs. Solid nodules in four cases showed adjacent areas of lymphangiomatosis. These vessels of the associated lymphangiomatosis were lined by a discontinuous flat endothelial cell layer (Fig. 2).
3.2. Immunohistochemical findings

3.2.1. C-Kit expression:
This study showed that 4 (40%) classic KS cases (1 in plaque & 3 in nodular stages) were c-KIT negative. The remaining 6 (60%) cases of classic KS showed focal positivity. Two (33.33%) of the later cases were in plaque stage and 4 (66.67%) were in nodular stage. The c-Kit positivity was detected as granular cytoplasmic staining in the spindle tumor cells, but no positivity was detected in endothelial cells of tumor vessels. Intensity of c-Kit positivity was strong (3+) in one case, moderate (2+) in 4 cases and weak (1+) in one case. Besides, focal c-Kit positivity of entrapped mast cells and basal keratinocytes that worked as internal positive control was seen in all cases included in this study (Fig. 3).

On the other hand, all (100%) KHE cases showed c-Kit negativity in tumor vessels & associated lymphangiomatosis lining cells as well, and focal positivity in tumor cells. The intensity of c-Kit positivity was weak (1+) in all cases of KHE (Fig. 4).

3.2.2. CD34 expression:
Diffuse CD34 positivity was present as a positive internal control in endothelial cells of tumor vessels of all classic KS cases. Besides, all (100%) cases showed positivity of spindle tumor cells that was diffuse in 6 (60%) cases (2 in plaque & 4 in nodular stages) and focal in the remaining 4 (40%) cases. But no (0%) case was negative for CD34 (Fig. 5: a-c).

In KHE cases, the tumor vessels of all (100%) cases showed positivity for CD34 and the tumor cells showed focal positivity in 2 (25%) cases, diffuse positivity in 4 (50%) cases, and were negative in the remaining 2 (25%) cases. Even the areas of associated lymphangiomatosis seen in 4 cases showed CD34 positivity in its lining cells (Fig. 5: d,e).

3.2.3. α-SMA expression:
α-SMA showed diffuse positivity in the spindle tumor cells of four (40%) KS cases (1 in plaque & 3 in nodular stages), focal positivity in 3 (30%) cases, and negative staining in 3 (30%) cases (2 in plaque & 1 in nodular stages). While all (100%) KHE cases showed negativity of tumor cells to α-SMA. All studied cases of both tumor groups showed α-SMA positivity in the walls of well formed blood vessels and in myofibroblastic cells in peritumoral area that worked as internal positive control (Fig. 6).

3.3. Statistical findings
As regards c-Kit staining, there was no statistical difference between KS and KHE on comparing the frequency and
the pattern of positivity (Table 1) of its expression (p=0.092 for both). However, a statistical significance was detected on comparing the intensity of positive staining in tumors of both studied groups (Table 2) as stronger c-Kit staining of scores 2+ & 3+ was significantly more frequent in KS than KHE (p=0.002).

For CD34 expression, there was no significant difference between KS & KHE as regards the frequency of expression (p=0.183), nor on comparing the pattern (Table 3) of its positivity (p=0.167).

While α-SMA showed significantly higher frequency of expression in studied KS cases than KHE cases (p=0.004) with also significant difference in pattern (Table 4) of its expression (p=0.003).

On correlating c-Kit expression to CD34 expression in all studied cases and in KHE cases, the correlation didn't reach

Table 1
Difference between KS and KHE as regards pattern of c-Kit expression:

|            | c-Kit Pattern | p -value Fisher exact |
|------------|---------------|-----------------------|
|            | Negative      | focal *               |
| Group      |               |                       |
| KS         | Count         |                       |
|           | % within c-Kit Pattern | 100.0% | 42.9% | 0.092 |
|           | % of Total    | 22.2% | 33.3% |
| KHE        | Count         | 0.0% | 57.1% |
|           | % within c-Kit Pattern | 0.0% | 44.4% |
| Total      | % of Total    |                       |

Fig. 3. Focal positivity of c-Kit in KS (a), positivity was detected as granular moderate to strong cytoplasmic staining in the spindle tumor cells (b-d) but no positivity was detected in endothelial cells of tumor vessels (black arrows) (d), c-Kit positivity was also seen in basal keratinocytes (white arrow) (a) and entrapped mast cells (e) [Immunoperoxidase X40 (a), X100(b, d), X400 (c, e)].

Fig. 4. C-Kit expression in KHE showed weak focal positivity in tumor cells (white arrows) (a, b) & negativity in tumor vessels (red arrows) and near-by lymphangiomatosis (black arrows) lining cells [Immunoperoxidase X40 (a), X100(b), X400 (c)].
Fig. 5. CD34 positivity in endothelial cells of tumor vessels & in spindle tumor cells of KS (a-c) & KHE (d,e), even the lymphangiomatosis lining cells were positive (d) [Immunoperoxidase X40 (a), X100(b-d), X400 (e)].

Fig. 6. α-SMA positivity in the spindle tumor cells of KS (a-c), negativity of tumor cells in KHE (d, e), positivity in the walls of well formed blood vessels and in myofibroblastic cells in peritumoral area (a-e) [Immunoperoxidase X40 (a), X100(b, d), X400 (c, e)].

statistical significance ($r=0.432$, $0.206$ & $p=0.074$, $0.624$ respectively). While on correlating between the 2 markers in KS cases, the correlation was statistically significant ($r=0.785$, $p=0.007$) which means that high c-Kit expression goes with high CD34 and vice versa in KS cases (Fig. 7; a).

On correlating c-Kit expression to α-SMA expression in studied cases, there was an inverse statistically significant relationship ($r=-0.745$, $p<0.0001$). Also, on correlating between the 2 markers in KS cases only, there was statistically significant inverse relationship ($r=-0.874$, $p=0.001$) which means that higher c-Kit expression was associated with lower α-SMA expression in KS cases (Fig. 7; b&c). However the correlation was of no significance in KHE as all cases were negative ($r=0.435$, $p=0.282$).

On correlating CD34 & α-SMA expression in all studied cases and in KHE group, the correlation was not statistically
significant (r=-0.374, 0.582 & p=0.127, 0.13 respectively). While in KS group, there was an inverse significant correlation (r=-0.88, p=0.001) which means that higher CD34 expression was associated with lower α-SMA expression in studied cases (Fig. 7; d).

4. Discussion

This study includes 10 classic KS adult cases and 8 KHE cases. In some countries the classic type of KS dominates over all other epidemiological types [19]. KHE is a rare vascular neoplasm that occurs in infants and young children especially in the first decade of life [20]. However in the last few years many cases have also been reported in adults [21–25]. In the current study, twenty five percent of KHE cases were in adult age.

This study shows that both KS and KHE have densely packed spindled tumor cells with slits and sieve-like vascular spaces in-between, however, the presence of nodules of more rounded endothelial cells and fibrin microthrombi together with the lobular growth pattern and the lack of chronic inflammatory infiltrate are more in favor of KHE and this was also proven by others [26]. The c-Kit proto-oncogene has tyrosine kinase activity. It acts as a stem-cell factors' receptor. Activation of c-Kit in KS stimulates cell proliferation by increasing the tumor cells response to growth factors. SCF-dependent proliferation is reported to be reserved by inhibition of c-Kit activity with either STI 571, a pharmacological inhibitor of c-Kit, or a dominant-negative c-Kit protein [27].

Our results show that C-Kit expression, when present, is detected in cytoplasm of tumor cells of studied cases in both tumor groups, but is lacking in endothelial cells of tumor vessels of any of them. It is expressed in 60% of KS cases and 100% of KHE cases. The difference between KS & KHE as regards the frequency and the pattern of c-Kit

| Table 2 | Difference between KS and KHE as regards intensity of c-Kit positivity: |
|--------------------------------------------------|----------------|
| c-Kit intensity | 1+ | 2+ | 3+ |
| Group | KS | KHE | KS | KHE |
| Count | 1 | 11.1% | 4 | 100.0% | 3 | 100.0% |
| % within c-Kit intensity | 7.1% | 28.6% | 7.1% | 28.6% |
| % of Total | 8 | 0 | 0 | 0 |
| Chi-square | X² | 12.842 | p-value | 0.002* |

*Significant

| Table 3 | Difference between KS and KHE as regards pattern of CD34 expression: |
|--------------------------------------------------|----------------|
| CD34 pattern | Negative | focal + | diffuse + |
| Group | KS | KHE | KS | KHE |
| Count | 0 | 0.0% | 3 | 60.0% | 7 | 63.6% |
| % within CD34 pattern | 0.0% | 16.7% | 0.0% | 38.9% |
| % of Total | 0 | 2 | 2 | 4 |
| Count | 2 | 100.0% | 2 | 40.0% | 100.0% |
| % of Total | 11.1% | 11.1% | 11 | 22.2% |
| Chi-square | X² | 3.580 | p-value | 0.167 |

| Table 4 | Difference between KS and KHE as regards pattern of α-SMA expression: |
|--------------------------------------------------|----------------|
| α-SMA pattern | Negative | focal + | diffuse + |
| Group | KS | KHE | KS | KHE |
| Count | 3 | 27.3% | 3 | 100.0% | 4 | 100.0% |
| % within α-SMA pattern | 16.7% | 0.0% | 16.7% | 0.0% |
| % of Total | 8 | 0 | 0 | 0 |
| Count | 72.7% | 0.0% | 44.4% | 0.0% |
| % within α-SMA pattern | 44.4% | 0.0% | 44.4% | 0.0% |
| % of Total | 11 | 3 | 4 |
| Chi-square | X² | 11.840 | p-value | 0.003* |

* Significant
Fig. 7. Correlation between c-Kit & CD34 in KS cases (a), Correlation between c-Kit & α-SMA in Studied cases (b) & in KS cases (c), and Correlation between CD34 & α-SMA in KS cases (d).

positivity in studied cases is not statistically significant; however, the intensity of positivity was significantly higher in KS (p=0.002). These findings reveal an essential role for c-Kit in KS and KHE tumorigenesis that can be targeted in pharmacological intervention in these tumors and this is also proved by others [27].

Raggo et al. reported that spindle-cell formation in dermal microvascular endothelial cells is caused by c-Kit activation [28]. To our knowledge no other studies have assessed c-Kit expression in KHE, and although a number of studies in the literature have scrutinized its expression in KS cases, their results exhibited notable controversies [3,6,9,29,30]. Whereas some authors found no expression [31], others detected the protein in 15.3% [24], 25.6% [26] or even in 43% of cases [9]. The figures of our results were closest to those reported by Pantanowitz et al. (56%) [9] and Kandemir et al [3] (62.9%) whose studies were conducted exclusively on classic KS. Kandemir et al. [3] ascribe this obvious contradiction to the fact the former two studies [6,31] did not specify the exact epidemiological type or histological stage under study. Also, they explained the deviation in results with respect to others was by the variation in technical parameters, as length of storage and fixation of tissues, the variation in immunohistochemical procedures employed [3], in addition to the possibility of sampling bias [9].

Comparing our results regarding c-Kit positivity in the different histological stages of KS, to others', reactivity in the plaque (66.67%) and nodular (57.14%) phases exceeded that obtained in the same stages by Pantanowitz et al. (53%, 47% respectively) [9]. It is worth noting, however, that the later study was conducted on epidemiologically heterogeneous types of KS. In the current study, c-Kit staining pattern was focal in all studied cases and this was comparable to Hussein et al., who reported diffuse in 61.5% and focal in 38.5% of positive cases of their study [19].

CD34 is a cell surface protein. Its gene is coded on chromosome 1q32. Human myeloid and lymphoid series of haematopoietic cells as well as endothelial cells express CD34. CD34 may have a role in regulation of early events of blood cell differentiation. Besides, it may function in endothelial cells and haematopoietic progenitor cells as an adhesion molecule [32].

Our results show CD34 expression in both studied tumor groups. The expression is detected in endothelial cells of all cases of both tumor groups, in tumor cells of all KS cases and in tumor cells of 75% of KHE cases with no significant difference between studied tumor groups as regards
the frequency of expression (p=0.183), nor on comparing the pattern of its positivity (p=0.167).

These results strongly favor a progenitor cell origin of the tumor cell elements in Kaposi sarcoma and KHE. Sidney et al. reported in 2014 that CD34 is not associated only with hematopoietic and endothelial cells, but it is a surface antigen that is suitable for selecting progenitor cell subpopulations from larger cell populations, including mesenchymal cells [33]. The presence or absence of CD34 is not an absolute indication of differentiation in a vascular tumor as it is expressed by blood vessel endothelium and in lymphatic endothelium in weaker but demonstrable levels [34].

In this study the well-formed capillaries, the small slit-like vascular spaces, the sieve-like areas and the spindle cells have all expressed CD34 in both KHE and KS cases. This observation is similar to others [22,32,35,36]. In addition, lymphangiomatoid elements within KHE cases shows CD34 positivity and this was similar to that is reported by Ramani, et al. [37].

High c-Kit expression goes with high CD34 and vice versa in cases of this study (r=0.432 & p=0.074). The correlation between both markers reached statistical significance in KS tumor group (r=0.785, p=0.007), but didn’t reach statistical significance in KHE group (r=0.206 & p=0.624).

These findings were similar to Gurzu et al. [18], who suggested a possible origin of KS from pluripotential mesenchymal stem cells of the connective tissue (PMCs) that were recognized in the connective tissue of dermis, skeletal muscles, and other organs [38]. These cells can originate from bone marrow mesenchymal stem cells [39,40], from reprogrammed fibroblasts [41], or from circulating fibrocytes [42,43]. They present genetic and epigenetic abnormalities that can be related to some oncogenic pathways. These modified PMCs secrete cytokines, integrins, and growth factors and possess a multilineage capacity [18]. According to the induction medium, these cells can differentiate into mesodermal or neuroectodermal lineage. C-Kit and CD34 positivity is obtained in the mesodermal lineage [44].

α-SMA expression was significantly of higher frequency (p=0.004) in KS than KHE with also significant difference in pattern of expression (p=0.003). KHE didn’t show any positivity in its tumor cells; however both studied groups showed α-SMA positivity in smooth muscle cells of well formed vessels and in myofibroblastic cells in peritumoral area.

Higher c-Kit expression was associated with lower α-SMA expression in studied cases (r=−.745, p<0.0001). This inverse correlation is highly significant in KS group (r=−.874, p=0.001) and was of no significance in KHE group (r=−0.435, p=0.282) as all cases were negative for α-SMA. Similarly, in correlating CD34 & α-SMA expression in all studied cases and in KHE group, the correlation was not statistically significant (r=−0.374, 0.582 & p=0.127, 0.13 respectively). While in KS there was an inverse significant correlation (r=−0.88, p=0.001) which means that higher CD34 expression was associated with lower α-SMA expression in studied cases.

A slight expression of α-SMA was also reported in KS spindled cells [45,46], but its significance is not known yet. This finding was also similar to Gurzu et al. [18] who reported that α-SMA positivity in KS suggests a differentiation to myofibroblast-like cells. They added that this supports a mesenchymal-endothelial rather than an endothelial-mesenchymal transition. Uldrick et al. reported that the lower rate of responders to the antiangiogenic therapy in KS also proves such transition. However, the cause and significance of this phenotypic heterogeneity are unclear yet [47]. Similar to our findings in KHE, others [48,49] reported α-SMA expression by pericytes that outlines tumor spindle cells, but not by the spindle tumor cells of KHE.

The aim of this work was to study the clinicopathological features of Kaposi sarcoma (KS) & kaposiform hemangioendothelioma (KHE) and analyze their immunohistochemical expression of c-Kit, CD34, α-SMA. It is potentially possible that KS & KHE represent stem cell tumors that can differentiate into smooth muscle cell-like phenotype in KS and to endothelial cell like in KHE. Presence of several dilated lymphatic channels, focal capillary formation and lack of nuclear atypia and mitosis within tumor cells, despite a Kaposiform pattern of tumor cells and the presence of eosinophilic bodies, suggest KHE rather than KS. C-Kit and CD34 seem to be help in labeling and diagnosis of KS and KHE, but they do not differentiate between them. If α-SMA also labeled the tumor, then KHE diagnosis can be ruled out. Much more studies are needed to clarify the significance of expression of such markers, their correlation to each other and to test the validity of using agents that inhibit c-Kit activity in such tumors.

Compliance with Ethical Standards

Authors declare that there are no conflicts of interest and state that this retrospective study followed the ethical standards of Helsinki and was approved by the Ethical Committee at our University.

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