Kaposiform haemangioendothelioma: a review with emphasis on histological differential diagnosis

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Summary
Kaposiform haemangioendothelioma (KHE) is a rare, locally aggressive/borderline vascular tumour primarily seen in neonates and children. KHE is occasionally associated with Kasabach–Merritt phenomenon and tends to have a poor clinical prognosis. While the histological features of tufted angiomas and KHE overlap, some believe tufted angiomas are a milder, benign, more localised counterpart of KHE. The other histological differential diagnoses of KHE include infantile haemangioma, congenital haemangioma, spindle cell haemangioma, verrucous malformation/haemangioma, and Kaposi sarcoma. Microscopically, KHE is characterised by confluent nodules of neoplastic spindle endothelial cells involving multiple planes of tissue which are positive for endothelial, lymphatic, and smooth muscle markers. Resection, once thought to be the definitive treatment for KHE, is often unattainable due to the extent of the lesion; thus, single or combination chemotherapies have been used to treat these patients. Sirolimus has recently been reported to be a successful agent to treat refractory and complicated cases of KHE.

Key words: Kaposiform haemangioendothelioma; vascular tumour; children; Kaposi sarcoma.

Received 1 August 2016, revised 3 February, accepted 21 March 2017
Available online: xxx

INTRODUCTION
The first histology-based scheme for understanding vascular lesions was published by Mulliken and Glowacki in 1982, which broadly divided vascular tumours into vascular neoplasms and vascular malformations. This classification was adopted by the International Society for the Study of Vascular Anomalies (ISSVA) group in 1996, and recently revised in 2014. The 2014 classification further divides the tumour group into benign, locally aggressive or borderline, and malignant tumours. Kaposiform haemangioendothelioma (KHE), initially introduced by Zukerberg et al. in 1993, is a locally aggressive vascular neoplasm occurring primarily in neonates and children. The designation of the term implies the similar histological appearance to Kaposi sarcoma ‘kaposiform’ and its borderline malignant behaviour ‘haemangioendothelioma’.

KHE typically presents as a plaque-like cutaneous lesion with ill-defined borders, and involves multiple planes of tissue. Occasionally it is associated with a life threatening condition known as Kasabach–Merritt phenomenon (KMP), a consumptive coagulopathy process. KHE is often mistaken for other vascular tumours including tufted angioma, infantile, congenital, verrucous malformation/haemangioma, or spindle cell haemangiomas which also occur in children. In addition, rare cases of children with Kaposi sarcoma involving the skin can also mimic KHE histology; thus, microscopic examination and immunohistochemical profiling is often indicated to distinguish KHE from other vascular lesions, when clinically uncertain. An accurate diagnosis is imperative for appropriate management and prognostication.

In this review, we highlight the histological characteristics and immunophenotype profile of KHE and its differential diagnosis.

CLINICAL FEATURES AND IMAGING
KHE is a rare vascular neoplasm with an estimated incidence rate of less than 1 per 100,000 children in the United States. Although the lesion is usually seen in infants and children, KHE has also been described in utero and in adults. The classic clinical presentation is a cutaneous lesion with infiltration into the adjacent subcutis, fascia, muscle, or bone. KHE most commonly involves the extremities, followed by trunk, retroperitoneal, and cervicofacial regions. Visceral locations including thymus, mediastinum, and spleen have been reported less frequently. The neoplasm is locally aggressive, but no distant metastasis has been reported. Other common presenting symptoms include thrombocytopenia and musculoskeletal dysfunction depending on the anatomical involvement. KHE often shows rapid growth and stabilises over time but only rarely completely regresses despite therapy. One of the most important clinical manifestations of KHE is its association with KMP, characterised by intravascular fibrin deposition, decreased levels of haemostatic components, including platelets, fibrinogen, and other clotting factors, with a mortality rate of 12–24%. Less frequently, KHE is also associated with lymphangiomatosis or congenital lymphoedema (Milroy disease). Magnetic resonance imaging findings of KHE include ill-defined borders, involvement of multiple tissue planes with cutaneous thickening and stranding of the subcutaneous fat, less prominent superficial vessels, and destructive changes of adjacent bone.

Print ISSN 0031-3025/Online ISSN 1465-3931 © 2017 Royal College of Pathologists of Australasia. Published by Elsevier B.V. All rights reserved.
DOI: http://dx.doi.org/10.1016/j.pathol.2017.03.001

Please cite this article in press as: Putra J, Gupta A, Kaposiform haemangioendothelioma: a review with emphasis on histological differential diagnosis, Pathology (2017), http://dx.doi.org/10.1016/j.pathol.2017.03.001
KAPOSIFORM HAEMANGIOENDOTHELIOMA WITH KASABACH–MERRITT PHENOMENON

In 1940, Kasabach and Merritt described a case of extensive purpura in a patient with a ‘capillary haemangioma’. The phenomenon carrying the names of these authors is now characterised by a consumptive coagulopathy (low fibrinogen level and elevated fibrin split products), with an enlarging vascular lesion in 50% of the cases. Thrombocytopenia seen in KMP is secondary to intralesional platelet entrapment. In addition to KHE, KMP has been associated with congenital haemangioma and rare reports of tufted angioma. Approximately 70% of KHEs are associated with KMP and these lesions tend to be greater than 8 cm in greatest dimension, and/or involve the retroperitoneum, mediastinum, or multiple anatomical regions.

PATHOGENESIS

The exact aetiopathogenesis of KHE has not been completely elucidated. The absence of human herpes virus 8 (HHV-8) in this lesion indicates a different pathogenesis from Kaposi sarcoma despite the histological resemblance. KHE has unique architectural features that favour turbulent blood flow and platelet activation, which explains its association with KMP.

PATHOLOGICAL FINDINGS

Cutaneous KHE lesions appear as a purplish to crimson, irregular, violaceous, often plaque-like area of discoulouration. On histology, the tumour is composed of confluent vascular masses/lobules composed of hypercellular, spindled endothelial cells. These lobules may focally exhibit a ‘cannonball’ pattern (Fig. 1A) where the spindled endothelial cells surround epithelioid endothelial cells resulting in a glomeruloid appearance. The clusters of spindled tumour cells exhibit multiple slit-like lumina (Fig. 1B) similar to the morphological findings in tufted angioma and Kaposi sarcoma. In addition, vacuolated red blood cells, haemosiderin, and platelet microthrombi (Fig. 1C) are commonly identified in the lesion. Mitotic figures are rare and the proliferative index is typically low except during infancy. These lobules are embedded in a fibrotic background. Elongated slit-like lymphatic channels are present at the periphery of the lobules (Fig. 1D).

Ultrastructural analysis of KHE is non-specific and it demonstrates capillaries with closely packed endothelial cells with poorly formed vascular lumina, and occasional discontinuous basement membrane. Histological examination is more helpful to distinguish KHE from its differential diagnoses.

IMMUNOHISTOCHEMISTRY AND MOLECULAR FEATURES

In addition to the aforementioned histology features, multi-plane involvement, and a lymphatic marker immunoreactivity (100% sensitive, but not specific) either with PROX-1 (Fig. 1E), lymphatic endothelial hyaluron receptor-1 (LYVE-1), or D2-40/podoplanin (Fig. 1F) within the neoplastic spindled endothelial cells support the diagnosis of KHE. In general, being a vascular lesion, non-specific endothelial markers like CD31, CD34, ETS-related gene/ERG, FLI-1, and von Willebrand Factor are immunoreactive within the lesional cells and adjacent non-lesional blood vessels. The epithelioid endothelial cells in the centre of the ‘glomeruloid’ foci are positive for endothelial markers but negative for lymphatic markers (Fig. 1F, podoplanin immunostain). However, immunohistochemistry should be interpreted cautiously as these immunostains are often not specific.

On literature review, no recurrent cytogenetic abnormalities have been described in KHE. However, Zhou et al. recently reported a balanced translocation t(13;16) (q14:p13.3) in a 7-year-old male patient with recurrent KHE involving the sacrum and thoracic vertebrae. Moreover, molecular features of KHE have not been elucidated to date.

DIFFERENTIAL DIAGNOSIS OF KAPOSIFORM HAEMANGIOENDOTHELIOMA

Several vascular lesions may resemble KHE clinically and/or histologically. These lesions include tufted angioma, infantile haemangioma, congenital haemangioma, spindle cell haemangioma, verrucous venous malformation/haemangiomma, and Kaposi sarcoma. Descriptions of KHE and its differential diagnosis are summarised in Table 1.

Tufted angioma (TA)

According to the 2014 ISSVA vascular tumour classification, TA is classified as a benign superficial vascular tumour, while KHE is included in the locally aggressive or borderline vascular tumour group. Previously known as ‘angio-blastoma of Nakagawa’ or ‘progressive capillary haemangioma’, TA resembles KHE on histology and many authors consider these two entities as part of the same neoplastic spectrum. The first detailed case series by Jones et al. described TA as a superficial, locally recurring vascular tumour which is distinctive from lobular capillary haemangioma. TA often appears as an erythematous or brown plaque or macule in children and young adults. The lesion maybe associated with KMP, however, less often than KHE. Histologically, TA involves a single plane of tissue (Fig. 2A) and it is characterised by small hypercellular tufts of endothelial cells rarely surrounded by crescentic lymphatic channels similar to KHE. The lesion has a ‘cannonball-like’ distribution of the lobules within the dermis and lacks confluency as seen in KHE. TA shows similar immunoreactivity to lymphatic markers as seen in KHE; however, Le Hua et al. found PROX1 immunoreexpression to be less frequent in TA compared to KHE, possibly due to the different proportion of neoplastic spindle cells in these lesions. The LYVE-1 expression pattern in KHE and TA is limited to the neoplastic cells and the surrounding lymphatic malformation-like areas, sparing the glomeruloid nodules within the lesion.

The histological similarities between KHE and TA were not emphasised in the initial publication by Zukerberg et al. However, the difficulty of distinguishing TA from KHE has been repeatedly demonstrated in the literature. Two of the five KHE patients reported by Mac-Moune Lai et al. were initially misdiagnosed with TA because the lesions were thought to be superficial. In his review, Allen described a thigh soft tissue mass in a 12-month-old infant which was misinterpreted as congenital haemangiopericytoma and TA before it was appropriately diagnosed as KHE based on the
additional information provided by magnetic resonance imaging. These examples emphasise the importance of radiological-pathological correlation to distinguish these lesions.

**Infantile haemangioma (IH)**

The most common tumour of infancy, IH is more frequently seen in females with a predilection to affect the cervicofacial region. The cutaneous lesion usually presents in the first few weeks of life, enlarges over a few months, and regresses over time. IH can be further classified based on its distribution (single, multifocal, or diffuse), and depth (superficial or deep)/location. During the proliferative phase, the lesion shows lobules (Fig. 2B) and sheets of thin basement membrane capillaries lined by plump endothelial cells surrounded by a layer of pericytes (Fig. 2B, inset). The lobules are not surrounded by thin walled, curvilinear lymphatic channels like KHE. As the lesion involutes, the number of capillary channels decrease with flattening of the endothelium, thickening of the basement membrane, and increased fibrous stroma in between the capillaries and lobules. The lesion is mostly composed of fibrofatty tissue with sparse individual or clustered capillaries during the involuted phase. Glucose transporter 1 (GLUT1) is a specific marker for IH (Fig. 2C).

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**Fig. 1** Key histology features of kaposiform haemangioendothelioma. Coalescing lobules of spindled endothelial cells (A), involving multiple planes of tissue by imaging (not shown here) (H&E). Higher magnification shows foci exhibiting a glomeruloid pattern with central more epithelioid tumour cells surrounded by spindled tumour cells with small central slit-like vessels (B, H&E). These tumour cells are associated with haemosiderin, extravasated red blood cells, and platelet microthrombi (C, H&E). The lobules of tumour cells are surrounded by curvilinear lymphatic channels (D, H&E). Neoplastic cells are positive for lymphatic markers including PROX-1 (E) and podoplanin/D2-40 (F).
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Demographic</th>
<th>Clinical presentation</th>
<th>Histology</th>
<th>Immunohistochemistry</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>Kaposiform haemangioendothelioma (KHE)</td>
<td>Congenital: young children; no gender predilection</td>
<td>Enlarged discolaration (skin, visceral, bone, retroperitoneal); rarely can regress</td>
<td>Confluent nodules of spindle cells in cannon-ball glomeruloid arrangement; spindle cells with slit-like features. Slit-like lymphatics around lobules</td>
<td>Endothelial markers (+), lymphatic markers (+), and smooth muscle actin (+) in spindled endothelial cells</td>
<td>70% associated with Kasabach–Merritt phenomenon (KMP), ectatic lymphatics, and Milroy disease</td>
</tr>
<tr>
<td>Tufted angioma (milder version of KHE)</td>
<td>Children and young adults</td>
<td>Skin lesions only</td>
<td>Similar to KHE, with smaller nodules and involves one plane</td>
<td>Similar to KHE pattern with only focal positivity of lymphatic markers</td>
<td>Occasionally associated with KMP</td>
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<tr>
<td>Infantile haemangioma</td>
<td>Present in the first few days to weeks after birth; female predominance</td>
<td>Proliferative phase followed by involution</td>
<td>Back to back capillaries lined by plump endothelial cells which upon involution flatten; the basement membrane hyalinises and stroma in between capillaries increases</td>
<td>GLUT1 (+), endothelial markers (+) and negative for lymphatic markers with the exception of LYVE-1 positivity during the proliferative phase</td>
<td>Most common tumour in infants</td>
</tr>
<tr>
<td>Congenital haemangioma</td>
<td>Fully-developed at birth</td>
<td>Rapidly involuting, partially involuting, or non-involuting</td>
<td>RICH: Similar sized lobules with central portion of lesion with haemorrhage, necrosis, or calcification. NICH: Varying sized lobules with capillaries lined by hobnailled endothelial cells; eosinophilic cytoplasmic inclusions may be present</td>
<td>Endothelial cells are GLUT1 (-)</td>
<td></td>
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<tr>
<td>Spindle cell haemangioma</td>
<td>Adolescents and young adults</td>
<td>Indolent vascular lesion in the distal of lower extremities</td>
<td>Solitary lesion with a venous malformation associated with extravascular elongated spindle cells. Phleboliths may occur within the malformation</td>
<td>Spindle cells are smooth muscle actin (+), endothelial cells and round-ovoid cells are endothelial markers (+)</td>
<td>Maffucci syndrome and Klippel–Trénaunay syndrome</td>
</tr>
<tr>
<td>Verrucous venous malformation/haemangioma</td>
<td>No gender predilection. Presents at birth or in early childhood</td>
<td>Most lesions occur in the extremities. The lesions usually slowly enlarge, become increasingly hyperkeratotic, and demonstrate bleeding episodes</td>
<td>Proliferation of small-to-medium-sized thick walled blood vessels in the dermis and subcutis and lobules of capillaries within the deep dermis. Epidermis shows hyperkeratosis and/or papillomatosis</td>
<td>Endothelial cells are (+) endothelial markers, GLUT1 (rarely +) in the deep lobules, and lymphatic markers (+) in most cases</td>
<td></td>
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<td>Kaposi sarcoma</td>
<td>Depends on the types: classic (older male from Mediterranean or Ashkenazi Jewish), endemic (Africans), epidemic (HPV infected population), iatrogenic (status-post transplant)</td>
<td>Three stages: patch stage, plaque stage, and tumour/nodular stage</td>
<td>Nodules with fascicles of spindle-shaped tumour cells with slit-like formation admixed with mixed inflammatory cells and haemosiderin-laden macrophages</td>
<td>HHV8 (+), endothelial markers (+), lymphatic markers (+)</td>
<td></td>
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NICH, non-involuting congenital haemangioma; RICH, rapidly involuting congenital haemangioma.
and it is not expressed in KHE. The endothelial cells are immunoreactive to vascular markers and Lewis Y antigen and merosin. Meanwhile, these cells are negative for lymphatic markers, with the exception of LYVE-1 positivity during its proliferative phase. LYVE-1 expression in IH is diffuse and restricted to the capillaries comprising the tumour lobules. Although IHs are mostly benign, rare malignant transformation has been reported.

**Congenital haemangioma (CH)**

CH is a benign vascular lesion which is present at birth and less common than IH. CH is further classified into rapidly involuting (RICH), non-involuting (NICH), and partially involuting (PICH) on the basis of its progression. CH is a circumscribed lesion composed of lobules of capillaries that may coalesce with one another (Fig. 2D); however, spindling of the endothelial cells and periblobular lymphatic channels are absent. These lobules are surrounded by abundant fibrous tissue. The capillaries in RICH consist of plump endothelium with a thin basement membrane surrounded by a layer of pericytes. The epicentre of the lesion often shows involution with absence of lobules, abundant fibrous tissue, and residual draining veins with thick fibromuscular walls which are not seen in KHE. NICH demonstrates similar histology appearances with greater elevation and coarse telangiectasia. Moreover, the endothelial cells have hyperchromatic nuclei that protrude into the lumen (hobnailed endothelial cells) with minimal cytoplasm (Fig. 2D, inset) and occasional cytoplasmic eosinophilic globules. Unlike IH, endothelial cells in CH are negative for GLUT1 antibody (Fig. 2E) and lymphatic markers.

**Spindle cell haemangioma**

Previously known as spindle cell haemangioendothelioma, spindle cell haemangioma is an indolent benign vascular lesion which is most frequently seen in the lower extremities of adolescents and young adults. The lesion has been associated with Maffucci syndrome, Klippel–Trénaunay syndrome, and other vascular anomalies. Histologically, spindle cell haemangioma appears well-circumscribed and non-capsulated. Thin-walled dilated, irregular veins with organised thrombi are commonly identified. Fascicles of spindle cells are seen among these dilated blood vessels (Fig. 2F). In addition, a second population of round-to-ovoid cells with vacuolated cytoplasm arranged in solid pattern may present. The endothelial cells lining the vessels and the round cells are positive for endothelial markers (CD31, CD34), while the spindle cells are positive for smooth muscle markers. The spindle cells have also been reported to be positive for the lymphatic markers.

**Verrucous venous malformation (VVM)**

Previously referred as verrucous haemangioma, VVM is a non-hereditary, congenital vascular anomaly which occurs...
predominantly in the extremities (91%). Clinically, VVM lesions grow proportionally with age, become hyperkeratotic, and are associated with bleeding episodes. Histological appearance of VVM is characterised by hyperkeratotic epidermis with small to medium sized, thin walled blood vessels (Fig. 2G) in the papillary dermis and capillaries with multilamellated basement membrane arranged in a vague lobular architecture in reticular dermis and/or subcutis (Fig. 2H). Immunohistochemical study occasionally shows GLUT1-immunoreactivity in the capillary endothelial cells and occasional positivity for lymphatic marker (D2-40 and PROX1) in the superficial dermal vascular component of the lesion.28,29

Kaposi sarcoma (KS)

A low grade malignant vascular neoplasm associated with HHV-8 infection, KS is classified into classic, African (endemic), AIDS-associated (epidemic), and iatrogenic form. The clinical subtype most commonly observed in children is the African/endemic-type. Most of these patients develop the clinical disease as a consequence of HIV infection. Ziegler and Katongole-Mbidde reported 100 cases of KS in children less than 15 years of age and they found that these patients usually present with lymphadenopathy and they lack skin manifestations. Clinical manifestations of KS lesion include early patch stage (maucles), plaque stage (plaques), and tumour stage (nodules). On histology, KS is characterised by hypercellular nodules composed of foci of spindle tumour cells with slit-like formation admixed with mixed inflammatory cells (Fig. 2I) and haemosiderin-laden macrophages. Eosinophilic and periodic acid–Schiff positive hyaline globules are a common finding in advanced lesions. The spindle cells are positive for endothelial and lymphatic markers. The HHV-8 immunoreactivity in the lesional spindle cells is helpful to distinguish KS from KHE lesions (Fig. 2J). Furthermore, podoplanin/D2-40 and PROX1 immunostains are expressed in KS.

TREATMENT AND PROGNOSIS

Historically, resection was the definitive treatment for KHE. However, given the extent of the lesion, this was not often possible as the lesion involved multiple planes of tissue, led to disfigurement, infections, organ dysfunction, and occasionally death secondary to profound bleeding associated with KMP. Available treatments include corticosteroids, conventional single or combination chemotherapies (vincristine, cyclophosphamide, actinomycin, doxorubicin, and gemcitabine), radiation therapy, and anti-fibrolintyotic therapy.

The mechanistic target of rapamycin (mTOR) pathway regulates vascular endothelial growth factor which is the key regulator of angiogenesis and lymphangiogenesis. Inappropriate activation of the PI3K/AKT/mTOR pathway has been associated with vascular anomalies. Sirolimus, a mechanistic target of rapamycin/mTOR inhibitor has recently been reported to be effective in treating complicated and refractory cases of KHE, by combining signals from the PI3K/AKT pathway to coordinate proper cell growth in assorted complex vascular neoplasms resulting in overall all tumour shrinkage. In their case study of 33 KHE patients, Lyons et al. reported two cases with regional perinodal soft tissue involvement. However, no cases of distant metastasis were identified. Spontaneous or complete post-treatment regression is rare. The reported mortality rate of KHE ranges from 12% to 24% and usually occurs in patients who develop KMP.

CONCLUSIONS

KHE is a rare vascular neoplasm with intermediate malignant behaviour seen in infants and children. KMP is seen in a significant number of KHE cases, and it is associated with an increased risk of mortality. The histological findings may overlap with other vascular lesions. Histological analysis with supportive lymphatic immunohistochemistry, and correlation with multiplane involvement by imaging is helpful to distinguish KHE from other vascular lesions.

Reference


