Int J Clin Exp Pathol 2015;8(10):13711-13718
www.ijcep.com /ISSN:1936-2625/IJCEP0013849

Original Article

Clinicopathological features of Kaposiform hemangioendothelioma

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Received August 2, 2015; Accepted September 25, 2015; Epub October 1, 2015; Published October 15, 2015

Abstract: Kaposiform hemangioendothelioma (KHE), an intermediate tumor of endothelial origin in childhood, is often associated with Kasabach-Merritt phenomenon (KMP). In this study, 22 cases of KHE were immunochemically studied for CD31, CD34, ERG, smooth muscle actin (SMA), D240, GLUT1 and Ki67. The patients (15 males and 7 females) ranged in age from 13 days to 7 years (median, 2 mo). Lesion developed on the extremities/joint (12 cases), chest/abdominal wall (6 cases), head/neck (4 cases), and presented both superficial and deep soft tissue. The superficial change was commonly enlarging cutaneous lesion with ill-defiined red to purple indurated plaque. 15 of the 22 cases (68%) developed KMP, with consumptive thrombocytopenia or bleeding complications. Tumors consisted of infiltrating nodules of fascicles of spindleshaped endothelial cells and slitlike vascular channels with irregular tumor margins. On immunohistochemistry (IHC), endothelial cells were diffusely positive for CD34, CD31 and ERG but negative for GLUT1, and the peripheral area of proliferative capillaries were markedly positive for D240. Adjuvant medical therapy and sclerotherapy were prepared for the tumor and the associated KMP, and then all patients were treated by complete surgical excision. Follow-up information was available in 22 patients (8 to 26 months, mean 15 mo), and indicated that 1 died of multiple organ failure and 21 were alive without residual disease. In conclusion, our results suggest that KHE can occur in the embryonic period, and patients with KMP often have earlier onset time and larger lesional size. KHE patients given with adjuvant corticosteroids and urea injection and complete resection rarely relapse.

Keywords: Hemangioma, kaposiform hemangioendothelioma, kasabach-merritt phenomenon, infancy

Introduction

Kaposiform hemangioendothelioma (KHE) is a rare vascular endothelial neoplasm of intermediate malignancy which usually occurs in infancy and early childhood, although adult cases have recently been reported [1-4]. The sites of predilection are the skin mainly, and deep anatomic regions such as retroperitoneum and so on. Typically KHE has a distinctive cutaneous blue-red lesion with ill-defined borders. Tumors have the characteristics of Kaposi sarcoma-like, spindle-shaped endothelial cells and slit-like vascular channels, with locally aggressive growth model. It is associated with lymphatic vessel proliferation and Kasabach-Merritt phenomenon (KMP). Due to age of presentation and the presence of a vascular cutaneous lesion, KHE may be confused with infantile hemangioma, juvenile hemangioma (JH) and tufted angioma (TA) for example. Our present study analyzes the clinical and pathological features of 22 cases retrospectively, to better understand the spectrum of this vascular tumor at the native place, including the clinical usual cure methods.

Materials and methods

All cases of KHE are retrieved from the medical records and database of the Henan province people's hospital in china from January 2013 to December 2014. Diagnoses were confirmed on the review of the hematoxylin and eosinstained sections by three of the authors before inclusion in the study. In the course of the reviewing, several features were specifically analyzed. These included morphology pattern, depth of

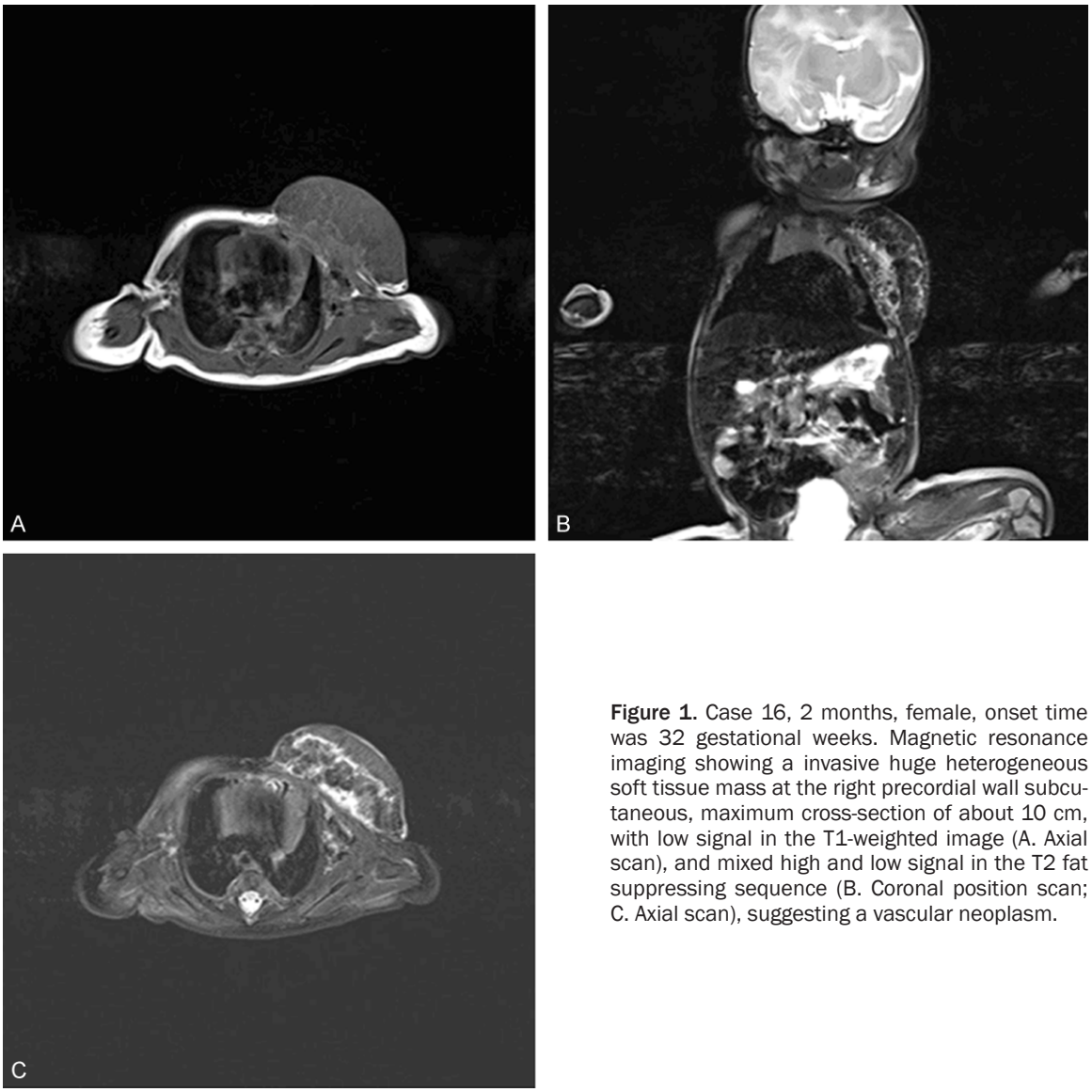

Figure 1. Case 16, 2 months, female, onset time was 32 gestational weeks. Magnetic resonance imaging showing a invasive huge heterogeneous soft tissue mass at the right precordial wall subcutaneous, maximum cross-section of about 10 cm, with low signal in the T1-weighted image (A. Axial scan), and mixed high and low signal in the T2 fat suppressing sequence (B. Coronal position scan; C. Axial scan), suggesting a vascular neoplasm.

infiltration, and mitotic index. On the other hand, we reviewed all the cases and reached consensus on the diagnosis of KHE based on review of clinical history, imaging (**Figure 1**), and laboratory data. Data collected included: sex, age, onset time, presenting signs, anatomic location, adjuvant therapy, prognosis, and platelet count to evaluate for KMP. KMP was broadly defined as a platelet count of less than 100,000 per microliter. Follow-up was obtained in 22 cases.

Immunohistochemistry

Immunohistochemistry was performed on all 22 cases of KHE using the following antibodies and conditions: CD31 (Dako QBEND10, No. M7165, dilution 1:150), CD34 (Dako QBEND10, No. M0823, dilution 1:100), ERG (ZSGB-BIO ZA-0545, clone EP111, ready to use), smooth muscle actin (Dako No. M0851, 1:200), D240 (Dako LOT 10079992, ready to use), GLUT1 (ZSGB-BIO ZA-0471, ready to use) and Ki67 (Dako QBEND10, No. M7248, dilution 1:100). The Envision Plus detection system (Dako) was used. Appropriate positive and negative controls were used throughout.

Results

Clinical finding

Clinical data are summarized in **Table 1**. 15 patients were males and 7 were females, ranging in age from 13 days to 7 years (median, 2 mo). 21 of the 22 cases (95%) occurred in

Table 1. Clinical Features and Outcome of 25 Cases of KHE

Case	Age	Onset time	Sex	Anatomic Site	KMP	Therapy	Metas-tases	Follow-up (Status)
1	21 days	birth	M	Right brachium	Yes	Steroid, Urea, SE	No	26 mo (ANED)
2	47 days	birth	M	Right hip	Yes	Steroid, Urea, SE	No	26 mo (ANED)
3	13 days	birth	M	Right neck, mandibular	Yes	Steroid, Interferon, SE	No	11 days (Dead)
4	1 mo	birth	F	Left lumbar region, hip, abdominal wall	Yes	Steroid, Urea, SE	No	21 mo (ANED)
5	13 days	birth	M	Left upper limb	Yes	Steroid, ATP, SE	No	21 mo (ANED)
6	5 mo	birth	M	Right upper limb	No	Urea, SE	No	21 mo (ANED)
7	2 mo	birth	M	Right lower extremity	Yes	Steroid, Urea, SE	No	21 mo (ANED)
8	28 days	birth	F	Left leg	Yes	Steroid, GG, SE	No	19 mo (ANED)
9	13 mo	7mo	F	Occiput	No	Urea, SE	No	18 mo (ANED)
10	2 mo	birth	M	Right neck, shoulder, chest	Yes	Steroid, SE	No	14 mo (ANED)
11	3 mo	birth	M	Left knee	Yes	Steroid, GG, SE	No	14 mo (ANED)
12	26 days	birth	M	Abdominal wall	Yes	Steroid, Urea, SE	No	13 mo (ANED)
13	3 mo	birth	M	Left shoulder and back	Yes	Steroid, Urea, SE	No	12 mo (ANED)
14	9 mo	7 mo	M	Left abdominal wall, inguinal and upper limb	Yes	Steroid, Urea, SE	No	11 mo (ANED)
15	1 mo	39 gestational weeks	M	Chest, abdominal wall	Yes	Steroid, Urea, GG, SE	No	9 mo (ANED)
16	2 mo	32 gestational weeks	F	Precordial wall	Yes	Steroid, GG, VK1, SE	No	8 mo (ANED)
17	7 yr	birth	M	Left face	No	SE	No	15 mo (ANED)
18	5 mo	1 mo	F	Left upper limb, inguinal	Yes	Urea, SE	No	14 mo (ANED)
19	15 days	birth	M	Scalp	No	SE	No	12 mo (ANED)
20	2 yr	2 mo	F	Right clavicle region	No	Urea, SE	No	13 mo (ANED)
21	5 yr	3 yr	F	Right stock department	No	Urea, SE	No	10 mo (ANED)
22	3 yr	birth	M	Right inguinal	No	Steroid, Urea, SE	No	8 mo (ANED)

KHE, Kaposiform hemangioendothelioma; KMP, Kasabach-Merritt phenomenon; ATP, adenosine triphosphate; GG, gamma globulin; VK1, vitamin K1; SE, surgical excision; ANED, alive, no evidence of disease.

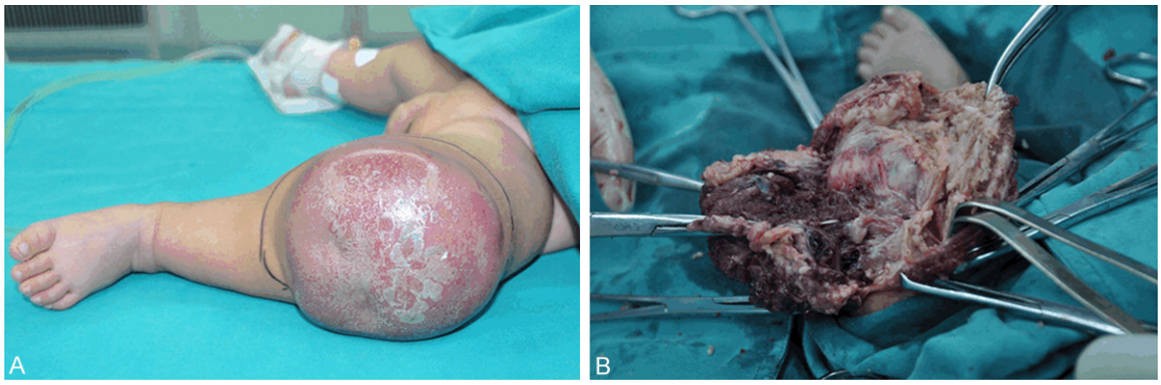

Figure 2. Case 11, 3 months, male, onset time was on birth. KHE in the left knee and the sample of the tumor (A). The section of tumor tissue showing dark red and riching in blood (B).

patients within the first year, 17 (77%) at birth, and 2 (9%) at embryonic period. Tumors developed on the extremities/joint (12 cases), chest/abdominal wall (6 cases), head/neck (4 cases). The most common presenting symptom was enlarging cutaneous lesion with ill-defiined red to purple indurated plaque (**Figure 2**); no patients had multi-focal lesions. There were incorporated the dermal ecchymosis in 2 patients, interspersed petechia around umbilical or total skin in 2 patients, cutaneous ulceration tendency in 1 patient. At the time of initial presentation, 15 of the 22 cases (68%) developed KMP, with consumptive thrombocytopenia or bleeding complications.

All patients were treated by complete surgical excision, among them 3 patients received two consecutive partial resection. At the same time, 22 cases were treated adjuvant medical therapy before operation, such as steroid, urea, interferon, gamma globulin, adenosine triphos-

Table 2. Pathological Features of 22 Cases of KHE

Case	Size (cm)	Margin	Nodule pattern	Infiltrating depth	Mitoses number (/10HPF)
1	6	Clear	Mixed	Adipose tissue	1
2	9	Clear	Fusional	Adipose tissue	0
3	8	Unclear	Mixed	Muscle tissue	3
4	9	Unclear	Mixed	Adipose tissue	2
5	7	Unclear	Isolated	Muscle tissue	1
6	4	Unclear	Fusional	Muscle tissue	4
7	10	Unclear	Isolated	Muscle tissue	2
8	10	Unclear	Fusional	Adipose tissue	5
9	3	Clear	Isolated	Adipose tissue	2
10	7	Clear	Isolated	Muscle tissue	2
11	14	Clear	Mixed	Adipose tissue	2
12	26	Unclear	Isolated	Muscle tissue	0
13	18	Unclear	Fusional	Muscle tissue	8
14	15	Unclear	Isolated	Adipose tissue	2
15	11	Unclear	Mixed	Muscle tissue	5
16	10	Clear	Fusional	Adipose tissue	2
17	2	Clear	Isolated	Adipose tissue	0
18	14	Unclear	Mixed	Adipose tissue	3
19	5	Unclear	Isolated	Adipose tissue	4
20	5	Unclear	Isolated	Adipose tissue	0
21	3	Unclear	Isolated	Adipose tissue	0
22	7	Unclear	isolated	Adipose tissue	0

KHE, Kaposiform hemangioendothelioma.

phate and so on. The most frequent therapy was a combination of systemic corticosteroids and (or) local injection of urea alone. No patients had the evidence of regional lymph node and distant metastasis. Follow-up data were available for all patients, ranging from 8 to 26 months (mean, 15 mo). 1 patient died of multiple organ failure 11 days after operation. The other 21 patients were alive with no recurrence of disease.

Pathologic finding

Pathological data are summarized in **Table 2**. The tumor size ranged from 2 to 26 cm (mean, 9 cm). Grossly, the affected skin was incomplete chunky. The mass under skin was dirty red with bleeding. All tumors infiltrated the adipose tissue, and among them 8 cases to muscular layer. In 1 case, the tumor neighbored the adjacent femoral vein and nerve, and another case with adhesion of periosteum.

Histologically, the tumors were dominated by infiltrating isolated and fusional nodules of spindle cells forming characteristic vascular pattern. The tumors of 11 cases were presented with isolated nodules mainly, 6 cases with fusional nodules, 5 cases with mixed pattern. The tumor nodules were composed of fascicles of spindleshaped endothelial cells and slitlike or crescentic vascular channels. Most cases (14 cases, 64%) had unclear and irregular tumor margins. In addition, there were extravasated red blood cells (RBC's), single cells with lumina containing RBC's, fibrin thrombi, eosinophilic globules and hemosiderin. There was mild nuclear variation, but no significant nuclear atypia, or necrosis, with rare mitoses (0-8/10HPF, mean 2/10HPF). In 2 cases, the tumors involved the skin nervelet. In all cases the stroma was predominantly collagenous, and discrete foci of irregular dilated vascular and lymphatic vessels. Only 1 case had a background of extensive lymphangiomatosis-like changes. And in another case there were focus calcification and lymphocytic infiltration in the stroma. It was be found that the trapping of RBC's and lymphocytes in the slitlike channels of the tumor nodules (**Figure 3**).

Immunohistochemical staining demonstrated a low Ki67 labeling index in most cases, but in few case with focus high index about 10-20%. The spindle cells were diffusely positive for vascular endothelial markers such as CD31, CD34, ERG except GLUT1. On the other hand, numerous GLUT1 positive RBC's were found in the channels. Smooth muscle actin (SMA) was focally positive, which suggested the existed perivascular cells. The areas comprising several dilated lymphatic vessels showed negative staining with CD31, CD34, ERG, but positive for D240. D240 was markedly immunoreactive in the peripheral area of proliferative capillaries, and mostly unreactive in the surrounding dilated vessels (**Figure 4**).

Discussion

KHE is a rare aggressive vascular tumor and first described and named occurring in childhood by Zukerberg and colleagues [1] in 1993.

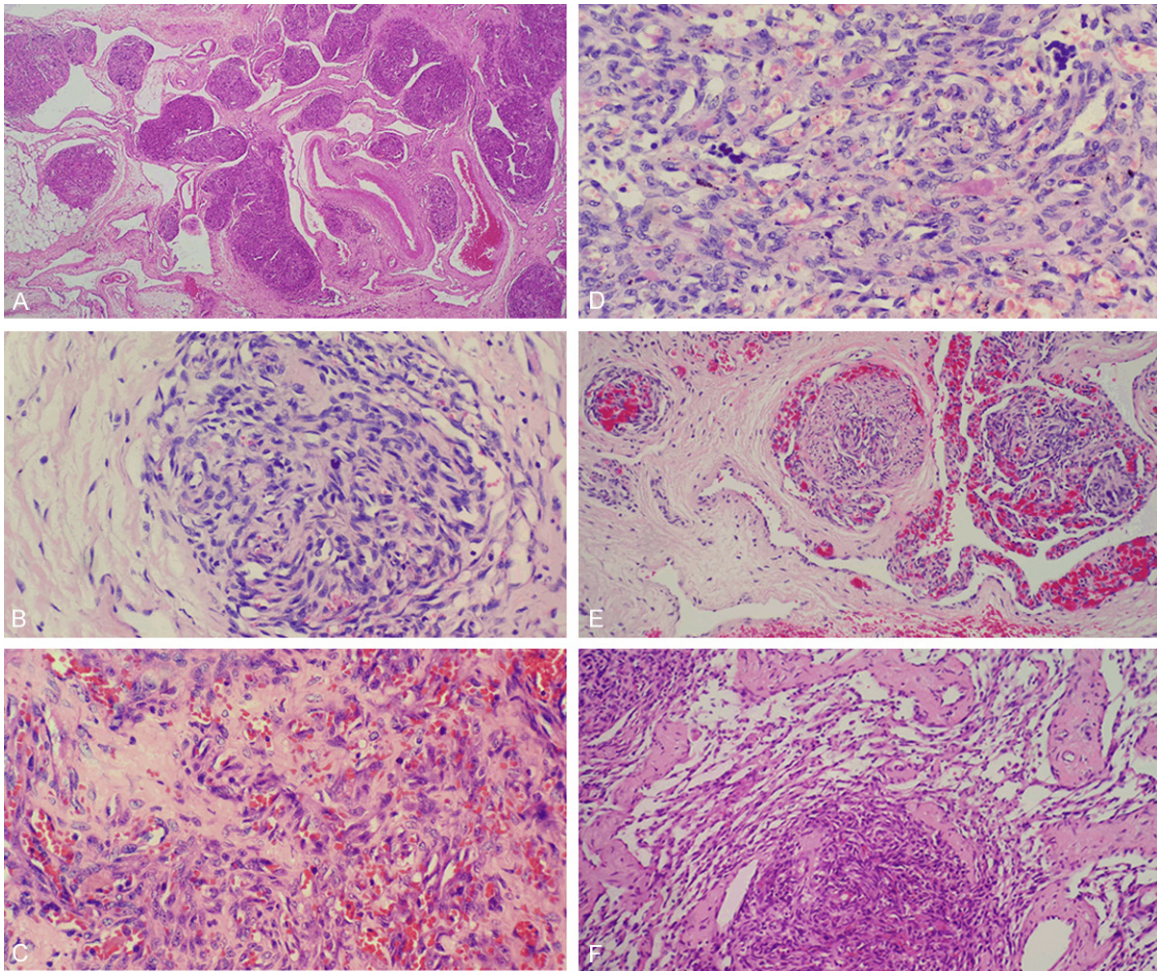

Figure 3. Histological features of KHE. A. Low power view showing irregular tumor nodules infiltrating through dermis and subcutaneous fat, and surrounding by dense collagenous stroma. H&E ×100. B. Some mitoses number in nodule along with fibrocollagenous stroma. H&E ×200. C. Higher magnification showing slit-like crescentic capillaries within spindle cells, including single cells forming lumina and containing RBC's. H&E ×400. D. Higher magnification showing micro thrombi, eosinophilic bodies and hemosiderin amid spindle shaped vascular cells, and also showing dilated lymphatic vessels containing lymphocytes. H&E ×400. E. Architectural pattern showing modality in which small convoluted vessels budding directly off larger vessels, and also showing the involved skin nervelet. H&E ×100. F. Background showing extensive lymphangiomatosis. H&E ×200.

Before this, there were similar tumors reported under a variety of other names, such as Kaposi-like hemangioma, hemangioma with Kaposi-like features, Kaposi-like infantile hemangioendothelioma, congenital hemangioendothelioma and so on [5]. Most of these earlier cases reported had similar histologic features of a multinodular infiltrative process and composed of complex vascular proliferations, which presented varying degrees of overlap with capillary hemangioma and Kaposi sarcoma (KS). At the same time, Zukerberg et al also pointed out a noticeable association between KHE, KMP, and lymphatic abnormalities. Up to now, approximately more than 200 cases have been reported.

As we know, KHE is usually identified in infancy and first decade of life without sex predilection. Sporadic or exceptional cases have been reported respectively in adolescents or adulthood. It typically occurs in the extremities, especially at the sites like the proximal arms and legs and the trunk, as superficial or deep soft tissue masses. Cutaneous is frequently involved and typically showed as violaceous papules or plaques. Our present study, the largest single study to date in Chinese, some different findings are extended based on many of those

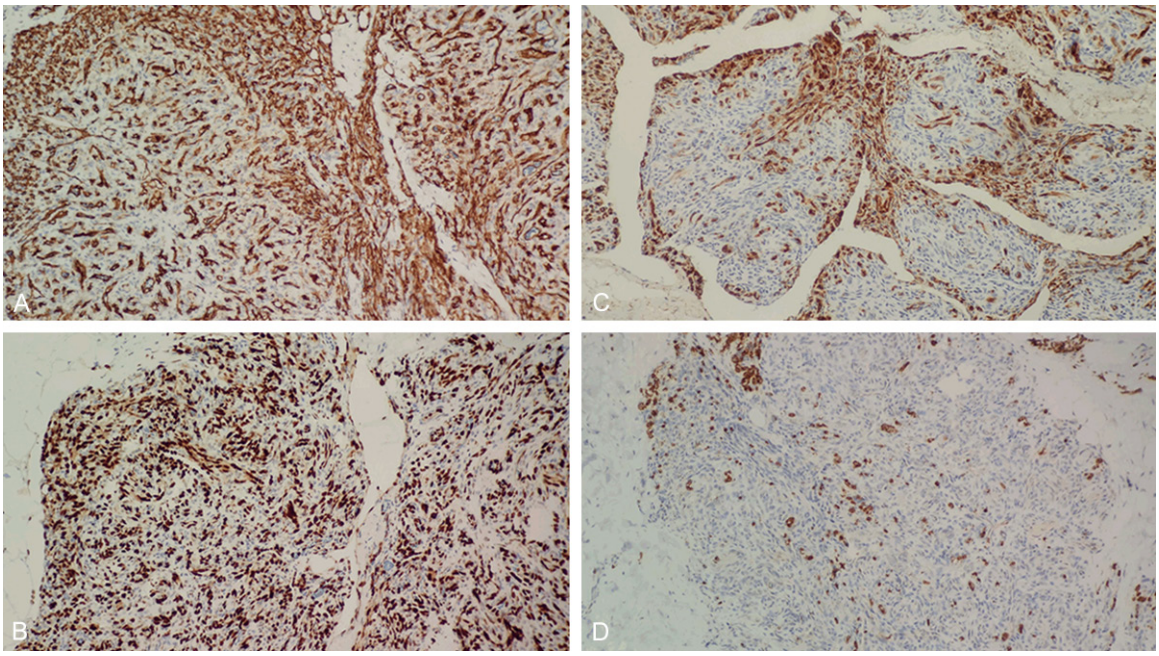

Figure 4. Immunohistochemical results. A. Nodule of infiltrating spindle cells and proliferating capillary vessels showing immunoreactivity to CD34 at cell membrane and cytoplasmic. 3'-3'-diaminobenzidine tetrahydrochloride. (DAB)×200. B. Nodule of infiltrating spindle cells and proliferating capillary vessels showing immunoreactivity to ERG at nucleus. DAB×200. C. Peripheral areas of capillary proliferation showing immunoreactivity to D240 at cytoplasmic. DAB×100. D. RBC's trapped in the slitlike channels of the tumor nodule showing immunoreactivity to GLUT1 at cytoplasmic. DAB×200.

earlier. In our cohort of KHE patients, there isn't obvious different in sex, too. Furtherly, 95% of cases occurred in patients within the first year, and 77% at birth. It is worth noted that there two cases occurred at embryonic period, which is the first report. It is suggested that tumorigenesis of KHE could be originated in the embryonic period. It lets us to have to think if there exists dysplasia of vascular endothelial cells or blood vessel during the period and maybe some research is necessary to do furtherly. Until now, there has not been a substantial genetic study on endothelial or perivascular cells in KHE. It was reported Prox1 played an important, previously unanticipated role in mediating the aggressive behavior of vascular neoplasms such as KHE in murine models, but there isn't any detection in human tumor tissue up to now [6]. In 22 cases, the pathogenic sites include the extremities, the trunk and head neck. There isn't obvious difference among them, but interestingly often multiple sites of the lesions occur at the same time.

KHE is be classified as intermediate (borderline) malignancy because of its invasive growth pattern, no self-healing tendency, secondary phenomenon of red cells destruction, thrombocytopenia and so on. It has marked histopathological features and can be sorted out from its other differentials like JH and KS. The infiltrating lobulated nodules with siltlike or crescentic vessels can grow in different organizational levels, subcutaneous fascia layer or muscular layer. The slitlike vessels are poorly canalized and lined by spindle shaped endothelial cells. These cells displayed focal lumen formation containing trapped RBC's, along with platelet thrombi, eosinophilic hyaline bodies and hemosiderin deposition. All of these are considered to be a manifestation of trapped red cells destruction, which don't extist often in JH and KS. IHC stains are useful in substantiating a definite diagnosis. For example, GLUT1 is noted to be strongly expressed in JH, especially cellular hemangioma of infancy, but is totally lacked for immunoreactivity in KHE [7]. Meanwhile in KHE, the epithelioid or glomeruloid areas, which have some CD31, CD34 and ERG staining, featured prominent SMA positive cells, suggesting sites of pericytic cells. On the other hand, tumorigenesis of KS mostly is related to HHV8 transcripts, but it isn't identified within KHE [5].

TA is another vascular tumor that representatively presents in children and adolescents as erythematous cutaneous macules and papules, which histologically comprises multiple lobulated clusters of capillary-sized vessels scattered in a “cannon ball” fashion through the dermis. Numerous similarities, both morphologically and immunophenotypically, between TA and KHE have been now shared the view that these 2 entities belong to the same biologic spectrum. But TA is be classified as benign tumor, the lesions is mainly located at dermis. In adverse, KHE is classified as an aggressive vascular tumor with infiltrative process, and it can grow in different organizational levels, subcutaneous fascia layer or muscular layer, even skeleton. Both KHE and TA have a mixed lymphatic and vascular endothelial immune-phenotype. In KHE, D240 is markedly immunoreactive in the peripheral area of proliferative capillaries, and mostly unreactive in the surrounding dilated vessels, but in TA, D240 has an adervse phenotype [8]. In addition, there were discrete foci of several dilated lymphatic vessels containing lymph and lymphocytes in KHE.

Another reason of KHE as an intermediate (borderline) malignancy is related to KMP mostly. Up to now, it has been reported that few vascular tumors are associated with KMP, including KHE, TA, and lymphangioendotheliomatosis, of which KHE is the most commonly reported. KMP, characterized by profound thrombocytopenia and consumptive coagulopathy resulting from the localized intravascular coagulation (LIC) in the tumor. Previous studies have suggested that the trapping of blood components, including platelets, may underlie the LIC in KHE. However, more evidence is needed to support this hypothesis. Yuan SM et al [7] found by the way of ultrastructural observation, there were the trapping of RBC’s, platelets, macrophages, and lymphocytes in the slit-like channels of the tumor nodules, and phagocytic vesicles in the cytoplasm of neoplastic cells, which may interpret the LIC in the tumor and subsequent consumptive coagulopathy. In this study, 15 of the 22 cases (68%) were complicated by KMP. Immunohistochemistry staining further showed numerous GLUT1 positive RBC’s in the channels. And on the other hand, KMP develops in the setting of KHE, which there isn’t any relation between KMP and clinical extant, mitoses number, or Ki67 index. But in all of cases of KMP, onset time is usually on birth or embryonic period, and lesional size is more often greater than 5 cm, even 10 cm. That is, the earlier onset time and the larger lesional size, the higher probability of KMP. In the cases of KMP, there were incorporated the dermal ecchymosis in 2 patients, and cutaneous ulceration tendency in 1 patient. All of the patients were in wake of different degree of anemia. Croteau SE et al [9] reported that the risk of KMP increases dramatically when tumor infiltrates muscle or when KHE arises in the retroperitoneum or mediastinum. And in our study, half of KHE cases with KMP infiltrated muscle. About KMP, there are some attractive explanations, which center around unique architectural and/or endothelial difference in KHE. In KHE, small convoluted capillaries arise directly from large vessels in a serial or linear fashion, arguably creating a situation that results in turbulence leading to platelet activation and aggregation. The more orderly tree-like branching vasculature of the JH in which blood passes through a series of vessels of gradually decreasing diameter would seem to favor laminar flow [5]. No further confirmation is obtained because of the paucity of information, although endothelial differences between the two tumors may well be important in the pathogenesis of KMP. So the development of KMP is still an intriguing problem.

KHE has no self-healing tendency, especially followed by KMP. Resection is the treatment of first choice for this type of tumor and adjuvant medical therapy is prepared for the associated KMP. The most frequent initial therapy for KHE+KMP was a combination of systemic corticosteroids and vincristine (VCR), or corticosteroids alone. Second-line treatments were VCR, rapamycin, and propranolol [10]. Management of KHE without KMP was variable; initial treatments included systemic corticosteroids alone or with VCR, monitoring without medication, VCR, propranolol, aspirin, and rapamycin [10-13]. But there aren’t standard protocols and consensus in different area. In our institution, the most common method is a combination of systemic corticosteroids and urea. Urea injection is a kind of sclerotherapy usually before resection. And patients with complete resection rarely relapse [14, 15].

Disclosure of conflict of interest

None.

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