Vascular Tumors of Intermediate Malignancy:
A Review and Update

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Vascular tumors of intermediate malignancy encompass a broad range of histologic entities. They are characterized clinically by having a high risk of local recurrence and limited risk of regional or distant metastasis. Vascular tumors of intermediate malignancy frequently present in the skin and often cause diagnostic difficulty. This article reviews the clinical and histologic features of kaposiform hemangioendothelioma, epithelioid hemangioendothelioma, Dabska tumor, retiform hemangioendothelioma, composite hemangioendothelioma, and epithelioid sarcoma-like hemangioendothelioma. The differential diagnosis of these entities is discussed. (Dermatol Sinica 27: 140-153, 2009)

Key words: Kaposiform hemangioendothelioma, Epithelioid hemangioendothelioma, Dabska tumor, Retiform hemangioendothelioma, Composite hemangioendothelioma, Epithelioid sarcoma-like hemangioendothelioma

INTRODUCTION
Vascular tumors of intermediate malignancy encompass a group of tumors whose biologic potential is intermediate between hemangiomas and angiosarcoma. Most frequently they have a risk of local recurrence and limited risk for lymph node or distant metastasis. There is a broad range of tumors with differing morphologies in this group of vascular neoplasms. Like fibrohistiocytic tumors of intermediate malignancy, vascular tumors of intermediate malignancy are frequently encountered in the skin. Therefore it is important to be familiar with the clinical and histologic features of this group of tumors.

KAPOSIFORM HEMANGIOENDOTHELIOMA
Clinical features
Kaposiform hemangioendothelioma typically occurs in childhood, with 45% of cases presenting within the first year of life, often present at birth. Rare adult cases have been reported. Cutaneous lesions present as large blue-red to violaceous plaque on the extremities, head and neck area, or trunk (Fig. 1). Kaposiform hemangioendothelioma is associated with Kasabach-Merritt phenomenon in approximately 40% of cases. Kasabach-Merritt phenomenon is a consumptive coagulopathy associated with thrombocytopenia. It is more common in deep-seated Kaposiform hemangioendothelioma, especially the retro-
peritoneum, but is also seen in cutaneous tumors. Prior to the recognition of kaposiform hemangioendothelioma, Kasabach-Merritt phenomenon was thought to be associated with infantile hemangioma. It is now recognized that virtually all cases of this consumptive coagulopathy are associated with kaposiform hemangioendothelioma.4

**Microscopic Features**

Cutaneous tumors show diffuse involvement of the dermis and subcutis. The tumor usually has a nodular growth pattern with ectatic lymphatic vessels surrounding the nodules (Fig. 2). The tumor varies from areas resembling a capillary hemangioma to solid areas (Fig. 3). The solid areas vary from ill-defined rounded nests of epithelioid to spindled endothelial cells resembling glomeruli to solid sheets of spindled endothelial cells with slit-like vascular lumens (Fig. 4). Within the glomeruloid areas and
slit-like lumens of the spindled zones, hemosiderin deposition, hyaline globules, and vacuolization are often present, indicative of platelet and erythrocyte destruction. Mitotic activity can be scant to occasional. Nuclear polymorphism is mild to moderate. By immunohistochemistry, the bulk of the tumor cells express CD31, CD34, and FLI1 protein. The peripheral lymphatic component is positive for podoplanin, a lymphatic-specific endothelial marker highlighted by the D2-40 antibody.

Recently, it has been reported that, the over expression of Prox1 in mouse hemangioendothelioma cells causes a kaposiform hemangioendothelioma lymphatic phenotype and a more infiltrative behavior. It has also been shown that the Prox1, a transcription factor, is induced by Kaposi’s sarcoma-associated herpes virus (KSHV). Prox1 induces lymphatic differentiation through podoplanin and vascular endothelial growth factor receptor-3 (VEGFR-3). It is possible that Prox1 over expression gives rise to over expression of VEGFR-3, which plays a role in the lymphatic proliferation associated with kaposiform hemangioendothelioma and the case reports of associated lymphangiomatosis.

**Differential Diagnosis**

The differential diagnosis of kaposiform hemangioendothelioma is varied. Because of the clinical presentation as a vascular tumor in infants, infantile hemangioma is frequently considered. Infantile hemangioma is usually circumscribed and predominantly composed of well-formed capillaries. Although the capillary hemangioma-like areas of kaposiform hemangioendothelioma can closely resemble areas of infantile hemangioma, the latter lacks the glomeruloid and solid spindled cell zones of kaposiform hemangioendothelioma. By immunohistochemistry, infantile hemangioma is immunoreactive for Glut-1 and Lewis-Y antigen; kaposiform hemangioendothelioma is negative for both of these markers.

Kaposiform hemangioendothelioma is also considered in the differential diagnosis of acquired tufted angioma. Both are lesions that typically present in young children, and both are associated with Kasabach-Merritt phenomenon. Histologically, acquired tufted angioma is characterized a distinctly nodular growth pattern likened to “cannonballs” in the dermis (Fig. 5). The cellular nodules are essentially identical to areas seen in kaposiform hemangioendothelioma. Given the clinical and histologic similarities, there is a growing consensus that acquired tufted angioma represents part of the spectrum of kaposiform hemangioendothelioma and is not a distinctly different tumor. Cases of combined lesions and transformations from tufted angioma to kaposiform hemangioendothelioma support this.

Kaposiform hemangioendothelioma has areas that strongly resemble Kaposi sarcoma. Arguably the spindled cell areas of kaposiform hemangioendothelioma are indistinguishable from the solid areas of plaque or tumor stage Kaposi sarcoma. Kaposi sarcoma

**Fig. 5**

Acquired tufted hemangioma has a nodular cannonball-like growth pattern similar to kaposiform hemangioendothelioma, supporting the idea that it may represent part of the morphologic spectrum of kaposiform hemangioendothelioma rather than a distinct entity.
has a different clinical presentation, presenting in immunocompromised or elderly patients. Early lesions of Kaposi sarcoma have thin neoplastic vessels that infiltrate between dermal collagen bundles and dissect around pre-existing structures of the dermis (so-called “promontory sign”). Kaposi sarcoma is also immunoreactive for HHV8 latent nuclear antigen. HHV8 infection is not a feature of kaposiform hemangioendothelioma.

**Prognosis**

Kaposiform hemangioendothelioma may metastasize to regional lymph nodes, but distant metastasis has not been demonstrated. The mortality rate of approximately 10% is usually related to Kasabach-Merritt phenomenon. Unlike other tumors in this group where surgery is the mainstay of treatment, treatment of kaposiform hemangioendothelioma is multifactorial. A variety of modalities are employed including excision, embolization and chemotherapeutic regimens with steroids, alpha interferon, and cytotoxic agents.15,16

**EPITHELIOID HEMANGIOENDOTHELIOMA**

**Clinical features**

Epithelioid hemangioendothelioma presents over a broad age range (9-93 years) but usually affects adults with a median age of 50 years. Epithelioid hemangioendothelioma is primarily found on the extremities (65%) with the remainder located on the head and neck, trunk, mediastinum, genitals, and retroperitoneum. The tumors are usually located in the deep soft tissue (60%) but a significant subset presents in the subcutis and dermis.17,21

Tumors presenting as cutaneous lesions usually present as a mass lesion, frequently painful, but without the violaceous hue of other vascular neoplasms.22 Therefore, a vascular tumor is suspected clinically in only a
minority of cases.

**Microscopic Features**

The histologic appearance of epithelioid hemangioendothelioma is varied. In epithelioid hemangioendothelioma the tumor cells are arranged in cords to small nests of spindled to epithelioid tumor cells embedded in a characteristic myxohyaline stroma (Fig. 6). The stroma may have a distinctly chondroid appearance (Fig. 7). Vascular channel formation is not obvious; instead there are small lumens that on cross section often appear as intracytoplasmic vacuoles that may contain erythrocytes (Fig. 8). Tumor cells with this vacuolated appearance have been termed “blister cells”. Epithelioid hemangioendothelioma sometimes has a distinctly angiocentric growth pattern with cords of tumor cells radiating out from the affected vessel (Fig. 9), but angiocentric growth is less frequent in cutaneous cases. The affected vessels are expanded and frequently occluded with dense collagen, tumor cells, and necrotic cellular debris. The tumor nuclei are relatively uniform and cytologically bland. Mitotic figures and necrosis are rare. In about 20% of cases, there may be significant nuclear atypia, mitotic rate > 1 mitotic figure/10 HPF, spindling, and/or tumor necrosis. By immunohistochemistry the tumor cells express CD31 and CD34, and approximately one fourth express cytokeratins. Cytokeratin expression is usually focal in nature, but occasional cases may show more diffuse keratin expression (Fig. 10).

**Differential Diagnosis**

Epithelioid hemangioendothelioma is frequently confused with nonvascular tumors owing to its subtle vascular differentiation. Epithelioid hemangioendothelioma can be confused with metastatic signet ring adenocarcinoma because of the vacuolated appearance of the tumor cells and mucinous appearing stromal background. This may be further complicated by expression of cytokeratin, but metastatic adenocarcinomas show stronger, diffuse expression of cytokeratin and are negative for vascular markers. Recognition of erythrocytes in the vacuoles and the cord-like growth pattern should prompt consideration of epithelioid hemangioendothelioma.

Epithelioid sarcomas can look histologically similar to epithelioid hemangioendothelioma in that they both are composed
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more atypia can be confused with epithelioid angiosarcoma. Epithelioid angiosarcoma typically has some areas with complex interanastomosing vessels, more severe cytologic atypia and a higher mitotic rate.

Finally, the differential diagnosis of epithelioid hemangioendothelioma includes epithelioid sarcoma-like hemangioendothelioma. This will be discussed in more detail below.

Prognosis and Treatment

Epithelioid hemangioendothelioma is arguably the most aggressive member in the family of vascular tumors of intermediate malignancy, and in the future it may be reclassified as a fully malignant sarcoma or subdivided into more indolent and aggressive subtypes. Overall, over 20% of patients develop metastasis with a mortality rate of approximately 15%. There is evidence suggesting that tumors with atypical features (i.e. nuclear atypia, increased mitotic rate, etc.) have the potential to behave in a more aggressive fashion. Recently, a novel study examined risk stratification within a cohort of epithelioid hemangioendothelioma cases and found that it is possible to separate epithelioid hemangioendothelioma into an indolent and aggressive categories based on size and mitotic activity. Tumors > 3.0 cm with a mitotic rate > 3 mitotic figures/50 high powered fields behaved more aggressively. Patients with high risk tumors had a higher rate of metastasis (32% vs. 15%) and a 5 year disease specific survival rate of 59%. No patients in the low risk tumor group died of disease during the follow-up period. Interestingly, other atypical features such as cytologic atypia and necrosis were not independent adverse indicators in this study.

DABSKA TUMOR

Clinical and histologic features

Originally described in 1969, the Dab-
Dabska tumor, also known as malignant endovascular papillary hemangioendothelioma, was a tumor thought to occur exclusively in children and neonates. More recently, Dabska tumor has been described over a broader age range with a number of cases occurring in adults. Overall, pediatric cases outnumber cases in adults approximately 3:1. Dabska tumor presents as a cutaneous lesion usually involving the distal extremities but a variety of locations have been reported. Clinically, the lesions range from nondescript subcutaneous masses, diffuse swelling, to multinodular violaceous lesions.

**Microscopic Features**

Dabska tumor involves the dermis and often the subcutis. Dabska tumor is characterized by variably well formed to interconnecting and dilated vessels (Fig. 11) with complex intravascular proliferations that can resemble renal glomeruli (Fig. 12) or appear as rosette-like structures (Fig. 13). The neoplastic vessels are lined by a single layer of endothelial cells with scant cytoplasm that protrude into the lumen in a hobnail or matchstick fashion (Fig. 13, 14). Within the lumina there may be mature lymphocytes that lie in close association to the hobnail endothelium. The surrounding stroma is sclerotic and contains a variably dense lymphoid infiltrate. Occasional cases have been documented arising in association with lymphangiomas or vascular malformations. The tumors cells express CD31 and CD34 typical of most vascular tumors. Dabska tumor also expresses podoplanin and VEGFR-3 consistent with lymphatic differentiation.

**Differential diagnosis**

Well differentiated angiosarcoma may have hobnail endothelium and intravascular tufting. Clinically, angiosarcoma occurs in sun damaged skin of elderly patients and usually has higher grade nuclear features and...
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Prognosis

In Dabska’s original series of six patients, two developed regional lymph node metastasis. Although no tumor related death was initially reported, both patients subsequently had tumor related deaths. The overall metastatic rate for Dabska’s tumor is <10%, and only one case of distant metastasis has been reported.

RETIFORM HEMANGIOENDOTHELIOMA

Clinical features

Retiform hemangioendothelioma is usually presents in adults with a minority of pediatric cases. Age at presentation of retiform hemangioendothelioma varies greatly, from 9-78 years of age, with the median age of 34 years. Most cases are located on the lower limbs with fewer on the upper extremities and trunk. Clinically they were either exophytic or plaque-like and ranged from 2-9 cm in size. The clinical features are somewhat nondescript and a vascular tumor is clinically suspected in only a minority of cases.

Microscopic Features

Histologically, retiform hemangioendothelioma extensively involves the dermis with frequent extension into the deep subcutaneous tissue. On a low power examination, the tumor is composed of elongated, thin branching vessels resembling the rete testis (Fig. 15). Like Dabska tumor, the vessels are lined by a single layer of hobnail endothelial cells (Fig. 16). The lumens may contain mature lymphocytes that are closely associated with the hobnail endothelium. Intravascular papillae are occasionally seen but they are less prominent and less developed than the intravascular papillary tufts seen in Dabska tumor. The endothelial cells are hyperchromatic but cytologically bland. Mitotic activity is absent to rare. The stroma surrounding the neoplasm is often sclerotic and contains

a more complex vascular pattern. Hobnail hemangiomma is a benign tumor but is circumscribed with well-formed vessels lacking intraluminal tufting. Acquired tufted angiomma, a variant in the spectrum of kaposiform hemangioendothelioma, and glomeruloid hemangiomma have intravascular proliferations that have a glomeruloid appearance but lack hobnail endothelial cells. The closest mimic is retiform hemangioendothelioma. Some consider Dabska tumor and retiform hemangioendothelioma to be related entities along a spectrum of hobnail hemangioendotheliomas. Retiform hemangioendothelioma is discussed in more detail below.
many lymphocytes. By immunohistochemistry, the tumor cells are positive for CD31 and CD34. They are negative for lymphatic specific markers podoplanin and VEGFR-3.\textsuperscript{41,42}

**Differential Diagnosis**

Dabska tumor and retiform hemangiendothelioma share many similar histologic features and it has been suggested they exist along a continuum under the sobriquet hobnail hemangiendothelioma.\textsuperscript{28} Both tumors have vessels lined by hobnail endothelium, intravascular endothelial proliferations and sclerotic stroma associated with lymphocytes. Dabska tumor predominantly occurs in children and lacks the retiform vessels of retiform hemangiendothelioma. Dabska tumor also has lymphatic differentiation not seen in retiform hemangiendothelioma. Therefore, though sharing similar histologic features, it seems reasonable at this time to consider them distinct entities.

As a result of the similar appearing hobnail endothelial cells, hobnail hemangioma can be confused with retiform hemangiendothelioma. Hobnail hemangioma, however, lacks the complex retiform vessels and is a circumscribed tumor.

A well differentiated angiosarcoma could also be considered in the differential diagnosis. Again, angiosarcoma usually present on sun damaged skin of the head and neck on elderly patients. Usually there is more nuclear atypia, mitotic activity, and multilayering of endothelial cells. The vessels of angiosarcoma are complex but usually do not have a retiform appearance.

**Prognosis**

Retiform hemangiendothelioma is prone to frequent local recurrence, understandable given its infiltrative nature and complex vascular pattern. Regional lymph node metastasis may occur but is uncommon. In the series of 15 cases of retiform hemangiendothelioma described by Calonje et al., only one case with documented lymph node metastasis was reported. We are not aware of any reports of distant metastasis.

![Fig. 17](image)

The histologic features of composite hemangiendothelioma are varied with significant variability from case to case. This composite image demonstrates areas resembling spindle cell hemangioma with ectatic vessels, hemorrhage and proliferation of spindled cells (top panels), areas resembling retiform hemangiendothelioma (bottom left panel), and a solid area with increased nuclear atypia resembling angiosarcoma (bottom right panel).
COMPOSITE HEMANGIOENDOTHELIO-MA

Clinical features

Composite hemangioendothelioma is a controversial entity first described in 2000 by Nayler et al. Since then, less than 20 total cases of this entity have been reported. Composite hemangioendothelioma can present at any age from birth to 71 years old, but is most common in young to middle aged adults. Composite hemangioendothelioma usually presents on the distal extremities, especially the lower leg and foot. The lesions may be skin-colored, erythematous or violaceous. They may be solitary or multinodular.

Microscopic Features

Composite hemangioendothelioma is a microscopically heterogenous tumor. Histologically, the most notable characteristic of composite hemangioendothelioma is its inter and intra lesional variability. It is composed of an admixture of components resembling benign, intermediate, and malignant vascular tumors. Composite hemangioendothelioma contains areas that resemble at least two of the following tumors: epithelioid hemangioendothelioma, retiform hemangioendothelioma, spindle cell hemangioma, or angiosarcoma areas (Fig. 17). Components resembling epithelioid hemangioendothelioma and retiform hemangioendothelioma are most common. Composite hemangioendothelioma may also have areas resembling lymphangioma, cavernous hemangioma or arteriovenous malformation. The tumors are positive for CD31 and CD34. The limited number of cases examined have been negative for podoplanin by D2-40, but this may not hold true for tumors associated with a lymphangioma component.

Differential Diagnosis

The differential diagnosis of composite hemangioendothelioma is highly dependent on the components present in the tumor. The most common differential diagnosis is epithelioid hemangioendothelioma and retiform hemangioendothelioma, the most common morphologic patterns seen in composite hemangioendothelioma. Recognition of the different components is key to the accurate diagnosis of this rare tumor. The argument that this is not a distinctive tumor but rather morphologic variants of other vascular neoplasms could be made. However, given the fairly consistent combination of retiform hemangioendothelioma and epithelioid hemangioendothelioma areas, two acknowledged distinctly different neoplasms, as well as other areas indistinguishable from other types of vascular tumors it is reasonable to consider composite hemangioendothelioma a distinct entity. This is especially true considering the similar behavior that composite hemangioendothelioma with different morphologies exhibit.

Prognosis

Interestingly, the different morphologies, including the presence of angiosarcoma like areas, do not appear to influence behavior. Owing to its infiltrative and sometimes multinodular growth pattern, local recurrence occurs in up to 50% of cases. Regional lymph node or soft tissue metastasis rarely occurs, but distant metastasis has not yet been reported.

EPITHELIOID SARCOMA-LIKE HEMANGIOENDOTHELIO-MA

Clinical features

Epithelioid sarcoma-like hemangioendothelioma is a very rare tumor, with fewer than ten reported cases. It occurs most commonly in young adults as a mass lesion usually involving the distal extremities. Some tumors present as ulcerated cutaneous lesions. Clinically it is not a distinctive tumor and lacks the violaceous hue of other
vascular neoplasms.

Microscopic features

On low-power examinations, epithelioid sarcoma-like hemangioendothelioma is characterized by vague nodularity, sheets, and short spindled fascicles, showing infiltrative borders and a desmoplastic response. The tumor cells most commonly are epithelioid with relatively abundant eosinophilic cytoplasm (Fig. 18), but all cases have demonstrated areas that transition to a more spindled, fascicular pattern (Fig. 19). The tumors are not angiocentric and evidence of vascular differentiation is inconspicuous, consisting of only rare intracytoplasmic lumens similar to the blister cells of epithelioid hemangioendothelioma seen in about half of cases. No multicellular vascular channels are found. Mitotic activity is usually low (<5 per 50 HPF) and necrosis has not been reported. This tumor has a unique immunophenotype; it is positive for CD31, FLI-1, and cytokeratin but negative for CD34.

Differential Diagnosis

As implied by the name of this tumor, the primary consideration in the differential diagnosis is epithelioid sarcoma. The growth patterns and cellular morphology are similar, but epithelioid sarcoma-like hemangioendothelioma lacks the granuloma-like necrosis of epithelioid sarcoma. The presence of intracytoplasmic vacuoles with erythrocytes, when present, is helpful. Epithelioid sarcomas may have a slightly higher mitotic rate, but this is not a consistent feature. In many cases it is not be possible to differentiate epithelioid sarcoma from epithelioid sarcoma-like hemangioendothelioma on routine histologic features. In many respects the differential diagnosis is dependent on immunohistochemical stains, specifically expression of CD31. Distinction is important, as epithelioid sarcoma-like hemangioendothelioma
appears to have a more indolent course than epithelioid sarcoma (see below).

The other entities in the differential diagnosis are epithelioid hemangioendothelioma and epithelioid angiosarcoma. Epithelioid sarcoma-like hemangioendothelioma lacks the angiocentric and cord-like growth pattern in epithelioid hemangioendothelioma. Epithelioid sarcoma-like hemangioendothelioma also has stronger cytokeratin expression and lacks CD34 expression, though this latter finding might not hold true as more experience is gained with this tumor. Epithelioid angiosarcoma usually has areas with multicellular vascular channels, a greater degree of cytologic atypia and a higher mitotic rate.

**Prognosis**

Though there is little experience with epithelioid sarcoma-like hemangioendothelioma, it appears to have in a relatively indolent fashion. Local recurrence and soft tissue metastasis has been reported, but not lymph node or distant metastasis to date. No tumor related deaths have been reported.

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