Kaposiform hemangioendothelioma (KHE) is a rare, potentially life-threatening vascular tumor first depicted in a case report in 1940 as a “capillary hemangioma” with purpura, but metastatic disease has not been reported.16 Signs and symptoms of this vascular tumor depend on the extent of the tumor and the tissue layers involved. When KHE infiltrates muscle and fascial layers, reduction of range of motion and pain may be observed with the risk of contracture development and chronic pain. Involvement of visceral organs is uncommon, but usually portends a more severe clinical course. Although classically KHE is diagnosed in infancy or early childhood, identification of KHE in adults is increasingly common.

Tufted angioma has a predilection for the upper back and neck. Tufted angioma (TA), described by Jones and colleagues in 1989, is a rare, benign, slow-growing vascular tumors that can develop at any stage of life, but predominantly during infancy or early childhood.4,11 Morphologic and histologic similarities between KHE and TA have led to a consensus that these vascular tumors exist along a spectrum.11,12 TA tends to be less extensive, localized predominantly in the epidermis and dermis; whereas, KHE can proliferate to include multiple body regions and infiltrate through skin, fascia, muscle and even bone. TA enlarge fairly slowly and spontaneous resolution has been reported.13,14 In contrast, KHE has been associated with a higher risk for KMP, and lesions may decrease in size or become dormant over time but do not completely involute.15

This review focuses on the characteristic clinical features of TA and KHE, current approaches to management, and opportunities for refining our clinical practice.

Clinical features
Kaposiform hemangioendothelioma typically presents as a solitary, indurated, red-purple plaque with an ill-defined border during infancy or early childhood. Skin manifestations may include a nodular appearance, warmth, hypertrichosis, hyperhidrosis, and telangiectasias (Figure 1A). Rapid enlargement occurring within days to weeks and multifocal KHE lesions have been reported.14,16 KHE has a slight predilection for the extremities, but also occurs on the head, neck, trunk, and groin. KHE may present without cutaneous findings, particularly in the retroperitoneum, mediastinum, or bone. Extension to adjacent viscera and lymph nodes can be seen, but metastatic disease has not been reported.16 Sign misidentifications and management. The rarity of KHE-spectrum lesions and an increasing number of providers across centers and an increasing number of providers across subspecialties with interest in this field are facilitating the development of standardized approaches to diagnosis and management. The rarity of KHE-spectrum lesions and the heterogeneity of clinical manifestations necessitate rationally designed, multisite clinical trials to investigate risk stratification schemas and formally evaluate the short- and long-term outcomes have been hindered by lesion misidentification, imprecise nomenclature, and lack of prospective, randomized clinical trials to assess therapeutic efficacy. The classic dermatologic features of these lesions can facilitate diagnosis for the astute provider; however, the absence of or unusual integumentary involvement or presentation in a less common age group (adolescents/ adults) poses a diagnostic challenge. Current approaches to the management of KHE/TA are often informed by lesion features such as presence of KMP extent and location of the tumor, and symptomatology. Evidence-based treatment guidelines are limited. Corticosteroids, vincristine, interferon, multi-agent regimens and newer therapies, such as sirolimus, have demonstrated efficacy in patient series. The use of surgical excision and interventional radiology-guided therapies have been described with mixed clinical benefit. Collaboration among emerging vascular anomaly centers and an increasing number of providers across subspecialties with interest in this field is facilitating the development of standardized approaches to diagnosis and management.

Kaposiform hemangioendothelioma (KHE) and tufted angioma (TA) are classified as vascular tumors with locally aggressive and benign growth potential, respectively, within the classification schema proposed by the International Society for the Study of Vascular Anomalies. A unique feature of these vascular tumors is the risk of Kasabach-Merritt phenomenon (KMP), a severe thrombocytopenia with mild to moderate coagulopathy resulting from intraleisonal platelet trapping. As with many vascular anomalies, accurate description of clinical course, responses to therapy, and long-term outcomes have been hindered by lesion misidentification, imprecise nomenclature, and lack of prospective, randomized clinical trials to assess therapeutic efficacy. The classic dermatologic features of these lesions can facilitate diagnosis for the astute provider; however, the absence of or unusual integumentary involvement or presentation in a less common age group (adolescents/adults) poses a diagnostic challenge. Current approaches to the management of KHE/TA are often informed by lesion features such as presence of KMP extent and location of the tumor, and symptomatology. Evidence-based treatment guidelines are limited. Corticosteroids, vincristine, interferon, multi-agent regimens and newer therapies, such as sirolimus, have demonstrated efficacy in patient series. The use of surgical excision and interventional radiology-guided therapies have been described with mixed clinical benefit. Collaboration among emerging vascular anomaly centers and an increasing number of providers across subspecialties with interest in this field is facilitating the development of standardized approaches to diagnosis and management. The rarity of KHE-spectrum lesions and the heterogeneity of clinical manifestations necessitate rationally designed, multisite clinical trials to investigate risk stratification schemas and formally evaluate the short- and long-term efficacy of available and novel therapies.

A unique feature of these vascular tumors is the risk of Kasabach-Merritt phenomenon (KMP), a severe thrombocytopenia with mild to moderate coagulopathy resulting from intraleisonal platelet trapping. As with many vascular anomalies, accurate description of the natural history and response to treatment difficult to interpret from the literature. In 1993, Zukerberg and colleagues provided a more detailed clinical and histopathologic description of this entity and coined the term KHE.4 Unfortunately, an association between “hemangioma” and KMP has persisted, in some cases leading to incorrect diagnosis and management.5,7

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with variable clinical presentations (ie, deep red to purple papules or plaques, or an indurated vascular stain with ill-defined borders; Figure 1B). Associated hypertrichosis with increased lanugo hairs and hyperpigmentation may be observed. TA tends to be warm and tender to the touch. TA often has an indolent course, enlarging slowly over time, and spontaneous resolution has been reported.

Kaposiform lymphangiomatosis
Kaposiform lymphangiomatosis (KLA) shares the histopathologic finding of “kaposiform” spindled lymphatic endothelial cells and the presence of abnormal, dilated lymphatic channels with KHE but otherwise seems to be a distinct clinical entity. KLA currently remains provisionally unclassified in the ISSVA classification for vascular anomalies; however, it is suspected to be a clinically aggressive subtype of generalized lymphatic anomaly (GLA). While KHE characteristically presents in infancy or early childhood as a localized, low-grade malignant vascular tumor, KLA presents more commonly in adolescence or adulthood with evidence of thoracic disease with presenting symptoms of cough, dyspnea, bleeding and findings of pleural and pericardial effusions, and moderate thrombocytopenia. A limited number of cases have been reported, and they likely reflect the most severe manifestations. All patients have had involvement of the thoracic cavity (mediastinum, lung parenchyma, pleural cavity) to some degree. Evidence of generalized lymphatic anomaly also involving the retroperitoneum, spleen, bones, soft tissue, or skin in these cases is common. Radiographic imaging features include: thickened interlobular septa, heterogeneous and infiltrative soft tissue masses in the mediastinal, paraspinal, or retroperitoneal regions. Lytic bony lesions with cortical sparing and cystic lesions in the spleen have been observed in the majority of patients. The natural history of KLA seems to be progressive, in some cases rapidly so. An early case series reported a 5-year survival of 51% with an overall survival was 34%. Accumulation of lymphatic fluid in the pericardium or pleural spaces is only temporarily relieved by interventional measures such as pleural and pericardial drainage, pleurodesis, sclerotherapy, and thoracic duct ligation. Given the rarity of this diagnosis and the variety of medical therapies tried, including vincristine, sirolimus, interferon, thalidomide, and doxycycline, the superiority of specific agents or therapeutic combinations has not yet been well studied.

Kasabach-Merritt phenomenon
KMP is a profound thrombocytopenia resulting from intralesional platelet trapping typically accompanied by mild coagulopathy as evidenced by elevation in d-dimer, slight prolongation of PT and aPTT and a moderate reduction in fibrinogen levels. Generally, the platelet count will be <50,000 per uL; the median platelet count reported in one large series was 11,500 per uL. KMP is distinct from the coagulopathy that can accompany other vascular anomalies (eg, venous malformation), which more closely resembles disseminated intravascular coagulation with a marked decrease in fibrinogen, prolongation of PT and aPTT, and a comparatively mild reduction in platelet count. KMP can arise in any patient with a lesion within the KHE/TA spectrum, but is more common in the neonatal and infant setting, and with KHE. To our knowledge, KMP has not been reported in adult-onset KHE. Predictors of KMP include age, size, and location of lesion. The proportion of infants who develop KMP is higher than that of older children. Lesions >8 cm are at increased risk for KMP. Anatomic location of cutaneous KHE lesions has not been demonstrated to correlate with KMP; however, lesions large enough to involve more than one anatomic region or with invasion of underlying muscle, bone, retroperitoneum, or the thoracic cavity have increased odds of KMP development compared to those limited to the skin. Even if the laboratories at the time of initial presentation do not suggest KMP, evidence of change in lesion characteristics (ie, enlarging lesion, deepening of color, increasing firmness, or pain) should prompt...
Croteau et al

a re-evaluation for KMP. Although most patients manifest KMP at the time of presentation, subsequent KMP can occur, generally within the first year after diagnosis.23

Diagnostic imaging

Imaging in kaposiform hemangioendothelioma can aid in diagnosis, determine extent of involvement, and monitor treatment effect. Magnetic resonance imaging (MRI) with and without gadolinium is the preferred imaging modality (Figure 2).24 MR angiography may be useful to obtain better resolution of the mass and provide information regarding arterial supply and venous drainage of the tumor. Ultrasound, computed tomography, and plain films have limited utility in KHE. There have also been reports of the resemblance of KHE to other tumors (ie, rhabdomyosarcoma or aggressive fibromatosis) on computed tomography.

Histopathology

KHE-spectrum lesions have a unique mixed lymphatic and vascular endothelial phenotype and share the same immunohistochemical phenotype and many histopathologic features (Figure 3). Therefore, a small specimen can make histopathologic distinction between these two entities challenging.12,25 KHE and TA can be further differentiated from previous misnomers of infantile hemangiomas as they are negative for GLUT-1 staining and unlike Kaposi sarcoma, stain negatively for HHV8.6 The pattern of the lymphatic marker D2-40 staining differs slightly between TA and KHE; KHE is markedly positive for D2-40, whereas TA is only positive in the surrounding tissues.26 Case reports of tumors with focal areas of both KHE and TA features on histopathology have been reported including one case of transformation from TA to KHE that was confirmed with serial biopsies of a progressively symptomatic lesion.27

Initial evaluation

The initial evaluation of KHE and TA should include baseline laboratory tests to determine whether or not there is concurrent KMP; ie, complete blood count (CBC) to evaluate for anemia and thrombocytopenia, coagulation panel, fibrinogen, and D-dimer to evaluate for any evidence of coagulopathy (Table 1).28 The diagnosis of KHE and TA should be supported by imaging, ideally MRI, to define the degree of infiltration of the musculature, fascia, and bone, which may be underestimated by the physical exam. The extent of the KHE/TA lesion is important for treatment decision-making. A tissue biopsy is not always required for diagnosis if clinical appearance and imaging characteristics are clear. Even minor trauma, such as biopsy, may aggravate a KHE lesion and result in acute

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**FIGURE 2.** Magnetic resonance imaging features of (A) kaposiform hemangioendothelioma and (B) tufted angioma. There is an ill-defined, homogeneous enhancement of an infiltrative tumor with varying extent of involvement depending on tumor type. KHE shows greater extension to the subcutaneous tissues and adjacent muscles versus TA, which is more confined within the epidermis and dermis. Stranding of the subcutaneous fat, surrounding edema-like pattern, and flow voids can be seen as well as ectatic vessels. Courtesy of Eric Monroe, MD.

**FIGURE 3.** (A) Kaposiform hemangioendothelioma: On histopathology, KHE shows nodules of infiltrating spindled endothelial, dilated and hyperplastic lymphatic channels, slit-like vascular channels, microthrombi and hemosiderin deposition. Mitosis and nuclear atypia are absent. Immunohistochemical profile is the same as TA and shows immunoreactivity for both lymphatic and endothelial cell markers; Prox 1+, LYVE-1+, D2-40+, CD31+, CD34+, VEGFR-3+ and negativity for markers suggestive of infantile hemangiomas GLUT-1- and Kaposi sarcoma HHV8-. (B) Tufted angioma: Characteristic histopathology features are the presence of tightly packed capillaries giving a so-called cannonball appearance, crescent-like peripheral clefts, and occasionally spindled endothelial cells lining ectatic lymphatic channels. Courtesy of Joe Rutledge, MD.
The clinical spectrum of kaposiform hemangioendothelioma and tufted angioma

**TABLE 1. Diagnostic evaluation for suspected KHE/TA**

- Complete blood count
- Coagulation studies: PT, PTT, fibrinogen, d-Dimer
- MRI of lesion with and without contrast
- Tissue biopsy (if diagnosis uncertain)

**Archetypes of kaposiform hemangioendothelioma and tufted angioma**

The spectrum of clinical presentation is broad, and a formal risk stratification schema requires prospective investigation. A few archetypes of KHE/TA have emerged and may help guide initial treatment decisions and clinical trial design: (1) fulminant KHE with KMP in a neonate/young infant, (2) large cutaneous/noncutaneous KHE/TA with KMP, (3) KHE/TA without KMP (Table 2).7,22,24,29,30

**Fulminant kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon in a neonate/young infant**

Patients in this archetype typically present in extremis and require intensive management for cardiovascular instability, respiratory compromise, or severe KMP potentially with bleeding.22,31 In some cases, recognition of the KHE lesion may be delayed because it is limited to the retroperitoneal region and there are no supportive physical exam cues for providers. This group has the highest morality rate, approaching 30% to 50%. Expedited recognition of the correct diagnosis and initiation of therapy is critical.

**Large cutaneous/noncutaneous KHE or TA with KMP**

This group represents the most common cases of KHE reported in the literature, but it is less frequently seen for TA. Affected patients tend to be younger, usually infants or toddlers. Depending on the clinical severity, inpatient versus outpatient management may be individualized. Diagnosis may be challenging if no characteristic integumentary findings are present.

**KHE or TA without KMP**

This group represents at least 30% to 40% of patients with KHE and a majority of patients with TA and is perhaps the most heterogeneous group. Proportionally more of these lesions are seen in toddlers, school-age children, and adults. Not all patients in this group will require treatment. Size, location, depth of infiltration, and associated symptomatology are all important factors in considering the appropriateness of observation versus pharmacotherapy or procedural intervention. Some patients with TA manifest flares of pain and increased induration of the mass that may be associated with low/normal fibrinogen, mild elevation of D-dimer, without thrombocytopenia. Case reports of administration of antiplatelet agents (eg, aspirin and ticlopidine) have led to resolution of symptoms and normalization of laboratories. It is hypothesized that there is a small degree of thrombin generation and microthrombi associated with TA that can lead to symptoms.30

**Treatment**

A wide range of therapeutic strategies used for the treatment of KHE/TA lesions with reported success. These treatments include pharmacological therapies, radiation therapy, and interventions such as surgical excision and embolization. Selection of an initial treatment regimen should be determined by the presentation. Observation, single-agent therapy, or aggressive multi-modal therapy may be indicated. A consensus statement by a self-selected group of vascular anomalies experts was recently published highlighting their expert opinion-based practice guidelines to help guide therapy for KHE with and without KMP.28 The presence of KMP is often the feature that prompts initiation of therapy. Even with severe thrombocytopenia, platelet transfusion is relatively contraindicated in KHE with KMP due to propagation of platelet trapping within

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**TABLE 2. Treatment considerations by KHE/TA archetype**

<table>
<thead>
<tr>
<th>Archetype</th>
<th>Suggested first-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulminant KHE with KMP* (neonate/young infant)</td>
<td>Multi-agent therapy often necessary. Consider consultation with a Vascular Anomalies Center for patient tailored recommendations.</td>
</tr>
<tr>
<td>KHE/TA with KMP*</td>
<td>Vincristine 0.05 mg/kg IV weekly AND prednisolone 2 mg/kg/day OR Methylprednisolone 1.6 mg/kg/day</td>
</tr>
<tr>
<td>KHE without KMP</td>
<td>Stable or minimally invasive lesion: Observation Lesion growth or symptoms: Prednisolone 2 mg/kg/day +/- antiplatelet therapy with aspirin 2 to 5 mg/kg/day</td>
</tr>
<tr>
<td>Symptomatic TA</td>
<td>Consider trial of an antiplatelet agent such as aspirin +/- ticlopidine</td>
</tr>
</tbody>
</table>

* Avoid platelet transfusion unless significant bleeding or intervention required

Abbreviations: KHE, kaposiform hemangioendothelioma; KMP, Kasabach-Merritt phenomenon; TA, tufted angioma.
the lesion resulting in lesion engorgement and enlargement. Platelet transfusion or fibrinogen replacement with cryoprecipitate may be necessary in certain clinical situations such as significant bleeding or the need for a procedure.

Surgical/interventional therapy
In rare cases, complete surgical excision is achievable and has been hallmarked as the gold standard of cure. The infiltrative nature of KHE makes surgical excision challenging. Incomplete surgical excision can actually result in aggravation and acute progression of the remaining tumor and precipitation of KMP. Intervventional therapies such as embolization have been reported without evidence of sustained response; but they may play an adjunctive role in tempering a severe lesion in an acute clinical setting.32

Pharmacologic therapy
Pharmacologic treatments have included corticosteroids, cytotoxic drugs (vincristine, cyclophosphamide), antiplatelet agents (ticlopidine, aspirin), antifibrinolytic agents, beta-blockers (propranolol), and now immunosuppressants (sirolimus) all with varying efficacy.29,33-38 A number of agents have been used both individually and in combination on a case-by-case basis. The most commonly used agents include corticosteroids and vincristine. The combination of corticosteroids plus vincristine is considered first-line therapy for patients with KHE complicated by KMP.34 Historically, interferon-α, was used with consistent success; however, the observation of spastic diplegia in infants, this therapy fell out of favor.39,40 Other than a recently published study of sirolimus for complex vascular anomalies,33 determinants for use of pharmacotherapy have not been consistent, including patient selection, dosage and duration of therapy, and standardized measurement of laboratories and outcomes. Emerging data suggests that sirolimus may result in more prompt resolution of KMP (1-2 weeks) rather than up to 3-4 weeks seen with vincristine. A randomized controlled trial (NCT# 02110069, https://clinicaltrials.gov/ct2 resultados?term=02110069&Search=Search) is currently investigating the comparative efficacy of vincristine versus sirolimus as first-line therapy for KHE patients requiring therapy.

Radiation therapy
Localized radiation therapy has been reported to have a therapeutic effect with regard to reduction of lesion size and improvement in KMP symptoms;42 however, this treatment modality carries considerable risk of long-term morbidity, particularly for the youngest (and most commonly affected) patients.39 Judicial use of this treatment modality is imperative.

Response to therapy
Timing of response to therapy is variable. Softening of the lesion and an increasing platelet count typically are observed first. If corticosteroids are effective, improvements (often small) may be seen within days. Other therapies may have a lag time of a few weeks. Overall improvement in KHE lesions often takes several months. The goals of therapy are to eliminate KMP and minimize the size and symptoms associated with the lesion. Those patients being treated for KHE without KMP or with modest-sized lesions may require several months to a year of therapy, while those with extensive lesions complicated by KMP, may require prolonged therapy. With the exception of complete surgical excision, no therapy to date has resulted in a “complete cure” of KHE. In all cases, there is some lesion remnant present, although it may be asymptomatic.

Long-term clinical outcomes
Descriptions of outcomes of KHE/TA with or without KMP, particularly long-term patient reported outcomes such as functionality and pain, are sparse. There have been few cases of spontaneous regression of TA in patients with a younger onset;13,14 but KHE remnants persist regardless of therapy. Enroljas et al presented the dermatologic outcomes of 42 patients treated with various treatment regimens. This group identified three types of KHE residual: (1) pseudo–port wine stains with papules, (2) telangiectasias with swelling, and (3) fibrotic subcutaneous infiltrates.15 Clinical features that impact these types of KHE resuduum, including presenting features and type of therapy administered, have not been explored. Long-term clinical outcome data for newer regimens including sirolimus are not yet available.

Conclusion
Refinement of the vascular anomalies classification and increased awareness of KHE and TA have led to a greater prevalence. This heightened awareness is also stimulating basic science investigation of the underlying vascular biology and causative genetic mutations as well as interest in prospective exploration of comparative and risk-stratified treatment regimens. The underlying etiology and genetic fingerprint of these tumors has yet to be elucidated. Increased activation of the P3K/AKT/mTOR pathway and genetic variants in PIK3CA have been associated with several vascular anomalies. Investigation of the dysregulation of this pathway in KHE is of interest given the growing number of reports of successful treatment with sirolimus, an mTOR inhibitor.

Most reported cases of KHE highlight the severe side of the phenotypic spectrum and are associated with KMP and high mortality rates. Increasingly, milder phenotypes are being recognized primarily in adults and older children. The biological differences that underlie this heterogeneity are unclear including the triggers for KMP.

As illustrated above, there is no shortage of therapeutic options reported to be “successful” in one or more KHE/TA cases. Prospective clinical trials in rare diseases require innovative design and multisite collaboration and are desperately needed in this field. Demonstration of the comparative efficacy among available and novel therapies is necessary for optimizing therapeutic response, minimizing toxicity, and tailoring care for our patients.

References
The clinical spectrum of kaposiform hemangioendothelioma and tufted angioma


