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Kaposiform hemangioendothelioma: atypical features and risks of Kasabach-Merritt phenomenon in 107 referrals

Stacy E. Croteau, MD, MMS,
Division of Pediatric Hematology/Oncology, Children's Hospital Boston

Marilyn G. Liang, MD,
Department of Dermatology, Children's Hospital Boston

Harry P. Kozakewich, MD,
Department of Pathology, Children's Hospital Boston

Ahmad I. Alomari, MD,
Division of Interventional Radiology, Children's Hospital Boston

Steven J. Fishman, MD,
Department of Surgery, Children's Hospital Boston

John B. Mulliken, MD, and
Department of Plastic Surgery, Children's Hospital Boston

Cameron C. Trenor III, MD
Division of Pediatric Hematology/Oncology, Children's Hospital Boston

Abstract

Objective—To examine the presentation characteristics of patients with kaposiform hemangioendothelioma (KHE) to describe the spectrum of disease and risk factors for Kasabach-Merritt phenomenon (KMP).

Study design—Retrospective review of 163 patients referred to the Vascular Anomalies Center at Children's Hospital Boston for KHE between 1991 and 2009 identified 107 patients with sufficient data for inclusion.

Results—The prevalence of KHE in Massachusetts is approximately 0.91/100,000 children. KHE manifested in infancy in 93% of cases; 60% as neonates. Common presenting features included enlarging cutaneous lesion (75%), thrombocytopenia (56%), and musculoskeletal pain or decreased function (23%). Cutaneous KHE favored the extremities, especially overlying joints. In our cohort 71% developed KMP (11% after initial presentation), and 11% of patients lacked cutaneous findings. Retroperitoneal and intrathoracic lesions, though less common, were complicated by KMP in 85% and 100% of cases, respectively. Compared with superficial lesions, KHE infiltrating into muscle or deeper was 6.3 fold more likely to manifest KMP, and 18-fold

Corresponding Author: Stacy E. Croteau, MD, MMS Vascular Anomalies Center Children's Hospital Boston 300 Longwood Avenue Boston, MA 02115 **Phone:** 617-355-5226 **Fax:** 617-730- 0752 Stacy.Croteau@childrens.harvard.edu.

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higher if retroperitoneal or intrathoracic. KHE limited to bone or presenting after infancy did not manifest KMP.

Conclusion—An enlarging lesion is the most common presenting feature of KHE in infancy. Older patients with KHE or those lacking cutaneous manifestations present with musculoskeletal complaints or atypical symptoms. The risk of KMP increases dramatically when tumor infiltrates muscle or when KHE arises in the retroperitoneum or mediastinum.

Keywords

Kasposiform hemangioendothelioma; Kasabach-Merritt phenomenon; Vascular Anomaly; Vascular Tumor

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor typically first seen in infancy as a distinctive cutaneous lesion with ill-defined borders.[1] KHE may be confused with infantile hemangioma due to age of presentation and the presence of a vascular cutaneous lesion. Prenatal and adult-onset KHE have been described. Although infantile hemangioma has a predictable natural history of proliferation for several months followed by slow involution over several years, the evolution of infantile KHE results in smaller, fibrous remnants with microscopic evidence of residual tumor, usually with persistent cutaneous stain.[2] Infantile hemangioma may present with multifocal cutaneous lesions with or without hepatic lesions. In contrast, few cases of multifocal KHE have been reported; only one has shown KHE in multiple biopsy sites.[3] Biopsy-proven hepatic KHE has never been reported, although a single case involving the common bile duct was recently described.[4] KHE is described as a “rare” vascular tumor; no epidemiologic studies have reported incidence or prevalence data.

KHE is an infiltrative tumor that may cross tissue planes from dermis into subcutis, fascia, muscle, and bone. Characteristic T_1–weighted MRI imaging reveals an ill-defined, hypo/isointense soft tissue thickening, often involving multiple tissue planes.[5] T_2–weighted MRI imaging typically demonstrates a hyperintense mass with reticular stranding in subcutaneous fat. Histopathologic features of KHE include: infiltrating nodules/sheets of variably spindled endothelial cells, focal immunopositivity for lymphatic endothelial markers, slit-like vascular channels, absence of mitosis or nuclear atypia, microthrombi, hemosiderin deposition, edema, fibrosis, and abnormal lymphatic channels.[1, 5-8]

Kasabach-Merritt phenomenon (KMP) is a profound thrombocytopenia resulting from intralesional platelet trapping.[9] The first report in 1940 described “extensive purpura” as a complication of “capillary hemangioma.” With refined definition of the term “hemangioma” in recent decades, it is now clear that KMP occurs with KHE and tufted angioma, not with infantile or congenital hemangiomas.[5, 10] Overuse of the term KMP to describe any low platelet count or coagulopathy observed in a patient with a vascular anomaly has caused considerable confusion with respect to the underlying biology and outcomes of this phenomenon, including broadly reported mortality rates of 12-30% for KHE.[5, 11] Localized or disseminated coagulopathy is more commonly attributed to other vascular malformations.[12]

Given the challenging diagnostic and management considerations for KHE, this study was designed to retrospectively evaluate a large cohort of patients, defined by interdisciplinary consensus, to better understand the spectrum of this vascular tumor, including atypical presentations and predictors of KMP.

METHODS

We reviewed the medical records and database of the Vascular Anomalies Center at Children's Hospital Boston from 1991 to 2009 using the search terms Kaposiform hemangioendothelioma, KHE, Kasabach-Merritt phenomenon, KMP, Kasabach-Merritt syndrome, and *KMS* to define a cohort of patients with probable KHE. Our Institutional Review Board approved this retrospective review. Our interdisciplinary team reviewed all cases and reached consensus on the diagnosis of KHE based on review of digital photos, imaging, clinical history, laboratory data and/or biopsy. Of the 163 patients in the initial search results, 118 patients carried a diagnosis of KHE, and 107 had sufficient clinical, imaging, and laboratory data for inclusion in this analysis. Data collected included: age of onset, presenting signs/symptoms, anatomic location, depth of infiltration, and platelet count to evaluate for KMP. KMP was broadly defined in this cohort as a platelet count of less than 100,000 per microliter. Depth of infiltration, as determined by radiographic findings or pathology, was designated as superficial or deep. Superficial lesions were those involving tissue layers from the dermis through subcutaneous tissue and involving the deep fascia. Deep lesions infiltrated muscle, bone, intrathoracic, or retroperitoneal sites. Histopathologic confirmation was not required for diagnosis. In 62 patients, a biopsy specimen was available and was reviewed by a pathologist with experience in vascular anomalies (HPK), confirming the diagnosis of KHE.

RESULTS

Epidemiology

This KHE cohort represented referrals from 30 states and 15 countries. We assume that our center was involved in the vast majority of cases from Massachusetts. Given the estimated 1.4 million children less than 18-years-old in Massachusetts in 2009[13] and 13 Massachusetts children with KHE, we estimate the prevalence of KHE as 0.91/100,000 children. Over the past decade there has been about one new case of KHE diagnosed in Massachusetts per year yielding an incidence of 0.071/100,000 children.

Demographics

KHE manifested before one month of age in 60% of cases and during infancy in 93% of cases (Figure, A). The median age of initial presentation was two months (range birth to 49-years-old). One patient had a lesion on prenatal ultrasonography that was ultimately diagnosed as KHE. There was a slight male predominance in our cohort of 1.33:1 (61 male; 46 female).

Presenting Signs and Symptoms

Eighty-nine percent of patients had a cutaneous vascular lesion; no patients had multi-focal lesions. Cutaneous discoloration and progressive enlargement of the tumor occurred in 75% of cases. Other common presenting features included: thrombocytopenia (56%) and musculoskeletal dysfunction with decreased range of motion or pain (23%) (Figure, B). Analysis of musculoskeletal complaints by patient age at presentation revealed an increase from 19% of infant presentations to 71% of presentations after 1-year-old (data not shown).

Anatomic Distribution

Four anatomic regions were used to categorize the location of KHE: cervicofacial, upper extremity/shoulder, lower extremity/hip, and torso (including intrathoracic cavity and retroperitoneum). KHE most frequently involved an extremity, followed by torso, then the cervicofacial region. Twenty-six percent (27/107) of KHE lesions extend into more than one of these anatomic regions. Superficial lesions tended to arise in the extremities (10/16). The

majority, 83%, of our KHE lesions were classified as deep lesions. Subgroups of deep lesions included: 3 bone only, 13 retroperitoneal and 9 intrathoracic lesions. KHE restricted to bone involved the femur, vertebrae or sacrum and presented with musculoskeletal pain without KMP.

Noncutaneous KHE

Eleven percent of our cohort did not have cutaneous involvement. Lesions arose in the torso (9/12) or the lower extremity (3/12). The median age at presentation of the noncutaneous KHE group was 6.5 months (range: birth to 6 years). Seven of twelve (58%) patients developed KMP. Five of these were retroperitoneal; all presenting in infants less than six-months-old. Presenting signs and symptoms in patients without cutaneous involvement are described in Table I. Pain and/or musculoskeletal dysfunction were more common in older patients.

Kasabach-Meritt phenomenon

Analysis of the frequency and risk factors for KMP was restricted to 96 patients with platelet counts. Although 56% of patients, overall, presented with symptoms of thrombocytopenia (bruising, petechiae, bleeding), subgroup analysis of the patients with known platelet counts revealed 71% of cases had KMP. Mean and median platelet nadirs for those the KMP were 17,300 and 11,500 platelets per microliter, respectively (data not shown). Anatomic location of cutaneous KHE lesions was not predictive of KMP; however, lesions large enough to involve more than one anatomic region did have increased KMP, odds ratio 7.93-15.90 (Table II). KHE superficial to muscle manifested KMP in only 36% lesions compared with 78% of lesions that invaded underlying muscle, bone, retroperitoneum or the thoracic cavity. The development of KMP in lesions involving the retroperitoneum or thoracic cavity was increased compared with superficial lesions, odds ratio 18.

Although most patients had KMP at time of presentation, 11% developed KMP later. The median interval to development of KMP for delayed cases was 6.5 weeks (range: 4 weeks to 2 years). Each of the eight patients who developed KMP subsequent to initial presentation was symptomatic at the time KMP was detected (enlarging lesion n=6; increased lesion firmness with change in cutaneous stain n=1, and respiratory distress n=1).

Twenty-eight cases in our cohort did not develop KMP, defined as a platelet count less than 100,000 per microliter (Table III). The median age for this group was 3.5 months (range: birth to 49 years). Eighty-five percent of these patients were offered treatment despite normal platelet levels. Novel presentation of KHE in patients older than 12 months did not include thrombocytopenia.

DISCUSSION

KHE involves a spectrum of lesions from small, superficial tumors without KMP to large, infiltrative lesions with life-threatening complications including KMP. We have characterized the largest cohort of KHE patients to date. Most patients have KMP and present in infancy with classic cutaneous lesions. Patients without cutaneous lesions present with atypical signs and symptoms and tend to be older. Numerous anatomic locations have been reported: cervicofacial region (sinuses,[14, 15] internal and external auditory canals,[16, 17] larynx,[18] thymus,[19] thyroid[3] and eyelid[20]), torso, extremities, mediastinum, and retroperitoneum[1]. Retroperitoneal tumors are frequently described in the literature because of their severity (publication bias); however, this location represented only 12% of tumors in our study, a lower proportion than previously published.[6, 21]

KMP is typically associated with more aggressive lesions and poorer outcomes.[22] No specific criteria have been established to risk-stratify patients with respect to the occurrence or recurrence of KMP. Previously, KHE lesions with a maximum cutaneous diameter greater than 8 centimeters or with infiltration of the retroperitoneum or mediastinum have been implicated as risk factors for KMP.[22] Our data suggest that KHE lesions extending into multiple anatomic regions confer an increased risk of KMP, though data available in our dataset did not permit for consistent analysis of maximal tumor dimensions.

The pathogenesis of KMP has yet to be elucidated. Clinically significant KMP is a severe thrombocytopenia, generally below 30,000 per microliter. We chose a generous platelet threshold of 100,000 per microliter to capture all cases and examine the distribution of platelet counts in KHE patients. Of 68 patients with platelet counts less than 100,000 per microliter, 47 had platelet count nadirs less than 30,000 per microliter. Mild thrombocytopenia may indicate a milder tumor, a quiescent tumor, partial response to successful therapy, or it may occur in other vascular lesions or have an etiology unrelated to vascular anomalies. KMP is refractory to transfused platelets, often causing painful tumor engorgement arguing against an intrinsic platelet defect. Abnormal platelet activation and aggregation may occur secondary to interaction with abnormal tumor endothelium resulting in localized trapping of platelets and consumption of clotting factors.[23] Others have hypothesized that the turbulent blood flow that results from the architecture of the small, convoluted capillaries seen in KHE triggers KMP.[8] The basal lamina of KHE endothelial cells has been shown to be discontinuous and poorly formed which may permit interaction of collagen with clotting factors.[1] In addition to the severe, persistent thrombocytopenia characteristic of KMP, patients often manifest elevated D-dimer and low fibrinogen. [5, 10, 24] Perturbations of prothrombin time, partial thromboplastin time, and hematocrit have been less uniformly described.[25, 26] Coagulopathy in addition to thrombocytopenia is associated with more aggressive presentations and may indicate concurrent infection or inflammation. Unfortunately, coagulopathy data were not routinely captured on patients in our cohort and were unavailable for retrospective review.

We have previously reported a series of patients without KMP [22] and have expanded from 10 to 28 cases in this study. Superficial tumors, tumors isolated to bone, or presentation at an older age are each characteristics associated with decreased frequency of KMP. Patients in our cohort with fascial involvement but not deeper invasion of muscle or bone had few complications of Kasabach-Merritt phenomenon, similar to “superficial” lesions involving skin and subcutaneous tissues alone. One theory explaining this is that repeated vessel microtrauma through muscle movement contributes to KMP. Anatomically, vascular lesions in bone may be physically constrained from expansion, altering their behavior compared with muscular lesions. Three cases of bone-only KHE in this study lacked KMP, and infiltrative lesions, including muscle and bone, developed KMP. Recent reports of adult-onset KHE also point to trauma as a possible trigger of the tumor proliferation.[27]

The cutaneous outcomes from KHE include three types of residuum: pseudo-port wine stains with papules, telangiectasias with swelling, and fibrotic subcutaneous infiltrates.[2] Importantly, patients with intramuscular, particularly peri-articular, KHE may develop decreased range of motion, contracture or chronic pain at the involved site over time.[2] Although fascial involvement may not predict KMP, it may conceivably promote scarring that may lead to long-term myofascial pain, this hypothesis warrants further investigation. Response to medical therapies, late effects of medical therapy and recurrence rates of KHE are not well delineated.

Referral bias at our center may under-represent adult patients and milder phenotypes, while over-representing severe, refractory or atypical patient presentations. Additionally, data

collected through referrals depends on the accuracy and quantity of referral data. Due to the severity of disease in infancy and wide geographic spread of patients represented in our cohort, not all patients were seen in person. Therefore, response to therapy and overall outcomes data for KHE lesions are currently lacking and are the subject of continued investigation.

As a major referral center for vascular anomalies we anticipate referrals from the vast majority of Massachusetts patients with KHE, permitting the first estimate of incidence and prevalence for KHE. Extrapolating our prevalence calculation in Massachusetts using the nationwide 2009 U.S. Census data estimating 74.5 million children less than 18 years old[13], we estimate 678 cases of KHE in the United States.

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Abbreviations

(KHE)	Kaposiform hemangioendothelioma
(KMP)	Kasabach-Merritt phenomenon

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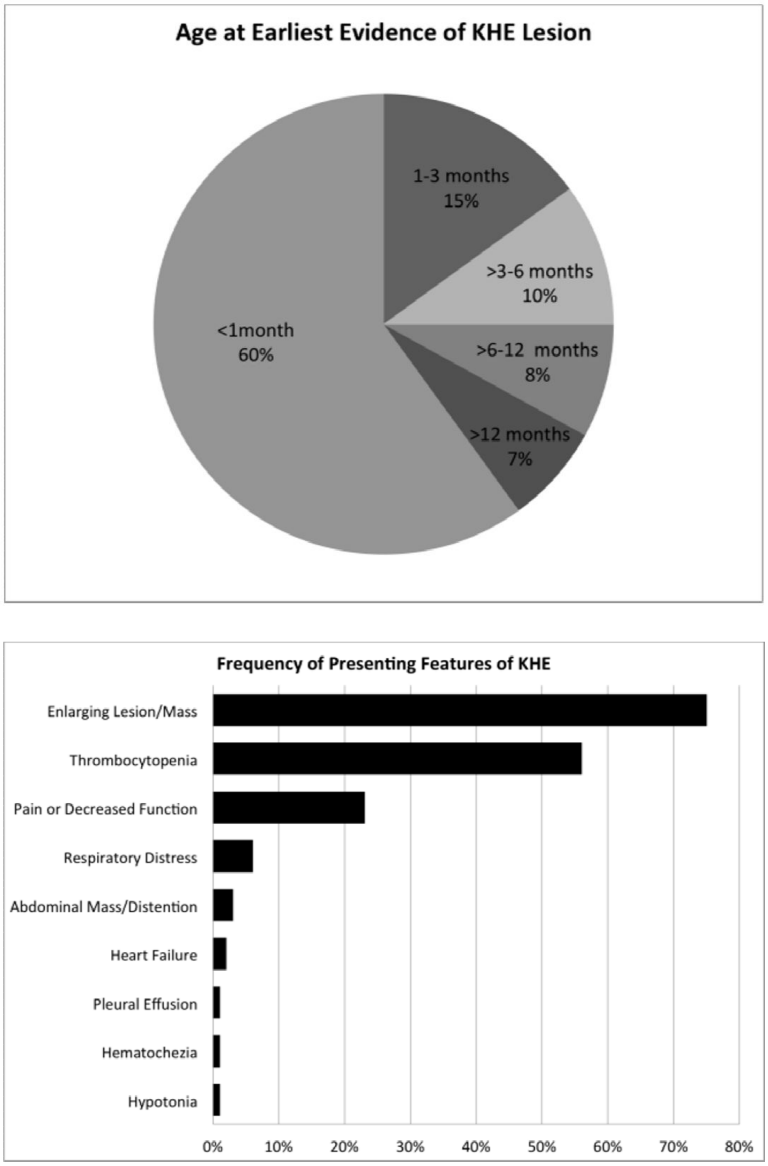

Figure 1.

KHE presentation characteristics. **A,** Age at first sign or symptom of KHE lesion. **B,** Frequency of presenting features of KHE. Individual patients commonly had more than one presenting sign or symptom.

Table 1

Patients with KHE without cutaneous involvement.

Age of Presentation	Presenting Symptoms	Depth of Infiltration	KMP
Birth	Thrombocytopenia/congestive heart failure	Retroperitoneum	Yes
Birth	Petechiae/Thrombocytopenia	Retroperitoneum	Yes
5 weeks	Ascites/respiratory distress	Retroperitoneum	Yes
4 months*	Bloody stool	Retroperitoneum	Yes
6 months	Abdominal mass/Thrombocytopenia	Retroperitoneum	Yes
3 years	Abdominal pain/distention	Retroperitoneum (pancreas)	No
4 months	Enlarging mass	Muscle (gluteus)	Yes
7 months	Hypotonia	Muscle (paraspinal)	No
10 months	Progressive lower extremity weakness	Muscle (paraspinal)	Yes
2 years	Extremity pain/limp	Bone (femur)	No
4 years	Hip pain/refusal to walk	Bone (sacrum)	No
6 years	Back pain	Bone (vertebrae)	No

Histopathology of all cases supported the KHE diagnosis, except one * without available histology.

Table 2

KHE by anatomic site, depth of infiltration, with frequency of KMP and ORs for KMP.

	Lesion Frequency	% Lesion Frequency	KMP	% KMP	OR	95% CI
Anatomic Location						
Extremity	39/107	36%	15/29	52%	**1**	
Truck	21/107	20%	15/20	75%	**2.80**	(0.80, 9.74)
Cervicofacial	20/107	19%	13/17	76%	**3.03**	(0.79, 11.54)
Truck & Extremity	19/107	18%	17/19	89%	**7.93**	(1.54, 40.74)
Cervicofacial & Truck +/− Extremity	8/107	8%	8/8	100%	**15.90**	(0.84, 301.03)
Depth						
Superficial	16/93	17%	5/14	36%	**1**	
Deep	77/93	83%	56/72	78%	**6.30**	(1.85, 21.47)
Bone Only	3/93	3%	0/3	0%	**0.25**	(0.01, 5.72)
Muscle & Bone	52/93	56%	36/50	72%	**4.63**	(1.17, 25.01)
Retroperitoneal	13/93	14%	11/13	85%	**18**	(2.92, 110.96)
Intrathoracic	9/93	10%	9/9	100%		

Table 3

KHE lesions without KMP.

Age of Presentation	Presenting Symptoms	Lesion Location	Treatment Offered
Birth*	Enlarging mass	Head	YES
2 years	Swelling	Head/Neck	YES
4 years	Swelling	Head	YES
1 month	Enlarging mass/FTT	Neck	YES
< 4weeks	Enlarging mass	Upper Extremity	YES
4 months‡	Enlarging mass	Upper Extremity	NO
5 months‡	Enlarging mass	Upper Extremity /Trunk	YES
7 months	Swelling/Cutaneous stain	Upper Extremity	YES
13 months	Pain/Swelling	Upper Extremity	Information Not Available
25 years*	Cutaneous stain/pain	Upper Extremity	YES
48 years	Pain/Swelling	Upper Extremity	YES
Birth	Decreased arm movement/swelling	Trunk	Information Not Available
Birth	Cutaneous stain	Trunk	NO
1 week*	Enlarging mass	Trunk	YES
1 month	Enlarging mass	Trunk	NO
7 months	Hypotonia	Trunk/Retroperitoneum	Information Not Available
14 months	Swelling/pain	Trunk	YES
6 years	Back pain	Trunk	YES
3 years	Abdominal pain/distention	Retroperitoneum (pancreas)	YES
Birth	Enlarging mass	Lower Extremity	YES
Birth	Enlarging mass	Lower Extremity	YES
Birth	Enlarging mass /pain	Lower Extremity	Information Not Available
1 month	Enlarging mass	Lower Extremity	YES
3 months	Ecchymotic stain	Lower Extremity	YES
3 months*	Swelling/ Cutaneous stain n	Lower Extremity	YES
<5 months*	Enlarging mass	Lower Extremity	YES
2 years	Extremity pain/limp	Lower Extremity	YES
4 years	Hip pain/refusal to walk	Lower Extremity	YES

Histology of all cases supported the KHE diagnosis, except two ‡ with “KHE-spectrum” and five * without available histology.