Kaposiform Hemangioendothelioma: Atypical Features and Risks of Kasabach-Merritt Phenomenon in 107 Referrals

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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 A 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 ~0.91 case per 100 000 children. KHE manifested in infancy in 93% of cases, with 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 higher if retroperitoneal or intrathoracic. KHE limited to bone or presenting after infancy did not manifest KMP.

Conclusion An enlarging cutaneous 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. *(J Pediatr 2013;162:142-7)*.

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor typically first seen in infancy as a distinctive cutaneous lesion with ill-defined borders.[1] Prenatal and adult-onset KHE have been described. KHE may be confused with infantile hemangioma due to age of presentation and the presence of a vascular cutaneous lesion. 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-proved 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 T1-weighted magnetic resonance imaging reveals an ill-defined, hypointense/isointense soft tissue thickening, often involving multiple tissue planes.[5] T2-weighted magnetic resonance imaging typically demonstrates a hyperintense mass with reticular stranding in subcutaneous fat. Histopathologic features of KHE include infiltrating nodules and 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."[9] With a 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

KHE	Kaposiform hemangioendothelioma
KMP	Kasabach-Merritt phenomenon

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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 photographs, imaging, clinical history, laboratory data, and/or biopsy results. 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 as a platelet count of <100 000/μL. 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 (H.K.), 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 <18 years old in Massachusetts in 2009[13] and 13 Massachusetts children with KHE in the same year, we estimate the prevalence of KHE as 0.91 case per 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 case per 100 000 children.

Demographics

KHE manifested before 1 month of age in 60% of cases and during infancy in 93% of cases (Figure, A). The median age of initial presentation was 2 months (range, birth to 49 years). 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 patients and 46 female patients).

Presenting Signs and Symptoms

Eighty-nine percent of patients had a cutaneous vascular lesion; no patients had multifocal 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 age of 1 year (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 (58%) of 12 patients developed KMP. Five of these cases were retroperitoneal, all presenting in infants <6 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.

KMP

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 (ie, 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 with KMP were 17 300 and 11 500 platelets/μL, 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 (OR 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 (OR 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