Kaposiform hemangioendothelioma without Kasabach-Merritt phenomenon

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Kaposahemangioendothelioma (KHE), tufted angioma, and possibly other vascular neoplasms. KHE presenting in the absence of Kasabach-Merritt phenomenon is rare, although tufted angioma frequently occurs without thrombocytopenia. We retrospectively reviewed 10 cases of KHE without Kasabach-Merritt phenomenon. The tumors appeared as soft tissue masses with the overlying skin being either normal, erythematous, or violaceous. There were no radiologic or microscopic differences in noncoagulopathic KHE as compared with coagulopathic KHE. Evidence of platelet trapping and hemosiderin deposition was seen histologically, despite normal serum platelet levels. All KHE were less than 8 cm in diameter, suggesting that tumors that grow no larger than this size are less likely to trap platelets in sufficient quantity to cause thrombocytopenia. Our series confirms that KHE appears with a wide spectrum of behavior and response to treatment. The decision as to whether or not to treat a noncoagulopathic KHE should be based on the size and location of the tumor and the possible side effects of therapy. (J Am Acad Dermatol 2005;52:616-22.)

In the 1940s, Kasabach and Merritt1 described a 2-month-old male infant who had thrombocytopenic purpura and a “giant capillary hemangioma” on his left thigh. Thereafter, the double eponym “Kasabach-Merritt syndrome” came to be used for hemangioma with platelet trapping. In the last decade, pathologists began to describe a distinctive vascular tumor, called kaposiform hemangioendothelioma (KHE), that often was associated with thrombocytopenia and lymphangiomatosis.2-4 However, it was not until the 1996 meeting of the International Workshop for the Study of Vascular Anomalies in Rome, Italy, that two clinical centers confirmed independently that thrombocytopenia occurs with the rare KHE and not with common infantile hemangioma.5,6

KHE appears as a single lesion at birth or early infancy in an equal sex ratio.6 There is a predilection for the trunk, extremities, and retroperitoneum, although lesions sometimes occur on the head and neck. KHE is typically an ill-defined, red to purple indurated plaque and looks quite different from infantile hemangioma.5 Histologically, KHE is composed of infiltrating nodules with slitlike or crescentic vessels that are poorly canalized and lined by spindle endothelium cells. Dilated hyperplastic lymphatic channels are sometimes seen, and this has been called “lymphangiomatosis.”4 Magnetic resonance imaging demonstrates a diffuse, enhancing, T2 hyperintense lesion with ill-defined margins. The lesions typically involve several tissue layers, with stranding in the subcutaneous fat, and signal voids, representing involvement of the septal fat by tumor, edema, and feeding and draining vessels.6

Tufted angioma (TA) is another vascular tumor that can manifest profound thrombocytopenia, although most lesions are not coagulopathic. TA can be present at birth or appear in infancy and childhood.7

Abbreviations used:
CS: corticosteroid
KHE: kaposiform hemangioendothelioma
KMP: Kasabach-Merritt phenomenon
TA: tufted angioma
VCR: vincristine
TA manifests as deep red-purple coalescent papules and plaques with ill-defined borders that are typically located on the upper aspect of the back and neck. The microscopic findings in TA are characteristic and consist of tightly packed capillaries located in the mid to reticular dermis in a cannonball pattern. The spindled cells seen in KHE are occasionally observed in TA, and the crescentlike peripheral clefts seen in TA also have been noted in KHE. Enjolras et al noted that TA was more commonly the histologic pattern in early Kasabach-Merritt phenomenon (KMP) or residual lesions, whereas the appearance of KHE was more prominent during active disease. Thus, it is possible that KHE and TA are part of the same neoplastic spectrum. Microscopic differentiation between KHE and TA can be difficult on a small specimen and pathologists often have differing interpretations. Because KHE, TA, and possibly hemangiopericytoma may all be associated with thrombocytopenia, Sarkar et al proposed that the

Table I. Patients with kaposiform hemangioendothelioma in the absence of Kasabach-Merritt phenomenon

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age of onset</th>
<th>Location</th>
<th>Size in diameter (initial and maximum if different)</th>
<th>Appearance</th>
<th>Age at follow-up evaluation</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F</td>
<td>2 y</td>
<td>Left cheek and mandible</td>
<td>1-1.7 cm, to 3 cm</td>
<td>Indurated ecchymotic mass with facial swelling</td>
<td>7 y</td>
<td>Improved on interferon alfa-2b and prednisone, recurred with discontinuation; no response to VCR; controlled on intermittent interferon alfa-2b until 3 y of age and incomplete excision.</td>
<td></td>
</tr>
<tr>
<td>2 F</td>
<td>Newborn</td>
<td>Right knee</td>
<td>1 cm, 3 cm (at 3 mo), to 5.5 cm</td>
<td>Indurated ecchymotic mass</td>
<td>3 y</td>
<td>Treated with CS for 3 mo to 2 y of age; softened and decreased in size</td>
<td></td>
</tr>
<tr>
<td>3 F</td>
<td>Newborn</td>
<td>Mons pubis</td>
<td>1 cm, to 5 cm</td>
<td>Indurated purple plaques with violaceous firm papules</td>
<td>6.5 y</td>
<td>Observation: no change</td>
<td></td>
</tr>
<tr>
<td>4 M</td>
<td>8-10 mo</td>
<td>Left arm intramuscular</td>
<td>6 × 2 cm</td>
<td>Firm mass, limiting elbow extension</td>
<td>15 mo</td>
<td>Observation: no change</td>
<td></td>
</tr>
<tr>
<td>5 M</td>
<td>2 mo</td>
<td>Right thigh</td>
<td>8 × 8 cm</td>
<td>Erythematous patch, changing to an indurated mass with hypertrichosis</td>
<td>3 y</td>
<td>CS and VCR without benefit; swelling associated with coxsackie viral infection; lymphedema dependent on lymphatic massage therapy; leg length discrepancy</td>
<td></td>
</tr>
<tr>
<td>6 M</td>
<td>2 mo</td>
<td>Left parotid area</td>
<td>2 × 2 cm</td>
<td>Firm mass without cutaneous changes</td>
<td>19 mo</td>
<td>Observation: decrease in size</td>
<td></td>
</tr>
<tr>
<td>7 F</td>
<td>Newborn</td>
<td>Left ear and neck</td>
<td>7 × 5 cm</td>
<td>Firm red to purple nodule</td>
<td>2 y</td>
<td>Treated with CS for 1 mo without improvement; VCR weekly for 14 doses with decrease in size and purpura and nontender; decrease in size off VCR</td>
<td></td>
</tr>
<tr>
<td>8 F</td>
<td>2 mo</td>
<td>Volar aspect and back of left wrist</td>
<td>2 × 5 cm</td>
<td>Ecchymotic, warm and tender mass</td>
<td>2 y</td>
<td>Treated with VCR every 3 weeks for 1 y with some regression and decrease in pain.</td>
<td></td>
</tr>
<tr>
<td>9 M</td>
<td>12 mo</td>
<td>Inferior aspect of right scapula</td>
<td>3 × 4 cm</td>
<td>Fixed mass without cutaneous changes</td>
<td>2 y</td>
<td>Observation: decreased in size</td>
<td></td>
</tr>
<tr>
<td>10 M</td>
<td>Infancy</td>
<td>Left knee</td>
<td>2.5 × 1.9 cm</td>
<td>Hyperpigmented nodule with hair</td>
<td>2 y</td>
<td>Observation: no change</td>
<td></td>
</tr>
</tbody>
</table>

CS, Corticosteroid; F, female; M, male; VCR, vincristine.
proper term should be “phenomenon” rather than “syndrome.”

It is well known that TA can occur in the absence of KMP. However, we have also observed children with KHE who never develop thrombocytopenia. We hypothesized that small KHE would be less likely to be associated with thrombocytopenic coagulopathy.

MATERIALS AND METHODS

A total of 9 patients with KHE in the absence of thrombocytopenia were culled from the Vascular Anomalies Center at Children’s Hospital, Boston, Mass, database by diagnosis. These patients were seen from 1990 to 2003. One patient was included from the Department of Dermatology, University of California at San Francisco. We reviewed the medical records, available radiology, and histology from all 10 patients.

RESULTS

Clinical features

The study group was composed of 10 infants and children (Table 1). Tumors were first noted from birth to 2 years of age; they were located on the trunk (n = 2), upper and lower extremities (n = 6), and cervicofacial region (n = 2). The lesions were 1 to 3 cm in diameter at presentation and grew up to 3 to 8 cm in diameter. The most common appearance was a soft tissue mass with cutaneous findings that ranged from an erythematous papule, plaque, or nodule to an indurated, purple, and firm tumor (Fig 1). Two tumors had normal overlying skin. Warmth and tenderness were noted in 8 lesions. Curious signs and symptoms before recognition of a tumor were documented in two cases: patient 4 had diminished mobility of the upper limb and patient 5 had a hyperpigmented nodule with hairs (Fig 2) mimicking a melanocytic neoplasm. None of the lesions ulcerated or evidenced ecchymosis.

Hematologic studies

All 10 patients had a normal platelet level throughout the follow-up evaluation of 6 months to 6 years. Platelet counts were checked at the initial visit and monthly if patients were treated with intravenous vincristine (VCR) or subcutaneous interferon. Only a few patients had D dimer and fibrinogen degradation products checked, which were normal.

Imaging studies

Of 10 patients, 9 had radiographic studies, 8 had magnetic resonance imaging, and one had computed tomography. The one computed tomography study showed multiple sclerotic and lytic areas in the mandible and maxilla with overlying soft-tissue infiltration. The lesion in patient 10 was biopsied without radiologic study.

The initial diagnoses based on these radiologic studies included hemangioma, venous malformation, lymphatic malformation, sarcoma, infantile
fibrosarcoma, neuroblastoma, fibromatosis, KHE, and TA. Magnetic resonance images showed an enhancing, ill-defined, soft tissue mass in all patients (Fig 3). This was a focal lesion in 5 patients, a diffuse lesion in two (patients 5 and 8), and one patient (patient 4) had bony involvement. In 4 patients, the mass predominately involved the subcutaneous fat; in two patients the mass was intramuscular (patients 4 and 9), and in another two patients (patients 5 and 8) all soft-tissue layers were involved. The lesions were hypotense or isointense compared with muscle on T1-weighted sequences, and hyperintense on T2-weighted or inversion-recovery sequences. The signals on T2- and postgadolinium T1-weighted sequences exhibited minor inhomogeneity in 7 patients and were uniform in one. Prominent vascular channels were evident as flow voids in the mass or as linear enhancing channels adjacent to the tumor in 5 patients (patients 3-6, and 7). Cutaneous thickening or enhancing subcutaneous stranding was evident in 4 patients (patients 2, 3, 6, and 8). Patient 8 had both diffuse subcutaneous stranding and focal enhancing nodules. Patient 3 had stranding of the subcutaneous tissues on T2 and postgadolinium images consistent with lymphatic involvement and mixed signal within the tumor on T2 consistent with hemosiderin deposition.

**Histopathologic findings**

Tissue was available from all patients. Histologic sections from 8 cutaneous and 2 intramuscular biopsy specimens (patients 1 and 9) were reviewed. All specimens had characteristic features of KHE.

There were mid and reticular dermal lobules of medium size with round or irregular margins; these lobules also extended directly into the subcutis and along the fibrous septa (Fig 4). The lobules were composed of small round or slitlike vascular channels lined by endothelial cells that were spindled, small with dark nuclei, or plump with vesicular nuclei. Pericytic cells had rather similar cytologic features. There was no nuclear atypia and mitoses were not seen or rare. Microthrombi, often consisting of platelet aggregates only, were noted in all specimens. Hemosiderin was present in all specimens within endothelial, pericytic, and stromal cells. All specimens had foci of dilated channels that were sometimes filled with congealed blood. Empty thin-walled channels, possibly lymphatics, were seen at the periphery of many of the lobules. In patient 2, individual lobules were subdivided into rounded clusters. The connective tissue surrounding the lobules was edematous with reactive fibroblasts and deposition of mucopolysaccharides. The two children who had intramuscular biopsies performed had the same histologic findings as described above.

**Treatment**

A total of 5 patients were treated pharmacologically because of increasing size of the tumor, notwithstanding the absence of thrombocytopenia. Patient 1 had several courses of interferon alfa in combination with tapering prednisone. She had been maintained on interferon alfa because of recurrent expansion whenever the drug was stopped. Patient 2 had a prompt response to oral corticosteroid (CS) with diminished size and firmness of the tumor. Patient 5 failed to respond to oral CS or intravenous VCR. He developed edema associated with a coxsackie infection and has been dependent on massage therapy to improve lymphatic drainage. Patient 7 had 1 month of oral CS therapy without

**Fig 3.** Patient 7: Postgadolinium axial magnetic resonance imaging through level of parotid showing inhomogeneous tissue enhancement that extends along multiple tissue planes with subcutaneous stranding and small flow voids.

**Fig 4.** Patient 6: Variably configured vascular channels and moderate spindling of endothelium and pericytes characteristic of kaposiform hemangioendothelioma. (Hematoxylin-eosin stain; original magnification: ×200.)
shrinkage and subsequently responded to intravenous VCR with continued improvement even with discontinuation of the drug. Patient 8’s tumor regressed on intravenous VCR. The remaining 5 of 10 patients were monitored without pharmacologic treatment. Of 5 tumors, 3 remained stable, and two tumors regressed.

**DISCUSSION**

We were curious as to why some infants with KHE develop thrombocytopenia whereas others do not. We looked at clinical, radiologic, and histologic features that might correlate with platelet trapping. It is generally accepted that KMP is far less likely with TA than with KHE. Wilson Jones et al., who were first to describe TA, later described 20 patients with TA without KMP, but they did not document lesional size. These tumors were most commonly located on the neck, upper aspect of chest, and shoulders. One half of the lesions were noted to have dilated lymphatic channels. Lesional size was not noted in 5 patients with TA and KMP in a report by Enjolras et al.,. These lesions were in similar locations as previously described, and all were associated with enlarged lymphatics.

There is little mention in the literature of possible determinants for the absence of platelet trapping with KHE, such as size, location, or histopathology. Zukerberg et al., described 3 patients with KHE without KMP and lymphangiomatosis. Size was not noted in this primarily histopathologic study. The tumors were all localized to the upper extremities and treated by excision. Mac-Moune Lai et al., reported 5 patients with KHE and two of them did not have KMP. One tumor was 4 cm in diameter located on the trunk and no size was noted for the tumor on the upper extremity. Neither tumor was associated with lymphangiomatosis.

The physical findings, imaging, and histologic features of all vascular tumors described in our series were characteristic of KHE. These noncoagulopathic KHE were similar with regard to a sex ratio, age of onset, and appearance to those with coagulopathic KHE., However, there were some differences in location in our patients as compared with patients with KHE and associated KMP. None of our tumors were located in the retroperitoneum or mediastinum or invaded visceral organs, where outcome is known to be poor., It is possible that small noncoagulopathic KHE could arise in these areas, but do not become clinically evident. Although the numbers are small, 2 of our 10 patients had tumors in the cervicofacial region, as compared with 3 of 22 in the series described by Enjolras et al., and 2 of 21 infants in the series of Sarkar et al., Shim hypothesized that larger vascular tumors are associated with thrombocytopenia more than smaller lesions. A critical size of more than 5 cm for KHE with KMP was suggested by Mulliken and Young., All 21 KHE described by Sarkar et al., had KMP and grew to greater than 5 cm in diameter. In our group of tumors without KMP, the size ranged from 1 to 3 cm at initial presentation. Tumors for patients 1 to 4, 6, 9, and 10 grew to a maximum diameter of 5 to 6 cm. The tumors for patients 5 and 7 enlarged to 7 to 8 cm in diameter. However, KMP has been reported in small (<5 cm) KHE.

In KHE, a platelet count should be checked for evidence of KMP. It would be ideal to also check D dimer and fibrinogen degradation products in all patients for evidence of chronic consumption.

Noncoagulopathic KHE exhibited similar imaging findings to KHE with KMP, including irregular margins, contrast enhancement, extension across tissue planes, stranding, and flow voids. However, these noncoagulopathic lesions tended to be more focal and were more likely to be small and superficial. Diffuse stranding of the subcutaneous fat was less common. Extensive areas of T2 hypointensity, which were believed to be related to hemosiderin deposition, were not seen.

The microscopic features in all tumors was characteristic of KHE, including evidence of microscopic coagulopathy, such as microthrombi, distended lesional vessels (possibly lymphatics) containing congealed blood and deposits of hemosiderin. Only one lesion had lobular subdivisions, typical of TA.

Several authors have described coagulopathic KHE and TA with dilated lymphatic channels., Lymphatic channels seen in KHE and TA may be either part of the vascular tumor or represent an underlying lymphatic malformation., Another possible explanation for the increased number of lymphatic channels is hyperplasia, secondary to lymphatic obstruction by the tumor., KHE without KMP also was noted in two patients with lymphangiomatosis. These authors suggested that KHE could “engraft” on a diffusely infiltrative lymphatic malformation. In their study, dilated lymphatic channels were almost always associated with the noncoagulopathic tumors; however, these were few in number.

KHE (or TA) with KMP has a high mortality., El-Dessouky et al., reported 12% deaths in 155 patients with KMP. Tumors in the viscera, retroperitoneum, neck, and mediastinum are associated with a particularly high mortality., Pharmacologic therapy is always indicated whenever the diagnosis is KHE with KMP and includes CsS, interferon alfa, epsilon-aminocaproic acid, cyclophosphamide, prednisone and epsilon-aminocaproic acid,
pentoxifylline, VCR and heparin. No single regimen has given consistently reproducible results with regard to the decrease in the size of the tumor and correction of thrombocytopenia. Iatrogenic complications, including infection and sepsis, can occur as a result of immunosuppressive therapy. Spastic diplegia can result from interferon therapy. Resection is possible in the rare instance of a small tumor. In addition, arterial embolization may be effective in initiating regression.

Zukerberg et al suggested that the prevalence of KHE is higher than indicated in published accounts because vascular tumors not manifested by coagulopathy and systemic involvement are less likely to be reported and examined histologically. Moreover, these authors hypothesized that localized tumors that were not associated with coagulopathy were likely to be misdiagnosed as unusual hemangiomas. The noncoagulopathic KHE in our series were small, superficial, stable lesions, and two slowly regressed. Some were treated, and it is theoretically possible that some of these might have developed KMP if left untreated. The two largest tumors in our series were treated. However, none of the untreated patients ever evidenced thrombocytopenia.

Treatment of patients with noncoagulopathic KHE is controversial. Based on our observations, KHE with a normal platelet count, limited extent, and without visceral involvement can be safely followed up without treatment. A total of 5 patients in our series did not receive any therapy. Of these patients, 4 remained stable with regard to tumor size during the follow-up period that ranged from 6 months to 6 years. Two patients’ tumors regressed without treatment. One untreated KHE increased in size and became swollen coincident with a coxsackie viral infection. KHE does not fully regress and, in fact, persists after resolution. Poor response to treatment appeared to be associated with residual and long-term complications. We suspect that in addition to the extent and location, unknown biologic differences probably influence the duration and timing of remission of KHE. For each infant, the decision whether or not to treat must be weighed against the risk of coagulopathy with increasing size and possible sequelae of persistent tumor, such as muscle fibrosis and joint contracture.

REFERENCES


