A newborn girl was transferred to this hospital because of a large cutaneous lesion, thrombocytopenia, and anemia.

The infant had been born at another hospital to a 33-year-old woman (gravid 2, para 1). She was delivered by cesarean section at 37 weeks’ gestation. The Apgar scores were 9 at one minute and 9 at five minutes. The weight was 2470 g. A large, dark-red cutaneous lesion, 2.5 mm thick, covered much of the child’s right hemithorax. Physical examination disclosed no other abnormalities. The oxygen saturation was 84 percent while the infant breathed ambient air. She was placed in a hood that initially provided 50 percent oxygen and then 100 percent oxygen. The blood pressure was initially stable, with mean arterial pressures of 39 to 42 mm Hg; the capillary refill was delayed at three seconds. Intravenous normal saline (10 ml per kilogram of body weight) was given. A chest radiograph was normal. Hematologic laboratory values are given in Table 1.

A specimen of blood was drawn for culture, and treatment with intravenous ampicillin and gentamicin was begun; 40 ml of platelets and 30 ml of fresh-frozen plasma were transfused. The skin lesion rapidly became darker, and its thickness increased to about 15 mm. While the infant was being transported to this hospital, the mean arterial pressure was 35 mm Hg and the respiratory rate was stable except for intermittent tachypnea at a rate of about 65 breaths per minute. Thirty milliliters of packed red cells was administered. The oxygen saturation was 93 percent or higher while the patient breathed flow-by oxygen.

The infant’s parents and older sibling were well. The father had had a vascular lesion on the right arm since birth, and a paternal uncle had a similar lesion on the wrist.

On the infant’s arrival at this hospital, the temperature was 37.2°C, the heart rate was 155 beats per minute, and the respiratory rate was 40 to 60 breaths per minute. The blood pressure ranged from 53/33 to 65/37 mm Hg. The oxygen saturation ranged from 84 to 89 percent while the infant was breathing room air and increased to 100 percent with the use of an oxygen hood.

On physical examination, the infant was sleeping comfortably, with minor subcos-
tal retractions. Petechiae were present over the right arm and back. There was a dark-red tumor that involved much of the right hemithorax to the sternum, with the right costal margin almost to the neck, including the latissimus dorsi, right axilla, right breast region and nipple, a third of the right scapula, and the upper third of the right humerus (Fig. 1A and 1B). At its greatest extent, the lesion was 16 by 9 cm, and the thickness was 15 mm. It was not pulsatile, and no bruit, thrill, or fluctuance was detected. The head, neck, lungs, heart, abdomen, and arms and legs were normal, and the results of a neurologic examination showed no abnormalities. Blood levels of glucose, sodium, potassium, and ionized calcium were normal. Other laboratory values are shown in Table 1. In peripheral blood there were 27 nucleated red cells per 100 white cells. There was anisocytosis (3+), macrocytosis (3+), hypochromia (2+), and poikilocytosis (1+). The blood type was A, Rh+, and the results of a screening test for antibodies were negative.

Computed tomographic (CT) scanning of the neck, thorax, abdomen, and pelvis (Fig. 2) disclosed a large extrathoracic soft-tissue mass. There was no evidence of intrathoracic or intraabdominal extension of the lesion.

Ampicillin, tobramycin, and ranitidine were given intravenously, and gentamicin was discontinued. On the second hospital day, the oxygen saturation was 100 percent while the infant was breathing ambient air; oxygen supplementation and blood-product transfusions were discontinued. Petechiae persisted over the infant’s right arm and back. Levels of glucose and thyroxine and the thyroid hormone–binding index were normal. Other laboratory values are shown in Tables 1 and 2.

A magnetic resonance imaging (MRI) scan of the thorax (Fig. 3A) showed a large, superficial subcutaneous mass that was hypointense on T₁-weighted images and isointense on T₂-weighted images. The mass appeared predominantly solid, with no evidence of fluid-filled cavities or invasion of the intercostal space or mediastinum. The underlying bones were normal. Images obtained with the use of the spin–echo technique revealed flow voids in the vicinity of the mass that probably represented en-

### Table 1. Hematologic Laboratory Values.

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Birth</th>
<th>Admission</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>31.7</td>
<td>31.2</td>
<td>35.1</td>
<td>36.8</td>
<td>40.5</td>
<td>40.5</td>
<td>36.2</td>
<td>34.7</td>
<td>30.9</td>
<td>20.4</td>
</tr>
<tr>
<td>White cells (per mm³)</td>
<td>16,900</td>
<td>10,400</td>
<td>17,300</td>
<td>12,800</td>
<td>7,500</td>
<td>7,500</td>
<td>7600</td>
<td></td>
<td></td>
<td>7700</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>60</td>
<td>62</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>29</td>
<td>20</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>7</td>
<td>8</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Band forms</td>
<td>7</td>
<td>8</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>8.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.8</td>
</tr>
<tr>
<td>Platelets (per mm³)</td>
<td>41,000</td>
<td>137,000</td>
<td>112,000</td>
<td>92,000</td>
<td>74,000</td>
<td>29,000</td>
<td>10,000</td>
<td></td>
<td>14,000</td>
<td>6000</td>
</tr>
<tr>
<td>d-dimer (µg/dl)</td>
<td>&gt;8.0</td>
<td>&gt;8.0</td>
<td>&gt;8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>88</td>
<td>38</td>
<td></td>
<td>&lt;35 (before transfusion)</td>
<td>&lt;35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>Normal</td>
<td></td>
<td></td>
<td>13.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial-thromboplastin time (sec)</td>
<td></td>
<td></td>
<td></td>
<td>39.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
gorged veins (Fig. 3B). There was heterogeneous enhancement after the injection of gadolinium (Fig. 3C). The magnetic resonance angiographic and venographic studies revealed no evidence of a large feeding artery, but the cephalic and lateral thoracic veins were enlarged (Fig. 3D). The subclavian and brachial arteries had normal diameters, with no evidence of an arteriovenous fistula. Treatment with prednisone (7.5 mg daily) and phototherapy were begun. The infant was breast-fed without difficulty. The lesion remained stable for the next three days. On the sixth day, the infant lost 2 to 3 ml of blood from a scratch on the skin over the hemangioma. Laboratory values for the 2nd through the 10th day are shown in Tables 1 and 2. Thirty milliliters of platelets was transfused.

On the seventh day, the lesion was unchanged; 30 ml of platelets was transfused. There was no more bleeding from the lesion, but on the next day
the infant passed two bloody stools. Thirty milliliters of platelets and 0.25 unit of cryoprecipitate were transfused. On the ninth day, there was no blood in the stools. Laboratory values on the 10th day are shown in Table 1.

Dr. John B. Mulliken: May we review the CT and MRI images?

Dr. Sudha Anupindi: CT scans of the infant’s neck, chest, and abdomen (Fig. 2), obtained after intravenous administration of contrast material, show a very large, extrathoracic soft-tissue mass that extends from the pectoralis region anteriorly to the region of the scapula posteriorly. There is edema of the subcutaneous tissues but no intrathoracic or intraabdominal extension.

An MRI scan (Fig. 3A) shows that the mass is solid and confined to the superficial subcutaneous
tissues. An image obtained with the use of the fast spin–echo technique shows some small flow voids, most likely representing engorged veins (Fig. 3B). There was heterogeneous enhancement after an injection of intravenous gadolinium (Fig. 3C). A magnetic resonance venogram (Fig. 3D) shows enlarged cephalic and lateral thoracic veins.

In summary, this is a large, superficial, subcutaneous, extrathoracic, solid mass without fluid-filled levels or cavities, with flow voids indicating fast-flowing blood. The arteriogram and venogram showed no enlarged feeding arteries or arteriovenous connections. These findings are characteristic of a vascular tumor. Arteriovenous malformations contain vessels with fast flow but without a soft-tissue mass. Venous and lymphatic malformations comprise fluid-filled cavities separated by septa, with no vessels containing fast-flowing blood.

**Dr. Mulliken:** This case highlights the confusion of terminology in the field of vascular anomalies. The term “hemangioma” has been used for a wide variety of cutaneous and visceral vascular anomalies that differ in both pathogenesis and behavior. The similarity in the appearance of these lesions and the imprecise nomenclature can lead to an incorrect diagnosis and improper therapy. Furthermore, interdisciplinary communication in the field of vascular anomalies has been limited, because each specialty has its own terminology.

In 1996, a meeting of the International Society for the Study of Vascular Anomalies produced a multidisciplinary consensus on a binary classification of vascular anomalies: “tumors” are lesions that arise by endothelial proliferation, and “malformations” are structural abnormalities that exhibit normal (slow) endothelial turnover (Table 3). As in any classification system, there are cases that are difficult to categorize. There are rare examples of infantile hemangioma associated with malformations. Vascular malformations can expand and exhibit endothelial proliferation, usually after trauma, endovascular or operative intervention, or hormonal changes. The infant in the case under discussion had a large, cutaneous vascular lesion, anemia, and thrombocytopenia at birth — the triad of findings known as the Kasabach–Merritt syndrome.

In 1940, Kasabach and Merritt described the case of a two-month-old boy who had thrombocytopenic purpura and a “giant capillary hemangioma” in the left thigh, which had been treated successfully by external-beam irradiation. Over the ensuing 60 years, the double eponym has been used indiscriminately for any coagulopathy associated with a vascular lesion, whether tumor or malformation. The clouds of confusion began to fade in the final decade of the 20th century. In retrospect, there had been a problem of mistaken identity. The Kasabach–Merritt syndrome or coagulopathy does not occur with the common hemangioma of infancy. Instead, it is associated with a more locally aggressive vascular tumor, described by pathologists as kaposiform hemangioendothelioma (KHE). There is little doubt that the infant described by Kasabach and Merritt had KHE, on the basis of their report of the physical findings and the histologic description.

**Table 3. Binary Classification of Vascular Anomalies, According to the International Society for the Study of Vascular Anomalies.**

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma</td>
<td>Slow flow</td>
</tr>
<tr>
<td>Hemangioendotheliomas</td>
<td>Capillary</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Lymphatic</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Venous</td>
</tr>
<tr>
<td></td>
<td>Fast flow</td>
</tr>
<tr>
<td></td>
<td>Arterial</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
</tr>
</tbody>
</table>

**Distinction Between Kaposiform Hemangioendothelioma and Infantile Hemangioma**

The differences between KHE and infantile hemangioma are listed in Table 4. Infantile hemangioma occurs in 1 to 2 percent of neonates and in up to 10 percent of white infants examined at one year of age. The median age of the child when the hemangioma appears is two weeks; however, approximately one third of cases of infantile hemangiomas are present at birth, manifested as an erythematous macular patch, a blanched area, telangiectasia, or a pseudoecchymotic stain. Infantile hemangioma can occur anywhere in the body. Visceral hemangiomas are more common in a child who has multiple cutaneous lesions. The most common locations are the...
head and neck (in 60 percent of affected infants), trunk (in 25 percent), and arms and legs (in 15 percent). Superficial cutaneous infantile hemangiomas are firm, raised, and bright red, whereas the skin overlying a deep tumor often appears normal. Infantile hemangiomas grow rapidly during the first year of life (the proliferating phase), regress slowly from 1 to 7 years (the involuting phase), and leave a variable fibrofatty residuum after 8 to 12 years of age (the involuted phase). Intrahepatic infantile hemangiomas can manifest initially as anemia, congestive heart failure, and minor thrombocytopenia, with a platelet count in the range of 50,000 to 60,000 per cubic millimeter.

About 50 percent of cases of KHE are present at birth; the remainder appear within the first year or, in rare cases, later in childhood. There is no sex predilection. In contrast to infantile hemangioma, KHE typically occurs in the proximal arms and legs and the trunk (including the retroperitoneum), whereas craniofacial lesions are uncommon. KHE is a solitary tumor; it is very rare for multifocal lesions to occur. It is unclear whether KHE arises in the viscera. It can invade a nearby organ — for example, retroperitoneal involvement of the pancreas, mesentery, and porta hepatitis or mediastinal extension into the pericardium, pleura, and thymus.

KHE is typically manifested as a slightly raised subcutaneous mass. Very early in its course, it can be pink and macular or telangiectatic and can be mistaken for infantile hemangioma. However, the overlying skin soon assumes a deep red–purple hue with an advancing ecchymotic margin; it may be shiny, with surrounding subcutaneous edema. The tumor can be indurated or soft, depending on the amount of trapped blood elements and the extent of intraleisonal bleeding. There are scattered petechiae, usually when the platelet levels fall below 10,000 per cubic millimeter. Tumors less than 10 cm in diameter may not cause thrombocytopenia. KHE can infiltrate across planes of tissue into muscle and bone, and there can be lytic bony lesions distal to the tumor. KHE does not completely regress spontaneously, nor does it metastasize.

**OTHER CONGENITAL VASCULAR AND NONVASCULAR LESIONS**

KHE can be mistaken for a congenital hemangioma, which is defined as a vascular tumor that is fully developed at birth. One type, the rapidly involuting congenital hemangioma, is protuberant, hemispherical, violaceous, and firm, often with a central ulceration, depression, or scar; it regresses by the age of 12 to 14 months.\(^8,9\) Other rare congenital hemangiomas do not regress.\(^10\) The incidence of congenital hemangiomas does not differ according to sex; the lesions are located with equal frequency in the head and neck region and in the arms and legs, and they have not been reported to trap platelets. They exhibit fast flow and can be associated with perinatal cardiac overload. In contrast, KHE rarely shunts enough blood to cause cardiac failure.

Infantile fibrosarcoma and other rare neoplasms, such as rhabdomyosarcoma and malignant rhabdoid tumor, can mimic a congenital vascular lesion but do not cause thrombocytopenia or fibrinolysis. A large lymphatic malformation on the trunk could manifest as a shiny, ecchymotic mass with minor thrombocytopenia caused by intraleisonal bleeding.

**ABNORMALITIES IN COAGULATION ASSOCIATED WITH VASCULAR LESIONS**

The differential diagnosis of the coagulopathy requires accurate interpretation of hematologic findings and precise nomenclature (Table 5). Unfortunately, the Kasabach–Merritt label continues to be applied to coagulation abnormalities in adults who...
Table 5. Abnormal Coagulation in Vascular Anomalies. *

<table>
<thead>
<tr>
<th>Feature</th>
<th>Kaposiform Hemangioendothelioma with KMP</th>
<th>Venous or Lymphaticovenous Malformation with LIC or DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>PT or PTT</td>
<td>Normal or ↑</td>
<td>↑</td>
</tr>
<tr>
<td>D-dimer</td>
<td>D-dimer ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Platelet trapping (primary) consumption of fibrinogen (secondary)</td>
<td>Stasis and activation of thrombin on abnormal vasculature</td>
</tr>
<tr>
<td>Management</td>
<td>Pharmacologic therapy, avoid platelets, heparin contraindicated</td>
<td>Sclerotherapy, resection, anticoagulation therapy</td>
</tr>
</tbody>
</table>

* KMP denotes the Kasabach–Merritt phenomenon, LIC localized intravascular coagulopathy, DIC disseminated intravascular coagulation, PT prothrombin time, and PTT partial-thromboplastin time. One downward arrow denotes mildly decreased, two downward arrows moderately decreased, three downward arrows markedly decreased, one upward arrow mildly increased, and two upward arrows moderately increased.

have a slow-flow venous or lymphaticovenous malformation. The confusion can be traced to the use of the obsolete term “cavernous hemangioma” for a venous malformation. The coagulopathy in these slow-flow anomalies is caused by stasis of blood within the abnormal vascular channels, which initiates the generation of thrombin and the local formation of clots. Activated clotting and fibrinolytic factors are found in blood taken from the lesions — evidence that this is a localized intravascular coagulopathy. In a patient with an extensive venous malformation, especially involving the trunk or an arm or leg, any perturbation (e.g., trauma, sclerotherapy, or an operation) can cause disseminated intravascular coagulopathy. The levels of fibrinogen are low, the prothrombin time and activated partial-thromboplastin time are prolonged, and the levels of D-dimer and fibrin degradation products are usually elevated — evidence of ongoing fibrinolysis. However, the platelet count is minimally depressed, in the range of 50,000 to 150,000 per cubic millimeter.

In contrast, an infant with KHE has profound thrombocytopenia (a platelet count of 3000 to 60,000 per cubic millimeter and, on average, less than 25,000 per cubic millimeter). Platelet trapping in the tumor is the primary event, as demonstrated by radioactive labeling and immunohistochemical markers. Hypofibrinogenemia and fibrinolysis are secondary. Usually, the prothrombin time and activated partial-thromboplastin time are normal or minimally elevated. The severe anemia is probably caused by the sequestration of red cells in the tumor. The findings on the peripheral-blood smear in this case do not suggest intravascular destruction of red cells (microangiopathic hemolytic anemia). In the absence of pulmonary involvement, the initial hypoxemia in this child was probably due to hypoventilation caused by the massive tumor that restricted movement of the chest.

**Other Vascular Tumors Associated with the Kasabach–Merritt Phenomenon**

Coagulopathy in which platelet trapping is considered to be the primary event may occur in lesions other than KHE. Thus, the Kasabach–Merritt phenomenon may be a more accurate designation than the Kasabach–Merritt syndrome. Congenital and acquired tufted angiomas have many similarities to KHE, and are probably on the same neoplastic spectrum. Tufted angioma usually appears as an erythematous, slightly tender, indurated macule or plaque in a child under the age of five years. Like KHE, it is typically located along the midline axis of the neck, upper trunk, and extremities. Although tufted angioma usually does not exhibit the Kasabach–Merritt phenomenon, it can occur.

A biopsy is necessary if there is uncertainty about the diagnosis of a vascular lesion. However, in this case, the diagnosis of KHE can be made on the basis of the combination of findings on physical examination, hematologic abnormalities, and findings on radiologic evaluation.

*Dr. Nancy Let Harris (Pathology): Dr. Kerzner, you followed this patient in the intensive care unit. Would you comment on your impressions and on the initial management?*

*Dr. Leslie S. Kerzner (Neonatology): The baby was remarkably stable, despite her coagulopathy. We in the Neonatology Division consulted our colleagues in the Pediatric Hematology and Dermatology Divisions. Most of the discussion centered on whether or not we should administer blood products when the infant had bleeding episodes.*

*Dr. Harris: Dr. Avram also saw this patient early in the course of her hospital stay. What were your thoughts about this case?*

*Dr. Mathew M. Avram (Dermatology): Given the
combination of the large vascular tumor and the profound thrombocytopenia, we thought it was likely that the infant had KHE with the Kasabach-Merritt phenomenon. We recommended withholding further transfusions, since the lesion had enlarged and the platelet count had not improved. We also recommended CT scanning and evaluation of the lesion with MRI studies, rather than a tissue biopsy to establish the diagnosis because of the risk of hemorrhage. Finally, we recommended topical treatment with hydrated petrolatum to prevent skin breakdown or drying, which could cause bleeding from the tumor.

Clinical Diagnosis

Kaposiform hemangioendothelioma with the Kasabach-Merritt phenomenon.

Dr. John B. Mulliken’s Diagnosis

Kaposiform hemangioendothelioma with the Kasabach-Merritt phenomenon.

Pathological Discussion

Dr. Martin C. Mihm, Jr.: KHE was described in 1991 in a series of retroperitoneal tumors. It was later recognized that this lesion, rather than infantile hemangioma, was the pathologic entity responsible for the Kasabach-Merritt syndrome. This lesion has distinctive histologic features.

At low magnification, there are zones of fibrosis containing dilated, thin-walled vessels surrounding and interspersed with large, expansile, coalescing nodules of closely packed spindled cells (Fig. 4A). The cells have pale cytoplasm and oval nuclei with delicate nuclear chromatin, delicate nuclear membranes, and inconspicuous nucleoli (Fig. 4B). The rate of mitosis is variable, but low overall. The cells form small, slit-like spaces filled with red cells in a pattern resembling that of Kaposi’s sarcoma. Mixed with these areas are nests of rounded, epithelioid cells of vascular origin, as well as aggregates of capillaries with round or irregularly shaped lumens containing platelet-rich fibrin thrombi (Fig. 4C).

Hemosiderin granules and hyaline globules are present in the neoplastic cells, as they are in Kaposi’s sarcoma. The nearly ubiquitous presence of abnormal lymphatics either within or at the periphery of the lesion suggests an underlying lymphatic abnormality, often referred to in the literature as lymphangiomatosis.

Immunohistochemical studies have shown that the neoplastic cells express CD34, CD31, and vascular endothelial growth factor receptor 3 (VEGFR-3) and focally factor XIIIa and von Willebrand factor. The cells are negative for factor VIII, Ulex europaeus, and actin and for the erythrocyte-type glucose-transporter protein isoform 1 (GLUT-1). Although the staining with VEGFR-3 has been cited as proof that the cells are of lymphatic origin, the development of antibodies with greater specificity will be needed to resolve this issue.

The ultrastructure of the endothelium appeared abnormal, with focal absence of basal lamina, prominent endothelial cell gaps, and the absence of Weibel-Palade bodies. In general, with the use of a monoclonal-antibody stain against the platelet and a megakaryocyte marker, CD61, platelet-rich fibrin thrombi and platelet trapping are observed. These findings support the interpretation that platelet trapping underlies the coagulopathy.

The most important disorder to rule out in the differential diagnosis of KHE is infantile hemangioma. The latter is characterized by the presence of lobulated masses of proliferating endothelial cells and pericytes that form small red cells containing lumens, without spindled cells or slit-like spaces. The cells of infantile hemangioma, unlike those of KHE, strongly express GLUT-1.

The lesion known as tufted angioma, unlike KHE, is characterized by rounded nodules, or tufts, of densely packed capillaries and pericytes in the middermis, which bulge into and compress large, thin-walled vessels at the periphery of the nodules. Tumors exhibiting gradations between KHE and tufted angioma and containing elements of both lesions have been described. These lesions may represent variations on a spectrum, since both can be associated with the Kasabach-Merritt phenomenon.

KHE differs from Kaposi’s sarcoma in its more prominent lobular pattern, its epithelioid nests, and in the presence of platelet-rich fibrin microthrombi. The plasma-cell infiltrate that is characteristic of Kaposi’s sarcoma is lacking in KHE, as is evidence of infection with human herpesvirus 8, which is commonly associated with Kaposi’s sarcoma.
Kaposiform hemangioendothelioma with the Kasabach–Merritt phenomenon.

Dr. Mulliken: Management of KHE should not focus on the thrombocytopenia. Severe hemorrhage is infrequent, and most children with this disorder do well for months or years with very low levels of platelets (10,000 to 15,000 per cubic millimeter), without bleeding. Platelets should not be given unless the patient is actively bleeding or is being prepared for an operation. Transfused platelets are quickly consumed by the tumor, with a half-life of between 1 and 24 hours. As observed in this infant, KHE expands rapidly after the administration of platelets, probably as the result of intralesional clotting. Furthermore, degranulating platelets release proangiogenic proteins that could stimulate the tumor and increase permeability by vascular endothelial growth factor. Neither drugs directed against platelet aggregation nor antifibrinolytic agents have been reproducibly successful in controlling the coagulopathy or shrinking the tumor. Heparin is contraindicated; clinical and experimental data show that it stimulates tumor growth. Cryoprecipitate treatment should not be given solely to correct a laboratory abnormality. Transfusion of packed red cells is indicated if there is symptomatic anemia.
**TREATMENT OF KAPOSIIFORM HEMANGIOENDOTHELIOMA**

The key to correcting the thrombocytopenia in infants with the Kasabach–Merritt phenomenon is to treat the tumor responsible for platelet trapping. Resection of KHE is rarely possible; however, in the few reported cases of a small tumor involving an arm or leg or the trunk, excision rectified the coagulopathy. Arterial embolization has been effective, but feeder vessels are often small in KHE, and embolization usually provides only temporary improvement. Radiotherapy has been used but should not be considered as first-line therapy because of its late effects on growth and the risk of the development of a secondary malignancy.

Pharmacologic treatments of KHE may include the use of a corticosteroid, interferon alfa-2a, vincristine, and cyclophosphamide. No single agent has been shown to be consistently effective. Because of the slow and unpredictable response to therapy with a single drug, there is a tendency to administer drugs in combination. However, there are no prospective studies showing that multimodality therapy has improved efficacy.

For this child, I would begin with a trial of a corticosteroid, at a starting dose of 2 to 3 mg per kilogram of body weight per day; however, in my experience, the response rate is only about 10 percent. I would measure urinary basic fibroblast growth factor levels, since they might reflect the activity of the tumor and possibly its responsiveness to interferon therapy. If after two weeks there is no improvement, and if the urinary basic fibroblast growth factor level is high, I would taper the corticosteroid and administer interferon alfa-2a or interferon alfa-2b. The response rate to interferon is 50 to 60 percent; however, the drug can cause reversible spastic diplegia in infants, so careful observation is necessary. If there is no response to interferon or if the initial urinary basic fibroblast growth factor level is low, I would switch to vincristine.

**MORTALITY AND MORBIDITY**

Infants with KHE and the Kasabach–Merritt phenomenon can die from hemorrhage (intrapleural, intraperitoneal, or intracranial), sepsis, or invasion of vital structures. The mortality rate ranged from 12 percent in 153 cases collected from the world literature to 24 percent in a small series. Retroperitoneal involvement has been associated with a poor outcome, although the prognosis may improve in the future as a result of better hematologic management and the availability of new drugs.

KHE can undergo partial spontaneous regression, complicating the analysis of the effectiveness of pharmacologic therapy. However, one important feature of this lesion is that it usually does not completely disappear, even after treatment. Biopsy specimens obtained from regressed or treated lesions may show residual viable tumor cells.

**Dr. Harris:** Dr. Ezekowitz, can you tell us how you cared for this patient?

**Dr. R. Alan B. Ezekowitz:** One of the most difficult problems in caring for children with this disorder is to know when to give platelets and blood products. We recognized that if the platelet count dropped below 5000 per cubic millimeter there was an increased chance of intracranial bleeding, but this risk needed to be weighed against the fact that infused platelets rapidly pool within the lesion and may cause proliferation of the endothelial cells. This infant had received platelets before her transfer to this hospital in order to minimize the possibility of intracranial bleeding. We administered platelets and cryoprecipitate because of episodes of bleeding, either from the tumor or from the gastrointestinal tract. The principle was to treat the patient, not the numbers.

Our approach to treating the underlying lesion was based on the principles of treating a malignant tumor. We began with a trial of a corticosteroid, but it was clear by day 9 that this treatment was not effective. We therefore tapered the corticosteroid and began a regimen of combination therapy, alternating cycles of cyclophosphamide (10 mg per kilogram given intravenously for three days) and vincristine (0.1 mg per kilogram given intravenously on alternate weeks) and interferon alfa (3 million units per square meter of body-surface area given subcutaneously each day). Interferon alfa-2a has been found to limit angiogenesis in vitro by inhibiting endothelial-cell migration. It was first used to treat a child with pulmonary hemangiomatosis. Subsequently, there have been other reports of its use in the treatment of life-threatening vascular tumors.

We planned to repeat this cycle three or four times and determine whether there was a clinical response as indicated by improvement in the coagulopathy, an increase in the platelet count, and stability in the growth of the lesion or its regression. Within four days after the start of interferon thera-

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py, the fibrinogen level rose to 47 mg per deciliter. The platelet count rose to 9000 per cubic millimeter on the 6th day of treatment, and at the time of the infant’s discharge on the 32nd hospital day, it was 25,000 per cubic millimeter. In addition, the lesion had begun to regress. After discharge, she received maintenance therapy with daily interferon for six months. One month after discharge, the platelet count was 137,000 per cubic millimeter. Six months after discharge, there was almost complete resolution of the tumor, with some residual staining (Fig. 1C). Her growth and development appeared to be appropriate at one year of age, and she has had no apparent neurologic complications from the interferon treatment.

REFERENCES

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