

Hemangiomas: Update on Classification, Clinical Presentation, and Associated Anomalies

Maria Garzon, MD, New York, New York

Infantile hemangiomas occur in 10% of children and are 3 times more common in female infants.^{1,2} The majority of hemangiomas are small, superficial tumors that require little, if any, treatment. During the last several years, new information regarding the classification, presentation, associations, and differential diagnosis of hemangioma has emerged and altered the management of these tumors. The purpose of this article is to briefly review some of these clinically relevant findings. A discussion of the pathogenesis and management of these potentially problematic tumors is beyond the scope of this article, but these topics have been addressed in several excellent reviews.²⁻⁵



FIGURE 1. Macular telangiectatic hemangioma at 2 months.

Update on Classification—Hemangiomas Versus Vascular Malformations

In 1982, Mulliken and Glowacki⁶ published a biologic classification for vascular birthmarks that distinguished hemangiomas from vascular malformations based on clinical characteristics, histopathology, and biologic behavior. Takahashi et al⁷ further investigated the cellular differences in 1994 and confirmed the distinct biologic characteristics of these 2 types of lesions.

Hemangiomas are proliferating tumors composed of endothelial cells that grow rapidly in the first year of life and spontaneously involute as childhood ensues. They are classified as superficial, deep, or combined hemangiomas based on their clinical appearance. Hemangiomas demonstrate increased cell turnover and express markers of proliferation, including proliferating cell nuclear antigen, type IV collagenase, vascular endothelial growth factor, and

basic fibroblast growth factor. Tissue inhibitor of metalloproteinase, which acts to inhibit blood vessel formation, is expressed during the involuting phase.

Vascular malformations are structural anomalies believed to represent errors in the normal vascular morphogenesis that persist throughout a patient's lifetime. Vascular malformations are composed of anomalous vascular channels demonstrating normal levels of endothelial cell turnover.⁷ Prior to the acceptance of this classification, many types of vascular anomalies, including those that were clearly malformations, were referred to as hemangiomas. By adopting this new classification, clinicians have been able to more accurately address prognosis and therapy. Moreover, recognition of the differences between these 2 types of vascular birthmarks has enabled researchers to investigate their pathogenesis more precisely.

The biologic classification was updated in 1996 by Mulliken and other members of the International Society for the Study of Vascular Anomalies (ISSVA) to reflect the results of their studies.⁴ Investigations indicated that vascular tumors resembling common hemangiomas could arise during infancy, but these lesions were distinct from hemangiomas in

Dr. Garzon is from the Department of Dermatology, Columbia University College of Physicians and Surgeons, New York, New York. REPRINT REQUESTS to Department of Dermatology, Columbia University, 161 Fort Washington Avenue, 14th Floor, New York, NY 10032.



FIGURE 2. Characteristic proliferation in portions of the hemangioma at 4 months.

their clinical characteristics, histopathologies, and biologic behaviors. Consequently, the ISSVA or modified biological classification now defines both vascular tumors and vascular malformations. Vascular tumors include common hemangioma of infancy, kaposiform hemangioendothelioma (KHE), tufted angioma hemangiopericytoma, spindle-cell hemangioendothelioma, and pyogenic granuloma. Vascular malformations are divided into simple or combined lesions and are further categorized based on their predominant anomalous channels: capillary, lymphatic, venous, or arterial.

Update on Clinical Presentation

Classic descriptions of hemangiomas often state that they are rarely present at birth, but usually become apparent within the first few weeks of life. Precursor lesions frequently are unrecognized within the first few days of life. Early authors described these precursors as telangiectatic macules, areas of pallor, or ecchymoses.^{8,9} The telangiectatic macules may be mistaken for capillary malformations on an initial assessment, but subsequent proliferation confirms the diagnosis of hemangioma (Figures 1 and 2). Superficial ulceration in the absence of clinically apparent hemangioma is an unusual precursor that may precede the development of a common hemangioma.¹⁰

An uncommon subset of fully developed hemangiomas that may be recognized on routine prenatal ultrasonography but that are rarely present at birth are called *congenital hemangiomas*. Congenital hemangiomas undergo proliferation during fetal life. At birth, they are fully developed vascular masses that present as violaceous tumors with ectatic veins, gray-violaceous tumors with overlying telangiectasia, or pale halo or flat infiltrative lesions with an overlying violaceous discoloration of the skin. Accelerated, spontaneous involution is a frequent occurrence in these tumors.^{4,11} It is necessary to differentiate con-



FIGURE 3. Kasabach-Merritt syndrome associated with tufted angioma (photo courtesy of I.J. Frieden, MD).

genital hemangiomas from other vascular tumors or sarcomas that may arise in the neonatal period. The diagnosis of congenital hemangioma is usually made on physical examination, but may require the assistance of magnetic resonance imaging (MRI) and Doppler ultrasonography.

Other uncommon presentations of the common hemangioma include superficial hemangiomas, which resemble capillary malformations, and deep subcutaneous masses with normal overlying skin. The latter contrasts with the majority of deep hemangiomas that are associated with bluish discoloration, dilated veins, or superficial telangiectasia. MRI evaluation and Doppler ultrasonography may help to confirm a diagnosis.¹²

Associated Anomalies

The majority of syndromes reported with vascular birthmarks occurs in association with vascular malformations. Familiar eponyms assigned to these associations include Sturge-Weber and Klippel-Trenaunay syndromes. It is uncommon to see hemangiomas associated with malformations, but it is essential to recognize the situations in which this may occur.

Large cervicofacial hemangiomas can be associated with a variety of intracranial anomalies, including structural malformations of the posterior fossa. These malformations include the Dandy-Walker malformation, arachnoid cyst, enlarged cisterna magna, and atrophy or hypoplasia of the cerebellum.¹³ Anomalies of the internal carotid artery, posterior or anterior cerebral artery, persistent trigeminal arteries, and coarctation of the aorta also occur in this setting.¹⁴ Patients with large facial hemangiomas and intracranial structural vascular anomalies may demonstrate progressive occlusive arterial changes and cerebral infarction.¹⁵

The acronym PHACE, which refers to Posterior fossa malformations, Hemangiomas, Arterial anom-

alies, Coarctation of the aorta and cardiac defects, and Eye abnormalities,¹⁶ has been proposed to describe the setting in which numerous malformations coexist with large facial hemangioma. Sternal agenesis, hypoplasia, or supraumbilical raphe may also occur concomitantly with large facial hemangiomas.¹⁷ Hemangiomas arising on the lower face in what has been described as a “beard” distribution may herald subglottic involvement and potential airway compromise. Large problematic facial hemangiomas appear to arise more commonly in female patients, which shows an even greater female predilection than hemangiomas in general.^{18,19} Hemangiomas arising over the lumbo-sacral spine may also be associated with congenital abnormalities of the gastrointestinal and genitourinary systems. In addition, they may herald underlying spinal dysraphism.^{20,21}

Kasabach-Merritt Syndrome and Vascular Tumors

Two recent reports^{22,23} support the finding that infants with Kasabach-Merritt syndrome do not have ordinary infantile hemangiomas. This syndrome, which is characterized by a rapid enlargement of “hemangioma” thrombocytopenia and a consumptive coagulopathy, is most commonly associated with 2 rare vascular tumors, KHE and tufted angioma (Figure 3).

KHE is a rare vascular tumor that often presents in the first few months of life, but it may also appear later. Although it has previously been reported under a variety of names, including hemangioma with Kaposi's sarcomalike features, Kaposilike infantile hemangioendothelioma, locally metastasizing vascular tumor, or hemangioendothelioma, KHE is the preferred term for this entity.²⁴ The true incidence of this tumor is unknown, and it may be more common than reported because of the confusion in identifying common hemangiomas. KHE often presents as a rapidly enlarging mass that arises on the trunk or extremities or in the retroperitoneum. Clinically, KHE arises almost equally in males and females, in contrast to the predominance in females of common hemangiomas. When it arises in the skin and soft tissues, it is often an infiltrative, edematous, purpuric plaque that may enlarge rapidly. The period of active proliferation may extend beyond the first several months of life, which also differs from the common hemangiomas. Moreover, KHE often responds poorly to the treatments that have been effective in the treatment of common hemangiomas, such as corticosteroids and interferon- α . The histologic characteristics of KHE are distinct from common hemangioma. The tumor is predominantly composed of spindled endothelial cells that show minimal atypia and rare mitoses and

line a slitlike lumen. Often, KHE extends beyond the deep dermis into the subcutaneous fat and is accompanied by lymphangiomatosis.²⁴

Enjolras et al²² reviewed 22 cases of patients with Kasabach-Merritt syndrome. Histopathologic specimens were available for 15 of the cases and none of the patients demonstrated features of common hemangioma in infancy. Moreover, histopathology revealed KHE or tufted angioma in all of the cases.²² Sarkar et al²³ reviewed 21 cases of patients with Kasabach-Merritt syndrome for which histopathologic specimens were available for 16 patients. Although all of the patients were reported to have KHE, none demonstrated the clinical or histologic features of common hemangioma. KHE may also display a distinctive pattern on MRI.²³ The first case of Kasabach-Merritt syndrome²⁵ was reported to have similar clinical features and the histopathology described “spindled-cells,” which is not a feature of common hemangioma. The natural history of this tumor is unpredictable. Cases that are associated with Kasabach-Merritt syndrome may respond poorly to treatment, and mortality rates between 20% and 30% are often cited.² Improvement may occur after successful treatment or spontaneously after several years of life-threatening coagulopathy.²¹⁻²⁴

Tufted angioma, which has been associated with Kasabach-Merritt syndrome, is another rare vascular tumor that may be mistaken for a common hemangioma. This tumor is more common in older infants and children, but congenital cases have occurred.⁴ Tufted angioma classically presents as erythematous indurated plaques, often on the limbs. The histologic features are characteristic. Discrete nodules of capillary vessels are distributed in the dermis in a “cannonball” pattern. The nodules are surrounded by clefts, giving rise to what has been described as a glomerular-like appearance.⁴ The natural history of tufted angioma is unpredictable. Lesions may regress spontaneously without treatment, others demonstrate a protracted course, and some are complicated by Kasabach-Merritt syndrome and require aggressive therapy.

The management of vascular lesions in the newborn is a challenge. The classification described in this brief review provides a useful framework for evaluating these lesions.

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