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Childhood Cutaneous Hemangiomas

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An hemangioma is a common benign growth of vascular endothelium that may have multiple clinical manifestations. Either identified at birth or shortly thereafter, hemangiomas have both proliferative and involutional phases. Certain varieties are associated with congenital anomalies. Numerous therapy options are discussed.

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Hemangiomas, the most common soft tissue tumors of infancy, are benign tumors of vascular endothelium, with a characteristic growth phase that consists of endothelial proliferation and hypercellularity for 8 to 18 months, followed by a spontaneous involutional phase usually over the next 5 to 8 years.[1] The exact classification of lesions as hemangiomas versus vascular malformations has been debated. Some distinguish hemangiomas from vascular malformations. Whereas vascular malformations are present at birth, subsequently grow with the child, and possess a normal rate of endothelial cell turnover, hemangiomas may or may not be present at birth (generally forming within the first few months of life) and have a distinctive proliferative phase characterized by high endothelial cell turnover followed by an involutional phase.[2] Occasionally, certain patients have both hemangiomas and vascular malformations.[3]

Epidemiology

Hemangiomas are the most common soft tissue tumors of infancy, with an incidence of 10% to 12% in white children by one year of age.[4] Hemangiomas are present at birth in 55% of cases, with the remaining cases forming within the first month of life.[5] They range from several millimeters to 5 cm or larger, occasionally affecting a large surface area. Hemangiomas are usually (80%) single lesions, primarily involving the head and neck (60%) or extremities (15%).[6] However, hemangiomas may occur in any organ system. Their pathogenesis is not completely known. Elevated levels of the angiogenic stimulators, basic fibroblastic growth factor and vascular endothelial growth factor protein, have been found in proliferative hemangiomas.[7] There is a 3-fold greater incidence of hemangiomas in females,[6] and a higher incidence is found in premature infants. Hemangiomas commonly are found in white infants but can affect all groups. A known family history of hemangiomas may be evident in 10% of affected children.[8] Cavernous hemangiomas can occur sporadically or in a familial pattern, with a presumed autosomal-dominant inheritance pattern with variable penetrance. In a study of 52 families, Siegel et al[9] discovered a genetic cause for anticipation of age (the process where the mean age of onset of disease decreases over subsequent generations) but no anticipation in disease severity (severity did not worsen with subsequent generations) in familial cavernous hemangiomas of the central nervous system. Multiple lesions are more common familially (70%) as opposed to sporadically (10%).[10,11] A 3-fold greater incidence of hemangiomas is found in the offspring of women who underwent chorionic villus sampling (particularly transcervical) versus amniocentesis during pregnancy.[12] Chorionic villus sampling may result in embryonically detectable hemorrhagic lesions of the fetus following placental disruption.[13] It has been speculated that hemangiomas may be predisposed to form on those hemorrhagic lesions.[12]

Clinical Manifestations

The clinical presentation of hemangiomas varies depending on their type. Hemangiomas may be

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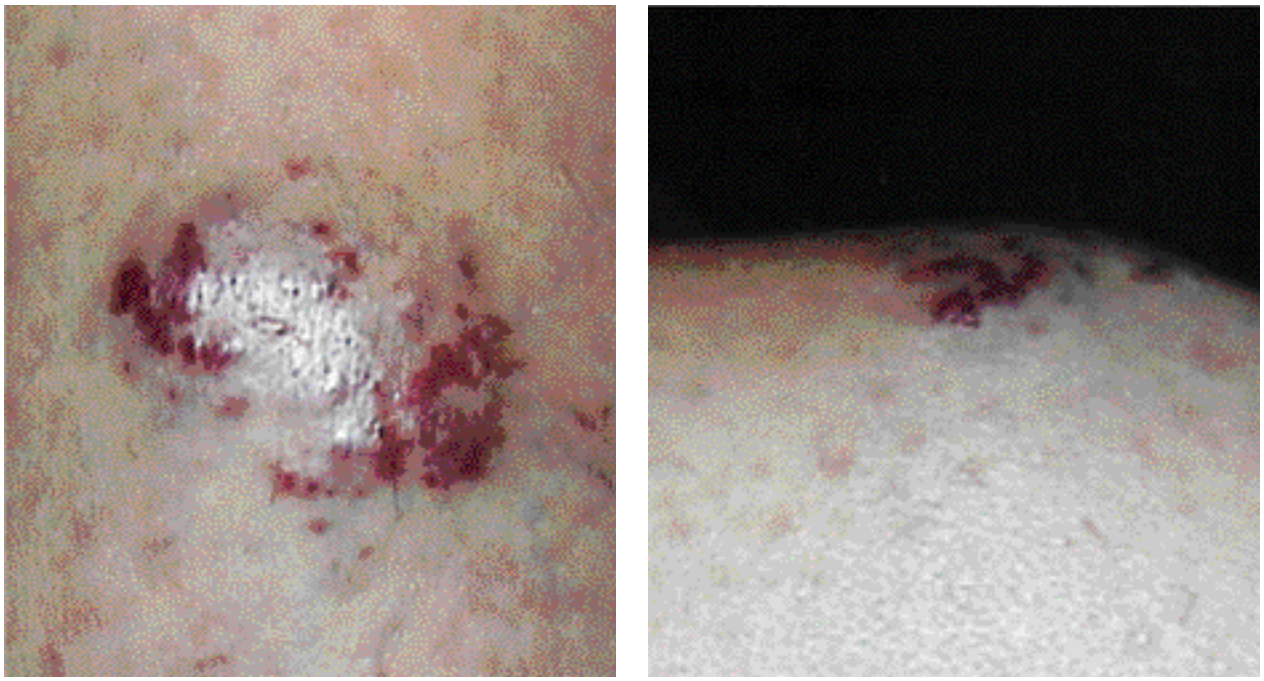

Figure 1. Vascular malformation of the leg (A and B). Labeled as a cavernous hemangioma when the patient was an infant, the lesion was an erythematous macule present at birth that subsequently grew with the patient.

superficial (capillary), deep (cavernous), or mixed (capillary-cavernous). Fifty to sixty percent of hemangiomas are capillary, 25% to 35% are capillary-cavernous, and 15% are cavernous.[14] At birth, lesions vary from erythematous to pale macules, birthmarks resembling ecchymoses, or localized telangiectasias, all of which enlarge, usually within the second to fourth weeks of life.[15,16] Congenital hemangiomas—defined as fully formed at birth—usually involute more rapidly (within 14 months) than other forms of hemangiomas,[17] which take several years to involute.

Superficial (capillary) hemangiomas are the most common. Composed of narrow blood vessels that are lined with minimal endothelium, these hemangiomas generally occur on the skin and less often in the viscera. They vary from soft, bright-red to purple nodules or plaques that are present at birth, or appear shortly afterward, subsequently grow, and spontaneously involute usually by the fifth year of life. Involution, initially marked by a change in color to white gray, leaves behind either no evidence of the former hemangioma or residual hypopigmentation, telangiectasias, or atrophy. Certain deeper lesions may not involute completely. Numerous capillary hemangiomas of infancy (diffuse hemangiomatosis) have been linked with hemangiomas in other visceral organ systems, including the liver, central nervous system, and gastrointestinal tract. The distinction between capillary and cavernous hemangiomas is based on the depth of the lesion.

Deep (cavernous) hemangiomas appear as dome-shaped, firm, rubbery, blue/purplish subcutaneous masses without an overlying superficial component (Figures 1 and 2). In the past, it was felt that large, rapidly expanding cavernouslike tumors rarely caused platelet sequestration and destruction resulting in thrombocytopenia, hemolytic anemia, and disseminated intravascular coagulation (the Kasabach-Merritt [K-M] syndrome),[18] which has no female preponderance[19] and a 20% mortality rate.[20] Recently, however, it was shown that patients with this syndrome have either kaposiform hemangioendotheliomas or tufted angiomas and that the K-M syndrome is not associated with classic hemangiomas.[19,21]

Mixed (capillary-cavernous) hemangiomas appear as red dermal tumors, with an underlying blue, flesh-colored subcutaneous mass.

Diagnosis is based on clinical presentation and history. Doppler ultrasound studies may reveal a high-flow pattern. Computed tomographic (CT) scans or, preferably, magnetic resonance imaging (MRI) is also helpful. Because of the risk for bleeding, biopsies are rarely performed to elucidate the diagnosis. Complications consist of ulceration

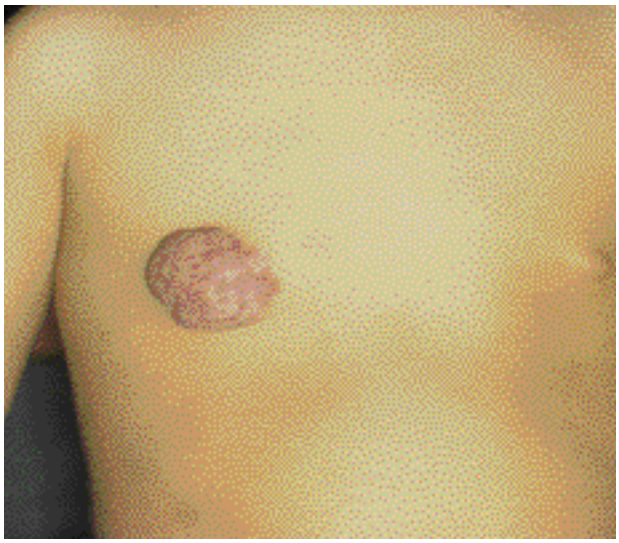

Figure 2. Large childhood hemangioma on the chest.

(often preceded by pain), secondary infection, hemorrhage, scarring, distortion of vital anatomic structures, and, rarely, mortality secondary to high-output cardiac failure (usually from visceral hemangiomas, primarily the liver). Hemangiomas may obstruct vision or the airway based on size and location. Multiple cavernous hemangiomas of the skin may be associated with neurologic abnormalities (seizures, intracerebral bleeding, and signs or symptoms of an intracranial mass).[22] If a patient has numerous cutaneous hemangiomas and either a personal or family history of neurologic symptoms, an examination of the patient and his or her family should be performed to rule out familial cavernous hemangiomatosis.[22] Intracranial cavernous hemangiomas are present in 0.5% to 0.7% of the population.[11]

Certain associations may be seen between hemangiomas and major congenital anomalies. Patients with large hemangiomas on their face and neck may have associated abnormalities. This usually occurs in females (9:1) and has been described as the PHACE syndrome (posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities).[23] Some believe that PHACE should be called *PHACES* because hemangiomas may occur in association with supraumbilical raphe, sternal clefting, and sacral and genitourinary defects.[24] Certain locales of hemangiomas warrant further diagnostic tests. For instance, lumbosacral hemangiomas should be evaluated with MRI because they may be indicative of spinal malformation. Hemangiomas located in the "beard" distribution (chin, lips, mandible, and neck) have a 60% incidence of associated hemangiomas of the airway, leading to airway occlusion,[5,25,26] and warrant visualization. Periorbital hemangiomas necessitate an ophthalmic examination because of the risk for the deleterious effects to vision secondary to amblyopia.

Histology

Hemangiomas are characterized by well-formed vascular spaces filled with blood and lined with endothelium, contained within the superficial and, occasionally, deep dermis. Capillary hemangiomas ordinarily are lobulated, unencapsulated clusters of densely packed, thin-walled capillaries that may be filled with blood or thrombosed.[27] Cavernous hemangiomas are well-defined masses of cavernous vascular areas filled with blood and commonly contain intravascular thromboses with dystrophic calcification.[27]

Differential Diagnosis

Hemangioma must be distinguished from tufted angioma, port-wine stain, venous malformation, lymphatic malformation, arteriovenous malformation, kaposiform hemangioendothelioma, adrenal carcinoma, pyogenic granuloma, nasal glioma, myofibromatosis, spindle cell and epithelioid cell nevi (Spitz), Dabska tumor, and dermoid cyst.[14,28,29] MRI and, less effectively, CT may be useful in delineating hemangiomas from vascular malformations.

Treatment

In the past, radiotherapy and surgical excision were the treatments of choice. Now, the theory is "to do no harm," adopting a watch-and-wait attitude. Regular follow-up with serial photographs to monitor for signs of change or involution, in addition to patient/family education regarding the natural course and evolution of hemangiomas, should be performed. Many treatments are available for hemangiomas, depending on the type, including both medical and surgical options. The dilemma facing physicians is who requires treatment. Unfortunately, we cannot predict how large a lesion will grow, when it will cease proliferating, and when and how effectively it will involute. Treatment should be based on the lesion's location, the presence of obstruction of the orifices, the cosmetic concerns, and the size, as well as the age of the patient.[30] Ultimately, the benefits and risks of treatment must be weighed on an individual basis.

Medical treatment options include topical, intralesional, and systemic glucocorticoids and interferon (IFN) alfa-2a and -2b. Both intralesional

glucocorticoids (3–5 mg/kg triamcinolone every 4 to 6 weeks, for a total of 1 to 5 times) and systemic corticosteroids (2–3 mg/kg prednisolone or prednisone for weeks to months) have been effective.[31] However, 70% of massive hemangiomas are not responsive to steroids.[32] Newer treatments, consisting of IFN alfa-2a or -2b (inhibitors of angiogenesis) in subcutaneous doses of 1 to 3 mU/m^2 per day for 8 to 18 months, also have been effective[32-34] in steroid-resistant cases. For life-threatening hemangiomas, 18 of 20 patients had a regression of over 50% with IFN alfa-2a therapy in subcutaneous doses of 3 mU/m^2 per day for 7.8 months, on average.[1] Side effects were transient and included fever, neutropenia, and skin necrosis.[1] The utility of IFN alfa-2a was shown in 4 of 5 patients with massive life-threatening hemangiomas. However, IFN alfa-2a may result in up to 20% of infants subsequently developing spastic diplegia.[35,36] Similar studies reveal the effectiveness of IFN alfa-2b, with and without concomitant use of granulocyte-macrophage colony-stimulating factor.[34,37] For ulcerated hemangiomas, topical care consisting of cleansing, topical or oral antibiotics, compresses, dressings, and pulsed dye laser therapy is effective.

Surgical treatment possibilities include cryosurgery, various forms of laser surgery, and surgical excisions. Cryosurgery provides good responses. Two forms include the use of liquid nitrogen and Kryomed®, a newer form that does not require cooling agents. Kryomed has been very effective, especially in capillary hemangiomas. However, cavernous hemangiomas proved to be considerably more difficult to treat using Kryomed. One study revealed a good response in one cavernous hemangioma but was ineffective in another one after 6 treatments.[38]

Numerous laser treatments have been tried and proven to be successful alternatives for superficial hemangiomas and for reducing erythema. The use of lasers for cosmetic purposes is offered to children who are beginning school. Several types of lasers exist, including flashlamp pulsed dye,[39,40] argon, copper, Nd:YAG,[41] and KTP.[42] One study of 100 pediatric patients with capillary-cavernous hemangiomas treated with intralesional laser therapy revealed no difference in effectiveness between Nd:YAG and KTP lasers. Both procedures, though not widely available, were highly effective in decreasing the size of even very large cavernous lesions.[42] Surgical excision in early childhood is appropriate if it is assumed that resection is inevitable. The scar would not be larger than if the excision was done at a later date, and the scar could be concealed easily.[43]

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