Vascular Anomalies: Hemangiomas

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Learning Objectives: After studying this article, the participant should be able to: 1. Differentiate clinically between hemangiomas and vascular malformations. 2. Describe indications and options for the treatment of hemangiomas. 3. List potential complications of hemangiomas.

Mulliken and Glowacki categorized vascular anomalies as either hemangiomas or malformations, with the former being the most common tumor of infancy. Despite distinct clinical, radiologic, and histologic findings, the two major types of vascular lesions are often confused. This complicates both patient care and interpretation of the medical literature. A thorough understanding of the presentation, natural history, treatment, and complications of vascular tumors (hemangiomas) and vascular malformations is essential to their proper management. A comprehensive review outlining the diagnosis and treatment of hemangiomas is presented. (Plast. Reconstr. Surg. 110: 572, 2002.)

Classification

Vascular anomalies are common, yet challenging, and their management is made more difficult by an inconsistent nomenclature. Numerous classification systems have been proposed over the years that reflected the understanding of disease processes at the time. These may be characterized as descriptive, anatomic, pathologic, embryologic, clinical, or biological in nature. Early methods of classifying vascular birthmarks were descriptive and likened the lesions to often-encountered items (e.g., foods). In the midnineteenth century, Virchow proposed a histopathologic classification based on the size and appearance of the constituent vessels. This system categorized vascular lesions as “angioma simplex,” “angioma cavernosum,” or “angioma racemosum” and was later extended to lymphatic lesions by Wegner. Further attempts at pathologic and embryologic classification were made, but they failed to correlate with clinical observations. In 1976, Edgerton proposed a clinical classification of angiomas based on their natural history. He divided angiomas into three categories: those that remain essentially unchanged if untreated, those that may be expected to resolve spontaneously, and those that progress or cause growth of adjacent structures. Although this scheme recognized the range of clinical outcomes, it did not identify the underlying basis that accounted for these observed differences. The biological classification of Mulliken and Glowacki, in 1982, defined the fundamental distinction between the two major types of vascular anomalies. Their system divided vascular anomalies into either tumors (principally hemangiomas) or malformations based on clinical and histologic findings. Subsequent radiologic and biochemical studies have confirmed the validity of their classification.

Biological Classification

Hemangiomas are proliferative lesions characterized by increased endothelial cell turnover. These tumors usually appear after birth, grow rapidly, and involute over the years. Vascular malformations are errors in morphogenesis populated by a stable, mature vascular endothelium. Although not always obvious, these are present at birth, grow commensurately with the child, and do not involute.

Many authors do not adhere to these definitions, so the medical literature is still replete with reports of “hemangiomas” that are actually malformations or a potpourri of vascular anomalies. It behooves all physicians involved in the care of vascular anomalies to critically evaluate study results.

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Hemangiomas are the most common tumor of infancy, occurring in up to 12 percent of Caucasian children by the age of 1 year.\textsuperscript{2,5,6} They are less common in African-Americans and Asians, with incidences of 1.4 percent and 0.8 percent, respectively.\textsuperscript{7,8} An especially high incidence of hemangiomas has been reported in premature infants weighing less than 1000 g (30 percent).\textsuperscript{2,9} About one-third of hemangiomas evidence early signs at birth, such as erythema, ecchymosis, pale patches, red papules, or telangiectasia. Boon et al.\textsuperscript{10} described congenital hemangioma, tumors that are fully developed at birth and do not show the typical proliferation. The majority of hemangiomas may be termed nascent and appear in the first 3 months of life. These exhibit the classic stages of early, rapid proliferation followed by slow involution over 5 to 7 years.

Girls are affected between two and five times as often as boys.\textsuperscript{11–13} This is in contrast to the 1:1 gender ratio seen in congenital hemangiomas, kaposiform hemangioendotheliomas, and vascular malformations.\textsuperscript{2,10,14,15} Sixty percent of hemangiomas are located in the cervicofacial region, although this accounts for only 15 percent of the body surface area.\textsuperscript{16} It is uncertain whether this disproportionate distribution reflects underreporting of trunk and extremity lesions or a true regional predilection for abnormal angiogenesis. Eighty percent of affected children have solitary lesions, whereas the remaining 20 percent have two or more.\textsuperscript{11}

Hemangiomas usually occur sporadically, and studies comparing their incidence in monozygotic and dizygotic twins do not suggest a genetic basis.\textsuperscript{12} Recent reports, however, have identified several examples of familial hemangiomas. These follow an autosomal dominant pattern of inheritance, and a possible locus has been identified on 5q.\textsuperscript{17}

Large cervicofacial lesions have been associated with other malformations in 10 percent of cases. These comprise the PHACES syndrome (P, posterior cranial fossa malformations; H, hemangiomas; A, arterial anomalies; C, cardiac anomalies; E, eye anomalies; S, sternal cleft). The causative event is unknown, but it occurs between 8 to 10 weeks of gestation. Anomalies include the Dandy-Walker malformation, absence of carotid/vertebral vessels, bifid or cleft sternum, and supraumbilical raphe. The vast majority of affected patients are girls (9:1 ratio), who are especially prone to occlusive cerebrovascular accidents at an early age.\textsuperscript{18–20}

Lumbosacral hemangiomas can be associated with tethered spinal cord or abnormalities of the anorectal or urogenital regions. These hemangiomas are flat and span the midline. Radiographic studies of the spine and pelvis should be obtained to identify associated anomalies.\textsuperscript{18,21}

Hemangiomas can be superficial, deep, or visceral in location. Although this does not affect the biological behavior, location determines the clinical appearance. Mulliken and Young’s\textsuperscript{2} caveats regarding the clinical appearance of vascular anomalies bear repeating: Not all strawberries are hemangiomas and not all hemangiomas look like strawberries. Superficial lesions often exhibit the classic crimson color of the so-called strawberry hemangioma (Fig. 1, above), whereas those within the deep dermis or subcutaneous tissues often present as pale blue or purple masses that may be confused with venous malformations (Fig. 2). Visceral lesions are not apparent on physical examination, and in 50 percent of cases, there are no accompanying cutaneous hemangiomas.\textsuperscript{18} In this setting, their presence may only be suggested by physiologic findings such as hepatomegaly, congestive heart failure, or stridor.

**Natural History**

Hemangiomas typically appear during the first 2 months of life either as an erythematous patch, a telangiectasia surrounded by a pale halo, or a blanched area.\textsuperscript{8,22} The following proliferative phase of rapid enlargement outpaces the growth of the child. This phase is often characterized by a bright crimson coloration that gives rise to the strawberry appellation. Palpation at this stage reveals a tense and noncompressible mass, with draining veins frequently seen around the periphery. Expansile growth continues for 4 to 8 months before plateauing. Involution is characterized by a decrease in cellularity and tumor size, formation of larger vascular channels, fibrofatty replacement, and development of a lobular architecture with septae. Early signs of involution are a decrease in turgidity and fading of color to a dullish or gray hue. This color change may be difficult to appreciate in deeply situated hemangiomas. The involutorial process begins at approximately 12 months of age and continues over the next 5 to 7 years.\textsuperscript{10} Involution and proliferation may be seen simultaneously.
within different parts of a given lesion or among hemangiomas in children with multiple lesions.\textsuperscript{2,11} Approximately 50 percent of hemangiomas have involuted by 5 years and 70 percent by 7 years of age. The remainder may continue to improve until the age of 12. Rate or completeness of involution is not influenced by lesion size, location, ulceration, depth, patient gender, or age of presentation. An early onset of involution is the only factor associated with improved outcome. As Bowers et al.\textsuperscript{11} noted, even with complete involution, signs of the hemangioma may persist in the form of residual tumor, loose skin, telangiectasias, or scarring.

**Pathogenesis**

Hemangiomas are the result of a derangement in angiogenesis that allows the uncontrolled proliferation of vascular elements. Folkman and Klagsbrun,\textsuperscript{23} Klagsbrun and D’Amore,\textsuperscript{24} and Folkman et al.\textsuperscript{25} elucidated the complex interplay of angiogenic and angiostatic forces involved in normal and pathologic processes. During the proliferative phase of rapid growth, many factors or markers of angiogenesis are increased in hemangiomas. These include basic fibroblast growth factor, vascular endothelial cell growth factor, matrix metalloproteinases, proliferating cell nuclear antigen, the endothelial cell adhesion molecule E-selectin, and type IV collagenase.\textsuperscript{26–28} Up-regulation of messenger RNA for the proangiogenic factors basic fibroblast growth factor and vascular endothelial cell growth factor has also been demonstrated in proliferative hemangiomas.\textsuperscript{29} With the exception of basic fibroblast growth factor, these factors decrease with the onset of involution and are not present in the fully involuted lesion. Basic fibroblast growth factor remains elevated through early involution in both hemangiomatous tissue and urine. Urinary levels of basic fibroblast growth factor can be monitored to assess the efficacy of treatment.\textsuperscript{25} In addition to the decrease in angiogenic factors, involution is characterized by a five-fold increase in endothelial cell apoptosis and abnormal levels of
angiogenic inhibitors. Tissue inhibitor of metalloproteinase, for example, is significantly increased in hemangiomas during the involuting phase.

Both the cellular and extracellular components of hemangiomas differ from normal tissues. The endothelial cells are plump with multilaminated basement membranes not seen in normal tissue or vascular malformations. The hyperplastic nature of hemangiomas is evidenced by frequent cellular mitoses, and unlike normal endothelial cells, those derived from hemangiomas readily grow in culture and demonstrate in vitro tubule formation. The extracellular matrix is composed of macromolecules that influence cell function through affects on growth, migration, and differentiation. The extracellular matrix also serves as a repository for growth factors and a modulator of cellular responses to them. The extracellular matrix of hemangiomas differs from that of normal skin and vascular malformations, with immunohistochemistry demonstrating increased vitronectin, perlecan, and laminin in hemangiomas. On a cellular level, hemangiomas in the involuting phase demonstrate a 30-fold to 40-fold increase in mast cells. Their specific role in the pathology of hemangiomas is uncertain, but mast cells are known to contain heparin and other vasoactive substances involved in neoangiogenesis. Electron microscopy reveals interactions between mast cells, fibroblasts, macrophages, and the endothelial basement membrane at the ultrastructural level.

**DIAGNOSTIC IMAGING**

Hemangiomas are readily distinguished from other tumors by computerized tomography, magnetic resonance imaging, and arteriography. Although hemangiomas can be diagnosed on clinical grounds in over 93 percent of cases, diagnostic imaging may be useful in questionable lesions to demonstrate visceral involvement, plan surgical excision, assess treatment efficacy, and define associated anomalous structures. Magnetic resonance imaging is the preferred method to study vascular lesions because of the wealth of information provided. T1-weighted and T2-weighted images demonstrate a lobulated soft-tissue mass with flow voids representing feeding and draining vessels. On T1-weighted imaging, hemangiomas are isointense or hypointense to muscle. With T2 imaging, the lesions are hyperintense. Hemangiomas demonstrate intense, homogeneous contrast enhancement with intravenous gadolinium.

Computerized tomography can be substituted if magnetic resonance imaging is unavailable. Findings are similar between the two studies, with demonstration of a distinctive soft-tissue mass that enhances with contrast. Angiography is usually reserved for equivocal cases or in patients undergoing therapeutic embolization. When performed, hemangiomas appear as well-circumscribed masses with persistent, intense parenchymal staining. Equatorial vessels are also seen and represent feeding arteries and draining veins. During the proliferative phase, hemangiomas appear as high-flow lesions, which then gradually diminish with involution.

**DIFFERENTIAL DIAGNOSIS**

Hemangiomas must be differentiated from macular stains, vascular malformations, and other vascular tumors of infancy. This may be done in greater than 93 percent of cases on a clinical basis, but radiographic studies and biopsy may be necessary in equivocal cases.

**Macular Stains**

The most common type of vascular birthmark is the macular stain. These are flat lesions, ranging in color from pink to red, seen in as many as 40 percent of newborns. Terms such as “angel’s kiss,” “salmon patch,” and “stork bite” are frequently applied. Typically seen in the neck, glabella, eyelid, and forehead, these probably are physiologic phenomena that will resolve with time. Yellow-green laser treatment is effective for lesions that persist.

**Vascular Malformations**

Vascular malformations are the other major category of vascular anomalies and must be distinguished from hemangiomas. Like hemangiomas, the terminology used to describe them is plagued by inconsistencies. Many physicians continue to use the terms “cavernous
hemangioma” for venous malformation and “port-wine stain” for capillary malformation. Malformations are the result of errors in morphogenesis and are divided into subtypes based on the constituent vessels: capillary, venous, arterial, lymphatic, and combined forms. Lesions are often mixed and contain more than one type of vascular element. Malformations may be further categorized based on flow characteristics. High-flow lesions consist of the arteriovenous malformations and arteriovenous fistulas. Low-flow lesions are the capillary, lymphatic, and venous malformations. Unlike hemangiomas, the endothelium in vascular malformations is not hyperplastic. These cells have a normal turnover rate and, thus, are no more susceptible to antiproliferative treatments than the surrounding tissues. This renders such treatments as radiation and chemotherapy ineffective in their management.

The natural history of vascular malformations is distinct from hemangiomas. Boys and girls are affected equally. As errors of morphogenesis, all malformations are present at birth. These may not be recognized immediately, however, and localized lesions may remain undetected into the teenage years. The physical appearance of vascular malformations is dependent on the type of vessels involved. Venous malformations may appear as bluish masses and be confused with subcutaneous hemangiomas, but they are distinguished by the ability to be emptied of blood with compression. Malformations grow commensurately with the child and do not undergo the rapid proliferative growth phase exhibited by hemangiomas. They are sensitive to hormonal modulation and may exhibit rapid enlargement during puberty and pregnancy. Infection and trauma may also cause a period of rapid expansion. The greatest distinction between hemangiomas and malformations is that the former spontaneously involute and the latter do not.

Malformations do not demonstrate the parenchymal staining seen with hemangiomas on computerized tomography and magnetic resonance imaging studies. They are less distinct and consist of multiple, ectatic channels. Histologic examination shows malformations to be composed of vascular channels with normal endothelium. Mast cells, growth factors, and cellular markers for endothelium are present in normal numbers and distribution.

The treatment of malformations differs from hemangiomas because they are not proliferative and do not involute. Antiangiogenic agents such as corticosteroids and interferon are ineffective, as are antiproliferative treatments such as radiation and chemotherapy. Sclerosis and embolization may be curative or might control some malformations. Capillary lesions are sensitive to laser therapy with pulsed dye and other yellow-green lasers. There is reported success in treating lymphatic malformations with streptococcal OK-432. Surgical resection with or without preoperative embolization is curative, but it may not be possible depending on lesion location and the proximity of vital structures.

Other Vascular Tumors of Infancy

**Pyogenic granuloma.** Pyogenic granuloma is an acquired vascular lesion that closely resembles hemangioma upon clinical and microscopic examination. They tend to occur on the skin and mucosa of older children and young adults, with a mean age of 6.7 years. Pyogenic granulomas arise suddenly and usually without a history of trauma. Frequently located on the cheeks, eyelids, extremities, and within capillary malformations (port-wine stains), they may be either sessile or pedunculated on a narrow stalk (Fig. 3). The natural history is one of superficial ulceration and repetitive episodes of bleeding, earning it the sobriquet “band-aid disease.” Treatment may consist of silver nitrate application, electrocauterization, laser ablation, or excision.

**Kaposiform hemangioendothelioma.** Kaposiform hemangioendothelioma is an aggressive vascular tumor of infancy that is frequently associated with severe thrombocytopenia. Kasabach and Merritt originally described this bleeding disorder in conjunction with
with a “giant hemangioma,” but it has recently been recognized that this coagulopathy does not occur with the common hemangioma of infancy.\textsuperscript{14,51} Rather, the Kasabach-Merritt phenomenon accompanies kaposiform hemangioendothelioma or tufted angioma.\textsuperscript{14,15,49–52} Kaposiform hemangioendothelioma is distinct from hemangioma clinically, radiographically, and histologically. As with hemangioma, it may present at birth or afterward, but it differs by having an equal gender distribution and usually occurring outside the cervicofacial region. Typically presenting in the trunk, extremities, and retroperitoneum, the lesions experience rapid growth. With cutaneous involvement, Kaposiform hemangioendothelioma often has a purplish, indurated appearance. Kaposiform hemangioendothelioma is distinguished on histologic examination by irregular lobules and sheets of cells that infiltrate the dermis and subcutaneous fat, spindle-shaped endothelial cells, microthrombi, hemosiderin deposits, and decreased pericytes and mast cells. Distinctive lymphatic-like vessels or channels may be evident as well.\textsuperscript{14,15} Mortality is particularly high with retroperitoneal tumors or when complicated by the Kasabach-Merritt phenomenon (>50 percent).\textsuperscript{14,40} Because a distinction between the two lesions has only recently been made, it is not surprising that the described treatment methods for kaposiform hemangioendothelioma and hemangiomas are similar. Corticosteroids, alpha-interferon, chemotherapy (vincristine, cyclophosphamide), embolization, ticlopidine, aspirin, radiation, and excision have been used.\textsuperscript{40,49,53,54} Combination therapy is often initiated because of the high mortality rate. Heparin should not be used for the thrombocytopenia of Kasabach-Merritt phenomenon because it causes the release of fibroblast growth factor and may be associated with accelerated tumor growth.\textsuperscript{40} 

\textit{Tufted angioma}. Tufted angioma, also known as angioblastoma of Nakagawa or angioblastoma, is another vascular tumor that may arise in the pediatric population. There are many similarities between tufted angioma and kaposiform hemangioendothelioma, and they may represent a pathologic spectrum rather than separate entities.\textsuperscript{40,55} The Kasabach-Merritt phenomenon may also complicate tufted angioma, and treatment options are similar to those for kaposiform hemangioendothelioma.\textsuperscript{40,52} 

\textit{Congenital hemangiopericytoma}. Hemangiopericytoma is a rare vascular tumor consisting of benign pericytes typically located on the extremities of newborns and young children. Biopsy may be required for diagnosis, and excision is indicated if the lesion does not spontaneously involute.\textsuperscript{40,56,57} 

\textit{Angiosarcoma}. Angiosarcomas are vascular tumors that are uncommon in children. When they do occur, these malignancies usually arise in the liver and frequently metastasize to the lungs. Because of their aggressive nature, prognosis is poor, with survival measured in months.\textsuperscript{10,38–40} 

\textit{Other}. Nonvascular neoplasms and masses may masquerade as hemangiomas, especially when situated subcutaneously. These include fibrosarcoma, rhabdomyosarcoma, neurofibroma, teratoma, nasal glioma, dermoid cyst, Spitz nevus, and myofibromatosis.\textsuperscript{5,36,40} Computed tomography, magnetic resonance imaging, and biopsy help differentiate these from hemangiomas.

\section*{Complications}

\subsection*{Ulceration}

The most common complication of hemangioma is ulceration,\textsuperscript{11,18} which occurs in less than 5 percent of cases and often involves perioral and perineal lesions.\textsuperscript{61} Treatment consists of wound care and topical antibiotic ointment. Excision of ulcerated lesions may be indicated (Fig. 4).

\subsection*{Infection}

Infection may develop in the presence of ulceration. Local wound care and topical antibiotic ointment is used, with systemic antibiotics reserved for cellulitis.
Visual Impairment

Periorbital hemangiomas may cause visual impairment by obstructing the visual axis or distorting the cornea (Fig. 1).40,62,63 The optic cortex is extremely sensitive to stimulus deprivation, as demonstrated in both kittens and baboons.62 During the first year of life, obstruction of the visual axis in humans may cause amblyopia in as little as 1 week. Anisometropia and failure to develop stereopsis may also occur. Obstruction is not the only mechanism by which vision may be impaired. The mass effect of a periorbital hemangioma, particularly of the upper eyelid, may deform the developing cornea. Proptosis may also result from intracranial lesions, and strabismus through involvement of the extraocular muscles.40

Ophthalmologic evaluation is indicated for children with periorbital hemangiomas. Lesions that do not compromise vision may be observed, but symptomatic lesions must be treated urgently to prevent visual compromise. Corticosteroids are used initially, although excision may be considered for smaller lesions. Direct injection of corticosteroids has also been advocated for periorbital hemangiomas, but direct injection does not have a faster onset of action, requires an anesthetic, and has been associated with complications, including blindness, globe penetration, and eyelid necrosis.18,63 Recent series of intralesional therapy with bare fiber neodymium:yttrium-aluminum-garnet or potassium-titanyl-phosphate lasers report significant regression of the hemangiomas, but these treatments have no documented improvement in vision, are accompanied by a high incidence of ulceration (17 to 25 percent), and are often confounded by the simultaneous use of corticosteroids.44–67

Airway Obstruction

Because infants are obligate nose breathers, intranasal hemangiomas may cause insidious airway obstruction. Subglottic lesions often present with stridor and can cause life-threatening obstruction.2,68 Because subglottic lesions are associated with cutaneous hemangiomas in only half the cases, endoscopy should not be reserved for children with skin lesions. When cutaneous lesions accompany laryngeal hemangiomas, they are often multiple and appear in a “beard” distribution.18

Intranasal lesions may be treated with corticosteroids. Submucosal resection is reserved for cases unresponsive to medical management.69 Subglottic hemangiomas may also be treated with a trial of corticosteroids if the airway compromise is not severe. Lesions causing severe obstruction or those unresponsive to initial management may be treated with carbon dioxide laser ablation.44,70,71 Because circumferential laser ablation may cause subglottic stenosis, interferon therapy should be considered as an alternative for extensive laryngeal involvement.11,44,72,73 Tracheostomy may be required if the above treatments are unsuccessful.

Auditory Canal Obstruction

Parotid gland hemangiomas may cause obstruction of the external auditory canal. Obstruction produces a conductive hearing loss that may affect speech development. Bilateral involvement that persists beyond 1 year of age should be treated to prevent this occurrence.2,18,44

Congestive Heart Failure

Congestive heart failure may complicate hemangiomas.18,40,44 This usually occurs in one of two settings: diffuse neonatal hemangiomatosis or large visceral hemangiomas.74–76 The latter are usually hepatic lesions that create symptomatic arteriovenous fistulas and cardiac decompensation. Medical management with diuretics and digitalis is usually combined with therapy directed at the hemangioma. Embolization, hepatic artery ligation, resection, systemic corticosteroids, alpha-interferon, and radiation have been used. Despite aggressive treatment, many patients succumb to persistent congestive failure, infection, or bleeding.72,73,75,81

Management

The appropriate management of hemangiomas is, first and foremost, dependent on an accurate diagnosis. In most instances, parental education and reassurance will suffice. Edgerton1 termed this “masterful neglect,” and Mul liken and Young2 advocated the principle primum non nocere. Because most hemangiomas undergo spontaneous involution, treatment may be reserved for those lesions of functional or psychological concern.

Hemangiomas obstructing the visual axis, airway, and auditory canals, or those associated with congestive heart failure, ulceration, or bleeding, should be considered for treatment.
The psychological effect of lesions on both the parents and child must be considered as well. Certain anatomic sites, such as the nasal tip, have an emotional significance that may warrant early treatment (Fig. 5). It is important for the counseling physician to be mindful that many hemangiomas do not fully involute and may leave unacceptable residua. In a study by Bowers et al., 25 percent of patients had significant deformity after maximal involution (Fig. 6).

**MEDICAL AND SURGICAL TREATMENT**

A number of options are available for the treatment of hemangiomas. Effective treatments may be divided into those that are non-specific (e.g., excision, cryotherapy); antiangiogenic (e.g., corticosteroids, interferon); and antiproliferative (e.g., chemotherapy, radiation). Corticosteroids are the first line of treatment, although multiple treatments may be used for massive or life-threatening hemangiomas.

**Steroids**

Zarem and Edgerton found that systemic corticosteroids rapidly induced involution in massive hemangiomas. Subsequent reports by many authors have confirmed the efficacy of prednisone and prednisolone in dosages of 2 to 3 mg/kg of body weight. In principle, the lowest dose administered for the shortest time is preferred. Mulliken suggests an initial 2-week course of therapy, which, if successful, should be continued and slowly tapered over several months. Therapy is slowly tapered over several months to prevent adrenal insufficiency. A clinical response is usually seen within 7 to 10 days of beginning treatment. Because the majority of hemangiomas begin to involute at 10 to 12 months, treatment usually can be discontinued before 1 year of age. Historical response rates for oral corticosteroid therapy vary from 30 to 90 percent, but many of these studies included other types of vascular lesions. The response rate for true hemangiomas to corticosteroids is closer to 90 percent. In lesions that respond, rebound growth may occur with tapering or discontinuance and reinstitution of therapy may be warranted. Adverse effects are frequent but are minor and temporary. These consist of cushingoid facies (71 percent), mental status changes such as irritability (29 percent), gastric upset (21 percent), yeast infection (6 percent), and growth retardation (35 percent). In those children with slowed growth, catch-up is seen with completion of steroid therapy. Hypertension and

![Fig. 5. “Cyrano de Bergerac” deformity in a 10-year-old following involution of nasal tip hemangioma.](image)
steroid myopathy are rare occurrences. All adverse effects are temporary, occur more frequently with increasing duration of treatment, and resolve with cessation of steroids. Edgerton suggested an alternate-day dosage schedule to minimize these unwanted effects, but most physicians use a daily morning dose. Although immunosuppression has not been documented, it is recommended that live virus vaccinations be delayed until the completion of therapy.

Intralesional injection of long-acting corticosteroids is advocated in the treatment of certain hemangiomas, particularly those involving the eyelids. This typically consists of triamcinolone and/or betamethasone administered under general anesthesia or sedation. Kushner reported rapid regression in 1 to 2 weeks, followed by gradual improvement over the next 6 to 8 weeks. The majority of patients required additional injections at that time for significant residual tumor. Intralesional injections purportedly localize the steroid effect to the given lesion and minimize unwanted systemic actions. This has not proved to be the case, and indeed, it is possible that intralesional steroids work by means of systemic absorption and recirculation of the drug. The accelerated involution of multiple lesions when one was injected (e.g., as seen in photographs in Kushner’s original article), the documented cases of adrenal suppression, and cushingoid facies in up to 10 percent of cases following intralesional injection are evidence of systemic effects. Severe complications related to intralesional injection of periorbital hemangiomas have also been described, including blindness, globe penetration, eyelid necrosis, and soft-tissue atrophy.

Interferon

Interferons are a class of cytokines produced by monocytes and dendritic cells. Alpha-interferon has 22 subtypes, three of which are commercially available for use as antiviral and antiproliferative agents. Alpha-interferon has many demonstrated effects, including the inhibition of endothelial, fibroblast, and smooth muscle cell proliferation; growth factor release; and collagen synthesis. Interferon seems to induce the involution of hemangiomas through a dose-dependent increase in endothelial cell apoptosis, or programmed cell death. Apoptosis is evident in spontaneously involuting hemangiomas and in 20 percent of endothelial cells of alpha-interferon–treated hemangiomas, but it is absent during the proliferative phase.

White et al. first described the use of alpha-2a–interferon for hemangiomas in the successful treatment of a 12-year-old with pulmonary hemangiomatosis. Subsequent series have confirmed its benefit in lesions unresponsive to steroids or in those requiring rapid regression. Interferon is usually reserved for serious cases in which steroids are contraindicated, have failed, or have had significant complications. Treatment regimens consist of the subcutaneous administration of 1 to 3 million units/m²/day of alpha-2a–interferon or alpha-2b–interferon. Initial therapy is instituted as an inpatient or as an outpatient with medical supervision to monitor for hemodynamic changes. Treatment is continued until the tumor is stabilized, which averages 20 months but may take up to 3 years. Regression is seen in 50 to 84 percent of lesions, with complete resolution in as many as 42 percent. As with steroid therapy, growth can recur with discontinuance of alpha-interferon and requires reinitiation. In rare cases, antibodies to alpha-interferon may develop and cause rebound growth during treatment. Serum antibody titers should be measured in such cases. Transitory adverse effects include fever and flulike
symptoms that respond to acetaminophen. Chronic neutropenia may persist for the length of therapy, and hepatic enzyme abnormalities often occur. Neurologic changes have recently been connected with alpha-2a–interferon therapy. Barlow and others have reported spastic diplegia developing in up to 25 percent of patients treated with long-term interferon. Affected children tended to begin therapy at an early age, and some demonstrated delayed central nervous system myelination on magnetic resonance imaging. Although myelination normalized on follow-up studies, not all children fully recovered. Because of this concern, neurodevelopmental testing should be performed before initiating, and then during, interferon therapy. Any abnormalities warrant magnetic resonance imaging evaluation to exclude other causes, and if negative, cessation of therapy or decreasing the dosage should be considered.

Surgical Excision

Surgical excision may be indicated in infancy for obstructing, ulcerating, or large hemangiomas unresponsive to pharmacologic therapy (Fig. 4). In the preschool years, resection may be chosen for prominent facial hemangiomas that interfere with the child’s developing self-image (Fig. 5). Later in childhood, involuting or involuted lesions may require surgical revision for residual tumor or skin atrophy (Fig. 6).

Laser

The several different types of lasers used in the treatment of hemangiomas include the carbon dioxide, flashlamp-pumped pulsed-dye, neodymium:yttrium-aluminum-garnet, potassium-titanyl-phosphate, and argon lasers. Relief of airway obstruction may be accomplished with carbon dioxide laser ablation. Care should be taken with extensive or circumferential subglottic hemangiomas because of the possible stenosis developing after laser treatment.

Superficial hemangiomas have been treated by delivering laser energy to the skin surface, whereas intraleralional delivery of laser energy has been used with more bulky lesions. Relief of airway obstruction may be accomplished with carbon dioxide laser ablation. Care should be taken with extensive or circumferential subglottic hemangiomas because of the possible stenosis developing after laser treatment.

Embolization

Selective embolization of hemangiomas may be effective for lesions associated with life-threatening coagulopathy, congestive heart failure, or airway and ocular obstruction refractory to other means. This is often adjunctive to surgical excision, although Burrows et al. reported rapid regression in five of six lesions embolized without resection.

Chemotherapy

Antineoplastic agents are successful in the treatment of hemangiomas because of their proliferative nature. Cyclophosphamide and vincristine have been used successfully in the treatment of the Kasabach-Merritt phenomenon. The associated lesions are kaposiform hemangioendothelioma, however, rather than true hemangiomas.
Radiation

Hemangiomas and other vascular tumors of infancy are very susceptible to radiation therapy because of their increased cellular turnover. Small dosages in the range of 400 centigray are used. Because of its long-term sequelae, however, radiation therapy is reserved for severe, life-threatening lesions refractory to other treatments.

Cryotherapy

Topical liquid nitrogen and carbon dioxide have been used in the treatment of superficial hemangiomas. Cryotherapy has poor acceptance in North America because it may be associated with unacceptable scarring and hypopigmentation. Edgerton found the resultant scarring particularly difficult to manage. Despite this, the method continues to have proponents in Europe.

Compression

A beneficial effect of compression on extremity hemangiomas has been described for lesions exhibiting symptomatic platelet trapping. In retrospect, these lesions were likely kaposiform hemangioendothelioma and not true hemangiomas of infancy.

Conclusions

Hemangiomas are the most common vascular tumor of infancy, found in upward of 10 percent of children. Their natural history is best described by the biological classification of vascular anomalies proposed by Mulliken and Glowacki. Hemangiomas are the result of pathologic angiogenesis and typically appear shortly after birth. They undergo rapid proliferation in the first year, followed by involution beginning by 1 year and continuing over the next 5 to 10 years. Apoptosis is associated with involution, beginning before age 1 year and peaking at age 2 years. Radiographic, histologic, and biochemical findings correspond to these phases. Congenital hemangiomas differ in that they are fully developed at birth, do not exhibit the rapid growth seen in nascent lesions, and often involute rapidly. Treatment is conservative in the majority of lesions, but ocular, airway, or auditory obstruction and congestive heart failure are indications for treatment. The psychological impact of a hemangioma should also be considered. First-line therapy consists of oral corticosteroids, with interferon and excision considered for unresponsive lesions. The Kasabach-Merritt phenomenon was previously thought to complicate hemangiomas of infancy, but has now been linked to the clinically distinct hemangioendothelioma and tufted angioma. The pathogenesis of hemangiomas likely involves a localized imbalance of factors that results in uncontrolled angiogenesis. Future therapies will likely be directed at restoring this balance through the administration of angiogenesis modulators.

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Acknowledgment

We thank Dr. John B. Mulliken for his careful review of the manuscript and his invaluable suggestions.

References


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Vascular Anomalies: Hemangiomas
by Thomas J. Gampper, M.D., and Raymond F. Morgan, M.D.

1. WHICH OF THE FOLLOWING CLASSIFICATION SYSTEMS OF VASCULAR LESIONS HAS THE GREATEST THERAPEUTIC IMPLICATION?
   A) Descriptive
   B) Anatomical
   C) Biological
   D) Embryological

2. HEMANGIOMAS ARE MOST COMMON IN WHICH OF THE FOLLOWING GROUPS?
   A) Males
   B) African-Americans
   C) Low birth weight infants
   D) Asians

3. WHICH OF THE FOLLOWING HISTOLOGIC OR HISTOCHEMICAL MARKERS IS PRESENT IN HEMANGIOMAS?
   A) Normal endothelial cell turnover
   B) Decreased expression of VEGF
   C) Decreased mast cell numbers
   D) Absent basement membrane
   E) Increased tissue bFGF

4. WHAT PERCENTAGE OF HEMANGIOMAS WILL SPONTANEOUSLY INVOLUTE BY 5 YEARS OF AGE?
   A) 10%
   B) 25%
   C) 50%
   D) 75%
   E) 90%

5. IN WHICH OF THE FOLLOWING VASCULAR LESIONS IS KASABACH-MERRITT PHENOMENON MOST LIKELY TO OCCUR?
   A) Venous malformation
   B) Angiosarcoma
   C) Hemangioma
   D) Pyogenic granuloma
   E) Kaposiform hemangioendothelioma

6. WHICH OF THE FOLLOWING TREATMENT MODALITIES IS RESERVED FOR SEVERE OR LIFE-THREATENING LESIONS THAT HAVE BEEN REFRACTORY TO OTHER TREATMENTS?
   A) Oral steroids
   B) Excision
   C) Radiation
   D) Interferon α
   E) Laser

To complete the examination for CME credit, turn to page 731 for instructions and the response form.