Vascular Tumors

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Semin Plast Surg 2014;28:49–57.

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Abstract

Vascular anomalies are divided into two main groups: tumors and malformations. Vascular tumors are a large and complex group of lesions, especially for clinicians with none or little experience in this field. In the past, these lesions caused a great deal of confusion because many appear analogous to the naked eye. Thankfully, recent advances in diagnostic techniques have helped the medical community to enhance our comprehension, accurately label, diagnose, and treat these lesions. In this article, we will review the most frequent vascular tumors and provide the reader with the tools to properly label, diagnose, and manage these complex lesions.

Keywords
- vascular anomalies
- vascular tumor
- hemangioma
- vascular malformation

Vascular anomalies can be broken down into two major categories: tumors and malformations. These clinical entities are extremely different, but often confused, as evidenced by the history and medical literature. A thorough medical history and physical exam is essential when it comes to defining any vascular anomaly. There are several different vascular tumors, but infantile hemangiomas are the most common. Others tumors that will be discussed include tuft angiomas, pyogenic granulomas, angiosarcomas, and kaposiform hemangioendotheliomas. Management of vascular tumors depends on their medical history, diagnosis, and most importantly their location.

History and Classification

Pathologists, clinicians, and radiologists have traditionally confused the diagnosis of vascular anomalies by using medical terminology that was not specific or defined. Given this inconsistency, the proper diagnosis of many of these tumors has been confusing for a great number of care providers. In a recent study, PubMed was queried for publications with the word "hemangioma" in either the title or abstract. In the 320 articles found, hemangioma was incorrectly used in 228 (71%).[1] In the articles that included management recommendations, they found that patients were incorrectly treated in 13 of 63 (21%) articles that used improper terminology, and zero of 42 who used the proper terminology.[1]

The word "birthmark" was one of the first ways used to described vascular anomalies, based on the folk belief that a mother's emotions can leave an imprint on her unborn fetus.[2] In the late 1860s, Dugas and Fisher disproved this belief and concluded that birthmarks were malformations resulting from flawed embryologic development.[2] Around the mid-19th century, Virchow proposed a histopathologic classification based on the size and appearance of the vessels.[3] Then in 1982, thanks to technologic advances Mulliken and Glowacki classified them based on histology, biology, and clinical presentation.[3] They divided vascular anomalies into two major categories: tumors and malformations.[2–8] In 1996, the International Society for the Study of Vascular Anomalies (ISSVA) adopted and modified Mulliken and Glowacki's original classification.[2] This classification system is now widely accepted to properly diagnose and manage vascular anomalies (►**Table 1**).[2,4]

In general, the suffix "-oma" is usually reserved for benign endothelial neoplasms that grow by endothelial hyperplasia.[4,6] All vascular tumors (except congenital hemangiomas) are not clinically present at birth, have a period of rapid growth, and spontaneously involute (except noninvoluting congenital hemangiomas [NICH]). A malformation is characterized as an error in development of vascular embryologic tissue. Vascular malformations can be capillary, venous, lymphatic, and/or arterial in nature. They differentiate from vascular tumors by the fact that they are present at birth, do

Issue Theme Vascular Anomalies; Guest Editor, Edward I. Lee, MD

DOI http://dx.doi.org/10.1055/s-0034-1376260.
ISSN 1535-2188.

Table 1 International Society for the Study of Vascular Anomalies classification of vascular anomalies

Vascular tumors	Vascular malformations
Infantile hemangioma Congenital hemangioma Rapidly involuting congenital hemangioma Noninvoluting congenital hemangioma Tufted angioma (± Kasabach-Merritt phenomenon (KMP) Kaposiform Hemangioendothelioma (± KMP) Spindle cell hemangioendothelioma Epithelioid hemangioendothelioma Other rare hemangioendotheliomas, i.e., composite, retiform, and others Dermatologic acquired, i.e., lobular capillary hemangioma (pyogenic granuloma) Angiosarcoma	Slow-flow: Capillary malformation Venous malformation Lymphatic malformation Fast-flow: Arterial malformation Arteriovenous malformation Combined vascular malformation (a mix of any of the above)

not have increased endothelial cell turnover, and grow proportionally with the child. An overview of the current clinical, histologic, and immunohistotypical features that distinguish the major types of vascular tumors presenting in infancy and childhood is provided. Diagnostic modalities and current management practices will be discussed.

Infantile Hemangiomas

Infantile hemangiomas (IHs) are the most common benign tumor in infancy, and occur approximately in 5% to 10% of the population (►**Fig. 1**).[2,4,7,9] These can appear anywhere in the body, but most commonly they affect the skin, especially of the head and neck (60%), trunk (25%), and extremities (15%).[2,4,9] The majority appear weeks to months after birth, but ~30% to 50% can present with a precursor lesion at birth.[7,9] Infantile hemangiomas are more prevalent in Caucasians, females, premature infants (birth weight < 1 kg), and children whose mothers have had in utero procedures (e.g., chorionic villus sampling).[2,3,5,7] Infantile hemangiomas undergo three distinctive phases—proliferation, involution, and involuted phase (►**Fig. 1**).

Pathogenesis

There are two dominant theories regarding the etiology of IHs. The first suggests IHs' endothelial cells arise from disrupted placental tissue embedded in fetal soft tissue. This is based on the presence of GLUT 1, Lewis Y antigen, and IGF2 in affected patients.[6,10] These markers are shared by placental capillaries, rather than normal cutaneous vasculature or other vascular tumors.[11] The second theory suggests that they arise from endothelial progenitor and stem cells because these cells are found circulating in patients with IHs.[6,10,12]

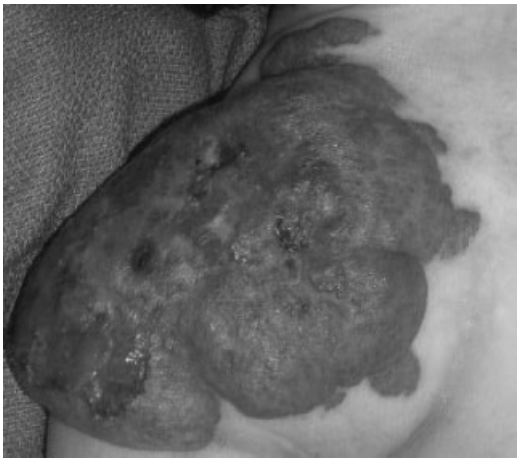

Fig. 1 Infantile hemangioma.

Clinical Presentation

At birth, the majority of IHs are not visible. A precursor lesion may be present in some cases, a superficial area of pallor often with fine thread-like telangiectasia throughout.[7] Infantile hemangiomas normally appear weeks after birth during the beginning of the proliferative phase. Superficial IHs involve the superficial dermis, and grossly appear as lobulated, bright red lesions with a thin, delicate-surface epithelium.[6,7,9,10,12] Deep IHs tend to appear later and involve the deep dermis and subcutaneous tissue. The epidermis retains its normal thickness and the overlying skin often has a bluish hue.[2,7,13] Infantile hemangiomas can be localized or segmental, and present as solitary (85%) or multiple (15%) lesions.[2,4,7,9] Large segmental IHs have been associated with structural anomalies, such as Dandy-Walker malformation, arterial anomalies, spinal cord tethering, genitourinary anomalies, and subglottic hemangiomas.[7] Large preauricular segmental IHs usually affect the parotid gland, but rarely affect the facial nerve. Multiple focal IHs have been associated with a higher risk of visceral hemangiomas, most notably affecting the liver, gastrointestinal system, and lungs.[7]

Proliferative Phase

During the proliferative phase, which usually peaks around the third or fourth months after birth, IHs grow at a very rapid rate. It is during proliferation that ulceration, the most common complication associated with IHs, usually occurs.[4,13,14] Depending on the location, IHs may present differently. Microscopically, lesions contain mitotically active cellular masses of plumped endothelial cells and pericytes, forming packed sinusoidal capillaries with small rounded lamina. There is marked cellularity with a jigsaw-like appearance. The blood vessels are small and difficult to find. Mast cells are prominent, with up to 40 times the normal levels.[2,6] They are believed to play a major role in proliferation.

Infantile hemangiomas continue to grow in the first year of life, and usually reach a maximum size by the end of the first or second year of life. On clinical exam, palpation at this stage reveals a tense, rubbery, and noncompressible mass with draining veins at the periphery.[2,3]

Involuting Phase

Involution occurs at a much slower rate than proliferation. It is visually impossible to differentiate the change in phases because during the transition both processes occur simultaneously. Involution typically starts ~12 to 18 months after birth, and may take 5 to 10 years to completely involute.[2,3,7,9] Clinical studies reveal the rate of involution in children to be ~50% by age 5, 70% by age 7, and 90% by age 9.[2,7] Involution is not influenced by race, sex, location, time the lesion was present, rate of growth, presence of ulceration, or clinical appearance. A more advanced involuting phase is distinguished by a change in color (not size) at the center of the lesion. The color changes from a bright red to a grayish or dull purple. It becomes less tense, and soft to palpation.[2,7] Immunostaining shows a slow decrease in expression of angiogenic markers.

Involuted Phase

Although 30% of IHs may completely involute by 3 years of age, some may take longer.[7,14] Near to normal skin is restored in ~50% of affected individuals, including those with small lesions or lesions with an early onset of involution (9 to 12 months). The other 50% demonstrate residual skin changes.[9] These changes are typically characterized by focal telangiectasias, atrophic wrinkling, hypopigmentation, or refined textural changes. In more severe cases, anetoderma (a crepe-like laxity scarring) due to destruction of elastic fibers, a fibrofatty residuum and swelling of the redundant skin is present.[3,7,9] Yellow discoloration or scarred patches can persist if ulceration occurred during the proliferative phase.[9]

Diagnosis

The correct diagnosis of any vascular anomaly is crucial to proceed with proper management. Vascular anomalies can be correctly labeled either as a tumor or malformation without the need of further tests ~90% of the time, based on appearance and typical growth characteristics.[7,9] Essential components for clinical evaluation of IHs should include (1) establishment of a rapport and open dialog with the parents or care providers, (2) confirmation of the diagnosis, (3) photographic documentation (provides reassurance for regression), (4) management consideration (pharmacologic vs. surgical), (5) determination of the need for complimentary studies to establish the extent of the hemangioma or to rule out associated anomalies, and (6) referral to sources of information and parental support.[9]

The initial physical examination is extremely important, and should be detailed. Key questions to consider during the first visit are (1) Is there dermatomal involvement, risk to vision, a bearded involvement, or stridor in the neck and head? (2) Is there ulceration? (3) Are there multiple cutaneous lesions? (4) Is there a lumbosacral or perineal involvement?[9]

Imaging is useful in questionable lesions either to demonstrate visceral involvement, plan surgical excision, assess treatment efficacy, and/or define associated anomalous structures. The best imaging technique to diagnose vascular anomalies is magnetic resonance imaging (MRI).[2,3,7,9,12] It allows for delineation of the lesion, and helps evaluate adjacent or visceral anomalies. During the proliferative phase, MRI and computed tomography (CT) scans can demonstrate well-circumscribed, densely lobulated, uniformly enhancing lesions with dilated feeding and draining vessels. The presence of an enhancing parenchymal mass with evidence of high-flow vessels on MRI is characteristic of hemangiomas.[7,9] On T1-weighted imaging, hemangiomas are isointense or hypointense to muscle. With T2-weighted imaging, the lesions appear hyperintense. Infantile hemangiomas demonstrate intense, homogenous contrast enhancement with intravenous gadolinium.[3,7,15]

In cases where MRI or CT is unavailable, ultrasound (US) with Doppler can be helpful. Ultrasound is inexpensive and noninvasive, but is operator dependent and gives less information than an MRI or CT. Ultrasound with Doppler in the proliferative phase demonstrates a nonspecific echogenic mass with increased color flow, high vessel density, and a high Doppler shift.[2,3,7] During the proliferative phase IHs appear as high-flow lesions, which gradually diminish as involution begins.[2,3]

Angiography is rarely used, but will show a well-circumscribed hypervascular mass with a dense, prolonged capillary blush.[2]

Immunohistochemistry

Advances in immunohistochemistry on vascular anomalies have allowed us to form hypotheses on their etiology, develop a more specific management, and evaluate treatment outcomes. Recent studies have discovered markers expressed by vascular tumors and malformations. The five most important markers are GLUT 1, merosin, Lewis Y antigen, CD34, and Fcy-RIIb.[6,7] The rest of the markers are type 3 iodothyronine deiodinase, indoleamine 2,3 dioxygenase, and insulin-like growth factor 2 (IGF2).[6,7] IHs (and placental capillaries) are the only vascular anomaly that express GLUT 1. Infantile hemangiomas express CD34 and Lewis Y antigen, indicating the possible origin to be angioblasts. High levels of angiogenic markers, such as basic fibroblast growth factor (FGF), VEGF, and high-molecular-weight matrix metalloproteinases (MMPs) can be detected in the urine during the proliferative phase, but not in the involuted phase.[4,6,12] These markers are good early predictors of treatment success, and especially helpful in cases where color change or size reduction is not apparent.

Differential Diagnosis

Infantile hemangiomas must be differentiated from macular stains, vascular malformations, and other vascular tumors of infancy. Ninety-three percent of cases can be diagnosed on a clinical basis, but radiographic studies and tissue biopsy may be necessary in questionable cases. ►**Table 2** summarized important differences between vascular tumors and malformations.[3,4,6,7]

Table 2 General differences between vascular tumors and malformations

Vascular tumors / IH	Vascular malformations
Proliferative	Congenital abnormality with proportional growth
30% visible at birth	No gender preference
70% become apparent during the first few weeks of life	May expand secondary sepsis, trauma, or hormonal chances
F to M ratio 3:1 (only IH)	Normal endothelial cell turnover
Rapid postnatal growth followed by slow involution (excluding CH)	Normal mast cell count
Endothelial cell proliferation	Do not involute
Increased mast cells	Localized consumptive coagulopathy possible
No coagulation abnormalities (excluding TA and KHE)	Slow-flow: phleboliths, ectatic channels
High percentage respond dramatically to corticosteroids in 2–3 weeks	Fast-flow: enlarged, tortuous vessels with AV shunting
Immunopositive for biologic markers (GLUT 1: only IH)	No response to corticosteroids or antiangiogenic agents
	Immunonegative for hemangioma biologic markers

Abbreviations: CH, congestive heart failure; F, female; IH, infantile hemangiomas; KHE, kaposiform hemangioendothelioma; M, male; TA, tufted angioma.

Management

When it comes to managing vascular anomalies, a multidisciplinary team approach remains key for optimal results.[14,15] The ultimate goal is to keep morbidity and mortality low, functionality high, and achieve the best possible aesthetic outcome. There is no "one size fits all" when it comes to treating IHs due to the broad spectrum of presentation and the potential for change in early infancy.[13] Infantile hemangiomas can be managed by active observation, pharmacological, or surgical means. Each patient should be evaluated and treated on an individual basis. After diagnosis, the age of the child, size, and location of the lesion are the most important features to help guide clinicians toward proper treatment.

Active Observation

The most common management of IHs is observation. The majority of IHs spontaneously involute around 10 to 12 months, with no or little residual skin changes or complications.[2,3,7,12,13] It is recommended to photograph the lesion on each visit to follow it through the phase changes. Observation is usually chosen for IHs that are small, focal, not located on the face, or ulcerated. It is critical to educate parents and caregivers about the natural life cycle of these lesions.[2,7] It is very helpful to show them pictures of previous successfully treated lesions. Parents should be informed that there are many documented cases where waiting for the lesion to involute will allow for a better cosmetic outcome.[2,13] Parental pressure should not force the surgeon to act prematurely.

Pharmacological Treatment

Corticosteroids

The decision to medically intervene during an IHs' proliferative phase depends on age of the child and the location and size of the lesion. Pharmacological treatment is usually applied if the lesion is large, rapidly growing (particularly on face or perineum), problematic (e.g., bleeding or ulcerated), endangering (e.g., vision), or life threatening (e.g., airway).[7,9,13] Systemic corticosteroids, specifically prednisone or prednisolone are the most common first-line pharmacological treatments.[3] The effectiveness of corticosteroids for vascular tumors was discovered by accident, and their mechanism of action is still a mystery. Systemic corticosteroids have a mean response rate of 85 to 90% for cutaneous IH.[2,3,7] Prednisone is frequently prescribed as a single morning dose of 2 to 4 mg/kg/d for an initial 2-week course.[2,7] Success is noted by color change and/or size reduction. Therapy is continued if successful and slowly tapered over a 2- to 4-week period.[2,7] Steroids are discontinued when the child reaches ~10 to 11 months of age. Rebound growth has been reported if treatment is stopped prior to the end of the proliferative phase. If rebound growth occurs, 4 to 6 more weeks of therapy is begun.[3]

Adverse effects from treatment include the usual adverse effects of long-term steroid use. Cushing facial appearance (71%), irritability (29%), gastric distress (21%), diminished weight and height gain, immunosuppression, hirsutism, and premature thelarche have all been described. The adverse effects of systemic steroids in children are mild and resolve with cessation of therapy.[3]

Intralesional and topical corticosteroids have been used with success for small, well-localized cutaneous IHs located on the nasal tip, cheek, lip, or eyelid. They slow the growth of tumors and minimize distortion of surrounding structures. Triamcinolone (25 mg/mL), at a dosage of 3 to 5 mg/kg, is injected slowly at a low pressure with a fine-gauge needle. Typically, 3 to 5 injections are needed at 6- to 8-week intervals with a response rate similar to that for systemic corticosteroids.[9,13] Potential adverse reactions include subcutaneous atrophy (usually temporary), anaphylaxis, ulceration, bleeding, infection, cutaneous necrosis, and adrenal insufficiency.[13] Intralesional injection for periorbital hemangiomas should be used cautiously because blindness (ipsilateral or bilateral) caused by retinal embolization and eyelid necrosis has been reported.[7]

Propranolol

Propranolol, a nonselective β-blocker, was accidentally discovered to produce involution of IHs after it was administered to an infant with both an IH and hypertrophic cardiomyopathy. Propranolol has been successfully used to manage IHs, with an administered dose 2 mg/kg/d, divided into three separate daily doses.[5,12,13] Complications associated with β-blockers in the pediatric population are generally low, but include bradycardia, hypotension, hypoglycemia, seizures, rash, and bronchospasm.[5,12] Patients usually need pulsed dye laser (PDL) therapy after medical treatment because although the subcutaneous tumor bulk is reduced, a cutaneous stain remains and it is slow to recede.[5]

Chemotherapy

Antineoplastics (vincristine) have been used with success, and considered as treatment for life-threatening or function-impairing hemangiomas resistant to corticosteroids. The most common adverse side effects related with vincristine use are peripheral neuropathy, hyponatremia, constipation, and hair loss, all which are corrected when therapy is finished.[3,7,13]

Recombinant Interferon Alfa

Interferons (IF) are a class of cytokines produced by monocytes and dendritic cells available for use as antiviral and antiproliferative agents. IF-α has demonstrated inhibition of endothelial, fibroblast, and smooth muscle cell proliferation. Recombinant IF-α 2A and 2B, were previously used as second-line pharmacotherapy for life-threatening vascular tumors unresponsive to corticosteroids, at a dosage of 3×10^6 IU/m^2/d as a subcutaneous injection.[7] It seems that IF-α induces involution of IHs though a dose-dependent increase in endothelial cell apoptosis. They are usually indicated for (1) lesions that do not respond to high-dose corticosteroid, (2) contraindications to prolonged systemic corticosteroid use, (3) complications of corticosteroid, and (4) parental refusal to use corticosteroid.[3,7] IF-α has a reported 50% to 80% regression rate after an average of 7 months of therapy, with complete resolution in as many as 40% of patients.[3] Use of IF has decreased mainly because of its slower response time compared with steroids, need for hospitalization for hemodynamic monitoring, and serious neurotoxic side effects such as spastic diplegia (20%).[7] Other common side effects include flu-like symptoms, irritability, neutropenia, and liver enzyme abnormalities.

Laser

There are various different lasers available to use on vascular tumors, including carbon dioxide, flashlamp-pumped pulsed dye (FPDL), neodynium: YAG (Nd:YAG), potassium-titanyl-phosphate (PTPL), and argon.[3] Each laser has different penetration depths. CO_2 laser ablation has been used to treat acute airway obstruction caused by a hemangioma. Flashlamp-pumped pulsed dye has a shallow penetration depth of ~1 mm, making it effective in treating relatively flat, and superficial hemangiomas.[12,14] Nd:YAG and PTP lasers have been used successfully for deeper and thicker vascular tumors (> 1.5 mm), but are associated with a higher risk of scarring and ulceration.[3]

Surgery

Excision of IHs may be considered during any phase. The majority of hemangiomas do not cause complications and surgery can be avoided. Even if surgery is indicated, medical treatment is usually started first to reduce the size of the lesion and the future surgical scar. Early surgical intervention is usually indicated for lesions causing: (1) obstruction— visual or subglottic; (2) deformation— periorbital distortion with secondary astigmatic amblyopia; (3) bleeding or ulceration unresponsive to medical or laser therapy; (4) scarring— ulceration more pronounced than surgical scar.[2,7,12,14] Infantile hemangiomas on the scalp are usually excised early because they can cause alopecia. During involution, removal of large IHs is considered because it is during this time that children normally become aware of physical differences. Excision during this phase is indicated if it is obvious that resection will be inevitable and there will be no difference in future scarring.[12] When possible, resection of IHs should be postponed until they have completely involuted. Indications for resection during the involuted phase include damaged skin, abnormal contour, and distortion of normal structures. Some lesions are amendable to single resections, whereas others will need a staged approach, most commonly those on the lips, cheek, glabella, and scalp.[7,12]

Complications

Life-threatening complications associated with IHs, such as tissue destruction, distortion, and obstruction, has been estimated to be around 10%. Its phase, size, and location are usually good predictors of future complications.

Ulceration

The most common complication is spontaneous epithelial breakdown, resulting in painful ulceration and often necrosis. This occurs in less than 5% of cases.[3] Ulceration usually starts at the center of the lesion during its proliferative phase.[7,9] The fast expansion of the tumor impedes blood to the center of the lesion, resulting in necrosis and ulceration. It can occur at any anatomical site, but the lips, perineum, anogenital region, and extremities are most commonly affected. With ulceration, there is an increased risk for deformity and scarring, especially on the lips, nose, and eyelids.[9] If not treated properly, ulcerations can become infected. In extreme cases, this can lead to cellulitis, septicemia, and death. If ulceration and spontaneous bleeding occur, local pressure is usually sufficient to control the bleeding. Further complications can be avoided with proper wound care, topical antibiotic, FPDL, and/or surgical excision of the lesion. Surgery is indicated if the lesion is located on the scalp, trunk, extremities, or face.[7,9] Superficial ulcerations usually heal within days to weeks, whereas deep ulcerations take much longer.

Visual Impairment

During the first year of life, the optic cortex is extremely sensitive to stimulus deprivation. Obstructing periorbital hemangioma, if not properly managed, can potentially cause visual impairment from deprivation amblyopia.[3,7] This can occur in as little as a week of obstruction. Presence of a mass and its pressure on the upper eyelid or supraorbital area can cause deformity of the developing cornea, resulting in astigmatic amblyopia.[9] In some cases, IHs can extend into the retrobulbar space, leading to ocular proptosis. Periorbital lesions have a high risk of ulceration (15–25%). Anisometropia and failure to develop stereopsis can occur.[3] If the lesion is small, it should be surgically removed. Corticosteroids and β-blockers are usually started immediately, even if surgical intervention is warranted.

Airway Obstruction

Intranasal hemangiomas can be problematic in infants because they are obligate nose breathers.[3] Most airway hemangiomas are usually located in the subglottic region and can be life threatening. Fifty percent of the infants with a subglottic hemangioma have cervical skin involvement.[9] Endoscopy is used for diagnosis. These lesions present with hoarseness and biphasic stridor 4 to 12 weeks after birth. When cutaneous lesions accompany laryngeal hemangiomas, they are often multiple, and typically appear in a "beard-" like distribution.[9] Intranasal, subglottic, and laryngeal hemangiomas can all be treated with corticosteroids except in acute life-threatening situations.[3] Resection is the best approach for these lesions. For extensive uncomplicated subglottic or laryngeal hemangiomas vincristine, propranolol, or interferon may be used to reduce its size.[3] Lesions causing severe airway obstruction can be treated with intralesional carbon dioxide laser ablation. Temporary tracheostomy should be considered for severe cases.[9]

Auditory Canal Obstruction

The external auditory canal can be obstructed by a hemangioma affecting the parotid gland. If the auditory canal is obstructed at an early age, conducting hearing loss can occur. Bilateral involvement that persists beyond 1 year of age can affect speech development.[3] These lesions are managed similar to hemangiomas of the airway, and should be addressed as soon as possible.

Congestive Heart Failure

Diffuse neonatal hemangiomatosis (multiple cutaneous or visceral IHs) or a single large visceral hemangioma (most notably in liver) can cause congestive heart failure (CHF).[7,9] Large visceral hemangiomas can create symptomatic arteriovenous fistulas and cardiac decompensation.[3] Managing these lesions usually involves the typical approach for hemangiomas combined with treatment for CHF. Embolization, hepatic artery ligation, resection, and even transplant have been used with variable success.[3,7] Despite aggressive treatment, patients usually succumb to persistent CHF, infection, or bleeding.

Associated Syndromes

Infantile hemangiomas have been found to be associated with certain syndromes, such as PHACES (posterior fossa abnormalities, hemangiomas, arterial intracranial anomalies, cardiac anomalies/coarctation, eye anomalies, sternal defects) and LUMBAR (lower body hemangioma, urogenital anomalies or ulceration, myelopathy, bony deformities, anorectal and arterial malformations, renal anomalies) syndromes.[4,] However, a full discussion of these syndromes is beyond the scope of this article and can be found elsewhere in literature.[4,16]

Congenital Hemangiomas

Although congenital hemangiomas (CHs) and IHs grossly appear very similar, they are histopathologically, pathogenetically, and immunophenotypically distinct. Congenital hemangiomas in general have no gender preference, are fully developed at birth, and test negative for the immunohistochemical marker GLUT 1.[6,7] Congenital hemangiomas exhibit proportional growth, are usually solitary, and more commonly present on the extremities. Congenital hemangiomas undergo the proliferative phase in utero, which makes it possible to be diagnosed with prenatal imaging.[4] They are separated into two main types: rapidly involuting congenital hemangiomas (RICHs) and noninvoluting congenital hemangiomas (NICHs).

Rapidly Involuting Congenital Hemangioma

Rapidly involuting congenital hemangiomas undergo rapid proliferation in utero and are grossly visible at birth. They usually start involuting weeks after birth and fully involute around 2 years of age.[4] They present as a raised, violaceous tumor with ectatic veins surrounded by a pale rim of vasoconstriction.[7] Histologically, variable-sized lobular capillaries with prominent endothelial cells are seen. Involution usually starts just after birth centrally and progresses toward the periphery, leaving behind a region of thin atrophied skin with little subcutaneous fat.[4,6] Treatment is similar to that of IHs. Lesions can be excised if they do not completely involute.

Noninvoluting Congenital Hemangioma

Noninvoluting congenital hemangiomas always appear fully formed at birth as a solitary tumor and are more common in males (►**Fig. 2**). They demonstrate proportional growth with the child and will never involute.[4] Typical lesions are round, average from 5 to 10 cm in diameter, with coarse overlying telangiectasias.[7] Most are warm to palpation with a component of fast arterial flow that can demonstrated by Doppler US.[7] Histology reveals lobular collections of small, thin-walled vessels with a large, often stellate central vessel.[6] Interlobular areas contain dilated dysplastic veins. Surgical excision is treatment of choice since they are solitary and do not involute (►**Fig. 2**).[4]

Pyogenic Granuloma (Lobular Capillary Hemangioma)

Lobular capillary hemangioma (LCH), commonly known as pyogenic granuloma, is the second most common vascular tumor seen in children (behind IHs).[7] Mean age of presentation is 6 years old, but can be found at any age. It is most commonly found in the head and neck region, but any part of the body can be affected. Lobular capillary hemangiomas resemble IHs, but microscopically these tumors show distinct

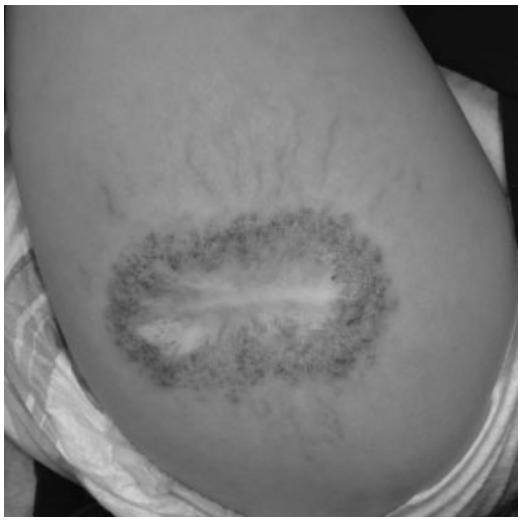

Fig. 2 Noninvoluting congenital hemangioma.

separations of capillary lobules by thick bands of fibrous tissue, unlike normal tissue that separates lobules of IHs.[6] These lesions are negative for GLUT 1. Lobular capillary hemangiomas arise as rapidly growing, bright red papules varying in size from a few millimeters up to 2 cm (►**Fig. 3**).[7,9] They are often pedunculated and can bleed easily, repeatedly, and profusely.[6,7] Management depends on the location and size. Small LCH can be removed by shave excision with curettage and light electrodessication to the base of the lesion.[7,9] Some of these tumors may also respond to treatment with silver nitrate. A worrisome, but rare complication is the development of multiple satellite lesions after its initial removal (►**Fig. 3**).[7]

Kaposiform Hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is a rare and aggressive vascular tumor of infancy (►**Fig. 4**). It is frequently associated with Kasaback-Merritt phenomenon (severe thrombocytopenia).[9] Kaposiform hemangioendothelioma can be present at birth or develop after, with 75% occurring in early infancy (usually before age 2).[7] Kaposiform hemangioendotheliomas frequently occur outside the cervicofacial region, affecting the trunk, extremities, and retroperitoneum. Clinically, they present as deeply seated, often bulging, indurated mass with a deep red-purple in color, edematous, and warm, with ecchymosis over and around the tumor.[6,9] Histologic studies reveal densely infiltrating nodules composed of spindled endothelial cells with minimal atypia and low mitotic activity.[6,7] Rarely, KHEs can occur without consumption coagulopathy. Immunohistochemistry reveals that spindle cells are positive for CD31, CD34 (a blood vascular marker), podoplanin, LYVE-1, PROX1 (all three lymphatic markers), and are negative for GLUT 1.[6] Kaposiform hemangioendothelioma is amenable to surgical excision if localized and superficial. However, pharmacological treatment is used for lesions not amenable for resection, such as those located in inaccessible areas such as the mediastinum or retroperitoneum, or those lesions that are too large for resection. Pharmacological options include IF-α 2a and vincristine.[9] Chemotherapeutic regimes consisting of cyclophosphamide, vincristine, and actinomycin D have also been used.[2] Corticosteroids alone are not effective, and heparin should not be used in the presence of Kasabach-Merritt phenomenon because it can cause the release of FGF, resulting in accelerated tumor growth (►**Fig. 4**).[6]

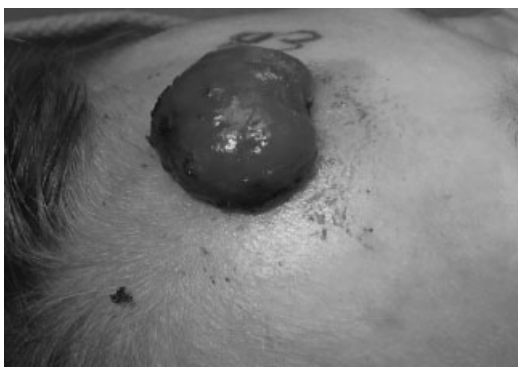

Fig. 3 Pyogenic granuloma.

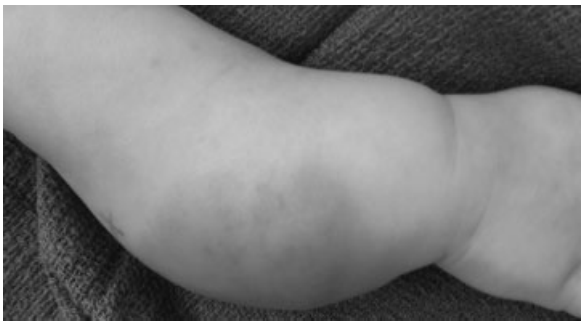

Fig. 4 Kaposiform hemangioendothelioma.

Tufted Angioma

Tufted angioma (TA), also known as angioblastoma of Nakagawa, is a rare vascular tumor closely related to KHE.[3] Tufted angiomas are milder and more superficial than KHEs. Onset is during infancy or early childhood (before 5 years), but occasionally is present at birth (15%).[7] They can present as solitary tumors, large infiltrated macules, or plaques with overlapping papules (►**Fig. 5**). They can spread slowly, leaving a "port-wine stain-like" cobblestone appearance.[7] The characteristic histology is vascular tufts of tightly packed capillaries dispersed throughout the dermis in a cannonball pattern.[6,7] The natural history of TAs is less predictable. Some cases involute, leaving minor cutaneous changes. Others can persist and expand overtime. Tufted angiomas are immunoreactive for lymphatic markers, such as podoplanin, LYVE-1, and PROX1, but also negative for GLUT 1.[6] Treatment options are similar to those for KHE and can be complicated by Kasabach-Merritt phenomenon (KMP) (►**Fig. 5**).

Kasabach-Merritt Phenomenon

Kasabach-Merritt phenomenon is a clinical finding that may accompany TAs and KHEs. Kasabach-Merritt phenomenon is

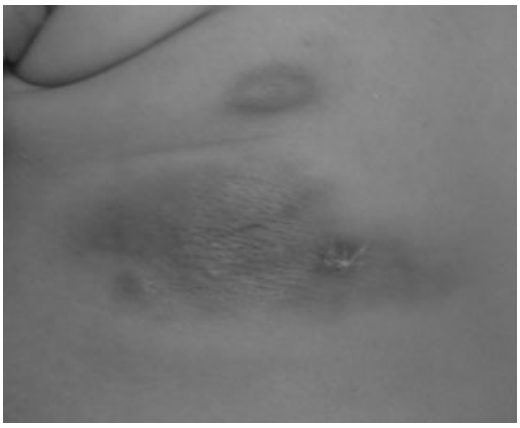

Fig. 5 Tufted angioma.

a consumption coagulopathy with thrombocytopenia ($< 10{,}000/mm^3$) and low fibrinogen levels. Hematologic abnormalities like anemia, elevated D-dimers, prothrombin time, and partial thromboplastin time may present.[7] This phenomenon occasionally presents at birth, but is more common in the first few months of life. It usually presents as tenderness, rapid growth, and bruising in a growing soft tissue tumor. Mortality of KHE and TA complicated by KMP can be as high as 50%.[3] Managing KMP, like any other vascular anomaly, should be done in a multidisciplinary manner. Corticosteroids alone are rarely effective, but are still used as first-line treatment. Surgery can be curative, but is rarely feasible. Vincristine has been demonstrated to be highly effective, but relapses are frequent. Supportive therapies like transfusions of fibrinogen and fresh-frozen plasma are helpful. Platelet transfusions should be avoided, except before surgical procedures or active bleeding because they can cause enlargement of the tumor.[7] Heparin, which is useful in consumption coagulopathy seen with vascular malformations, should not be used in the presence of KMP. Heparin causes the release of FGF, resulting in accelerated tumor growth and increased bleeding.[7] Kasabach-Merritt phenomenon can easily be confused with the coagulopathy that occurs in the setting of large vascular malformations. The coagulopathy associated with vascular malformations usually has a later onset and is characterized by consumption of clotting factors and elevated D-dimers, but has a platelet count and fibrinogen level not as low as in KMP.[7]

Angiosarcoma

Angiosarcomas (ASs) are rare and aggressive vascular tumors, rapidly proliferating with extensively infiltrating anaplastic cells derived from blood vessels and lining irregular blood-filled spaces. They can occur at any age, and in any part of the body, but most commonly arise on the skin, liver, breast, and spleen. Lymphedema, radiation, and exposure to carcinogens, such as vinyl chloride, arsenic, and thorium dioxide, have been indicated as possible risk factors.[16,17] Angiosarcomas can resemble a skin infection, a bruise, or a nonhealing wound. They form distinct vascular channels that are irregular in size and shape. Initially, they can resemble infantile hemangiomas. Unlike IHs, angiosarcoma vascular channels disrupt tissue planes and form a connecting network of sinusoids. Surgery is the primary method of treatment for angiosarcomas. Chemotherapy or radiation therapy can be an important part of the treatment plan. The chemotherapy of choice for angiosarcomas has been doxorubicin. Some institutions use a combination of mesna, doxorubicin, and ifosfamide (MAI).[17] Paclitaxel and docetaxel have shown effectiveness against angiosarcomas of the head, neck and scalp.[18] Long-term prognosis is poor for these patients, with a 5-year overall survival rate of less than 30%.[17,18]

Conclusion

Vascular tumors are the result of pathologic angiogenesis and are quite common. Out of these, infantile hemangiomas have the highest frequency and appear shortly after birth. Today, the available medical treatments are nonspecific, have an efficacy rate around 85% to 90%, and are usually applied if there is the possibility of future complication. The majority is usually left alone until involution is complete, and usually surgery is required to correct the resultant atrophied skin. There is still the need to know more from these lesions to possibly discover a more specific treatment.

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