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Hemangiomas of Infancy – A Clinical Review

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SUMMARY Hemangiomas of infancy are the most common benign tumors of childhood. They are composed of proliferating endothelial tumor cells and usually manifest as cutaneous birthmarks. In most cases, these tumors characteristically follow a natural course of regression. However, they can cause a tremendous amount of anxiety. Hemangiomas can threaten vital life processes if located in certain areas of the body. They may also be part of larger syndromes associated with high rates of life-changing morbidity and mortality. In all of these situations, hemangiomas are often referred due to the uncertainties that exist regarding the most efficacious diagnosis and management.

KEY WORDS: hemangiomas, infancy, cutaneous birthmarks, vascular tumors

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INTRODUCTION

Cutaneous birthmarks are often the result of vascular tumors and malformations. Over the past several decades some of the underlying processes behind these lesions have been elucidated. In doing so, hemangiomas are now recognized as well-defined vascular tumors. However, misleading terms from the past are still used to describe them. These are often inaccurate and used interchangeably. Mulliken and Glowacki proposed a set of criteria to differentiate vascular tumors and malformations that have gained wide acceptance (Tables 1 and 2) (1). These have been modified over the past two decades to incorporate new information, and the International Society for the Study of Vascular Anomalies has recently acknowledged an updated version (Table 3) (2). These criteria provide a well-defined foundation from which a clinician may study, diagnose, and accordingly treat these lesions.

Hemangioma of infancy is the accepted term used to describe the most common benign tumor in children (3). In the past, it has been used carelessly to describe a variety of cutaneous birthmarks. It should only be used for the entity discussed here (Tables 1 and 2). Culinary adjectives such as strawberry and cherry are sometimes used to further describe some hemangiomas, but are not particularly clear. Modifiers such as conventional ones characterize lesions with respect to their location at different depths of the skin. Subtypes of hemangiomas have been documented, such as noninvoluting (4) and lobular capillary hemangiomas (5), but should be distinguished from the common, benign form that is the focus of this article.

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Table 1. Mulliken and Glowacki classification of vascular anomalies

Vascular tumors	Vascular malformations
Proliferating hemangiomas	Capillary malformations
Involuting hemangiomas	Venous malformations
	Arterial malformations
	Lymphatic malformations
	Fistulous malformations

Table 2. Distinguishing characteristics between vascular tumors and malformations

Vascular tumors	Vascular malformations
Endothelial cell proliferation	Normal endothelial cell cycle
40% present at birth	90% present at birth
Rapid postnatal growth, followed by involution	Grow commensurately with child growth

EPIDEMIOLOGY

Hemangiomas of infancy are apparent at birth in 1.0%-2.6% of term neonates, but the incidence may be as high as 10%-12% in white children as the proliferative phase progresses in the first year of life (6). They affect females more than males with a 3:1 ratio (7,8). Approximately 30% of these birthmarks are apparent while the infant is in the newborn nursery. Their frequency tends to be higher in infants who are preterm, weigh less than 1500 g (7), or were subject to chorionic villus sampling in utero (9). The incidence might be lower in children of African or Asian descent (3). Segmental hemangioma, a lesion with a plaque-like morphology, is more common in Hispanic infants (10). In patients aged 2-6 years, hemangiomas may be encountered in the involutive phase. Complete involution usually occurs by age 7-10, and they are uncommon in children older than this.

Some patients may have multiple lesions occurring all over the body. This occurs uncommonly, and is referred to as hemangiomatosis. It is apparent at birth in 61% and by one month of age in 86% of cases (11). The two major classifications of hemangiomatosis will be described later.

ETIOLOGY AND PATHOLOGY

Hemangiomas result from abnormal changes in angiogenesis that lead to over-proliferation of vascular entities. There may be a complex interplay of angiogenic and angiostatic forces involved in both normal and pathologic processes that lead to their formation (12). At this time, however, fetal vascular development remains poorly understood. Angiogenic markers such as proliferating cell nuclear antigen, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), E-selectin, and type IV collagenase are found at increased levels during the proliferative phase (13-15). During the involutive phase, there is a subsequent decrease of angiogenic factors

Table 3. International Society for the Study of Vascular Anomalies classification

Vascular tumors	Vascular malformations
Hemangiomas of infancy	Capillary malformations (port-wine stain)
Rapidly involuting hemangioma	Venous malformations
Noninvoluting hemangioma	Lymphatic malformations
Kaposiform hemangioendothelioma	Arterial malformations
Tufted angioma	Mixed malformations
Pyogenic granuloma	
Malignant endovascular papillary angioendothelioma (Dabska tumor)	

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with a 5-fold increase in endothelial cell apoptosis (16). This increase in cell death may be significant in overcoming the proliferation of endothelial cells, and may mark the beginning of involution. These alterations in angiogenesis may account for the increased vascular proliferation that occurs in hemangiomas.

Antigens relatively unique to hemangiomas have been identified that are not found in normal skin or vascular entities such as pyogenic granuloma, granulation tissue, tufted angioma, kaposiform hemangioendothelioma, or vascular malformations (17). The glucose transporter GLUT1 is normally expressed in various cell types throughout the body, but not the skin. GLUT1 was found in samples taken from hemangiomas during all stages of its natural course (18), and has been found to be specific for this cutaneous birthmark. Markers such as merosin, Lewis Y antigen, and Fcγ receptor are also tissue-specific (17). Curiously, chorionic villi also share this constellation of antigens, giving rise to a hypothesis of placental origin for hemangiomas (17,19).

Most hemangiomas develop sporadically and are believed to be the result of developmental errors that occur between the 4th and 10th week of gestation. One series noticed a higher concentration of focal hemangiomas in the center of the face, an area that contains the highest density of embryonic fusion lines on the face (19). Rarely, they are inherited in an autosomal dominant fashion with moderate to high rates of penetrance (20). One study suggests that the formation of hemangiomas may be associated with mutational events that result in the loss of heterozygosity at a specific locus on chromosome 5 (21). Three genes involved in angiogenesis map to this chromosomal region, namely fibroblast growth factor receptor-4, platelet derived growth factor receptor-beta, and fms-related tyrosine kinase-4 (22).

Microscopic examination of hemangioma tissue reveals proliferating groups of endothelial cells. During involution, these cells flatten, the vessel lumina dilate, and fibrous tissue is deposited. Histologic examination of residual tissue reveals few feeding and draining vessels in a dense stroma of collagen and reticulin fibers (1).

CLINICAL FEATURES AND CONSIDERATIONS

The natural history of hemangiomas usually follows a predictable course (23). The proliferative phase usually begins at 3-6 months and is complete by 9-12 months of age. Few remain stable in size and appearance from birth, and exhibit no proliferative phase. Involution typically begins by 12-18 months of age, and progresses at a rate of about 10% per year (24). It is usually complete by age 7-10, at which time only 50% of patients will have completely normal appearing skin, the rest exhibiting some form of residuum.

Hemangiomas are most commonly located on the head and neck (59%), followed by the trunk (24%), lower extremities (10%), and upper extremities (7%) (25). Most are less than 2.0 cm in diameter, but in some instances can cover large portions of the body. Approximately 30% of these lesions are developed at birth. One-half of infants have premonitory skin findings that range from hypopigmented to a “bruise-like” macule (26). The clinical appearance of developed hemangiomas varies with the location of the tumor within the skin. Superficial hemangiomas are situated in the superficial dermis, and appear as bright-red, raised nodules. This appearance gave rise to the term strawberry hemangioma. Lesions located deep in the reticular dermis or subcutaneous fat appear as normal appearing skin overlying soft masses with a bluish tone (27). These have often been referred to as deep or cavernous hemangiomas. Cases with both superficial and deep elements have also been described (23).

During the involutive phase, superficial hemangiomas transform from a “strawberry” appearing neoplasm to a duller, gray one. The tumor becomes softer to palpation as the vascular elements are replaced by connective tissue. In most cases, the more superficial and centrally located elements will show signs of involution first. Similarly, deep hemangiomas also tend to lose their pigmented appearance as they enter the involutive phase.

One half of involuted hemanigomas will display some form of residual scar (23,25). The other 50% may exhibit telangiactasias, localized atrophy and alopecia, or a hyperpigmented residuum. The timing of all of these changes and their ultimate appearance is, however, difficult to predict.

Hemangiomatosis is a relatively rare entity that is characterized by multiple cutaneous tumors. Lesions of hemangiomatosis are usually bright red, as in solitary hemangiomas, but range anywhere in size from 2 mm to 2 cm (28,29). Diffuse neonatal hemangiomatosis is characterized by the aforementioned skin findings and coexisting visceral involvement (11,29-31). The most common site of involvement is the liver, although nearly any

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organ may be involved. Patients may show signs of high-output congestive heart failure, hemorrhage from the gastrointestinal or respiratory tract, or signs of hepatic involvement such as increased abdominal girth, hepatomegaly or obstructive jaundice (28,31). These infants have a relatively poor prognosis.

Benign neonatal hemangiomatosis has only cutaneous involvement or asymptomatic visceral involvement. It is commonly associated with complete resolution of physical findings by the age of 3 (11,31). Patients who present with multiple lesions should have a thorough history and physical examination. Suspicious clinical findings should guide the appropriate imaging studies (32). Although hemanigomas are most often benign and located on the skin, tumors in alternate sites may threaten vital life processes. These sites include the eye and the airways.

Hemangiomas are the most common orbital tumor of infancy, and may threaten the development of the visual axis (29,33). Periocular tumors may impinge upon external structures of the eye, or may be located deep in the orbit, producing proptosis. They may become large enough to physically obstruct the visual system or place pressure on the cornea, especially when located on the upper eyelid (33). Because of the high rate of visual complications, infants with periocular tumors should be promptly referred to an ophthalmologist for evaluation.

Laryngeal disease often causes stridor or croup-like symptoms, and 50% of cases have concurrent dermatologic manifestations. One study found that 63% of children with a “beard-like” distribution of vascular tumors had simultaneous airway hemangiomas (34). Respiratory symptoms should be evaluated in any infant with hemangiomatous disease in such a distribution.

Hemangiomas may also be a part of a constellation of associated anomalies termed the PHACE(S) syndrome. One should search for features of this syndrome that includes posterior fossa malformations, arterial anomalies, coarctation of the aorta, cardiac defects, eye abnormalities, and sternal defects (35-37).

DIFFERENTIAL DIAGNOSIS

The defining feature of hemangiomas is their natural course of proliferation and subsequent involution. Upon initial presentation of a patient with vascular tumor-like lesion, one must also consider vascular malformations, noninvoluting hemangiomas (4), lobular capillary hemangiomas (5), Dabska tumors (38), tufted angiomas, port-wine stains, or fibrosarcoma.

EVALUATION

The diagnosis of a vascular tumor is based on history and physical examination alone in about 95% of cases (39). Laboratory tests are not indicated for the common cutaneous lesion, but may be performed in situations that have concurrent gastrointestinal or respiratory manifestations.

When the history and physical examination are equivocal, imaging studies are sometimes utilized to distinguish hemangiomas from other entities mentioned in the differential diagnosis. Distinct criteria are being developed that will allow the physician to diagnose an atypical lesion on magnetic resonance imaging (MRI) (40). This imaging modality is of limited value unless contrast is used (40). MRI also allows for precise localization of the lesion, and can detect associated nervous system abnormalities. Ultrasound with Doppler interrogation is the most cost-effective and noninvasive imaging technique (41). Results are operator dependent, and ultrasound does not illustrate the lesion relationship to other structures. These characteristics make ultrasound suitable for following the course of internal lesions. Tissue biopsy is diagnostic, but high risk of bleeding makes this a somewhat unpopular method of diagnosis. It may be used to differentiate atypical hemangiomas from other soft-tissue tumors such as kaposiform hemangioendothelioma, myofibromatosis, and rhabdomyosarcoma (39).

MANAGEMENT AND TREATMENT

The goals of management are to prevent or avoid life- or function-threatening complications, to prevent permanent disfigurement, to minimize the psychological impact on the patient and his/her parents, to avoid aggressive or scarring treatments, and to avoid/treat ulceration to minimize pain or scarring (39). Most hemangiomas of infancy involute without intervention and are in anatomically benign locations (24). It is therefore important to educate parents about their child’s condition and describe its typical course, but also mention that the rate of involution and the nature of the residuum might be unpredictable. This may ease anxiety if the lesion grows in the early stages. With effective patient education, one can avoid being pressured into instituting hasty medical therapy that may lead to a less desirable outcome. Regular follow up visits should be scheduled to monitor

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the course of the lesion and to provide continuous reassurance. Second opinions from other physicians may also be helpful. Parent education has been shown to significantly alleviate stress caused by hemangiomas and is a crucial part of treatment (42).

MEDICAL THERAPY

Early medical intervention is indicated when hemangiomas are located in areas that hinder normal development, interfere with vital life processes, or cause severe pain (3,33,34,39). These locations include the eye, nose and airways. Another indication is a large facial lesion, since these almost inevitably will leave highly visible involutive scars.

Systemic glucocorticoids have been considered first-line therapy for severely deforming or life-threatening lesions for several decades (39,43-45). Recent reviews have reported efficacy rates of 84% in infants treated with prednisone equivalent doses of 2.9 mg/kg when administered during the proliferative phase (45). Doses of 2 to 4 mg/kg in a single morning or divided dose have been recommended, with larger doses being used for tumors that compromise the airways (39). Complications have been reported in approximately 35% of patients, with no catastrophic results (45,46). Common side effects such as irritability, cushingoid appearance, and adrenal suppression are temporary. Bacterial infection secondary to immune suppression is uncommon (46). To avoid adrenal crisis, steroids should not be stopped abruptly and the patient will require stress doses for months following treatment.

The use of intralesional triamcinolone in treating problematic cases was first demonstrated in the treatment of periorbital hemangiomas (39). Its effectiveness in treating localized cutaneous hemangiomas has since been demonstrated (47). One therapeutic regimen entails multiple injections of a 50:50 mix of triamcinolone (40 mg/mL) and betamethasone (6 mg/mL) at doses of 3-5 mg/kg per treatment every four to six weeks (48,49). Complications are relatively rare. An ophthalmologist should evaluate orbital hemangiomas.

Interferon alfa-2a is used for life-threatening or deforming hemangiomas that have not responded to glucocorticoid therapy (50-52). This treatment is administered subcutaneously at a dose of 1 to 3 million U per square meter of body surface area. Common side effects include fever, malaise, neutropenia and elevated liver enzymes (50-53). One series reported on 100% of patients exhibiting some degree of toxicity (53). Interferon is not regularly used due to its potential for neurotoxicity (53). The spectrum of neurologic side effects ranges from agitation and irritability to seizure and permanent spastic diplegia (53,54).

Newer laser treatments have rapidly risen to the forefront of the hemangioma management due to their safety and efficacy (39,55). With recent technological innovations, the flash-lamp, pumped, pulse-dye laser (FPDL) is considered the most effective laser treatment for superficial hemangiomas and residual lesions (39,55). The FPDL produces short pulses of light at 585 nm, and the typical time of exposure is 0.45 ms (39,56-58). For proliferating lesions, treatments are spaced at 2- to 3-week intervals, and at 4 to 6 weeks for nonproliferative lesions (59). Atrophic scarring is less common than with argon laser, still producing side effects (56,60). The FPDL, however, is limited by its depth of penetration, and is ineffective on deep hemangiomas (55,57,58,61). The neodymium:yttrium-aluminum-garnet laser has produced promising results in deep hemangiomas (54,61). Treating uncomplicated hemangiomas with the FPDL has yet to be proven more effective than the conservative approach (56). New generations of FPDLs that are less painful are currently being studied (63). For now, clear indications for early laser treatment remain ulcerated lesions after topical therapies have failed, and residual telangiectasias (3,39,57).

Local wound care for alleviation of pain and reduction of infection rate has been the foundation for treatment of ulcerated lesions (3,64-66). Ulceration affects between 5% and 15% of hemangiomas, and is the most frequent complication (64,65). Along with infection, ulceration can lead to disfigurement and pain. Compresses are a readily available measure that can be used to debride the ulcer (3,64,65), and can be used in conjunction with topical mucoprin, bacitracin, or metronidazole (64).

SURGICAL THERAPY

The technique and timing for surgical resection of hemangiomas is still a topic of contentious debate. The surgeon must identify situations where an excision procedure will produce a more cosmetically acceptable result than conservative or medical treatment. The timing of resection is also a factor since facial deformities can have a psychological impact on children, especially when they enter their school-age years. Some still advo-

cate postponing excision until after the involution phase. Specific situations where surgical intervention is indicated include abnormal scar or excess tissue following natural involution, ulcerated lesions that bleed excessively or are associated with pain, and lesions that interfere with the development and/or activities necessary for life including vascular tumors of the eye, ear, or larynx (33,34,39,64,65,67-70). One study evaluated the outcome of a circular excision with purse-string closure using a single 4-0 or 5-0 suture versus a standard lenticular excision (67). Circular excision resulted in an average scar that was 15% of its original area. In addition, the scar length with circular excision was by 72% shorter than with lenticular excision. There was no significant variation between the phase in which the procedure was performed. There was no variation in the result if the circular or lenticular excision was performed as a follow-up procedure to further reduce the scar size either. To date, no other excision and closure technique results in a smaller scar.

CONCLUSIONS

Hemangiomas are rather unsightly lesions, and parents of these children, understandably, will often pressure physicians to deliver definitive medical or surgical treatment. The physician should be well versed in the natural history of the lesion, the risks and benefits of available treatment modalities, and educate parents to alleviate the psychological stress placed upon the family. One should be concerned if there are multiple tumors, periorbital lesions, signs of airway obstruction, or symptoms of visceral hemangiomas. Better understanding of these lesions and new generations of the FPDL may soon lead to effective early interventions for nonproblematic lesions. For now, the physician should provide ongoing assurance that the child is healthy, and that the appearance of the lesion will improve with time.

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