Ten Lessons Learned from a Hemangioma Clinic

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ABSTRACT

Infantile hemangiomas are the most common tumors seen in pediatrics. Recent clinical research has led to marked advances in understanding, including the recognition that a wide spectrum of clinical severity exists and that these tumors are significantly more complex than originally thought. This article addresses some of the most common clinical questions and scenarios surrounding infantile hemangiomas, based on the most recent research to date.

KEYWORDS: Hemangioma, PHACES syndrome

True Infantile Hemangiomas Appear a Few Weeks to Months after Birth and Are Dynamic Tumors That Have Phases of Growth and Involution

Despite Dr. John Mulliken's landmark classification of vascular birthmarks in 1982, there remains a great deal of confusion within both the medical and nonmedical communities, with just about everything vascular on the skin or elsewhere often being called "hemangioma."¹ Although this definitely makes any hemangioma clinic that much more interesting, prior misdiagnosis leads to inaccuracies in both treatment and discussion of prognosis.

For example, it is now recognized that infantile hemangiomas are probably never "fully formed" at birth. Such lesions are either another type of vascular tumor or a vascular malformation. One entity that has been increasingly reported is the rapidly involuting congenital hemangioma or RICH. Despite the name, RICH is not a hemangioma at all but a hybrid between a benign vascular tumor and vascular malformation. RICHs are fully formed at birth, most commonly located on an extremity, have a characteristic gray-purple or sometimes deep purple color (because of intralesional hemorrhage),

and involute rapidly within the first year of life with characteristic atrophy (Fig. 1A, B). The counterpart to RICH, the noninvoluting congenital hemangioma (NICH), most commonly arises on the trunk as a congenital, oval to round plaque with coarse, central telangiectasias and a surrounding rim of pallor (Fig. 2). NICH may feel warm to palpation, has a slight bruit, and, as the name implies, remains unchanged over time. RICH and NICH may be on two ends of a spectrum, as there are known cases of RICH that later evolve into NICH. Like RICH, the tufted angioma (TA), another relatively rare type of benign vascular tumor, can also be congenital and self-regress.² TA is one of two types of vascular tumors associated with the Kasabach-Merritt phenomenon (KMP), the other being the kaposiform hemangioendothelioma (KHE). As with RICH/NICH, it is believed that TA and KHE are also variants of the same entity, although associated KMP is much more common with KHE.³

Although the aforementioned entities are histopathologically benign, any congenital, vascular tumor that is firm and grows rapidly after birth, *especially* when located on the hands or feet, can also represent malignancy (particularly infantile fibrosarcoma or

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Figure 1 (A) Rapidly involuting congenital hemangioma (RICH) in early infancy. (B) Rapidly involuting congenital hemangioma (RICH) at 1 year.

rhabdomyosarcoma) (Fig. 3). In any case suspicious for such, it is best to obtain tissue pathology for definitive diagnosis and not rely solely on imaging. Lastly, vascular lesions present at birth that do not change significantly during early childhood are usually vascular malformations, which are structural, nondynamic anomalies of blood vessels. Vascular malformations can be slow-flow (capillary, venous, lymphatic, or a combination) or fast-flow (arteriovenous malformation).¹

Current Nomenclature Describes Hemangioma Appearance by Level of Skin Involvement: Superficial (Most Common), Deep, or Combined (Fig. 4)

The terms “strawberry” and “cavernous” are best abandoned. The former term began in medieval times when it was believed that if a pregnant woman ate strawberries, this could somehow be imprinted on her fetus, and the latter term is also used to describe venous malformations, leading to further confusion. Furthermore, this terminology implies that hemangiomas of different morphol-

ogy also have different pathology, when it is believed that all infantile hemangiomas probably have the same histopathology. Most also behave similarly. Although “abortive” hemangiomas do occur, almost all others demonstrate phases of growth (generally rapid for the first 3 to 4 months of life and then slow for 6 to 12 months) and involution, which occurs slowly over several years. Individual rate of growth and improvement is still difficult to predict but is often proportionate to size, with larger hemangiomas generally having longer periods of growth and involution. “Deep” hemangiomas are often not noticed by families until 3 to 4 months of age because proliferation is occurring more deeply and

Figure 2 Noninvoluting congenital hemangioma (NICH), with central scarring related to prior ulceration.

Figure 3 Infantile fibrosarcoma.

Figure 4 Combined (superficial and deep) hemangioma.

the appearance can be subtle at first. Some small “pin-point” hemangiomas, which are often multiple, can appear a little later than expected (3 to 4 months of age sometimes), often do not proliferate to a significant degree, and then involute more rapidly than expected, often within the first year.

It Is Important to Be Realistic with Families about Prognosis

A not uncommon clinical scenario involves the parents of a 2-year-old child with a hemangioma who present worried because their pediatrician said that the hemangioma would go away by age 2. There are two problems with this statement. First, complete involution by age 2 certainly happens but is not very common. Second, “go away” implies to parents that the skin will look completely normal when involution is complete, when in reality, up to 50% of the time, that is not the case. Risk factors for scarring include ulceration, significantly raised and/or pedunculated *superficial* hemangiomas (which can result in redundant tissue), and location, especially when hemangiomas occur on the nasal tip or cross the vermilion border. Deep hemangiomas, which by definition do not involve the epidermis to a significant degree, tend to heal extremely well with essentially normal skin.

“Multiple” Hemangiomas Probably Are Not as Worrisome as Once Thought

First of all, how many is multiple? The current (albeit artificial) definition is five or more hemangiomas. It is now recognized that an association exists between multiple births and multiple hemangiomas, so that as average maternal age and number of women undergoing treatment for infertility rise, the incidence of multiple hemangiomas may increase.⁴ The potential association between multiple skin hemangiomas and internal (particularly hepatic) hemangiomas is well known, but it is

now realized that there are different categories of liver involvement, and the most worrisome, life-threatening type of liver hemangioma arises with no cutaneous hemangiomas at all.⁵

What is the recommended protocol for a child who presents with multiple skin hemangiomas? Although no consensus exists, an abdominal ultrasound study is still advised for infants younger than 6 months of age until more is known. However, the simple presence of liver hemangiomas in an otherwise healthy, asymptomatic infant is *not* an indication for treatment. It is likely that most asymptomatic infants with multiple skin and liver hemangiomas will remain healthy, do not require treatment, and can simply be observed clinically. Furthermore, if an otherwise healthy infant older than 6 months of age presents with multiple hemangiomas, an evaluation for visceral involvement is not generally necessary. As with the situation with hemangiomas in a mandibular or “beard” facial distribution and potential airway hemangiomas, if a child has not developed symptoms by 6 months of age, it is very unlikely that he or she will, and their discovery will only serve to increase parental anxiety.

Ulceration Is Not a “Good” Sign of Improvement

Ulceration generally occurs early, during the rapid growth phase, and is more common with superficial, large hemangiomas, especially those in trauma-prone locations such as the lip, diaper area, posterior scalp or back, or folds. Most ulceration is superficial and can be healed with gentle wound care, antibiotic ointment or a similar barrier, and reasonable protection from trauma. Less commonly, however, ulceration can be aggressive, quickly becoming deep and extensive. In most cases this probably results from secondary infection with organisms such as *Pseudomonas*, for which hospitalization for intravenous antibiotics is often necessary.

Also, any hemangioma, especially when ulcerated, can bleed. However, parents often worry that their child’s raised, superficial hemangioma, if traumatized, will “pop like a balloon” with dramatic bleeding, and thus it is important to provide reassurance that *most* hemangioma bleeding is slow, minor, and can be controlled with 10 to 15 minutes of direct pressure. Another treatment reported for aggressive ulceration that fails to respond to standard wound care is platelet-derived growth factor or becaplermin 0.01% gel (Regranex, Ortho-McNeil Pharmaceutical, Raritan, NJ), applied in a thin layer once daily. Although concerns about the potential promotion of hemangioma growth have not, at least thus far, been substantiated, this product is costly (approximately \$500 U.S. dollars for a 15-g tube).⁶

Hemangiomas That Are "Segmental" (Large, Plaque-like) in Morphology Are Much Less Common but Much More Likely to Be Problematic (Fig. 5)

Segmental hemangiomas are more likely to ulcerate or result in a poor cosmetic outcome, or both, and thus are more likely to require treatment.⁷ In addition, like multiple cutaneous hemangiomas, solitary segmental hemangiomas of the skin can be associated with visceral hemangiomas, although the clinical significance is unknown.⁸ Furthermore, segmental hemangiomas may be associated with birth defects. Most physicians are aware that the rare segmental hemangioma crossing midline over the lumbosacral spine can be associated with spinal dysraphism, particularly tethered cord. Ultrasound evaluation of the spine is adequate for infants younger than 4 months of age, but if any abnormalities are seen or the child is older, magnetic resonance imaging MRI (without contrast) is necessary.

PHACES syndrome (Online Mendelian Inheritance in Man [OMIM] 606519) should be considered in any child who presents with a large, segmental hemangioma, especially when located on the face. PHACES is an acronym that stands for posterior fossa abnormalities, large segmental facial hemangiomas, cerebrovascular arterial anomalies, coarctation of the aorta and cardiac defects, eye anomalies, and sternal defects or supraumbilical raphe.⁹ The diagnosis of PHACES requires the presence of a typical segmental, facial infantile hemangiomas (IH) in association with only one other congenital anomaly, as affected infants rarely suffer from the complete spectrum. Infants at risk for PHACES should receive a formal ophthalmologic examination and undergo imaging of the head, neck, and cardiovascular, which is institution dependent but often specifically performed with head and neck MRI and magnetic resonance angiography and an echocardiogram.¹⁰ Sternal pits or defects are usually visible on skin examination, and a supraumbilical raphe is simply a midline defect

Figure 5 Large, segmental facial hemangioma in a newborn girl with PHACES syndrome.

that consists of a well-healed scar that extends upward from the umbilicus and usually does not require repair.

PHACES is uncommon but not rare and appears to be even more common than Sturge-Weber syndrome. Anomalies of the brain are the most common finding and potentially greatest source of morbidity in PHACES. For example, it is now recognized that PHACES-associated cerebrovascular anomalies can develop progressive vasculopathies during infancy that can lead to acute arterial ischemic stroke. Progressive changes may also occur within the cardiovascular anomalies of PHACES, although the true incidence and clinical significance are unknown. The etiology of PHACES is elusive, although about 90% of cases occur in female infants. Unlike hemangiomas overall, PHACES tends to occur in term, singleton pregnancies of normal birth weight. A PHACES patient registry has been developed at Texas Children's Hospital in Houston in an effort to promote collaborative research. Patients or their caregivers will be able to enroll in the registry and will not need physician referral.^{11,12}

It Is Important to Understand What Treatment Can and, Perhaps Even More Important, Cannot Do for Patients

Systemic corticosteroids are still first-line therapy for most life-threatening or life-altering hemangiomas but, as often explained to parents, are intended to "put a brake on the growth phase." Corticosteroids are thus effective only when administered during the proliferative phase, and the earlier initiated, the better. It is estimated that an average of 80% of hemangioma growth often occurs by age 3 to 4 months; thus, in many infants who may not present until 6 months of age, it may be too late for corticosteroids to have a significant impact. Parents must also understand that systemic corticosteroids do not remove the hemangioma, nor do they always reduce size to a significant degree. Most pediatric dermatologists use prednisolone at a starting dose of 2 to 3 mg/kg/day, with simultaneous ranitidine. How steroids are then tapered varies between clinicians; other variables include the age of the patient when therapy is started, the severity of the case, and individual response.⁵

Interferon, once considered the second-line agent for life-threatening, corticosteroid-unresponsive cases, has fallen somewhat out of favor because of legitimate concerns about neurotoxicity, specifically spastic diplegia. Many clinicians thus now use vincristine as a second-line agent. Intralesional steroids are generally most useful for ulceration or focal periocular hemangiomas causing visual compromise, as sometimes the response to systemic corticosteroids with the latter is suboptimal. However, the hemangioma needs to be well defined enough that a reasonably even distribution of medication can be obtained with injection. Concerning periocular hemangiomas,

most ophthalmologists recommend MRI for retro-orbital involvement if there is any thickening of the lid or any displacement of the globe.⁵

Systemic side effects still occur with intralesional (and topical) corticosteroids in addition to very rare but concerning reports of blindness and eyelid necrosis resulting from periocular injection. Intralesional steroid concentrations vary among clinicians but should not exceed 3 mg/kg per dose. Topical steroids are not appropriate for any hemangioma of medical concern but are sometimes used for minimally raised, superficial hemangiomas of minor cosmetic concern, usually on the face. Many clinicians use clobetasol cream once or twice daily for one to a few months during the proliferative phase and advise parents to apply a zinc oxide-based or other visible barrier to the hemangioma edges to avoid contact of the steroid with normal skin.

Lastly, parents often believe (or have been told) that lasers will “remove” hemangiomas. However, the flashlamp pulsed-dye laser was designed not for hemangiomas but for port-wine stains and penetrates the skin only about 1.2 mm. Lasers thus do very little for a hemangioma that is raised to any significant degree. The most widely accepted indications for lasering hemangiomas are ulceration and residual telangiectasias, following some degree of involution. The use of a laser for early, proliferating hemangiomas is controversial because of the potential for promoting ulceration within large, segmental hemangiomas and also, even with smaller, focal hemangiomas, for causing a worse cosmetic outcome (i.e., more scarring, atrophy, and dyschromia) than if the lesion had been left to involute naturally.¹³ Surgery is, of course, the only way to remove a hemangioma definitively and is generally a straightforward measure for redundant tissue after some degree of involution has taken place. However, as plastic surgeons well know, the decision to remove an early hemangioma surgically depends on the individual case and can sometimes be difficult, as one must predict whether the resultant scar would be better than the results of natural involution.

Never Underestimate the Wide Range of Parental Perception

The degree of parental anxiety surrounding hemangiomas is not surprising given our appearance-driven society and the fact that hemangiomas are most common in girls and on the face. Parents may feel harassed by insensitive comments from strangers and/or pressure (usually from other family members) to “do something.” Lastly, the Internet can be a less than helpful resource, particularly when it comes to hemangiomas. Not uncommonly, the parents of an infant with a relatively small, focal hemangioma see a picture of a large, severe (often segmental) lesion and fail to understand where their child fits within the severity spectrum.

Education Is Very Important

As with most medical conditions, physicians may take for granted what parents understand about hemangiomas. Addressing common concerns is important: “this growth is not cancer and will not turn into cancer; there is nothing we know of that you could have done to cause this; it is going to grow and then improve,” and so forth. Physicians should attempt to provide parents with their best estimate of prognosis and discuss risks and realistic benefits of treatment versus waiting for (at least some) natural involution. Even when observation alone is the best treatment decision, this can often be much more difficult for both the family and physician, with frequent follow-up for reassurance often needed, particularly during the growth phase. Parents are often relieved to know that their physician shares their concerns about any potential cosmetic implications, especially before the start of school.

There Is Still So Much to Be Learned about Hemangiomas

I am continually humbled by the atypical hemangioma case: the infant with a large, segmental hemangioma of the trunk (not face) or multiple hemangiomas who has other typical features of PHACES syndrome and the hemangioma that involutes as expected but then starts to grow again at age 6 years. These are the patients who teach me and inspire me to learn more, and this is why hemangiomas are one of the most challenging and fascinating parts of my practice. Although we have learned a great deal, there are still so many unanswered questions: What exactly causes hemangiomas and what is their relationship with the placenta? Why do they not develop until *after* birth? Why are they so common in female and low-birth-weight infants? Why do some infants have segmental hemangiomas, and why are these lesions so much more complicated? Given that hemangiomas are the most common tumor seen in pediatrics, it is hoped that ongoing research efforts will be able to answer these and other questions in the near future.

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