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PICTORIAL ESSAY

Hemangiomas revisited: the useful, the unusual and the new

Part 1: overview and clinical and imaging characteristics

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Abstract Hemangiomas are common vascular tumors occurring in children. Though most of the lesions present in infants and young children with a typical appearance, it is important to understand that they all do not behave in the same way. Rather, they are a group of vascular lesions with different clinicopathological subtypes, with their clinical behavior varying with the stage of the tumor as well. As such, they can and do have a varied clinical, imaging and pathological appearance according to the location of the tumor and also the stage at which the patient is seen. In this pictorial essay, the classification, pathogenesis, clinical appearance, natural history and imaging characteristics of hemangiomas are reviewed and illustrated.

Keywords Infantile hemangioma · Congenital hemangioma · US · MR

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Introduction

Hemangiomas are the most common tumors of infancy. Despite the fact that the classification of vascular tumors and malformations by Mulliken and Glowacki [1] was published almost three decades ago, significant confusion still exists about hemangiomas, mainly related to the inappropriate use of the terms utilized to refer to these lesions [2, 3]. This confusion frequently yields inaccurate information provided to parents regarding the natural course, prognosis and treatment of the condition.

Knowledge of the features of hemangiomas allows the radiologist to play an important role in the appropriate approach to these patients. In the first part of this article, we review and illustrate the classification, clinical appearance, natural history and pathogenesis of hemangiomas. Lastly, the role of imaging and the features of infantile and congenital hemangiomas are discussed.

Nosology of hemangiomas

The importance of adhering to an accepted classification system when dealing with vascular anomalies cannot be overstated. Much of the confusion that prevails even now regarding the diagnosis and treatment of hemangiomas stems not only from the complex nature of the vascular anomalies but also from the indiscriminate application of the term "hemangioma" to a number of vascular lesions [4]. Terms to be avoided when describing these lesions include strawberry, nascent, common or capillary hemangioma, juvenile hemangioma, cavernous hemangioma and hepatic hemangioendothelioma. Hemangiomas are true vascular tumors with two types recognized according to the

International Society for the Study of Vascular Anomalies classification: infantile and congenital [5].

International Society for the Study of Vascular Anomalies classification

The classification and the terminology used for vascular lesions have been very confusing. In 1982, Mulliken and Glowacki [1] described a classification of vascular anomalies based on endothelial cell characteristics. This classification, which was later adopted by the International Society for the Study of Vascular Anomalies in Rome (June 1996), differentiates lesions with a proliferative endothelium (for example, hemangiomas) from lesions with structural anomalies (for example, vascular malformations) as shown in Table 1 [6]. This classification has been widely accepted and is very helpful in standardizing the terminology.

It is important that pediatric radiologists adhere to the classification to use the correct terms. Especially in the adult literature, there is still misuse of the terms, with hemangioma and venous malformation frequently used interchangeably. Some syndromes frequently associated with venous malformations, not with hemangiomas as erroneously described in older literature, are listed in Table 2 [3, 7]. Port-wine stain is a term that refers to capillary malformation and does not represent a hemangioma. These lesions are flat, geographical and confined to one of the trigeminal branch territories; as the name implies, they display a very intense dark red color.

Table 1 Classification of vascular tumors and malformations

Tumors	Vascular malformations
• Infantile hemangioma	• Simple
• Congenital hemangioma	- Venous
- Rapidly involuting congenital hemangioma (RICH)	- Lymphatic
- Non-involuting congenital hemangioma (NICH)	- Capillary
• Kaposiform hemangioendothelioma	• Combined
• Tufted angioma	- Arteriovenous fistula
• Hemangiopericytoma	- Arteriovenous malformation
• Pyogenic granuloma	- Venolymphatic malformation
• Spindle cell hemangioendothelioma	- Any other combination

Table 2 Syndromes associated with venous malformations

- Klippel-Trenaunay
- Proteus
- Maffucci
- Gorham-Stout
- Blue-rubber bleb nevus
- Bockenheimer

Infantile hemangiomas (IHs): clinical characteristics

Infantile hemangioma is the most common tumor of childhood, with a reported incidence of 3–10% in Caucasian infants [8]. Multiple lesions are found in 15–30% of patients with infantile hemangiomas [9]. Recognized risk factors for the development of hemangiomas include prematurity, fair skin and female sex, with ratios ranging from 1.4:1 to 3:1. Infantile hemangiomas affect whites more commonly than they do Hispanics or African Americans. Compared with the general population, mothers of patients with IHs are of higher maternal age, have a higher incidence of pre-eclampsia or placenta previa and are more likely to have multiple gestation pregnancies [10–13]. Infantile hemangiomas are the only lesions positive for a marker called GLUT-1, independent of the stage [14–16].

Infantile hemangiomas usually are superficial involving the skin and therefore obvious on physical examination, but they can also be deep (subcutaneous) with or without skin changes. IHs can be focal, segmental or indeterminate. Focal hemangiomas are more common and present as localized, raised and tumor-like lesions (Fig. 1). Segmental hemangiomas are flat, larger, plaque-like and geographical in a segmental distribution (Fig. 1). Indeterminate lesions do not entirely encompass an accepted embryological segment or arise from a single focus and can demonstrate mixed features (Fig. 1). On occasion, IHs are completely confined to the subcutaneous soft tissues, presenting as a bluish lump with intact overlying skin (Fig. 2) [17].

Infantile hemangiomas follow a fairly characteristic pattern of evolution [10, 11]. The lesions are not fully developed at birth. Instead, approximately 30% have a precursor lesion indicated by the presence of a macule, an area of discoloration or telangiectasia (Fig. 3). The lesions start to grow shortly after birth during the proliferating, highly angiogenic phase, reaching a peak at about a year of age. During this phase, the IHs become raised (Fig. 3), resembling a strawberry (hence the usage of the outdated term strawberry hemangiomas). The proliferative phase is followed by an involuting phase characterized by spontaneous regression of the angiogenesis causing a decrease in size. Deep hemangiomas, however, might have a longer

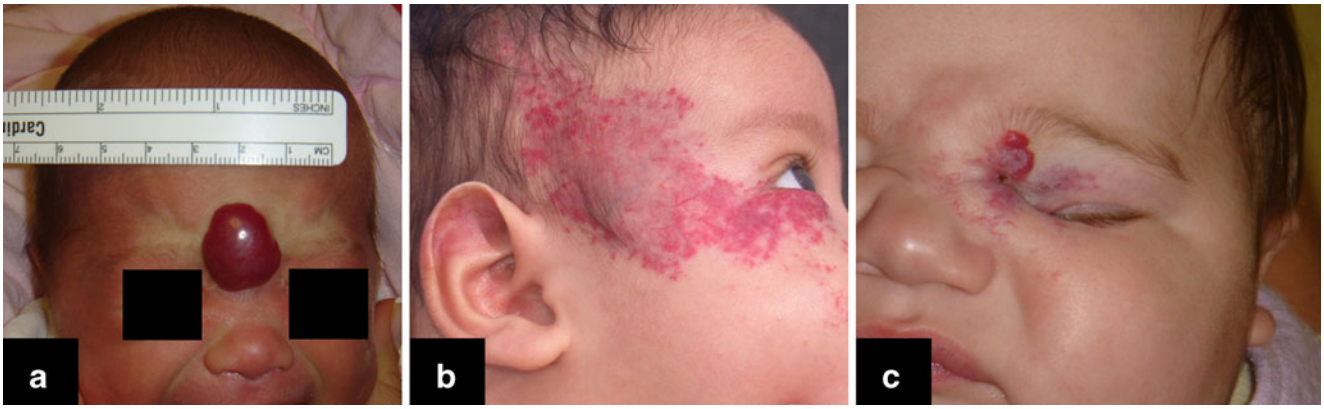

Fig. 1 Cutaneous infantile hemangioma. **a** Focal hemangioma: red, well-circumscribed, raised lesion. **b** Segmental hemangioma: larger, plaque-like and geographical in a segmental distribution. **c** Indeterminate hemangioma: mixed features of both focal and segmental hemangiomas

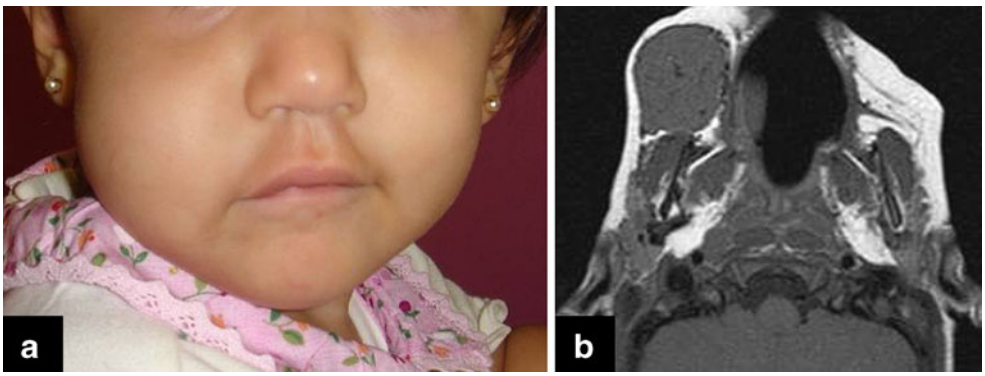

Fig. 2 Subcutaneous infantile hemangioma. **a** Clinical image: mass in the right cheek without skin involvement. **b** Axial T1-W MR image demonstrates a solid mass isointense to muscle with few flow voids. Note the normal skin/subcutaneous fat overlying the lesion

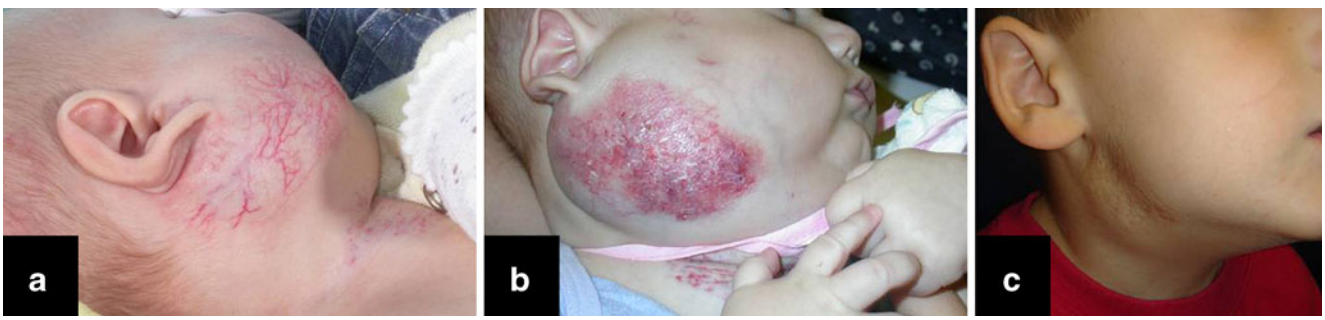

Fig. 3 Infantile hemangioma, clinical characteristics. **a** Precursor lesion: multiple telangiectasias in a beard distribution. **b** A few months later, the lesion has proliferated and is raised with superficial erythema. **c** After involution, a residual scar is seen

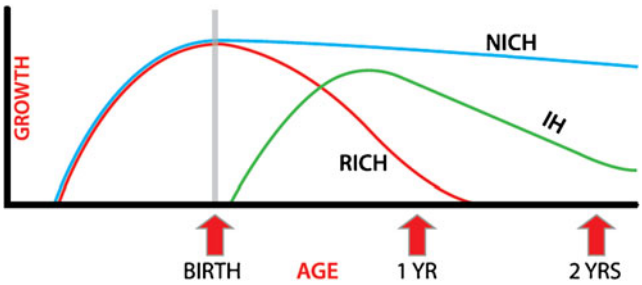

Fig. 4 Growth patterns of hemangiomas: congenital hemangioma versus infantile hemangioma (*RICH* = rapidly involuting congenital hemangioma, *NICH* = non-involuting congenital hemangioma, *IH* = infantile hemangioma)

proliferative phase [17]. The final stage of the process is the fibrotic stage, characterized by a small area of residual, loose fibrofatty tissue. Contrary to the common belief that IHs completely involute, a scar of variable size is always present (Fig. 3).

Theories of the pathogenesis of IHs

Endothelial cells of IHs express glucose transporter isoform 1 (GLUT-1) that is associated with placental vessels. This marker is not expressed by any other vascular tumor or even scar tissue, which makes it very useful to make the diagnosis. Other antigens expressed by IHs include FC

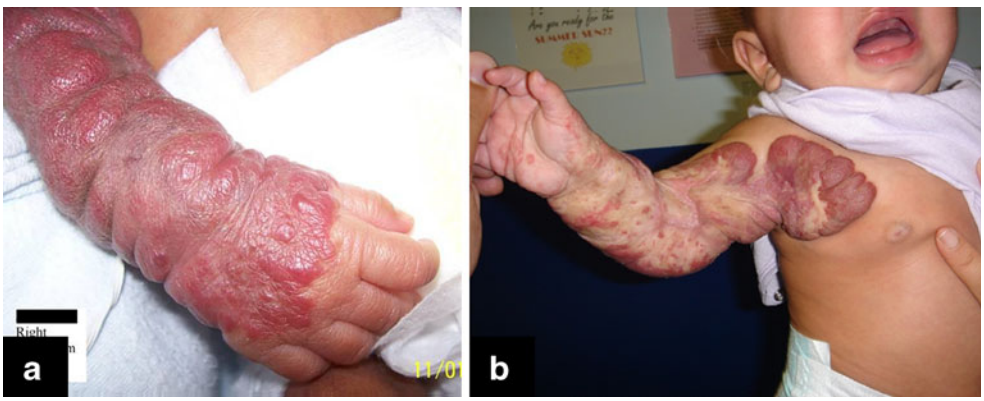

Fig. 5 Rapidly involuting congenital hemangioma involving the right upper extremity. **a** Lesion fully developed at birth. **b** The lesion was GLUT-1-negative with significant involution in 10 months (GLUT-1 = Glucose transporter-1)

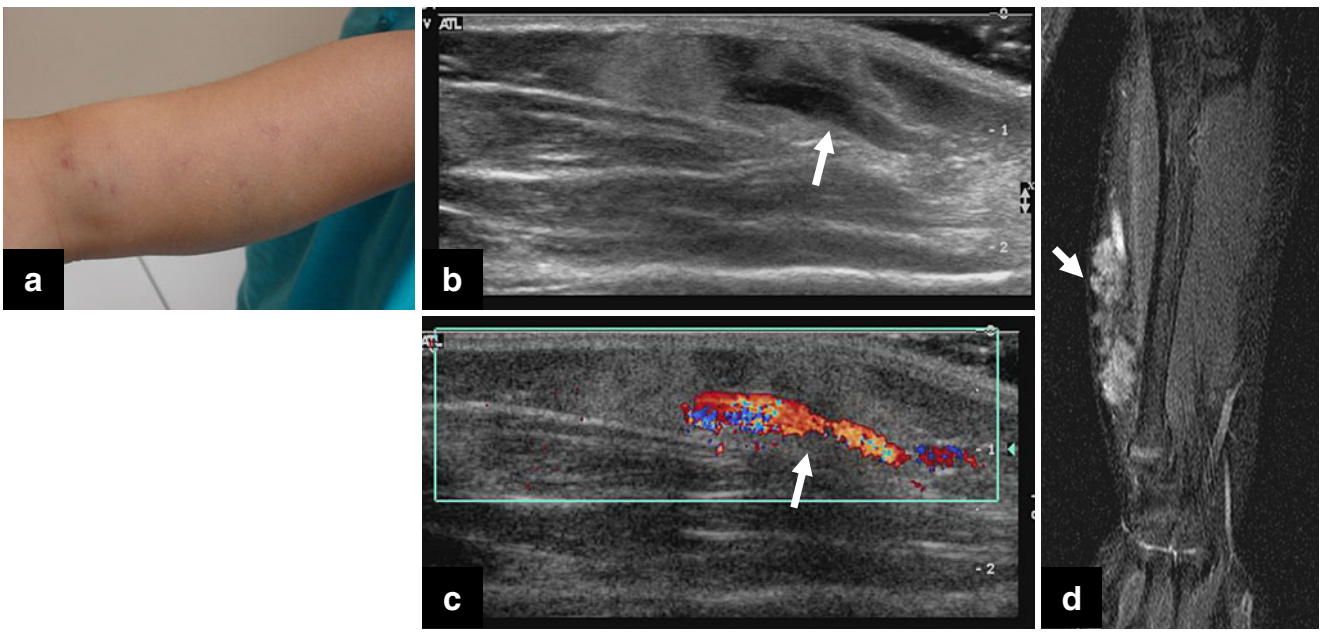

Fig. 6 Non-involuting congenital hemangioma. **a** A soft-tissue mass with reddish discoloration present since birth in a 6-year-old girl. **b** The lesion is predominantly echogenic on US. A vessel is seen within (*arrow*). **c** Color Doppler confirms flow within (*arrow*), a finding more commonly seen in congenital hemangiomas. **d** Coronal STIR image demonstrates a lobulated subcutaneous lesion (*arrow*)

Table 3 Features of hemangiomas: infantile versus congenital

Infantile hemangiomas	Congenital hemangiomas
• Common lesion: occurs in as many as 10% of children	• Rare lesions
• Most present shortly after birth	• Fully developed at birth; sometimes diagnosed prenatally
• 30% have precursor lesion at birth: macule or discoloration	• GLUT-1-negative
• GLUT-1-positive independent of stage	• Two subtypes:
• Also positive for Lewis Y antigen, Fc gamma receptor II	- RICH: rapidly involuting congenital hemangioma
• Follow typical course consisting of proliferation, involution, fibrosis	- NICH: non-involuting congenital hemangioma
	• RICH – Involution complete about 1 year of age
	• NICH – Do not involute

gamma receptor II (FcγRII), Lewis Y antigen and merosin [14]. This gene expression pattern differs from that of endothelial cells in normal skin but resembles that of endothelial cells lining fetal microvessels in human placenta [18].

The presence of antigens that are expressed in placental tissues in hemangiomas has led to the hypothesis that IHs result from embolization of placental cells into receptive tissues. Furthermore, the observation that chorionic villus sampling increases the risk of developing hemangiomas supports this theory [19]. More recently, Mihm et al. [20] hypothesized that whether IHs result from embolized cells from the placenta or not, the sites where hemangiomas form are prepared by humoral factors secreted by the placenta. Recent studies suggest that IHs exhibit an imbalance in vascular endothelial growth factor (VEGF) signaling that leads an increase in proliferation, migration and survival of the endothelial cells in these tumors [21, 22].

Another theory is the multipotential stem cell hypothesis, which explains the link between the IH and placenta with a common origin. This supports the idea that IHs arise from somatic mutation and clonal expansion of progenitor stem cells. Multipotential stem cells have been isolated from IHs that gave rise to hemangioma-like lesions in immunodeficient mice [23]. In a related hypothesis, Yu et al. [24] identified mesenchymal stem cells residing in the tumor that preferentially differentiate into adipocytes during spontaneous regression and found that these cells might not be clonally derived.

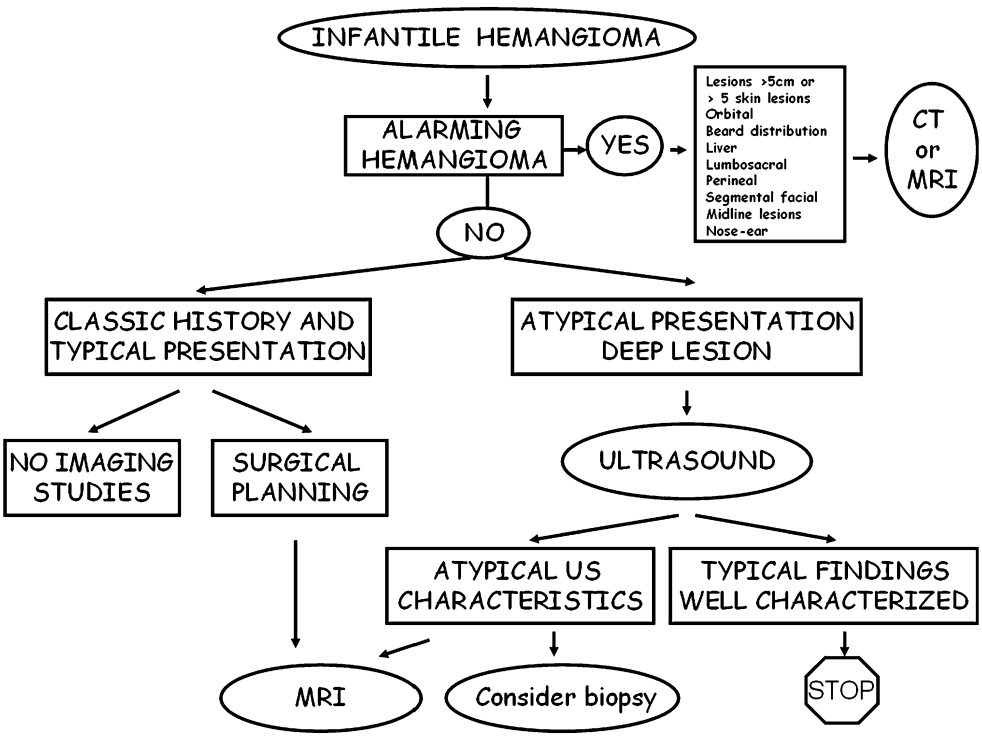

Fig. 7 Suggested diagnostic imaging algorithm to approach infantile hemangiomas

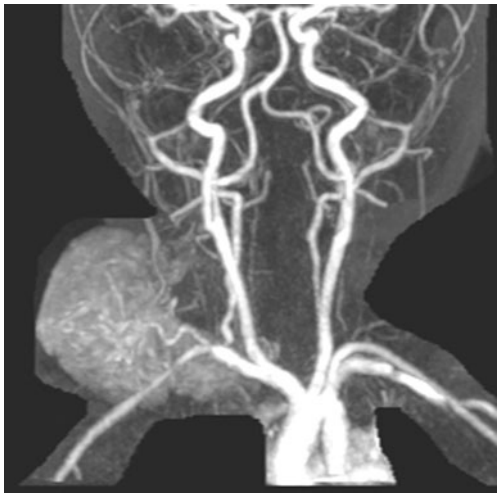

Fig. 8 MR angiogram of an infantile hemangioma. Contrast-enhanced MR angiogram demonstrates a vascular mass in the right neck with arterial feeders from the right subclavian artery

During the proliferative phase, hemangiomas are characterized by abundant immature endothelial cells; during the involuting phase, by prominent endothelial-lined vascular channels and endothelial apoptosis; and after having involuted, by the few remaining capillary-like vessels surrounded by loose fibro-fatty tissue [25].

It has been reported that IHs in the head and neck region have a non-random distribution along embryonic segments. There is, though, some controversy as to the exact nature of such a distribution pattern. Waner et al. [26] suggested that segmental hemangiomas have a distribution along the facial placodes and that focal hemangiomas tend to occur at the lines of embryological fusion. Haggstrom et al. [27] found that observed patterns of IHs were distinctly different on the upper face but resembled the previously described facial developmental units on the lower face. Accordingly, they suggested that neural crest derivatives play a role in the development of facial hemangiomas [27].

Congenital hemangiomas (RICH/NICH): Clinical characteristics

Congenital hemangiomas are rare lesions that, unlike IHs, are fully developed at birth [5, 16]. In utero diagnosis of congenital hemangiomas has been reported. These lesions do not grow after birth and do not follow the involution pattern of IHs. However, two types have been identified: rapidly involuting congenital hemangiomas (RICH) and non-involuting congenital hemangiomas (NICH) (Fig. 4) [28, 29]. RICHs are defined by a spontaneous and complete resolution that can start soon after birth and usually occurs before 14 months (Fig. 5). On the other hand, NICHs are characterized by a growth commensurate to the child's growth and never involute (Fig. 6). Congenital hemangiomas are GLUT-1-negative, in contrast to IHs.

RICH and NICH can appear as bossed plaques or tumors. Three morphological variants of RICH have been described: (1) a lesion with a characteristic red-purple color, often with coarse telangiectasia present on a portion of its surface or at the periphery of the tumor; (2) a flat infiltrative tumor with violaceous overlying skin; and (3) a raised grayish tumor with multiple tiny telangiectasias, surrounded by a pale halo.

NICHs have a very different clinical appearance, tending to be plaque-like with a pink or purple color and prominent overlying coarse telangiectasia. Peripheral blanching is characteristic of NICHs, although it may be seen in RICHs as well [29]. Table 3 illustrates the main differences between the infantile and congenital hemangiomas [10–16, 28].

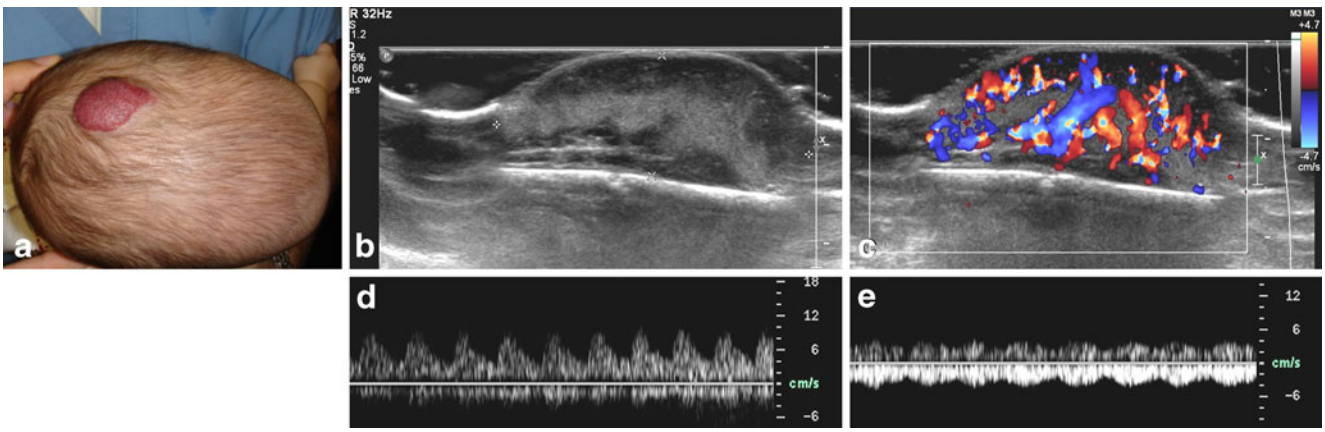

Fig. 9 Infantile hemangioma: imaging characteristics on US. **a** Clinical image shows a raised red lesion in the scalp. **b** A well-defined, heterogeneous solid mass is seen. **c** On color Doppler the lesion is vascular. **d, e** Arterial and venous waveforms on spectral Doppler

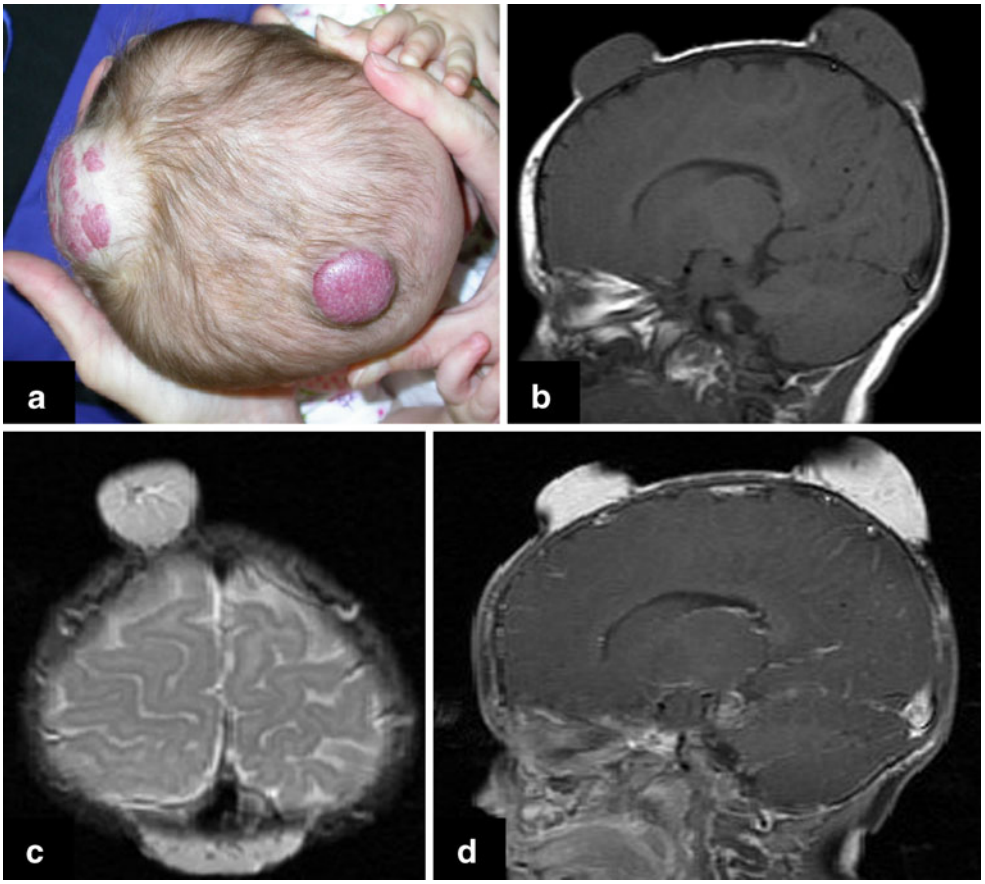

Fig. 10 Infantile hemangioma: imaging characteristics on MR. **a** Clinical image demonstrates two focal hemangiomas in the scalp. **b** Sagittal T1-W image shows two raised, focal soft-tissue masses of intermediate signal intensity with internal flow voids. **c** Axial T2-W image shows the characteristic high signal intensity with flow voids within. **d** Contrast-enhanced fat-saturated sagittal T1-W image shows intense homogeneous enhancement

Imaging appearance of infantile and congenital hemangiomas

The clinical appearance and the imaging appearance of hemangiomas depend upon the type (IH versus congenital hemangioma), the stage and the location [30]. Most hemangiomas are easily recognized and diagnosed clinically, requiring no imaging.

As pediatric radiologists, it is important to be familiar with the clinical appearances of hemangiomas. The first step in the evaluation of hemangiomas is to ask the parents, while examining the child, about the appearance of the lesion at birth, the presence of a precursor lesion and the pattern of growth and involution.

Clear guidelines have not been established; however, there is agreement about some indications of when to image

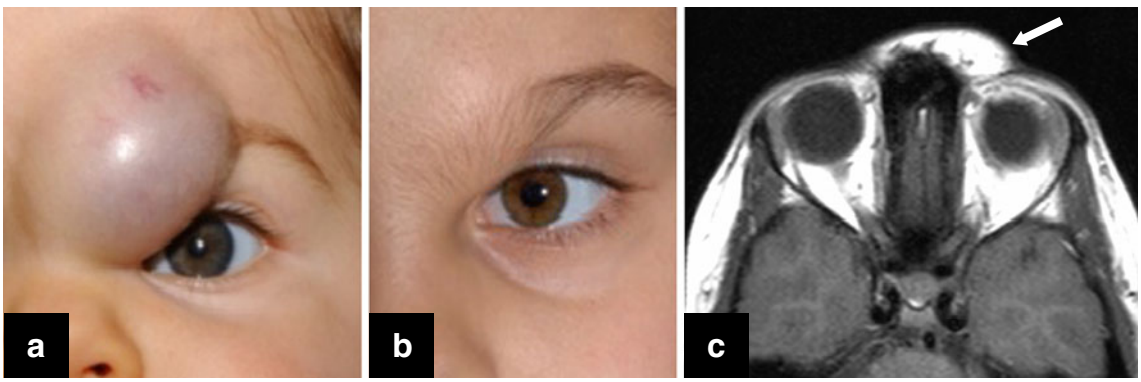

Fig. 11 Infantile hemangioma: involution. **a** An infantile hemangioma in the superomedial aspect of the left orbit in a 7-month-old girl. **b** The lesion has involuted by 6 years of age, leaving a mild focal soft-tissue prominence. **c** Axial T1-W image shows residual fibroadipose tissue (*arrow*)

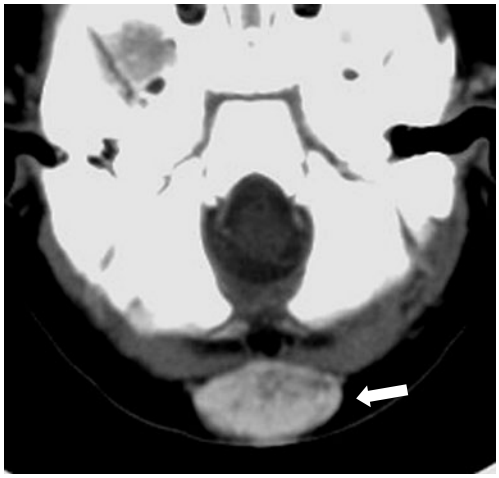

Fig. 12 Infantile hemangioma: imaging characteristics on CT. Contrast-enhanced axial CT image demonstrates a well-circumscribed intensely enhancing solid lesion in the subcutaneous soft tissues of the occipital region (*arrow*)

hemangiomas (Fig. 7) [31]. Indications for imaging IHs include (1) the assessment of the extension and depth of the lesion; (2) the evaluation of the relationship with adjacent organs/structures, particularly for treatment planning; (3) evaluation of a lesion with atypical features either on physical exam or when a hemangioma-like lesion develops after 6 months of age to exclude different pathologies such as kaposiform hemangioendothelioma, infantile fibrosarcoma and rhabdomyosarcoma; and (4) when there are more than five or six cutaneous lesions or a single lesion larger than 5 cm due to the increased risk of associated visceral hemangiomas or PHACE or PELVIS syndromes/LUMBAR association. Miliary or disseminated hemangiomatosis is a term used when there are at least 30–100 papular lesions of very small size, red to blue–black color and sharply demarcated with associated extra-cutaneous hemangiomas, most commonly hepatic. On the other hand, the term multifocal cutaneous hemangiomas is applied to 5 or more cutaneous hemangiomas of the focal type that have a potential for concomitant visceral lesions [32, 33].

Table 4 Imaging differences between infantile hemangiomas and congenital hemangiomas

Imaging summary	Infantile hemangiomas IH	Congenital hemangiomas	
		NICH	RICH
1. US visible vessels	15%	72%	63%
2. US calcification	None	17%	38%
3. US heterogeneity	42%	72%	63%
4. CT/MRI – well-defined limits	100%	67%	60%
5 CT/MRI – fat stranding	8%	29%	29%

US and MRI are the preferred imaging modalities to evaluate hemangiomas, each one with its own advantages and disadvantages. In general, US exam is frequently the initial test, as it is readily available, lacks ionizing radiation, does not require sedation and is inexpensive. A limitation of US is operator dependence [30]. In certain locations such as the orbit or the spine that could prompt a referral to a specialist, or when the full extension of the lesion is not seen on US exam, contrast-enhanced MRI plays an important role. MRI is definitely superior in the evaluation of deeper lesions, the relationship with adjacent structures and the presence of associated malformations. The MRI protocol should include a dynamic MRA with gadolinium to evaluate the supplying and draining vessels as well as the pattern of enhancement (Fig. 8) [34].

Contrast resolution and tissue characterization by CT are inferior to that of MRI; however, with modern scanners the study can be performed without sedation and high-quality angiograms can be obtained. Because of the radiation involved and in accordance with the Image Gently campaign at our institution, contrast-enhanced CT is not routinely used except when airway involvement is suspected [35]. Hemangiomas can sometimes be seen when the CT scan is performed for other indications. CT is an acceptable alternative when MRI is not available. US at our institution, with high frequency images of the liver, spleen and brain, is the imaging modality for screening when visceral hemangiomas are suspected. Currently, angiography is seldom performed except when endovascular therapy is indicated to control bleeding not responsive to pharmacotherapy and when there is high-output cardiac failure [36, 37]. Conventional radiography has no role in the evaluation of hemangiomas.

On US, proliferating IHs appear as a relatively well-circumscribed mass of variable echogenicity with a high vessel density of greater than 5 vessels/cm^2 (Fig. 9). With IHs, there is no arteriovenous shunting (arterialization of venous flow); however, the mass is supplied by high-flow vessels with low-resistance waveforms and drained by veins (Fig. 9). Mean arterial peak, flow velocity and mean resistance values do not allow differentiating hemangioma from arteriovenous malformation [38]. During the involuting phase, IHs decrease in size with a reduced number of vessels and with high systolic flow. Congenital hemangiomas appear similar to infantile hemangiomas, but more vessels can be seen on gray scale with occasional calcifications (Fig. 6).

On MRI, IHs are well-circumscribed, solid, lobulated masses with intermediate signal on T1-W images and hyperintense signal on T2-W images (Fig. 10). During the proliferative phase, rapid and vivid homogeneous contrast enhancement with different degrees of washout is displayed (Fig. 10). Flow voids representing feeding and draining vessels can be seen during this phase as well. During

involution, there is a steady decrease in vascular flow and thus less contrast enhancement. The increase in fibrofatty tissue seen as hyperintense areas on T1-W images makes the lesions more heterogeneous during this phase (Fig. 11). Findings on CT imaging are similar to those of MRI, with a homogeneous solid soft-tissue mass that shows intense enhancement during the proliferative phase (Fig. 12). Involuting hemangiomas appear as heterogenous masses with less prominent enhancement and fibrofatty replacement.

The CT and MRI imaging appearance of congenital hemangiomas has been described as being very similar to that of infantile hemangiomas (Fig. 6), with some RICH lesions having areas of inhomogeneity and larger flow voids [39]. These lesions can simulate an AVM; however, the presence of an associated solid parenchymal component supports the diagnosis of RICH. Clinical history rather than imaging is the key to differentiate between the types of hemangioma. Only a few characteristics have been found to be different between IHs and congenital hemangiomas (Table 4). Gorincour et al. [39] found that significant fat stranding occurred in 29.4% of congenital hemangiomas examined by CT and/or MRI, compared with 7.4% of infantile hemangiomas. Also, well-defined margins were less common in congenital hemangiomas as compared with infantile hemangiomas (67% of NICH and 60% of RICH vs. 100% of IH). However, they thought that NICH and RICH could be imaged adequately by US alone, even though the imaging findings might not be pathognomonic.

Conclusion

When talking about hemangiomas, the first step as a pediatric radiologist is to adhere to the terms infantile hemangioma and congenital hemangioma. Certain terms such as capillary or strawberry hemangioma, among others, are discouraged. It should be clear that hemangiomas are vascular tumors and not malformations. All hemangiomas follow a fairly anticipated course that helps in differentiating and characterizing them. Congenital hemangiomas are fully developed at birth and have two distinct courses: rapidly involuting hemangiomas (RICH) that could start involuting soon after birth and usually before 1 year of age, and the non-involuting hemangiomas (NICH) that never involute. On the other hand, infantile hemangiomas initially present as precursor lesions that grow soon after birth, and most involute in the first few years of life. Therefore, the clinical appearance and the growth characteristics of the hemangioma are the most important determinant in the type of lesion, especially given the similarity of the lesions on imaging. Beware of a suspected hemangioma presenting initially after 6 months of age or having an atypical clinical or imaging appearance, as it probably represents a different vascular lesion or neoplasm. Most hemangiomas require no imaging; however, when indicated, US and in some cases contrast-enhanced MRI are the modalities of choice.

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