Infantile Hemangiomas
Current Management

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KEY POINTS

- Management of infantile hemangioma (IH) includes a combination of observation, medical therapy, laser treatments, and surgery.
- The nomenclature to describe these lesions has been standardized and should be adhered to.
- The goal of treatment is to obtain the best possible result commensurate with known developmental milestones.
- Current knowledge of the biology of these tumors as well as experience allows obtaining this goal.
- "Leave it alone, it will go away" is no longer universally acceptable advice for treatment of IH.

Infantile hemangioma (IH) is a vascular anomaly and the most common benign tumor of infancy. In spite of it being so prevalent, there is still a widespread lack of understanding in the medical community leading to mismanagement of affected children. The purpose of this article is to review the current knowledge on pathogenesis, diagnosis, and management of IH.

Vascular anomalies are a group of disorders that are categorized as either tumors or malformations according to the accepted classification of the International Society for the Study of Vascular Anomalies (April 2014; http://www.issva.org). The tumors are further divided into benign, locally aggressive, or malignant entities. IH is one of the benign vascular tumors along with congenital hemangiomas, pyogenic granulomas, and a few other less common entities.

IH are true neoplasms of endothelial cell origin exhibiting up-regulated cell growth, increased mitosis, and cellular hyperplasia. Endothelial cells in IH have a clonal origin but the exact source of the progenitor cell is not clear. Striking commonality in the mRNA transcriptome have been found between IH and placental tissue, which suggests that progenitor cells from placenta may be associated with these tumors.[1] In addition to morphologic similarities between endothelial cells of IH and placenta, IH uniquely coexpresses glucose transporter protein 1 (GLUT-1) and other markers with placenta.[2] The only vascular anomaly that expresses GLUT-1 is IH, making this an important marker to histologically confirm a diagnosis of IH and distinguish from all other vascular lesions in the occasional case requiring a tissue biopsy. Endothelial and mesenchymal progenitor cells have been identified in both IH and placenta but the exact source of these progenitor cells is not clear. One theory suggests that fetal angioblasts differentiate into a placental vascular phenotype at locations that are prepared by circulating factors secreted by the placenta thus making the predisposed sites fertile ground for the growth of IH.[3] This metastatic niche theory has been shown to be true in some cancers. The other theory posits that embolic progenitor cells from the placenta deposit in the developing fetus and differentiate into IH.[4] These embolic cells may be more likely to deposit in the head and neck due to the increased vascularity in this region with the sites of predilection occurring at the end arteries of the developing facial placodes.[5] Neither theory

has yet to been proven or explains the peculiar natural history of IH, which consists of a period of rapid postnatal proliferation followed by a phase of involution.

Histologically, during proliferation, IH is characterized by a high mitotic activity in the endothelial cells and pericytes as the tumor enlarges. Involution is accompanied by an increase in apoptosis, endothelial cells flatten with enlargement of their lumina, and the lesions become dominated by fibrofatty stroma. Alterations in several cytokines important in angiogenesis have been demonstrated during the various phases. The proliferation phase is dominated by vascular endothelial growth factor (VEGF), which is a primary mitogen for benign and malignant vascular tumors and promotes cell survival while inhibiting apoptosis. Serum levels of VEGF are elevated in infants with proliferating IH compared with involuting IH and controls.[6] VEGF activates angiogenesis via the mammalian target of rapamycin (mTOR) signaling pathway. Also elevated during this time are basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF)-2, matrix metalloproteinase (MMP)-9, and type IV collagenase, whereas levels of endogenous interferon are decreased. During involution, levels of VEGF, bFGF, and IGF-2 decline, whereas levels of regulatory cytokines such as interferon and tissue inhibitor of MMP-1 (TIMP-1) increase. These factors and pathways are potential targets for clinical intervention.

Clinically, these hallmark phases form the basis for diagnosis and management. IH are typically not visible at birth; however, up to 30% are evident as precursor lesions with variable findings including a telangiectatic macule, pale vasoconstrictor area, vascular stain, or bruised appearance. Within the first weeks of life, IH becomes visible as an erythematous macule or slightly raised papular lesion. The lesions then undergo a classic progression of rapid proliferative growth followed by involution that is variable in length and extent. The period of most rapid growth occurs in the early proliferative stage and is largely complete by about 4 to 6 months of age with tumors reaching roughly 80% of their final size at this point. Despite the increase in size during proliferation, IH tend not to expand beyond the defined anatomic site of the original lesion. The late proliferative phase is complete by 9 months in most children with very little growth occurring after this point as the lesion enters the plateau phase. Involution begins as early as 6 months and may last for several years. Clinically, lesions become lighter in color and softer to palpation with diminution in the volume of the mass. If one includes all IH (scalp to soles of feet) nearly 60% of IH will involute to aesthetically and functionally acceptable endpoints; however, 40% of lesions leave a remnant that may require further treatment.[7] They may appear as hypopigmented or telangiectatic macules, with loose, expanded soft tissue, and/or fibrofatty residual masses, depending on the nature of the original tumor. The threshold for what is considered acceptable varies with location and size. For example, a small focal lesion of the nasal tip will have a very different impact than a larger, segmental lesion of the lower back. For this reason, even though 100% of IH involute, a large number of patients will seek improvement as the threshold for acceptability is high because most occur in the face and head or neck areas (**Fig. 1**).
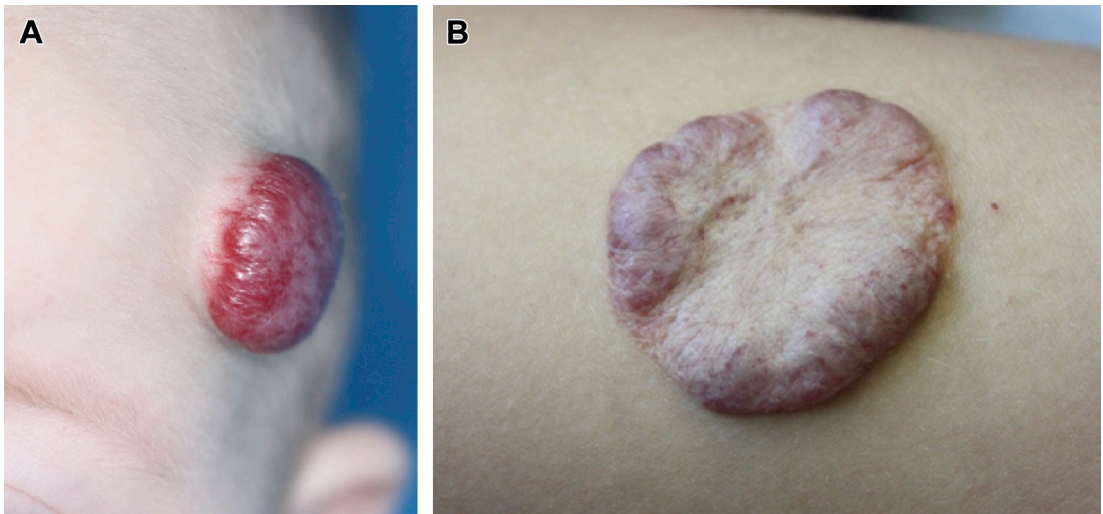
Fig. 1. Proliferating and involuting IHs. (*A*) Proliferating compound IH of the temple. (*B*) Involuting thick superficial IH of the arm.