Infantile hemangiomas

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INTRODUCTION

Infantile hemangiomas (IHs), also known as "hemangiomas of infancy," are common benign tumors of endothelial cells characterized by a unique pattern of rapid proliferation that occurs in the first months of life, followed by slow involution that may take years to complete. They reportedly occur in as many as 10% of children and are frequently brought to the attention of both pediatricians and dermatologists. Although most are ultimately of little significance, a portion have the potential to produce complications of concern.

Confusion often arises regarding the diagnosis and management of IH, in part because the term "hemangioma" has been applied indiscriminately to a variety of vascular anomalies with diverse biologic and pathologic features. Clinical observations and pathologic studies, however, have clearly distinguished IHs, which are dynamic, from other vascular tumors and from vascular malformations. Because of this distinction, the terms "infantile hemangioma" or "hemangioma of infancy" should be used to describe these lesions, and older terms such as "strawberry" or "capillary" hemangioma should be discouraged. During the past decade, there have been an increasing number of studies and publications on IH. Highlights include the identification of specific immunohistochemical markers shared by placental microvasculature that distinguish IH from other vascular tumors, the recognition that Kasabach-Merritt phenomenon is not a complication of IH but rather of other vascular tumors, the description of an IH-specific neurocutaneous syndrome (PHACE(S) syndrome; *p*osterior fossa malformation, *h*emangioma, *a*rterial anomalies, *c*oarctation of the aorta, *e*ye abnormalities, and *s*ternal defects), and the recognition of specific IH patterns that help in risk-stratification.

This periodic synopsis is by no means a complete compendium, but attempts to highlight those articles viewed by the authors as being among the most relevant and important. As the scope of all vascular tumors is broad and varied, we have restricted our focus (apart from issues of differential diagnosis) to the subject of IHs.

Abbreviations used:

GLUT:	glucose transporter
HH:	hepatic hemangioma
IH:	infantile hemangioma
MRI:	magnetic resonance imaging
PCP:	*Pneumocystis carinii* pneumonia
PDL:	pulsed dye laser
PHACE(S):	*p*osterior fossa malformation, *h*emangioma, *a*rterial anomalies, *c*oarctation of the aorta, *e*ye abnormalities, and (*s*ternal defects)
VEGF:	vascular endothelial growth factor

REVIEW ARTICLES

Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003;48:477-93.

Gampper TJ, Morgan RF. Vascular anomalies: hemangiomas. Plast Reconstr Surg 2002;110:572-85.

These recent reviews (although written for different audiences) provide comprehensive overviews of the subject at hand. Both include discussions of hemangioma classification, natural history, and management options. Bruckner and Frieden also focus on "worrisome presentations," those hemangiomas most likely to produce significant sequelae.

Metry D. Update on hemangiomas of infancy. Curr Opin Pediatr 2004;16:373-7.

This succinct review focuses on recent advances in the field of IH: the relationship between IH and placental tissue and the discovery of immunohistochemical markers identifying IH, the association of morphology and risk for complications, and the use of becaplermin 1% gel to treat ulceration.

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This report reflects the best data available at the time the report was prepared, but caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations set forth in this report.

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J Am Acad Dermatol 2006;55:671-82.
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Frieden IJ, Haggstrom AN, Drolet BA, Mancini AJ, Friedlander SF, Boon L, et al. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas, April 7-9, 2005, Bethesda, Maryland, USA. Pediatr Dermatol 2005;22:383-406.

This article details the proceedings of a recent workshop sponsored by the National Institutes of Health about IH that was attended by researchers and physicians from multiple specialties. Summaries of the plenary talks highlight the current best practices and state of knowledge about clinical care and research of IH. In addition, summaries of the breakout sessions emphasize current research questions that need to be addressed.

PATHOLOGY/PATHOGENESIS

IHs are primarily composed of endothelial cells but also contain pericytes, fibroblasts, interstitial cells, and mast cells. The pathophysiologic mechanisms leading to endothelial cell proliferation and involution are poorly understood, and the variety of articles on the subject reflects many competing theories.

Reviews

Bauland CG, van Steensel MA, Steijlen PM, Rieu PN, Spauwen PH. The pathogenesis of hemangiomas: a review. Plast Reconstr Surg 2006;117:29e-35e.

Friedlander SF, Ritter MR, Friedlander M. Recent progress in our understanding of the pathogenesis of infantile hemangiomas. Lymphat Res Biol 2005;3:219-25.

Both articles present well-organized summaries of recent findings about the pathogenesis of IH and highlight potential future research directions.

Immunohistochemistry

Bree AF, Siegfried E, Sotelo-Avila C, Nahass G. Infantile hemangiomas: speculation on placental trophoblastic origin. Arch Dermatol 2001;137:573-7.

North PE, Waner M, Mizeracki A, Mihm MC Jr. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 2000;31:11-22.

North PE, Waner M, Mizeracki A, Mrak RE, Nicholas R, Kincannon J, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol 2001;137:559-70.

GLUT1 is an erythrocyte-type glucose transporter that is expressed in the endothelia of blood-tissue barriers. North et al (2000) discovered that GLUT1 expression was marked in IH, regardless of stage, while its expression was negative in other vascular tumors and malformations, making it a specific and useful immunohistochemical marker for IH. North et al (2001) further recognized that IH and placenta both express GLUT1, as well as the vascular antigens FcγRII, Lewis Y antigen, and merosin. They speculate that IH may result from angioblasts that differentiate toward a placental phenotype or, alternatively, derive from embolized placental cells. Conversely, Bree et al showed that IHs lack placental trophoblastic markers, suggesting that placental trophoblast, which is distinct from placental microvasculature, is not the source of IH.

Dadras SS, North PE, Bertoncini J, Mihm MC, Detmar M. Infantile hemangiomas are arrested in an early developmental vascular differentiation state. Mod Pathol 2004;17:1068-79.

Nguyen VA, Kutzner H, Furhapter C, Tzankov A, Sepp N. Infantile hemangioma is a proliferation of LYVE-1-negative blood endothelial cells without lymphatic competence. Mod Pathol 2006;19:291-8.

Yu Y, Flint AF, Mulliken JB, Wu JK, Bischoff J. Endothelial progenitor cells in infantile hemangioma. Blood 2004;103:1373-5.

Yu et al examined tissue from 12 proliferating IHs and detected the coexpression of CD34 and CD133 in 11. Whereas CD34 is a known marker for endothelial cells, CD133 is expressed in primitive cell populations. The coexpression of both markers suggests endothelial progenitor cells are involved in the pathogenesis of IH. Similarly, Dadras et al showed that proliferating IHs express CD31 (another vascular marker) and LYVE-1, a marker for lymphatic vessels. Expression was markedly reduced or absent in involuting IHs and other vascular tumors and malformations. The authors conclude that proliferating IH endothelial cells display an immature immunophenotype, similar to that of cardinal vein endothelial cells, which have the capacity to become either lymphatic or blood vessels. They hypothesize that this maturational arrest may lead to their rapid proliferation postnatally. Nguyen et al, however, found that the majority of proliferating IHs do not express LYVE-1 and that IHs do not express the lymphatic markers Prox-1, podoplanin, and D2-40. The authors do not dispute the findings of Dadras et al, but postulate that subsets of IH that are LYVE-1-positive and -negative may exist.

Genetics

Barnes CM, Huang S, Kaipainen A, Sanoudou D, Chen EJ, Eichler GS, et al. Evidence by molecular profiling for a placental origin of infantile hemangioma. Proc Natl Acad Sci U S A 2005;102:19097-102. Epub 2005 Dec 19.

Using DNA-based microarrays, the authors compared the gene expression profiles of IH and placenta and found a "striking similarity" between the two as compared to other tissues. These observations strengthen the proposed relationship between hemangioma and placental endothelia, suggesting that a common genetic program is shared by both.

Boye E, Yu Y, Paranya G, Mulliken JB, Olsen BR, Bischoff J. Clonality and altered behavior of endothelial cells from hemangiomas. J Clin Invest 2001;107:745-52.

Walter JW, North PE, Waner M, Mizeracki A, Blei F, Walker JW, et al. Somatic mutation of vascular endothelial growth factor