Hemangiomas: What Every Dermatologist Should Know

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DISCLOSURE

- Conflict of Interests: None
- Off-label discussion:
  I do intend to discuss unapproved/investigative use of commercial products/devices in my presentation. There are NO FDA-approved medications for hemangioma therapy

Overview

- Background
- Diagnosis
- Epidemiology and Pathogenesis
- Management: When to Worry and What to Do
- Management options

What makes Infantile Hemangiomas so Interesting?

- Their genomic DNA is virtually identical to placental blood vessels but they are primarily a skin tumor
- They involute spontaneously: We know *how* (via apoptosis) but we don't know what triggers cell death.
- Varied in size, morphology, and natural history makes them a "moving target"

Hemangioma Investigator Group (HIG)

- Not well studied and virtually no funding for studies
- HIG, a group of 8 pediatric dermatology centers, formed in 2001
- Felt that dermatologists (with our understanding of skin and both medical *and* surgical expertise) should play an important role in hemangioma research and care
- Embarked on studies with help from Derm Foundation, ASA, SDRF and private donors
- Enrolled cohort 1000 patients in 14 month period

The Hemangioma Investigator Group

Ilona Frieden and Anita Haggstrom	UC San Francisco
Beth Drolet	Medical College WI
Sarah Chamlin and Tony Mancini	Northwestern
Maria Garzon	Columbia University
Amy Nopper, Brandon Newell and Kim Horii	Mercy Children's Kansas City
Anne Lucky	Cincinnati Childrens
Denise Metry	Baylor Med College
Eulalia Baselga	Barcelona, Spain

And many of our colleagues, fellows who helped us…

Diagnosis

The Word "Hemangioma" Means Many Things to Many People

- "Hemangioma" has been used to describe a wide array of diverse diseases
- Examples: Lobular capillary, Rapidly-involuting congenital, Non-involuting congenital, and Intramuscular, …
- The word "hemangioma" needs an *adjective* to be specific

Which "Hemangioma" are we talking about today?

- **Infantile hemangioma (**AKA Hemangioma of Infancy, "Strawberry", etc)
- A unique tumor arising *only* in infancy
- Absence at birth or present as so-called precursor lesions(s)
- Characteristic phases of growth, proliferation early infancy followed invariably by involution phase

Terminology to Avoid Confusion

- Superficial, Deep and Superficial and Deep (or "Mixed") to describe location in skin
- Localized and Segmental hemangiomas to describe morphologic patterns
- NOT "Cavernous hemangioma" or "capillary hemangioma"

Specific Immunohistochemical Markers

- GLUT-1, an erythrocyte-type glucose transporter protein is found *in all stages* of hemangioma of infancy
- Not found in other vascular tumors or malformations
- Commercially available stain
- IH also stain with merosin and other "placental blood vessel markers:

North PE et al. Hum Pathol 2000;31:11-22

Epidemiology and its Implications for Pathogenesis: Who Gets Infantile Hemangiomas and Why?

Are Hemangiomas Derived from Placental Blood Vessels?

- Have immunohistochemical and molecular signatures virtually identical to placental blood vessels
- Evidence that placental injury (CVS) associated with increase in hemangiomas
- Intrinsic vs extrinsic hypotheses
- Regardless of original unique phenotype has clinical relevance

HIG Study Results (I) : Demographic/Perinatal

Hemangioma Group vs population (NVSS) data

Female gender	(p<0.0001)
White, Non-Hispanic	(p<0.0001)
Prematurity (also get MORE hemangiomas)	(p<0.0001)
Low Birth Weight	(p<0.0001)
Product of a Multiple Gestation	(p<0.001)
Advanced maternal age	(p<0.0001)

Haggstrom et al. J Pediatr. 2007 Mar;150(3):291-4.

Working Hypothesis: Hemangiomas are Immature Endothelial Precursor Cells

- Could explain prematurity/low birth weight connection
- Could explain why hemangiomas are so common
- Might help explain why hemangiomas go away (immune recognition)
- Low birthweight/tissue hypoxia may put the HIF pathway into overdrive

Management: When to Worry, What to Do

Management Dilemmas

- Real-life issue: Common *very heterogeneous* condition
- *Which* Hemangiomas to Worry About
- What are the clinical features most predictive of complications and/or need for treatment?
- Is there an optimal time to treat?

Considerations in Management:

- Location
- Segmental pattern
- Nature of Dermal Involvement
- Age/Timing
- Ulceration

Hemangiomas: When To Worry LOCATION

"Endangering"

- Periocular
- Airway
- Multiple (>5): risk of extracutaneous
- Lumbosacral

Disfiguring Potential

- **Central face**
- Nasal tip
- Perioral
- Ear
- Glabella

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Localized vs Segmental: Study of 327 infants

- 72% localized
- 18% segmental
- 8% indeterminate
- 3% multifocal (8 or more)

Chiller, Passaro and Frieden. Arch Dermatol. 2002;138:1567-76

Segmental Hemangiomas: Worse Prognosis

- Structural anomalies
- Complications
- Greater need for treatment
- Poorer outcome

p>0.001

Chiller, Passaro and Frieden. Arch Dermatol. 2002 Dec;138(12):1567-76

Hemangioma Patterns Localized and Segmental

- Segmental: Broad anatomic region or recognized developmental unit (such as the entire ear)
- Localized: Confined spatially, often appear to arise from central focal point

HIG Treatment findings

- Complications in 24%; Some form of treatment 38%
- Major indications for treatment(s)
  - Risk of disfigurement (67.5%)
  - Ulceration (35.4%)
  - Parental anxiety (31.6%
  - Rapid growth (29.3%)
  - Threat to vision (16.9%)
- Therapies used: Wound care (13%), oral corticosteroids (12%), topical corticosteroids (9%), pulsed-dye laser therapy (8%), surgical excision (5%), intralesional corticosteroids (4%).

Segmentals: Need for Treatment

- Segmental hemangiomas were 11 times more likely to experience complications and 8 times more likely to receive treatment than localized hemangiomas, even when controlled for size.
- Segmental facial hemangiomas 43x more likely to receive systemic treatment compared to non-facial, non-segmental IH.
- Segmentals presented mean 1 month earlier BUT were 10x as large

Haggstrom et al. Pediatrics 2006 Sep;118(3):882-7

Dispelling the "red dot" theory

- "If we could have only treated it when it was a tiny red dot…"
- Superficial treatments (e.g. laser, imiquimod, topical steroid) can halt growth of hemangiomas destined to be superficial and typically small
- Hemangiomas "mark out their territory" (before birth)
- Main growth is volumetric not true radial growth

PHACE SYNDROME

- P: Posterior fossa and other brain anomalies
- H: Large facial hemangiomas
- A: Arterial anomalies especially CNS and facial
- C: Cardiac defect and right-sided coarctation of the aorta
- E: Eye defects especially cataract, vascular anomalies, microphthalmia

Frieden et al. Arch Dermatol 1996;132:307-11

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What do we know about hemangioma Growth?

- Characteristic **rapid growth** during infancy
- Involution approximately 10% per year
- 50% by age 5
- 90% by age 9
- **Complete involution** does not necessarily mean **complete resolution**

Growth during Infancy

- Study of over 1000 patients followed minimum 8 to maximum 22 months
- Hemangiomas reach 80% of maximum size at a mean age of 3 month
- Segmental hemangiomas and deep hemangiomas grow longer
- Average age of first visit to dermatology was 5 months

Key Concepts re: Growth

- 80% of hemangioma growth completed by 5 months of age
- Hemangiomas mark out their territory early: Segmentals presented 1 month earlier yet were 10x larger
- Essential ***no radial growth phase:*** Hemangioma growth is mainly volumetric not centrifugal

Implications of Growth Characteristics: Hemangioma Crisis Period

- High-risk hemangiomas (segmental, large, central face) require prompt referral and urgent visit to specialist
- Watch "like a hawk" first few weeks to months
- Worry less after 6 months and much much less after 1 year

TREATMENT OVERVIEW

- "No one-size-fits-all" treatment approach
- Treatment MUST be individualized based on location, morphology, age of patient, parental preferences, etc.
- Treatments we have are good but not great, effective but not foolproof
- 3 examples

Simplified Treatment Schema

- Big Bad hemangiomas: Usually need systemic steroids
- Little ones: Observation alone or a superficial treatment (laser/topical steroid/imiquimod/etc)
- Medium or small but problematic (eg nasal tip, small lip, etc: IL steroids, systemic steroids, surgical excision
- Recognize when the "cat is out of the bag"

Rx of hemangiomas: Yes BUT…

TREATMENT	LIMITATIONS
Systemic steroids	Many side effects, need high doses for months
Intralesional steroids	Smaller lesions, intra-arterial injection; benzyl alcohol
Topical steroids	Effect is very superficial
Pulsed dye laser	Effect superficial; NOT an eraser; Risk ulceration
Interferon	Risk spastic diplegia ~20%

Topical CS & Imiquimod

- Imiquimod anecdotal and case series (largest #22 in 18 patients; next 10; then single case reports)
- In largest, all superficials improved; resolution 4/22 but no change in deeps
- **Crusting (5/22)**
- Topical CS case series 34 patients- 35% demonstrated good response, 38% partial response, and 27% no response

Ho NT et al. J Am Acad Dermatol. 2007;56:63-8.

Garzon et al JAAD 2005;52:281-6

Intralesional Laser Therapy

- Reports “bare fiber” KTP or Nd-YAG into hemangiomas >1cm thickness
- Summary of >500 patients reports positive results with modifications of older techniques.
- Clearly quite operator-dependent
- Need for multiple Rx under GA
- No comparison to other modalities and many received other Rx as well.

Burstein FD et al. J Craniofacial Surg 2006;17:756-61

Surgical Approaches

- For pedunculated or large protuberant lesions if resection is inevitable
- Upper eyelid lesion not responding to Rx
- Scar easily hidden (scalp)
- Residual permanent skin changes

Purse-string closure technique to minimize scar length

Mulliken. Curr Probl Surg 2000, 37:517-84

Mulliken Plast Reconstr Surg 2002;109:1544-54

TREATMENT OF ULCERATION

Treatment of Ulcerated Hemangiomas: 1st Line Therapy

- Treat pain
- Topical occlusive ointment or occlusive environment
- Barrier creams, pastes diaper area (Ilex, Triple Paste) sometimes helpful

Ulcerated Hemangiomas: Other Treatments

- Regranex® –my current favorite 2nd line. Cost is about $600 for a tube
- Pulsed Dye laser –sometimes very helpful
- Hemangioma-specific Rx (eg steroid, interferon, etc)
- Excision – great option if well-localized and good anatomic site

Metz B et al. Arch Dermatol. 2004 ;140:867-70

Infantile Hemangiomas: The Future

- Unique vascular phenotype – **not** just “regular blood vessels” best illustrated by paradoxical growth with Endostatin
- Huge need for more research – both clinical and : animal models and good *in vitro* systems to study IH