Classification, Pathogenesis and Treatment of Benign Vascular Anomalies in Children

With a review of the pathology

Martin C. Mihm Jr., MD
Director, Melanoma Program
Brigham and Women's Hospital
Harvard Medical School

Conflict of Interest

- Chairman Scientific Advisory Board - Caliber I.D. Inc.
- Member Scientific Advisory Board - MELA Sciences Inc.

Vascular anomalies are either hemangiomas or malformations

- 10% of all children are born with a vascular birthmark
- 90% resolve by age 2; the remaining are either a problematic hemangioma (infantile), or type of hemangioma (NICH/RICH) or a vascular malformation (the most common is a port wine stain)

Mulliken & Young (1988)
Hemangiomas-Clinical Presentation

- Typically *infantile hemangiomas* appear 3 to 4 weeks after birth
- Start as a flat blanched lesion
- Begin proliferation at 4 to 6 weeks
- Can be both superficial/deep

Waner and Suen (1999)
One prominent histological feature of infantile hemangiomas, the presence of endoneurial pseudoinvasion, led us to investigate blood-nerve barrier competency in these lesions.

**GLUT1**

1. One of a family of facilitative glucose transporter protein isoforms, each with a limited tissue distribution in vivo.
2. Expression found in normal tissues highly restricted to erythrocytes, perineural cells, endothelial cells at blood-tissue barriers as brain, nerve and placenta, and some epithelial barriers.
3. Up-regulation in many malignant cells, but not in benign tumors.

**Pyogenic Granuloma**
Hemangioma

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Gene</th>
<th>Locus</th>
<th>Pathway</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IH</td>
<td>VEGFR3; PDGFR-beta; FLT4; VEGFR2; TEM7</td>
<td>5p31-33</td>
<td>VEGF receptor pathway; EC proliferation; tubular morphogenesis; sprouting integrin-like receptor</td>
<td>Propranolol; acebutolol; corticosteroids</td>
</tr>
</tbody>
</table>

Uebelhoer M., Boon LM, Ikkula M. CSH Perspectives; 2012

Preferred Treatment of Infantile Hemangiomas

- Early proliferating superficial lesions, especially segmental, should be treated with pulse dye laser or topicals

- Steroids are still preferred for intraleisonal injection into small focal hemangiomas since propranolol has not been found to be effective when injected directly into a lesion

- Propranolol is first line oral/systemic treatment for large, disfiguring and problematic segmental and focal hemangiomas

- Surgery is considered for lesions that fail drug and/or laser therapy or when a vital structure is impaired and there is insufficient time to wait for drug therapy to take effect

Labreze, de la Roque, Hubiche, Boralevi, Bordeau Children's Hospital, June 2008 (New England Journal of Medicine) 358--2649--2651

The Unique Vascular Phenotype of Infantile Hemangioma

GLUT1, Le Y, PEG perfection, MEROSIN
POSSIBLE MECHANISMS FOR SHARED HEMANGIOMA-PLACENTAL PHENOTYPE

1. Embolization of placentally-derived vascular cells or precursors to fetal tissues during gestation or birth (North P. et al.; Hum Path; 2001; Mihm MC. Nelson S.; 2010).

2. Colonization by angioblasts (Boye E. et al.; JCI; 2001) aberrantly "switched" to the placental phenotype by either:
   a. Somatic mutation.
   b. Abnormal local inductive influences.

3. Infantile hemangioma stem cells give rise to both endothelial and pericytic cells. (Boscolo E. et al.; Arterioscler Thromb Vasc Biol; 2013)

Recent Investigations (Cont.)

- Striking similarities of transcriptomes between placenta and hemangioma when studying hierarchical and nonhierarchical clustering analysis of >7,800 genes from a variety of tissues
- Comparing the two studying arrays of 21 endothelial cell genes in 1000 polymorphisms, great similarities were found. (Barnes et al. PNAS, 2005)
<table>
<thead>
<tr>
<th>Vascular Malformations</th>
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<tbody>
<tr>
<td><strong>High Flow</strong></td>
</tr>
<tr>
<td>Arteriovenous Malformations</td>
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<tr>
<td>Arteriovenous Fistulas</td>
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<tr>
<td><strong>Low Flow</strong></td>
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<tr>
<td>Lymphatic</td>
</tr>
<tr>
<td>Capillary</td>
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<tr>
<td>Venous</td>
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<tr>
<td>Mixed</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Arteriovenous Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most cases occur sporadically</td>
</tr>
<tr>
<td>Heritable AVMs have been associated with a cutaneous capillary malformation and hereditary hemorrhagic telangiectasia (HHT)</td>
</tr>
<tr>
<td>Arterio-venous fistulae are commonly trauma associated</td>
</tr>
<tr>
<td>Lesions present as often small pulsatile cutaneous plaques or nodules with overlying normal or Port Wine Stain-like skin</td>
</tr>
</tbody>
</table>

HHT-associated AVMs involve endoglin and activin receptor-like kinase 1 genes
Loss of function results in impaired TGF-beta signaling, necessary for AV differentiation
The cutaneous capillary malformation associated with AVM involve mutations in RASA 1 that affects the RAS/MAP Kinase pathway

Whitehead KJ et al. 2013; CHS Perspectives on medicine
Theory

- Relative or absolute absence of pre-capillary sphincters/sphincter control.
- Results in continuous shunting of blood across the nidus.
- This in turn results in expansion of the nidus, venous dilatation and arterial hypertrophy.
Theory
- Primary nidus - capillary malformation
- Arterial hypertrophy and venous dilatation-secondary changes
- No way of clinically differentiating between primary nidus and secondary changes.
- Difficulty in determining “tumor margins”, assuming that the nidus is fixed.

Treatment of AVMs
- Requires multidisciplinary team approach with Interventional Radiologist and Surgeon
- Goal is to manage, attempt to cure
- Embolization/Angiographic
- Sclerotherapy
- Combination with surgery. Must remove the NIDUS
- All tissue must be removed

Arteriovenous Malformation

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<tr>
<td>AVM</td>
<td>RASA1</td>
<td>5q13-22</td>
<td>Ras/MAPK inhibitor; Cell motility; Survival</td>
<td>mTOR Inhibitors? Ras Inhibitors?</td>
</tr>
</tbody>
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Glomulovenous Malformation

“Glomangioma”

Differential diagnosis in infancy:
- Blue Rubber Bleb Nevus Syndrome
- Leukemia Cutis (Blueberry Muffin Syndrome)
- Venous Malformations
Glomulovenous Malformation

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<tr>
<td>Glomulovenous</td>
<td>GLMN</td>
<td>1p21-22</td>
<td>SMC differentiation; Protein synthesis/</td>
<td>mTOR inhibitors</td>
</tr>
<tr>
<td>Malformation</td>
<td></td>
<td></td>
<td>degradation; TGF-beta, HGF</td>
<td></td>
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Low Flow – Lymphatic Malformation

- Lymphatic malformations (cystic hygroma or lymphangioma are classified as microcystic, macrocystic, or mixed.
- Most lymphatic malformations (approximately 75%) occur in the cervicofacial region.
- The overlying skin can be healthy, or it may have tiny characteristic vesicles.

Lymphatic Malformations

- Lesions often first present or become more extensive at times of hormonal change, such as puberty, or associated with infection
- Recurring infections lead to extensive growth and often require prophylactic antibiotics
Lymphatic Malformation, Macrocystic
(Cystic Hygroma)
Management of Lymphatic Malformations

- Surgical resection
- Laser therapy
- OK 432
- Management with antibiotics
- Studies currently underway with Rapamycin and Viagra (Sildenafil)

Low Flow – Capillary Malformation
Port Wine Stains

- Also known as port wine stains
- Sometimes referred to as venular malformations
- Present at birth as a flat red/purple birthmark
- Never regress
- Some can thicken, cobble, and cause tissue overgrowth
Port Wine Stain Treatment

- Laser treatment
- Sometimes require tissue debulking

Photos courtesy of www.birthmark.org
Port Wine Stain Treatment

- Pulse Dye Laser (PDL) is current treatment of choice
- Selectively destroys subsurface targets without inducing thermal damage in adjacent normal tissue
- PDL first generation used 577 nm. wavelength and 300 us. pulse duration
- Now 585 nm. wavelength available for adult PWS treatment

Angiogenesis inhibitor Rapamycin (RPM) has been combined with PDL to potentially enhance PWS therapeutic outcome
- RPM can suppress the VEGF/PI3K/AKT/mTOR pathway and inhibit reperfusion of blood vessels post PDL in PWS patients
- Further study is needed for more efficient therapeutic modalities

Venous Malformation

- Clinical Features
  - Incidence is 1 in 5,000 to 1 in 10,000 persons
  - Thrombosis common and associated with pain as well as clinical nodularity
  - Occur in complex syndromes including Klippel-Trenaunay, Maffucci, and Blue Rubber Bleb Nevus syndrome
Low Flow - Venous Malformations

Venous Malformations are usually soft and easily compressible soft-tissue mass that is associated with bluish skin discoloration.

Increasing engorgement with dependency is typical.

These birthmarks can be small and localized or extensive and involve the entire extremity or body part.
Venous Malformation Treatment
- Surgical resection
- Embolization
- Sclerotherapy
- Rapamycin
- NdYag
- Laser

Venous Malformation

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<tr>
<td>VM</td>
<td>TIE2/TEK</td>
<td>9p21</td>
<td>Tyrosine kinase receptor; EC migration, proliferation, survival; SMC recruitment; Vascular sprouting; Maturation, stability; Hematopoietic quiescence</td>
<td>TIE2 inhibitors?</td>
</tr>
</tbody>
</table>

Uebelhoer M., Boon LM, Ikksu M. CSH Perspectives; 2012
**Low Flow - Mixed Malformation**

- Lympho-venous malformations are often referred to as mixed lesions.
- They contain both abnormal lymphatic and venous channels.
- They may be scattered in one extremity or may be a focal malformation.
- Treatment consists of embolization, sclerotherapy, compression management, and laser.

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**Malformation Syndromes**

- Klippel-Trenaunay Syndrome
- Sturge-Weber Syndrome

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**Klippel-Trenaunay Syndrome**

- Affects one or more limbs or trunk region.
- Triad of stain, tissue hypertrophy, and bone overgrowth.
- Most cases, girth of limb is larger but in some cases, the non-affected limb can be clinically smaller.
- Stain is different than typical port wine stain.
- Lateral Marginal Vein varicosity diagnostic.
KTS Treatment/Management
- Compression
- Water therapy
- Laser
- Elevation of extremity
- Low dose aspirin
- Debulking when necessary
- Amputation as a last resort

Sturge-Weber Syndrome
- Involves 3 components: vascular stain of the V1 (eye area), calcification on the brain, and glaucoma from increased ocular pressure
- 30% to 70% of individuals with a stain in the V1 region are suspect for SWS
- Brain involvement may be unilateral or bilateral

Sturge-Weber Syndrome
- A typical vascular nevus

Ellison D., Neuropathology; 3rd Ed.
Sturge-Weber Syndrome

- Bilateral meningeal angiomatosis.

Coronal slices of a surgical specimen show the narrowed dark granular cortical ribbon.

Microscopy shows the abnormal leptomeningeal venous plexus and a linear array of superficial calcifications in the thin atrophic cortex.
Sturge-Weber Syndrome

- Severe astrogliosis with Rosenthal fiber formation and many calcospherites in the superficial cortex.

Ellison D., Neuropathology; 3rd Ed.

Sturge-Weber Syndrome

- The leptomeningeal venous angioma lacks elastic fibers.

Ellison D., Neuropathology; 3rd Ed.

Vascular Tumors and Malformations associated with Coagulopathy

- Mild-to-moderate chronic consumptive coagulopathy – large venous and lymphatic malformations
- Severe thrombocytopenia due to platelet trapping (Kasabach-Merritt phenomenon) – kaposiform hemangioendothelioma and tufted angioma
Kaposiform hemangioendothelioma

Infantile hemangioma

Kasabach-Merritt Phenomenon

<table>
<thead>
<tr>
<th>Infantile hemangioma</th>
<th>TA</th>
<th>KHE</th>
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<tbody>
<tr>
<td>GLUT1 positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No KMP</td>
<td></td>
<td></td>
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<tr>
<td>GLUT1 negative</td>
<td></td>
<td></td>
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<tr>
<td>+/- KMP</td>
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TA
Intramuscular “Hemangiomas”

- Large vessel malformations (mostly venous)
- Small vessel type (vascular malformations or tumors?)
- Mixed small and large vessel type
- No infantile hemangiomas

Most are low-flow venous malformations.

The cellular, “small-vessel” type mimic infantile hemangioma in histology somewhat, but are negative for GLUT1, etc. These present as “masses” by MRI and typically show angiographic and/or clinical features of AV-shunting. They are clinically consistent with vascular malformations and do not regress.
Intramuscular venous malformation

Intramuscular “hemangioma”

In Summary

- Vascular tumors of childhood represent a number of distinct entities with diverse etiologies – many with diagnostic histopathological features.

- Some lesions continue to defy classification and are best viewed as complex, dynamic processes responding to as yet unidentified factors. For these, the object for the pathologist is not to “pigeon hole”, but to describe as accurately as possible.
Everyone has the right to look normal

Photos courtesy of VBF

Acknowledgments

- Paula North, MD, PhD
- Milton Waner, MD
- Teresa O, MD
- Adriano Piris, MD
- Ignacio Carpintero, MD
- Larry Eichenfield, MD
- Ilona Frieden, MD
- Christine Lian, MD
- Labib Zakka, MD
- Linda Rozell-Shannon, PhD

Thank you for your kind attention