Histopathology of Pediatric Vascular Anomalies using the International Society of Vascular Anomalies Classification - a must know for all

Anita Gupta, MD Assistant Professor in the Department of Pathology, Cincinnati Children’s Hospital Medical Center, Cincinnati, USA

Abstract: All vascular lesions are not “hemangiomas” and vascular lesions in adults are not “hemangiomas”. In 1982 Mulliken and Glowacki proposed a classification of vascular anomalies based on clinical characteristics and biologic properties. Ten year later, in 1992, the International Society for the Study of Vascular Anomalies (ISSVA) was established and their classification scheme was accepted by ISSVA in 1996. Since then yearly and bi-yearly ISSVA members have meet with the latest being 3 months ago in March 2014 with revisions in the classification revealing over 50 different subtypes of vascular anomalies. Unfortunately, even today confusing terminology and misconceptions are still being propagated throughout the medical community world-wide even when clearly there is a distinct difference between vascular anomalies. The focus of my talk today will be to familiarize all of you with basic histopathology of pediatric vascular anomalies using the International Society of Vascular Anomalies Classification.

Key words: International Society of Vascular Anomalies (ISSVA), infantile hemangioma, congenital hemangioma, kaposiform hemangioendothelioma, capillary malformation, venous malformation, glomuvenous malformation, arteriovenous malformation, and PTEN Hamartoma of Soft Tissue

In 1982 Mulliken and Glowacki proposed a classification of vascular anomalies based on clinical characteristics and biologic properties. In 1992, the International Society for the Study of Vascular Anomalies (ISSVA) was established and their classification scheme was accepted by ISSVA in 1996 with revisions in 1997. Patient advocacy groups were formed nationally and internationally. Further revisions to include anomalies such as Kaposiform Lymphangiomatosis (KLA), PTEN Hamartoma of Soft Tissue (POST), Fibroadipose Vascular Anomalies (FAVA), and others were made in March 2014 at the ISSVA conference in Melbourne Australia. However, despite this decade worth of accomplishments medical textbooks continued to use outdated terminology like capillary hemangioma, lymphangioma, cavernous hemangioma, arteriovenous hemangioma and several others.

International Society of Vascular Classification breaks down vascular anomalies broadly into vascular tumors and vascular malformations. Vascular tumors mainly include infantile hemangioma, congenital hemangioma (rapidly involuting, partially involuting, and noninvoluting), kaposiform hemangioendothelioma, and others. Vascular malformations can be broadly broken down to capillary, venous, lymphatic, arterial, and mixed malformations.
Why do I have to know the ISSVA Classification?
Most important reasons are alterations in treatment modalities thus better patient outcome.

- Drugs: steroids, propranolol, chemotherapy
- Phototherapy: capillary malformation; does not really work for hypertrophic or deep CM
- Sclerotherapy: venous and macrocystic lymphatic malformation
  various sclerosing agents depending on type of malformation
  a. Doxycycline
  b. Bleomycin
- Surgery: excision, debulking, amputation
- Cytogenetics: PTEN mutation, RASA 1 mutations

Vascular Tumors: Key Points

1. **Infantile Hemangioma**
   a. Appears few days *after* birth
   b. Quarter of all premature infants
   c. Head and neck is most common location
   d. Growth phases
   e. Proliferative phase (0-9 months)
      i. Lobules of back to back capillaries with little intervening stroma
   f. Plateau phase (9-18 months)
      i. Lobules of capillaries with increased intervening stroma and hyalinized capillary basement membrane
   g. Involutes completely by 6-10 years
      i. Few scattered hyalinized capillaries interspersed between fat
   h. ALL PHASES capillary endothelium immunoreactive to Glucose 1 transporter protein (GLUT-1)
   i. Lumbosacral cutaneous anomalies “Port Wine Stain” may be either capillary malformation or infantile hemangioma; and the later are often associated with dermal sinus tracts.
   j. Liver infantile hemangiomas previously known as infantile hemangioendothelioma type 1, is the most common mesenchymal tumor of the liver accounting for 20% of all liver tumors from birth till 21 years of age. These lesions are more common in females. They are typically clinically silent with 80% occurring in the first 6 months of life. The three clinical subgroups of infantile hepatic hemangioma recognized by the Liver Hemangioma Registry of the Vascular Anomalies Center at the Children’s Hospital of Boston are focal, multifocal, and diffuse. About 20% of cutaneous IHs are multiple and often have visceral involvement with the liver being the most common region of involvement. A small subset of multifocal and diffuse hepatic IH are symptomatic with signs of cardiac failure secondary to high volume shunting, hypothyroidism...
secondary to overproduction of type 3 iodothyronine deiodinase, abdominal compartment syndrome, and fulminant hepatic failure. Thus if you treat the hypothyroidism you can often times alleviate some symptoms.

2. **Congenital Hemangioma**
   a. Fully grown at birth
   b. May be associated with consumptive coagulopathy and heart failure
   c. On histology: Rapidly Involuting, Partially Involuting, and Non Involuting
      i. The endothelial cells are GLUT-1 negative

3. **Kaposiform Hemangioendothelioma**
   a. Aggressive neoplasms
   b. Focal or Diffuse
   c. Involves multiple planes of tissue
   d. Half are congenital
   e. Lesions larger than 5cm are often associated with Kasabach Merritt Phenomenon
   f. Histology: classic pattern is of coalescing lobules of spindled endothelial cells with are immunoreactive to smooth muscle actin and lymphatic endothelial marker like PROX-1 or D240; platelet microthrombi, hemosiderin laden macrophages, and extravasated red blood cells.

   In 2012 Malmo Sweden ISSVA conference, poster presentation, upon evaluation of all the KHE at our institute – we recognized the “vascular pattern “of KHE which was exclusively seen in neonates – sheets of small vessels that are GLUT-1 negative, and smooth muscle actin/lymphatic marker positive.
   g. Latest Treatment includes Sirolimus

---

**Vascular Malformations**

1. **Capillary malformation (CM),** is used in a generic sense by clinical colleagues to indicate a vascular stain rather than a specific type of lesion and it therefore includes stains produced by various vascular malformations such as the common facial “port-wine” stains (veno-capillary malformation), venous and
arteriovenous malformations and those observed in syndromes such as Klippel-Trenaunay and Parkes Weber. The most common and well known CM is the facial nevus flammeus or “port-wine” stain. Biopsies of lesions in young children may demonstrate normal histology or only rare dilated “capillaries” in the papillary dermis. With increasing age, CM are characterized by haphazardly arranged ectatic vessels with small venular morphology in the papillary and occasionally reticular dermis. The channels have flat endothelial cells, thin collagenous walls, and a layer of pericytes. Vascular size and the mean vessel area increase with age and correlate with the change in color of the lesion. A small minority of individuals with a facial CM will develop cutaneous thickening and nodularity, soft tissue and skeletal overgrowth, and in Sturge Weber syndrome, approximately 50% will do so. The histopathologic correlates of this phenomenon include nodular aggregates of large channels, many with thickened walls composed of collagen and smooth muscle surrounded by abundant fibrous tissue.

2. **Venous malformations (VMs)**, even today, are still called “cavernous hemangioma”, “venous hemangioma”, and “cavernous angiomas” in medical text books. VMs vary in size and can involve the dermis, subcutaneous tissue, skeletal muscle, and viscera including liver and brain. Histopathologically, VMs are composed of irregular venous-type channels, lined by flat endothelium and surrounded by smooth muscle that is often focally absent or scant relative to channel size. Luminal thrombi are frequently present, sometimes showing papillary endothelial hyperplasia.
   a. **Glomuvenous malformation (GVM)**, previously known as “glomangioma”, are single or multiple venous malformations of a special type. These lesions are characterized by ecstatic and malformed veins with smooth muscle replaced by one or multiple layers of cuboidal “glomus” cells which are immunoreactive for smooth muscle actin. Glomus tumors differ from GVM in that the former almost always occurs in adults as a small well-circumscribed subungual proliferation of clusters and sheets of glomus cells lacking a malformed venous component.
   b. **Blue Rubber Bleb Nevus Syndrome** is characterized by soft blue, nodular venous malformations involving the dermis, subcutaneous tissue, and all layers of the gastrointestinal tract. Cutaneous lesions have large channels with thin walls and little or no smooth muscle. The deeper ones have a layer of smooth muscle although it may be discontinuous.

3. **Lymphatic malformations (LMs)** reflect the abnormal development of the lymphatic system. LMs used to be called “lymphangioma” or “cystic hygroma” depending on whether the size of the channels was small or large, respectively. Localized LMs of the skin and subcutis have lymphatic channels that do not connect with the deep (intramuscular) lymphatics. Abnormalities of large lymphatic trunks including the thoracic duct, such as ectasia, lack of valves or atresia, have been demonstrated in extensive or generalized lesions.

   LM is an invariably prominent component in Klippel-Trenaunay syndrome and may occur in other syndromes such as Trisomy 21 and Noonan. If involvement was extensive or generalized, the term “lymphangiomatosis” was
used. LMs vary from small, localized sponge-like lesions to diffuse involvement of a region or organ, to generalized involvement including viscera and bone. They are often classified as microcystic, macrocystic (spaces larger than 1cm), or combined.

Generalized LM and Gorham-Stout syndrome, also known as “disappearing bone disease” have histopathology similar to solitary LM, but in some lesions, the channels are smaller, complex and permeative, the lymphatic endothelial cells are larger, focal endothelial hyperplasia may be present, and the proliferative index is increased in these areas.

4. **Arteriovenous malformations (AVMs)** were known previously as “arteriovenous hemangioma”. These high flow lesions involve skin, soft tissue and viscera with the head and neck region including brain being the most common location. Approximately 50% of these lesions are visible at birth. The majority of these lesions are sporadic; however some AVM are part of inherited syndromes: hereditary hemorrhagic telangiectasia, Parkes Weber syndrome, CM-AVM, and PTEN hamartoma tumor syndrome. Generally, there are large and tortuous arteries, large and thick-walled veins, thin-walled structures that are probably abnormal veins, and some number of smaller indeterminate vessels. Some arteries show disruption of the arterial internal elastic lamina highlighted by the elastic or Verhoeff-van Gieson Stain (VVG) and a transition to hypertensive veins, representing sites of shunting. A small vessel component of a variable degree is present in most AVMs and is where the proliferative component resides. The reason for this proliferation is unknown; however it has been hypothesized to be a consequence of abounding blood flow or alternatively may be intrinsic to the genesis of AVM itself. Pyogenic granuloma-like, infantile hemangioma-like (the endothelial cells are negative for GLUT-1), and pseudokaposiform like patterns may also occur. These patterns are not of any known significance; however, they are important for the pathologist to recognize as a common component of AVM and not be mistaken for tumor.

a. **PTEN hamartoma of soft tissue**. These lesions occur most often in children and young adults and are usually intramuscular. Some extend to skin and soft tissue producing an irregular cutaneous capillary stain. The lesions are composed of an overgrowth of fibromyxoid and adipose tissue, tortuous arteries and veins with marked transmural muscular hyperplasia, labyrinthine veins, arteriovenous shunts, lymphoid nodules with germinal centers and sometimes bone formation and Schwann cell hyperplasia within nerves.

References:

Anita Gupta, MD
Pathology and Lab Medicine
Cincinnati Children's Hospital
MLC 1035, 3333 Burnet Avenue
Cincinnati, OH 45229-3039
USA
Anita.Gupta@cchmc.org
513-636-3924

Graduated from Mahadevappa Rampure Medical College, Gulbarga, Karnataka. I did my residency in Anatomic and Clinical Pathology at Northwestern Memorial Hospital in Chicago followed by a pediatric pathology fellowship at The Children's Hospital of Denver. Currently, I am an Assistant Professor transpiring into an Associate Professor as of July 1, 2014, at Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio, USA with certification in pediatric and anatomic pathology by the American Board of Pathology. In addition to general pediatric pathology, specialties include vascular anomalies, pediatric liver tumors, ciliopathies, and cardiac biopsies. I have twenty-three publications in peer reviewed journals primarily in vascular anomalies and pediatric GI/Liver. I have over 50 posters/or platform presentations at national and international meetings (United States Canadian Anatomic Pathology Meeting, Society of Pediatric Pathology, and International Society of Vascular Anomalies). Lastly, I also teach/give didactic lectures to medical students, residents, fellows, and multidisciplinary physicians locally and nationally.

Vascular Anomalies Treatment Questions:
Denise Adams, MD
Professor in Hematology/Oncology at Cincinnati Children’s Hospital
Director of the Vascular Anomalies Group
Denise.Adams@cchmc.org