Multifocal vascular anomalies:
Common, less common, and rare

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Conflict of interests:
Pierre Fabre Dermo-Cosmétique
Medimetriks Pharmaceuticals, Inc.
Menlo Therapeutics
Pfizer Inc.
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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DISCLOSURES

Menlo Therapeutics
Bridge BioServices
Pfizer
Pierre Fabre Dermatology
Overview

- Emphasis on early presentations
- Legacy of “diffuse neonatal hemangiomatosis”
- Multifocal vascular tumors
  - Infantile hemangioma
  - Multifocal lymphangioendotheliomatosis
  - Other
- Multifocal vascular malformations
  - Venous malformations
  - Glomuvenous malformations
  - CM-AVM
Not on the List

- Not Hereditary hemorrhagic telangiectasia (HHT)
  - Multifocal vascular typically later in life
- Rarely Cerebral Cavernous Malformations
  - If early onset usually only 1 or 2
“Diffuse Neonatal Hemangiomatosis”
Case from Literature

- More than 100 lesions at birth
- Lytic lesions in virtually every long bone
- Brain, GI mucosa, pleura, kidneys all studded with vascular growths (post-mortem)
- Died despite corticosteroids and supportive care

Not all “hemangiomas” are Infantile Hemangioma

- Natural history of IH: *not* dozens of vascular tumors at birth
- Immunohistochemical markers now allow specific diagnosis
- Distinguishing different diseases: Better able to define extra-cutaneous associations

North PE et al. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol. 2000 Jan;31(1):11-22
MLT and CAT

We reported his case and 2 others:


Short time later:

Revisiting “Diffuse Neonatal Hemangiomatosis”

- We performed a systematic review of 180 articles.
- Looked at clinical, laboratory, and histopathology.
- 73 cases had sufficient information to categorize into 3 groups:
  - IH/probable IH (59%)
  - MLT (23%)
  - Multifocal vascular lesions, NOS (18%)

Multifocal Vascular Tumors

- Infantile Hemangiomas
- MLT/CAT
- Other:
  - Multifocal PGs
  - Multifocal RICH
  - Others yet to be defined
Multifocal Infantile Hemangiomas

- Most common of the multifocal vascular tumors
- Numbers from a few to hundreds
- Main risk of extra-cutaneous involvement is hepatic IH
- Other sites much less common
  - GI IH is more likely with segmental IH not multifocal
  - Rare outliers; evaluation based on signs symptoms, not routine
Multifocal IH: Evaluation and Management

- 5 of more IH: Liver ultrasound (yield ~15%)
- If liver hemangiomas
  - Thyroid function tests
  - Is there evidence increased blood flow to and from liver?
  - Are hepatic hemangiomas diffuse or not?

Hepatic IH

- Like cutaneous IH most don’t need treatment
  - If mild disease, repeat monthly until going away
- Ultrasound less important after age 6 months
- Two major morbidities in hepatic IH
  - High-output CHF
  - Diffuse liver IH with consumptive hypothyroidism
- Propranolol 1st line treatment for H-IH

MLT/CAT

- Multifocal vascular tumors – often present at birth
  - Usually increase in numbers
- Main extracutaneous features are GI bleeding and fluctuating thrombocytopenia
- Many additional organs systems can be involved e.g. CNS, lungs, liver, kidneys, spleen
- Several skin clinical phenotypes
MLT/CAT Summary

- 2\textsuperscript{nd} most common multifocal vascular tumor of infancy
- Varied clinical presentations
- Clinicopathologic correlation essential
  - Genomics may prove helpful but no gene reported...yet
- Sirolimus emerging as important treatment
Other Multifocal Vascular Tumors: Still a lot to Learn...
• ~20-30 friable papules especially scalp
• Mother had PG during pregnancy
• Histopath c/w PG
• More recurred after removal of largest scalp PGs

Congenital PG-like presentation: Case 2

- Decreased fetal movements
- Anemia and coagulopathy at birth
- New papules appeared
- Dozens removed – path c/w PG
- Eventually slowly regressed and at age 19 years reportedly healthy
Funk T, Lim Y, Kulungowski AM, Prok L, Crombleholme TM, Choate K, Bruckner AL.

JAMA Dermatol. 2016 Sep 1;152(9):1015-20
Details of Case

- Mass on back detected *in utero* at 30 weeks GA
- At birth huge mass and hundreds of other cutaneous lesions
  - Platelets 8K, anemia, elevated D-Dimers
  - DIC resolved after resection of large mass
- Pathology was most c/w Rapidly-involuting CH
- Somatic mutation in GNA11 both back & leg but not saliva
- Suggests best dx is multifocal RICH
- This report points out importance of genomics in solving these mysteries!
Multifocal Vascular Malformations

- Multifocal venous malformations AKA “Blue rubber bleb nevus syn”
- Glomuvenous malformations
- CM-AVM
Multifocal Venous Malformations

- Familial (Autosomal dominant)
- Sporadic Multifocal VM
- Blue-rubber bleb nevus syndrome (Multifocal VM plus GI tract involvement)
- All 3 forms due to mutations in TEK
Blue Rubber Bleb Nevus syndrome

Skin lesions:
- Often a dominant VM (frequently congenital)
- Others VMs are generally small, < 1-2 cm, blue to purple in color, compressible, often hyperkeratotic, favoring palms and soles
- GI tract involvement typical
- Usually not inherited
- Due to double cis mutations in TEK

GVM as a cause of multifocal malformations

- Most common inherited vascular malformation
  - 90% penetrance so parents may be clinically unaffected
  - Genetic testing (germline) needed to confirm

- Regional /segmental stains at birth with unusual appearance

- Multifocal disease often appears in first few years

- Variable pain –often present

- Skin/SQ but occasionally IM

Recent discovery of EphB4 as cause of “CM-AVM2”
- 50% of CM-AVM have germline RASA1 mutations
- Telangiectasias more common
- CNS AVMs may be less common

Significant minority with CM-AVM have neither RASA1 or EphB4

CM-AVM: Some Take-aways

- High-flow stains & multifocal stains important clues
  - Capillary refill almost instantaneous
  - Parkes Weber may be somatic variant OR type II mosaicism
- Always ask about FH of birthmarks, brain vascular incidents
- Refer for genetic counselling and testing: RASA1 or EphB4
- 10% risk of spinal or brain AVM
  - MR imaging of brain and spine…when and how often?
- High-risk OB for mother even if father is carrier

Revençu N et al Hum Mutat. 2013;34:1632-41