Vascular Malformations

By Jennifer Eyler, MD and Patricia Todd, MD

### CAPILLARY MALFORMATIONS
Present at birth as well-demarcated pink to dark red macular stain. Can be isolated lesion or associated with a syndrome. Proportional growth with child and may darken and become nodular over time.

**NEVUS SIMPLEX** (Salmon Patch) Most common vascular lesion of infancy occurring in 30-40% of newborns. Dull pink macular lesion on posterior neck, scalp, glabella, forehead, and upper eyelids. Isolated lesion with no associated findings. No treatment necessary as many fade in 1-2 years. Those on the nape of the neck are more likely to persist.

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<th>ASSOCIATED SYNDROMES</th>
<th>GENETICS</th>
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<th>ADDITIONAL CLINICAL FEATURES</th>
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<tr>
<td>Sturge-Weber</td>
<td>Somatic mutations in GNAQ</td>
<td>Facial CM (variably V1, increased risk if bilateral V1 or V1 + V2 and V3)</td>
<td>Ipsilateral leptomeningeal angiomatosis, calcifications, and cerebral atrophy; ipsilateral ocular abnormalities. Neurologic symptoms include: seizures, cognitive and developmental delay, emotional or behavior problems, and attention deficit. Endocrine complications include growth hormone deficiency and central hypothyroidism.</td>
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<tr>
<td>Phakomatosis Pigmentovascularis</td>
<td>Twin spotting</td>
<td>Types I-V (CM) Type V (CMTC)</td>
<td>I – CM + epidermal nevus II – CM + dermal melanocytosis (\pm) nevus anemicus III – CM + nevus spilus (\pm) nevus anemicus IV – CM + dermal melanocytosis + nevus spilus (\pm) nevus anemicus V – CMTC + dermal melanocytosis</td>
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<tr>
<td>Cutis Marmorata Telangiectatica Congenita</td>
<td>Localized or generalized reticulated violaceous vascular network with focal atrophy; network persists with rewarming.</td>
<td>Limb hypoplasia on affected side; less commonly neurologic and ophthalmologic complications</td>
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<td>MACROCEPHALY-CM</td>
<td>PIK3CA, AKT3, PIK3R2</td>
<td>CM, often central facial (philtrum and glabella) or persistent nevus simplex</td>
<td>Developmental delay, neurologic abnormalities, asymmetric overgrowth, syndactyly, polydactyly, joint laxity, and hyperelastic skin; possible increased risk of Wilm’s tumor.</td>
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### TELANGIECTASIAS
Dilated capillary-type blood vessels with localized, segmental, or widespread distribution.

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<th>CUTANEOUS FEATURES</th>
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<tr>
<td>Hereditary Hemorrhagic Telangiectasia</td>
<td>Autosomal Dominant, ENG (HHT1), ALK1 (HHT2), SMAD4</td>
<td>Mucocutaneous telangiectasias typically appearing after puberty.</td>
<td>Visceral AVMs with a propensity to bleed including pulmonary (often HHT1), cerebral, GI, GU, and hepatic AVMs (often HHT2); complications include: intracranial hemorrhage, stroke, high-output heart failure, and portal hypertension.</td>
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<tr>
<td>Ataxia-Telangiectasia</td>
<td>Autosomal Recessive, ATM</td>
<td>Telangiectasias on conjunctiva (i.e. bulbar), face, and ears at 4-6 years of age.</td>
<td>Presents first with ataxia in toddlers; immunoglobulin deficiencies (IgG, IgA) and defective cell-mediated immunity lead to sinopulmonary infections (lymphoma and leukemia).</td>
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### ANGIOKERATOMAS
Ectasias of dermal capillaries associated with hyperkeratotic and acanthotic epidermis.

Subtypes:
- Solitary or multiple angio keratomas – lower extremities of young adults
- Angiokeratomas of Fordyce – scrotum or vulva in adults
- Angiokeratoma circumscriptum – plaque composed of multiple red-purple papules on extremity (present since birth or early childhood)
- Angiokeratoma of Mibelli – digits or interdigital spaces during childhood or adolescence, autosomal dominant
- Angiokeratoma corporis diffusum – widespread lesions in bathing trunk distribution (associated with Fabry disease and \(a\)-fucosidase deficiency)

### VENOUS MALFORMATIONS
Soft, compressible, blue nodules that expand in dependent position. Can affect face, including lips or oral mucosa (cephalic VMs), as well as trunk and limbs. Commonly penetrate deep into muscles, joints, and bones. Monitor for thrombosis and coagulopathy.

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<td>Familial Cutaneous and Mucosal VM</td>
<td>TEK/TIE2</td>
<td>Small, superficial cutaneous and mucosal VMs</td>
<td>Visceral VMs of intestines, lungs, and CNS. Cardiac malformations.</td>
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<td>Blue Rubber Bleb Nevus Syndrome</td>
<td></td>
<td>Small black-blue papules and skin-colored nodules involving palms and soles</td>
<td>Soft tissue and intestinal VMs. Hemorrhage can lead to iron-deficiency anemia. Lesions can be tender.</td>
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<tr>
<td>Glomuvenous Malformation</td>
<td>Glomulin</td>
<td>Painful, partially compressible, cobblestoned plaques on trunk and limbs</td>
<td>Rare joint or visceral involvement.</td>
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<tr>
<td>Maffucci Syndrome</td>
<td>Somatic mutations in IDH1 and IDH2</td>
<td>VM-like lesions with spindle cell hemangioma on biopsy, phleboliths</td>
<td>Enchondromas (cause orthopedic complications, 90% on the hands and feet), increased risk of chondrosarcoma, visceral VMs.</td>
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<tr>
<td>Cerebral Cavernous Malformation (CCM, Cerebral Capillary Malformation)</td>
<td>Autosomal (d)Dominant, KRT17 (CCM1), MGC4607 (CCM2), PDCD10 (CCM3)</td>
<td>Hyperkeratotic dark red to purple con genital plaque located on extremities</td>
<td>Neurologic manifestations including headaches, seizures, and cerebral hemorrhage.</td>
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LYMPHATIC MALFORMATIONS

**PRIMARY LYMPHEDEMA**
- Abnormalities of lymphatic vessels and nodes leading to inadequate clearance of lymph. Affects extremities. Increased risk of bacterial infection.
  - Subtypes:
    - Generalized – associated with intestinal or pulmonary lymphangiectasias, exudative enteropathy, and pleural effusions
    - Milroy Disease – AD mutation in FLT4, congenital lymphedema of lower extremities
    - Lymphedema-Distichiasis Syndrome – AD mutation in FOXC2, peri-pubertal onset of lymphedema, congenital distichiasis and venous varicosities

**SOLITARY LM**
- Consist of irregular, ectatic lymphatic channels. Classified as macrocystic, microcystic, or combined based on the size of cystic spaces present.
  - Macrocystic LM (cystic hygroma): large, soft, skin-colored, subcutaneous mass, detectable by ultrasound, CT, or MRI. Seen in Turner Syndrome (45 XO), Noonan Syndrome (PTPN11), and Down Syndrome (trisomy 21).
  - Microcystic LM (lymphangioma circumscriptum): most common type of LM occurring on proximal limbs, trunk, and mouth.
  - Plaques with overlying clear or hemorrhagic vesicles. Swelling occurs following injury or infection around the lesion.

Complications of LM
- Cervicofacial – bony involvement common, leads to mandibular overgrowth and prognathism
- Intracranial – bleeding in setting of dental or upper respiratory infection, leads to growth of LM
- Oropharyngeal – airway compromise
- Orbital – chemosis, amblyopia, strabismus, proptosis, vision loss
- Multifocal truncal lesions – may have associated visceral lymphangiomatosis
- Gorham-Stout Disease – LM with bony involvement leading to massive osteolysis causing pathologic fractures and deformity

**ADDITIONAL CLINICAL FEATURES**
- Fast-flow vascular malformations with direct communication between arteries and veins. 40% visible at birth; head and neck are most frequent locations. May worsen with puberty, pregnancy, and trauma.
  - Classified into 4 stages:
    - Quiescent/dormant – muscular or slightly infiltrated, red, and warm lesions that mimic CMs
    - Expansion – warm masses with throbbing and thrill over dilated draining veins
    - Destruction – necrosis, hemorrhage, ulceration, lytic bone lesions
    - Cardiac decompensation

**ASSOCIATED SYNDROMES**

**GENETICS**

- **Cobb**
  - Dermatomal CM or AVM overlying spinal cord +/- associated hyperkeratosis

- **Bonnet-Dechaume-Blanc**
  - Facial AVM
  - AVM extends to the orbit and brain, may be asymptomatic, may cause seizures or hemiplegia/paresis

- **CM-AVM**
  - Autosomal dominant; RASAL
  - Multiple small CMs, cutaneous AVMs in 11%, typically underlying largest CM
  - Cerebral AVM/AVF, Parkes Weber Syndrome in 12%

**OVERGROWTH SYNDROMES ASSOCIATED WITH VASCULAR MALFORMATIONS**

**OVERGROWTH SYNDROMES**

**GENETICS**

- **PTEN hamartoma tumor (includes Bannayan-Riley-Ruvalcaba)**
  - PTEN
  - AVMs (intramuscular), CMs, and venous varicosities
  - Genital lentigines and lipomas. Macrocephaly, segmental excess of hypervascularized fat, cerebral venous anomalies. Increased risk of thyroid or breast malignancy

- **Parkes Weber**
  - RASAL
  - Unilateral diffuse red CM, underlying AV fistula, lymphatic anomaly
  - Limb overgrowth, excess fat, lytic bone lesions and heart failure. Poor prognosis after puberty

- **CLOVES**
  - Somatic mutations in PIK3CA
  - CM, CLVM, less commonly AVM
  - Congenital lipomatous overgrowth, vascular anomalies, Epidermal Nevi, Scoliosis and other skeletal abnormalities

- **Klippel-Trenaunay**
  - Somatic mutations in PIK3CA
  - Capillary stain, venous varicosities usually involving lower limb, thrombophlebitis
  - Soft tissue/bony hypertrophy, coagulopathy, congestive heart failure, pulmonary embolism, stasis dermatitis, cutaneous ulcerations, and bleeding. Sharply demarcated “geographic” stains with increased risk of massive limb overgrowth, lymphatic involvement, and cellulitis

- **Proteus**
  - AKT1
  - CM, VM, LM, CLVM
  - Epidermal nevi, cerebrocutaneous connective tissue nevi of palms and soles, café au lait spots, lipomas. Learning disabilities. Disproportionate overgrowth leading to deformity and disabling orthopedic consequences

**ADDITIONAL CLINICAL FEATURES**

**VASCULAR FEATURES**

- Intramedullary spinal AVMs + vertebral vascular anomaly of same segment cause neurologic symptoms as lesions expand or bleed including back pain, radiculopathy, rectal/bladder dysfunction, paraplegia

**References:**