## 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.

<table>
<thead>
<tr>
<th>NEVUS SIMPLEX (Salmon Patch)</th>
<th>VASCULAR FEATURES</th>
<th>ADDITIONAL CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td></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 behavioral problems, and attention deficit. Endocrine complications include growth hormone deficiency and central hypothyroidism.</td>
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### GENETICS

Somatic mutations in GNAQ

### Phakomatosis Pigmentovascularis

Twin spotting

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<th>Types I-IV (CM)</th>
<th>Type V (CMTC)</th>
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### Ectasias of dermal capillaries associated with hyperkeratotic and acanthotic epidermis.

### GENETICS

Twin spotting

### Associated Syndromes

#### Sturge-Weber

Autosomal Recessive, CM, often central facial (philtrum and Type I-IV (CM)

#### Phakomatosis Pigmentovascularis

Twins spotting

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### CUTANEOUS FEATURES

#### Sturge-Weber

Facial CM (variably V1, increased risk if bilateral V1 or V1 + V2 and V3)

### ADDITIONAL CLINICAL FEATURES

Ipsilateral leptomeningeal angiomatosis, calcifications, and cerebral atrophy; ipsilateral ocular abnormalities. Neurologic symptoms include: seizures, cognitive and developmental delay, emotional or behavioral problems, and attention deficit. Endocrine complications include growth hormone deficiency and central hypothyroidism.

### DILATED CAPILLARY-MALFORMATION SYNDROMES

#### Cerebral Cavernous Malformation (CCM)

Autosomal Dominant, KRIT1 (CCM1), MGC4607 (CCM2), PDCD10 (CCM3)

### 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>V - CMT + dermal melanocytosis</td>
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### Associated Syndromes

#### Macrocephaly-CM

PIK3CA, AKT3, PIK3R2

| CM, often central facial (philtrum and glabella) or persistent nevus simplex |

### Telangiectasia

Localized or generalized reticulated violaceous vascular network with focal atrophy; network persists with rewarming.

### Reticulated cutaneous vascular network with focal atrophy.

### ADDITIONAL CLINICAL FEATURES

Limb hypoplasia on affected side; less commonly neurologic and ophthalmologic complications

### Telangiectasia

Autosomal Recessive, ATM

| Telangiectasias on conjunctivae (i.e. bulbar), face, and ears at 4-6 years of age. |

### Ataxia-Telangiectasia

Autosomal Dominant, ENG (HHT1), ALK1 (HHT2), SMAD4

| Mucocutaneous telangiectasias typically appearing after puberty. |

### Hereditary Hemorrhagic Telangiectasia

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<td>Cutaneous features</td>
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### ANGIKERATOMAS

### Vascular Features

Ectasias of dermal capillaries associated with hyperkeratotic and acentric epidermis.

#### Subtypes:

- Solitary or multiple anginokeratoma – lower extremities of young adults
- Angiokeratoma 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 α-fucosidase deficiency)

#### Vascular Features

Small black-blue papules and skin-colored nodules involving palms and soles

### ADDITIONAL CLINICAL FEATURES

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.

### Ataxia-Telangiectasia

Autosomal Recessive, ATM

| Telangiectasias on conjunctivae (i.e. bulbar), face, and ears at 4-6 years of age. |

### Presents first with ataxia in toddlers; immune globulin deficiencies (IgG, IgA) and defective cell-mediated immunity lead to sinopulmonary infections (lymphoma and leukemia).

### VESSELS AFFECTIONED

#### Familial Cutaneous and Mucosal VM

| KE1/KE2 |
| Small, superficial cutaneous and mucosal VMs |

### Additional Clinical Features

Visceral VMs of intestines, lungs, and CNS. Cardiac malformations.

### Blue Rubber Bleb Nevus Syndrome

| Small black-blue papules and skin-colored nodules involving palms and soles |

### Glomuvenous Malformation

| Painful, partially compressible, cobblestoned plaques on trunk and limbs |

#### Glomulin

### Maffucci Syndrome

| VM-like lesions with spindle cell hemangio blast, phleboliths |

### Zygostatic nodules in IDH1 and IDH2

### Cerebral Cavernous Malformation (CCM, Cerebral Capillary Malformation)

| Autosomal Dominant, KRIT1 (CCM1), MGC4607 (CCM2), PDCD10 (CCM3) |

### Hyperkeratotic dark red to purple con genital plaque located on extremities

### Neurologic manifestations including headaches, seizures, and cerebral hemorrhage.

Jennifer Eyler, MD is a PGY-3 dermatology resident at Loyola University Medical Center in Maywood, Illinois.

Patricia Todd, MD is a PGY-4 dermatology resident at Loyola University Medical Center in Maywood, Illinois.
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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.

Macrocytic 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
Cerebrocerebral – bony involvement common, leads to mandibular overgrowth and prognathism
Intracranial – bleeding in setting of dental or upper respiratory infection, leads to growth of LM
Orbital – chemosis, anophthalmia, strabismus, proptosis, vision loss
Orbital – neoplasms, optic nerve compression
Orbital – cavernomas, optic atrophy
Orbital – enophthalmos, diplopia
Orbital – chemosis, amblyopia, strabismus, proptosis, vision loss
Orbital – proptosis, optic atrophy

Cardiac – heart failure, valvular dysfunction, atrial septal defect, pulmonary hypertension
Neurologic – seizures, developmental delay, cognitive and developmental delay
Endocrine – hypothyroidism, central hypothyroidism
Gastrointestinal – enteric dysmotility, gastrointestinal bleeding
Genitourinary – hirsutism, hypospadias, cryptorchidism
Central nervous system – cranial nerve abnormalities, seizures
Orthopedic – limb length discrepancy, limb deformities
Cutaneous – café au lait spots, lipomas
Hematologic – coagulopathy, anemia
Psychiatric – anxiety, depression

ASSOCIATED SYNDROMES

GENETICS
Cobb
Dermatomal CM or AVm overlying spinal cord +/- associated hyperkeratosis

Bonnet-Dechaume-Blanc
Facial AVM

CM-AVM
Autosomal dominant; RASA1

VASCULAR FEATURES
Multiple small CMs, cutaneous AVMs in 11%, typically underlying largest CM

Cerebral AVM/AVF, Parkes Weber Syndrome in 12%

ADDITIONAL CLINICAL FEATURES
Intramedullary spinal AVMs + vertebral vascular anomaly of same segment cause neurologic symptoms as lesions expand or bleed including back pain, radiculalgia, rectal/bladder dysfunction, paraplegia.

AVM extends to the orbit and brain, may be asymptomatic, may cause seizures or hemiplegia/paresis.

OVERGROWTH SYNDROMES ASSOCIATED WITH VASCULAR MALFORMATIONS

OVERGROWTH SYNDROMES

GENETICS
PTEN hamartoma tumor (includes Bannayan-Riley-Ruvalcaba)

PTEN

VASCULAR FEATURES
AVMs (intramuscular), CMs, and venous varicosities

CM, CLVM, less commonly AVm

UNILATERAL DIFFUSE RED CM, UNDERLYING AFLATULA, LYMPHOMATIC ANOMALY

SUCCESSFUL EXTENSION OF TUMOR TISSUE INTO NORMAL TISSUE

CLOVES
Somatic mutations in PIK3CA

Skeletal abnormalities.

Klippel-Trenaunay
Somatic mutations in PIK3CA

Capillary stain, venous varicosities usually involving lower limb, thromboembolitis

Soft tissue/bony hypertrophy, coagulopathy, congestive heart failure, pulmonary embolism, stasis dermatitis, cutaneous ulcerations, and bleeding

Shortened/lengthened limb, varicose veins, phlebitis, and decreased calf muscle volume

Proteus
AKT1

CM, VM, LM, CLVM

ADDITIONAL CLINICAL FEATURES
Genital lentigines and lipomas.

Macrocystic LM (cystic hygroma): large, soft, subcutaneous mass, detectable by ultrasound, CT, or MRI. Seen in Turner Syndrome (45 XO), Noonan Syndrome (PTPN11), and Down Syndrome (trisomy 21).

CMs are less common than VMs and LMs in congenital or acquired vascular anomalies.


References: