Vascular Malformations

By Jennifer Eyler, MD and Patricia Todd, MD

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

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

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.

ASSOCIATED SYNDROMES	GENETICS	VASCULAR FEATURES	ADDITIONAL CLINICAL FEATURES
Sturge-Weber	Somatic mutations in *GNAQ*	Facial CM (invariably V1, increased risk if bilateral V1 or V1 + V2 and V3)	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.
Phakomatosis Pigmentovascularis	Twin spotting	Types I-IV (CM) Type V (CMTC) May be associated with Sturge-Weber or Klippel-Trenaunay	I – CM + epidermal nevus II – CM + dermal melanocytosis ± nevus anemicus III – CM + nevus spilus ± nevus anemicus IV- CM + dermal melanocytosis + nevus spilus ± nevus anemicus V – CMTC + dermal melanocytosis
Cutis Marmorata Telangiectatica Congenita		Localized or generalized reticulated violaceous vascular network with focal atrophy; network persists with rewarming.	Limb hypoplasia on affected side; less commonly neurologic and ophthalmologic complications
Macrocephaly-CM	*PIK3CA, AKT3, PIK3R2*	CM, often central facial (philtrum and glabella) or persistent nevus simplex	Developmental delay, neurologic abnormalities, asymmetric overgrowth, syndactyly, polydactyly, joint laxity, and hyperelastic skin; possible increased risk of Wilm's tumor.

TELANGIECTASIAS	Dilated capillary-type blood vessels with localized, segmental, or widespread distribution.

ASSOCIATED SYNDROMES	GENETICS	CUTANEOUS FEATURES	ADDITIONAL CLINICAL FEATURES
Hereditary Hemorrhagic Telangiectasia	Autosomal Dominant, *ENG (*HHT1), *ALK1* (HHT2), *SMAD4*	Mucocutaneous telangiectasias typically appearing after puberty.	Visceral AVMs with a propensity to bleed including pulmonary (often HHTI), 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; immunoglobulin deficiencies (IgG, IgA) and defective cell-mediated immunity lead to sinopulmonary infections (lymphoma and leukemia).

ANGIOKERATOMAS	Ectasias of dermal capillaries associated with hyperkeratotic and acanthotic epidermis. Subtypes: Solitary or multiple angiokeratomas – 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 α-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.

ASSOCIATED SYNDROMES	GENETICS	VASCULAR FEATURES	ADDITIONAL CLINICAL FEATURES
Familial Cutaneous and Mucosal VM	*TEK/TIE2*	Small, superficial cutaneous and mucosal VMs	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	Soft tissue and intestinal VMs. Hemorrhage can lead to iron-deficiency anemia. Lesions can be tender.
Glomuvenous Malformation	*Glomulin*	Painful, partially compressible, cobblestoned plaques onf trunk and limbs	Rare joint or visceral involvement.
Maffucci Syndrome	Somatic mutations in *IDH1* and *IDH2*	VM-like lesions with spindle cell hemangioma on biopsy, phleboliths	Enchondromas (cause orthopedic complications, 90% on the hands and feet), increased risk of chondrosarcoma, visceral VMs.
Cerebral Cavernous Malformation (CCM, Cerebral Capillary Malformation)	Autosomal dDominant, *KRIT1* (CCM1), *MGC4607* (CCM2), *PDCD10* (CCM3)	Hyperkeratotic dark red to purple congenital plaque located on extremities	Neurologic manifestations including headaches, seizures, and cerebral hemorrhage.

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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 Intraoral – bleeding in setting of dental or upper respiratory infection, leads to growth of LM Oropharyngeal – airway compromise Orbital – chemosis, ambylopia, 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	
ARTERIOVENOUS MALFORMATIONS	
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 – macular or slightly infiltrated, red, and warm lesions that mimic CMs Expansion – warm masses with throbbing and thrills over dilated draining veins Destruction – necrosis, hemorrhage, ulceration, lytic bone lesions Cardiac decompensation	

ASSOCIATED SYNDROMES	GENETICS	VASCULAR FEATURES	ADDITIONAL CLINICAL FEATURES
Cobb		Dermatomal CM or AVM overlying spinal cord +/- associated hyperkeratosis	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.
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; RASA1*	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			
OVERGROTH SYNDROMES	**GENETICS**	**VASCULAR FEATURES**	**ADDITIONAL CLINICAL FEATURES**
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	*RASA1*	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	**C**ongenital **L**ipomatous **O**vergrowth, **V**ascular anomalies, **E**pidermal Nevi, **S**coliosis and other **S**keletal 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, cerebriform connective tissue nevi of palms and soles, café au lait spots, lipomas. Learning disabilities. Disproportionate overgrowth leading to deformity and disabling orthopedic consequences.

Abbreviations:
CM: capillary malformation, **CMTC:** cutis marmorata telangiectatica congenital, **GI:** gastrointestinal, **GU:** genitourinary, **VM:** venous malformation, **LVM:** lymphatic venous malformation, **LM:** lymphatic malformation, **AVM:** arteriovenous malformation.

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