OVERGROWTH SYNDROMES

The Salim Afshar Laboratory

	STURGE-WEBER SYNDROME	PARKES WEBER SYNDROME	PROTEUS SYNDROME	CLOVES SYNDROME	KLIPPEL-TRENAUNAY SYNDROME	MAFFUCCI SYNDROME
AKA				congenital lipomatosis overgrowth vascular malformations epidermial, Scoliosis/skeletal/spinal anomalies (CLOVES),		1 of 7 Endochonromatosis syndromes (subtype 2) Spindle cell hemangioma or soft tissue vascular anomaly
General	incidence 1/50,000 newborns facial + leptomeningeal CM + eye anomalies +/- bone and/or soft tissue overgrowth defined by CM in V1 trigeminal nerve involvement but can also involve V2 & V3 Increased risk for GH deficiency and central hypothyroidism commonly has soft tissue and/or bony overgrowth (60-83%) extracraniofacial capillary malformations (29%)	CM + AVF +limb overgrowth diagnosis confirmed by detection of bruit or thrill patients have subcutaneous and intramuscular microshunting	CM, VM and/or LM + assymetrical somatic overgrowth 100 cases in literature neurology, opthamology, pulmonology consultations needed M:F = 2:1 high risk of developing DVT	M = F LM + VM + CM +/- AVM + lipomatous growth Lipomatosis mass associations (capillary malformations [skin above mass] OR lymphatic malformations within mass) (83%) AVM within or around lipomatous masses in paraspinal area (28%) Venous malformations (phlebectasia) involving truncal lesions (16%)	CM + VM +/- LM + limb overgrowth venous component of the syndrome manifests as phlebectasia/abnormal drainage pathognomonic: emrbyonic marginal vein of Servelle in the subcutaneous tissue is isolated in the lateral calf/thigh	VM +/- spindle-cell hemangioma + endochondroma patients have normal intelligence multiple endochondromas & soft tissue vascular lesions At risk of developing other tumors [brain, pancreatic, ovarian, & AML possibly fatal due to pulmonary metastasis from chondrosarcoma
Head & Neck	Morbidity: Glaucoma (65-77%), blindness, retinal detachment		opthalmologic findings (40%) = stabismus, epibulbar cysts, epibulbar dermoids			spindle cell: head & neck (25%) endochondromas: head (18%)
Intracranial	neurologic problems (87-93%) & leptomeningeal anomalies common Morbidity: refractory seizures, contralateral hemiplegia, and/or delayed motor and cognitive development, 75% of seizures occur during the first year of life		cerebral anomalies (40%) = development delays, seizures, malformations	spine, neural tube defects (ex: encephalocele, spina bifida), tethered cord Lipomatous mass -> infiltrate adacent areas (retroperitoneum, mediastinum, paraspinal muscles, and epidural space)		
Trunk		can develop symptomatic congestive heart failure (6%)		Truncal Lipomatous mass in posterolateral, back or flank = all patients spine, neural tube defects -->; lipomatous mass -->; MSK anomalies - scoliosis	CM distributed over lateral side of extremity, buttock, or thorax Pelvic involvement can cause hematuria, bladder outlet obstructure, cystitis, and hematochezia Lymphatic abnormalities: macrocystic in pelvis/thigh; microcystic buttock, abdominal wall, distal limb	spindle cell: trunk (29%) endochondromas: scapula (20%), ribs (27%)
Groin						endochondromas: pelvis (25%) --> 3.8X higher risk of transformation in any area
Extremity	generalized extracraniofacial capillary malformations in (29%) often misdiagnosed in the extremity as Klippel-Trenaunay syndrome, or Parkes Weber syndrome unlike the other two syndromes, pts with Sturge-Weber do not have venous, lymphatic, or arterial anomalies in an extremity	most commonly involves one lower extremity symmetrical enlargement Parkes weber via RASA1 mutation = upper limb (33%), lower limb (67%)	cerebriform CT nevi (palmar aspects of hands, plantar surface of feet, chest). Significant progression and pathognomonic. progressive, asymmetrical, disproportionate overgrowth of body parts (typically skeletal/limbs), adipose overgrowth	MSK anomalies: wide triangular feet, large hands, macrodactyly (usually middle toe or finger), widened "sandal gap" typically first web space of toot	10% can be hypoplastic Lower limb (95%), Upper extremity (5%), contralateral foot or hand may be enlarged, exhibit macrodactyly association: thrombophlebitis (20%-45%) and PE (4-24%)	spindle cells hands (57%), foot (41%), arm (39%), leg (38%) endochondromas: tibia/fibula (32%), foot (36%), femur (36%), humerus (34%), radius/ulna (29%) Long bone & axial skeleton higher risk of transformation (44%). hand & foot 14% transf.
Visceral			adipose overgrowth, cystic lung disease (9%), renal:urologic anomalies (9%), bone disorders (skull hyperostoses, megaspondylodysplasia)	renal agenesis or hypoplasia		
Multifocal?		overlying CM is heterogenous (single, multiple, localized, diffuse)				
Present at Birth?		Yes	Yes	Yes		
Growth Progression			significant progression			average age presentation: 4 yrs old 27% patients diagnosed at birth 78% patients present prior to puberty
Appearance			Differential is CLOVES syndrome: but proteus patients have significant progression, cerebriform CT nevi & differentiated via AKT1 genetic mutation			Spindle cell occurs due to likely VM, blue in color, and empitied with pressure/elevation. Contains phleboliths Endochondromas are endosteal & cause progressive skeletal deformity such as bowing, shortening of extremities, leg-length discrepancy, and scoliosis
Size						
Symptoms			commonly have tumors: ovarian, cystadenoma, meningioma, testicular tumor, parotid adenoma	pain with lipomatous masses		*see above*
Blood Flow		Fast flow		slow flow vascular formations fast flow paraspinal malformations		
Imaging		MRI: confirm dx & determine extent of malformation MR angiography & venography (non-specific) Ultrasound (non-specific)	CT/MRI: evaluate pulomnary cystic lesions, intraabdominal lipomas, CNS anomalies Skeletal radiographs to rule out magaspondylodysplasia or vertebral body asymmetry	MRI: determine if spinal cord threatened by lipomatous lesion or AVM; delineates thoracic phlebectasia Renal ultrasound: Wilm's tumor	MRI: confirm tissues above AND below muscle fascia are affected; other causes of extremity overgrowth only involve the area above the muscle fascia	
Histopathology	not indicated	non-specific	non-specific	non-specific, biopsy if malignancy is indicated	not indicated	nondiagnositc
Gene	GNAQ	sporadic or familial RASA1 mutation	AKT1	non-familial, somatic mosaic activating mutation in PIK3C4	somatic mosaic PIK3CA mutations, with 5 specific PIK3CA mutations accounting for most cases	IDH1/IDH2

	LYMPHATIC MALFORMATION	MACROCYSTIC	MICROCYSTIC	COMBINED (MACRO + MICRO)	GENERALIZED LYMPHATIC ANOMALY (GLA)	KAPOSIFORM LYMPHANGIOMATOSIS (KLA)	GORHAM-STOUT DISEASE	PRIMARY LYMPHEDEMA
AKA	cystic hygroma lymphangioma							discontinue use of congenital, pracox, tarda to define age of onset
General	high risk of infection (71%) adolescence > childhood (2.6x)	accessed by needle	too small to be cannulated	macro > micro ratio = better prognosis	M = F appendicular > axial skeleton	M:F = 2:1 Mean age presentation = 8 — Bone involvement 40% Poor prognosis/ high mortality	M = F	1.2/100,000 people under age 20 M = F — Males more likely to present in infancy [68%] / Females more likely present in adolescence [55%] associated w/ turner syndrome *chronic lymphedema: predisposes to lymphangiosarcoma (0.07-.45%), recurrence and pulmonary metastasis*
Head & Neck		most common is neck	face				cranium, cervical spine	FOXC2 mutation = Lymphedema Distichiases: extra row eyelashes SOX18 mutation — Hypotrichosis-Lymphedema-Telangiectasia [sparse hair & cutaneous telangiectasias] / Hennekam Syndrome [generalized, developmental delay, flat face, hypertelorism, broad nasal bridge
Intracranial								
Trunk	axilla (most common)	axilla			most common ribs thoracic spine	Mediastinum (95%0 Retroperotineum (30%)	most common is ribs clavicle	
Groin								4% isolated genital involvement
Extremity			extremities common		humerus femur			Distal limb is ALWAYS effected & swelling can migrate proximally 91.7% lower extremity [50% unilateral, 50% bilateral], 16% upper extremity positive stemmer sign: inability to pinch dorsal skin of hand/foot due to edema + dermal thickening
Visceral						Spleen 35%		Hennekam Syndrome: visceral involvement Milroy Disease: infant with lower extremity lymphedema presents at birth. + family OR VEGFR3mutation Meige Disease: adolescent with lower extremity lymphedema. Only with family history.
Multifocal?					multiple bones (mean 30 bones inolved), non-contagious		multiple bones (mean 7 bones involved = always contagious)	
Present at Birth?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Growth Progression	increase							progressive: overtime edema replaced with subcutaneous adipose tissue, increasing circumference of limb Occurrence — [Infancy 49.2%], [Childhood 9.5%], Adolescence [55%]
Appearance	soft and compressible, blueish hue, pink vesicles				*56% overlying soft tissue abonormality*		disappearing bones 95% overlying soft tissue abnormality	*see above*
Size		5 mm or larger	<5 mm					
Symptoms	psychosocial morbidity infection & bleeding		bleeding & leaking [cutaneous vessel]		Discrete lytic areas/radiolucency confined to medullary cavity 50% macrocystic, 63% splenic lesions, 50% pleural effusion	Thrombocytopenia (30%) Cough/dyspnea (55%) Pericardial/pleural effusion (85%) Cutaneous stain/nodule (25%)	pain & pathologic fractures pleural effusion (42%), splenic/hepatic lesions (21%)	painless, progressive, risk of infection & cellulitis, distal limb always effected, ulceration rare
Blood Flow	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow
Imaging							osteolysis, cortical loss	Lymphoscintigraphy
Histopathology								
Gene	PIK3CA	PIK3CA of lymphatic endothelial cells	PIK3CA of lymphatic endothelial cells	PIK3CA of lymphatic endothelial cells	Somatic Mutation NRAS			FOXC2, SOX18, VEGFR3, CCBE1 [Hennekam]

	CAPILLARY MALFORMATION	MACROCEPHALY-CAPILLARY MALFORMATION (M-CM)	CLAPO	DIFFUSE CAPILLARY MALFORMATION W/ OVERGROWTH (DCMO)	FADING CAPILLARY STAIN	HETEROTOPIC NEURAL NODULE	CUTIS MARMORATA TELANGIECTATICA CONGENITA (CMTC)	CUTIS MARMORATA
AKA	port-wine stain capillary hemangioma							
General	7 Phenoypic Subtypes >> Involves integument M = F	Lesion does not ulcerate of fade (unlike CMTC)	lower lip CM + face and neck LM + asymmetry & partial/generalized overgrowth lympathic malformation = microcystic and oral cavity	overgrowth of soft tissue and bony overgrowth of limbs	most common vascular birthmark (50% of whitenewborns)	ring of long hair contains heterotopic leptomeningeal tissue	cutaneous marbling at birth pronounced in low temperature	low temperature induced not pathologic
Head & Neck	dermatomal distribution, more progression CLAPO, Fading capillary stain , M-CM	Philtrum/upper lip 75% and neuro macrocephaly	lower lip is pathognomic		'angel kiss' on forehead, eyelids, nose, upper lip 'Stork Bite' on posterior neck	parietal of occipital scalp nodule Overlying alopecia		
Intracranial	heterotopic neural nodul, m-cm					Extends intracranially		
Trunk	less progression	Diffuse capillary malformation Patchy and reticular		Axial overgrowth			Yes, common location	
Groin								
Extremity	less progression	Diffuse capillary malformation		DCMO (lower > upper, increased circumfrence & possible axial overgrowth)			CMTC (69%) common location, limb commonly hypoplastic	
Visceral								
Multifocal?	localized, extensive, multiple, generalized							
Present at Birth?	Yes (0.3% newborns)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Growth Progression	lesion darkens, more purple				lightens over first 2 years of life		improves during first year	
Appearance	generally most have pink-purple skin discoloration	lesion does not ulcerate or fade (unlike CMTC) patchy and reticular	Midline, symmetrical, smooth, well defined	overgrowth of soft tissue & bony overgrowth of limbs Extremity has increased circumfrence and may have axial overgrowth	port wine stain-colored birth mark		depressed, purple serpiginous reticulated pattern Subtopic 11 usually unilateral	Accentuated normal cutaneous vascularity pattern
Size								
Symptoms								
Blood Flow	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow
Imaging	*not needed for diagnosis* MRI for dura involvement)					MRI to check for dura involvement		
Histopathology	rarely indicated					contain heterotopic leptomeningeal tissue		
Gene	GNAQ (Sturge-Weber Syndrome), GNA11	PIK3CA	PIK3CA	GNA11			ARL6IP6	

	VENOUS MALFORMATION	BLUE RUBBER BLEB NEVUS SYNDROME	FIBROADIPOSE VASCULAR ANOMALY (FAVA)	GLOMUVENOUS MALFORMATION (GVM)	CUTANEOMUCOSAL VENOUS MALFORMATION (CMVM)	CEREBRAL CAVERNOUS MALFORMATION (CCM)	VERRUCOUS VENOUS MALFORMATION (VVM)	DIFFUSE PHLEBECTASIA OF BOCKENHEIMER	FAMILIAL INTRAOSSEOUS VASCULAR MALFORMATION (VMOS)
AKA	phlebectasia						verrucous hemangioma		
General	may be part of a combined malformation, particularly lymphatic 3 forms → sporadic phlebectasia (congenital); associated with lymphatic malformation; syndromic (lateral embryonal vein in Klippel-Trenaunay syndrome)	M = F	shares clinical, radiographic, histologic w/ intramuscular venous malformation different: significant pain (89%), nonspongiform venous cutanous part (44%), poor response to sclerotherapy		less common than GVM	low temperature induced not pathologic	similar to hyperkeratoic venous malformation clincally, radiographically, hisologically		severe blood vessel expansion within craniofacial bones accompanied by midline abonormalities (diastasis recti & supraumbilibical raphe) hereditary, documented in literature within families very rare. intraosseous vascular malformations 0.2% all bony tumors
Head & Neck	47% lesions involve skin, mucosa, subcutaneous tissue 50% affect muscle, bone, joints, viscera primary morbiity psychosocial. airway or orbital compromise due to bleeding	60% skin and soft tissue		10% skin & subcutaneous tissue 50% intramuscular lesions	50%; affect skin and oral mucosa (muscle maybe)	CCM defined by effecting brain and spinal cord			
Intracranial					May present in brain	brain & spinal cord affected			
Trunk	13% lesions involve skin, mucosa 50% affect muscle, bone, joint, viscera	80% skin and soft tissue		14% skin $ subcutaneous 50% intramuscular lesion	13%; skin & possible muscle	9% skin lesions Association: risk for new intracranial lesions, seizures, hemorrhages	affect the skin & subcutis of tunk (95)		
Groin			affects gluteal area (7%)						
Extremity	40% skin, mucosa, 50% muscle, bone, joint, viscera	93% skin and soft tissue	affects calf (70%), thigh (12%), forearm (8%), ankle/foot (3%)	76% skin & subcutaneous tissue 50% intramuscular lesion	37%; skin & possible muscle	9% skin lesions	affect the skin & subcutis of extremity (9%)	defines disease: all tissues of an extremity Association: hypoplastic limb, arthiritis	
Visceral	association w/ chronic bleeding/ anemia	GI (usually small intestine) 75% bleeding requiring transfusion			May present in GI, lung				
Multifocal?	10% multifocal → 8% glomuvenous (GVM), 2% cutaneomucosal (CMVM)	can have hundreds of lesions		73% lesions are multiple	73%				
Present at Birth?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Growth Progression	2.6x more likely adolescence than during childhood 26% before adolescence, 75% before adulthood								prior to puberty malformation & bone enlargement restricted to mandibular/ maxillary region after puberty rapid expansion to all cranial bones
Appearance	blue, soft, compressible. hard, calcified phleboliths may be palpable						becomes hyperkeratotic and frequently bleeds		
Size	>5 cm (56%)	< 2cm		<5cm (66.6%)	<5 cm (76%)		2-8 cm		
Symptoms	pain		differentiated via pain & contractures	painful particularly on palpation				pain	
Blood Flow	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow
Imaging			MRI to differentiate FAVA FAVA more fat or fibrosis, not as bright on T2 images, hetergenous, smaller/less defined channels, nonspongiform-appearing vessels						no findings yet
Histopathology			FAVA infiltrative & greater fibroadipose tissue						critical to determine differential diagnosis
Gene	TIE2, PIK3CA	TIE2	PIK3CA	LOF of glomulin gene	TIE2	CCM1/KR1T1, CCM2/malcavernin, CCM3/PDCD10			loss-of-function mutations in ELMO2 via impaired RAC1 signaling

	CONGENITAL HEMANGIOMA	INFANTILE HEMANGIOMA	INFANTILE MYOFIBROMA (IM)	PYOGENIC GRANULOMA	TUFTED ANGIOMA (TA)	KAPOSIFORM HEMANGIOENDOTHELIOMA (KHE)	ENZINGER INTRAMUSCULAR HEMANGIOMA	CUTANEOVISCERAL ANGIOMATOSIS W/ THROMBOCYTOPENIA (CAT)	EPITHELIOID HEMANGIOENDOTHELIOMA (EHE)	ANGIOSARCOMA
AKA		capillary/ cavernous,/strawberry hemangioma	infantile myofibromatosis	hemangioma		capillary hemangioma				
General	M = F RICH [rapidly involuting] NICH [non involuting]	most prevalent in white F:M = 4:1 40% increased risk in prematurity	M: F = 1.6:1 Benign fibrous tumor of infancy 3 Types: solitary, multifocal, generalized	Age 6-7 onset	Less aggressive than Kaposiform Hangioendothelioma counterpart Locally invasive Kasabach-Merritt (K-M) phenomenon	Locally aggressive (no metastasis) 1/100,000 children M = F 80% male in adult onset Kasabach-Merritt (K-M) Phenomenon: 85% increased risk retroperitoneal, intrathoracic, muscle involvement	Benign tumor of skeletal muscle 25% pediatrics Median age diagnosis 25 yrs	Affects skin & GI tract Thrombocytopenia Hematemesis/Melena	Malignant endothelial tumor Affecting Skin, bone, liver, and lung	99% affects adults in 70s 1% Pediatrics M = F
Head & Neck	RICH 42% NICH 43%	60% PHACES: Eye/Endocrine; LUMBAR: Myelopathy	most common	62% Cheek 29%, Lips 9%, Oral Cavity 14%, Scalp 11%, Eyelid 9%, Forehead 10%	common location	40% Association with K-M, muscle involvement	30%			Sun & Radiation exposed areas in adults
Intracranial		PHACES: posterior fosa brain malformation, arterial cerebrovascular anomalies								
Trunk	RICH 6% NICH 19%	25% PHACES: sternal clefting, supralumbilical raphe	second most common	20% Association: Hx of trauma/ underlying cutaneous condition	common location	30% Association K-M: retroperitoneal, intrathoracic, muscle involvement	32%		Yes	Breast (13%) Mesentery (%)
Groin		Check for spinal anomaly. LUMBAR: urogential anomalies, anorectal malformation								Peds: Pelvis (7%)
Extremity	RICH 52% NICH 38%	15%	third most common	Upper 13% Lower 5%		30% . Association K-M muscle involvement	Upper Limb 23% Lower Extremity 15%			Peds: Upper (7%)
Visceral		Hepatic = Check thyroid levels. PHACES: coarctation of aorta & cardiac defects. LUMBAR: renal anomaly	25-40% with multifocal subtype have visceral involvement					GI tract , Melena, Lung involvement causes hemoptysis	Liver	Peds: Heart & pericardium (46%) Peds: Liver (13%) Peds: Spleen (7%)
Multifocal?	No	Yes	Affects viscera	Usually solitary		No - solitary		Yes	Yes	
Present at Birth?	Yes	Yes	Yes (60% cases)	No	During early infancy & childhood	Yes				
Growth Progression	In utero Rapidly Involuting: 50% regression by 7 months Non Involuting: no postnatal regression	Proliferating Phase: 80% growth by 3 months Involuting Phase: begins 9-12 month, cont. 3.5 yrs	Grows during infancy Diagnose before 2 yrs (80% cases)	Grows rapidly & forms stalk Age 6-7 onset		60% noted neonatal 93% in infancy Mean age 42.9 onset Enlarges until age 2, then partially regresses			unpredictable	Malignant, High Mitotic Index
Appearance	ALWAYS SOLITARY Violaceous with coarse telangiectasia and a peripheral pale halo	80% Superficial [bright red] 20% Deep [blue] 80% Single Lesion	reddish-pruple	small, red, bleeding lesion	Pink-red, violaceous plaque Solitary tumor, diffuse stain	reddish-purple	painless soft tissue welling	reddish-brown w/ blue macules and pupules		
Size		Infants with >5 lesions [<5mm] = 16% risk visceral lesion	0.5-7 cm	6.5 mm (2-20 mm range) 75% <1 cm		> 5 cm				Mean 8 cm *range 3.5 - 13 cm*
Symptoms		may ulcerate during infancy (16%) rarely bleeds	ulcerate	Bleeding (64.2%), Ulcerate (36.3%)	K-M phenomenon	chronic pain, stiffness & contractures		melena/hemoptysis		
Blood Flow	Fast	Fast	Fast		Fast		Fast Flow & Enhancement	Fast	Fast	N/A
Imaging	Rarely indicated, Prenatal ultrasonography, Doppler	Ultrasonography [first line, check for hepatic lesions], Doppler, MRI	Doppler, MRI, Ultrasound			MRI for diagnosis confirmation & severity	findings = tumor			
Histopathology	Rarely indicated	GLUT1 positivity	often necessary to diagnose	indicated	"cannonballs" or round vascular nodules	indicated	biopsy required for dx		indicated	indicated (racemose vessels and solid sheet of cells)
Gene	GNA11		PDGFR-β	RAF(BRAF), GNA14	GNA14	GNA14			CAMTA1 & WWTR1?	

	ARTERIOVENOUS MALFORMATION	PTEN-ASSOCIATED VASCULAR ANOMALY (PTEN-AVA)	CAPILLARY MALFORMATION-ARTERIOVENOUS MALFORMATION (CM-AVM)	HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)	COBB SYNDROME	WYBURN-MASON SYNDROME
AKA	arteriovenous hemangioma	PTEN hamartoma tumor syndrome cowden syndrome, bannayan-riley-ruvalcaba syndrome		osler-weber-rendu syndrome		bonnet-dechaume-blanc syndrome; retinocephalofacial vascular malformation syndrome
General	progresses over time Schobinger Staging: I. Quiescence: warm, pink-blue Doppler; II. Expansion: enlargement & pulsation; III. Destruction: ulceration, bleeding; IV: Decompensation: cardiac failure	m = f 85% are intramuscular Lesions replace muscle with disorganized fat (non syndromic muscular AVMs cause symmetrical overgrowth without adipose tissue) Genetic testing is confirmatory	1/100,000 prevalence parkes weber syndrome (12%)	clinical hht: epistaxis, mucocutaneous telangiectasias clinical hht: visceral AVM, 1st degree relative	patients likely has CLOVES or CM-AVM	extremely rare (121 cases in literature)
Head & Neck	most common, risk of CHF	Macrocephaly seen in PTEN Hamartoma Syndrome	80% spinal arteriovenous lesions	mucocutaneous telangiectasias (lips, oral cavity, fingers, nose) morbidity: chronic anemia from epistaxis		defined by retinal arteriovenous malformations with or without a brain (47%) AVM or facial vascular malformation
Intracranial			intracerebral AVM (7%): associated with vein of Galen aneurysmal malformations, seizures, hydrocephalus, developmental delay Extra cerebral AVM (11%) 5% tumor of CNS (neurofibroma, optic fioma)	cerebral arteriovenous malformations Morbidity: stroke and brain abscess , hemorrhage		22% have retinal AVM with brain arteriovenous malformation and facial vascular malformation
Trunk	risk of CHF					
Groin		Penile freckling seen in hamartoma syndrome				
Extremity	risk of chf		Parkes weber - diffuse extremity AVM causes overgrowth of limb. One lower extremity usually affected & capillary malformation present over AVM			
Visceral	risk of CHF	thyroid lesions (31%) GI polyps 30%		Morbidity: upper GI bleeding (25%) & high-output heart failure/portal HTN		
Multifocal?		57% of patients	as many as 53 CM. 6% only have 1 lesion			
Present at Birth?	Yes	Yes	Yes	Yes	Yes	Yes
Growth Progression	enlarges, becomes symptomatic Twofold risk of progression in adolescence	Patients at risk for developmental delay/autism (19%), thyroid lesions (31%), GI polyps (30%) Patients should be followed closely for tumors of endocrine and GI origin				
Appearance	pink-red cutaneous stain, warm, palpable thrill/bruit		small, multifocal, round, pinkish-red 50% surrounded by pale halo			
Size	Pink-red cutaneous stain, warm, palpable thrill/bruit		1- 15 cm range			
Symptoms	Disfigurement, destruction of tissues, obstruction of vital structures pain, ulceration, bleeding, CHF, arteries may rupture	Exam should be done to determine PTEN Harmatoma Syndrome: macrocephaly, penile freckling				
Blood Flow	Fast	Fast	Fast	Fast	Fast	Fast
Imaging	if dx equivocal after doppler & HPE = confirm using Ultrasound, MRI. Use Angiogram if still unclear after all options.	Often found after MRI or angiogram of patient thought to have sporadic AVM	MRI usually indicated for brain/spine associated lesions			doppler ultrasound first line MRI to confirm angiogram CT (when involving bone)
Histopathology	rarely indicated. Only if dx equivocal/ malignancy suspected	can aid diagnosis tortuous vessels with arterialized veins, fibromyxoid areas, adipose tissue, lymphoid clusters . arteries have transmural muscular hyperplasia & small lumens				
Gene	MAP2K1	genetic testing should be done. patients should be genetic counseled about transmitting disease to offspring	LOF mutation RASA1			