Congenital vascular anomalies: current perspectives on diagnosis, classification, and management

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Abstract: The term "congenital vascular anomalies" encompasses those vascular lesions present at birth. Many of these lesions may be detected in utero. This review serves to apprise the readership of newly identified diagnoses and updated classification schemes. Attention is focused on clinical features, patterns of presentation, clinical manifestations and behavior, diagnostic tools, and treatment modalities. It is an invigorating period for this field, with a surge in vascular anomalies-related basic and clinical research, genetics, pharmacology, clinical trials, and patient advocacy. A large number of professional conferences now include vascular anomalies in the agenda, and trainees in multiple specialties are gaining expertise in this discipline. We begin with a summary of classification schemes and introduce the updated classification adopted by the International Society for the Study of Vascular Anomalies. Disease entities are described, with liberal use of photographs, as many diagnoses can be established based on a thorough history and visual appearance and it is thus essential to develop a familiarity with diagnosis-specific physical features. Peripheral (non-central nervous system) vascular anomalies are the focus of this review. We focus on those entities in which diagnostic radiology is routinely used and accentuate when histologic confirmation is essential. We also underscore some differences in approach to the pediatric vs adolescent or adult patient. A list of Internet-based resources is included, with hyperlinks to informative sites. References are limited to seminal discoveries and review articles. We hope that our enthusiasm in writing this review will be shared by those who read this review.

Keywords: vascular anomalies, hemangiomas, vascular malformations, overgrowth syndromes

Introduction

The term "vascular anomalies" refers to a heterogeneous group of disorders with distinct clinical and radiologic features. Diagnoses can often be determined by incorporating the history, physical examination, imaging (for some diagnoses), and chronologic course. An updated classification provides structure and allows for clarity and consistency in terminology. Recent interest and advances in clinical and basic research have contributed to a more profound understanding of vascular anomalies and new treatment modalities.

The classification of anomalies has evolved based on anatomic and clinical features and is reviewed by Wassef and Blei.[1] The most widely accepted classification is based on the original observations by Mulliken and Glowacki,[2,3] whereby vascular anomalies are divided into those that are proliferative during all or part of the life cycle (vascular tumors – benign) and those that are predominantly structural anomalies

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(vascular malformations). Vascular malformations (VMs) are further characterized by the predominantly affected vessel (arterial, venous, lymphatic, capillary – individually or combined) and subclassified into truncular and extratruncular vessels. Staging systems based on escalating clinical symptoms or anatomic extent have been developed by Schöbinger[4] (for arteriovenous malformations [AVMs]) and de Serres et al[5] (lymphatic malformations [LMs]). The original Mulliken classification was recently expanded and updated to incorporate new entities, genetic information, and syndromes.[6] Terminology in this review is aligned with the classification of the International Society for the Study of Vascular Anomalies (ISSVA) (Table 1), available at http://www.issva.org/content.aspx?page_id=22&club_id=298433&module_id=152904. Figure 1 provides a schematic representation of the development of the vasculature in vascular anomalies.

Congenital vascular anomalies are those that are evident at birth and can be VMs or vascular tumors. If present at birth, it is likely that the lesion could be diagnosed prenatally, although this is not always appreciated. Vascular tumors that are present at birth include the congenital hemangiomas (rapidly involuting congenital hemangioma [RICH], noninvoluting congenital hemangioma [NICH]), Kaposiform hemangioendothelioma (KHE), and multifocal lymphangioendotheliomatosis. VMs present prenatally and at birth, however, may not be visible. Early detection of vascular anomalies is important, as this may affect childbirth decisions. Additionally, early awareness of vascular lesions and potentially associated syndromic features can inform evaluation and management strategies.[7]

Imaging for vascular anomalies has been well reviewed in several manuscripts. Nozaki et al,[8,9] in a pictorial review titled "Syndromes associated with vascular tumors and malformations", as well as an article titled "Imaging of vascular tumors with an emphasis on ISSVA classification", impart a well-organized logical presentation based on the ISSVA classification (albeit the earlier version). Calvo-Garcia et al,[10] in "Imaging of fetal vascular anomalies", provide an update of prenatal diagnosis with ultrasonography and fetal magnetic resonance imaging (MRI). We also refer the readers to review published consensus statements regarding the diagnosis and treatment of VMs.[7,11,12]

Nozaki et al[9] present a simple flowchart for radiologic evaluation of patients with vascular anomalies (Figure 2), and a more complex algorithm is presented by Tekes et al.[13] Burrows[14] and Rosen et al[15] provide thorough reviews of the role of interventional radiology in VMs. Waner and O[16] provide a review of the role of surgery in VMs.

Congenital hemangioma

Congenital hemangiomas include RICH, NICH, and partially involuting congenital hemangioma (PICH), although the latter two diagnoses are temporally determined, when the initial lesion involutes only partially (in the case of PICH) or not at all (as in NICH).[17] In contrast to infantile hemangiomas, which are either undetectable at birth or minimally apparent with a precursor mark or discoloration, congenital hemangiomas are more easily discernable. Histologically, the congenital hemangiomas are negative for the glucose transporter type 1 (GLUT-1) marker, whereas hemangiomas of infancy stain strongly positive.[18] Figure 3 demonstrates the stages of proliferation and involution of hemangiomas of infancy, as well as the associated features. RICH-type lesions can be associated with high flow, causing a fetal and postnatal high cardiac output state, and they may

Table 1 ISSVA classification of vascular anomalies, 2014

| Vascular tumors | Vascular malformations | | | |
	Simple	Combined	Of major named vessels	Associated with other anomalies
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations Arteriovenous fistula	Capillary-venous, capillary-lymphatic, lymphatic-venous, capillary-lymphatic-venous, capillary-arteriovenous, capillary-lymphatic-arteriovenous	(aka "channel-type" or "truncal" vascular malformations) Further characterized by involvement of artery, lymphatic vessel, or vein and by anomaly of origin, course, number, length, diameter, etc	For example, Klippel–Trenaunay Sturge–Weber Mafucci CLOVES Proteus Bannayan–Riley– Rubacalva Others

Notes: Adapted from ISSVA International Society for the Study of Vascular Anomalies [webpage on the Internet]. Available from: http://www.issva.org/content.aspx?page_id=22&club_id=298433&module_id=152904.[88] http://creativecommons.org/licenses/by/4.0/.
Abbreviations: CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and spinal/skeletal scoliosis; ISSVA, International Society for the Study of Vascular Anomalies.
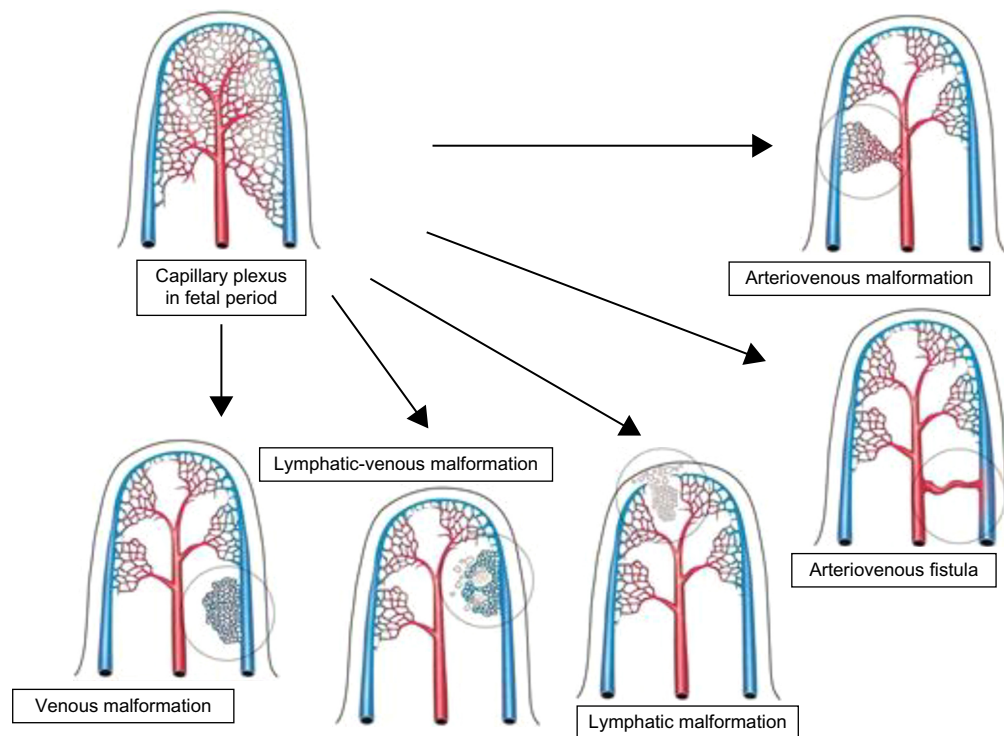
Figure 1 Proposed mechanism of development of vascular malformations from fetal capillary plexus.
Notes: Used with permission from Nozaki T, Nosaka S, Miyazaki O, et al. Syndromes associated with vascular tumors and malformations: A pictorial review, *RadioGraphics*, 2013;33:175–195, Copyright: The Radiological Society of North America (RSNA®).[9]

ulcerate and hemorrhage.[19] There is one other presentation termed "rapidly involuting congenital hemangioma with fetal involution", which has a distinctive appearance.[20,21] Images of congenital hemangiomas are shown in Figure 4.

Imaging of RICH and NICH

Case reports and studies predominantly demonstrate ultrasound and MRI findings in congenital hemangiomas. RICH can occur in many locations, often sparing the face. When RICH occurs in the liver, it is important to characterize the lesion and differentiate it from other liver lesions. RICH should be suspected in a neonate with a solitary liver lesion and normal-for-age serum alpha-fetoprotein levels. On ultrasonography, RICH has a variable appearance, although typically characterized as a solid mass with a heterogeneous echotexture. A minority of cases contain small calcifications. On color Doppler imaging,
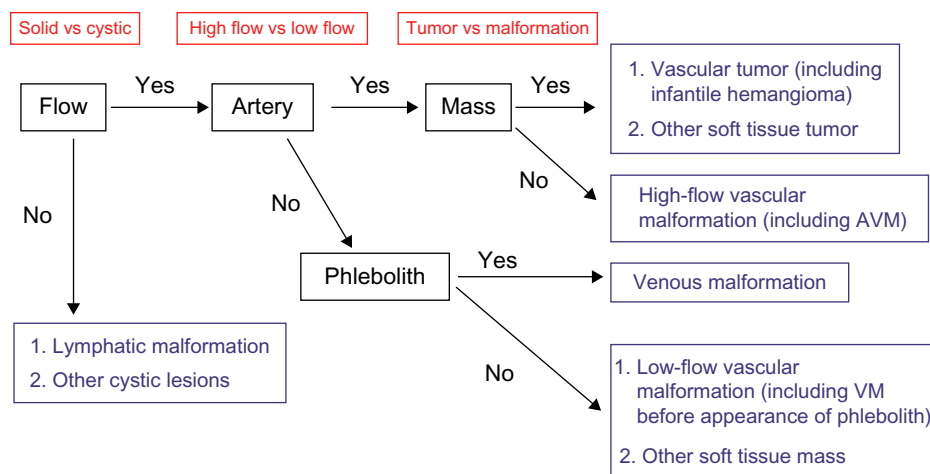

Figure 2 Algorithm for radiologic evaluation of vascular malformations.
Notes: Used with permission from Nozaki T, Nosaka S, Miyazaki O, et al. Syndromes associated with vascular tumors and malformations: A pictorial review, *RadioGraphics*, 2013;33:175–195, Copyright: The Radiological Society of North America (RSNA®).[9]
Abbreviations: AVM, arteriovenous malformation; VM, vascular malformation.
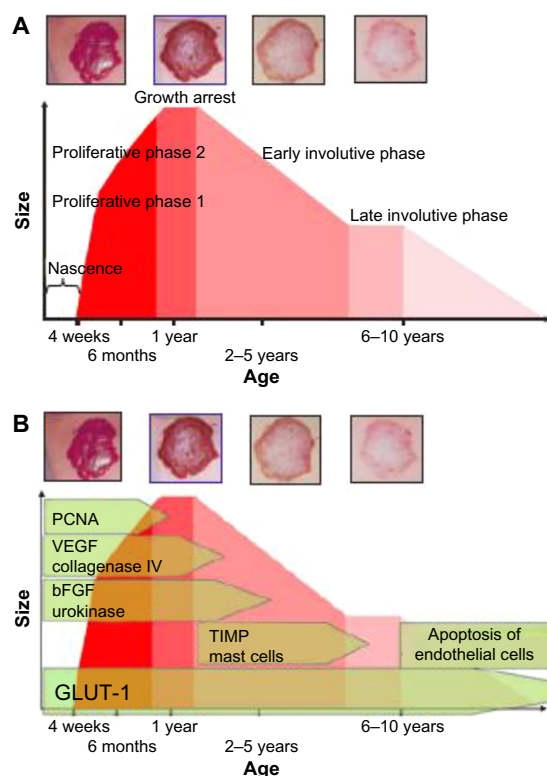
Figure 3 Schematic growth and regression curve of hemangioma of infancy.
Notes: Photographs of different stages of hemangioma proliferatoin and involution (**A**); corresponding cellular markers expressed during different phases of proliferation and involution (**B**). Copyright © 2010. John Wiley and Sons. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol.* 2010;163(2):269–274.[86]
Abbreviations: bFGF, basic fibroblast growth factor; GLUT-1, glucose transporter type 1; PCNA, proliferating cell nuclear antigen; TIMPs, tissue inhibitor of metalloproteinases; VEGF, vascular endothelial growth factor.

fibrosis. Small lesions may be homogeneous on T2-weighted imaging. On T1-weighted imaging, they are hypointense relative to normal liver parenchyma and may contain foci of bright signal due to internal hemorrhage. On arterial phase postgadolinium images, the enhancement pattern is peripheral and nodular, which follows the signal of the blood pool. Portal venous and delayed phase imaging shows progressive centripetal enhancement.[23] Computed tomography (CT) is not the preferred modality due to the potential harmful effects of ionizing radiation to the newborn. Findings with noncontrast CT include a well-defined mass that is hypodense to the adjacent liver. The postcontrast enhancement pattern is similar to that observed with MRI, ie, peripheral nodular enhancement and centripetal enhancement on delayed phase images. Serial ultrasonography of the liver is commonly performed to ensure progressive shrinkage of the lesion. If there is interval growth, then a biopsy is recommended.

Congenital hemangiomas, in contrast to the more commonly seen hemangiomas of infancy, do not typically appear in full form prenatally; at birth, there may be small red spots or a pale white or pink precursor area. Postnatally, hemangiomas of infancy proliferate for several months and then naturally involute. Small retrospective imaging studies have attempted to distinguish infantile hemangioma from congenital hemangiomas. On sonography, RICH and NICH are more often heterogeneous in echotexture compared with infantile hemangioma, which is usually homogeneously echogenic. Congenital hemangiomas more commonly have detectible vessels compared with the infantile form. Calcifications have not reported in infantile hemangioma but have been identified in a subset of congenital hemangiomas.[24]
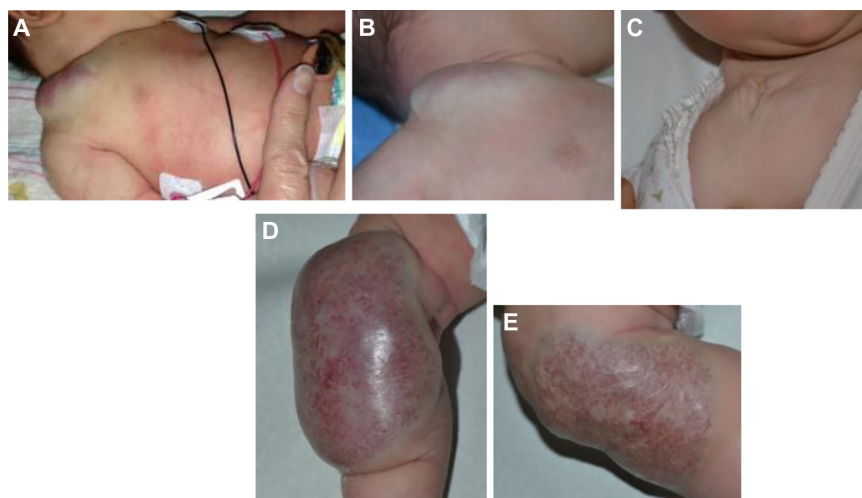
prominent vessels are often detected in the periphery of the lesion with a relatively hypovascular center.[22] RICH are markedly hyperintense on T2-weighted MRI, and larger lesions are often heterogeneous due to central thrombosis, necrosis, and/or

Figure 4 Rapidly involuting congenital hemangioma (RICH).
Notes: Images of patient over time. (**A–C**) Without treatment, lesion is involuted. (**A**) Present at birth; (**B**) at 1 month of age; (**C**) at 7 months of age. Note the circumferential halo. (**D**) At 10 days of age (note circumferential halo); (**E**) 3 months later (after short course of oral corticosteroids to decrease vascularity).

Location, size, morphology, and any functional impairment caused by the hemangioma influence decisions regarding imaging and/or treatment. Despite the now-historical temptation to leave hemangiomas alone because they will "go away on their own", in fact, early treatment allows for an optimal esthetic and functional outcome. Segmental hemangiomas of the cervicofacial and upper arm regions prompt evaluation for possible PHACES syndrome (Posterior fossa/other central nervous system [CNS] structural malformations, segmental Hemangiomas, Arterial anomalies, Cardiovascular anomalies, Eye abnormalities, and Sternal cleft/supraumbilical raphe or other midline abnormality).[25] Similarly, segmental hemangiomas on the lower back/lumbosacral area, buttocks, and/or perianal area dictate an evaluation for possible LUMBAR association (Lower body segmental hemangioma, Urogenital anomalies and ulceration, Myelopathy, Bony abnormalities, Anorectal and/or Arterial anomalies, and Renal anomalies).[26]

Representative images of patients with PHACE and LUMBAR symptoms are shown in Figures 5 and 6. Imaging for PHACE includes MRI with and without contrast to evaluate CNS structure, as well as magnetic resonance angiography of the brain, neck, and upper chest for evaluation of arteriopathies, which usually occur on the side ipsilateral to the facial hemangioma. Arteriopathies may include presistent embryonic arteries, atretic dysplastic tortuous vessels, and/or those with abnormal branching, as well as aortic arch anomalies. There is a high incidence of a funnel-shaped enlarged internal auditory canal, many of which have a hemangioma within their enlarged structure.[11,27–29] Dandy–Walker malformation (which is characterized by vermian hypoplasia, cystic dilatation of the fourth ventricle, and an enlarged posterior fossa with torcular–lambdoid inversion) is the most common posterior fossa malformation associated with PHACES syndrome. Large cervicofacial hemangiomas are the hallmarks of PHACES, classically with a segmental distribution.

Figure 5 Segmental hemangioma/PHACE syndrome.
Notes: (**A**) Segmental facial hemangioma. (**B**) MRI demonstrates periorbital and subcutaneous involvement of hemangioma. (**C**) MRA demonstrates contralateral right carotid hypoplasia.
Abbreviations: MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PHACE, Posterior fossa/other central nervous system structural malformations, segmental Hemangiomas, Arterial anomalies, Cardiovascular anomalies, Eye abnormalities, and Sternal cleft/supraumbilical raphe or other midline abnormality.
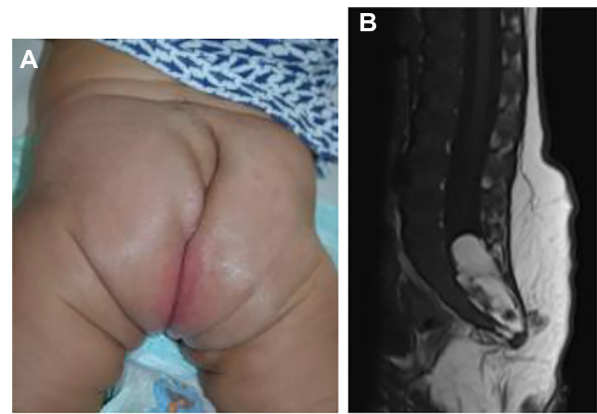

Figure 6 LUMBAR associations.
Notes: (**A**) Asymmetry and fullness of the midline lower back and buttock crease was noted in an infant who had a segmental hemangioma of the perianal area, which had ulcerated. Ultrasonography was not informative due to ossification of the bony structures. There were no genital, renal, or anorectal anomalies. MRA has not been performed yet. (**B**) MRI demonstrated an 11.6×1.8×4.0 cm lipoma protruding through a defect in the inferior sacrum and tethering the cord at the L5 level, with syringomyelia extending from the terminal cord superiorly to the level of the superior endplate of L2.
Abbreviations: LUMBAR, Lower body hemangioma and other cutaneous defects, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies, and Renal anomalies; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

Although rare, stroke is a reported complication of the arterial cerebrovascular anomalies associated with PHACES syndrome. Aortic coarctation is the most common cardiovascular abnormality identified in this patient population. Other cardiac and aortic anomalies described in PHACES include patent ductus arteriosus, septal defects, pulmonary stenosis, aberrant subclavian artery, tetralogy of Fallot, and aortic aneurysms.

Prenatal PHACE may be suspected with ultrasonographic or MRI detection of unilateral cerebellar hypoplasia, other posterior fossa anomalies, sternal clefting, aortic arch, or other vascular dysplasias.[30–35] Adults have been diagnosed retrospectively with PHACE (ie, questioning if the patients had facial segmental hemangiomas in infancy), after incidental findings of arteriopathies, cerebellar hypoplasia, and other abnormalities are found on CNS MRIs (obtained for other reasons).[36–38]

Imaging of LUMBAR association

Ultrasonography of the lower spine, abdomen, and pelvis is indicated for midline segmental vascular lesions of the lower back, perineum, and buttock areas. The optimal age to perform a spinal ultrasound investigation in a neonate is less than 3–4 months due to lack of ossification of the posterior elements of the spine. Sonography of the spine beyond 6 months of age is often limited.[39] MRI with contrast confirms suspected abnormalities after an abnormal ultrasound result and is the first-line study in elderly patients for whom ultrasonography is technically limited.

Subcutaneous hemangiomas often warrant evaluation to confirm reassuring radiologic findings. If any concerns arise clinically or radiologically, histologic confirmation should be considered. The differential diagnosis includes pilomatrixoma, pericytoma, sarcoma, lymphoma, rhabdomyosarcoma, neuroblastoma, and other diagnoses.

KHE, which may be seen in the newborn period, can present as a boggy, red/purple mass with ill-defined borders (Figure 7). Kasabach–Merritt phenomenon (with profound thrombocytopenia and hypofibrinogenemia) may accompany this diagnosis, although several cases without a hematologic abnormality have been described.[40] Patients with Kasabach–Merritt syndrome can be quite ill, with hemorrhage into the lesion or elsewhere. This is generally treated medically with vincristine, sirolimus, steroids, or other agents.[41–45] A study comparing the efficacy of sirolimus vs vincristine is under way (NCT02110069).

Imaging of KHE

KHE involves a spectrum of lesions ranging from small superficial lesions to large infiltrative lesions with potential life-threatening complications. KHE is usually unifocal and is most commonly located in the extremity. The torso (thoracic cavity and retroperitoneum) and cervicofacial locations are the next most commonly affected locations. MRI is the most useful modality to assess KHE. On MRI, KHE is characterized as an infiltrative lesion with poorly defined borders. It often crosses tissue planes and involves the skin, subcutaneous soft tissues, with deep extension into the muscles, and possibly bone. Due to this appearance, it can mimic an infiltrative neoplasm such as sarcoma. On T1-weighted imaging, it is hypointense or isointense relative to skeletal muscle. On T2-weighted imaging, KHE is hyperintense in signal, with reticular edema-like signal within the subcutaneous fat,

often referred to as "stranding".[8,43,46] In contrast, infantile hemangioma does not typically demonstrate an infiltrative growth pattern. After contrast administration, KHE demonstrates marked enhancement. Flow voids are often depicted along the periphery of the lesion, although these are less prominent compared with common hemangiomas.[47]

CT shows an infiltrative soft tissue mass with ill-defined margins, skin thickening, and fat stranding within the subcutaneous fat. There is often homogeneous postcontrast enhancement. Ultrasonography often shows a solid mass with a heterogeneous echotexture with poorly defined borders. Color Doppler imaging demonstrates hypervascularity with high-resistance arterial waveforms. Sonography may be limited in determining the full extent of the lesion; therefore, MRI is the preferred modality.

Multifocal lymphangioendotheliomatosis ± thrombocytopenia (MLT) is a rare but important vascular anomaly.[48,49] There are cutaneous (macular and popular red/purple) lesions of variable size, which may crust and bleed, as well as gastrointestinal, lung, or other parenchymal vascular lesions. Patients with MLT are at risk of severe gastrointestinal hemorrhage.[50]

Vascular malformations
Capillary malformation

Imaging is not usually necessary to make a diagnosis of capillary malformation (CM), which is diagnosed clinically. When imaging is performed, subtle signal abnormality is often seen superficially within the subcutaneous fat. CM may be a clue to an underlying structural malformation, with imaging playing an important role in its detection and characterization. Patients at risk for Sturge–Weber syndrome (SWS) represent a particular case, wherein patients with CMs should undergo neuroimaging.

Two recent studies have challenged the previously accepted notion that CMs over the distribution of the trigeminal nerve places patients at highest risk of SWS.[51,52] In these papers, upper facial port-wine stains (forehead and temple areas) are correlated
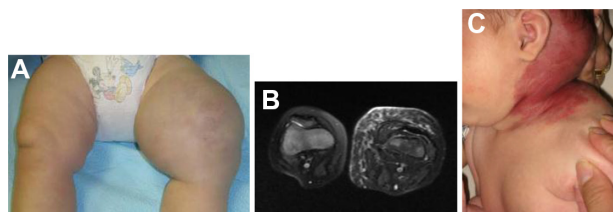

Figure 7 Kaposiform hemangioendothelioma.
Notes: (**A**) Image of 10-month-old patient with boggy fullness. Presented at 6 months of age with purple swollen thigh, initially thought to be trauma related. Platelet count was 28,000; low fibrinogen levels and elevated levels of D-dimers were found. Biopsy demonstrated Kaposiform hemangioendothelioma. Patient is improving with medical therapy. (**B**) Axial T fat-saturated image of Kaposiform hemangioendothelioma. Note the intramuscular stranding and ill-defined borders. (**C**) Infant with progressively enlarging cervical mass, profound thrombocytopenia, and hypofibrinogenemia, representing Kaposiform hemangioendothelioma and Kasabach–Merritt phenomenon.
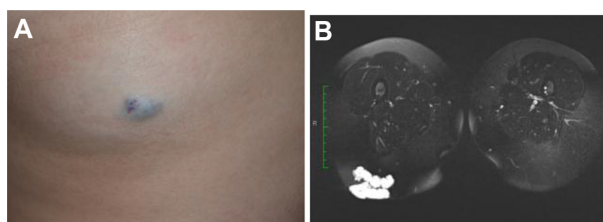

Figure 8 Venous malformation.
Notes: (**A**) Soft, tender vascular mass on buttock, which has been present since birth and is progressively tenderer, in an adolescent. (**B**) MRI demonstrates large focal area of subcutaneous vascularity with flow characteristics of venous malformation.
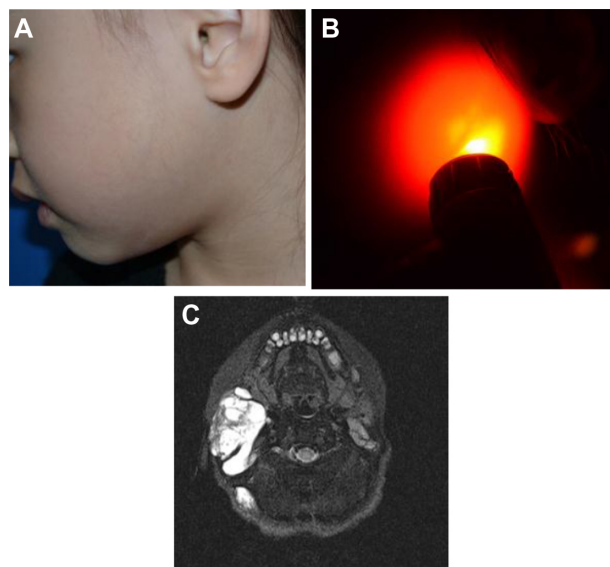**Abbreviation:** MRI, magnetic resonance imaging.

Figure 9 Lymphatic malformation.
Notes: (**A** and **B**) Soft, nontender mass on cheek, present since birth without change. Area transilluminates, with suggestion of septations. (**C**) MRI (of a similar patient) supports diagnosis of lymphatic malformation.
Abbreviation: MRI, magnetic resonance imaging.

with neurologic involvement. A somatic mutation in the *GNAQ* gene in port-wine stains of patients with and without SWS has been identified.[53] It is believed that the earlier the mutation occurs, the more the cell types will be affected (eg, SWS), suggesting that SWS occurs due to an early somatic mosaicism.

Arteriovenous malformation

On sonography, low-resistance arterial flow is depicted within the arteries of an AVM. Sampling of the veins shows arterial waveforms due to shunting. The characteristic findings of an AVM on MRI include tortuous and enlarged vascular channels with a dilated draining vein. AVMs may have perilesional edema, but are not associated with a soft tissue mass. The high-flow vessels seen with AVM are hypointense curvilinear flow voids on spin-echo imaging. MRA is helpful in showing the high-flow nature of the malformation and can identify the supplying vessel.

Venous malformation

Although radiographs often have a limited role in the workup for suspected VM, radiographs may reveal pathognomonic phleboliths caused by thrombosis and calcification. When VMs reach a significant size, bony distortion from mass effect may occur. The most commonly observed bony finding is cortical thickening involving the bone adjacent to the VM due to venous stasis and venous hypertension, which leads to organized periosteal reaction.[54] VMs involving the bone result in hypoplasia, cortical thinning, demineralization, or osteolysis.

On grayscale ultrasound imaging, VMs appear heterogeneous and are typically hypoechoic relative to adjacent tissue. Tubular hypoechoic channels are seen in <50% of cases.[55] Although rarely identified on ultrasonography, phleboliths appear as well-defined echogenic foci with posterior acoustic shadowing. When superficial, VMs are compressible when pressure is applied to the transducer. Color Doppler imaging typically demonstrates venous monophasic flow within the malformation. In a minority of cases, flow is not demonstrated, which may be related to thrombosis or flow below a detectible level.[55]

CT plays a limited role in the workup for VMs mainly due to poor contrast resolution and due to the effects of ionizing radiation. When a VM is encountered on CT, it is typically hypodense on noncontrast imaging with internal calcified phleboliths. After contrast administration, there is tubular enhancement of the malformation because of the opacification of the venous channels.

VMs are best demonstrated and characterized on MRI (Figure 8). VMs may be small and localized or diffuse and

Table 2 Syndromic vascular anomalies: hemangioma syndromes

Syndrome	Findings	Radiology assessment	References
PHACE	Posterior fossa malformation	MRI with contrast	11,25
OMIM 606519	Hemangioma	MRA	
	Arterial anomalies	Brain to thoracic aorta	
	Cardiac anomalies	Sternal assessment	
	Eye anomalies		
	Sternal/midline anomalies		
LUMBAR	Lower body hemangioma		26
	Ulceration, Urogenital defects		
	Myelopathy		
	Bony deformities		
	Anorectal anomalies		
	Renal anomalies		

Abbreviations: MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; OMIM, Online Mendelian Inheritance in Man.

Table 3 Syndromic vascular anomalies: vascular malformation syndromes

Disorder	Manifestations	Comments	Mutation	References
Hereditary hemorrhagic telangiectasia Type I OMIM 187300 Type 2 OMIM 600376 Type 3 OMIM 175050	Mucosal and gastrointestinal telangiectasias and arteriovenous malformations in brain, lungs, and liver	Higher incidence of pulmonary AVMs Higher incidence of hepatic AVMs and gastrointestinal bleeding Juvenile polyposis	Type I 9q34.11 endoglin (ENG) Type 2 12q13.13 activin receptor-like kinase I (ACVRLI) Type 3 18q21.2 SMAD-related protein 4 (SMAD4)	57
CLOVES syndrome OMIM 612918	Congenital lipomatous overgrowth, vascular malformation, epidermal nevus, skeletal/spinal abnormalities (macrodactyly, polydactyly, syndactyly, limb length/girth asymmetry, thumb deformities, progressive scoliosis), occult spinal dysraphism, renal asymmetry/structural anomalies, inguinal hernias, undescended testicles, increased risk of pulmonary embolism (especially in patients with thoracic and central phlebectasia), may have complex spinal-paraspinal fast-flow lesions	Wilms tumor	3q26.32 PIK3CA gene somatic mosaic activating mutations	63–68
Proteus syndrome OMIM 176920	Asymmetric progressive, disproportionate overgrowth, hyperostosis, cerebriform connective tissue nevus, vascular malformation (capillary, venous, ± lymphatic), phenotypic facies (dolichocephaly, open mouth, wide nares, down-slanting palpebral fissures) cystic lung disease, obstructive sleep apnea	Bilateral ovarian cystadenoma, parotid adenoma	AKT1 gene somatic mosaic activating mutations 14q32.33	69,70
Megalencephaly–capillary malformation–polymicrogyria syndrome MCAP;M-CM OMIM 602501	Megalencephaly with brain malformation (polymicrogyria), prenatal overgrowth asymmetry, cutaneous vascular malformation, syndactyly ± polydactyly, connective tissue dysplasia	N/A	PIK3CA-activating mutation 3q26.32	71,72
Klippel–Trenaunay Syndrome OMIM 149000	Capillary malformation, soft tissue overgrowth, vascular malformation	N/A	PIK3CA	73,74
Parkes Weber Syndrome OMIM 608355	Capillary malformation, arteriovenous malformation, ± soft tissue overgrowth	N/A	Somatic RASA1 5q14.3	75
Capillary malformation–arteriovenous malformation OMIM 608354	Capillary malformation, soft tissue overgrowth, vascular malformation, and arteriovenous fistula	N/A	Germline RASA1-activating mutation 5q14.3	76,77
Sturge–Weber syndrome OMIM 185300	Facial capillary malformation (PWS), glaucoma, CNS leptomeningeal angiomatosis (encephalotrigeminal angiomatosis), bone ± soft tissue overgrowth	N/A	Somatic GNAQ 9q21	53
PTEN hamartoma syndrome Bannayan–Riley–Ruvalcaba syndrome OMIM 153480 Cowden syndrome OMIM 158350	Macrocephaly, vascular malformation, lipomas, thyroid disorders, penile lentigines (BRRS), trichilemmomas, papillomatous papules	High risk of malignancy, especially those of breast, thyroid, endometrium; Lhermitte–Duclos cerebellar gangliocytoma	Germline PTEN 10q23.31	78–82

(*Continued*)

Table 3 (Continued)

Disorder	Manifestations	Comments	Mutation	References
Facial infiltrating lipomatosis	Unilateral facial soft tissue with skeletal overgrowth, premature dentition with macrodontia, hemimacroglossia, mucosal neuromas	N/A	Somatic PIK3CA-activating mutation	83
Maffucci syndrome OMIM 614569	Venous malformation, ± spindle cell hemangioma, + enchondromas	Malignant transformation of enchondromas (chondrosarcoma) Increased incidence of malignancies – brain, ovarian, pancreatic	Somatic (isocitrate dehydrogenase [IDH] 1 or 2), IDH1 IDH2	84
SOLAMEN	Segmental proportional Overgrowth, Lipomatosis, Arteriovenous Malformation and Epidermal Nevus	N/A	PTEN 10q23.3 Mosaic PTEN wild-type allelic loss	85

Abbreviations: AVMs, arteriovenous malformations; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and spinal/skeletal scoliosis; CNS, central nervous system; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; N/A, not applicable; OMIM, Online Mendelian Inheritance in Man; PIK3CA, Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase Catalytic Subunit, Alpha Isoform; PTEN, phosphatase and tensin homolog; PWS, port wine stain.

extensive involving an entire limb or body part. Most VMs are hyperintense on T2-weighted imaging and hypointense on T1-weighted imaging and typically have a lobulated margin. Phleboliths are rounded hypointense signal voids, best demonstrated on T2-weighted imaging. Fluid–fluid levels are uncommon.[56] Enhancement is typically present within the low-flow vascular channels. The presence of enhancement is an important differentiating feature from nonenhancing cystic lesions such as LM.

Lymphatic malformation

Clinically, LMs (Figure 9) may present as soft compressible masses with normal overlying skin. A diagnostic feature is the transillumination of these lesions (Figure 9B). LMs may be classified as macrocystic or microcystic depending on their imaging appearance. On sonography, macrocystic LMs appear as hypoechoic cystic spaces with thin internal septations. Although ultrasonography may be adequate to define subcutaneous cystic nonvascular prominent masses, MRI with contrast is the preferred method to define the anatomic extent of the process and, importantly, its juxtaposition with other structures. This will also help in treatment planning. Microcystic LMs appear as echogenic areas on soft tissue thickening.[56] The cysts in a microcystic LM are usually too small to identify as discrete structures on MRI and usually appear as diffuse areas of low T1 signal and increased signal on T2-weighted imaging, with absence of or mild postcontrast enhancement. On MRI, macrocystic LMs appear as well-defined cysts characterized by hypointense signal on T1-weighted imaging and marked hyperintense signal on T2-weighted imaging. Fluid–fluid levels are common, due to internal hemorrhage or proteinaceous material, although a feature that is not pathognomonic for LM as they can be seen in a minority of VMs. After gadolinium administration, there is septal and peripheral enhancement, but the cystic spaces are not internally enhanced, which is a helpful differentiating feature from VM. Edema and enhancement of the adjacent soft tissue may be present in the setting of an inflamed LM.

Syndromic VMs

Syndromic hemangiomas and VMs are summarized in Tables 2 and 3, respectively. Many patients with VMs have skeletal, soft tissue, adipose, and/or parenchymal overgrowth. They are phenotypically distinct, and causative genetic mutations have been identified for many. In most cases, the identified mutation presents mosaic expression due to a somatic (postzygotic) mutational event; thus, these syndromes

are not familial. These patients in particular require ongoing surveillance, collaboration among multiple specialists, and – in some cases – early screening for potential malignancies. Syndromes which include slow- and fast-flow lesions are: blue rubber bleb nevus syndrome (Figure 10), Proteus syndrome, Klippel–Trenaunay syndrome (CM, VM, and/or LM, soft tissue hypertrophy and/or skeletal anomalies), RASA-1 AVM-CM (AVMs with multiple cutaneous CMs), and hereditary hemorrhagic telangiectasia (HHT), the latter which is inherited as an autosomal dominant trait (Figure 11), Parkes Weber syndrome (CM, VM with arteriovenous fistula), CLOVES (congenital lipomatous overgrowth, VMs, epidermal nevus, and spinal/skeletal scoliosis – Figure 12), and SWS. Many new treatments are derived from basic and genetic studies, which have identified signaling pathways that are operative in the evolution of vascular anomaly syndromes (Figure 13).

Hereditary hemorrhagic telangiectasia

Several genetic mutations (most commonly affecting one of two genes in the transforming growth factor-beta/bone morphogenetic protein [BMP] signaling family: endoglin or activin receptor-like kinase-1 [ACVRL1], or less commonly SMAD4 [Mothers Against Decapentaplegic, Drosophila Homolog of 4] or growth/differentiation factor [GDF2; BMP9]) have been identified in this disorder, which has been recently reviewed by McDonald et al.[57] Patients experience epistaxis due to telangiectatic vessels, as well as gastrointestinal and parenchymal AVMs in the gastrointestinal tract, lungs, brain, and/or liver. There may be subungual, facial, lip, tongue, and/or intraoral telangiectasias (Figure 11).

On radiography, pulmonary AVMs demonstrate a well-defined lobulated pulmonary nodule with a draining vein. CT with contrast demonstrates an enhancing well-circumscribed mass with an enhancing feeding artery and draining vein.

Blue rubber bleb nevus syndrome

Patients with blue rubber bleb nevus syndrome have multiple small soft blue VMs of variable size in the skin,
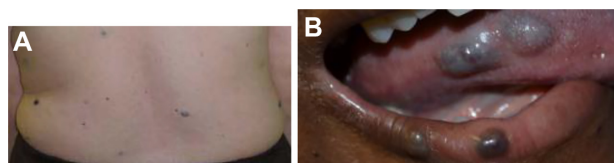

Figure 11 Hereditary hemorrhagic telangiectasia.
Note: Telangiectasia in subungual (**A**), tongue (**B**), and palate (**C**) locations, in a patient with recurrent oral bleeding and epistaxis, with multiple affected family members in at least three generations.

gastrointestinal tract, and other organs (Figure 10). On imaging, gastrointestinal tract VMs are characteristic, with the small bowel most commonly affected. Fluoroscopic examinations demonstrate multiple polypoid filling defects, potentially mimicking a polyposis syndrome. Radiographs and CT images demonstrate multiple calcifications, reflecting phleboliths. MRI is useful in detecting the VMs in the musculoskeletal system and solid organ involvement. As detailed in the section on VMs, VMs are typically hypointense on T1-weighted imaging, hyperintense on T2-weighted sequences, and enhanced after gadolinium administration. Phleboliths are common, manifesting as round T2 hypointense filling defects.

Maffucci syndrome

Maffucci syndrome is a nonhereditary enchondromatosis characterized by multiple enchondromas and soft tissue spindle cell hemangioendotheliomas.[58] On the basis of the Mulliken and Glowacki classification scheme,[3] the "hemangioendotheliomas" may represent a form of VM as they often contain phleboliths. Patients with enchondromatoses have an increased risk of chondrosarcomatous transformation, seen in up to 15%–30% of cases.[59,60] Radiographs are often pathognomonic, showing enchondromas of the small bones of the hands and feet and soft tissue calcifications representing phleboliths. On radiographs, the enchondromas

Figure 10 Blue rubber bleb nevus syndrome.
Notes: Multifocal blue vascular lesions are seen. (**A**, left panel) Vascular lesions on skin, (**B**, right panel) mucosal surfaces, and gastrointestinal tract, often associated with severe gastrointestinal bleeding.
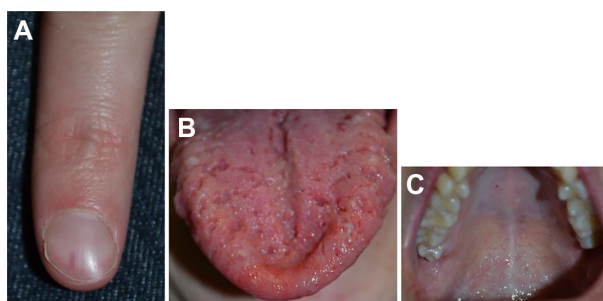

Figure 12 CLOVES syndrome in two patients.
Note: Patients have congenital lipomatous overgrowth (**A**), vascular malformation, epidermal nevus (**B**), and skeletal/spinal abnormalities (macrodactyly, syndactyly, sandal toe deformity, and limb length/girth asymmetry) (**C**).
Abbreviations: CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and spinal/skeletal scoliosis.
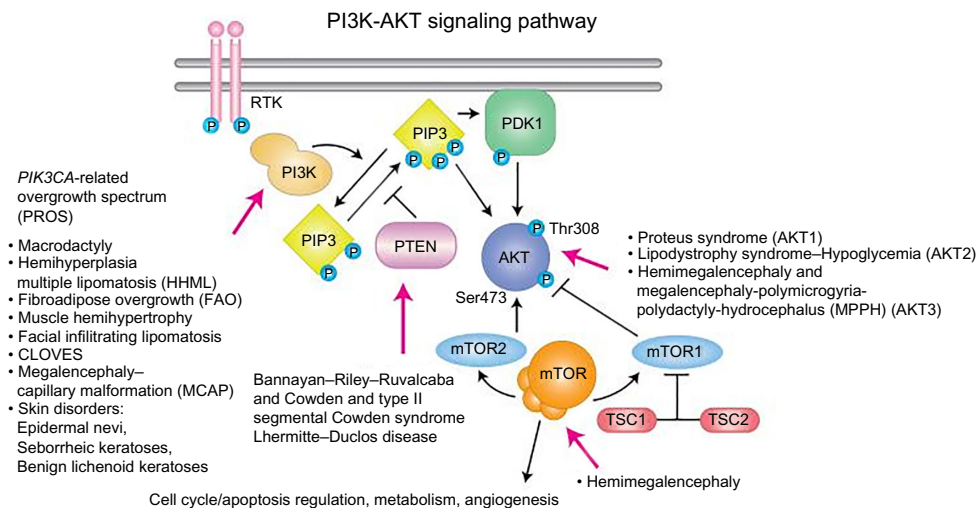
Figure 13 *PIK3CA*-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation.
Notes: Copyright © 2010. John Wiley and Sons. Keppler-Noreuil KM, Rios JJ, Parker VE, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A*. Feb 2015;167A(2):287–295.[87]
Abbreviations: CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and spinal/skeletal scoliosis; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin; PI3Ks, phosphoinositide 3-kinases; RTKs, tyrosine kinase receptors; PDK1, phosphoinositide-dependent protein kinase 1; AKT, v-akt murine thymoma viral oncogene homolog 1; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; TSC, Tuberous Sclerosis Complex.

are defined, expansile lucent bony lesions with endosteal scalloping and cortical thinning. There is often a mineralized matrix with an ring-and-arc pattern. On MRI, enchondromas have similar signal intensity as cartilage on all pulse sequences; they are hypointense or isointense on T1-weighted imaging, hyperintense on both T2-weighted and cartilage-sensitive sequences, and may demonstrate peripheral enhancement.

Prenatal diagnosis of vascular anomalies

Antenatal detection of vascular anomalies can be important for parental anticipation, fetal monitoring, pre-and postnatal management, and obstetrical decision-making. Marler et al[61] reported 29 patients in a 12-month period prenatally diagnosed with a vascular anomaly, 42% of whom were incorrectly diagnosed. In this series, patients correctly diagnosed had optimal decision-making with regard to in utero

therapy and mode of delivery (vaginal, cesarean section, ex utero intrapartum treatment procedure).[61]

Radiologic evaluation provides noninvasive detection of prenatally diagnosed vascular anomalies, including dysmorphic or asymmetrical organs/limbs or abnormal growth patterns, which may be detected with prenatal ultrasonography. Fetal MRI can confirm and refine diagnoses suspected on ultrasonography and assist in arranging the most appropriate type of delivery.[10,62]

For disorders with identified genomic mutations in a proband, molecular genetic testing may be utilized. Preimplantation genetic diagnosis, amniocentesis, or chorionic villus sampling may be feasible for future offspring.

Resources

Currently, there are several vascular anomalies-related therapeutic trials, registries, and observational and genetic studies. A database of clinical trials and other studies in the USA and

Table 4 Online resources for genetic and further information

Online Mendelian Inheritance in Man (OMIM) – online catalog of human genes and genetic disorders	http://www.omim.org
Genetics Home Reference	http://ghr.nlm.nih.gov
Genetic Testing Registry	http://www.ncbi.nlm.nih.gov/gtr/
GeneTests – includes gene reviews, tests, disorders, genes, laboratories, and clinics	https://www.genetests.org
GeneReviews	http://www.ncbi.nlm.nih.gov/books/NBK1116/
Vascular Anomaly and Lymphedema Mutation Database	http://www.icp.ucl.ac.be/vikkula/VAdb/home.php
NORD (National Organization for Rare Diseases) – rare disease database	https://www.rarediseases.org
ORPHANET – portal for rare diseases and orphan drugs	http://www.orpha.net
International Society for the Study of Vascular Anomalies (ISSVA) – updated classification	http://www.issva.org

Table 5 Disease-specific advocacy groups

Group	Web site
Klippel–Trenaunay Support Group	http://k-t.org
Vascular Birthmark Foundation	http://www.birthmark.org
CLOVES Syndrome	http://www.clovessyndrome.org
The PTEN Hamartoma Tumor Syndrome Foundation	http://www.ptenfoundation.org
Hereditary Hemorrhagic Telangiectasia	http://curehht.org
Sturge–Weber Foundation	http://www.sturge-weber.org
Lymphangiomatosis and Gorham's Disease	http://www.lgdalliance.org
National Lymphedema Network	http://www.lymphnet.org
Proteus Syndrome Foundation	http://www.proteus-syndrome.org
Lymphatic Malformation Institute	http://www.lmiresearch.org/institute/

Abbreviations: CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and spinal/skeletal scoliosis; PTEN, phosphatase and tensin homolog.

internationally, including those open to recruitment, is available at https://clinicaltrials.gov. At this time, pharmacologic studies for vascular anomalies include A Study to Compare Vincristine to Sirolimus for Treatment of High Risk Vascular Tumors (NCT02110069), Sirolimus for VMs with or without hypertrophy syndromes (NCT00975819, NCT02509468, NCT01811667, NCT02428296, and NCT02443818), Laser and oral or topical sirolimus vs laser alone for port-wine stain–type CMs (NCT00830466, NCT02214706), Bevacizumab or Timolol Nasal Spray for HHT-related epistaxis (NCT02106520, NCT02157987, NCT02484716, and NCT01752049), Thalidomide or Pazopanib for HHT (NCT01485224, NCT02204371), as well as several registries and imaging and sclerotherapy studies.

Instructive Web sites are listed in Table 4 and include the following: Online Mendelian Inheritance in Man (OMIM®; http://www.omim.org), which provides OMIM numbers for each disorder as well as academic summaries and links to relevant publications. *Genetics Home Reference* (http://ghr.nlm.nih.gov) provides, in layman's terms, medical and genetic information. The Genetic Testing Registry® is particularly robust, synthesizing information from various Web sites to include available clinical and research tests, diagnoses/phenotypes, genetic mutations, and approved state and Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories worldwide. GeneTests (https://www.genetests.org) links to OMIM and other sites, as well as providing a comprehensive database of international laboratories performing genetic testing, including availability for research and/or clinical test method and availability of prenatal and carrier testing. *GeneReviews®* provides peer-reviewed concise summaries of clinical and genetic information with links to PubMed; however, this may not be as updated (last viewed August 9, 2015) as other sites. The Vascular Anomaly and Lymphedema Mutation Database, maintained by the Laboratory of Human Molecular Genetics, de Duve Institute, Brussels (Belgium) is an excellent resource for recognized mutations for several vascular anomalies-related disorders, with links to PubMed references and an analysis of types of variants reported.

Patient- /family-initiated foundations and support groups provide patient/family education, advocacy, guidelines, direct research funding, links to outside funding opportunities, and financial assistance (Table 5). Many funding agencies now encourage patient advocates as panel members and grant reviewers. Patient advocacy groups have become extremely important in moving the field forward, with patient/family education, support, activism, guidelines, fundraising, direct research funding, links to outside funding opportunities, and liaisons with professional organizations and government agencies.

Summary and conclusion

It should be apparent that the term "vascular anomalies" does indeed represent a spectrum of vascular disorders, and that evaluation, diagnosis, and management is a multidisciplinary process. Experts in medical and surgical subspecialties (otolaryngology, plastic/reconstructive surgery, dermatology, orthopedics, ophthalmology, neurosurgery, urology, and general medicine), as well as geneticists, physiatrists, and others, work as a team.

It is important to recognize the clinical presentation and to establish an appropriate diagnosis to most appropriately evaluate and manage the patients. Some congenital vascular anomalies require no or minimal intervention, while others require a cohesive multidisciplinary approach. Understanding these nuances and complexities is essential for the most comprehensive care and optimal clinical outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

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