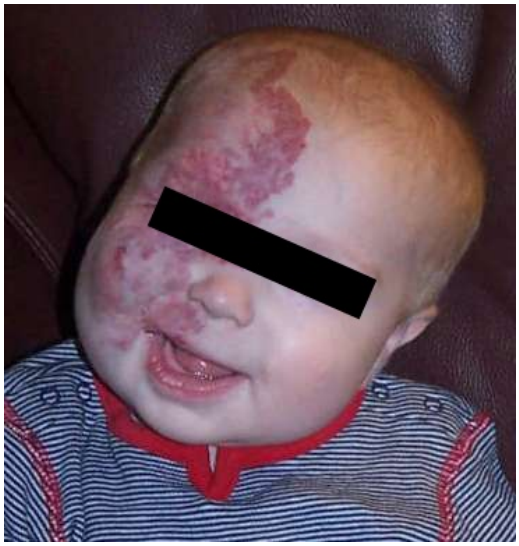
COURSE 01: ORIENTATION

Dr. Francine Blei

Orientation: History and classification of vascular anomalies



Historically, few individuals and institutions have been interested in or experienced with vascular anomalies. As a result, patients have often been misdiagnosed and inappropriately managed. Within the past several years, however, understanding about the clinical and scientific aspects of vascular anomalies has improved. Consequently, efforts to formalize evaluation and treatment protocols and to collaborate in research studies are underway.

Research has identified the potential mechanisms underlying the development of vascular anomalies as well as somatic and germline mutations, leading to clinical trials with new targeted therapies.

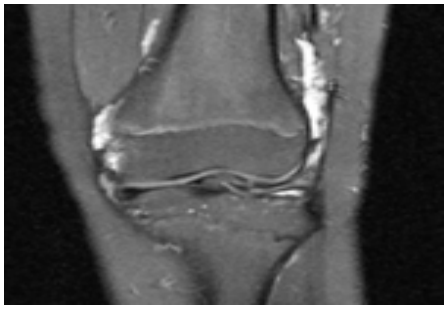
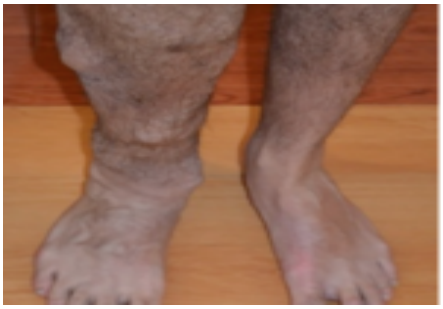
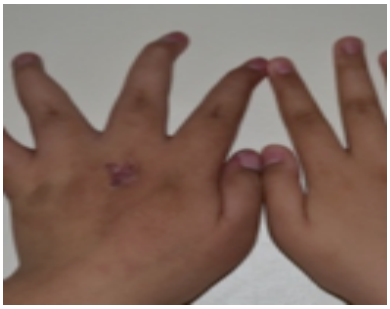
Patient support groups have often taken the lead to support patients and research, and to increase public awareness. The intent of this module is to describe the past nomenclature used to describe vascular anomalies and to define and describe the current terminology, stressing the importance of consistency. The module focuses on topics most relevant to adult patients with vascular anomalies. It provides not only a background for the general practitioner and specialist, but also an appreciation for when patients should be referred to a dedicated vascular anomalies program. The module helps clarify misconceptions and to address the most common questions which arise in the management of patients. Since it is important to recognize the appearance and/or patterns of vascular lesions, images of patients are used liberally throughout this course. Links to relevant internet sites are included to reinforce knowledge and provide ongoing resources for learning.

Objectives

Upon successful completion of this activity, participants should be able to:

- Identify and describe the basic categories of vascular anomalies
- Define criteria to distinguish various vascular anomalies
- Explain the importance of understanding the classification of vascular anomalies, as well incorrect terminology is often used
- Identify syndromal vascular anomalies
- Classify types of vascular anomalies with known genetic mutations
- Identify specialists who may be necessary for a given patient
- Locate reliable resources to keep up-to-date

Depictions of vascular anomalies

What is a vascular anomaly?

Vascular anomalies are functionally divided into two categories, based on their propensity to proliferate. The separation between vascular anomalies into proliferative lesions vs. static malformations represented an important advance, as the prognosis and management for each type varies. These two types of entities differ substantially. From a medical standpoint, this distinction enhances three crucial aspects to clinical management: early detection, proper evaluation, and appropriate treatment.

Generally, several specialists are required to manage patients with vascular anomalies. Multidisciplinary Vascular Anomalies Teams provide the optimal mechanism to coordinate care and may be comprised of the following: radiologists (diagnostic and interventional), surgeons (ENT, plastic, general), pathologists, hematologists, dermatologists, ophthalmologists, orthopedists, obstetricians, gynecologists, gastroenterologists, pulmonologists, geneticists, and other specialists.

References: 1,2

Common inaccuracies and conundrums

Not every vascular lesion is a hemangioma!
In fact, in the adult population, no vascular anomaly is a hemangioma.
Is there a genetic basis for vascular anomalies? Yes. Many genes have been identified, with genomic or somatic mutations.
Are there specific obstetric and gynecologic issues for women with vascular anomalies? Potentially, yes.

Historical classification of vascular anomalies

Several classification schemes for vascular anomalies have existed, based on severity and associated symptoms. However, the seminal classification was suggested by Mulliken and Glowacki, based on functional and cellular differences (1). This classification scheme was adapted as the 1996 International Society for the Study of Vascular Anomalies (ISSVA) Classification. (3)

Proliferative vascular lesions	Static vascular lesions (vascular malformations) Simple or combined
Hemangiomas	**Arterial**
Kaposiform hemangioendothelioma	**Venous**
Tufted angioma	**Capillary**
Pyogenic granuloma	**Lymphatic**
Kaposi's sarcoma	
Angiosarcoma	
Other	

Updated ISSVA classification

In 2014, ISSVA updated its classification to incorporate new diagnoses, syndromes, and genetic information. (The full classification is available as a dynamic Powerpoint document. Click on CLASSIFICATION on the left sidebar.
A detailed explanation of the diagnoses and rationale for this classification is available in a manuscript.) (3)

Unfortunately, many practitioners continue to call most benign vascular lesions "hemangioma(s)," which may confuse patients and lead to incorrect treatment. It is hoped that all physicians and researchers will utilize the updated classification and share this common vernacular.

Please note that in the ISSVA Classification, the distinction between vascular tumors (proliferative) and vascular malformations (static) remains.

Vascular Tumors are further separated into "benign," "locally aggressive or borderline," and "malignant."

Vascular Malformations are separated by the predominant affected vessels and can be simple or combined (affecting ≥ 1 vessel type), truncular (anomalies of major named vessels), or associated with other anomalies (skeletal, CNS, etc.).

Updated ISSVA classification table (Table 1)

		Vascular Anomalies		
Vascular Tumors (Benign)	Vascular Tumors (Simple)	Vascular Tumors (Combined)	Vascular Malformations Of Major named vessels	Vascular Malformations Associated with other anomalies
Locally aggressive or borderline	Capillary Malformations	CVM,CLM	See details	See list
Malignant	Lymphatic Malformations	LVM,CLVM		
	Venous Malformations	CAVM		
	Arteriovenous Malformations	CLAVM		
	Arteriovenous fistula	others		

Vascular malformations associated with anomalies

Klippel-Trenaunay Syndrome:	CM + VM +/- limb overgrowth
Parkes Weber Syndrome:	CM + AVF + limb overgrowth
Servelle-Martorell Syndrome:	Limb VM + bone overgrowth
Sturge-Weber Syndrome: overgrowth	Facial + leptomeningeal CM + eye anomalies +/- bone and/or soft tissue
Limb CM + congenital non-progressive limb hypertrophy	
Maffucci Syndrome:	VM +/- spindle-cell hemangioma + enchondroma
Macrocephaly - CM (M-CM / MCAP)	
Microcephaly - CM (MICCAP)	
CLOVES Syndrome:	LM + VM + CM +/- AVM + lipomatous overgrowth
Proteus Syndrome:	CM,VM and/or LM + asymmetrical somactic overgrowth
Bannayan-Riley-Ruvalcaba sd:	AVM + VM + macrocephaly, lipomatous overgrowth

Simple vascular malformations

Primary Lymphedema

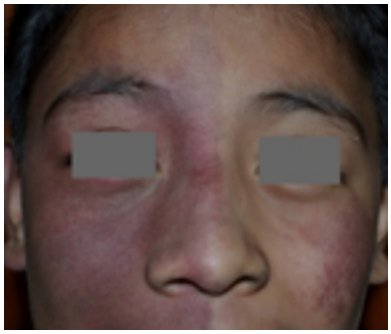
- Nonne-Milroy Syndrome
- Primary hereditary lymphedema
- Lymphedema – distichiasis
- Hypotrichosis – lymphedema – telangiectasia
- Primary lymphedema with myelodysplasia
- Primary generalized lymphatic anomaly (Hennekam lymphangiectasia – lymphedema Syndrome)
- Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome
- Lympedema – choanal atresia

Provisionally unclassified vascular anomalies

- Verrucous hemangioma
- Angiokeratoma
- Multifocal lymphangioendotheliomatosis with thrombocytopenia / cutaneovisceral angiomatosis with thrombocytopenia (MLT / CAT)
- Kaposiform lymphangiomatosis (KLA)
- PTEN (type) hamartoma of soft tissue / “angiomatosis” of soft tissue

Anomalies	**Hematological disorder (some vascular anomalies are associated with a hematologic disorder)**
Tufted angioma Kaposiform hemangioendothelioman	Profound and sustained thrombocytopenia with profound hypofibrinogenemia, consumptive coagulopathy, and elevated D-dimer (Kasabach-Merritt phenomenon)
Rapidly involuting congential hemangioma	Transient mild/moderate thrombocytophenia, +/- consumptive coagulopathy, and elevated D-dimer
Venous malformations/Lymphatic-venous malformations	Chronic localized intravascular coagulopathy with elevated D-dimer , +/-hypofibrimogenemia, and +/- moderate thrombocytopenia (may progress to DIC after trauma or operation)
Lymphatic malformations	Chronic localized intravascular coagulopathy with elevated D-dimer, +/- mild to moderate elevated D-dimer, and +/- mild to moderate thrombocytopenia *(consider Kaposiform lymphangiomatosis)* (may progress to disseminated intravascular coagulopathy (DIC) after trauma or operation)
Multifocal lymphangioendotheliomatosis with thrombocytopenia / Cutaneovisceral angiomatosis with thrombocytopenia	Sustained, fluctuating, moderate to profound thrombocytopenia with gastrointestinal tract bleeding or pulmonary hemorrhage
Kaposiform lymphangiomatosis	Mild to moderate thrombocytopenia, +/- hypofibrimogenemia, and D-dimer elevation

Case 1

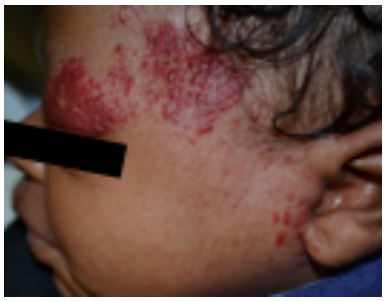


Sturge-Weber Syndrome

Patient with macular red facial vascular lesion, a history of seizures and glaucoma

Sturge- Weber Foundation's Learning Center Medscape®'s Overview of Struge-Weber Syndrome

Case 2

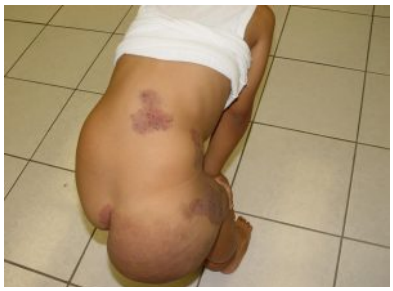


PHACE Syndrome

Adult patient who presents with transient ischemic attack; radiologic evaluation demonstrates cerebellar hypoplasia and arteriopathy. Query whether patient had a segmental vascular lesion in infancy, then suspect PHACE Syndrome: posterior fossa anomaly, hemangioma (segmental), arteriopathy, cardiac anomaly, eye anomaly

Case 3

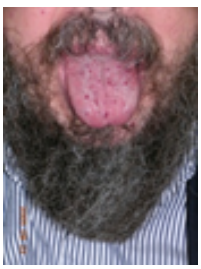
Klippel-Trenaunay Syndrome



Female patient with severe pain and swelling in limb; venous malformation after starting oral birth control
Suspect thrombosis

Klippel-Trenaunay Syndrome Foundation

Case 4

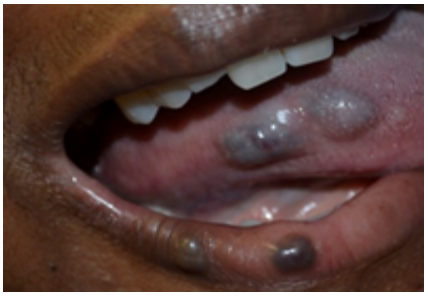
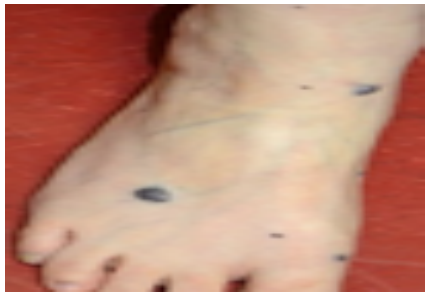


HHT

Multiple family members with epistaxis, mucosal and gastrointestinal bleeding, and clubbing. Suspect Hereditary Hemorrhagic Telangiectasia(HHT)

Case 5

Blue Rubber Bleb Nevus Syndrome

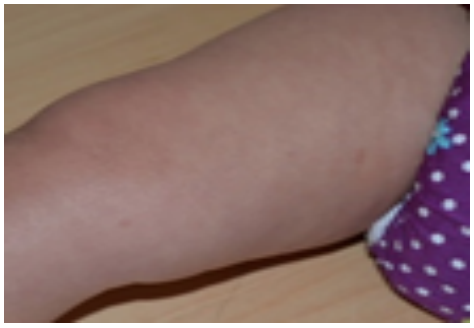
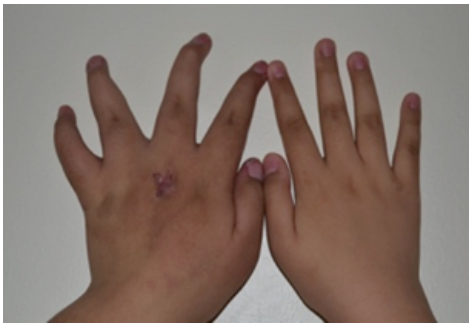



Two different patients, both with multiple small blue vascular lesions, gastrointestinal bleeding, anemia.

Suspect Blue Rubber Bleb Nevus Syndrome
Blue Rubber Bleb Nevus Syndrome at Pubmed

Case 6

Capillary Malformation-Arteriovenous Malformation (CM/AVM)

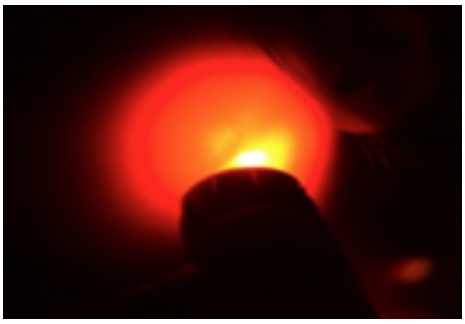
Left photo: Patient with many small flat, pink cutaneous lesions, and history of embolizations in brain in infancy. See ISSVA Classification.

Right photo: Similar patient with asymmetry of hands and fingers, affected hand larger, left arm thrill and bruit, heart murmur, and multiple small macular, red blanching lesions on trunk and face.

Suspect Capillary Malformation-Arteriovenous Malformation
(RASA-1 mutation)

Case 7

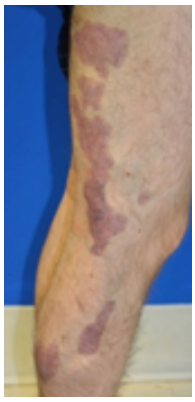
Lymphatic malformation

Patient with soft mass, occasional inflammation. Transilluminates on examination.
Suspect Lymphatic Malformation

Case 8

Klippel-Trenaunay Syndrome



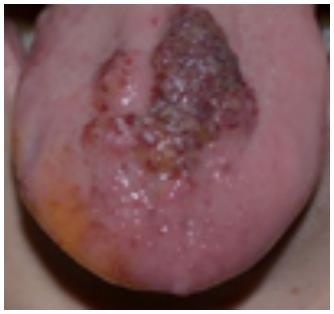
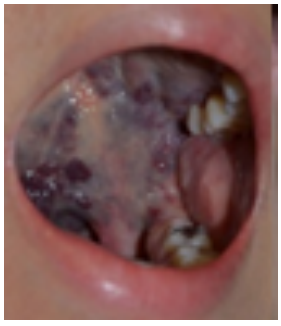
Patient with “geographic” macular red/purple discoloration
with occasional blebs, ipsilateral dilated veins, limb length and girth discrepancy, pain with small tender nodules.

Suspect capillary venous malformation with hypertrophy.

May have LIC (localized intravascular coagulopathy) with modest thrombocytopenia and hypofibrionogenemia.

Case 9

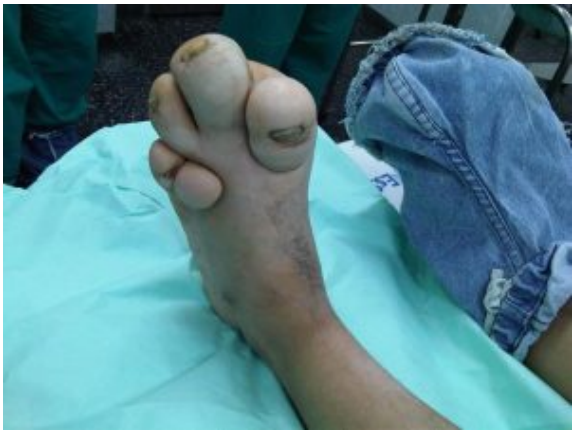
Lymphatic / venous / arteriovenous malformation

Patient with large tongue and/or lips, malocclusion, intra-oral oozing, mandibular overgrowth, orthopnea. Suspect lymphatic, venous, or arteriovenous malformation, depending on clinical and radiologic features.

Case 10

Proteus Syndrome

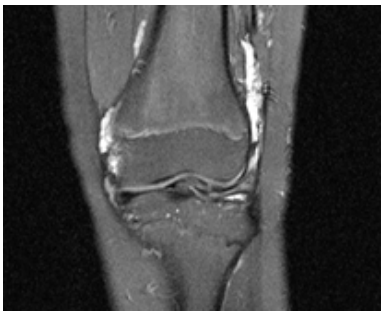


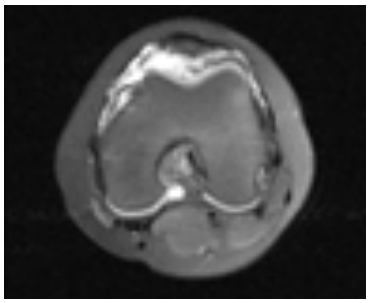
Prominent leg veins, limb length, and girth discrepancy in a patient with asymmetric overgrowth, distinctive facial features, bullous lung lesions, epidermal nevus, fatty masses, and blood clots.

Suspect Proteus Syndrome

Case 11

Venous malformation

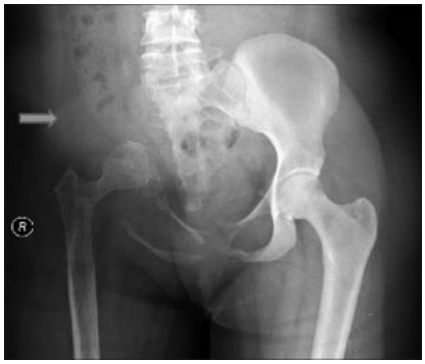




Patient with chronic knee pain and swelling, MRI with gadolinium demonstrates slow-flow lesion of knee with serpentine vessels infiltrating the infra-patellar fat pad with some cartilage loss.
Suspect venous malformation of knee.

Case 12

Gorham Stout Disease

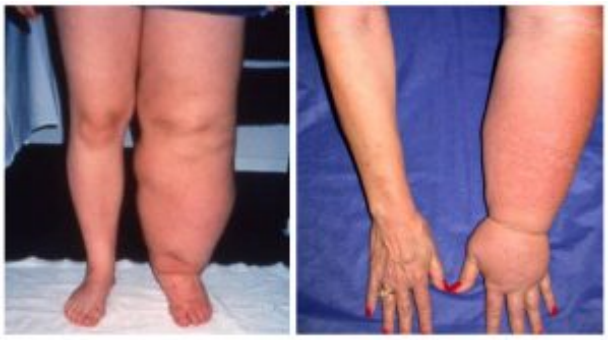


Patient with history of multifocal fractures, facial deformity, dental issues, and history of hospitalization for pulmonary effusion with chylous effusion.

Suspect Gorham Stout Disease
Lymphangiomatosis & Gorham's Disease Alliance

Case 13

Lymphedema



A patient has swollen legs, no history of trauma, surgery, or radiation. She occasionally experiences cellulitis, which improves with antibiotics. She is dependent upon a special kind of massage therapy, a compression pump at night, and compression stockings. Many relatives have the same diagnosis. Suspect Familial Lymphedema improving with decompressive lymphatic massage therapy. National Lymphedema Network

Online resources for genetic information

Online Mendelian Inheritance in Man (OMIM) – OMIM is an online catalog of human genes and genetic disorders

Genetics Home Reference – Genetics Home Reference provides consumer-friendly information about the effects of genetic variations on human health.

Genetic Testing Registry – The Genetic Testing Registry (GTR®) provides a central location for voluntary submission of genetic test information by providers. The scope includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials. The overarching goal of the GTR is to advance the public health and research into the genetic basis of health and disease.

Gene Tests and **Gene Reviews**– By providing current, easy-to-access information on genetic testing and its use in diagnosis, management, and genetic counseling, Gene Tests promotes the appropriate use of genetic services in patient care and personal decision making.

Vascular Anomaly and Lymphedema Mutation Database – This organization's purpose is to develop new information technologies to aid in the understanding of fundamental molecular and genetic processes that control health and disease. More specifically, the NCBI has been charged with creating automated systems for storing and analyzing knowledge about molecular biology, biochemistry, and genetics; facilitating the use of such databases and software by the research and medical community; coordinating efforts to gather biotechnology information both nationally and internationally; and performing research into advanced methods of computer-based information processing for analyzing the structure and function of biologically important molecules.

Informative Websites

NORD (National Organization for Rare Diseases) Rare Disease Database – NORD is a 501(c)(3) patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 230 patient organization members, is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

ORPHANET Portal for rare diseases and orphan drugs – Orphanet is the reference portal for information on rare diseases and orphan drugs, for all audiences. Orphanet's aim is to help improve the diagnosis, care, and treatment of patients with rare diseases.

MEDLINE®/PubMED® – The National Library of Medicine (NLM), on the campus of the National Institutes of Health in Bethesda, Maryland, has been a center of information innovation since its founding in 1836. The world's largest biomedical library, NLM maintains and makes available a vast print collection and produces electronic information resources on a wide range of topics that are searched billions of times each year by millions of people around the globe. It also supports and conducts research, development, and training in biomedical informatics and health information technology. In addition, the Library coordinates a 6,000-member National Network of Libraries of Medicine that promotes and provides access to health information in communities across the United States.

Advocacy groups

Vascular Birthmarks Foundation -Since its inception in 1994, VBF has successfully networked thousands of children and adults into treatment, sponsored significant research, and educated physicians, patients, and families about the diagnosis and treatment of vascular birthmarks. VBF has established chapters all over the world.

Cloves Syndrome Community – CLOVES Syndrome Community supports, educates, empowers, and improves the lives of those affected by CLOVES Syndrome.

CLOVES Syndrome Foundation – The CLOVES Syndrome Foundation is a 501(c)3 not-for-profit organization, is focused on improving the lives of CLOVES patients by funding Overgrowth and Vascular Anomaly research.

Hereditary Hemorrhagic Telangiectasia – The HHT Foundation's new brand, Cure HHT, deepens and renews our commitment to the HHT community. We have one mission that drives everything we do: to find a cure for HHT disease, a genetic blood vessel disorder that affects 1 in 5,000 people, 90% of whom are undiagnosed.

Klippel-Trenaunay Support Group – The Klippel-Trenaunay Support Group (K-T Support) was founded in 1986. We welcome patients and their families as members and provide information about the group and about Klippel-Trenaunay (K-T, KT, KTS) Syndrome, a combined vascular malformation.

Lymphangiomatosis and Gorham's Disease – The mission of the LGD Alliance is to improve the care of patients with lymphangiomatosis and Gorham's disease by promoting research that will identify effective treatments and, ultimately, a cure for these diseases. The Alliance is committed to providing support and education to members of the patient community and their families, education for professionals and the general public, and hope to those affected by these rare lymphatic malformations.

National Lymphedema Network – The National Lymphedema Network (NLN) is an internationally recognized non-profit organization founded in 1988 by Saskia R.J. Thiadens, RN, to provide education and guidance to lymphedema patients, healthcare professionals, and the general public by disseminating information about risk reduction and the management of primary and secondary lymphedema.

Proteus Syndrome Foundation – The Proteus Syndrome Foundation is a 501c3 not-for-profit organization dedicated to improving the lives of Proteus patients by funding AKT1 research. We offer education support for patients and families, help to create networks among individuals affected by Proteus syndrome, and connect those individuals to medical professionals.

Sturge- Weber Foundation – The Sturge-Weber Foundation's (The SWF) international mission is to improve quality of life and care for people with Sturge-Weber syndrome and Port Wine Birthmark conditions through collaborative education, advocacy, research and friendly support.

The PTEN Hamartoma Tumor Syndrome Foundation – The PTEN Hamartoma Tumor Syndrome Foundation was founded with a mission to educate about PTEN syndromes, provide financial support to patients, support research, and to promote awareness.

Course 01: Orientation - Lesson Quiz

1. Which type of vascular malformation may fill in the dependent position, with valsalva or straining?
    A. Arteriovenous malformation
    B. Capillary malformation
    C. Venous malformation
    D. Lymphatic malformation

2. Which type of vascular anomaly may transilluminate?
    A. Arteriovenous malformation
    B. Venous malformation
    C. Lymphatic malformation
    D. Capillary malformation

3. Has the classification of vascular anomalies that was established many years ago been updated?
    A. No, it was a very comprehensive classification which still applies today.
    B. The classification has been updated every 2 years since it was first established.
    C. There is no standard classification for vascular anomalies.
    D. Yes. Many new entities have been discovered and the classification has been updated.

4. Are most physicians “fluent” in vascular anomaly terminology so that most patients receive the correct diagnosis when first seen?
    A. Yes, because textbooks and medical training are very up-to-date on this topic.
    B. Yes, because these diagnoses are very common so most physicians are aware them.
    C. Yes, because the presentation of most of these disorders is very typical.
    D. No, many patients spend years trying to find a physician well-versed in their condition.

5. Are most vascular lesions seen in adults called hemangiomas?
    A. No. It is erroneous to use that term for most vascular anomalies in adult patients.
    B. Yes. "Hemangiomas" is a catch-all phrase that is correct to use for most adult vascular anomalies.
    C. No, most vascular lesions in adults are called "Proteus malformations."
    D. No, most vascular lesions in adults are called "blebs" or "nevi."

6. Which would be considered as a reliable resource to keep updated on research and findings concerning vascular anomalies?
    A. OMIM
    B. MEDLINE®/PubMED®
    C. Cancer.org
    D. A&C

7. Which are considered the two basic categories of vascular anomalies in the ISSVA Classification?
    A. Surgically treated vs. medically treated
    B. Malignant vs. non-malignant
    C. Infantile vs. adult
    D. Vascular tumors vs. vascular malformations

8. Which would not be considered a vascular malformation syndrome?
    A. CLOVES syndrome.
    B. Blue rubber bleb nevus (Bean) syndrome.
    C. Cushing's syndrome.
    D. Proteus syndrome.

9. Which type of vascular anomaly is known to have genetic mutations?
    A. Rapidly Involuting Congenital Hemangioma (RICH)
    B. Proteus Syndrome
    C. Verrucous hemangioma Servelle-
    D. Martorell syndrome

10. You are seeing a 29-year old female who has just relocated. She has an enlarged left leg, some areas are firm and erythematous. This has been present since birth and progressing somewhat with age. She is unable to wear regular shoes since the ipsilateral foot is larger and oozes on occasion. She feels better when her legs are elevated, when she wears compression stockings, and when she swims. Several other family members have similar findings. She asks you what can be done and whether there are any tests to see if this is genetic?
    A. She should have a PET scan and total body x-rays.
    B. Unfortunately, no treatments are available.
    C. It is most likely a familial lymphedema; there may be a genetic mutation in the family, and she can be seen by the lymphedema specialist and geneticist.
    D. It is most likely not a familial familial lymphedema; there is probably no genetic mutation and she can continue to be seen by her primary doctor.

Course 01: Orientation - Lesson Quiz Answer Key

1. C
2. C
3. D
4. D
5. A
6. D
7. D
8. C
9. A
10. C

AUTHOR
PROFILES

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Dr. Blei is Board-certified in Pediatrics and Pediatric Hematology-Oncology. Her clinical practice is limited to vascular anomalies (prenatal to adult): patients with hemangiomas, vascular malformations, Kaposiform Hemangioendothelioma, lymphedema, and many syndrome-associated vascular anomalies. She has worked in a laboratory studying the molecular mechanisms of endothelial cells.

Dr. Blei has co-authored many original articles, reviews, textbook chapters, is the Associate Editor of the journal, and Section Editor for Vascular Anomalies of Lymphatic Research and Biology and co-author of"100 Questions and Answers About Vascular Anomalies," a practical guide for patients, families, and physicians. She is currently the Scientific Chair of the International Society for the Study of Vascular Anomalies (ISSVA).

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A Foundation in Vascular Anomalies- Course 1: Orientation

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