VASCULAR ANOMALIES CENTER

Multidisciplinary Approaches to Vascular Anomalies (MAVA)

An International Web Series

In Partnership with The Hendren Project

Editors:

Annie Kulungowski MD, Pediatric Surgery, Surgical Director
Taizo Nakano MD, Pediatric Hematology-Oncology, Medical Director
Vascular Anomalies Center, Children's Hospital Colorado
University of Colorado School of Medicine

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

VASCULAR ANOMALIES CENTER

Multidisciplinary Approaches to Vascular Anomalies (MAVA)

An International Web Series

Partners:

- **The Hendren Project**

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

VASCULAR ANOMALIES CENTER

Multidisciplinary Approaches to Vascular Anomalies (MAVA)

An International Web Series

Guest speakers:

Dr. Max Itkin
Dr. Deborah Rabinowitz
Dr. Motoi

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

Mission Statement

1. To increase awareness of and advocate for pediatric patients with vascular anomalies
2. To understand how to establish proper diagnosis and treatment of pediatric vascular anomalies
3. To create an international forum for debate, discussion and dialog

International Society for the Study of Vascular Anomalies (ISSVA) (www.issva.org)

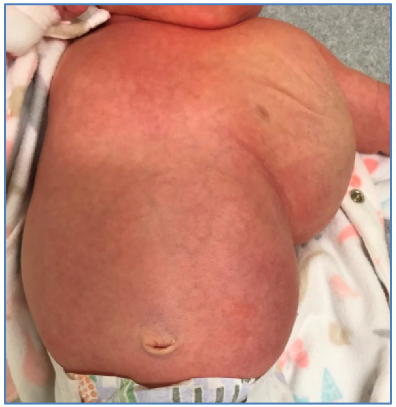
Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined °**	**of major named vessels**	**associated with other anomalies**
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

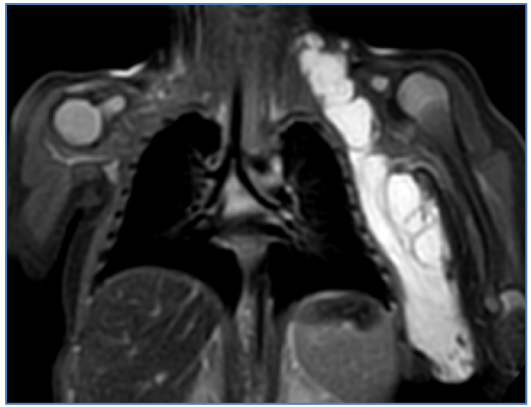
Simple vascular malformations IIa	
Lymphatic malformations (LM)	
Common (cystic) LM *	PIK3CA
Macrocystic LM	
Microcystic LM	
Mixed cystic LM	
Generalized lymphatic anomaly (GLA)	
Kaposiform lymphangiomatosis (KLA)	
LM in Gorham-Stout disease	
Channel type LM	
"Acquired" progressive lymphatic anomaly (so called acquired progressive "lymphangioma")	
Primary lymphedema (different types)	
Others	

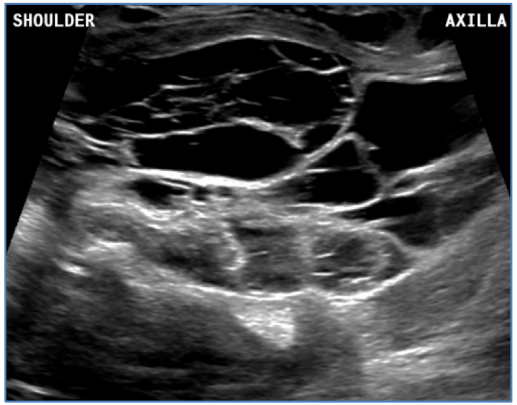
History

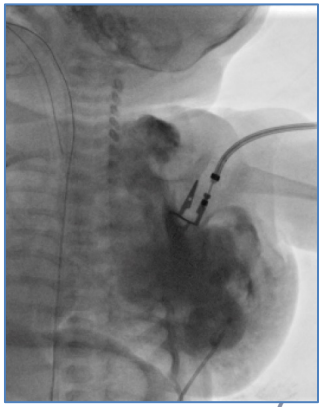
Baby girl presented with prenatal diagnosis of macrocystic lymphatic malformation of the left chest and axilla

- Enlarging cyst on 20-week Ultrasound
- Fetal MRI: multi-septated mass, axillary and left thoracic soft tissues
- Birth hx: Cesarean at 39 weeks GA

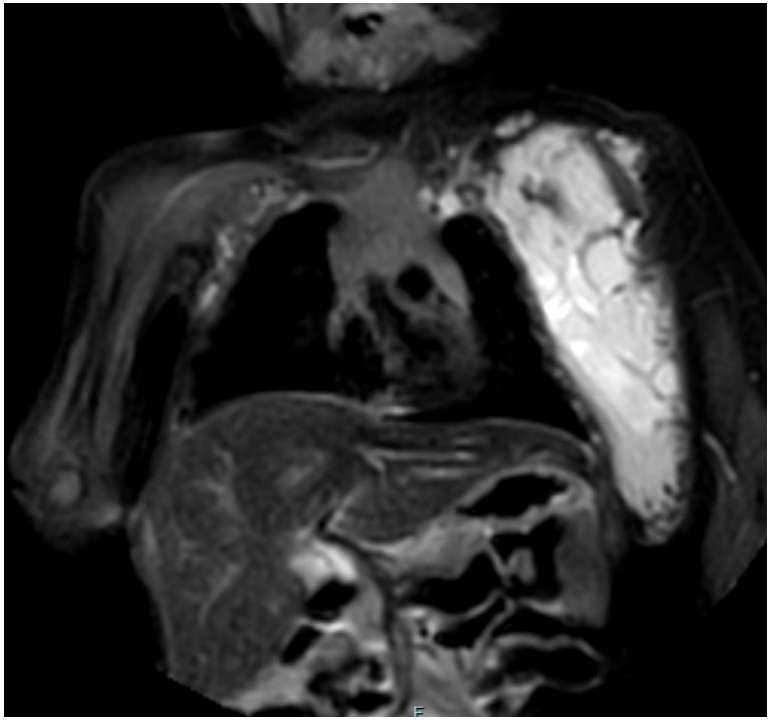


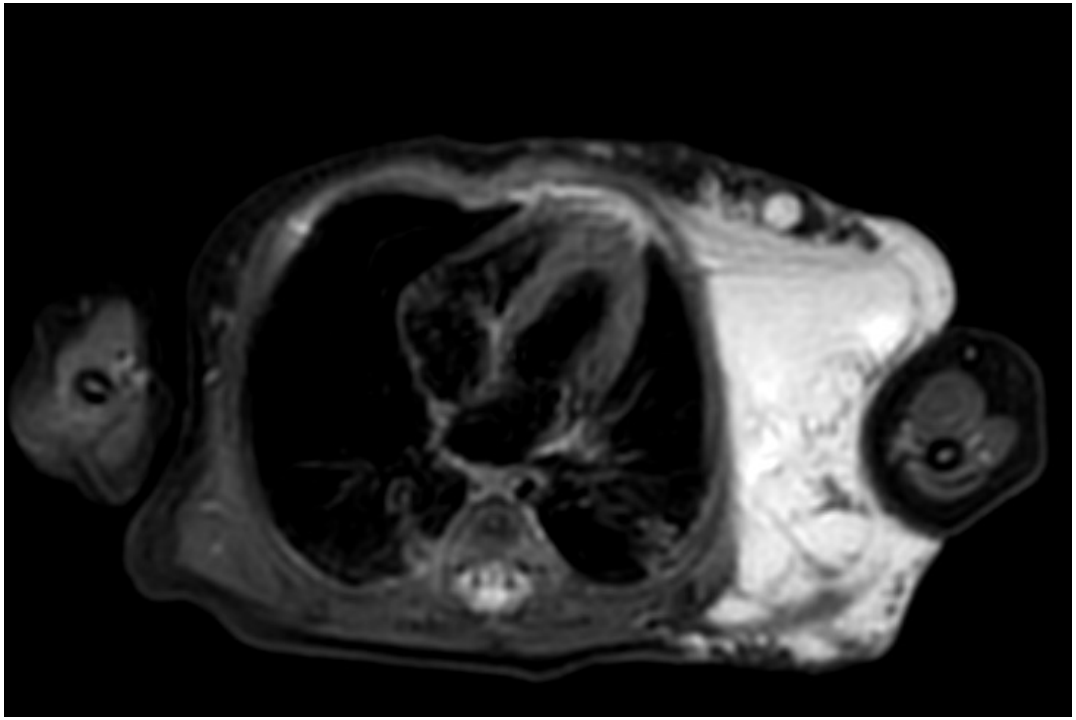






MRI 12/2018



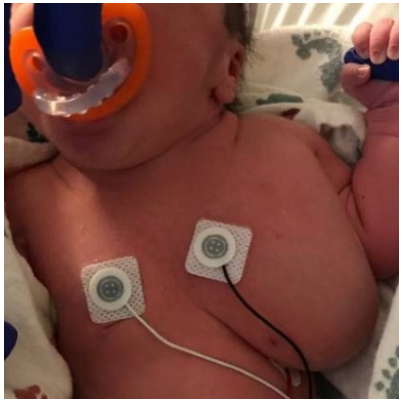


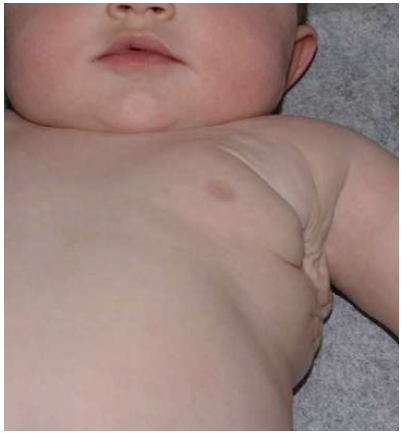
History

Baby girl presented with prenatal diagnosis of macrocystic lymphatic malformation of the left chest and axilla

- Enlarging cyst on 20-week Ultrasound
- Fetal MRI: multi-septated mass, axillary and left thoracic soft tissues
- Birth hx: Cesarean at 39 weeks GA

Symptomatic (mobility) lesion treated with sclerotherapy x 3.



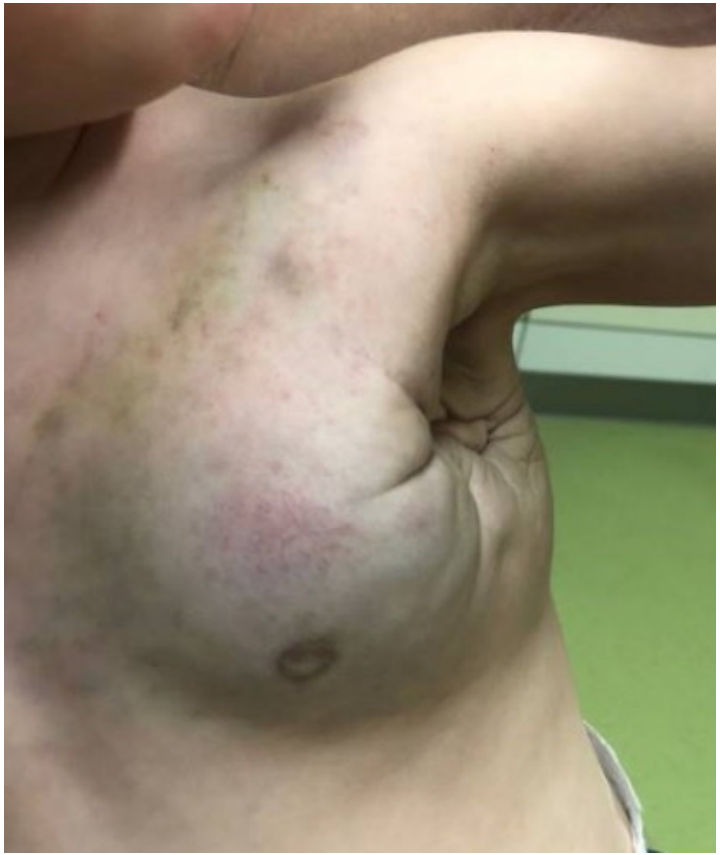


How early should one treat?

History

Follow up at ~ 2 years of age reporting that the malformation took on more bluish hue, concern for venous component, with palpable phleboliths

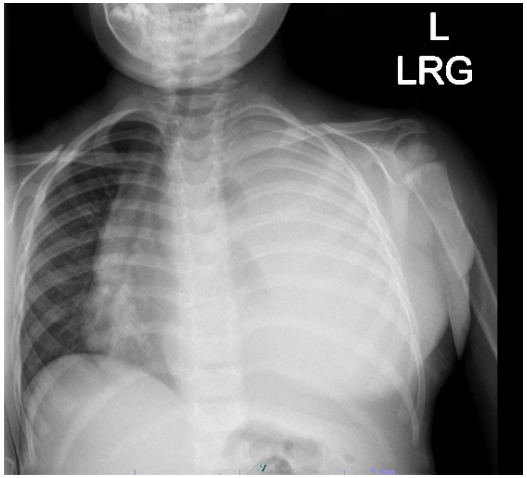
MRI imaging recommended, but not pursued

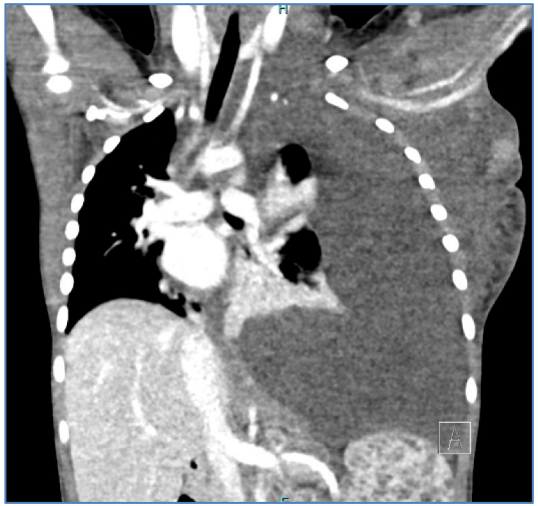


History

Patient acutely presented with increased WOB

- Large left pleural effusion with mediastinal shift
- Admitted with placement of chest tube
- Output confirmed Chylous
- Initiation of complete NPO/TPN

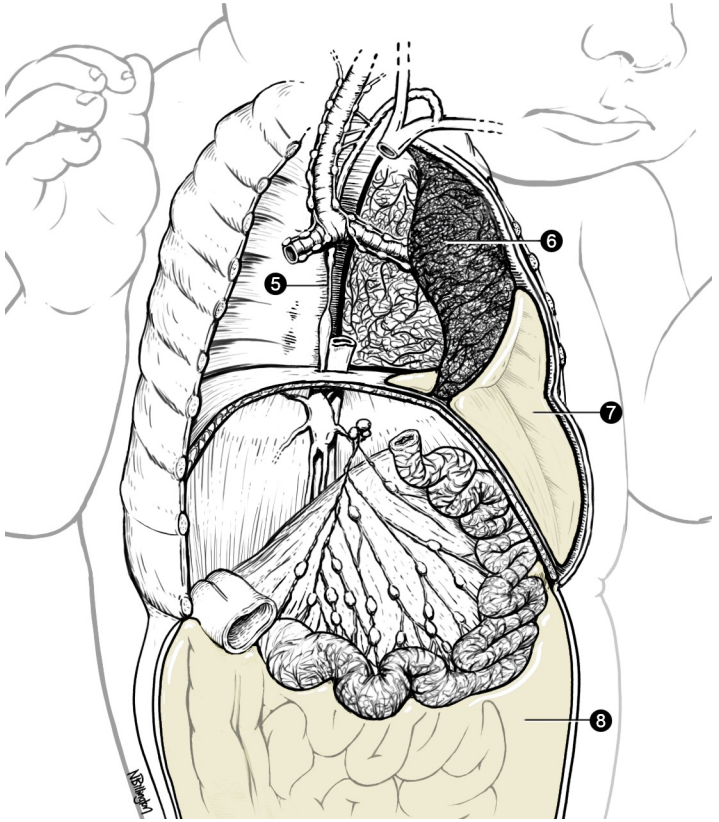




How can lesions evolve over time?

Chylous Effusion or Ascites

Fluid Appearance	Cloudy, milky white to serosanguinous, turbid and thick
Fluid:Serum protein ratio	Fluid should be sent for total protein concentration, Fluid:Serum protein ratio of 0.5 or more
Fluid LDH	Elevated fluid lactic dehydrogenase (LDH) > 160 IU/L
Fat levels (chylomicrons)	Increased Sudan III staining for fat globules, protein analysis demonstrating increased chylomicrons (lipoprotein electrophoregram)
Glucose level	Elevated fluid glucose > 100 mg/dL
Triglycerides	Elevated fluid triglyceride >110 mg/dL associated with lymphatic fluid (< 50 mg/dL inconsistent with lymphatic fluid)
Lymphocytes	Increased lymphocyte cell count, > 50% lymphocytes (ALC of > 500)

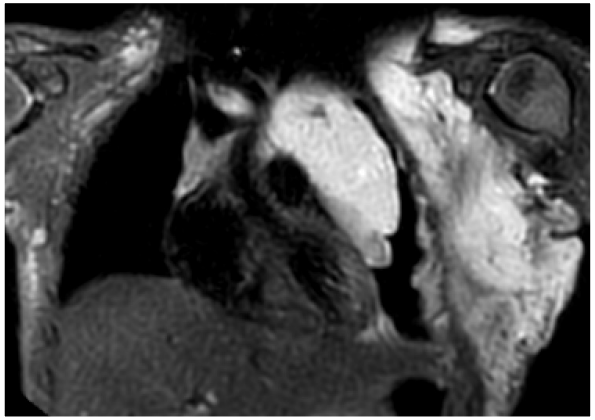


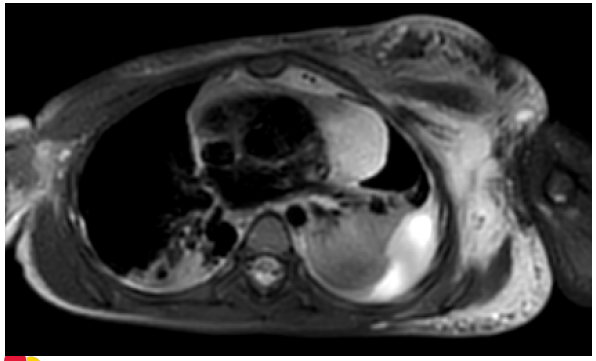
Children's Hospital Colorado
Here, it's different.™

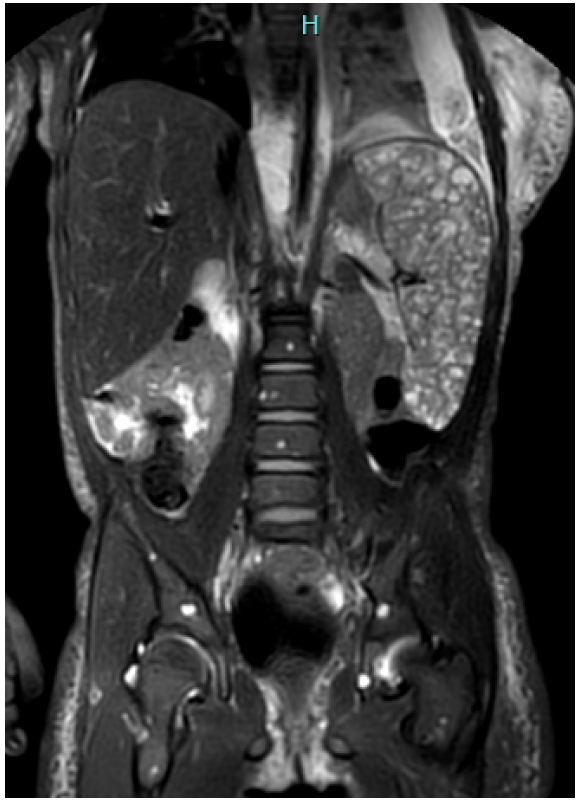
Affiliated with
University of Colorado
Anschutz Medical Campus

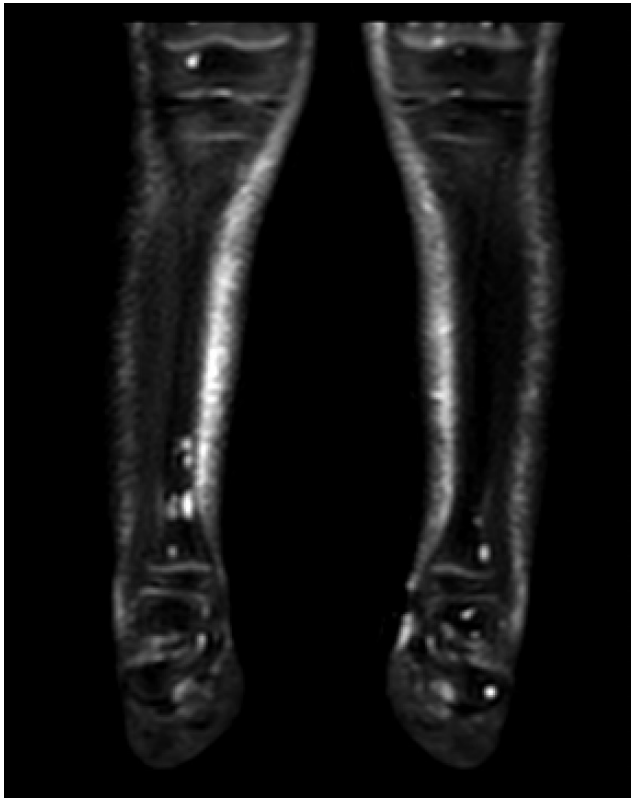
Nakano TA, et al. How We Approach: Congenital Chylous Effusion and Ascites. Pediatric Blood & Cancer. 2021

MRI C/A/P and Total Body MRI









What is the proper diagnosis?

Complex congenital lymphatic anomalies

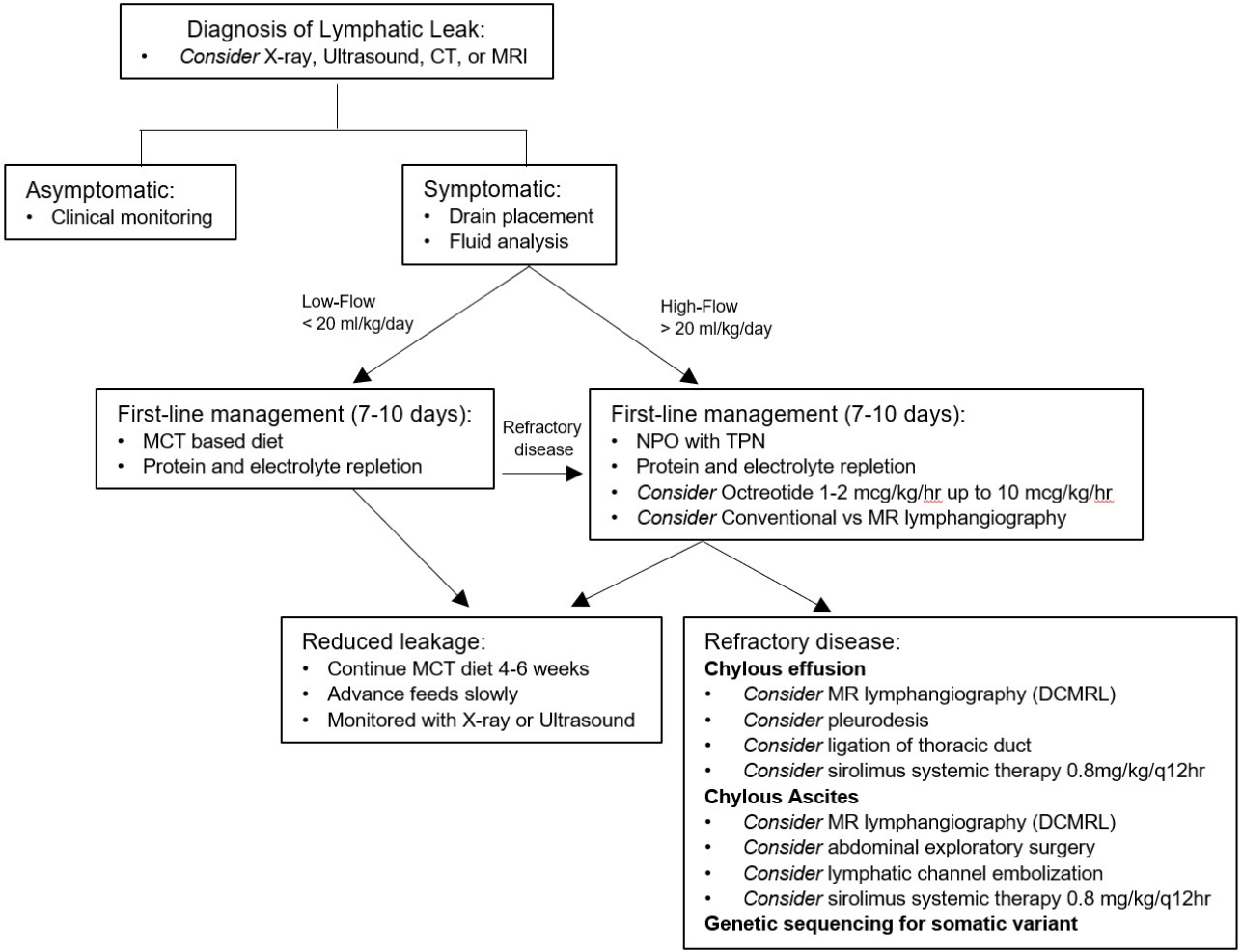
Gorham-Stout Disease (GSD):	A rare complex vascular anomaly syndrome characterized by the infiltration of lymphovascular channels in bone and the surrounding soft tissues.[42] Also referred to as Gorham Stout syndrome, massive osteolysis, or vanishing bone disease, the remarkable feature of this condition is progressive osteolysis and cortical bone destruction without adequate signs of repair. The clinical features can vary greatly depending on the site of disease involvement and is often described as focal vs regional (multiple contiguous bones) involvement.
Generalized Lymphatic Anomaly (GLA)	(Previously referred to as lymphangiomatosis, cystic angiomatosis, generalized cystic lymphangiomatosis) Diffuse or multifocal dilated, cystic lymphatic malformation in association with multifocal bone lytic skip lesions. Bone lesions preserve the cortex, are generally stable and more often associated with the appendicular skeleton. Skin, superficial soft tissue, spleen, intestine, liver, lung can also be involved.
Central Conducting Lymphatic Anomaly (CCLA)	(Previously referred to as lymphangiectasia) Enlarged lymphatic malformations with abnormal structure and function of lymphatic channels with dysmotility of flow and distal obstruction that inhibits adequate clearance of lymph. Obstructed and static flow causes retrograde reflux of lymphatic fluid. Often involves dysfunction at the level of the thoracic duct or cisterna chyli.
Kaposiform Lymphangiomatosis (KLA)	A rare subtype of GLA with predominance of intrathoracic and extrathoracic effusions. Dilated lymphatic channels contribute to dysmotility, stasis, and reflux similar to CCLA. Lymphatic channels can be blood-filled. Effusions more commonly demonstrate frank hemorrhage. Histologic analysis demonstrates clusters of spindle endothelial cells without nuclear atypia; a pattern seen in Kaposiform hemangioendothelioma. The combination of both CCLA features and Kaposiform features results in an aggressive, proliferative complex malformation that manifests as refractory hemorrhagic effusions. Extrathoracic disease can manifest as pericardial effusions, cystic lesions of the spleen, and bone lesions. Bone involvement tends to present as multiple non-contiguous lytic lesions that spare the cortex most often involving the thoracic spine.

Nakano TA, et al. How We Approach: Congenital Chylous Effusion and Ascites. Pediatric Blood & Cancer. 2021

History

High-flow: 3-4L/day output, 12 kg child (250-300 ml/kg/day lymphatic leak)

- Chest-tubes
- Fluid & electrolyte replacement
- Albumin replacement (albumin > 2)
- Complete NPO, on TPN with IL
- Octreotide
- Sirolimus (trough 10-15)
- IVIG replacement (IgG >400 in context of fevers)
- Pain control
- Central line access
- NG placement
- BiPAP support



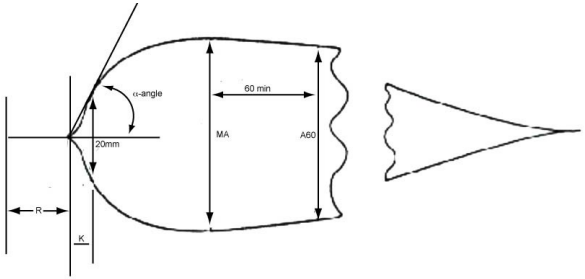
Nakano TA, et al. How We Approach: Congenital Chylous Effusion and Ascites. Pediatric Blood & Cancer. 2021

Acquired Coagulopathy of High-Flow Lymphatic Leak

	NORMAL VALUE	ADMISSION	AFTER 1 WEEK	AFTER 2 WEEKS
Platelet Count	(150,000 – 500,000)	214,000	93,000	263,000
Fibrinogen	(150 – 400 mgs/dL)	136 mgs/dL	124 mgs/dL	241 mgs/dL
D-dimer	< 0.48 mcg/mL	6.8 mcg/mL		2.2 mcg/mL
Von Willebrand Ag	(44 – 144 %)		47 %	88 %
PT	(12 – 15 sec)	17.3 sec	24.7 sec	16.6 sec
INR		1.4	2.2	1.4
PTT	(22-37 sec)	28 sec	68 sec	37 sec
Factor VII	(52 – 120 %)		45 %	53 %
Factor VIII	(58% - 132 %)		50 %	122 %
THROMBOELASTOGRAM				
Reaction Time	(5 – 10 min)		6.3 min	4 min
K-Clot Kinetics	(1 – 3 min)		3.2 min	1.2 min
Alpha Angle	(53 – 72 degree)		53 degree	70 degree
Maximum Amplitude	(50 – 70 mm)		40 mm	62 mm

WEEK 2 INTERVENTIONS:

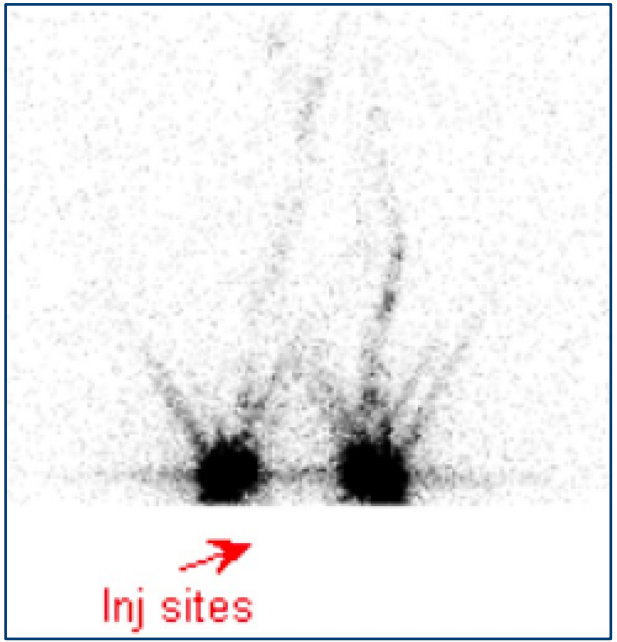
- Continue full medical supportive care
- Lipiodol lymphangiogram
- Cryoprecipitate x 1
- PRBC x 2

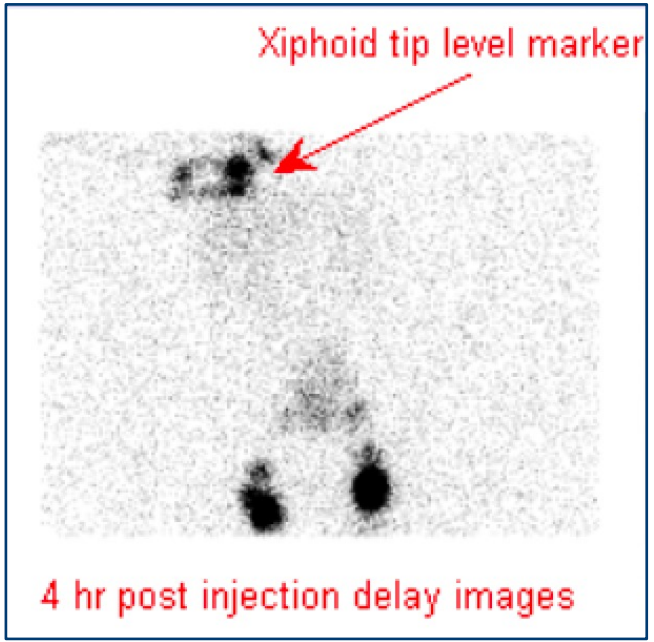


What are our diagnostic imaging options?

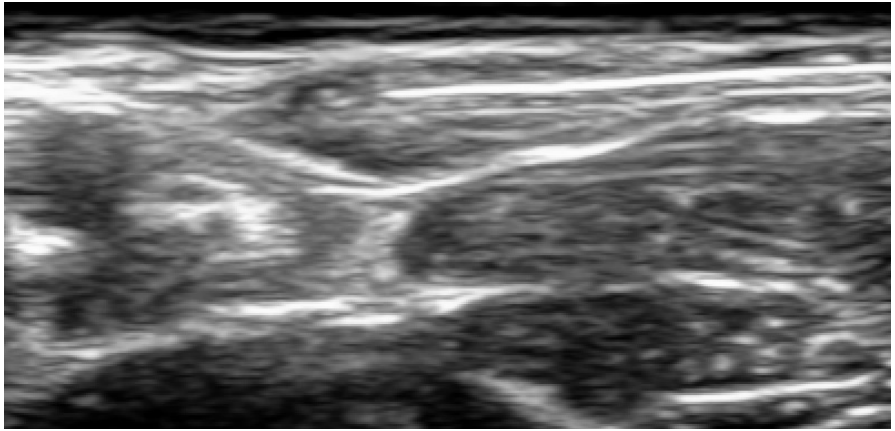
What are our interventional therapeutic options?

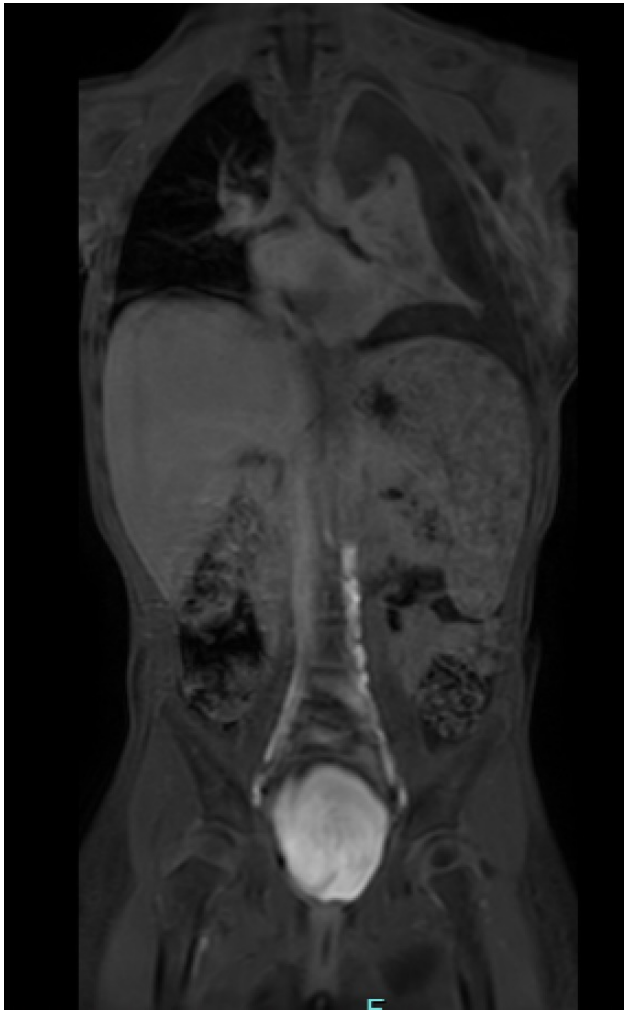
Lymphoscintigraphy (different patient)



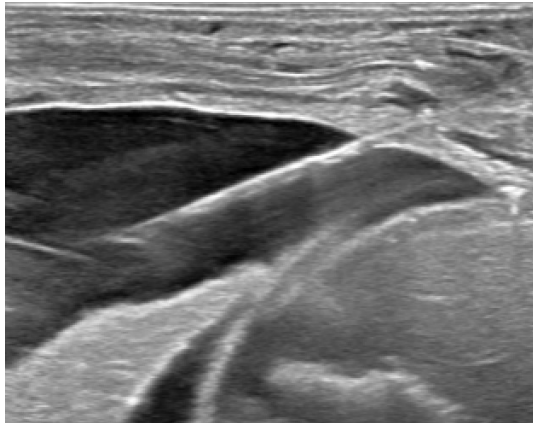


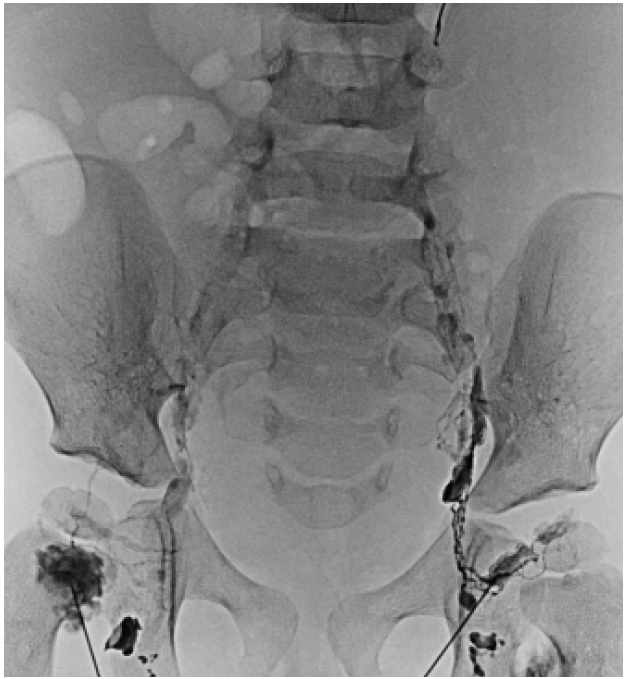
MR Lymphangiogram

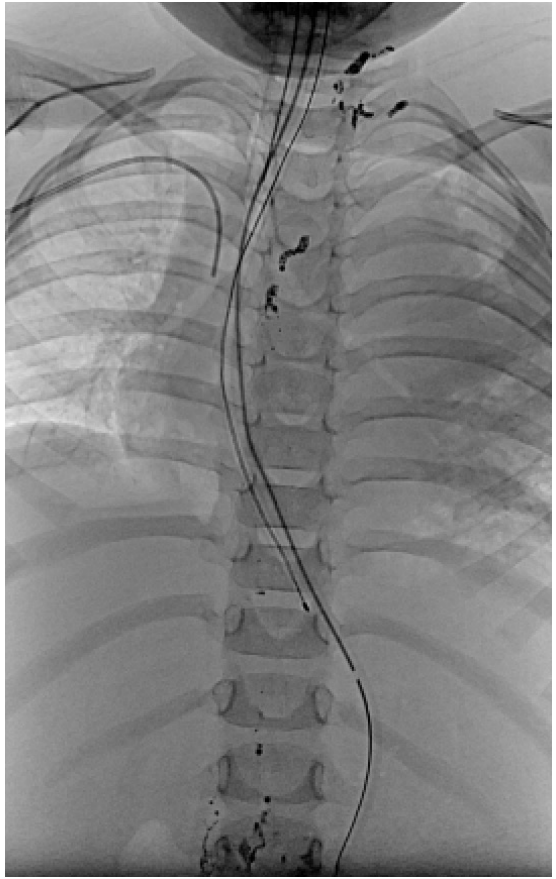




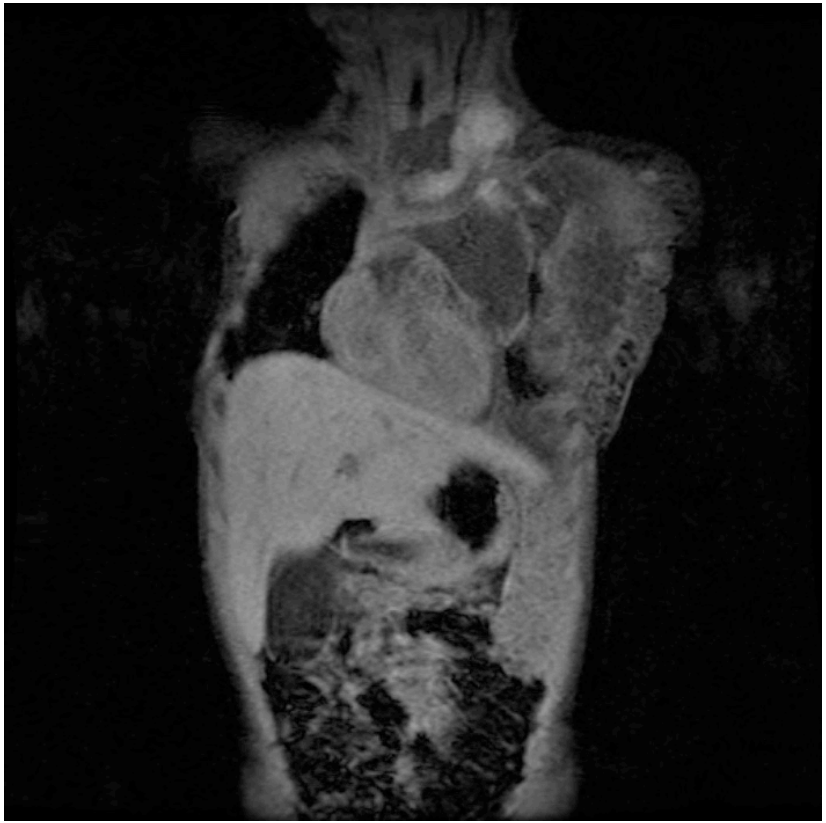
Lipiodol Lymphangiogram

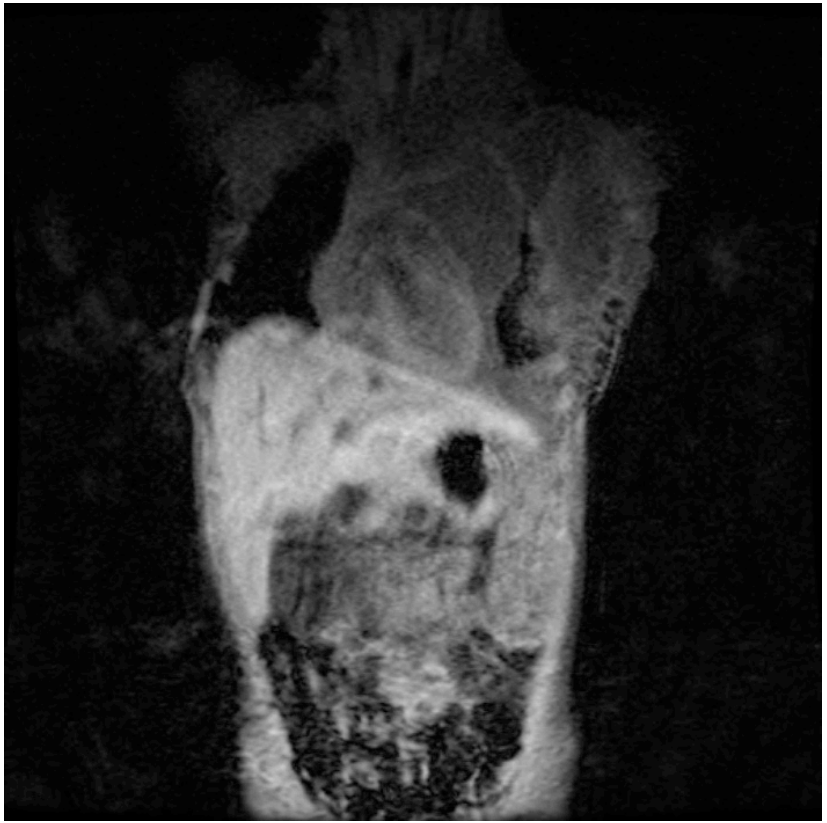


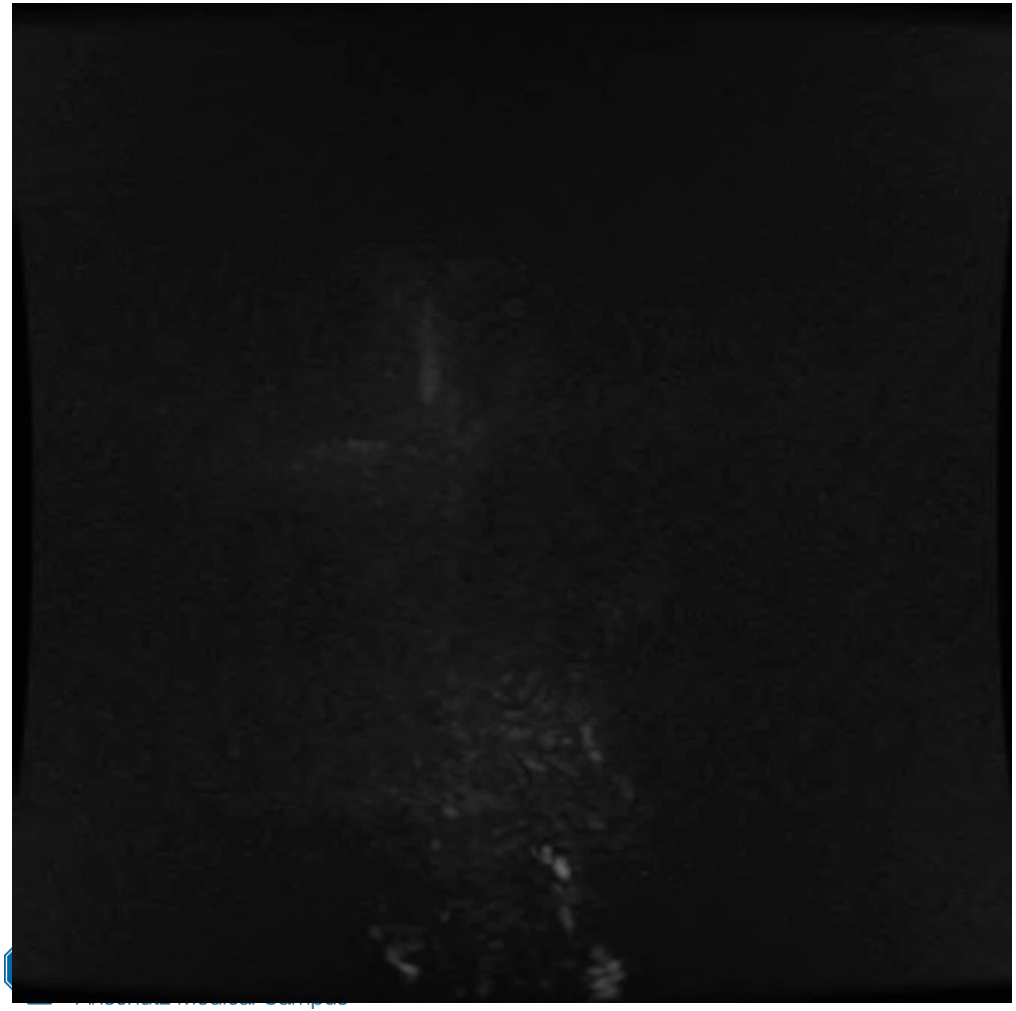




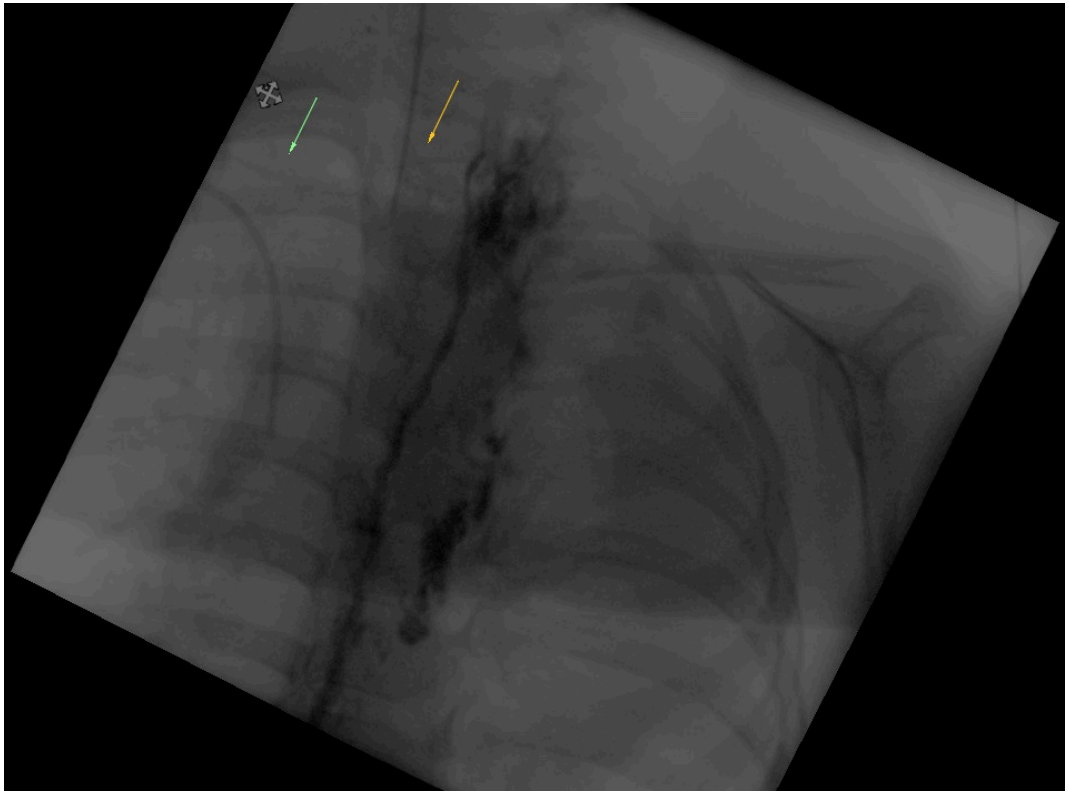
Consultation with Nemours Lymphatics Team

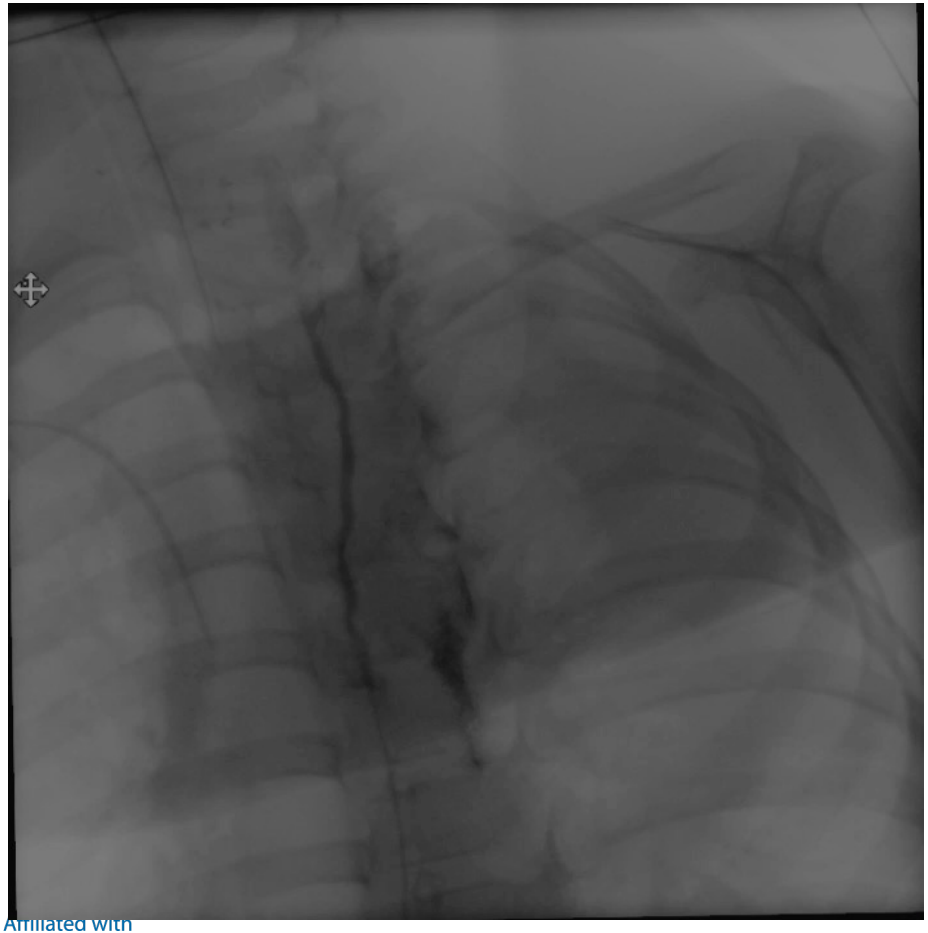


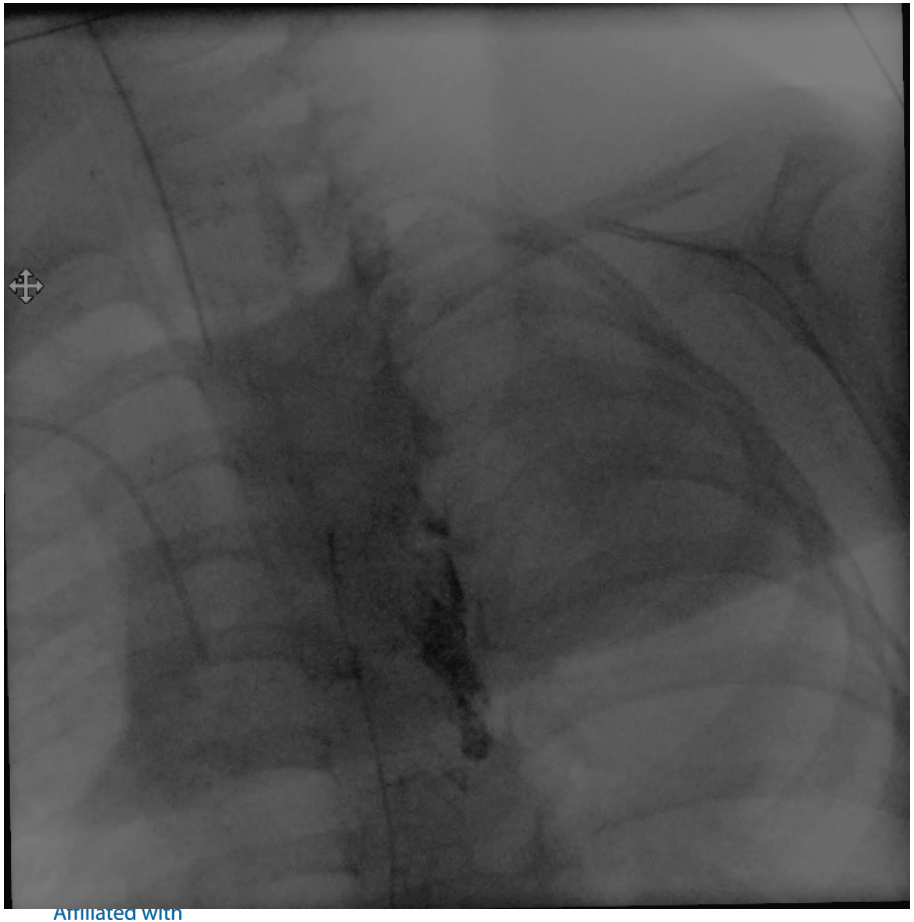




Consultation with Nemours Lymphatics Team







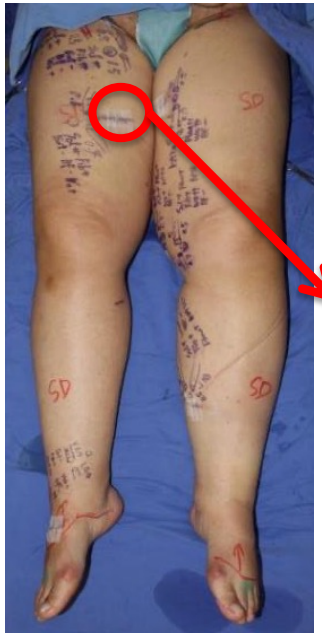
Treatment options

- Medical management
- Interventional
- Surgical

What are our surgical therapeutic options?

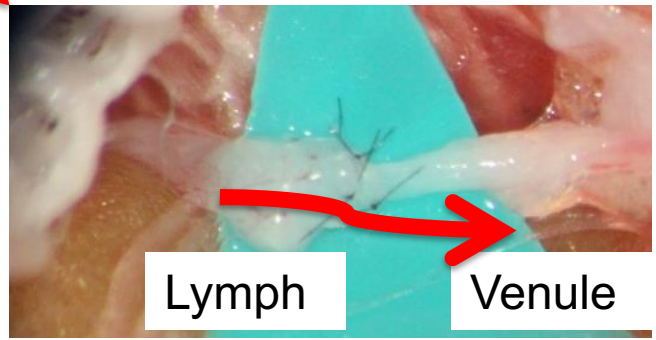
Lymphatic venous anastomosis (LVA) for Lymphatic disorders

Motoi Kato, The University of Tokyo

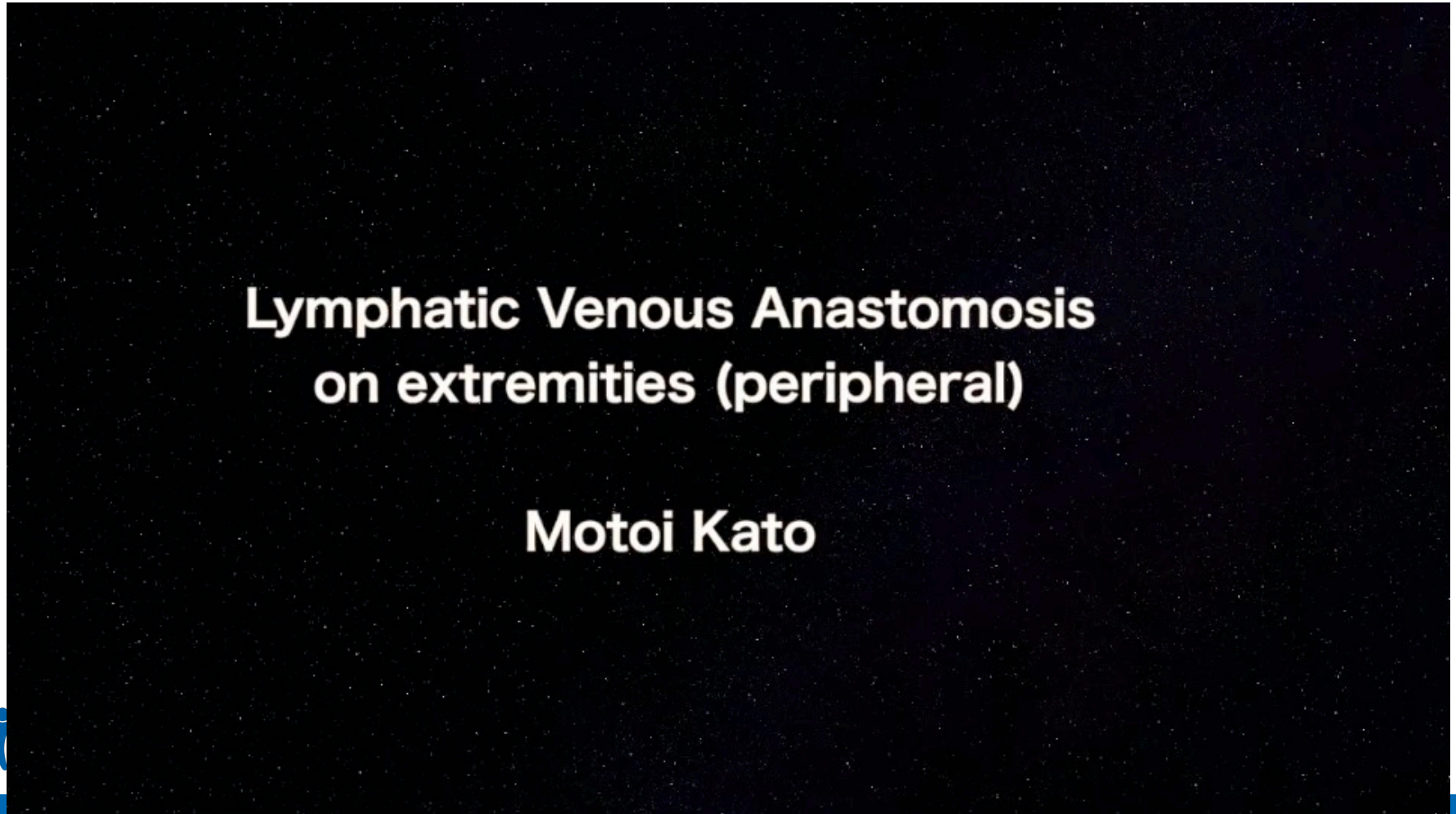


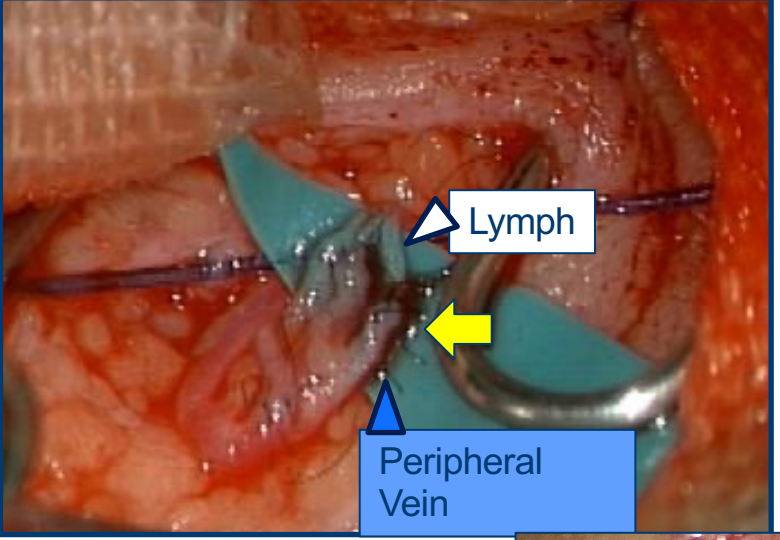
- Anastomosis Lymph to vein
- Minimally invasive：1-2cm skin incision
- Super microsurgery technique required

* **Became popular for lymph edema**

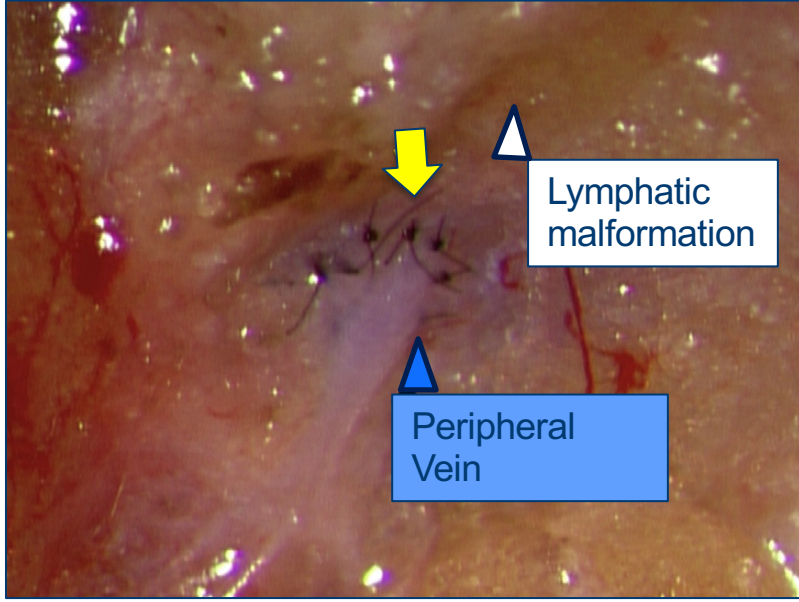


Short video about LVA (peripheral)

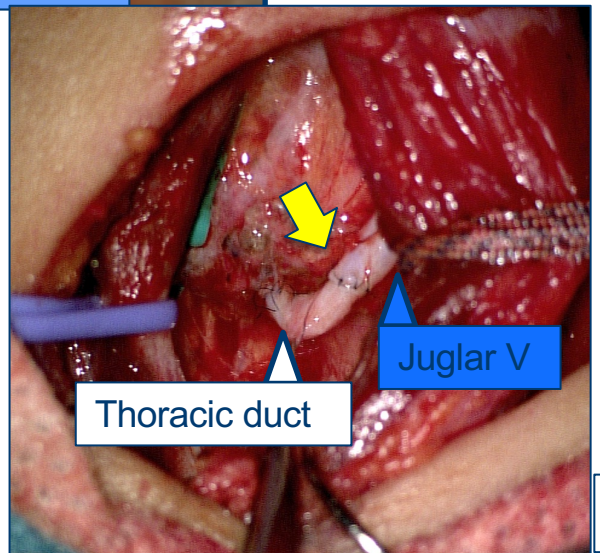




Peripheral LVA



LVA on LM



Cervical LVA

Anastomosis site

Generalized Lymphatic Anomaly (GLA)

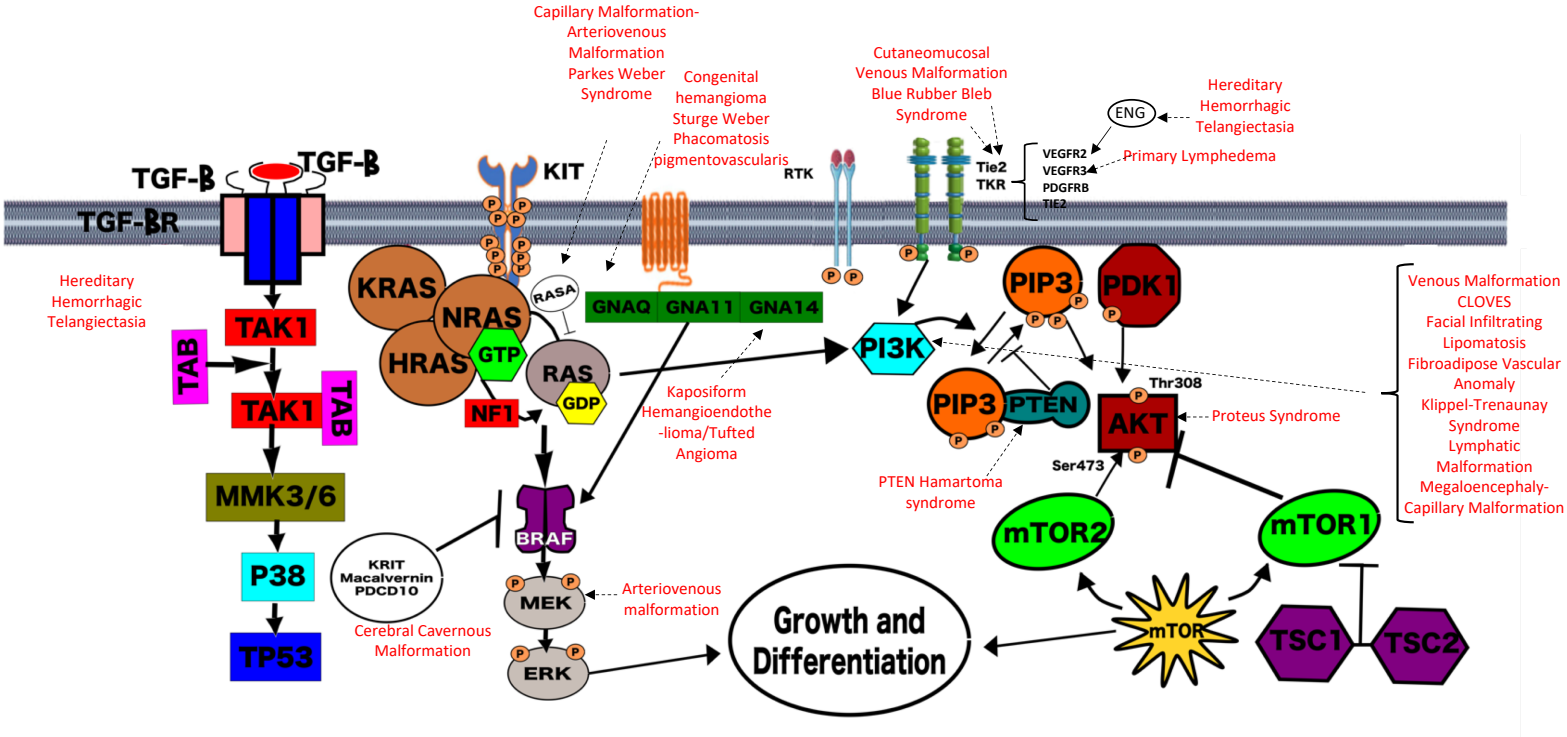
- Historically referred to as lymphangiomatosis

- Abnormal overgrowth of lymphatic vessels
  - Bones
  - Lungs and pleural
  - Soft tissue

Management options

- Sirolimus
- Bisphosphonates
- Trametinib?
- Apelisib?

Figure 1. Genetic Pathways Implicated in Vascular Anomalies



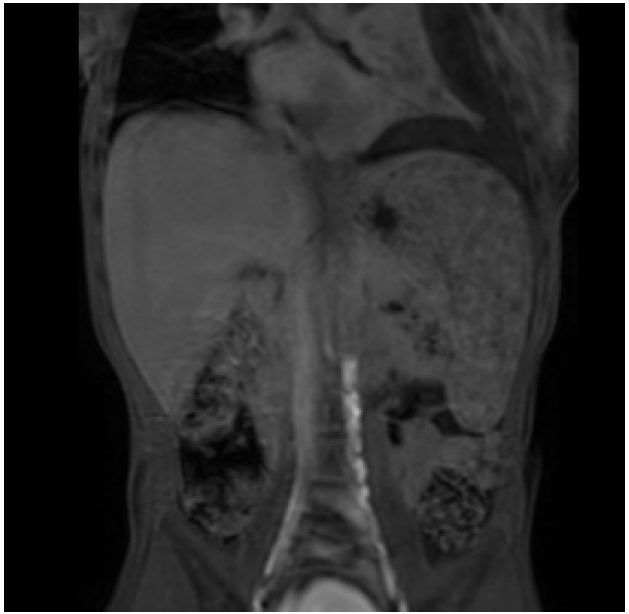
Children's Hospital Colorado
Here, it's different.™

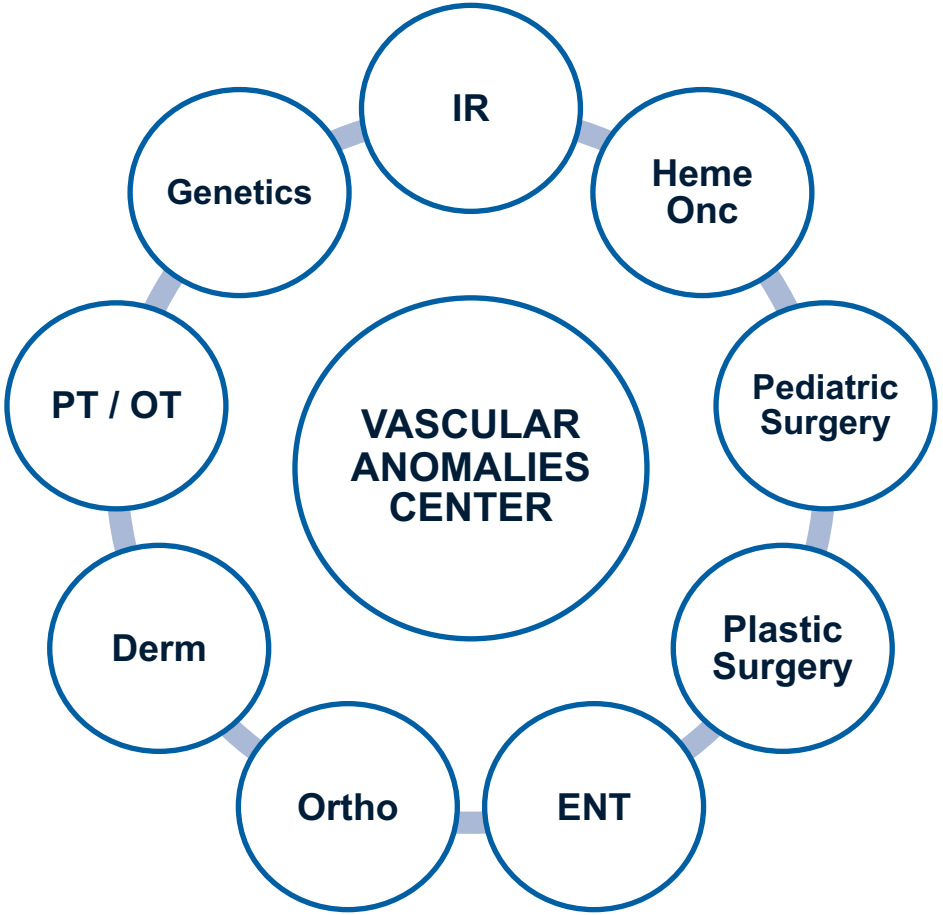
Affiliated with
University of Colorado
Anschutz Medical Campus

Borst AJ, A Primer on a Comprehensive Genetic Approach to Vascular Anomalies. Frontiers in Pediatrics 2020.

Ongoing management

- Medication
  - Sirolimus for GLA disease
- Genetics
  - University of Pennslyvania panel negative
  - Seattle Children's panel negative
  - **Is affected tissue being sent?**
  - **Unidentified mutation?**
  - Consideration of cell free DNA
- Follow-up Imaging
  - MRI total body after 6m sirolimus therapy
  - Timing of repeat lymphatic imaging
- Question about how to manage a painful, enlarged spleen




IR
Heme Onc
Pediatric Surgery
Plastic Surgery
ENT
Ortho
Derm
PT / OT
Genetics
VASCULAR ANOMALIES CENTER

VASCULAR ANOMALIES CENTER

Multidisciplinary Approaches to Vascular Anomalies (MAVA)

An International Web Series

In Partnership with The Hendren Project

Save the date for Winter 2021

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

VASCULAR ANOMALIES CENTER

Multidisciplinary Approaches to Vascular Anomalies (MAVA)

An International Web Series

In Partnership with The Hendren Project

VASCULAR ANOMLIES CENTER

Dermatology
Anna Bruckner, MD
Carla Torres-Zegarra, MD

Ear, Nose, and Throat
Christian Francom, MD
Owen Darr, MD

Hematology-Oncology
Taizo Nakano, MD, Medical Director

Interventional Radiology
Aparna Annam, DO, IR Director
Roger Harned, MD
Patricia Ladd, MD
Vaz Zavaletta, MD
PJ Rochon, MD

Pediatric Surgery
Ann Kulungowski MD, Surgical Director

Plastic Surgery
Leahthan Domeshek, MD
Aaron Mason, MD

Advanced Practice Provider
Becky Hill, MSN, CPNP-PC/AC

Nurse Coordinator
Lauren Larroque, RN, BSN, CPN

Program Coordinator
Anna Brentlinger, BA

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

VASCULAR ANOMALIES CENTER

Multidisciplinary Approaches to Vascular Anomalies (MAVA)

An International Web Series

In Partnership with The Hendren Project

Webinar Administration

Taizo Nakano, MD
Assistant Professor of Pediatrics
Medical Director, Vascular Anomalies Center
Center for Cancer and Blood Disorders
Children's Hospital Colorado
taizo.nakano@childrenscolorado.org

Annie Kulungowski, MD
Associate Professor, Surgery
Surgical Director, Vascular Anomalies Center
Division of Pediatric Surgery, Department of Surgery
Children's Hospital Colorado
ann.kulungowski@childrenscolorado.org

Advanced Practice Provider:
Becky Hill, MSN, CPNP-PC/AC
Lauren.Hill@childrenscolorado.org

Nurse Coordinator:
Lauren Larroque, RN, BSN, CPN
Lauren.Larroque@childrenscolorado.org

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus

VASCULAR ANOMALIES CENTER

Multidisciplinary Approaches to Vascular Anomalies (MAVA)

An International Web Series

In Partnership with The Hendren Project

Please take a moment to take our survey!

Children's Hospital Colorado
Here, it's different.™

Affiliated with
University of Colorado
Anschutz Medical Campus