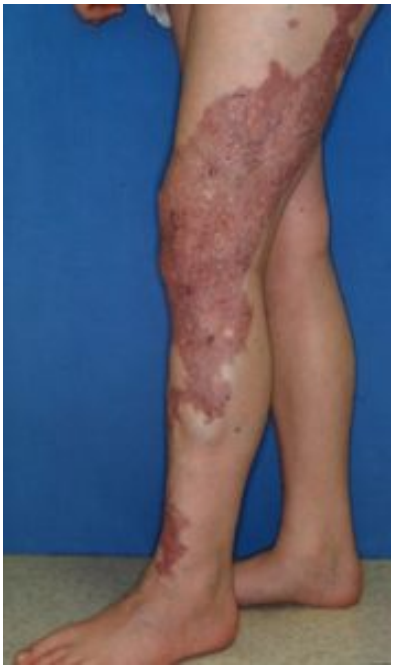
COURSE 02: DIAGNOSIS AND TREATMENT OF KLIPPEL-TRENAUNAY SYNDROME

Dr. Patricia Burrows



Klippel-Trenaunay Syndrome is one of the vascular overgrowth syndromes in which patients have combined capillary, lymphatic, and venous anomalies, usually associated with overgrowth of the affected limb. It most commonly involves the lower extremities, but can also involve the trunk and upper extremities, and can be bilateral. Overgrowth is usually due to either increased subcutaneous fat, or infiltration with lymphatic malformation, in addition to increased length of the extremity involving bony overgrowth. The components of KTS are variable and form a spectrum, from mild to severe and deforming. The type and severity of symptoms are variable and correlates with the vascular anomalies present. Somatic mutations in PIK3 have been identified in patients with KTS. Because of their need for multidisciplinary care, these patients should be managed in a vascular anomalies center.

This module will describe:

- clinical spectrum of features corresponding to the diagnosis of Klippel-Trenaunay Syndrome [capillary lymphatic venous malformation [CLVM] with overgrowth]
- current knowledge regarding etiology of KTS and related vascular overgrowth syndromes
- symptomatology related to the vascular malformation
- appropriate imaging to evaluate KTS, and
- expected findings and treatment guidelines

Objectives

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

- Identify KTS and distinguish it from other vascular overgrowth syndromes
- Describe vascular anomalies present in KTS
- Explain the pathophysiology underlying the symptoms of KTS and their progression
- Locate published information about KTS
- Recognize the complications of KTS
- Choose appropriate treatment, including referral to a vascular anomalies center

KTS

Capillary malformation (CM)

A capillary malformation (CM), often called a port-wine stain, is typically bright or dark red and extends in a patchy or geographic distribution from the waist to the foot. The intensity of the color and the extent of the CM is quite variable. Some patients have only small red areas on the skin. CM is usually asymptomatic, but when combined with lymphatic vesicles, can be associated with sanguinous drainage.

Lymphatic malformation (LM)

Extent and severity of LM is also variable, ranging from a few clusters of cutaneous vesicles to massive tissue swelling due to the presence of microcystic, macrocystic, or combined LM. Microcystic LM often causes the most severe overgrowth and swelling at the level of the foot, but can involve all of the affected tissues. Macrocysts are most often in the pelvis but can be seen in the muscle and subcutaneous fat of the limb as well. When the entire limb is involved, LM often extends from the lower extremity through the ischiorectal space into the pelvis. Cutaneous vesicles may be clear or blood-filled. When associated with hypertensive underlying veins, bleeding from vesicles can be significant. Vesicles, especially in the perineal region, are major portals for cellulitis, which can progress rapidly to life-threatening sepsis.

…Venous anomalies

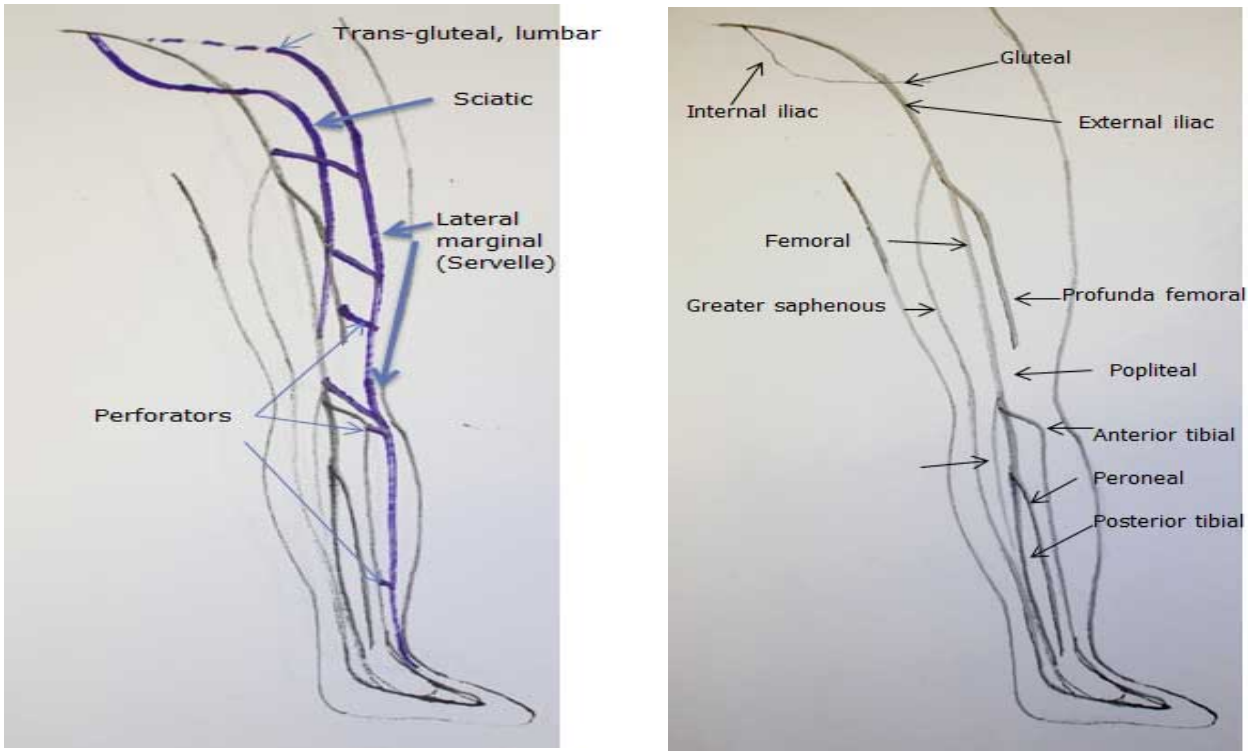
Anomalies of the conducting veins are typical of KTS and follow some well-defined patterns. Typically, patients have dilated anomalous subcutaneous veins thought to be remnants of the fetal marginal venous system. Patterns of distribution are well described. Usually, the veins extend from the lateral margin of the foot to the knee or hip. They often communicate with deep veins at the level of the knee, thigh, or pelvis. In the thigh and pelvis, they frequently follow patterns described as persistent sciatic veins.

Anastomoses with intrafascial veins occur at many levels, from the lesser saphenous or anterior tibial veins below the knee to proximal popliteal or deep femoral veins, or to gluteal and lumbar veins. Typically, the anomalous channels, especially the marginal veins, are valveless, leading to severe venous insufficiency. Over time, the subcutaneous veins elongate and become large and tortuous, forming a reservoir for thrombi and pulmonary emboli. Unfortunately, there is an inverse relationship between the size of the anomalous superficial veins and the size of the femoral veins in KTS.

While deep veins can always be identified, they can be threadlike and interrupted. The femoral vein is most often interrupted. In this case, most of the flow from the distal lower extremity is through the anomalous marginal system as well as sciatic and other anomalous intrafascial veins. This flow pattern may contribute to underdevelopment of the deep veins. In addition to anomalous veins in the lower extremities, patients with KTS may have intra-abdominal venous anomalies, especially involving the portal system. This contributes to rectal bleeding, which can be severe and may result in portal vein thrombosis.

Venous anatomy of the lower extremities

Normal (left) and lateral marginal vein with potential anastomoses with deep veins (right)



KTS

Differential diagnosis

Other vascular overgrowth syndromes include the following:

- Parks-Weber Syndrome: diffuse AVM of the extremity with overgrowth, often associated with multiple capillary malformations due to RASA1 mutation.
- CM with venous enlargement and tissue overgrowth: similar to mild KTS without a lymphatic component: venous anomalies are usually less severe and often involve the greater saphenous distribution.
- CLOVE Syndrome: congenital lipomatous overgrowth with vascular anomalies and ectodermal dysplasia caused by germline *PIK3CA* mutations and associated with severe progressive tissue overgrowth, progressive lymphatic and venous malformations, massive enlargement of truncal veins, and spinal AVMs. Acral (sandal foot deformity) and renal anomalies as well as increased incidence of malignant tumors may occur. For more information, please see: http://rarediseases.org/rare-diseases/cloves-syndrome/ and http://www.clovessyndrome.org/research-and-genetics
- PTEN tumor hamartoma Syndrome: germline PTEN mutations lead to macrocephaly, autism spectrum, ectodermal dysplasia, hamartomas, and multifocal AVMs, as well as increased potential for tumors. http://www.ncbi.nlm.nih.gov/books/NBK1488/

Progression

Symptoms correlate with the type and severity of vascular anomalies present and include:

- Limb length discrepancy and tissue overgrowth, causing difficulties with ambulation and secondary orthopedic problems such as scoliosis and arthritis.
- Venous insufficiency, leading to painful varicosities, venous hypertension with distal limb pigmentation, ulceration and bleeding, syncope due to orthostatic hypotension, thromboembolism, abdominal/pelvic venous insufficiency causing rectal varices, G.I. bleeding and portal vein thrombosis.
- Lymphedema, with fluid leakage, repeated cellulitis, and sepsis which lead to progressive fibrosis in the soft tissues, contributing to pain and difficulty with ambulation.

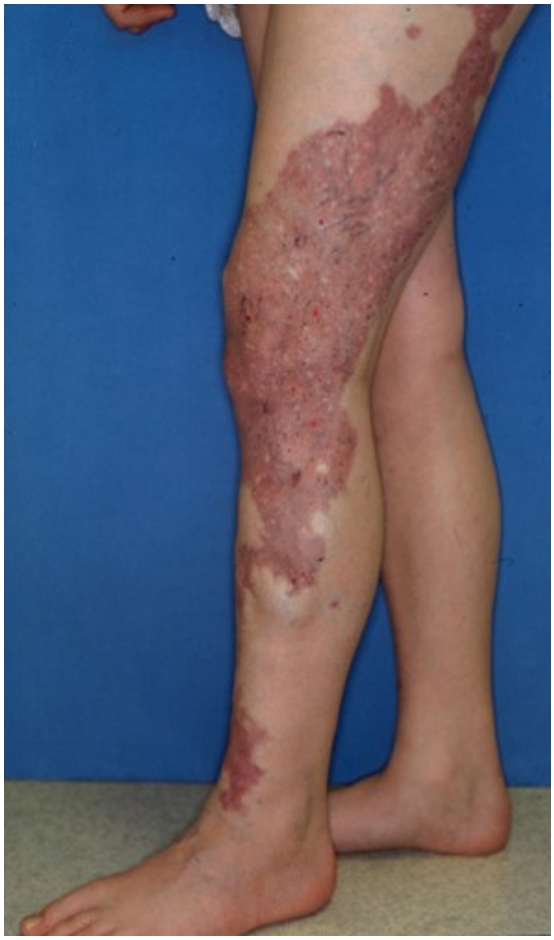
Imaging evaluation

- MRI with time-resolved, contrast-enhanced MR angiography from pelvis to foot is the best way to evaluate the vascular anomalies and overgrowth. Typical findings are expansion of the subcutaneous tissues due to fatty overgrowth and anomalous veins, especially in the lateral subcutaneous plane but also intramuscular. Lymphatic malformation, often extending into the pelvis, can involve the retroperitoneal tissues and spleen. Hypoplasia of the deep veins can occur at any level, but most commonly in the calf and thigh. Iliac veins can be dilated. Hemorrhoidal and portal veins may be dilated or thrombosed.
- Orthopedic radiographs are useful to follow leg length discrepancy, and typically show elongation on the affected limb without significant deformity.
- Ultrasonography is useful to evaluate superficial veins, especially in the context of thrombophlebitis

KTS treatment

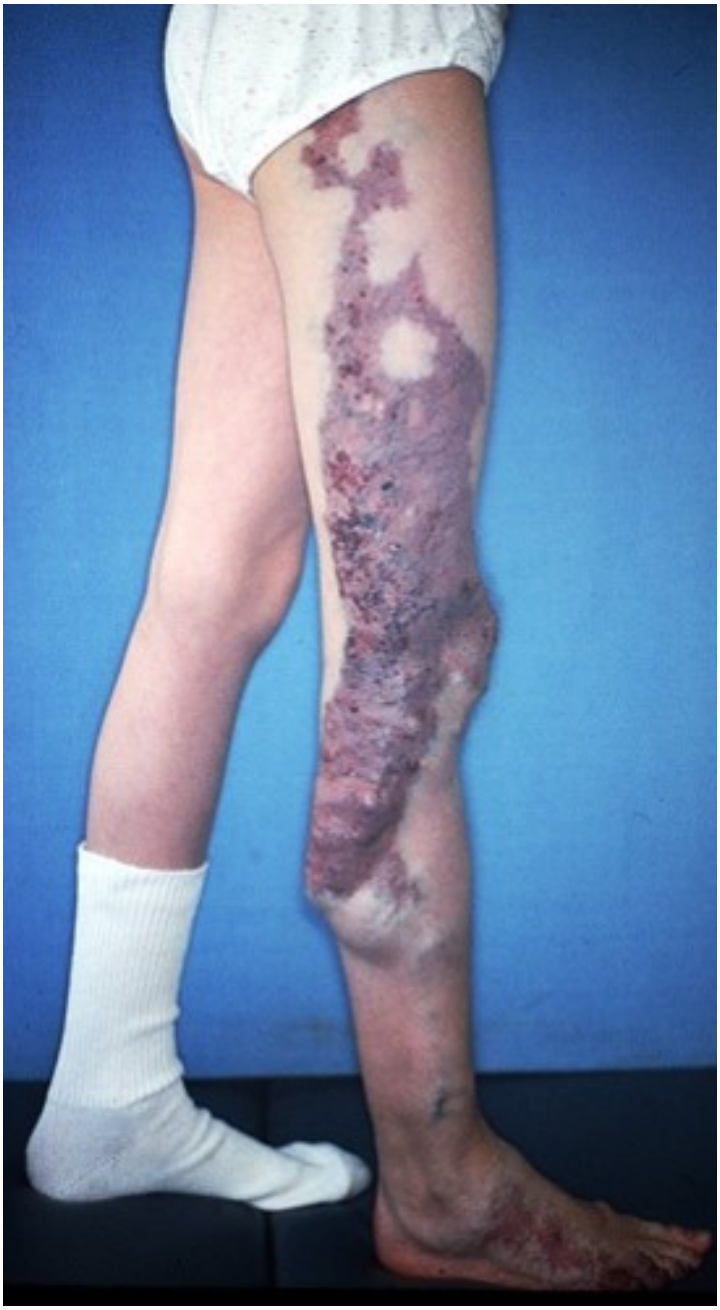
- Treatment guidelines are published by the K-T support group at https://k-t.org/resources/guidelines
- Venous insufficiency is treated with compression garments and patient education to minimize trauma and avoid infection.
- Thrombophlebitis and/ or pulmonary thromboembolic disease must be managed by hematologists, often with lifelong anticoagulation.
- Invasive treatment of venous insufficiency (stripping, resection, or endovascular ablation of superficial anomalous veins) should only be carried out by physicians within a multidisciplinary vascular anomalies group, after careful evaluation of venous anatomy and trial of noninvasive treatment.
- Lymphedema is managed with compression, lymphedema therapy, and careful hygiene. In the presence of recurrent cellulitis, intermittent prophylactic antibiotic is often considered. Sup¯erficial CO2, diode or Yag laser, or sclerotherapy may be helpful in decreasing the fluid leakage or bleeding from vesicles. Certified lymphedema therapists and pediatric dermatologists are consulted for these issues.
- Leg length discrepancy is managed by pediatric orthopedic surgery within a vascular anomalies program. Epiphysiodesis is often needed to minimize the final leg length difference. Secondary problems such as scoliosis and joint problems also need care.
- Severe tissue overgrowth may require staged surgical debulking, but this must be done by experienced surgeons in vascular anomalies centers.
- Pharmacologic treatment using sirolimus may be helpful in minimizing lymphatic fluid leakage, decreasing swelling due to lymphedema and improving the related pain.

KTS with severe venous hypertension, pain, and cutaneous bleeding



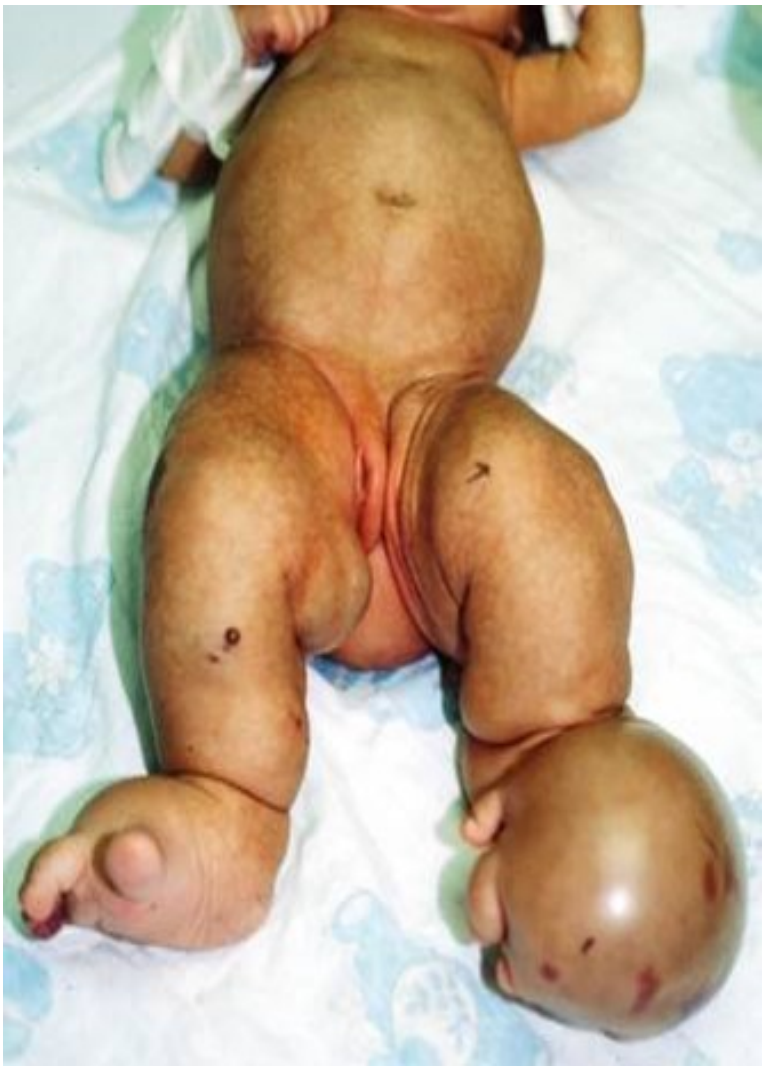
- Female presented at puberty with increasing pain, varicosities, and severe bleeding from vesicles.
- Endovenous ablation of the subcutaneous varicosities was carried out, with sclerotherapy of vesicles. Bleeding improved, but patient developed progressive swelling and severe pain, limiting activity.
- Note the typical overgrowth, cutaneous capillary malformation, dark-colored vesicles, and subcutaneous varicosities.

KTS with severe venous anomalies



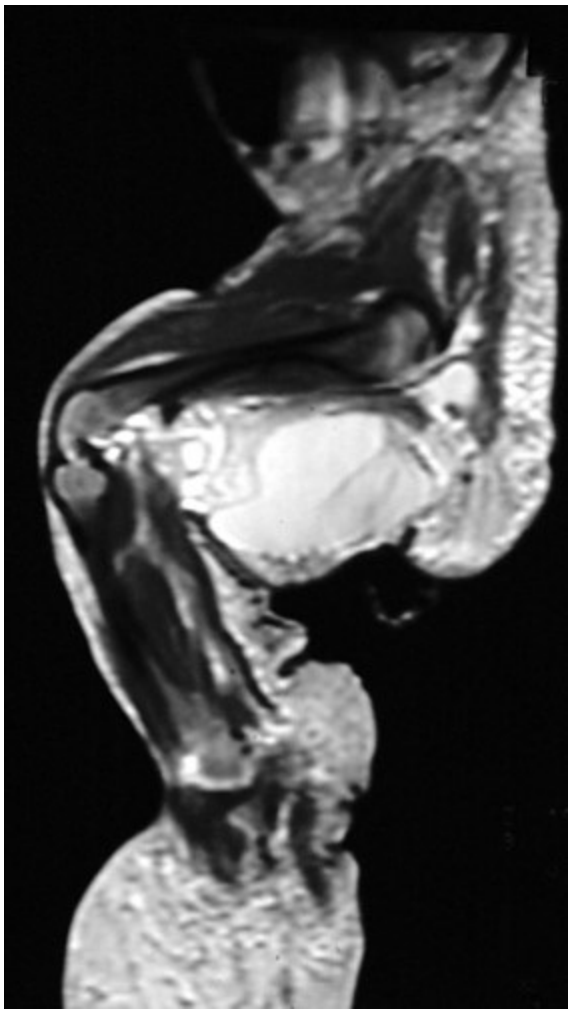
Severe venous insufficiency of the lower extremity, rectal bleeding, massive recurrent pulmonary emboli. Management included compression, resection and ablation of superficial and competent veins, IVC filter, lifelong anticoagulation, embolization of hemorrhoidal varicosities, and pulmonary thrombectomy. The patient is functioning well and working as a professional.

KTS: bilateral

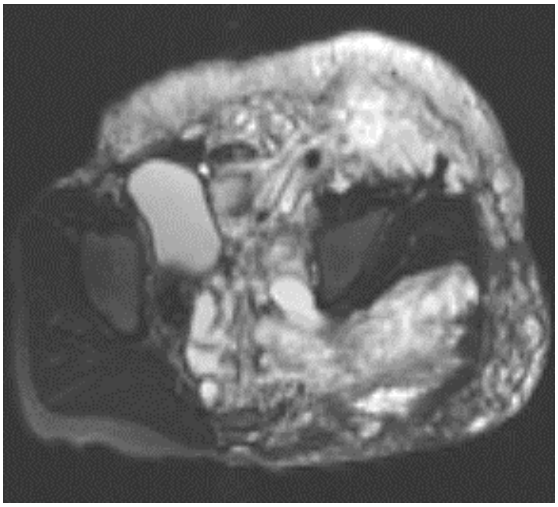


Bilateral CLVM with massive swelling of the foot due to microcystic LM. This patient would likely require a type of amputation and ambulate with a prosthesis.

KTS:imaging



T2-weighted MRI shows extensive lymphatic malformation in the lower extremity and pelvis.



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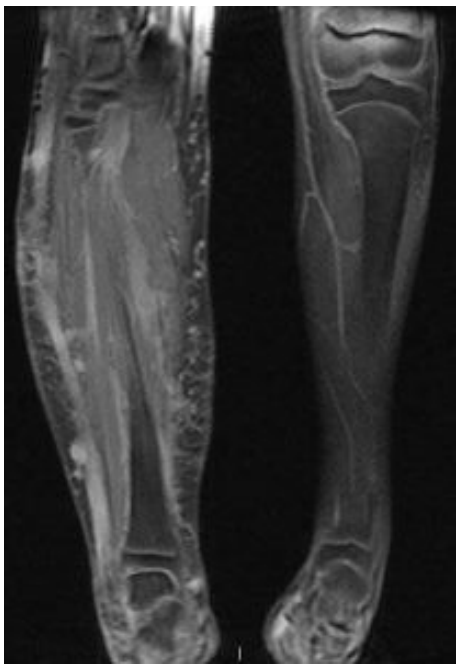
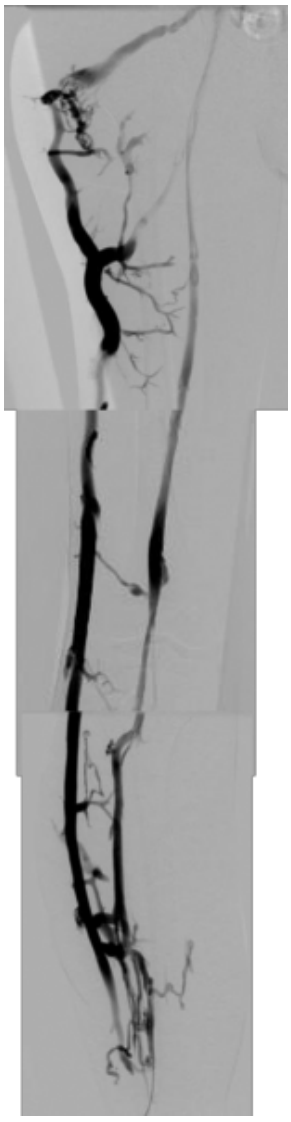


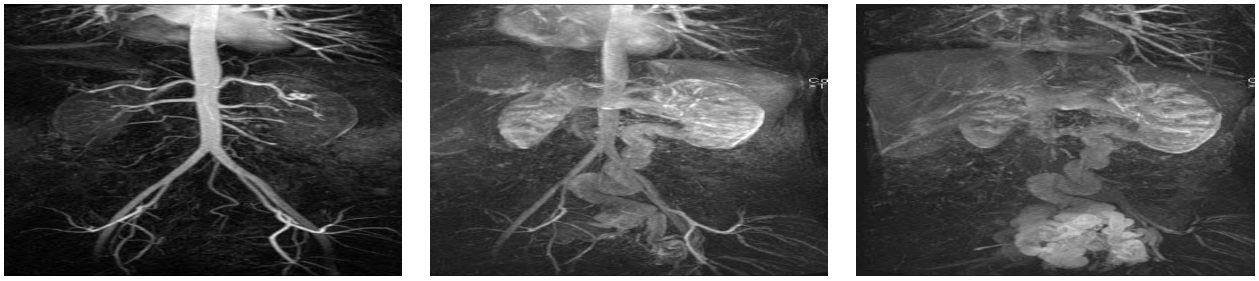
Coronal T1-weighted MRI with contrast and fat suppression shows dilated marginal vein in the lateral subcutaneous fat of the calf.



Ascending pedal venogram shows large, valveless marginal vein to gluteal vein, and relatively normal deep veins.

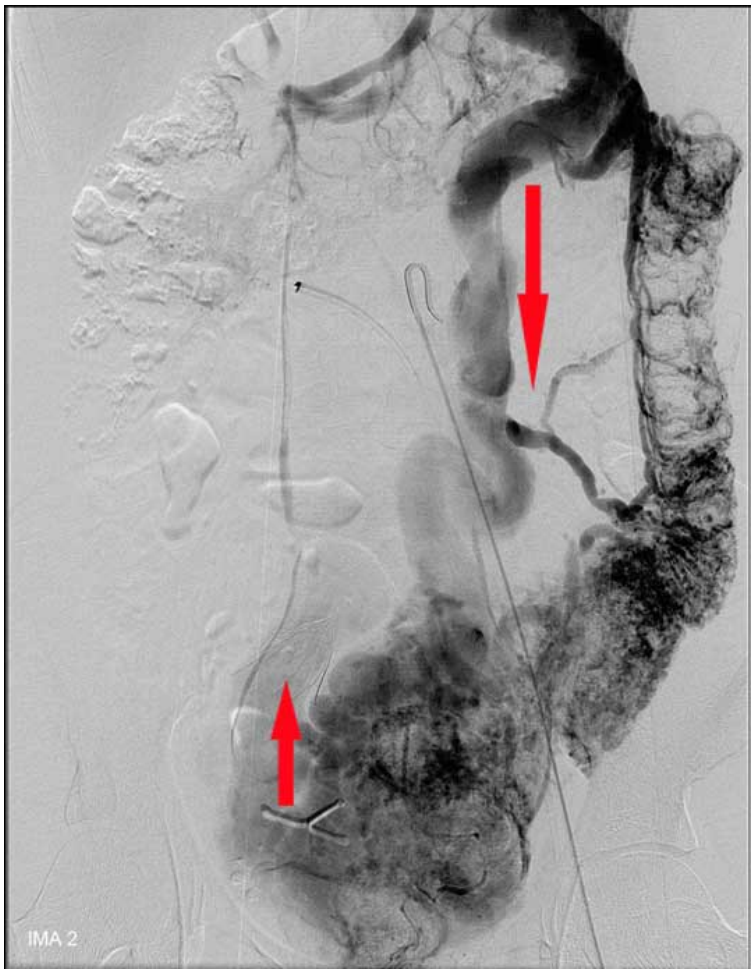
More imaging

Dysplastic, incompetent inferior mesenteric vein with rectal varices in a patient with KTS, rectal bleeding and pulmonary emboli, shown by dynamic contrast-enhanced MRA.



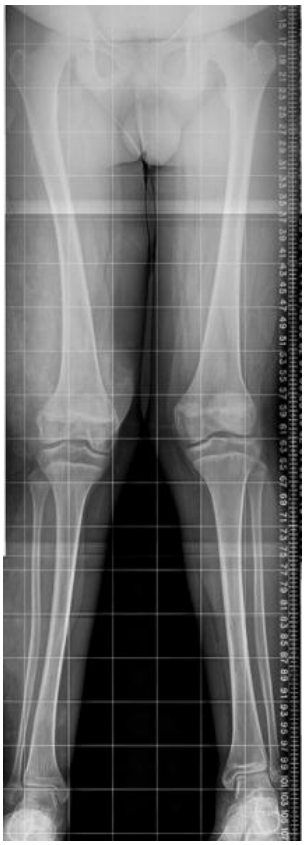
More imaging

Inferior mesenteric angiogram, venous phase. Arrows show direction of blood flow. Up arrow is in right iliac vein.



Case study 1

15-year old male with CLVM, overgrowth RLE, pain worse with standing, walking, bleeding from vesicles. Improved with compression.



Scanogram shows mild LLD.

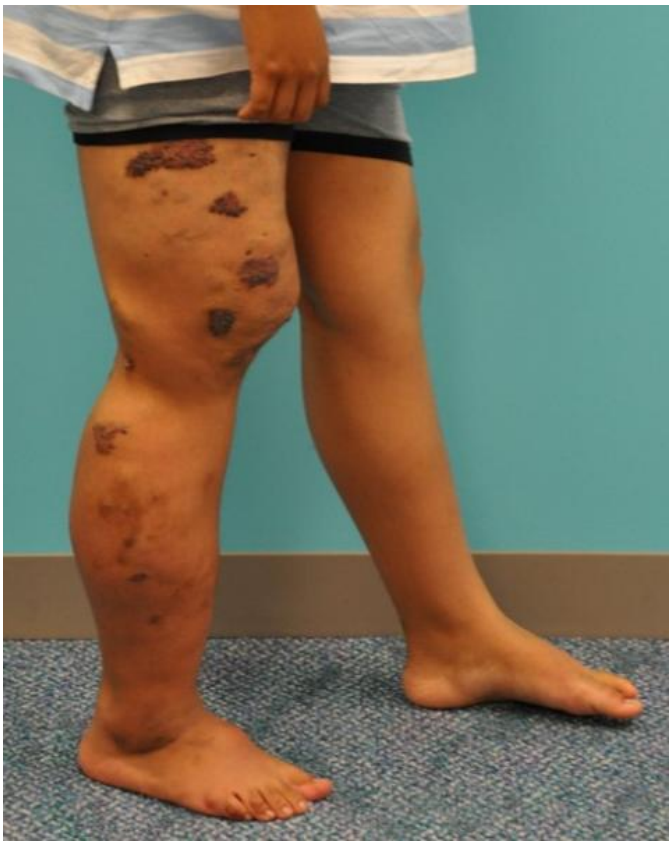
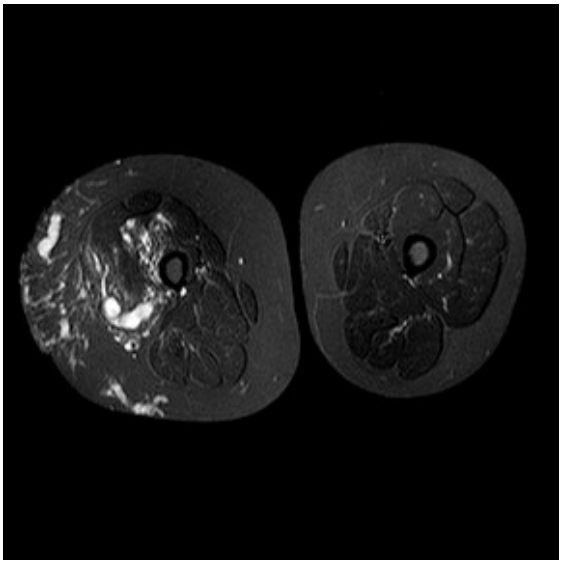


Photo shows overgrowth, varicosities, vesicles.



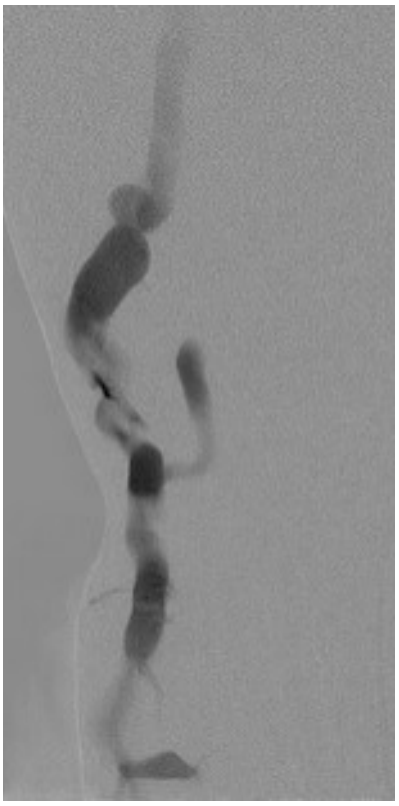
T2-weighted MRI shows anomalous veins, increased fat, muscle atrophy.

Case study 1

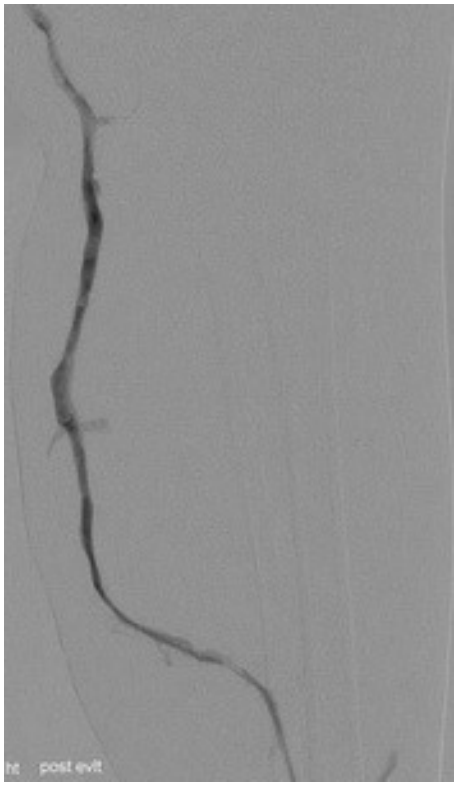
Endovascular procedure

Ascending pedal venogram before treatment shows preferential flow in large tortuous marginal vein.

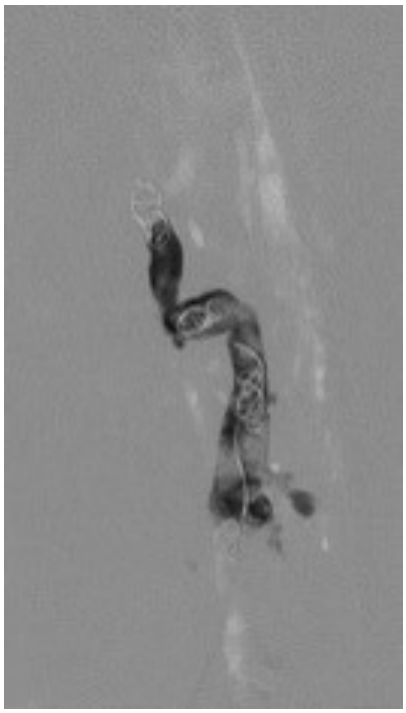
…Ascending posterior tibial venogram shows adequate deep veins.



Marginal vein prior to endovenous laser.



Marginal vein after endovenous laser.

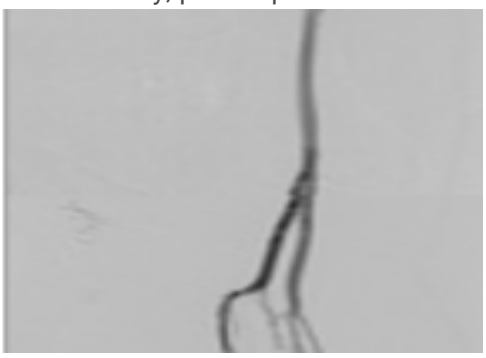


Additional varicosities embolized with coils, NBCA glue, and STS foam.

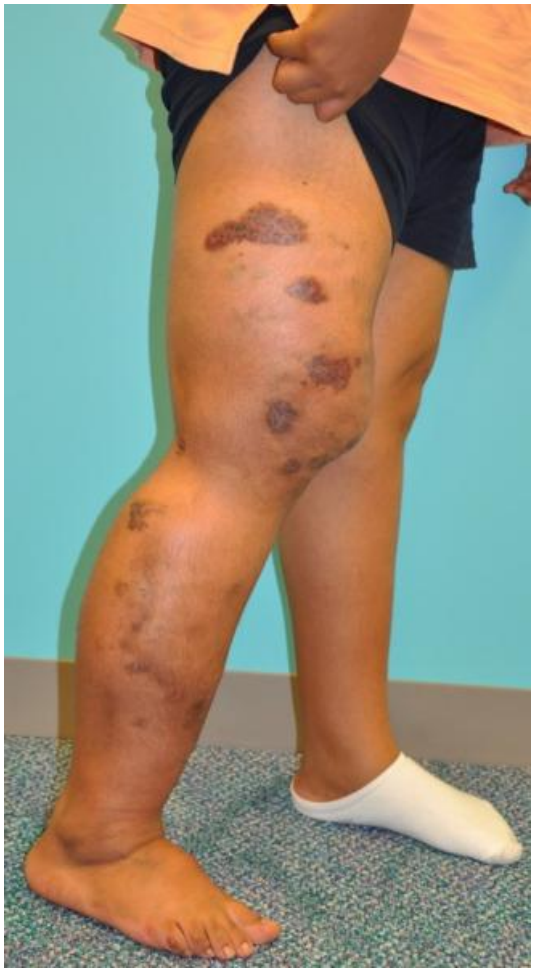
Case study 1

Post-endovascular treatment

After recovery, pain improved with standing and walking.



Ascending pedal venogram after percutaneous and trans-catheter ablation of the large, tortuous marginal veins shows competent deep veins.



4 weeks after the procedure. Bruising over the marginal vein from laser ablation; note flattening of vesicles after surface laser treatment.

Case study 1

Discussion

This patient has appropriate anatomy to justify ablation or removal of the marginal vein. The deep veins are anatomically normal but underfilled due to preferential flow to the anomalous superficial veins. The patient would be expected to benefit from the elimination of the anomalous veins by having decreased pain from venous insufficiency and decreased risk of thromboembolism.

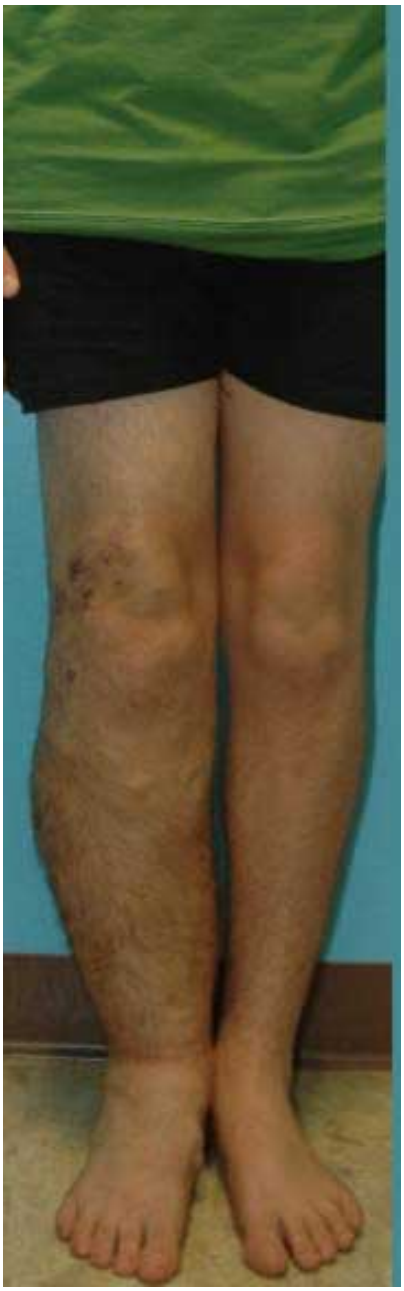
Clinic-based, ultrasound-guided sclerotherapy would be both ineffective (due to the large size of the channels) and risky
(because of communications between the superficial veins and the deep veins).

Pulsed dye laser is usually inadequate to treat the vesicles. CO2 laser or bare laser fiber used for endovenous ablation is more effective.

Surgical vein stripping and resection of diseased skin are feasible and appropriate, but may require a longer recovery.

Case study 2

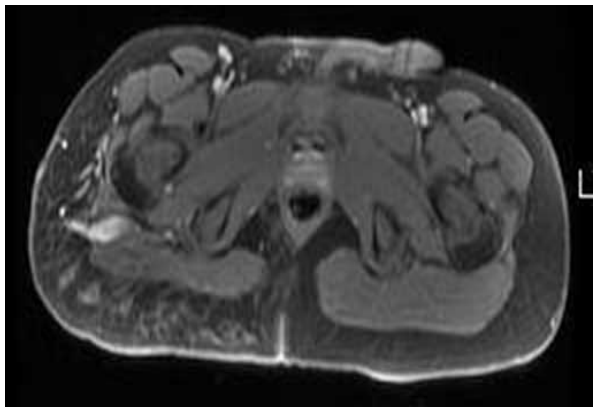
- 15 year-old boy with CLVM
- Bleeding from vesicles
- Swelling of calf
- Pain worse on dependency

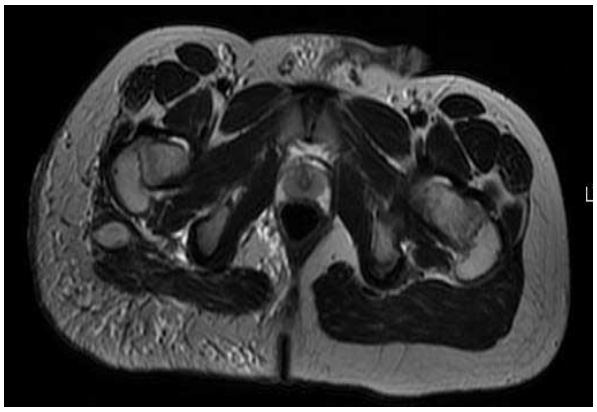


Causes of pain in KTS:

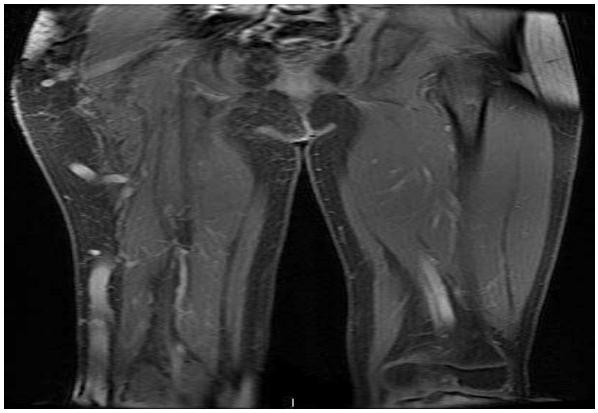
- Venous anomalies
  < Engorgement, thrombophlebitis
- Lymphatic cysts
  < Hemorrhage, infection
- Lymphedema
  < Heaviness, cellulitis
- Primary neuronal anomalies

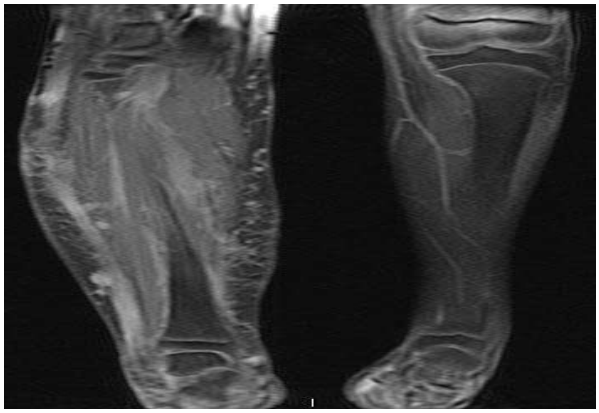
Case study 2: imaging



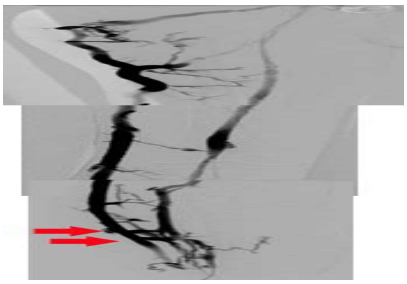


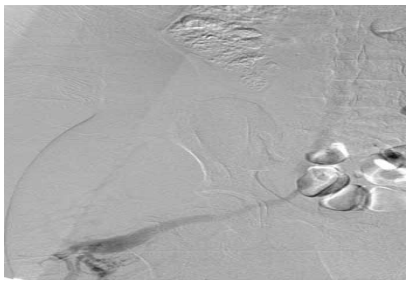
VENOUS ANOMALIES

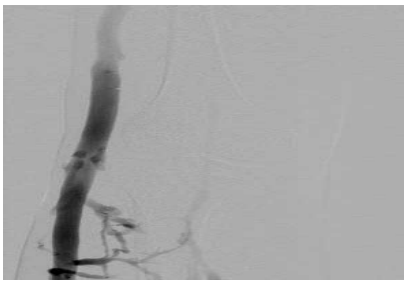




Case study 2: Marginal vein

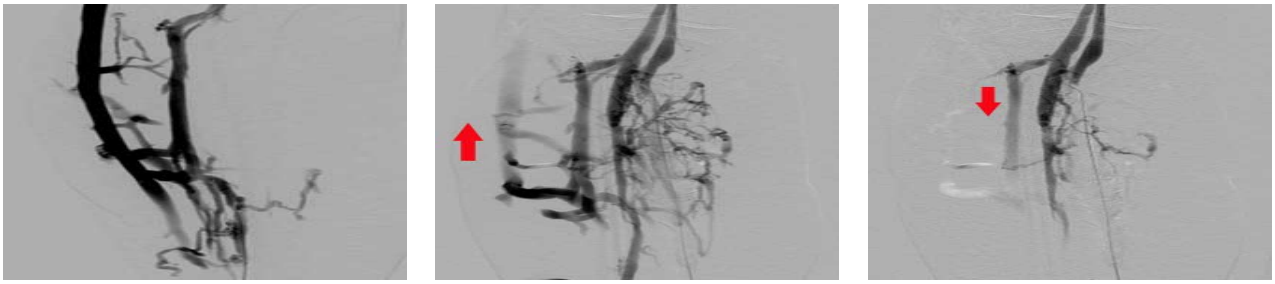




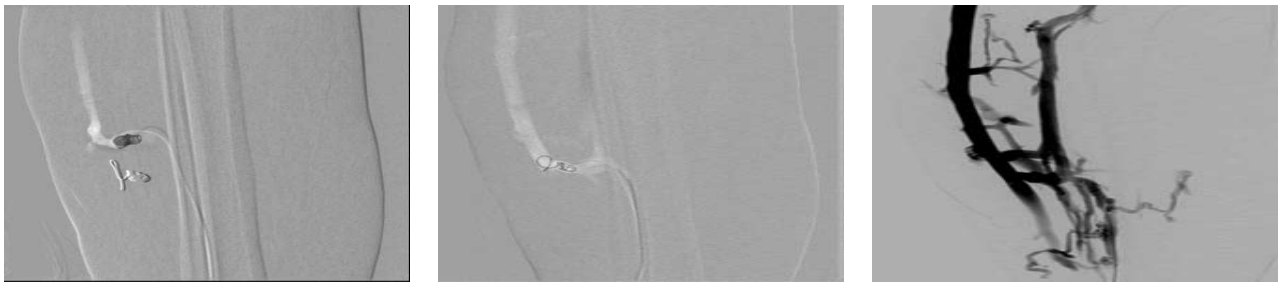


Anterior tibial venography shows marginal vein from foot to buttock, with large perforators (arrows) and patent deep veins.

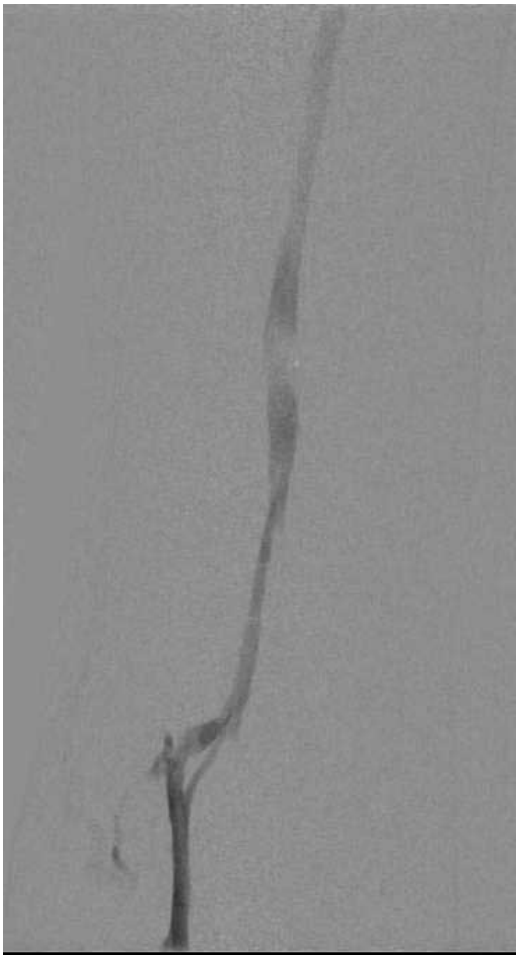
Posterior tibial vein



Embolization of incompetent perforators



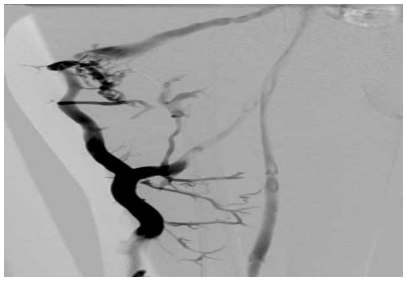
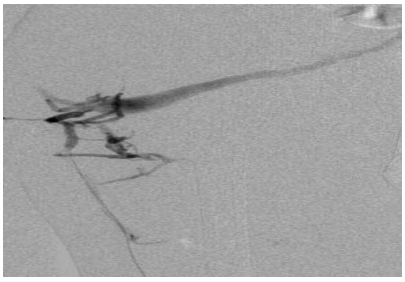
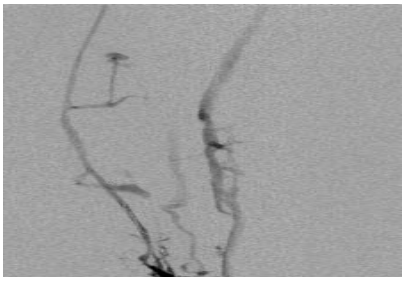
Deep veins after embolization



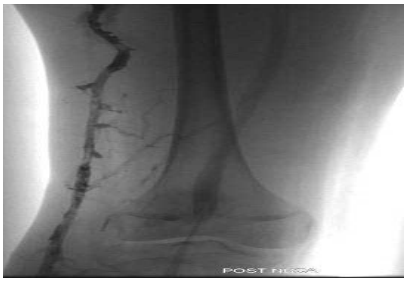
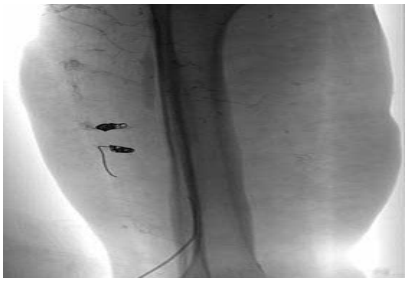
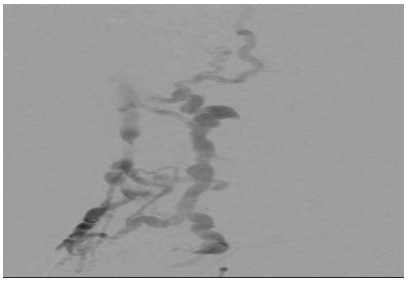
EVLT of marginal vein

Endovenous Laser Therapy of the Marginal Vein (MV), usually done after coil or glue embolization of the proximal extent to protect against pulmonary emboli. If the marginal vein is not occluded after laser, it is injected with foam or glue.

Left: Marginal vein before laser
Middle: Catheter in proximal MV
Right: Narrowed MV after laser

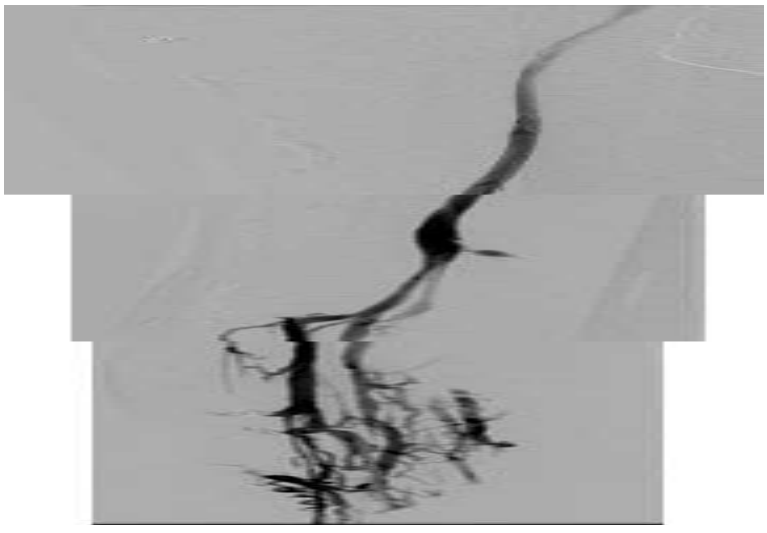




After coils, EVLT, and embolization

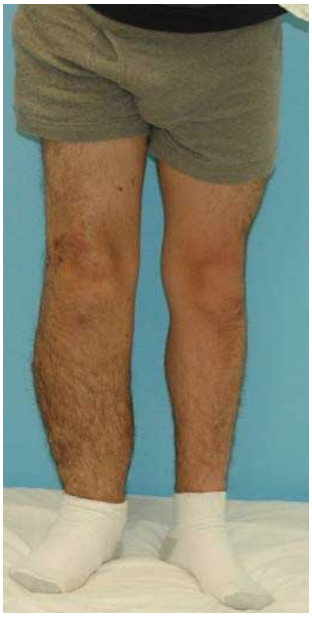




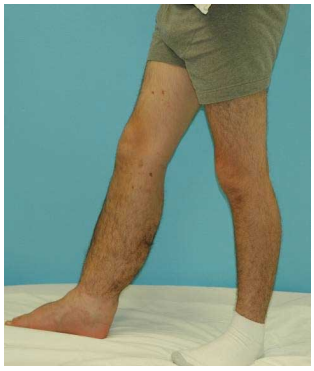
Post-occlusion

Post-occlusion anterior tibial venogram shows intact deep venous system without reflux.

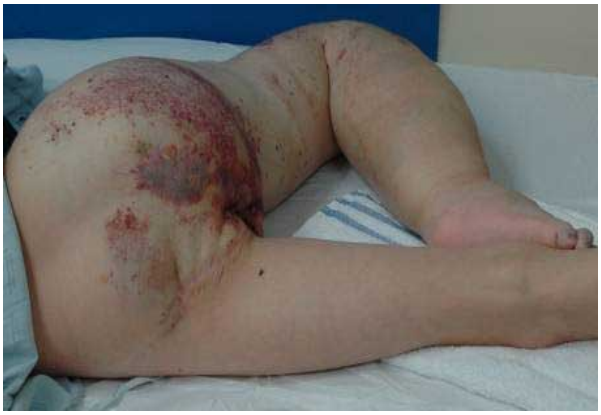


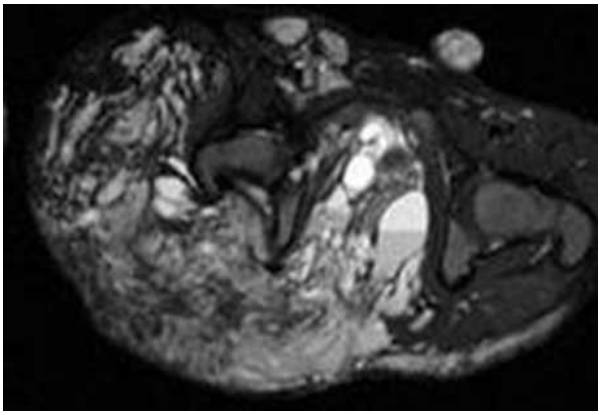
After venous ablation

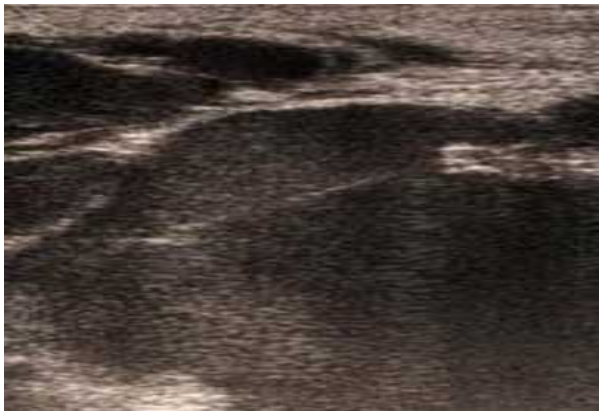


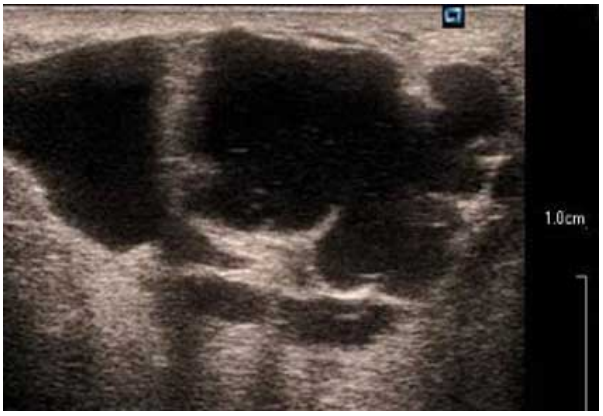


>KTS post debulking, severe bleeding from LM



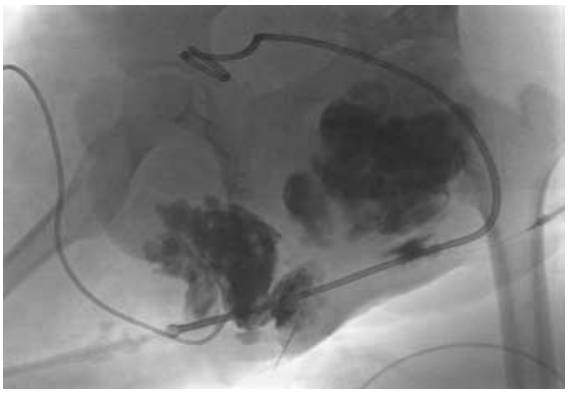


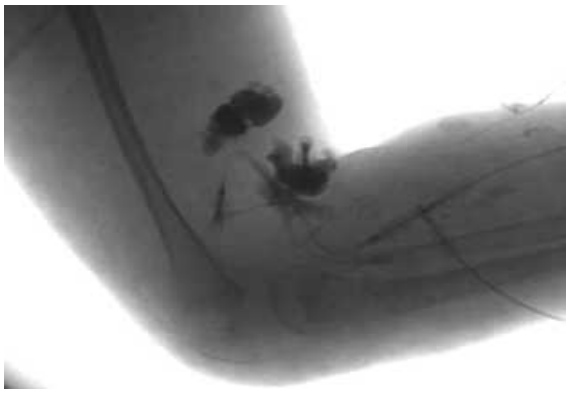




Lymphatic malformation

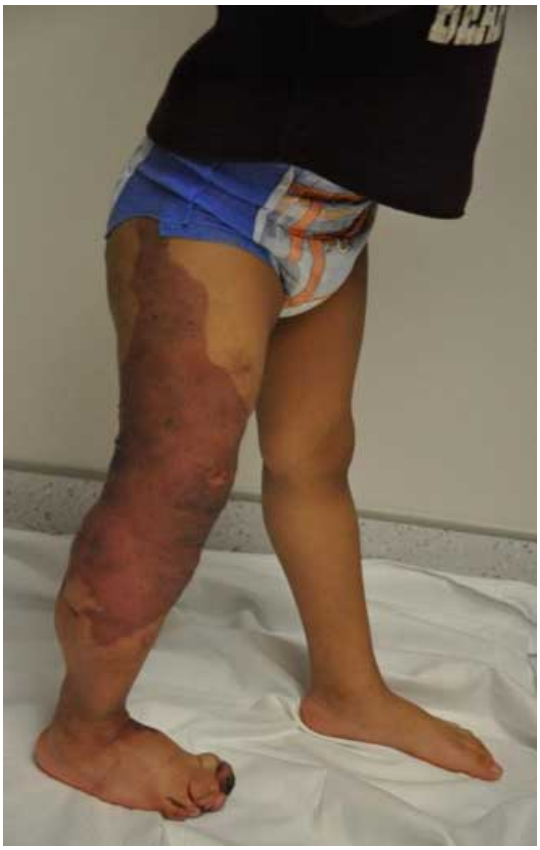
LM aspiration and doxycycline injection:
300 ml of bloody fluid was aspirated. Sclerotherapy resulted in decreased bulk and control of bleeding.





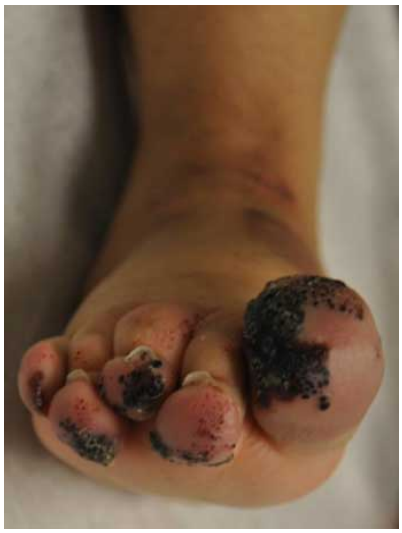
Before and after

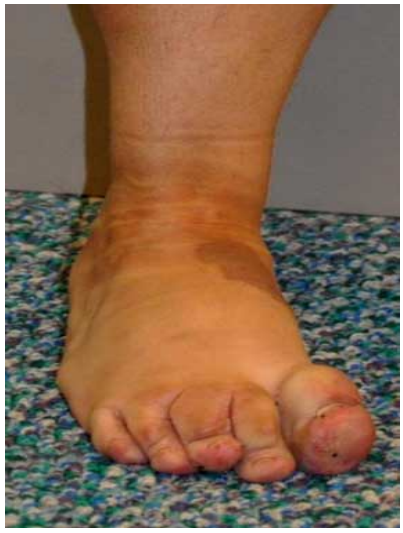
KTS before and after doxycycline sclerotherapy and laser treatment of LMs



Before and after

Nd-YAG 1320 laser and sclerotherapy





Course 02: Lesson Quiz

1. Leg ulcers in KTS are caused by:
   A. Venous hypertension
   B. Macrocystic lymphatic malformation
   C. Peripheral arterial ischemia
   D. Infection of the capillary malformation

2. Which of the following venous anomalies are frequently seen in KTS?
   A. Developmental venous anomaly
   B. Intra-articular venous malformation of the knee
   C. Interruption or hypoplasia of the femoral vein
   D. Marginal artery of Servelle

3. Genetic mutations identified in KTS include:
   A. Germline PIK3 mutations
   B. Germline RASA1 mutations
   C. Somatic PIK3 mutations
   D. Somatic RASA1 mutations

4. Typical symptoms of KTS include:
   A. Pain, bleeding, high output cardiac failure
   B. Intra-articular venous malformation of the knee
   C. Infection of the capillary malformation
   D. Pain, venous insufficiency, lymphedema

5. Which of the following are appropriate surgical procedures for KTS?
   A. epiphysiodesis
   B. both debulking of massive tissue overgrowth and epiphysiodesis
   C. thoracic duct ligation to control lymphatic fluid leak
   D. debulking of massive tissue overgrowth

6. Appropriate imaging for KTS is:
   A. Transfemoral angiography
   B. MRI with MR venography
   C. Microangiography
   D. Conventional lymphangiography

7. The definition of KTS is:

A. Capillary venous malformation with overgrowth
B. Capillary malformation with overgrowth and venous enlargement
C. Capillary lymphatic venous malformation with overgrowth
D. Capillary lymphatic malformation with overgrowth

8. Which of the following is NOT appropriate treatment for bleeding microcystic lymphatic malformations in KTS?

A. Pulse dye laser therapy
B. Compression therapy
C. Sclerotherapy Surgical
D. debulking

9. Initial treatment of painful varicosities in KTS should include:

A. Stripping of the greater saphenous vein
B. A trial of sirolimus
C. Graded elastic compression stockings Endovenous
D. ablation of the greater saphenous vein

10. In a patient with typical KTS involving one lower extremity, which of the following should be ruled out?

A. Hypoplasia of the deep extremity veins
B. Spinal AVM
C. Wilms tumor
D. Inferior vena cava hypoplasia

AUTHOR PROFILES

Patricia Burrows, MD

Dr. Patricia Burrows has been involved in the diagnosis and treatment of vascular anomalies since her Pediatric Special Procedures fellowship at Boston Children's Hospital in 1981. In 1985, she obtained additional training in neurovascular intervention in order to provide endovascular treatment of children with vascular malformations at the Hospital for Sick Children in Toronto. She was director of pediatric interventional radiology and co-director of the Vascular Anomalies Center at Boston Children's Hospital, and served as both president and executive board member of ISSVA for several years. She is a co-editor of the second edition of Mulliken and Young's Vascular Anomalies.

Presently, Dr. Burrows is an active member of the Vascular Anomalies Program at Children's Hospital of Wisconsin and Professor of Radiology at the Medical College of Wisconsin.

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Course 02: Lesson Quiz Answer Key

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