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Techniques in Vascular and Interventional Radiology

Klippel-Trenaunay Syndrome

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Klippel-Trenaunay syndrome or KTS is a complex vascular syndrome associated with overgrowth occurring as a result of somatic mutations in the *PIK3CA* gene. Patients are diagnosed on the basis of physical findings, sometimes with supportive imaging, of commonly a segmental anomaly with a cutaneous port-wine stain, lymphatic and venous malformations and overgrowth. The severity of the component vascular malformations and the degree of overgrowth varies from patient to patient which demands care given by a multi-professional team with regular follow-up in a specialist clinic. Some patients may present with acute life-threatening problems, often as a result of veno-thromboembolic events (VTEs) especially following surgical and invasive radiological procedures. Awareness of such problems is vital and prophylactic measures to reduce such risks are paramount. The interventional radiologist is vital to the care team as he/she can undertake procedures including endovascular closure of significant venous anomalies which predispose to such VTEs. Although these procedures can be lengthy and complex, they can now provide a minimally invasive means to reduce the risk from life-threatening and sometimes fatal VTEs. The results however from such interventions will require long-term studies which to date are unavailable.
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Klippel-Trenaunay Syndrome (KTS)

The molecular basis for many vascular malformations is now much better understood and provides a genetic framework for many well-recognised vascular anomaly phenotypes. It is now known that KTS belongs to the so-called PIK3CA-related overgrowth spectrum (PROS).[1]

The phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian Target of Rapamycin (mTOR) pathway is an intracellular signalling pathway important in regulating cell cycles ensuring normal cellular growth and differentiation. These cellular functions involve PI3Ks (phosphoinositide 3-kinases, otherwise known as phosphatidylinositol 3-kinases) which are an enzyme family of 4 classes.

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When somatic gain-of-function PIK3CA gene mutations occur (ie, the so-called PROS-causing PIK3CA mutations) there is activation of class 1 PI3K enzyme activity, resulting in dysregulated cellular growth and malformed vascular channels.

KTS is one of a number of recognised segmental overgrowth phenotypes with vascular malformations occurring as a result of somatic mutations in the PIK3CA gene.[2,3]

Diagnosis and Associated Features of KTS

Two French physicians, Maurice Klippel and Paul Trenaunay, in 1900 first described the association of vascular abnormalities and hypertrophy of a limb as "noevus variqueux osteohypertrophique" which subsequently became known as the Klippel-Trenaunay Syndrome.[4,5] KTS was diagnosed on the basis of 3 clinical features usually in one affected extremity : A cutaneous port-wine stain, varicosities and tissue hypertrophy. The lower limb is commonly affected, however upper limb and truncal involvement can occur. Lymphatic anomalies are also present and nowadays, it is preferable to name this condition by the combined malformed vascular channels of which it is composed, that is, CLVM (capillary, lymphatic, and

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venous malformation) associated with overgrowth. CLVM is therefore a combined low-flow vascular malformation.

Therefore the diagnosis of KTS is based on the physical findings of a CLVM associated with overgrowth.[6,7,8] No imaging or laboratory/genetic testing is needed to diagnose KTS.

CLVM often involves the proximal portion of the embryonic limb bud. If the upper limb and trunk are affected, vascular anomalies may be seen in the posterior mediastinum and retropleural space, and rarely within the abdominal cavity. CLVM in the lower limb often extends into the genitalia and pelvis involving the bladder, vagina, and rectum.[9]

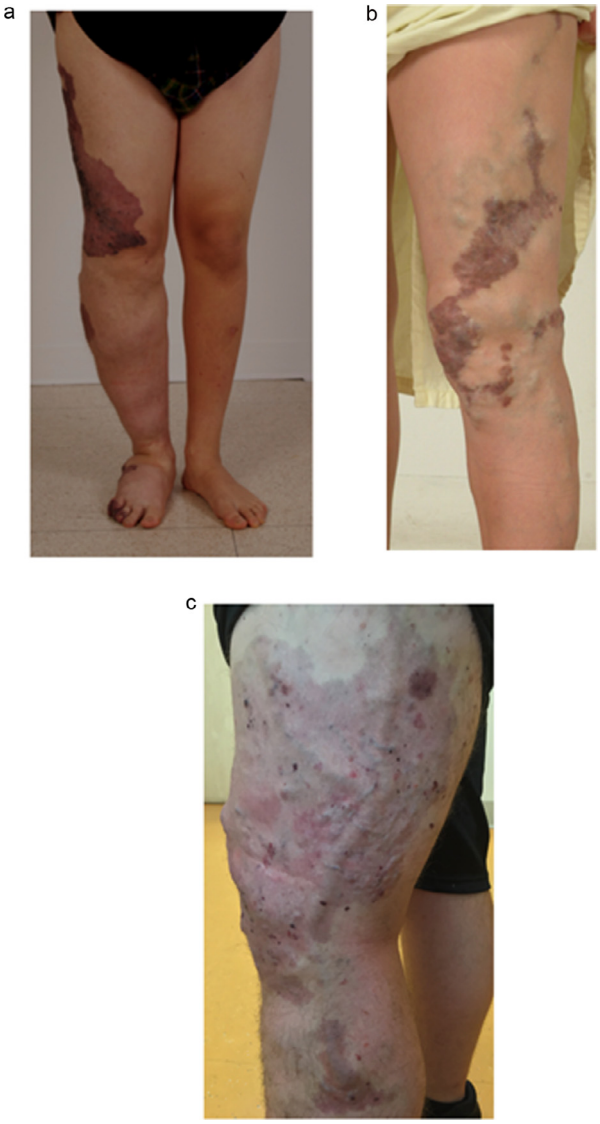

Figure 1 Typical physical features of KTS. (a) Right leg overgrowth (longitudinal and axial) including foot overgrowth. Geographic port-wine stain on leg and foot. Microcystic lymphatic malformations (LMs) present as small dark lesions on the surface of the port-wine stain. (b) (Different patient). Left leg KTS with lateral varicosities and port-wine stain. (c) (Different patient). CLVM diagnosed on physical findings with leg overgrowth and the following vascular malformations: port-wine stain on the skin (CM), microcystic LMs on surface of stain, lateral varicosities and a thick wall, protuberant embryonic lateral marginal vein of Servelle (VM). Leg enlarged from overgrowth. (Color version of figure is available online.)

The port-wine stain is one type of a capillary malformation and when present on the lower extremity in KTS, is often seen on the lateral side of the extremity, mainly on the thigh and upper aspect of the calf (Figs. 1a to c). Lymphatic malformations (LMs) including lymphedema are common; hypoplasia of lymphatic collecting systems and cystic lymphatic malformations (macro, micro, and mixed cystic types) including dermal lymphatic vesicles, due to microcystic lymphatic malformations on the surface of the port-wine stains occur. The dermal microcystic LMs are small and often dark in colour as they are hemorrhagic (Figs. 1a to c) and can bleed recurrently. Rarely they leak chyle because of chylous reflux into the limb. Intrapelvic cystic LMs are predominantly macrocystic (Figs. 2 and 3). Macrocystic LMs occur more frequently in the pelvis than in an extremity. Usually these pelvic macrocysts are asymptomatic; however, they can displace the bladder, causing outlet obstruction, or can compress the rectum, causing constipation. Intestinal lymphangiectasia resulting in a protein-losing enteropathy can be seen with truncal CLVM.

Venous anomalies are the predominant vascular malformation in this disorder with malformed venous channels affecting the superficial and deep venous systems.

The so called "lateral marginal vein" (LMV) otherwise known as the "vein of Servelle", is the most common venous anomaly being present in up to 70% of patients (Figs. 1c, 4a and b).[10] It is one of 2 persistent embryonic veins (PEVs) otherwise known as anomalous veins, seen in KTS. The other PEV is the persistent sciatic vein (PSV).[11,12] Embryonic veins usually regress before birth, however in KTS they persist.

The LMV is located deep in the subcutis and as such may not be visible, although it may be palpated as it progressively becomes thick walled and ectatic with increasing age (Fig. 1c). Perforating veins can occur along the full length of the anomaly. The vein is incompetent, may be valveless and sometimes can be composed of several interconnecting channels rather than a single longitudinal channel (Fig. 4b). It begins on the dorsum and lateral side of the foot as a venous plexus and extends up the limb for a variable length (Figs. 1c, 4a, 5b), terminating in different veins such as the popliteal vein (in 11%), the superficial femoral vein (in 17%), the profunda femoris vein (in 19%), or the external iliac vein (in 6%) (Figs. 4a, 5b, 6, 7a and b). In approximately one-third

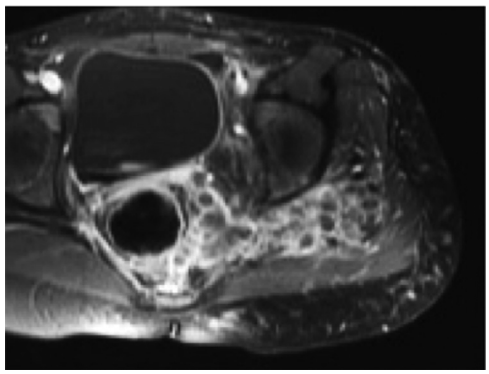

Figure 2 MR pelvis in KTS patient with recurrent left buttock pain from infected macrocystic LM. Post Gad T1 showing multiple small macrocystic LMs in left buttock extending into pelvis.

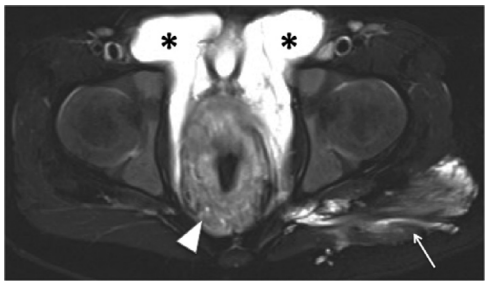

Figure 3 Axial T2 MR pelvis in KTS infant with severe rectal bleeding, and elevated D-Dimer. Diffuse soft tissue rectal and peri-rectal thickening (arrowhead) due to recto-sigmoid venous malformation. The venous malformation involved the recto-sigmoid wall and mucosa. Bilateral pelvic lymphatic macrocysts (asterisk) and left gluteal venous malformation (single arrow).

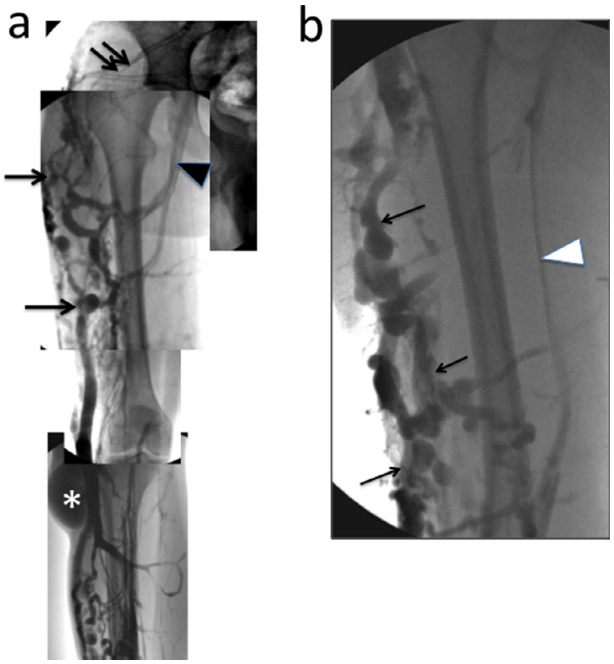

Figure 4 Venography of LMV. Injection done into dorsal foot vein with an ankle tourniquet applied during injection. (a) Extra-fascial LMV is predominantly a single channel up to the mid-thigh and superiorly is several smaller channels. LMV has a large superficial varix (asterisk) in the lower leg, LMV becomes intra-fascial (single arrows) connecting with systemic veins in the mid-thigh, by several larger posterior channels joining the femoral vein at the groin (arrowhead) and by small trans-gluteal channels to the iliac veins (double arrow). (b) (Different patient to a). LMV composed of multiple interconnecting longitudinal channels (single arrows). The superficial femoral vein is present, patient and "hypoplastic" (arrowhead).

of patients, the LMV extends the full length of the leg passing through the lateral aspect of the buttock, entering the internal iliac system via the gluteal veins, sometimes by multiple transgluteal channels where there may be a large dominant channel.

The PSV is superficial, under the skin on the posterior aspect of the thigh. In its complete form the vein originates at the popliteal vein, ascends the thigh, passes through the sciatic notch and drains into the internal iliac vein. Incomplete variants occur where the vein does not cross the entire thigh and buttock.[12]

These PEVs are typically incompetent, exhibit stagnant flow and consequently are a major cause of symptomatic venous engorgement, painful superficial thrombophlebitis, venous thrombosis (DVT), and pulmonary thromboembolism.

Laterally located varicosities in affected lower extremities are typical in KTS (Fig. 1b) and are related to the lateral location of the embryonic vein, the LMV. Eczema, varicose changes, frank lipodermatitis secondary to venous hypertension and progression to ulceration are rare. There is no association between superficial varicosities and deep venous anomalies in KTS.

Deep venous system anomalies occur with some debate as to their incidence. Obstructions affecting the popliteal and femoral veins (from extrinsic fibrous band occlusions and atresias) and malformations of the iliac vein and inferior vena cava are reported. What is interesting is that when the LMV is closed and blood flow is redirected preferentially into the deep system, the so called "deep vein hypoplasia" (Fig. 4b) improves. Therefore there is no true hypoplasia of the superficial femoral vein in many KTS patients and the "small size" is secondary to reduced flow. When flow is restored, this deep vein increases in size because of its plasticity.

The intestinal lesions are predominantly venous, sometimes extending into the spinal canal and sigmoid or left colon. In some instances, the entire colon may be involved. In the pelvis, thick circumferential involvement of the anorectum (Fig. 3) and surrounding fat by lymphatic and venous malformations often result in chronic rectal bleeding and pain. Similar involvement, particularly by the venous anomaly, of the mucosa and wall of the urinary bladder and urethra can cause chronic bleeding per urethra.[13]

Limb enlargement is due to longitudinal and axial tissue overgrowth (Fig. 1a). Extremity overgrowth is obvious at birth and although progressive, major changes after birth are unusual. The overgrowth of an affected limb can involve the entire extremity including the hand and foot. Interestingly macrodactyly can be seen in an otherwise uninvolved limb in a patient with KTS with classical features affecting another extremity. Longitudinal bony overgrowth follows the soft tissue and accounts for the longitudinal extremity overgrowth. There is little increase in bony diameter. Axial overgrowth is unpredictable and due to excessive extra-fascial/subcutaneous fat and vascular tissue. Usually extremity muscles are normal in size and intra-fascial infiltration of fat and cystic lymphatic malformations may occur. In a few patients with otherwise classic CLVM, there is undergrowth (hypotrophy) and shortening of the affected limb.

The CLVM phenotype at birth defines the appearance of the child and young adult with few exceptions such as the port-wine stain which may lighten/ darken, dermal lymphatic vesicles on the port-wine stain surface can erupt and bleed (Figs. 1a to c), the latter causing black/purple colouration of the port-wine stain, varicosities become more prominent over time and limb length discrepancy may increase.

Cellulitis and septicemia can occur in CLVM, presumably due to bacterial proliferation in the abnormal lymphatic spaces. Pelvic and gastrointestinal lesions are likely to be

the origin of the cellulitis in the buttock, perineum, or proximal thigh, due to bacterial translocation (usual *E. coli*) across an abnormal mucosal barrier. Localized signs of infection may be noted in the proximal thigh or buttock; however, they may be absent, despite obvious septicaemia. Micro-organisms are difficult to culture from the blood. Rarely, gram-negative bacteria have been identified, possibly due to bacterial seeding originating in the lower gastrointestinal tract.

There are several incorrect reports in the literature including the mention of hemangiomas in KTS. Such vascular tumors are not a component of KTS. Also the term "Klippel-Trenaunay Weber syndrome" should be avoided as this entity does not exist. Parkes Weber syndrome (PKWS) is sometime confused with KTS however it is very different. There are many differentiating features between PKWS and KTS. In PKWS there are high flow vascular malformations, overgrowth and vascular skin stains. Some patients with PKWS have a germline mutation of the RASA 1 gene, inherited in an autosomal dominant manner. In these cases, the skin stains are usually multiple. In PKWS, micro AV shunts are present in the subcutaneous fat and focal AV fistulae are present in or adjacent to bone. Cardiac decompensation and cardiac failure may toccur in PKWS and not in KTS as the latter is not a high-flow vascular malformation. Macrocystic LMs and intra-fascial infiltration of fat and LM seen in KTS, are not seen in PKWS.

Imaging in KTS

We routinely perform magnetic resonance imaging (MR) on all our KTS patients as this demonstrates the full extent of the disease deep to the skin and the nature of the underlying vascular malformations. The diagnosis of KTS is based on physical findings and imaging is not needed to establish the diagnosis. There is no medical urgency in getting routine MR imaging done in infancy. However, as we now advocate for PEV closure in the older toddlers (about 4 years of age), it is useful to get the MR done at this age. Ultrasound (US) can be very useful to see the presence and size of PEVs in superficial locations although is limited when assessing the deeper continuation of these channels. When KTS affects the lower extremity and pelvis, imaging should include an assessment of the IVC and iliac veins for patency and size. Ectasia of the IVC can occur. US is excellent as a quick "bedside tool" when patients present with acute focal extremity pain. Macrocystic LMs, which may be infected and superficial blood clot can easily be identified. We rarely use CT unless looking for acute pulmonary thromboembolic disease and chronic thromboembolic pulmonary hypertension.

The size of the LMV may be underestimated when patients are supine in position during MR, US, and venography. Because of this, we ultrasound patients upright in position if possible, to better assess the size of the superficial PEVs.

Routine extremity venography is not needed in KTS patients unless surgical or endovascular closure of the anomalous veins is planned. Often venography can be done at the time of endovascular closure, which makes this a lengthy procedure and always done under general anaesthesia.

General Care of Patients With KTS

Many patents are managed conservatively with graded compression garments if needed to reduce limb swelling, venous engorgement and discomfort. Above 4 years of age yearly monitoring of leg length is done when the malformation affects the lower extremity to assess for a leg length discrepancy (LLD).[14] Low-dose biplanar radiography (EOS), CT scanogram or MR monitoring of leg length is done in those children with a LLD who are older than the toddler age group to assess the need for timed surgical correction with an epiphysiodesis.[15] Skin hygiene advice to minimise infection and care of skin bleeds is important, measures taken to reduce venothromboembolic risk factors (including progesterone only oral contraceptives), undertaking early treatment of infections and optimising obstetric care during pregnancies must always be considered.[16] Extremity pain or pain in areas affected by the malformation, demands an accurate diagnosis and appropriate treatment.[17,18] This includes radiological sclerotherapy for macrocystic lymphatic malformations. Maintenance of extremity function is vital in those with a functioning affected extremity. Amputation of digits and portions of an extremity should only be undertaken to improve function or for uncontrollable recurrent severe infection. It is important never to sacrifice function to achieve an improved appearance.

Nowadays, the optimum care of KTS patents is preferably by a multi-professional collaborative team, bringing together the experience of different specialties. Some KTS patients have benefited from being treated with Sirolimus.[19] Sirolimus offsets the progression of vascular malformations, can improve selected symptoms and the quality of life of patients through inhibition of the PI3K/AKT/mTOR pathway (see Table 1).

The mTOR inhibition seems helpful for KTS patients with troublesome LMs, particularly those with troublesome microcystic LMs and lymphatic leaks. Although a more favourable response with Sirolimus can be seen in selected vascular malformations when commenced early, not all patients with KTS require Sirolimus. Sirolimus is a long-term oral medication and patients need regular follow-up and monitoring of potential Sirolimus-related complications.[20] See Table 1 for KTS-related problems and recommended treatments.

Intralesional coagulopathies and venothromboembolic events (VTEs) pose significant and sometimes life-threatening problems for patients with KTS.[21,22,23,24] In my practice, I have seen KTS patients with unprovoked acute large pulmonary emboli including a 21 year-old patient die from a massive PE. Sepsis can also be challenging as it can be difficult to recognise in young children as we have seen one 6 year-old patient die from unrecognised sepsis. Appropriate early treatment of infection is needed and patients may need admission for IV antibiotics.

Providing long-term care and follow-up is necessary to manage a range of problems as outlined in Table 1. Hematologic evaluation, pain management, social support, and education of the families and patients should never be forgotten and are important in optimising care.

Table 1 KTS-related Problems

Clinical Feature	Management Consideration
Limb "heaviness"	Graded compression garment
Extremity overgrowth	Longitudinal – monitor (shoe lift for mild difference & if significant timed surgical epiphysiodesis) Axial – extra-fascial debulking for massive disabling overgrowth. Avoid liposuction because of fat embolism & infection risk.
Mobility, ambulation, and post-surgical rehabilitation issues	Physical and rehabilitation therapy
Massive overgrowth with deformed limb, chronic severe pain, irreversible flexion contracture	Limb amputation
Extremity pain	Investigate and treat cause eg, cellulitis, DVT, thrombophlebitis, osseous venous malformation, arthropathy, neuropathy, growing pains
Bleeding from GI/GU tracts and	Investigate (d-Dimer + fibrinogen levels) and Rx appropriately Acute GI/GU bleeds : give supportive Rx and consider LMWH + fresh frozen plasma if intravascular coagulopathy present. For GI bleeds exclude splanchnic venous anomaly, portal hypertension and GI low-flow malformations
Severe chronic rectal bleeding needing repeat blood transfusions	Iron supplements, stool softeners, sclerotherapy/resection with surgical endorectal pull-through
Skin bleeds from dermal lymphatic vesicles	Rx topically (inc. topical Sirolimus) and graded compression garment
All troublesome recurrent bleeding	Consider Sirolimus
Macrocystic LM	Sclerotherapy
Large disabling LM	Surgical debulking, Sirolimus
LM infection	Antibiotics for cellulitis, ? elective sclerotherapy for macrocysts
Lymph leakage	Sirolimus and consider radiological embolization of conducting lymphatics
Cutaneous lymphatic vesicles	CO_2 laser photovaporisation, Sirolimus if troublesome (inc topical Sirolimus)
Venous malformation (embryonic veins, and other venous anomalies)	Hematologic evaluation early in life Perioperative prophylactic anticoagulation Elective early closure of embryonic veins
Veno-thromboembolic events	Assess and Rx appropriately including long-term anticoagulation
Capillary malformation (ie the skin port-wine stain)	Pulse dye laser (lower extremity results often poor because of venous hypertension)
Cachexia	Nutritional evaluation and support (enteral feeding may be needed)
Social support	Involve local social worker
Patient and family education	Patient and family education days KTS support group
Chronic disability	Address the cause & involve rehabilitation
Psychological issues	Psychological support

Localised Intravascular Coagulopathies (LIC) in KTS

Patients with KTS are prone to intravascular coagulopathies with elevated D-Dimer and low fibrinogen levels.[25,26] We use the following normal reference values: D-Dimer <0.5 μg/mL ($<$ 250 ng/mL) and fibrinogen 1-4 g/L. Abnormal venous anatomy with venous ectasia, slow blood flow and lymphatic anomalies are some of the recognised contributory factors leading to the coagulopathies. Most intravascular coagulopathies are localised (the so-called "localized intravascular coagulopathy" or LIC). In LIC, that is, there are abnormalities in D-Dimer and fibrinogen levels without spontaneous bleeding or clotting. In general, LICs are categorised as mild (with elevated D-Dimer and normal fibrinogen levels) or severe (with elevated D-Dimer and low fibrinogen levels). It is important to know that an LIC can progress to a disseminated type (DIC), that is, where there are abnormalities in D-Dimer and fibrinogen levels with spontaneous bleeding, petechiae and clotting. This conversion of an LIC into a DIC is recognised occurring with surgical or radiological interventional procedures including sclerotherapy and then aggravated by immobilization after these procedures.

Veno-Thromboembolic Events (VTEs) in KTS

Table 2 outlines our practice management for KTS patients with VTEs. Thrombotic events in KTS, including potentially

Table 2 Suggested Treatments for KTS-related Coagulopathies and VTEs

Problem	Treatment
Superficial thrombosis in embryonic vein	Anticoagulate with LMWH / Rivaroxaban (proximity of clot to embryonic – systemic vein junction can help guide the length of Rx)
Recurrent superficial thrombosis in embryonic vein	Anticoagulate with LMWH / Rivaroxaban
Deep venous thrombosis in affected extremity	Supportive care including thrombolytics and anticoagulate with LMWH / Rivaroxaban
Established pulmonary embolus	Supportive care including thrombolytics / embolectomy and anticoagulation (for 3-6 months ? life-long) with LMWH/Rivaroxaban. Elective extremity venography + embryonic vein(s) closure
Patient undergoing procedures (check D-Dimer & fibrinogen on all patients) :- 1. Surgery inc. leg debulking, embryonic vein closure (except minor procedures, eg, dental) 2. Interventional radiologic procedures (including endovenous embryonic vein closure)	Prophylactic anticoagulation (LMWH / Rivaroxaban) except when surgical bleeding causes high risk (eg, neuro- or eye surgery). For leg debulking surgery, close embryonic veins before surgery (preferably by endovenous approach)

fatal pulmonary emboli, are not uncommon especially after surgical and radiological interventional procedures and trauma, however, they can also occur spontaneously.[21] We recommend avoiding oestrogen in oral contraceptive pills for female KTS patients wanting oral contraception and if possible using alternative contraceptive methods. VTE frequency is reported ranging from 4%-22% which includes superficial and deep venous thrombotic events. Pulmonary emboli (PE) have been reported in 4% KTS patients. Age, as in all patients, is a risk factor for VTE in KTS patients, as following puberty the VTE risk increases. Chronic thromboembolic pulmonary hypertension thought to be due to recurrent PE has been observed in KTS patients.[27] Superficial thrombophlebitis in the non-KTS patient is often treated symptomatically without anticoagulation. However in KTS patients, superficial thrombophlebitis occurs particularly in the PEVs, which despite some variation in their drainage, all eventually connect into systemic veins (Figs. 4a, 5a and b, 6, 7a and b). It is thought that large draining veins may increase the likelihood that if a venous thrombus is present, a resulting pulmonary embolus could be large. In this high-risk patient group anticoagulation with low molecular weight heparin (LMWH) in children and Rivaroxaban (oral Factor Xa inhibitor) in adults, can be given to treat superficial thrombophlebitis in the embryonic veins. To date, the anticoagulation literature for treating PE is based largely on non-KTS patients, with length of treatment depending on whether or not the VTE was "provoked or unprovoked". Interestingly, although the PEVs are often the source of the thrombosis, PEs have been observed in KTS patients without PEVs. The usage of prophylactic anticoagulation is also important (see Table 2). In our practice we routinely use LMWH as our anticoagulant of choice. We do not use Coumadin and to date Rivaroxaban is not licensed for routine usage in infants and children in Canada. It has been suggested that lifelong prophylactic anticoagulation in KTS patients with proven pulmonary embolism should be considered. The usage of temporary IVC filters varies and their effectiveness remains in debate in the KTS population. In our practice in children we do not routinely place temporary IVC filters during endovascular closure of PEVs as what is needed is appropriate prophylaxis with LMWH.

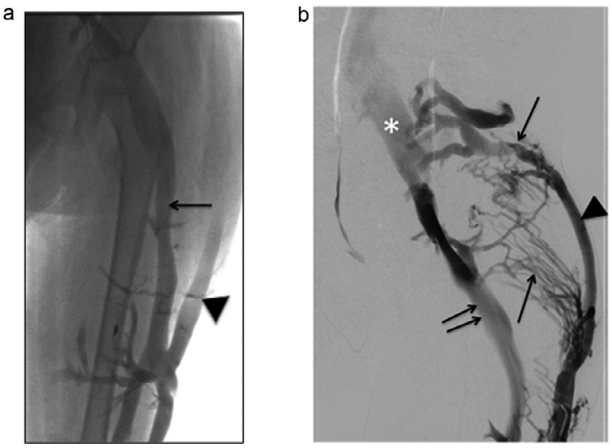

Figure 5 Venography of lower extremity PEVs. (a,b) (Same patient). Contrast injected by catheter into LMV). (a) Persistent sciatic vein (single arrow) and LMV (arrowhead) connect in mid-thigh. (b) Multiple trans-gluteal channels with dominant channel (arrowhead) drain the LMV into the left common iliac vein (asterisk). Multiple small channels (arrows) drain into the common and internal iliac veins. The persistent sciatic vein (double arrows) drains directly into the left internal iliac vein. There is no left external iliac vein.

Bleeding in KTS

If KTS patients have an un-treated LIC, they are at risk of major intra-operative haemorrhage. The treatment of choice in such cases is immediate heparin, usually LMWH and other supportive therapy. Fresh frozen plasma may be needed if the fibrinogen level is <1 g/L. Surgeons who operate on extremity vascular anomalies sometimes encounter bleeding with using a tourniquet for resection of a CLVM. It is presumed that stagnant blood during tourniquet inflation changes clotting factors and leads to bleeding and further DIC. This transient coagulopathy, demands that surgeons compress a wound and wait before closure.

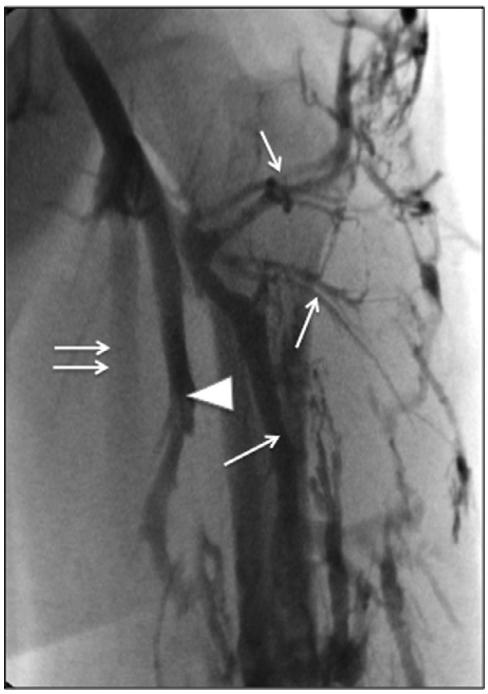

Figure 6 Venography by retrograde catheter injection of left common femoral vein (catheter placed via right femoral vein) and simultaneous injection into lower LMV. To enhance retrograde filling of the left femoral vein, the left external iliac vein was compressed during catheter injection. Communicating small channels from the upper end of the LMV to the deep system shown (single arrows). There is no filling of the superficial femoral vein due to its absence. Filling of embryonic (double arrow) and profunda femoris vein (arrowhead).

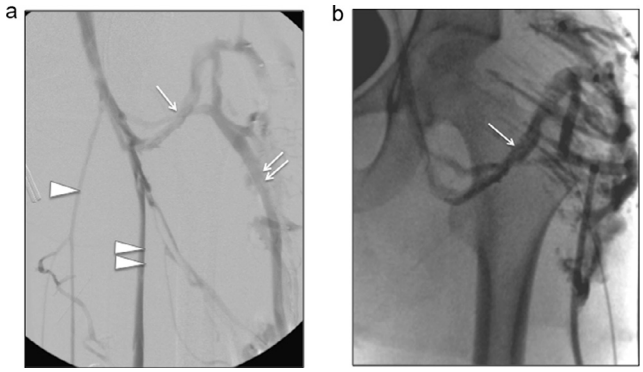

Figure 7 (a and b) (Different patients). Venography showing variant drainage of the LMV via recognised channels (arrow) anterior to the femoral neck draining into the common femoral vein. (a) Greater saphenous vein (arrowhead), superficial femoral vein (double arrowhead) and LMV (double arrows) shown. (b) Patient also has "dual" LMV drainage via trans-gluteal and anterior femoral channels.

Pulmonary Arterial Hypertension (PAH) in KTS

KTS patients can develop pulmonary hypertension. Chronic thromboembolic pulmonary hypertension is caused by recurrent or unresolved pulmonary embolism caused by LIC and it hypercoagulable state.[27] Small vessel abnormalities of these vascular anomalies can lead to PAH without evidence of pulmonary embolism.[28] Significant PAH has been correlated with high levels of D-dimer in patients with extensive venous malformations and KTS compered to health controls.[29] Echocardiography can be useful in the workup of these patients.

Management of Coagulopathies

It is important to discuss these potentially coagulopathic patients in a multi-professional collaborative team. Careful planning is required when KTS patients undergo surgical and interventional radiologic procedures, as not only are these patients at risk of peri/post procedural VTEs but also intra-procedural bleeding. To date with few evidence-based therapeutic regimens reported, the Special Interest Group (SIG) in Vascular Anomalies within the American Society of Pediatric Hematology/Oncology, has made recommendations for peri-procedural anticoagulation in vascular malformations. KTS patients are "high-risk" and can be stratified into a higher-risk subgroup if they have low fibrinogen levels, venous ectasia (ie, PEVs), D-Dimer levels x 5 normal, thrombocytopenia (without other explanation) and a positive personal/family history of thrombosis. They recommend that all such higher-risk subgroup of KTS patients, if undergoing invasive radiological or surgical procedures should receive 2 weeks of LMWH pre-procedure, rechecking the D-Dimer and fibrinogen levels and to continue LMWH post-procedure for a further 2 weeks or until baseline ambulation is achieved, whichever is the longer. When fibrinogen levels are normal, we start LMWH on the day of the procedure and continue for one week following the procedure.

To date there is no evidence base for using aspirin in KTS patients. Graded compression garments reduce the amount of blood stasis in these lesions. They can be of significant clinical benefit provided they are of the appropriate design and pressure, are worn regularly and renewed every 3 months.

Venography and Endovascular Closure of Embryonic Veins in KTS

Closure of embryonic veins, i.e. the lateral marginal vein (LMV) and the persistent sciatic vein (PSV) can be done as a prophylaxis to reduce the risk from pulmonary embolic events. Embryonic veins are often the source of the thrombus and pulmonary emboli from these can be massive and fatal in childhood.[21] We would consider endovascular closure of embryonic veins in all KTS patients with such venous anomalies. It is advantageous to undertake this at an early age, such as in the toddler age group, before the veins increase significantly in size and become thick walled. Embryonic vein closure should also be done in all KTS patients undergoing planned surgical debulking on the affected extremity, prior to surgery. Detailed venography of the affected lower extremity is needed prior to endovascular closure and can be done at the time of endovascular closure. All catheter venography and endovascular approaches to close embryonic veins require coverage with anticoagulation (see Table 2).

Anatomically, the LMV inferiorly is extra-fascial and as it ascends in the leg it becomes intra-fascial with connecting channels to the deep veins. Some variation is seen regarding the venous drainage into the deep veins (Figs. 4a, 5b, 6, 7a and b).

Anatomic variants of the PSV are also seen. The so-called "complete" PSV arises from the popliteal vein, ascends the posterior thigh superficially close to the skin, enters the sciatic notch and drains into the internal iliac vein.

Venography is done to demonstrate the venous anatomy of the embryonic vein, its draining veins and the deep veins. When embryonic veins are present, venous return from an extremity can be predominantly through these channels. Consequently the deep veins are often difficult to demonstrate on venography although in most cases they are present, albeit small and "hypoplastic".

Although some of this venous anatomy can be evaluated with MR and US, detailed venography is required in all cases where endovascular closure is being undertaken. MR and US often fail to demonstrate the entire anatomy of the embryonic veins, connecting veins and the deep veins.[30] Venography can be challenging as affected limbs have anatomic and functional venous disease with complex venous reflux patterns, severe valvular incompetence, calf muscle pump impairment, and venous hypertension. Several venographic methods, including ascending and descending techniques may be required to demonstrate the PEVs and the deep veins (see below).

In the presence of a LMV, conventional ascending venography by pedal vein injection is inadequate to demonstrate the deep venous system. Descending venography supplemented with venous compression may also be inadequate. Diversion venography can be very useful to demonstrate the deep venous system in KTS patients with a LMV.[31] Here, multiple tourniquets are placed at the level of large perforators to prevent blood flow from the smaller deep veins to the larger embryonic veins. When ascending venography is done (either by pedal vein puncture or direct puncture of tibial and popliteal veins and US guidance) with multiple tourniquets applied over the large perforators, the deep veins are better demonstrated.

Direct catheterisation of the LMV and/PSV will best demonstrate the anomalous venous anatomy (Figs. 5a and b, 7b, 8a to c). It is optimal to access the LMV by a lateral puncture in the calf and for the PSV, just above the knee posteriorly. A 4F micropuncture introducer set with US guidance is useful for access and can be used for venography however a 4/5F angiographic catheter advanced through this access superiorly in the PEV will enable excellent venography to be done. Sometimes more than one access may be needed if the extra-fascial vein is long, to enable catheterisation of the entire channel. It is best to secure multiple access sites before commencing endovascular closure.

Radiological endovascular closure of the embryonic vein can be done once venography is completed.[7] For LMV closure, we now routinely perform coil embolization of the intra-fascial vein(s), followed by EVLA of the extra-fascial vein.[32,33] Initial coiling is important to prevent possible clot migration and EVLA can provide closure with minimal clot risk. Alternative

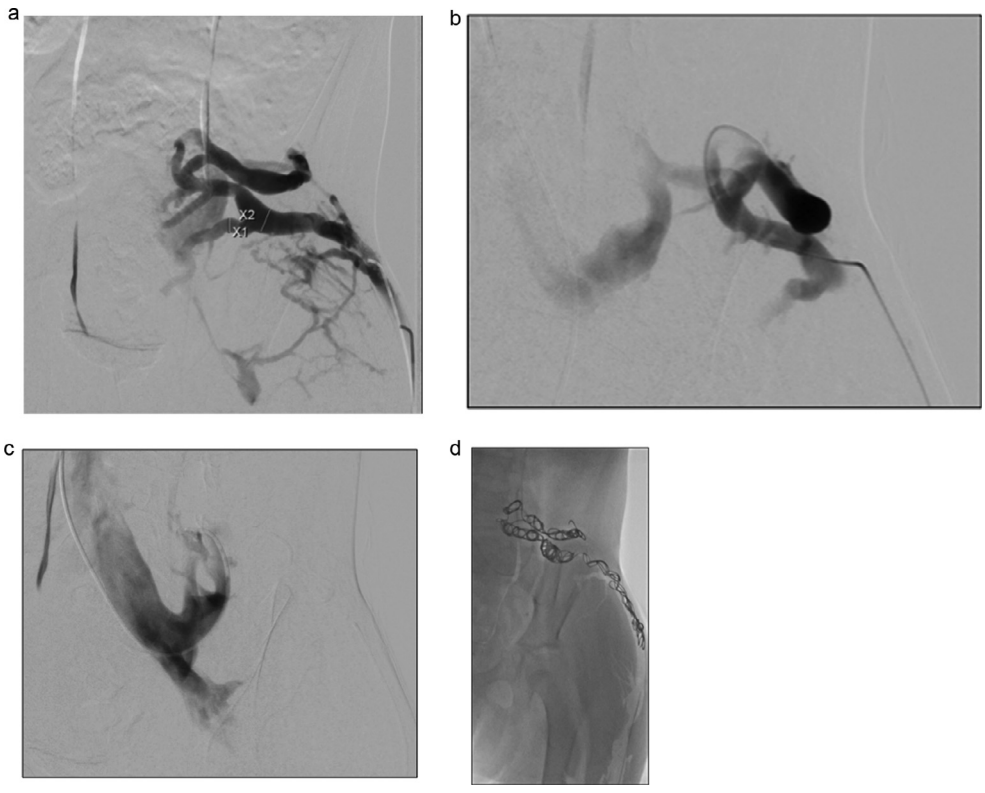

Figure 8 (a to d) (Same patient as in Figs. 5a and b). Endovascular closure of LMV. Detailed venography followed by coil embolization using a 4 F angiographic catheter placed into the lower LMV. (a to c) Catheter venography of LMV showing its connection with the common iliac vein. (d) Post "loose packing" of coils in the intra-fascial connecting veins immediately before EVLA of the extra-fascial LMV.

techniques using EVLA with no coil embolization or radiofrequency ablation alone have been reported.[34,35] A 4/5F angiographic catheter used for venography of the embryonic veins can be used for coil embolization of the intra-fascial veins. Large diameter 0.035 inch fibered platinum macro-coils can be used and for patients of all ages and "loose packing" of the coils should suffice as the aim of the coil embolus is to act as a filter against the passage of clot (Fig. 8d). If there is a large dominant gluteal channel, an Amplatzer plug can be used in this deep location. Larger vascular plugs can be placed by direct trans-gluteal puncture with US and venographic guidance (Figs. 9a and b). Although some suggest alternative embolic materials such as the long PTFE coating from a stripped Benston guide, we have found that PTFE does not coil satisfactorily. We would caution against using other embolic agents such as glue/other adhesives, sclerosant foam or liquid sclerosants to embolise the intra-fascial connecting veins.

If the intra-fascial venous channels from a LMV, such as the trans-gluteal veins, are small, then coil embolization of these may not be required as such small channels themselves can act as a satisfactory filter against clot migration.

Once the intra-fascial veins have been coiled embolised, the extra-fascial LMV channel is closed by EVLA using a conventional technique with some modifications. After placing the laser guide sheath and laser fibre to an appropriate position as high as possible in the extra-fascial vein, perivenous tumescence is then done.

For tumescence, we use normal saline or Ringers Lactate in a 250 ml bag as a reservoir to hand inject the fluid around the vein with a 22 gauge needle with US guidance. For children under general anaesthesia, local anaesthetic need not be added to the tumescent fluid, thus avoiding concern regarding local anaesthetic dosing. Achieving adequate tumescence for safe EVLA of anomalous veins in KTS can be challenging. Numerous small venous channels immediately surrounding the LMV making injection and maintenance of tumesence difficult. This may be overcome if only a short length of perivenous tumescence followed by immediate endovenous lasing over this short venous segment is done and then repeated along the entire length of vein to be treated. (Fig. 10). If the embryonic vein is located immediately under the skin it may be difficult to inject an adequate amout of tumescent fluid and EVLA may not be possible.

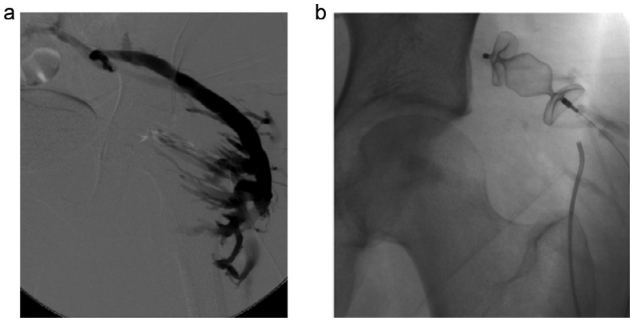

Figure 9 (a and b) (Same patient). Embolisation of dominant trans-gluteal vein with Amplatzer Vascular "Plug 2". This was placed by percutaneous puncture using a Neff Percutaneous Access Set with ultrasound guidance after venography was completed.

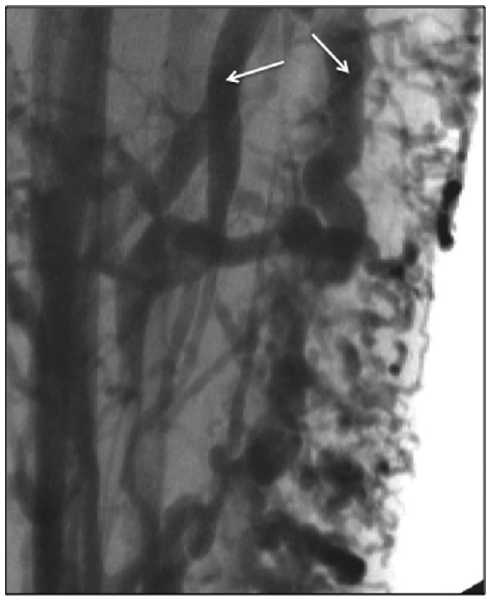

Figure 10 Venography showing the LMV (arrows) with numerous small superficial venous channels. These small channels make tumescence difficult when undertaking EVLA of the extra-fascial LMV.

Chemical ablation with sclerosants including alcohol of the PEV is not a safe alternative to EVLA because of the cardiopulmonary and VTE risk. We have seen one fatality when alcohol was injected into the LMV and the patient died from recurrent massive PEs. If there are small tributaries draining into the lower LMV, these can be treated after the main channel of the LMV has been successfully closed. These tributaries can injected with sclerosant foam or closed with EVLA, the latter being done by passing the laser fibre through the small sheath of a 4F micropuncture introducer set. It is useful to map out such tributaries with US before commencing EVLA of the main channel of the LMV, mark their location on the skin and establish access into these channels (Fig. 11).

Endovascular closure of a PSV requires coil embolization of the entire vein (ie, both the intra-fascial and extra-fascial channels). The extra-fascial channel in the PSV is unsuitable for EVLA as it is superficial and located immediately under the skin. "Loose packing' of coils should suffice when embolising the PSV, using similar coils as for the LMV.

Surgical excision is an option to close embryonic veins, especially when the extra-fascial vein (LMV/PSV) is too large or too superficial for endovascular closure.[36,37] If needed, endovascular coil closure of the intra-fascial connecting channels can be done prior to surgical excision of the extra-fascial embryonic vein.

Endovascular closure of embryonic veins offers a minimally invasive approach to close embryonic veins in KTS patients and provides a prophylactic treatment option to minimise pulmonary embolic events. It can be used in 2 senarios 1) a useful primary treatment option to surgical closure and 2) as a pre-surgical adjunct before major lower extremity debulking procedures to reduce extra-fascial fat and vascular tissue. This minimally invasive approach offers advantages over surgical vein closure, as the surgeon cannot always close the deeper intra-fascial veins, extra-fascial intra-fascial which may partly explain the high recurrence of symptoms after surgery. It is important

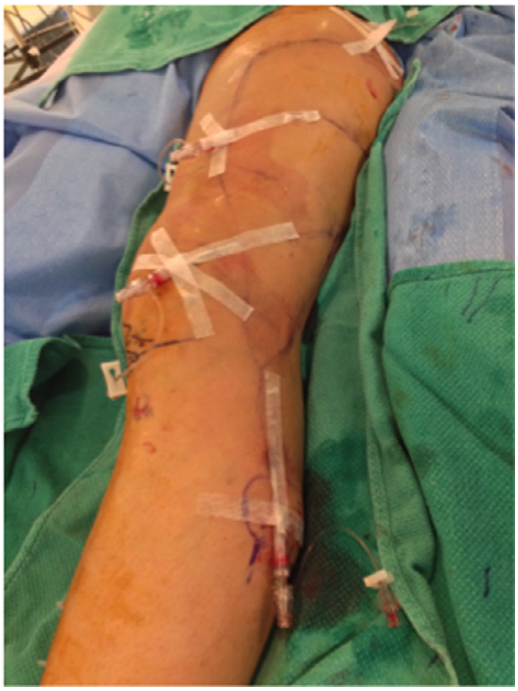

Figure 11 Mapping and establishing access into the tributaries of the LMV for treatment of the tributaries occasionally. (Color version of figure is available online.)

however for physicians to recognise that despite these procedures being minimally invasive, patients require expert periprocedural care including prophylactic anticoagulatuion, procedures can be complex and lengthy, need general anaesthesia, require hospital stays and sometimes lengthy recovery periods with possible thrombotic risks.

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