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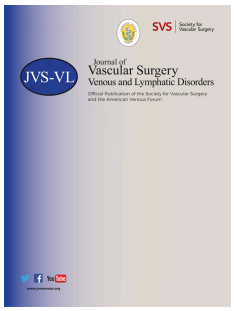

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Clinical presentation and outcomes following endovascular management in a mixed pediatric and adult Klippel-Trenaunay Syndrome population

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Article Highlights

Type of Research: Single center, retrospective cohort study

Key Findings: Fifteen of 20 KTS patients underwent endovascular intervention for symptoms related to venous pathology of KTS refractory to compression therapy. Technical success was 97.8%, clinical success was 100%, and complication rate was 6.7% (1 patient, Grade II Clavien-Dindo).

Take home message: Endovascular intervention is safe and effective for KTS patients who fail conservative management.

Table of Contents Summary

In this retrospective study of 20 KTS patients, endovascular intervention for refractory symptoms related to venous pathology of KTS had 97.8% technical success, 100% clinical success, and 6.7% complication rate. Endovascular intervention is safe and effective for KTS patients who fail conservative management.

Abstract

Objective: To retrospectively study the clinical presentations and outcomes of endovascular management in a mixed pediatric and adult Klippel-Trenaunay Syndrome (KTS) population at a single academic medical center.

Methods: Retrospective study of patients with KTS and referred for endovascular intervention following evaluation and diagnosis by a multidisciplinary team at a single academic medical center over a 10-year period was performed. Patient demographics, areas affected, presenting symptoms, prior treatments, imaging modalities, endovascular treatment types, number of treatments, and complications were assessed. Technical and clinical success percentages were calculated.

Results: Twenty-six patients with suspected KTS were evaluated. Twenty patients, ages 2-75 years, were diagnosed with KTS based upon ISSVA criteria and referred for endovascular management. Left lower extremity was most affected. Presenting symptoms were pain (80%), edema (70%), bleeding (10%), numbness (25%), claudication (25%). Sixteen patients (80%) received treatment for KTS before presenting to our institution. MRI and US were the most common imaging modalities. Fifteen patients underwent 46 endovascular treatments during the study period. Treatment included 5 endovenous ablations only, 4 US-guided sclerotherapies with

endovenous ablation, 5 US-guided sclerotherapies only, and 32 catheter-directed venograms with additional interventions. Localized intravascular coagulopathy (LIC) was the only procedure-related complication and occurred in 1 patient following 3 treatments. Technical success was 97.8%. Clinical success was 100%.

Conclusion: Endovascular intervention is safe and effective for KTS patients who fail conservative management. Pain and edema are the most common presenting symptoms in KTS patients and may be related to pathology of anomalous and orthotopic superficial veins or deep veins. Venous claudication may be present in KTS despite patency of the deep venous system. MRI and duplex US are frequently used modalities for venous assessment. Complications of endovascular treatment are rare but include LIC.

Keywords: Klippel-Trenaunay syndrome, endovascular, anomalous vein, localized intravascular coagulopathy, venous claudication

Conflict of Interest Statement: The authors have no relevant disclosures.

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Introduction:

Klippel-Trenaunay Syndrome (KTS) is a rare, complex, congenital vascular anomaly defined by the International Society for the Study of Vascular Anomalies (ISSVA) as the combination of a capillary vascular malformation (port wine stain birthmark), venous malformation (VM), and limb overgrowth, with or without lymphatic malformation (LM) [1]. In the last decade, an association with PIK3CA somatic gene mutation has been identified, although this is not a criterium for KTS diagnosis nor is it universally present in KTS patients [2,3,4]. Although up to 50% of people with KTS have no clinically significant issues or debilitation, the remainder of patients are significantly impacted by their clinical condition, often requiring more than

conservative management with compression [5]. In patients with patent deep venous systems and symptoms secondary to vascular congestion in anomalous or diseased orthotopic venous structures, vascular intervention may be considered. Over the last decades, vascular intervention in KTS has shifted from open surgery to an endovascular approach [5,6,7,8,9,10,11]. The literature pertaining to endovascular management of KTS is limited and largely comprised of case reports. The largest KTS studies to date involve surgical management or a combination of surgical and endovascular management [6,8]. The purpose of this study is to review the clinical presentations and outcomes for patients undergoing endovascular management in a mixed pediatric and adult KTS population at a single academic medical center.

Methods:

Following IRB approval, including IRB approved waiver of patient consent, patients with congenital anomalies and presumed diagnosis of KTS referred for multidisciplinary evaluation at a single academic medical center from 2009-2019 were retrospectively identified. All patients undergoing evaluation had cross-sectional imaging. Outside cross-sectional imaging of the affected area, when available, was reviewed. Patients without cross-sectional imaging or requiring additional imaging underwent Magnetic Resonance Imaging (MRI) with time-resolved Magnetic Resonance Arteriography (MRA) and Magnetic Resonance Venography (MRV). Anesthesia support for MRI was available for patients of all ages, on an as needed basis. Formal duplex ultrasound was obtained, as needed, for diagnosis and/or clarification of deep venous patency and was performed in compliance with Intersociety Accreditation Committee (IAC) standards for peripheral venous testing [12]. Inclusion criteria included diagnosis of KTS based upon ISSVA criteria after multi-disciplinary evaluation, symptoms not relieved by conservative management with compression, venous pathology identifiable by imaging or physical exam,

patent deep veins and performance of endovenous intervention at our institution. Exclusion criteria included failure to meet ISSVA criteria for KTS, absence of a deep venous system in the affected anatomic area, resolution of symptoms with conservative measures, absence of superficial or deep venous pathology suitable for intervention and no endovenous intervention at our institution. Patient age was documented as age at the time of initial referral for endovascular intervention at a single academic medical center. Patient age was assessed by defined categories: infant 0-1y, child 2-12y, adolescent 13-18y, and adult >18y. Mean patient age was calculated. Sex was documented in binary fashion, male or female. Affected area was defined as the extremity involved with or without adjacent truncal extension. Presenting symptoms were assessed as reported by the patient and/or family, and included pain, subjective worsening of edema, recurrent bleeding, numbness/tingling, and claudication defined as debilitating muscle cramping with activity that was not attributable to underlying deep venous pathology or to underlying arterial disease. Prior treatments were documented as reported by the patient, family, or outside medical records.

Technical success was defined as the successful completion of the intended intervention, with intent of occlusion of vessels undergoing embolization, endovenous ablation or sclerotherapy. Clinical success was defined as the complete or partial resolution of pre-procedure symptoms following endovascular treatment, assessed at the initial post-procedure clinic follow-up. Complete response was defined as resolution of presenting symptoms. Partial response and no response were defined as improvement versus no change, respectively, in the frequency, severity and degree of debilitation of presenting symptoms. Complications related to treatment were assessed using Clavien-Dindo classification, which has been validated across surgical

subspecialties [13]. A standard complication classification has not been defined for KTS. Treatment response was assessed at the initial post-procedure clinic follow-up.

Technique

Procedures for patients 18 years of age or younger were performed under general anesthesia. Procedures for patients over the age of 18 years were performed under moderate sedation or general anesthesia depending upon anticipated procedure length, expected procedure-related pain, and patient comorbidities. Complete blood count (CBC), activated partial thromboplastin time (aPTT) and prothrombin time (PT)/international normalized ratio (INR), and basic chemistry panel were obtained prior to all procedures. Fibrinogen and D-dimer were obtained in patients with extensive VM, defined as those with VM with intramuscular or bony involvement or involving greater than 25% of the surface area of the affected region. Standard sterile technique was utilized. Pre-procedural antibiotics were utilized for patients undergoing sclerotherapy, coil embolization and stent placement. Technical details for venous access, venography, sclerotherapy, venoplasty, stent placement, coil embolization, and endovenous ablation are provided in Appendix 1. Intra-procedural nerve monitoring was performed during endovenous radiofrequency and laser ablation of persistent sciatic and lateral marginal veins. At the conclusion of each procedure, immediately following placement of sterile dressings, the patient's pre-fitted compression garment was applied. Early ambulation or mobilization occurred in the recovery area as soon as deemed safe by the recovery nurse. With the exception of patients who were from out of town, who were kept in the hospital for overnight observation, patients were discharged on the day of intervention following anesthesia or sedation recovery and ambulation.

Phone follow-up was performed 2-5 days post-procedure. Initial post-procedure clinic follow-up was scheduled at 8 weeks. Subsequent clinic follow-up was generally scheduled every 6-12 months. Clinic follow-up for patients with extensive venous malformations requiring staged treatment were scheduled every 2-3 months. Patients were also seen in clinic, as needed, for new, recurrent, or worsening symptoms. US with Doppler was performed by the interventional radiologist during clinic visits for new, recurrent, or worsening symptoms, and for treatment planning during pre-procedure visits. Post-procedure duplex US to assess for deep venous thrombosis (DVT) was performed at one week. Follow-up MRI was not routinely performed following treatment, but was obtained for new, recurrent, or worsening symptoms which were not clarified by duplex US.

Statistics

Descriptive statistics were performed for anatomic areas affected by KTS and presenting symptoms, and percentage of patients previously treated for KTS at outside institutions was calculated. Pre-treatment non-invasive imaging modalities were tallied. All types of MRI, including time-resolved MRA and MRV, were included as MRI. Total number of procedures was tallied, and mean treatment number per patient was calculated. Endovascular treatments were categorized by type and site, and the number of each endovascular treatment tallied. Median clinical follow-up after initial procedure and last procedure were calculated. Clinical and technical success percentages were calculated. Kaplan-Meier estimation for re-intervention free survival was performed using Stata version 16 (StataCorp, College Station, TX).

Results:

From 2009-2019, 26 patients with congenital anomalies were referred to a single academic medical center with presumed diagnosis of KTS. After multidisciplinary review, 20 patients were confirmed to have a diagnosis of KTS based upon ISSVA criteria. Patients not meeting ISSVA criteria for KTS included 4 diagnosed with isolated capillary vascular malformation and 2 patients diagnosed with Parkes Weber syndrome based upon identification of underlying arteriovenous malformation on MRI with time-resolved MRA.

The 20 patients with confirmed diagnosis of KTS included 3 males (15%) and 17 females (85%). Average patient age at presentation was 23.1 years, (range 2-75 years) including 1 infant, 5 children, 2 adolescents and 12 adults. Areas primarily affected by KTS included left lower extremity in 8, left lower extremity and pelvis in 5, right lower extremity in 4, right lower extremity and pelvis in 2, and left upper extremity in 1 patient. Two patients had accompanying microcystic lymphatic malformations (MCLM) of the affected areas. Presenting symptoms included pain in 16 (80%), subjective worsening of edema in 14 (70%), recurrent bleeding in 2 (10%), numbness/tingling in 5 (25%), and claudication in 5 patients (25%) (Table I). Of the 2 KTS patients with accompanying microcystic lymphatic malformations, one had primary complaint of bleeding from scrotal varicosities and from the urethra, and the other presented with subjective worsening of edema.

Sixteen of the 20 patients (80%) with KTS diagnosis had been previously treated for KTS before presenting to our institution. Prior treatments included compression only in 1 patient, pulsed-dye laser of capillary vascular malformation in 10, surgical debulking with stab phlebectomy in 2, surgical limb lengthening in 1, deep venous thrombectomy of the affected limb in 1, and sclerotherapy with pulsed-dye laser in 1. Prior treatments of three patients included treatment of anomalous veins or varicose veins, two with stab phlebectomy at the time of surgical debulking

and one with sclerotherapy. All three patients had clinical success without recurrence of the treated veins. All previously treated patients presented to our institution with new, progressive or recurrent symptoms. Non-invasive imaging modalities utilized prior to evaluation and/or prior to treatment included MRI in 18, CT in 2, and formal duplex US performed by the vascular lab in 3 patients. Fifteen patients underwent additional pre-treatment bedside planning duplex US in clinic for assessment of venous insufficiency, interrogation of veins in areas of symptomatology and interrogation of MRI or CT abnormalities to assist treatment planning.

Five of 20 patients with confirmed KTS diagnosis were excluded from the study. Two patients had resolution of presenting symptoms after obtaining custom compression garments. One patient who had previously been treated at an outside institution for incompetent superficial veins and presented with ongoing venous claudication underwent catheter venography which failed to demonstrate a deep venous stenosis reported on outside MRI, so intervention was not performed. One patient underwent treatment at another institution. One patient with accompanying MCLM and subjective worsening of edema was lost to follow-up after initial evaluation. Fifteen patients met inclusion criteria and underwent 46 endovascular treatments (mean 3.1, median 2 treatments per patient, range 1-15) over a ten-year period (Figure 1). Seven patients underwent multiple procedures. Four underwent staged treatments for extensive venous malformations and were reassessed after each procedure. Two of the four staged patients had new or recurrent symptoms after the initial staged treatments which prompted additional treatment. Three patients underwent additional treatment for new varicosities or symptoms arising after the initial treatment and follow-up. Additional treatments were for new or progressive pathology in previously untreated veins, not involving previously treated venous structures.

Treatment details are presented in Table II. Treatments included 5 endovenous ablations only (radiofrequency or laser), 4 US-guided sclerotherapies with endovenous ablation, 5 US-guided sclerotherapies only, and 32 catheter-directed venograms with additional interventions, including sclerotherapy, coil embolization, endovenous ablation, venoplasty, and stent placement. Ten lateral marginal veins and 3 persistent sciatic veins were treated. Lateral marginal veins were treated with sclerotherapy alone in 8 patients, sclerotherapy with coil embolization in one patient, and sclerotherapy with ablation in another. Persistent sciatic veins were treated with sclerotherapy in one patient, sclerotherapy with coil embolization in one patient and endovenous ablation with nerve monitoring in another. Mean age at treatment of symptomatic anomalous veins was 10.0 years (6-17 years) and 17.7 years (2-33 years) for persistent sciatic and lateral marginal veins, respectively. Mean age at treatment of symptomatic orthotopic veins was 37.1 years (26-75 years), 30.0 years (29-31 years), and 20.8 years (4-33 years) for great saphenous, small saphenous and anterior accessory saphenous veins, respectively. Symptoms related exclusively to orthotopic veins were only present in adult patients. One pediatric patient presented with symptoms related to insufficiency of an orthotopic vein in addition to an anomalous vein. One patient in our study was noted to have ipsilateral common iliac vein compression on imaging, later confirmed with catheter venography and intravascular ultrasound, and ultimately treated with angioplasty and stent placement. Following this intervention, the patient proceeded to treatment of incompetent anterior accessory saphenous and lateral marginal veins and associated varicosities with endovenous ablation and foam sclerotherapy. The patient experienced partial improvement of her venous hypertension symptoms after iliac stent placement, and complete resolution of her symptoms was documented following treatment of the superficial veins on the affected extremity. In one patient for whom endovenous laser ablation of

the lateral marginal vein was intended, adequate tumescent anesthesia could not be obtained; therefore, catheter directed foam sclerotherapy was instead performed. The intended endovenous intervention was successfully performed in all other procedures. Technical success was 97.8%.

Median follow-up was 2.5 years (range 2 months- 8 years) from first treatment, and median follow-up was 1 year (range 2 months- 4 years) from last treatment. There were no major complications. There were no incidences of post-treatment deep vein thrombosis (DVT), endovenous heat-induced thrombosis (EHIT), skin burn, ulceration, motor nerve injury, or non-target embolization. There were 3 Clavien-Dindo grade II complications, all of which were localized intravascular coagulopathy (LIC) which occurred following 3 treatments in 1 patient. One patient with extensive muscular venous channels affecting her left lower extremity and pelvis developed LIC at age 14 years after undergoing multiple prior treatments uncomplicated by LIC. In her case, D-dimer was elevated beyond the upper limits of detection, and she was started on therapeutic low molecular weight heparin (LMWH). This patient's follow-up and ongoing LIC management were coordinated with hematology colleagues. Following the initial LIC event, the patient was managed with prophylactic LMWH in the post-operative period alone, but experienced LIC despite prophylactic LMWH and experienced sporadic LIC unrelated to treatments. Subsequently, ongoing prophylactic dose LMWH was utilized for prevention of sporadic LIC events unrelated to treatment, and therapeutic dose LMWH was utilized in the peri-procedural period for the remainder of her treatment course. The patient's LIC was controlled without progression to disseminated intravascular coagulopathy (DIC).

Clinical success was 100% (Table 1). There was complete or partial resolution of pain in 14 of 14 treated patients: complete resolution in 12 (85.7%), partial resolution in 2 (14.2%). Two of the patients who initially presented with pain were not treated. There was complete or partial

improvement in swelling/edema in 13 of 13 patients: complete resolution in 11 (84.6%), partial resolution in 2 (15.4%). One patient with swelling was not treated. There was resolved or decreased bleeding in 2 of 2 patients: 1 resolved (50%), 1 decreased (50%). There was resolution or improvement of numbness/tingling in 5 of 5 patients: 2 resolved (40%), 3 improved (60%). There was complete resolution of venous claudication in 4 of 4 patients (100%). One patient with venous claudication was not treated.

Discussion:

Compression therapy is considered the cornerstone of management of KTS [5,6,7,9,10,11]. Many KTS patients require additional treatment or intervention. Medical management of KTS is increasing. Sirolimus (Rapamycin) was introduced in 2011 as the first pharmacologic treatment for complicated vascular anomalies [3]. KTS is part of the PIK3CA-related overgrowth spectrum (PROS), and PIK3CA somatic mutations are present in the majority of KTS patients [3]. PIK3CA mutation results in physiologically inappropriate activation of the PI3K/AKT/mTOR pathway resulting in dysregulated cellular growth and malformed vascular channels [2,3,4,14]. The use of Sirolimus, an mTOR inhibitor and immunosuppressant, has demonstrated improvement in volume of affected areas in some patients with variable improvement in quality of life. Adverse events including blood/bone marrow toxicity have occurred in a significant percentage of patients even at low dose [14, 15]. Study of Sirolimus in KTS is ongoing. As a therapy, Sirolimus is a suppressive, not curative, treatment and may require indefinite use [14,15]. For these reasons, use of Sirolimus in KTS is considered on a case-by-case basis.

Open surgery was traditionally the therapeutic option for venous complications of KTS refractory to conservative management but has fallen out of favor due to wound complications and persistent bleeding [7]. Endovascular interventions for venous complications of KTS have been explored and adopted, although data is limited. This study demonstrates the safety and efficacy of a variety of adjunctive, minimally invasive endovascular therapies for symptomatic venous pathology in KTS, including thermal and chemical ablation, coil embolization, venoplasty and stenting.

Pain and edema were common presenting complaints at 80% and 70%, respectively, and are the most frequently reported symptoms of KTS in the literature [5,6,8,9]. Insufficient anomalous and orthotopic veins may be symptomatic in KTS. Symptomatic anomalous veins were treated in the majority of patients in this study. Symptomatic orthotopic veins presented both with and without accompanying symptomatic anomalous veins and were far more frequent in adult patients. This finding highlights the ongoing effects of venous hypertension in KTS patients which may lead to development and need for treatment of orthotopic veins not typically associated with KTS.

Claudication was a presenting symptom in 25% of patients. All patients with claudication were pre-menopausal adult women with extensive capillary vascular malformations of the affected limb. All had widely patent deep venous systems and absence of underlying arterial disease. All patients reported complete resolution of claudication following endovascular intervention. Venous claudication is generally attributed to vascular inflow-outflow mismatch due to underlying venous outflow restriction [16]. In this study, venous claudication occurred in patients with patent deep veins, indicating that venous claudication in KTS is related to a different vascular inflow-outflow mismatch. In addition to the expected increase in inflow related to exercise, increased inflow also occurs in the presence of extensive capillary vascular

malformations [6], which were present in all claudication patients in this study. When this increased inflow is coupled with the presence of venous insufficiency, which impairs outflow, debilitating venous hypertension with claudication occurs despite the presence of patent deep veins.

Multiple imaging modalities are capable of anatomically assessing the deep and superficial venous systems, including CT, catheter-directed venography, MRI, and duplex US. As with surgery, ensuring the presence of an intact and patent deep venous system is mandatory before considering endovascular treatment of varicosities and VM. MRI and duplex US are the preferred methods for assessing the patency and anatomy of the deep and superficial venous systems [4,17] both in this series and previous published literature due to lack of ionizing radiation. Though widely available, duplex US is operator dependent and therefore, should be performed by experienced vascular technologists. The anatomic complexity of KTS can prove challenging. For this reason, the study institution favors initial KTS evaluation with MRI (including time-resolved MRA and MRV) to assist diagnosis, to characterize the extent of disease, and to demonstrate presence and patency of deep veins. Formal Duplex US is obtained, as needed, for clarification of deep venous patency. Bedside duplex US is performed in clinic after careful history, physical exam, and review of the patient's MRI to assess extent of venous insufficiency, to interrogate veins in areas of symptomatology and to interrogate other MRI abnormalities to assist treatment planning. Diversion venography has a demonstrated role in characterization of suspected hypoplastic or atretic deep veins and should be considered, as needed [18]. Failure to accurately identify occluded or absent deep venous structures in patients undergoing intervention may result in limb loss.

Anatomic deep venous compression may exacerbate KTS. Popliteal vein entrapment requiring release in KTS has been described [10]. Iliac vein compression may co-exist with KTS, as present in one patient in this study, and may be assessed on cross-sectional imaging [11]. Deep venous evaluation in patients with KTS must include assessment for treatable deep venous pathology, as deep and superficial venous interventions are complimentary in managing symptoms. As in the non-KTS venous hypertension population, lesions of deep venous outflow should be addressed prior to treatment of superficial venous disease.

Multiple endovascular therapies for superficial veins are available for patients with KTS and commonly involve sclerotherapy, endovenous ablation, and embolization [2,7,8,9,10,11,19]. These interventions may be employed for both insufficient orthotopic veins and anomalous veins [7,9,19,20]. In this study, incompetent and symptomatic superficial veins were initially addressed with thermal endovenous ablation (RFA or laser) if anatomically feasible; however, microfoam sclerotherapy and cyanoacrylate adhesive may also be used. Excessively tortuous superficial veins and symptomatic varicosities were most frequently treated with US-guided foam sclerotherapy. While stab phlebectomy of varicosities underlying capillary vascular malformations may be safely performed with proper technique [6], some institutions have moved towards catheter-mediated techniques and away from open surgery for KTS as with other venous insufficiency syndromes. In KTS patients with extensive anatomic variation and complex anatomy, venography is used in addition to US to guide superficial venous treatment.

Intervention for persistent sciatic vein and lateral marginal vein warrants special attention, as these veins may exist in proximity to the sciatic nerve and peroneal nerve, which are motor nerves. Intra-procedural nerve monitoring may be considered with endovenous ablation to avoid devastating nerve injury. Even with nerve monitoring, thermal endovenous ablation should only

be considered when the vein and nerve are not intimately associated or can be separated with tumescent anesthesia. Alternatively, non-thermal, chemical ablation of anomalous veins may be performed, with or without coil embolization. Both endovenous ablation with nerve monitoring and chemical ablation were used to treat the lateral marginal vein and persistent sciatic vein in this study, without complication.

The abnormal blood flow associated with VM in KTS, including superficial phlebectasia and multi-compartment venous malformation, may lead to thrombophlebitis and DVT. Venous thromboembolism risk increases in the peri-procedural period. Graduated compression and early ambulation decrease venous stagnation. Anticoagulation is utilized when indicated by patient history or laboratory testing. Despite precautions, activation of the coagulation cascade may result in DVT or LIC, requiring heightened awareness. The development of LIC has been associated with VM surface area, intramuscular involvement, bony involvement, truncal location and VM progression during puberty [21,22]. The formation of focal thrombus seen with LIC usually manifests as significant focal pain. Laboratory analysis demonstrates elevated D-dimer [22,23]. In severe instance, LIC can be characterized by low fibrinogen in addition to elevated D-dimer conveying a high risk of hemorrhage and possible progression to DIC [23]. Aspirin and non-steroidal anti-inflammatory drugs may alleviate pain but are not useful in treating the underlying cause, as it is not a platelet driven process [22,23]. LIC is traditionally treated with LMWH which improves pain associated with thrombosis and prevents progression to DIC. The successful use of oral anti-Xa agents for treatment of LIC has been published in case reports [22,24]. The potential for LIC to progress to DIC or to precipitate life-threatening thrombo-embolic complications underscores the need for pre-operative CBC, PT/INR, aPTT, D-dimer, and fibrinogen levels in high-risk patients. The occurrence of LIC in this study, in a KTS patient with extensive VM,

confirms the existing literature [22]. Clinician awareness is essential, and periprocedural prophylaxis and treatment should be initiated when indicated.

There are limitations to this study, including single-center, retrospective design, with patient reported metrics. Given the complexity and variability of KTS anatomy and pathology, endovascular treatment plan varied by patient and by operator. Finally, as KTS is a rare disease, the study size is small.

Conclusion:

KTS is a rare, complex, congenital vascular anomaly with variable clinical presentation. Consistent with this study, pain and edema are the most commonly reported symptoms. Symptoms may be related to pathology of anomalous and orthotopic superficial veins or deep veins. KTS patients with patent deep venous systems may present with venous claudication due to increased vascular inflow from extensive capillary vascular malformations and impaired outflow related to superficial venous insufficiency. MRI and duplex US evaluation are frequently used modalities to assess deep venous patency and superficial venous anatomy. Compression remains central to management of KTS. Study of Sirolimus in KTS is ongoing. Endovascular intervention is safe and effective for KTS patients who fail conservative management. Clinical success, with complete or partial response to treatment, is expected following endovascular intervention for symptoms related to venous hypertension in KTS. Complications are rare but include localized intravascular coagulopathy.

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Appendix 1

All venous access was performed under real-time ultrasound (US) guidance utilizing 12-5 MHz or 15-7 MHz frequency transducers (Philips, Cambridge, MA). Venous access was obtained with 21-gauge micro puncture needle (Merit Medical, Jordan, Utah), 23- gauge butterfly needle (BD, Franklin Lakes, NJ) or 25-gauge butterfly needle (BD, Franklin Lakes, NJ) based upon operator preference and vessel size. Venography was performed with 50% or greater dilution of iohexol 350 contrast material (GE Healthcare, Chicago, IL). Sclerotherapy was performed with 1% or 3% sodium tetradecyl sulfate (Mylan, Canonsburg, PA) injected directly or injected mixed with air as foam in up to a 1:3 ratio. Sclerotherapy was performed under direct ultrasound guidance or under fluoroscopic guidance following venography. Sclerosant was delivered through butterfly needle, micro puncture needle, 4 French micro puncture sheath (Merit Medical, Jordan, Utah), or via 5 French angiographic catheters (Cook Medical, Bloomington, IN). Venoplasty was performed with non-compliant balloon catheters (BD, Franklin Lakes, NJ). Self-expanding stent (Boston Scientific, Marlborough, MA) was used for persistent venous stenosis refractory to angioplasty. Coil embolization with 0.035” fibered detachable coils (Boston Scientific, Marlborough, MA) was performed for enlarged (diameter 5mm or greater) and incompetent (reflux > 0.5 seconds) draining perforator veins prior to sclerotherapy of persistent embryonic veins. Endovenous ablation was performed following tumescent anesthesia with either radiofrequency system (Medtronic, Fridley, MN) or 1,470 nm diode laser (Angiodynamics, Latham, NY) per manufacturer’s guidelines.

Symptom	Age range (years)	N presenting (%)	N treated	CR (%)	PR (%)
Pain	3-77	16 (80)	14	85.7	14.2
Swelling/edema	2-77	14 (70)	13	84.6	15.4
Bleeding	1-32	2 (10)	2	50	50
Numbness/tingling	29-49	5 (25)	5	40	60
Claudication	29-45	5 (25)	4	100	--

Table I: Presenting symptoms and treatment response of KTS patients

Abbreviations: N presenting= number of patients with that symptom; N presenting (%)= percentage of all patients presenting with that symptom; N treated=number of patients with that symptom who underwent treatment; CR (%)= percentage of patients who demonstrated complete response of that symptom to treatment; PR (%)= percentage of patients who demonstrated partial response of that symptom to treatment.

	Age	Treatment	TreatmentSite	Vein	Anesthesia	Dose(mGy)	#sites	Sclerosant	Complications
1	7	V+sclero	LLE, pelvis	Lat, VM	GA	1.59	3	4mL STS 3%	None
2	7	V+sclero	LLE, pelvis	VM	GA	7.86	6	6mL STS 3%	None
3	8	V+sclero	LLE, pelvis	VM	GA	5.15	3	4mL STS 3%	None
4	8	V+sclero	LLE, pelvis	VM	GA	2.78	5	5mL STS 3%	None
5	9	V+sclero	LLE, pelvis	VM	GA	7.63	4	4mL STS3%	None
6	7	V+sclero	LLE, pelvis	PS, VM	GA	--	4	4 mL STS3%	None
7	8	V+sclero	LLE	VM	GA	--	3	4mL STS3%	None
8	8	V+sclero	LLE	VM	GA	--	3	3mL STS3%	None
9	9	V+sclero	LLE, pelvis	VM	GA	--	3	5mL STS3%	None
10	10	V+sclero	LLE	VM	GA	--	3	5mL STS3%	None
11	11	V+sclero	LLE,	VM	GA	23.60	4	4mL	None

			pelvis					STS3%	
12	11	V+sclero	LLE	VM	GA	2.30	5	4mL STS3%	None
13	11	V+sclero	LLE	VM	GA	1.00	4	3mL STS3%	None
14	12	V+sclero	LLE	VM	GA	--	5	--	None
15	12	V+sclero	LLE	VM	GA	6.72	4	6mL STS3%	None
16	13	V+sclero	LLE	VM	GA	1.68	3	4mL STS3%	None
17	13	V+sclero	LLE	VM	GA	7.23	6	10mL STS3%	None
18	14	V+sclero	LLE, pelvis	VM	GA	12.67	7	8mL STS3%	LIC
19	14	V+sclero	LLE, pelvis	VM	GA	9.96	6	5mL STS3%	LIC
20	15	V+sclero	LLE	VM	GA	2.05	4	4mL STS3%	LIC
21	17	V+sclero +abl	RLE	Lat, PS	GA	1.14	3	2mL STS3%	None
22	26	Abl	LLE	GSV	Sedation	n/a	1	n/a	None
23	26	US abl+ sclero	LLE	Perf x 2, vv	Sedation	n/a	4	--	None

24	30	V+sclero + abl	LLE	GSV, SSV, Lat	Sedation	0.35	4	1mL STS3%	None
25	29	V+PTA+ stent	Pelvis	CIV	Sedation	32.00	1	n/a	None
26	29	Abl	LLE	GSV, SSV	Sedation	n/a	2	n/a	None
27	30	V+sclero	LLE	GSV, vv	Sedation	9.6	1	1mL STS3%	None
28	30	US abl+ sclero	LLE	Lat, perf	Sedation	n/a	2	--	None
29	31	US sclero	LLE	SSV	Sedation	n/a	1	1mL STS3%	None
30	33	US abl+ sclero	LLE	AASV, Lat	Sedation	n/a	2	4mL STS3%	None
31	29	US sclero	LLE	Lat	Sedation	n/a	1	--	None
32	33	V+sclero + abl	LLE	GSV, Lat	GA	1.27	2	--	None
32	32	V+sclero	Pelvis	vv	GA	17.00	1	1mL STS3%	None
34	45	Abl	RLE	GSV	Sedation	n/a	1	n/a	None
35	46	US sclero	RLE	GSV, vv	Sedation	n/a	1	--	None

36	75	Abl	LLE	GSV	Sedation	n/a	1	n/a	None
37	1	V+sclero	LLE	VV	GA	4.0	2	0.4mL STS3%	None
38	2	US sclero	LLE	Lat	GA	n/a	4	--	None
39	3	V+sclero	LLE	VV	GA	4.26	3	0.5mL STS3%	None
40	4	V+sclero + abl	LLE	AASV, Lat	GA	0.68	3	1mL STS3%	None
41	6	V+sclero + coils	LLE	Lat, PS	GA	12.56	4	4mL STS3%	None
42	31	US abl+ sclero	RLE	GSV, AASV, vv	GA	n/a	3	--	None
43	33	Abl	LLE	GSV	Sedation	n/a	1	n/a	None
44	30	V+sclero + abl	LLE	GSV, AASV, vv	Sedation	--	2	2mL STS1%	None
45	33	US abl+ sclero	LLE	GSV, vv	Sedation	n/a	4	--	None
46	16	US sclero	RLE	Lat	Sedation	n/a	1	0.5mL STS1%	None

1

2 **Table II: Endovascular treatment details**

Abbreviations: LLE= left lower extremity, RLE= right lower extremity, # sites= number of treatment access sites per session, V = venography, abl = endovenous radiofrequency or laser ablation, sclero = sclerotherapy, US = ultrasound, PTA = angioplasty, VM= multi-compartment venous malformation, GSV= great saphenous vein, SSV= small saphenous vein, AASV= anterior accessory saphenous vein, Lat= lateral marginal vein, PS= persistent sciatic vein, Perf= perforator vein, vv= varicose veins (unnamed), CIV= common iliac vein, -- not available, n/a = not applicable.

Figure 1: Kaplan-Meier estimation of reintervention free survival

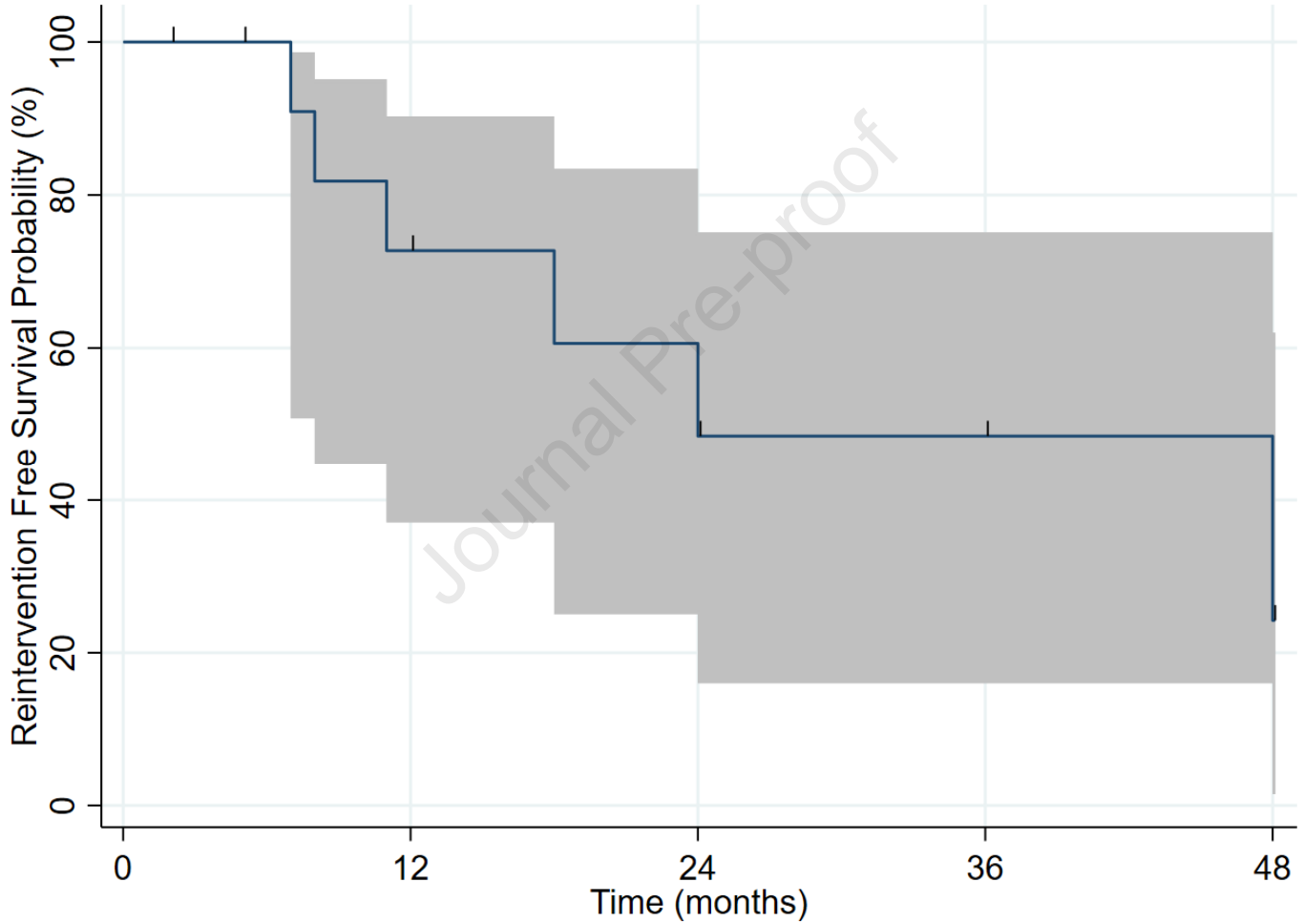

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Figure 1: Kaplan-Meier estimation for reintervention free survival

The number of patients at risk and the number of censored patients are shown below each respective time point. Censored patients are demarcated on the survival curve with a hash mark. The 95% confidence interval is outlined in gray. Median re-intervention free survival time is 24 months with a standard error of 13.70 months.