Clinical presentation and outcomes after endovascular management in a mixed pediatric and adult Klippel-Trenaunay syndrome population

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ABSTRACT

Objective: We retrospectively studied 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: We performed a retrospective study of patients with KTS who had been referred for endovascular intervention after evaluation and diagnosis by a multidisciplinary team at a single academic medical center during a 10-year period. The patient demographics, areas affected, presenting symptoms, previous treatments, imaging modalities, endovascular treatment types, number of treatments, and complications were assessed. The technical and clinical success rates were calculated.

Results: Twenty-six patients with suspected KTS were evaluated. Of these 26 patients, 20, aged 2 to 75 years, had been diagnosed with KTS using the International Society for the Study of Vascular Anomalies criteria and referred for endovascular management. The left lower extremity was affected most often. The presenting symptoms were pain (80%), edema (70%), bleeding (10%), numbness (25%), and claudication (25%). Of the 20 patients, 16 (80%) had undergone treatment of KTS before presenting to our institution. Magnetic resonance imaging and ultrasound (US) were the most common imaging modalities. Fifteen patients underwent 46 endovascular treatments during the study period. The treatments 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 was the only procedure-related complication and occurred in one patient after three treatments. The technical success rate was 97.8%, and the clinical success rate was 100%.

Conclusion: Endovascular intervention is safe and effective for KTS patients for whom conservative management has failed. Pain and edema were the most common presenting symptoms. Presenting symptoms may be related to pathology of anomalous veins, orthotopic superficial veins or deep veins. Venous claudication can be present in those with KTS despite patency of the deep venous system. Magnetic resonance imaging and duplex US are frequently used modalities for venous assessment. The complications of endovascular treatment are rare but include localized intravascular coagulopathy. (J Vasc Surg Venous Lymphat Disord 2021;■:1-9.)

Keywords: Anomalous vein; Endovascular; Localized intravascular coagulopathy; Klippel-Trenaunay syndrome; Venous claudication

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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 malformations.[1] In the past decade, an association with a PIK3CA somatic gene mutation has been identified, although this is not a criterion for a diagnosis of KTS nor is it universally present in those with KTS.[2-4] Although ≤50% of those with KTS will have no clinically significant issues or debilitation, the remainder will be significantly affected 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 can be considered. During the past decades, vascular intervention for those with KTS has shifted from open surgery to an endovascular approach.[5-11] The literature pertaining to the endovascular management of KTS is limited and largely composed of case reports. The largest KTS studies to date involved surgical management or a combination of surgical and endovascular management.[6,8] The purpose of the present study was 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.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, retrospective cohort study
- **Key Findings:** Of 20 patients with Klippel-Trenaunay syndrome (KTS), 15 had undergone endovascular intervention for symptoms related to venous pathology of KTS refractory to compression therapy. The technical success rate was 97.8%, clinical success rate was 100%, and complication rate was 6.7% (one patient; Clavien-Dindo classification, grade II).
- **Take Home Message:** Endovascular intervention is safe and effective for KTS patients for whom conservative management has failed.

METHODS

After institutional review board approval, including an institutional review board–approved waiver of informed patient consent, patients with congenital anomalies and a presumed diagnosis of KTS who had been referred for multidisciplinary evaluation at a single academic medical center from 2009 to 2019 were retrospectively identified. All of the patients who underwent multidisciplinary evaluation had undergone cross-sectional imaging studies. Cross-sectional imaging studies of the affected area that had been performed at outside institutions, when available, were reviewed. Patients without cross-sectional imaging studies or requiring additional imaging studies had undergone 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 examinations were obtained, as needed, for diagnosis and/or clarification of deep venous patency and were performed in compliance with the Intersociety Accreditation Committee standards for peripheral venous testing.[12] The inclusion criteria included a diagnosis of KTS using the ISSVA criteria after the multidisciplinary evaluation, symptoms not relieved by conservative management with compression, venous pathology identifiable by imaging studies or physical examination, patent deep veins, and performance of endovenous intervention at our institution. The exclusion criteria included failure to meet the ISSVA criteria for KTS, the absence of a deep venous system in the affected anatomic area, resolution of symptoms with conservative measures, the absence of superficial or deep venous pathology suitable for intervention, and no endovenous intervention performed at our institution. Patient age was documented as the age at the initial referral for endovascular intervention at our academic medical center. Patient age was assessed using defined categories: infant, 0 to 1 year; child, 2 to 12 years; adolescent, 13 to <18 years, and adult, ≥18 years. The mean patient age was calculated. Sex was documented in binary fashion as male or female. The affected area was defined as the extremity involved with or without adjacent truncal extension. The 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, which was defined as debilitating muscle cramping with activity that was not attributable to underlying deep venous pathology or underlying arterial disease. Previous treatments were documented as reported by the patient or family or from the outside medical records.

Technical success was defined as the successful completion of the intended intervention, with the intent of occlusion of the vessels undergoing embolization, endovenous ablation, or sclerotherapy. Clinical success was defined as the complete or partial resolution of the preprocedure symptoms after endovascular treatment, assessed at the initial postprocedure clinic follow-up examination. A complete response was defined as resolution of the presenting symptoms. A partial response and no response were defined as improvement and no change, respectively, in the frequency, severity, and degree of debilitation of the presenting symptoms. Complications related to treatment were assessed using Clavien-Dindo classification, which has been validated across surgical subspecialties.[13] A standard complication

classification system has not been defined for KTS. The treatment response was assessed at the initial postprocedure clinic follow-up examination.

Technique. The procedures for patients aged ≤18 years were performed with the patient under general anesthesia. The procedures for patients aged >18 years were performed with the patient under moderate sedation or general anesthesia, depending on the anticipated procedure length, expected procedure-related pain, and patient comorbidities. The complete blood count, activated partial thromboplastin time, prothrombin time or international normalized ratio, and basic chemistry panel were obtained before all procedures. The fibrinogen and D-dimer levels were measured for patients with extensive VM, defined as those with VMs with intramuscular or bony involvement or involving >25% of the surface area of the affected region. A standard sterile technique was used. Preprocedural antibiotics were given to the patients undergoing sclerotherapy, coil embolization, and stent placement. The technical details for venous access, venography, sclerotherapy, venoplasty, stent placement, coil embolization, and endovenous ablation are provided in the Appendix (online only). Intraprocedural nerve monitoring was performed during endovenous radiofrequency and laser ablation of persistent sciatic and lateral marginal veins. At the conclusion of each procedure, immediately after placement of sterile dressings, the patient's prefitted compression garment was applied. Early ambulation or mobilization was performed 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, the patients were discharged on the day of intervention after anesthesia or sedation recovery and ambulation.

Telephone follow-up was performed 2 to 5 days after the procedure. The initial postprocedure clinic follow-up visit was scheduled for 8 weeks after treatment. Subsequent clinic follow-up visits were generally scheduled every 6 to 12 months. Clinic follow-up examinations for patients with extensive VMs requiring staged treatment were scheduled every 2 to 3 months. The patients were also seen in the clinic, as needed, for new, recurrent, or worsening symptoms. Doppler US was performed by the interventional radiologist during the clinic visits for new, recurrent, or worsening symptoms and for treatment planning during the preprocedure visits. Duplex US to assess for deep vein thrombosis (DVT) was performed at 1 week after the procedure. Follow-up MRI was not routinely performed but was obtained for new, recurrent, or worsening symptoms that were not clarified by the duplex US findings.

Statistical analysis. Descriptive statistics were performed for the anatomic areas affected by KTS and presenting symptoms, and the proportion of patients previously treated for KTS at outside institutions was calculated. The pretreatment noninvasive imaging modalities were recorded. All types of MRI, including time-resolved MRA and MRV, were included as MRI. The total number of procedures was tallied, and the mean treatment number per patient was calculated. Endovascular treatments were categorized by type and site, and the number of each was tallied. The median clinical follow-up after the initial procedure and after the last procedure was calculated. The clinical and technical success rates were calculated. A Kaplan-Meier estimation for reintervention-free survival was performed using Stata, version 16 (StataCorp, College Station, Tex).

RESULTS

From 2009 to 2019, 26 patients with congenital anomalies had been referred to a single academic medical center with a presumed diagnosis of KTS. After multidisciplinary review, 20 patients were confirmed to have a diagnosis of KTS using the ISSVA criteria. The patients not meeting the ISSVA criteria for KTS included four with a diagnosis of isolated capillary vascular malformation and two with a diagnosis of Parkes-Weber syndrome following identification of underlying arteriovenous malformations using MRI with time-resolved MRA.

The 20 patients with a confirmed diagnosis of KTS included 3 males (15%) and 17 females (85%). The average patient age at presentation was 23.1 years (range, 2-75 years), including 1 infant, 5 children, 2 adolescents, and 12 adults. The areas primarily affected by KTS included the left lower extremity in eight, left lower extremity and pelvis in five, right lower extremity in four, right lower extremity and pelvis in two, and left upper extremity in one patient. Two patients had had accompanying microcystic lymphatic malformations of the affected areas. The 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 two patients with accompanying microcystic lymphatic malformations, one had had primary complaint of bleeding from scrotal varicosities and the urethra, and the other had presented with subjective worsening of edema.

Of the 20 patients with a KTS diagnosis, 16 (80%) had been previously treated for KTS before presenting to our institution. The previous treatments included compression only in 1 patient, pulsed-dye laser of a 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. The previous treatments of three patients included treatment of anomalous veins or varicose veins, two with stab phlebectomy at surgical debulking and one with sclerotherapy. All three patients had had clinical success

Table I. Presenting symptoms and treatment response of KTS patients

Symptom	Age range, years	Patients presenting with symptom, no. (%)	Patients treated, No.	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	0

CR, Complete response; *PR*, partial response.

without recurrence of the treated veins. All previously treated patients had presented to our institution with new, progressive, or recurrent symptoms. The noninvasive imaging modalities used before evaluation and/or before treatment included MRI in 18, computed tomography (CT) in 2, and formal duplex US performed by the vascular laboratory in 3 patients. Fifteen patients had undergone additional pretreatment bedside planning duplex US in the clinic for assessment of venous insufficiency, interrogation of the veins in the areas of the symptoms, and interrogation of MRI or CT abnormalities to assist in treatment planning.

Of the 20 patients with a confirmed KTS diagnosis, 5 were excluded from the present study. Two patients had experienced resolution of their presenting symptoms after obtaining custom compression garments. One patient who had previously been treated at an outside institution for incompetent superficial veins and had presented with ongoing venous claudication underwent catheter venography, which failed to demonstrate a deep venous stenosis reported on an outside MRI study; thus, intervention was not performed. One patient had undergone treatment at another institution. One patient with accompanying microcystic lymphatic malformations and subjective worsening of edema was lost to follow-up after the initial evaluation. The remaining 15 patients met the inclusion criteria and had undergone 46 endovascular treatments (mean, 3.1; median, 2 treatments per patient; range, 1-15) during a 10-year period (Fig). Seven patients had undergone multiple procedures. Four had undergone staged treatments for extensive venous malformations and were reassessed after each procedure. Two of these four patients had experienced new or recurrent symptoms after the initial staged treatments, which prompted additional treatment. Three patients had undergone additional treatment of new varicosities or symptoms arising after the initial treatment and follow-up. The additional treatments were for new or progressive pathology in previously untreated veins, not involving the previously treated venous structures.

The treatment details are presented in Table II. The 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 three persistent sciatic veins were treated. Lateral marginal veins were treated with sclerotherapy alone in eight patients, sclerotherapy with coil embolization in one patient, and sclerotherapy with ablation in one patient. Persistent sciatic veins were treated with sclerotherapy in one patient, sclerotherapy with coil embolization in one patient, and endovenous ablation with nerve monitoring in one patient. The mean age at the treatment of symptomatic anomalous veins was 10.0 years (6-17 years) and 17.7 years (range, 2-33 years) for persistent sciatic and lateral marginal veins, respectively. The mean age at the treatment of symptomatic orthotopic veins was 37.1 years (range, 26-75 years), 30.0 years (range, 29-31 years), and 20.8 years (range, 4-33 years) for great saphenous, small saphenous, and anterior accessory saphenous veins, respectively. Symptoms related exclusively to orthotopic veins were

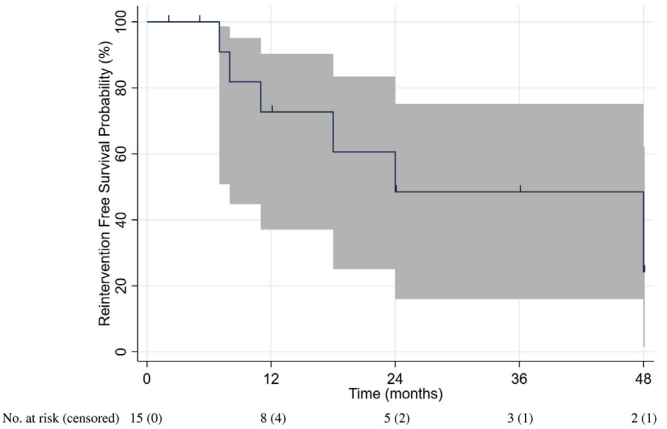

Fig. Kaplan-Meier estimation for reintervention-free survival. The number of patients at risk and the number of censored patients are shown below each respective time point. Censored patients are demarcated on the survival curve with a *hash mark*. The 95% confidence interval is outlined in *gray*. The median reintervention-free survival time was 24 months, with a standard error of 13.70 months.

Table II. Endovascular treatment details

Procedure No.	Age, years	Treatment	Treatment site	Vein	Anesthesia	Dose, mGy	Treatment access sites, No.	Sclerosant	Complications
1	7	V + S	LLE, pelvis	LMV, VM	GA	1.59	3	4 mL STS 3%	None
2	7	V + S	LLE, pelvis	VM	GA	7.86	6	6 mL STS 3%	None
3	8	V + S	LLE, pelvis	VM	GA	5.15	3	4 mL STS 3%	None
4	8	V + S	LLE, pelvis	VM	GA	2.78	5	5 mL STS 3%	None
5	9	V + S	LLE, pelvis	VM	GA	7.63	4	4 mL STS 3%	None
6	7	V + S	LLE, pelvis	PS, VM	GA	NR	4	4 mL STS 3%	None
7	8	V + S	LLE	VM	GA	NR	3	4 mL STS 3%	None
8	8	V + S	LLE	VM	GA	NR	3	3 mL STS 3%	None
9	9	V + S	LLE, pelvis	VM	GA	NR	3	5 mL STS 3%	None
10	10	V + S	LLE	VM	GA	NR	3	5 mL STS 3%	None
11	11	V + S	LLE, pelvis	VM	GA	23.60	4	4 mL STS 3%	None
12	11	V + S	LLE	VM	GA	2.30	5	4 mL STS 3%	None
13	11	V + S	LLE	VM	GA	1.00	4	3 mL STS 3%	None
14	12	V + S	LLE	VM	GA	NR	5	NR	None
15	12	V + S	LLE	VM	GA	6.72	4	6 mL STS 3%	None
16	13	V + S	LLE	VM	GA	1.68	3	4 mL STS 3%	None
17	13	V + S	LLE	VM	GA	7.23	6	10 mL STS 3%	None
18	14	V + S	LLE, pelvis	VM	GA	12.67	7	8 mL STS 3%	LIC
19	14	V + S	LLE, pelvis	VM	GA	9.96	6	5 mL STS 3%	LIC
20	15	V + S	LLE	VM	GA	2.05	4	4 mL STS 3%	LIC
21	17	V + S + A	RLE	LMV, PS	GA	1.14	3	2 mL STS 3%	None
22	26	A	LLE	GSV	Sedation	NA	1	NA	None
23	26	US-guided A + S	LLE	PV × 2, VVs	Sedation	NA	4	NR	None
24	30	V + S + A	LLE	GSV, SSV, LMV	Sedation	0.35	4	1 mL STS 3%	None
25	29	V + PTA + stenting	Pelvis	CIV	Sedation	32.00	1	NA	None
26	29	A	LLE	GSV, SSV	Sedation	NA	2	NA	None
27	30	V + S	LLE	GSV, VV	Sedation	9.6	1	1 mL STS 3%	None
28	30	US-guided A + S	LLE	LMV, PV	Sedation	NA	2	NR	None
29	31	US-guided S	LLE	SSV	Sedation	NA	1	1 mL STS 3%	None
30	33	US-guided A + S	LLE	AASV, LMV	Sedation	NA	2	4 mL STS 3%	None
31	29	US-guided S	LLE	LMV	Sedation	NA	1	NR	None
32	33	V + S + A	LLE	GSV, LMV	GA	1.27	2	NR	None
32	32	V + S	Pelvis	VVs	GA	17.00	1	1 mL STS 3%	None
34	45	A	RLE	GSV	Sedation	NA	1	NA	None
35	46	US-guided S	RLE	GSV, VVs	Sedation	NA	1	NR	None
36	75	A	LLE	GSV	Sedation	NA	1	NA	None
37	1	V + S	LLE	VVs	GA	4.0	2	0.4 mL STS 3%	None
38	2	US-guided S	LLE	LMV	GA	NA	4	NR	None
39	3	V + S	LLE	VVs	GA	4.26	3	0.5 mL STS 3%	None
40	4	V + S + A	LLE	AASV, LMV	GA	0.68	3	1 mL STS 3%	None
41	6	V + S + coils	LLE	LMV, PS	GA	12.56	4	4 mL STS 3%	None
42	31	US-guided A + S	RLE	GSV, AASV, VVs	GA	NA	3	NR	None

(Continued on next page)

Table II. Continued.

Procedure No.	Age, years	Treatment	Treatment site	Vein	Anesthesia	Dose, mGy	Treatment access sites, No.	Sclerosant	Complications
43	33	A	LLE	GSV	Sedation	NA	1	NA	None
44	30	V + S + A	LLE	GSV, AASV, VVs	Sedation	NR	2	2 mL STS 1%	None
45	33	US-guided A + S	LLE	GSV, VVs	Sedation	NA	4	NR	None
46	16	US-guided S	RLE	LMV	Sedation	NA	1	0.5 mL STS 1%	None

A, Endovenous radiofrequency or laser ablation; *AASV*, anterior accessory saphenous vein; *CIV*, common iliac vein; *GSV*, great saphenous vein; *LLE*, left lower extremity; *LMV*, lateral marginal vein; *NA*, not applicable; *NR*, not reported; *PS*, persistent sciatic vein; *PTA*, percutaneous angioplasty; *PV*, perforator vein; *RLE*, right lower extremity; *S*, sclerotherapy; *SSV*, small saphenous vein; *STS*, sodium tetradecyl sulfate; *US*, ultrasound; *V*, venography; *VM*, multicompartment venous malformation; *VVs*, varicose veins (unnamed).

only present in the adult patients. One pediatric patient had 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, which was later confirmed by catheter venography and intravascular US. The patient was ultimately treated with angioplasty and stent placement. After this intervention, the patient proceeded to treatment of the 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 after treatment of the superficial veins on the affected extremity. For 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 performed. The intended endovenous intervention was successfully performed in all other procedures. The technical success rate was 97.8%.

The median follow-up was 2.5 years (range, 2 months to 8 years) from the first treatment and 1 year (range, 2 months to 4 years) from the last treatment. No major complications developed. No cases of post-treatment DVT, endovenous heat-induced thrombosis, skin burn, ulceration, motor nerve injury, or nontarget embolization developed. Three Clavien-Dindo grade II complications occurred, all of which were localized intravascular coagulopathy (LIC). LIC had occurred after three treatments in one patient. One patient with extensive muscular venous channels affecting her left lower extremity and pelvis had developed LIC at age 14 years after undergoing multiple previous treatments uncomplicated by LIC. In her case, the D-dimer level was elevated beyond the upper limits of detection and therapeutic low-molecular-weight heparin (LMWH) was started. This patient's follow-up and ongoing LIC management were coordinated with our hematology colleagues. After the initial LIC event, the patient received prophylactic LMWH in the postoperative period alone. However, she experienced LIC despite prophylactic LMWH and sporadic LIC unrelated to the treatments. Subsequently, an ongoing prophylactic dose of LMWH was used for the prevention of the sporadic LIC events unrelated to treatment, with a therapeutic dose LMWH used in the periprocedural period for the remainder of her treatment course. The patient's LIC was controlled without progression to disseminated intravascular coagulopathy (DIC).

The clinical success rate was 100% (Table I). Complete or partial resolution of pain was documented in all 14 treated patients, with complete resolution in 12 (85.7%) and partial resolution in 2 (14.2%) patients. Two of the patients who had initially presented with pain had not undergone treatment. Complete or partial improvement in swelling/edema occurred in all 13 treated patients, with complete resolution in 11 (84.6%) and partial resolution in 2 (15.4%). One patient with swelling was not treated. Bleeding had resolved or decreased in two patients, with resolution in one (50%) and a reduction in one (50%). Resolution or improvement of numbness/tingling had occurred in all five patients, with resolution in two (40%) and improvement in three (60%). Complete resolution of venous claudication had occurred in all four treated patients (100%). One patient with venous claudication was not treated.

DISCUSSION

Compression therapy is considered the cornerstone of management of KTS.[5-11] Many KTS patients will require additional treatment or intervention. The medical management of KTS has been increasing. Sirolimus (rapamycin) was introduced in 2011 as the first pharmacologic treatment of complicated vascular anomalies.[3] KTS is a part of the PIK3CA-related overgrowth spectrum, and PIK3CA somatic mutations are present in most patients with KTS.[3] A PIK3CA mutation results in physiologically inappropriate activation of the PI3K/AKT/mTOR pathway causing dysregulated cellular growth and malformed vascular channels.[2-4,14] The use of sirolimus, an mTOR

inhibitor and immunosuppressant, has demonstrated improvement in the volume of the affected areas in some patients, with variable improvement in their quality of life. Adverse events, including blood/bone marrow toxicity, have occurred in a significant proportion of patients even at low doses.[14,15] The study of sirolimus to treat KTS is ongoing. Sirolimus is a suppressive, not curative, treatment and might require indefinite use.[14,15] For these reasons, the use of sirolimus to treat KTS should be considered on a case-by-case basis.

Open surgery has traditionally been the therapeutic option for venous complications of KTS refractory to conservative management but has fallen out of favor because of wound complications and persistent bleeding.[7] Endovascular interventions for venous complications of KTS have been explored and adopted, although the reported data are limited. The results from the present study have demonstrated 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 have been the most frequently reported symptoms of KTS in the literature.[5,6,8,9] Insufficient anomalous and orthotopic veins can be symptomatic in those with KTS. Symptomatic anomalous veins were treated in most of the patients in the present study. Symptomatic orthotopic veins had been present 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 can lead to the development and need for treatment of orthotopic veins not typically associated with KTS.

Claudication was a presenting symptom in 25% of our patients. At the time of presentation, all of the patients with claudication had been premenopausal adult women with extensive capillary vascular malformations of the affected limb. All had had widely patent deep venous systems and the absence of underlying arterial disease. All the patients had reported complete resolution of claudication after endovascular intervention. Venous claudication is generally attributed to a vascular inflow–outflow mismatch due to underlying venous outflow restriction.[16] In the present 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 will also occur in the presence of extensive capillary vascular malformations,[6] which were present in all the patients with claudication in the present study. When this increased inflow is coupled with venous insufficiency, which impairs outflow, debilitating venous hypertension with claudication will occur 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 VMs. MRI and duplex US are the preferred methods for assessing the patency and anatomy of the deep and superficial venous systems,[4,17] in both the present series and previous reported data owing to the lack of ionizing radiation. Although widely available, duplex US is operator dependent and, therefore, should be performed by experienced vascular technologists. The anatomic complexity of KTS can prove challenging. Thus, we have favored an initial KTS evaluation with MRI (including time-resolved MRA and MRV) to assist in the diagnosis, characterize the extent of disease, and demonstrate the presence and patency of the deep veins. Formal Duplex US will be obtained, as needed, for clarification of deep venous patency. Bedside duplex US will be performed in the clinic after careful history, physical examination, and a review of the patient's MRI studies to assess the extent of venous insufficiency, interrogate the veins in the areas of symptoms, and interrogate other MRI abnormalities to assist in treatment planning. Diversion venography has a demonstrated role in the 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 could result in limb loss.

Anatomic deep venous compression can exacerbate KTS. Popliteal vein entrapment requiring release in KTS has been described.[10] Iliac vein compression can coexist with KTS and was present in one patient in the present study. Iliac vein compression can be assessed using cross-sectional imaging.[11] Deep venous evaluation of patients with KTS must include an assessment of treatable deep venous pathology, because 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 before the treatment of superficial venous disease.

Multiple endovascular therapies for superficial veins are available for patients with KTS and usually involve sclerotherapy, endovenous ablation, and embolization.[2,7-11,19] These interventions can be used for both insufficient orthotopic veins and anomalous veins.[7,9,19,20] In the present study, incompetent and symptomatic superficial veins were initially addressed with thermal endovenous ablation (radiofrequency or laser ablation) if anatomically feasible. However, microfoam sclerotherapy and cyanoacrylate adhesive can also be used. Excessively tortuous

superficial veins and symptomatic varicosities were most frequently treated with US-guided foam sclerotherapy. Although stab phlebectomy of varicosities underlying capillary VMs can be safely performed with proper technique,[6] some institutions have moved toward catheter-mediated techniques and away from open surgery for KTS just as for other venous insufficiency syndromes. In KTS patients with extensive anatomic variation and complex anatomy, venography can be used, in addition to US, to guide superficial venous treatment.

Intervention for persistent sciatic veins and lateral marginal veins warrants special attention, because these veins can exist in proximity to the sciatic nerve and peroneal nerve, which are motor nerves. Intraprocedural nerve monitoring can 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, nonthermal, chemical ablation of the anomalous veins can be performed, with or without coil embolization. Both endovenous ablation with nerve monitoring and chemical ablation were used to treat lateral marginal veins and persistent sciatic veins in the present study, without complications.

The abnormal blood flow associated with VMs in KTS, including superficial phlebectasia and multicompartment venous malformation, can lead to thrombophlebitis and DVT. The venous thromboembolism risk increases in the periprocedural period. The use of graduated compression and early ambulation decrease venous stagnation. Anticoagulation should be used when indicated by the patient history or laboratory test results. Despite precautions, activation of the coagulation cascade can result in DVT or LIC, requiring heightened awareness. The development of LIC has been associated with the VM surface area, intramuscular involvement, bony involvement, truncal location, and VM progression during puberty.[21,22] The formation of focal thrombus seen with LIC will usually manifest as significant focal pain. Laboratory analysis will demonstrate elevated D-dimer levels.[22,23] In severe cases, LIC can be characterized by low fibrinogen levels, in addition to elevated D-dimer, conveying a high risk of hemorrhage and possible progression to DIC.[23] Aspirin and nonsteroidal anti-inflammatory drugs can be used to alleviate pain but are not useful in treating the underlying cause, because it is not a platelet-driven process.[22,23] LIC has traditionally been treated with LMWH, which will improve the pain associated with thrombosis and prevent progression to DIC. The successful use of oral anti-Xa agents for the treatment of LIC has been described in case reports.[22,24] The potential for LIC to progress to DIC or to precipitate life-threatening thromboembolic complications underscores the need for preoperative testing of the complete blood count, prothrombin time or international normalized ratio, activated partial thromboplastin time, D-dimer, and fibrinogen levels in high-risk patients. The occurrence of LIC in the present study in a KTS patient with extensive VMs has confirms the reported data.[22] Clinician awareness is essential, and periprocedural prophylaxis and treatment should be initiated when indicated.

The present study had limitations, including the single-center, retrospective design, with patient-reported metrics. Given the complexity and variability of KTS anatomy and pathology, the endovascular treatment plan varied by patient and operator. Finally, because KTS is a rare disease, the study size was small.

CONCLUSION

KTS is a rare, complex, congenital vascular anomaly with a variable clinical presentation. Consistent with the results from the present study, pain and edema are the most commonly reported symptoms. The symptoms can be related to pathology of the anomalous and orthotopic superficial veins or deep veins. KTS patients with patent deep venous systems can 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 the management of KTS. The study of sirolimus to treat KTS is ongoing. We found that endovascular intervention is safe and effective for KTS patients for whom conservative management has failed. Clinical success, with a complete or partial response to treatment, can be expected after endovascular intervention for symptoms related to venous hypertension in KTS. Complications are rare but include LIC.

AUTHOR CONTRIBUTIONS

Conception and design: KN, AL, NA
Analysis and interpretation: KN, RB, AL, LF, KK, JN, NA
Data collection: KN, RB, HJ, LF
Writing the article: KN, RB, NA
Critical revision of the article: KN, RB, AL, HJ, LF, KK, JN, NA
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APPENDIX (online only).

All venous access was performed under real-time ultrasound (US) guidance using 12.5-MHz or 15.7-MHz frequency transducers (Philips, Cambridge, Mass). Venous access was obtained with a 21-gauge micropuncture needle (Merit Medical, Jordan, Utah), 23-gauge butterfly needle (BD, Franklin Lakes, NJ), or 25-gauge butterfly needle (BD, Franklin Lakes, NJ) based on operator preference and vessel size. Venography was performed with ≥50% dilution of iohexol 350 contrast material (GE Healthcare, Chicago, Ill). 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 US guidance or fluoroscopic guidance after venography. The sclerosant was delivered through a butterfly needle, micropuncture needle, or 4F micropuncture sheath (Merit Medical) or via 5F angiographic catheters (Cook Medical, Bloomington, Ind). Venoplasty was performed with noncompliant balloon catheters (BD). A self-expanding stent (Boston Scientific, Marlborough, Mass) was used for persistent venous stenosis refractory to angioplasty. Coil embolization with 0.035-in. fibered detachable coils (Boston Scientific) was performed for enlarged (diameter, ≥5 mm) and incompetent (reflux, >0.5 second) draining perforator veins before sclerotherapy of persistent embryonic veins. Endovenous ablation was performed after tumescent anesthesia with either a radiofrequency system (Medtronic, Fridley, Minn) or 1470-nm diode laser (Angiodynamics, Latham, NY) in accordance with the manufacturer's guidelines.