

# Diagnosis and management of the venous malformations of Klippel-Trénaunay syndrome



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## ABSTRACT

**Objective:** A dearth of information exists in the literature regarding current practice in the management of Klippel-Trénaunay syndrome (KTS), a rare condition. We review and describe the etiology, diagnosis, and treatment of KTS.

**Methods:** Relevant data were synthesized from a Medline review using a combination of the keyterms "Klippel" and "Trénaunay." The majority of hits described singular case reports and were subsequently excluded. The remaining papers were then reviewed and included on the basis of the quality of evidence and the authors' discretion.

**Conclusions:** KTS is characterized by a clinical triad of extremity varicosities, cutaneous vascular malformations, and hypertrophy of soft tissues and long bones. The diagnosis is clinically supplemented with magnetic resonance imaging and computed tomography. Although this syndrome is associated with significant comorbidities, such as pain, edema, ulcerations, and pruritus, it is rarely the cause of death. The backbone of treatment is nonoperative in nature but should be supplemented with minimally invasive, endovascular, and rarely open surgical procedures for refractory cases. (J Vasc Surg: Venous and Lym Dis 2017;5:587-95.)

Vascular malformations of Klippel-Trénaunay syndrome (KTS) usually affect the capillary, venous, and lymphatic systems of the lower extremities. Rarely, these defects are seen in the upper extremities, are bilateral, or involve the trunk. Although first described by Hilaire in 1832, KTS was truly recognized as an entity in itself by its namesakes at the turn of the 20th century.<sup>1</sup> The duo of Frenchmen defined a cohort of patients presenting with a triad of asymmetric limb hypertrophy, localized capillary malformation (*nevus flammeus*, "port-wine stain"), and congenital lower extremity varicosities. Although KTS is generally benign in course, the diseased limb can exhibit pain, swelling, hyperpigmentation, thrombophlebitis, variceal bleeding, and ulceration.

Shortly after description by Klippel and Trénaunay, Weber designated a similar vascular syndrome with the addition of arteriovenous fistulas termed the Parkes Weber syndrome.<sup>2</sup> This separate pathologic process has been the source of much confusion since the mid-20th century as clinicians have often ascribed one as the other. However, there are crucial differences that affect the clinical course. With the addition of high-flow arteriovenous fistulas, those suffering from Parkes Weber syndrome have a decreased life span and more

significant arterial complications compared with the more benign KTS.

Much effort has been made to unify the criteria of KTS to clarify the clinical condition, the first step in diagnosis and management. Currently, the best classification of venous malformations, of which KTS is one, is the Hamburg classification of congenital vascular malformations. By use of this tool, KTS would be classified as a predominantly venous defect of the truncular anatomic form presenting with aplasia, obstruction, or dilation. Truncular forms arise after developmental arrest and during vascular trunk formation; in other words, these lesions do not have the ability to proliferate after removal.<sup>3,4</sup>

The true pathogenesis of KTS has been elusive. Whereas most patients demonstrate a normal karyotype, sporadic translocations have been reported of chromosomes 5 to 11 and 8 to 14; a supernumerary ringed chromosome 18 has also been described. Familial cases are rarely (and often unreliably) reported.<sup>5</sup> The affected limbs tend to exhibit increased blood flow; this has been thought to be related to vascular endothelial growth factor-mediated angiogenesis, but no definitive evidence has been brought forth. There also may be involvement of gain-of-function *PIK3CA* gene mutations causing upregulation of AKT and mammalian target of rapamycin (mTOR) signaling.<sup>6</sup> Phosphoinositide 3-kinase and mTOR inhibitors are currently being investigated as treatment options with promising results in mice and humans.<sup>7-9</sup> At least six hypothetical causes of KTS have been suggested in the literature, of which none completely explains the entire clinical spectrum.<sup>5</sup>

## PRESENTATION

KTS is clinically diagnosed by the observation of a triad of cutaneous capillary malformations, varicosities, and hypertrophy of soft tissues and long bones. However, a

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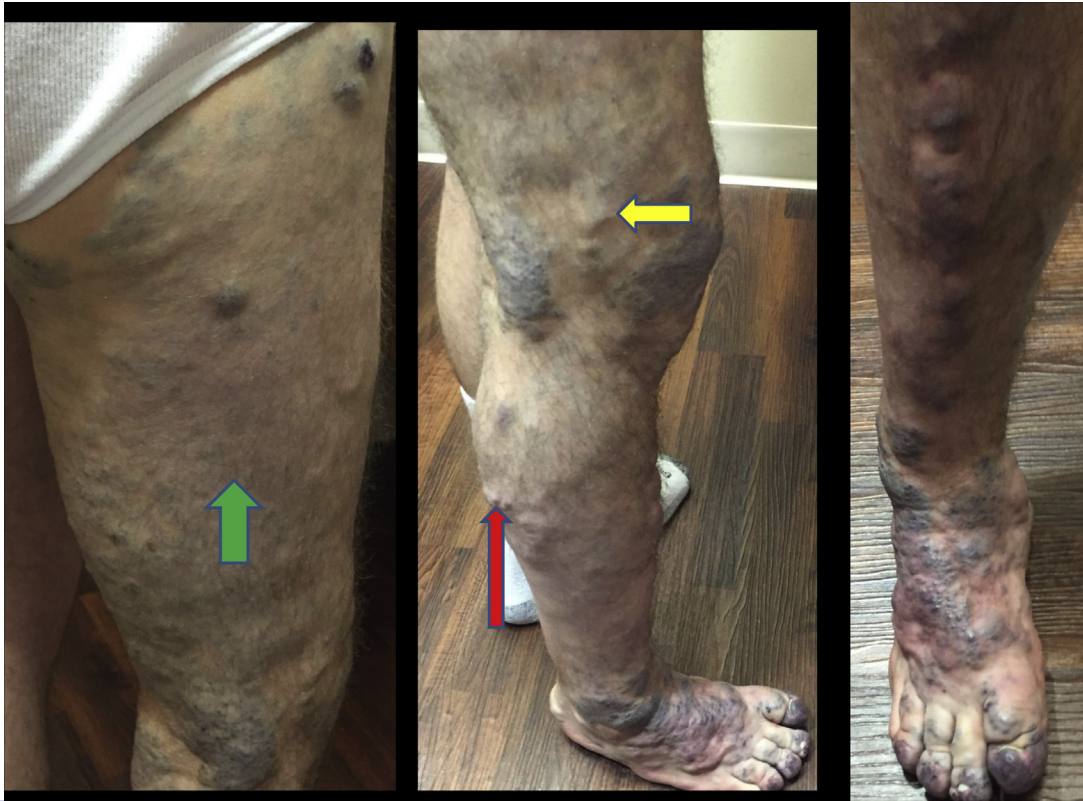
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**Fig 1.** Patient with unilateral limb swelling secondary to persistent lateral marginal vein (yellow arrow) and varicosities (red arrow) since birth. A large and diffuse port-wine stain is noted over the posterior aspect of the right thigh (green arrow).

spectrum and combination of these is usually appreciated in the real world. In addition, although this classical presentation is usually observed in a singular limb, multiple and even whole body cases have been described.<sup>10</sup>

Limb length discrepancy is most often secondary to underlying soft tissue growth but can be associated with long bone hypertrophy. The difference in growth occurs during childhood before stabilizing in young adulthood with minimal changes after the teenage years.<sup>11</sup>

Capillary malformations present on the hypertrophied limb and clinically appear as flat hemangiomas. In contrast, true flow-limiting arterial disease is exceedingly rare in KTS and more characteristic of the more pathologic Parkes Weber syndrome. A cutaneous capillary malformation is often the first and most obvious sign on examination of the patient thought to have KTS. This is often referred to in the literature as a port-wine stain. Frequently dermatomal in distribution, these lesions tend to bleed and persist as the patient ages. The frequency with which these skin findings coexist in KTS cannot be understated; in fact, the prevalence of capillary malformations approaches 100% in the reported literature.<sup>12</sup>

Varicosities usually appear on the lateral aspect of the limb, resulting from persistent embryonic veins,

superficial venous malformations, or deep venous aberrations consisting of hypoplasia, segmental aplasia, and aneurysmal degeneration.<sup>2,13</sup> Varicosities are slightly less common than capillary malformations and range from 76% to 100% in small case series (Fig 1).<sup>12</sup> These pathologic vessels disappear proximally as the diseased veins dive into the proximal femoral and iliac systems. Patients mainly complain of swelling, often with pain, but may also experience more advanced clinical signs and symptoms of chronic venous disease.<sup>14,15</sup>

Frequently, patients present with a persistent embryonic vein on the lateral aspect of the distal leg termed a lateral marginal vein or persistent sciatic vein. Prevalence rates in the literature range from 9% to 68%.<sup>13,15-19</sup> Animal fetal studies have demonstrated that these embryonic veins form and regress by 12 weeks of life, but this has yet to be demonstrated in humans.<sup>19</sup>

Yamaki et al reported the frequency of venous and lymphatic malformations in 61 KTS patients clinically diagnosed with duplex ultrasound and magnetic resonance imaging (MRI). Capillary malformations were detected in 89%, among which port-wine stain was most prominent (66%), followed by telangiectasia (51%) and angiokeratoma (30%). A persistent embryonic vein was detected in 53% of the patients. Reflux was observed

in the great saphenous vein (20%), embryonic vein (15%), and small saphenous vein (7%). Deep vein hypoplasia/aplasia was observed in 20%. Extratruncular and truncular lymphatic malformations were observed in 21% and 28% of the patients, respectively.<sup>20</sup>

The signs and symptoms of KTS are often related to the obstruction or insufficiency present in the venous outflow and can be scored by the CEAP classification system for chronic venous disease (clinical presentation, etiology, anatomic involvement, and pathophysiology).<sup>3,21</sup> Furthermore, the results of any treatment should be determined by venous severity scores and quality of life questionnaires used for more familiar forms of chronic venous disorders.<sup>3,15,22</sup>

If internal organs are affected by vascular malformations, patients may report mild hematuria or hematochezia.<sup>23</sup> In a small and unfortunate subpopulation, bleeding may be intractable and necessitate bowel resection.<sup>10</sup>

## DIAGNOSIS

The diagnosis of KTS is clinical and difficult to make even for the experienced physician as there is no true pathognomonic test. However, an elevated D-dimer level and mutation of the *ACGF1* gene may suggest the diagnosis.<sup>4</sup> The status of the *PIK3CA* gene does not currently add diagnostic value but may yield useful information in the future.<sup>24</sup> Duplex ultrasound, MRI, and computed tomography (CT) imaging may show soft tissue hypertrophy and associated vascular malformations. Plain films can be used to screen long bones for limb length discrepancies.

Patients thought to have KTS should be initially evaluated with noninvasive imaging. The purpose of this is to determine the extent and severity of disease along with delineation of any significant arteriovenous shunting that may be present.<sup>21</sup>

The high sensitivity and specificity of lower extremity duplex ultrasound imaging in regard to venous and arterial anatomy and function make it the best initial diagnostic study.<sup>16</sup> Confirmation can be easily obtained of valvular incompetence, low-flow regions, compressible vascular channels, and anatomic abnormalities, such as aneurysms and atretic segments, quickly, at low cost, and without the need for sedation in the pediatric population. In addition to B mode and color flow, hemodynamic studies such as ankle-brachial indices, segmental pressures, and pulse volume recordings may be useful in flushing out suspected arterial anomalies, such as the blunted waveforms and reduced digital pressures observed distal to a high-flow arteriovenous malformation.

Most consider MRI essential in the diagnostic evaluation of patients with KTS as it allows differentiation of the soft tissues. This modality can provide the first assessment of the involvement of muscles, joints, and bones.

Also, the addition of intravenous gadolinium contrast agent can discriminate venous from the more insidious arterial malformations and help the classification of patients into the Hamburg system.<sup>21</sup>

CT imaging incurs a radiation dose along with potential renal toxicity, depending on the patient's prestudy renal function and contrast material use. It may not provide detail of muscle and surrounding soft tissue involvement, for which MRI excels. In addition, many patients undergoing initial evaluation for KTS are children, making the avoidance of radiation all the more important. However, contrast-enhanced CT imaging with venous-phase protocols may be of particular use in preinterventional planning and cannot be avoided at times despite the best intentions.

Last, ascending venography should be employed to assist with preoperative planning when superficial vein-eliminating procedures, such as ablation, sclerotherapy, ligation, or stripping, are planned as it can be performed concurrently. If documentation of a patent deep venous system has not been performed previously, venography can assist with this as well.

The differential diagnosis for patients being considered for KTS should include Sturge-Weber syndrome, Parkes Weber syndrome, lymphatic filariasis, Beckwith-Wiedemann syndrome, Russell-Silver syndrome, congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, neurofibromatosis 1, triploid syndrome, and Proteus syndrome.<sup>24</sup> The differences in presentation of these complex disease states are briefly delineated in the [Table](#). The plethora of named syndromes makes the Hamburg classification so appealing in that it provides a structure and delivers direction to treatment.

## MEDICAL MANAGEMENT

Nonoperative medical management is the main modality in the treatment of symptomatic KTS patients. Rarely, and only in patients refractory to medical management, should operative intervention be considered. For example, in a series of 19 KTS patients described by Sung et al, only 4 underwent operative intervention during a mean follow-up of 4.1 years with no major adverse outcomes regardless of management style.<sup>14</sup>

Patients with KTS should be managed similarly to those with more common varieties of chronic venous disorders with appropriate consideration of potentially extenuating circumstances, such as deep venous agenesis ([Fig 2](#)), which may make the remaining superficial veins an important egress for lower extremity outflow.

Patients presenting with symptoms of chronic venous disease should be initiated on a regimen of compression and elevation. This is the fundamental basis of all treatment related to limb edema. Compression stockings should extend from above the affected area to the digits and should be fitted to the individual limb. The correct

**Table.** Differential diagnosis and the presentation of the various syndromes and diseases in the patient thought to have Klippel-Trénaunay syndrome (KTS)

Sturge-Weber syndrome	Parkes Weber syndrome	CHILD syndrome	Neurofibromatosis type 1	Triploid syndrome
Facial cutaneous capillary malformations (port-wine)	High-flow vascular malformations (AVM)	Usually lethal in males	Café au lait macules	Hydrocephalus, CNS malformations
Leptomeningeal angiomas	Limb overgrowth	Ichthyosiform nevus along Blaschko lines	Skinfold freckling	Craniofacial malformations
Glaucoma	Capillary, venous, and lymphatic malformations	Variable limb abnormalities	Neurofibromas	Clubfoot, syndactyly
			Lisch nodules	
			Optic pathway gliomas	
			Bone dysplasia	

AVM, Arteriovenous malformation; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; CNS, central nervous system.

pressure may vary for the patient but typically ranges from 20 to 40 mm Hg. However, compliance to this garment can be difficult in the pediatric population with rapidly growing limbs along with other social factors. Low-dose aspirin should be considered as there is limited benefit to pain and swelling in patients with vascular malformations.<sup>25</sup> If symptoms are refractory to compression alone, intermittent pneumatic compression can be a useful adjunct in lower extremity edema mobilization.<sup>26</sup> Some clinicians will trial a course of diuretics in the patient with continued symptomatic edema despite compression, mobilization, and elevation; however, there is no evidence of efficacy in reduction of limb edema.<sup>17</sup>

If soft tissue inflammation develops, it should initially be managed with over-the-counter analgesics and elevation. Be mindful that this presentation is often initially sterile; therefore, antibiotics should be reserved until cellulitis with virulent organisms is suspected.<sup>17</sup> Wound cultures can be performed, but organisms are rarely isolated. There is currently no evidence for prophylactic antibiotics in this population. In addition, the need for careful wound care and personal hygiene should be reinforced with each clinic visit.

No role for anticoagulation has been identified early in the clinical course; however, it should be initiated if patients develop deep venous thrombosis. In addition, adults who have had a venous intervention should be considered for a short perioperative course of prophylaxis as they have increased risk for thromboembolic events.<sup>11</sup> Women with severe venous malformations should avoid oral contraceptives as this has been associated with a higher risk of thromboembolic events.<sup>17</sup>

Limb length discrepancies can be appropriately managed with heel inserts or compensatory shoes to avoid scoliosis as long as discrepancies are <1.5 cm. However, if the discrepancy in limb length is >2 cm, surgical intervention should be considered in the form of osteotomy or epiphysiodesis by the appropriately trained orthopedic surgeon.

Using the CEAP classification, operative vascular intervention should be considered when the severity of

disease progresses to greater than class 3 or potentially class 2 in some symptomatic cases.<sup>27</sup> The largest experience of vascular malformations intervened on is reported by the Mayo Clinic. In their practice, absolute indications for intervention consist of continuing hemorrhage, refractory ulcerations, and acute thromboembolism. Relative indications consist of pain, functional impairment, swelling secondary to venous insufficiency, limb asymmetry, and cosmesis.<sup>21</sup>

Because of the rarity and complexity of KTS, early referral to specialist centers should be considered.<sup>24</sup> The varying presentations and severity of disease necessitate that each treatment plan be individualized for the specific KTS patient. A multidisciplinary team should be involved with the patient's care so that all needs are addressed as they are manifested. Perhaps the most important member of the team is the patient. He or she should be educated about the nature of the disease as compliance to any proposed treatment is essential to ultimate success and only increases with education.

## ENDOVASCULAR AND MINIMALLY INVASIVE INTERVENTION

The role of endovascular therapy and minimally invasive intervention in KTS is not well established secondary to the low prevalence of the disease; however, it should be offered over open surgery after failed nonoperative management. The basis of the success of sclerotherapy, embolization, ablation, and laser treatments in KTS is built from the parallel experience in chronic venous and capillary disease.

A plastic surgery group from South Korea described pulsed dye laser therapy in their KTS population for capillary malformations, namely, port-wine stains; 4 of their small series of 19 patients were treated with laser without morbidity. The 585-nm wavelength has also been effectively used in the treatment of facial telangiectasias and hemangiomas.<sup>14</sup> The clinician should keep in mind that lighter colored lesions in the pediatric population respond best, whereas darker lesions in adults are more refractory to treatment; however, these darker



**Table.** Continued.

Lymphatic filariasis	Beckwith-Wiedemann syndrome	Russel-Silver syndrome	Proteus syndrome
Parasitism of filarial nematodes in tropical regions Hydroceles, lymphedema	Overgrowth syndrome with macroglossia, organomegaly, and increased childhood tumor risk	Growth retardation Hemihypertrophy, macrocephaly, clinodactyly, and triangular facies	Capillary, venous, and lymphatic malformations Pulmonary restriction Scoliosis, limb asymmetry Fatty hypertrophy

lesions are responsive to nontraditional krypton and copper lasers.<sup>28</sup>

After failed nonoperative management of varicosities, sclerotherapy or embolization (Fig 3) techniques with various agents can be attempted. However, before intervention is performed, the deep venous system should be documented to be patent by imaging of choice. These techniques, over radiofrequency ablation, should be considered for persistent embryonic and large superficial veins to avoid postoperative persistence of hard cords and thermal injury.<sup>24</sup> In particular, the persistent sciatic vein should be treated with sclerotherapy or embolization secondary to proximity of the sciatic nerve.<sup>24,29</sup>

Burrows and Mason reported their series of consecutive sclerotherapy patients with low-flow vascular malformations and noted a good or excellent result in up to 90% of patients by clinical survey. However, there was a complication rate of 12% per treatment and a 28% complication rate per patient. Almost 15% of the patients in this series had some evidence of skin necrosis. To decrease the high risk of complications, the authors cautioned against injection of agents, especially ethanol, close to major nerves or cutaneous lesions.<sup>30</sup> Later reports have echoed these initial findings.<sup>31</sup>

Foam sclerotherapy has also been well documented in the literature. Smith reported a series of 808 mostly CEAP class 2 patients undergoing ultrasound-guided injection with diluted sodium tetradecyl. Although follow-up was marginal, there was a significant decrease in CEAP classification 6 months after the procedure. Minor complications were minimal, and the author reported no major complications.<sup>32</sup>

Endovascular radiofrequency ablation of the persistent embryonic or great saphenous vein has also increasingly gained popularity in the last 10 years. Weiss et al reported 934 consecutive radiofrequency and laser thermal ablations of superficial veins with 6-month, 1-year, and 5-year ablation rates at 92%, 86%, and 72%, respectively.<sup>33</sup> No differences were noted in the laser and radiofrequency ablation groups. Smaller series of KTS patients also mirror these excellent results, although re-treatment is common, with minimal complications.<sup>34</sup> As with

superficial veins in any patient, care has to be taken when these modalities are used and no heat sink can be provided during the procedure. The result could be significant cutaneous burns.<sup>35</sup>

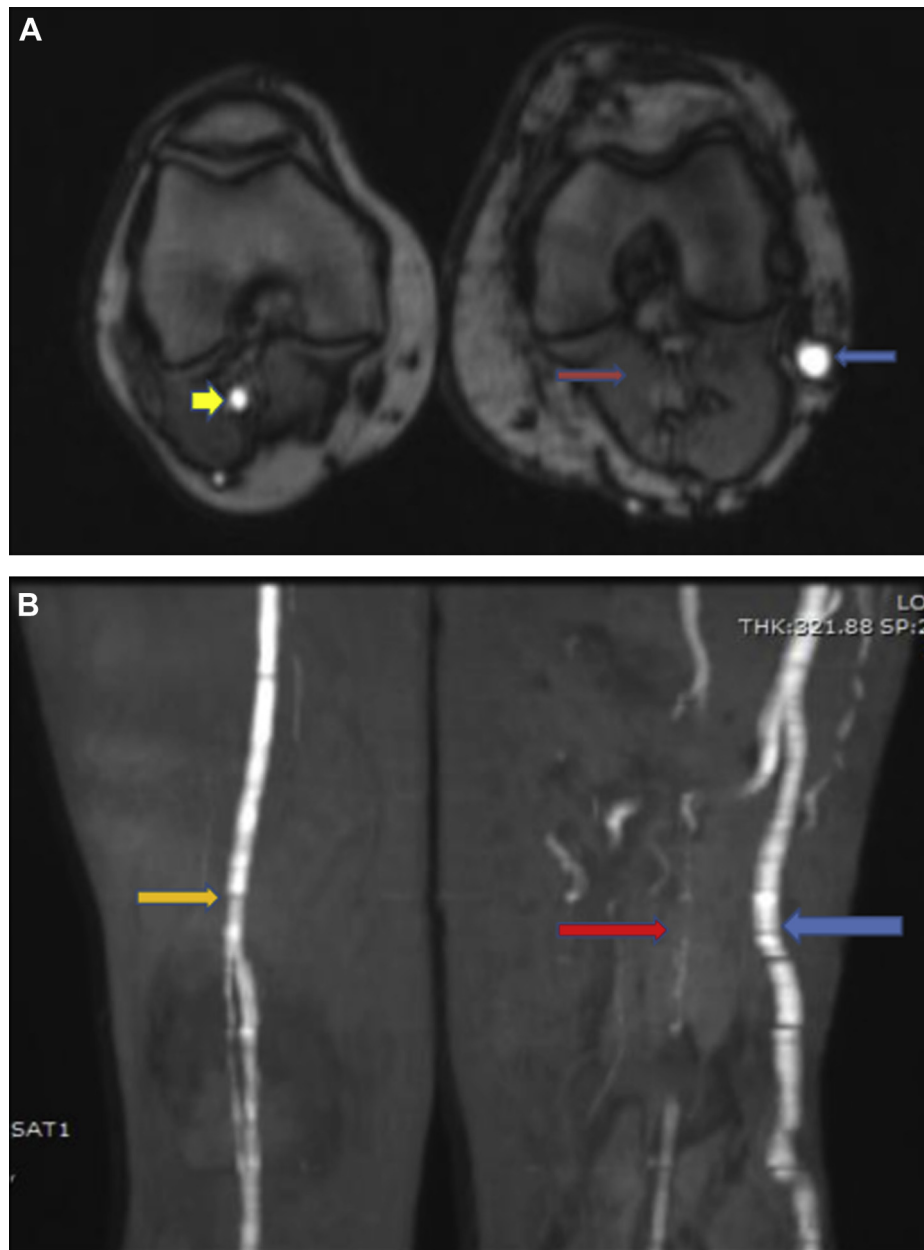
### OPEN SURGERY

Although some advocate for early surgical intervention,<sup>36</sup> open surgical volume has drastically decreased during the last several decades and become more of historical interest secondary to wound complications and persistent bleeding. Currently, open operations are reserved for patients who are not candidates for minimally invasive techniques and therefore mainly consist of a combination of high ligation of persistent embryonic veins, vein stripping, and stab phlebectomies. Subfascial endoscopic perforator surgery has been useful in the select group of patients with large and incompetent perforating veins, but new available percutaneous interventions are making this of historical significance as well.

Ulcerated or bleeding lesions may be excised when possible; however, the clinician should keep in mind the poor wound healing potential of the KTS limb.<sup>37</sup> Therefore, postoperative edema should be kept to a minimum with compression and elevation as tolerated. Before intervention, the venous anatomy should be meticulously documented to avoid destroying the superficial venous system in patients with an atretic deep system.

Because of the robust venous network that can develop in these patients, consideration should be given to the potential blood loss during an open operation. Blood should be available in the operating room to be transfused as needed. In addition, tourniquets can be an important adjunctive tool and should be used when appropriate.<sup>12</sup>

The largest open surgical series comes from the French surgeon Servelle, who described 768 "KTS" operations during 40 years of practice in 1985. Although the author claimed all patients were clinically diagnosed with KTS, 71% of the operations were performed for venous compression release in the extremities, not a problem



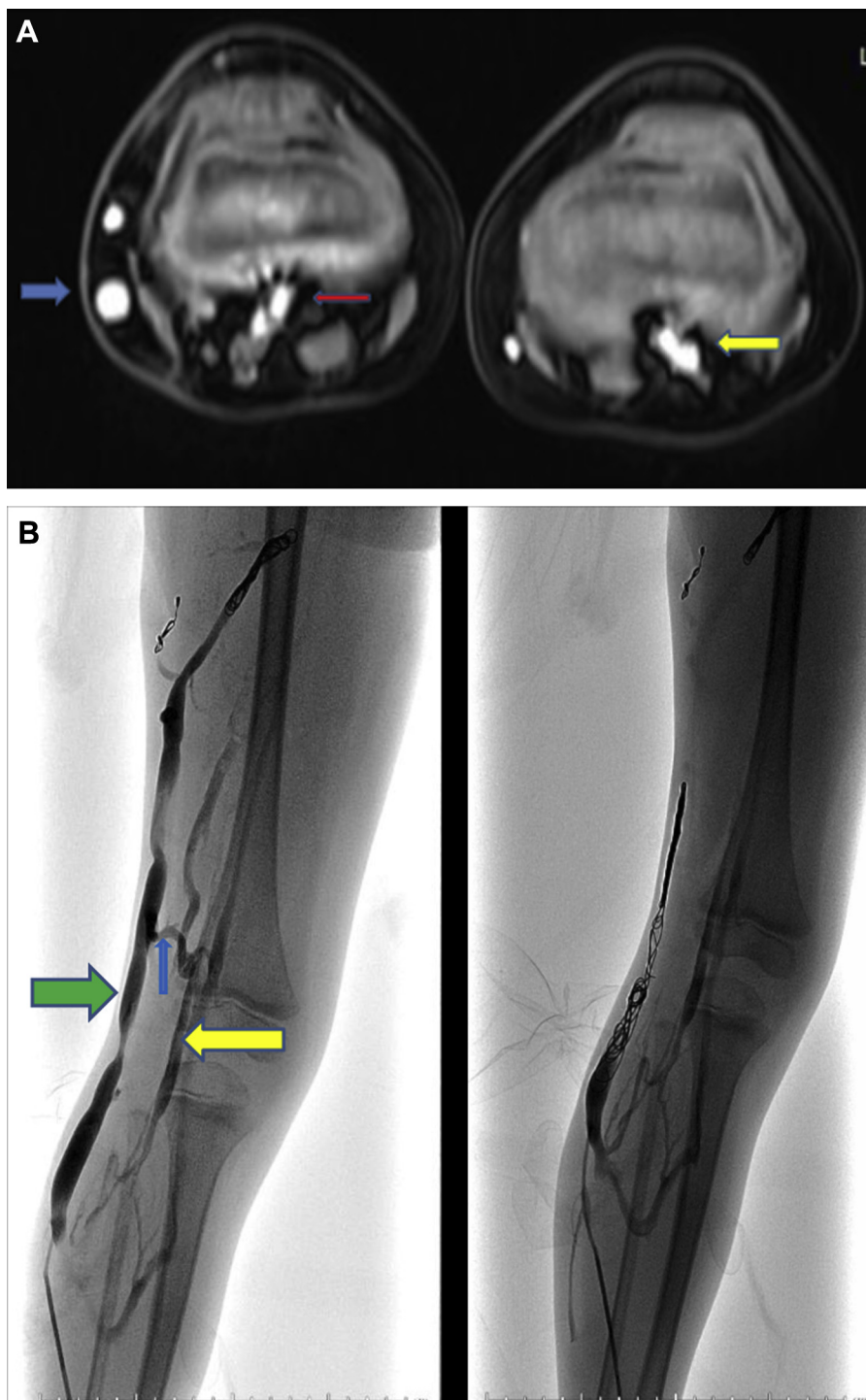
**Fig 2. A,** Representative axial cut of lower extremity magnetic resonance venography in which an absent deep vein is noted in the left lower extremity (*pink arrow*). A large persistent and patent lateral marginal vein appears to drain most of the left lower extremity. Normal venous anatomy is noted in the right lower extremity and highlights the normal popliteal vein (*yellow arrow*). **B,** Coronal section of the patient in (**A**) demonstrating a normal deep vein on the right side (*yellow arrow*). On the left side, the deep veins are atretic (*red arrow*), and there is a large lateral subcutaneous vein (*blue arrow*) draining the left lower extremity.

often seen in the KTS population. Only 36% of the cohort had clinically apparent varicosities, whereas port-wine stains were present in only 32%. Follow-up and outcomes were not reported.<sup>18</sup>

Baraldini et al reported their experience of 29 pediatric KTS patients undergoing a combination of open and minimally invasive interventions for venous disease. The average age at intervention was 10.3 years. The procedures were all technically successful. No deaths or major complications were noted on

6-month and 2-year follow-up. The authors suggested that early intervention is safe and efficacious in minimizing long-term venous hypertension and its sequelae.<sup>36</sup>

The Mayo Clinic group documented their surgical experience longitudinally in consecutive KTS patients during two decades previous to the widespread adoption of radiofrequency ablation and laser ablation. One such report described intervention in 53 limbs of 49 patients. The average length of follow-up was 73 months. All had



**Fig 3. A,** Axial sections from magnetic resonance venography demonstrating a large left lower extremity persistent lateral marginal vein (*blue arrow*) in addition to a normal patent popliteal vein (*red arrow*). The opposite side is normal, with the popliteal vein highlighted by a *yellow arrow*. **B,** Representative intraoperative imaging of the same patient as in **(A)** in which the lateral marginal vein was cannulated and subsequently embolized using metal coils. The *left panel* is an image of the large lateral vein (*green arrow*) with only a perforator vein (*blue arrow*) connecting it to the popliteal vein (*yellow arrow*). The *right panel* demonstrates occlusive coils lying within the abnormal lateral vein.

varicosities, 73% had limb hypertrophy, and all patients met two of the three diagnostic KTS criteria. The most common presenting symptom was disabling pain

(88%). Stripping of the great saphenous vein, small saphenous vein, and lateral embryonic vein was undertaken in 32%, 36%, and 28%, respectively. Short-term

morbidity included a 4% deep venous thrombosis risk and a 14% thrombophlebitis rate, and 10% experienced at least one episode of cellulitis. There were no deaths; 13 of 49 patients required reintervention. Nonetheless, 50% reported significant pain relief, and statistically significant decreases in Venous Clinical Severity Score and CEAP class were reported.<sup>12</sup>

## CONCLUSIONS

KTS is characterized by a triad of cutaneous vascular malformations in the form of port-wine stains, limb length discrepancies, and venous insufficiency secondary to venous malformations.

The diagnosis of this disease is clinical but can be supplemented with noninvasive imaging, such as duplex ultrasound, to define the lower extremity venous anatomy. Radiologic studies, such as MRI (primarily) and CT, can further delineate the deep and superficial venous anatomy as well as adjacent soft tissue, joint, muscle, and bone involvement so needed for preoperative planning.

Primary treatment consists of nonoperative management with lifestyle modification, local wound care, orthotics, extremity elevation, and compression therapy. Operative intervention is rarely required. If symptom progression occurs, patients should be offered a combination of pulsed laser therapy, embolization, sclerotherapy with foam or ethanol, and radiofrequency or laser ablation.

Patients who are not candidates for minimally invasive techniques may benefit from open surgery consisting of vein stripping, stab phlebectomies, or more aggressive venous reconstructions. It is important to image the deep system to confirm patency before removal of flow from the superficial system.

## AUTHOR CONTRIBUTIONS

Conception and design: SW, MD

Analysis and interpretation: SW, MD

Data collection: SW, MD

Writing the article: SW, ND, FM, AG, MD

Critical revision of the article: SW, ND, FM, AG, MD

Final approval of the article: SW, ND, FM, AG, MD

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