



CLINICAL CASE REPORT

Klippel-Trénaunay syndrome: a case report of a rare vascular disorder identified in a rural Canadian hospital

AUTHORS

Osman Kaan Yilmaz¹ Medical student

Lauren E Smithson² MPhil, MD, FRCSC, FACS, General Surgeon *

CORRESPONDENCE

*Dr Lauren E Smithson lauren_smithson@yahoo.com

AFFILIATIONS

¹ University of Heidelberg, Grabengasse 1, 69117 Heidelberg, Germany

² Department of Surgery and Endoscopy, Charles S. Curtis Memorial Hospital, 178-200 West Street, St. Anthony, NL A0K 4S0, Canada

PUBLISHED

14 November 2019 Volume 19 Issue 4

HISTORY

RECEIVED: 22 February 2019

REVISED: 14 September 2019

ACCEPTED: 24 September 2019

CITATION

Yilmaz OK, Smithson LE. Klippel–Trénaunay syndrome: a case report of a rare vascular disorder identified in a rural Canadian hospital. Rural and Remote Health 2019; 19: 5348. <https://doi.org/10.22605/RRH5348>

This work is licensed under a Creative Commons Attribution 4.0 International Licence

ABSTRACT:

Context: Klippel–Trénaunay syndrome (KTS) is a very rare congenital vascular anomaly. It is characterized by the presence of capillary malformation, venous malformation as well as limb overgrowth, generally affecting one extremity. Although clinical characteristics of KTS are well known, the epidemiology and pathophysiology still remain to be defined. Awareness of these disorders is important for rural physicians for managing potential complications.

Issue: A 60-year-old male presented with symptomatic varicosities and chronic venous insufficiency of the left leg. The patient had a history of several episodes of ulceration and thrombophlebitis on the left side. Physical examination revealed extensive varicosities and a large port-wine stain on the lateral side of the left leg,

despite a previous ligation of the saphenofemoral junction. The left leg was circumferentially larger than the right leg. Additional investigations were conducted to rule out arterial disorders and confirm the venous nature of the abnormalities. The patient was clinically diagnosed with KTS and his varicosities were treated surgically using phlebectomy with stab avulsion technique.

Lessons learned: KTS is a distinct entity that belongs to the vascular malformations group. In a rural practice, identification and accurate diagnosis are challenging, as these patients often require a multidisciplinary approach and do not present until later in the course of the condition. An understanding of the correct nomenclature and associated complications is imperative for proper assessment and management in rural and remote settings.

Keywords:

Canada, Klippel-Trénaunay syndrome, PIK3CA-related overgrowth spectrum, port-wine stains, rural medicine, vascular anomalies, vascular malformations.

FULL ARTICLE:

Context

Vascular diseases such as varicose veins and chronic venous insufficiency are common patient presentations in rural medicine. Due to their high prevalence, they are considered to be widely investigated and well understood. Congenital vascular anomalies, however, still represent a challenge in diagnosis and management¹. Multiple disorders of the vascular system exist under this umbrella term, including Klippel-Trénaunay syndrome (KTS). KTS is a very rare congenital disorder consisting of a triad of anomalies that typically affect only one limb: capillary malformations, venous malformations and limb hypertrophy^{1,2}. Despite the well-defined and described clinical features of KTS, the epidemiological data are still unsatisfactory.

This report presents the case of a 60-year-old male from a rural community who had previously been treated for, but not diagnosed with, KTS. This case demonstrates how complex congenital vascular malformations can present in rural populations and require physicians in remote areas to have a high index of suspicion for clinical presentations that may harbor more complex disorders than initial assessment suggests. An awareness of the panorama of vascular anomalies will allow for earlier recognition and management of these rare conditions, even in areas where advanced healthcare services or specialists are not available.

Issue

In September 2018, a 60-year-old Caucasian male presented to the surgical clinic at the Charles S. Curtis Memorial Hospital in St Anthony, Newfoundland, with extensive varicosities of the left leg and chronic venous insufficiency. The patient had been recently diagnosed with an advanced osteoarthritis of the right knee, and a total knee replacement was recommended. There was, however, a concern of possible venous thrombosis intraoperatively, so he was referred to the general surgeon for possible phlebectomy prior to the orthopedic surgery.

The patient reported symptoms of fatigue and heaviness in the left leg while walking and moderate swelling at night. He denied having pain or any history of recent trauma. The patient had a longstanding history of varicose veins on the left, affecting both the greater and lesser saphenous distribution. He also experienced multiple episodes of ulceration with severe pain and edema. In 1987, he was hospitalized due to a left popliteal superficial

thrombophlebitis. Additionally, he underwent a left-sided saphenofemoral ligation and multiple stab avulsions of his varicosities in 2004. The surgery was uneventful; however, there was a recurrence of the symptomatic varicosities within a few years.

The patient's past medical history included gastroesophageal reflux disease, chronic obstructive pulmonary disease, non-ST-elevation myocardial infarction and occasional rectal bleeding. Past surgical history included an open cholecystectomy, and a Hartmann's procedure with subsequent reversal for perforated diverticulitis. No family history of varicosities, port-wine stains or other vascular anomalies were recorded. He had smoked 20 cigarettes a day for 30 years but quit smoking in 2013. His occupation as a fisherman included prolonged periods of standing.

The physical examination confirmed visible varicosities on the left leg. The left foot was warm, with normal capillary refill and strong, palpable pulses. The most striking observation was the port-wine birthmark on the lateral aspect of the left leg, extending from the mid-thigh to the toes. The stain was dark red, raised in some areas, and had sharply demarcated borders, whereas some areas were less well defined. There was no discrepancy in leg length; however, the left leg was larger in circumference than the right. The right leg was normal. Laboratory tests showed normal complete blood count and coagulation parameters, but hyperuricemia (10.3 mmol/L).

A Doppler ultrasound and the ankle-brachial index of the left leg were normal. There were no signs of arteriovenous fistula. The patient underwent a Trendelenburg test in 2004, which showed the incompetence of the saphenofemoral junction. Based on the presence of the triad of a large port-wine stain, extensive varicosities and a larger left leg, KTS was identified in this previously undiagnosed patient.

Due to his symptoms, the patient opted for surgical intervention. The phlebectomy was conducted under spinal anesthesia. At his 6-week postoperative visit, he reported having severe burning pain over the lateral aspect of the left lower leg. This pain resolved slowly over time, but he continued to have reduced sensation to touch over the same area. This also resolved with time. The initial symptoms of swelling, fatigue and heaviness subsided completely after surgery (Fig1).

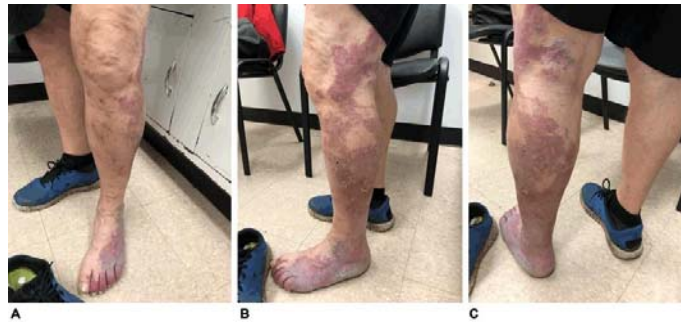


Figure 1: Postoperative images of the patient, showing the large violaceous port-wine stain with sharply demarcated borders and less well defined areas throughout. Multiple black dots on the left leg indicate the areas where the phlebectomy was performed. A. Anterior view; B. lateral view; C. posterior view.

Lessons learned

Vascular disorders are very common and believed to be well known and widely understood. Regardless, congenital anomalies remain an intriguing area in the field of vascular medicine. Missed diagnoses and mistakes in terminology increase the risk of inaccurate evaluation and treatment^{1,3}.

According to the International Society for the Study of Vascular Anomalies' 2014 classification, vascular anomalies are divided into vascular malformations and vascular tumors. 'Malformations associated with other anomalies' represent a further subgroup of vascular malformations to which KTS also belongs. KTS is defined by the triad of capillary and venous malformations as well as limb overgrowth, whereas lymphatic malformation may or may not be present¹. Although KTS was first described more than a century ago, the epidemiology and pathophysiology remain to be defined⁴. KTS, along with other vascular malformations, usually does not regress spontaneously, but can regress with puberty, trauma or infections^{5,6}. KTS is believed to be mostly sporadic, but there is also evidence of familial occurrence^{7,8}. Several studies have found that most KTS patients have somatic phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) mutations⁹. These mutations eventually lead to an activation of mammalian target of rapamycin (mTOR) and increased angiogenesis, which explains the therapeutic potential of mTOR inhibitor Sirolimus in KTS. Sirolimus has been shown to be an efficacious and safe alternative in reducing the symptoms and complications of vascular malformations, especially in younger patients^{5,6,10,11}. Recent studies investigated additional inhibitors of the PI3K (phosphoinositide-3-kinase)-Akt-mTOR signaling pathway in KTS. Di Blasio et al have demonstrated in mouse models that a dual therapy with PI3K/mTOR inhibitor BEZ235 or mTOR inhibitor Everolimus could significantly reduce vascular lesions. On the other hand, therapy with Akt inhibitor has been found to be less successful¹². A study by Venot et al revealed that BYL719, a *PIK3CA* inhibitor, could ameliorate disease symptoms in patients with associated overgrowth syndromes¹³. In the present case, the patient did not have genomic testing nor did he undergo targeted medical therapy.

The cutaneous capillary malformation in KTS manifests as a port-wine stain (nevus flammeus). As proposed by a recent study, the

stains can be stratified into 'geographic' or 'blotchy/segmental' types¹⁴. Geographic stains are described as dark red and sharply demarcated throughout the entire nevus, while segmental stains are rather indistinctly demarcated and light pink. Interestingly, the same study put forward that geographic stains, and not segmental stains, are strongly associated with both lymphatic malformations and other complications in KTS patients¹⁴. In this case, the patient had mostly well-defined violaceous stains, although the demarcation in the lateral aspect of the shin was less distinct. The features of both geographic and segmental stains increases the likelihood of a lymphatic malformation.

For physicians in rural areas managing patients with KTS, identification is important in order to manage possible complications. These complications can include coagulopathy, thromboembolism and thrombophlebitis^{2,15}. A previous study revealed that, in a cohort of 75 KTS patients, 29 patients (39%) had had thromboembolic complications. Moreover, some patients had clinically silent thrombosis identified by ultrasonography. As reported by the same study, the KTS patients had significantly higher D-dimer levels and plasmin-antiplasmin complexes, whereas protein C levels were lower compared to controls¹⁶. It should be noted that the patient in this case previously had an episode of thrombophlebitis on the affected limb. His coagulation profile was normal during the current evaluation, but he will need further education on identifying symptoms of thromboembolic complications. Symptomatic patients should undergo diagnostic imaging such as Doppler ultrasound¹⁷. Low-dose aspirin therapy provided promising results in patients with vascular malformations, reducing the pain and soft tissue swelling¹⁸. It may be helpful in case of hypercoagulability. Lifelong anticoagulation is required in patients with deep venous thrombosis or pulmonary embolism¹⁶.

Laboratory investigations in this patient revealed only hyperuricemia. Ulrich et al reported hyperuricemia as an independently associated laboratory value in a KTS patient with pulmonary arterial hypertension (PAH)¹⁹. Further studies should be undertaken to determine if and how KTS is associated with hyperuricemia and PAH. No studies have yet been performed on this patient to evaluate for pulmonary hypertension, but it is worth considering.

Another possible complication of KTS is bleeding from abnormal

vessels. The vascular malformations are often not restricted only to the superficial venous system but may also involve the gastrointestinal and genitourinary tract. This can lead to life-threatening hemorrhages, most frequently from the rectum and bladder²⁰⁻²². The patient in this case report had a history of occasional rectal bleeding, which points to the possibility of a visceral manifestation of KTS. If clinically significant bleeding occurs, CT or MR angiography may be considered to assess the extent of visceral manifestations²⁰.

Differential diagnosis of KTS includes a number of syndromes with capillary malformations and overgrowth, such as Parkes–Weber syndrome (PWS) and CLOVES syndrome (congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi and skeletal anomalies)²³. Most of these syndromes have their own distinct features (Table 1). It can, however, be challenging to distinguish between KTS and PWS¹. In this patient’s case, the absence of fast-flow arteriovenous fistulae effectively ruled out PWS and indicated instead a diagnosis of KTS. The fact that the patient was diagnosed at an advanced age clearly demonstrates the need of early diagnostic tools in suspected patients to prevent or decelerate possible complications. An important starting point could be

genetic testing in pediatric patients with associated clinical findings. In this regard, there has been growing interest in investigating the genetic background of KTS and related disorders. In recent years, the hypernym ‘*PIK3CA*-related overgrowth spectrum (PROS)’ was established to classify diseases linked to somatic *PIK3CA* mutations²⁴. This includes CLOVES syndrome, fibroadipose hyperplasia or overgrowth, megaencephaly-capillary malformation and, more recently, KTS^{24,25}.

Vascular anomalies define a broad scope of disorders ranging from a benign nevus to a syndrome with severe complications. Precise diagnosis of complex vascular anomalies often requires a multidisciplinary approach to ensure appropriate management. Since the presence of medical or surgical subspecialists in rural areas is rare, diagnosis and management fall to the general practitioner. Awareness of the breadth of congenital vascular anomalies and the impact of their possible complications are critical for the rural and remote physician in delivering safe and effective health care. This report seeks to address this challenge and raise awareness of lesser known causes underlying vascular disorders for remote healthcare providers.

Table 1: Differential diagnosis of Klippel–Trénaunay syndrome

Characteristic	Klippel–Trénaunay syndrome	Diffuse capillary malformation with overgrowth	Parkes–Weber syndrome	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies syndrome	Macrocephaly-capillary-malformation
Capillary malformation†	+	+	+	+	+
Venous malformation and/or varicosities	+	+/-	+/-	+	+/-
Arteriovenous malformation	-	-	+	+/-	-
Lymphatic malformation	+/-	-	-	+	-
Overgrowth‡	+	+	+	+	+
Digital anomalies	+	-	-	+	+
Epidermal nevus	-	-	-	+	-

† Capillary malformation is often dark red/purple and geographic in KTS, compared with DCMO, where stain is pink, diffuse and reticulated.
 ‡ Overgrowth is non-progressive in DCMO but can be progressive in KTS. Lipomatous overgrowth is a prominent feature of CLOVES syndrome and can primarily involve the trunk.
 CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies syndrome. DCMO, diffuse capillary malformation with overgrowth. KTS, Klippel–Trénaunay syndrome.
 Source: Reproduced with permission from Frieden IJ, Chu DH. Klippel–Trénaunay syndrome: Clinical manifestations, diagnosis, and management. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on 25.01.2019.) Copyright © 2019 UpToDate, Inc. For more information visit www.uptodate.com.

Acknowledgements

The authors thank Kweku Dankwa at Charles S. Curtis Memorial Hospital, Newfoundland, Canada.

REFERENCES:

- Wassef M, Blei F, Adams D, Alomari A, Baselga E, Berenstein A, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics* 2015; **136(1)**: e203-e214. <https://doi.org/10.1542/peds.2014-3673> PMID:26055853
- Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Glociczki P. Klippel-Trenaunay syndrome: spectrum and management. *Mayo Clinic Proceedings* 1998; **73(1)**: 28-36. [https://doi.org/10.1016/S0025-6196\(11\)63615-X](https://doi.org/10.1016/S0025-6196(11)63615-X)
- Hassanein AH, Mulliken JB, Fishman SJ, Greene AK. Evaluation of terminology for vascular anomalies in current literature. *Plastic and Reconstructive Surgery* 2011; **127(1)**: 347-351. <https://doi.org/10.1097/PRS.0b013e3181f95b83> PMID:21200229
- Klippel LM, Trenaunay P. Du naevus variqueux ostéohypertrophique. *Archives of General Internal Medicine (Paris)* 1900; **185**: 641-672.
- Nadal M, Giraudeau B, Tavernier E, Jonville-Bera AP, Lorette G, Maruani A. Efficacy and safety of mammalian target of rapamycin inhibitors in vascular anomalies: a systematic review. *Acta Dermato-Venereologica* 2016; **96(4)**: 448-452. <https://doi.org>

/10.2340/00015555-2300 PMID:26607948

6 Bessis D, Vernhet H, Bigorre M, Quere I, Rossler J. Life-threatening cutaneous bleeding in childhood Klippel-Trenaunay syndrome treated with oral Sirolimus. *JAMA Dermatology* 2016; **152(9)**: 1058-1059. <https://doi.org/10.1001/jamadermatol.2016.1008> PMID:27167017

7 Craven N, Wright AL. Familial Klippel-Trenaunay syndrome: a case report. *Clinical and Experimental Dermatology* 1995; **20(1)**: 76-79. <https://doi.org/10.1111/j.1365-2230.1995.tb01292.x> PMID:7671406

8 Aelvoet GE, Jorens PG, Roelen LM. Genetic aspects of the Klippel-Trenaunay syndrome. *The British Journal of Dermatology* 1992; **126(6)**: 603-607. <https://doi.org/10.1111/j.1365-2133.1992.tb00107.x> PMID:1319193

9 Luks VL, Kamitaki N, Vivero MP, Uller W, Rab R, Bovee JV, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *The Journal of Pediatrics* 2015; **166(4)**: 1048-1054 e1-5. <https://doi.org/10.1016/j.jpeds.2014.12.069> PMID:25681199

10 Adams DM, Trenor CC, 3rd, Hammill AM, Vinks AA, Patel MN, Chaudry G, et al. Efficacy and safety of Sirolimus in the treatment of complicated vascular anomalies. *Pediatrics* 2016; **137(2)**: e20153257. <https://doi.org/10.1542/peds.2015-3257> PMID:26783326

11 Boscolo E, Limaye N, Huang L, Kang KT, Soblet J, Uebelhoer M, et al. Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. *The Journal of Clinical Investigation* 2015; **125(9)**: 3491-3504. <https://doi.org/10.1172/JCI76004> PMID:26258417

12 di Blasio L, Puliafito A, Gagliardi PA, Comunanza V, Somale D, Chiaverina G, et al. PI3K/mTOR inhibition promotes the regression of experimental vascular malformations driven by PIK3CA-activating mutations. *Cell Death & Disease* 2018; **9(2)**: 45. <https://doi.org/10.1038/s41419-017-0064-x> PMID:29352118

13 Venot Q, Blanc T, Rabia SH, Berteloot L, Ladraa S, Duong JP, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* 2018; **558(7711)**: 540-546. <https://doi.org/10.1038/s41586-018-0217-9> PMID:29899452

14 Maari C, Frieden IJ. Klippel-Trenaunay syndrome: the importance of 'geographic stains' in identifying lymphatic disease and risk of complications. *Journal of the American Academy of Dermatology* 2004; **51(3)**: 391-398. <https://doi.org/10.1016/j.jaad.2003.12.017> PMID:15337982

15 Huiras EE, Barnes CJ, Eichenfield LF, Pelech AN, Drolet BA. Pulmonary thromboembolism associated with Klippel-Trenaunay syndrome. *Pediatrics* 2005; **116(4)**: e596-e600. <https://doi.org/10.1542/peds.2004-1607> PMID:16166386

16 Oduber CE, van Beers EJ, Bresser P, van der Horst CM, Meijers JC, Gerdes VE. Venous thromboembolism and prothrombotic parameters in Klippel-Trenaunay syndrome. *The Netherlands Journal of Medicine* 2013; **71(5)**: 246-252.

17 Hoffmann WH, Toonder IM, Wittens CHA. Value of the Trendelenburg tourniquet test in the assessment of primary varicose veins. *Phlebology* 2004; **19(2)**: 77-80. <https://doi.org/10.1258/026835504323080353>

18 Nguyen JT, Koerper MA, Hess CP, Dowd CF, Hoffman WY, Dickman M, et al. Aspirin therapy in venous malformation: a retrospective cohort study of benefits, side effects, and patient experiences. *Pediatric Dermatology* 2014; **31(5)**: 556-560. <https://doi.org/10.1111/pde.12373> PMID:25040175

19 Ulrich S, Fischler M, Walder B, Pfammatter T, Speich R. Klippel-Trenaunay syndrome with small vessel pulmonary arterial hypertension. *Thorax* 2005; **60(11)**: 971-973. <https://doi.org/10.1136/thx.2004.023184> PMID:16263952

20 Wilson CL, Song LM, Chua H, Ferrara M, Devine RM, Dozois RR, et al. Bleeding from cavernous angiomas of the rectum in Klippel-Trenaunay syndrome: report of three cases and literature review. *The American Journal of Gastroenterology* 2001; **96(9)**: 2783-2788. <https://doi.org/10.1111/j.1572-0241.2001.04110.x> PMID:11569713

21 Servelle M, Bastin R, Loygue J, Montagnani A, Bacour F, Soulie J, et al. Hematuria and rectal bleeding in the child with Klippel and Trenaunay syndrome. *Annals of Surgery* 1976; **183(4)**: 418-428. <https://doi.org/10.1097/0000658-197604000-00016> PMID:178278

22 Cha SH, Romeo MA, Neutze JA. Visceral manifestations of Klippel-Trenaunay syndrome. *Radiographics* 2005; **25(6)**: 1694-1697. <https://doi.org/10.1148/rg.256055042> PMID:16284144

23 Frieden IJ, Chu DH. *Klippel-Trenaunay syndrome: clinical manifestations, diagnosis, and management*. Post TW, ed. *UpToDate*. Waltham, MA: UoToDate Inc. Available: <https://www.uptodate.com/contents/klippel-trenaunay-syndrome-clinical-manifestations-diagnosis-and-management> (Accessed 25 January 2019).

24 Keppler-Noreuil KM, Rios JJ, Parker VER, Semple RK, Lindhurst MJ, Sapp JC, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *American Journal of Medical Genetics Part A* 2015; **167a(2)**: 287-295. <https://doi.org/10.1002/ajmg.a.36836> PMID:25557259

25 Vahidnezhad H, Youssefian L, Uitto J. Klippel-Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). *Experimental Dermatology* 2016; **25(1)**: 17-19. <https://doi.org/10.1111/exd.12826> PMID:26268729