

Klippel-Trenaunay syndrome: case report and literature review

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Abstract

Klippel-Trenaunay syndrome (KTS) is a rare congenital disease, characterized by a triad of clinical features: (1) capillary malformations, manifesting as a “port wine stain”, (2) vascular anomalies, mostly varicose veins and (3) bone and/or soft tissue hypertrophy, usually of one lower extremity. The symptoms are frequently accompanied by lymphatic abnormalities that in some cases may lead to lymphedema. KTS is mostly benign in the course. Nevertheless, patients with KTS are at higher risk of developing deep vein thrombosis (DVT), pulmonary thromboembolism, recurrent episodes of thrombophlebitis, dermatolymphangitis or internal bleeding. Management in KTS should be individualized, minimally invasive and involve multidisciplinary care of the patient. We report a case of a man with fully symptomatic KTS, after incident pulmonary thromboembolism in the past and with severe phlebolymphe-dema, effectively treated with decongestive lymphatic therapy (DLT). We also provide a review of the literature on the clinical aspects of this complex syndrome.

Key words: phlebolymphe-dema, lymphatic malformations, port wine stain, varicose veins, compression therapy

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Introduction

Klippel-Trenaunay syndrome (KTS) is an unusually seen congenital vascular disorder, mostly occurring sporadically and characterized by a triad of presentations: (1) capillary malformations, manifesting as a “port wine stain”, (2) vascular anomalies, mostly varicose veins and (3) bone and/or soft tissue hypertrophy of usually one lower extremity.

The diagnosis of KTS is mostly made clinically when at least two of these features are present [1, 2]. Characteristic clinical symptoms are usually noticed during infancy or in early childhood [1–4]. Lymphatic malformations and abnormal lymphatic drainage are present in

the majority of patients [2, 5]. In some cases, lymphatic disorders may lead to lymphedema [6]. Because of difficulties in recognition of lymphatic abnormalities, they might have been under-reported in many studies.

KTS is mostly benign in the course. Nevertheless, it associates with a higher risk of developing deep venous thrombosis, pulmonary thromboembolism, superficial thrombophlebitis, recurrent dermatolymphangitis or internal bleeding [3, 7–9].

Management in KTS requires a multidisciplinary approach including careful diagnosis, prevention and treatment of complications.

We present a case of a 56-year-old patient with fully symptomatic KTS, after incident pulmonary thrombo-

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embolism in the past and with severe phlebolymphe-
dema, effectively treated with decongestive lymphatic
therapy (DLT).

Case report

56-year-old men were admitted to the Department of Internal Medicine in the 4th Military Hospital in Wrocław due to the right lower limb edema. The patient was complaining about increasing discomfort, heaviness, swelling, ulceration and increasing lymphorrhoea within the right lower extremity. Lymphedema had appeared in the patient at the age of 30 and gradually increased. Medical history of the patient was also relevant for arterial hypertension, deep vein thrombosis of the right lower limb and the pulmonary thromboembolism diagnosed 8 years earlier. The patient has been on chronic anticoagulation (acenocumarol) as secondary prophylaxis of deep vein thrombosis.

During physical examination, the following abnormalities within the right lower extremity were found: hypertrophy of the limb, large flat cutaneous capillary malformation (port wine stain) extending to the abdominal skin, severe phlebolymphe-
dema, numerous varicose veins and skin lesions secondary to venous and lymphatic insufficiency, including hyperpigmentation, thickening and keratosis of swollen skin and minor ulceration on the calf (Fig. 1A–C).

Laboratory examination showed mild normocytic anemia (hemoglobin level 13.2 g/dL; normal range > 14.0 g/dL) and slightly elevated D-dimer level (0.92 ug/mL; normal range < 0.50 ug/mL). ECG revealed right bundle branch block. Echocardiography showed moderate aortic, tricuspid and pulmonary regurgitation, right atrial and ventricular enlargement due to

atrial septal defect with left to right shunt, without evidence of pulmonary hypertension (RVSP 22 mm Hg). Lymphoscintigraphy revealed numerous lymphatic malformations and cutaneous lymph stasis within the right lower extremity (Fig. 2). Doppler ultrasound of the lower limbs showed the insufficiency of the right saphenous vein, numerous varicose veins and an arteriovenous fistula located on the medial side of the right knee joint. Computed tomography angiography (angio-CT) confirmed the presence of the arteriovenous fistula: it revealed a small arterial vessel with a diameter of approximately 0.2 cm, originating from the right femoral artery, approximately 15.0 cm above the right knee joint, and supplying the right saphenous vein, approximately 2.5 cm below the right knee joint and causing it to widen to a diameter of about 1.0 cm in the whole further course.

During the next hospitalization, the patient underwent arteriography with embolization of the arteriovenous fistula with histoacryl glue with a good clinical effect. Arteriography also showed numerous micro-arteriovenous fistulas within the right lower extremity. The treatment of phlebolymphe-
dema consisted of decongestive lymphatic therapy (DLT), involving the following components: multilayer short-stretch compression bandages, manual lymphatic drainage (MLD), sequential intermittent pneumatic compression (SIPC), skin care, and decongestive exercises. It resulted in significant edema reduction, improvement of the skin condition of the lower limb, including healing of the ulcer, and reduction of previously reported symptoms, such as discomfort and heaviness of the right leg. The patient requires regular follow-up visits.

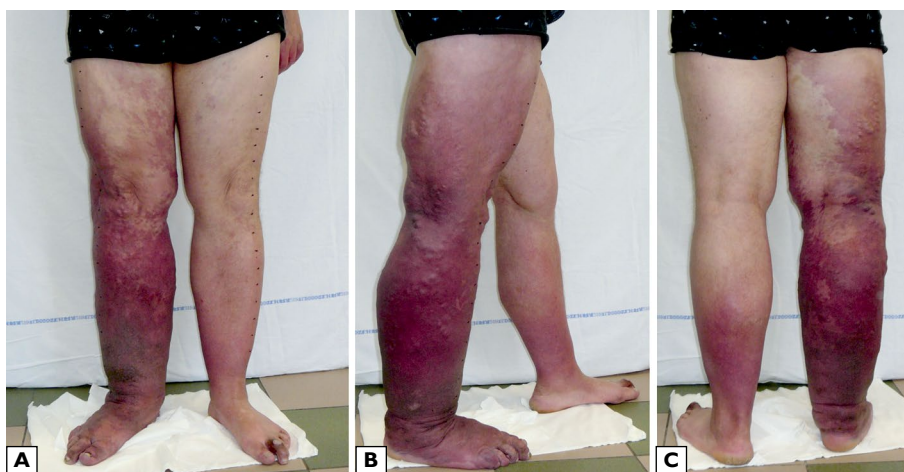


Figure 1. Clinical features of KTS within right lower extremity in our patient: limb hypertrophy, port wine stain, phlebolymphe-
dema, large varicose veins and skin lesions secondary to venous and lymphatic insufficiency; **A** — front view; **B** — side view; **C** — back view

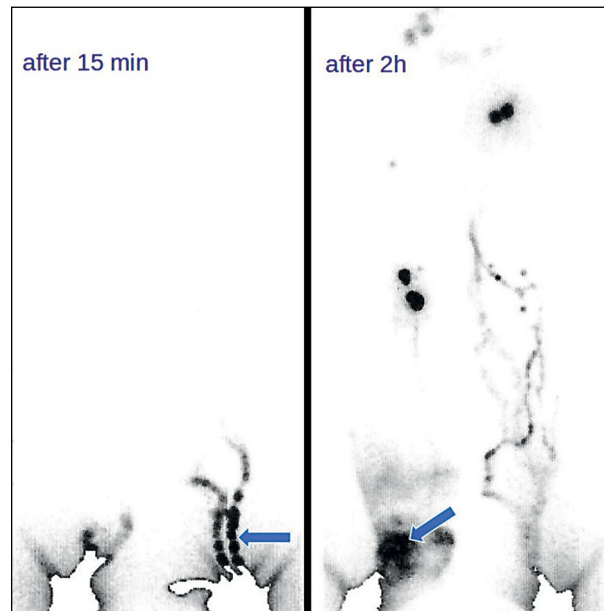


Figure 2. Lymphoscintigraphy demonstrating numerous lymphatic malformations (marked with arrows)

Discussion

KTS in the literature is known by various names, including angioosteohypertrophy syndrome or capillary-lymphaticovenous malformation [3, 10, 11]. The first case was reported in 1900 by Maurice Klippel and Paul Trenaunay [12].

KTS affects men and women in all ethnic groups equally [13]. The aetiology of the syndrome remains unknown and many theories have been proposed. It is generally accepted that KTS is a congenital disorder, in which blood and lymph vessels do not properly form during intrauterine development [11, 14–16]. KTS is postulated to be the result of sporadic mutations, including chromosomal translocations such as: $t(5;11)(q13.3;p15.1)$ [17, 18] or $t(8;14)(q22.3;q13)$ [19], supernumerary ringed chromosome 18 [20], mutations in the *PIK3CA* gene [21], and somatic mutations in *RASA1* gene [22–24]. Other possible theories deal with embryonic disturbed vasculogenesis [25, 26], mesodermal defects or somatic mosaicism of a dominant lethal gene [27]. Nevertheless, none of the hypotheses could explain the entire manifestation of KTS.

The spectrum of clinical features in KTS is wide [2, 3, 28, 29]. Typically, the syndrome affects unilaterally, however, the involvement of all 4 extremities have also been reported [1, 30]. In the study of 252 patients with KTS, port wine stain was found in 98%, varicose veins or venous malformations in 72% and limb hypertrophy in 67%. All three features of KTS were present in 63% of patients, and 37% had 2 of them [1].

The capillary malformations, commonly called “port wine stain”, manifest as red to purplish geographic discolourations on the skin. The port wine stain is usually located on the affected limb, however, it may be present in any area of the body [6, 30, 31]. Present at birth, the port wine stain is usually flat and will not regress. Later, it can become studded with vascular nodules and its colour may decrease [4]. Dermatopathological, it consists of many vascular channels lined by a single layer of endothelial cells localized on the surface of the skin [4]. The term “hemangioma” for the port wine stain is incorrect because the vessels in KTS are remodelled and incorrectly formed. The port wine stain remains the same size, whereas, in blood vessel tumours, the endothelial cells grow excessively [32, 33].

Asymmetric enlargement of the affected extremity can include long bones elongation, soft tissue hypertrophy and, less commonly, muscular hypertrophy, accompanied by increasing skin thickness and vascular tissue [2]. Soft tissue enlargement can be localized or spreading along the entire limb, sometimes reaching the trunk [28]. In the majority of cases, hypertrophy involves one limb (in 80–85% of cases) [4, 6, 30], usually lower extremity. However, cases with affected two up to four limbs have been also reported [30, 31]. Significant limb-length discrepancy (greater than 2 cm) that requiring surgical intervention is estimated at 14% of all cases [32]. The severity of hypertrophy is unpredictable and varies widely among individuals [2]. Polydactyly, syndactyly and macrodactyly are also relatively common [1, 6, 30].

Venous anomalies can involve both the superficial and deep venous system. Tortuous superficial varicose veins are the most common manifestation, as a result of venous hypertension [34] and abnormal drainage. The main factors are valvular incompetence, venous obstruction, vein insufficiency, hypoplasia, aplasia, and venous aneurysm of deep veins [3, 35, 36]. Varicosities usually occur along the lateral side of the affected extremity [12, 23].

Persistent embryonic veins, such as the lateral marginal vein (“vein of Servelle”, “Klippel-Trenaunay vein”) and the persistent sciatic vein are characteristic for KTS. The prevalence rate of these veins is estimated from 9% to 68% [1, 2, 15, 16, 21, 26, 30]. The lateral vein starts from a dorsal venous, runs along the lateral side of the lower limb, and attaches to the profunda femoris vein, the superficial femoral vein, the popliteal vein, the internal vein via gluteal veins, or the external iliac vein [15]. The persistent sciatic vein is a deep vein originating from the popliteal fossa, running along the sciatic nerve and terminating in the internal iliac vein [26, 37].

Venous malformations in KTS are commonly associated with lymphatic abnormalities [5, 36]. In the literature, the prevalence rate of the lymphatic component in KTS has widely ranged from 10% to 84% [1, 6, 32, 36] and it is frequently underestimated [4, 5]. It has been shown that lymphatic anomalies may be observed also in asymptomatic individuals if appropriate imaging tests are used (e.g. lymphangiography, lymphoscintigraphy, MRI, CT) [4]. In a study by Liu *et al.*, the coexistence of lymphatic and venous malformations were found in almost all (in 31 of 32) patients [5]. Lymphatic malformations in KTS may be macrocytic and microcystic [3, 5]. Patients with microcystic lymphatic anomalies have asymmetry in the inguinal lymph nodes, seen as irregularities in outline, heterogeneity in texture, increase or decrease in number and size, or even absence of the lymph nodes [5]. Microcystic lymphatic malformation includes aplasia, hypoplasia or hyperplasia of lymph vessels. All abnormalities described above can lead to lymphatic outflow insufficiency and deep lymphatic system congestion. Reduced flow and stasis of lymph result in accumulation of proteins, glycosaminoglycans, and cellular metabolites within the skin and subcutaneous tissues. The raising tissue osmotic pressure results in the fluid gathering and, in consequence, the formation of edema or cutaneous lymphatic vesicles [2, 38]. Reflux of chyle contributes to lymphorrhea (lymph leakage). Patients with abnormal lymphatic drainage are at higher risk of recurrent dermatolymphangitis and bacteriemia [3, 6].

In 1957, Servelle *et al.* [36, 39] made a hypothesis that lymphatic abnormalities in KTS occur as a consequence of the obstruction of the anomalous deep veins

The lymphatic system has a strong structural and functional relationship with the venous system. According to a centrifugal theory of lymphangiogenesis, that the primitive lymph sacs originate from embryonic veins, the lymphatic malformations may arise as a result of the vascular anomalies.

Patients with KTS complain mostly about pain, edema, the heaviness of the limb, and movement difficulties. Vascular anomalies can lead to such complications as bleeding, thrombophlebitis, cellulitis, ulcerations [2, 16, 30]. They are the main reason for seeking medical help.

KTS associates with a higher risk of developing serious complications as deep vein thrombosis (DVT), pulmonary embolism (PE), congestive heart failure, and recurrent internal bleeding from abnormal vessels in the gastrointestinal tract, kidney and genitalia [2, 6, 8, 14, 21, 41, 42]. Heart defects are also common presentations [41, 43].

The relationship between large venous abnormalities and hypercoagulability have been documented but the exact pathomechanism requires further study. In the theory of “localized intravascular coagulation” (LIC) proposed by Mazoyer *et al.* [44], vascular anomalies cause blood stagnation. As a result, blood stagnation within the deformed, slow-flow venous channels generates consumption of coagulation factors and cause the formation of thrombin and fibrin. Laboratory evidence of LIC process includes elevated D-dimer level, prolonged prothrombin time, decreased fibrinogen level, and moderately low platelet count. The larger and more complex vascular malformation, the higher the risk for thromboembolic events [7, 44]. Deep vein thromboses can lead to chronic thromboembolism and recurrent pulmonary embolism [9]. It is worth noticing that LIC can progress to disseminated intravascular coagulation (DIC) under acute systemic conditions, such as sepsis, surgery, neoplasm, pregnancy, trauma, prolonged immobility, or even menstruation [7, 44].

The diagnosis of Klippel-Trenaunay syndrome is primarily clinical, based on an interview, past history, current patient’s complaints and physical examination. Imaging tests, including Duplex ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), lymphoscintigraphy, standard radiography are useful to confirm the diagnosis and evaluate the severity of the disease and its complications [1, 2, 32].

KTS should be distinguished from Parkes-Weber syndrome (PWS). Despite many similarities in the clinical features, the diseases are different in terms of aetiology, course and prognosis [32, 33, 45]. PWS is distinguishable from KTS primarily by the presence of one or more hemodynamically significant arteriovenous fistulas. Due to the presence of the high-flow arterio-

venous fistula, the treatment and prognosis of PWS vary greatly in comparison to KTS and these two entities should be considered as different diseases [2, 6, 11, 15, 31, 33, 36, 46]. Patients with KTS may have arteriovenous fistulas but the shunts are usually not clinically important [11, 15]. Moreover, lymphatic anomalies are uncommon in PWS and show different patterns [47].

At present, there is no causative treatment for KTS. Generally, management of the disease should be individualized and minimally invasive [1–3, 16, 28, 30, 48]. It includes local wound and skin care, rehabilitation, the elevation of the limbs, compression therapy, lifestyle modification and psychological support [2, 21].

The decongestive lymphatic therapy (DLT) is the primary complex treatment for lymphedema [49–52] with the purpose of preventing dermatolymphangitis, elephantiasis and ulcerations. The DLT includes four components: (1) compression therapy with use of short-stretch multilayer compression bandaging, compression sleeves, garments, and sequential intermittent pneumatic compression (SIPC), (2) manual lymph drainage (MLD), (3) skin and nail care, and (4) decongestive exercises [50].

Surgery should be considered in patients refractory to conservative care, in life-threatening symptoms such as hematuria, vaginal, rectal or esophageal bleeding, or in cases where the limb hypertrophy leads to impairment [2, 27, 41]. A decision about invasive treatment of varicose veins, ligation, or stripping should be carefully considered after detailed imaging of blood and lymphatic vessels [2, 16, 31, 48, 53]. Endovascular therapy and minimally invasive procedures (e.g. pulsed-dye laser treatment, sclerotherapy, ablation, embolization) are promising methods in the management of KTS and they may provide an alternative for operative interventions [21, 54]. Due to little treatment evidence and a large variety of clinical pictures of KTS, it is not possible to establish a clear strategic procedure for all the patients.

Generally, it is recommended that patients with KTS should be treated by a multidisciplinary team of medical doctors, physiotherapists and psychologists [3, 16, 21].

Conflict of interest

None.

References:

- Jacob AG, Driscoll DJ, Shaughnessy WJ, et al. Klippel-Trénaunay syndrome: spectrum and management. *Mayo Clin Proc.* 1998; 73(1): 28–36, doi: [10.1016/S0025-6196\(11\)63615-X](https://doi.org/10.1016/S0025-6196(11)63615-X), indexed in Pubmed: [9443675](https://pubmed.ncbi.nlm.nih.gov/9443675/).
- Capraro PA, Fisher J, Hammond DC, et al. Klippel-Trénaunay syndrome. *Plast Reconstr Surg.* 2002; 109(6): 2052–2060; quiz 2061, indexed in Pubmed: [11994613](https://pubmed.ncbi.nlm.nih.gov/11994613/).
- Kulungowski AM, Fishman SJ. Management of combined vascular malformations. *Clin Plast Surg.* 2011; 38(1): 107–120, doi: [10.1016/j.cps.2010.08.009](https://doi.org/10.1016/j.cps.2010.08.009), indexed in Pubmed: [21095476](https://pubmed.ncbi.nlm.nih.gov/21095476/).
- Mulliken JB, Burrows PE, Fishman SJ. Mulliken and young's vascular anomalies: hemangiomas and malformations. 2nd ed. Oxford University Press, Oxford 2013: 606–609.
- Liu NF, Lu Q, Yan ZX. Lymphatic malformation is a common component of Klippel-Trénaunay syndrome. *J Vasc Surg.* 2010; 52(6): 1557–1563, doi: [10.1016/j.jvs.2010.06.166](https://doi.org/10.1016/j.jvs.2010.06.166), indexed in Pubmed: [20800418](https://pubmed.ncbi.nlm.nih.gov/20800418/).
- Volz K, Kanner C, Evans J, et al. Klippel-Trénaunay Syndrome. *Journal of Ultrasound in Medicine.* 2016; 35(9): 2057–2065, doi: [10.7863/ultra.15.08007](https://doi.org/10.7863/ultra.15.08007).
- Huiras EE, Barnes CJ, Eichenfield LF, et al. Pulmonary thromboembolism associated with Klippel-Trénaunay syndrome. *Pediatrics.* 2005; 116(4): e596–e600, doi: [10.1542/peds.2004-1607](https://doi.org/10.1542/peds.2004-1607), indexed in Pubmed: [16166386](https://pubmed.ncbi.nlm.nih.gov/16166386/).
- Douma RA, Oduber CEU, Gerdes VEA, et al. Chronic pulmonary embolism in Klippel-Trénaunay syndrome. *J Am Acad Dermatol.* 2012; 66(1): 71–77, doi: [10.1016/j.jaad.2010.12.002](https://doi.org/10.1016/j.jaad.2010.12.002), indexed in Pubmed: [21571392](https://pubmed.ncbi.nlm.nih.gov/21571392/).
- Oduber CEU, Gerdes VEA, van der Horst CM, et al. Vascular malformations as underlying cause of chronic thromboembolism and pulmonary hypertension. *J Plast Reconstr Aesthet Surg.* 2009; 62(5): 684–689; discussion 689, doi: [10.1016/j.bjps.2007.12.062](https://doi.org/10.1016/j.bjps.2007.12.062), indexed in Pubmed: [18571489](https://pubmed.ncbi.nlm.nih.gov/18571489/).
- Uihlein LC, Liang MG, Fishman SJ, et al. Capillary-venous malformation in the lower limb. *Pediatr Dermatol.* 2013; 30(5): 541–548, doi: [10.1111/pde.12186](https://doi.org/10.1111/pde.12186), indexed in Pubmed: [23829172](https://pubmed.ncbi.nlm.nih.gov/23829172/).
- Calvo-Garcia MA, Kline-Fath BM, Adams DM, et al. Imaging evaluation of fetal vascular anomalies. *Pediatr Radiol.* 2015; 45(8): 1218–1229, doi: [10.1007/s00247-014-3248-x](https://doi.org/10.1007/s00247-014-3248-x), indexed in Pubmed: [25492302](https://pubmed.ncbi.nlm.nih.gov/25492302/).
- Klippel M, Trénaunay P. Du naevus variqueux osteo-hypertrophique. *Arch Gen Med.* 1900; 185: 641–672.
- Jacob AG, Driscoll DJ, Shaughnessy WJ, et al. Klippel-Trénaunay syndrome: spectrum and management. *Mayo Clin Proc.* 1998; 73(1): 28–36, doi: [10.1016/S0025-6196\(11\)63615-X](https://doi.org/10.1016/S0025-6196(11)63615-X), indexed in Pubmed: [9443675](https://pubmed.ncbi.nlm.nih.gov/9443675/).
- Genetics Home Reference [Internet]. U.S. National Library of Medicine. 2019; p. 1–5. [Genetics Home Reference \[Internet\]. U.S. National Library of Medicine.](https://ghr.nlm.nih.gov/condition/klippel-trenaunay-syndrome)
- Baskerville PA, Ackroyd JS, Browse NL. The etiology of the Klippel-Trénaunay syndrome. *Ann Surg.* 1985; 202(5): 624–627, indexed in Pubmed: [2996451](https://pubmed.ncbi.nlm.nih.gov/2996451/).
- Noel AA, Gloviczki P, Cherry KJ, et al. Surgical treatment of venous malformations in Klippel-Trénaunay syndrome. *J Vasc Surg.* 2000; 32(5): 840–847, doi: [10.1067/mva.2000.110343](https://doi.org/10.1067/mva.2000.110343), indexed in Pubmed: [11054214](https://pubmed.ncbi.nlm.nih.gov/11054214/).
- Whelan AJ, Watson MS, Porter FD, et al. Klippel-Trénaunay-Weber syndrome associated with a 5:11 balanced translocation. *Am J Med Genet.* 1995; 59(4): 492–494, doi: [10.1002/ajmg.1320590416](https://doi.org/10.1002/ajmg.1320590416), indexed in Pubmed: [8585570](https://pubmed.ncbi.nlm.nih.gov/8585570/).
- Tian XL, Kadaba R, You SA, et al. Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trénaunay syndrome. *Nature.* 2004; 427(6975): 640–645, doi: [10.1038/nature02320](https://doi.org/10.1038/nature02320), indexed in Pubmed: [14961121](https://pubmed.ncbi.nlm.nih.gov/14961121/).
- Wang Q, Timur AA, Szafranski P, et al. Identification and molecular characterization of de novo translocation t(8;14)

- (q22.3;q13) associated with a vascular and tissue overgrowth syndrome. *Cytogenet Cell Genet.* 2001; 95(3-4): 183–188, doi: [10.1159/000059343](https://doi.org/10.1159/000059343), indexed in Pubmed: [12063397](https://pubmed.ncbi.nlm.nih.gov/12063397/).
20. Timur AA, Sadgephour A, Graf M, et al. Identification and molecular characterization of a de novo supernumerary ring chromosome 18 in a patient with Klippel-Trenaunay syndrome. *Ann Hum Genet.* 2004; 68(Pt 4): 353–361, doi: [10.1046/j.1529-8817.2004.00095.x](https://doi.org/10.1046/j.1529-8817.2004.00095.x), indexed in Pubmed: [15225160](https://pubmed.ncbi.nlm.nih.gov/15225160/).
 21. Wang SK, Drucker NA, Gupta AK, et al. Diagnosis and management of the venous malformations of Klippel-Trenaunay syndrome. *J Vasc Surg Venous Lymphat Disord.* 2017; 5(4): 587–595, doi: [10.1016/j.jvsv.2016.10.084](https://doi.org/10.1016/j.jvsv.2016.10.084), indexed in Pubmed: [28624001](https://pubmed.ncbi.nlm.nih.gov/28624001/).
 22. Revencu N, Boon LM, Domp Martin A, et al. Germline mutations in RASA1 are not found in patients with Klippel-Trenaunay syndrome or capillary malformation with limb overgrowth. *Mol Syndromol.* 2013; 4(4): 173–178, doi: [10.1159/000349919](https://doi.org/10.1159/000349919), indexed in Pubmed: [23801933](https://pubmed.ncbi.nlm.nih.gov/23801933/).
 23. Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Genet.* 2003; 73(6): 1240–1249, doi: [10.1086/379793](https://doi.org/10.1086/379793), indexed in Pubmed: [14639529](https://pubmed.ncbi.nlm.nih.gov/14639529/).
 24. Wetzel-Strong SE, Dettler MR, Marchuk DA. The pathobiology of vascular malformations: insights from human and model organism genetics. *J Pathol.* 2017; 241(2): 281–293, doi: [10.1002/path.4844](https://doi.org/10.1002/path.4844), indexed in Pubmed: [27859310](https://pubmed.ncbi.nlm.nih.gov/27859310/).
 25. Dimopoulos A, Sicko RJ, Kay DM, et al. Copy number variants in a population-based investigation of Klippel-Trenaunay syndrome. *Am J Med Genet A.* 2017; 173(2): 352–359, doi: [10.1002/ajmg.a.37868](https://doi.org/10.1002/ajmg.a.37868), indexed in Pubmed: [27901321](https://pubmed.ncbi.nlm.nih.gov/27901321/).
 26. Oduber CEU, Young-Afat DA, van der Wal AC, et al. The persistent embryonic vein in Klippel-Trenaunay syndrome. *Vasc Med.* 2013; 18(4): 185–191, doi: [10.1177/1358863X13498463](https://doi.org/10.1177/1358863X13498463), indexed in Pubmed: [23966121](https://pubmed.ncbi.nlm.nih.gov/23966121/).
 27. Sharma D, Lamba S, Pandita A, et al. Klippel-trenaunay syndrome — a very rare and interesting syndrome. *Clin Med Insights Circ Respir Pulm Med.* 2015; 9: 1–4, doi: [10.4137/CCRPM.S21645](https://doi.org/10.4137/CCRPM.S21645), indexed in Pubmed: [25861232](https://pubmed.ncbi.nlm.nih.gov/25861232/).
 28. Głowiczki P, Driscoll DJ. Klippel-Trenaunay syndrome: current management. *Phlebology.* 2007; 22(6): 291–298, indexed in Pubmed: [18274338](https://pubmed.ncbi.nlm.nih.gov/18274338/).
 29. Sreekar H, Dawre S, Petkar KS, et al. Diverse manifestations and management options in Klippel-Trenaunay syndrome: a single centre 10-year experience. *J Plast Surg Hand Surg.* 2013; 47(4): 303–307, doi: [10.3109/2000656X.2013.766201](https://doi.org/10.3109/2000656X.2013.766201), indexed in Pubmed: [23710784](https://pubmed.ncbi.nlm.nih.gov/23710784/).
 30. Głowiczki P, Hollier LH, Telander RL, et al. Surgical implications of Klippel-Trenaunay syndrome. *Ann Surg.* 1983; 197(3): 353–362, indexed in Pubmed: [6299216](https://pubmed.ncbi.nlm.nih.gov/6299216/).
 31. LINDENAUER SM. The Klippel-Trenaunay Syndrome: varicosity, hypertrophy and hemangioma with no arteriovenous fistula. *Ann Surg.* 1965; 162: 303–314, indexed in Pubmed: [14327016](https://pubmed.ncbi.nlm.nih.gov/14327016/).
 32. Berry SA, Peterson C, Mize W, et al. Klippel-Trenaunay syndrome. *Am J Med Genet.* 1998; 79(4): 319–326, indexed in Pubmed: [9781914](https://pubmed.ncbi.nlm.nih.gov/9781914/).
 33. Cohen MM. Klippel-Trenaunay syndrome. *Am J Med Genet.* 2000; 93(3): 171–175, indexed in Pubmed: [10925375](https://pubmed.ncbi.nlm.nih.gov/10925375/).
 34. Servelle M. Klippel and Trenaunay's syndrome. 768 operated cases. *Ann Surg.* 1985; 201(3): 365–373, indexed in Pubmed: [2983626](https://pubmed.ncbi.nlm.nih.gov/2983626/).
 35. Eifert S, Villavicencio JL, Kao TC, et al. Prevalence of deep venous anomalies in congenital vascular malformations of venous predominance. *J Vasc Surg.* 2000; 31(3): 462–471, indexed in Pubmed: [10709058](https://pubmed.ncbi.nlm.nih.gov/10709058/).
 36. Servelle M. Klippel and Trenaunay's syndrome. 768 operated cases. *Ann Surg.* 1985; 201(3): 365–373, indexed in Pubmed: [2983626](https://pubmed.ncbi.nlm.nih.gov/2983626/).
 37. Rovira OJ, Repollet-Otero C, Rodriguez LE, et al. Symptomatic, unilateral, isolated, complete persistent sciatic vein. *J Vasc Surg Venous Lymphat Disord.* 2018; 6(1): 104–106, doi: [10.1016/j.jvsv.2017.09.002](https://doi.org/10.1016/j.jvsv.2017.09.002), indexed in Pubmed: [29129803](https://pubmed.ncbi.nlm.nih.gov/29129803/).
 38. Szuba A, Rockson SG. Lymphedema: anatomy, physiology and pathogenesis. *Vasc Med.* 1997; 2(4): 321–326, doi: [10.1177/1358863X9700200408](https://doi.org/10.1177/1358863X9700200408), indexed in Pubmed: [9575606](https://pubmed.ncbi.nlm.nih.gov/9575606/).
 39. Servelle M, Albeaux Fernet N, Laborde N. Lesions des vaisseaux lymphatiques dans les malformations congénitales des veines profondes. *Press Med.* 1957; 65: 531–534.
 40. Sabin F. On the origin of the lymphatic system from the veins and the development of the lymph hearts and thoracic duct in the pig. *American Journal of Anatomy.* 1902; 1(3): 367–389, doi: [10.1002/aja.1000010310](https://doi.org/10.1002/aja.1000010310).
 41. Cha SH, Romeo MA, Neutze JA. Visceral manifestations of Klippel-Trenaunay syndrome. *Radiographics.* 2005; 25(6): 1694–1697, doi: [10.1148/rg.256055042](https://doi.org/10.1148/rg.256055042), indexed in Pubmed: [16284144](https://pubmed.ncbi.nlm.nih.gov/16284144/).
 42. Kundzina L, Lejniece S. Klippel-Trenaunay-Weber syndrome with atypical presentation of hypersplenism and nephrotic syndrome: a case report. *J Med Case Rep.* 2017; 11(1): 243, doi: [10.1186/s13256-017-1413-1](https://doi.org/10.1186/s13256-017-1413-1), indexed in Pubmed: [28823249](https://pubmed.ncbi.nlm.nih.gov/28823249/).
 43. Sahin ON, Atik T, Coğulu O, et al. The spectrum of clinical features associated with Klippel-Trenaunay-Weber syndrome. *Genet Couns.* 2015; 26(2): 249–251, indexed in Pubmed: [26349197](https://pubmed.ncbi.nlm.nih.gov/26349197/).
 44. Mazoyer E, Enjolras O, Laurian C, et al. Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach-Merritt syndrome. *Clin Lab Haematol.* 2002; 24(4): 243–251, indexed in Pubmed: [12181029](https://pubmed.ncbi.nlm.nih.gov/12181029/).
 45. Meier S. Klippel-Trenaunay syndrome: a case study. *Adv Neonatal Care.* 2009; 9(3): 120–124, doi: [10.1097/ANC.0b013e-3181a68b15](https://doi.org/10.1097/ANC.0b013e-3181a68b15), indexed in Pubmed: [19542774](https://pubmed.ncbi.nlm.nih.gov/19542774/).
 46. Banzic I, Brankovic M, Maksimović Ž, et al. Parkes Weber syndrome-diagnostic and management paradigms: a systematic review. *Phlebology.* 2017; 32(6): 371–383, doi: [10.1177/0268355516664212](https://doi.org/10.1177/0268355516664212), indexed in Pubmed: [27511883](https://pubmed.ncbi.nlm.nih.gov/27511883/).
 47. Young AE. Congenital mixed vascular deformities of the limbs and their associated lesions. *Birth Defects Orig Artic Ser.* 1978; 14(6B): 289–296, indexed in Pubmed: [728569](https://pubmed.ncbi.nlm.nih.gov/728569/).
 48. Baskerville PA, Ackroyd JS, Lea Thomas M, et al. The Klippel-Trenaunay syndrome: clinical, radiological and haemodynamic features and management. *Br J Surg.* 1985; 72(3): 232–236, indexed in Pubmed: [2983819](https://pubmed.ncbi.nlm.nih.gov/2983819/).
 49. Szuba A, Rockson SG. Lymphedema: classification, diagnosis and therapy. *Vasc Med.* 1998; 3(2): 145–156, doi: [10.1177/1358836X9800300209](https://doi.org/10.1177/1358836X9800300209), indexed in Pubmed: [9796078](https://pubmed.ncbi.nlm.nih.gov/9796078/).
 50. Drodz K, Chachaj A, Szuba A. The decongestive lymphatic therapy in the massive primary lower limb lymphedema treatment. *Acta Angiologica.* 2017; 23(3): 130–134, doi: [10.5603/aa.2017.0011](https://doi.org/10.5603/aa.2017.0011).
 51. Phillips GN, Gordon DH, Martin EC, et al. The Klippel-Trenaunay syndrome: clinical and radiological aspects. *Radiology.* 1978; 128(2): 429–434, doi: [10.1148/128.2.429](https://doi.org/10.1148/128.2.429), indexed in Pubmed: [208102](https://pubmed.ncbi.nlm.nih.gov/208102/).
 52. Warren AG, Brorson H, Borud LJ, et al. Lymphedema: a comprehensive review. *Ann Plast Surg.* 2007; 59(4): 464–472, doi: [10.1097/01.sap.0000257149.42922.7e](https://doi.org/10.1097/01.sap.0000257149.42922.7e), indexed in Pubmed: [17901744](https://pubmed.ncbi.nlm.nih.gov/17901744/).
 53. Głowiczki P, Stanson AW, Stickler GB, et al. Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. *Surgery.* 1991; 110(3): 469–479, indexed in Pubmed: [1653464](https://pubmed.ncbi.nlm.nih.gov/1653464/).
 54. Blaise S, Charavin-Cocuzza M, Riom H, et al. Treatment of low-flow vascular malformations by ultrasound-guided sclerotherapy with polidocanol foam: 24 cases and literature review. *Eur J Vasc Endovasc Surg.* 2011; 41(3): 412–417, doi: [10.1016/j.ejvs.2010.10.009](https://doi.org/10.1016/j.ejvs.2010.10.009), indexed in Pubmed: [21111641](https://pubmed.ncbi.nlm.nih.gov/21111641/).

