Přehledový článek | Review article

Klippel–Trénaunay syndrome: the etiology, clinical presentation, and treatment options

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SÚHRN

Cieľ: Klippelov–Trénaunayov syndróm (KTS) je zriedkavá kombinovaná cievna malformácia spojená s nadmerným rastom končatiny. Cieľom tejto prehľadovej práce je zhrnúť súčasné poznatky o predpokladanej etiológii, najčastejších anomáliách spojených s KTS, diagnostickom prístupe a liečebných stratégiách.
Metódy: V období od januára do mája 2025 bola vykonaná analýza literatúry s využitím databáz PubMed a Google Scholar so zameraním na kľúčové pojmy Klippelov–Trénaunayov syndróm a *PIK3CA*-related overgrowth spectrum (PROS).
Záver: KTS sa prejavuje ako súbor vrodených malformácií postihujúcich končatinu a typicky postihuje jednostranne dolnú končatinu. Je dôsledkom postzygotnej aktivačnej mutácie v géne *PIK3CA*, ktorá vedie k nadmernej aktivácii signálnej dráhy *PI3K*–AKT–mTOR. Klinický obraz je variabilný, od miernych foriem až po závažné ochorenie s postihnutím viscerálnych orgánov a trombohemoragickými komplikáciami. Preferovanou zobrazovacou metódou na posúdenie rozsahu cievnych malformácií a postihnutia tkanív je MR angiografia. Liečba KTS si často vyžaduje multidisciplinárny prístup. V roku 2022 FDA schválila alpelisib ako systémovú liečebnú možnosť pre pacientov s ťažkými formami KTS.

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Keywords:
Alpelisib
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ABSTRACT

Objective: Klippel–Trénaunay syndrome (KTS) is a combined slow-flow vascular malformation associated with excessive growth of limbs. The aim of this review is to summarize the knowledge about the presumed etiology, the most common anomalies associated with KTS, the diagnostic approach, and the treatment strategies.
Methods: A literature search was conducted between January and May 2025 using PubMed and Google Scholar databases, focusing on terms such as Klippel–Trénaunay syndrome and *PIK3CA*-related overgrowth spectrum (PROS).
Conclusions: KTS manifests as a cluster of congenital malformations affecting the limb and typically affects the lower extremity unilaterally. It results from a postzygotic activating mutation in the *PIK3CA* gene which leads to overactivation of the *PI3K*-AKT-mTOR signaling pathway. The clinical presentation is variable, ranging from mild forms to severe disease with the visceral organ involvement and thrombo-hemorrhagic complications. MRI-angiography is the preferred imaging modality to assess the extent of vascular malformations and tissue involvement. Management of KTS often requires a multidisciplinary approach. In 2022, the FDA approved alpelisib as a systemic treatment option for patients with severe forms of KTS.

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Introduction

Although Klippel–Trénaunay syndrome (KTS) has been known since 1832, it was first described as a distinct clinical entity in 1900 by the French physicians Maurice Klippel and Paul Trénaunay.[1,2] The clinical diagnosis of KTS is based on the characteristic triad of capillary malformation, venous malformation (unilateral, extensive veins), and segmental overgrowth, which most commonly occur in the lower extremity.[3] Many patients also have lymphatic malformations. Although clear diagnostic criteria are lacking, the presence of two of the three typical symptoms is required for the diagnosis.[4,5] Vascular malformations and overgrowth may involve the gastrointestinal tract, bladder, kidney, spleen, liver, and mediastinum.[6] Visceral organ involvement is likely when the capillary malformation extends to the abdomen and trunk. It is thought to affect both men and women equally without racial predisposition.[7] The prevalence of KTS is low, mild forms are probably underreported and its estimated incidence ranges from 1 to 5 per 100,000 individuals.[8,9]

Pathophysiology of Klippel–Trénaunay syndrome

KTS belongs to the *PIK3CA*-related overgrowth spectrum (PROS), a group of rare congenital disorders characterized by segmental or lateralized overgrowth of various tissues and anatomical regions. These conditions share a mosaic, postzygotic, somatic gain-of-function mutation in the *PIK3CA* gene, which arose during embryogenesis and fetal development.[10,11]

The *PIK3CA* gene encodes the p110α catalytic subunit of class I phosphatidylinositol-3-kinase (PI3K), which has a role in cellular processes such as proliferation, motility, invasion, and death through its involvement in the PI3K/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway. This mutation leads to activation of the PI3K signaling cascade, including downstream effectors such as AKT and mTOR.[3,10,12–14] Experimental studies using animal models have demonstrated that activating mutations in *PIK3CA* gene are associated with hyperplastic vasculature, increased endothelial cell proliferation, enhanced angiogenesis, spontaneous hemorrhage, and pronounced phenotypic anomalies.[15]

Cells that arise from a mutated cell carry the mutation, resulting in mosaicism (an organism has cells with different genetic content). Different distribution of healthy and pathological cells in tissues leads to variable phenotypic expression. The presence of a somatic mutation does not confer disease risk to the offspring of the patient.[16]

Increased expression of the *AGGF1* gene (angiogenic factor with G patch and FHA domains 1) has also been documented in individuals with KTS. Overexpression of the *AGGF1* gene enhances angiogenesis through phosphorylation of the p110α catalytic subunit and the p85α regulatory subunit of the PI3K.[10,17] In addition, sporadic chromosomal translocations between chromosomes 5 and 11 and 8 and 14 have been reported as other, less common genetic events potentially involved in KTS pathogenesis.[18]

Slow-flow vascular malformations in Klippel–Trénaunay syndrome

According to the International Society for the Study of Vascular Anomalies classification, KTS is characterized by the presence of capillary malformation, venous malformation, and limb overgrowth with/without lymphatic malformation.[19] In a study including 252 patients with KTS conducted at the Mayo Clinic in Rochester, all three characteristics were observed in 63% of cases, while 37% of patients showed two of these features.[20] Unilateral lower limb involvement was described in 71% of cases in the study conducted by Alwalid et al., and bilateral but asymmetric lower limb involvement was described in the remaining 29% of cases.[8] The upper limbs are less frequently affected. KTS is a trunkal vascular malformation, therefore it does not have the ability to proliferate after removal.[21]

Capillary malformations (nevus flammeus) are usually present at birth (**Figs 1–3**). This lesion consists of a flat, well-circumscribed, pink, red, or purple patches resembling a map-like distribution, referred to as a port wine stains. It occurs in 98% of patients and often is the first clinical manifestation of KTS.[20] The lesions tend to grow proportionally with the child. Its proximal extension in the gluteal region, pelvis, and abdominal wall is associated with a risk of visceral vascular and organ involvement.[3,22]

Venous malformations occur in 70–100% of patients and most commonly manifest as dilated veins.[8] Both the superficial and deep venous systems may be affected,

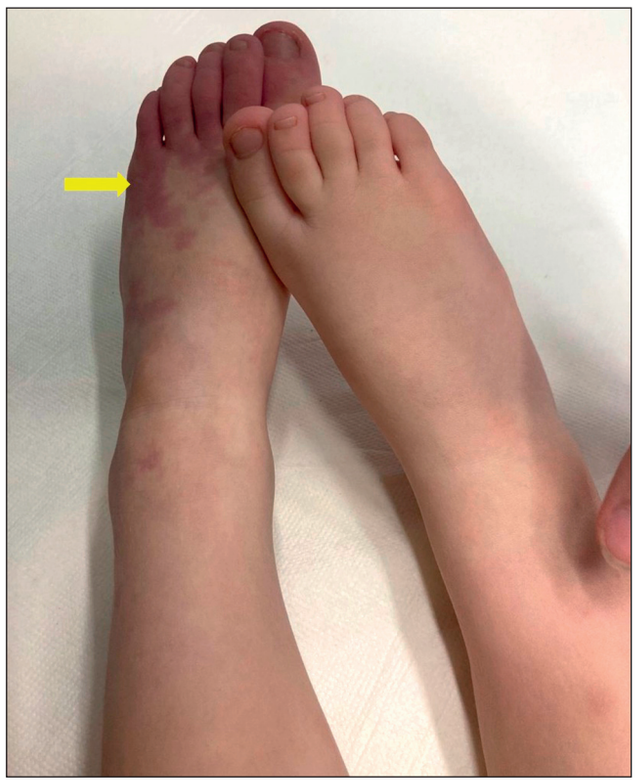

Fig. 1 – Capillary malformation (nevus flammeus) of left leg and toes (yellow arrow), longer left leg in child with KTS (archive of the VÚSCH).

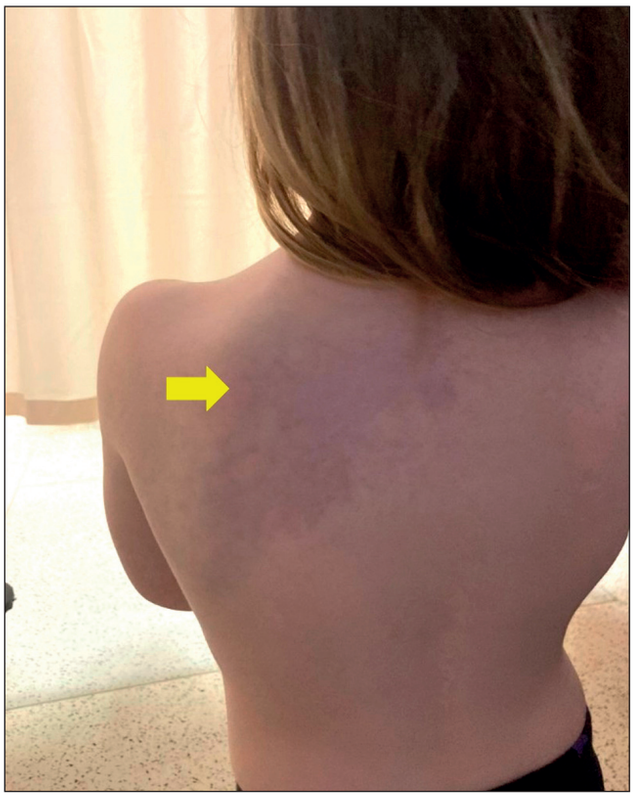

Fig. 2 – Capillary malformation (nevus flammeus) (yellow arrow) in a patient with KTS (archive of the VÚSCH).

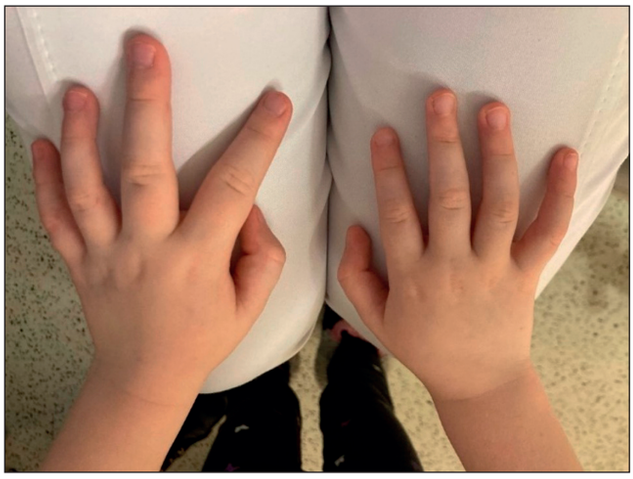

Fig. 3 – Macrodactyly of the index finger and middle finger of the left hand in patients with KTS (archive of the VÚSCH).

with manifestations ranging from small vein ectasia to persistent embryonic veins, and extensive venous malformations. Large embryonic veins may be present in 17–72% of patients.[21] These anomalous veins include the sciatic vein, the lateral marginal vein, gluteal and pelvic-retroperitoneal venous malformations. Approximately 17–56% of patients with KTS have a lateral marginal vein, also known as the vein of Servelle or the vein of Klippel–Trénaunay. It arises from the metatarsal region, is located on the lateral part of the calf and thigh, enters the deep venous system at various anatomical levels and is frequently associated with deep venous hypoplasia or aplasia.[14] It communicates via large perforators with the deep and superficial veins and may divide into multiple channels.

The persistent sciatic vein, present in almost 50% of patients, starts at the level of knee, follows the anatomical course of the sciatic nerve and terminates into internal iliac vein.[23,24] Avalvular dilated embryonic veins with abnormal thin-walled structure, are a source of venous reflux, subsequent venous insufficiency, and a source of intravascular coagulation.[8]

The deep venous system is often dysplastic with abnormalities including agenesis, atresia, hypoplasia, duplication, valvular insufficiency, stenosis, ectasia, and aneurysmal dilatation.[14] Deep vein hypoplasia/aplasia was observed in 20% of patients.[21] Popliteal vein was affected in 51% of cases, superficial femoral vein in 16% of cases, both in 29% of cases, iliac veins in 3% of cases and inferior cava vein in 1% of cases.[20] Venous return from the limb is often diverted from the smaller, underdeveloped deep venous system into anomalous valveless veins that function as a collateral compensatory venous drainage system.

The prevalence of lymphatic malformations in the study conducted by Liu et al. was comparable to the prevalence of venous malformations.[25] In this study, lymphatic hypoplasia and aplasia were identified in 64% of patients, while lymphatic hyperplasia was observed in 36% of patients. Lymph node abnormalities, including hyperplasia, hypoplasia, or aplasia, were present in 71% of cases. Patients with lymphatic hyperplasia may have concomitant lymph node aplasia, whereas individuals with normal lymph nodes may have hypoplasia or aplasia of superficial lymphatic vessels.[25]

Primary lymphedema worsens chronic venous insufficiency, contributes to limb swelling, overgrowth, and increases the risk of elephantiasis, erysipelas, cellulitis, and leg ulcers. Recurrent cellulitis further damages the lymphatic system, and leads to progressive lymphedema. The most common symptoms include pain, swelling, bleeding, heaviness in the extremities and cosmetic problems.

The frequent coexistence of venous and lymphatic malformations supports the hypothesis of a close developmental relationship between these two circulatory systems and is consistent with the hypothesis that primitive lymphatic sacs originate from endothelial cells of embryonic veins.[25] Lymphatic malformations, similarly to venous malformations, could also occur in the pelvis, bladder, gastrointestinal tract, and in the spleen.[26]

Hematologic complications of Klippel–Trénaunay syndrome

Patients with venous malformations are at risk of thrombotic and bleeding complications. Localized intravascular coagulopathy (LIC) occurs in approximately 40–60% of patients with venous malformations and is explained by blood stasis and degenerative changes in the venous wall. It is characterized by elevated D-dimers, and in severe forms with low fibrinogen levels.[27,28] Elevated D-dimers are seen in 42–58% of patients, and hypofibrinogenemia is present in 6–10% of patients.[27]

LIC may be chronic and asymptomatic; however, if symptomatic, it may cause swelling and pain due to thrombosis or bleeding within the malformation.[27] Over time, intralesional thrombi develop into phleboliths (intraluminal calcified thrombi or focal calcifications of the vein wall), which may be palpable as hard nodules.[27] LIC carries a risk venous thromboembolism (VTE) which has been reported in 8–30% of patients with KTS. The presence of a lateral marginal vein 2.7-fold increases the risk of VTE.[27,29] Other factors that increase the risk of VTE include venous ectasia, previous thrombosis, thrombophilic states, and a recent history of surgical or endovascular procedures.

Risk factors (trauma, surgical or endovascular procedures, infection, immobilization, pregnancy) can cause LIC progression to disseminated intravascular coagulation (DIC).[26,27] Structural abnormalities of the venous wall and venous hypertension further increase the bleeding risk. Bleeding most commonly occurs in the gastrointestinal and urogenital tracts, but depending on the anatomical location of the KTS, bleeding may also occur in other visceral organs.

Tissue overgrowth and visceral involvement

The most variable feature of KTS is excessive growth of the affected limb due to hypertrophy of soft tissues and/or bones, which occurs in 67–100% of patients.[20,22] Hypertrophy may be isolated, e.g. macrodactyly, but the entire lower limb could be affected. Polydactyly, clinodactyly, syndactyly, camptodactyly, and ectrodactyly were also described.[14] The limb increases in width and length.[2,3,22] Limb differences are variable, but after the growth plates close, the bone does not grow in length. Overgrowth may lead to secondary problems such as early arthritis, contractures, stiff joint, joint instability, gait disturbances, spinal stenosis, muscle atrophy and scoliosis.[30] Orthopedic manifestations occur in almost two thirds of patients.[31] In the analysis conducted by Schoch et al. which included 410 patients with KTS, 84% of patients had a limb length discrepancy, 10% angular limb deformity, 9% scoliosis, 7% osteopenia/osteoporosis, 6% pathological fracture, and 5% had a contracture.[31]

The progression of limb hypertrophy/overgrowth is deteriorating by chronic venous insufficiency and lymphedema therefore it is difficult to predict it. Tissue hypertrophy/overgrowth could occur in the pelvic, gluteal, and abdominal regions. Maxillary and mandibular involvement in cases of upper limb involvement has also been described.[21]

Gastrointestinal involvement is present in approximately 20% of patients with lower extremity venous malformation. "Hemorrhoids" can be the tip of the iceberg of gastrointestinal manifestation.[24] Bleeding from gastrointestinal venous malformations can be mild or occult (e.g. from perianal lymphatic vesicles), but cases of fatal intraabdominal bleeding have been documented.[5,26,32,33,34]

The pathophysiology of complications differs in the anorectal and anorectosigmoid regions. In the anorectal region, blood from venous malformations drains to the internal iliac vein. Venous malformations in this region may present with enterorrhagia, as well as LIC with phlebolith formation.

In anorectosigmoid venous malformations, blood drains into the internal iliac vein, superior rectal vein, and inferior mesenteric vein. Stasis and venous hypertension in these veins, in addition to the complications mentioned above, increase the risk of portal vein thrombosis, portal hypertension, gastroesophageal varices, and ascites.

In the urogenital tract KTS may manifest as cryptorchidism, phimosis, megaureter, penile hypertrophy/deformity, scrotal overgrowth, megauterus, unilateral renal hypertrophy, and bladder wall thickening.[8,20] Hematuria has been reported in 1% of patients and it may originate from the bladder, urethra, and kidneys.[33,35] Uterine venous malformations may cause menorrhagia.[36] Splenic lesions may present with multifocal or diffuse lymphatic malformations and splenomegaly. Intestinal lymphangiectasia may cause protein-losing enteropathy.

Diagnosis of Klippel–Trénaunay syndrome

Diagnosis is based on history, physical signs and symptoms.[6] The length and circumference of the affected limb, hand, and foot should be measured at each examination. Plain radiograph is used for evaluation and follow-up of limb length discrepancy, bone abnormalities such as scoliosis, joint dislocation and it can show phlebolits which are pathognomic for venous malformations.[8] Ultrasonography is used to diagnose superficial and deep vein involvement. Patients with recurrent thromboses and LIC should be examined by echocardiography for the presence of pulmonary hypertension. MRI-angiography is the examination of first choice for visceral venous malformations and tissue hypertrophy; if unavailable, CT-angiography is used (**Figs 4–8**).[6] Lymphoscintigraphy is used to diagnose lymphatic malformation. Depending

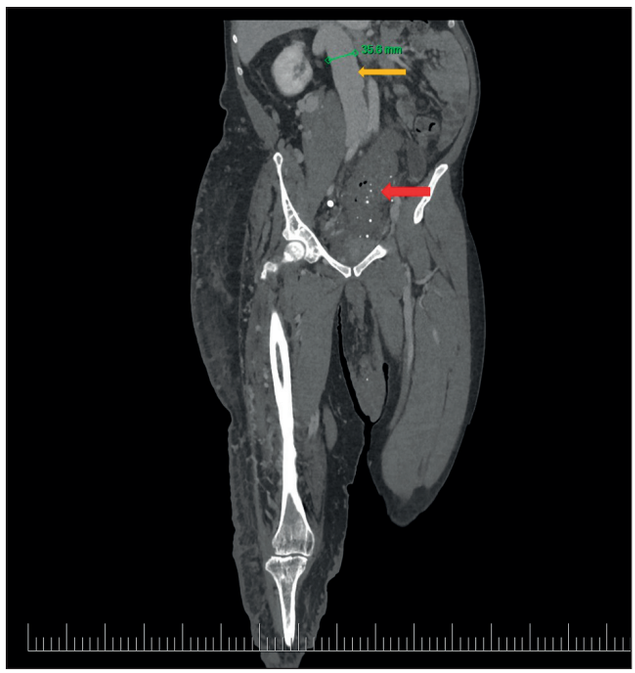

Fig. 4 – CT-angiography of patient with KTS. Phlebolits in venous malformations in the rectum (red arrow), megacava with diameter of 35.6 mm (yellow arrow), hypertrophy of the right gluteal region (archive of the VÚSCH).

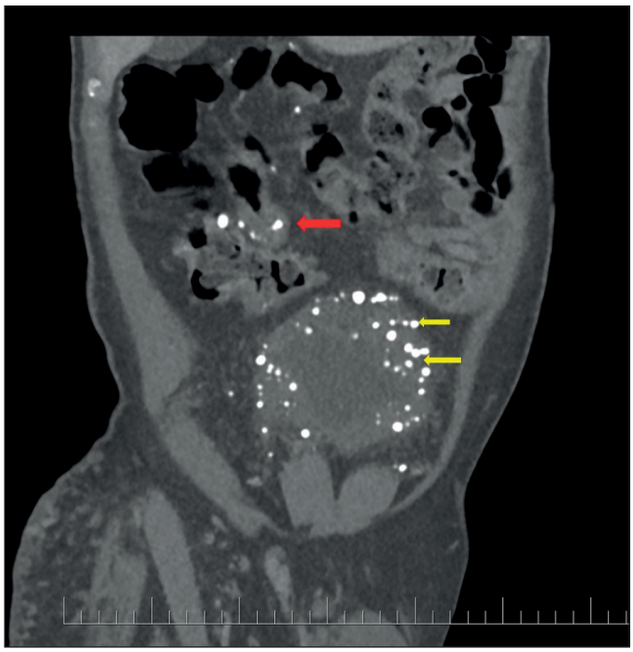

Fig. 5 – CT-angiography of a patient with KTS. Phlebolits in venous malformations in bladder (yellow arrow) and in venous malformations of the intestine (red arrow) (archive of the VÚSCH).

on the affected organs and complications, further examinations are indicated (dermatological, urological examination, and cystoscopy, endoscopic examination of the gastrointestinal tract, gynaecological examination). If the diagnosis is not confirmed by clinical examinations, malignancy is suspected, a biopsy for genetic testing is performed. The biopsy must be performed from overgrown limb or from the area of vascular malformation. Laboratory evaluation includes monitoring of D-dimers, fibrinogen, hemoglobin, platelets, prothrombin time, activated partial thromboplastin time. Normal hemoglobin and iron levels decrease probability of occult bleeding from the gastrointestinal or urogenital tract.

General principles of Klippel–Trénaunay syndrome therapy

Depending on the extent of the disease, treatment is led by a multidisciplinary team that includes a dermatologist, gastroenterologist, urologist, orthopedist, angiologist, vascular surgeon, hematologist, radiologist, and gynaecologist. Its goal is to improve the quality of life; a full recovery is not yet possible.

Patients with symptoms of chronic venous disease and lymphedema should be treated similarly to patients with more common forms of these diseases with compression therapy (graduated compression stockings, e.g. class II–III). Compression therapy reduces pain, the risk of superficial thrombophlebitis, ulceration, LIC and slows the lymphedema progression.[27]

Patients should avoid factors that increase thrombotic risk, such as exogenous estrogens, immobility, smoking, and obesity. Anticoagulation is individualized and can

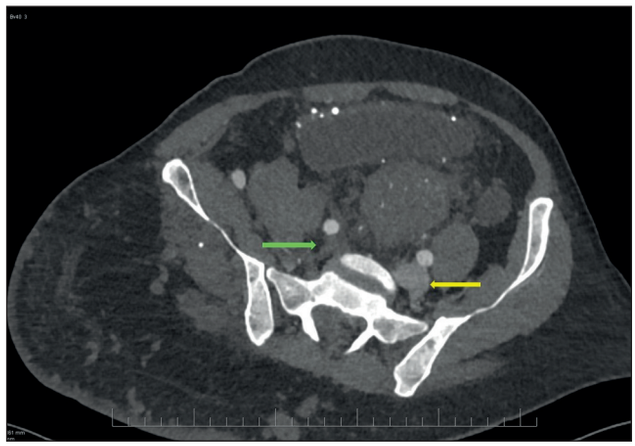

Fig. 6 – CT-angiography of a patient with KTS, absence of the right common iliac vein (green arrow) presence of left common iliac vein (yellow arrow) (archive of the VÚSCH).

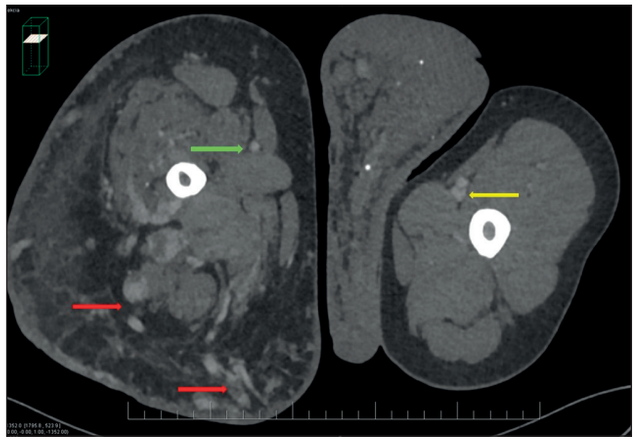

Fig. 7 – CT-angiography of a patient with KTS, absence of the right superficial femoral vein (green arrow), venous malformations in the posterior part of right thigh (red arrows), left superficial femoral vein (yellow arrow) (archive of the VÚSCH).

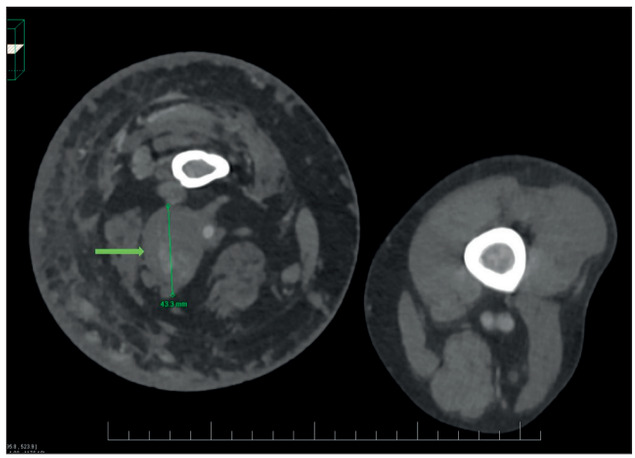

Fig. 8 – CT-angiography of a patient with KTS. Ectasia of right popliteal vein with diameter of 43.3 mm (green arrow), asymmetrical soft tissue thickening of the right leg (archive of the VÚSCH).

be prophylactic or therapeutic; short-term, long-term or lifelong. In high-risk situations (perioperatively, after trauma, immobilization, pregnancy, postpartum), prophylactic anticoagulation therapy for 1–2 weeks pre- and 2 weeks post-procedural in recommended.

Long-term anticoagulation therapy is used in patients with persistently elevated D-dimer and decreased fibrinogen, to treat bleeding associated with low fibrinogen levels, to prevent conversion of LIM to DIC, and in patients with multiple phleboliths, recurrent thrombosis, thrombophlebitis, pulmonary embolism, and pulmonary hypertension.[24] Some authors suggest long-term anticoagulation therapy in all patients with KTS after phlebothrombosis and pulmonary embolism.[22] It is not yet certain whether the efficacy of NOACs in LIC is the same as that of LMWH.[28]

Treatment of vascular malformations

A collaborative approach among professionals of a multidisciplinary team is important to provide optimal care for these patients. Hematologists are involved due to high thrombosis risk. Dermatologists treat capillary malformations. A variety of vascular-selective lasers may be employed, with the pulsed dye laser being the most common and well studied. Vascular experts are required for chronic venous insufficiency. Removal of superficial veins in patients with deep vein agenesis/aplasia worsens the symptomatology and swelling of the legs, therefore, an examination of the deep vein patency before any invasive procedure is necessary.

Indications for the treatment of superficial limb venous malformations are severe symptoms and recurrent bleeding. Endovascular therapy is the treatment of first choice and foam sclerotherapy, radiofrequency and laser thermal ablation are used.[26]

Vascular surgery (high ligation of persistent embryonic vein, vein stripping, and stab phlebectomy) is associated with high recurrence rate, poor wound healing and may be used in selected patients. The ligation and excision of large venous lakes are considered futile.[32]

Treatment of gastrointestinal and rectal bleeding depends on severity. Patient should be evaluated by a gastroenterologist and general surgeon. Conservative treatment including blood transfusion and stool softeners is possible in spontaneously resolving bleeding.[26] In case of recurrent gastrointestinal bleeding, endoscopic treatment is used for localized lesions, and surgery when endoscopic treatment fails. Sclerotherapy is the safe choice for anorectal venous malformations.[26] However, it is not suitable for anorectosigmoid venous malformation, as it increases the risk of acute portal thrombosis, so surgical treatment is considered a better option.[26]

Abnormalities of urogenital tract and hematuria due to urogenital complications should be evaluated by an urologist. Mild hematuria may be treated with intravenous hydration and transfusion, however, in the presence of refractory or life-threatening hematuria, more invasive treatment such as laser coagulation, selective embolization of the internal iliac arteries, cauterization and partial cystectomy are used.[6]

Macrocystic lymphatic malformations are treated with sclerotherapy, lymphatic skin vesicles with CO_2 laser, large complex lymphatic malformations with fatty overgrowth with surgical debulking. Splenomegaly and splenic lesions usually carry little clinical significance and therefore do not require intervention. Rarely, massive splenomegaly is treated with splenectomy.

Early involvement of the orthopaedist is crucial in limb-length discrepancy to determine the optimal timing of intervention and to improve limb symmetry. In the study conducted by Schoch et al., limb length correction by epiphysiodesis was performed in 62.4% of patients, debulking in 6.8% of patients, and amputation in 32.3% of patients.[31]

Despite multidisciplinary efforts, endovascular and surgical treatment of KTS is not completely curative.[7] These treatment modalities treat patients' symptoms without affecting the underlying molecular etiology of KTS.[30] After identification of the underlying cause of PROS in 2012 and genetic definition in 2015, drugs targeting the *PI3K* pathway, previously used in the treatment of malignancies, began to be investigated as new therapeutic options for KTS.[7,36,37]

The mTOR (mammalian target of rapamycin) inhibitor sirolimus, is a direct inhibitor of the protein kinase mTOR. It is used in the prevention of kidney transplant rejection.[22] Sirolimus may stop the progression of vascular malformations, tissue hypertrophy and improve the quality of life. It could be an alternative treatment for patients in whom standard therapy is either not efficacious or not tolerated.[27] Most of its adverse effects are dose-dependent. Headaches, gastrointestinal complaints, elevation of cholesterol, and triglycerides, stomatitis, bone marrow suppression, increased risk of infections, impaired wound healing, and rarely interstitial pneumonia have been described.[22,38]

In 2022, the Food and Drug Administration approved alpelisib for the treatment of *PIK3CA* disease in patients who require systemic therapy. Alpelisib is a competitive, selective inhibitor of the catalytic subunit of *PI3K* (*PI3K*α) approved for the treatment of advanced or metastatic breast cancer with a *PIK3CA* mutation. Treatment with alpelisib in patients with PROS was well tolerated and associated with a clinical improvement.[7] In the EPIK-P1 study, at 24 weeks after treatment initiation, 37.5% of patients experienced ≥20% reduction in target lesion volume, 74% of patients showed reduction in target lesion volume with a mean reduction of 13.7%, and no patients experienced disease progression at the time of the primary analysis.[39] Withdrawal of alpelisib resulted in asymmetric hypertrophy in animal model, suggesting that continuous administration of alpelisib may be needed.[40] Glucose levels should be monitored during treatment as hyperglycaemia is common. The use of alpelisib in Europe for KTS is considered off-label, and the European Medicines Agency does not yet recommend its routine use in this indication. Other drugs being tested include serabelisib, a selective *PI3K* inhibitor, which appears to be effective and well tolerated.[39] The protein kinase B (AKT) inhibitor miransertib was not shown to be effective in the MOSAIC trial.[39,41] Taselisib, an inhibitor of PI3Kα, PI3Kγ,

and PI3KΔ isoforms, had a negative safety profile in the TOTEM study.[42]

Conclusions

Klippel–Trénaunay syndrome is a complex slow-flow vascular malformation with excessive growth of the affected limb due to hypertrophy of soft tissues and/or bones. The clinical presentation is variable, ranging from mild forms to severe disease with the visceral organ involvement and thrombo-haemorrhagic complications. The diagnosis is clinical, and a somatic PIK3CA mutation in affected tissue confirms Klippel-Trénaunay syndrome. To determine the venous anatomy of the extremities, duplex ultrasonography is used. MRI imaging is recommended to examine the extent of vascular malformations, soft tissue, joints, muscles, and bone involvements.

Treatment depends on the extent of the disease. In general, it is aimed at improving chronic venous insufficiency, lymphedema, and thrombo-hemorrhagic complications. Patients with symptoms of chronic venous disease should be treated similarly to patients with more common forms of chronic venous disease, taking into account the possible agenesis of deep veins. Genetic studies have opened up the prospect of alternative or complementary treatments to the current therapies, which address the symptoms rather than the underlying cause of Klippel–Trénaunay syndrome. Alpelisib, a selective PI3Kα inhibitor, targets the etiology of this syndrome and thus offers a new therapeutic approach.

Authors' contributions

All authors contributed equally to the manuscript, read and approved the final version of the manuscript.

Conflict of interest

None.

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Ethical statement

This review article is based on previously published literature. The authors affirm that this manuscript adheres to the ethical standards of academic publishing.

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