Wound-Healing Problems Associated with Combined Vascular Malformations in Klippel–Trenaunay Syndrome

Kosuke Ishikawa,¹ Yuhei Yamamoto,¹ Emi Funayama,¹ Hiroshi Furukawa,² and Satoru Sasaki^{3,*}

Satoru Sasaki, MD, PhD

Submitted for publication August 7, 2018.
Accepted in revised form September 18, 2018

*Correspondence: Department of Plastic and Reconstructive Surgery, Center for Vascular Anomalies, Tonan Hospital, Kita 4, Nishi 7, Chuo-ku, Sapporo 060-0004, Japan
(e-mail: satoru-s@tonan.gr.jp).

¹Department of Plastic and Reconstructive Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan.

²Department of Plastic and Reconstructive Surgery, Aichi Medical University, Nagakute, Japan.

³Department of Plastic and Reconstructive Surgery, Center for Vascular Anomalies, Tonan Hospital, Sapporo, Japan.

Significance: In Klippel–Trenaunay syndrome (KTS), management of a wound in the affected limb can be difficult because of the underlying vascular malformations present. This review describes the characteristics of KTS with wound complications in light of the genetic and molecular mechanisms of the disease.

Recent Advances: KTS is a slow-flow combined vascular malformation characterized by the triad of capillary malformation, venous malformation with or without lymphatic malformation, and limb overgrowth. KTS is encompassed within the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)-related overgrowth spectrum (PROS), having recently been linked to activating mutations in the *PIK3CA* gene. This clearly has implications for both molecular diagnosis and potential treatment strategies for the disease.

Critical Issues: KTS should be distinguished from Parkes Weber syndrome, a fast-flow-type combined vascular malformation with limb overgrowth. Individualized management is needed for KTS and should be focused on the treatment of symptoms.

Future Directions: Targeted therapies that inhibit the phosphoinositide 3-kinase signaling pathway are a potential treatment option for PROS.

Keywords: wounds and injuries, wound healing, contracture, ulcer, vascular malformations, Klippel–Trenaunay–Weber syndrome

SCOPE AND SIGNIFICANCE

VASCULAR MALFORMATIONS associated with other anomalies are a diagnostic and therapeutic challenge for physicians. Klippel–Trenaunay syndrome (KTS) is a congenital vascular malformation with limb overgrowth.¹ Although chronic leg ulcers are less common in patients with KTS than in patients with diabetes or peripheral arterial disease, wounds on affected limbs tend to be difficult to manage because of the underlying disease. This review describes the

characteristics of KTS with wound complications taking into account the genetic and molecular mechanisms of the disease. This should lead to better understanding of the complex medical conditions of KTS and thus to better management, which is typically needed from childhood.

TRANSLATIONAL RELEVANCE

Considerable progress has been made in understanding the underlying genetics of vascular malformations.²

KTS has been linked to activating mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene^{3,4} encoding the 110-kDa catalytic α -subunit of the phosphoinositide 3-kinases (PI3Ks) and belongs to the *PIK3CA*-related overgrowth spectrum (PROS).⁵ PI3Ks are key signaling enzymes in the regulation of fundamental cell processes, including growth, proliferation, motility, survival, and metabolism.⁶ Activating mutations in the *PIK3CA* gene have been identified in various human cancers⁷ and the critical role of the PI3K signaling pathway in wound healing have been documented.^{8–11}

CLINICAL RELEVANCE

Development of anticancer drugs targeting the PI3K signaling pathway is now a major research focus for the pharmaceutical industry.¹² PROS is a progressive condition and therefore a potential target for medical therapy in its early stages because downregulation of the pathway may prevent disease progression and overgrowth.¹² A recent study provided the first evidence that inhibition of *PIK3CA* is a promising therapeutic strategy for patients with PROS.¹³

BACKGROUND AND OVERVIEW

International Society for the Study of Vascular Anomalies classification for vascular anomalies

Vascular anomalies are divided into vascular tumors and vascular malformations according to the 1996 International Society for the Study of Vascular Anomalies (ISSVA) classification.^{14,15} Vascular tumors are defined as proliferative endothelial lesions and include infantile hemangioma, tufted angioma, kaposiform hemangioendothelio-

ma, and angiosarcoma. Vascular malformations are composed of malformed vessels that do not show endothelial cell proliferation; the majority of these lesions tends to worsen over time and are associated with cosmetic problems and functional disability.¹⁶

Vascular malformations can be subcategorized based on their flow characteristics¹⁷ as slow-flow lesions that include capillary malformations (CMs), venous malformations (VMs), and lymphatic malformations (LMs), or as fast-flow lesions that include arteriovenous malformations and arteriovenous fistulae (AVF). There are also various types of combined vascular malformations, such as capillary–venous and capillary–lymphatic–venous malformations.¹⁴ Various eponymous syndromes include such malformations and associated hypertrophy or hypotrophy of the affected limbs.¹⁶

Definition of KTS

According to the updated 2014 ISSVA classification, KTS is a slow-flow type of combined vascular malformation characterized by a constellation of anomalies, including CM, VM with or without LM, and limb overgrowth.¹⁸ KTS was first reported as a distinct disease entity in 1900 by physicians Maurice Klippel and Paul Trenaunay. In their report they described the three clinical findings of port wine stains (*i.e.*, CMs), varicose veins (*i.e.*, VMs), and bony and soft tissue hypertrophy of the involved limb.¹

Several definitions of KTS have been proposed to date,^{19–21} making it difficult to compare between reports in the literature. For example, Jacob *et al.*²² defined it as the presence of any two of the three abovementioned features, based on their experience of 252 patients with KTS. However, Enjolras *et al.*¹⁶ stressed that not all slow-flow vascular malformations in limbs with altered limb growth fall under KTS, such as diffuse CM with congenital hypertrophy of the affected limb and diffuse VM

Table 1. Vascular malformations associated with other anomalies according to the 2018 ISSVA classification

		Causal genes
Klippel–Trenaunay syndrome*	CM + VM $\pm$ LM + limb overgrowth	<i>PIK3CA</i>
Parkes Weber syndrome	CM + AVF + limb overgrowth	<i>RASA1</i>
Servelle–Martorell syndrome	Limb VM + bone undergrowth	
Sturge–Weber syndrome	Facial + leptomeningeal CM + eye anomalies $\pm$ bone and/or soft tissue overgrowth	<i>GNAQ</i>
Limb CM + congenital nonprogressive limb overgrowth		<i>GNA11</i>
Maffucci syndrome	VM $\pm$ spindle-cell hemangioma + enchondroma	<i>IDH1/IDH2</i>
Macrocephaly : CM (M-CM/MCAP)*		<i>PIK3CA</i>
Microcephaly: CM (MICCAP)		<i>STAMBP</i>
CLOVES syndrome*	LM + VM + CM $\pm$ AVM + lipomatous overgrowth	<i>PIK3CA</i>
Proteus syndrome	CM, VM and/or LM + asymmetric somatic overgrowth	<i>AKT1</i>
Bannayan–Riley–Ruvalcaba syndrome	AVM + VM + macrocephaly, lipomatous overgrowth	<i>PTEN</i>
CLAPO syndrome*	Lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth	<i>PIK3CA</i>

Source: Reference 5. *These lesions belong to the *PIK3CA*-related overgrowth spectrum.

AVF, arteriovenous fistula; AVM, arteriovenous malformation; CLOVES syndrome, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome; CM, capillary malformation; ISSVA, International Society for the Study of Vascular Anomalies; LM, lymphatic malformation; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; VM, venous malformation.

with extensive muscle involvement of the affected limb.¹⁶ Vascular malformations associated with other anomalies are summarized in Table 1 along with the established genetic mutations, in accordance with the updated 2018 ISSVA classification.⁵

Differential diagnosis of Parkes

Weber syndrome

KTS should be distinguished from Parkes Weber syndrome (PWS), a fast-flow-type combined vascular malformation with limb hypertrophy that was first described in 1907 by the dermatologist Frederick Parkes Weber.²³ PWS is defined by the presence of CM, AVF, and limb overgrowth¹⁸ and is linked to germline inactivating mutations in the *RASA1* gene.^{24,25} KTS is distinguishable by the absence of one or more hemodynamically significant AVFs.²⁰ However, very small localized arteriovenous malformations may occur in CM and/or VM lesions in KTS patients²⁶ and are detectable only by detailed investigation techniques.²¹

The overlap in phenotypic features between KTS and PWS often leads to misdiagnosis and inappropriate management.²⁵ Given the clinical implications of AVF, the prognosis and treatment of these two syndromes are very different.²⁷ In contrast to KTS, the deformity in PWS tends to progress relentlessly with time, resulting in a poor prognosis for limb viability.²⁸ Adding further to this complexity is the coining of the term “Klippel–Trenaunay–Weber syndrome” that has been used interchangeably with both KTS and PWS^{21,27} in some reports^{29–31} and was introduced as a MeSH (Medical Subject Headings) term in 1994. These syndromes are frequently difficult to differentiate at birth or in infancy.

PIK3CA-related overgrowth spectrum

The phenotypic features of KTS may also overlap with manifestations of other segmental overgrowth disorders with vascular malformations (Table 1). These phenotypic similarities result from somatic mosaic activating mutations in the *PIK3CA* gene and have been included under the umbrella term of PROS.^{12,32} Given the importance of the PI3K signaling pathway, germline mutations upregulating the pathway would likely be lethal during embryonic development. However, mosaic mutations can cause segmental overgrowth disorders.³³ These mutations occur in a postzygotic stage during embryonic development, resulting in phenotypic features of the disease that vary from individual to individual.³² A recent study identified somatic mosaicism for *PIK3CA* mutations in 19 of 21 patients with KTS.⁴ Given the overlapping clinical features of PROS, accurate diagnosis may require the identification of a specific mutation in the affected tissues.^{34,35}

Characteristics of KTS

Although there is overlap of findings in patients with segmental overgrowth disorders, various body parts can be affected generally in a mosaic pattern. In most cases, KTS manifests as unilateral overgrowth limited to a lower limb³⁶ with CM and VM with or without deep venous anomalies (Fig. 1); however, there have been reports of involvement of the upper extremities, trunk, and rarely the internal organs.^{32,37} In most cases, at least one of the three features (most commonly CM) is noted shortly after birth,³⁶ whereas the remaining features (VM and subsequent limb overgrowth) become evident as the child begins to ambulate.^{38,39} Most commonly involved are the lower extremities (88%–95%) followed by the upper extremities (26%–29%).^{22,36} Unilateral lower limb involvement has been reported in 72% of cases³⁶ and upper and lower limb involvement in 18%.^{22,36}

KTS shows an equal sex distribution and occurs sporadically.²⁰ In a Japanese survey of the prevalence of congenital anomalies in 27,472 consecutive newborn babies at a large maternity hospital, one case of KTS was diagnosed, indicating a prevalence of 0.04 per 1000 births.⁴⁰ The severity of KTS ranges from mild to severe with potentially life-threatening complications.⁴¹ Possible symptoms and complications associated with this condition include the following: pain; bleeding from the affected skin, gastrointestinal tract, or genitourinary tract; superficial thrombophlebitis; cellulitis; lymphedema; skin ulceration; coagulopathy; deep venous thrombosis; and pulmonary embolism.^{21,22,36,41–43} Moreover, the physical disabilities that occur in KTS patients can impair their ability to perform activities of daily living.³⁷

Management of KTS

Individualized management is needed and it should be focused on the treatment of symptoms based on their severity.^{27,38,44} However, surgical treatment of symptomatic or cosmetically worrisome lesions has been controversial because of the wide spectrum of symptoms and impairments associated with KTS.³⁶ Management of KTS consists of combinations of the therapeutic options described in the following sections and generally entails multiple treatment sessions continued over the long term. Moreover, KTS patients should receive multidisciplinary medical care with regard to the physical, psychological, and social aspects of the disease.^{37,45} Given that KTS cannot be totally cured at present, developing good doctor–patient relationships are also important to provide adequate social support.⁴⁶

Figure 1. A female patient with Klippel–Trenaunay syndrome and unilateral lower limb overgrowth. (A, B) At the age of 2 years. (C) At the age of 6 years. A coronal T2-weighted magnetic resonance image shows extensive lesions in the subcutaneous tissues and muscles suggesting lymphatic–venous malformations. (D, E) At the age of 7 years after multiple treatment sessions including sclerotherapy, pulsed dye laser therapy, carbon dioxide laser ablation, surgical soft tissue debulking, and sclerotherapy with high ligation of the lateral marginal vein. (F) At the age of 1 year before therapeutic intervention. Angiokeratoma lesions on capillary malformations can be seen on the second to fifth toes. (G) At the age of 5 years, 12 days after sclerotherapy, with formation of blisters as an acute complication. (H) At the age of 6 years. Note that a reduction in redness and angiokeratoma contributed to relief of pain. Color images are available online.

DISCUSSION

Capillary malformations

CMs manifest as either geographic or blotchy stains^{41,43} and occur predominantly on the lateral side of the limb with extension onto the adjacent truncal skin.^{44,47,48} They almost never regress²² and tend to darken in color with age.⁴⁷ Patients with geographic stains are more likely to have associated LMs and complications, such as cellulitis, pain, and bleeding.⁴¹ Skin ulcerations on CMs that later bleed may require surgical excision of the lesion, and the affected skin tends to heal rather poorly.^{38,49}

With the recent advent of laser therapy, pulsed dye lasers (PDLs) have been the mainstay of therapy for CMs.⁵⁰ Current PDLs that emit a wavelength of 595 nm with longer pulse durations can provide a greater depth of dermal penetration, without compromising vascular specificity.^{38,50} Complications of PDLs, although not frequent, can include pigmentary alteration and scarring.⁵⁰ PDLs may be effective in reducing the redness of CMs in patients with KTS to some extent,⁵¹ but large CMs associated with soft tissue overgrowth and those located in a distal limb tend to respond

less well to laser therapy than CMs in the face and neck.^{50,52} Sclerotherapy targeting underlying VMs has also been reported to be effective for CMs.^{27,53}

Patients with KTS may have angiokeratoma lesions on the CMs,⁵⁴ resulting in troublesome bleeding. Angiokeratoma, a provisionally unclassified vascular anomaly in the ISSVA classification,⁵ is characterized by aggregates of hyperkeratotic erythematous papules and nodules that may coalesce to form verrucous plaques.⁵⁵ Therapeutic options for angiokeratoma include carbon dioxide laser, Nd:YAG laser, electrocoagulation, cryotherapy, or excision.⁵⁶ Laser therapy may be suitable for multiple lesions, but in cases with recurrent bleeding from angiokeratoma, electrocoagulation using electrocautery with a fine-tipped needle can be effective for stopping bleeding from underlying vascular lesions that heal with minimal scarring (Fig. 2).

VMs and varicose veins

VMs are often less conspicuous in infancy and early childhood, but they are diagnosable if subtly dilated veins are present in comparison with the unaffected limb.⁴¹ Persistent embryonic veins

Figure 2. A male patient with Klippel-Trenaunay syndrome and bilateral involvement of the lower limbs with macrodactyly. **(A)** At the age of 1 year, when capillary malformations can be seen as geographic stains on the lower limbs bilaterally. **(B)** At the age of 4 years after multiple treatment sessions including sclerotherapy and pulsed dye laser therapy. **(C)** At the age of 4 years a coronal T2-weighted magnetic resonance image shows extensive lesions in the subcutaneous tissues and muscles. **(D)** At the age of 14 years. Note the reduced redness. **(E)** Hematoxylin and eosin staining of the angiokeratoma associated with capillary malformations showing a dilated vessel with hyperkeratosis in the dermis, and a number of thin-walled vascular channels with narrow lumens in the reticular dermis and subcutis. Bar, 200 μ m. **(F)** At the age of 10 years angiokeratoma lesions can be seen on the right foot and lower leg. Lesions with episodes of frequent bleeding are marked for electrocoagulation. **(G)** At the age of 14 years, when the frequent episodes of bleeding from the angiokeratoma lesions ceased after carbon dioxide laser ablation and electrocoagulation. Color images are available online.

frequently appear on the lateral aspect of an affected lower limb in patients with KTS, including the lateral marginal and persistent sciatic veins.⁵⁷ These avascular embryonic veins⁴⁸ are frequently disfiguring and can be associated with pain, a sensation of heaviness, superficial thrombophlebitis, lymphedema, venous stasis ulceration, and bleeding.^{27,38,43,47} These embryonic veins may exist in conjunction with deep venous insufficiency that includes atresia, hypoplasia, aplasia, or valvular incompetence of the deep veins.^{20,27} Servelle⁵⁸ proposed that these deep venous conditions were the causes of the chronic venous hypertension and resulted in hypertrophy of the limb.^{27,41} However, 60% of patients with KTS have normal deep veins,⁴⁴ so it is currently thought that deep venous abnormalities are not the etiology of KTS but are part of its clinical features.^{27,41,43}

Generally, varicose veins in patients with KTS are managed conservatively with intermittent rest, limb elevation, and continued reminders of the importance of wearing graduated compression garments.³⁸ Thrombophlebitis in the varicose veins should be treated with analgesic and anti-inflammatory medications.⁴⁷ If the thrombophlebitis recurs, sclerotherapy with high ligation or excision of varicose veins can be considered.³⁸ Evaluation of the deep venous system by duplex ultrasonography, magnetic resonance imaging, or venography^{38,47} is required before proceeding to these invasive forms of treatment.

Common VMs with muscle involvement have been reported to occur in 69% of patients with KTS.²² VMs may have an intra-articular extension, commonly in the knee joint. Range of motion may be

limited because of the pain and lead to joint contractures.⁴⁷ Sclerotherapy for VMs can improve pain and decrease the size of the lesions.^{47,59} Chronic venous stasis ulcers may improve after sclerotherapy.⁴⁷ Multiple sclerotherapy sessions are generally required to alleviate symptoms regardless of the sclerosing agent used,⁴⁷ such as absolute ethanol^{60,61} and detergent sclerosants (including polidocanol,⁶² ethanolamine oleate,⁶² and sodium tetradecyl sulfate).⁶³ Local complications of sclerotherapy include blistering (Fig. 1), skin necrosis, and damage to local nerves, and systemic complications include deep venous thrombosis and subsequent pulmonary embolism, hemolysis, and a potential for renal toxicity and cardiac arrest.^{59,61,64}

Limb overgrowth and digital anomalies

Limb overgrowth is caused by hypertrophy of the soft tissues and bones. Associated LMs contribute to the appearance of limb gigantism.⁴³ Soft tissue hypertrophy may be localized or diffuse in the subcutaneous tissue and/or muscle.^{27,65} Evaluation of the hypertrophied components by magnetic resonance imaging is important³⁶ when considering surgical debulking procedures,⁴⁷ although delayed wound healing is a troublesome complication.⁶⁶ Bony hypertrophy often results in limb-length discrepancy (LLD) that may be accompanied by digital anomalies.²²

Regular clinical and radiologic measurement of limb length is necessary in patients with KTS,^{43,67} because progression is unpredictable.⁴³ An LLD of 2 cm or less may be managed with a shoe lift on the contralateral side to compensate for the discrepancy. However, an LLD of 2–3 cm or more is likely to result in significant ambulatory difficulties, abnormal posture, and compensatory changes on the contralateral side.³⁸ Before these discrepancies become permanent and irreversible, they should be addressed individually by limb-shortening procedures.³⁸ Epiphysiodesis of the distal femoral or proximal tibial epiphysis, or both,⁶⁶ is considered to be reliable and should be performed at ~11–12 years of age,¹⁶ as long as accurate measurements and predictions can be made.³⁸ Epiphysiodesis may improve quality of life in patients with KTS, probably because there is an improvement in walking as a result of the decreased LLD.³⁷

KTS may also be associated with digital anomalies, including syndactyly, polydactyly, and macrodactyly (Fig. 2).^{20,22} In patients with these toe anomalies, foot size for shoe fitting can be controlled by ray amputation, often combined with metatarsal epiphysiodesis or soft tissue debulking.^{68,69} Wound healing problems should be anti-

cipated in patients with KTS and a transmetatarsal or higher amputation that requires debridement, prolonged hospitalization, or skin grafting.^{66,69} Moreover, several studies have noted difficulties in fitting of a prosthesis in patients with KTS after a transverse amputation.^{66,68,69}

LMs and lymphedema

LMs have been found in 56% of patients with KTS,⁴¹ resulting in lymphedema or cutaneous lymphatic vesicles with an increased risk of cellulitis.^{27,38} LMs can be localized to the subcutaneous tissues or can extend into the muscles.⁴⁷ Macrocystic LMs are usually found in the pelvis and thigh; microcystic LMs occur mainly in the abdominal wall, buttock, and distal limbs. Macrocystic LMs can be treated with ethanol sclerotherapy using an injection and aspiration technique.⁷⁰ Cutaneous lymphatic vesicles may be managed by intravesicular sclerotherapy, carbon dioxide laser ablation, electrocoagulation, or excision.⁴⁷

Lymphedema can be a component of limb hypertrophy in patients with KTS. In the later stages, the affected limbs may develop elephantiasis and chronic skin ulcers.⁷¹ The initial management of lymphedema begins with education of the patient and family on skin hygiene, with the end goal of minimizing skin infections.³⁸ Inappropriate treatment, such as removal of functional varicose veins or surgical debulking, may damage the already impaired venous and lymph circulation and worsen lymphedema further. Early diagnosis and appropriate treatment with graduated compression garments may prevent or slow the course of lymphedema in patients with KTS.⁷¹ These garments can also protect the limb from minor trauma.⁴³

Localized intravascular coagulopathy

KTS patients might develop localized intravascular coagulopathy (LIC)⁷² as a complication of the disease (Fig. 3).²⁰ LIC is a chronic consumptive coagulopathy characterized by an elevated D-dimer level and a minimally depressed platelet count.^{73,74} When there is extensive VMs of the limbs, blood pooling with activation of coagulation can occur.⁷³ LIC causes thromboses within the lesions, resulting in formation of phleboliths and development of pain and impaired function. Severe LIC, which is characterized by low fibrinogen, a high D-dimer level, and the presence of soluble fibrin complexes, may progress to disseminated intravascular coagulation subsequent to surgery or trauma.⁷³ Graduated compression can reduce the amount of blood trapped within the VMs. Low-molecular-weight heparin therapy once daily for a few months can decrease the risk of thrombosis within the lesions

Figure 3. A female patient with Klippel-Trenaunay syndrome and unilateral lower limb overgrowth associated with localized intravascular coagulopathy. She had undergone excision of the capillary-venous malformations of the left thigh and a subsequent split thickness skin graft at the age of 22 years. She walked using a crutch because of a fixed left knee contracture. She had pain and anemia because of intermittent bleeding from cutaneous vascular lesions. **(A)** At the age of 57 years, capillary-venous malformations can be seen on the left lumbar and thigh region. These were episodes of prolonged bleeding at this site. **(B)** A sagittal T2-weighted magnetic resonance image shows extensive lesions in the subcutaneous tissues and muscles. **(C)** At the age of 59 years after multiple treatment sessions, including sclerotherapy, pulsed dye laser therapy, and carbon dioxide laser ablation. Note the reduced redness that contributed to relief of pain and cessation of bleeding. **(D)** At the age of 57 years capillary-venous malformations with angiokeratoma are seen on the left toes. There were episodes of prolonged bleeding and infection at this site. She also presented at this time with a painful ingrown first toe nail that was difficult to manage. **(E)** After surgical procedures that included amputations of the first and second toes and sclerotherapy to the third and fourth toes. **(F)** At the age of 59 years, after the third toe amputation, that contributed to relief of pain and cessation of bleeding. Color images are available online.

and may alleviate the inflammation and pain.⁷³ Low-molecular-weight heparin is also effective for stopping bleeding from an accidental or surgical wound in a lesion caused by VMs.⁷³

LIC should be distinguished from Kasabach-Merritt phenomenon (KMP).⁷⁵ This life-threatening condition is defined as profound thrombocytopenia related to trapping of platelets inside a vascular tumor of infancy, as occurs in kaposiform hemangioendothelioma or tufted angioma.⁷³ Although fibrinogen consumption and D-dimer elevation can occur in KMP, platelet consumption (on average 25,000/mm³) tends to predominate, unlike in LIC where coagulation factor consumption predominates.^{72,73} Therapeutic options for KMP include corticosteroids, interferon alpha, vincristine, and antiplatelet agents such as aspirin and ticlopidine.⁷³

Wound healing problems in KTS

Wound complications in KTS include skin ulcers and/or bleeding from the cutaneous vascular le-

sions,^{21,22,41-43,76} and wound healing problems after surgery have also been reported.^{31,66-69} Various options for local treatment of skin ulcers in KTS patients have been reported, including negative pressure wound therapy,⁷⁷ low-level laser therapy,⁷⁸ and topical application of recombinant human platelet-derived growth factor-BB.^{79,80} Oral systemic agents have also been used, including sunitinib,⁸¹ a multitargeting tyrosine kinase inhibitor with anti-angiogenic properties, and sirolimus, an inhibitor of mammalian target of rapamycin (mTOR).⁸² Recent publications emphasize future targeted therapies as treatment options for PROS, such as inhibition of PI3K signaling pathway including its downstream target mTOR.⁸³

The literature contains some reports of rare cases in which skin cancer developed, including basal cell carcinoma^{80,84} and squamous cell carcinoma,^{84,85} in association with skin ulceration on an affected lower limb in KTS. Moreover, there is a report of a case of Stewart-Treves syndrome, an angiosarcoma that

occurs with chronic lymphedema,⁸⁶ in the affected lower limb with skin ulceration in PWS.⁸⁷ Although an association between KTS and malignancy is difficult to prove, chronic skin ulcers in KTS patients may indicate an underlying cancer.^{80,84}

SUMMARY

KTS is a rare slow-flow combined vascular malformation that has been recently linked to mutations in the *PIK3CA* gene. Despite the overlapping features in patients with segmental overgrowth disorders, a correct diagnosis is essential and can be based on flow characteristics and the type of dysmorphic vascular channel. In this review, we have described the characteristics of KTS with possible wound complications. Management of KTS should be individualized and it should focus on the treatment of symptoms. Patients benefit from multidisciplinary medical care. Future targeted therapies that inhibit the PI3K signaling pathway could offer new treatment options for PROS.

ACKNOWLEDGMENTS AND FUNDING SOURCES

This work was supported by JSPS KAKENHI Grant Number JP18K16974.

AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article.

TAKE-HOME MESSAGES

- KTS is a congenital slow-flow vascular malformation with limb overgrowth.
- KTS is categorized under PROS, so there are implications for molecular diagnosis and potential treatment.
- Wounds are difficult to manage in KTS because of the underlying vascular malformations.
- Management of KTS should be individualized and focused on the treatment of symptoms.
- Targeted therapies that inhibit PI3K signaling pathway may be therapeutic options in the future.

ABOUT THE AUTHORS

Kosuke Ishikawa, MD, is a fellow in the Department of Plastic and Reconstructive Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University. **Yuhei Yamamoto, MD, PhD**, is a professor in the Department of Plastic and Reconstructive Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, and is the President of the Japan Society for Surgical Wound Care. **Emi Funayama, MD, PhD**, is an associate professor in the Department of Plastic and Reconstructive Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University. **Hiroshi Furukawa, MD, PhD**, is a professor in the Department of Plastic and Reconstructive Surgery, Aichi Medical University. **Satoru Sasaki, MD, PhD**, is a director at the Center for Vascular Anomalies, Department of Plastic and Reconstructive Surgery, Tonan Hospital, and is the President of the Japanese Society for the Study of Vascular Anomalies.

REFERENCES

1. Klippel M, Trenaunay P. Memoires originaux: du naevus variqueux osteo-hypertrophique. Arch Gen Med (Paris) 1900;3:641–672.
2. Vikkula M, Boon LM, Mulliken JB. Molecular genetics of vascular malformations. Matrix Biol 2001;20:327–335.
3. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in *PIK3CA* cause CLOVES syndrome. Am J Hum Genet 2012;90:1108–1115.
4. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in *PIK3CA*. J Pediatr 2015;166:1048–1054.
5. ISSVA Classification of Vascular Anomalies ©2018 International Society for the Study of Vascular Anomalies. "issva.org/classification" (last accessed July 31, 2018).
6. Vanhaesebroeck B, Stephens L, Hawkins P. PI3K signalling: the path to discovery and understanding. Nat Rev Mol Cell Biol 2012;13:195–203.
7. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the *PIK3CA* gene in human cancers. Science 2004;304:554.
8. Squarize CH, Castilho RM, Bugge TH, Gutkind JS. Accelerated wound healing by mTOR activation in genetically defined mouse models. PLoS One 2010;5:e10643.
9. Karrasch T, Spaeth T, Allard B, Jobin C. PI3K-dependent GSK3 α (Ser9)-phosphorylation is implicated in the intestinal epithelial cell wound-healing response. PLoS One 2011;6:e26340.
10. Lima MH, Caricilli AM, de Abreu LL, et al. Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial. PLoS One 2012;7:e36974.

11. Jin Y, Tymen SD, Chen D, et al. MicroRNA-99 family targets AKT/mTOR signaling pathway in dermal wound healing. *PLoS One* 2013;8:e64434.
12. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Clinical delineation and natural history of the *PIK3CA*-related overgrowth spectrum. *Am J Med Genet A* 2014;164A:1713–1733.
13. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with *PIK3CA*-related overgrowth syndrome. *Nature* 2018;558:540–546.
14. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). *Adv Dermatol* 1997;13:375–423.
15. Enjolras O. Classification and management of the various superficial vascular anomalies: hemangiomas and vascular malformations. *J Dermatol* 1997;24:701–710.
16. Enjolras O, Chapot R, Merland JJ. Vascular anomalies and the growth of limbs: a review. *J Pediatr Orthop B* 2004;13:349–357.
17. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982;69:412–422.
18. Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics* 2015;136:e203–214.
19. Boyd JB, Mulliken JB, Kaban LB, Upton J, 3rd, Murray JE. Skeletal changes associated with vascular malformations. *Plast Reconstr Surg* 1984;74:789–797.
20. Cohen MM, Jr. Klippel-Trenaunay syndrome. *Am J Med Genet* 2000;93:171–175.
21. Oduber CE, van der Horst CM, Hennekam RC. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. *Ann Plast Surg* 2008;60:217–223.
22. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Głowiczki P. Klippel-Trenaunay syndrome: spectrum and management. *Mayo Clin Proc* 1998;73:28–36.
23. Weber FP. Angioma formation in connection with hypertrophy of limbs and hemi-hypertrophy. *Br J Dermatol* 1907;19:231–235.
24. 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;73:1240–1249.
25. Revencu N, Boon LM, Mulliken JB, et al. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by *RASA1* mutations. *Hum Mutat* 2008;29:959–965.
26. Malan E, Puglionisi A. Congenital angiodysplasias of the extremities. Note I: Generalities and classification; venous dysplasias. *J Cardiovasc Surg (Torino)* 1964;5:87–130.
27. Volz KR, Kanner CD, Evans J, Evans KD. Klippel-Trenaunay syndrome: need for careful clinical classification. *J Ultrasound Med* 2016;35:2057–2065.
28. Roebuck DJ. Klippel-Trenaunay and Parkes-Weber syndromes. *AJR Am J Roentgenol* 1997;169:311–312.
29. Mullins JF, Naylor D, Redetski J. The Klippel-Trenaunay-Weber syndrome: naevus vasculosus osteohypertrophicus. *Arch Dermatol* 1962;86:202–206.
30. Viljoen DL. Klippel-Trenaunay-Weber syndrome (angio-osteohypertrophy syndrome). *J Med Genet* 1988;25:250–252.
31. Guidera KJ, Brinker MR, Kousseff BG, et al. Overgrowth management in Klippel-Trenaunay-Weber and Proteus syndromes. *J Pediatr Orthop* 1993;13:459–466.
32. Vahidnezhad H, Youssefian L, Uitto J. Klippel-Trenaunay syndrome belongs to the *PIK3CA*-related overgrowth spectrum (PROS). *Exp Dermatol* 2016;25:17–19.
33. Lindhurst MJ, Parker VE, Payne F, et al. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in *PIK3CA*. *Nat Genet* 2012;44:928–933.
34. Mirzaa GM, Riviere JB, Dobyns WB. Megalencephaly syndromes and activating mutations in the PI3K-AKT pathway: MPPH and MCAP. *Am J Med Genet C Semin Med Genet* 2013;163C:122–130.
35. Youssefian L, Vahidnezhad H, Baghdadi T, et al. Fibroadipose hyperplasia versus Proteus syndrome: segmental overgrowth with a mosaic mutation in the *PIK3CA* gene. *J Invest Dermatol* 2015;135:1450–1453.
36. Głowiczki P, Stanson AW, Stickler GB, et al. Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. *Surgery* 1991;110:469–479.
37. Oduber CE, Khemlani K, Sillevs Smitt JH, Hennekam RC, van der Horst CM. Baseline Quality of Life in patients with Klippel-Trenaunay syndrome. *J Plast Reconstr Aesthet Surg* 2010;63:603–609.
38. Capraro PA, Fisher J, Hammond DC, Grossman JA. Klippel-Trenaunay syndrome. *Plast Reconstr Surg* 2002;109:2052–2060.
39. Lindenauer SM. The Klippel-Trenaunay syndrome: varicosity, hypertrophy and hemangioma with no arteriovenous fistula. *Ann Surg* 1965;162:303–314.
40. Higurashi M, Oda M, Iijima K, et al. Livebirth prevalence and follow-up of malformation syndromes in 27,472 newborns. *Brain Dev* 1990;12:770–773.
41. Maari C, Frieden IJ. Klippel-Trenaunay syndrome: the importance of “geographic stains” in identifying lymphatic disease and risk of complications. *J Am Acad Dermatol* 2004;51:391–398.
42. Harvey JA, Nguyen H, Anderson KR, et al. Pain, psychiatric comorbidities, and psychosocial stressors associated with Klippel-Trenaunay syndrome. *J Am Acad Dermatol* 2018. [Epub ahead of print]; DOI: 10.1016/j.jaad.2018.05.1245.
43. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations. Part II: associated syndromes. *J Am Acad Dermatol* 2007;56:541–564.
44. Baskerville PA, Ackroyd JS, Browse NL. The etiology of the Klippel-Trenaunay syndrome. *Ann Surg* 1985;202:624–627.
45. Kihiczak GG, Meine JG, Schwartz RA, Janniger CK. Klippel-Trenaunay syndrome: a multisystem disorder possibly resulting from a pathogenic gene for vascular and tissue overgrowth. *Int J Dermatol* 2006;45:883–890.
46. van der Ploeg HM, van der Ploeg MN, van der Ploeg-Stapert JD. Psychological aspects of the Klippel-Trenaunay syndrome. *J Psychosom Res* 1995;39:183–191.
47. Kulungowski AM, Fishman SJ. Management of combined vascular malformations. *Clin Plast Surg* 2011;38:107–120.
48. Telander RL, Kaufman BH, Głowiczki P, Stickler GB, Hollier LH. Prognosis and management of lesions of the trunk in children with Klippel-Trenaunay syndrome. *J Pediatr Surg* 1984;19:417–422.
49. Baskerville PA, Ackroyd JS, Lea Thomas M, Browse NL. The Klippel-Trenaunay syndrome: clinical, radiological and haemodynamic features and management. *Br J Surg* 1985;72:232–236.
50. Maguiness SM, Liang MG. Management of capillary malformations. *Clin Plast Surg* 2011;38:65–73.
51. Berry SA, Peterson C, Mize W, et al. Klippel-Trenaunay syndrome. *Am J Med Genet* 1998;79:319–326.
52. Lanigan SW. Port wine stains on the lower limb: response to pulsed dye laser therapy. *Clin Exp Dermatol* 1996;21:88–92.
53. Nitecki S, Bass A. Ultrasound-guided foam sclerotherapy in patients with Klippel-Trenaunay syndrome. *Isr Med Assoc J* 2007;9:72–75.
54. Yamaki T, Konoeda H, Fujisawa D, et al. Prevalence of various congenital vascular malformations in patients with Klippel-Trenaunay syndrome. *J Vasc Surg Venous Lymphat Disord* 2013;1:187–193.
55. Somasundaram V, Premalatha S, Rao NR, Razack EM, Zahra A. Hemangioectatic hypertrophy with angiokeratoma circumscriptum. *Int J Dermatol* 1988;27:45–46.
56. Zeng Y, Zhan K, Xie WL, Lin QZ. Angiokeratoma of Fordyce response to long pulsed Nd:YAG laser treatment. *Dermatol Ther* 2016;29:48–51.
57. Oduber CE, Young-Afat DA, van der Wal AC, van Steensel MA, Hennekam RC, van der Horst CM. The persistent embryonic vein in Klippel-Trenaunay syndrome. *Vasc Med* 2013;18:185–191.
58. Servelle M. Klippel and Trenaunay's syndrome. 768 operated cases. *Ann Surg* 1985;201:365–373.
59. Cabrera J, Cabrera J, Jr., Garcia-Olmedo MA, Redondo P. Treatment of venous malformations with sclerosant in microfoam form. *Arch Dermatol* 2003;139:1409–1416.
60. Furukawa H, Sasaki S, Oyama A, et al. Efficacy of percutaneous ethanol sclerotherapy for venous malformation in lower extremities: a retrospective review of 21 cases. *Eur J Plast Surg* 2013;36:105–110.
61. Lee BB, Do YS, Byun HS, Choo IW, Kim DI, Huh SH. Advanced management of venous malformation

- with ethanol sclerotherapy: mid-term results. *J Vasc Surg* 2003;37:533–538.
62. Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations. *J Vasc Surg* 2008;47:578–584.
 63. Scorletti F, Patel MN, Hammill AM, Ricci KW, Myer CMt, Dasgupta R. Sclerotherapy for intramuscular vascular malformations: a single-center experience. *J Pediatr Surg* 2018;53:1056–1059.
 64. Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. *J Vasc Interv Radiol* 2004;15:431–445.
 65. Funayama E, Sasaki S, Oyama A, Furukawa H, Hayashi T, Yamamoto Y. How do the type and location of a vascular malformation influence growth in Klippel-Trenaunay syndrome? *Plast Reconstr Surg* 2011;127:340–346.
 66. Letts RM. Orthopaedic treatment of hemangiomatous hypertrophy of the lower extremity. *J Bone Joint Surg Am* 1977;59:777–783.
 67. Stringel G, Dastous J. Klippel-Trenaunay syndrome and other cases of lower limb hypertrophy: pediatric surgical implications. *J Pediatr Surg* 1987;22:645–650.
 68. Sooriakumaran S, Landham TL. The Klippel-Trenaunay syndrome. *J Bone Joint Surg Br* 1991;73:169–170.
 69. Gates PE, Drvaric DM, Kruger L. Wound healing in orthopaedic procedures for Klippel-Trenaunay syndrome. *J Pediatr Orthop* 1996;16:723–726.
 70. Furukawa H, Sasaki S, Oyama A, et al. Ethanol sclerotherapy with 'injection and aspiration technique' for giant lymphatic malformation in adult cases. *J Plast Reconstr Aesthet Surg* 2011;64:809–811.
 71. Liu NF, Lu Q, Yan ZX. Lymphatic malformation is a common component of Klippel-Trenaunay syndrome. *J Vasc Surg* 2010;52:1557–1563.
 72. Enjolras O, Ciabrini D, Mazoyer E, Laurian C, Herbreteau D. Extensive pure venous malformations in the upper or lower limb: a review of 27 cases. *J Am Acad Dermatol* 1997;36:219–225.
 73. Mazoyer E, Enjolras O, Laurian C, Houdart E, Drouet L. Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach-Merritt syndrome. *Clin Lab Haematol* 2002;24:243–251.
 74. Domp Martin A, Acher A, Thibon P, et al. Association of localized intravascular coagulopathy with venous malformations. *Arch Dermatol* 2008;144:873–877.
 75. Kasabach H, Merritt K. Capillary hemangioma with extensive purpura: report of a case. *Am J Dis Child* 1940;59:1063–1070.
 76. 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;47:303–307.
 77. Chung CJ, David LR, Morykwas MJ, Argenta LC. Case review: management of life-threatening sepsis and wound healing in a Klippel-Trenaunay patient using serial surgical débridements and vacuum-assisted closure. *Eur J Plast Surg* 2003;26:214–216.
 78. Dixit S, Maiya AG, Umakanth S, Shastry BA. Closure of non-healing chronic ulcer in Klippel-Trenaunay syndrome using low-level laser therapy. *BMJ Case Rep* 2012;2012: pii: bcr2012006226.
 79. Danikas D, Theodorou SJ, Wurmser E. Successful treatment of chronic wound in Klippel-Trenaunay syndrome with recombinant human platelet-derived growth factor-BB. *Plast Reconstr Surg* 2002;109:2608–2609.
 80. Langner D, Heining B, Schonlebe J, et al. Foot ulcers in Klippel-Trenaunay syndrome: two case reports and one metatypical basal cell carcinoma. *J Biol Regul Homeost Agents* 2015;29:27–30.
 81. Nguyen S, Franklin M, Dudek AZ. Skin ulcers in Klippel-Trenaunay syndrome respond to sunitinib. *Transl Res* 2008;151:194–196.
 82. Bessis D, Vernhet H, Bigorre M, Quere I, Rossler J. Life-threatening cutaneous bleeding in childhood Klippel-Trenaunay syndrome treated with oral sirolimus. *JAMA Dermatol* 2016;152:1058–1059.
 83. Vahidnezhad H, Youssefian L, Uitto J. Molecular genetics of the PI3K-AKT-mTOR pathway in genodermatoses: diagnostic implications and treatment opportunities. *J Invest Dermatol* 2016;136:15–23.
 84. Salman SM, Phillips T, Rogers GS. Klippel-Trenaunay syndrome and cutaneous carcinomas. *J Dermatol Surg Oncol* 1993;19:582–584.
 85. De Simone C, Giampetruzzi AR, Guerriero C, De Masi M, Amerio P, Cina G. Squamous cell carcinoma arising in a venous ulcer as a complication of the Klippel-Trenaunay syndrome. *Clin Exp Dermatol* 2002;27:209–211.
 86. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema; a report of six cases in elephantiasis chirurgica. *Cancer* 1948;1:64–81.
 87. Simas A, Matos C, Lopes da Silva R, Brotas V, Teófilo E, Albino JP. Epithelioid angiosarcoma in a patient with Klippel-Trenaunay-Weber syndrome: an unexpected response to therapy. *Case Rep Oncol* 2010;3:148–153.

Abbreviations and Acronyms

AVF	= arteriovenous fistula
CM	= capillary malformation
ISSVA	= International Society for the Study of Vascular Anomalies
KMP	= Kasabach-Merritt phenomenon
KTS	= Klippel-Trenaunay syndrome
LIC	= localized intravascular coagulopathy
LLD	= limb-length discrepancy
LM	= lymphatic malformation
mTOR	= mammalian target of rapamycin
PDL	= pulsed dye laser
PIK3CA	= phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PI3K	= phosphoinositide 3-kinase
PWS	= Parkes Weber syndrome
PROS	= PIK3CA-related overgrowth spectrum
VM	= venous malformation