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Recurrent Cellulitis as Clinical Presentation of Klippel–Trénaunay Syndrome: A Case Report

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Keywords

Cellulitis, Lymphedema, Edema, Capillaries, Vascular medicine, Antibiotics, Skin infections, Recurrent cellulitis, Klippel–Trénaunay syndrome, Lymphatic malformations, Venous malformations

Abstract

A 32-year-old man presented with a history of recurrent cellulitis since his teenage together with nonpitting unilateral edema of the left leg. Further clinical examination and imaging studies revealed port-wine stains along the torso with extrathoracic capillary, lymphatic, and venous malformations. A diagnosis of Klippel–Trénaunay syndrome was established, and the patient was treated with complex decompression therapy. After 7 months, the left leg volume was reduced by more than half, and he was able to reinstate physical activity with no new recurrences. This case highlights the importance of considering subjacent causes in patients with recurrent cellulitis episodes and lymphedema.

Background

Cellulitis is a common bacterial infection of the skin and subcutaneous cellular tissue that occurs primarily in the lower extremities. This condition generates high health care costs, with more than 650 000 admissions per year in the United States alone (1). Recurrent cellulitis (RC) (defined as 1–2 episodes in less than 3 years) occurs in up to 30% of people suffering from an initial episode. This is usually associated with predisposing conditions such as obesity, eczema, edema, venous insufficiency, and lymphedema (2, 3). Early suspicion of these conditions is pivotal for their adequate management and prevention of further recurrences.

Objective

Here, we describe the case of an adult patient with several RC episodes with concomitant progressive unilateral nonpitting edema of the left leg. After we made the diagnosis of Klippel–Trénaunay syndrome (KTS), multimodal treatment reduced more than half of the initial leg volume, and the patient did not return for RC episodes.

Case Report

A 32-year-old man presented to the emergency department with a 6-hour history of sudden oppressive pain and redness over his left leg. He had a history of recurrent left lower-leg cellulitis since his teenage years (this being the third episode during the last year) treated with multiple courses of antibiotics, including cephalexin and clindamycin in the last year. His medical records were relevant for obesity, sedentarism, asymmetric lipomatosis of the back with previous liposuction, heavy smoking, social drinking habits, and a family history of cervical cancer and arterial hypertension. He was allergic to dicloxacillin, dipyrone, and loratadine. On physical examination, he was found to be tachycardic, normotensive, and afebrile. He presented with edema and erythema of the left leg with angiokeratomas on the ankle and foot. Initial blood tests revealed leukocytosis and neutrophilia with elevated C-reactive protein levels. A Doppler ultrasonography of the left limb ruled out deep venous thrombosis but revealed lymphatic vessel dilatation with loculated lymphedema. The patient received empirical



Figure 1. Clinical and radiologic findings on admission. (A) Dorsal lumbar lipomatosis with port-wine stains representing capillary malformations. (B) Elephantiasis nostra verrucosa of the left leg. (C) Computed tomography angiography of the abdomen showing venous low-flow extrapulmonary malformations (arrow).

treatment with tigecycline due to the previous use of antibiotics, which raised suspicion of methicillin-resistant *Staphylococcus aureus*-related cellulitis. Further examination of the skin revealed dorsal lumbar asymmetric lipomatosis with port-wine stains (Figure 1A) and elephantiasis verrucosa nostra of the left leg (Figure 1B). Additional imaging testing included a whole-body computed tomography angiography which revealed low-flow extrathoracic venous malformations and subcutaneous honeycombing of the left leg (Figure 1C). By considering capillary, lymphatic, and venous malformations together with unilateral limb overgrowth, KTS was established. After normalizing clinical and laboratory inflammatory variables, he completed an outpatient 14-day antibiotic course and he started lymphatic drainage therapy sessions together with oral micronized purified flavonoid fraction. Table 1 and Figure 2

provide the patient's volumetric and clinical follow-up while he received multimodal therapy. After 7 months, the patient experienced a reduction of approximately 62% of the initial left leg volume with no further cellulitis recurrences. In addition, he reported increasing levels of independence and no new recurrent episodes.

Discussion

RC is a common condition that remains as a clinical challenge for physicians due to the repetitive nature of the disease, overlapping presentation of other conditions, and underlying risk factors. Important differential diagnoses to consider include chronic lymphedema, venous stasis dermatitis, deep venous thrombosis, dermatomycosis, and cutaneous lymphangitis, among others. When RC is confirmed, it is of paramount

Table 1. Leg Measurements at Basal and Subsequent Controls During Multimodal Therapy

Side	Control (Right Leg)		Intervention (Left Leg)		
	Basal	Seven Months After Discharge	Basal	One Week After Discharge	Seven Months After Discharge
Thigh, cm	47	46	N/A	51	47.50
Calf, cm	37	41	60	40	36
Ankle, cm	35	23	40	33	31
Metatarsal, cm	29	27.50	40	31	29.50
Calf–ankle volume, cm ³ *	1134.70	920	2217.60	1169.80	984.20

N/A = not available.

*Volumetric estimation by using the cone formula: $h(C^2 + Cc + c^2)/12 \pi$, where C is the larger cone circumference, c is the smaller one, and h is the interval between the 2 measurements. Calf–ankle volume was taken as an approximation of whole leg volume, given the cone shape of this segment.

importance to assess predisposing factors for prompt diagnosis and appropriate treatment to reduce recurrences. Rare vascular pathologies, such as KTS, should be considered when more common conditions are excluded.

KTS was first described in 1900 as a rare congenital disorder, with an estimated incidence of 1:100 000 population without race or sex predilection (4). It is characterized by a distinctive triad of capillary malformations, venous varicosities, and abnormal growth of 1 or more extremities (4). Although not entirely understood, the cause is related to mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic

subunit alpha (*PIK3CA*) gene responsible for regulating signaling pathways involved in cell proliferation, adhesion, motility, and survival (5, 6).

The classic triad of capillary and venous malformations, along with limb hypertrophy, often appears early in life. Capillary involvement presents as dark red or purple “port-wine stains,” while venous malformations lead to varicose veins and venous stasis. The deep venous system also may be affected, with venous aplasia or hypoplasia (7). Excessive limb growth may result from soft-tissue or bone growth, making it difficult to distinguish from lymphedema or venous congestion. Diagnosing KTS requires clinical suspicion, the 3 key manifestations, and supportive radiologic studies.

Lymphedema and cellulitis are interconnected in KTS. Lymphedema impairs local immune responses, increasing susceptibility to cellulitis (8). Chronic venous insufficiency in KTS can cause stasis dermatitis and lipodermatosclerosis, elevating the risk for ulcers and infections. This relationship creates a vicious cycle, with each cellulitis episode further damaging the lymphatic system, leading to progressive lymphedema and an increased cellulitis risk (7, 9). In patients with KTS, a combined presentation of RC and lymphedema occurs in 13% to 25% of cases. Despite this association, microbiologic studies for cellulitis and erysipelas are not routinely recommended in clinical guidelines (3).

A multidisciplinary approach is key to treat symptoms and prevent future complications by investigating and treating predisposing causes. Complex decompression therapy in 2 stages is the management of choice. The reductive phase includes an intense period of manual lymphatic drainage combined with skin care and compression with inelastic systems to restore the pumping action of the limb muscles. The maintenance phase consists of elastic compression garments worn during the day (10). A recently published randomized clinical trial demonstrated that the use of compression therapy for patients with chronic edema of the limb significantly reduced the incidence of RC (hazard ratio: 0.37; $P = 0.02$) at a 6-month follow-up (11). Another randomized clinical trial in patients with cancer treatment–associated lymphedema estimated that compression therapy reduced excess limb volume between 48% and 60% without the additional benefit of adding manual



Figure 2. Follow-up after 10 physical and lymphatic therapy sessions.

lymphatic drainage (12). However, intervention techniques and volume measurements are heterogeneous among studies with no current established guidelines (13).

In addition to complex decompression therapy, numerous pharmacologic agents including coumarin and benzopyrones have been evaluated without demonstrating conclusive efficacy for limb-volume reduction (14). Despite these findings, micronized purified flavonoid fraction has been shown to improve several leg symptoms, functional discomfort, quality of life, and ankle circumference in patients with chronic venous disease of lower limbs (15). This warranted its use for symptomatic venous malformations in our case.

Finally, antibiotic therapy for cases of KTS, although occasionally reported, should be reserved for situations in which infection is confirmed or highly suspected (7). Once controlled, the primary focus should be on comprehensive management of the underlying lymphedema and venous stasis to prevent RC (3, 11, 12). Current guidelines suggest the possibility of administering prophylactic antibiotics to prevent infection recurrence (2, 3). However, this approach should be limited to patients who persistently experience confirmed RC despite comprehensive conservative management of KTS (3).

RC is a frequent condition that must raise the suspicion of predisposing risk factors, whose prompt identification and treatment are essential in the prevention of recurrences and related complications. KTS is a rare condition characterized by capillary, venous, and/or lymphatic malformations resulting in venous insufficiency and unilateral lymphedema of the limb. A comprehensive multimodal treatment improved the patient's quality of life in this case.

References

- Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA*. 2016;316:325-37. [PMID: 27434444] doi:10.1001/jama.2016.8825
- Dalal A, Eskin-Schwartz M, Mimouni D, et al. Interventions for the prevention of recurrent erysipelas and cellulitis. *Cochrane Database Syst Rev*. 2017;6:CD009758. [PMID: 28631307] doi:10.1002/14651858.CD009758.pub2
- Stevens DL, Bisno AL, Chambers HF, et al. Executive summary: practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:147-59. [PMID: 24947530] doi:10.1093/cid/ciu296
- Procaccini L, Consorte B, Gabrielli D, et al. Klippel–Trénaunay syndrome (KTS): a report of two patients and review of literature. *Imaging*. 2021;13:80-3. doi:10.1556/1647.2020.00008
- Vahidnezhad H, Youssefian L, Uitto J. Klippel–Trénaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). *Exp Dermatol*. 2016;25:17-9. [PMID: 26268729] doi:10.1111/exd.12826
- Ligresti G, Militello L, Steelman LS, et al. PIK3CA mutations in human solid tumors: role in sensitivity to various therapeutic approaches. *Cell Cycle*. 2009;8:1352-8. [PMID: 19305151] doi:10.4161/cc.8.9.8255
- Jacob AG, Driscoll DJ, Shaughnessy WJ, et al. Klippel–Trénaunay syndrome: spectrum and management. *Mayo Clin Proc*. 1998;73:28-36. [PMID: 9443675] doi:10.1016/S0025-6196(11)63615-X
- Lurie F, Malgor RD, Carman T, et al. The American Venous Forum, American Vein and Lymphatic Society and the Society for Vascular Medicine expert opinion consensus on lymphedema diagnosis and treatment. *Phlebology*. 2022;37:252-66. [PMID: 35258350] doi:10.1177/02683555211053532
- Cox N, Al-Niami F. Cellulitis and lymphoedema: a vicious cycle. *Wounds Int*. 2014;4.
- Manrique OJ, Bustos SS, Ciudad P, et al. Overview of lymphedema for physicians and other clinicians: a review of fundamental concepts. *Mayo Clin Proc*. 2022;97:1920-35. [PMID: 32829905] doi:10.1016/j.mayocp.2020.01.006
- Webb E, Neeman T, Bowden FJ, et al. Compression therapy to prevent recurrent cellulitis of the leg. *N Engl J Med*. 2020;383:630-9. [PMID: 32786188] doi:10.1056/NEJMoa1917197
- Andersen L, Hojris I, Erlandsen M, et al. Treatment of breast-cancer–related lymphedema with or without manual lymphatic drainage—a randomized study. *Acta Oncol*. 2000;39:399-405. [PMID: 10987238] doi:10.1080/028418600750013186
- Badger C, Preston N, Seers K, et al. Physical therapies for reducing and controlling lymphoedema of the limbs. *Cochrane Database Syst Rev*. 2004;4:CD003141. [PMID: 15495042] doi:10.1002/14651858.CD003141.pub2
- Badger CMA, Preston NJ, Seers K, et al. Benzo-pyrones for reducing and controlling lymphoedema of the limbs. *Cochrane Database Syst Rev*. 2004;2004:CD003140. [PMID: 15106192] doi:10.1002/14651858.CD003140.pub2
- De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's choice—European Society for Vascular Surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. *Eur J Vasc Endovasc Surg*. 2022;63:184-267. [PMID: 35027279] doi:10.1016/j.ejvs.2021.12.024