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PROLONGED ANTICOAGULATION WITH RIVAROXABAN IN KLIPPEL-TRÉNAUNAY SYNDROME: A CASE REPORT WITH 7-YEAR FOLLOW-UP

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ARTIGO ORIGINAL

RESUMO

INTRODUÇÃO: A síndrome de Klippel-Trénaunay (SKT) é uma malformação vascular congênita rara associada a coagulopatia intravascular localizada (LIC) e risco tromboembólico elevado. Os anticoagulantes orais diretos (DOACs) emergiram como alternativa à heparina de baixo peso molecular (HBPM), porém dados de segurança e eficácia a longo prazo permanecem escassos. **OBJETIVO:** Relatar o seguimento mais prolongado documentado de terapia contínua com rivaroxabana para profilaxia trombótica na SKT. **RELATO DE CASO:** Paciente do sexo feminino, 30 anos, com SKT diagnosticada na infância, apresentou primeiro episódio de trombose venosa superficial (TVS) aos 23 anos. Rivaroxabana 20 mg/dia foi iniciada, porém suspensa após 4 meses, com recorrência imediata de TVS. A anticoagulação foi reinstituída em 20 mg/dia e mantida de forma contínua por aproximadamente 7 anos, sem eventos tromboembólicos recorrentes. A Doppler venosa revelou veia perfurante insuficiente, malformação venosa de baixo fluxo e sistema venoso profundo competente. Hipermenorreia severa com anemia ferropriva exigiu inserção de dispositivo intrauterino de levonorgestrel para mitigação do sangramento, preservando a anticoagulação em dose plena. Redução para 10 mg/dia foi planejada mediante estabilização clínica. **CONCLUSÃO:** Sete anos de rivaroxabana 20 mg/dia sem recorrência tromboembólica representam o seguimento mais prolongado reportado para DOACs na SKT. A recorrência imediata de TVS após suspensão reforça a natureza persistente da coagulopatia intravascular localizada (LIC), fundamentando a anticoagulação contínua e individualizada nesta população.

Palavras-chave: Síndrome de Klippel-Trénaunay; Trombose venosa superficial; Rivaroxabana; Anticoagulação oral; Profilaxia tromboembólica.

PROLONGED ANTICOAGULATION WITH RIVAROXABAN IN KLIPPEL-TRÉNAUNAY SYNDROME: A CASE REPORT WITH 7-YEAR FOLLOW-UP

ABSTRACT

INTRODUCTION: Klippel-Trénaunay syndrome (KTS) is a rare congenital vascular malformation associated with localized intravascular coagulopathy (LIC) and elevated thromboembolic risk. Direct oral anticoagulants (DOACs) have emerged as alternatives to low-molecular-weight heparin (LMWH), but long-term safety and efficacy data remain scarce. **OBJECTIVE:** To report the longest documented follow-up of continuous rivaroxaban therapy for thrombotic prophylaxis in KTS. **CASE REPORT:** A 30-year-old female with KTS diagnosed in infancy developed first superficial vein thrombosis (SVT) at age 23. Rivaroxaban 20 mg/day was initiated but discontinued after 4 months, resulting in immediate SVT recurrence. Anticoagulation was reinstated at 20 mg/day and maintained continuously for approximately 7 years without recurrent thromboembolic events. Doppler ultrasound revealed insufficient perforating vein, low-flow venous malformation, and competent deep venous system. Severe hypermenorrhea with iron-deficiency anemia required levonorgestrel intrauterine device insertion for bleeding mitigation while preserving full-dose anticoagulation. Dose reduction to 10 mg/day was planned upon clinical stabilization. **CONCLUSION:** Seven years of rivaroxaban 20 mg/day without thromboembolic recurrence represents the longest follow-up reported for DOACs in KTS. Immediate SVT recurrence upon discontinuation underscores the persistent nature of LIC, supporting continuous and individualized anticoagulation in this population.

Keywords: Klippel-Trénaunay syndrome; Superficial vein thrombosis; Rivaroxaban; Oral anticoagulation; Thromboembolic prophylaxis.

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INTRODUCTION

Klippel-Trénaunay syndrome (KTS) is a rare congenital vascular malformation, with an estimated incidence of 1:20,000 to 1:40,000 births, characterized by the classic triad of capillary malformation (port-wine stain), venous and lymphatic malformations, and segmental soft tissue and/or bone hyperplasia, predominantly affecting the lower extremities [1]. It results from activating somatic mutations in the PIK3CA gene, placing it within the spectrum of PIK3CA-related overgrowth syndromes (PROS), and its diagnosis remains essentially clinical, although vascular imaging—particularly color Doppler ultrasonography—is essential for identifying aberrant venous anomalies with predictive value for thromboembolic risk [1,2]. The pathophysiology of KTS involves chronic blood stasis within malformed low-flow venous channels—notably the lateral marginal vein, present in up to 70% of patients—generating localized and persistent activation of the coagulation cascade, termed localized intravascular coagulopathy (LIC) [1,3]. This pathological cycle of thrombosis and fibrinolysis translates biochemically into elevated D-dimer levels, fibrinogen consumption, and, in extreme cases, thrombocytopenia, which may progress to disseminated intravascular coagulation (DIC) in the setting of invasive procedures or immobilization [3]. The clinical consequence is a substantially elevated thromboembolic risk: cohort studies demonstrate that approximately one-third of patients with KTS experience at least one thromboembolic event during their lifetime, with a prevalence of pulmonary embolism between 5.8% and 9.2% and a mean age at first severe event in the third to fourth decades of life [2,4]. Specific venous anomalies—lateral marginal vein (OR = 2.71), incompetent perforating vein of the thigh (OR = 4.01), and intramuscular venous convolutes (OR = 2.67) constitute independent risk factors, enabling anatomical stratification of individual risk [2]. Conventional anticoagulant management relies on low-molecular-weight heparin (LMWH), which is recognized as effective in interrupting the consumptive cycle and controlling pain associated with LIC [3,5]. However, its prolonged subcutaneous administration represents a significant barrier to adherence and is additionally associated with a risk of heparin-induced thrombocytopenia and osteoporosis with chronic use [5]. Vitamin K antagonists (VKAs) present particularly challenging laboratory control in states of factor consumption, with therapeutic fluctuation and the need for

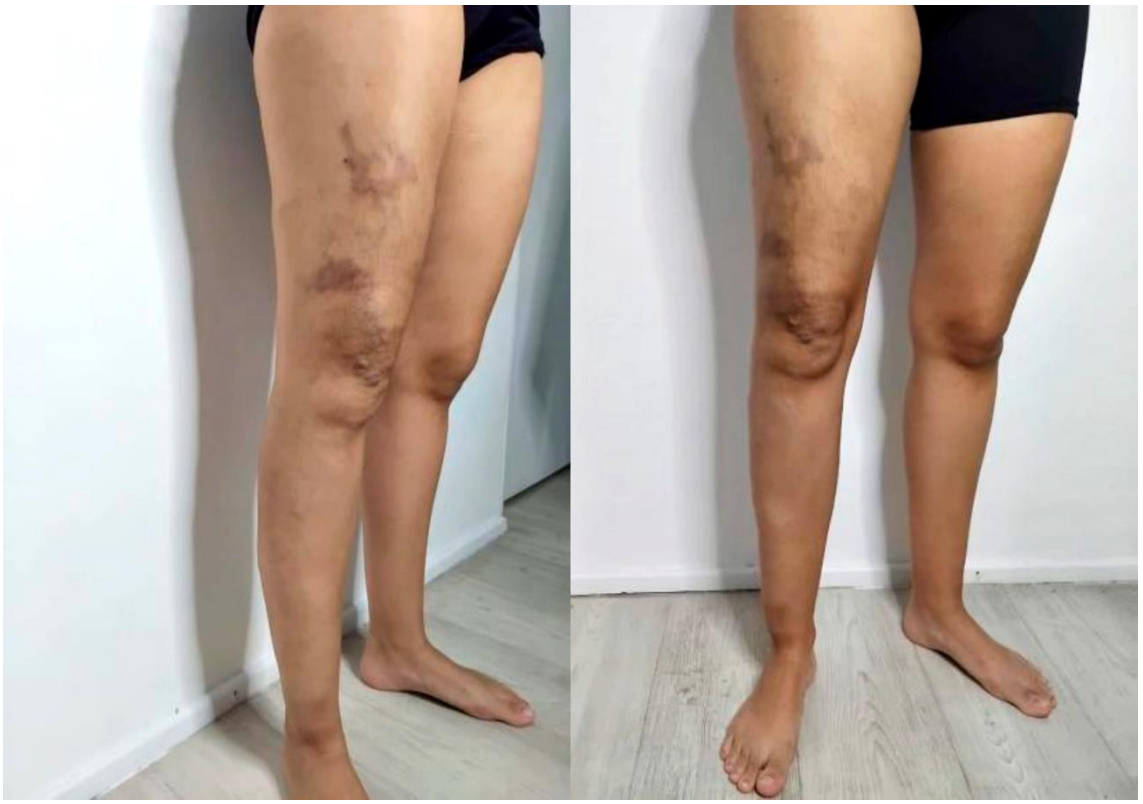
frequent monitoring [3]. The absence of standardized prophylaxis protocols for this population reflects the lack of randomized clinical trials to support evidence-based guidelines [4]. In this context, direct oral anticoagulants (DOACs)—particularly rivaroxaban, a selective factor Xa inhibitor—have emerged as a potentially advantageous alternative [6]. Rivaroxaban has an oral bioavailability of 80%–100%, a terminal half-life of 5–9 hours, dual metabolism (renal and via CYP3A4/P-glycoprotein), and a fixed-dose regimen without routine laboratory monitoring, conferring pharmacokinetic predictability and enabling prolonged outpatient management [6]. The accumulated evidence for its use in low-flow vascular malformations has progressed progressively: from the first documented report in KTS with DIC in 2013 [3], followed by cases of successful transition from LMWH to the oral route [7], to the largest published retrospective series (n = 29), which demonstrated pain improvement in 85% of cases and D-dimer reduction in 86%, without major bleeding [5]. More recently, the first prospective multicenter study (n = 45), employing the validated Pediatric Quality of Life Inventory (PedsQL) quality-of-life instrument, documented a statistically significant improvement in quality of life, reduction in pain, and decrease in D-dimer levels as early as the first two weeks, with persistence of benefits at 12 weeks [10]. Despite this growing body of evidence, critical gaps persist. No randomized clinical trials exist; the available evidence derives from retrospective, single-center, small-scale studies, with heterogeneity in doses, agents, and populations [4,5,10]. Long-term safety, the optimal dose for continuous prophylaxis, perioperative management, and differential response according to genetic profile (TEK vs. PIK3CA) remain to be elucidated [5,9]. Data in pediatric populations are scarce, limiting the generalizability of the findings [11]. The present report describes the experience of prolonged clinical follow-up of a patient with KTS under continuous oral anticoagulation with rivaroxaban as a prophylactic strategy for thromboembolic events, in a context of clinical stability and interdisciplinary management. The case illustrates the challenges of dose individualization, monitoring of coagulopathy biomarkers, and decision-making in rare vascular diseases, contributing to the emerging literature on DOACs in low-flow vascular malformations.

CASE REPORT

Presentation and Medical History

A 30-year-old female patient, born and residing in Maceió, State of Alagoas, Brazil, with Klippel-Trénaunay syndrome (KTS) diagnosed in childhood, with clinical manifestations restricted to the right lower extremity (RLE). There is no history of known prenatal gestational complications. At birth, an erythematous-wine-colored macule was observed on the anterior aspect of the right thigh, consistent with a capillary malformation (port-wine stain) (**Figure** 1). At approximately 12 months of age, asymmetry of hip height was identified, prompting initiation of specialized follow-up in pediatric angiology and clinical diagnostic confirmation of KTS. Conservative treatment with graduated compression stockings (20–30 mmHg) was instituted and maintained into adulthood. No additional relevant comorbidities; no family history of vascular malformations or venous thromboembolism.

Figure 1. Erythematous-wine-colored macule (capillary malformation) and superficial venous dilatations of the right lower extremity.



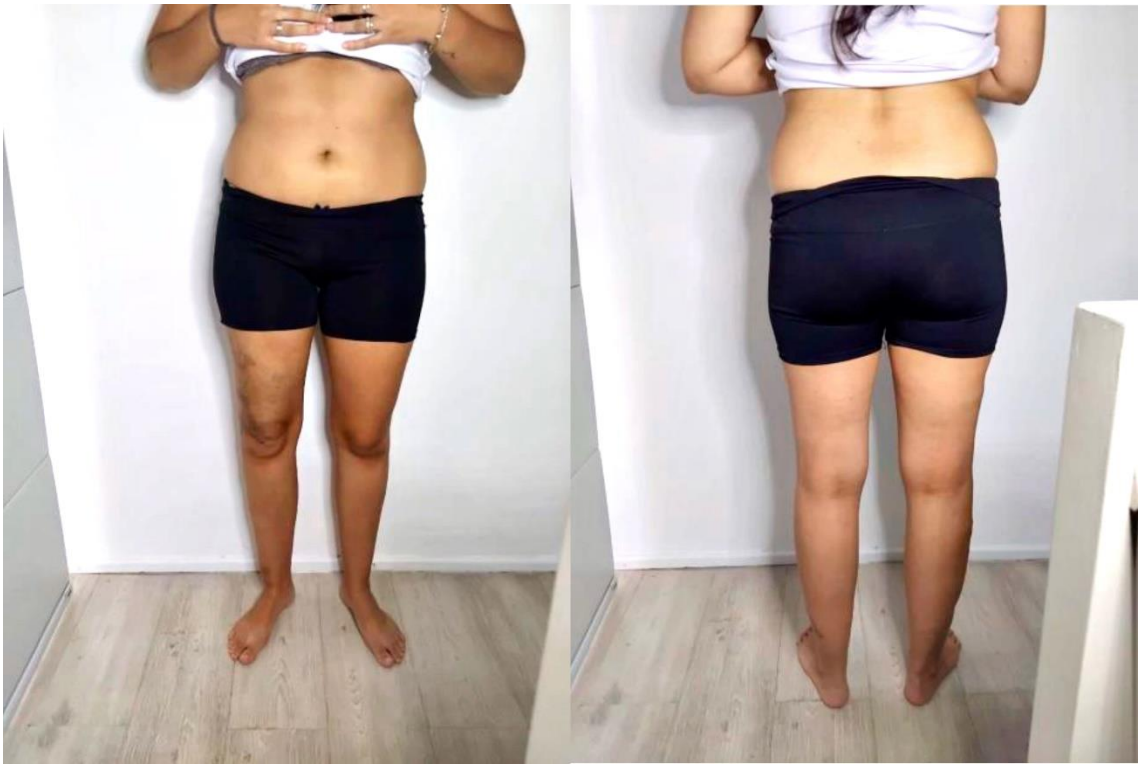
Clinical Course

At age 23, the patient presented with a first episode of superficial venous thrombosis (SVT) of the RLE and was seen in the emergency department, where treatment with oral rivaroxaban 20 mg/day was initiated and maintained for 4 months. After discontinuation of the drug, she developed a second, recurrent episode of SVT of the RLE. At that time, she was referred to the hematology team, which restarted rivaroxaban 20 mg/day orally, with continuous use to date. No new thromboembolic events have occurred since the resumption of anticoagulation, totaling approximately 7 years of sustained anticoagulant treatment.

Current Presentation

On current angiological evaluation, the patient reports moderate-intensity pain, edema, and hypersensitivity in the right tibial region, with evening predominance. She also reports severe menorrhagia and intense menstrual cramping, with a prior diagnosis of endometriosis and chronic iron-deficiency anemia secondary to exacerbated uterine bleeding. She is on continuous rivaroxaban 20 mg/day.On physical examination, she is conscious, oriented to time and place, in good general condition, well-perfused, hydrated, afebrile, anicteric, acyanotic, and eupneic, with atypical facies and gait. A compensatory pelvic tilt is observed secondary to hypertrophy of the RLE, with increased circumference and length compared with the left lower extremity (LLE) (**Figure** 2). Visible capillary malformations (port-wine stains) and superficial venous dilatations are distributed along the entire extent of the RLE, from the root of the thigh to the ankle (**Figure** 1). Peripheral arterial pulses (femoral, popliteal, dorsalis pedis, and posterior tibial) are palpable and symmetric. There are no signs of ulceration, pigmentation, or lipodermatosclerosis. The contralateral limb shows no apparent trophic or vascular changes.

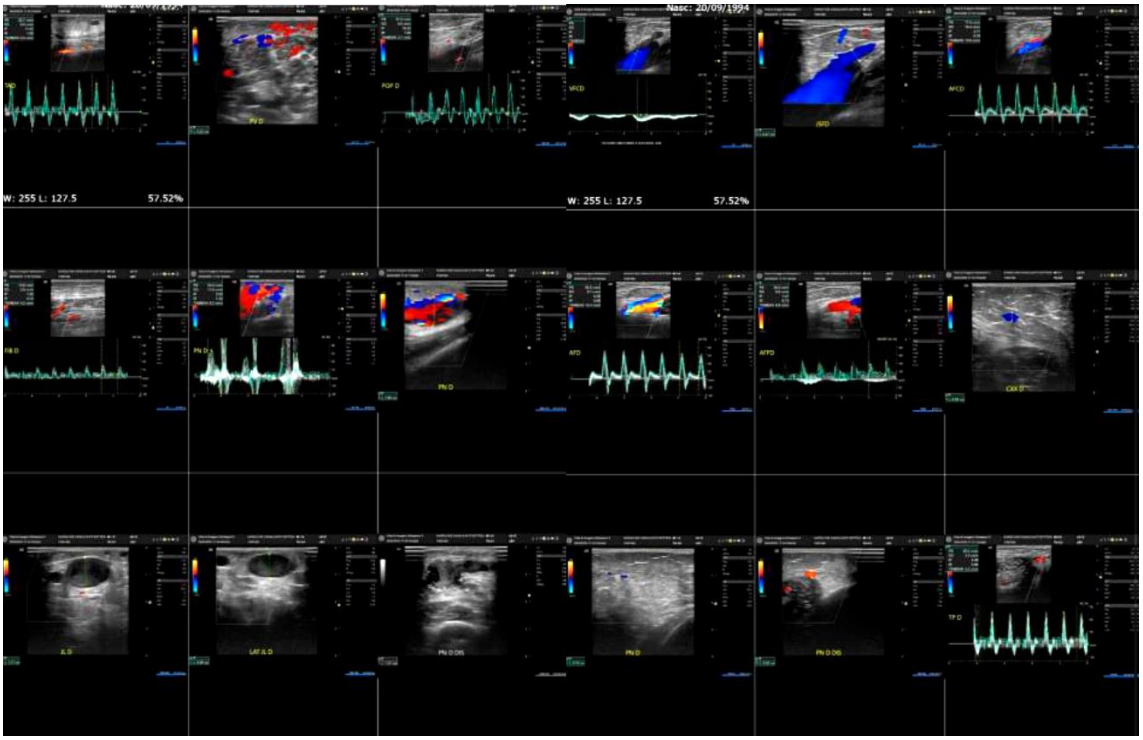
Figure 2. Body asymmetry secondary to hypertrophy of the right lower extremity, with compensatory pelvic tilt.



Diagnostic Studies

Venous Doppler ultrasonography of the RLE revealed an incompetent perforating vein located 23 cm from the plantar surface, on the lateral aspect of the right leg, with reflux on Valsalva maneuver; venous dilatations on the anterior and lateral aspects of the right thigh, knee, and leg, without fistulous pattern; confirmed low-flow venous malformation, with no signs of an arteriovenous component (**Figure** 3). The deep venous system demonstrated phasic flow with respiration and competence on Valsalva maneuver, without reflux. No deep or superficial venous thrombosis was present at the time of the examination. Arterial Doppler ultrasonography of the RLE showed no abnormalities.

Figure 3. Venous Doppler ultrasonography demonstrating a low-flow venous malformation and venous dilatations of the right lower extremity.



Management and Clinical Course

The instituted management comprised multidisciplinary referral. Gynecological evaluation confirmed indication for insertion of a levonorgestrel-releasing intrauterine device (Mirena®) as a measure to control menorrhagia, with the aim of stabilizing the hemorrhagic presentation and improving quality of life. The hematology team maintained the strategy of continuous anticoagulation with rivaroxaban 20 mg/day, considering the history of recurrent SVT upon prior discontinuation. A plan for joint reassessment was established after adaptation to the intrauterine device and control of menstrual bleeding, with the prospect of potential dose reduction of rivaroxaban to 10 mg/day, based on the absence of new thromboembolic events over the past 7 years and maintained clinical stability. The patient remains under regular outpatient follow-up.

Ethical Considerations

The patient signed the informed consent form, voluntarily and knowingly authorizing the use of her clinical information and images for academic and scientific purposes, with her privacy and anonymity guaranteed at all stages of the study. This

work was also approved by the Research Ethics Committee of Centro Universitário CESMAC (CAAE: 93071825.4.0000.0039).

DISCUSSION

The patient in the present report presents a clinical course that emblematically illustrates the pathophysiological spectrum of Klippel-Trénaunay syndrome (KTS) and the therapeutic dilemmas inherent to the prolonged management of the associated localized intravascular coagulopathy (LIC). The early diagnosis, established at approximately 12 months of age based on the classic clinical triad—capillary malformation, venous malformations, and segmental hypertrophy—corroborates the contemporary guidance that the diagnosis of KTS is essentially clinical, obviating the need for confirmatory genetic testing in most cases, although molecular characterization (PIK3CA vs. TEK) is acquiring increasing relevance in the era of personalized medicine [1,9].

The identification, on Doppler ultrasonography, of an incompetent perforating vein in the right lower extremity assumes particular significance in light of the findings of Zwerink et al. (2021), who demonstrated that perforating vein insufficiency of the thigh was the strongest anatomical risk factor for thromboembolic events in KTS (OR = 4.01; 95% CI: 1.64–10.18; p = 0.003) [2]. Although the perforator identified in this case is located on the lateral aspect of the leg—rather than the thigh, the site of highest risk in the Zwerink cohort—the presence of a low-flow venous malformation associated with extensive venous dilatations constitutes the anatomical-hemodynamic substrate that predisposes to stasis, activation of the coagulation cascade, and development of LIC, as modeled by John (2019) and Randrianarisoa et al. (2013) [1,3]. The occurrence of the first episode of superficial venous thrombosis (SVT) at age 23 is fully compatible with the available epidemiological data: van der Vleuten et al. (2022) reported a mean age at first thromboembolic event of 28.13 years (SD = 16.44), with a peak incidence between the second and fourth decades of life [4], and Zwerink et al. (2021) documented an overall prevalence of thromboembolic events in 32.4% of patients with KTS [2].

The recurrence of SVT immediately after discontinuation of rivaroxaban—after only 4 months of treatment—constitutes a finding of clinical relevance that directly engages

with the emerging literature. Vandenbriele et al. (2014) demonstrated that reducing the rivaroxaban dose from 10 mg to 5 mg/day resulted in a decrease in fibrinogen below 1.0 g/L and a spontaneous hemorrhagic episode, with complete reversal upon restoration of the 10 mg/day dose [7]. Lagneaux et al. (2024) reported that six of their 29 patients experienced thromboembolic events during treatment, most at subtherapeutic doses or in the postoperative setting [5]. These findings, together with the present case, support the hypothesis that LIC in KTS constitutes a dynamic and persistent process, requiring continuous and individualized anticoagulation—inadequate interruption or dose reduction exposes the patient to reactivation of the thrombosis-fibrinolysis cycle and clinical recurrence.

The maintenance of rivaroxaban 20 mg/day for approximately 7 years, without new thromboembolic events, represents one of the longest follow-up periods reported in the literature for DOACs in KTS. For comparison, the mean follow-up periods in the available studies range from 6 to 32 months: Randrianarisoa et al. (2013) reported 12 months [3]; Vandenbriele et al. (2014), 6 months [7]; Mack et al. (2018), a minimum of 6 months [8]; Lagneaux et al. (2024), a mean of 3.4 years (range, 1 month to 10 years) [5]; Boccara et al. (2025), 6 to 24 months [11]; and the prospective study by Mack et al. (2026) evaluated only 12 weeks [10]. This extended follow-up at full therapeutic dose (20 mg/day) adds long-term safety evidence that, although restricted to a single case, partially fills the gap identified by multiple authors regarding the tolerability and sustained efficacy of DOACs in low-flow vascular malformations [4,5].

The choice of rivaroxaban as the maintenance anticoagulant finds solid pharmacological rationale. Kvasnicka et al. (2017) systematized its pharmacokinetic profile—oral bioavailability of 80%–100%, terminal half-life of 5–9 hours, dual metabolism (renal and via CYP3A4/P-glycoprotein), and a fixed-dose regimen without routine laboratory monitoring—conferring a predictability that contrasts with the limitations of vitamin K antagonists (VKAs), which are particularly challenging in states of factor consumption such as LIC [6]. Additionally, Randrianarisoa et al. (2013) demonstrated that VKAs are particularly difficult to control in KTS with DIC, whereas rivaroxaban maintained laboratory stability for 12 months without therapeutic fluctuations [3]. LMWH, although effective, requires prolonged subcutaneous administration, and is associated with a risk of heparin-induced thrombocytopenia and osteoporosis with chronic use—limitations

that motivated the transition to the oral route in multiple reports [3,5,7]. In the present case, the initial choice of rivaroxaban at the first thrombotic event, in the emergency department, anticipated the current trend in the literature of replacing LMWH as first-line therapy in this population.

The severe menorrhagia with iron-deficiency anemia observed in this case represents the most frequent and clinically significant adverse event of DOAC use in women of childbearing age with vascular malformations. Lagneaux et al. (2024) reported heavy menstrual bleeding in 4 of 29 patients (13.8%) [5]; Mack et al. (2026), in 6 of 45 patients (13.3%), with 2 patients requiring discontinuation of anticoagulation due to clinically relevant bleeding [10]; and Oo et al. (2022) reported heavy menstrual bleeding after 10 months of rivaroxaban 10 mg/day, resolved with insertion of a levonorgestrel-releasing intrauterine device [9]. The recurrence of this pattern across independent series confirms heavy menstrual bleeding as the main safety concern in the female population receiving DOACs for vascular malformations, justifying proactive gynecological evaluation and consideration of local hormonal contraceptive measures as a mitigating strategy concomitant with anticoagulation—rather than as a late response to the complication. The indication of a levonorgestrel intrauterine device (Mirena®) in this case aligns with the management adopted by Oo et al. (2022) and represents a first-line strategy for the control of abnormal uterine bleeding in anticoagulated women, with a dual benefit: gynecological control and enabling the maintenance of full-dose anticoagulation [9].

The prospect of reducing the rivaroxaban dose from 20 mg to 10 mg/day after control of menstrual bleeding warrants critical analysis. The literature demonstrates wide dose variability: Vandenbriele et al. (2014) demonstrated efficacy of 10 mg/day with sustained normalization of fibrinogen [7]; Mack et al. (2018) used 10 mg/day as the initial dose in all four patients, with escalation to 20 mg in only one case [8]; Boccara et al. (2025) selected rivaroxaban 7.5–10 mg/day for children <12 years of age [11]; and Lagneaux et al. (2024) reported that 55% of their cohort remained on a low dose, with 86% showing a D-dimer reduction ≥25% [5]. Oo et al. (2022) achieved a 91% reduction in D-dimer with 10 mg/day in a venous malformation associated with a TEK variant [9]. However, Vandenbriele et al. (2014) demonstrated that 5 mg/day was insufficient [7], and the present case showed recurrence of SVT after discontinuation of 20 mg/day—

suggesting that LIC in this patient requires a full therapeutic dose. The decision to reduce to 10 mg/day should, therefore, be conditioned on laboratory documentation of coagulopathy control (serum D-dimer and fibrinogen), biomarkers whose serial assessment was not performed in this case, constituting a significant limitation. The absence of D-dimer and fibrinogen monitoring over the 7 years of treatment represents the main gap in the documentation of this report, precluding the correlation between biochemical control of LIC and the absence of clinical events—a correlation that constitutes a central pillar of the accumulated evidence [3,5,7,9,10].

From a broader therapeutic perspective, it is relevant to consider that the management of KTS is not restricted to systemic anticoagulation. John (2019) advocates prophylactic endovascular occlusion of persistent embryonic veins (PEVs)—notably the lateral marginal vein (LMV)—ideally at preschool age, by means of coil embolization combined with endovenous laser ablation (EVLA), with the aim of eliminating the anatomical substrate of stasis and reducing the long-term risk of thromboembolic events [1]. In the present case, Doppler ultrasonography did not identify an LMV; however, the incompetent perforating vein and the extensive venous dilatations could, theoretically, constitute targets for endovascular approaches complementary to anticoagulation. The decision to maintain an exclusively clinical management strategy, without surgical or endovascular intervention, reflects the observed clinical stability but also illustrates the absence of standardized protocols to guide patient selection for interventional versus conservative treatment in this population—a central controversy in the current literature [1,4].

The functional and psychosocial impact of KTS, although underestimated in most case reports, warrants rigorous scientific consideration. Mack et al. (2026), in the first prospective multicenter study to employ validated quality-of-life instruments (PedsQL), demonstrated a statistically significant improvement in physical, emotional, social, and school functioning scores as early as the first two weeks of anticoagulation, with persistence at 12 weeks [10]. The patient in the present report has experienced, for three decades, functional limitations (chronic pain, evening edema, restriction from sports participation), body image distortion (pelvic tilt, limb asymmetry), and psychosocial repercussions that transcend the strict control of coagulopathy. The multidisciplinary approach integrating angiology, hematology, and gynecology, as

advocated by John (2019) [1], represents the ideal model of care, although the absence of formal quality-of-life assessment with validated instruments (PedsQL, DLQI, or SF-36) constitutes an additional limitation of this report.

Among the limitations of the present report, the following stand out: (i) the retrospective and single-center nature, inherent to the case report design; (ii) the absence of serial monitoring of LIC biomarkers (D-dimer, fibrinogen, platelets) over the 7 years of treatment; (iii) the absence of molecular genetic characterization (PIK3CA vs. TEK), which could contribute to the understanding of the individual therapeutic response, given the emerging evidence of genotype-dependent differential response [5,9]; (iv) the absence of standardized quality-of-life assessment; (v) the concomitant use of elastic compression as an uncontrolled confounding variable; and (vi) the impossibility of establishing a definitive causal relationship between anticoagulation and the absence of events, given the absence of a control group.

Within the context of current controversies, three central questions remain unresolved by robust evidence. First, no randomized clinical trials compare DOACs, LMWH, or VKAs in low-flow vascular malformations—the available evidence derives from retrospective series, case reports, and a single uncontrolled prospective study, precluding grade A recommendations [4,5,10]. Second, the optimal dose for continuous prophylaxis has not been established: whereas some authors report efficacy with 10 mg/day [7-9], others use 20 mg/day [3] or progressive titration regimens [5], without standardized criteria for escalation or reduction. Third, the role of prophylactic endovascular approaches (occlusion of PEVs, embolization of incompetent perforators) as a complement to systemic anticoagulation remains undefined, lacking long-term comparative studies [1]. The present case, by documenting prolonged clinical stability with anticoagulation alone at full therapeutic dose, contributes to this discussion by suggesting that, in patients without large-caliber PEVs and with sustained clinical control, pharmacological therapy may constitute an effective strategy as monotherapy—a hypothesis that requires prospective validation.

CONCLUSION

The present report documents the longest clinical follow-up described in the literature of a patient with Klippel-Trénaunay syndrome (KTS) under continuous oral

anticoagulation with rivaroxaban at full therapeutic dose (20 mg/day for approximately 7 years), without recurrence of thromboembolic events. This finding, although restricted to a single case, adds preliminary evidence to the emerging literature regarding the sustained efficacy and safety of direct oral anticoagulants (DOACs) in the management of localized intravascular coagulopathy associated with low-flow vascular malformations.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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