Deep vein thrombosis in the setting of Klippel-Trenaunay syndrome and sirolimus treatment

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ABSTRACT

Klippel-Trenaunay syndrome (KTS) is a congenital vascular disorder characterized by the triad of cutaneous capillary malformation, lymphatic and venous anomalies, and soft tissue and bone overgrowth. Sirolimus is a mechanistic target of rapamycin inhibitor used as an immunosuppressive drug. It has also been used to improve and treat vascular malformations that can predispose to intravascular coagulopathy. We have described the case of a patient with KTS receiving a therapeutic anticoagulation dose, for whom sirolimus was initiated, and who had presented with an extensive venous thromboembolism. Correlations between the use of sirolimus in patients with KTS are limited, and cautious use and monitoring could be necessary. (J Vasc Surg Cases Innov Tech 2021;7:524-8.)

Keywords: Deep venous thrombosis; Klippel Trenaunay syndrome; Sirolimus

Klippel-Trenaunay syndrome (KTS) is a clinical diagnosis of a rare congenital disorder that includes cutaneous capillary malformations ("port-wine stain"), asymmetric hypertrophy of the bones and overlying soft tissues, and congenital varicosities and venous and lymphatic malformations.[1] The incidence has been estimated at 1 in 20,000 to 40,000 live births.[2] KTS has been reported more often in male than in female patients. However, no racial predilection has been observed.[3] Most often, it is a sporadic condition, although rare familial cases have been reported.[4] Several studies have indicated that most patients with this syndrome carry a postzygotic somatic gain-of-function mutation in the phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) gene.[1,5] This mutation leads to protein kinase B (AKT) activation and further activation of the mechanistic target of rapamycin (mTOR). This activation is responsible for the accumulation of endothelial cells due to reduced apoptosis and defective recruitment of vascular smooth muscle cells, which results in enlarged, convoluted venous channels.[6] The reported incidence of venous thromboembolism (VTE) in KTS patients has ranged from 14% to 22%.[7]

Sirolimus is indicated to induce immunosuppression and prevent organ rejection, as an anti-angiogenic medication on coated coronary stents, and as a cytostatic agent to treat breast and renal cancer.[6] Recently, some studies have shown benefits as therapy for vascular malformations.[8-12] Furthermore, sirolimus has been emerging as a new medical treatment option for both vascular tumors and vascular malformations as an allosteric inhibitor of mTOR with further downstream inhibition of abnormal signaling through the PI3K/AKT pathway to coordinate proper cell growth and proliferation. Sirolimus seems ideal for "proliferative" vascular tumors through the control of tissue overgrowth disorders caused by inappropriate activation of the PI3K/AKT/mTOR pathway as an antiproliferative agent.[13] Seront et al[14] reported that sirolimus is slowly establishing itself as the reference standard molecular therapy for recalcitrant malformation lesions. Some of the most known side effects include oral ulcerations, interstitial lung disease, metabolic disturbances, gastrointestinal symptoms, nephrotoxicity, anemia, and thromboembolic disease.[15] Several studies in the transplant literature have reported a possible association between sirolimus use and the development of VTEs.[16-20] The etiology of the increased risk of VTE remains unclear. One theory is that higher levels of procoagulant factors are present in transplant patients, including von Willebrand factor, prothrombin fragments 1 and 2, thrombin-activatable fibrinolysis inhibitor, and plasminogen activator inhibitor-1. Also, studies of drug-eluting stents and sirolimus with thrombosis have shown increased endothelial tissue factor expression and platelet aggregation.[19] We have described a case of a large deep vein thrombosis (DVT) in a patient with a history of KTS receiving active stable anticoagulation therapy, treated recently with sirolimus for his venous malformation. The patient provided written informed consent for the report of his case.

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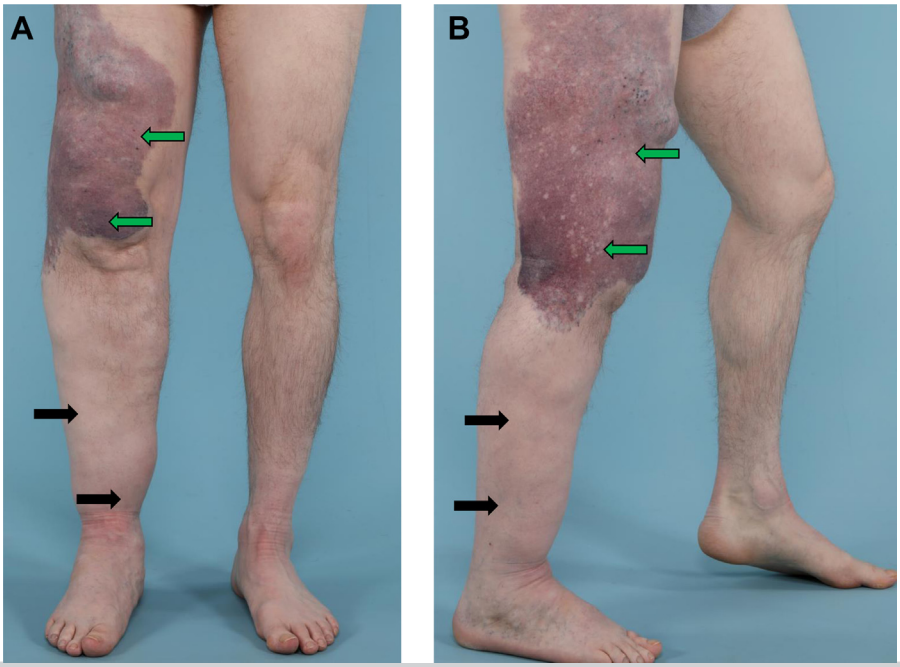

Fig 1. Anterior **(A)** and lateral **(B)** photographs of bilateral lower extremity findings from a patient with Klippel-Trenaunay syndrome (KTS). *Green arrow* indicates port-wine stain (nevus flammeus) due to capillary malformation in the skin, and *black arrows* indicate bulging varicosities of the superficial veins.

CASE REPORT

A 35-year-old male patient with a history of KTS (Fig 1) was transferred to our institution because of extensive lower extremity DVT from enlarged iliac veins to the suprahepatic inferior vena cava (IVC) abutting the right atrium (Fig 2), bilateral pulmonary embolisms (PEs) with associated pulmonary hypertension, and acute kidney injury requiring hemodialysis. He had a history of previous recalcitrant VTEs for which he had been receiving active anticoagulation therapy with fondaparinux and had a suprarenal IVC filter in place. He had been previously treated with warfarin, apixaban, dabigatran, and enoxaparin sodium (Lovenox) without success. The latest regimen with fondaparinux had resulted in no VTEs for the previous 6 months. He had also undergone a hypercoagulable state evaluation, with negative findings. Because of the severe symptomatic superficial varicose veins and an absent deep venous system causing orthostatic hypotension, he had started sirolimus 1 month before presentation. The initial dose was 1.5 mg twice daily for 2 weeks and, subsequently, 2.5 mg twice daily. Sirolimus therapy helped with the management of the skin changes and severe dilatation of his superficial veins causing orthostasis. The patient's sirolimus blood levels were lower than, or within, the normal range of the levels considered to be therapeutic in the transplant setting (Table I).

During the current hospital admission, sirolimus was discontinued. Intravenous heparin was started, and he underwent extensive mechanical thrombectomy using the ClotTriever device (Inari Medical, Irvine, Calif; Fig 3). The previously placed suprarenal IVC filter was replaced with an infrarenal filter. After 12 days of hospitalization, his kidney function had recovered, and hemodialysis was not required since that hospitalization. At the last follow-up, his anticoagulation regimen included dabigatran, and he was without VTE recurrence for the previous 6 months.

DISCUSSION

KTS is a rare congenital disorder with a typical triad of physical findings that include port-wine stain (capillary malformations in the skin), unilateral bone and soft tissue hypertrophy, and venous varicosities and venous and lymphatic malformations.[21] KTS is thought to result from a gain-of-function mutation in the protein PIK3CA, leading to activation of the mTOR protein.[6] Consequently, an accumulation of endothelial cells occurs due to reduced apoptosis and defective recruitment of vascular smooth muscle cells, resulting in enlarged, convoluted venous channels.[6] The reported incidence of VTEs in KTS patients has ranged from 14% to 22%.[7] Choosing the appropriate anticoagulation therapy to prevent VTEs in patients with KTS can be very challenging. Asnake et al[22] reported the case of one patient with KTS who had received anticoagulation therapy with warfarin. The patient had presented with bilateral segmental PEs. The patient's international normalized ratio was 3.2 during the event.[22] Another similar case reported by Gianlupi et al[23] described the case of a patient with KTS with recurrent PE despite an international normalized ratio of 2.3 on presentation.

No cure is available for KTS.[3] However, recent studies have demonstrated sirolimus as a potential new

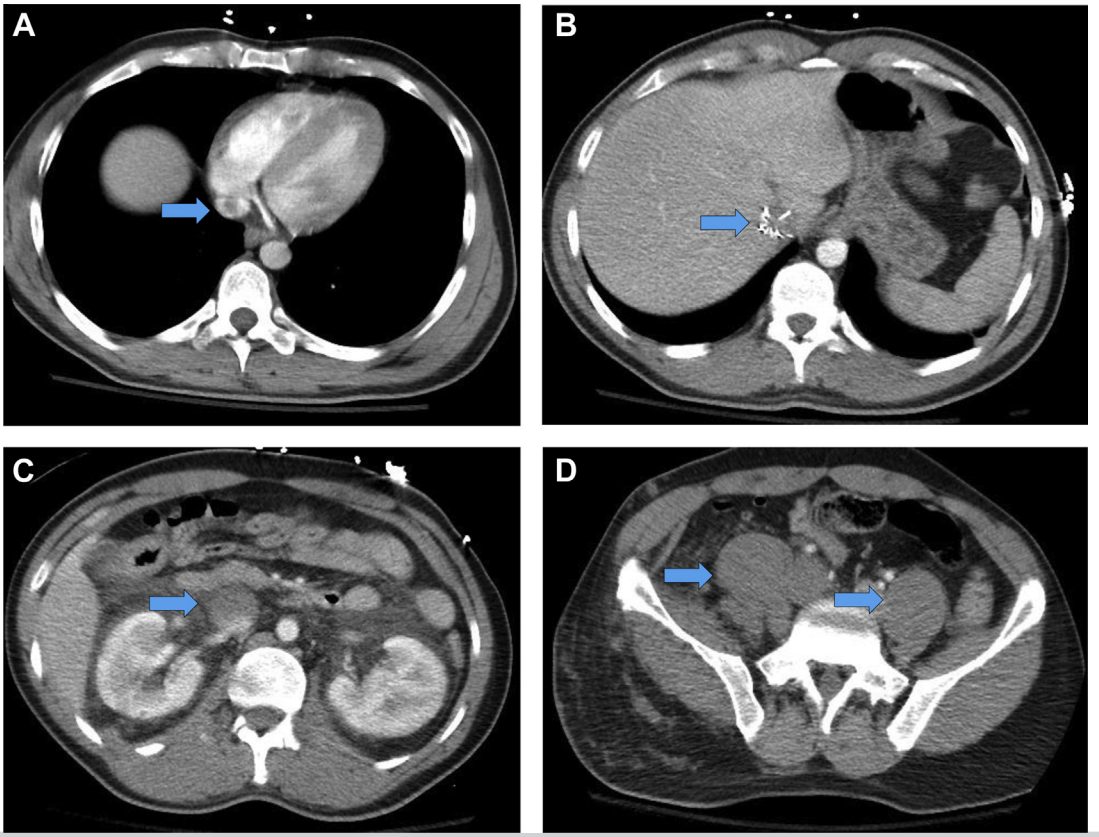

Fig 2. Axial cuts of computed tomography venography at different levels of the inferior vena cava (IVC) depicting extensive thrombus (*blue arrows*) at IVC–right atrium junction **(A)**, suprarenal IVC region with filter **(B)**, infrarenal IVC region, and bilateral dilated common iliac vein region **(D)**.

Table I. Patient's sirolimus blood levels stratified by date

Date	Sirolimus blood level, ng/mL
11/7/2020	3.2
11/14/2020	6.7
12/29/2020	<1.0

medication for the management of venous malformations.[8-12] The mechanism of action of sirolimus is to inhibit the mTOR protein, which is partially responsible for the pathogenesis of KTS.[6] Sirolimus has been used successfully in >80 case reports of vascular anomalies with lymphatic components.[24] Sandbank et al[25] reported clinical improvement with the use of sirolimus in 79% of patients included in their study. Similar results were reported in a phase II study,[6] which had included two patients with KTS. Those two patients reported a significant and rapid improvement in their symptoms and quality of life with the introduction of sirolimus as a treatment option.[14] It has been suggested by Mack et al[12] that sirolimus improves coagulopathy in slow-flow vascular malformations, although how it behaves in patients with KTS could be different.

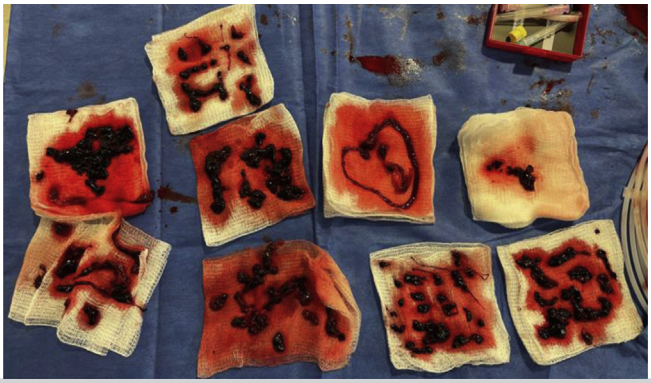

Fig 3. Thrombi removed from the iliac veins and inferior vena cava (IVC) using the ClotTriever device (Inari Medical, Irvine, Calif).

The known side effects associated with mTOR inhibitors in the transplant literature include oral ulcerations (10%-19%), interstitial lung disease (4%-17%), metabolic disturbances (30%-64%), gastrointestinal symptoms (15%-20%), nephrotoxicity (2%-10%), anemia (12%-76%), and VTEs (17%).[15] Several studies have reported VTE as a concerning side effect in transplantation patients with immunosuppression induced by sirolimus,[16-20] which

Table II. PubMed review of association between VTE and sirolimus therapy and VTE and KTS

Investigator	VTE with sirolimus therapy	VTE without sirolimus therapy	*P* value
Association of VTE with sirolimus therapy			
Ahya et al[16]	15/87 (17.2)	3/94 (3.2)	<.01
Thibodeau et al[18]	8/67 (12)	9/134 (7)	.03
Lingaraju et al[26]	33/59 (56.7)	35/143 (24.4)	<.001
Verhave et al[27]	13/68 (19)	22/60 (9)	<.05
Witkowsky et al[20]	Multivariable analysis of risk factors for VTE: HR, 1.97; 95% CI, 1.20-3.32		
Association of VTE with KTS	**KTS**	**VTE**	**NA**
Huiras et al[30]	10 (100)	8 (80)	
Douma et al[29]	48 (100)	8 (17)	
Baskerville et al[28]	49 (100)	11 (22.4)	

CI, Confidence interval; *HR*, hazard ratio; *KTS*, Klippel-Trenaunay syndrome; *NA*, not applicable; *VTE*, venous thromboembolism.
Data presented as number/total (%) or number (%).

has been suggested to be related to the presence of higher levels of procoagulant factors.[19] We have summarized the currently available evidence in PubMed regarding the association between VTEs with sirolimus therapy and between VTEs with KTS in Table II.[16,18,20,26-30] It is also very probable that, in addition to sirolimus therapy and KTS, the thrombogenic aspect of the presence of IVC filters could have been an exacerbating factor for the acute, extensive DVT in our present patient.[31]

To the best of our knowledge, no study has previously reported an extensive DVT in a patient with KTS receiving therapeutic anticoagulation, who had recently started sirolimus for management of venous malformations. Information regarding the association of sirolimus with VTEs in patients with KTS remains limited. However, before the introduction of sirolimus to his treatment, his KTS had been successfully managed with therapeutic anticoagulation, without the development of VTE. Therefore, cautious implementation of sirolimus in KTS patients could be warranted.

CONCLUSIONS

KTS is a rare congenital disease, and its treatment has challenged conventional management for venous malformations in the presence of anticoagulation therapy. Sirolimus has shown promising efficacy in reducing the symptoms related to KTS. However, its association with VTEs is a factor to consider. Further investigations on the safety of sirolimus therapy for adult patients with KTS are required.

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