Klippel–Trenaunay Syndrome: An Often Overlooked Risk Factor for Venous Thromboembolic Disease

Albert Ndzengue, MD¹ Richard B. Rafal, MD¹ Simon Balmir, MD¹ Dinker B. Rai, MD¹ Eric A. Jaffe, MD¹

¹ Department of medicine, Interfaith Medical Center, Brooklyn, New York

Address for correspondence and reprint requests Albert Ndzengue, MD, Department of medicine, Interfaith Medical center, 1545 Atlantic Avenue, Brooklyn, NY 11213 (e-mail: albertndzengue@yahoo.com).

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Abstract

Klippel–Trenaunay syndrome (KTS) is a congenital condition redefined by Oduber et al (2008) by the coexistence of vascular malformations and disturbed soft tissue or bony growth, including hypertrophy or hypotrophy in the same or opposite sides of the body. The anomalies may involve part of a limb, a whole limb, a limb girdle, or a hemibody. Vascular malformations may involve veins, capillaries, or lymphatics although venous or capillary malformations are essential for the diagnosis. Associated venous anomalies include dysplasia, valvular malformations, and varicosities. Congenital venous anomalies are often associated with disturbances of blood flow and should be considered as prothrombotic states. However, such anomalies are not considered in Wells scores and used to determine the risk for venous thromboembolism (VTE). We present the case of a male with unrecognized crossed dissociated form of KTS and unsuspected VTE. The pathophysiology and the treatment of VTE in KTS are discussed. We suggest physicians to be aware of KTS and that its recognition in a critically ill patient should prompt consideration for appropriate prophylaxis for high-risk category for VTE. Dedicated duplex sonography should be obtained if VTE is suspected. We also suggest a modification of the Wells scores to reflect the association of KTS and VTE.

Keywords

- ▶ anticoagulation
- ▶ DVT
- ▶ hemangioma
- ▶ duplex
- ▶ lower extremity
- ▶ risk factors varicose veins

A 25-year-old man presented to the emergency room (ER) with a short history of altered mental status and dyspnea. Paramedics noted pinpoint pupils and the patient was given naloxone, after which he became alert and oriented. Before lapsing into bradypnea and a comatose state requiring intubation and ventilation, the patient admitted to smoking 10 cigarettes daily, and stated that he had taken a 40-mg morphine tablet to relieve right-sided chest pain. He sustained a traumatic right pneumothorax 5 years previously, and claimed to have experienced chest pain ever since. At this time, he denied any family history of Klippel–Trenaunay syndrome (KTS) or venous thromboembolism (VTE).

On examination, he was afebrile with pulse 86, respiration 15, blood pressure 120/66 mm Hg, and oxygen saturation 99% on 40% FiO₂ on mechanical ventilation. His pupils were 3 mm and reactive to light, and no focal neurological deficit was

noted. A 10-cm subcutaneous mass was noted on the posterior chest wall. Lung and cardiovascular examinations were normal. The right foot was nonedematous but bigger than the left foot with disproportionate toes sizes (third and fourth toes bigger than the second toe and a relatively small big toe), and macrodactyly and syndactyly were evident. The right leg was slightly erythematous, not edematous or tender, and 2 cm larger in circumference than the left at mid-calf. Port-wine stains were seen as patches on the left foot and toes and varicose veins were confirmed on the left lower limb at late reassessment (▶ **Fig. 1**). arterial blood gas (ABG) on 40% oxygen was: pH 7.35 (normal 7.35 to 7.45), pCO₂ 49.1 mm Hg (normal 35 to 45), pO₂ 204 mm Hg, bicarbonate 26.4 mmol/L (normal 22 to 28), and alveolar-arterial (A-a) gradient 19.95 (normal 4 to 21). Laboratory values showed: hemoglobin 11.5 g/dL and white blood cells 11,000/μL. His complete

Fig. 1 Lower limbs lesions suggestive of cross dissociated variant of KTS. Note prominent varicose veins (horizontal arrows), syndactyly and macrodactyly of third and fourth toes (stars). The skin hue of the hypertrophic right leg is secondary to autonomic dysfunction in KTS. The purple patches (vertical arrows) on the left foot are representative of port-wine stains. KTS, Klippel-Trenaunay syndrome.

metabolic panel and blood glucose were normal. A D-dimer was sent from the ER. Urine toxicology screen was positive for benzodiazepine, opiates, and cannabinoids. Electrocardiography and computed tomography (CT) of the brain were normal. Chest radiograph demonstrated fibrotic stranding of left lung. Noncontrast CT of the chest showed small bilateral pleural effusions and a lipoma in the right posterior chest wall.

Fig. 2 Computed tomography scan of chest with intravenous contrast. Note emboli in the branches of the pulmonary artery bilaterally (arrows).

Respiratory depression secondary to opiate intoxication was felt to be the cause of his respiratory distress. Subcutaneous heparin at 5,000 U every 8 hours was prescribed for deep vein thrombosis (DVT) prophylaxis. However, when the D-dimer results became available 18 hours later ($> 5,000$ ng/L, normal < 500 ng/L), the patient was started on Lovenox (enoxaparin) 1 mg/kg twice daily. Thrombophilia work-up result was as follows: prothrombin time 12.0, international normalized ratio 1.25, partial thromboplastin time 27, protein C antigen 50% of normal, free protein S 122%, protein S 100%, antithrombin III antigen 93%, antithrombin III activated 90%, and factor V Leiden negative. The patient was extubated 36 hours later. The postextubation ABG on 28% oxygen was 7.43/43.6/72.1/95.8%, A-a gradient 73.79 (expected normal < 33.53). Contrast-enhanced CT of the chest showed bilateral pulmonary embolism (PE) (→ **Fig. 2**). Venous Doppler of the lower limbs did not show any DVT in the commonly screened veins. No mention was made of abnormal development of this patient's visualized deep venous system in the radiology report. The patient was started on Coumadin (warfarin) and discharged.

Discussion

KTS is a sporadic congenital condition due to failure of blood vessels and/or lymph vessels to form properly. Although Klippel and Trenaunay initially described KTS as the triad of venous varicosities, ipsilateral cutaneous capillary malformations, and bony and soft tissue overgrowth of the affected limbs, Oduber et al expanded the definition to cover more anatomic variations.^{1,2} KTS is now recognized as a congenital defect of angiogenesis in which vascular malformations and disturbed growth (hypertrophy or hypotrophy) coexist on the same or opposite sides involving part of a limb, a whole limb, a hemibody, or a limb girdle.^{2,3} Hypertrophy of soft tissues may be prominent in small body parts such as toes (macrodactyly).² Capillary malformations (port-wine stains) and venous malformations are both considered as major diagnostic features, whereas small congenital lymphatic malformations simply support the diagnosis of KTS.^{2,4} Limb dystrophic disorders which are nonessential but still support the diagnosis of KTS include polydactyly, syndactyly, and clinodactyly.² Complications that also support the diagnosis include thrombosis, thrombophlebitis, emboli, cellulitis, edema, hemorrhage from the involved epithelia, and autonomic dysfunction as evidenced by skin atrophy or hyperhydrosis.² Abnormal development (dysplasia) of the venous system involves mostly the deep veins of the lower limbs with valvular defects, phlebectasia, and hypoplasia.^{1,2} The common superficial venous system anomalies in KTS are the persistence of the embryonic lateral marginal vein and varicose veins.^{2,5} Varicose veins are tortuous and dilated superficial veins. The abnormal veins (in particular, the lateral marginal thigh vein, the persistent sciatic vein, the profunda-popliteal vein, and the muscular thigh veins) where there is stasis are the unsuspected site of thrombi which the noninformed sonographer will omit at DVT screening.⁶ This may have been so in our case where the duplex was reported

as negative for DVT. A thrombus formed in a persistent and large superficial marginal thigh vein may propagate through its multiple connections to deep veins in the thigh and the pelvis, and cause a PE.⁶

Our patient had the crossed dissociated form of KTS based on the nonsided occurrence of the anomalies.^{1,2} The positive major criteria were (1) varicose veins and port-wine stains, and (2) localized and regional growth disturbances (respectively, macrodactyly and leg hypertrophy).² Syndactyly, autonomic dysfunction of the skin (the skin hue), and venous complications such as edema and thromboembolism observed in our patient corroborate the diagnosis of KTS.² That KTS was the cause of the VTE is more plausible than causation by low protein C in our patient because his protein C levels were above 49% of normal, the critical value under which VTE events are found.⁷ No other thrombotic predispositions were observed or reported in this patient to account for VTE. KTS is a documented cause of VTE-related fatalities in children.⁸ The incidence of VTE in KTS is between 14 and 22% which is equal to or higher than the incidence associated with most other risk factors for VTE.⁶ These other risk factors include prior history of VTE, unilateral leg swelling, recent surgery, active cancer, and a history of thrombophilia.^{9,10} These risk factors but KTS are integrated into the Wells scores to determine the likelihood of VTE in given clinical situations.⁹

The Wells scores estimate the probability of VTE, guide the investigations, and dictate the need for early anticoagulation. Since congenital venous malformations such as those found in KTS are not a part of the scoring system, our patient would have scored 0 on both pretest probabilities for DVT and PE.^{11,12} Therefore, anticoagulation could not have been considered until after the D-dimer result was suggestive of VTE. Besides, the finding of opiate intoxication, the patient's positive response to the antidote naltrexone, and his normal initial A-a gradient caused us not to consider any treatment for PE early in the hospital course. Our failure to recognize KTS had the following two significant implications:

1. Preventative measures for high-risk status for VTE such as stockings in addition to high prophylactic doses of heparin were not used.
2. When the D-dimer came positive, unusual sites for thrombosis were not screened with the duplex ultrasound, leading to a probable false-negative result.

The surgical indications in KTS include excessive leg length discrepancy, symptomatic varicosities, and localized superficial venous malformations in selected patients. Stripping of a large lateral embryonic vein is indicated to treat the symptoms associated with varicosities and may contribute to decreasing the incidence of VTE.^{3,5} Lifelong anticoagulation is indicated after the first VTE in KTS.⁸ Coumadin therapy alone reportedly fails to prevent recurrences of VTE; combined use of low molecular weight heparin with elastic compression stocking is preferred.^{8,13} Invasive adjunctive therapy with cava filters may be required if above treatments are not sufficient, particularly if extension of the venous anomaly to the vena cava is confirmed.^{8,13}

Conclusion

Recognition of KTS could help observed appropriate VTE prophylaxis and optimize the diagnosis yield for DVT or PE in the appropriate clinical situation. A modification of the Wells scores to reflect the association of KTS and VTE could be a life-saving reminder to caregivers.

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Conflict of Interest

There are no conflicts of interest.

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