Use of Rivaroxaban for Prophylaxis of Superficial Venous Thrombosis in Klippel-Trenaunay-Weber Syndrome: Case Report and Systematic Review

Hina Qamar and Cynthia Wu

About the Authors

Hina Qamar is with the Department of Medicine, University of Alberta. Cynthia Wu is with the Department of Medicine, Division of Hematology, University of Alberta.
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Abstract

Klippel-Trenaunay-Weber syndrome (KTWS) is a congenital malformation syndrome involving blood and lymph vessels and disturbed bone and soft tissue growth. Complications of KTWS include deep-vein thrombosis, pulmonary embolism, gastrointestinal bleeding, and vascular (usually lymphatic) blebs within capillary malformations. We present a case of a young male patient with KTWS who presented with superficial venous thrombosis and microangiopathic hemolytic anemia in a presentation similar to disseminated intravascular coagulation. He was ultimately maintained on prophylactic rivaroxaban to prevent recurrent thrombotic events. We performed a literature search to identify similar cases and to summarize common presenting features and treatment modalities that were offered.

Résumé

Le syndrome de Klippel-Trenaunay-Weber (SKTW) est une malformation qui touche les vaisseaux sanguins et lymphatiques et qui se caractérise par une anomalie de la croissance des os et des tissus mous. Les complications liées au SKTW incluent : la thrombose veineuse profonde, l'embolie pulmonaire, des hémorragies gastro-intestinales et la présence de vésicules vasculaires (habituellement lymphatiques) à l'intérieur de capillaires difformes. Nous rapportons le cas d'un homme jeune atteint d'un SKTW qui présente une thrombose veineuse superficielle et une anémie microangiopathique qui ressemble à une coagulation intravasculaire disséminée. Le patient a finalement été mis sous rivaroxaban de manière prophylactique pour prévenir des épisodes thrombotiques récurrents. Nous avons effectué une revue de la littérature pour répertorier d'autres cas similaires et faire une synthèse des manifestations courantes et des traitements offerts.

Case Report

An 18-year-old man from Edmonton with known Klippel-Trenaunay-Weber syndrome (KTWS) had a history of a slowly increasing vascular mass on his left chest and left arm. He began tetradecyl (sclerosant) injection in December 2009. His fifth dose was on 20 May 2010. The goal of these injections was to reduce the size of these malformations and decrease symptoms. After his fifth injection, he experienced flu like symptoms accompanied by worsening pain in his left arm over the site of venous malformation with swelling and ecchymosis. His fatigue and pain had progressed such that he was largely bed bound at home for three days before presenting to the emergency room.

Examination revealed: BP 128/73, temperature 39.5 degrees Celsius, O2 saturation 100% on 6L non-rebreather mask. He was profoundly icteric. A large vascular malformation was present on his left posterior thorax and there was a significant swelling of his left arm extending from the shoulder down to his hand and fingers. Smaller hemangiomata were noted on his left arm and hand. The venous malformation and left arm were extremely tender with significant bruising and provoked by even minimal movement.

When investigated, his hemoglobin was 24g/L, white blood cell count was 21.4 with a neutrophil count of 19, platelets 98. Electrolytes and creatinine were normal. Markers of hemolysis were positive with a total bilirubin 588, unconjugated bilirubin 212 and LDH 1597. Direct antiglobulin test was negative. D-dimer greater than 20. Computed tomography angiogram ruled out any obvious sources of bleeding. Blood cultures were negative for any source of infection.

The patient was diagnosed with Kasabach-Merritt syndrome - coagulopathy resulting from coagulation factor consumption within vascular malformations. It was felt that the precipitating factor was his preceding tetradecyl injection. He was treated with aggressive supportive care/blood product transfusion. After bleeding was ruled out as a cause for the anemia, he was commenced on routine deep-vein thrombosis (DVT) prophylaxis with low dose low-molecular-weight heparin (LMWH). Interestingly, he noted that the painful symptoms immediately started to improve after anticoagulation was started. An ultrasound of his left arm over the venous malformation revealed old superficial venous thrombosis with recanalization. His coagulopathy eventually settled and his complete blood count and biochemical parameters started to normalize. He was discharged in stable condition. Table 1 summarizes the laboratory parameter trends from initial disseminated intravascular coagulation presentation to recovery.

He was referred to outpatient Hematology for evaluation of preventative measures prior to undergoing further sclerosing therapy for his KTWS. He had a few minor attacks largely characterized by significant arm pain requiring time off work. These occurred even in the absence of sclerosing therapy. Subsequent magnetic resonance imaging of the arm in December 2010 confirmed evidence of thrombosis in the areas of malformation including the left hemithorax, axilla, arm, 4th and 5th fingers. It was suggested that he commence long term low dose LMWH to try and prevent further symptomatic superficial thromboses.

Due to expense and inconvenience of injections, other options were explored. After discussion regarding off-label use of rivaroxaban in this situation, he was commenced on low dose rivaroxaban 10 mg daily. He tolerated this well. He has been on treatment since 2013, aside from one episode of pain recurrence during anticoagulation interruption for dental surgery and one episode of recurrent arm pain/swelling (ultrasound negative for

Table 1. Laboratory Parameter Trends from Initial Disseminated Intravascular Coagulation Presentation to Recovery

	DAY 0	DAY 10-15	DAY 30-35	3 YRS LATER*	5 YRS LATER*
Hemoglobin	24	79	122	145	148
Platelet	98	231	120	138	176
PT-INR	1.9	1.3	1.3	1.2	1.2
PTT	32	31	35	37	32.9
Fibrinogen	1.1	2.3	0.7	1.0	0.8
D-dimer	>20.00	-	-	>20.00	>10.00
Bilirubin	529	471	87	18	14
LDH	1597	1504	340	212	206

**denotes to labs on rivaroxaban.*

LDH = lactate dehydrogenase; PT-INR = prothrombin time-international normalized ratio; PTT = partial thromboplastin time.

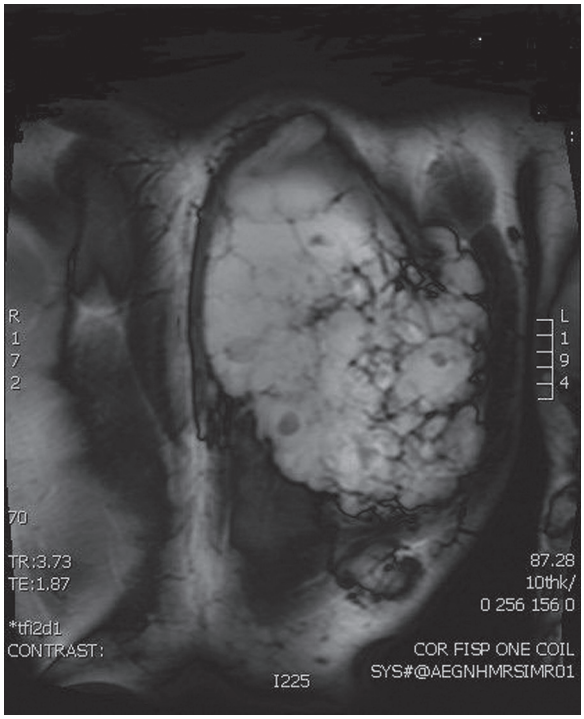

Figure 1. Magnetic resonance imaging of patient showing hemangioma within venous malformation.

DVT) after heavy manual labour and upper extremity exertion. His acute thrombotic event was managed on low-molecular-weight heparin.

Methods

To review how thrombotic manifestations of KTWS are managed, we performed a comprehensive literature search on PubMed using MESH terms: KWS, thrombosis, DIC and Kasabach-Merritt coagulopathy. Of the 97 publications found, 81 were excluded as they were focused on non-thrombotic complications of KTWS. Two randomized control trials were excluded as they examined assessment and recurrence of thrombosis but not treatment and 2 cases reports were excluded as they were not in English. One case report was excluded as description of thrombosis was not reported. Results of the remaining 11 case reports are summarized in Table 2.

Discussion

This case describes a young man with KTWS and complex coagulopathy. KTWS is a congenital malformation syndrome involving blood and lymph vessels and disturbed bone and soft tissue growth.[1]

The main characteristics of coagulopathy in KTWS are moderate reduction in platelets, reduction in fibrinogen and other plasma coagulation factors, evidence of fibrinolysis, and the presence of fibrin split products. In studying this phenomenon, Gilon et al demonstrated a relative decrease in the peripheral blood platelet count as opposed to an increase in platelets within the haemangioma in patients with this disorder.[23] Gilon et al theorized that the tortuosity of the vessels within the haemangioma resulted in the trapping and subsequent destruction of platelets which, in turn led to the activation of the coagulation mechanism and a localized intravascular coagulopathy.[23] Localized intravascular coagulation rarely progresses to disseminated intravascular coagulation, especially under acute conditions (e.g., sclerotherapy of the venous malformation, surgery, bone fracture, or menstruation).[2]

Treatment of KTWS includes: sclerotherapy, embolization, compression stockings (to reduce lymphedema) and anticoagulation to prevent venous thromboembolism in vascular anomalies.[7] When coagulopathy – local or more disseminated – results, treatment is supportive in nature. This include fresh frozen plasma, platelets, human activated protein C. In critically ill, non-bleeding patients with DIC, prophylaxis for venous thromboembolism with prophylactic doses of heparin or low-molecular-weight heparin is recommended.[8]

Our patient was considered for use of anticoagulation for secondary prevention of thrombotic events as his recurrent debilitating pain syndromes were assumed secondary to microthrombotic events within his venous malformation. There is data to support the use of short term low dose anticoagulation in the treatment of acute superficial vein thrombosis (SVT).[9] Randomized controlled studies have demonstrated the efficacy and safety of systemic anticoagulation with therapeutic/intermediate doses of LMWH or prophylactic doses of fondaparinux administered for 4–6 weeks.[9] Fondaparinux 2.5 mg/day is currently the only anticoagulant with a license for the treatment of SVT.[23] With a large permanent venous malformation and previous recurrent thrombotic events within this vascular system, we elected to extend anticoagulation to indefinite duration. We chose to use rivaroxaban 10 mg daily due to inconvenience of daily subcutaneous heparin injections. Secondly, therapeutic rivaroxaban has been shown to be as safe and as effective compared to standard warfarin therapy in the treatment of DVT and PE.[10] Thirdly, prophylactic rivaroxaban (10 mg daily) has been shown to be effective and safe as a DVT prophylactic regimen in the those undergoing major orthopedic surgery.[11] Finally, prophylactic dose anticoagulation has been shown to be effective in the treatment of SVT.[9]

In conclusion, KTWS is a rare condition that can be complicated by a variety of thrombotic manifestations. Recurrent overt thrombotic events may be successfully treated with anticoagulation. Our patient despite symptomatic and frequent recurrent events of SVT have remained stable for over five years on, though still off label, low dose newer anticoagulant.

Table 2. Review of KTWS cases with Thrombotic Complications

Case ID	Venous Malformation	SVT*	DVT*	DIC*	LIC*	Treatment	Outcome
Muluk et al 1995[12]	left leg and arm	no	yes	not reported	not reported	therapeutic coumadin	stable
Stone et al 1997[13]	left leg	no	yes	not reported	not reported	cavotomy+ angioplasty	stable
Gianluppi et al 1999[14]	right hand, back,leg	no	yes	not reported	not reported	therapeutic coumadin	patient died from cor pulmonate
Awada et al 2003[15]	cephalic vein	no	yes	not reported	not reported	therapeutic lmwh*	stable
Randrianrisoa et al 2013[16]	right leg	no	yes	yes	not reported	rivaroxaban 20mg daily	stable
Ndzengue et al 2012[17]	right leg	no	yes	not reported	not reported	therapeutic coumadin	stable
Aronoff et al 1998[18]	left neck, arm, chest, spleen, illiopsoas	no	no	yes	not reported	therapeutic LMWH + antithrombin III	stable
Neubert et al 1995[19]	vulva	no	no	yes	not reported	therapeutic lmwh + aminocaproic acid	stable
Gungor et al 2010[20]	right leg	yes	no	not reported	not reported	therapeutic lmwh + thrombectomy	stable
Karalezli A 2006[21]	spleen and spinal	no	yes	not reported	not reported	therapeutic coumadin	stable
Garg A 2009[22]	perineum and thigh	no	yes	not reported	not reported	therapeutic LMWH	stable

SVT = superficial vein thrombosis; DVT = deep vein thrombosis; DIC = disseminated intravascular coagulation; LIC = local intravascular coagulation, LMWH = low-molecular-weight heparin.

References

1. Oduber CE, van der Horst CM, Hennekam RC. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. Ann Plast Surg 2008.
2. D'Amico JA, Hoffman GC, Dyment PG. Klippel-Trenaunay syndrome associated with chronic disseminated intravascular coagulation and massive osteolysis. Cleve Clin Q 1997.
3. Heit JA, Mohr DN, Silverstein MD, et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 2000.
4. Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB. Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med2007.
5. Lorenzo Loffredo, Ludovica Perri, Maria Del Ben, Francesco Angelico, Francesco VioliNew oral anticoagulants for the treatment of acute venous thromboembolism: are they safer than vitamin K antagonists?A meta-analysis of the interventional trials. Intern Emerg Med 2014.
6. Arcelus J, Dome`nech, Ferna´ndez-Capitan PMC, et al Rivaroxaban in the treatment of venous thromboembolism and the prevention of recurrences: a practical approach. Clinical and Appl Thrombo Hemostas 2014.
7. Gloviczki P, Driscoll DJ. Klippel-Trenaunay syndrome: current management. Phlebology 2007.
8. Levi M, Toh CH, Thachil J, Watson HGGuidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology Br J Haematol 2009.
9. Scott G[1], Mahdi AJ, Alikhan R.Superficial vein thrombosis: a current approach to management. Br J Haematol 2014 Dec 17.
10. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010 Dec 23.
11. Van Thiel D[1], Kalodiki E, Wahi R, Litinas E, Haque W, Rao G.Interpretation of benefit-risk of enoxaparin as comparator in the RECORD program: rivaroxaban oral tablets (10 mg) for use in prophylaxis in deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery. Clin Appl Thromb Hemost. 2009 Jul-Aug.
12. Muluk SC, Ginns LC, Semigran MJ, Kaufman JA, Gertler JP. Klippel-Trénaunay syndrome with multiple pulmonary emboli--an unusual cause of progressive pulmonary dysfunction. J Vasc Surg 1995 Apr.
13. Stone DH1, Adelman MA, Rosen RJ, Riles TS, Lamparello PJ, Jacobowitz GR, Rockman CB. A unique approach in the management of vena caval thrombosis in a patient with Klippel-Trénaunay syndrome. J Vasc Surg 1997 Jul.
14. Gianlupi A, Harper RW, Dwyre DM, Marelich GP. Recurrent pulmonary embolism associated with Klippel-Trenaunay-Weber syndrome. Chest 1999 Apr.

15. Awada A, Al Jumah M, Al Ayafi H. Two unusual complications of the Klippel-Trénaunay syndrome: carpal tunnel syndrome and cerebral venous thrombosis. Rev Neurol (Paris) 2003 Jul.
16. Randrianarisoa E, Kopp HG, Balletshofer BM, Jaschonek K, Kanz L, Haering HU, Rittig K. Management of disseminated intravascular coagulopathy with direct factor Xa inhibitor rivaroxaban in Klippel-Trénaunay syndrome. Blood Coagul Fibrinolysis 2013 Oct.
17. Ndzengue A1, Rafal RB, Balmir S, Rai DB, Jaffe EA. Klippel-trenaunay syndrome: an often overlooked risk factor for venous thromboembolic disease. Int J Angiol 2012 Dec.
18. Aronoff DM, Roshon M. Severe hemorrhage complicating the Klippel-Trénaunay-Weber syndrome. South Med J 1998 Nov.
19. Neubert AG, Golden MA, Rose NC. Kasabach-Merritt coagulopathy complicating Klippel-Trenaunay-Weber syndrome in pregnancy. Obstet Gynecol 1995 May.
20. Gündoğan TG and Jacquemyn Y Klippel-Trenaunay Syndrome and pregnancy. Obstet Gynecol Int 2010.
21. Karalezli A, Sevgili S, Ernam Turgut D, HasanoLIN A, HasanoLIN HC. Pulmonary embolism in a patient with Klippel Trenaunay-Weber syndrome. Tuberk Toraks 2006.
22. Garg A, Trent ME, Strouse JJ, Mitchell SE, Rowe PC. Delayed diagnosis of iliac vein thrombus in a sexually-active adolescent with Klippel- Trenaunay syndrome. J Pediatr Adolesc Gynecol 2009 Jun.
23. Gilon E, Ramot B, Sheba C. Multiple hemangiomata associated with thrombocytopenia: remarks on the pathogenesis of the thrombocytopenia in this syndrome. Blood 1959.

PATIENT CONSENT

Informed consent was obtained from all patients for being included in the study.