Case Report

A Rare Case of Klippel Trenaunay Syndrome with Von Willebrand Factor Deficiency and Multiple Accessory Spleens: A Case Report and Brief Literature Review

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Abstract

Klippel Trenaunay Syndrome (KTS) is an uncommon inherited syndrome identified by venous varicosities and capillary abnormalities. von Willebrand Disease is the most common inherited hemorrhage disturbance in humans, leading to insufficiency in von Willebrand Factor, which is a complex multimeric protein with two functions: it forms a bridge between the platelets and injured vascular areas and it attaches factor VIII and stabilizes it. We present a 13-year-old son with a typical clinical manifestation of KTS, including "port-wine stains" as capillary malformation, venous malformation, and hypertrophy of the left lower extremity, who also suffers from von Willebrand Disease type 3. He has been suffering from these two rare conditions since birth. The occurrence of KTS with von Willebrand Factor deficiency in a patient has so far not been reported, which may propose a mutation in the putative common regulatory gene that caused this uncommon phenotype.

Keywords: Factor VIII, Klippel Trenaunay weber syndrome, von Willebrand disease, von Willebrand factor

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Introduction

Klippel Trenaunay Syndrome (KTS) is a rare inherited disease with blended vascular malformation. KTS was first demonstrated by Klippel and Trenaunay in 1900.[1] It is determined by a triad of hemangiomas (secondary to capillary dysplasia), venous abnormalities, and soft tissue or bone hypertrophy.[2] Its pathogenesis remains uncertain, but last studies have proposed that a mutation in the PIK3CA gene may be the cause.[3] Another pathogenetic mechanism of the elevated angiogenesis is thought to be mutations in the angiogenic agent (VG5Q) gene via transcription and elevated activity.[4] VG5Q gene has been recognized in blood vessels, which is secreted during angiogenesis with the function of increasing endothelial cell proliferation.[5]

Von Willebrand Disease (VWD) is generally introduced to be "the most common human inherited hemorrhage disturbance." VWD which is found in about 1% of the overall population was first demonstrated.[6] VWD is caused by qualitative or quantitative defects in Von Willebrand Factor (vWF), a complex plasma protein with several functions that contribute generally to platelet thrombus creation at damage sites to help prevent bleeding.[4] vWD is an intricate genetic disturbance in which three forms have been characterized. vWD type 3 is rare

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and is described by decreased rates of FVIII and untraceable levels of vWF.[7] According to the Iranian Hemophilia Society (IHS) report, the overall number of patients with hemostatic diseases in Iran is 10,944 (a prevalence of 131 per million), while the number of recorded patients with vWD is 1,617 and 1,516 according to the IHS and annual global study, respectively (prevalence about 19 per million).[8] We present a rare case of a 13-year-old boy who suffers from both of these conditions (KTS and vWD type 3) since birth.

Case Report

A 13-year-old boy who had been referred to our pediatric hospital to receive his routine drug haemate *P* (human coagulation factor VIII and human vWF) for vWD type 3. Medical history, examination, and imaging revealed that he is also a case of KTS. He presented with capillary malformation at birth, venous malformation, multiple accessory spleens (AS) progressive left leg enlargement, and lymphedema in early childhood. AS generally described as an isolated asymptomatic mass of splenic tissue detached from the body of the real spleen.[9]

The laboratory data of our case revealed as follows: Activated Partial Thromboplastin Time (PTT or APTT) was prolonged while Prothrombin Time (PT) and fibrinogen range were typical. The rest laboratory data displayed factor VIII level at 5% but the factor IX level was normal. The vWF Ag evaluation results were decreased at 2%, confirming a severe form of vWD type 3.

After falling down at the age of one and severe gingival bleeding that was not cured despite necessary medical procedures, he was referred to a more advanced center to evaluate coagulopathy disorder and was diagnosed with a severe form of vWD type 3. The child was discharged with recommendation of relative stationary lifestyle in blend with prophylactic treatment in minor surgical with dental work. In infancy, there was no abnormal umbilical cord bleeding. His height, weight, and psychomotor expansion were normal. There was no family history of KTS or vWD. Until the age of 1 year, he had no complaints of spontaneous bleeding or bruising. He was circumcised at the age of 5 years. Few days after the circumcision, he suffered from severe bleeding at the suture site, which was controlled by receiving high dose of factor without the need for a blood transfusion. He then suffered from a skull fracture at school age, the bleeding was so severe that he was given a blood transfusion but the brain CT was normal and there was no evidence of ICH, SDH, IVH, and epidural hematoma. He was hospitalized twice due to hemarthrosis and three times due to hematuria. He also had experienced many episodes of epistaxis. He has a normal clinical presentation of KTS with extensive "port-wine stains'' as capillary malformation [Figure 1a-d] venous malformation on trunk [Figure 1b] and hypertrophy of left lower extremity [Figure 1c]. There was extensive port-wine stain on his trunk, back, and also on lower and upper limbs.

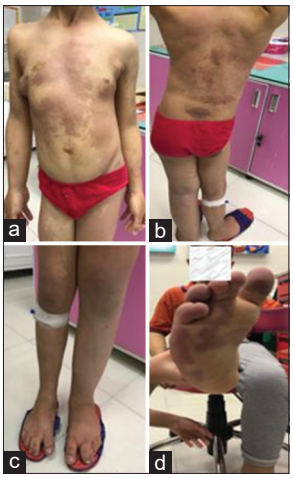

Figure 1: A 13-year-old patient (a) extensive "port-wine stains'' as capillary malformation and venous malformation on the trunk, (b) skeletal deformity such as scoliosis, (c) hypertrophy of left leg with syndactyly of the second and third toes of both feet, and (d) extensive "port-wine stains'' as capillary malformation in the sole of the foot

Bruises were seen on the right knee as well as on the left eyelid. There was a venous malformation measured 8 × 5 cm on his right midaxillary lines of trunk as a soft and rubbery mass. Additional findings include skeletal deformity such as scoliosis [Figure 1b] and syndactyly [Figure 1c] and gingival hypertrophy. On physical investigation, the respiratory and cardiac examinations were typical. The patient had a gingival hypertrophy and high arched palate. On abdominal assay, there were no remarkable abnormality and organomegaly. Without joint swelling, tenderness, or erythemas (hemarthrosis) were detected.

During the musculoskeletal examination, the lower limbs showed length and width discrepancy, hypertrophy of left leg with syndactyly of the second and third toes of both foots [Figure 1c], which is a rare feature of KTS. Scoliosis was present. The neurologic examination was unremarkable except decreased deep-tendon reflexes of left leg. Genitalia examination showed left scrotal enlargement but there was not any other abnormality such as hypospadias. Gastrointestinal bleeding and iron deficiency were not found and there was no evidence of capillary malformation on colonoscopic examination.

The Doppler ultrasound of all four extremities, trunk, and midaxillary lesion revealed: 1: There was venous malformation in the right midaxillary. 2: Extensive capillary malformation has been found in all four limbs and trunks. 3: No evidence of DVT reported. Magnetic resonance imaging of the thorax with and without contrast reported a septated lesion with decreased signal intensity in T1. It suggested venous malformation.

His medications for vWD were iron supplement (200 mg ferrous sulfate three times daily) with haemate p (1,500 IU three times weekly). Compression stockings or bandages were used 8 hours/day for his left leg lymphedema. There was no invasive therapy or surgery in his history till now.

Discussion

KTS can be characterized as a combined vascular abnormality affecting the lymphatic systems, capillary, and venous.[1] It is an uncommon idiopathic disorder described by hemihypertrophy of the soft tissues and bones, low-flow vascular abnormality, and variceal enlargement of the veins in the involved extremity. The appearance of KTS has a widespread ability to affect each organ system. This is due to the unpredictable nature of vascular abnormalities. KTS is often related with genitourinary manifestations, hemimegalencephaly, polydactyly, developmental delays, macrodactyly, syndactyly, pulmonary embolism, heart failure, osteomyelitis, coagulopathy, seizures thrombophlebitis, hemothorax, susceptibility to fractures, hydronephrosis, and in uncommon cases, ophthalmic alterations, such as orbital varix, oculosympathetic palsy, conjunctival telangiectasia, strabismus, retinal and chiasmal varicosities, cataracts, iris coloboma, and heterochromia. Gastrointestinal KTS is an uncommon event.[10-13]

In addition, KTS has been related to Kasabach-Merritt occurrence in which platelet sequestration with secondary depletion of coagulation factors happens in the venous sinusoids of the vascular abnormality.[14] The pathophysiology is not well recognized for their pathogenesis, although there are concepts explained in the literature, such as 1: inherited occlusion of the deep veins relating to the involved limb (typically the varicose veins and popliteal that drain directly to the internal iliac vein, leading to circulatory overload),[15] 2: mesodermal abnormalities, which demonstrate poor creation of soft tissues and vascular during the fetal life,[13] 3: gene mutations that regulate growth and cellular differentiation, combined with deficiencies of chromosome 5q (locus CMC1), which is required for angiogenesis.[16-18] Many recent studies have presented that KTS seems to be associated with mutations in the PIK3CA gene and that Parkes-Weber syndrome is caused by mutations of the RASA1 gene, both genes that are accountable for mediating cellular growth, proliferation, and differentiation (through the tyrosine kinase pathway).[3,18,19] Several forms of therapy have been used to manage KTS, such as radiotherapy, cryotherapy, sclerotherapy, and laser therapy. Surgery should be kept for complicated cases in which the KTS is extremely symptomatic.[15]

vWD is the most common inherited hemorrhage disease, with a prevalence of about 1%-2% according to population investigation.[6] It is mostly transmitted in an autosomal dominant manner and is created by the abnormality or deficiency of vWF, which is required for platelet adhesion to subendothelium to serve and occur as a carrier of FVIII, inhibited by the activated protein C system.[20] VWD is categorized into three types. Types 1 and 3 vWD reflect the partial or complete quantitative defect of vWF, respectively, while type 2 vWD reflects qualitative defects of vWF. Type 3 vWD is inherited as an autosomal recessive trait and is described by untraceable ranges of vWF (typically <3 U/dL) and very little rates of FVIII (usually 1-5 U/dL), which may cause a more severe hemorrhage trend described not only by mucocutaneous bleedings but also by hematomas and hemarthroses as in moderately severe hemophilia.[21] The identification of vWD is based on biological and clinical data. When patients present with mucocutaneous hemorrhage symptoms suggestive of a primary hemostatic disorder, a qualitative or quantitative defect of normal vWF is a possible cause or contributory factor. Screening assays contain classically platelet count, activated partial thromboplastin time (aPTT), and closure time (PFA-100 analyzer). Second-rate–specific vWF evaluates are crucial to diagnose vWF deficiency and they contain the evaluation of vWF antigen (vWF: Ag), FVIII activity (FVIII: C), and vWF ristocetin cofactor activity (vWF: RCo) allowing the calculation of ratios (vWF: RCo/vWF: Ag and FVIII: C/vWF: Ag) and the evaluation of ristocetin-induced platelet aggregation. Third-rate vWF evaluates are dedicated to a better characterization of vWD types and they include structural evaluates (vWF propeptide [vWFpp], vWF multimers analysis) and functional evaluates (VWF binding to platelet GPIb, to FVIII [VWF: FVIIIB] and to collagen [VWF: CB]).[22,23] In fact, many cases of vWD go undiagnosed, and hemorrhage during dental treatment may be the first sign of underlying disease.[24,25] Treatments which pertain on the type of vWD include all ways that increase the endogenous plasma concentration of vWF.[26,27]

We present a rare case of a 13-year-old boy who has suffered from both of these conditions since birth. He has a typical clinical presentation of KTS: extensive "port-wine stains" as capillary malformation [Figure 1a-d], venous malformation on trunk [Figure 1b], hypertrophy of left lower extremity [Figure 1c], and syndactyly of the second and third toes of both feet [Figure 1c]. Although concurrency of KTS with antithrombin III, factor VII, and factor XIII deficiency have been reported in some journals,[28,29] but we could not find any report of concurrency of KTS and vWD.

On this issue, Endo Y *et al*. a woman with factor XIII defect was reported. The patient had no consanguinity, but familial traits were present (unlike our case(. A hemorrhage affinity and poor lesion healing had been noted in the patient since birth (like our case). Hematologic research shown cryofibrinogenemia, hypofibrinogenemia, platelet dysfunction, and mild chronic disseminated intravascular coagulation with elongated PT and PTT, mild increase of fibrinogen-fibrin degradation products, and beta-thromboglobulin and platelet factor 4. The evaluation of subunits A and S were 16% and 29%, respectively, by the electro-immunoassay technique, and the evaluation of the factor XIII rate was 10% by the antiserum inhibition technique.[28]

A patient with KTS, a copper metabolism disorder, and a factor VII deficiency was reported. The KTS involved histologically the liver and left leg. A long PT prompted clotting studies illuminating a factor VII deficiency while the other factors were at the typical level.[29]

A case of a patient presenting with KTS and stroke was reported. The biological assay showed antithrombin inefficiency.[29]

All of the three cases above were rare. Apart from these three articles, the article that links the relationship between KTS and factor deficiency (including vWF deficiency) as the cause of bleeding has not been reported so far. The absence of deep vein thrombosis (DVT) in this case despite the presence of lymphedema may be due to its co-occurrence with type 3 vWD.

Conclusion

As a result, the event of these two rare pathologies in a single patient has not been characterized so far, which may propose a mutation in a hypothetical common regulatory gene cause this uncommon phenotype.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained and the informed consent of the patient is available upon request.

Availability of data and materials

Not applicable.

Author contributions

Conceptualization and design: Vahid Falahati, Mahsa Fallahi, Kazem Ghaffari, and Ali ghasemi. Drafting of the manuscript: Kazem Ghaffari and Mona Shahriarpour. Critical revision of the manuscript for important intellectual content: Kazem Ghaffari and Ali Ghasemi.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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