CASE REPORT

A Woman with Klippel-Trenaunay Syndrome Reproductive Tract Bleeding Case Report and Review of the Literature

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ABSTRACT

Klippel-Trenaunay syndrome (KTS) is a rare congenital vascular disorder characterized by wine stains, abnormal tissue and bone growth, and vascular malformations. Genital involvement is uncommon. We report a case of a 12-year-old female with KTS who experienced recurrent profuse vaginal bleeding and provide a comprehensive literature review on KTS cases with genital involvement. The literature reports 7 cases, mainly in individuals aged 25 to 45, presenting with uncontrollable vaginal bleeding and anemia. Endovascular interventions were the primary treatment, although surgery was necessary in some cases. Recent studies have identified a potential association between KTS and the PIK3CA gene mutation, offering insights for pharmacological treatment. (*Altern Ther Health Med.* 2024;30(10):66-69).

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INTRODUCTION

Klippel-Trenaunay Syndrome (KTS) is a rare and complex congenital disorder characterized by a triad of symptoms including port-wine stains, varicosities, and bone and soft tissue hypertrophy. This syndrome can cause a range of symptoms such as pain, swelling, lymphedema, bleeding, thrombophlebitis, and deep vein thrombosis, which significantly impact the quality of life and pose challenges in management. First described by Maurice Klippel and Paul Trenaunay in 1900, our understanding of KTS has evolved since then.[1] Despite its rarity, KTS has been reported to have an estimated incidence of one per 100 000.[2] It is more commonly observed in males, although no racial predilection has been observed. However, there is a scarcity of literature specifically addressing adolescent females with KTS, particularly those with genitourinary tract involvement.[3]

In this report, we present a case of a 12-year-old girl who experienced heavy non-menstrual vaginal bleeding and was subsequently diagnosed with KTS. Additionally, we conducted a systematic review of the peer-reviewed literature from 1988 to 2023, focusing on patients with KTS and genital involvement. Our objective is to provide new insights and contribute to the understanding of KTS, particularly in the context of adolescent females. By highlighting the rarity and complexity of KTS, elaborating on its clinical manifestations, and emphasizing the scarcity of literature on adolescent females with KTS, we aim to set the stage for the detailed case report and the findings of the literature review.

CASE REPORT

Background

Our patient is a 14-year-old female with no relevant medical history. She experienced her first menstruation at the age of 12 in May 2019. Her menstrual cycles ranged from 26 to 90 days with normal bleeding volume and no dysmenorrhea. The patient had no history of vaginal sexual intercourse, and her last menstrual period was on November 21, 2019.

Symptomatology and Diagnosis

In December 2019, the patient came to our hospital for a sudden onset of heavy vaginal bleeding. Ultrasound images showed a thin endometrium, a liquid dark area measuring approximately 70 mm × 44 mm in the middle of the pelvis posterior to the uterus, an oval hypoechoic mass about 50 mm × 38 mm was seen inside, considered hematoma formation, no

Table 1. Key characteristics of the included case report or series.

Year of publication	Nationality	Age (years)	Performance	Treatment	prognosis
1988[4]	United Kingdom	25	Heavy bleeding during menstruation	Blood transfusion, compounded oral contraceptives	N
1998[5]	United States	30	Heavy vaginal bleeding after cervical LEEP	Repeated transfusion, cervical suture, uterine artery mbolization, Hysterectomy, secondary abdominal exploration, low molecular heparin, antithrombin III	Effective control
2014[6]	France	30	Postpartum hemorrhage at 38 weeks gestation	Uterine artery mbolization, suturing, blood transfusion, erinatal heparin anticoagulation	Effective control
2016[7]	Japan	23	Cesarean section at 37 weeks of gestation, blood loss 3792 g	Blood transfusion, postpartum use of enoxaparin	N
2019[8]	China	26	Heavy vaginal bleeding 10 days after cesarean section in full-term pregnancy	Blood transfusion, uterine artery embolization, hysterectomy, secondary abdominal exploration, heparin, warfarin anticoagulation	Follow up for 5 years
2019[9]	Canada	45	Heavy menstrual flow	GnRH-a combined with directional addition therapy/uterine artery embolization/hysterectomy	Effective control
2021[10]	Korean	31	Severe increased menstrual flow/ progressive clitoral-vaginal enlargement	Oral Acetylclofenac	Effective control

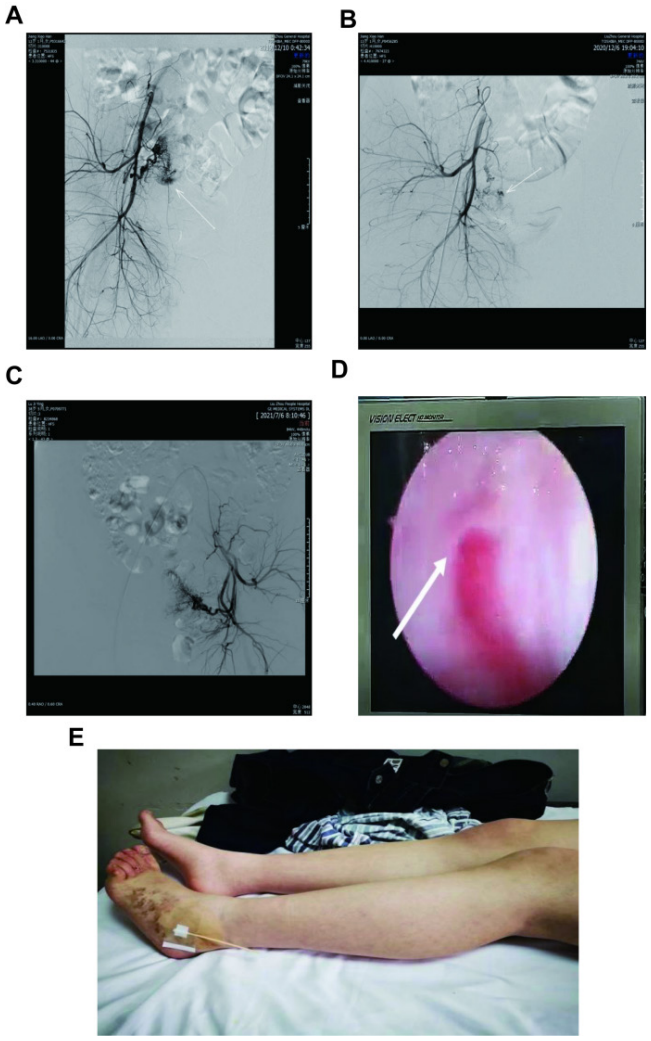

Figure 1. A treatment case of a 12-year-old girl with significant vaginal bleeding outside of menstruation. (A) In December 2019, the patient exhibited abnormal thickening of blood vessels in the anterior fornix of the vagina. (B) In December 2020, the patient showed abnormal patchy vascular shadowing in the uterine adnexal region. (C) In July 2021, the patient's uterine arteries exhibited patchy staining in the distal region. (D) In July 2021, the patient experienced bleeding from the blood vessels on the left anterior wall of the cervix under hysteroscopy. (E) On March 12, 2023, there was no abnormal vaginal bleeding at 18 months of follow-up.

abnormalities in the uterine body and bilateral adnexal regions; CT showed that occupancy in the posterior wall of the cervix and abnormal thickened vessels in the anterior fornix of the uterus, excluding hematoma and vascular malformation. The patient's hemoglobin level dropped to 32.40 g/L. Angiography suggested an arteriovenous fistula of the left inferior superficial femoral artery and an arteriovenous fistula of the left dorsalis pedis - small saphenous vein (Figure 1A). The patient was diagnosed with KTS in combination with the ancillary tests and clinical presentation and underwent the first emergency bilateral uterine artery embolization on December 10, 2019. After the bleeding stopped, the patient underwent two more lower extremity angiograms and embolization of the left popliteal arteriovenous fistula. The patient's menstrual periods were normal after treatment.

Treatment Course

In January 2020 and December 2020, the patient was admitted to the hospital with heavy vaginal bleeding 3 days after finishing a regular menstrual cycle. Angiograms suggested that arteriovenous fistula of the left external and internal iliac veins (Figure 1B). Both underwent uterine artery embolization and the bleeding gradually decreased and stopped.

In July 2021, the patient had another heavy vaginal bleeding episode and had a Hemoglobin level concentration of 68 g/L when admitted to the hospital. Ultrasound images showed a cystic, solid mixed echogenic area of about 55 mm × 52 mm in the cervical region, which is poorly demarcated from the cervix (Figure 1C). The patient underwent two internal iliac artery embolizations because of recurrent disease. After excluding reasons such as functional and blood disorders and no free peritoneal fluid in the abdominal cavity, the physicians planned to perform a hysteroscopy to investigate malignant causes. Under hysteroscopy, we saw an accumulation of approximately 250 ml of blood in the vagina and active bleeding from the vessels at the upper cervical lip at 1 o'clock, about 1 cm from the ectocervix (Figure 1D), electrocoagulation was performed on the bleeding point, and the anterior cervical lip was sutured. The bleeding gradually stopped after the operation, and the patient was discharged in stable condition with no abnormal vaginal bleeding at 18 months of follow-up (Figure 1E).

The patient is currently stabilized with abnormal growths in the lower extremities after venous embolization of the lower extremities, but hypertrophy of the left lower extremity, increased skin temperature, and persistent symptoms of skin pigmentation nevus.

LITERATURE REVIEW

There are few case reports and series reported in the literature on reproductive tract bleeding in women with KTS. We performed a literature search in PubMed, Embase, Web of Science, and NKI for case reports and case series published from 1988 to 2023 using the keywords with 'Klippel-Trenaunay syndrome', 'KTW', 'leg overgrowth', 'venous malformation', 'hemorrhage','colporr-hagia' and 'vaginal bleeding'. The literature was screened according to the International Society for the Study of Vascular Anomalies (ISSVA) diagnostic criteria, such as the literature must suggest the clinical presentation and diagnostic basis in words or pictures and excluded articles in letters, commentaries, and series that did not provide raw data. Finally, we included 7 case reports of reproductive tract bleeding in women with KTS. Table 1[4-10] contains the included studies and their key characteristics.

In our literature search, we found that venous malformations often involve multiple organ systems, such as involvement of the digestive system, leading to dilated intestinal lymphatics that can cause protein-losing enteropathy; varicose veins in the gastrointestinal tract can cause pain, bleeding, and diarrhea. However, they are often overlooked in asymptomatic patients.[11] The most frequently reported source of gastrointestinal bleeding is diffuse cavernous hemangiomas of the distal colon and rectum, which account for an estimated 1%-12.5% of KTS cases.[12] Portal venous insufficiency can also cause upper gastrointestinal bleeding, and portal hypertension leads to esophageal varices.[13] The Mayo Clinic performed a neuroimaging evaluation of 116 patients with combined K-T and found 19 cases of spinal nerve and vascular anomalies (19/116, 16.4%), including cavernous venous malformations, arteriovenous malformations and arteriovenous fistulas, presenting as extremity pain, varicose veins, back pain, headache, paraplegia, deep and superficial venous thrombosis. Specifically, an 18-year-old male presented with a painful paravertebral mass, which was found to be a venous malformation on MRI, CTA and DSA.[14]

In contrast, the genitourinary tract is less likely to be involved. Tepeler A reported that about 3-6% of patients had urethral venous and/or lymphatic malformations, commonly involving the kidneys, bladder, and scrotum.[15] Hematuria was the most common symptom (3/10, 30%). One case presented with recurrent hematuria requiring blood transfusion treatment and some cases were treated with endoscopy and endoscopic laser ablation.[16]

In the literature, vaginal bleeding as the first symptom is more rare. As shown in Table 1, the mean age of patients was 35 years (25-45 years). Three cases of vaginal bleeding occurred from the time of delivery to 10 days after delivery, and one case after cervical cerclage. In the present case, four cases presented for spontaneous vaginal bleeding, and two cases with menstrual bleeding. In contrast, this patient presented with sudden non-menstrual bleeding, which has not been reported in the previous literature. All cases presented with uncontrollable heavy bleeding from the genital tract, with anemia, and even hemorrhagic shock.

How to stop the bleeding has become the focus in the management of this group of patients. Currently, there is no uniform treatment protocol due to the small number of cases. Endovascular treatment, including sclerotherapy, endovenous ablation, and embolization, is commonly used in patients with KTS.[17] Four patients in this series underwent endovascular embolization with inconclusive results and finally underwent follow-up surgery. Zhang J et al.[8] reported a case of postpartum women in China who developed a life-threatening hemorrhage and was treated with endovascular embolization along with conventional hemostatic transfusion support. However, the hysterectomy was eventually removed due to poor results. The patient developed diffuse intravascular coagulation (DIC) after surgery due to persistent bleeding from the trauma and finally accepted the anticoagulation therapy - low molecular heparin and antithrombin III. There were no abnormalities at the 5th year of follow-up. Aronoff DM et al.[5] reported a case of a 30-year-old woman in the United States who presented with vaginal trauma bleeding after cervical LEEP. The condition gradually improved and stabilized after cervical suturing, uterine artery embolization, hysterectomy, blood transfusion, and anticoagulation therapy - low molecular heparin and antithrombin III. Koch A[7] reported a case of a French pregnant woman presenting with vulvar hemangioma and perineal laceration resulting in 2000 ml of bleeding, which was controlled and stabilized with endovascular embolization and surgical suturing without involving the visceral vessels. In view of genital tract bleeding, hormone therapy has also been reported. Lawlor F et al.[4] reported a case of a 25-year-old British woman who presented with heavy menstrual bleeding and therefore had a sequential infusion of 30u of red blood cell concentrate followed by a 21+7 day pattern of combined oral contraceptives (ethinyl estradiol 30 mcg + levonorgestrel 250 mcg), with lifetime contraceptive medical advice mentioned in the article, but follow-up information was lacking. Milman T et al.[9] reported a Canadian case of a 45-year-old Canadian woman who had failed GnRH-a therapy after intravascular embolization and underwent hysterectomy for symptomatic relief.

DISCUSSION

The 2018 Amsterdam meeting updated the classification of vascular anomalies, emphasizing the broad spectrum of clinical problems caused by these abnormalities, including Klippel-Trenaunay Syndrome (KTS). Patients with KTS often experience progressive symptoms and a decreasing quality of life, with skin pigmentation and skeletal overgrowth being typical manifestations. These symptoms can have a significant impact on patients' daily lives.[3] Capillaries appear as wine-like pigmentation of the skin due to swelling and rupture of small blood vessels under the skin. Most of the skeletal overgrowth involves one lower extremity, which is characterized by bilateral lower extremity inequality and uneven thickness. It creates an imbalance that reduces movement and leads to pain, scoliosis, and walking problems. Overgrowth increases with age and stabilizes around age 12.[18]

Managing KTS requires a multidisciplinary approach due to its complex nature. Surgeons, interventional radiologists, and geneticists, among others, need to work together to develop an effective treatment plan for each patient. This collaborative approach is necessary to address the various clinical challenges posed by KTS.

Recent studies have shown that vascular malformations and overgrowth disorders may be associated with PIK3CA somatic mutations, now collectively referred to as PIK3CA-related overgrowth syndromes (PROS). In addition to KTS, these disorders include the more common congenital lipomatous overgrowth vascular malformations epidermal nevi and skeletal abnormalities (Congenital lipomatous overgrowth vascular malformations epidermal nevi and skeletal abnormalities, CLOVES), Megalencephaly capillary malformation (MCAP). Postzygotic somatic activating mutations in PIK3CA are responsible for the PIK3CA-related overgrowth clinical spectrum. PIK3CA encodes p110a, a critical component of the PI3-kinase enzyme, which activates signaling pathways involved in cellular proliferation, survival, and growth. One of the key downstream effectors of this pathway is mTOR1 via phosphorylation of AKT. Activating hotspot mutations in PIK3CA were first identified in ovarian clear cell carcinoma.[19] Mutations are usually undetectable in blood and observed only in the affected tissue, which carries variable mutational burdens ranging from 33 to 67%.[20] A Korean case of a 31-year-old woman with KTS presented with bulging of the clitoris and vagina. IK3CA mutation was not detected by analysis of whole genome sequencing variant data using peripheral blood.[10] However, tissue was relatively difficult to obtain, and a new method was used for circulating blood specimens.

The somatic mutations in the PI3K/mTOR pathway provide the molecular rationale for mammalian target of rapamycin (mTOR) inhibition treatment. Freixo C et al. reviewed the current literature on the use of mTOR inhibitors for vascular malformations, including 2 randomized controlled studies, 2 nonrandomized prospective studies, 22 case series, and 47 case reports. A total of 373 individuals were treated with sirolimus at an oral dose of 5 mg/d (62.1%) or 0.8 mg/m2 (17.2%) twice daily. In patients with vascular malformations, there was no significant improvement in lesions or clinical symptoms. The genetic status of the patients was not mentioned in the article.[22] Venot Q et al. constructed a PIK3CACAGG-CreER mouse model expressing a dominantly active PI3KCA transgene. After treatment with an inhibitor of PIK3CA (BYL719), mice treated with BYL719 were found to gain longer survival time and improved vascular and organ abnormalities compared to mice treated with placebo. Based on this result, they treated 19 patients with a diagnosis of PROS with BYL719, of which 17 patients had detectable PIK3CA gene mutations. All patients were found to have improved clinical symptoms, such as smaller recalcitrant vascular tumors, improved congestive heart failure, reduced hypertrophy, and reduced scoliosis. No significant side effects were observed during the 180-day treatment period and subsequent follow-ups.[23] Preliminary evidence for the effectiveness of PIK3CA gene-related targeted therapy for PROS.

In conclusion, KTS is a complex vascular anomaly with diverse symptoms and challenges in management. A multidisciplinary approach is necessary for effective treatment. Genetic insights into KTS have revealed the association between PIK3CA mutations and the disease. However, further research is needed to confirm this correlation. Emerging targeted therapies show promise, but more clinical evidence is required. This discussion has important implications for clinical practice and patient management in the field of KTS.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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AUTHOR CONTRIBUTIONS

Xiaohong Luo and Tianyu Ruan contributed equally to this work. XL, TR and YC designed the study and performed the experiments, CGL and FM collected the data, DY and ZT analyzed the data, XL, TR and YC prepared the manuscript. All authors read and approved the final manuscript.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Liuzhou People's Hospital. Signed written informed consent were obtained from the patients and/or guardians.

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