Klippel–Trénaunay Syndrome – A Very Rare and Interesting Syndrome

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ABSTRACT: Klippel–Trénaunay syndrome (KTS or KT) is an infrequently seen dermatological syndrome, which is often viewed as a triad of vascular malformation (capillary malformations or port-wine brands), venous varicosity, and soft tissue and/or bony hypertrophy. We report a case of a 12-year-old male who presented to us with the symptoms of varicose plaques over both lower limbs and was diagnosed as a case of KTS. Management is normally conservative and includes stockings for compression of the branches to reduce edema because of chronic venous insufficiency; modern devices that cause on and off pneumatic compression; and rarely, surgical correction of varicose veins with lifelong follow-up. The orthopedic abnormalities are treated with epiphysiodesis in order to prevent (stop) overgrowing of limb and correction of bone deformity.

KEYWORDS: Klippel–Trénaunay syndrome, capillary malformations, port-wine stains, venous varicosity, soft tissue and/or bony hypertrophy, compression stockings

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Introduction

Klippel–Trénaunay syndrome (KTS or KT) is an unusually seen dermatological syndrome with typical combinations of delicate tissue or bony overgrowth, dermatological vessel abnormalities, and associated venous capillary or lymphatic malformations. KTS is now termed capillary-lymphatic-venous malformation (CLVM). This is a low-flow vascular malformation and not an arteriovenous malformation, which is a high flow condition. The latter is termed Klippel–Trénaunay–Weber syndrome and is a separate syndrome. The vascular abnormalities are usually seen in a single limb, but in rare cases, multiple limbs can be involved. This syndrome should be diagnosed properly and early and differentiated from similar-looking conditions such as Parkes–Weber syndrome (PWS), lymphatic filariasis, Beckwith–Wiedemann syndrome, Proteus syndrome, Russell–Silver syndrome, Maffucci syndrome, CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects), neurofibromatosis type 1 (NF1), and triploid syndrome. Management is usually conservative with lifelong follow-up.[1] We describe a male kid who had KTS and is today in regular follow-up.

Case Presentation

A 12-year-old boy presented to us with the symptoms of verrucous plaques over both lower limbs of sizes 12 cm × 6 cm × 11 cm; certain areas over the plaque showed ulceration and occasional bleeding on minor trauma. In summation, the patient had multiple fluid-filled lesions intermingled with verrucous papules and plaques with enlargement of the left lower limb. On detailed physical examination, he had severe anemia (hemoglobin 6 mg/dL). His heart rate was 100/minute, which was regular, and blood pressure was 100/68 mmHg in the right upper arm. He had normothermia, with the absence of any jaundice, cyanosis, clubbing, and lymph node enlargement. He had marked hypertrophy of the left lower limb. There was a large port-wine stain on most of the left lower limb, except the upper medial portion of the thigh (Fig. 1). Detailed examination showed multiple distinct red to bluish black papulonodular angiokeratomas present over the port-wine stain. Similar lesions were also present over the right lower half of thigh extending over the knee joint and left buttock (Fig. 2). Gross hypertrophy was evident over the right knee joint. A few lesions were on the right buttock with involvement of the perianal area (Fig. 3). Lymphangiectatic lesions were abundant in the perianal area. The left foot had oligodactyly and syndactyly (Fig. 4). In measuring both the lower limbs, they were found to be of equal length. The mental condition according to the index event was as per age, and he did not have any intellectual deficits.

Routine investigations showed 6 mg/dL of hemoglobin; peripheral smear did not show any parasite. X-ray of both lower limbs did not show any limb discrepancies. Doppler ultrasound showed venous malformation with diffuse hypertrophy of soft

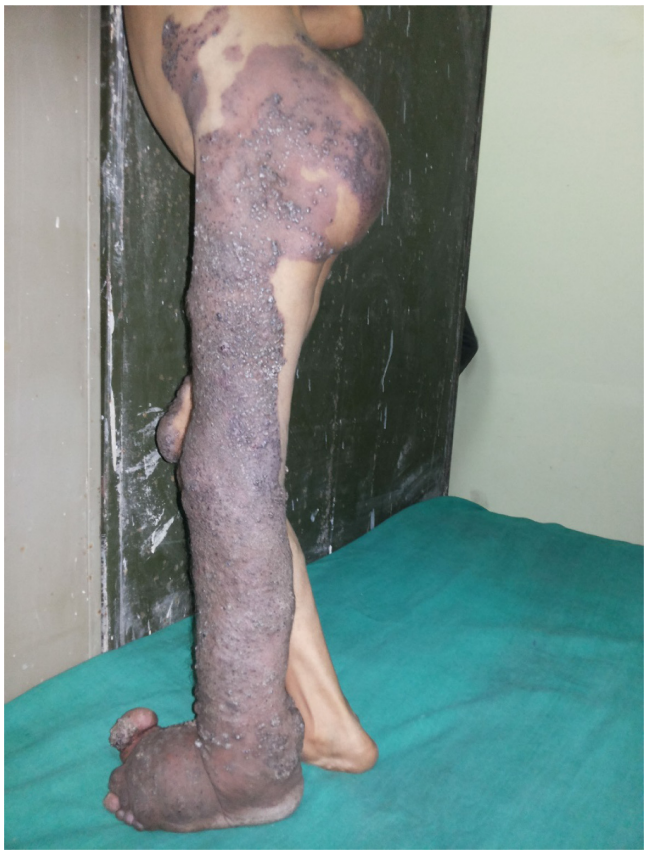

Figure 1. Large port-wine stain on most of the left lower limb. Note multiple discrete and grouped deep red to bluish-black papules, and nodules such as angiokeratomas were present over the port-wine stain. There is marked hypertrophy of the left lower limb.

tissue of the left leg and thigh with no obvious arterial malformation in the lower arm. The patient is now in regular follow-up.

Discussion

KTS or KT is known by various names, including angio-osteohypertrophy syndrome or hemangiectatic hypertrophy.

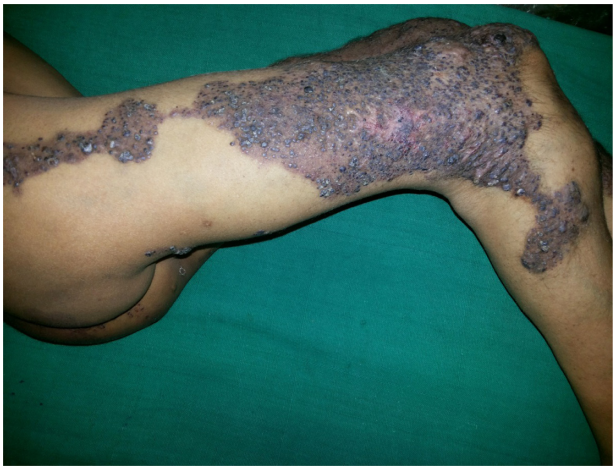

Figure 2. Lesions present over the right lower half of the thigh extending over the knee joint.

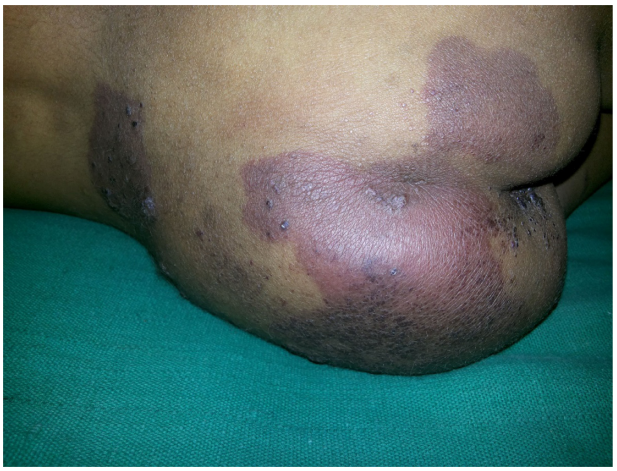

Figure 3. Few lesions were present over the right buttock with involvement of the perianal area. Also note predominance of lymphangiectatic lesions over the perianal area.

The first case was reported in 1900 by Maurice Klippel and Paul Trénaunay in a patient who had unequal growth of delicate tissue and bone along with hemangioma of the skin.[1] The etiology of KTS is unknown, and many theories has been postulated that include a list like paradominant inheritance pattern, somatic mosaicism of an otherwise dominant lethal gene' embryonic disturbed vasculogenesis, and mesodermal defects, and there have been case reports showing various translocations and mutations, but none of them have been proved to have any definite association with the disease. These include genetic translocation at (8;14) (q22. 3; q13),[2] de novo supernumerary ring chromosome 18,[3] terminal deletion 2q37.3,[4] and 5:11 balanced translocation.[5] The incidence of KTS reported is two to five shells per 100,000 live births.[6,7]

Clinical manifestation spectrum. The severity of KTS can be classified based on the type of dysplasia of the blood vessels involved[5]: (1) venous dysplasia; (2) arterial dysplasia; (3) arterial and associated venous dysplasia (a) with no AV-shunt

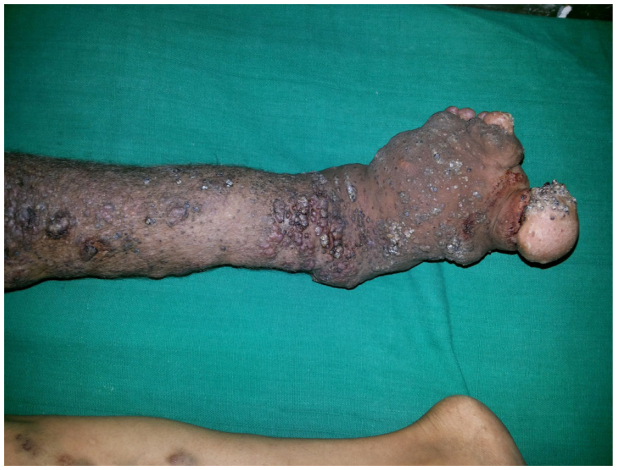

Figure 4. The left foot shows oligodactyly and syndactyly.

and (b) with AV-shunt; and (4) mixed angiodysplasias (a rare form of KTS).

Hypertrophy. Hypertrophy of the affected region of the physical structure is common because of excessive increase in underlying soft tissue and the associated adipose tissue hyperplasia, although bony hypertrophy leading to difference in limb length may also be seen in a few cases.[8] Unusually or rarely, there is inverse KTS, which is characterized by wasting of the affected limb in contrast to hypertrophy, which is usually viewed and is reckoned to be the result of postzygotic recombination.[9]

Capillary malformations. This is the most common cutaneous presentation of KTS. Usually, capillary malformations are seen in the hypertrophied limb, though dermatological changes can be noted in any location of the body. The most common site of capillary malformations is the lower limb and is usually seen in around 95% cases. The dermatological vascular malformation is usually present as a flat, red or purple-colored capillary hemangioma. The overlying skin is usually hard, dry, thickened, and hyperpigmented.[10]

Varicose veins. They are seen predominantly in all patients of KTS with its usual location along the lateral side of the affected arm/branch. Both the superficial and deep venous systems can be affected in KTS with varied manifestations ranging from ectasia of small veins to persistent embryologic veins and large venous malformations of superficial venous systems. Deep venous abnormalities include aneurysmal dilatation, agenesis, hypoplasia, duplications, and venous regurgitation.[10]

Other organ association. The different organs involved are gastrointestinal tract, genitourinary tract, and central nervous system. Bleeding from rectum and bladder is life threatening and is an emergency condition in all the complications of various visceral vascular malformations and has a reported incidence of around 1%.[11] The diverse clinical manifestations include:

1. *Gastrointestinal tract*: It involves bleeding that changes from minor or occult bleeding to massive, life-threatening hemorrhages and Disseminated intravascular consumptive coagulopathy (DIC). The most usual sites of participation are the distal colon and rectum, and esophageal variceal bleeding is also seen.[12] The splenic involvement is discovered in the form of splenic hemangiomas.[13]
2. *Genitourinary tracts*: Its involvement is normally experienced in very serious events. It is characterized by recurrent, painless, and gross hematuria and renal enlargement.[14]
3. *Skeletal manifestations*: These are usually secondary to leg-length differences and a few are dislocations of the ipsilateral hip and scoliosis.[15] The associated developmental defects usually seen are various and include polydactyly,[16] oligodactyly, macrocephaly, blue nevi, pulmonary vein varicosities, cerebral aneurysm,[17] and pulmonary embolism.[18]

Forbes et al described a lawsuit of a 12-year-old son who received an enlarged right lower limb with varicosities. They found extensive superficial and deep venous varices, with dilatation of the right common iliac and external iliac veins in the patient.[19]

Akcali et al described a case of a 14-year-old young woman who was a diagnosed case of KTS with associated multiple port-wine stain-type vascular anomalies and varicose veins involving the upper limb.[20]

In the majority of instances, the diagnosis is done by examination of the patient clinically, but usually, confirmation requires laboratory studies, such as higher D dimer assay, gene analysis of AGGF1, and radiological imaging such as x-ray study of lower limb bones, color Doppler of arteries and veins, MRI, MR angiography, and catheter angiography can be considered. Ultrasound, CT, and MRI show the presence of soft tissue hypertrophy in KTS and can also identify the associated various vascular malformations present throughout the branch. These imaging modalities can also identify the involvement of vascular lesions in the pelvis and abdomen. The complications of KTS, which can be picked up with these diagnostic modalities, include thrombophlebitis, deep venous thrombosis, pulmonary embolism, and congestive heart failure.[21,22]

The management is normally conservative, symptomatic, and medical, and only in a few rare cases, surgical intervention is warranted.[23] The patient needs regular follow-up to the medical personnel and also regular radiological monitoring of one of the affected branches. Several treatment modalities are available and can be used, which include[24]:

- compression stockings for chronic venous insufficiency,
- intermittent pneumatic compression devices,
- flash lamp-pumped pulsed dye laser for port-wine stains,
- surgical correction of varicose veins, and
- epiphysiodesis for orthopedic abnormalities in order to prevent (stop) overgrowing of limb and correction of bone deformity.

Compression therapy has been the backbone of conservative treatment in the course of an elastic garment or compression bandage. This has been shown to have beneficial effect in managing both lymphedema and chronic venous insufficiency. Local wound care, compression dressings, special orthopedic footwear, and lifestyle adjustment may also be asked to supervise activities of daily living and improve the use of the limb.[25] Vascular operations to treat venous insufficiency are mostly unsuccessful because of very high recurrence rate. The ligation and excision of large venous lakes is futile. A less invasive and, therefore, a better solution is either ultrasound-guided foam sclerotherapy (USFS) or steam vein sclerosis (SVS) followed by foam sclerotherapy. The USFS has been presented as a very effective and also minimally invasive ambulatory technique

with minimum pain and has shown indication of excellent results in patients with KTS.[26]

The close differential to KTS is PWS, which needs to be found out. KTS is characterized by the triad of port-wine stain (capillary malformations), varicose veins, and limb hypertrophy, whereas PWS is characterized by varicose veins, limb hypertrophy, and associated AV malformations. The gene mutation involved in KTS is AGGF1, whereas in PWS, it is RASA1. In KTS, abnormalities are in the mesodermal layer, whereas in PWS, they are in both ectodermal and mesodermal layers. The other important marking point is a type of menstruation that is slow in KTS and fast in PWS. With regard to the aspect of prognosis, KTS has a favorable prognosis, whereas it is poor and fatal in PWS.[27]

KTS is usually not life threatening and has a favorable prognosis, but the severity depends on the type of dysplasia of the blood vessels involved. There has been a case report of KTS presenting with life-threatening hematochezia and symptoms of iron deficiency anemia as an outcome of gastrointestinal vascular malformations.[12,28] KTS can also present as renal hemangioma with complicating perirenal hematoma requiring nephrectomy.[29] There has been a case report of pulmonary vascular malformations of KTS leading to thromboembolism[30] and leading to death of the patients.[31]

Conclusion

KTS is a very rare congenital syndrome of vascular malformations and soft tissue and bone hypertrophy. It can involve multiple organ systems, and the patients can have visceral organ complications that are very dreadful complications of KTS. Treatment is normally cautious, and regular follow-up of the patients is to be taken care of.

Author Contributions

Conceived and designed the experiments: DS, SL, AP. Analyzed the data: DS, AP. Wrote the fist draft of the manuscript: DS. Contributed to the writing of the manuscript: SL, AP, SS. Agree with manuscript results and conclusions: DS, SL, AP, SS. Jointly developed the structure and arguments for the paper: SL, DS, AP, SS. Made critical revisions and approved final version: DS, SL, AP, SS. All authors reviewed and approved of the final manuscript.

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