KLIPPEL-TRENAUNAY SYNDROME INVOLVING UPPER LIMB AND CHEST WALL: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract. *The group of congenital limb overgrowth syndromes associated with vascular malformations include various disorders, often with variable clinical expression. Klippel-Trenaunay syndrome is the most common syndrome in this group, compared to other similar disorders such as Proteus, Parkes-Weber, Sturge-Weber, Cobb, Maffucci and CLOVES syndromes. We present a case of a 55-year-old male who presented with swelling, pain, heaviness, numbness and increased local temperature, involving the right upper extremity and the right side of the chest wall and associated with a livid erythema. The patient had several comorbidities including arterial hypertension and ischemic heart disease. He also had a family history of diabetes mellitus. A multidisciplinary team-based treatment approach, including physicians with expertise in various medical and surgical specialties was applied with the patient being “the unifying focus” of all these experts and their efforts. A personal approach tailored to the patient’s preferences was the key to a successful treatment.*

Key words: *Klippel-Trenaunay syndrome, port-wine stain, tissue overgrowth, venous varicosity*

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INTRODUCTION

Klippel-Trenaunay syndrome (KTS) is a very rare congenital vascular malformation defined by triad of a port-wine stain, venous varicosity and progressive overgrowth of the affected extremity [1,2]. Lymphatic abnormalities can often be present and range from hypoplasia to aplasia. Lymphedema can exacerbate limb hypertrophy and venous congestion. This disorder is usually sporadic and associates with mutation in PIK3CA gene [3]. Men are equally or slightly more often affected and the disease has no predilection for race [4]. The vascular malformation is usually limited to a single limb, although multiple limbs can be involved. KTS is also

called angio-osteohypertrophy syndrome or osteohypertrophic angioectasia. Diagnosis is mainly based on clinical signs and symptoms and supported by laboratory and instrumental investigations.

CASE REPORT

A 55-year-old male presented with swelling, pain, heaviness, numbness and increased local temperature, involving the right upper extremity and the right side of the chest wall and associated with an overlying discoloration. The patient reported three episodes of erysipelas on the same limb. The patient had several comorbidities including arterial hypertension and ischemic heart disease, controlled with bisoprolol

and olmesartan medoxomil/hydrochlorothiazide. The patient also had a family history of diabetes mellitus.

Clinical examination revealed a port-wine stain over the right upper limb and hemithorax extending from the base of the neck to the T3 dermatome limited by the midline, with a hypertrophy of the ipsilateral limb (Fig. 1A, B). The other limbs had no abnormalities. Laboratory investigations revealed only increased levels of uric acid – 919 $\mu\text{mol/l}$ (200-420 $\mu\text{mol/l}$) and C-reactive protein – 59.4 mg/l (< 5 mg/l), while the blood count and other biochemical tests were within normal ranges. Histological examination showed dilated capillaries in the upper reticular dermis without an increase in their numbers (Fig. 2). The X-ray examination found no bone hypertrophy but significant soft tissue enlargement was evident (Fig. 3). The difference between both arms was 40 cm at the level of 5 cm above olecranon process. In our patient we observed finger abnormalities like jar grip, which presents with large gap between the thumb and the index finger (Fig. 1C). The treatment with intravenous ceftriaxone 2 g/d for 7 days as well as diclofenac sodium for pain relief was initiated and the patient was discharged with improvement.

DISCUSSION

Klippel-Trenaunay syndrome is a rare congenital disorder that affects one in every 20,000 to 40,000 children [5]. The first description of KTS is presumed to belong to Hilaire in 1832, but was termed on names of French physicians Maurice Klippel and Paul Trenaunay [6]. Although the cause of KTS is still unknown, the leading hypothesis is somatic mutation in PIK3CA gene. This mutation results in an increased expression of the insulin receptor which can cause segmental overgrowth [7]. This syndrome is generally not thought to be hereditary, and the risk of KTS in the offspring of parents with the disease is similar to the general population risk. The syndrome is present at birth or in early childhood and often the only visible sign is port-wine stain [5]. The varicose veins may be congenital but usually present throughout puberty. While the limbs may have unequal size at birth, more often this becomes apparent as the child grows. The soft and/or bone tissue hypertrophy resulting in gigantism of the involved extremity. The involved limb is often painful and may become edematous as was seen in our

Fig. 1. **A** – Port-wine stain over the right upper limb and hemithorax extending from the base of the neck to the thorax, with a hypertrophy of the ipsilateral limb; **B** – the same lesions in profile; **C** – jar grip with large gap between the thumb and index finger and hyperkeratosis and ridges of right palm.

Fig. 2. Dilated capillaries in the upper reticular dermis without an increase in their numbers (H&E stain, x 200).

Fig. 3. The X-ray examination of thorax and right upper limb found no bone abnormalities but significant soft tissue enlargement.

patient. Lower-limb involvement occurs in approximately 95% of patients, while only 5% of patients have upper limb involvement [8-10], as was in our case. Moreover, when the chest is affected, the malformation almost never crosses the midline.

KTS is a progressive disorder and complications may be life-threatening. They include stasis dermatitis, thrombophlebitis, cellulitis [11], limb disparity and more serious sequelae such as thrombosis, coagulopathy, gastro-intestinal bleeding [12], pulmonary embolism [13], aortic aneurism [14] and congestive heart failure [15]. Recurrent cellulitis was a serious medical problem in our patient. Finger deformations are also common in KTS. Furthermore, many of the patients have visceral vascular malformations, oral vascular lesions [1], as well as digital and musculoskeletal abnormalities [16].

The differential diagnosis has to be made on first place with Parkes-Weber syndrome, in which arteriovenous malformations are associated with KTS triad: port-wine stain, varicosities and hypertrophy of the limb [17]. Proteus syndrome is a hamartoma type disorder due to mosaic mutation in AKT1 gene, presented with irregular asymmetric overgrowth of multiple mesodermal body tissue abnormalities as well as varicosities [18]. Maffucci syndrome appears due to somatic mutations in IDH1 and IDH2 genes and presents clinically with enchondromas, venous malformations and spindle cell hemangiomas [19]. CLOVES syndrome is a newly described disorder, caused by mosaic mutations in the PIK3CA gene and characterized by congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal or spinal anomalies [20].

There is no standardized treatment for KTS. Port-wine stains can be treated with pulsed dye or Nd:YAG lasers [21]. Compression therapy and elastic garment are essential for varicose veins and lymphedema. Surgical treatment of tissue overgrowth and venous varicosity with excisions, ligation, stripping, sclerotherapy [22] or endovascular radiofrequency ablation

[23] are effective in some cases. The management should be multidisciplinary and aim to reduce the symptoms and complications of the disease. Targeted therapies with inhibitors of phosphoinositide 3-kinase signaling pathway could be a potential treatment option for KTS patients in future.

In conclusion, we present a case of a 55-year-old male with KTS who had two signs of the triad of this disease. This case serves to highlight the variable presentation of patients with KTS. The prognosis is unpredictable and depends upon the extent of the disease and presence of complications.

Conflict of interest

The authors have nothing to declare.

REFERENCES

1. Miteva LG, Dourmishev AL, Schwartz RA, et al. Oral vascular manifestations of Klippel-Trenaunay syndrome. *Cutis* 1998; 62:171-174.
2. Kihiczak GG, Meine JG, Schwartz RA, et al. Klippel-Trenaunay syndrome: a multisystem disorder possibly resulting from a pathogenic gene for vascular and tissue overgrowth. *Int J Dermatol.* 2006;45(8):883-890.
3. Vahidnezhad H, Youssefian L, Uitto J. Klippel-Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). *Exp Dermatol.* 2016;25(1):17-19. doi:10.1111/exd.12826
4. Sung HM, Chung HY, Lee SJ, et al. Clinical Experience of the Klippel-Trenaunay Syndrome. *Arch Plast Surg.* 2015;42(5):552-8.
5. Jacob AG, Driscoll DJ, Shaughnessy WJ, et al. Klippel-Trenaunay syndrome: spectrum and management. *Mayo Clin Proc.* 1998;73(1):28-36.
6. Klippel M, Trenaunay P. Klippel-Trenaunay syndrome. *Archives Generales de Medicine* 1900; 185:641-72.
7. Lacerda Lda S, Alves UD, Zanier JF, et al. Differential diagnoses of overgrowth syndromes: the most important clinical and radiological disease manifestations. *Radiol Res Pract.* 2014; 2014:947451.
8. Ralph R, Chrispa A. Klippel-Trenaunay syndrome of the upper limb--a rare congenital anomaly. *J Assoc Physicians India.* 2013;61(5):337.

9. Gober-Wilcox JK, Gardner DL, Joste NE, et al. Limb hyperplasia: case report of an unusual variant of Klippel-Trenaunay syndrome and review of the literature. *Cutis*. 2009;83(5):255-262.
10. Rajaonarivony T, Randriamananjara N, Rakotoarisoa AJ, et al. Un cas de syndrome de Klippel-Trenaunay-Weber de la main: description et revue de la littérature. *Ann Cardiol Angeiol (Paris)*. 2005;54(5):289-291.
11. Viljoen D, Saxe N, Pearn J, et al. The cutaneous manifestations of the Klippel-Trenaunay-Weber syndrome. *Clin Exp Dermatol*. 1987;12(1):12-17.
12. Samo S, Sherid M, Husein H, et al. Klippel-Trenaunay Syndrome Causing Life-Threatening GI Bleeding: A Case Report and Review of the Literature. *Case Rep Gastrointest Med*. 2013;2013:813653. doi:10.1155/2013/813653
13. Chu ST, Han YH, Koh JA, et al. A Case of Klippel-Trenaunay Syndrome with Acute Submassive Pulmonary Thromboembolism Treated with Thrombolytic Therapy. *J Cardiovasc Ultrasound*. 2015;23(4):266-270.
14. Böckler D, Erhart P, Haußer-Siller I, et al. Klippel-Trénaunay-Weber syndrome associated with abdominal aortic aneurysm in childhood. *J Vasc Surg Cases*. 2015;1(2):174-176.
15. Gwinn JL, Lee FA. Congestive heart failure secondary to peripheral arteriovenous malformation. Klippel-Trenaunay syndrome. *Am J Dis Child*. 1977;131(1):89-90.
16. McGrory BJ, Amadio PC, Dobyns JH, et al. Anomalies of the fingers and toes associated with Klippel-Trenaunay syndrome. *J Bone Joint Surg Am*. 1991;73(10):1537-1546. doi:10.2106/00004623-199173100-00012.
17. Banzic I, Brankovic M, Maksimović Ž, et al. Parkes Weber syndrome-Diagnostic and management paradigms: A systematic review. *Phlebology*. 2017;32(6):371-383.
18. Turner JT, Cohen MM Jr, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. *Am J Med Genet A*. 2004;130(2):111-22.
19. Prokopchuk O, Andres S, Becker K, et al. Maffucci syndrome and neoplasms: a case report and review of the literature. *BMC Res Notes*. 2016; 9:126.
20. Bloom J, Upton J 3rd. CLOVES syndrome. *J Hand Surg Am*. 2013;38(12):2508-2512.
21. Zini L, Amara N, Graziana JP, et al. Syndrome de Klippel-Trenaunay et hémangiomes vésicaux multiples: traitement par laser Neodymium:YAG. *Prog Urol*. 2001;11(6):1282-1284.
22. Malgor RD, Gloviczki P, Fahrni J, et al. Surgical treatment of varicose veins and venous malformations in Klippel-Trenaunay syndrome. *Phlebology*. 2016;31(3):209-215.
23. Frasier K, Giangola G, Rosen R, Ginat DT. Endovascular radiofrequency ablation: a novel treatment of venous insufficiency in Klippel-Trenaunay patients. *J Vasc Surg*. 2008;47(6):1339-1345.

Accepted December, 2019