Scrotal hemangioma misdiagnosed as a malignant tumor in Klippel-Trénaunay syndrome: a case report and review of the literature

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ABSTRACT

The paper discusses a challenging medical case of a 29-year-old male patient who was diagnosed with a scrotal hemangioma in association with Klippel-Trénaunay syndrome (KTS). In this case, the patient experienced an increase in size and pain in the right scrotum, which was initially suspected to be a malignant tumor of the right testis based on B-ultrasound and magnetic resonance imaging findings. This case is particularly rare and notable because KTS involvement in the scrotum is uncommon in clinical practice, complicating the diagnostic process. The patient had a history of surgical intervention for KTS, which included high ligation of the right great saphenous vein. The case underscores the importance of clinicians being aware of the clinical features of KTS to ensure accurate diagnosis and appropriate management when presented with similar scrotal symptoms. This report serves to highlight the diagnostic challenges and considerations necessary in cases where symptoms may mimic those of more common conditions, such as testicular tumors. (J Vasc Surg Cases Innov Tech 2024;10:101631.)

Keywords: KTS; Klippel-Trénaunay syndrome; Noevus variqueux osteohypertophique; Scrotum hemangioma; Scrotum tumor; Case report

Klippel-Trénaunay Syndrome (KTS) was initially identified by French physicians Maurice Klippel and Paul Trénaunay in 1900. Originally termed "noevus variqueux osteohypertrophique," this condition is characterized by vascular anomalies and limb hypertrophy and is now commonly known as Klippel-Trénaunay Syndrome.[1,2] Recent studies have categorized KTS within the PIK3CA-related overgrowth spectrum, which comprises a group of disorders marked by mixed low-flow vascular malformations and limb overgrowth.[3] KTS is typically diagnosed based on the presence of at least two of the following three criteria: (1) cutaneous vascular nevus (capillary malformation) on the affected limb; (2) limb soft tissue and bone hypertrophy; and (3) varicose veins or venous malformations.[4] This report discusses a case of KTS affecting the genitourinary system, illustrating the diverse manifestations of KTS symptoms and underscoring the importance of awareness and understanding of this complex condition.

CASE REPORT

A 29-year-old male noted a progressive enlargement of the right scrotal mass over 10 years, initially without discomfort. The patient mistakenly believed it to be a normal aspect of scrotal development and, therefore, did not pay it much attention. In September 2020, the patient was diagnosed with KTS and was admitted for high ligation of the great saphenous vein due to varicosity. Over time, he experienced intermittent, dull pain and swelling, exacerbated by physical activity but not radiating to the ipsilateral lower abdomen. The mass's size remained constant regardless of the patient's position or respiratory maneuvers. During the history taking, the patient observed an enlargement of the right testicle and mistakenly believed that a testicle had always been present in the right scrotum. Consequently, the patient repeatedly asserted that there had been no prior abnormalities in either testicle.

Physical examination revealed a drooping right scrotum with an oval, firm mass not clearly separable from surrounding tissues and tender upon palpation. No abnormalities were detected in the left testis. A surgical scar was evident below the right groin. Additionally, the right lower limb appeared swollen and thick with variegated skin texture, pronounced superficial vascular dilations, and localized pigmentation and peeling. Scattered vascular nevi were present (Fig 1).

Laboratory analysis showed normal tumor markers, including alpha-fetoprotein, carcinoembryonic antigen, ferritin, and various carbohydrate antigens (CA125, CA15-3, CA19-9). A 1.5 T magnetic resonance imaging of the testicular region displayed an enlarged right scrotum with mixed patchy signal abnormalities; T1-weighted images showed slightly lower signals compared with slightly higher signals on T2-weighted and diffusion-weighted images. Contrast-enhanced scans revealed minimal enhancement, although tortuous and thickened blood vessels were noted.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2468-4287

https://doi.org/10.1016/j.jvscit.2024.101631

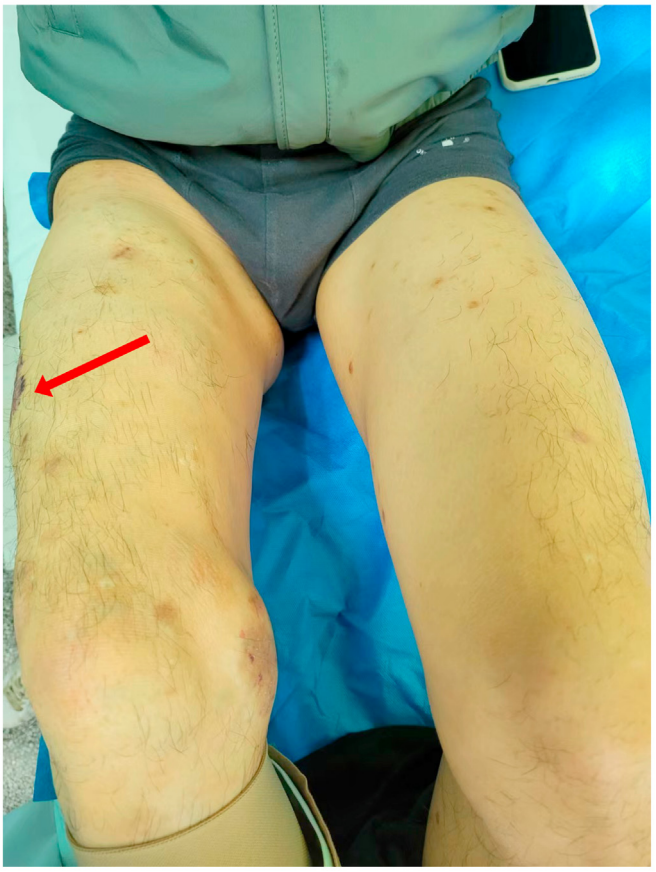

Fig 1. The patient's right lower limb is swollen and bulky; multiple uneven areas can be seen on the skin surface. Multiple superficial blood vessels protruded, dilated, bent, and curled into clusters, and scattered vascular nevus could be seen on the surface.

Further imaging included tortuous and patchy signal abnormalities across the right inguinal area, right iliac fossa, major psoas, gluteus maximus, and right thigh, suggesting varicose veins. The right external iliac vein showed localized stenosis. A chest computed tomography scan identified several pulmonary nodules, likely indicative of inflammatory granulomatous or fibroproliferative lesions. There was also evidence of bone destruction at the sternum and bilateral clavicles. This complex presentation underscores the need to differentiate between vascular and neoplastic lesions in such ambiguous cases. Bilateral lower limb X-rays reveal that the right femur is slightly longer than the left, with localized cortical thickening in the mid-to-lower segment of the right tibia's lateral aspect (Fig 2 and Fig 3).

Due to progressive swelling and discomfort in the scrotum and considering the patient's report of a persistent right testicle since childhood and the examination findings, the possibility of a scrotal tumor and potential bone metastasis could not be dismissed. Consequently, the patient, expressing a preference for surgical intervention and after being cleared of any surgical contraindications, underwent scrotal tumor resection.

During the surgery, an 8 × 7 × 6 cm tumor was found in the right scrotum, firmly attached to the skin and the dartos muscle layer. The surgical team carefully separated the tumor upward toward the inner ring and excised the tumor along with a portion of the scrotal skin. The postoperative assessment revealed no apparent testicular tissue or vas deferens in the right scrotum or inguinal canal, confirming the tumor's adherence to the dartos muscle and skin.

Pathological analysis of the right scrotal mass post-surgery indicated microscopic characteristics consistent with a mixed-type hemangioma. Immunohistochemical testing further confirmed this diagnosis, showing positive markers for smooth muscle actin, vascular endothelial cell (F8), and vascular endothelial cell (ERG), which supported the vascular nature of the tumor (Fig 4).

Three months post-surgery, a semen analysis of the patient indicated no abnormalities. Five months after the initial procedure, the patient returned to our hospital due to varicose veins in his right lower extremity. Subsequently, he underwent surgical resection of cavernous hemangiomas located in his right thigh and right knee.

In this case report, we detail the diagnostic process, treatment plan, and outcomes for a patient. Before the publication of this article, the patient was fully informed that their case details would be used for academic research and public dissemination and expressed understanding and consent. The patient also granted explicit authorization for the publication of their medical images and personal health information. All personal information involved in this case report has been de-identified to protect patient privacy. The patient has signed a written consent form agreeing to the use of their case and images for medical education and research purposes.

DISCUSSION

This case involves a young male exhibiting symptoms characteristic of the triad associated with KTS. Although diagnosing KTS itself is straightforward, determining the nature of the scrotal mass presents complexities. Although numerous cases of KTS with manifestations in the genitourinary and digestive systems have been documented since the syndrome's initial report, they are predominantly noted for bleeding symptoms. Furness and colleagues have reported two cases and reviewed 18 articles encompassing 1174 cases of genitourinary manifestations of KTS.[5] These symptoms generally appear in more severe forms of the syndrome, with superficial vascular malformations typically affecting the trunk, pelvis, and genitals. Among these, scrotal vascular malformations were observed in 12 of 130 patients, as noted across nine studies, representing an incidence of 8.5%. However, instances of testicular absence are rare in the literature. Notably, in male patients with KTS, vascular abnormalities may impair the blood supply to the testicles. If venous malformations or obstructed venous return occur in patients with KTS, it could lead to compromised testicular blood flow, potentially resulting in ischemic injury, testicular atrophy, or even complete testicular loss. Additionally, complications such as

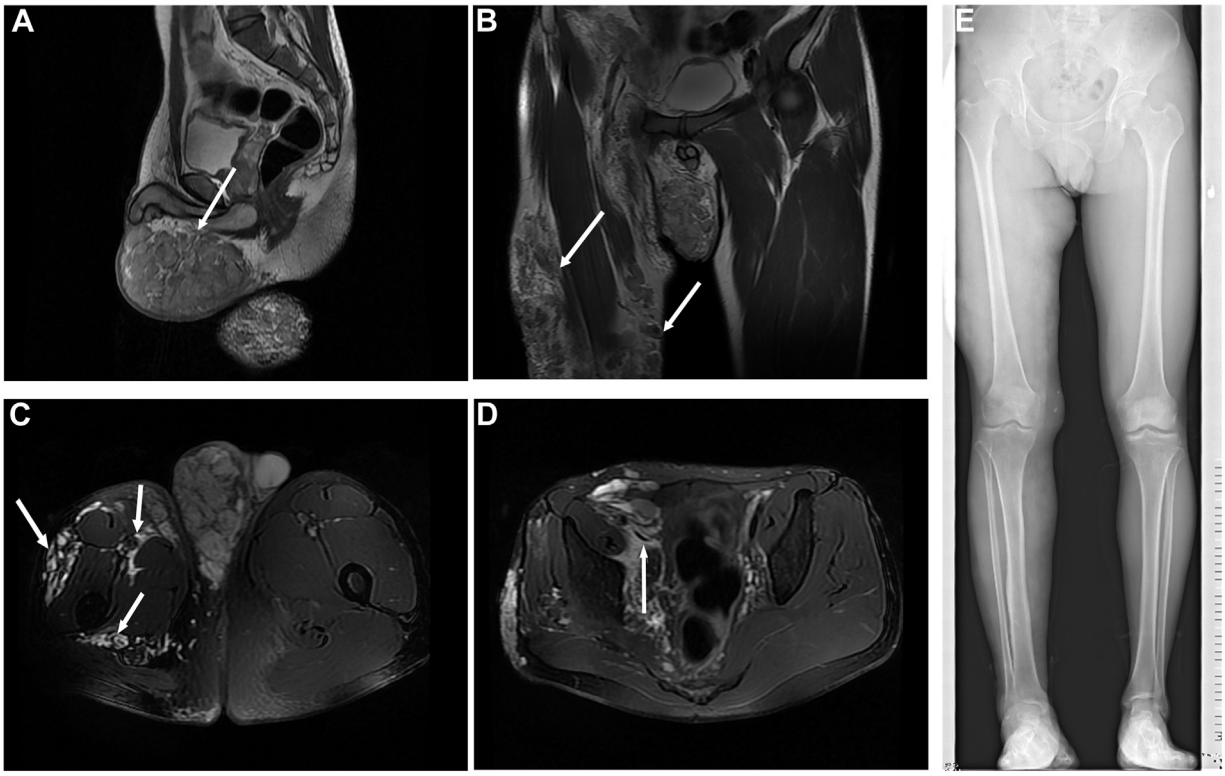

Fig 2. A, A mixed patchy abnormal signal shadow in the right scrotum of the patient. **B** and **C,** Images were divided into the right groin area, right iliac fossa, psoas major, gluteus maximus, proper thigh muscle gap, and right thigh muscle buttocks. Multiple tortuous strips and patchy mixed abnormal signal shadows were seen under the skin. **D,** Local stenosis of right external iliac vein. **E,** The right femur is slightly longer than the left, with localized cortical thickening observed in the mid-to-lower segment of the right tibia's lateral aspect.

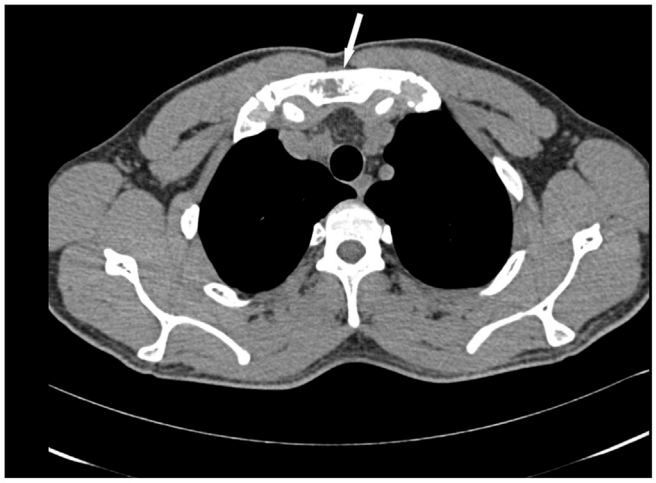

Fig 3. Sternal and bilateral clavicle bone destruction.

thrombosis and venous hypertension may exacerbate this condition. Padhi and colleagues, in 2004, reported a case of KTS with ipsilateral testicular loss,[6] and Biswas et al described a case involving an undescended testis.[7] In this case, the patient's testicular absence is likely closely related to these vascular abnormalities.

KTS affecting the scrotum is a rarity in clinical practice, which limits the understanding of its pathophysiological mechanisms. Recent findings suggest a genetic underpinning for this sporadically occurring disease. Genes responsible for pathological angiogenesis and vascular malformations have been identified, shedding light on the molecular basis of the syndrome. Notably, mutations in the AGGF1 (VG5Q) gene have been observed in patients diagnosed with KTS. This condition is also linked to the PI3K enzyme, which is part of the phosphoinositide 3-kinase pathway encoded by the PIK3CA gene. This pathway plays a crucial role in the growth of embryonic cells in the uterus, categorizing associated diseases under the umbrella of PIK3CA-related overgrowth syndrome. Literature suggests that KTS involving the scrotum may stem from abnormalities in the venous system and lymphatic circulation, leading to hemodynamic disorders in the scrotum. These disturbances can manifest as symptoms like pain, swelling, and pigment changes.[8] Therefore, when two of the three characteristic features of KTS are present—particularly scrotal enlargement or hematuria—there should be a suspicion of KTS involvement in the urogenital system. Diagnosis should primarily be based on clinical signs, supported by imaging studies and pathological confirmation.

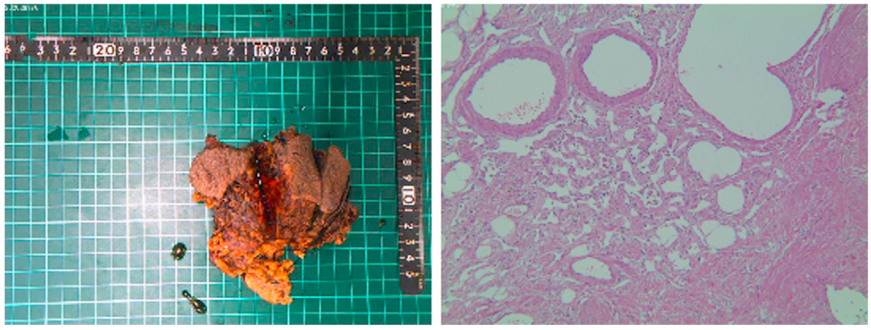

Fig 4. The pathology of the right scrotum tumor.

In this case, the destruction of the sternal bone may be linked to congenital vascular dilatation and hypertrophy. Research indicates that congenital anomalies in arteries, veins, and lymphatic vessels are associated with various bone abnormalities. These can include bone sclerosis, overgrowth, the formation of chondromas, and osteolysis, highlighting the complex interplay between vascular anomalies and skeletal development.[9]

In the differential diagnosis, it is essential to distinguish KTS from several other conditions, including Sturge-Weber syndrome, Parkes-Weber syndrome, lymphatic filariasis, Beckwith-Wiedemann syndrome, Russell-Silver syndrome, and CHILD syndrome.[4] Sturge-Weber syndrome, a neurocutaneous disorder, is characterized by port-wine stains along the ophthalmic branch of the trigeminal nerve, ipsilateral leptomeningeal hemangioma, glaucoma, epilepsy, and intellectual disability. Notably, Sturge-Weber syndrome and KTS can coexist in the same individual.[10] Parkes-Weber syndrome, unlike KTS, is a complex vascular malformation involving both high-flow and low-flow blood vessels, characterized by arteriovenous shunting and limb bone hypertrophy, whereas KTS primarily involves simple low-flow vascular anomalies.[11]

Managing KTS when it involves the scrotum presents significant challenges. Effective evaluation and treatment planning for patients with KTS benefit from advanced imaging techniques such as multi-slice spiral computed tomography and three-dimensional magnetic resonance venography. These tools provide detailed insights into the vascular anomalies associated with the syndrome, facilitating a more comprehensive approach to treatment. Multiple therapeutic options should be considered to tailor the management strategy to the individual needs of the patient, ensuring a holistic and effective intervention.[12]

Drug therapy, including non-steroidal anti-inflammatory drugs and anticoagulants, plays a critical role in managing inflammation and alleviating pain in patients with KTS. Local treatment options such as sclerotherapy and radiotherapy are also viable considerations, depending on the specifics of the case. The treatment plan should be tailored to the individual's condition and developed in collaboration with the patient to ensure a consensus and understanding of the approach. For patients presenting severe venous abnormalities, anticoagulant therapy is recommended due to the increased risk of deep vein thrombosis and pulmonary embolism. Although surgical intervention is necessary for only a minority of cases, it becomes a pivotal option for those experiencing severe deformity or pain, where surgical resection may provide significant relief.[13]

In this case, the patient presented with progressive enlargement of a scrotal mass. During the preoperative medical history review, the patient repeatedly affirmed the presence of a testis in the right scrotum, which made it difficult to completely rule out the possibility of a malignant tumor. Consequently, surgical resection was deemed necessary. Postoperatively, the pathology confirmed the mass as a vascular anomaly rather than a malignancy. The surgery not only alleviated the patient's scrotal pain but also dispelled his concerns about a potential testicular tumor. The results of the semen analysis indicated normal semen quality, suggesting that the surgery did not negatively impact the function of the remaining testicle. However, because no preoperative semen analysis was conducted, we cannot conclusively determine the positive effect of surgical intervention on the fertility of patients with KTS.

Prognosis and potential complications are critical considerations in treating KTS when it involves the scrotum. The prognosis largely depends on the severity of the vascular malformations associated with KTS. Although early diagnosis and intervention can mitigate symptoms, these malformations may continue to develop, leading to ongoing overgrowth and worsening venous insufficiency. Additionally, acute hemorrhage from gastrointestinal malformations can result in significant blood loss, and, if untreated, pose a mortal risk. Recurrent deep vein thrombosis further increases the likelihood of potentially fatal pulmonary embolism. Moreover, complications such as deep vein thrombosis, infection, and ulcers can significantly impair the patient's quality of life.[14] Therefore, the possibility cannot be excluded that

testicular vascular abnormalities and deep vein thrombosis could lead to ischemia and necrosis of testicular tissue, further exacerbating chronic pain and discomfort. Although the efficacy of testicular vein embolization has been extensively studied and applied in the treatment of varicocele and pelvic congestion syndrome, there is limited literature on its use in patients with KTS. Patients with KTS often present with more complex venous malformations and abnormal blood flow patterns. Currently, research on the outcomes of testicular vein embolization in patients with KTS remains insufficient, which may impact the procedure's success rate and its long-term efficacy. Ongoing research is essential to enhance the understanding of the pathogenesis and to improve the diagnostics of KTS, particularly when it affects the scrotum, to develop more effective treatments.

DISCLOSURES

None.

REFERENCES

1. Klippel M, Trenaunay P: Noevus variqueux osteohypertrophique. J des Praticiens 14:65, 1900 (abstr).
2. Klippel M, Trenaunay P: Noevus variqueux osteohypertrophique. Arch Gen Med Tome 111: 641, 1900(b).
3. Vahidnezhad H, Youssefian L, Uitto J. Klippel–Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). *Exp Dermatol*. 2016;25:17–19.
4. Wang SK, Drucker NA, Gupta AK, Marshalleck FE, Dalsing MC. Diagnosis and management of the venous malformations of Klippel-Trénaunay syndrome. *J Vasc Surg Venous Lymphat Disord*. 2017;5:587–595.
5. Furness PD, Barqawi AZ, Bisignani G, Decter RM. Klippel-Trénaunay syndrome: 2 case reports and a review of genitourinary manifestations. *J Urol*. 2001;166:1418–1420.
6. Padhi T, Mishra S, Sirka CS. Klippel–Trenaunay syndrome: association with absence of ipsilateral testis. *Indian J Dermatol Venereol Leprol*. 2004;70:379–380.
7. Biswas K, Sarkar AK, Sarkar S, Mukhopadhyay B, Ganguly S. Klippel Trenaunay Weber syndrome associated with abdominal hamartoma with undescended testis. *Indian Pediatr*. 1995;32:95–99.
8. Harnarayan P, Harnanan D. The Klippel-Trénaunay syndrome in 2022: Unravelling its genetic and molecular Profile and its Link to the limb overgrowth syndromes. *VHRM*. 2022;18:201–209.
9. Kessler HB, Recht MP, Dalinka MK. Vascular anomalies in association with osteodystrophies?A spectrum. *Skeletal Radiol*. 1983;10:95–101.
10. Sakaguchi Y, Takenouchi T, Uehara T, Kishi K, Takahashi T, Kosaki K. Co-occurrence of Sturge–Weber syndrome and Klippel–Trenaunay–Weber syndrome phenotype: consideration of the historical aspect. *Am J Med Genet A*. 2017;173:2831–2833.
11. Abdel Razek AAK. Imaging findings of Klippel-Trenaunay syndrome. *J Comput Assist Tomogr*. 2019;43:786–792.
12. Bastarrika G, Redondo P. Indirect MR Venography for evaluation and therapy planning of patients with Klippel-Trénaunay syndrome. *Am J Roentgenol*. 2010;194:W244–W245.
13. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-trénaunay syndrome: spectrum and management. *Mayo Clin Proc*. 1998;73:28–36.
14. Asghar F, Aqeel R, Farooque U, Haq A, Taimur M. Presentation and management of Klippel-Trenaunay syndrome: a review of Available Data. *Cureus*. 2020;12:e8023.

Submitted May 14, 2024; accepted Aug 23, 2024.