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Ocular manifestations of **Klippel-Trenaunay** Syndrome: A Case Report

Lara Linhares Pierre, Lucas Linhares Pierre, Erika Teles Linhares Pierre, Virna Fonteles de Sousa Lima, Paulo de Tarso Ponte Pierre-Filho

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CASE REPORT

RESUMO

A síndrome de Kippel-Trenaunay (SKT) é uma doença congênita esporádica, cujo diagnóstico clínico se dá pela presença de duas características da sua tríade clássica: manchas vinho do porto, varizes e hipertrofia óssea e/ou de tecidos moles. Mutações gênicas da subunidade catalítica da fosfatidilinositol-4,5-bisfosfato 3-quinase também foram identificadas nesta condição, sendo, portanto, classificada como espectro de crescimento excessivo relacionado ao PIK3CA. Alterações oculares relacionadas à SKT são incomuns e podem incluir anormalidades vasculares orbitárias, da íris, da retina, da coroide e do nervo óptico. Relata-se o caso de uma criança com SKT encaminhada por um clínico geral para exame oftalmológico. Exame revelou uma lece coloraçãoo avermelhada na face esquerda. Para evitar erros no manejo, é importante reconhecer a síndrome. Como múltiplos órgaõs estão envolvidos na SKT, cuidado multidisciplinar pode ser necessário para controlar suas complicações e otimizar os resultados.

Descritores: Síndrome de Klippel-Trenaunay, Manifestações oculares, Malformações vasculares, Manchas vinho do porto,

ABSTRACT

Klippel-Trenaunay syndrome (KTS) is a sporadic congenital disorder, which is clinically diagnosed by the presence of two features of its classical triad of port-wine stains, varicose veins and bone and/or soft tissue hypertrophy. Mutations in the Phosphatadylinositol-4-5-biphosphate 3 Kinase Catalytic subunit (PIK3CA) gene have also been identified in this condition, therefore, it is classified as a PIK3CA-related overgrowth spectrum . Ocular changes associated with KTS are uncommon and may include vascular, orbit, iris, retina, choroid and optic nerve abnormalities. A case involving a child with KTS referred from a general physician to ophthalmologic examination is reported. Examination revealed a faint reddish discolouration over the left face. To avoid errors in management, it is important to recognize the syndrome. Because multiple organs are involved in KTS, a multidisciplinary care can be necessary to manege its complicattions and optimize overall outcomes.

Keywords: Klippel-Trenaunay syndrome, Ocular manifestations, Vascular malformations, Port-wine stain, Case report.

Instituição afiliada:
[1] School of Medicine Uninta, Sobral, Ceará, Brazil.
[2] Pierre Ophthalmology Clinic, Sobral, Ceará, Brazil.

[*]Corresponding author: Paulo de Tarso P. Pierre-Filho, Av. Gerardo Rangel, 803 ap.1400 Sobral - CE, Brazil CEP:62042-240. Email:paulopierre@hotmail.com

INTRODUCTION

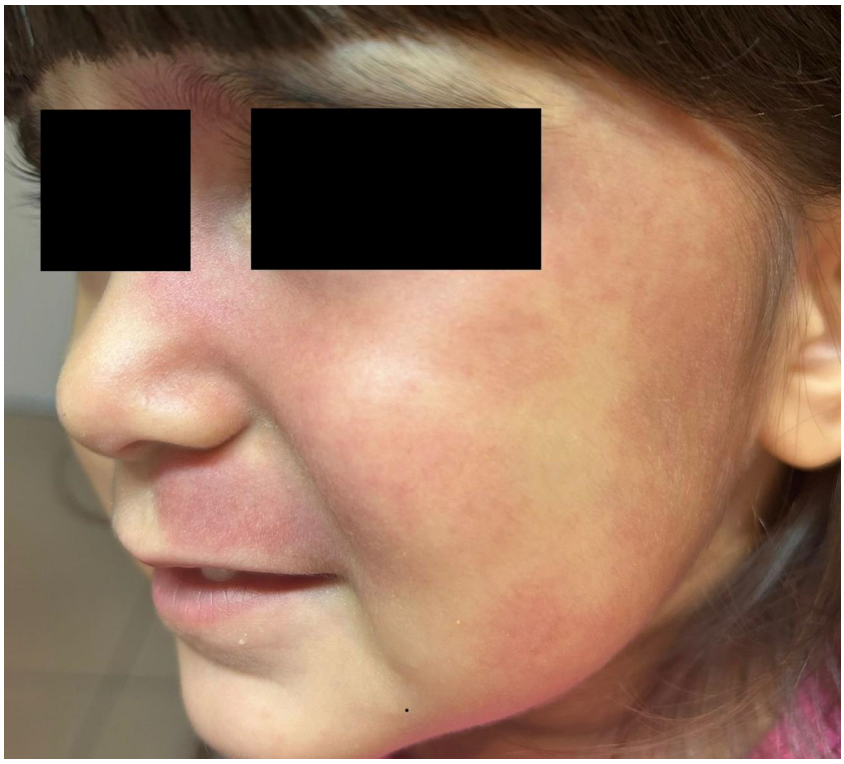
Klippel-Trenaunay Syndrome (KTS) is a rare congenital phakomatosis clinically characterized by triad: cutaneous nevi (port-wine stains), venous abnormalities, and hemihypertrophy of bones and soft tissues, usually involving one of the extremities. Diagnosis is made if at least two of the three classic signs are present. KTS was first described in 1900 by two French physicians Klippel and Trenaunay, under the name of "naevus varicosus osteohypertrophicus" [1]. This syndrome has an incidence estimated at around 2–5 in 100,000 with no race, sex or geographic area predilection [2]. Recognition is usually possible at birth or early childhood, and evaluation and treatment are important because morbidity may be minimized.

Although the exact etiology of KTS remains indistinct, it is thought to be secondary to abnormality of mesodermal tissues in embryologic development. Most cases of KTS are sporadic and no causative gene or etiology has been firmly established. The syndrome has usually a benign course, but serious complications involving various organs, such as pulmonary, gastrointestinal and genitourinary organs, as well as nervous system, may be observed [3]. Reported ophthalmological features include conjunctival, retinal, choroidal, and orbital varicosities, iris coloboma and heterochromia, cataracts, neuro-ophthalmologic manifestations, strabismus and secondary glaucoma [4-7]. Here, we have discussed a patient previously diagnosed with KTS referred from a general physician to the clinic for suspected ocular abnormalities.

CASE REPORT

A 3-year-old girl was referred to our service for ophtalmologic evaluation. The child was born following uncomplicated vaginal delivery at full term, with a discrete asymmetry, with a bigger left leg and foot. On examination, the patient had a red-colored patch (port-wine stain) on the left face, extending to the midline (Figure 1). There was no history of medication use. Laboratory work-up were normal. She had no family history of similar disorder. The remaining general and neurological physical

examination were normal. Her visual acuity was 20/25 in both eyes (OU). Intraocular pressure measured by Perkins tonometer was 14mmHg in the right eye and 16mmHg in the left eye. Pupils were equal and reactive without an afferent pupillary defect, and extraocular movements were normal. Corneal topography revealed normal pattern bilaterally. Anterior segment examination was unremarkable. Fundus findings were apparently normal in OU (Figure 2). The hematologic, biochemical, and urinary laboratory tests were normal. Abdominal ultrasound, cranial and orbital magnetic resonance revealed no abnormality. As there were no ophthalmologic manifestations of posterior segment or optic nerve, the patient did not require specific treatment. Regular follow-up was recommended.



F**igure 1.** Port-wine stains in the left hemiface.

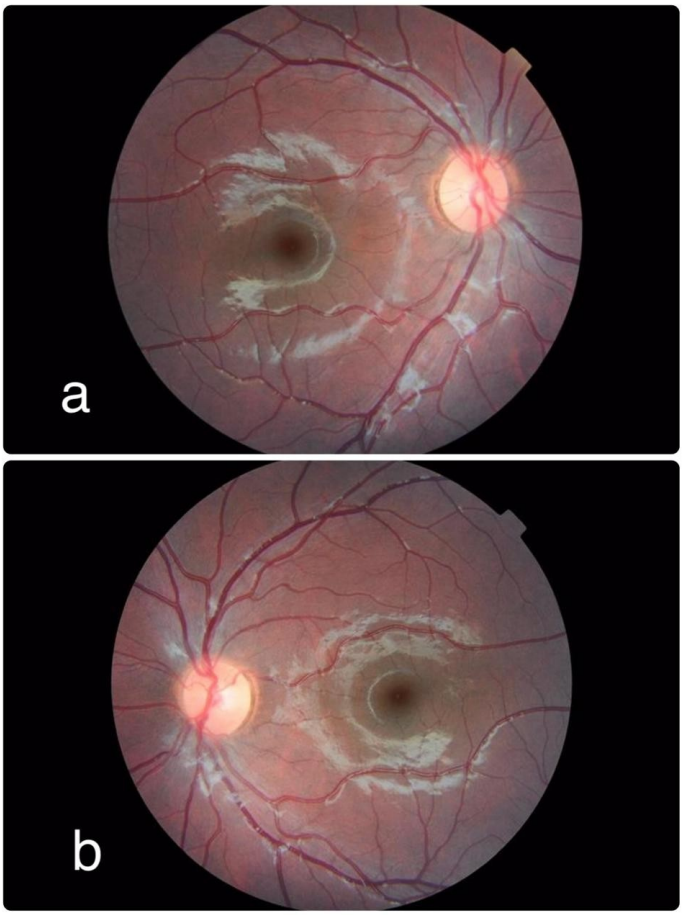


Figure 2. Funduscopy showed optic discs, retina and vessels with a normal appearance.

DISCUSSION

KTS is a sporadic condition caused due to somatic phosphatidylinositol-4,5 bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations and it has been included in the PIK3CA-related overgrowth spectrum. It has been postulated that the mechanism of malformation and overgrowth during embryogenesis is due to the alteration of multiple signalling pathways including the insulin-like growth factor, vascular endothelial growth factor, and fibroblast growth factor path ways [8], leading to capillary, venous and lymphatic malformations. Klippel–Trenaunay syndrome manifests both overgrowth and vascular malformations.

KTS is a clinical diagnosis and often diagnosed at birth or childhood. The phenotypic spectrum is variable, with clinical manifestations ranging from mild cutaneous lesions to severe limb asymmetry and functional impairment. In the present case, port-wine stains and soft-tissue hypertrophy were present at birth. Varicose veins

generally become prominent at a later stage and progress until adolescence, reflecting hormonal influence over vascular proliferation. The main differential diagnoses are Sturge-Weber syndrome (SWS), Parks Weber Syndrome, Maffucci syndrome, Proteus syndrome, Russell-Silver Syndrome, and other capillary malformations not associated with any syndrome [6,9].

A study of 252 patients with KTS (136 females and 116 males) found the classic triad in 63% of cases, and two of the three features were foud in 37%. Capillary malformations in the form of port-wine stains were found in 98% of patients, whereas 72 % of the patients had atypical veins and 67 % had soft tissue hypertrophy [10]. Another study conducted with 144 patients found that hemangioma was present in 95.1%, varicosity in 76.4%, and hypertrophy of the soft tissues or bones in 93.1% [11].

Ocular involvement is variable and there is no epidemiologic data revealing its prevalence among KTS patients. The most common ophthalmological alterations encountered in the KTS are choroidal hemangiomas similar to those described for the SWS. They are often ipsilateral to a facial cutaneous hemangioma. Glaucoma, also frequently observed, has been associated with malformations of the anterior chamber angle, vascular malformations or raised episcleral venous pressure, leading to aqueous obstruction. The incidence of associated glaucoma is believed to be lower thas SWS, estimated betwwen 50-70%. Treatment may be challenging as the disease can be refractory, unresponsive to medical and surgical management [8].

The facial port-wine stain is a common characteristic of the SWS and KTS and the association between these two rare phakomatoses have been reported [8]. There is a suggestion that SWS and KTS are the same disease with different manifestations, but it should be considered as separate entities. The pathogenesis of port-wine stain remains unclear, but it is linked to progressive ectasia of the superficial cutaneous vascular network, and there is no malignant. The lesion often start out looking pink at birth and, into adulthood, tend to become thicker and darker violaceous color color as a result of progressive vascular ectasia. The lesions may appear anywhere in the body but the face is vastly more affected (90%), as observed in our patient, followed by the neck, trunk, legs, and arms [12].

Retinal vascular abnormality such as macular telangiectasis, retinal dysplasia and retinal arteriovenous communications also have been reported in patients with KTS [7]. Brod et al reported a young girl with KTS who had bilateral, exudative, outer retinal vascular masses involving the peripheral fundus in one eye and the foveal area in the other eye [13].Good and Hoyt [14] reported a case of a 10-year-old girl with KTS that had enlargement of optic nerve. Olcaysu et al. [15] present a 17-year old boy with KTS that had unilateral mature cataract and vitreoretinopathy. Spoor et al. [16] described an 18-year-old girl with KTS that had bilateral optic nerve meningiomas. Bothun et al.[17] reported a 16-year-old girl with KTS who was found to have bilateral optic nerve and chiasmal gliomas, optic disk drusen, and acquired myelination of the retinal nerve fiber layer. Optic nerve hypoplasia and tilted optic nerves associated with endocrine abnormalities was reported by Lambert et al. [18].

Patients with KTS are managed symptomatically and require multidisciplinary approach involing various medical specialties. Treatment plans are individualized to avoid life-threating complications. Recently, targeted therapies such as PIK3CA inhibitors have emerged as treatment options for more severe cases [19]. These inhibitors can block abnormal vascular formation and proliferation, potentially alleviating symptoms and improving disease prognosis. Our patient's ocular manifestation were mild, with the presence port-wine stain affecting the face and eyelid region. As there were no signs of cataract, retinal or choroidal neovascularization and no evidence of glaucoma, we suggested regular follow up, including ophthalmic examination and IOP measurements.

CONCLUSION

Our patient presented with port-wine stain on the left side of the face, soft tissue hypertrophy of the left leg, which were compatible with Klippel- Trenaunay syndrome. This case emphasizes the need for vigilante monitoring of ocular manifestations in KTS patients. Physicians recognizing early signs of this condition is critical for improving long-term patient outcomes. Patients diagnosed with KTS or other forms of mesodermal phakomatoses should have an ophthalmologic assessment as soon as possible to

optimize outcomes and improve quality of life. Further research is needed to enhance treatment strategies for this rare condition.

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Research Ethics Committee Approval: We declare that the patient approved the study by signing an informed consent form and the study followed the ethical guidelines established by the Declaration of Helsinki.

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Conflicts of Interest: The authors declare no conflicts of interest.

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