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Klippel-Trenauney syndrome with axillary hyperhidrosis

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Abstract

Klippel-Trenaunay syndrome (KTS) is a rare, clinically variable congenital disorder involving capillary malformations, soft tissue or bone hypertrophy, and venous malformations or varicose veins. We report a 28-year-old man who presented with a hypertrophic right arm as well as markedly increased ipsilateral axillary hyperhidrosis and erythematous patches on the back, chest, and arm. This case of KTS is unusual because our patient presented with a markedly increased unilateral axillary hyperhidrosis ipsilateral to the hypertrophic limb.

Keywords: Klippel-Trenauney syndrome, hyperhidrosis, AKT, PI3K

Introduction

Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder characterized by the triad of capillary malformations such as port wine stains, soft tissue or bone hypertrophy involving limb asymmetry, and venous malformations or varicose veins [1-5]. Complications of delayed diagnosis of KTS include thrombophlebitis, pulmonary embolism, stasis dermatitis, cutaneous ulcerations, and bleeding [6].

Case Synopsis

A 28-year-old man presented to our dermatology clinic for treatment of red bumps on his right arm and back that occasionally bled when irritated. He had similar lesions cauterized in the past, which improved the bleeding. The patient stated the bumps had been present for years and had not grown in size. They were not painful or itchy. In addition, the patient reported axillary hyperhidrosis present for several years that was markedly pronounced on the right side. He reported that aluminum chloride hexahydrate had failed to improve hyperhidrosis in the past but he had responded well to Botox injections in the past.

On examination, we found several erythematous, well-demarcated patches in a somewhat blashkoid pattern on the upper right back, chest, and arm as well as a few scattered cherry angiomas. The patches were present since birth. We also noted more notable hyperhydrosis on the right axilla compared to the left. The length and girth of the right arm were mildly increased compared to the left (**Figure 1**). The patient stated that he was previously told the patches were port wine stains. He previously tried pulsed dye laser treatment to reduce these patches. However, he found it extremely painful and it was not effective. The patient was not bothered by the patches. He confirmed that the right arm was longer, stronger, and colder than the left arm.

For treatment of hyperhidrosis, Botox was administered to both axillae. Upon follow-up one-month post Botox, the patient reported significantly reduced hyperhidrosis on both axillae. Electrocautery to five cherry angiomas was performed, as requested by patient. To address the port wine stain with limb length discrepancy, work-up in vascular anomalies clinic was recommended. Review of systems was negative, with no palpitations, chest pains, or any difficulty with exercise. There was no family history of vascular lesions or hyperhidrosis.

On magnetic resonance imaging of the right upper arm and chest, the great vessels, superior vena cava,

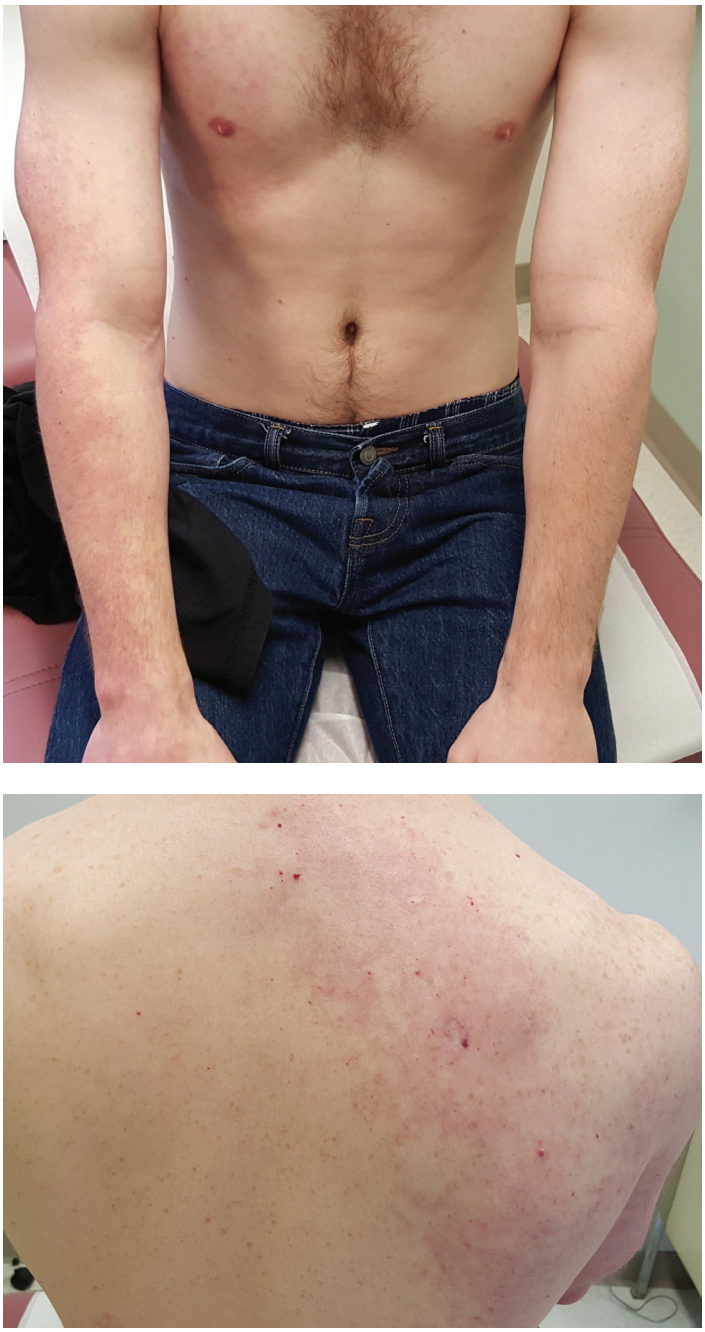

Figure 1. *(Top) Port-wine stain and on the right arm and chest. Hypertrophy of the right arm was also present. (Bottom) Port-wine stain and scattered cherry angiomas on the right upper back.*

and brachial, cephalic, and basilic veins appeared normal. No thrombus, atriovenous shunting, venous malformation, or collateral vessels were detected. The right subclavian and axillary veins were poorly visualized.

Case Discussion

KTS is often associated with three symptoms [7, 8]: cutaneous vascular malformation (birthmark), superficial venous varicosity, and hyperplasia of soft tissue and bone of the affected limb. In our patient, two of the three criteria were present.

Diagnosis is based on the classic triad with absence of arteriovenous shunting by imaging, which differentiates it from Parkes Weber syndrome, an important condition in the differential diagnosis. Doppler and duplex ultrasound are usually necessary to determine the type and severity of the vascular malformation. Furthermore, D-dimer level ≥ 500 mcg/ml has been noted to be highly specific for the diagnosis of venous malformations, differentiating KTS from Parkes-Weber syndrome [9]. The etiology of KTS has not yet been elucidated. Servelle proposed that obstruction or atresia of the deep veins in the leg produces chronic venous hypertension, which causes port-wine stains, varicose veins, and limb hypertrophy [10]. Other authors have hypothesized that KTS is a mesodermal disorder and that the deep vein abnormalities are part of the syndrome, but not its cause [11]. Defects of the angiogenic factor VG5Q [12], RASA1 mutations [13], and de novo supernumerary ring chromosome 18 have also been detected in patients with KTS [14]. More recently, mosaic activating mutations in PIK3CA were discovered in patients with KTS [15, 16].

Although dermatologists generally regard KTS as a distinct syndrome, Vahidnezhad et al. recently postulated that KTS belongs to the PIK3CA-related overgrowth spectrum (PROS) as several KTS patients were noted to have somatic mutations in the PIK3CA gene [17]. Indeed, heterozygous gain-of-function mutations in components of the PI3K-AKT pathway have now been identified in syndromes with features similar to KTS, such as Proteus syndrome-AKT1, CLOVES syndrome, megalencephaly-capillary malformation (MCAP) syndrome, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome, and mosaic overgrowth with fibroadipose hyperplasia [15, 18, 19].

We are presenting this case because of its rare coexistence with marked pronounced ipsilateral axillary hyperhidrosis and to suggest that the PIK3CA-AKT pathway may be causing the hyperhidrosis. Although KTS is associated with many symptoms mentioned above, hyperhidrosis has not previously been reported in KTS patients. In 1981, Sakai et al. reported hyperthermia without hyperhidrosis in

the hypertrophic limbs in a 3-year-old KTS patient [6]. However, our patient's KTS may be unrelated to hyperhidrosis. Some causes of unilateral hyperhidrosis are trauma, tumor, stroke, idiopathic, Pourfour du Petit syndrome, and Holmes-Adie syndrome.

Mounting evidence has shown the association between the PI3K/AKT pathway and KTS, but our literature search shows that PI3K/AKT pathway may also be linked to eccrine gland anomalies including hyperhidrosis. An increased expression of p-AKT1/2/3 was linked to proliferation of human eccrine sweat gland epithelial cells (hESGc) and inhibition of its apoptosis [20]. The eccrine glands of axilla are derived from embryonic ectoderm and the formation of the sweat gland requires an induction between epithelial cells and mesenchyma. Since activation of the PI3K/AKT pathway has an important role in epithelial-mesenchymal transition (EMT), we postulate that our KTS patient's hyperhidrosis is related to over-induction of sweat glands secondary to an overactive PI3K/AKT pathway [21-23]. Mutations of PIK3CA and AKT-1 have been reported in apocrine-eccrine carcinomas and other tumors [24, 25] such as eccrine angiomatous hamartoma, tufted angioma, and with a nevoid proliferative condition that shows increased numbers of eccrine glands and dilated vascular channels in the deep dermis and subcutaneous tissue [26].

Increased AKT signaling can explain both overgrowth and vascular malformation in KTS. AKT is the key signaling protein of the PI3K/AKT signal channel. It mediates cell growth and proliferation, cell movement and invasion, and cell apoptosis that leads to skeletal muscle hypertrophy and general tissue growth in KTS. AKT also is found to be involved with angiogenesis, which is coincidentally thought to be increased in KTS. For example, AKT1 deficient mice displayed inhibited physiological angiogenesis and enhanced pathological angiogenesis [27]. Moreover, KTS patients have shown a higher incidence of cerebral cavernous malformations, a common vascular malformation of the brain, associated with abnormal angiogenesis [28].

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