Limb Hyperplasia: Case Report of an Unusual Variant of Klippel-Trenaunay Syndrome and Review of the Literature

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The estimated time to complete this activity is 1 hour.

GOAL

To understand Klippel-Trenaunay syndrome (KTS) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Differentiate generalized and localized somatic overgrowth syndromes.
2. List the classic triad of symptoms of KTS.
3. Identify the differential diagnosis for KTS.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and generalists.

CME Test and Instructions on page 263.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: April 2009.

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Klippel-Trenaunay syndrome (KTS) is a rare disorder involving a triad of cutaneous capillary malformations (port-wine stain), varicose veins or venous malformations, and bony or soft tissue hyperplasia of an extremity. It is one of many heterogeneous disorders known as overgrowth syndromes that are characterized by either generalized or localized somatic overgrowth. Overgrowth syndromes each have unique clinical, behavioral, and genetic features, but some of

these features overlap, causing diagnostic difficulty. Cutaneous manifestations, however, can be key to distinguishing the various syndromes. We present a patient with an unusual variant of KTS consisting of right upper extremity hyperplasia, lymphedema, and cutaneous and visceral lymphangiomas. We review several closely related syndromes and discuss the differential diagnosis of limb hyperplasia.

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Overgrowth syndromes are a heterogeneous group of disorders characterized by either generalized or localized somatic overgrowth. Overgrowth is present either at birth or may occur postnatally, with some combination of increased weight, increased length, and/or increased head circumference.[1] Most of the overgrowth syndromes have associated anomalies; mental deficiency often is a feature and development of tumors is a common characteristic. Generalized somatic overgrowth disorders include Simpson-Golabi-Behmel syndrome, Sotos syndrome, and Weaver syndrome. Localized somatic overgrowth disorders include Klippel-Trenaunay syndrome (KTS), Proteus syndrome, isolated hemihyperplasia (hemihypertrophy), Parkes Weber syndrome, and Maffucci syndrome. Beckwith-Wiedemann syndrome is characterized by both generalized and localized somatic overgrowth.[2]

Overgrowth syndromes are classified by age at onset (prenatal and postnatal) and are further categorized as primary or secondary, representing intrinsic cellular hyperplasia as seen in some of the congenital overgrowth syndromes or overgrowth caused by humorally mediated factors outside the skeletal system (eg, diabetic macrosomia), respectively.[3] Diagnostic categorization of these disorders often is difficult because they share common clinical features. Our discussion focuses primarily on the differential diagnosis of limb hyperplasia with concurrent cutaneous and visceral lesions.

Case Report

In April 2004, an 8-year-old girl with a medical history of congenital limb hyperplasia presented to the dermatology department with areas of dyspigmentation over her right arm and right scapula as well as "blisters" on her right hand. Her adoptive mother stated that the "blisters," which were weeping, painful, and resistant to multiple treatments, developed at approximately 5 years of age. Right upper extremity hyperplasia was first noted at approximately 2 months of age by her adoptive mother and was confirmed on comparative radiography of her arms, which showed that her right humerus was longer than the left. No skin changes or soft tissue hyperplasia were noted at that time; however, at 2 years of age, she began to develop enlargement of her right upper extremity. Magnetic resonance imaging of the right hand showed a normal marrow signal with normal bony architecture, marked soft tissue thickening over the dorsal aspect of the metacarpals, and increased fluid on short TI inversion recovery sequence suggesting edema. At 7 years of age, multiple splenic lesions were noted on abdominal computed tomography and subsequently biopsied because of concern for neoplasia. The lesions were capillarylike vascular proliferations that proved to be splenic lymphangiomas by staining with D2-40, an immunohistochemical marker specific for lymphatic endothelium (Figure 1). She had no other remarkable medical history and no evidence of a learning disability or mental deficiency.

On physical examination, she had substantial hyperplasia of the right hand, which measured 1 cm longer than the left hand from the wrist crest to the fingertips (Figure 2). There were hypopigmented macules over her right forearm following Blaschko lines. Surrounding the dorsal and palmar aspects of the first, second, third, and fourth digits were multiple discrete areas of hyperkeratotic verrucous or frogspawn-like plaques (multiple, grouped, small vesicles filled with clear serosanguineous fluid) with tiny areas of punctate hemorrhage (Figure 3). Additionally, the patient had an area of hyperpigmentation over her right scapula. Her lower extremities were symmetric. There were no varicosities appreciated. A 2×3-cm capillary vascular malformation was present on her left buttock. The remainder of her physical examination was unremarkable.

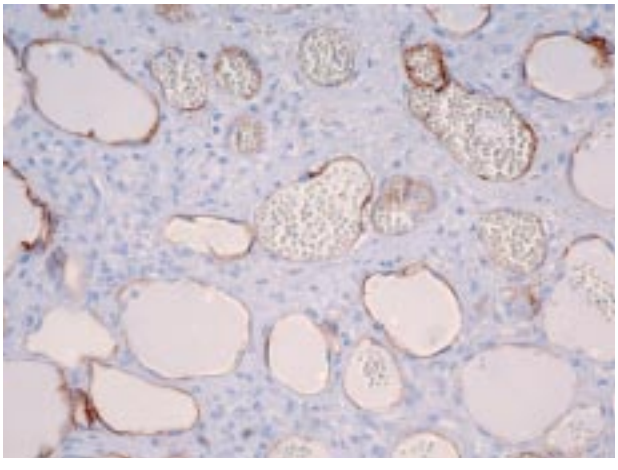

Figure 1. Immunohistochemical staining with D2-40 demonstrates capillarylike vascular formations of splenic lymphangiomas (original magnification ×40).

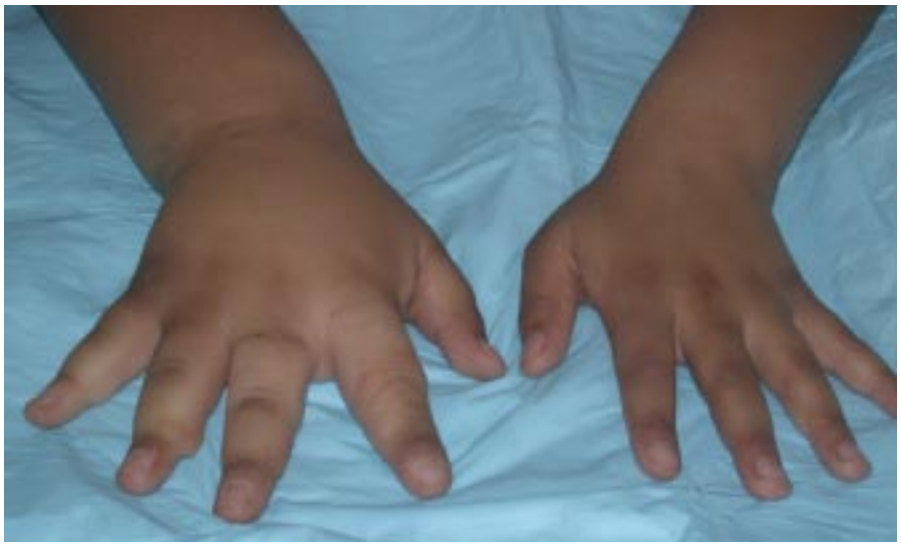

Figure 2. Comparison of patient's hands demonstrating right hand hyperplasia.

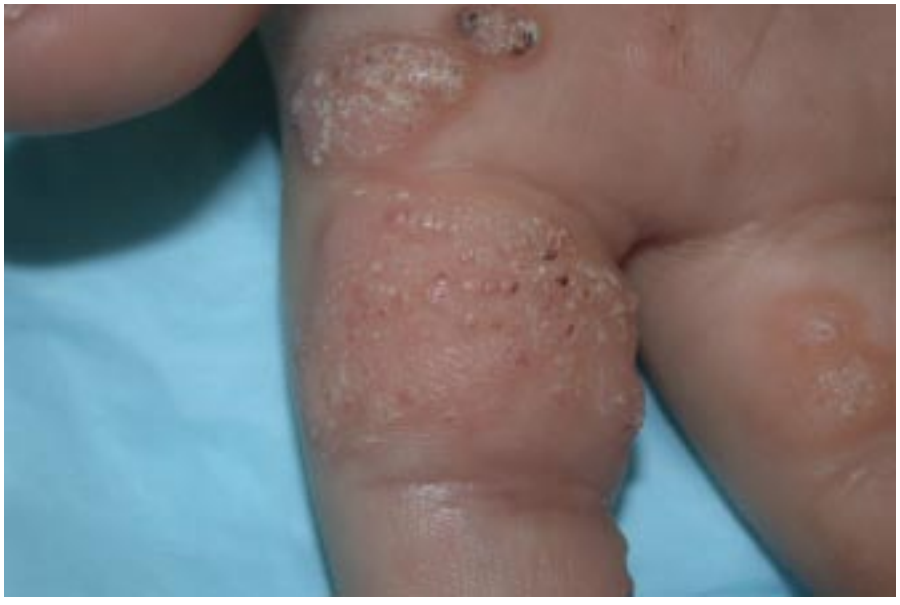

Figure 3. Frogspawn-like plaques with tiny areas of punctate hemorrhage on the palmar aspects of digits.

Two skin shave biopsies were obtained, one from a frogspawn-like plaque on the dorsum of her first finger and one from a more hyperkeratotic lesion. Both specimens demonstrated grouped ectatic lymphatics located in the papillary dermis, accompanied by epidermal hyperplasia and hyperkeratosis consistent with cutaneous lymphangioma.

After a pediatric dysmorphologic evaluation, the patient was diagnosed as having atypical KTS based on her limb hyperplasia and cutaneous and splenic lymphangiomas. She was treated with a compression glove for lymphedema.

At a follow-up evaluation in March 2007 (11 years of age), the patient's right upper extremity hyperplasia remained stable since her last visit 1.5 years prior. She received annual abdominal ultrasonography to monitor her splenic lymphangiomas, which also remained stable over time. Several months prior to the follow-up visit, the patient was hospitalized for an episode of right upper extremity cellulitis secondary to cutaneous lymphangiomas, which subsequently resulted in left hip septic arthritis.

Comment

Klippel-Trenaunay Syndrome—Klippel-Trenaunay syndrome was first described in 1900 by French physicians Klippel and Trenaunay[4] in 2 patients presenting with port-wine stains, varicosities, and hyperplasia of soft and bony tissue affecting a limb. They termed the syndrome *naevus vasculosus osteohypertrophicus*.[4] It is a rare disorder that is characterized by the triad of cutaneous capillary malformations (typically a port-wine stain), varicose veins or venous malformations, and bony or soft tissue hyperplasia of an extremity.[5] These findings usually are isolated to one extremity;

however, multiple extremity, unilateral, and even whole-body involvement has been reported.[6]

The port-wine stain presents as an irregular, macular, red to violaceous patch, usually of the nevus flammeus type.[4,7] It is typically noted at birth on the lateral aspect of a limb and may be cutaneous but also may involve visceral organs, such as the spleen, liver, bladder, or colon, and can confer greater morbidity due to internal hemorrhage.[6,8-10] It may follow a dermatomal distribution with either a geographic pattern with sharply demarcated borders or a blotchy pattern that is ill-defined. One study found that the presence of a port-wine stain with a geographic pattern in patients with KTS was predictive of both an underlying lymphatic abnormality and associated complications.[11] Venous malformations can occur in superficial, deep, and perforating veins. Superficial venous anomalies can range from ectasia of small veins to large venous malformations. Deep venous anomalies include atresia and agenesis, hypoplasia, duplications, and aneurysmal dilatation. Complications can include stasis dermatitis, thrombophlebitis, cellulitis, and pulmonary embolism. Patients also can have lymphatic system anomalies and can present with lymphedema, cutaneous lymphatic vesicles, lymphorrhea, and susceptibility to infection and cellulitis.[10,12] Bony tissue hyperplasia leads to increased length, while soft tissue hyperplasia leads to increased thickness of the extremity. Usually, hyperplasia and vascular lesions occur in the same extremity and rarely occur in different limbs. Affected sites (in order of decreasing frequency) include the leg, arm, and trunk. The incidence is equal in females and males and there is no mental deficiency.[4-6]

The etiology of KTS is unknown. There are a few case reports in the literature suggesting a familial or paradominant inheritance pattern,[13,14] and there is one report of a patient with a balanced translocation [46,XX,t(5;11)(q13.3;p15.1)] suggesting a single gene mutation etiology.[15]

In our patient, congenital limb hyperplasia of the right upper extremity and lymphatic malformation of the limb with resultant lymphedema were consistent with a diagnosis of KTS. She also had visceral involvement evidenced by multiple splenic lymphangiomas. Features atypical of KTS in our patient were lack of varicosities and port-wine stain, though the patient did have a 2×3-cm capillary vascular malformation on the left buttock.

Differential Diagnosis—At our patient's initial presentation, the differential diagnosis included Milroy disease and Proteus syndrome. Milroy disease, also called primary congenital lymphedema, is a rare autosomal dominant condition that is characterized by painless lymphedema present from birth, toenail changes, and recurrent cellulitis. The failure of lymphatic vessels to form correctly in utero results in hypoplasia, dilation, and tortuosity. Patients are susceptible to prolonged lymphedema and recurrent bacterial infections.[16] The genetic basis of most cases of Milroy disease has not been established; however, defects in the vascular endothelial growth factor receptor 3 gene, *VEGFR3*, have been described in the literature. *VEGFR3* codes for a tyrosine kinase receptor that is specific to lymphatic vessels.[17,18] In our patient, lymphedema was not present at birth and developed at 2 years of age. Additionally, patients with Milroy disease do not have bony hyperplasia, as was evident in our patient.

Proteus syndrome is a rare and complex disorder involving malformations and overgrowth of multiple tissues. The presentation is highly variable and is characterized by asymmetric localized somatic overgrowth; plantar or palmar cerebriform connective tissue nevi; linear verrucous epidermal nevi; lipomas and/or lipohypoplasia; café au lait spots; hyperpigmentation or hypopigmentation; and vascular malformations of capillary, venous, or lymphatic vessels, such as port-wine stain, angiokeratoma, cavernous hemangioma, lymphangioma, varicosities, and combined capillary-venous or capillary-lymphatic malformation. Pathognomonic for Proteus syndrome, soft tissue cerebriform hyperplasia presents as well-demarcated, gyriform, flesh-colored plaques representing cerebriform connective tissue nevi that usually occur on palms and soles but have been noted on other areas such as the forearm and trunk. Epidermal nevi present as tan or brown, flat-topped, hyperkeratotic to verrucous papules following Blaschko lines, typically on the trunk and neck. Lipomas can be found on the abdomen, head, groin, or legs, and are well-demarcated, soft, flesh-colored nodules. Lipohypoplasia presents as areas with loss of subcutaneous adipose tissue, while dermal hypoplasia appears as depressed violaceous plaques with prominent veins.[19,20] Macrodactyly and syndactyly also can occur and moderate mental deficiency occurs in approximately 1 of 5 cases. Males are twice as likely to be affected than females.[21,22]

The 3 general criteria for diagnosing Proteus syndrome include a mosaic pattern or distribution, progressive course, and sporadic presentation. The disorder is thought to be caused by a somatic genetic alteration, but the etiology remains unknown.[7,20,23] Although our patient had the specific characteristics of Proteus syndrome, such as asymmetric growth and lymphatic malformations, her course was not

Cutaneous Features of Klippel-Trenaunay Syndrome, Proteus Syndrome, and Maffucci Syndrome

Syndrome	Lesion	Appearance	Location	Onset	Pathology
Klippel-Trenaunay syndrome	Port-wine stains	Irregular, macular, red to violaceous patches	Unilateral, lateral aspect of limb	Congenital, prenatal	Ectatic capillaries in the papillary dermis without endothelial cell proliferation
	Varicose veins or venous malformations	Large, usually lateral superficial veins	Lateral aspect of limb, usually lower extremities; pelvic area; rare reports of varicosities located in bladder, colon	Congenital	Tortuous and dilated venules and lymphatic spaces with separation of collagen bundles
	Lymphangiomas	Hyperkeratotic, verrucous, frogspawn-like plaques (multiple grouped, small vesicles filled with clear serosanguineous fluid)	Usually superficial but can involve internal organs	Variable	Proliferation of vascular channels in papillary dermis or subcutis
Proteus syndrome	Cerebriform connective tissue nevi	Well-demarcated, gyriform, flesh-colored plaques; cerebriform/rugated	Usually on palms and soles but have been noted on forearm and trunk	Postnatal	Irregular proliferation of highly collagenized fibrous tissue
	Epidermal nevi	Tan or brown, flat-topped, hyperkeratotic to verrucous papules	Linear, follow Blaschko lines, typically on the trunk and neck	Congenital, prenatal	Acantholysis, hyperkeratosis, papillomatous hyperplasia
	Lipomas	Well-demarcated, soft, flesh-colored nodules	Abdomen, head, groin, legs	Postnatal	Adipose tissue encapsulated by fibrous capsule
	Lipohypoplasia	Lipohypoplasia presents as regions of skin with minimal fat, dermal hypoplasia appears as depressed violaceous plaques with prominent veins	Trunk, lower extremities	Postnatal	Loss of subcutaneous adipose tissue

TABLE CONTINUED ON PAGE 260

Table. (continued)

Syndrome	Lesion	Appearance	Location	Onset	Pathology
Proteus syndrome (continued)	Café au lait spots	Uniformly light or dark brown, sharply demarcated macules or patches	Trunk, extremities	Variable	Epidermal melanin macroglobules
	Hyperpigmentation	Tan or brown, irregular macules or patches	Linear, follow Blaschko lines	Variable	Increased melanin in melanocytes/basal keratinocytes without melanocytic proliferation
	Hypopigmentation	Hypopigmented, irregular macules or patches	Face, trunk	Variable	Reduced melanin
	Vascular malformations (highly variable): port-wine stain, angiokeratoma, cavernous hemangioma, lymphangioma, varicosities, combined capillary-venous or capillary-lymphatic malformation		Trunk, lower extremities	Congenital	
Maffucci syndrome	Hemangiomas	Blue, compressible, subcutaneous nodules that do not completely blanch	Unilateral or bilateral and can be anywhere on the body, most commonly hands and feet; rare reports of hemangiomas found in leptomeninges, eyes, pharynx, tongue, intestines, trachea	Birth to 30 years of age	Proliferation of endothelial cells in dermis/subcutaneous tissue
	Enchondromas	Irregular hard nodules	All parts of the skeleton, including hands, feet, long bones, ribs, pelvis, and skull	Birth to 30 years of age	Lobules of intramedullary benign chondrocytes, frequently rimmed by a band of new osteoid

progressive and therefore did not meet the criteria for a diagnosis of Proteus syndrome.

Although not considered in the differential diagnosis for our patient, Maffucci syndrome also demonstrates limb overgrowth and cutaneous features. It is a rare genodermatosis characterized by cutaneous and deep hemangiomas and multiple enchondromas. Hemangiomas present as blue, compressible, subcutaneous nodules that can be found anywhere on the body but are most commonly located on the hands and feet, typically adjacent to the enchondromas. Rare instances of hemangiomas occurring in the leptomeninges, eyes, and gastrointestinal tract have been reported. Venous-lymphatic malformations also are rare presentations. Enchondromas appear as irregular hard nodules that can occur in all parts of the skeleton, including hands and feet; long bones, such as the tibia, fibula, femur, and humerus; ribs; pelvis; and skull. They are thought to be caused by generalized mesodermal dysplasia.[24] Malignant transformation of enchondromas occurs in approximately 23% to 37% of cases and most commonly involve chondrosarcomas. Other malignancies include fibrosarcomas, angiosarcomas, lymphangiosarcomas, and osteosarcomas. This syndrome affects females and males equally and does not appear to follow simple mendelian patterns of inheritance. The average age at onset is 4 years, and in 27% of cases, the bony abnormalities are congenital. There is no mental deficiency in patients with Maffucci syndrome.[7,24,25] The Table compares the cutaneous features of KTS, Proteus syndrome, and Maffucci syndrome.

Diagnosis—The nosology of overgrowth syndromes continues to challenge clinicians, which is particularly true for patients with Proteus syndrome because there is considerable variability of disease severity and extent of involvement. One review of the literature found that the rate of misdiagnosis of Proteus syndrome was 39%.[26] Most but not all patients with KTS present with the triad of cutaneous capillary malformations (port-wine stain), varicose veins or venous malformations, and bony or soft tissue hyperplasia of an extremity. For instance, not all patients with KTS have a cutaneous capillary malformation. While most studies report that almost all patients with KTS have a cutaneous capillary malformation,[5,6,27] a series by Servelle[28] found flat angiomata in 32% of 614 patients examined. Furthermore, in a series of 252 patients assessed at the Mayo Clinic in Rochester, Minnesota, 159 patients (63%) had all 3 features and 93 (37%) had 2 of 3 features.[29] As described in one case report, a 20-year-old man presented with features suggestive of KTS, including hemangiomas, varicosities, and right iliac vein agenesis, but without limb hyperplasia.[30]

Patients presenting with atypical features that do not directly correspond to recognized overgrowth syndromes raise interesting questions about current diagnostic criteria. Correct classification of these patients greatly aids in determining prognosis and making therapeutic decisions. Advances in the molecular characterization of these syndromes holds some promise in addressing some of these complicated issues.

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