Diagnosis and management of extensive vascular malformations of the lower limb

Part I. Clinical diagnosis

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After completing this learning activity, participants should be able to describe the etiopathogeny of vascular malformations and to accurately distinguish between the nine types of vascular malformations which occur in the lower limbs.

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There is significant confusion in the literature when describing vascular anomalies, and vascular malformations are often misnamed or incorrectly classified. Part I of this two-part series on the diagnosis and management of extensive vascular malformations of the lower limbs will discuss the dermatologist's role in the diagnosis of these lesions. At least nine types of vascular malformations with specific clinical and radiologic characteristics must be distinguished in the lower limbs: Klippel–Trénaunay syndrome, port-wine stain with or without hypertrophy, cutis marmorata telangiectatica congenita, macrocephaly–capillary malformation, Parkes Weber syndrome, Stewart–Bluefarb syndrome, venous malformation, glomuvenous malformation, and lymphatic malformation. This article highlights the differences in clinical appearance and discusses the differential diagnosis of extensive vascular malformations in an attempt to ensure earlier diagnosis and better outcomes for these patients. (J Am Acad Dermatol 2011;65:893-906.)

Key words: cutis marmorata telangiectatica congenita; embolization; glomuvenous malformation; port-wine stain; Klippel-Trenaunay syndrome; laser; localized intravascular coagulation; lymphatic malformation; Macrocephaly-capillary malformation; magnetic resonance; multi-detector computed tomography; Parkes Weber syndrome; pulmonary hypertension vascular malformations; Stewart-Bluefarb syndrome; sclerotherapy; surgery; venous malformation.

In 1982, Mulliken and Glowacki[1] published a biologic classification of congenital vascular anomalies based on the pathologic characteristics of the predominant endothelium and their natural progression. Vascular anomalies were divided into two main categories: vascular tumors, produced by cell proliferation, and vascular malformations, characterized by abnormal distorted vascular channels. This classification was accepted at the 1996 biennial meeting of the International Society for the Study of Vascular Anomalies (ISSVA)[2,3] and remains, with minimal changes (Table I). The Hamburg classification, which was established in 1988 and subsequently endorsed by the ISSVA, describes the malformation according to its predominant vascular component, defining it as truncal or extratruncal according to the embryonic stage in which the development defect was produced.[4]

Vascular malformations are rare disorders of vascular development present at birth that occur in approximately 0.3% to 0.5% of the population.[5] Despite the above classifications and the numerous publications in which the appropriate terminology has been developed by specialists, considerable nosologic uncertainty persists, and vascular malformations are often misnamed or incorrectly classified. For example, adult musculoskeletal or visceral "hemangiomas" are misnamed in the current literature because, according to the ISSVA classification, the term hemangioma should not be applied to adult lesions, with the rare exception of noninvoluting congenital hemangiomas.[1,2] The present review only addresses extensive vascular malformations involving the lower limbs and their clinical characteristics and does not refer to the clinical manifestations of vascular malformations at other anatomic sites. The port-wine stain (PWS) with no other associations is the most prevalent vascular malformation. The combined malformations are also frequent in the lower limbs, notably Klippel–Trénaunay syndrome (KTS). But not even all vascular malformations of lower limbs are KTS and not all the KTS have the same clinical course. From a practical point of view for the dermatologist, and without trying to create a new classification, we propose a diagnostic algorithm based initially on whether or not a PWS is present on the lower limbs (Fig 1).

CAPSULE SUMMARY

- Confusion exists regarding the nomenclature and management of extensive vascular malformations of the lower limb.
- From a practical point of view for the dermatologist, a diagnostic algorithm is proposed, based initially on whether or not a port-wine stain is present on the lower limbs.
- The port-wine stain with no other associations is the most prevalent vascular malformation. Klippel–Trénaunay syndrome is the most representative example of combined vascular malformation.
- The diagnoses of Parkes Weber and Stewart–Bluefarb syndromes are confirmed by the detection of arteriovenous fistulae.
- Port-wine stain–like purplish lesions (pseudo-Kaposi sarcoma) in Stewart–Bluefarb syndrome and the port-wine stain in macrocephaly–capillary malformation because of its tendency to turn pale are considered atypical port-wine stains.
- The presence of phleboliths, morning pain, and emptying with compression are characteristic of venous malformations.
- Glomuvenous malformations are not compressible, they do not empty when raised above the level of the heart, and they do not contain phleboliths.

KLIPPEL–TRÉNAUNAY SYNDROME

Key points

- **Klippel–Trénaunay syndrome (KTS) is defined as a capillary malformation of the**

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Table I. Modified classification of the International Society for the Study of Vascular Anomalies (Rome, Italy, 1996)

Tumors	
Hemangiomas	Superficial (capillary or strawberry hemangiomas)
	Deep (cavernous hemangiomas)
	Combined
Others	Kaposiform hemangioendothelioma
	Tufted angioma
	Hemangiopericytoma
	Spindle-cell hemangioendothelioma
	Glomangiomas
	Pyogenic granuloma
	Kaposi sarcoma
	Angiosarcoma
Vascular malformations	Single capillary (C) (port-wine stain or nevus flammeus)
	Venous (V)
	Lymphatic (L) (lymphangioma or cystic hygroma)
	Arterial (A)
	Combined arteriovenous fistula (AVF)
	Arteriovenous malformation (AVM)
	CLVM (includes most cases of Klippel–Trénaunay syndrome)
	CVM (includes some cases of Klippel–Trénaunay syndrome)
	LVM
	CAVM
	CLAVM

affected extremity, underlying bony and soft tissue hypertrophy, and varicose veins and/or venous malformation

- **KTS is the most representative example of combined vascular malformation. Some cases have genetic defects of the angiogenic factor VG5Q and RASA1 mutations**
- **Clinically, there are two types of KTS: simple and complex. Simple KTS has a blotchy/segmental port-wine stain (PWS) and a better prognosis. Complex KTS features geographic PWSs, often includes deep venous system aplasia or hypoplasia, and has a higher risk of lymphatic involvement and a greater number of complications**
- **The differential diagnosis of KTS includes all the vascular malformations described in this review, with special consideration of Proteus, Bannayan-Riley-Ruvalcaba, and Mafucci syndromes**

KTS is a congenital malformation with a low incidence (<1:10000) that was first described in 1900.[7] It is characterized by a triad of capillary malformation (PWS), atypical varicose veins (also known as marginal or anomalous lateral veins) or venous malformations (VMs), and hypertrophy of soft tissues and/or bone. According to the biologic classification of Mulliken and Glowacki,[1] KTS is the most representative example of combined vascular malformation, with a similar incidence in males and females.

Increased angiogenesis appears to be a pivotal molecular mechanism in the pathogenesis of KTS. Although the genetic transmission of KTS is sporadic, there were recent reports of two genetic defects of the angiogenic factor VG5Q,[8] RASA1 mutations,[9] and de novo supernumerary ring chromosome 18 in KTS patients.[10] The unilateral lower limb is involved in 85% of patients, bilateral in 12.5%, crossed-bilateral in 2.5%, and in 10% both the upper and lower extremities are affected.[11,12]

KTS can be diagnosed if only two of the three clinical features described above are present. In a series of 252 patients, all three clinical features were present in 63% of patients and two of them in the remaining 37%.[13]

Capillary or venular malformation

Capillary or venular malformation, also known as PWS, telangiectatic, or flammeus nevus, is the most frequently observed lesion at birth in most KTS patients. It is present in 98% of KTS patients and clinically presents as a pink or reddish stain with linear borders whose intensity can increase with age, becoming more violaceous in color. Nodular lesions appear in up to 10% of older patients, apparently corresponding to ectatic venous channels.[14] They are histologically characterized by ectatic capillaries or superficial dermal venules.[14] It is not uncommon to observe areas of hyperhidrosis coinciding with PWS.

Some authors recently classified capillary malformations into two groups: "geographic" or "blotchy/segmental." The former are defined as very well defined lesions of irregular shape and dark red or purple color. In contrast, blotchy/segmental malformations have a poorly defined border with normal skin and are very large and distributed in light pink or pink-red segments or blotches. The presence of a geographic vascular stain predicts a risk of associated lymphatic malformation and complications in KTS patients.[15] Lymphatic malformations may result from lymphatic hypoplasia, which is present in more than 50% of patients, and is associated with lymphedema and isolated lymphatic macrocysts on the pelvis or trunk or microcysts on the abdominal wall, the gluteal region, or the distal limbs. In these latter

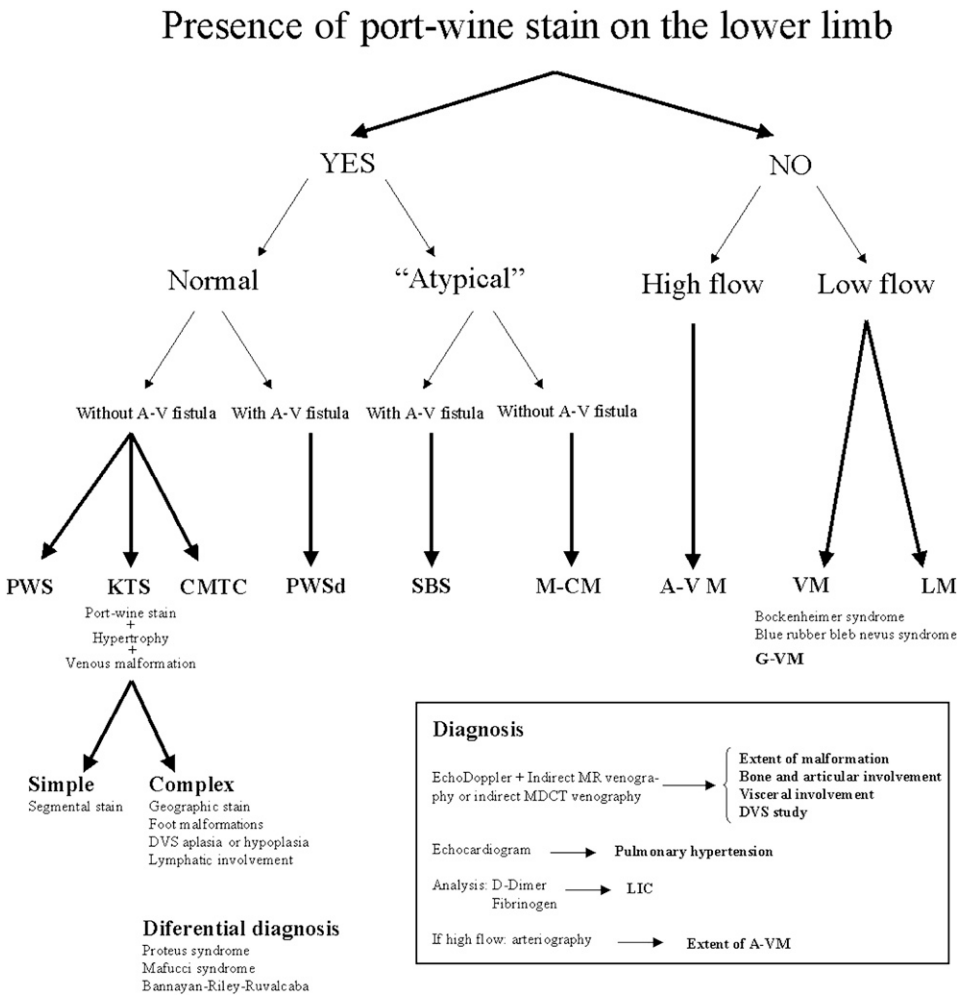

Fig 1. Algorithm for the initial evaluation of patients with extensive vascular malformations in the lower limbs. *A-VM*, Arteriovenous malformation; *CMTC*, cutis marmorata telangiectasica congenita; *DVS*, deep venous system; *G-VM*, glomuvenous malformation; *KTS*, Klippel—Trénaunay syndrome; *LIC*, localized intravascular coagulation; *LM*, lymphatic malformation; *M-CM*, macrocephaly-capillary malformation; *MDCT*, multidetector computed tomography; *MR*, magnetic resonance; *PWS*, port-wine stain; *PWSd*, Parkes Weber syndrome; *SBS*, Stewart—Bluefarb syndrome; *VM*, venous malformation.

cases, the malformation is usually predominantly subcutaneous or diffusely infiltrates the muscle.[12] Vesicles arranged irregularly in groups on the skin are frequent.

Atypical varicose veins

Atypical varicose veins or anomalous lateral veins and VMs are observed in 72% of KTS patients but not always at birth, becoming more evident when the child starts walking. Large varicose veins or VMs are most frequently present in the anterolateral and medial aspects of the calf or thigh. Atypical varicose veins are persistent embryonic veins of the superficial venous system (SVS) and correspond to the lateral thigh vein (marginal vein) or sciatic vein. They are usually long and tortuous veins that are avalvular, producing heaviness in the legs.[16,17]

The presence of ulcers and trophic changes of the skin usually accompany venous involvement. Limbs with KTS have a high propensity for triple venous system incompetence (ie, superficial, deep, and perforator reflux). The large amount of venous reflux is associated with a significant impairment in calf muscle pump function and with venous hypertension. The deep venous system (DVS) is involved in more than 25% of KTS patients and in a similar percentage of vascular malformations of venous predominance. DVS alterations include aneurysmatic dilatations, duplications, hypoplasia, aplasia, and external compression from anomalous vessels or fibrotic bands. The popliteal and superficial

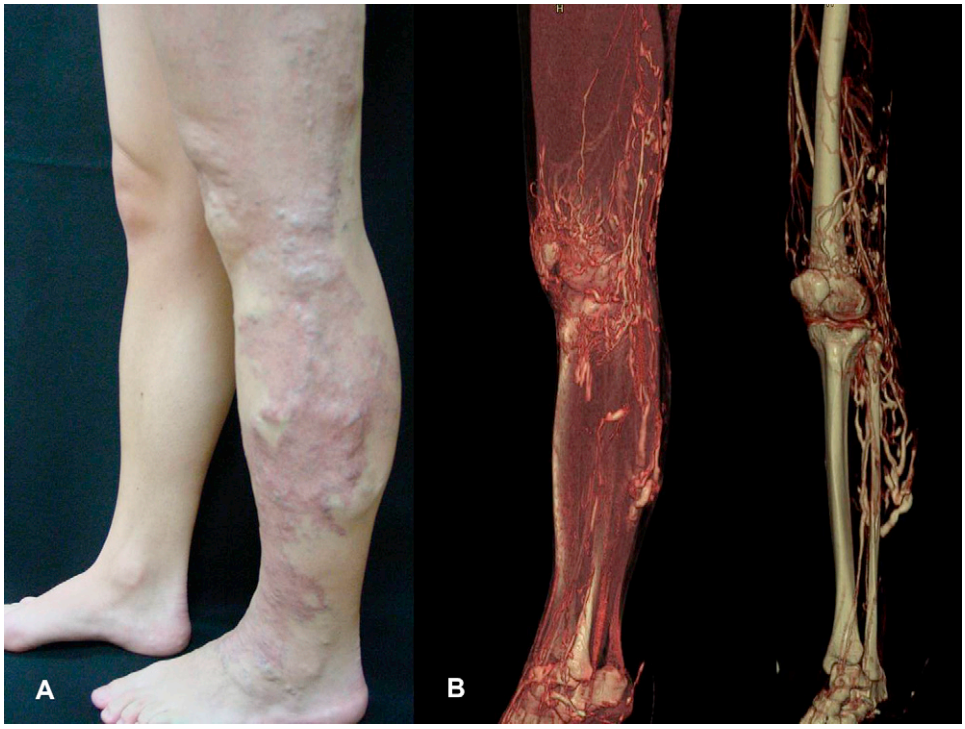

Fig 2. A, A 27-year-old woman with simple Klippel–Trénaunay syndrome, characterized by segmental nongeographic port-wine stain without deep venous system anomaly. **B**, Direct multidetector computed tomography venography with maximum intensity projection and volume rendering reconstructions, showing the anomalous veins.

femoral veins are the most frequently involved, although any vein, including the inferior vena cava, can be affected. Some patients may also present with varicose perianal and perirectal veins, possibly because of a high flow in the internal iliac vein. The presence of large suprapubic veins can be a sign of atresia of the iliac vein.[18]

Hypertrophy

Hypertrophy is the most variable feature of KTS and is generally present at birth. The increase in limb size can be either in girth or length. The progression of a hypertrophic limb cannot be predicted, but it is usually axial and slow. The affected limb is short or hypotrophic in some KTS patients. In total, 67% of KTS patients present with some dissymmetry between the affected and collateral limbs.[13] A recent study of KTS patients suggested that a large difference in arterial blood flow between the limb with the PWS and the normal limb is linked to a limb length discrepancy or exacerbation of an existing limb length discrepancy.[19]

Up to 25% of KTS patients have malformations in the hands and feet. In a recent retrospective investigation, we found malformations at these sites in nine of the 51 patients studied—above all macrodactyly and syndactyly, but also ectrodactyly, clinodactyly, and camptodactyly. These malformations, present at birth, have been significantly correlated with agenesis or malformation of the DVS.[20] Our group previously correlated these DVS anomalies with the presence of geographic PWSs.[21]

By considering recently published clinical data, it is possible to visually differentiate between two types of KTS (Fig 1). One type, simple KTS, is characterized by the classic triad of features with a blotchy/segmental PWS and has a greater or lesser impact on function and on quality of life as a function of the degree of dissymmetry and the severity of the venous malformation (Fig 2). Complex KTS is characterized by the same triad of features but with geographic PWSs and a higher risk of associated lymphatic malformations. Patients with complex KTS can have DVS aplasia or hypoplasia, malformations in the feet, marked lymphatic involvement in the form of superficial vascular blebs and/or lymphangiectasia, severe lymphedema, pseudoverrucous hyperplasia, cellulitis, and macrocystic lymphatic disease (Fig 3). They also typically have a greater number of complications, including genitourinary or gastrointestinal bleeding, hemothorax, and heart failure. This clinical phenotype should always be borne in mind, above all in neonates, because the detection of major involvement permits a closer

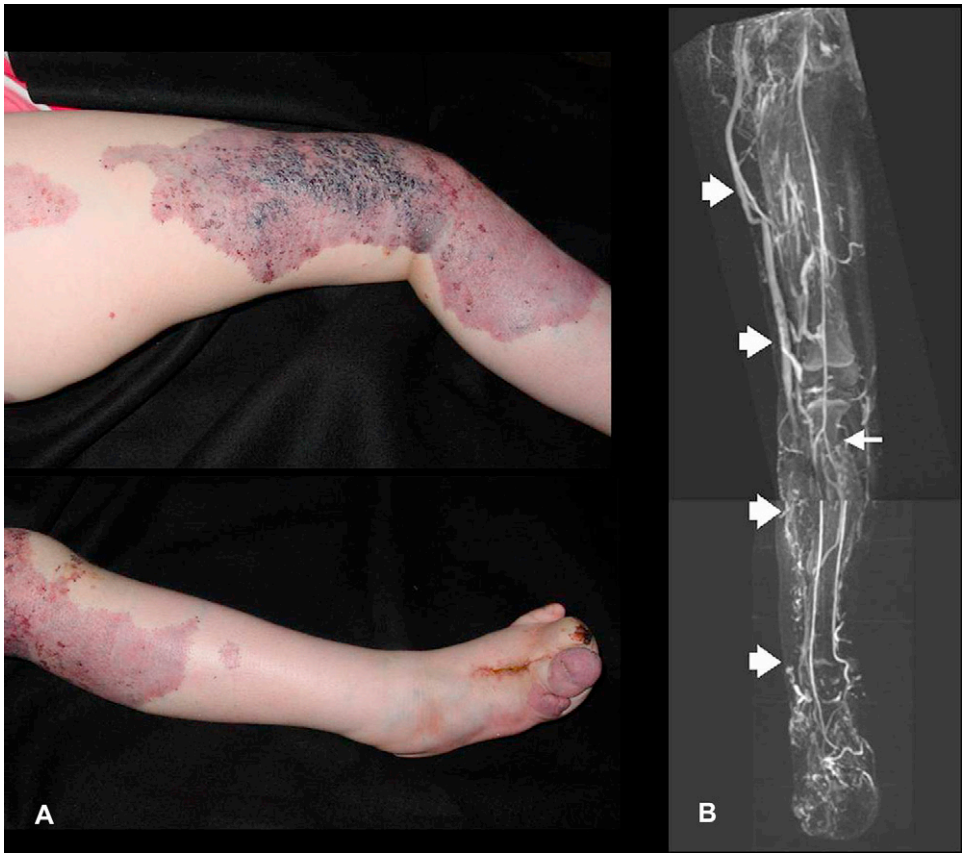

Fig 3. A, A 9-year-old girl with complex Klippel–Trénaunay syndrome, characterized by geographic port-wine stain, deep venous system anomalies, lymphatic malformation, and foot malformations (hypertrophy of the first, second [amputated], and third toes, with plantar expansion). **B**, Direct magnetic resonance venography with maximum intensity projection, revealing popliteal vein aplasia (*arrow*). Note communication of entire venous drainage of leg with a large marginal vein (*bold arrows*).

follow-up and possibly an earlier (but limited) treatment.

The differential diagnosis of KTS includes the other subgroups of VMs in this review but must especially consider Proteus, Bannayan-Riley-Ruvalcaba, and Mafucci syndromes.

Proteus syndrome

Proteus syndrome (PS) is a complex hamartomatous disorder defined by local overgrowth (macrodactyly or hemihypertrophy), subcutaneous tumors, and various bone, cutaneous, and/or vascular anomalies. A possible association between PS and heterozygous germline PTEN mutations have been described.[22] PS is always characterized by lipomatosis, macrocephalia, asymmetry of limbs (with partial gigantism of hands and feet or both), and a striking cerebriform plantar thickening that histologically corresponds to a collagenoma.[23] Like KTS, its onset is sporadic. PS is the most difficult entity to distinguish from KTS, especially with respect to vascular anomalies. Several studies have shown that patients with PS had previously been diagnosed with KTS. There have been case reports illustrating an overlap between PS and KTS and describing overgrowth management in both syndromes.[24] Unlike in Parkes Weber syndrome, high-flow lesions have never been reported.

Bannayan-Riley-Ruvalcaba syndrome

Bannayan-Riley-Ruvalcaba syndrome (BRRS) is an autosomal dominant condition with macrocephaly, developmental delay, pseudopapilledema, pigmented macules on the glans penis, and hamartomatous growths, including subcutaneous and visceral lipomas, gastrointestinal polyposis, and VMs (capillary and combined malformations).[25] Mutations in the PTEN gene have been detected in BRRS patients, and several patients have been reported to have overlapping features of Cowden syndrome and BRRS.[26]

Mafucci syndrome

Mafucci syndrome involves the presence of exophytic VMs with bone exostoses and enchondromas.

Unlike KTS, it is not usually present at birth and the bone lesions arise during infancy and vascular lesions at a later stage. It can be unilateral or bilateral and more frequently involves the upper limbs, but can also affect the lower limbs. The malformation is of venous type, although it can also be capillary or even lymphatic,[27] but it is histologically a spindle cell hemangioendothelioma. Some authors do not consider them to be true tumors but rather vascular proliferations within a preexisting VM, often triggered by a repeated trauma.[28] Malignant transformation to chondrosarcoma occurs in 20% to 30% of cases.[29]

Port–Wine stain on the limbs

Key points

- **Port-wine stain is a segmental or geographic capillary malformation. It may be associated with limb dissymmetry, but this association is not typical (incomplete KTS)**
- **No venous malformation or abnormal veins are seen on imaging studies in either group**

There are two groups of patients with PWS. One group has a segmental or geographic capillary–venular malformation in the limb not associated with anomalous lateral veins, VMs, or limb dissymmetry. A PWS with no other association is the more prevalent vascular lesion. The other group, incomplete KTS, has PWS on the limbs that may also be associated with nonprogressive congenital hypertrophy of the underlying bone and soft tissues.[30] No VM or abnormal veins are seen on imaging studies in either group. Although the presence of two characteristics of the triad has classically been sufficient to define KTS,[13] some authors have proposed that the combination of PWSs and hypertrophy could be considered an incomplete or abortive KTS.[31,32] Care must be taken with young children, because varicosities or VMs are reported to be present in around 72% of KTS patients, with an incidence of less than 60% in patients under 5 years of age; this prevalence increases with age.[13]

A priori, all of these patients will have fewer complications and a better quality of life in comparison to classic KTS patients, whose main functional limitation derives from a venous or lymphatic malformation.

Cutis marmorata telangiectatica congenita

Key points

- **Cutis marmorata telangiectatica congenita is a congenital reticulated erythema that may or may not be associated with telangiectasies and typically improves over time**
- **Cutis marmorata telangiectatica congenital can be associated with body assymmetry and vascular anomalies (PWS and superficial varicose veins)**

Cutis marmorata telangiectatica congenita (CMTC) is a congenital vascular anomaly of unknown origin that was described by van Lohuizen[33] in 1922. CMTC is histologically characterized by the presence of multiple dilated capillaries and veins in the reticular dermis.[34] The main clinical finding is a congenital reticulated erythema that may or may not be associated with telangiectasias and typically improves over time (Fig 4). There may be atrophic areas and ulcerations on the skin. CMTC can be seen in association with a PWS and superficial varicose veins, either distant from the CMTC or within the same area. The segmental distribution, often with a sharp midline separation, suggests that CMTC may be a disorder characterized by genetic mosaicism.[35]

A recent study of 27 patients with CMTC reported body asymmetry (hypertrophy or hypotrophy of the affected limb) in nine patients (33%).[36] All of the lesions were evident at birth and preferentially involved the lower limbs (74%), followed by the trunk (67%) and face (15%). Associated vascular anomalies were found in 15% of patients, 50% of which were PWSs.[37] Syndactyly and CMTC are also associated in Adams–Oliver syndrome.[38]

Criteria were recently defined for the diagnosis of lesions compatible with CMTC.[36] Major criteria are as follows: (1) the presence of congenital reticulated erythema (cutis marmorata); (2) the absence of response to local heat, as in physiologic cutis marmorata secondary to the cold; and (3) the absence of venous lesions (venectasias) in the affected areas, evaluated at 1 year of age. Minor criteria include: (a) the progressive disappearance of the erythema within the first 2 years (in around 50% of patients); (b) the presence of telangiectasias in the affected area; (c) PWSs outside the CMTC area; and (d) skin ulceration and atrophy.

The differential diagnosis must include livedo racemosa and other extensive VMs.

Macrocephaly-Capillary malformation

Key points

- **Reticulated or telangiectatic PWS is the most characteristic cutaneous vascular anomaly seen in macrocephaly-capillary malformation affecting the lower limbs**
- **Many patients have considerable fading of their PWS during the first years of life**

Although macrocephaly associated with CMTC (MCMTC) has been reported in more than 50% of cases in one series,[39] this entity may correspond to a

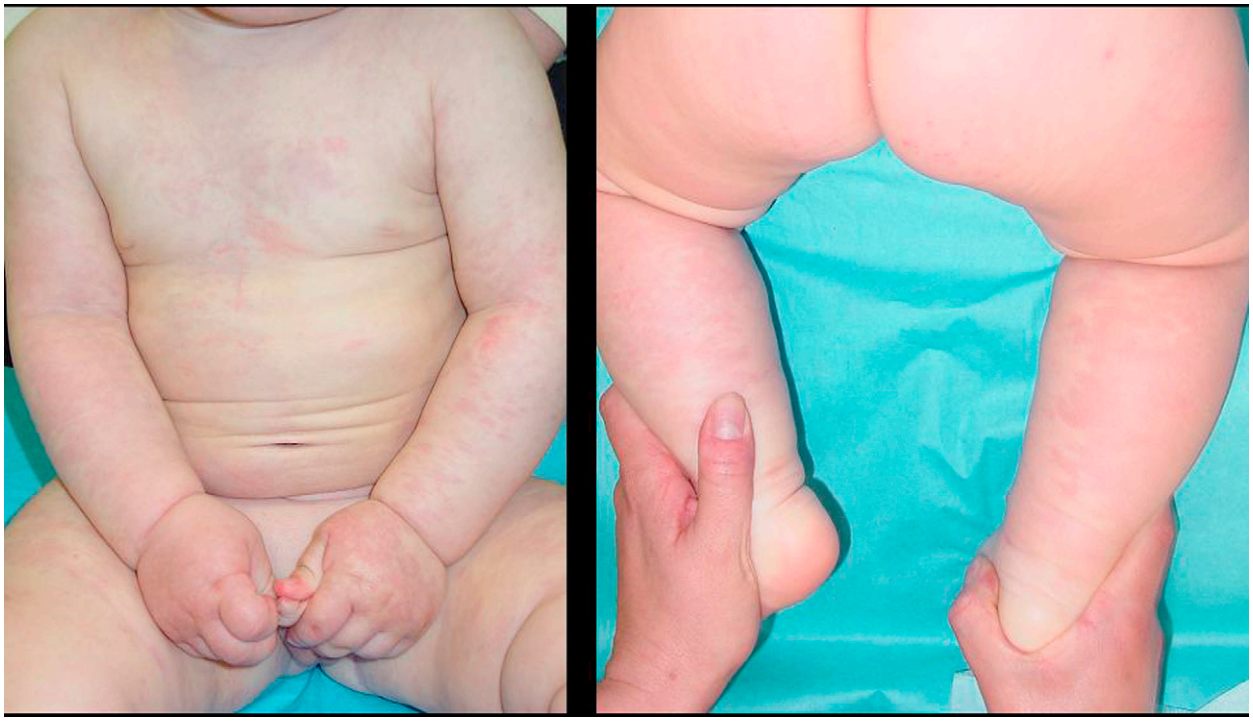

Fig 4. Macrocephaly-capillary malformation with "atypical" port-wine stain in patient at 11 months of age.

different syndrome associated with other vascular lesions. Toriello and Mulliken[40] clarified that the VMs associated were neither capillary malformations (CMs) nor CMTCs, and instead argued that the majority of patients have CMs. They proposed that this condition be renamed macrocephaly-capillary malformation (M-CM). VMs associated with MCMTCs are not true CMTCs but rather PWSs (often reticulated or telangiectatic) and persistent central facial vascular stains (salmon patches). The syndrome is characterized by macrocephaly, neonatal hypotonia, development delay, segmental overgrowth, syndactily, asymmetry, connective tissue defects, and PWSs. Many M-CM patients had considerable fading of their PWS during the first years of life. Some evolved into a finer, more telangiectatic pattern. Others faded overall, becoming barely perceptible or disappearing completely in some areas.[41] We consider "atypical" the PWS in M-CM for its trend to turn pale.

Parkes Weber syndrome

Key points

- **Combined vascular malformation clinically very similar to KTS**
- **The diagnosis of Parkes Weber syndrome is confirmed by detection of arteriovenous fistulae**
- **Parkes Weber syndrome is differentiated from KTS by the presence of arteriovenous fistulae, the usual absence of marginal vein and lymphatic malformations, and lesser musculoskeletal involvement**
- **The differential diagnosis of Parkes Weber syndrome includes other syndromes presenting with PWS and high-flow shunts in the lower limbs (capillary malformation–arteriovenous malformation, *RASA1* mutation, and CLOVES syndrome)**

Parkes Weber syndrome is a capillary arteriovenous malformation that is similar in its presentation to KTS; it is classified by the ISSVA as a combined malformation. It preferentially involves the lower limbs (77%), although with a lesser frequency in comparison to KTS. Parkes Weber syndrome onset is usually sporadic, but some familial cases have been reported in association with a mutation in *RASA1* gene.[42] Unlike conventional PWSs, however, local temperature is increased, a pulse or thrill can be palpated, and a murmur is heard on auscultation. It is differentiated from KTS by the high flow of the vascular lesion, the presence of arteriovenous fistulas, the usual absence of abnormal lateral veins and lymphatic malformations (almost always), and lesser musculoskeletal involvement. The increase in soft tissues is in muscle and bone

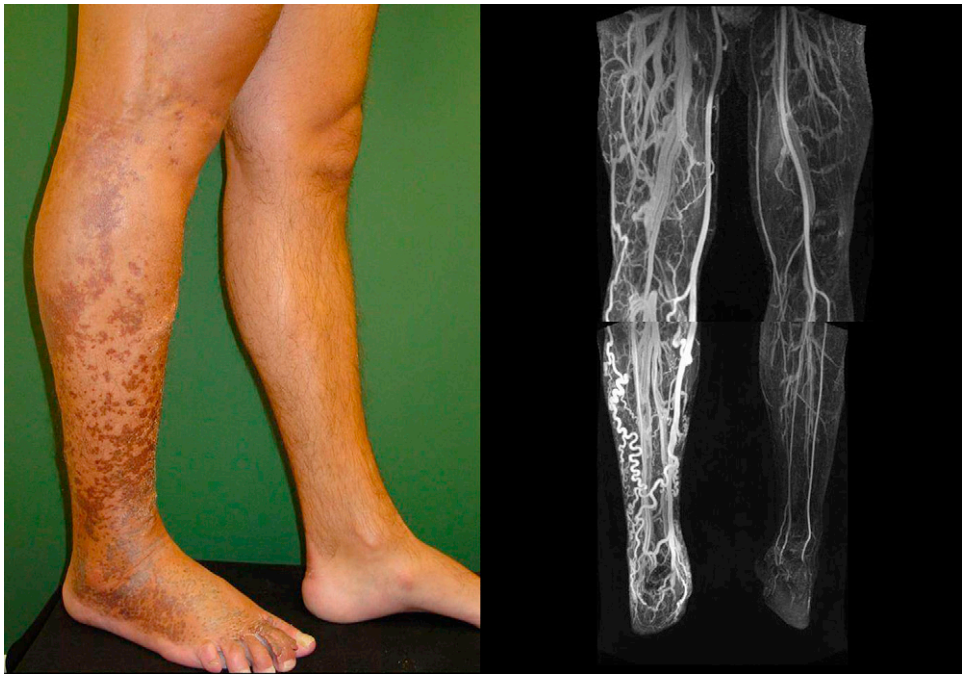

Fig 5. Three-dimensional magnetic resonance venography of a patient with Stewart–Bluefarb syndrome showing the early filling of dilated venous structures caused by arteriovenous microfistulae. This is associated with pseudo-Kaposi lesions, clinically similar to "atypical" port-wine stains, and arteriovenous fistulae.

in Parkes Weber syndrome, whereas it is in subcutaneous cell tissue (and occasionally bone) in KTS. Instead of thrombophlebitis and the risk of pulmonary embolism, the main complication of Parkes Weber syndrome is increased cardiac load that might lead to heart failure and cutaneous ischemia.[43]

As in Parkes Weber syndrome, the association of PWSs and high-flow shunts in the lower limbs can be observed in some rare syndromes such as CM–arteriovenous malformation syndrome (CM-AVM; *RASA1* mutation)[44] and CLOVES syndrome. In CM-AVM, the high-flow lesions may be located in the skin and subcutaneous tissue, bone, or muscle, and some of these patients have the clinical features of Parkes Weber syndrome. CLOVES syndrome (*c*ongenital *l*ipomatous *o*vergrowth, *v*ascular malformations, *e*pidermal nevi, and *s*coliosis, seizures, and spinal/skeletal anomalies) is a recently described phenotype.[45]

Stewart Bluefarb syndrome

Key points

- **Stewart–Bluefarb syndrome is an arteriovenous malformation of the leg with multiple fistulae and port-wine stain–like purplish lesions that are either congenital or acquired (Mali's acroangiodermatitis or pseudo–Kaposi sarcoma)**

Stewart–Bluefarb syndrome (SBS) is characterized clinically by an AVM of the leg with multiple fistulae and PWS-like purplish lesions that can be congenital or appear in the first years of life, designated Mali's acroangiodermatitis or pseudo–Kaposi sarcoma.[46-48] The syndrome is diagnosed in young adults, usually by the detection of underlying congenital arteriovenous fistulas during the study of skin lesions (Fig 5). Etiopathogenically, it is a reactive vascular proliferation caused by chronic venous insufficiency with capillary venous hypertension or secondary to arteriovenous fistulae that augment the tension in the capillary bed.

Clinically, the affected limb features brown macules ("atypical" PWS) and violaceous or purplish nodules and plaques (especially on the dorsal surface of the foot, the ankles, and the calves) that may become verrucous or even develop ulcerations. Frequent findings include edema, varicose veins, hypertrichosis, skin ulceration, and elevated temperature associated with a palpable thrill and audible bruit, with different pulses. Musculoskeletal hypertrophy is not uncommon, with enlargement of the affected limb. Clinical suspicion is confirmed by localization of the anomalous vessels using echo

Doppler, angio–magnetic resonance imaging (MRI), or arteriography.

SBS is characterized histologically by the proliferation of small blood vessels and fibroblasts, extravasation of erythrocytes, and the deposit of hemosiderin within the dermis. This "pseudo-Kaposi" entity can be distinguished from a genuine Kaposi sarcoma by the regularity of the proliferation in the dermis, the limited presence of vascular slits in the upper part of the dermis (found in the whole dermis in Kaposi sarcoma), and the absence of atypical mitoses in endothelial cells or fibroblasts.[49]

The most frequent complications are skin ulceration or necrosis (steal syndrome), hemorrhage and infection, regional osteoporosis, and congestive heart failure.

Venous malformations

Key points

- **Venous malformations (VMs) are formed by ectatic vessels with low blood flow that are morphologically and histologically similar to veins**
- **Characteristics of VMs include phleboliths, morning pain, and emptying with compression**
- **VMs in the lower limbs have a deep segmental extension larger than its external appearance**
- **Muscle and joint involvement and musculoskeletal hypotrophy are not uncommon**
- **Blue rubber bleb nevus syndrome is characterized by cutaneous and gastrointestinal VMs with the risk of life-threatening gastrointestinal hemorrhage**

VMs are the most common vascular anomalies of the extremities and account for approximately one-half to two-thirds of all VMs. A recent study of 118 patients found that the lower limbs were affected in 58% of cases and the upper limbs were affected in 30% of cases; the authors also reported a higher prevalence of female patients (64%) with limb involvement.[50]

VMs are formed by ectatic vessels with low blood flow that are morphologically and histologically similar to veins. The skin that covers them varies in color as a function of the degree of ectasia and depth of the lesion, being purple over more superficial lesions and more bluish or green or even showing no color change over deeper lesions. The lesions, which are sometimes of nodular appearance, are soft to the touch and can be emptied with compression. When the patient is in the prone position, the malformation re-fills with blood, emptying if the affected area is raised above the level of the patient's heart. The presence of small venous thromboses, also called phleboliths, is not uncommon in very ectatic lesions, appearing at young ages and serving as radiologic markers of this type of VM. Morning pain that disappears with movement is also characteristic of VMs, and symptoms are exacerbated in women who are pregnant or undergoing hormonal changes, which may be explained by the presence of estrogen receptors on endothelial cells or by the prothrombotic effect of estrogen, favoring painful thromboinflammatory events within the lesion.[2,6]

VMs are commonly observed in the extremities, often with a deep segmental extension larger than its external appearance. There is almost always muscle involvement in these patients, and involvement of joint and bone is not uncommon. Gonalgia is frequently experienced when the knee is involved, with functional limitation and hemoarthrosis, and arthropathy with synovial siderosis can develop into degenerative arthritis with amyotrophy of the leg, flexion contractures, and progressive ankylosis of the knee, resulting in severe functional impairment. Diffuse VM of the lower limb characteristically affects the entire leg and adjacent trunk. Unlike KTS-type combined malformations, there is not usually musculoskeletal hypertrophy of the affected limb, which tends to be normal or atrophic/hypotrophic.[51] Amyotrophy, detectable with MRI, can be intensely marked and progressive. Pain is mainly related to muscle involvement or episodes of thrombosis or hematoma.[52] DVS anomalies were reported in 47% of VM patients.[18]

The term "phlebectasia" is used to describe enlarged and irregularly dilated veins in the superficial and deep dermis. "Genuine diffuse phlebectasia of Bockenheimer," "Bockenheimer syndrome." and "extensive VM" are synonymous terms that apply to a slow-flow VM affecting all tissues in the limb.[53,54] It represents a variant of VM characterized by an extensive circumscribed venous dilatation that is visible beneath the skin of the limb. Bockenheimer syndrome does not include PWSs or arteriovenous fistulae.

Servelle–Martorell syndrome is another synonymous term for pure VMs with slight underdevelopment of the affected limb, although this term has also been applied to patients with KTS.[55]

Blue rubber bleb nevus syndrome (BRBNS) is a rare disorder that is characterized by multiple and distinctive cutaneous and gastrointestinal VMs. Cutaneous lesions may number from a few to more than 100 and preferentially involve the trunk and lower limbs. They are typically compressible blue subcutaneous nodules that can be painful and range from a few millimeters to several centimeters in

diameter. They may or may not increase in size and number with age. Early diagnosis and management of this entity is vital because of the risk of life-threatening gastrointestinal hemorrhage.[56] Patients frequently present with consumptive coagulopathy and iron deficiency anemia secondary to occult bleeding episodes.[57]

Glomuvenous malformations or glomangiomas

Key points

- **The cause of glomuvenous malformations or glomangiomas is several loss-of-function mutations in glomulin (protein encoded in the p21 locus of chromosome 9)**
- **Disseminated or metameric forms of glomuvenous malformations or glomangiomas are found in the lower limbs, are purple or blue in color, and have a cobblestone-like appearance**
- **Contrary to VMs, they are limited to the skin and subcutaneous tissue, they are not compressible, they do not empty when raised above heart level, and they do not contain phleboliths**

Some VMs have an increased number of rounded cells in their walls, known as glomus cells. In the past, these were known as glomus tumors or glomangiomas,[58] but the term glomuvenous malformation (GVM) now appears to be more correct.[59] Although classified within the group of venous or low-flow malformations, GVM is a clinically and pathologically distinct entity. GVMs represent 5% of all VMs; 63% of them are hereditary. Recent studies suggest that GVMs are caused by several loss-of-function mutations in glomulin, a protein encoded in the p21 locus of chromosome 9.[59,60] The multiple lesions can be subdivided into localized, disseminated, and congenital plaque-type forms. Congenital plaque-type GVMs are severe, have an extensive distribution, and can be initially difficult to diagnose.[61] Disseminated or metameric forms affect the limbs in around 80% of cases, preferentially the lower limbs. Lesions are pinkish during the first years of life and then become more purple or blue in color with a thickening of the skin, which acquires a cobblestone-like appearance with minor hyperkeratosis. Unlike VMs, which infiltrate deep planes, GVMs are almost always limited to the skin and subcutaneous cell tissue and rarely involve the mucosa. GVMs also differ from VMs in other ways: they are not compressible to palpation, they do not empty when raised above heart level, they do not contain phleboliths, they are not affected by hormonal changes, and they are not associated with localized intravascular coagulation (LIC)—type fibrinolysis disorders. GVMs do not respond to compression and are painful to even light palpation. Interestingly, 17% of a large series of patients with familial GVM reported the appearance of new lesions in previously unaffected areas after a local trauma.[62] Histologically, they are poorly defined, nonencapsulated lesions reminiscent of hemangiomas and are made up of irregular and dilated and occasionally thrombosed vascular channels with small clusters of glomus cells on their walls. These cells are monomorphic and round or polygonal with eosinophilic cytoplasms and hyperchromatic central nuclei; they are positive for vimentin and alfa—smooth muscle actin stains but are negative for desmin stain.[63]

Lymphatic malformations

Key points

- **Lymphatic malformations are superficial crops of thin-walled vesicles or hyperkeratotic papules arranged irregularly in groups that are connected to deeper subcutaneous lymphatic cisterns**
- **Patients with lymphatic malformations can have skeletal hypertrophy or bone resorption phenomenon (Gorham—Stout syndrome)**

Lymphatic malformations (LMs) show no predilection for sex or race; 65% of cases are detected at delivery, 80% by 1 year of age, and 90% by 2 years of age. Although present at birth, they can be missed when deep, subsequently becoming evident because of increased size, distension, inflammation, or infection.[64]

The Hamburg classification divides lymphatic vascular malformations between truncular forms, also designated lymphedemas, and extratruncular forms, known as cystic or cavernous lymphangioma or cystic hygroma.[4,65] We include the former in this review. The Hamburg classification also describes a group of patients with hemolymphatic malformations, corresponding to KTS-type combined malformations in the ISSVA classification, in which truncal and extratruncal lesions usually overlap.

The clinical appearance of LMs varies according to their size, depth, and localization. There is a frequent presence of multiple persistent crops of thin-walled vesicles or hyperkeratotic papules arranged irregularly in groups. The surrounding skin is normal, sometimes with a bluish color. These superficial lesions are connected to deeper subcutaneous lymphatic cisterns.

Superficial complications include ulceration, bleeding, and secondary infection. Large LMs involving limbs frequently produce pain, inflammation, and gigantism through the growth of musculoskeletal tissue.[66] Skeletal hypertrophy has been reported in 83% of patients, causing functional repercussions in 33% of patients with LMs. This hypertrophy is not explained, as in other VMs, by an increase in the blood supply. The opposite phenomenon can also be produced—as in Gorhan–Stout syndrome or "disappearing bone disease" or "phantom bone disease"—by a progressive osteolysis induced by an LM in soft tissue and skeleton.[67] It is often present in children with a history of minor trauma resulting in a pathologic fracture. Although the degree of bone resorption is variable, complete resorption of the bone has been reported in several cases. This syndrome is occasionally associated with different lymphatic vascular malformations.[68] In fact, the ISSVA now assigns the designation of Gorham–Stout to the phenomenon of bone resorption in patients with lymphatic vascular malformations.[69] It is histologically characterized by the complete replacement of the bone with fibrovascular or lymphatic tissue associated with significant capillary proliferation.[70]

CONCLUSION

There is significant confusion in the literature when describing vascular anomalies and, not infrequently, vascular malformations are misnamed or incorrectly classified. A PWS with no other association is the most prevalent vascular malformation. Combined malformations are also frequent in the lower limbs, notably KTS. But not all vascular malformations of the lower limbs are related to KTS, and not all cases of KTS have the same clinical course. This article provides a guideline for understanding and managing this class of lesions, with a classification of extensive vascular malformations according to the presence or absence of PWS.

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REFERENCES

1. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristic. Plast Reconstr Surg 1982;69:412-20.
2. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol 1997;13:375-423.
3. Hand JL, Frieden IJ. Vascular birthmarks of infancy: resolving nosologic confusion. Am J Med Genet 2002;108:257-64.
4. Belov S. Classification of congenital vascular defects. Int Angiol 1990;9:141-6.
5. Mulliken JB, Young AE, editors. Vascular birthmarks: hemangiomas and malformations. Philadelphia: Saunders; 1988.
6. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations: Part I. J Am Acad Dermatol 2007;56:353-70.
7. Klippel M, Trenaunay P. Du noevus variqueux osteohypertrophiques. Arch Gen Med 1900;3:641-72.
8. Tian XL, Kadaba R, You SA, Liu M, Timur AA, Yang L, et al. Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trenaunay syndrome. Nature 2004;427:640-5.
9. Eerola I, Boon LM, Mulliken JB, Burrows PE, Dompmartin A, Watanabe S, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet 2003;73:1240-9.
10. Timur AA, Sadgephour A, Graf M, Schwartz S, Libby ED, Driscoll DJ, et al. Identification and molecular characterization of a de novo supernumerary ring chromosome 18 in a patient with KlippeleTrenaunay syndrome. Ann Hum Genet 2004;68:353-61.
11. Gloviczki P, Hollier LH, Telander RL, Kaufman B, Bianco AJ, Stickler GB. Surgical implications of Klippel-Trenaunay syndrome. Ann Surg 1983;197:353-62.
12. Samuel M, Spitz L. Klippel-Trenaunay syndrome: clinical features, complications and management in children. Br J Surg 1995;82:757-61.
13. Jacob AG, Driscol DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trénaunay syndrome: spectrum and management. Mayo Clin Proc 1998;73:28-36.
14. Mills CM, Lanigan SW, Hughes J, Anstey AV. Demographic study of port-wine stain patients attending a laser clinic: family history, prevalence of nevus anaemicus with results of prior treatment. Clin Exp Dermatol 1997;22:166-8.
15. Maari C, Frieden IJ. Klippel-Trenaunay syndrome: the importance of "geographic stains" in identifying lymphatic disease and risk of complications. J Am Acad Dermatol 2004;51:391-8.
16. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol 1998;13:375-422.
17. Mulliken JB, Young AE. Vascular birthmarks: hemangiomas and malformations. Philadephia: Saunders; 1988.
18. Eifert S, Villavicencio JL, Kao TC, Taute BM, Rich NM. Prevalence of deep venous anomalies in congenital vascular malformations of venous predominance. J Vasc Surg 2000;31:462-71.
19. Samimi M, Maruani A, Bertrand P, Arbeille P, Lorette G. Arterial blood flow in limbs with port-wine stains can predict length discrepancy. Br J Dermatol 2009;160:219-20.
20. Redondo P, Bastarrika G, Aguado L, Martínez-Cuesta A, Sierra A, Cabrera J, et al. Foot or hand malformations related to deep venous system anomalies of the lower limb in Klippel-Trenaunay syndrome. J Am Acad Dermatol 2009;61:621-8.
21. Bastarrika G, Redondo P, Sierra, Cano D, Martínez-Cuesta A, López-Gutierrez JC, et al. New techniques for the evaluation and therapeutic planning of patients with Klippel–Trénaunay syndrome. J Am Acad Dermatol 2007;56:242-9.
22. Smith JM, Kirk EP, Theodosopoulos G, Marshall GM, Walker J, Rogers M, et al. Germline mutation of the tumour suppressor PTEN in Proteus syndrome. J Med Genet 2002;39:937-40.
23. Wiedemann HR, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E. The Proteus syndrome. Eur J Pediatr 1983;140:5-12.
24. Hoeger PH, Martinez A, Maerker J, Harper JI. Vascular anomalies in Proteus syndrome. Clin Exp Dermatol 2004;29:222-30.
25. Gorlin RJ, Cohen MM Jr, Condon LM, Burke BA. Bannayan-Riley-Ruvalcaba syndrome. Am J Med Genet 1992;44:307-14.

26. Marsh DJ, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ, Ahme SF, et al. PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet 1999; 8:1461-72.
27. Cohen MM Jr, Neri G, Wesberg R. Overgrowth syndromes. New York: Oxford University Press; 2000.
28. Perkins P, Weiss SW. Spindle cell hemangioendothelioma. An analysis of 78 cases with reassessment of its pathogenesis and biologic behavior. Am J Surg Pathol 1996;20: 1196-204.
29. Kaplan RP, Want JT, Amron DM, Kaplan L. Maffucci's syndrome: two cases reports with a literature review. J Am Acad Dermatol 1994;29:894-9.
30. Enjolras O, Chapot R, Merland JJ. Vascular anomalies and the growth of limbs: a review. J Pediatr Orthop B 2004;13:349-57.
31. Gloviczki P, Driscoll DJ. Klippel—Trenaunay syndrome: current management. Phlebology 2007;22:291-8.
32. Atiyeh BS, Musharrafieh RS. Klippel-Trenaunay-type syndrome: an eponym for various expressions of the same entity. J Med 1995;26:253-60.
33. Van Lohuizen CHJ. Cutis marmorata telangiectatica congenita [in German]. Acta Derm Venereol 1922;3:202-11.
34. Fujita M, Darmstadt GL, Dinulos JG. Cutis marmorata telangiectatica congenita with hemangiomatous histopathologic features. J Am Acad Dermatol 2003;48:950-4.
35. Devillers ACA, de Waard-van der Spek FB, Oranje AP. Cutis marmorata telangiectatica congenita. Clinical features in 35 cases. Arch Dermatol 1999;135:34-8.
36. Kienast AK, Hoeger PH. Cutis marmorata telangiectatica congenita: a prospective study of 27 cases and review of the literature with proposal of diagnostic criteria. Clin Exp Dermatol 2009;34:319-23.
37. Amitai DB, Fichman S, Merlob P, Morad Y, Lapidoth M, Metzker A. Cutis marmorata telangiectatica congenita: clinical findings in 85 patients. Pediatr Dermatol 2000;17:100-4.
38. Patel MS, Taylor GP, Bharya S, Al-Sanna'a N, Adatia I, Chitayat D, et al. Abnormal pericyte recruitment as a cause for pulmonary hypertension in Adams—Oliver syndrome. Am J Med Genet 2004;129:294-9.
39. Lapunzina P, Gairí A, Delicado A, Mori MA, Torres ML, Goma A, et al. Macrocephaly-cutis marmorata telangiectatica congenita. Report of six new patients and a review. Am J Med Genet A 2004;130A:45-51.
40. Torriello HV, Mulliken JB. Accurately renaming macrocephaly-cutis marmorata telangiectatica congenita (M-CMTC) as macrocephaly-capillary malformation (M-CM). Am J Med Genet A 2007;143:3009.
41. Wright DR, Frieden IJ, Orlow SJ, Shin HT, Chamlin S, Schaffer JV, et al. The misnomer ''macrocephaly-cutis marmorata telangiectasica congenita syndrome.'' Arch Dermatol 2009; 145:287-93.
42. Hershkovitz D, Bergman R, Sprecher E. A novel mutation in RASA1 causes capillarymalformationand limb enlargement. Arch Dermatol Res 2008;300:385-8.
43. Enjolras O, Logeart I, Gelbert F, Lemarchand-Venencie F, Reizine D, Guichard JP, et al. Arteriovenous malformations: a study of 200 cases [in French]. Ann Dermatol Venereol 2000; 127:17-22.
44. Eerola I, Boon LM, Mulliken JB, Burrows PE, Dompmartin A, Watanabe S, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet 2003;73:1240-9.
45. Alomari AI. Characterization of a distinct syndrome that associates complex truncal overgrowth, vascular, and acral anomalies: a descriptive study of 18 cases of CLOVES syndrome. Clin Dysmorphol 2009;18:1-7.
46. Mali JW, Kuiper JP, Hamers AA. Acro-angiodermatitis of the foot. Arch Dermatol 1965;92:515-8.
47. Bluefarb SM, Adams LA. Arteriovenous malformation with angiodermatitis. Arch Dermatol 1967;96:176-81.
48. Stewart WM. False Kaposi's angiosarcoma caused by multiple arteriovenous fistulas [in French]. Bull Soc Fr Dermatol Syphiligr 1967;74:664-5.
49. Zutt M, Emmert S, Moussa I, Haas E, Mitteldorf C, Bertsch HP, et al. Acroangiodermatitis Mali resulting from arteriovenous malformation: report of a case of Stewart-Bluefarb syndrome. Clin Exp Dermatol 2007;33:22-5.
50. Mazoyer E, Enjolras O, Bisdorff A, Perdu J, Wassef M, Drouet L. Coagulation disorders in patients with venous malformation of the limbs and trunk: a case series of 118 patients. Arch Dermatol 2008;144:861-7.
51. Malan E, Puglionisi A. Congenital angiodysplasia of the extremities. J Cardiol Surg 1964;5:87-130.
52. Enjolras O, Ciabrini D, Mazoyer E, Laurian C, Herbreteau D. Extensive pure venous malformations in the upper or lower limb: a review of 27 cases. J Am Acad Dermatol 1997;36: 219-25.
53. Kubiena HF, Liang MG, Mulliken JB. Genuine diffuse phlebectasia of Bockenheimer: dissection of an eponym. Pediatr Dermatol 2006;23:294-7.
54. Osawa R, Kato N, Yanagi T, Yamane N. A case of Bockenheimer's syndrome (genuine diffuse phlebectasia): venous involvement inside muscles was detected by magnetic resonance imaging. Clin Exp Dermatol 2007;32:664-7.
55. Matassi R. Differential diagnosis in congenital vascular bone syndromes. Semin Vasc Surg 1993;6:223-44.
56. Crosher RF, Blackburn CW, Dinsdale RC. Blue rubber-bleb naevus syndrome. Br J Oral Maxillofac Surg 1988;26:160-4.
57. Hofhuis WJ, Oranje AP, Bouquet J, Sinaasappel M. Blue rubber bleb naevus syndrome: report of a case with consumption coagulopathy complicated by manifest thrombosis. Eur J Pediatr 1990;149:526-8.
58. Bailey OT. The cutaneous glomus and its tumors: glomangiomas. Am J Pathol 1935;11:915-35.
59. Brouillard P, Boon LM, Mulliken JB, Enjolras O, Ghassibé M, Warman ML, et al. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations (''glomangiomas''). Am J Hum Genet 2002;70:866-74.
60. Boon LM, Brouillard P, Irrthum A, Karttunen L, Warman ML, Rudolph R, et al. A gene for inherited cutaneous venous anomalies (''glomangiomas'') localizes to chromosome 1p21-22. Am J Hum Genet 1999;65:125-33.
61. Mallory SB, Enjolras O, Boon LM, Rogers E, Berk DR, Blei F, et al. Congenital plaque-type glomuvenous malformations presenting in childhood. Arch Dermatol 2006;142:892-6.
62. Boon LM, Mulliken JB, Enjolras O, Vikkula M. Glomuvenous malformation (glomangioma) and venous malformation distinct clinicopathologic and genetic entities. Arch Dermatol 2004;140:971-6.
63. Kaye VM, Dehner LP. Cutaneous glomus tumor: a comparative immunohistochemical study with pseudoangiomatous intradermal melanocytic nevi. Am J Dermatopathol 1991;13:2-6.
64. Gross RE. Cystic hygroma. In: The surgery of infancy and childhood. Philadelphia: W.B. Saunders; 1953. pp. 960-70.
65. Belov ST. Anatomopathological classification of congenital vascular defects. Semin Vasc Surg 1993;6:219-24.
66. Boyd JB, Mulliken JB, Kaban LB, Upton J, Murray JE. Skeletal changes associated with vascular malformations. Plast Reconstr Surg 1984;76:789-97.

67. Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone): its relations to hemangiomatosis. J Bone Joint Surg Am 1955; 37-A:986-1004.
68. Somoza Argibay I, Díaz González M, Martínez Martínez L, Ros Mar Z, López-Gutiérrez JC. Heterogenicity of Gorham-Stout syndrome: association with lymphatic and venous malformations [in Spanish]. An Pediatr (Barc) 2003;58:599-603.
69. Bruch-Gerharz D, Gerharz CD, Stege H, Krutmann J, Pohl M, Koester R, et al. Cutaneous vascular malformations in disappearing bone (Gorham-Stout) disease. JAMA 2003;289: 1479-80.
70. Dunbar SF, Rosenberg A, Mankin H, Rosenthal D, Suit HD. Gorham's massive osteolysis: the role of radiation therapy and a review of the literature. Int J Radiat Oncol Biol Phys 1993;26: 491-7.