Actas Dermosifiliogr. 2007;98:141-58

REVIEW ARTICLE

Vascular Malformations (I). Concept, Classification, Pathogenesis and Clinical Features

P Redondo
Departamento de Dermatología, Clínica Universitaria de Navarra, Pamplona, Spain

Abstract. Vascular malformations are anomalies always present at birth that, contrary to hemangiomas, never regress and may grow during lifetime. Clinical presentation of vascular malformations is extremely variable and ranges from asymptomatic spots of mere aesthetic concern to lesions with high blood flow or located in critical sites that may be life-threatening. Given the low incidence of these disorders it is difficult to establish therapeutic guidelines. In addition to a correct classification of vascular anomalies, it is necessary a multidisciplinary approach for the follow-up and management of these patients. The first part of this review focuses on the different classifications of vascular anomalies, maintaining as reference the one proposed by the International Society for the Study of Vascular Anomalies (ISSVA). Additionally, clinical features of the different subtypes of vascular anomalies as well as their association in certain syndromes are reviewed.

Key words: vascular malformation, Klippel-Trenaunay, venous, lymphatic, arteriovenous.

MALFORMACIONES VASCULARES (I). CONCEPTO, CLASIFICACIÓN, FISIOPATOGENIA Y MANIFESTACIONES CLÍNICAS

Resumen. Las malformaciones vasculares son anomalías presentes siempre en el nacimiento que, al contrario que los hemangiomas, nunca desaparecen y pueden crecer durante toda la vida. La presentación clínica de las malformaciones vasculares es extremadamente variable y va desde manchas asintomáticas con repercusión meramente estética, hasta lesiones de alto flujo o localizaciones peculiares que pueden incluso poner en peligro la vida del enfermo. También al tratarse de enfermedades relativamente raras es difícil alcanzar la suficiente experiencia en su manejo para establecer pautas contrastadas de tratamiento. Además de una correcta clasificación de las anomalías vasculares, es necesario un enfoque multidisciplinar respecto del seguimiento y las posibilidades terapéuticas de estos pacientes. En la primera parte de esta revisión se abordan las diferentes clasificaciones de las malformaciones vaculares, manteniendo como referencia la sugerida por la ISSVA *(International Society for the Study of Vascular Anomalies)*. Además se incide en las características clínicas de los diferentes subtipos de malformaciones vasculares así como sus asociaciones en determinados complejos sindrómicos.

Palabras clave: malformación vascular, Klippel-Trenaunay, venosa, linfática, arterio-venosa.

Introduction

Almost all congenital vascular abnormalities affect the skin and are evident from birth or become so during the first few weeks of life. Up to almost 12% of newborns are thought to have a hemangioma, although most of these disappear during the first year of life.[1] For centuries, these lesions have been recognized as cutaneous vascular nevi, attributed in some cultures to whims or excessive consumption of red fruits by the mother during pregnancy. In the 19th century, with the first steps in histopathology, they began to be known as angiomas, although other types of lesion have often erroneously been described using this term. For example, the term hemangioma, the most important, has been generically applied to all types of vascular lesion regardless of the pathogenesis, histology, or clinical course.

At first glance, the 2 most common types of vascular birthmarks—hemangiomas and vascular malformations—may appear to be very similar but their course and treatment are different. Hemangiomas appear in the first few weeks of life, whereas vascular malformations are always present from birth even though they might not be apparent. Hemangiomas usually regress spontaneously over time

Correspondence:
Pedro Redondo.
Departamento de Dermatología.
Clínica Universitaria de Navarra. 31080 Pamplona. Spain
predondo@unav.es

Manuscript accepted for publication January 24, 2007.

whereas vascular malformations never disappear and often grow during a person's lifetime.[2] Thus, in general, most hemangiomas can be considered insignificant tumors that do not require treatment except in certain exceptional circumstances and that represent an esthetic rather than a medical problem. Nevertheless, they may have a large psychological impact in the family setting. Just as there are congenital hemangiomas with intrauterine development that begin to regress from the moment of birth and that will completely resolve in a few months, some hemangiomas with normal development may not involute and will persist throughout a person's life. This group, defined initially by Enjolras et al,[3] and characterized clinically by a solitary lesion located almost always on the head and neck, and histologically by glucose-transporter-1 negativity, is the only one that might be confused with a vascular malformation.

Thus, in summary, with the above exception, no vascular birthmark present in an adolescent or adult should be described as a hemangioma or angioma because it is really a vascular malformation. There is much confusion concerning vascular abnormalities, even within the scientific community. Indeed, it has been found that more than half the patients attending referral clinics with vascular abnormalities had been diagnosed and followed incorrectly.[4] Some physicians familiar with this entity often rightly describe children with vascular malformations as "nomadic patients" because they have visited different specialists according to the anatomical site and possible consequences for specific organs, and in each case a different diagnosis has been made and treatment has followed different therapeutic criteria. Often, at the best of times, treatment and follow-up consist of "phototherapy," a term that does not refer to the therapeutic properties of ultraviolet radiation but rather to the periodic photographs to assess the lesion course. In this case, "at the best of times" means that disproportionate or inappropriate treatments are not applied because of erroneous diagnosis.

Table 1. Mulliken and Glowacki Classification of Congenital Vascular Lesions

Hemangiomas
Vascular Malformations
Capillary
Venular
Venous
Lymphatic
Arteriovenous
Combined
Venous-lymphatic
Venous-venular

Modified by Waner and Suen.[12]

Therefore, in addition to a correct classification of vascular malformations, a multidisciplinary approach to the follow-up and management of these patients is needed. In 1982, Mulliken and Glowack[5] published a biological classification of vascular lesions based on the main endothelial characteristics. This classification has become widely accepted and is reviewed every 2 years by the International Society for the Study of Vascular Anomalies (ISSVA). Despite this, there is currently substantial confusion in the classification of these lesions. For example, in an analysis of the latest editions of 5 text books of genetic medicine, an inappropriate use of the terms hemangioma and vascular malformation could be found,[6] attributable to the even more frequent confusions found in clinical journals.[7,8]

The ISSVA was founded in 1992 in Budapest with the aim of achieving consensus among health care professionals from different medical fields who are in contact with these patients. Specialists include pediatricians, dermatologists, interventional radiologists, plastic and vascular surgeons, pediatric surgeons, ear, nose, and throat specialists, ophthalmologists, pathologists, and geneticists. The common aim was to further the knowledge of the pathogenesis, diagnosis, and treatment of patients with vascular lesions. Treatment of these lesions is often very complex and consensus should be reached among a broad group of specialists who, working as a team, arrive at definitive or palliative solutions for patients with vascular malformations, limiting "phototherapy" to those patients in whom the maxim "do no harm" really can be applied after detailed examination. We all bear the responsibility of training and inspiring those professionals in contact with these patients so that they are able to send them to referral clinics and thus ensure that the vascular malformations get the best diagnosis, treatment, and follow-up.

Classification of Vascular Malformations

It was more than 20 years ago when Mulliken and Glowacki[5] described a biological classification of congenital vascular malformations based on the main pathological characteristics of the endothelium and the natural course of the lesion (Table 1). This classification was later redefined by Mulliken and Young[9] and adopted by the ISSVA in 1996. Today, it is the most widely used classification with minimal changes to the original version (Table 2). In 1998, the so-called Hamburg classification was published (and subsequently approved by the ISSVA). This classification describes the malformation in terms of the predominant component of the vascular lesion, which is then classified as truncular or extratruncular according to the embryonic stage when the malformation begins to develop[10,11] (Table 3). This classification does not include hemangiomas or

Table 2. 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, nevus flammeus)
	Venous (V)
	Lymphatic (L) (lymphangioma, cystic hygroma)
	Arterial (A)
Combined	Arteriovenous fistula (AVF)
	Arteriovenous malformation (AVM)
	CLVM (includes most of the Klippel-Trenaunay syndromes)
	CVM (includes some cases of Klippel-Trenaunay syndrome)
	LVM
	CAVM
	CLAVM

Table 3. Classification of Vascular Malformations: Hamburg, Germany 1988

	Anatomic Form	
Type of Defect:	*Truncular*	*Extratruncular*
Mainly arterial	Aplasia	
	Obstruction	Infiltrating
	Dilation	Limited
Mainly venous	Aplasia	
	Obstruction	Infiltrating
	Dilation	Limited
Mainly arteriovenous shunt	Superficial arteriovenous fistula	Infiltrating
	Deep arteriovenous fistula	Limited
Combined defects	Arterial and venous	Infiltrating
	Hemolymphatic	Limited

lymphatic malformations, but it is useful for making diagnoses according to clinical and anatomic characteristics, forms the basis for defining the treatment of choice, and aids dialogue between different specialists.

Waner and Suen[12] made 2 minor changes to the Mulliken classification: they considered the term "arteriovenous malformations" to be erroneous and suggested using the term capillary malformations instead because it is in the capillary bed where the small arteriovenous shunts are found, and all other characteristic findings (afferent arterial hypertrophy and dilation of the efferent venous system) are secondary to these malformations. This first modification does not alter the previous classification, as the authors were of the opinion that rather than clarifying matters it could lead to confusion. The second modification does however affect the classification. Thus, they introduced the term venular malformation to refer to the port wine stain or nevus flammeus, were of the opinion that these lesions correspond to postcapillary ectatic venules of the papillary plexus, and subclassified these malformations according to size. The classification is as follows:

1. Vessels between 50 and 80 µm in diameter, characterized clinically as pink macules.
2. Vessels between 80 and 120 µm, with a darker coloring than the previous classification.
3. Vessels between 120 and 150 µm with red-violaceous color.
4. Vessels greater than 150 µm, corresponding to dilated vessels that form palpable nodules, of cobblestone appearance and violaceous coloring. This group also includes the so-called venule malformations of the midline, known in lay terms as salmon patch, stork bite, or angel's kiss.

Other specialists have also classified venous malformations according to anatomic site and hemodynamic characteristics,[13] an approach which is particularly useful for assessing the efficacy of sclerotherapy. Phlebography is necessary to define the hemodynamic characteristics of the lesion, although as we shall see later, this test may be supplanted in the future by computed tomographic (CT) angiography. Thus, venous malformations can be divided into 4 groups: *a)* isolated malformations with no peripheral drainage; *b)* malformations that drain into normal veins; *c)* malformations that drain into dysplastic veins; and *d)* venous distension. The first 2 types are the easiest to treat and show a better response to sclerotherapy.

Finally, the natural history of an arteriovenous malformation can be divided into different stages according to the moment in its development. Schobinger[8] divides these stages as follows:

I. Quiescence: characterized by a pink-violaceous mark and the presence of an arteriovenous shunt detectable by echo-Doppler ultrasound.
II. Expansion: as in stage I, but clinically pulsatile, with obvious presence of tortuous vessels and tight turns.
III. Destruction: as for stage II, along with dystrophic skin changes, ulceration, bleeding, and continuous pain.
IV. Decompensation: similar to stage III, associated with heart failure.

Pathophysiology

Vascular malformations are benign, nontumorous lesions that are always present from birth, although they may not always be visible until weeks or months later.[14,15] Their incidence is 1.5%, approximately two-thirds are predominantly venous,[16] and they are evenly distributed according to sex and race. They are considered diffuse or localized defects in embryonic development and have been traditionally attributed to sporadic mutations. However, recent evidence points to a possible familial hereditary component. Vikkula et al[17,18] identified a mutation characterized by increased activity of the tyrosine kinase receptor tunica internal endothelial cell kinase-2 (Tie-2) in 2 families with venous malformations. Tie-2 is essential for early vessel development and increased activity can lead to abnormal growth of the primary vascular plexus.[19] The same authors also found glomulin to be implicated in patients with glomuvenous malformations.[20] Furthermore, some genetic mutations have been reported in cerebral cavernous malformations[21] and combined vascular malformations such as Klippel-Trenaunay syndrome[22] and Proteus syndrome.[23] Likewise, at least 2 types of vascular malformation have been implicated in abnormalities in neural modulation of blood vessels[24,25]; thus, venular malformations are probably due to a relative or absolute deficit in autonomic innervation of the postcapillary venular plexus, whereas arteriovenous malformations may be due to the same abnormality, but at the level of the precapillary sphincters[26] (Table 4).

To explain the etiology of port wine stains, the term "sick dermatome" has been coined whereby a lesion is due to completely or partly defective sensory and autonomic vascular innervation giving rise to growth of the affected vessels, which may even take on a cobblestone appearance. In the case of complete defects, the changes over time will be quicker. Histologic study of hypertrophy in such vessels has revealed, in addition to the vascular abnormalities, diffuse hamartomatous changes affecting epithelial connective tissue and neural elements of the skin, an observation which points to a somatic mutation in the affected area.[27] Moreover, precapillary sphincters are responsible for regulating blood flow through the nidus. Defective autonomic innervation or neuroreceptor deficit at this site might possibly be the cause of arteriovenous malformations. The age of onset and the clinical course will depend on whether the defect is complete or partial.

Unlike hemangiomas, vascular malformations do not have a growth cycle and subsequent spontaneous regression but rather persist throughout a person's lifetime, growing slowly, sometimes in response to injury, changes in blood or lymph pressure, infections, hormonal changes, etc. Characteristically, these lesions progressively produce ectasia of vascular structures, increasing the diameter of vessels without increasing their number. Expansion is therefore by hypertrophy but not by hyperplasia, as is the case for hemangiomas. In any case, there are nuances to this traditional concept as many exceptions can be found. For example, arteriovenous malformations often grow through hyperplasia and may behave like actual tumors. Despite an apparent endothelial quiescence, some vascular malformations can expand rapidly during pregnancy, after surgery, or in response to injury. Further clarification of the pathogenesis of vascular malformations is still needed but their formation and progression are closely related to angiogenesis. Angiogenesis is a complex process regulated by many angiogenic factors leading to the formation of new functional vasculature. This includes differentiation of endothelial and mural cells (pericytes), cell proliferation and migration, and specification of arterial, venous, and lymphatic fate.[28] Although to our knowledge studies in

Table 4. Genetics of Vascular Malformations

Vascular Malformation	*Chromosomal Localization*	*Gene*	*OMIM #*
Type 1 cerebral cavernous malformation	7q11.2-q21	KRIT1	
Type 2 cerebral cavernous malformation	7p15-p13	MGC4607	#603284
Type 3 cerebral cavernous malformation	3q25.2-27	PDCD10	#603285
Klippel-Trenaunay syndrome	5q13.3	AGGF1	#149000 and *608464
Arteriovenous-capillary malformations	5q13.3	RASA 1	#608354
Venous malformation with cutaneous and mucosal involvement	9p21	TIE2	#600195
Glomuvenous malformation	1p22-p21	lomulin	#138000
Proteus syndrome	10q23.31	PTEN	#176920 and *601728

Adapted from Wang QK. Update on the molecular genetics of vascular anomalies. Lymphat Res Biol. 2005;3:226-33.
Abbreviation: OMIM, Online Mendelian Inheritance in Man. Available from: http://www.ncbi.nlm.nih.gov/omim/

adult patients with vascular malformations have yet to show an angiogenic serum profile, theoretically, such an observation might be expected, and some unpublished preliminary results from our group support it. Marler et al[29] observed elevated metalloproteinases and basic fibroblast growth factor (bFGF) in urine from children with hemangiomas and vascular malformations compared to controls. Another study showed elevated serum levels of bFGF in a patient with glomangiomas.[30] In addition, some clinical findings and molecular studies have found that cerebral arteriovenous malformations show angiogenesis and vascular remodeling.[31] We have recently observed elevated plasma levels of angiopoietin-2 (as in some cerebral lesions[32]) and Tie-2 receptor in a patient with extensive and active arteriovenous malformation.[33] All these findings point to a significant role for angiogenesis in the development and maintenance of vascular malformations, perhaps not as abrupt and circumscript in time as in the proliferative phase of hemangiomas,[34,35] but still important for explaining the pathophysiology of these lesions.

Clinical Characteristics

We will now follow the Mulliken and Glowacki classification[5] with the aforementioned modifications concerning venular and arteriovenous malformations.[12]

Venular Malformations

In the Mulliken and Glowacki[5] classification, venular malformations are denominated capillary malformations even though they would be better classed as venular because of the abnormal histopathological findings in the postcapillary venules of the papillary plexus.[12] Venular malformations can be divided into midline malformations and traditional venular malformations known as port wine stains, telangiectatic nevus, or nevus flammeus.

Midline lesions are pink macules, may or may not be confluent, are always present from birth, appear on the midline of the head, and are commonly known as "salmon stains," "stork bites," or "angel kisses." They occur in 40% of white newborns and 30% of black ones. They are usually transient and tend to disappear during the first year of life in 65% of boys and 54% of girls,[36] particularly in the case of lesions on anterior sites. Unlike port wine stains, they never progress, and hypertrophy or cobblestone appearance is extremely uncommon. When they affect anterior parts of the body, they characteristically spread in a wedge-shaped pattern on the glabella and forehead along territory innervated by the supratrochlear and supraorbital nerves. Often the nose in the supraalar region and the upper lip in the two-thirds of the philtrum are affected.

Port wine stains are reddish-pink macules that darken over time. Although they are always congenital, they do not become visible until several days after birth. They occur in 0.4% of newborns and equally in boys and girls. In 83% of cases, they appear on the head and neck[37] (Figure 1) and, interestingly, they affect the right side of the face more often than the left side.[38]

Port wine stains are located on one or more facial dermatomes defined by branches of the trigeminal nerve. The V2 dermatome is the one most often implicated (57%), followed by the mandibular one (V3), and the ophthalmic one (V1).[37] When more than one dermatome is affected, the most common association is V2 with V1 or V3, accounting for 90% of the cases. The lesion usually shows a geographic confluent morphology, and in such cases response to laser therapy is better than in patchy lesions.[37] When the V2 dermatome is affected, the mucosa adjacent to or close to the cutaneous lesion may be compromised. Mucosa such as the vermillion border, labial mucosa, and maxillary and gingival mucosa tend to be affected in this case. Unlike lesions of the midline, these venular malformations darken and thicken with age, acquiring a more violaceous tone and a cobblestone appearance, although the course may vary among individuals and is much more evident in the head and neck region than at other anatomic sites (Figure 2). They may sometimes be associated with small skeletal changes in the form of bone hypertrophy, particularly when the V2 lesion extends to the gingival and maxillary mucosa. This localized hypertrophy may lead to gaps between the teeth and a striking increased volume of the affected lip that requires surgical correction (Figure 3).

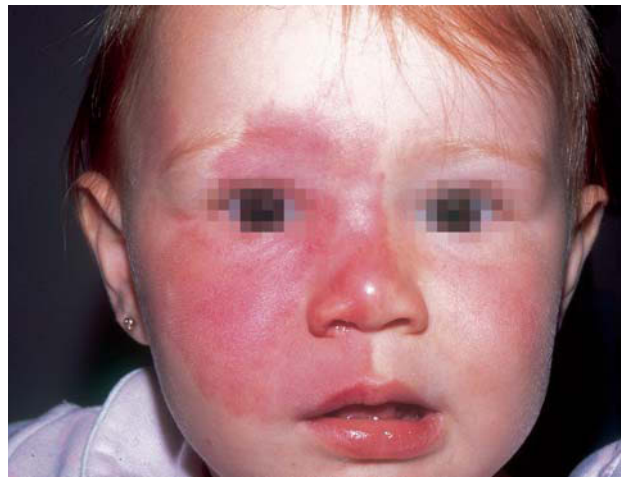

Figure 1. Port wine stain on the right side of the face without exceeding the midline. V1 and V2 involvement.

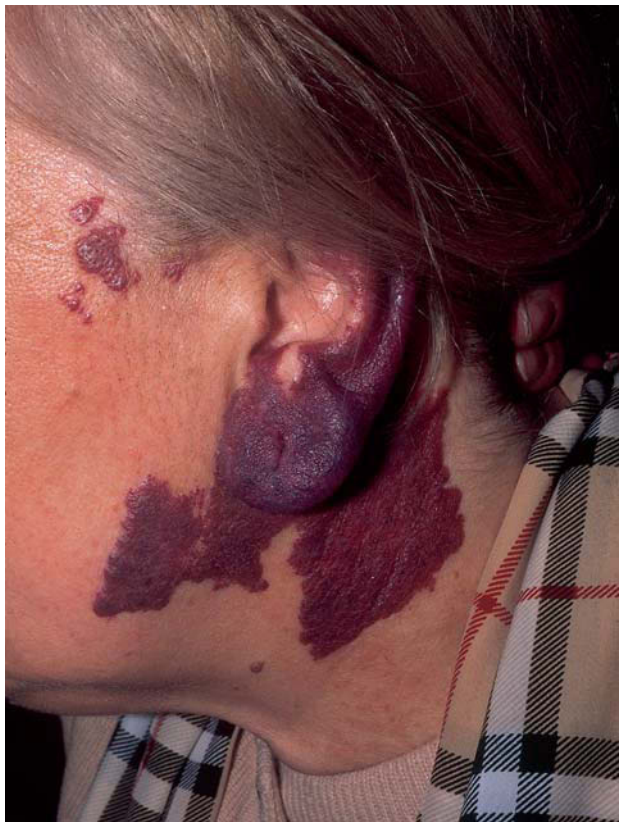

Figure 2. Adult patient with port wine stain. Note the purple coloration and hypertrophy of the pinna.

Table 5. Syndrome Complexes Associated With Vascular Malformations

Vascular Malformations	*Syndromes*
Single	
Venular	Sturge-Weber syndrome Cobb syndrome Sacral venular malformation Cutis marmorata telangiectatica congenita Phacomatosis pigmentovascularis Von Hippel-Lindau syndrome
Venous	Blue rubber bleb nevus syndrome Maffucci Syndrome Glomuvenous malformations
Combined	
Venular-venous-lymphatic	Klippel-Trenaunay syndrome Proteus syndrome
Venular-venous with arteriovenous fistula	Parkes-Weber syndrome
Arteriovenous	Rendu-Osler-Weber syndrome
Venous or venous-lymphatic	Maffucci Syndrome Gorham disease

Syndromes Associated With Venular Malformations

Certain venular malformations, when present at a specific anatomic site, are associated with syndromes that are diagnosed or suspected due to the cutaneous vascular anomaly (Table 5).

Sturge-Weber Syndrome or Encephalotrigeminal Angiomatosis

The Sturge-Weber syndrome occurs due to sporadic mutations, and has a prevalence of 1 case per 50 000 neonates. Clinically, it is characterized by a facial venular malformation associated with leptomeningeal vascular malformation and ocular abnormalities,[39,40] although not all lesions may be apparent and leptomeningeal abnormalities may even occur without venular malformation. Increased expression of the fibronectin gene in fibroblasts taken from damaged tissues in some patients has been attributed a pathogenic role.[41]

The V1 dermatome is always compromised in the case of port wine stains. Although the lesion is generally unilateral, it may affect both sides of the face or extend to the lower half of the face and trunk (Figure 4). It is often associated with gingival, labial, or hemifacial hyperplasia due to expansion of soft or bony parts; hyperplasia is greater with more extensive port wine stains.[42] The most important clinical ocular manifestation is glaucoma, which should be treated early.[43] However, the most frequent manifestation is increased choroidal vascularization that gives a characteristic image at the back of the eye know as "tomato ketchup." This lesion is usually asymptomatic in childhood but can lead to retinal detachment in adult life.[44]

Leptomeningeal angiomatosis usually occurs on the same side as the venular malformation and is manifest clinically as epileptic symptoms with focal tonic-clonic seizures on the contralateral side of the body, with onset during the first year of life.[43] Response to treatment is variable and most seizures usually become resistant to antiepileptic drugs, leading to slow progressive hemiparesis. Half of the patients are mentally retarded during childhood as a result of chronic consumption of antiepileptics, local hypoxia resulting from prolonged epileptic seizures, and progressive cerebral atrophy.[45]

Although diagnosis is essentially clinical, magnetic resonance imaging (MRI) can indicate whether leptomeningeal vascular abnormalities and cerebral atrophy are present. This technique is also useful for detecting the so-called "tram-track" cerebral calcifications which appear over time in patients.[46] An annual ophthalmological check-up that includes examination of the back of the eye and determination of intraocular pressure should be undertaken. In 22 patients with Sturge-Weber syndrome (aged between 8 days and 25 months), single photon emission tomography

(SPECT) was done with xenon 133 to determine the regional cerebral blood flow at the same time as an MRI scan. At times when a seizure was documented, SPECT revealed decreased blood flow, confirming hypoperfusion and hypometabolism in the damaged side. Surprisingly, when SPECT was done in patients before the seizures, the most affected side showed hyperperfusion in 75% of the cases. This test can therefore help in the early diagnosis of damage in children with the Sturge-Weber syndrome, a possibility that is beneficial because early treatment of convulsions can help limit anoxia and neurological damage.[47]

Cobb Syndrome or Cutaneomeningospinal Angiomatosis

In Cobb syndrome, a venular malformation with a metameric distribution on the trunk or proximal part of the limbs occurs above a vascular malformation of the spinal cord. The onset of symptoms from the spinal malformation takes place during childhood and adolescence. Symptoms take the form of paraplegia or spastic paraparesis and sensory loss below the level of the affected spinal cord. A metameric port wine stain present on the trunk should raise suspicion of Cobb syndrome before neurologic symptoms appear and some patients with a spinal lesion may be candidates for surgery. Diagnostic confirmation is obtained by MRI.[48]

Although to a lesser extent than with hemangiomas, the presence of a venular malformation in the lumbosacral region might be associated with spinal dysraphism, which should be ruled out by an imaging technique (ultrasound or MRI).

Cutis Marmorata Telangiectatica Congenita

Although cutis marmorata telangiectatica congenita is classified as a simple venular malformation, it is actually a mixed malformation that combines venular and venous elements. One out of every 3000 neonates is affected and it has a recessive autosomal character.[49,50] It is characterized clinically as livedo reticularis, which takes on a marble-like appearance, with flat or depressed lesions and superficial telangiectasias. In the case of segmental disease, hypotrophy or atrophy of the skin or—less frequently—ulceration of the affected limb may occur. Over time, the lesions of some patients tend to get progressively lighter until completely disappearing.[51] When the lesions are diffuse, follow a mosaic pattern, or the head is involved, further tests are recommended to rule out other associated diseases such as retinal abnormalities, secondary neovascular glaucoma, patent ductus arteriosus, or spina bifida.[52]

Phacomatosis Pigmentovascularis

The term phacomatosis pigmentovascularis refers to congenital processes characterized by the combination of vascular and melanocytic nevi in the same patient, in whom "twin spotting" is a manifestation of mosaicism. Most patients can be classified into 4 types. Type 1 is associated with a venular malformation with melanocytic nevus and verrucous epidermal nevus. In type 2, venular malformation

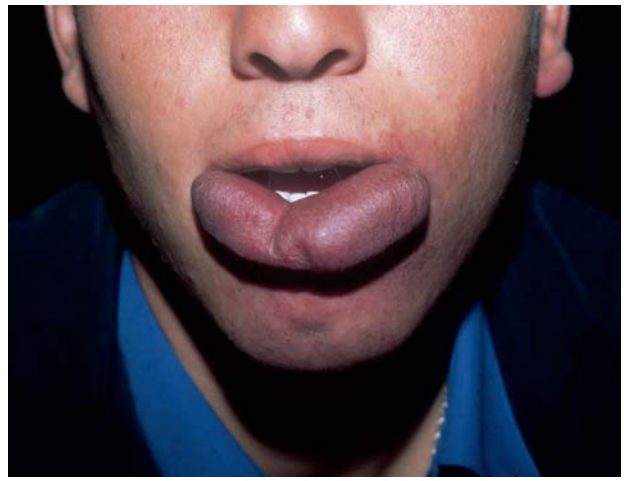

Figure 3. Adolescent with bilateral port wine stain limited to V3 with substantial labial hypertrophy susceptible to surgery.

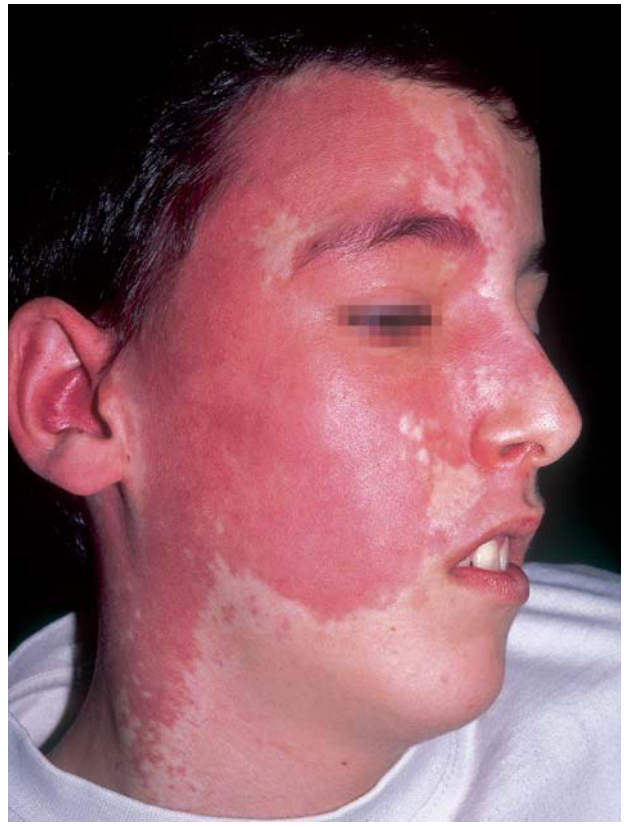

Figure 4. Sturge-Weber syndrome with port wine stain at the V1 and V2 level, glaucoma, and leptomeningeal involvement.

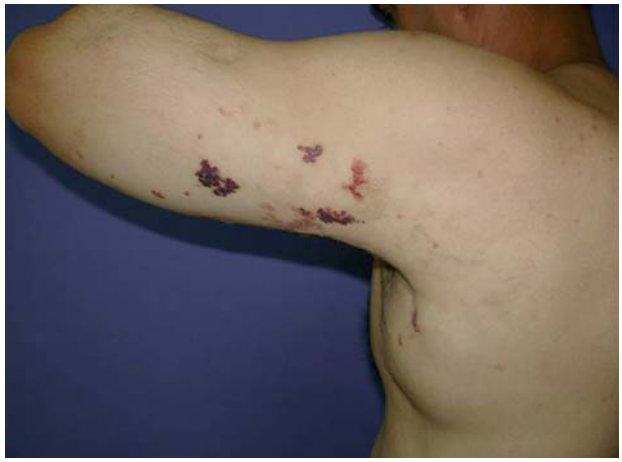

Figure 5. Lymphatic malformation. Note the bulky axillary macrocystic lesion and hemorrhagic vesicles on the flexor surface of the proximal forearm.

is observed in association with dermal melanocytosis in the form of aberrant Mongolian spots. In type 3, venular malformation is combined with nevus spilus. Type 4 corresponds to the association of venular malformation, nevus spilus, and aberrant Mongolian spots. The last 3 may also present with an anemic nevus. Recently, type 5 has been described in which extensive cutis marmorata telangiectatica congenita and aberrant Mongolian spots can be seen.[53] In turn, each type is subdivided into A and B depending on whether involvement is exclusively cutaneous (type A) or whether some systemic repercussion (ophthalmologic, central nervous system, or skeletal abnormalities) or relationship with Sturge-Weber syndrome, Klippel-Trenaunay syndrome, and/or Ota nevus is found (type B).[54]

Lymphatic Malformations

Traditionally, lymphatic malformations have been described as lymphangioma, cystic hygroma, lymphangioma circumscriptum, and lymphangiomatosis.[55] Like other vascular malformations, lymphatic malformations are always congenital, although only 65% to 75% are diagnosed at birth; by the end of the second year of life, 80% to 90% have been diagnosed.[56] The most common site is the head and particularly the neck (90%)[57]; the high incidence at this site is explained by some authors in terms of the complexity of the cervical lymphatic system.[58] Other typical sites are the axilla, thorax, mediastinum, retroperitoneum, buttocks, and anogenital region. The clinical appearance varies according to the size, depth, and site of the lesion. Often, multiple translucent vesicles containing a viscous fluid are present at the level of the skin or mucosa, which resembles "frog spawn" (Figure 5). The surrounding skin is normal, sometimes with a bluish hue. The surface lesions are connected to deeper cisternae for lymph fluid lying in the subcutaneous or submucosal tissue. Depending on depth, malformations are divided into the microcystic or diffuse variant (also known as lymphangioma), characterized by poorly defined edges and massive generalized edema, and a macrocystic or localized variant comprising multiseptate cysts. In general, mucosal lesions (which affect the floor of the mouth, jugal mucosa, and tongue) belong to the first type and are hard to eradicate with surgery, whereas cervical lesions, the most common type, also known as cystic hygromas, are macrocystic and easier to resect. The latter type of malformation presents as painless nonpulsatile masses with a rubbery consistency that are covered by normal colored skin.

Often, microcystic mucosal lesions may be exacerbated by accidental injury or surgery, intralesional hemorrhage, or infection.[59] When they spread, cervical lesions may compress the pharynx or trachea when the mediastinum is involved and those close to the orbit may induce proptosis. Sudden growth of a cervical lymphatic malformation may be an emergency because the airways can be compromised, sometimes leading to respiratory distress. Some studies have reported episodes of sepsis in up to 16% of cervical lesions,[60] possibly triggered by oral bacteria.[10] Deep lesions cause skeletal hypertrophy in 83% of those affected, and distortion is evident in 33%.[61] Such observations are not due to increased blood supply as is the case for other vascular malformations. Specifically, mandibular hypertrophy may cause prognathism and poor jaw closure. Lymphatic abnormalities in the thorax, and particularly those in the thoracic duct, may first become manifest with pleural symptoms in the form of chylothorax. Abnormalities in the gastrointestinal tract cause hypoalbuminemia due to protein-losing enteropathy. Pelvic lesions may become manifest through urinary obstruction, diarrhea, and recurrent infections. When such lesions affect a limb, large lymphatic malformations often cause pain, inflammation, and gigantism due to growth of musculoskeletal tissue. In combined malformations such as Klippel-Trenaunay syndrome, the greater the extent of the lymphatic malformation, the greater the number of complications and secondary effects.

There is a syndrome known as Gorham-Stout syndrome, also known as "phantom bone," characterized by the presence of lymphatic and venous malformations affecting the skin, mediastinum, and bone. Bone lesions are usually unilateral and cause osteolysis with secondary fibrosis. Extensive lesions may lead to the disappearance of entire bones.[62,63]

Some cases of regression of lymphatic malformations have been reported, explainable in theory by the appearance over time of a lymphatic-venous shunt.[64] In such cases, it is advisable to delay treatment,[10,58,59] although some of these supposedly implicated lesions may actually correspond to

subcutaneous hemangiomas following their natural course. At present, it is possible to detect the involvement of lymphatic vessels in some vascular malformations that do not a priori appear particularly lymphatic through the use of selective lymphatic cell markers (such as lymphatic vessel endothelial hyaluronan receptor [LYVE]-1 and D-240). Some authors suggest that the presence of these cells is associated with a greater number of coagulation disorders—this is discussed later in the article.[65]

Venous Malformations

Venous malformations occur in ectatic vessels that have low blood flow and that are morphologically and histologically similar to veins. They are classed as either superficial or deep, and as localized, multicentric, or diffuse. The skin or mucosa that covers such malformations varies in color according to the depth and degree of ectasia of the lesion. The most superficial ones are a purple color whereas the deeper ones appear more bluish or greenish, or may not even be visible. These lesions are soft to the touch, sometimes have a nodular appearance, and empty on applying pressure (Figure 6). In certain positions, such as those on the head and neck after the Valsalva maneuver, the malformation fills with blood, whereas malformations at other sites drain when the affected area is raised above the level of the heart. In highly ectatic lesions, the presence of small venous thrombi is not uncommon. The lesion may become infected and the infection may spread rapidly, causing pain and inflammation. Phlebolites, that is, radiologic markers of this type of malformation, may be present and such malformations appear at early ages. A particularly characteristic feature is that first thing in the morning, patients may experience pain that gradually remits with movement. Symptoms may also be exacerbated in pregnant women and women with hormonal imbalances[10] (Figure 7).

In the head and neck region, venous malformations may often compromise the mucosa, with the tongue, palate, lips, and jugal mucosa affected and infiltration of the muscle, salivary glands, and even bone structures (Figures 8 and 9). Specifically, mandibular or maxillary involvement is not uncommon in the form of painless slow-growing masses. The most noteworthy manifestation is gaps between the teeth, which may be moveable or fall out prematurely with heavy bleeding. In the radiograph, the affected bone appears with a honeycomb pattern.[66] Hypertrophy of soft tissues and perilesional bone occurs relatively frequently in large lesions. When such lesions affect the periorbital region or the neck, growth may cause ocular problems or airway obstruction, respectively. Relatively frequently, venous malformations are found in the limbs, and are often longer and deeper than can be

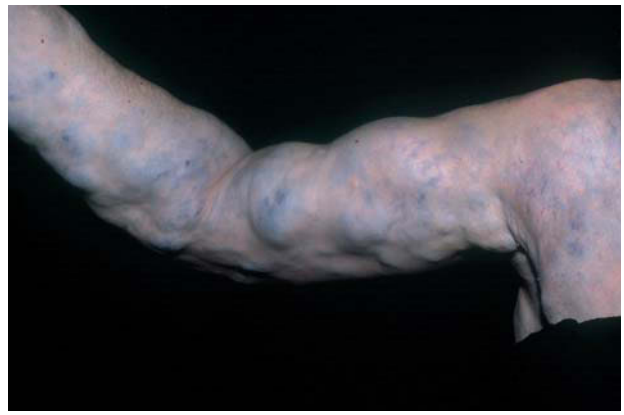

Figure 6. Extensive venous malformation on the right arm. Compressible lesions that partially empty on lifting the arm.

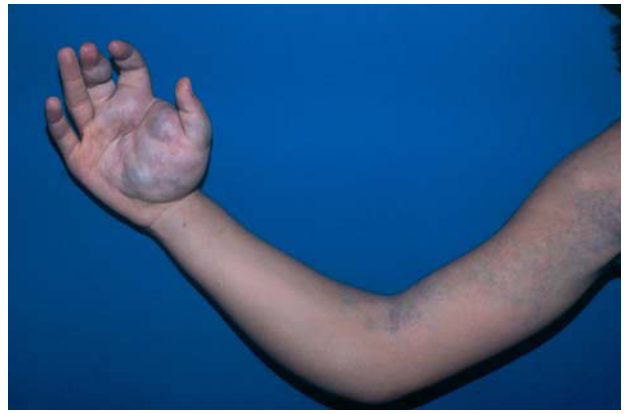

Figure 7. Well-defined venous malformation of the hand that extends diffusely along the upper right arm.

appreciated externally. Muscle is almost always involved, and joints and bones are also often affected. Unlike combined vascular malformations such as Klippel-Trenaunay syndrome, musculoskeletal atrophy or hypotrophy rather than hypertrophy of the affected limb is usually observed (Figure 10). When the knee is affected, gonalgia is common with functional impairment and hemarthrosis. It is not unusual for arthropathy due to hemosiderin to eventually progress to degenerative arthritis. In a series of 176 patients with venous malformations affecting skeletal muscle tissue, the incidence was twice as high in women and two-thirds of the patients had been diagnosed at birth, whereas the remaining ones had been diagnosed during childhood or adolescence. The most common sites were the head, neck, and limbs, and the main symptoms were pain and inflammation.[67]

In another series of 27 patients with extensive venous malformations in the limbs, all had muscular involvement, 81% joint involvement (elbow or knee), and 63% of 19

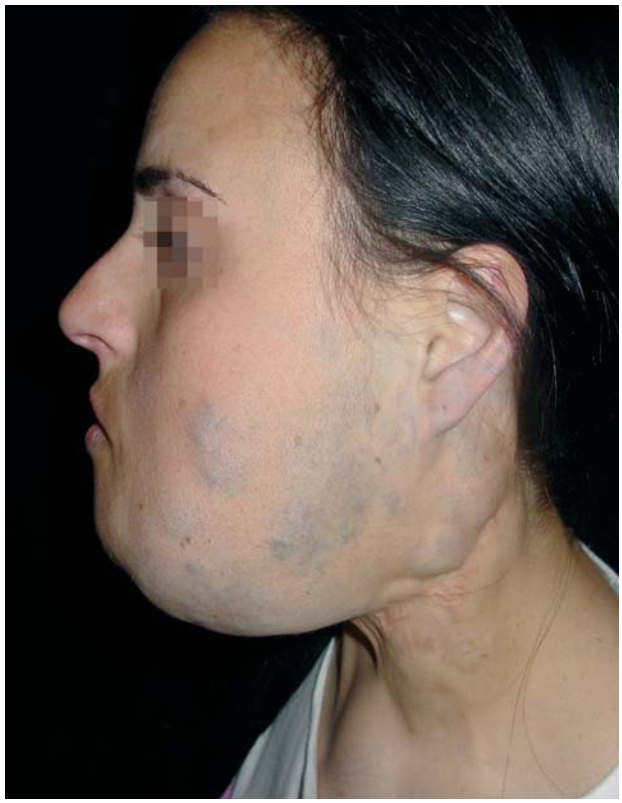

Figure 8. Large venous malformation on one side of the face with spread towards the neck in a young woman. Postoperative scarring can be seen on the neck.

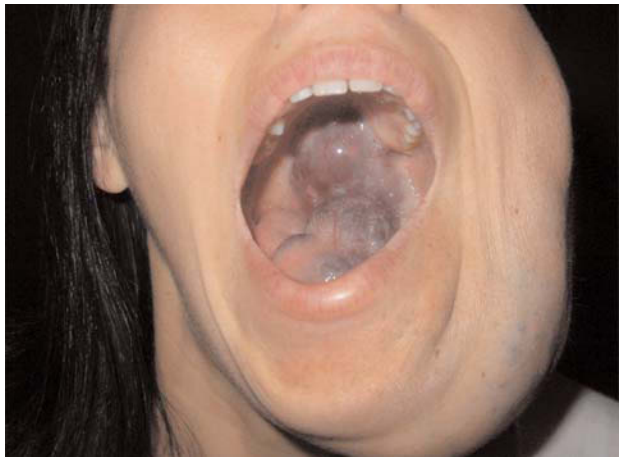

Figure 9. Detail of the previous patient with extensive involvement of the palate and oral mucosa.

patients studied had bone abnormalities (thinning, demineralization, or lysis).[68] Another group showed local bone demineralization in 71% of the patients, and this might be associated with pathological fractures.[61] When large venous malformations of the limbs are present, spread to the trunk and visceral involvement—specifically spread from the arms to the pleura, mediastinum, and lungs and from the legs to the pelvis and abdominal cavity—should be ruled out. Thus, a complete imaging study (CT or MRI angiography) has been proposed to assess the extent of the lesion.

In this group of purely segmental venous malformations or in combined extensive venous-lymphatic malformations (such as Klippel-Trenaunay syndrome, discussed below), coagulation disorders have been reported. Specifically, localized intravascular coagulation, which is different to the disseminated intravascular coagulation of the Kasabach-Merrit syndrome, has been described. It is important to mention here that this syndrome, characterized by hemolytic amenia, thrombocytopenia, and coagulation disorders, is specific to some vascular tumors such as kaposiform hemangioendothelioma or tufted hemangioma, but not to common hemangiomas or vascular malformations, regardless of type.[69] Recently, a new entity has been described denominated multifocal lymphangioendotheliomatosis with thrombocytopenia, characterized by congenital cutaneous and gastrointestinal vascular lesions on the borderline between being a tumor and a vascular malformation and by coagulation disorders, also on the borderline between a disseminated intravascular coagulation of the Kasabach-Merritt syndrome type and a localized intravascular coagulation.[70] Curiously, both in this new entity and in the 2 types of tumor, investigators have described abnormal lymphatic vessels, which in addition to being positive for LYVE-1 are positive for vascular endothelial growth factor-R3, a tyrosine kinase receptor expressed by lymphatic endothelial cells.[71] We would thus postulate that these coagulation disorders with platelet trapping appear mainly in tumors or vascular malformations with lymphatic differentiation. In localized intravascular coagulation, characteristic of some vascular malformations, local uptake of coagulation factors within the malformation or secondary to venous ectasia occurs, leading to the formation of microthrombi and phlebolites. In these patients, fibrinogen levels are usually low (<0.5 g/L) and D-dimer levels are high. Baseline measurement of these parameters is useful when undertaking a therapeutic intervention, as withdrawal of compression stockings, surgery, or sclerotherapy may worsen the condition, predisposing patients to possible thromboembolism, which requires anticoagulation therapy with low molecular weight heparin.

Finally, in patients with extensive venous malformations of the limbs and in Klippel-Trenaunay syndrome, abnormalities of the deep venous system can be found in 47% of the cases, specifically, phlebectasia (36%), aplasia or hypoplasia of venous trunks (8%), aneurysms (8%), and avalvulia (7%).[16] These findings require studies of the deep venous system of the affected limb, particularly before

performing a therapeutic procedure, in view of the possible complications that may arise.

Conditions with Their Own Characteristics

Glomus Tumors and Glomangiomas

These are uncommon tumors that originate in the smooth muscle cells in acral arteriovenous shunts. Although the most common site is cutaneous or subcutaneous, they have also been described outside the skin in bone and in the stomach, colon, trachea, and mediastinum.[72] When multiple tumors are present, they are called glomangiomas, which are sometimes hereditary,[73] and should be differentiated from blue rubber bleb nevus syndrome (Table 5).

The natural course and clinical manifestations can help differentiate between venous malformations and glomuvenous ones. Glomuvenous malformations are nodular or plaque lesions with pink or dark blue coloration and a cobblestone appearance. Sometimes hyperkeratotic areas are present, particularly in localized segmental lesions on a limb (Figure 11). They generally affect the skin and subcutaneous cellular tissue without invading deep layers and are painful on palpation.[74] In contrast, venous malformations have a more bluish green color, are compressible, readily invade the muscle and joints, present phlebolites, and are painful, particularly in the morning, with increased pain also associated with hormonal changes. Patients with such malformations may present symptoms of localized intravascular coagulation unlike those with glomuvenous malformations. In case of doubt, the presence of glomus cells in the pathological study is conclusive for diagnosis.[75]

Blue Rubber Bleb Nevus Syndrome[76,77]

Blue rubber bleb nevus syndrome is associated with multiple venous malformations in the skin and gastrointestinal tract. Skin lesions, which are generally present from birth or appear progressively in early childhood, present in the form of small bluish or purplish nodules. At times, they may form more extensive tumors or bluish macules. Characteristically, they are compressible to palpation to form a rubbery bleb. They typically cause spontaneous pain. Within the digestive tract, the most common site of the lesions is in the small intestine. These malformations may cause bleeding in the digestive system with secondary anemia and require endoscopic monitoring and surgery depending on their severity. From the histopathological point of view, the lesions are vascular ectasias with irregular sizes and forms found in the deep dermis and subcutaneous cellular tissue. MRI is useful for diagnosing the extent of visceral involvement and is used for studying asymptomatic family members. Most of the cases published correspond to sporadic mutations, although a dominant autosomal hereditary pattern has been described in some.[78]

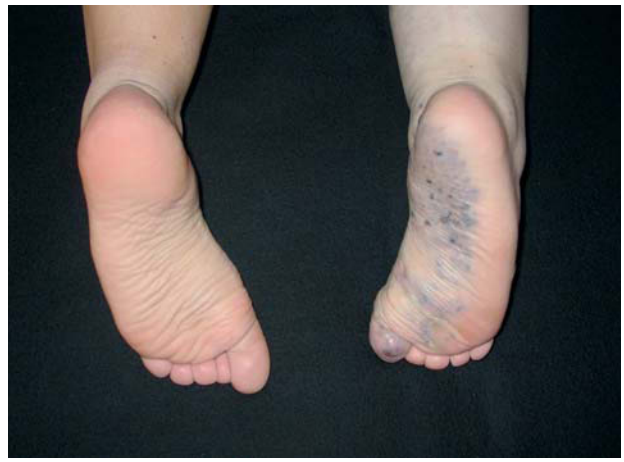

Figure 10. Venous malformation in the leg with plantar involvement. Bone and musculoskeletal atrophy is noted contrary to the usual presentation in combined malformations of the Klippel-Trenaunay type.

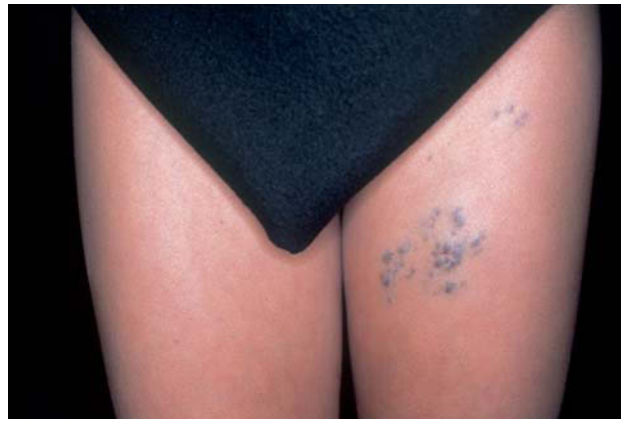

Figure 11. Sixteen-year-old boy with plaque-like glomuvenous malformation following a dermatome arrangement on the thigh.

Familial Cutaneomucosal Venous Malformation

This type of malformation is due to a mutation in the Tie-2 receptor that is inherited according to a dominant autosomal pattern.[17] Clinically, these malformations are characterized by the presence of multiple small venous lesions that may affect the skin and mucosas.[18]

Cerebral Venous Malformations (Also Known as "Cavernous Angiomas")

Like the malformations discussed earlier, cerebral venous malformations also run in families and show the same hereditary pattern. A subgroup of patients with such malformations have cutaneous capillary-venous lesions with a hyperkeratotic appearance[79]; an ocular venous malformation

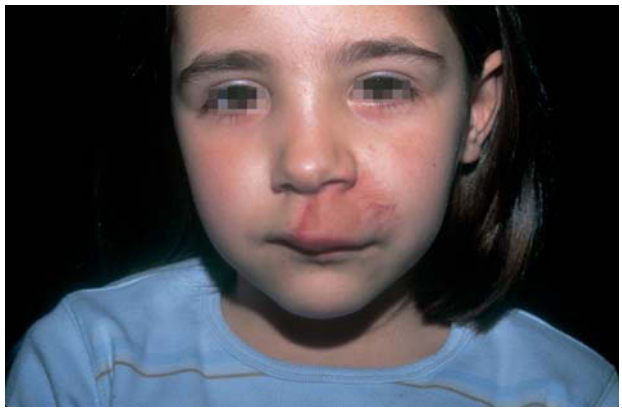

Figure 12. Six-year-old girl with port wine stain on the upper lip associated with hypertrophy. Angiographic study confirmed diagnosis of arteriovenous malformation.

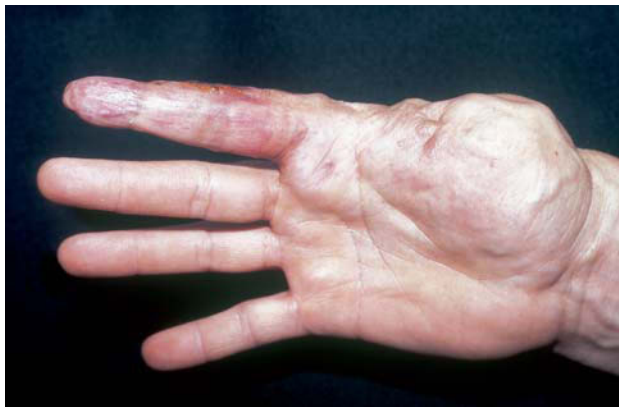

Figure 13. Arteriovenous malformation of a hand with steal syndrome and distal necrosis, with amputation of the thumb and substantial trophic abnormalities in the index finger.

is often also present. In some families, an abnormality has been detected at 7q11-22.[80]

Arteriovenous Malformations

Arteriovenous malformations refer to a group of congenital malformations made up of several fistulous tracts that create arteriovenous shunts. In the scientific literature, other synonyms can sometimes be found such as birthmark with discernible pulsation, cirsoid aneurysm, or arteriovenous aneurysm. Mulliken and Young[12] prefer to reserve the term arteriovenous fistula for the acquired traumatic variant comprising a solitary fistula. The histological analysis of the arteriovenous malformations in children and newborn babies shows that the nidus of this lesion is comprised of capillaries. As the malformation matures, the degree of ectasia increases and the development of venous dilation and arterial hypertrophy become apparent.

The most common site of the arteriovenous malformations is the cranium, followed in descending order of frequency by the head, neck, limbs, trunk, and viscera. Of the vascular malformations, the arteriovenous ones—although congenital like the others—are the group that is diagnosed latest, sometimes during the forth or fifth decade of life.[10] They may erroneously be confused with hemangioma or, more often, with a port wine stain (Figure 12), but the arteriovenous malformations are usually slightly raised macules that are warmer and sometimes pulsatile. Ulceration, intense pain, intermittent bleeding, and hypertrophy of the bone underlying the lesion are also common. A proximal arteriovenous malformation with high blood flow may increase cardiac load and lead to congestive heart failure,[81] although the increased cardiac load is usually compensated for years[15,82]; in contrast, if the malformation is distal there is a propensity to lower flow and peripheral ischemia (steal syndrome) (Figure 13). The natural history of an arteriovenous malformation is documented using the clinical staging published by Schobinger[8] that we discussed earlier. Unlike venous malformations, these lesions do not fully empty on compression, refill quickly, and are firmer to palpation. As in other malformations, partial removal, manipulation, injury, and hormonal changes can favor growth. Within the group of vascular malformations, arteriovascular ones are the most active, with the greatest chance of expansion and growth and, at the same time, the hardest to treat.[83] Generally, their histological extension exceeds the visible extension, with microscopic infiltration of the underlying tissue that favors relapse after partial removal. Moreover, as mentioned earlier, such lesions have shown a pattern that favors angiogenesis and therefore growth and activation.

Mixed or Combined Malformations

These malformations are complex syndromes that are associated with overgrowth of musculoskeletal tissue (Table 5). They can be classified according to high or low blood flow.

Low Flow

Klippel-Trenaunay Syndrome

The Klippel-Trenaunay syndrome is characterized by the association of a venular, lymphatic, and venous malformation along with skeletal hypertrophy and soft tissue enlargement in one or more limbs.[10,84] Although the cause has yet to be determined, Servelle[85] postulated that obstruction or atresia of the deep venous system causes chronic venous

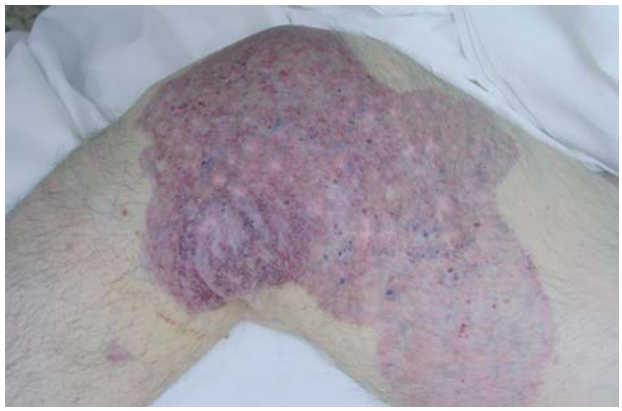

Figure 14. Geographic port wine stain on the knee of a patient with Klippel-Trenaunay syndrome. A violaceous color can be seen with well defined edges.

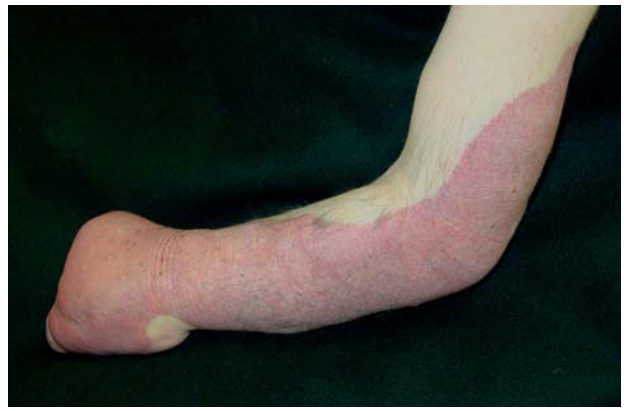

Figure 15. Geographic port wine stain on the arm of a patient with Klippel-Trenaunay syndrome affecting one side of the body. The stain is associated with distal deformity of the affected limb

hypertension responsible for the port wine stain, varicose veins, and hypertrophy of the limb.[86] Although the presentation is sporadic, familial cases with genetic mutations have recently been reported.[22,87,88] Venular malformations or port wine stains are usually multiple, generally affecting a lower limb (95% of cases) and often spreading to the glutea and thorax. In more than 10% of patients the lesion extends beyond the limb with involvement of the trunk and may even affect the entire side of the body. A recent publication distinguished between "geographical stains" (irregular well-defined border resembling a continent) with an intense reddish or violaceous color (Figures 14 and 15) and other "blotchy" marks with a segmental distribution and pink coloration (Figure 16). Geographic stains show greater lymphatic involvement and are associated with more complications.[89] The new diagnostic techniques open up new perspectives in patients with Klippel-Trenaunay syndrome. Advances in noninvasive angiographic techniques such as 3-dimensional MRI venography and/or multislice CT venography allow a complete evaluation of these patients from a single image. Using these procedures, we were able to observe how geographic stains are also often associated with hypoplasia or atresia of the deep venous system in a small but significant series of patients.[90]

Venous malformation manifests as anomalous lateral veins or persistent embryonic veins that are prominent due to valvular insufficiency and due to the frequently associated abnormalities in the deep venous system.[91] Although it may be detected at birth, it appears more frequently when the patient starts to walk. Lymphatic hyperplasia is seen in more than half the patients, generally in the form of vesicles containing a clear fluid or hemorrhagic vesicles at the surface of the skin, which are associated with lymphedema and lymphatic macrocysts (Figures 17 and 18).

The increased volume of the affected limb becomes more noticeable with age. Of particularly note is soft tissue

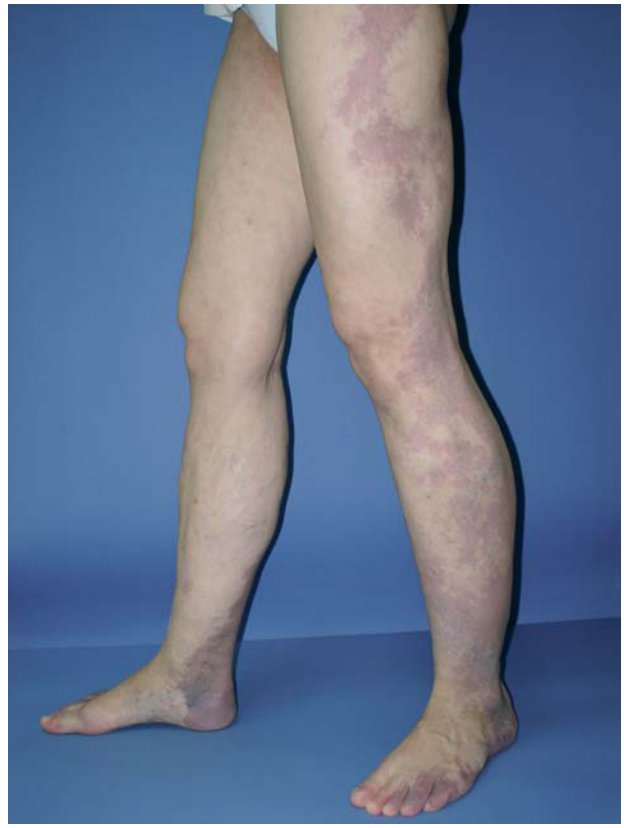

Figure 16. Diffuse port wine stain with poorly defined edges and tenuous coloration on the external aspect of the leg of a patient with Klippel-Trenaunay syndrome.

enlargement and macrodactyly, which require monitoring and specific treatment; in a small percentage of patients atrophy and shortening of the limb is observed.[92] The main complication of Klippel-Trenaunay syndrome is thrombophlebitis, which is reported in 20% to 45% of patients[93,94] and causes pulmonary embolism in 4% to 25%

Figure 17. Venous-lymphatic malformation with genital involvement. Characteristic blackish (hemorrhagic) vesicles on a violaceous geographic stain.

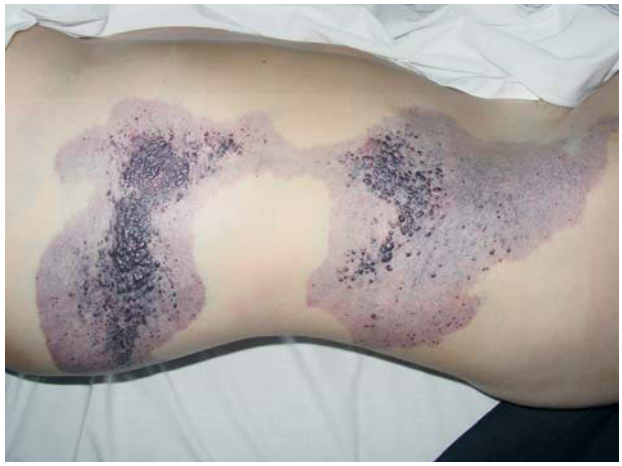

Figure 18. Woman affected by extensive venous-lymphatic malformation with geographic stain on the thorax-abdomen and similar lesions extending to the leg

of cases.[95] Coagulation disorders are also common in the form of localized intravascular coagulation, hemothorax, and intestinal or urinary bleeding due to focal disease. The risk of recurrent cellulitis and bacteremias increases with greater lymphatic involvement.[96]

Proteus Syndrome

Proteus syndrome is a heterogenous condition defined by the presence of asymmetric vascular, skeletal, and soft-tissue lesions of varying size.[97] Linear verrucous skin lesions, lipomas and lipomatosis, macrocephalia, asymmetric limbs with partial gigantism of the hand, foot, or both, and a plantar cerebriform thickening corresponding histologically to collagenoma can be observed. In a series of 55 patients, 98.2% showed asymmetric body growth and macrodactyly.[98]

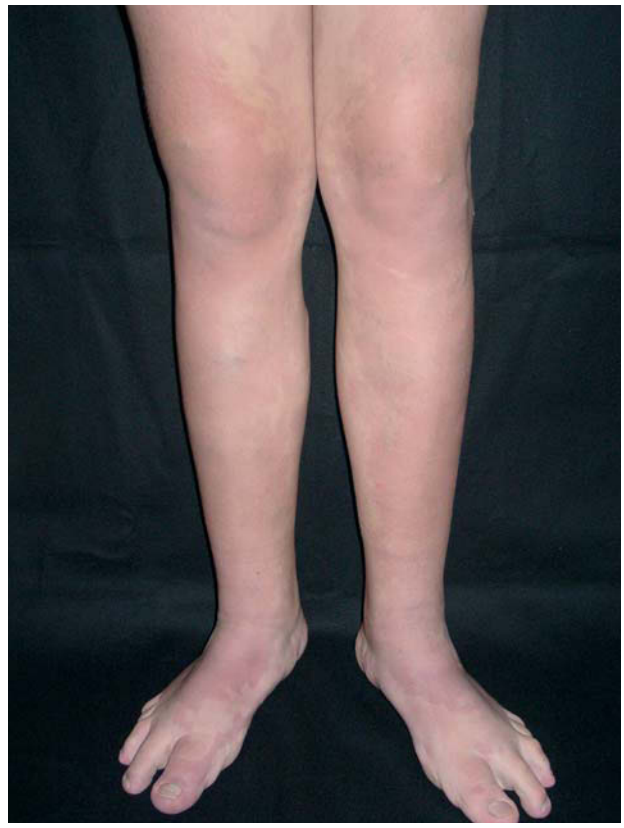

Figure 19. Seventeen-year-old boy with Proteus syndrome. Bilateral port wine stain and hypertrophy of the feet with macrodactyly.

Vascular lesions occur in 69% of the cases and are of the following types, in descending order of frequency: venular malformations such as port wine stains (Figure 19), lymphatic malformations (micro- and macrocystic), and combined low-flow malformations such as Klippel-Trenaunay syndrome. High-flow lesions such as the Parkes-Weber syndrome have never been described.

Maffucci Syndrome

The Maffucci syndrome is a congenital and sporadic mesenchymal dysplasia that is associated with venous, capillary, and occasionally lymphatic malformations, with exostosis and enchondromas.[99-101] Occasionally, spindle-cell hemangioendotheliomas may appear in preexisting vascular lesions. Lesions can be localized, usually to the hands or feet, or generalized. They may be present at birth although it is more common for there to be an early and progressive development of multiple bluish subcutaneous nodules with a soft consistency and often containing phlebolites.

At the same time, enchondromas develop, characterized clinically as hard nodules in the long bones, particularly in the hands and feet. They cause more or less evident

deformities and pathological fractures depending on the degree of involvment.[102] In the radiograph, enchondromas appear as hypodense regions. Their main complication is the risk of onset of malignant disease, particularly chondrosarcomas, the high incidence of which—around 40%—make biopsy of any painful lesion obligatory.

High Flow

Parkes-Weber Syndrome

The Parkes-Weber syndrome is a venular arteriovenous malformation. It appears at birth and affects the legs (77%) more often than the arms, but to a lesser extent than Klippel-Trenaunay syndrome. It is characterized by a diffuse reddish pink macule with geometric or blotchy borders that spread evenly in all directions. Unlike the Klippel-Trenaunay syndrome, the vascular lesion is a high-flow one with arteriovenous fistulas. Lateral venous anomalies are uncommon, and lymphatic malformations and musculoskeletal involvement does not usually occur. Twenty-three percent of the cases occur on the arms.[103,104] Instead of thrombophlebitis and the risk of pulmonary embolism, the main complication in the Parkes-Weber syndrome is increased cardiac load that might lead to heart failure and cutaneous ischemia.[12,105]

Conflicts of Interest

The author declares no conflicts of interest.

References

1. Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol. 2003;48:477-93.
2. Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy. Clinical characteristics, morphologic subtypes, and their relationship to race, ethnicity, and sex. Arch Dermatol. 2002;138:1567-76.
3. Enjolras O, Mulliken JB, Boon L, Wassef M, Kozakewich HP, Burrows PE. Noninvoluting congenital hemangioma: a rare cutaneous anomaly. Plast Reconstr Surg. 2001;107: 1647-54.
4. Konez O, Burrows PE. Magnetic resonance of vascular anomalies. Magn Reson Imagin Clin N Am. 2002;10:363-88.
5. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69: 412.
6. Hand JL, Frieden IJ. Vascular birthmarks of infancy: resolving nosologic confusion. Am J Med Genet. 2002;108: 257-64.
7. Ly JQ, Sanders TG, San Diego JW. Hemangioma of the triceps muscle. AJR Am J Roentgenol. 2003;181:544.
8. Kuo P-H, Chang Y-C, Liou J-H, Lee J-M. Mediastinal cavernous haemangioma in a patient with Klippel-Trenaunay syndrome. Thorax. 2003;58:183-4.
9. Mulliken JB. Vascular malformations of the head and neck. In: Mulliken JB, Young AE, editors. Vascular birthmarks: Hemangiomas and vascular malformations. Philadelphia: WB Saunders; 1988.
10. Belov S. Classification of congenital vascular defects. Int Angiol. 1990;9:141-6.
11. St. Belov DA, Loose J, Weber, editors. Vascular malformations. Einhorn Presse Verlag. Periodica Angiologica; 1989. p25-7.
12. Waner M, Suen JY. A classification of congenital vascular lesions. In: Waner M, Suen JY, editors. Hemangiomas and vascular malformations of the head and neck. Chapter 1. New York: Wiley-Liss; 1999. p. 1-12.
13. Puig S, Aref H, Chigot V, Bonin B, Brunelle F. Classification of venous malformations in children and implications for sclerotherapy. Pediatr Radiol. 2003;33:99-103.
14. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. J Pediatr Surg. 1983;18:894.
15. Sako Y, Varco R. Arteriovenous fistula: results of management of congenital and acquired forms, blood flow measurements, and observations on proximal arterial degeneration. Surgery. 1970;67:40.
16. 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.
17. Vikkula M, Boon L, Carraway KL 3rd, Calvert JT, Diamonti AJ, Goumnerov B, et al. Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. Cell. 1996;87:1181.
18. Boon LM, Mulliken JB, Vikkula M, Watkins H, Seidman J, Olsen BR, et al. Assignment of a locus for dominantly inherited venous malformations to chromosome 9p. Hum Mol Genet. 1994;3:1583-7.
19. Sato TN, Tozawa Y, Deutsch U, Wolburg-Buchholz K, Fujiwara Y, Gendron-Maguire M, et al. Distinct roles of the receptor tyrosine kinases Tie-1 and Tie-2 in blood vessels formation. Nature. 1995;376:70-4.
20. 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.
21. Sahoo T, Johnson EW, Thomas JW, Kuehl PM, Jones TL, Dokken CG, et al. Mutations in the gene encoding KRIT1, a Krev-1/rap1a binding protein, cause cerebral cavernous malformations (CCM1). Hum Mol Genet. 1999;8:2325-33.
22. 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.
23. Eng C. PTEN: one gene, many syndromes. Hum Mutat. 2003;22:183-98.
24. Smoller BR, Rosen S. Port-wine stains: a disease of altered neural modulation of blood vessels. Arch Dermatol. 1986;122:177.
25. Rydy M, Malm M, Jernbeck J, Dalsgaard C. Ectatic blood vessels in port-wine stains lack innervation: possible role in pathogenesis. Plast Reconstr Surg. 1991;87:419.

26. Ornstein E, Blesser WB, Young WL, Pile-Spellman J. A computer simulation of the haemodynamic effects of intracranial arteriovenous malformation occlusion. Neurol Res. 1994;16:345-52.
27. Sánchez-Carpintero I, Mihm MC, Mizeracki A, Waner M, North PE. Epithelial and mesenchymal hamartomatous changes in a mature port-wine stain: morphologic evidence for a multiple germ layer field defect. J Am Acad Dermatol. 2004;50:608-12.
28. Enciso JM, Hirschi KK. Understanding abnormalities in vascular specification and remodeling. Pediatrics. 2005;116: 228-30.
29. Marler J, Fishman SJ, Kilroy SM, Fang J, Upton J, Mulliken JB, et al. Increased expression of urinary matrix metalloproteinases parallels the extent and activity of vascular anomalies. Pediatrics. 2005;116:38-45.
30. Kapur N, Lambiase P, Rakhit RD, Pearce J, Orchard G, Calonje E, et al. Local and systemic expression of basic fibroblast growth factor in a patient with familial glomangioma. Br J Dermatol. 2002;146:518-22.
31. Hashimoto T, Wu Y, Lawton MT, Yang GY, Barbaro NM, Young WL. Coexpression of angiogenic factors in brain arteriovenous malformations. Neurosurgery. 2005;56:158-65.
32. Hashimoto T, Lam T, Boudreau NJ, Bollen AW, Lawton MT, Young WL. Abnormal balance in the angiopoietintie2 system in human brain arteriovenous malformations. Circ Res. 2001;89:111-3.
33. Redondo P, Martínez-Cuesta A, García-Quetglas E, Idoate A. Active angiogenesis in an extensive arteriovenous vascular malformation: a posible therapeutic target? Arch Dermatol. 2007. In press.
34. Soto J. Pathology and pathogenesis of haemangiomas. An Sis Sanit Navar. 2004;27 Suppl 1: 27-31.
35. Takahashi K, Mulliken JB, Kozakewich HP, Rogers RA, Folkman J, Ezekowitz RA. Cellular markers that distinguish the phases of hemangioma during infancy and childhood. J Clin Invest 1994;93:2357-64.
36. Oster J, Nielson A. Nucha naevi and interscapular telangiectasis. Acta Paediatr Scand. 1970;59:416.
37. Orten S, Waner M, Flock S, Roberson P, Kincannon J. Port-wine stains: an assessment of 5 years of treatment. Arch Otolaryngol Head Neck Surg. 1996;122:1174.
38. Barsky SH, Rosen S, Geer DE, Noe J. The nature and evolution of port wine stains: a computer assisted study. J Invest Dermatol. 1980;74:154.
39. Dahan D, Fenichel GM, El-Said R. Neurocutaneous syndromes. Adolesc Med. 2002;13:495-509.
40. Alonso EM, Sánchez J, Lalanza JJ. Síndrome de Sturge Weber. Med Clin (Barc). 2001;117:320.
41. Comi AM, Hunt P, Vawter MP, Pardo CA, Becker KG, Pevsner J. Increased fibronectin expression in Sturge-Weber syndrome fibroblasts and brain tissue. Pediatr Res. 2003;53: 762-9.
42. Tallman B, Tan OT, Morelli JG, Piepenbrink J, Stafford TJ, Trainor S, et al. Location of port-wine stains and the likelihood of ophthalmic and/or central nervous system complications. Pediatrics. 1991;87:323-7.
43. Sujansky E, Conradi S. Sturge-Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children. J Child Neurol. 1995;10:49-58.
44. Ikeda N, Ikeda T, Nagata M, Mimura O. Ciliochoroidal effusion syndrome secondary to Sturge-Weber syndrome. Jpn J Ophthalmol. 2003;47:233. Author reply 233-4.
45. Kramer U, Kahana E, Shorer Z, Ben-Zeev B. Outcome of infants with unilateral Sturge-Weber syndrome and early onset seizures. Dev Med Child Neurol. 2000;42:756-9.
46. Vilela PF. Sturge-Weber syndrome revisited. Evaluation of encephalic morphological changes with computerized tomography and magnetic resonance. Acta Med Port. 2003; 16:141-8.
47. Pinton F, Chiron C, Enjolras O, Motte J, Syrota A, Dulac O. Early single photon emission computed tomography in Sturge-Weber syndrome. J Neurol Neurosurg Psychiatry. 1997;63:616-21.
48. Pascual-Castroviejo I, Frutos R, Viano J, Pascual-Pascual SI, González P. Cobb syndrome: case report. J Child Neurol. 2002;17:847-9.
49. Danarti R, Happle R, Konig A. Paradominant inheritance may explain familial occurrence of cutis marmorata telangiectatica congenita. Dermatology. 2001;203:208-11.
50. Nagore E, Torrelo A, Zambrano A. Cutis marmorata telangiectática congénita. Revisión de 28 casos. Actas Dermosifiliogr. 1999;90:433-8.
51. 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.
52. Shields JA, Shields CL, Koller HP, Federman JL, Koblenzer P, Barbera LS. Cutis marmorata telangiectatica congenita associated with bilateral congenital retinal detachment. Retina. 1990;10:135-9.
53. Torrelo A, Zambrano A, Happle R. Cutis marmorata telangiectatica congenita and extensive mongolian spots: type 5 phacomatosis pigmentovascularis. Br J Dermatol. 2003; 148:342-5.
54. Vidaurri-de la Cruz H, Tamayo-Sánchez L, Durán-McKinster C, Orozco-Covarrubias Mde L, Ruiz-Maldonado R. Phakomatosis pigmentovascularis II A and II B: clinical findings in 24 patients. J Dermatol. 2003;30:381-8.
55. Levine C. Primary disorders of the lymphatic vessels. A unified concept. J Pediatr Surg. 1989;24:233.
56. Gross RE. Cystic hygroma. En: The surgery of infancy and childhood. Philadelphia: WB Saunders; 1953. p. 960-70.
57. Ward GE, Hendrick JW, Chambers RG. Cystic hygroma of the head and neck. Surg Obstet Gynecol. 1950;58:41-7.
58. Kennedy TL. Cystic hygroma-lymphoma: a rare, still unclear entity. Laryngoscope. 1989;99:1-10.
59. Broomhead IW. Cystic hygroma of the neck. Br J Plast Surg. 1964;17:225.
60. Nihn TN, Nihn TX. Cystic hygroma in children: report of 126 cases. J Pediatr Surg. 1974;9:191.
61. Boyd JB, Mulliken JB, Kaban LB, Upton J, Murray JE. Skeletal changes associated with vascular malformations. Plast Reconstr Surg. 1984;76:789.
62. Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone): its relations to hemangiomatosis. J Bone Joint Surg. 1955; 37:986-1004.
63. Somoza I, Díaz M, Matínez L, Ros Z, López-Gutiérrez JC. Heterogenicidad del síndrome de Gorham-Stout: asociación a malformaciones linfáticas venosas. An Pediatr (Barc). 2003;58:599-603.

64. Sabin FR. The lymphatic system in human embryos, with a consideration of the morphology of the system as a whole. Am J Anat. 1909;9:43.
65. Kaipainen A, Korhonen J, Mustonen T, van Hinsbergh VW, Fang GH, Dumont D, et al. Expression of the fms-like tyrosine kinase 4 gene becomes restricted to lymphatic endothelium during development. Proc Natl Acad Sci USA. 1995;92:3566-70.
66. Schmidt GH. Hemangioma in the zygoma. Ann Plast Surg. 1982;3:330.
67. Hein KD, Mulliken JB, Kozakewich HP, Upton J, Burrows PE. Venous malformations of skeletal muscle. Plast Reconstr Surg. 2002;110:1625-35.
68. 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.
69. Enjolras O, Wassef M, Mazoyer E, Frieden IJ, Rieu PN, Drouet L, et al. Infants with Kasabach-Merritt syndrome do not have «true» hemangiomas. J Pediatr. 1997;130: 631-40.
70. North PE, Khan T, Cordisco MR, Dadras SS, Detmar M, Frieden IJ. Multifocal lymphangioendotheliomatosis with thrombocytopenia. A newly recognized clinicopathological entity. Arch Dermatol. 2004;140:599-606.
71. Folpe AL, Veikkola T, Valtola R, Weiss SW. Vascular endothelial growth factor receptor-3 (VEGF-R3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. Mod Pathol. 2000;13:180-5.
72. Brindley GV. Glomus tumor of the mediastinum. J Thorac Surg. 1949;18:417-20.
73. Pepper MC, Laubenheiner R, Cripps DJ. Multiple glomus tumors. J Cutan Pathol. 1977;4:244-57.
74. Iqbal A, Cormack GC, Scerri G. Hereditary multiple glomangiomas. Br J Plast Surg. 1998;51:32-7.
75. Boon LM, Mulliken JB, Enjolras O, Vikkula M. Glomuvenous malformation (glomangioma) and venous malformation. Distinct clinicopathologic and genetic entibies. Arch Dermatol. 2004;140:971-6.
76. Oranje AP. Blue rubber bleb nevus syndrome. Pediatr Dermatol. 1986;3:304-10.
77. Tyrell RT, Baumgartner BR, Montemayor KA. Blue rubber bleb nevus syndrome: CT diagnosis of intussusception. Am J Radiol. 1990;154:105-6.
78. Wong CH, Tan YM, Chow WC, Tan PH, Wong WK. Blue rubber bleb nevus syndrome: a clinical spectrum with correlation between cutaneous and gastrointestinal manifestations. J Gastroenterol Hepatol. 2003;18:1000-2.
79. Labauge P, Enjolras O, Bonerandi JJ, Laberge S, Dandyrand, Joujoux JM, et al. An association between autosomal dominant cerebral cavernomas and a distinctive hyperkeratotic cutaneous vascular malformation in 4 families. Ann Neurol 1999;45:250-4.
80. Gil-Nagel A, Dubovsky J, Wilcox KJ, Stewart JM, Anderson VE, Leppik IE, et al. Familial cerebral cavernous angioma: a gene localized to a 15-cM interval on chromosome 7q. Ann Neurol. 1996;39:311-4.
81. Flye MW, Jordan BP, Schwartz MZ. Management of congenital arteriovenous malformations. Surgery. 1983;94:740.
82. Natali J, Jue-Denis P, Kieffer E, Benhamou M, Tricot JF, Merland JJ, et al. Arteriovenous fistulae of the internal iliac vessels. J Cardiovasc Surg. 1984;25:165-72.
83. Kohout MP, Hansen M, Pribaz JJ, Mulliken JB. Arteriovenous malformation of the head and neck: natural history and management. Plast Reconstr Surg. 1988;102:643-54.
84. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P, et al. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc. 1998;73: 28-36.
85. Servelle M. Klippel and Trenaunay's syndrome. 768 operated cases. Ann Surg. 1985;201:365-373.
86. Bastida M, Iturbe R. Asimetría de extremidades inferiores con manchas «en vino de Oporto». An Pediatr (Barc). 2004; 60:589-90.
87. Enrola 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.
88. Timar 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 Klippel-Trenaunay syndrome. Ann Hum Genet. 2004;68:353-61.
89. 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.
90. Bastarrika G, Redondo P, Sierra A, Cano D, Martínez-Cuesta A, López-Gutiérrez JC, et al. New techniques for the evaluation and therapeutic planning of patients with Klippel-Trenaunay syndrome. J Am Acad Dermatol. 2007; 56:242-9.
91. Dogan R, Faruk Dogan O, Oc M, Akata D, Gumus B, Balkanci F. A rare vascular malformation, Klippel-Trenaunay syndrome. Report of a case with deep vein agenesis and review of the literature. J Cardiovasc Surg (Torino). 2003;44:95-100.
92. Berry SA, Peterson C, Mize W, Bloom K, Zachary C, Blasco P, et al. Klippel-Trenaunay syndrome. Am J Med Genet. 1998;79:319-26.
93. Gloviczki P, Stanson AW, Stickler GB, Johnson CM, Toomey BJ, Meland NB, et al. Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. Surgery 1991;110:469-79.
94. Samuel M, Spitz L. Klippel-Trenaunay syndrome: clinical features, complications and management in children. Br J Surg. 1995;82:757-61.
95. Baskerville PA, Akroyd JS, Thomas ML, Browse NL. The Klippel-Trenaunay syndrome: clinical, radiological, and hemodynamic features and management. Br J Surg. 1985; 72:232-6.
96. Bauza A, Redondo P. Síndrome de Klippel-Trenaunay. Piel. 2005;20:373-82.
97. Wiedemann HR, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E. The Proteus syndrome. Eur J Pediatr. 1983;140:5-12.
98. Hotamisligil GS. Proteus syndrome and hamartoses with overgrowth. Dysmorphol Clin Genet. 1990;4:87-102.
99. Cohen MM Jr, Neri G, Wesberg R. Overgrowth syndromes. New York: Oxford University Press; 2000.

100. 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.
101. Moreno JC, Valverde F, Medina I, Marchal J. Síndrome de Mafucci. Actas Dermosifiliogr 2002;93:321-4.
102. Kaplan RP, Wang JT, Amron DM, Kaplan L. Maffucci's syndrome: two case reports with a literature review. J Am Acad Dermatol. 1993;29:894-9.
103. Berger TM, Caduff JH. Hemodynamic observations in a newborn with Parkes-Weber syndrome. J Pediatr. 1999; 134:513.
104. Ziyeh S, Spreer J, Rossier J, Strecker R, Hochmuth A, Schumacher M, et al. Parkes Weber or Klippel-Trenaunay syndrome? Non-invasive diagnosis with MR projection angiography. Eur Radiol. 2004;14:2025-9.
105. Cohen MM Jr. Vasculogenesis, angiogenesis, hemangiomas, and vascular malformations. Am J Med Gen. 2002; 108:265-74.