

Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies

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Vascular anomalies represent a spectrum of disorders from a simple “birthmark” to life-threatening entities. Incorrect nomenclature and misdiagnoses are commonly experienced by patients with these anomalies. Accurate diagnosis is crucial for appropriate evaluation and management, often requiring multidisciplinary specialists. Classification schemes provide a consistent terminology and serve as a guide for pathologists, clinicians, and researchers. One of the goals of the International Society for the Study of Vascular Anomalies (ISSVA) is to achieve a uniform classification. The last classification (1997) stratified vascular lesions into vascular malformations and proliferative vascular lesions (tumors). However, additional disease entities have since been identified that are complex and less easily classified by generic headings, such as capillary malformation, venous malformation, lymphatic malformation, etc. We hereby present the updated official ISSVA classification of vascular anomalies. The general biological scheme of the classification is retained. The section on tumors has been expanded and lists the main recognized vascular tumors, classified as benign, locally aggressive or borderline, and malignant. A list of well-defined diseases is included under each generic heading in the “Simple Vascular Malformations” section. A short definition is added for eponyms. Two new sections were created: one dealing with the malformations of individually named vessels (previously referred to as “truncular” malformations); the second groups lesions of uncertain or debated nature (tumor versus malformation). The known genetic defects underlying vascular anomalies are included in an appendix. This classification is meant to be a framework, acknowledging that it will require modification as new scientific information becomes available.

Vascular anomalies (vascular tumors and vascular malformations), often named “angioma” or hemangioma, in fact represent a broad spectrum of disorders from a simple “birthmark” to life-threatening entities, which affect mainly infants, children, and young adults. Certain vascular anomalies, such as salmon patch (nevus simplex) or infantile hemangioma, are very

common. Others such as port wine stain are uncommon, and still others are quite rare. Despite long-standing efforts to promulgate standard classification, nomenclature terminology of vascular anomalies continues to be confusing.¹⁻⁴ The term “hemangioma” is, for example, commonly used to name different types of vascular tumors as well as

abstract

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vascular malformations, despite the different constitution, natural evolution, and treatment of these 2 groups of lesions. Incorrect nomenclature and misdiagnoses are commonly experienced by patients with vascular anomalies.² Accurate diagnosis and common terminology are crucial for appropriate evaluation and management, often requiring multidisciplinary specialists.

One of the goals of the International Society for the Study of Vascular Anomalies (ISSVA) is to achieve a uniform classification. The 1996 ISSVA classification stratified vascular anomalies into vascular malformations and proliferative vascular lesions (tumors) (Table 1).^{5,6} This classification was then “unofficially” updated on the basis of evolving knowledge a decade later.⁷ However, since then, knowledge about these disorders has increased considerably. The genetic basis of many types of vascular malformations has been elucidated and additional disease entities have been identified that need more precise classification rather than generic headings such as capillary malformation (CM), venous malformation (VM), lymphatic malformation (LM), etc, which have been used previously. The ISSVA Classification of Vascular Anomalies was recently updated by the Society’s Scientific Committee and Board to incorporate these changes and was adopted at the last workshop in

TABLE 1 1996 ISSVA Classification Scheme

Vascular Anomalies		
Vascular tumors	Vascular Malformations	
	Simple	Combined
Hemangioma	Capillary	AVF, AVM
Others	Lymphatic	CVM, CLM
	Venous	LVM, CLVM
	Arterial	CAVM
		CLAVM

AVF, arteriovenous fistula; AVM, arteriovenous malformation; CAVM, capillary-arteriovenous malformation; CLAVM, capillary-lymphatic-arteriovenous malformation; CLM, capillary-lymphatic malformation; CLVM, capillary-lymphatic-venous malformation; CVM, capillary-venous malformation; LVM, lymphatic-venous malformation.

TABLE 2 2014 ISSVA Classification of Vascular Anomalies

Vascular Anomalies				
Vascular Tumors	Vascular Malformations			
	Simple	Combined	Of Major Named Vessels	Associated With Other Anomalies
Benign	CM	See Table 5	See text	See Table 6
Locally aggressive or borderline	LM			
Malignant	VM			
	AVM			
	Arteriovenous fistula			

Melbourne, Australia (April 2014). The goal of this article is to briefly discuss some of the present classifications and to introduce the 2014 updated ISSVA classification. The interactive document is available at www.issva.org. This classification is meant to represent the state-of-the-art in vascular anomalies classification, acknowledging that it will require modification as new scientific information becomes available.

Several classifications of vascular anomalies are available; some are general classifications, and others deal with specific organs or tissues or only with vascular tumors or vascular malformations. The earliest classification was that of Virchow, which was a pathologic classification that classified vascular anomalies as “angioma simplex, angioma cavernosum, angioma racemosum and lymphangioma.”^{8–10} This was a primitive classification system but appropriate for the time. The World Health Organization (WHO) classifications are generally considered as the reference classification for tumors and tumorlike diseases. The WHO classification of skin vascular “tumors”¹¹ is a nonhierarchical list of a series of different diseases, irrespective of their tumor, malformation, reactive, or infectious nature. The WHO classification of soft tissue tumors¹² uses the word “hemangioma” to describe a tumor or a malformation, further confusing the terminology.¹³

These inconsistencies in classification and nomenclature make the WHO

classifications misleading and confusing.^{8–10} It is then difficult for clinicians across specialties to communicate using a common language specific for each entity, and confusion in the naming of lesions creates inaccuracies in scientific advances and the dissemination of knowledge that may help patients. It also makes coding and statistical data about the prevalence and incidence of these lesions inaccurate.

The 1996 ISSVA classification scheme⁵ is based on the fundamental separation of vascular anomalies into

TABLE 3 Classification of Vascular Tumors

Benign vascular tumors
Infantile hemangioma/hemangioma of infancy
Congenital hemangioma
Rapidly involuting CH (RICH) ^a
Noninvoluting CH (NICH)
Partially involuting CH (PICH)
Tufted angioma ^{a,b}
Spindle cell hemangioma
Epithelioid hemangioma
Pyogenic granuloma (or lobular capillary hemangioma)
Others
Locally aggressive or borderline vascular tumors
Kaposiform hemangioendothelioma ^{a,b}
Retiform hemangioendothelioma
Papillary intralymphatic angioendothelioma, Dabska tumor
Composite hemangioendothelioma
Kaposi sarcoma
Others
Malignant vascular tumors
Angiosarcoma
Epithelioid hemangioendothelioma
Others

Reactive proliferative vascular lesions are listed with benign tumors.

^a Some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy.

^b Many experts believe that these are part of a spectrum rather than distinct entities.

those lesions with a proliferative component (named “vascular tumors”) versus relatively static “vascular malformations,” following Mulliken and Glowacki’s¹⁴ seminal work. Vascular malformations, which are due to inborn errors in vascular morphogenesis, are further classified on the basis of the main type of vessel they are composed of: capillary, venous, lymphatic, arterial, and combined malformations (Table 1). Another proposed classification schema, the Hamburg classification, uses vessel type as the basis of classification of vascular malformations. In each class, “truncular malformations” affecting (individual) large vessels and “extratruncular malformations” composed of smaller vessels intimately embedded in the host tissue are recognized. This distinction is clinically relevant, because “truncular” malformations seems to behave differently, and are more often associated with pulmonary embolism when affecting veins and with chylous effusion when affecting lymphatic vessels.¹⁵ However, this distinction was not considered in the 1996 ISSVA classification.

Beginning in 2013, a group of ISSVA leaders from both the scientific committee and board, with mindful consideration given to the various existing classifications, sought to update and improve the classification of vascular anomalies, both to make it more clinically relevant and flexible and to acknowledge new knowledge including new genetic and histologic information available since its 1996 classification was approved. This updated consensus classification is intended to be applicable and functional for all medical and surgical specialties and for every organ or tissue.

THE 2014 UPDATED ISSVA CLASSIFICATION

Because the updated classification lists a large number of different diseases, it is presented as a general table (Table 2) containing the main

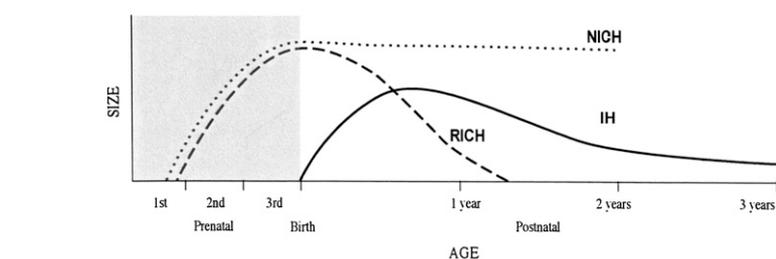


FIGURE 1

Evolution scheme of untreated IH, RICH, and NICH. IH appears after birth, grows generally until the end of the first year of life, then stabilizes and gradually involutes most significantly during years 1 to 2 and continues to improve over the ensuing years. CHs are fully grown at birth and rapidly involute (RICH) or persist indefinitely (NICH). Reprinted with permission from Mulliken JB and Enjolras O.²⁷ NICH, noninvoluting congenital hemangioma; RICH, rapidly involuting congenital hemangioma. The Y axis show relative size.

classes of vascular anomalies and with reference to other tables. The online version of the classification, which is available on the ISSVA Web site (www.issva.org), contains hypertext links that facilitate the navigation in the classification and its appendices.

Vascular Tumors

A list of the main vascular tumors was added in the section on tumors, divided into benign, locally aggressive

or borderline, and overtly malignant (Table 3). Reactive vascular proliferative lesions were grouped with benign tumors. The distinction between the reactive or tumor nature of a lesion is not always straightforward and is debated for several lesions (pyogenic granuloma/lobular capillary hemangioma,¹⁶ spindle cell hemangioma,¹⁷ epithelioid hemangioma¹⁸). Some rare vascular tumors are not included in the table and are listed as “others,”

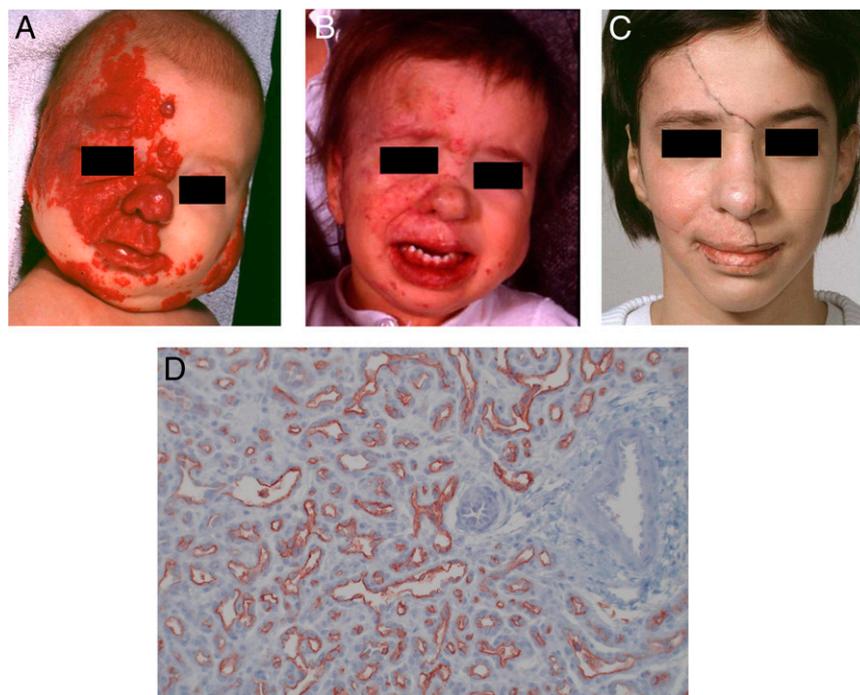


FIGURE 2

Infantile hemangioma. A, A large segmental lesion of the face in an infant. Such lesions may be part of a PHACE syndrome. B, Involution of the lesion at age 24 months. C, Residual lesion at 10 years. D, IH endothelial cells express Glut-1, contrary to those of the normal artery (on the right side of the panel).

because the number of such rare lesions is rapidly increasing and because they can be found in review articles¹⁹⁻²⁴ or in dermatology or soft tissue textbooks.

Infantile hemangioma (IH; also named hemangioma of infancy) is the most common tumor of infancy with an incidence estimated between 4% and 10% of all infants and children.^{25,26} IHs, which are more frequent in females and in cervicofacial locations, appear within the first few weeks of life as a solitary cutaneous lesion that progressively enlarges over months and then gradually regresses²⁵⁻²⁷ (Fig 1). IHs are subclassified as focal, multifocal, segmental, and indeterminate depending on their morphology, extent, or distribution (Fig 2)²⁸ and as superficial, deep, and mixed depending on their location in the skin and/or hypodermis. Segmental IHs may be associated with other vascular and nonvascular anomalies, especially in PHACE (posterior fossa anomaly, hemangioma, arterial anomalies, cardiovascular anomalies, eye anomalies, sternal clefting and/or supraumbilical raphe) and LUMBAR (lower body hemangioma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies) syndromes.²⁹⁻³¹ IHs are mainly composed of proliferating endothelial cells and pericytes. These endothelial cells possess unique immunohistochemical markers (glucose transporter 1 [Glut-1], Lewis Y antigen, FC γ II receptor [Fc γ RII], and merosin),^{32,33} which are also present on placental blood endothelial cells and other blood-tissue barrier vessels (eg, brain, retina).

Congenital hemangiomas (CHs) are less common. They are present and are fully grown at birth. They often regress rapidly,^{27,34} before 1 year of age, or can remain stable or partially involute (Fig 1). On the basis of this natural history, these 3 types are named, respectively, rapidly

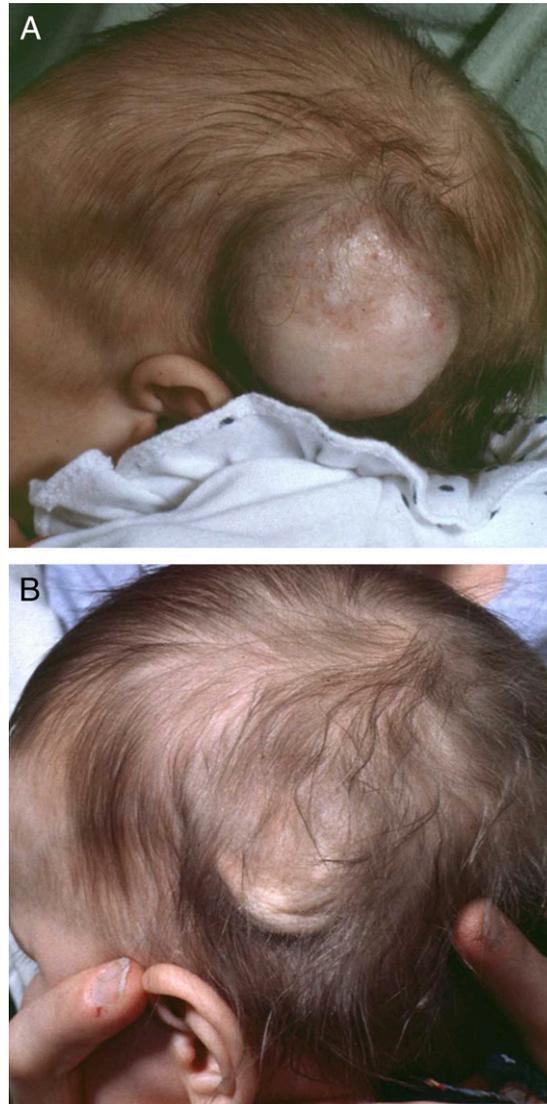


FIGURE 3 Rapidly involuting congenital hemangioma. A large bulky lesion on the scalp at birth (A) and at age 9 months (B), without treatment.

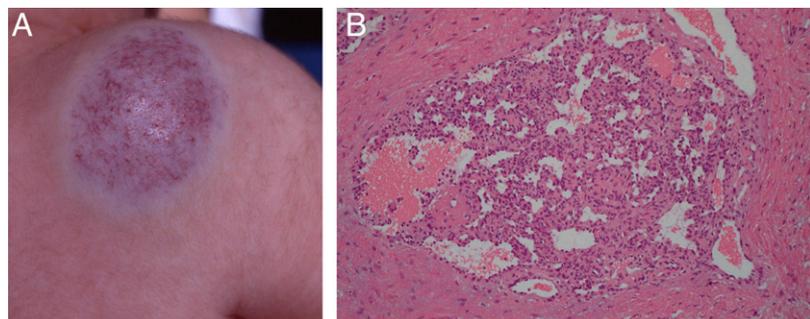


FIGURE 4 Noninvoluting congenital hemangioma. A, A plaque-like round lesion of the shoulder, with coarse central telangiectasia and blue peripheral halo. B, The tumor lobules are made of vessels of various size, with a virtual or an open lumen. Some lumina are large and stellate.

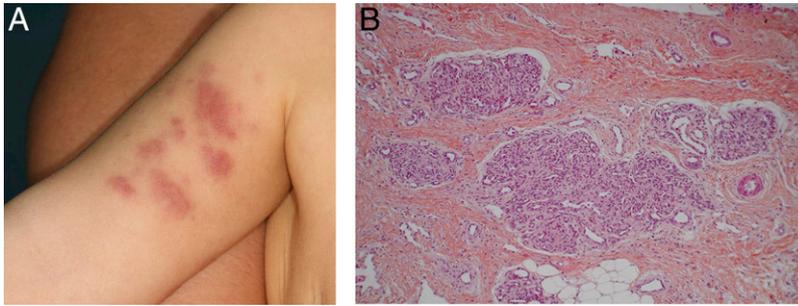


FIGURE 5 Tufted angioma. A, Red vascular lesion with leathery quality on the arm of an infant. B, Histologically, the lesion is composed of small vascular tufts or lobules in a fibrous dermis.

involving CH,^{27,35} noninvolving CH,^{27,36} and partially involuting CH³⁷ (Figs 3 and 4). They are composed of capillary lobules where endothelial cells do not express Glut-1 and are associated with large extralobular veins, arteries, and lymphatics. Rapidly involuting CH may be associated with transient thrombocytopenia and consumption coagulopathy.³⁸ Other clinically significant benign or locally aggressive and borderline vascular tumors are tufted angiomas and kaposiform hemangioendotheliomas. Tufted angiomas appear as erythematous or brown plaques or

macules (Fig 5) in children and young adults.³⁹ A few cases are present at birth or are associated with hyperhidrosis or hypertrichosis. Some lesions regress spontaneously, especially in congenital cases. Tufted angiomas are composed of small tufts of capillaries, characteristically surrounded by a crescentic slitlike vessel, in the dermis and subcutis, with a cannon-ball distribution. Kaposiform hemangioendothelioma may affect the skin and subcutis but often involves the deep tissues, presenting as a locally aggressive tumor (Fig 6). It histologically resembles tufted angioma with larger

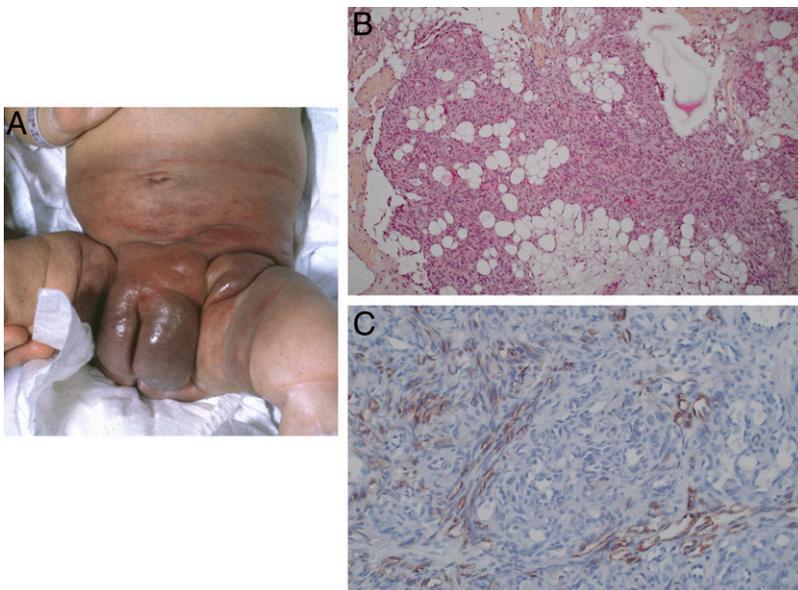


FIGURE 6 Kaposiform hemangioendothelioma in a child with Kasabach-Merritt phenomenon. A, Large, infiltrated, edematous and boggy lesion of the trunk, thighs, and labia majora, associated with petechiae. B, Compared with tufted angioma, the lobules are larger and coalescent and infiltrate the hypodermis fat. C, a subset of tumor cells, often situated at the periphery of the lobules, express the lymphatic endothelial marker podoplanin (D2-40 antibody).

TABLE 4 Simple Vascular Malformations

CMs	
Cutaneous and/or mucosal CM (“port wine” stain)	
CM with bone and/or soft tissue overgrowth	
CM with CNS and/or ocular anomalies (Sturge-Weber syndrome)	
CM of CM-AVM	
CM of microcephaly-CM (MICCAP)	
CM of megalencephaly-CM-polymicrogyria (MCAP)	
Telangiectasia	
Hereditary hemorrhagic telangiectasia (HHT; different types)	
Others	
Cutis marmorata telangiectatica congenita (CMTC)	
Nevus simplex/salmon patch/ “angel kiss,” “stork bite”	
Others	
LMs	
Common (cystic) LMs	
Macrocytic LM	
Microcystic LM	
Mixed cystic LM	
Generalized lymphatic anomaly (GLA)	
LM in Gorham-Stout disease	
Channel-type LM	
Primary lymphedema	
Others	
VMs	
Common VM	
Familial VM cutaneo-mucosal (VMCM)	
Blue rubber bleb nevus (Bean) syndrome VM	
Glomuvenous malformation (GVM)	
Cerebral cavernous malformation (CCM; different types)	
Others	
AVMs	
Sporadic	
In HHT	
In CM-AVM	
AVFs	
Sporadic	
In HHT	
In CM-AVM	
Others	

and confluent tumor lobules, with a more infiltrating pattern. Both lesions focally express lymphatic endothelial markers (podoplanin, Prospero homeobox 1 [Prox-1])⁴⁰ but do not express Glut-1. Both tumors may be associated with the life-threatening Kasabach-Merritt phenomenon, characterized by profound thrombocytopenia and consumption of blood coagulation factors.^{41–43} Many authors consider tufted angioma and kaposiform hemangioendothelioma as part of

a spectrum rather than distinct diseases.⁴² The description of the many other types of even rarer vascular tumors is beyond the focus of this article.

Vascular Malformations

Vascular malformations are divided into 4 groups: simple malformations, combined malformations, malformations of major named vessels, and malformations associated with other anomalies. "Malformations of major named vessels" was the name chosen for those malformations named "truncular" in the Hamburg classification.

Simple Vascular Malformations

Most simple malformations are composed mainly of only 1 type of vessel (capillaries, lymphatics, or veins), with the exception of arteriovenous malformation, which contains arteries, veins, and capillaries (ie, not a combined venous malformation with an arterial malformation but rather a separate disease composed of several types of vessels). Similarly, nonacquired arteriovenous fistula is not considered a combined malformation. For each type of simple malformation, a list of the well-defined diseases is proposed (Table 4).

Capillary malformations (CMs; Table 4) mainly affect the skin and mucosa, appearing as pink to red macules (often referred to as "port wine" stains) (Fig 7). They are present at birth and generally persist throughout life. These lesions may thicken and darken with time and may be associated with soft tissue or bone overgrowth. Some variants, which affect the midline of the head, in the forehead, eyelids, glabella, or nape (named nevus simplex or salmon patch, or so-called angel kiss or stork bite) may lighten and disappear with time, generally before 5 years of age. CMs consist of dilated capillaries and/or postcapillary venules. Lesions associated with soft tissue or bone overgrowth may



FIGURE 7 Capillary malformation: macular vascular lesion that blanches upon pressure.

contain deep lobular aggregates of venous-like vessels. CMs may be associated with other vascular and nonvascular anomalies and syndromes (see below).

Lymphatic malformations (LMs; Table 4) are made up of variously

dilated lymphatic channels or cysts, lined by endothelial cells with a lymphatic phenotype. They are classified as microcystic, macrocystic, and mixed subtypes. There is no uniform consensus regarding the definition of macrocystic and

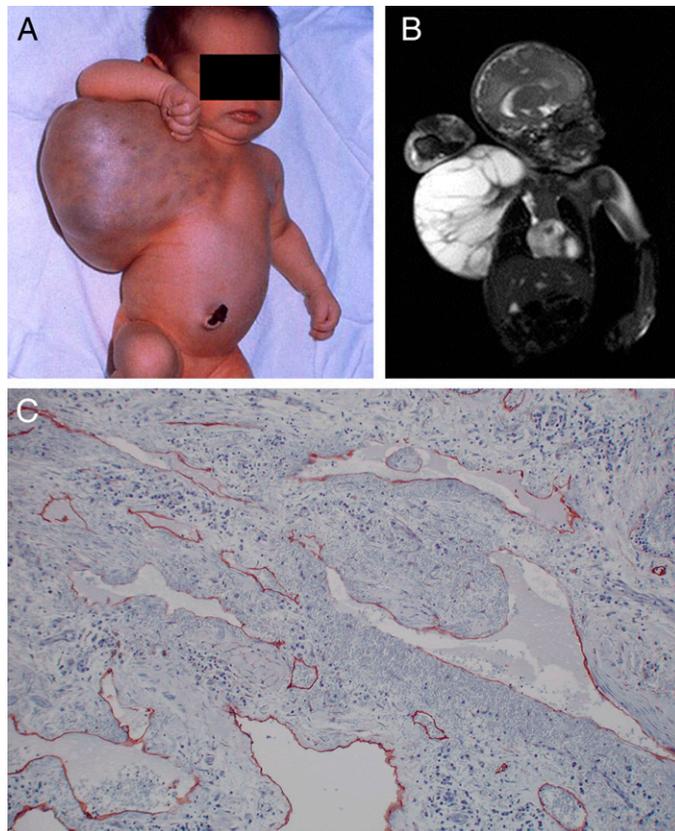


FIGURE 8 Lymphatic malformation. A, Large macrocystic LM of the axillary region. B, MRI of a macrocystic LM of the neck after contrast injection. Thin septae are visible between the large cysts. C, The endothelial cells of LM present a lymphatic phenotype (anti-podoplanin D2-40 antibody).

microcystic LMs. A useful distinction is whether the cysts can be successfully aspirated/sclerosed, resulting in a decrease in LM size,⁴⁴ with the smaller cysts being more challenging. Radiographic features also can help to define the difference because macrocystic LMs are often evident as discernible fluid-filled areas. Common LM develops mainly in the cervicofacial and axillary region, generally under normal-colored skin (Fig 8), except when intralesional hemorrhage occurs. Generalized lymphatic anomaly is defined as a multifocal LM that may affect the skin and superficial soft tissue and abdominal and thoracic viscera, and often involve bone, with bone disease that is generally nonprogressive and spares the bone cortical boundaries. Chylous effusions (pericardial, pleural, or peritoneal) can be present. In contrast, Gorham-Stout disease, also named disappearing or vanishing bone disease, is characterized by LM affecting a single or multiple bones and often neighboring soft tissue, with a progressive osteolysis also affecting the cortical bone. Patients with Gorham-Stout disease can also have abdominal and thoracic visceral involvement as well as effusions. Pathologic fractures may occur in both entities. Primary lymphedemas are considered a subtype of LM due to a primary dysgenesis of the lymphatic network. The causal mutations underlying many types of primary lymphedemas are now elucidated (list available on the ISSVA Web site, www.issva.org). LMs may be associated with other vascular and nonvascular anomalies (see below).

Venous malformations (VMs) (Table 4) generally manifest as a blue skin discoloration when superficial (Fig 9) or as a soft subcutaneous mass and may affect every tissue or viscera. Common VMs are soft and compressible and tend to increase in volume with an increase in venous pressure (eg, Valsalva maneuver or straining) when the affected segment

is dependent or with exercise. Because of sluggish flow of blood through the malformed vessels, thrombosis may occur, resulting in pain and the formation of rounded hyaline organized thrombi (phleboliths) that may be palpable or visible on imaging when calcified. Morphologically, VMs may be focal, multifocal, or diffuse, the

latter typically involving an entire muscle or limb. Common VMs are generally sporadic. They may be evident at birth, but many cases, particularly those with predominantly intramuscular disease, often present later in life with pain provoked by vigorous physical activity.⁴⁵ Familial VMs present generally as small

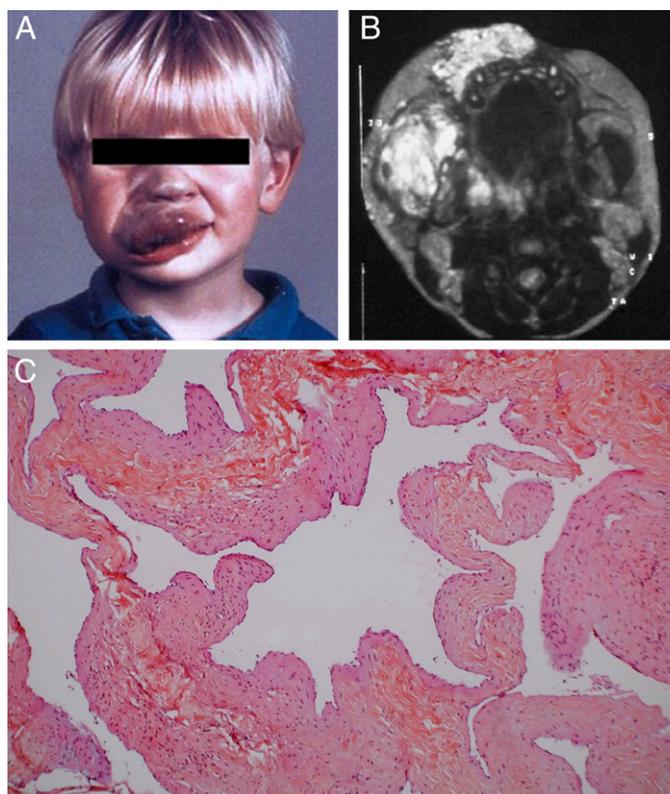


FIGURE 9 Venous malformation. A, Blue, soft, ill-defined mass involving the lips, nose, and cheek. B, MRI of the same child showing a hyperintense lobulated lesion, extending to the pharynx, on T2-weighted images. C, Histologically, VMs are made up of thin-walled stellate, generally empty vessels, dissecting the host tissue.

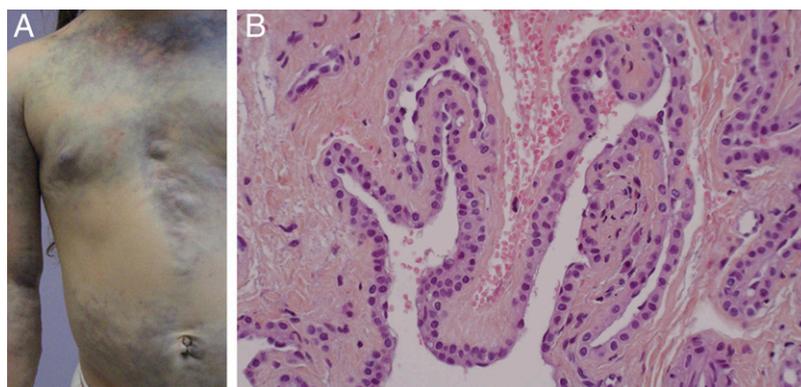


FIGURE 10 Glomuvenous malformation. A, Multifocal dilated veins in checkerboard pattern with blue-colored skin. B, Vessel walls of glomuvenous malformation contain distinctive round or cuboidal glomus cells.

multiple lesions affecting the skin and mucosa. These familial cutaneo-mucosal VMs are caused by germ-line autosomal dominant mutations in the tyrosine kinase with immunoglobulin-like and EGF-like domain 2 (Tie2) gene.⁴⁶ A proportion of sporadic VMs also are caused by somatic mutations in the same Tie2 gene.⁴⁷ Both common and familial VMs are composed of a network of veins with thin walls, defective in smooth muscle cell media, dissecting the host tissue. Patients affected by the blue rubber bleb syndrome (Bean syndrome) present with multiple VMs affecting the skin, soft tissue, and gastrointestinal tract, the latter responsible for chronic bleeding and anemia. Some of the skin VMs, especially on the soles and palms, present as small, round, dark hyperkeratotic bleblike or nipple-like lesions. Glomuvenous malformations, formerly known as glomangioma or glomangiomas, form nodular or plaque-like lesions, sometimes with a cobblestone appearance, affecting the skin (Fig 10), with rare mucosal localization. They are generally of darker blue to purple color and less compressible compared with bluish soft common VMs and are usually painful to palpation. Their histologic appearance is similar to common VMs except for the presence, at least focally, in the vein walls of rounded “glomus” cells corresponding to modified smooth muscle cells. Glomuvenous malformations are related to an inactivating mutation in the glomulin gene.⁴⁸ Cerebral cavernous malformations (CCMs) are solitary or multiple nodular aggregates of thin-walled, round, closely packed veins, progressively appearing in the brain of affected patients. Contrary to other VMs, no normal tissue structures are enclosed in the lesion between the abnormal veins. CCMs are related to mutations in several different genes: *KRIT1* (Krev interaction trapped 1; *CCM1*), malcavernin (*CCM2*), and *PDCD10* (programmed cell death 10; *CCM3*).⁴⁹ VMs may be associated with

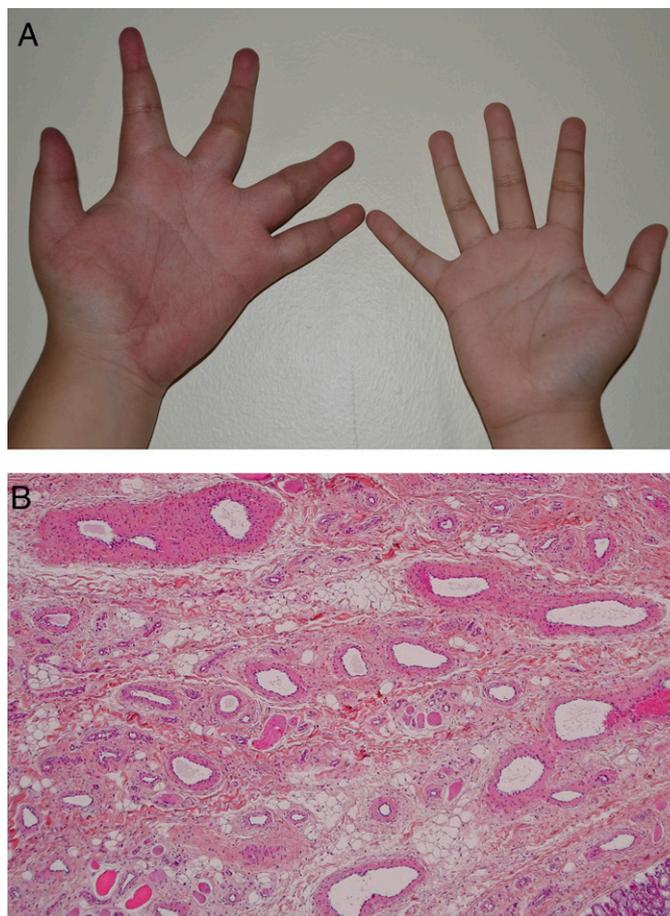


FIGURE 11

Arteriovenous malformation. A, Bright-red enlarged hand and distorted fingers in a patient with AVM of the arm treated with multiple embolizations. The patient was born with cardiomegaly, a high-flow cardiac state, and bruit in the affected arm. B, AVMs are made of round or oval thick-walled vessels of various size, evenly distributed in the tissue, along with various amounts of small capillary vessels.

other vascular and nonvascular anomalies (see below).

Arteriovenous malformations (AVMs) are potentially the more aggressive type of vascular malformation. They are composed of malformed arteries, veins, and capillaries, with direct arteriovenous communications resulting in arteriovenous shunting. They may present as a pseudo-CM

with pulsation at palpation or a bruit; as an enlarging red, warm, painful lesion (Fig 11); as an ulcerated and bleeding lesion due to trophic skin lesions; or rarely, with a shunt-related cardiac overload. Individual lesions may progress from a quiescent to a more aggressive lesion, following the 4 stages defined by Schobinger.⁵⁰ AVMs and congenital arteriovenous

TABLE 5 Combined Vascular Malformations

	Combined Vascular Malformations
CM + VM	Capillary-venous malformation
CM + LM	Capillary-lymphatic malformation
CM + AVM	Capillary-arteriovenous malformation
LM + VM	Lymphatic-venous malformation
CM + LM + VM	Capillary-lymphatic-venous malformation
CM + LM + AVM	Capillary-lymphatic-arteriovenous malformation
CM + VM + AVM	Capillary-venous-arteriovenous malformation
CM + LM + VM + AVM	Capillary-lymphatic-venous-arteriovenous malformation

fistulas may be sporadic or observed in patients presenting with hereditary hemorrhagic telangiectasia⁵¹ or CM-AVM RASA1 (RAS p21 protein activator [GTPase activating protein])–related disease.⁵² AVMs and arteriovenous fistulas may be associated with other vascular and nonvascular anomalies (see below).

Combined Vascular Malformations

Combined vascular malformations associate ≥ 2 vascular malformations in 1 lesion. These may be simple malformations, malformations of major named vessels, or a combination of both types. Some combined malformations associate a cutaneous CM and an underlying VM, LM, or AVM, or a VM with an LM. Others are also associated with nonvascular anomalies (see below). A list of the different existing combinations is presented in Table 5.

Malformations of Major Named Vessels

These malformations affect veins, arteries, or lymphatics of generally large caliber, often axial or conducting vessels. They consist of anomalies in the origin, course, number, length,

diameter (aplasia, hypoplasia, ectasia/aneurysm) or valves. Congenital arteriovenous fistulas and the persistence of embryonic vessels are also included in this group of malformations.

Vascular Malformations Associated With Other Anomalies

Vascular malformations (simple and/or of major named vessels) may be associated with anomalies of bone, soft tissue, or viscera. These nonvascular anomalies are often overgrowth of soft tissue and/or bone or, rarely, undergrowth. Most of these associations are eponymous syndromes. Most of these syndromes or diseases are listed in Table 6 along with their most common associations

Provisionally Unclassified Vascular Anomalies

A small number of vascular anomalies remain unclassified, because it is still unclear whether they are tumors or malformations or because their definition and clinicopathologic characteristics are still incompletely understood. The main unclassified lesions are verrucous hemangioma and angiokeratoma,^{53,54} multifocal lymphoendotheliomatosis with thrombocytopenia/cutaneous angiomatosis with thrombocytopenia, kaposiform lymphangiomatosis,^{55,56} phosphatase and tensin homolog (PTEN) (type) hamartoma of soft tissue, and “angiomatosis” of soft tissue.^{57,58}

GENETIC CAUSES OF VASCULAR ANOMALIES AND OTHER APPENDICES

In recent years, our knowledge of the genetic causes of vascular anomalies has increased considerably. Many of the identified genes cause inherited diseases, but the genetic anomalies underlying some sporadic malformations with postzygotic somatic mutations have also been unraveled. Because the list of causative genetic anomalies is rapidly lengthening, it has not been included in the body of the classification but is

presented in an appendix. Other appendices include a list of abbreviations used in the classification or recommended, a list of vascular anomalies possibly associated with thrombocytopenia or coagulation disorders, and some additional information on IH, the most common vascular tumor. These appendices as well as the complete classification are freely available on the ISSVA Web site (www.issva.org). It is anticipated that this comprehensive updated classification will provide a consistent framework, encourage common terminology, and aid in both management of affected patients and research.

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ABBREVIATIONS

AVM: arteriovenous malformation
 CH: congenital hemangioma
 CCM: cerebral cavernous malformation
 CM: capillary malformation
 Glut-1: glucose transporter 1
 IH: infantile hemangioma
 ISSVA: International Society for the Study of Vascular Anomalies
 LM: lymphatic malformation
 VM: venous malformation
 WHO: World Health Organization

TABLE 6 Vascular Malformations Associated With Other Anomalies

Klippel-Trenaunay syndrome: CM + VM +/- LM + limb overgrowth
Parke-Weber syndrome: CM + AVF + limb overgrowth
Servelle-Martorell syndrome: limb VM + bone undergrowth
Sturge-Weber syndrome: facial + leptomenigeal CM + ocular anomalies +/- bone and/or soft tissue overgrowth
Limb CM + congenital nonprogressive limb hypertrophy
Maffucci syndrome: VM +/- spindle cell hemangioma + enchondroma
Macrocephaly-CM (M-CM)/megalencephaly-CM-polymicrogyria (MCAP)
Microcephaly-CM (MICCAP)
CLOVES syndrome: LM + VM + CM +/- AVM + lipomatous overgrowth
Proteus syndrome: CM, VM and/or LM + asymmetric somatic overgrowth
Bannayan-Riley-Ruvalcaba syndrome: AVM + VM + macrocephaly, lipomatous overgrowth

CLOVES, congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi and spinal/skeletal anomalies and/or scoliosis.

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