Introduction: ISSVA Classification

The International Society for the Study of Vascular Anomalies (ISSVA) was born in 1992 after 16 years of biennial international workshops. Interdisciplinary and international collaboration has been the guiding principle of the ISSVA, with a primary goal of improving our understanding and management of these lesions. This continuing workshop has taken place every two years in various countries around the world.

Multiple nomenclatures for "angiomas" or "vascular birthmarks" have long been an important obstacle to communication amongst the various medical specialists (pediatricians, dermatologists, surgeons, radiologists, angiologists, ophthalmologists, ENT surgeons, pathologists, etc.) involved in the management of these patients (13).

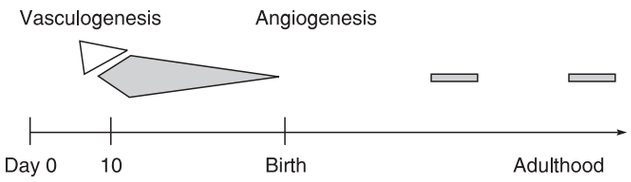
During discussions among members of the workshop it was decided to discard the old terms "angioma" and "birthmark." A very basic classification system was adopted by the ISSVA during its 1996 workshop, to give us a common language.

We now distinguish two main types of vascular anomalies: vascular tumors (the most common type is infantile hemangioma, but other rare vascular tumors occur in children as well as in adults) and vascular malformations (10).

This system is based on the founding biological investigation of Mulliken and Glowacki published in 1982, which provided the groundwork for a proper identification of vascular birthmarks (16). Vascular tumors have been differentiated from vascular malformations based on their clinical appearance, radiological and pathological features (21), and biological behavior. The suffix "oma" (used in the term "angioma") means proliferation of a tumor, and thus the words "angioma," "hemangioma," "lymphangioma" are erroneous when used for vascular malformations (10, 16).

Vascular tumors grow by cellular (mainly endothelial) hyperplasia: the very common infantile hemangioma is in reality a benign vascular tumor. In contrast, vascular malformations have a quiescent endothelium and are considered to be localized defects of vascular morphogenesis, likely caused by dysfunction in pathways regulating embryogenesis and vasculogenesis (Table 1). Vascular tumors

Table 1 Vasculogenesis, angiogenesis. As vasculogenesis begins (day 7 in the mouse embryo), the hemangioblasts, then the angioblast, are in a milieu rich in angiogenic factors (high levels of VEGF) and depleted in angiostatic factors (for instance, low levels of interferon, INF). Then, angiogenesis begins, slightly overlapping with vasculogenesis. Slowly over time, angiogenic factors taper and are accompanied by a parallel rise in angiostatic factors. This change in milieu leads to a slow and gradual decline in the relative amount of angiogenic activity, such that by birth, the angiogenic and angiostatic axis meet and global angiogenesis ends.



Reproduced with permission from: Chiller KC, Frieden IJ, Arbiser JL. Molecular pathogenesis of vascular anomalies, classification in three categories based upon clinical and biochemical characteristics. *Lymph Res Biol* 2003; **1**: 267–81 (Figure 2).

Table 2 The first "biological" classification of vascular anomalies.

Vascular tumors	*Vascular malformations*
Infantile hemangioma	Slow-flow vascular malformations: • Capillary malformation (CM) • Venous malformation (VM) • Lymphatic malformation (LM) Fast-flow vascular malformations: • Arterial malformation (AM) • Arteriovenous fistula (AVF) • Arteriovenous malformation (AVM)

can regress or persist depending on their type. Vascular malformations never regress, they persist throughout life. Most of them have commensurate growth during childhood, and some worsen over time if not treated (11, 17). Differentiating between vascular tumors and malformations is essential as not only their clinical, radiological and pathologic features and their morbidity, but also their management are quite different.

In addition to separation between vascular tumors and vascular malformations, a subdivision of vascular malformations, based on hemodynamics and on

Table 3 Main differences between the very common vascular tumor, infantile hemangioma, and vascular malformations.

	Infantile hemangioma	*Vascular malformations*
Age of occurrence and course	Infancy and childhood	Everlasting if not treated
Course	Three stages: proliferating, involuting, involuted	Commensurate growth or slow progression
Sex prevalence	3–9 girls/1 boy	1 girl/1 boy
Cellular	Increased endothelial cellular turnover. Increased mastocytes. Thick basement membrane	Normal cellular turnover. Normal number of mastocytes. Normal thin basement membrane
Immunohistochemical expression	Proliferating hemangioma: PCNA +++, VEGF +++, bFGF +++, collagenase IV +++, urokinase ++, TIMP-1 -, mast cells −, LYVE-1/CD31 +++, PROX1 − Involuting hemangioma: PCNA -, VEGF +, bFGF ++, collagenase IV -, urokinase ++, TIMP-1+++, mast cells +++, LYVE-1/CD31 −, PROX1 −	Barely detectable: PCNA, VEGF, bFGF, urokinase Not detectable: collagenase IV Variable staining for TIMP 1
Factors causing flare	None (or unknown)	Trauma, hormonal changes
Pathology	Distinctive aspects of the three phases of the tumor. GLUT1 +	CM, VM, LM, AVM, depending on the type. GLUT1 −
Radiological aspects on MRI	Well-delineated tumor with flow voids	Hypersignal on T2-sequences with VM or LM. Flow voids without parenchymal staining with AVM
Treatment	Spontaneous involution, or pharmacological treatment, or surgery, lasers	Lasers, or surgery and/or embolization/ sclerotherapy depending on the type

VEGF=vascular endothelial growth factor; bFGF=basic fibroblast growth factor; TIMP=tissue inhibitor matrix proteinase; GLUT1=glucose transporter 1; CM=capillary malformation; VM=venous malformation; LM=lymphatic malformation; AVM=arteriovenous malformation; MRI=magnetic resonance imaging.

predominant anomalous channels, was created (10, 11, 21). Vascular malformations are either slow-flow or fast-flow, and they are subcategorized into capillary malformation (CM), venous malformation (VM), lymphatic malformation (LM), and arteriovenous malformation (AVM) (Tables 1–4). This is quite important, since their management, with regard to both diagnosis (Table 5) and treatment (Table 6), will also be quite different depending on their subtype (5–9, 17, 21). Some patients have complex-combined vascular malformations, defined as capillary venous malformation (CVM), capillary lymphatic malformation (CLM), capillary lymphatic venous malformation (CLVM), lymphatic venous malformation (LVM), capillary arteriovenous malformation (C-AVM), or lymphatic arteriovenous malformation (L-AVM). Many of these syndromes are still labeled using eponymous terminology (Table 7).

Since 1982, a number of biological investigations have confirmed obvious differences between vascular tumors and malformations. Markers of cellular proliferation, such as cell nuclear antigen, type IV collagenase, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF), are elevated in proliferating hemangiomas, and not in vascular malformations (19). Serum levels

Table 4 Updated ISSVA classification of vascular anomalies.

Vascular tumors	*Vascular malformations*
• Infantile hemangiomas • Congenital hemangiomas (RICH and NICH) • Tufted angioma (with or without Kasabach–Merritt syndrome) • Kaposiform hemangioendothelioma (with or without Kasabach–Merritt syndrome) • Spindle cell hemangioendothelioma • Other, rare hemangioendotheliomas (epithelioid, composite, retiform, polymorphous, Dabska tumor, lymphangioendotheliomatosis, etc.) • Dermatologic acquired vascular tumors (pyogenic granuloma, targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma, etc.)	*Slow-flow vascular malformations*: • Capillary malformation (CM) Port-wine stain Telangiectasia Angiokeratoma • Venous malformation (VM) Common sporadic VM Bean syndrome Familial cutaneous and mucosal venous malformation (VMCM) Glomuvenous malformation (GVM) (glomangioma) Maffucci syndrome • Lymphatic malformation (LM) *Fast-flow vascular malformations*: • Arterial malformation (AM) • Arteriovenous fistula (AVF) • Arteriovenous malformation (AVM) *Complex-combined vascular malformations:* • CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM

C=capillary; V=venous; L=lymphatic; AV=arteriovenous; M=malformation. RICH=rapidly involuting congenital hemangioma; NICH=noninvoluting congenital hemangioma.

Table 5 Diagnostic imaging devices and the various vascular anomalies.

	Infantile hemangioma	*CM*	*VM*	*LM*	*AVM*
Ultrasonography/Doppler	+++	++	++	++	+++
Plain radiographs	–	–	++ (phleboliths, bone)	+/– (bone)	+ (bone)
MRI, MRA, MRV	++	–	+++	+++	++
CT	+	–	+	+	+
Angio-CT scans	–	–	+	–	++
Lymphoscintigraphy	–	–	–	+	–
Biopsy	+	+	+	+	+
Angiography	–	_	+	–	+++

MRI=magnetic resonance imaging; MRA=magnetic resonance angiography; MRV=magnetic resonance venography; CT=computed tomography; CM=capillary malformation; VM=venous malformation; LM=lymphatic malformation; AVM=arteriovenous malformation.

Table 6 Main therapeutic strategies depending on the type of vascular anomaly.

Modality	*Vascular tumors*	*Vascular malformations*
Pharmacological therapies (glucocorticosteroids, interferon alpha 2a or 2b, vincristine, cyclophosphamide, bleomycine, etc.)	+++	+/−
Lasers (FPDL, Nd-YAG, Diode, etc.)	+	CM +++ VM and LM +
Surgical excision/resection	++	++
Direct puncture sclerotherapy	−	VM and LM +++ AVM +
Arterial superselective embolization	+/− (liver hemangiomas, hemangiomas with congestive cardiac failure	AVM +++ VM +/−

FPDL=flashlamp pulsed dye laser; CM=capillary malformation; VM=venous malformation; LM=lymphatic malformation; AVM=arteriovenous malformation.

of VEGF are significantly higher in proliferating hemangiomas than in involuting hemangiomas, vascular malformations, and normal controls (23).

The origin of endothelial cells within the common hemangiomas of infancy has been discussed since it was established that they express GLUT1, merosin, Lewis Y antigen, and $F_C\gamma$ receptor II, during the three stages of hemangioma life (proliferating, involuting, and involuted stages) (18). These markers are also present on endothelial cells of placenta microvessels. These proteins are not expressed on endothelial cells of vascular malformations: the placenta-like microvascular phenotype is lacking in all types of vascular malformations (18). As GLUT1 positivity is lost in hemangioma cultures further experiments would determine if hemangioma endothelial cells actually originate from placenta or if both hemangioma endothelial cells and placenta endothelial cells simply share a similarly immature phenotype.

LYVE-1/CD 31 double staining gave positive results in proliferating hemangioma and not in involuting hemangioma, while PROX-1 was negative in both phases of hemangioma, and Dadras et al. concluded that these infantile tumors are arrested in an early developmental vascular differentiation state (8) (Table 3). New, mainly immunohistological, data let us update and complete the ISSVA classification (Table 4).

In roughly half of cases a hemangioma regresses to result in normal-appearing skin; however, it has long been observed that some involuted hemangiomas develop into a prominent fibro-fatty residuum. According to Bischoff (4) and Yu et al. (22) mesenchymal stem cells with adipogenic potential are present in proliferating hemangioma, and these cells probably contribute to this adipogenesis.

Table 7 Syndromes including slow-flow vascular malformations.

Syndrome	*Type of vascular malformation*	*Other main signs and symptoms*
Klippel–Trenaunay syndrome	CM, VM (varicose veins), LM (lymphedema, lymphatic vesicles)	Progressive overgrowth of the affected extremity, possible GI tract and urinary involvement
Proteus syndrome	CM, LM, VM	Disproportionate asymmetric overgrowth, cerebriform connective tissue nevus
Bannayan–Riley–Ruvalcaba syndrome	CM, VM?	Macrocephaly, developmental delay, GI tract polyposis
Cutis marmorata–macrocephaly syndrome	CM	Ocular anomalies, developmental delay
Cutis marmorata telangiectatica congenita	CM	Hypotrophy of affected limbs
Adams–Oliver syndrome	CM	Transverse limb defects, aplasia cutis of scalp
Rendu–Osler–Weber (hereditary hemorrhagic telangiectasia) syndrome	CM	Visceral AVMs
Ataxia telangiectasia	CM	Ataxia, immune deficiency, malignancies
Bean (blue rubber bleb nevus) syndrome	VM	GI tract lesions with hemorrhages, coagulopathy
Maffucci syndrome	VM	Enchondromas
Gorham–Stout syndrome	LM	Bone resorption

CM=capillary malformation; VM=venous malformation; LM= lymphatic malformation; AVM=arteriovenous malformation.

Various theories concerning the pathogenesis of hemangioma have been developed (3). Some suggest an intrinsic defect of hemangioma endothelial cells (hem ECs): the clonality of hem ECs has been demonstrated and a somatic mutation in a single progenitor cell has been hypothesized as the cause of hemangioma. The intrinsic theory is reinforced by the demonstration of loss of heterozygosity in 5q and by paradoxical response to endostatin of cultured hem ECs (3). Other theories suggest that hemangioma endothelial cells respond to extrinsic defects present in the local environment. These are based on various experiments: release of VEGF from in vitro cultured proliferating hemangioma was found (1), and alteration of expression of interferon-β in the epidermis overlying proliferating hemangioma, but not in the keratinocytes distant to the hemangioma, was demonstrated (2).

A balance between intrinsic and extrinsic factors, and between stimulators and inhibitors of angiogenesis, might account for the rapid growth and slow subsequent involution of infantile hemangiomas (3, 12).

It is currently hypothesized that infantile hemangiomas are primarily the consequence of excess angiogenesis (“hemangiogenesis”), while vascular malformations could be the result of errors in vessel remodeling (6). It has long been unclear whether true angiogenesis occurs in some vascular malformations that

exhibit a clear propensity to thicken over the years, or expand, or even multiply. An example can be found with the lifelong increasing number of venous lesions in Bean syndrome (also known as blue rubber bleb nevus syndrome). Another example is the lethal, inexorably expanding, unalleviated course of some visceral thoracic and abdominal microcystic lymphatic malformations. New findings indicate that vascular malformations may also be angiogenesis-dependent disorders: urinary high-molecular-weight matrix metalloproteinases (hMW MMPs) and bFGF levels are elevated not only in vascular tumors but also in some vascular malformations, such as lymphatic or lymphatico-venous malformations and arteriovenous malformations (15). It is noticeable that this urinary increase in bFGF and hMW MMPs parallels the extent and progression of the vascular anomaly in patients with expanding, unremitting vascular malformations, while urinary VEGF levels do not (15).

Fewer data are available concerning the pathogenesis of vascular malformations, compared with what is currently known about infantile hemangioma. The excess of proteolytic enzymes like the hMW MMPs probably parallels the tissue remodeling observed in diffuse and expanding vascular malformations, such as some AVM or some LM, and the work of Marler et al. suggests that drugs targeting bFGF or MMPs might be an adequate therapeutic strategy for these patients (15).

The existence of inherited forms of vascular malformations, although rare, has permitted a new insight into the complex process of vasculogenesis and the molecular pathways physiologically involved in vascular malformations (7). As genetic defects are being identified in various types of vascular malformations (VM, glomuvenous malformation, familial lymphedema, arteriovenous-capillary malformation), the objective is to understand how such gene alterations, and modifications in signaling pathways (Table 8) result in abnormal vascular channels, with changes in embryonic blood or lymphatic vessels remodeling, ending in the familial forms of vascular malformations (3, 6, 20).

Molecular biology may completely change our approach to the classification of the various vascular anomalies (20). However, as we do not know whether the biological mechanisms of the sporadic vascular malformations, the most frequent ones, are similar to those of inherited forms, it is currently highly speculative to propose a shift to a genetic classification.

In addition, current progress in the understanding of the pathogenesis of angiogenesis-dependent vascular anomalies offers novel targets for their treatment. As an example, the knowledge of the enzyme defect in Fabry disease has resulted in enzyme replacement therapy with agalsidase alpha treatment, and this has changed the prognosis of this severe familial vascular disease (14). Future therapies for other types of vascular anomalies should be tailored to their specific defects once they are identified.

Treatments for the various vascular anomalies have become more specifically adapted over the last 30 years. Some treatments appeared to have more risks than benefits and were discarded. This was the case for the various types of ionizing radiation therapy. Therapeutic embolization through the arterial route and

Table 8 Genetics defects elucidated in some familial vascular malformations.

Diagnosis	*Transmission*	*Chromosomal location*	*Gene mutated*
VMCM (familial cutaneous and mucosal venous malformation)	AD	9p21	*Tie2* (TEK domain)
GVM (glomuvenous malformation, glomangioma)	AD	1p21–22	*Glomulin gene*
CM–AVM (capillary malformation–arteriovenous malformation)	AD	5q13.3	*RASA1*
Lymphedema of Milroy	AD	5q34–q35	*VEGFR3*
Lymphedema–distichiasis	AD	16q24	*FOXC2*
Cerebral cavernous malformations	AD	CCM1=7q11.2-q21, CCM2=7p15–p13, CCM3=3q25.2–27	*CCM1:KRIT1*, ligand de Krev/Rap1a
Bannayan–Riley–Ruvalcaba syndrome	AD	10q23	*PTEN*
Ataxia telangiectasia	AR	11q22–23	*ATM*
HHT (Rendu–Osler–Weber syndrome)	AD	HHT1=9q33, HHT2=12q13, HHT3=5q31.5–32	HHT1=ENG (endoglin), HHT2=ALK1(activin receptor-like kinase 1), HHT3=*gene*?

HHT=hereditary hemorrhagic telangiectasia; AD=autosomal dominant; AR=autosomal recessive; VEGFR=vascular endothelial growth factor receptor.

sclerotherapy through direct puncture of the lesion now have clear indications for use. Surgical procedures have been adapted and customized by both plastic and vascular surgeons. The development of laser technology, since the early 1960s, has resulted in major progress in the treatment of capillary malformations, with better clinical results as the devices have been improved. When successful, early laser treatment of port wine stains provides better results than the surgical treatments previously performed, and they allow the children to develop a positive self-image, reducing the subconscious psychological impact of the CM. A great deal of progress has been achieved in the field of vascular anomalies, but much still remains to be accomplished, in particular to improve our knowledge of their pathogenesis and the results of therapy.

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