1 Nomenclature of Vascular Anomalies: Evolution to the ISSVA 2018 Classification System

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The term "vascular anomalies" embraces a heterogeneous group of vascular lesions, involving one or more vessel type (capillary, artery, vein, and/or lymphatic). This chapter will focus on the historical context of "birthmarks" and evolution of the current most updated comprehensive classification of vascular anomalies. Detailed descriptions of diagnoses (clinical, radiologic, and pathologic features) and their treatment are discussed in subsequent chapters of this book.

Clinically, "vascular anomalies" represent a spectrum of disorders, from a simple cutaneous "birthmark" to life-threatening entities that may be associated with a high incidence of morbidity and mortality. Recognition of temporal and physical patterns of presentation has contributed to the identification of *syndromic* vascular anomalies (e.g., segmental hemangiomas associated with PHACE and LUMBAR syndromes and CLOVES, Proteus, and hereditary hemorrhagic telangiectasia syndromes with vascular malformations), enabling appropriate preemptive evaluation, patient/parent education, and treatment [1–5].

Historically, the field of vascular anomalies has been absent in medical training syllabi, and knowledge was acquired when physicians rotated in centers with recognized vascular anomalies programs (which attracted a broad range of vascular anomalies patients of varying complexity). As more physicians have become exposed to and interested in this field, there has been a quantum increase in vascular anomalies practitioners.

Purported causes of birthmarks are wrought with folklore (in Jewish, Greek, Christian, and Indian cultures) and negative connotations, from ancient times to the present [6]. Birthmarks were attributed to "constellations in human form," supernatural influences, or a result of parental (usually maternal) "impression" – due to images seen or thoughts at the time of conception or during pregnancy affecting

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fetal development. Despite scientific interest in embryologic development and teratology, throughout the nineteenth and early twentieth century, the notion of maternal/parental impression persisted [7–9] and https://embryo.asu.edu/pages/teratogens#sthash.6Ow0mlSl.dpuf. Terms for "birthmark" often convey a negative context. In Italy, the term for birthmark is "voglia di fragole" or "desire for strawberries," reflecting the perception that the birthmark in the child was due to the mother's craving for strawberries during pregnancy. Similarly, the French term for birthmark, "envie," is thought to refer to the mother's unsatisfied desires during pregnancy. Similarly, in German "muttermal" means "mother's mark." The Finnish translation of Nathaniel Hawthorne's haunting short story, *The Birthmark*, is *Paholainen käsikirjoituksessa* meaning "The devil in the script" [10].

Despite the early recognition of birthmarks, descriptive categories did not emerge until the late eighteenth and early nineteenth centuries, with treatises by Virchow, Plenck, Willan, and then Alibert, and reviewed in great detail in the first chapter of *Mulliken and Young's Vascular Birthmarks* [11]. In the 1960s, Malan and Puglionisi described arterial, venous, and lymphatic dysplasias in the extremities [12, 13]. In 1988, the Hamburg classification divided vascular malformations into "truncular" (containing major axial vessels) or "extratruncular" (comprising branches of major vessels) [14]. Dr. John Mulliken and Dr. Anthony Young began a series of workshops in 1976, subsequently occurring every other year, to discuss vascular anomalies among various subspecialists with similar interests. This evolved and was formalized into the International Society for the Study of Vascular Anomalies (ISSVA) in 1992, after an International Workshop in Vascular Anomalies, which occurred 2 years earlier. From a handful of physicians, this group currently has over 290 active members (05/2019) from 5 continents representing multiple medical subspecialties, clinicians, and researchers (http://www.issva.org/). ISSVA has emerged from obscurity and is now a sought after professional organization, attracting new members at an increased rate.

Mulliken and Glowacki were first to clearly separate vascular anomalies into two distinct categories based on endothelial characteristics and clinical features [15], with further refinement based on in vitro, biologic, and radiologic differences [15, 16]. In this classification, vascular anomalies are divided into hemangiomas or vascular malformations, the former having a proliferative phase and the latter representing simple (with one vessel type) or complex (with two or more vessel types) vascular abnormalities (Table 1.1). The framework for an ISSVA classification of vascular anomalies, which built upon the Mulliken and Glowacki classification, was

Table 1.1 1982 Classification of vascular anomalies – Mulliken and Glowacki [15]

Hemangioma	Vascular malformation
Proliferative phase	Simple
Involuting phase	Capillary
	Venous
	Arterial
	Lymphatic
	Combined
	Capillary venous
	Arteriovenous
	Capillary venous/lymphatic

established at the 1996 ISSVA workshop and later published by Enjolras et al. (Table 1.2) [17]. This updated classification included newly recognized entities and separated vascular malformations into slow- or fast-flow lesions. Proliferative lesions in this classification scheme included subcategories of hemangiomas: infantile hemangiomas (GLUT-1 positive), congenital hemangiomas (rapidly involuting congenital hemangiomas (RICH) and noninvoluting congenital hemangiomas (NICH)), tufted angiomas, kaposiform hemangioendothelioma, pyogenic granuloma, and rare hemangioendotheliomas and acquired dermatologic vascular tumors. Syndromic vascular malformations and those with known genetic mutations at the time were included. This taxonomy provided a framework for updated nomenclature and characterized vascular anomalies, which could help direct evaluation and management. Further updates and refinements to this classification are discussed in the latter portion of this chapter.

Table 1.2 1996 ISSVA classification of vascular anomalies

Vascular tumors	Vascular malformations
Infantile hemangiomas **(Hemangiomas of infancy)** **(GLUT-1 positive)**	*Slow-flow vascular malformations:* Capillary malformation (port-wine stain, telangiectasia, angiokeratoma) Venous malformation(VM) (common sporadic VM, Bean syndrome, familial cutaneous and mucosal VM, glomovenous malformation, Maffucci syndrome) Lymphatic malformation
Congenital hemangiomas **RICH (rapidly involuting congenital hemangioma)** **NICH (noninvoluting congenital hemangioma)**	*Fast-flow vascular malformations* Arterial malformation, arteriovenous fistula, arteriovenous Malformation
Tufted angioma (with or without Kasabach-Merritt syndrome)	*Complex-combined vascular malformations:* CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM
Kaposiform hemangioendothelioma (with or without Kasabach-Merritt syndrome)	
Spindle cell hemangioendothelioma	
Other rare hemangioendotheliomas (epitheliod, composite, retiform, polymorphous, Dabka tumor, lymphangioendothelioma, etc.)	
Dermatologic acquired vascular tumors (pyogenic granuloma, targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma, etc.)	

Enjolras et al. [17]

C capillary, *V* venous, *L* lymphatic, *AV* arteriovenous, *M* malformation, *GLUT1* erythrocyte glucose transporter protein 1

[a]International Society for the Study of Vascular Anomalies

In addition to the classification updates, staging systems may help guide management decisions. Examples include the Schobinger staging of arteriovenous malformations based on clinical aggressiveness and staging systems for cervicofacial lymphatic malformations corresponding to anatomic location and extent [18, 19].

Patients with vascular anomalies may have focal aberrations of vascular development (in vascular malformations) or vascular proliferation (in hemangiomas). Syndromic vascular anomalies, a "developmental field defect," include the blood/lymphatic vessels as well as skeletal, soft tissue, and/or organ involvement. The cardiovascular system is the first functioning organ in the developing fetus. Research in the past decades has elucidated factors mediating the differentiation and development of normal blood and lymphatic vessels. Over time, a more complex series of well-orchestrated intricate processes continues to emerge, defining a myriad of growth and transcription factors, rheologic influences, and molecular signaling pathways involved in normal vascular development [20–23].

In recent years, additional breakthroughs have been published, defining molecular and genetic mechanisms implicated in the development of vascular anomalies. Germline genetic mutations causing inherited vascular anomalies (e.g., HHT, RASA-1, EPH4, FLT4, TIE2, KRIT1, PTEN, Glomulin) [5, 24–33] or genetic mutations expressed mosaically in somatic, affected tissue (e.g., GNAQ, PIK3CA, AKT1, KRAS, NRAS) [34–44] have been identified, providing insight into potential mechanisms implicated in the development of vascular anomalies and allowing for more targeted therapies for prevention and/or treatment [45–49].

Since 1996, there has been an increase in the quantity and quality of clinical, basic, and genetic research in vascular anomalies, along with the identification of new therapies (e.g., propranolol for hemangiomas and sirolimus for some vascular malformations and kaposiform hemangioendothelioma, advanced sclerotherapy procedures), which have drawn attention and interest to the field. Typically, more than one subspecialist is involved with the evaluation and management of patients with vascular anomalies, and Vascular Anomalies Centers, which centralize physicians of many disciplines, have become a model for multidisciplinary care and research. It is essential that all team members be fluent in the updated nomenclature.

Despite clearly different clinical presentations, chronological course, and symptoms, terminology for vascular anomalies has been fraught with errors, and patients are frequently misdiagnosed and diagnostic inaccuracies have dominated this field. Most frequently, the term "hemangioma" inaccurately used to describe any benign vascular lesion in a patient of any age, irrespective of the lesion's clinical appearance and behavior. One study found "terminological imprecision" in medical journals, incorrectly using the word "hemangioma" in the majority of manuscripts reviewed [50]. Additionally, diagnoses of patients referred to vascular anomalies centers are often incorrect [51]. Some of these nomenclature misnomers are historic in nature - experienced pathologists, radiologists and other diagnostic clinicians may be unaware of the evolution of newer subdivided classification systems for vascular anomalies, leading to continued use of outdated terminology. Aligning the vocabulary among providers, educators, and researchers is essential, and use of a comprehensive updated classification system is indispensable.

The 1996 ISSVA classification became outdated, since new diagnoses, causative genes, and syndromes have been recognized [39, 46, 52–58]. The classification was updated and approved by the ISSVA Board and membership in 2014 and is published in a comprehensive manuscript [59]. The original stratification of proliferative (tumor) vs malformation remains; however, two new categories were added – malformations of individually named vessels ("truncular" in the Schobinger classification) and lesions of unclear etiology (tumor vs malformation). The ISSVA classification is increasingly referred to in peer-reviewed publications, and a further update was approved in 2018 (issva.org/classification) [60–63].

An interactive PowerPoint® version of the classification is available for download and reference (issva.org/classification). Each slide is summarized in Table 1.3.

Table 1.3 Detailed table of ISSVA 2018 classification, http://www.issva.org → CLASSIFICATION, or http://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

Slide #	Title of slide	Entitles included
1	Overview vascular anomalies	Most general separation of vascular tumors and vascular malformations
2	Benign vascular tumors 1	Hemangioma subtypes, other
3	Benign vascular tumors 2	Hobnail hemangioma, other
4	Locally aggressive and malignant vascular tumors	Kaposiform hemangioendothelioma, etc. Angiosarcoma, epithelioid hemangioendothelioma
5	Simple vascular malformations I	Capillary malformations
6	Simple vascular malformations IIa	Lymphatic malformation subtypes Generalized lymphatic anomaly, kaposiform lymphangiomatosis, Gorham's disease, channel-type lymphatic malformation
7	Simple vascular malformations IIb	Primary lymphedema (link to genetic mutations)
8	Simple vascular malformations III	Venous malformations (link to genetic mutations and different types of cerebral cavernous malformations)
9	Simple vascular malformations IV	Arteriovenous malformations Arteriovenous fistulae (link to Genetic mutations)
10	Combined vascular malformations	CM +/− VM +/− LM +/−AVM combinations
11	Anomalies of major named vessels	Affected vessel Anomaly type
12	Vascular malformations associated with other anomalies	Syndromic vascular malformations (link to genetic mutations)
13	Provisionally unclassified vascular malformations	(link to genetic mutations)
14	Appendix 1	Abbreviations used (excluding gene names)
15	Appendix 2-a	Causal genes
16	Appendix 2-b	Causal genes
17	Appendix 2-c	Causal genes
18	Appendix 3	Infantile hemangioma Pattern of distribution, type, syndromes
19	Appendix 4	Vascular anomalies possibly associated with platelet count/coagulation disorders
20	Appendix 5	PIK3CA-related overgrowth spectrum

The first slide of the updated ISSVA classification (ISSVA PowerPoint) expands the original framework of Mulliken and Glowacki's schema (Table 1.1), replacing "hemangioma" with "vascular tumors" and maintaining "vascular malformations" as the main headings. Clicking on the underlined blue word or abbreviation links to another slide, which provides further information (e.g., subcategories of the diagnostic category or the known genetic mutation) for the respective entity.

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