Vascular Anomalies

A Guide for the Hematologist/ Oncologist

Cameron C. Trenor III
Denise M. Adams
Editors

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We dedicate this book to those who have provided support and inspiration in the field of vascular anomalies, primarily the patients, families, family support groups, and other collaborators.

Our patients are truly heroes, and they provide the needed resilience and drive to accomplish much of our efforts to seek diagnoses and develop the best treatment options. They inspire collaboration and our desire to develop interdisciplinary education and the development of vascular anomaly centers. The steady encouragement and inquisitive nature of this cohort help stipulate continuous feedback and modifications to the delivery of care. Their willingness to participate in vital research studies has fostered an environment of unity as we strive to forward our mutual goals of best practices and distinction in care. Their desire to expand the awareness of this mission through lobbying of federal agencies and donors to support and provide resources for continuous exploration of treatments is noteworthy. For without these dedicated individuals, we would not be achieving results for the betterment of our field/patients. We are forever grateful for this support.

Preface

This book was conceptualized by two pediatric hematologists/oncologists, bringing complementary experience - one from oncology and one from hematology - to a shared passion for vascular anomalies. The purpose was to enhance the education of pediatric hematologist/oncologists in the field of vascular anomalies and entice their interest in joining the growing numbers of "vascular anomalists." It is an exciting time with new discoveries and opportunities in medical therapies and comprehensive care of patients with vascular anomalies.

Surgeons and radiologists were the first professionals to form groups to study vascular anomalies. Initial investigation of vascular anomalies was led by Dr. Judah Folkman, the founder of angiogenesis. He mentored Dr. John Mulliken, the founder of the Vascular Anomalies Center at Boston Children's Hospital. These are two of our luminaries in the field.

Twenty years ago, Dr. Mulliken and colleagues reported a simple classification of vascular anomalies (tumors and malformations). Pattern recognition was the basis for diagnostic classification and was best performed by astute clinicians. Most treatment options were surgical and interventional, and there were limited medical options with no clinical trials. There were no consortiums or cooperative groups for the organization of clinical trials. In contrast, 20 years ago in Pediatric Hematology/Oncology, clinicians worked together in cooperative groups. There were multiple active clinical trials. Diseases were risk-stratified and outcome measures were being studied. Furthermore, the start of genetic discovery was changing treatment paradigms.

Thanks to warm mentorship from the pioneers in this field, pediatric hematologist/oncologists with an interest in vascular anomalies were actively deemed "having the vascular anomaly gene" and were welcomed as partners into vascular anomaly centers. We are forever grateful for the guidance and support of Drs. Judah Folkman and John Mulliken.

Currently, the classification system for vascular anomalies was revised by the scientific committee of the International Society for the Study of Vascular Anomalies (ISSVA), including significant contributions from hematologist/oncologists on this committee. There are better standards of practice for vascular anomalies; some of these are medical practices formulated by pediatric hematologists/oncologists. Today, hematologists/oncologists have a central role in many vascular anomaly centers. Furthermore, there are precise phenotypes of disease that can be linked to

genotypes. This genotype/phenotype partnering has led to treatment options and clinical trials that are improving the outcomes for patients with vascular anomalies. Translational and clinical providers are teaming with basic scientists to continue to move this field forward. An interdisciplinary approach is essential in the treatment and care of vascular anomalies, and this collaboration is essential.

This book exemplifies this interdisciplinary collaboration. We are honored that today's leaders in the field of vascular anomalies agreed to contribute their expertise and content - and even more honored to call these international experts our friends. We hope that this book sparks the interest of other hematologists/oncologists who have "the gene" to join this exciting bandwagon and help improve the outcomes for these patients.

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

Francine Blei

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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Diagnosis of Vascular Anomalies

2

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Abbreviations

CLOVES	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal/spinal anomalies
D2-40	Podoplanin
FAO	Fibroadipose overgrowth
GLUT-1	Glucose 1 transporter protein -1
HHML	Hemihyperplasia-multiple lipomatosis
HHT	Hereditary hemorrhagic telangiectasia
MCAP	Megalencephaly-capillary malformation
MPPH	Megalencephaly-polymicrogyria-polydactyly-hydrocephalus
PHACE syndrome	Posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, and eye anomalies
TRICKS	Time-resolved MRA sequences

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Clinical Features

As with any patient, the diagnosis of vascular anomalies starts with a careful history. Vascular anomalies present with a variety of symptoms, including a mass or effects of that mass on involved structures, effusions, bleeding, or thrombosis. Overlying skin changes, including a vascular "stain," blebs, brownish or bluish discoloration may be present. Consideration of the age at presentation, the rate of growth or factors related to growth such as trauma or hormonal changes, characteristics and location of the lesion, and associated clinical or laboratory features can aid in the diagnosis of vascular anomalies. Increasing evidence points to a genetic component to many vascular malformations and the family history may provide clues to an inherited syndrome.

Age at Presentation The age at presentation is a key consideration in the diagnosis of vascular anomalies. Capillary and lymphatic malformations are typically diagnosed at birth. Infantile hemangiomas may be initially inconspicuous but grow rapidly in the first weeks to months of life. Kaposiform hemangioendothelioma is most common in infants and young children, but presentation can range from in utero [1] to young adulthood [8]. Venous and arteriovenous malformations are present at birth but often become more apparent in late childhood or with puberty. Lymphatic malformations are generally diagnosed at birth but may enlarge in association with trauma, hemorrhage or infection, or at puberty. Telangiectasias in hereditary hemorrhagic telangiectasia (HHT) typically do not appear until adulthood.

Growth Vascular anomalies are mainly classified into tumors and malformations based on growth characteristics. Vascular tumors (e.g., hemangiomas, hemangioendotheliomas, angiosarcomas) grow rapidly due to vascular proliferation. Most are benign, though they may be locally invasive (kaposiform hemangioendothelioma), and rare tumors can metastasize (angiosarcoma, epithelioid hemangioendothelioma). Vascular malformations, in contrast, represent developmental anomalies; they are present at birth and grow in proportion to the child. However, injury, inflammatory stimuli, or hormonal changes may stimulate growth, and, thus, some malformations may become more apparent in late childhood or adolescence.

Physical Exam Findings and Location The color of the lesion should be noted; a red color is most commonly associated with hemangiomas and capillary malformations, whereas venous malformations may appear bluish if superficial. Lymphatic malformations are often flesh-colored, unless acutely inflamed, but they may appear red or bluish if there has been hemorrhage into a macrocyst. Lesions can be flat, plaque- or mass-like, with borders that are discrete or infiltrating. Capillary malformations are flat and well-demarcated, whereas vascular tumors tend to be plaque- or mass-like (Fig. 2.1a). A compressible lesion that fills when in a dependent position suggests a venous malformation. The presence of an overlying bruit, thrill or warmth suggests a high-flow component as in an arteriovenous malformation (Fig. 2.1b). However, the appearance of a lesion can be affected by its depth or presence of additional vascular components, and can change with growth of the lesion or with intralesional hemorrhage or thrombosis.

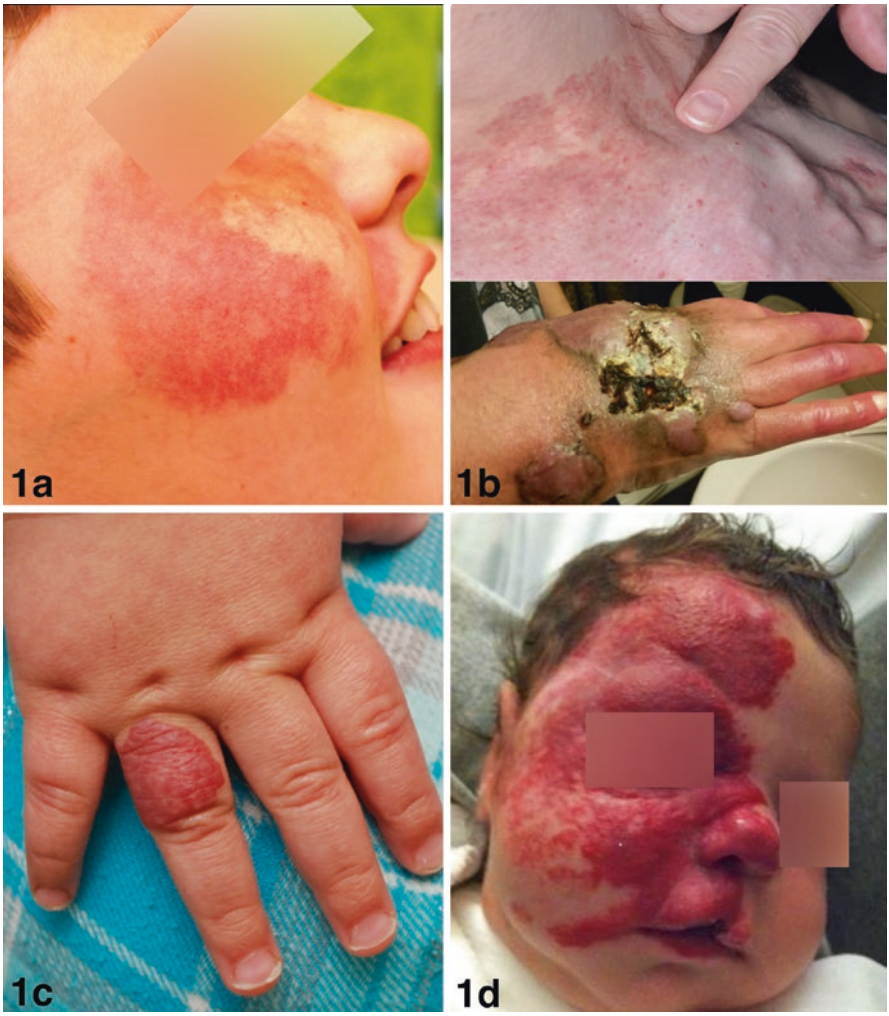

Fig. 2.1 (**a**) Capillary malformation. (**b**) Arteriovenous malformation. (**c**) Infantile hemangioma. (**d**) Infantile segmental hemangioma

In addition to the appearance of the lesion, the location of the vascular anomaly may influence presenting symptoms and provide clues to the diagnosis as well as trigger a search for associated features or syndromes. Infantile hemangiomas are commonly found in the head and neck region or less often the trunk and limbs (Fig. 2.1c). Periorbital and orbital hemangiomas in infants may affect development of visual acuity; even if they only partially obstruct vision [18]. Blockage of the tear duct may also occur. PHACE syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, and eye anomalies) should be considered if any hemangioma is >5 cm and segmental (Fig. 2.1d). Capillary malformations involving the face in the distribution of the first branch of the trigeminal nerve

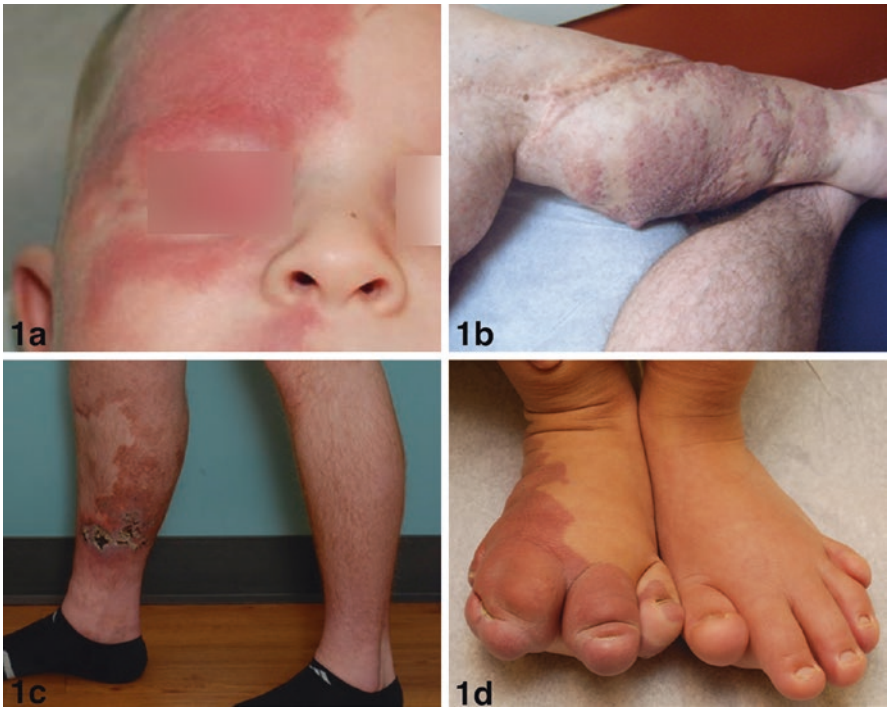

Fig. 2.2 (**a**) Sturge-Weber. (**b**) Klippel-Trenaunay syndrome. (**c**) Parkes Weber. (**d**) CLOVES

are often associated with leptomeningeal angiomas, choroidal hemangioma, and glaucoma (Sturge-Weber syndrome) (Fig. 2.2a). Airway obstruction may complicate vascular anomalies in the head and neck region. Infantile hemangiomas in the "beard" distribution (preauricular areas, chin, anterior neck, and lower lip) have a propensity to compress the airway as they enlarge, or they may be associated with additional subglottic lesions [13, 14]. Infantile hemangiomas in the midline lumbosacral region can be associated with spinal dysraphism [5, 10]. Hemangiomas may also be present in viscera, most commonly the liver. The presence of multiple (5 or more) cutaneous infantile hemangiomas increases the likelihood of hepatic involvement [16]. Large hepatic congenital or multifocal infantile hemangiomas are associated with an increased risk of high-output cardiac failure and diffuse hepatic infantile hemangioma may cause consumptive hypothyroidism [7]. Lymphatic malformations frequently involve the head and neck, including oral structures such as the tongue, which can also lead to airway obstruction. In addition, lymphatic malformations that involve the neck, axillary, or intrathoracic sites may be associated with pleural effusions. Mediastinal involvement is less common in lymphatic malformation, but is the most common location for kaposiform lymphangiomatosis [3]. Bony lesions are characteristic of generalized lymphatic anomaly and Gorham-Stout disease; involvement of the appendicular skeleton is more common in the former. Pelvic and lower extremity involvement is common in the mixed capillary lymphaticovenous malformations of Klippel-Trenaunay syndrome, as well as in primary lymphedema. Limb overgrowth