Diagnosis of Vascular Anomalies

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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.

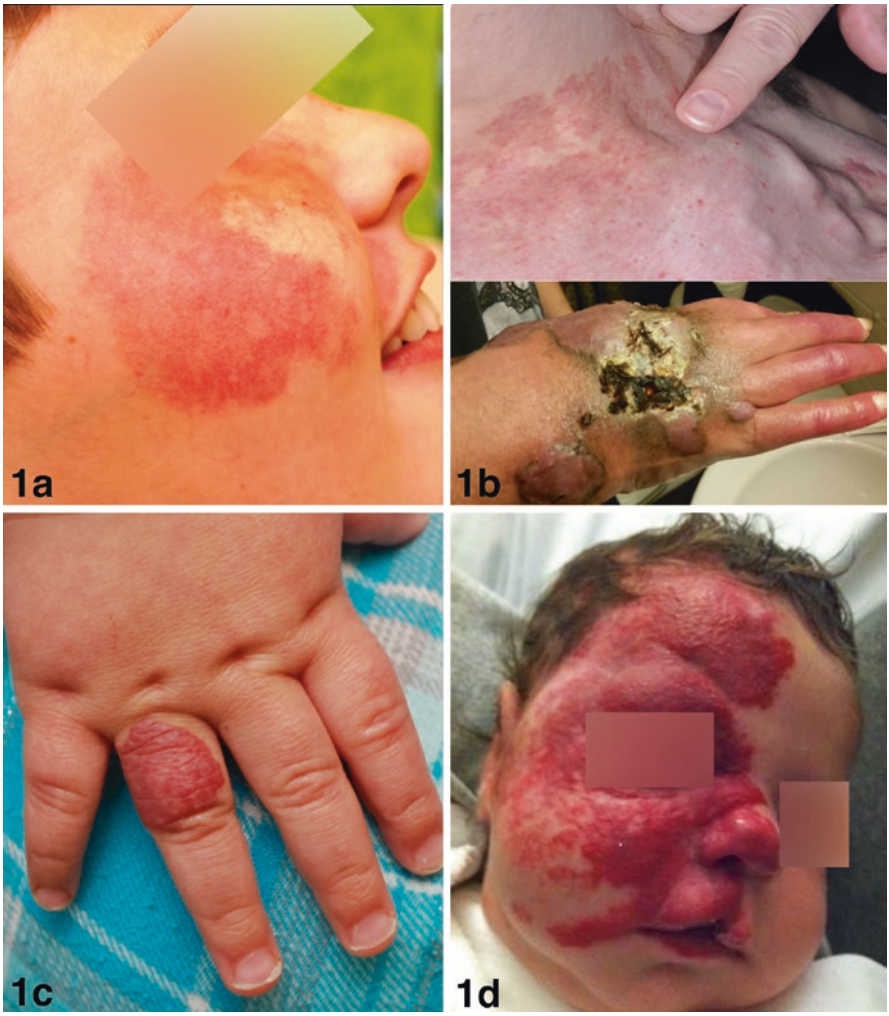

Fig. 2.1 (**a**) Capillary malformation. (**b**) Arteriovenous malformation. (**c**) Infantile hemangioma. (**d**) Infantile segmental hemangioma

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

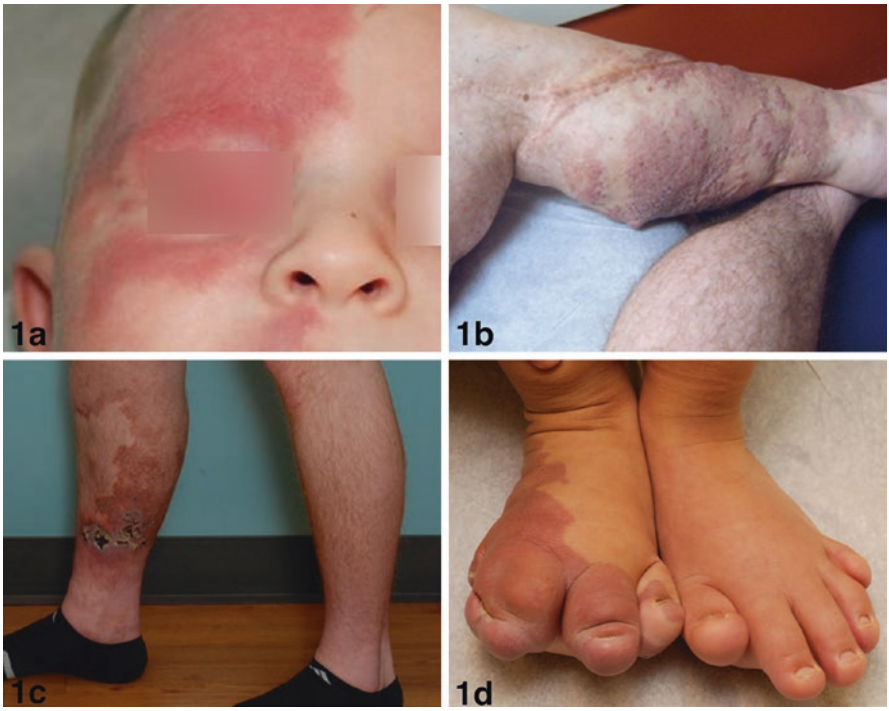

Fig. 2.2 (**a**) Sturge-Weber. (**b**) Klippel-Trenaunay syndrome. (**c**) Parkes Weber. (**d**) CLOVES

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

and megalencephaly may be a complication of multiple vascular malformation syndromes including Klippel-Trenaunay syndrome (Fig. 2.2b); Parkes Weber syndrome (Fig. 2.2c); congenital lipomatous overgrowth, vascular malformations, epidermal nevi, spinal/skeletal/scoliosis anomalies (CLOVES) (Fig. 2.2d); fibroadipose overgrowth (FAO); hemihyperplasia-multiple lipomatosis (HHML); Proteus syndrome; megalencephaly-capillary malformation (MCAP); and megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) [19].

Associated Clinical Laboratory Features Coagulopathy and thrombosis are frequent complications in slow-flow vascular anomalies. Kasabach-Merritt syndrome is a life-threatening coagulopathy with severe thrombocytopenia, hypofibrinogenemia, and elevated D-dimers associated with kaposiform hemangioendotheliomas or tufted angiomas. Venous malformations or mixed malformations with a venous component may also have localized intralesional coagulopathy with mild to moderate thrombocytopenia, hypofibrinogenemia, and elevated D-dimers [11]. Phleboliths, round calcified thrombi, may be noted on imaging and are often painful. Venous thrombosis and pulmonary embolism can occur, especially in Klippel-Trenaunay and CLOVES syndrome where there may be failure of regression of large embryonic veins and/or abnormal development of the deep venous system of the lower limbs; valvular defects, phlebectasia, and hypoplasia are frequently present [12, 15]. In particular, the persistence of the embryonic lateral marginal vein is a potential site for development of thrombi that may propagate to the deep veins in the thigh and pelvis and subsequently embolize to the lungs. Pulmonary hypertension and embolic stroke may occur as a complication of pulmonary arteriovenous malformations [2]. Bleeding can also be associated with vascular lesions, even in the absence of coagulopathy. Patients with hereditary hemorrhagic telangiectasia suffer from recurrent severe epistaxis and can bleed from intestinal telangiectasia as well; iron deficiency should alert the clinician to the possibility of gastrointestinal hemorrhage. Chronic intestinal bleeding and iron deficiency may also complicate blue rubber bleb syndrome and cutaneovisceral angiomatosis with thrombocytopenia. Rectal bleeding, hemorrhoids, and hematuria can be seen in Klippel-Trenaunay syndrome with pelvic involvement [17]. Finally, intra-articular venous malformations can lead to hemarthrosis.

Family History Genetic mutations have been described in several of the vascular malformation syndromes, and in general, three patterns have emerged. Affecting the majority of patients, Somatic mutations have been identified in abnormal vascular tissue from patients with capillary malformations and segmental overgrowth syndromes, sporadic venous malformations, and lymphatic malformations. Chromosomal translocations have been identified in tumor tissue from patients with epithelioid and pseudomyogenic hemangioendothelioma. Germline inherited mutations are the basis of familial syndromes such as hereditary hemorrhagic telangiectasia, some lymphedema syndromes, hereditary venous malformations, capillary malformation-arteriovenous malformation, and Proteus syndromes. A familial predisposition with incomplete penetrance, due to the inheritance of one mutated allele and the somatic acquisition of a second mutation within the abnormal vascular tissue, is seen in patients with glomuvenous and cerebral cavernous malformations.

Diagnostic Evaluation

The diagnosis of a vascular anomaly often depends largely on the clinical history and exam. Blood work, radiographic imaging, and biopsy may, in different situations, help define the type of vascular anomaly or rule out alternative diagnoses. More recently, genetic testing may facilitate diagnosis and counseling. A multidisciplinary approach is required, especially for malformations that are complex or have associated syndromic features.

The *clinical history and exam* will take into account the patient's age at presentation, growth characteristics, appearance and location of the lesion(s), and associated features. It is important to identify symptoms that demand acute management as well as those that inform the differential diagnosis (see above). Digital photos of the lesions are a helpful addition to the medical record.

Laboratory studies useful in the evaluation of vascular anomalies include a complete blood count and coagulation studies (PT, aPTT, fibrinogen, and D-dimers); this will identify associated complications such as Kasabach-Merritt syndrome or localized intralesional coagulopathy. Severe thrombocytopenia (platelet counts <50 K) strongly suggests Kasabach-Merritt syndrome, consistent with the diagnosis of Kaposiform hemangioendothelioma or tufted angioma. D-dimers are also frequently elevated in slow-flow lesions with a venous component, but rarely in pure lymphatic malformations and arteriovenous malformations [4]. If microcytic anemia is present, iron studies should be performed. In infants with liver lesions, the concomitant presence of cutaneous hemangiomas favors diagnosis of infantile hepatic hemangioma. Serum alpha fetoprotein should be obtained in those children in whom hepatoblastoma is suspected; however, since AFP is elevated at birth, serial AFPs monitoring the rate of fall with age may be required in order to interpret the results. Thyroid studies (T4, TSH) should be obtained in infants with hepatic hemangiomas to screen for consumptive hypothyroidism.

Radiographic imaging is useful for defining the extent of the lesion and to identify fast flow or slow flow as well as lymphatic components. Imaging is also important in the evaluation of complications such as thrombosis and in the planning of interventional approaches. Additional studies may be indicated in vascular lesions with syndromic associations to identify occult vascular and nonvascular abnormalities. Ultrasound is frequently employed as a first step in imaging because it does not expose the patient to radiation and often does not require sedation. Ultrasound is especially sensitive for identification of cystic or fluid filled spaces and, in combination with Doppler, can distinguish high- and low-flow lesions as well as areas of impaired flow due to thrombosis. Fast flow is characteristic of arteriovenous malformations and hemangiomas, whereas slow flow is seen in venous and capillary malformations. Ultrasound may also identify pleural effusions or ascites. In young infants, ultrasound of the spine can detect spinal dysraphism. Magnetic resonance imaging provides a cross-sectional overview of the lesion and is the most frequently used modality in the evaluation of large or complex vascular anomalies. Enhancement characteristics can identify lymphatic components (T2-bright, non-enhancing) versus venous, arterial, or capillary components (enhance with contrast). Additional sequences, such as time-resolved MRA sequences "TRICKS" or "TWIST" can identify lesions as "fast" or "slow" flow by measuring the rate at which contrast

enters, dwells, and then is washed out of a vascular lesion. Phleboliths, which are small, rounded, calcified structures having evolved from chronic clot, typically indicate a venous component. Lymphoscintigraphy may be used in the evaluation of lymphedema; this involves the injection of Tc99m-labeled antimony sulfur or albumin distally into the web space between the first and second digit of the affected area and tracing the flow of the labeled colloid proximally through the lymphatics [9]. CT may be useful in specific circumstances to define bony involvement. An echocardiogram should be obtained if there is a risk of high-output cardiac failure, especially in children with large hepatic lesions or with AVMs.

Biopsy is not always required to make a diagnosis and may be contraindicated in the face of severe coagulopathy or some anatomic locations. In addition, biopsy of lymphatic rib lesions is discouraged as it can lead to the formation of a chronic pleural effusion. Nevertheless, when the diagnosis is unclear, biopsy can provide useful information to aid the diagnosis and rule out alternative processes. In addition to morphologic review [6], immunohistochemical stains can differentiate between different types of vascular anomalies. GLUT-1 (glucose 1 transporter protein-1) is expressed in infantile hemangiomas and not expressed in other cutaneous vascular anomalies of infancy, congenital hemangiomas and pyogenic granulomas. PROX-1 and/or podoplanin (i.e., D2-40) immunostains are reactive in lymphatic malformations and kaposiform hemangioendothelioma and negative in venous malformations. Smooth muscle actin highlights glomus cells lining venous channels. In addition, tissue can be analyzed for somatic genetic mutations (see below). Pleural effusions or ascites should be tapped, which may provide diagnostic information as well as therapeutic benefit. Pleural or ascitic fluid with elevated triglycerides and lymphocytes indicates a chylous effusion and suggests dysfunction of the central conducting lymphatics.

Genetic testing for a number of germline and somatic mutations may be clinically available and facilitate diagnosis. Somatic mosaic mutations can be assayed from biopsied tissue, whereas genomic mutations are typically assayed from peripheral blood leukocytes. Clinical testing is currently available for a number of genetic mutations associated with vascular anomalies including ACVRL1, AKT1, AKT2, AKT3, ENG, GNAQ, GLMN, MTOR, PIK3CA, PIK3R2, PTEN, RASA1, and SMAD4. The field is rapidly changing; current information can be found on the website GeneTests.org.

In summary, the approach to an accurate vascular anomalies diagnosis requires a comprehensive clinical assessment, thorough personal and family history, complete blood count and coagulation studies, correlation with imaging, biopsy, or resection of the lesion in some cases, and increasingly, genetic testing.

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