A Basic Introduction to Pediatric Vascular Anomalies

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Vascular malformation classifications were first described by Mulliken and Glowacki in 1982, eventually forming the International Society for the Study of Vascular Anomalies (ISSVA) classifications. Due to confusion with nomenclature and classification, in 2014 ISSVA simplified nomenclature for all practitioners, particularly for those less involved with direct treatments of vascular anomalies but critical to the initial evaluation and diagnosis of these lesions. This change was implemented to prevent patients receiving incorrect treatments secondary to mislabeling, misdiagnosis, and inappropriate referrals.

The major classification modification that was made during the 1982 Congress was the separation of vascular anomalies into two broad categories: vascular malformations and vascular tumors or hemangiomas. The definition of hemangioma is a neoplasm with pathologic cell proliferation, while malformation is broadly defined as abnormally formed channels within a vascular apparatus lined by endothelial cells that do not undergo abnormal cellular turnover.¹ In this review, we will discuss the most common vascular birthmarks, according to the most recent ISSVA classification, and provide a pictorial guide to assist the practitioner with diagnosis.

Definitions

- **Telangiectasia:** small dilated blood vessels near the surface of the skin or mucous membranes.
- **Ecchymosis:** extravasation of blood into tissues from ruptured blood vessels.
- **Anetoderma:** loose skin due to loss of elastic fibers in the dermis. The affected skin can appear as a flesh-colored protuberance or soft, thin, and wrinkled.
- **Kasabach-Merritt phenomenon:** a life-threatening consumptive coagulopathy due to significant thrombocyto-

penia caused by platelet trapping within the tumor.² Presenting clinical findings include petechiae and easy bleeding.

- **Phlebolith:** small, round calcification within a vein (precursor is blood clot).

Vascular Tumors

Vascular tumors are classified into benign, locally aggressive/borderline, and overtly malignant.

- Benign:** infantile hemangioma (IH), congenital hemangioma (CH), tufted angioma, spindle cell hemangioma, epithelioid hemangioma, pyogenic granuloma.
- Locally aggressive:** Kaposiform hemangioendothelioma (KHE), retiform hemangioendothelioma, Kaposi sarcoma (KS).
- Malignant vascular tumors:** epithelioid hemangioendothelioma, angiosarcoma.

Benign Vascular Tumors

Infantile Hemangioma

The most common benign vascular neoplasm is IH with an estimated prevalence of 4 to 5%.³ IH can be further subclassified based on level of skin involvement as superficial, deep, or combined. It can also present in mucous membranes or visceral organs.³ IH is GLUT-1 positive, a unique identifying marker that distinguishes IH from other vascular birthmarks. The pathophysiology of IH is proliferation of endothelial cells and pericytes.

Clinically, IH presents more frequently in premature, low-birth-weight infants, Caucasians, and females.² The tumor most commonly presents within the first few weeks of life as a solitary cutaneous lesion on the cervicofacial area. Sixty percent of IH lesions present on the head/neck, 25% on the trunk, and 15% on the extremities.² Thirty percent to 50% are evident at birth as a telangiectatic stain or ecchymotic patch. Twenty percent of patients with IH have more than one

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lesion. While it is common to have two or three hemangiomas, infants with 5 years or more are at an increased risk of IH of their internal organs, most commonly the liver.

The most common differential diagnoses of IH are other benign tumors especially congenital hemangiomas (CHs) and tufted angioma/KHE, vascular malformations, infantile myofibromatosis, and, rarely, malignant tumors such as infantile fibrosarcoma, lymphoma, or metastatic neuroblastoma.

Various classification systems exist. Classification by skin depth includes superficial, deep, or mixed. Superficial lesions only involve the outer layers of the skin and are typically bright red in color (►Fig. 1a). In comparison to deep lesions, superficial IH will often both appear and involute earlier in age.⁴ Deep lesions grow under the skin and into the adipose tissue. They appear flesh-colored with a bluish hue and often overlying telangiectasias (►Fig. 1b). Mixed lesions exhibit both superficial and deep features (►Fig. 1c).

Alternatively, IH can be classified by anatomic configuration⁴—focal, segmental, facial segmental, indeterminate, and multifocal. Focal tumors arise from a single local point and are round, popular, or nodular. Segmental lesions are plaque-like and involve a larger region of skin. Facial segmental IH can be defined as frontotemporal, maxillary, mandibular, and/or frontonasal (►Fig. 1d, e). Indeterminate IH is classified into this category when the lesion cannot be definitively

determined either focal or segmental. Multifocal tumors are classified by multiple IH lesions, typically five or more.

IH tends to follow three distinct growth patterns.² The *proliferative* phase is rapid growth which occurs early within the first year of life, with the majority of growth achieved by 3.2 months. During the rapid growth phase, IH may ulcerate.⁴ The *involution* phase generally begins around 6 to 18 months of age and can occur simultaneously with the growth phase. On average, this phase is complete by age 4 to 5 years. During involution, superficial IH will involute from the center outward commonly observed as “central clearing.”⁴ After *complete involution* (aka “involved”), approximately half of IH will leave residual telangiectasia, anetoderma, scarring, fibrofatty residuum, redundant skin, or destroyed anatomic structures.

Up to 24% of patients with IH develop complications.⁴ The most common complication is ulceration (►Fig. 1e). In comparison to focal IH, segmental IH is at higher risk of ulcerating. Larger, superficial, or mixed IH in pressure or trauma-prone locations are also at greater risk. Depending on the character of the lesion and its location to other vital structures, other complications include bleeding, visual impairment, auditory impairment, and airway obstruction. Diffuse IH of the liver is rare but life-threatening, as this can result in consumptive hypothyroidism, congestive heart failure, hepatic failure, and abdominal compartment syndrome.

Fig. 1 IH is classified into three different subtypes based on their depth. (a) Superficial IH also known as “strawberry type” is only localized to the surface of the skin with no subcutaneous component. (b) Deep IH is deep to the skin and involves the adipose tissue and can either be blue in color or have no surface involvement. In this case, the baby exhibits a cranial lesion blue in color. (c) Mixed IH exhibits both components with a purple-red color and subcutaneous presentation. (d) Patterns of segmental IH. 1 = frontotemporal, 2 = maxillary, 3 = mandibular, 4 = frontonasal. (e) Segmental right maxillary IH demonstrates local scalp ulceration. (f) Infantile hemangioma in a patient with PHACES. (g) Anterior chest wall infantile hemangioma. Ultrasound demonstrates a well-defined mass with mixed echogenicity. (h) Anterior chest wall infantile hemangioma. Color Doppler demonstrates increased flow within the lesion. (i) The image demonstrates gray scale and color Doppler ultrasound of an intraparotid lesion. The left-sided MRI image demonstrates a noncontrast T1-weighted MRI image with a hypointense lobulated parotid mass. With contrast, the T1-weighted MRI image demonstrates enhancement.

IHs may have associated syndromes,⁵ two of which go by the acronym PHACES and LUMBAR syndromes. PHACES syndrome consists of posterior fossa anomaly, hemangioma (typically segmental, >5 cm in diameter, and located on the head or neck; ►Fig. 1f), cerebrovascular arterial anomalies, cardiovascular anomalies, eye anomalies, and sternal defects and/or supraumbilical raphe. LUMBAR syndrome consists of lower body hemangioma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, and renal anomalies.

IH is usually diagnosed clinically, but some imaging modalities can be implemented. In any infant found to have a hemangioma in any location, color Doppler is the imaging modality of choice³ because it does not require sedation or radiation exposure. Ultrasound is especially useful during the proliferative phase, as it will show a well-circumscribed mass with variable echogenicity and enlarged channels (►Fig. 1g). Color Doppler will demonstrate high-flow vessels in and around the mass (►Fig. 1h).⁶

Extensive or complicated hemangiomas may occasionally require evaluation with MRI to better characterize and determine disease extent, for preoperative planning. If MRI is implemented, IH will demonstrate contrast enhancement of the mass with serpiginous flow on fat-saturated T1 images. Masses on T2 will have mild hyperintensity in comparison to muscle⁶ (►Fig. 1i).

The approach to management is dependent on multiple contributing factors including the lesion's size and location as well as current or potential complications, possible disfigurement, the patient's age, and rate of growth or involution upon evaluation.

Since IH often begins to spontaneously involute beginning at the first year of life, watchful waiting is the most common management option for the small, localized, uncomplicated lesions.

However, local therapies for the uncomplicated small or superficial hemangiomas generally involve expectant management or medical therapies.⁷ Topical β -blockers such as timolol (first line) or propranolol are used as treatment for the small lesions located in areas of minor cosmetic concern. Timolol is applied two to three times daily for 6 to 12 months.

In the past, topical corticosteroids were used for superficial hemangiomas at risk for ulceration. However, since the introduction of topical β -blockers, corticosteroids are less frequently used given their adverse effects including skin atrophy and hypopigmentation.

Intralesional corticosteroids are used for small, localized, deep hemangiomas. Individual doses should not exceed 3 mg/kg and it is notable that treatment response begins at 2 weeks and continues for a total of 8 weeks of treatment.

Complicated hemangiomas are lesions that result in severe ulceration, scarring, or disfigurement; are life-threatening; or affect the function of its neighboring organs. Treatment for complicated hemangiomas generally is medical or surgical.⁷

A systemic nonselective β -blocker-like propranolol is the first-line agent for hemangiomas that are at increased risk for causing permanent disfigurement or result in local impaired function. By inducing vasoconstriction and decreasing the

expression of the vascular endothelial growth factor, propranolol induces lesion regression and inhibits growth. The patient must undergo pretreatment evaluation, specifically cardiac and respiratory assessment. All patients should have a thorough history of cardiac and pulmonary abnormalities. A cardiovascular family history, specifically arrhythmia or heart block, should also be obtained. Children with a below-baseline heart rate or history of arrhythmia should have an electrocardiogram. Patients at risk for PHACE should get a cardiac ultrasound or MRI to exclude aortic coarctation.

Oral propranolol is started at 0.5 to 1 mg/kg daily in two to three divided doses with feedings. It can be increased by 0.5 mg/kg daily as tolerated to reach a target dose of 2 mg/kg within 1 to 2 weeks. Oral propranolol should be initiated in the hospital setting if the patient is younger than 5 weeks, preterm with a corrected age greater than 5 weeks, has conditions that affect blood glucose maintenance, or has other morbidities that would affect the cardiovascular or respiratory system. Children are followed up every 1 to 3 months with an average duration of treatment of 6 to 12 months depending on the size and location of the hemangioma. Often, patients continue this therapy up until 12 to 18 months of age. Upon propranolol discontinuation, rebound growth can occur in 14 to 25% of patients.

For children with a contraindication to propranolol, systemic corticosteroids are the treatment of choice. Prednisolone is started at 2 to 3 mg/kg daily. Treatment is continued for several months depending on the child's age and treatment response. Treatment should be slowly discontinued to avoid the risk of rebound proliferation.

Interferon alfa can be used as an alternative therapy for hemangiomas that are unresponsive to glucocorticoids. However, this is rarely used due to the adverse effects of motor developmental complications and permanent spastic diplegia.

Interventional treatment can also be considered for each individual case. However, the following are not often recommended due to the potential risk of scarring.⁷ Pulsed-dye laser (PDL) is targeted toward superficial hemangiomas as it can penetrate only up to a depth of 1.2 mm. It is used in the cases of ulceration, postinvolution erythema, and telangiectasias. Excisional surgery is reserved for hemangiomas that have not involuted after the age of 4, pedunculated cutaneous hemangiomas, localized periorbital hemangiomas, and hemangiomas in areas of cosmetic concern. Since excisional surgery can also create a surgical scar, the benefits and risks should be considered for each case. Arterial embolization can be used for large visceral hemangiomas that have failed medical therapy.

First-line therapy for IH resulting in complications may depend on their anatomic location.⁷ Ulcerated hemangiomas should get wound care to avoid trauma or infection. Topical antibiotics and barrier creams are commonly used. Oral propranolol can be used in addition to wound care for the lesions that may interfere with daily life activities or cause permanent disfigurement. For ulcerated IH that have failed first-line therapy, PDL can be used as an adjunctive treatment. Airway hemangiomas are approached with systemic propranolol as first-line therapy followed by laser ablation as second-line

therapy. Superficial periocular hemangiomas are treated with topical timolol. In patients with vision-threatening periocular IH, oral propranolol is first line with intralesional corticosteroids as a second option for patients who have a contraindication to the β -blocker or fail first-line therapy.

Congenital Hemangioma

Congenital hemangiomas are the second most common benign vascular tumors and can present as one of three subtypes; rapid involuting CH (RICH), noninvoluting CH (NICH), and partially involuting CH (PICH). Histologically, these neoplasms are composed of capillary lobules with endothelial cells. Unlike IH, they do not express GLUT-1.^{2,5} They can also be associated with large extralobular veins, arteries, and lymphatics.²

Their clinical features may further help distinguish them from IH. Unlike IH, CH is fully developed at birth (i.e., congenital). The lesions can occur as visceral, soft-tissue, or intracranial extra-axial lesions.⁸ RICH presents as a raised, blue, violaceous mass with prominent peripheral veins. RICH will begin rapidly regress by 14 months of age with the majority of the lesion involuting by the first 3 months of life⁸ (►Fig. 2). NICH presents as a round telangiectatic plaque with a rim of pallor and grow proportionally with the patient's growth⁶. The NICH neoplasms will not involute and rarely cause ulcerations (►Fig. 3). The PICH neoplasms will partially involute within the first year of life. The rapid involution satisfies the RICH criteria. The residual tumor resembles NICH. CH commonly affects the head, neck, and limbs and, less often, the trunk.

As with IHs, CHs (primarily RICH) may also have complications.⁹ RICH is known to be associated with mild transient thrombocytopenia and consumption coagulopathy which typically self resolves within a few weeks. RICHs have been associated with Kasabach-Merritt phenomenon (KMP), although rare. RICH is rarely associated with high output cardiac failure due to arteriovenous or portovenous shunting.¹⁰ In the first few months of life, RICH can more commonly ulcerate and bleed particularly during the involution phase.

Fig. 2 This was classified as RICH. The shoulder lesion was fully formed at birth with rapid, progressive regression.

Fig. 3 This was classified as NICH. The lesion did not regress with time.

Often, CH is diagnosed clinically. Its presence at the time of birth is an important diagnostic clue that helps differentiate from IH. Imaging can be used for further evaluation when the diagnosis is unclear. Both RICH and NICH are high-flow vascular lesions on Doppler examination and demonstrate a heterogeneous structure with diffuse vascularity on ultrasound. On MRI, RICH and NICH demonstrate lesions of ill-defined borders with heterogeneous enhancement, T2-weighted hyperintensity, and absent peripheral edema.

RICH can generally be observed due to the rapid regression. Periodic clinical examination is recommended to ensure complete resolution and monitor for ulceration. To prevent ulceration, petrolatum can be applied throughout the day. Superficial ulcerations are treated with wound care which involves barrier creams, frequent dressings, and topical antibiotics. Patients may require surgical excision if the CH persistently ulcerates.

NICH is most often observed because it less commonly causes complications. Surgical excision or laser can be considered to improve cosmesis. Patients with CH-induced heart failure require embolization and/or surgical excision. Although transient thrombocytopenia often self-resolves, systemic corticosteroids have been used in a small number of patients. However, the efficacy of this therapy is unknown.

Locally Aggressive or Borderline Vascular Neoplasms

Kaposiform Hemangioendothelioma

Kaposiform hemangioendothelioma is a rare vascular neoplasm with an incidence of 0.07/100,000 children yearly with 50% of the cases presenting at birth and the remainder presenting in the neonatal period. KMP occurs in 70% of patients.¹¹ Although KHE is histopathologically benign, it is locally aggressive and potentially life-threatening when associated with KMP.

The lesion(s) of KHE often present as raised, red-purple, subcutaneous mass with a purpuric appearance. Often, the lesions can rapidly enlarge and involve the deep tissues

Fig. 4 (a) A newborn child with a flat red-purple lesion consistent with KHE. (b) Axial T2 MRI image demonstrates diffuse superficial abnormality with infiltration of deeper musculature in a 2-year-old.

resulting in persistent chronic pain and visible deformities² (► **Fig. 4a**). Rarely, KHE can involve the retroperitoneum, mediastinum, and internal organs. Among these noncutaneous locations, retroperitoneal involvement is the most common.

However, KHE can also present without an obvious mass but, rather, with a clinical presentation of KMP. Patients with lesions located in the retroperitoneum or mediastinum or with congenital lesions are at the highest risk of developing KMP.⁸ Unlike IH, it presents in equal sex distributions, but usually larger (>5 cm) typically involving deep tissue. These lesions often affect the head and neck (40%), trunk (30%), and extremity (30%).²

KHE is often diagnosed clinically with the aforementioned features. When cutaneous lesions are not easily identifiable and/or confirmation is needed, MRI is the imaging modality of choice. On MRI, it presents as a T2 hyperintense lobular lesion in subcutaneous tissue and T1 enhancement postgadolinium lesion with poorly defined margins, small vessels, and invasion into adjacent tissues² (► **Fig. 4b**). Prominent vessels extending to the lesions can be identified; however, vessels within the lesion are rarely identified.⁸ Although less distinct than MRI, ultrasound can also be used which will demonstrate a poorly defined mass that extends from the skin and infiltrates the subcutaneous tissue. Focal edema can also be seen which contributes to the difficulty in identifying the tumor margins.⁸

Management depends on the size of the lesion, symptoms, and presence or absence of KMP.

Patients with KHE without KMP can be managed with surgical excision, PDL, and various chemotherapy agents.¹² Asymptomatic lesions without involvement of neighboring structures or functional compromise can be observed. Symptomatic tumors can undergo surgical excision. However, this

is not recommended since KHE often has poorly defined margins or involves neighboring vital structures. Furthermore, tumors do not fully regress and can return with pain and inflammation, often around puberty. There are various pharmacologic approaches to symptomatic, nonresectable tumors which include aspirin, corticosteroids, and chemotherapy agents.

Management of KHE with KMP involves treating both the tumor and maintaining hemostasis.¹² Systemic corticosteroids are first-line therapy and started at 2 to 3 mg/kg daily; however, response is variable. If thrombocytopenia resolves within 1 to 2 weeks of initiating treatment, corticosteroids can be tapered over 4 weeks. However, if thrombocytopenia relapses, agents such as vincristine, sirolimus, or interferon- α should be added.

The chemotherapeutic agent Vincristine is another first-line therapy which helps minimize fibrosis and pain. It can also be used in conjunction with corticosteroids. It is initially given weekly and can be increased to every 2 weeks for 2 months then every 3 weeks for 2 months if treatment response is appreciated. A response includes tumor regression or reduction in size and/or hematologic response.

Alternatively, in patients with refractory KMP, recent studies have shown a good response to the mammalian target of rapamycin (mTOR inhibitor, Sirolimus), which blocks platelet trapping and inhibits lymphangiogenesis.¹³

Recent case reports have also noted the use of aspirin in conjunction with sirolimus or vincristine. Not only does this help with pain, but it also prevents platelet aggregation.^{14,15}

Malignant Vascular Tumors

Malignant vascular tumors make up 2% of vascular tumors⁸ and include childhood angiosarcoma, epithelioid hemangioendothelioma, and infantile fibrosarcoma. However,

although pediatric cases have been reported, they are usually present in the older patient population. Therefore, since their pediatric presentation is rare, there is little information about their clinical history and management.

Angiosarcoma

Angiosarcoma^{8,16} is a high-grade tumor that makes up 0.5% of all pediatric sarcomas. Otherwise, they often do not present until after the second decade of life. However, when they do occur during childhood, they are more aggressive than those that present during adulthood and are similarly associated with a poor prognosis.

Cases have been reported in children between 3 months and 16 years of age with a 4:3 male:female ratio. They present as a painful, enlarging mass that lasts for several weeks. Occasionally, patients will also present with acute hemorrhage, anemia, and coagulopathy. Twenty-seven percent of patients present with tumor rupture and hemoperitoneum. These tumors frequently occur in the liver and deep soft tissue and prefer the trunk, pelvis, head, neck, and mediastinum. Sixty percent have metastasized upon presentation.

Diagnosis is difficult in poorly differentiated angiosarcomas. It is often a histological diagnosis often relying on immunohistochemical studies if vasoformative architecture is not well identified. Immunohistochemistry is important for diagnosis, as it can confirm vascular differentiation from other vascular tumors such as from Kaposi sarcoma, epithelioid hemangioendothelioma, hemangiopericytoma, and spindle cell hemangioendothelioma. One helpful histologic characteristic is that angiosarcoma is immunoreactive to CD34 and CD31. MRI can provide information regarding extent of lesion and its involvement with other tissue structures. On MRI, the lesion is T1 hyperintense and T2 hypointense with an internal fluid–fluid level from the layering blood product.

Management of these tumors varies based on the behavior of the tumor (well vs. poorly differentiated) and the involvement of other structures. Poorly differentiated neoplasms and mitotic count are independent prognostic factors.¹⁶ Resection can be considered if the tumor is local. Although the role of chemotherapy is unknown, since angiosarcoma originates from endothelial cell, paclitaxel has been studied due to its antiangiogenic activity.¹⁶ Theoretically, paclitaxel can target both the tumor cells and its vascularization.

Infantile Fibrosarcoma

Infantile fibrosarcoma is a very rare childhood malignancy characterized as a spindle cell tumor originating from soft tissue. It makes up less than 1% of childhood tumors and more commonly presents in the first 5 years of life. It often presents as an infiltrating, local, rapidly enlarging, soft-tissue mass commonly located in the distal extremities, head, and neck. Larger infantile fibrosarcomas have the potential to present with necrotic or ulcer surface resulting in anemia. Recurrence (local) is common but metastasis is rare. If metastasis does occur, the lung is the most common site. As there are no distinguishing radiologic characteristics, this tumor can only be definitively diagnosed with biopsy.

However, MRI remains beneficial, as it can be used for initial staging, help select which part of the tumor is appropriate for biopsy, and can help in the surgical planning.¹⁷ Images will demonstrate a heterogeneously intense mixed cystic and solid structure with heterogeneous enhancement. Some nonspecific malignant features include invasion to bone or adjacent vascular nervous structures, measure larger than 6 cm, and disrupt the superficial aponeurosis. However, these features are more often seen in aggressive, near incurable tumors.¹⁷

The preferred therapeutic approach is wide surgical excision with negative margins, ideally with a nonmutilating outcome. However, often, the tumor is inoperable due to its invasion or encasement of neurovascular bundles. In patients in whom surgery will result in long-term morbidity, recent studies have favored preoperative neoadjuvant chemotherapy to decrease tumor size and allow for complete tumor resection with decreased morbidity.¹⁸ Adjuvant chemotherapy is also preferred in patients with positive surgical margins.¹⁸ Radiation therapy is often avoided to preserve growth potential and function,¹⁷ particularly in the younger patients.

Vascular Malformations

Vascular malformations are divided into four groups: simple malformation, combined malformations, malformations of major named vessels, and malformations associated with other anomalies. These can further be divided into low-flow versus high-flow malformations.

1. Simple malformations:

- i. Capillary malformations (multiple subtypes), “port wine” stain, telangiectasia, cutis marmorata telangiectatica congenita, nevus simplex/salmon patch (e.g., “angel kiss,” “stork bite”).
- ii. Lymphatic malformations (LMs; multiple subtypes), generalized lymphatic anomaly, LM in Gorham-Stout disease, channel-type LM, primary lymphedema.
- iii. Venous malformations (multiple subtypes), common VM, blue rubber bleb nevus syndrome (BRBNS), familial VM cutaneomucosal, glomuvenous malformation (GVM), cerebral cavernous malformation.
- iv. Arteriovenous malformations (AVMs).
- v. Arteriovenous fistulas (AVFs).

2. Combined malformations:

More than two vascular malformations in one lesion. These may be simple malformations, malformations of major named vessels, or a combination of both types.

3. Malformation of major named vessels:

These malformations affect veins, arteries, or lymphatics of generally large caliber, often axial or conducting vessels.

Simple Vascular Malformations

These are composed of a single type of vessel (capillaries, lymphatics, or veins). The exception to this rule is AVMs which are composed of arteries, veins, and capillaries.

Capillary Malformations

This simple malformation is composed of dilated capillaries in the superficial dermis. They are most commonly known as “port-wine stains” due to their darkly erythematous presentation on the skin.

Capillary malformations (CMs) are usually present at birth, acquired cases are rare, and affect the skin and mucosa, appearing as flat pink or red blanching flat lesions with irregular borders² (►Fig. 5). Their presentation can vary from small and localized to extensive or rarely generalized. Bony and/or soft-tissue hyperplasia can also be seen. CMs are sometimes referred to as “sick dermatome” due to a complete or partially deficient autonomic and sensory vascular innervation at a level of a dermatome resulting in hypertrophy of the affected vessels.² On the face, CM is most commonly seen in a V1, V2, and/or V3 distribution (►Fig. 5). Patients with a V1 distribution are at risk for CNS and ocular involvement; particularly, patients should be worked up for Sturge-Weber syndrome.^{5,6,19} Sturge-Weber syndrome is caused by a somatic mutation in the GNAC gene.²⁰

As the child ages, the CM can thicken, darken, and become nodular, because they infiltrate deeper tissue. Local complications include the development of pyogenic granulomas and eczematous dermatitis overlying the CM.²¹ The differential diagnosis for these lesions consists of nevus simplex, IH, and vascular stain associated with AVM (AVM precursor).

IH can be differentiated by CM by the presence of surrounding pallor that is seen in hemangiomas due to vasoconstriction. Furthermore, CM remains flat while IH can become raised and develop vascular blebs. IH can also be differentiated from CM due to the presence of a proliferative phase. Clues to differentiate this from AVMs are done by Doppler to assess flow rates. If bruit and/or thrill to palpation are found, AVM is the most likely diagnosis.

CMs also have association with other syndromes. Sturge-Weber syndrome (the most common): facial CM plus capillary-venous vascular malformations of the brain and/or eye

anomalies.⁶ Klippel-Trenaunay syndrome: CMs, lymphatic malformation, abnormal soft tissue and bone overgrowth (usually limited to one limb), and superficial venous varicosities, generally related to maldevelopment of the deep venous system. Patients with deep vein malformations are at increased risk for deep vein thrombosis. Parkes-Weber syndrome: CMs, AVFs (often microvascular), abnormal growth of one limb.

In most cases, CM is a clinical diagnosis based on appearance, evolution of the skin lesion, and time of onset. Clues include the unilateral distribution of a blanchable red patch at birth that does not regress. Although imaging studies are not routinely performed, they may be done to evaluate suspicion of associated syndromes.

In patients with facial CM, particularly in the V1 dermatomal distribution, or demonstrating neurologic symptoms, a contrast-enhanced MRI should be conducted to exclude Sturge-Weber syndrome.²² Patient with Sturge-Weber syndrome will demonstrate the presence of leptomeningeal CM.⁶

In general, management of CM is expectant, but there are specific instances where treatment may be necessitated or preferred. Patients with CMs of cosmetic concern, most commonly facial, often elect to undergo laser treatment.² The gold standard treatment for CMs is PDL therapy (aka selective photothermolysis) which irreversibly damages the capillary vessel wall with minimal damage to the epidermis. This involves an initial consecutive series of treatments followed by maintenance treatments over time as improvement is not permanent.⁶ PDL is most effective in patients with lighter skin types, as greater amounts of melanin may interfere with treatment response.² While PDL is relatively safe, uncommon risks include ocular damage, blistering, scarring, dyspigmentation, and inefficacy. For patients who respond inadequately to PDL, alternative lasers such as long-pulsed neodymium:yttrium-aluminum-garnet (Nd:Yag) laser can be tried.²¹

Fig. 5 Craniofacial V1 and V2 distribution of a red and pink flat lesion which respects the midline.

Lymphatic Malformations

Lymphatic malformation lesions are the second most common type of vascular malformations. They are low-flow lesions caused by dilation of lymphatic channels or cysts lined by endothelial cells. LMs are classified by the size of the malformed channels: macrocystic (>2 cm), microcystic (<2 cm), and mixed subtypes.^{5,19}

Macrocystic LMs have a strong predilection for the cervicofacial and axillary region, which accounts for 75% of the lesions. Ninety percent occur in children before the age of 2. Microcystic LMs, also known as lymphangioma circumscriptum, are more common and generally present later than macrocystic LM. They are usually soft but noncompressible and appear as clear (or red due to intralesional bleeding) vesicles when they involve the superficial skin or mucous membranes⁶ (►Fig. 6a). This subtype of LM is commonly located in the proximal extremities, trunk, axilla, and oral cavity.

Macrocystic LMs, colloquially referred to as cystic hygroma, often present at birth. They often appear as large,

Fig. 6 (a) Microcystic lymphatic malformation of the buttock appears as red mucosal vesicles. (b) A 4-year-old boy with macrocystic lymphatic malformation of the right neck. (c) Lymphatic malformation involving the right mandible resulting in mandibular hypertrophy. (d) Gray scale ultrasound demonstrates multiple anechoic cystic spaces consistent with simple macrocystic LM. (e) Ultrasound image demonstrates a complex chest wall macrocystic lymphatic malformation. Coronal T2 MRI image of the neck demonstrates a well-defined hyperintense lesion extending from the supraclavicular fossa into the neck.

skin-colored or translucent, soft, spongy, nontender masses⁶ (►Fig. 6b). This subtype of LM is commonly located in the lateral chest wall, axilla, or cervicofacial region. They rarely regress and can temporarily fluctuate in size based on the amount of intracystic fluid present. Such changes are often dependent on exacerbating factors such as infection, trauma, and hormonal changes during puberty or pregnancy.

Macro- and microcystic LMs are usually asymptomatic. Independent of location, these lesions can cause intralesional bleeding resulting in pain and/or recurrent inflammation which can lead to cellulitis. Depending on their location to nearby structures, they can also cause various complications as they grow. In the tongue, trachea, or mouth, LMs may cause dysphagia, dyspnea, difficulties with speech, or difficulties with eating. Thoracic LMs may result in chest pain or shortness of breath. Periosteal or intraosseous lesions can lead to osseous maldevelopment and even occasional pathologic fractures²³ (►Fig. 6c).

LMs (particularly microcystic LM) may be associated with Klippel-Trenaunay syndrome. Fifty percent of the macrocystic LM identified in the first trimester of pregnancy are associated with Down's syndrome, Turner's syndrome, and Noonan's syndrome.

LMs are usually diagnosed by clinical presentation with appropriate imaging characteristics. Ultrasound and color flow Doppler can help confirm the cystic appearances. Macrocystic LM will demonstrate anechoic lesions with internal septa (►Fig. 6d). Microcystic LM will appear hyper-echoic which is artifact due to their small size.⁶ Ultrasound also helps evaluate for fluid-fluid levels which indicates intralesional hemorrhage or infection. Doppler ultrasound will show no intracystic flow,⁶ which is useful to help

distinguish from venous malformation. However, ultrasound might identify cyst wall flow, which needs to be carefully interrogated to ensure it is not within the cyst itself.

MRI is most useful in defining the LM based on its superiority in soft-tissue imaging. Macrocystic LM will demonstrate a septated cystic hypointense mass on T1-weighted images. The septated mass will be hyperintense on T2-weighted images (►Fig. 6e). Postcontrast T1 images can also help differentiate from VM. Except the septations, LM masses will not enhance after contrast injection.⁶ Microcystic LMs are diffusely T1 hypointense and T2 hyperintense. On CT, LM will demonstrate nonenhancing low-attenuation masses. If intralesional hemorrhage or infection is involved, MRI can demonstrate a fluid-fluid level.

Indications for treatment of lymphatic malformations include recurrent infections or hemorrhages, impairment or threat to local structures, and disfigurement.¹⁹ Conservative management includes physical therapy, physical activity, compression garments, and lymphatic massage. The goal of these therapeutic modalities is to decrease the risk of cellulitis and improve mobility/comfort.

For complex LM, if interventional treatment is recommended, options include sclerotherapy, radiofrequency ablation, and/or surgical excision depending on the LM size, degree of disfigurement, functional deficit, and involvement of neighboring structures. Currently, sclerotherapy with the sclerosants doxycycline or bleomycin (particularly for areas intolerant of an aggressive inflammatory response/swelling) is the main approach toward complex (predominantly macrocystic) LM with surgical excision as a complementary therapy. It works by irritating the vessels

which activates the immune system resulting in increased endothelial permeability and therefore increased drainage and lymph flow causing contraction of the lesion.²³ Cyst wall inflammation may also allow closure of the cyst space. Intralesional injection of a sclerosant is beneficial over other therapies due to its ability to access the LM without compromising nearby structures. The only curative measure is surgical resection, but complete resection is not often achievable due to the regeneration of the remaining channels and location of the LM. Therefore, to prevent local recurrence, an extensive radical resection is required which could consequentially affect surrounding and/or vital structures as well as potential disfigurement.

Many recent case reports have demonstrated the mTOR inhibitor, sirolimus, to be efficacious for complex unresectable LMs by reducing size and “softening” the lesions, making them more tolerable and amenable to interventional or surgical therapy. Sirolimus directly inhibits mTOR, therefore blocking downstream protein synthesis, decreasing the expression of VEGF, and creating an antiangiogenic and antitumoral effect.¹³ Many questions remain surrounding mTOR utilization, including appropriate length of therapy, inability to prevent rebound growth of the lesion, peritherapy immunosuppressive risks, and others.

Fig. 7 (a) Blue discoloration of the oropharyngeal mucosa. (b) Blue discoloration of the left hand consistent with venous malformation. (c) Gray scale and color Doppler of the left labia demonstrates multiple tubular venous channels with low flow. Compression of the lesion results in “flash-filling.” (d) T2-weighted MRI image demonstrates hyperintensity within the multiple tubular structures of the left labia.

Venous Malformations

This is the most common type of congenital vascular malformations with an incidence of 1 in 10,000 patients²² and most commonly sporadic in nature. They are slow-flow lesions composed of clusters of veins and venules lined by a single endothelial layer with minimal connection to adjacent veins.

Venous malformation can present at birth, but often, especially if intramuscular, will present later in life as pain provoked by physical activity. They generally present as a deep bluish skin discoloration with a superficial or soft subcutaneous mass that can affect any tissue or viscera in the body²⁴ (►Fig. 7a, b). VMs are soft, compressible, and increase in volume with increase in venous pressure or with exercise. These lesions can expand or contract based on patient positioning and thus are “dependent.”⁵ If the lesion involves multiple tissue layers (muscle, subcutaneous fat, and skin), patients can suffer from pain with reduced physical function due to disfigurement/impairment of neighboring structures and organs. Furthermore, large VMs can be associated with intravascular coagulopathy (elevated D-dimer and decreased fibrinogen levels).

The most common symptom of VM is pain depending on their size and location. Phlebotic syndrome results in local pain and swelling due to stagnant blood flow and local intravascular coagulopathy. Other complications include skin changes and tissue/limb overgrowth.²² Depending on the area of involvement, there may be specific local issues.²³ In the lower limbs, these are pathologic fractures, weakness, bone growth disorders, and/or muscular hypertrophy. In the face or temporal muscle, patients may experience migraine headaches. In the tongue, palate, and oropharynx, if the deformity is significant, this can cause life-threatening invasion to the airway and/or dental malocclusion.

Venous malformations may also be associated with Klippel-Trenaunay syndrome or BRBNS (aka Bean syndrome): a rare disorder that consists of many VMs which most commonly involve the skin and gastrointestinal tract as well as other visceral organs.⁵

To diagnose venous malformations, color Doppler is the first-line imaging modality when investigating VM. It demonstrates a very slow-flow tubular lesion and the vascular anatomy (►Fig. 7c). Sixteen percent of lesions may not demonstrate any flow due to its low-flow velocity and/or static state.²² In some instances, flow can only be elucidated with a rapid compression release of the ultrasound probe (so-called “flash-filling”). If phleboliths are present, they demonstrate acoustic shadowing upon compression.

MRA and contrast-enhanced MRI are preferred for pre-procedural planning and for postprocedural clinical concerns. In our practice, the routine use of posttreatment MRI is not recommended. In general, T2-weighted imaging will demonstrate multiple hyperintense signals within tubular channels (►Fig. 7d). T1-weighted imaging will demonstrate a lobulated, often hypointense lesion. However, the intensity can vary in the setting of thrombosis or hemorrhage.²² On postcontrast imaging, the channels will

either homogeneously or heterogeneously enhance depending on the presence of a phlebolith or thrombosis within the lesion.⁶

Management is dependent on patient's preference, cosmetic disfigurement, pain, functional impairment of neighboring structures, hemorrhage, and thromboembolic risk.²² Many institutions prefer to treat only in the presence of clinical symptoms or gross cosmetic issues.

For small VMs, conservative therapies include the use of compression garments, pain management, low-molecular-weight heparin, and physical/occupational therapy. Compression garments are indicated for VMs of the extremities to help reduce the risk of thrombosis, pain, and further enlargement.²¹ Contraindications include GVMs as the garments will increase pain. Pain control with low-dose aspirin and/or anti-inflammatory drugs is used in VMs with persistent pain despite compression therapy or in anatomic sites not amenable to compression. In patients with localized intravascular thrombosis, low-molecular-weight heparin is introduced for 20+ days.²¹ Physical therapy/occupational therapy may provide soft-tissue strengthening techniques and accommodative techniques to help patients improve their functionality and reduce their pain.

In general, for symptomatic venous malformations, sclerotherapy is the first-line treatment and diminishes the volume of the malformation by damaging the vascular endothelium. It can be performed alone or prior to surgical treatment.^{6,19} Surgery is considered in patients with small VMs that can be completely excised or larger VMs with well-defined margins. However, larger VMs with ill-defined margins require sclerotherapy first to reduce the risk of relapse.

Arteriovenous Malformations

Arteriovenous malformations are congenital vascular malformations with an abnormal shunt between artery and vein that develops from an identifiable source vessel (nidus) which is not a capillary. The nidus is an abnormal connection of arterial and venous systems.¹⁹ Since the nidus allows blood flow to bypass the high-resistance capillary beds, AVMs are high-flowing lesions.

Often AVMs are present at birth, but may not become noticeable or symptomatic until puberty and trauma when growth of the lesion is triggered. They can present as warm pink-bluish skin lesions possibly with a palpable, warm thrill. AVMs commonly occur in soft tissues and bone and most frequently in the midface, oral cavity, and limbs.⁸ Early complications include dystrophic skin, bleeding (which can be life-threatening) and ulcerations.^{6,25} Later complications may include congestive heart failure and tissue necrosis.

AVMs may be associated with Parkes-Weber syndrome; hereditary hemorrhagic telangiectasia (HHT)—arteriovenous malformations of the skin, mucous membranes, and visceral organs resulting in diffuse hemorrhage; Maffucci's syndrome—arteriovenous malformations, multiple enchondromas, and, occasionally, lymphangiomas; and CM-AVM syndrome—multiple small CMs with high-flow AVMs and AVFs in the soft tissues, bone, or central nervous system. It is associated with a mutation of the RASA-1 gene.

Fig. 8 (a) T2-weighted axial and coronal MRI image at the level of the ankle demonstrates a conglomerate of flow voids in and around the osseous structures of the ankle. (b) Color Doppler ultrasound demonstrates a conglomerate of tangled vessels with arterialized waveforms.

MRI, MRA, and CTA help identify the extent of the lesion. MRI will demonstrate a tangle conglomerate of arteries and veins with multiple hypolucent arterial flow voids.^{6,25} T1-weighted postcontrast images will demonstrate contrast enhancement of the arterial vessels with early venous enhancement.⁶ MRA is important for pretreatment planning, as it demonstrates the feeding vessels, amount of volume that is being shunted, and the location of the nidus.⁶ Besides demonstrating features similar to that of MRA, CTA can provide further evaluation of soft tissues and, especially, the bones. CT can demonstrate intraosseous changes including erosions. Ultrasound and color Doppler will demonstrate high systolic and diastolic flow and arteriovenous shunting. It will also show arterial waveforms in venous structures⁶ (► Fig. 8b).

AVMs can be difficult to treat due to its high recurrence rate and replacement of normal tissue by these lesions.²⁵ The goal is not curative but rather to control ischemic pain, recurrent ulcers/bleedings, and cardiac function. First-line therapy is embolization alone or with surgical resection. The goal is to obliterate the nidus. However, lesion recurrence is common if the nidus is not destroyed, as it will recruit new vessels to collateralize with.¹⁹ Few but recent studies have

attempted the immunosuppressive agent, Sirolimus, for AVM management. However, results have shown it not to be an efficacious treatment.¹³

Conclusions

The field of vascular anomalies has begun to enter a period of marked improvement of our understanding and classifications of these disorders. As this knowledge base increases, it becomes increasingly more important for all practitioners to have basic understanding of diagnosis, treatment, and associated syndromes. This can lead to rapid treatment of these patients before more debilitating complications arise.

Disclosure

The authors report no conflict of interest concerning the findings specified in this article.

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