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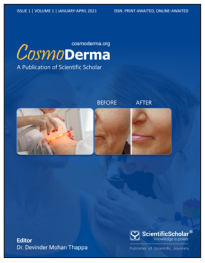

Review Article

Vascular malformations – A review article

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Received: 16 September 2023
Accepted: 27 November 2023
Published: 09 January 2024

DOI
10.25259/CSDM_175_2023

Quick Response Code:

ABSTRACT

Vascular malformations are deviations in blood vessel growth that poses a serious threat to mortality, morbidity, and hemorrhage. We address just vascular malformations in this article, covering basic nomenclature, etiology, and diagnostic criteria for each subclass as well as current treatment options. Optimizing the outcome requires the capacity to understand basic physiology, make an accurate diagnosis, and apply appropriate diagnostic and therapeutic procedures.

Keywords: Vascular, Malformation, Review

INTRODUCTION

Congenital defects in the development of the arteries are known as vascular malformations (VM). Vascular disorders are a broad group that includes a variety of vascular developmental diseases, and clinicians continue to encounter challenges in diagnosing and treating them. The terminology used to characterize and classify vascular ailments is essential to accurate diagnosis and treatment.

The International Society for the Study of Vascular Abnormalities (ISSVA) has devised a categorization system that now divides vascular abnormalities into two categories: (1) Vascular malformations and (2) vasoproliferative or vascular malignancies, such as hemangiomas.[1]

All vascular malformations and cancers are included in the ISSVA classification of vascular anomalies, which uses a system of globally standardized terminology. The International Society for the Study of Vascular Anomalies is referred to as ISSVA.[2] The first categorization published by Mulliken and Glowacki in 1982 served as its foundation, and it has since been revised to reflect the identification of causative genetic alterations. Because all vascular malformations have a single endothelial cell lining, they are classed together based on their shared embryonic origin.[3] It is believed that anomalies in the development of the embryo, such as aberrant signaling pathways that control vascular apoptosis, maturation, and growth, are the source of vascular malformation units. The choroid plexus cells maintain some of their unique characteristics as a result of these abnormalities.[4] Based on the characteristics of its flow, vascular malformations are classified into four basic categories: Fast flow (arteriovenous malformation [AVM]) and slow flow (capillary malformation [CM], venous malformation, and lymphatic malformation [LM]).[2] The fact that these lesions frequently contain elements of several malformations, such as combined lymphatic and VM, further complicates the issue of proper nomenclature. While the majority of VMs exist from birth, they can occasionally arise during post-natal development. The remaining 95% are

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random in origin, meaning that they are caused by gain-of-function mutations, which emerge after fertilization in a group of nongametes. The remaining 5% are present at birth because of inherited loss-of-function germline mutations with a somatic second hit.[2] These mutations affect one of two key cell signaling pathways that control angiogenesis, cell growth and proliferation, motility, and apoptosis: The PI3KCA-AKT-mTOR and the RAS-RAF-MEK-ERK pathways. Due to the involvement of both pathways in a range of malignancies, targeted medicines that target various components of these intricate cascades have been developed as a result of their evaluation in these populations. It has also been noted that mosaic variations of the KRAS pathway's constituents (KRAS, NRAS, BRAF, and MAP2K1) work as activation drivers in the extracranial AVM formation process.

Certain genetic variations have been associated with intracerebral abnormalities[5] and mixed vascular malformations such as Klippel–Trenaunay syndrome[6] and Proteus syndrome.[7] In contrast, at least two different kinds of vascular malformations have been connected to abnormalities in vascular neuromodulation.[8,9] Consequently, AVMs may result from the same defect but at the capillary sphincter level, whereas vascular malformations are most likely caused by a partial or whole loss of autonomic innervation of the capillary venous plexus[10] [Table 1].

CLASSIFICATION OF VASCULAR MALFORMATIONS

Mulliken and Glowacki[11] developed a biological categorization of congenital vascular malformations more than 20 years ago. This classification was based on the natural evolution of the lesion and the primary pathological features of the endothelium [Table 2].

Mulliken and Young[12] later revised this categorization, which was then accepted by ISSVA in 1996. With little alterations from the first classification, this is currently the most popular one [Table 3].

The ISSVA later accepted the so-called Hamburg classification, which was first made public in 1998. Based on the stage of development at which the deformity begins to develop, the principal component of the vascular lesion is used to classify the malformation, which is further split into truncular and extratruncular categories[13,14] [Table 4]. This classification is useful for diagnosing clinical and anatomical characteristics, providing physicians with a starting point for treatment decisions, and easing communication between specialists. Hemangiomas and lymph node abnormalities are not included in it.

Since all other features including small arteriovenous shunts are located at the capillary bed, they advised using the term "capillary malformations" rather than "arterial malformations."[15] They believed that "arterial malformations" was an imprecise term. The findings, which include afferent artery enlargement and efferent venous dilatation, are primarily due to these anomalies. It does not change the current classification because the authors believe that this first change could lead to more confusion than clarity. However, there is one more change that affects the classification. As a result, they identified port-wine stain or nevus flammeus as VM, categorized these malformations according to size, and thought of these lesions as ecstatic vasculature in the capillaries of the associated papillary plexus. The classification is as follows:

1. Veins 50–80 μm in diameter are clinically characterized as pink dots
2. Vessels 80–120 μm in size and darker in color than the previous classification
3. Vessels 120–150 μm in diameter and red-violet color
4. Vessels larger than 150 μm corresponding to dilated vessels forming cobblestone-like and brown palpable nodules and also included in this group are so-called midline deformities, which in layman's terms are called salt spot, stork bite, or angel's kiss.

Anatomical location and hemodynamic features have also been used by other specialists to categorize VM,[16] which are especially helpful when assessing the efficacy of sclerotherapy. To ascertain the hemodynamic properties of the lesion, phlebography is required; however, as we shall see later, computed tomography (CT) angiography may eventually

Table 1: Genetics of vascular malformations.

Vascular malformation	Chromosomal localization	Gene
Type 1 cerebral cavernous malformation	7q11.2-q21	KRIT1
Type 2 cerebral cavernous malformation	7p15-p13	MGC4607
Type 3 cerebral cavernous malformation	3q25.2-27	PDCD10
Klippel-Trenaunay syndrome	5q13.3	AGGF1
Arteriovenous capillary malformation	5q13.3	RASA1
Venous malformation with cutaneous and mucosal involvement	9p21	TIE2
Glomuvenous malformation	1p22-p21	lomulin
Proteus syndrome	10q23.31	PTEN

Table 2: Mulliken Glowacki classification.

Vascular malformation
Capillary
Venular
Venous
Lymphatic
Arteriovenous
Combined
Venous-lymphatic
Venous- venular

Table 3: Modified classification of International Society for the Study of Vascular Anomalies (Rome, Italy, 1996).

Tumour hemangiomas	Superficial
	Deep
	Combined
Others	Kaposiform
	Hemangioendotheliomas
	Tufted angioma
	Hemangiopericytoma
	Spindle cell hemangioendothelioma
	Glomangiomas
	Pyogenic granuloma
	Kaposi sarcoma
	Angiosarcoma
Vascular malformations	Capillary
Single	Venous
	Lymphatic
	Arterial
Combined	Arteriovenous fistula
	Arteriovenous malformation
	Venous, Lymphatic and Arterial malformations in various combinations

Table 4: Classification of Vascular Malformations: Hamburg, Germany 1988.

Type of defect	Truncular anatomic form	Extratruncular anatomic form
Mainly arterial	Aplasia	Infiltrating
	Obstruction	Limited
	Dilation	
Mainly venous	Aplasia	Infiltrating
	Obstruction	Limited
	Dilation	
Mainly arteriovenous shunt	Superficial arteriovenous fistula	Infiltrating
	Deep arteriovenous fistula	Limited
Combined defects	Arterial and venous hemolymphatic	Infiltrating
		Limited

replace this investigation. Thus, VM can be divided into four groups:

a. Isolated malformations without peripheral drainage;
b. Deformities that drain into normal blood vessels;
c. Malformations flowing into dysplastic blood vessels; and
d. Swelling of veins.

The first two types are the easiest to treat and respond better to sclerotherapy.

Finally, the natural history of AVM can be divided into different stages according to the time of its development.[17]

i. Quiescence: Characterized by a pink-violet trace and arteriovenous shunt, which can be detected by echo-Doppler ultrasound
ii. Enlargement: As in stage I, but clinically pulsatile with obvious tortuous vessels and tense turns
iii. Destruction: For example, stage II, dystrophic skin changes, ulcers, bleeding, and constant pain
iv. Decompensation: Similar to stage III, associated with heart failure.

CM

CMs are abnormalities of the capillaries in the papillary skin that typically manifests as a permanent, pink, or purple patch that is present from birth. "Port-wine stain" is an ill-defined term that has endured because it is frequently used in literature. The majority of facial CMs often affects the trigeminal distribution, particularly the eyes (V1) and chin (V2).[18] Since capillary abnormalities in the V1 or midline distribution are closely linked to leptomeningeal involvement and subsequent seizure disorders (e.g., Sturge–Weber syndrome), clinicians should be aware of potential involvement and appropriate imaging procedures. The spots can alter facial characteristics, including bone structures, and have a tendency to darken and thicken into "pebbles" as the patient ages. As of right now, no imaging method is needed to help with the diagnosis, although magnetic resonance imaging (MRI) is strongly advised to rule out central nervous system (CNS) involvement. Gyral enlargement, ipsilateral thickening and enlargement of the choroid plexus, gradual cerebral atrophy, and calcification are positive findings.[17] Both cortical problems linked to CNS function and parenchymal contrast retention can be detected with cerebral angiography. The majority of therapies, including pulsed dye laser (580–595 nm), are ablative in nature.[12] Macular color improves noticeably when laser therapy is performed with lateral CM and started in youth. A significant reduction in weight is often seen in over 75% of individuals. It is advised to begin treatment before 6 months because early intervention yields better effects.

VM

Similar to other vascular anomalies, VM exist from birth. These are the most prevalent vascular malformations, affecting

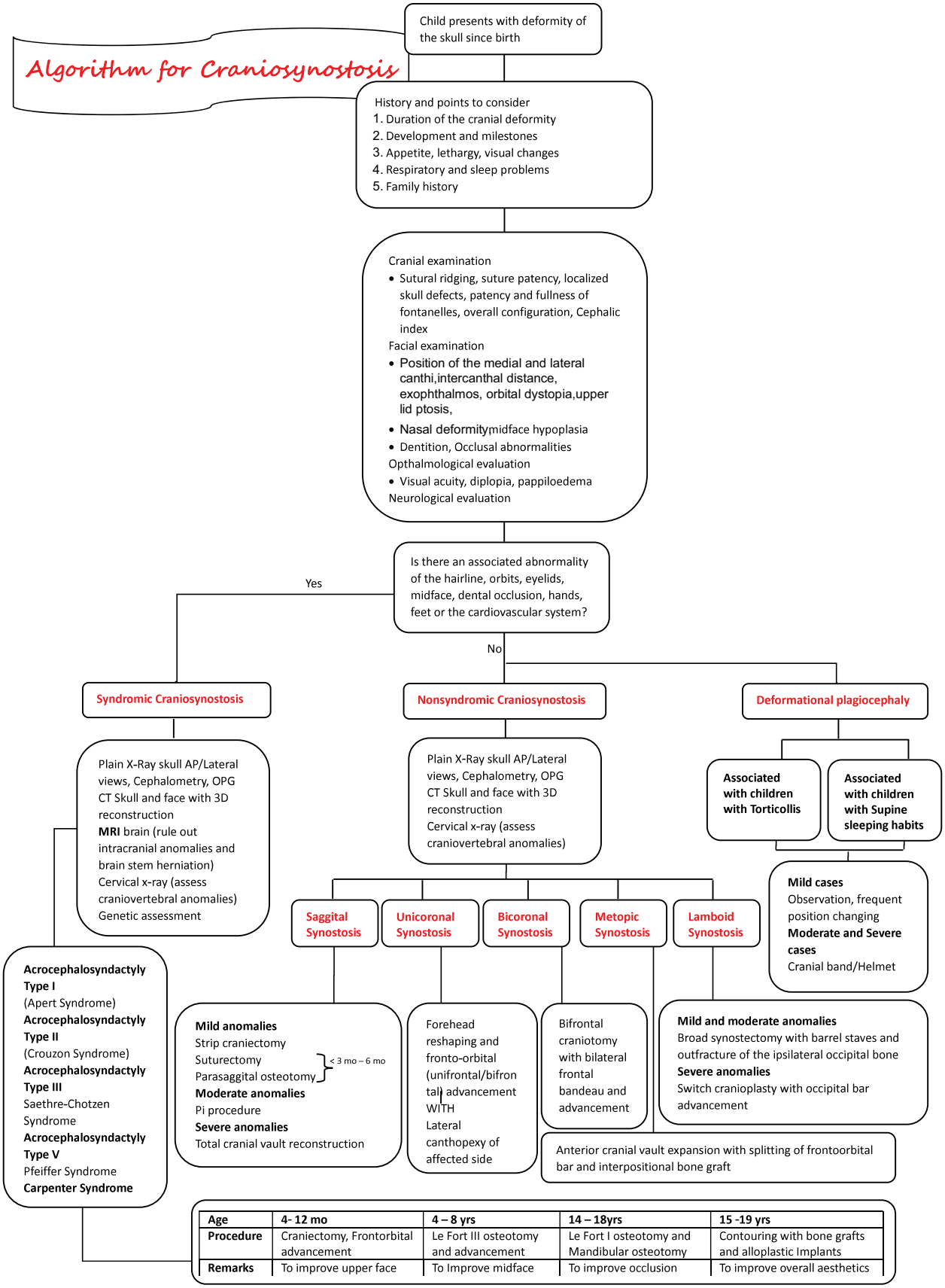

Figure 1: Algorithm for treatment of vascular malformations.

1–4% of people and typically affecting the face, limbs, or trunk. Clinically, they appear as bluish soft compressible lesions. A single endothelium layer covers several blood vessels of varying diameters in VM. VM are dependent lesions, meaning that the patient's posture affects how big or small the lesion is. They frequently expand during puberty, hormonal changes, or illnesses and have a tendency to become larger than the youngster.[14] Phleboliths, which are pathognomonic for VM and can be diagnosed by imaging investigations, are formed when they thrombose. Intralesional calcifications known as phleboliths are brought on by inflammation and venous stasis.[15,16] The most helpful diagnostic technique for identifying low-flow lesions with phleboliths is MRI, but ultrasound (US) and color Doppler are also effective.[13] Finding the extent of the disease can also be done with angiography, which is helpful in cases of deep or tiny lesions. VMs include gastric VM or cerebral sinus pericranii because these lesions are harder to find with traditional MRI and magnetic resonance angiography.[19] A coagulation profile should occasionally be obtained in addition to imaging if a patient has a large VM due to the possibility of local intravascular coagulopathy.[20] VM, the location, and the degree of the damage determine the available therapy choices. Treatment beginning is typically guided by limits that are either functional or esthetic. Interventional radiology can assist with pre-operative or intraoperative embolization, or it can do primary care tasks such as staged sclerotherapy and embolization. Absolute ethanol sclerotherapy works well for treating big, extensive VMs, but it should be used carefully as it might result in systemic toxicity, nerve damage, and epidermal necrosis.[21,22] Bleomycin and 3% sodium tetradecyl sulfate (STS) are two more typical sclerosants. Surgery is rarely the first course of treatment, but it might be in some circumstances, such as (1) ligating efferent vessels to enhance sclerotherapy outcomes, (2) removing residual VM following sclerotherapy, (3) removing lesions that are resistant to sclerotherapy, or (4) a localized lesion that can be removed entirely.[23] It is important to understand that resection can be labor-intensive and technically demanding; thus, it should not be undertaken without a thorough discussion of all operational risks.

LM

Seventy-five percent of LMs are found in the cervical and face areas. LM is lymphatic fluid-filled vascular channels, sacs, or vesicles with a single lining of endothelial cells. Because LM cells do not exhibit cellular hyperplasia, the term "lymphangioma" used to refer to them is misleading. Lymphatic abnormalities are categorized as macrocystic (>2 cm), microcystic (>2 cm), or mixed based on the size of the lymphatic chamber. The lymphatic system's malformations never go away; instead, they enlarge and contract based on the quantity of lymph nodes present, as well as on inflammation or bleeding.[24] These lesions, which are frequently present from birth, are caused by intralesional bleeding and manifest as tiny red dome-shaped nodes. A huge number of macrocystic LM can expand to the point where the anatomy is distorted, particularly the face's soft tissues and bones. Procedures are required due to tissue deformations, recurrent bleeding, and cellulite. The majority of LM instances can be diagnosed clinically, and imaging is not necessary in most circumstances. Imaging methods such as ultrasound (US) and color flow Doppler are very useful in the diagnosis when the diagnosis is not evident.[11] To determine the distinctive cystic appearance of these tumors, ultrasound is used. In addition to helping with diagnosis, MRI is helpful in determining the severity of the illness. A minor upgrade to the walls and partitions that provide the familiar ring and arch pattern gives the MRI a classic appearance. MRI is also useful in differentiating between microcystic lesions and macrocystic lesions, as the treatment methods for the two differ.[19] Treatment options for LM begin with expectant management of symptomatic lesions, such as pain control and compression for intralesional bleeding and antibiotics for infection. Given that there are differences in the treatment approaches for macrocystic and microcystic lesions, MRI can also be used to distinguish between the two.[19] Beginning with expectant management of symptomatic lesions – which is frequently possible – treatment options for LM include pain management, compression for intralesional hemorrhage, and medications for infection. The first-line treatment [Figure 1] is sclerosants; other options are pisibanil (OK-432), 100% ethanol, doxycycline, or STS.[19] These substances damage endothelium irreversibly, which results in inflammation locally and eventually fibrosis. Surgical resection is the only potentially curative procedure. Resection aims to minimize harm to neighboring structures, minimize blood loss, and remove a specific anatomical region in its entirety. It is important to remember that complete resection is usually not possible, because the remaining canals regenerate and extensive radical resection usually occurs at the expense of surrounding normal structures.[5,25]

AVM

AVMs represent a class of vascular malformations that develop from an identifiable primary vessel called the "nidus," which forms an abnormal connection with the arterial and venous systems.[6] This type of shunt is usually present at birth but does not develop. Occurs until the first or second decade of life. AVMs may be slightly compressible and pulsatile with palpable tenderness. This type of lesion is most often found intracranially and can increase in response to certain stimuli such as trauma or puberty. Clinically, AVMs can occur in soft tissue or bone and are

not usually associated with pain but with fairly frequent bleeding episodes.[7] These lesions have a reliable natural history consisting of four distinct phases: Quiescence, growth, symptoms, and decompensation.[8]

Imaging plays an important role in the diagnosis of AVM, but even more so in operative planning. As with other vascular malformations, US and MRI can detect high flow and determine the extent of the lesion. In Color Doppler US, lesions are often multispace and hypervascular. MRI is particularly useful in determining the extent of an AVM, as it usually shows multiple flow cavities and a hyperintense signal without an obvious mass.[17] Unlike other vascular malformations, CT can be particularly valuable in bony AVMs. Angiography can also be used to determine vascular nutrition and drainage before sclerotherapy or surgery.[11] AVM treatment is based on the concept of nidus loss, which is thought to cause the lesion to grow due to the involvement of new blood vessels from nearby areas. Sclerotherapy and embolization remain the main options for safer intraoperative resection with less blood loss.[9,26] Nutrient ligation should never be performed because it leads to rapid collateral recruitment and increased vascularity. When considering AVM resection, it is extremely important to understand that these lesions are rarely curable, focusing instead on disease control. Indications for intervention include ischemic pain, recurrent ulceration/bleeding, or heart failure.[10] Resection of these lesions can result in extensive damage that may require flap coverage or formal reconstruction and should be performed only when the benefits clearly outweigh the risks.

RECENT ADVANCES

1. All the studies predate a seminal discovery in 2017 that the overwhelming majority of sporadic brain AVMs harbor activating KRAS mutations in nidal endothelial cells and sporadic extracranial AVMs have mutations in MAP2K1. With deeper genomic sequencing depths, KRAS mutant prevalence increases to almost 90% of brain and spine AVMs and is sufficient to induce AVMs in pre-clinical models. Mosaic variants in components of the KRAS pathway (KRAS, NRAS, BRAF, and MAP2K1) were discovered as activating drivers in the development of extracranial AVMs as well. Their aberrant features were reversed through *in vitro* and pre-clinical *in vivo* experiments with MEK inhibition. Hence, there is a growing body of knowledge that KRAS mutations drive sporadic AVM development; this pathway then serves as a logical target for therapeutic drug discovery with MEK inhibition.[27]
2. There are some key differences in the approach to vascular anomalies in children. Interventional radiologist (IR) play a crucial role in ensuring the most common, self-limiting vascular tumors are left alone, while the rare aggressive life-threatening types receive emergent embolization and diagnostic biopsy when required.[28]
3. The acute bleomycin pulmonary toxicity syndromes include interstitial pneumonitis and eosinophilic hypersensitivity pneumonitis. Interstitial pneumonitis is dose dependent and can lead to pulmonary fibrosis within 2 weeks. Eosinophilic hypersensitivity pneumonitis, on the other hand, is not dose dependent and can occur within hours. In the current literature, there are only three bleomycin-related deaths for the intralesional treatment of vascular malformations. Previously, these deaths were caused by either comorbid pulmonary disease or respiratory failure resulting from airway compression by large cervical malformations. Recently, the etiologies were likely related to the eosinophilic hypersensitivity pneumonitis variant, which usually occurs shortly (1–2 days) after administration.[29]
4. The ISSVA is based on the initial classification published by Mulliken and Glowacki in 1982 and has since been updated with the recognition of causal genetic mutations. This was the latest modification in 2018.[30]

CONCLUSION

Vascular malformations are a source of great concern and anxiety not only for patients and their families but also for the treating physicians. Proper identification as well as a multidisciplinary approach is paramount for proper treatment. Understanding the clinical aspects, tools available for diagnosis, and options for interventions of each subtype of lesion will enable appropriate care to be provided and results to be maximized.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Chittoria RK, Reddy JB. Vascular malformations – A review article. CosmoDerma. 2024;4:3. doi: 10.25259/CSDM_175_2023