Vascular Malformations

Abstract

Vascular malformations are intricate anomalies of the circulatory system, presenting a diverse array of clinical manifestations, and posing significant challenges in diagnosis and treatment. The pathogenesis of vascular malformations is explored through the lens of genetic and molecular mechanisms, shedding light on the pivotal role of somatic mutations and dysregulated signaling pathways. Clinical presentations of vascular malformations are widely variable, ranging from cosmetic concerns to life-threatening complications. The utility of imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), and angiography, are discussed in detail, emphasizing their role in precise delineation and characterization. Therapeutic strategies for vascular malformations are multifaceted, considering factors such as lesion size, location, potential complications, and patient-specific factors. Traditional interventions, including surgical excision and embolization, are appraised alongside emerging approaches like targeted molecular therapies and minimally invasive procedures. The manuscript underscores the need for an individualized treatment approach, optimizing outcomes while minimizing risks and complications. In summation, this manuscript offers a comprehensive analysis of vascular malformations, encompassing their underlying pathogenesis, clinical nuances, diagnostic methods, and therapeutic considerations. By synthesizing current knowledge and highlighting gaps in understanding, this review serves as a valuable resource for clinicians, researchers, and medical practitioners, fostering an enhanced comprehension of vascular malformations and paving the way for improved patient care and innovative research endeavors.

Keywords: *Arterial, lymphatic, vascular malformations, venous*

Neetu Bhari, Akash Agarwal[1], C. V. V. Asritha[2], Maitreyee Panda[2], Rahul Mahajan[3]

Department of Dermatology, All India Institute of Medical Sciences, New Delhi, Delhi, [1]Department of Dermatology, All India Institute of Medical Sciences, [2]Department of Dermatology, IMS and SUM Hospital, Bhubaneswar, Odisha, [3]Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence:
Dr. Rahul Mahajan, Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012, India. E-mail: drrahulpgi@yahoo.com

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Introduction

Vascular malformations are a group of congenital anomalies that involve abnormalities in the formation, structure, or function of blood vessels during fetal development. These malformations can affect different types of blood vessels, including arteries, veins, capillaries, or a combination of these vessels, but the lining of these dysplastic vessels is a normal endothelium. Vascular malformations can be seen involving multiple body parts and can present with a wide range of symptoms and complications. They are typically classified into capillary malformation (CM), venous malformation (VM), arteriovenous malformation (AVM), and lymphatic malformation (LM).[1] Diagnosis of vascular malformations involves a thorough clinical evaluation, imaging studies, and rarely histopathological examination. Treatment options depend on the specific type and characteristics of the malformation and may involve a multidisciplinary approach to address symptoms, improve function, and minimize complications associated with the malformation. The article reviews the various vascular malformations with special mention regarding the syndromes associated with various types of malformations. A clinical approach algorithm for vascular malformations has been illustrated in Figure 1.

International Society for the Study of Vascular Anomalies (ISSVA) classification of Vascular malformations is summarized in Table 1.[2]

Capillary malformation

a. **Nevus simplex (Medial telangiectatic nevus; MTN):**
Nevus simplex (NS), also known as a salmon patch, angel kiss (glabella), or stork bites (nape of neck), represents one of the commonest birthmarks noted in the newborn period. They present as pink to red irregular patches,

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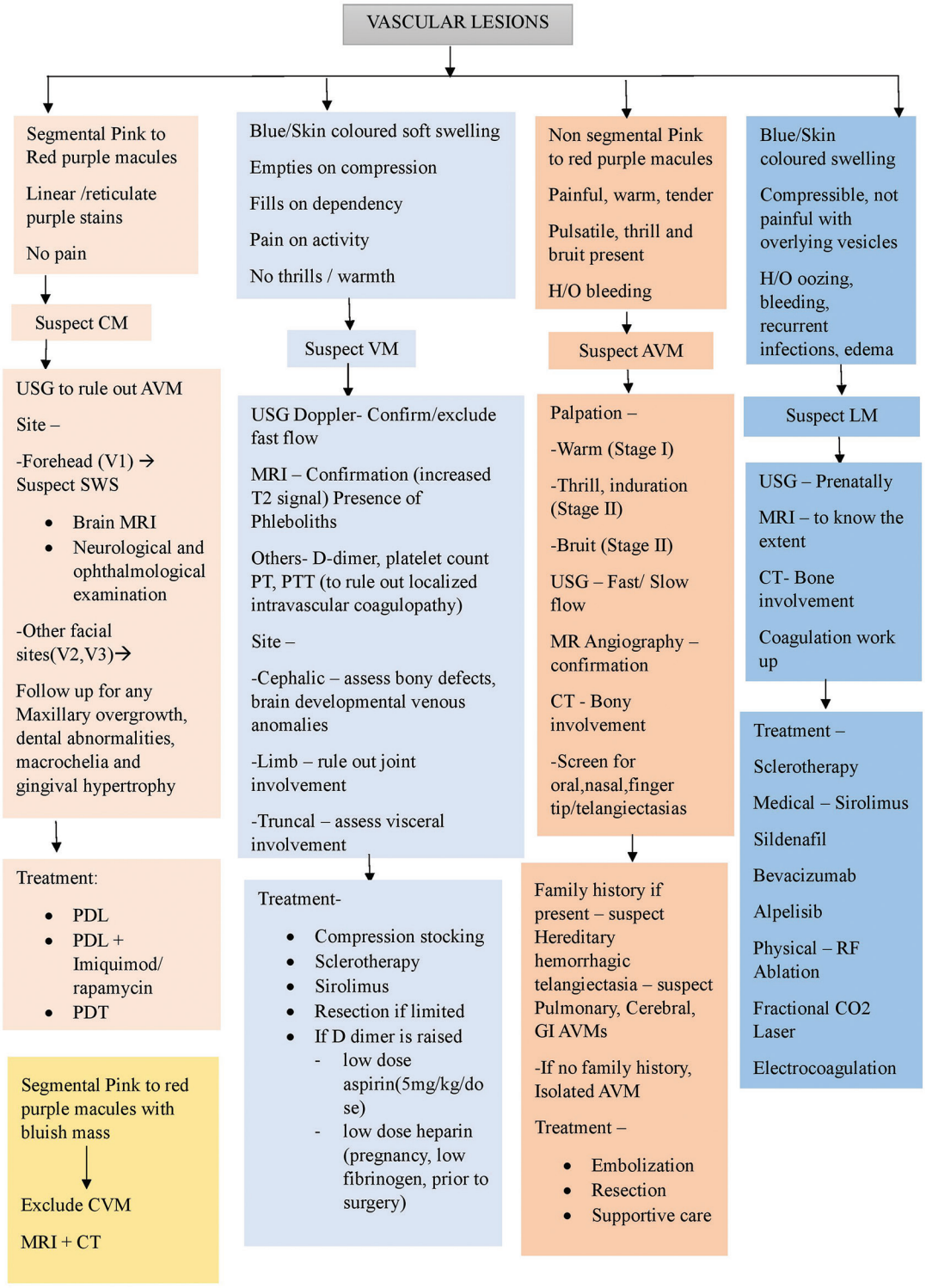

Figure 1: An algorithmic approach to vascular lesions

affecting up to 40-50% of newborns. They are partially blanchable and tend to become more prominent during crying or by temperature changes. Meyerson's phenomenon (eczematous changes occurring around the naevus) over NS is also described.[3]

Underlying pathomechanisms are believed to be a defect in the neural regulation of small capillaries, which is perhaps a maturational defect. This is why the entity tends to resolve with age, unlike port wine stain (PWS). They characteristically fade during infancy and that is why the terminology "fading macular stains" has been used.[4] Mostly sporadic, but autosomal

Table 1: ISSVA classification of vascular anomalies

Simple	Combined	Of major vessels	Associated with other anomalies
Slow flow	Combined channel malformations	Abnormalities in the origin or course or number of major blood vessels (arteries/veins/lymphatic) that have anatomical names	Klippel–Trenaunay syndrome
Capillary (CM)	E.g.: CVM		Sturge-Weber syndrome
Venous (VM)	CLM		Maffucci syndrome
Lymphatic (LM)	LVM		CLOVES
High flow	CLVM		Proteus syndrome
Arteriovenous malformations (AVM)	CAVM		Bonnet–Dechaume–Blanc Syndrome
Arteriovenous fistulas (AVF)	CLAVM		Solamen syndrome

dominant inheritance is seen in familial cases.[5,6] The terms "persistent MTN" and "residual MTN" have been used to describe lesions persisting beyond 5 years and incompletely resolved, respectively. The majority of cases with NS have no underlying associations, but persistent or large prominent lesions may have syndromic associations.

The common associations include Beckwith–Wiedemann syndrome (congenital overgrowth syndrome: macroglossia, anterior abdominal wall defects, gigantism, and a prominent and persistent NS involving the glabella), macrocephaly-cutis marmorata telangiectatic congenita, hyperextensions of the joints as well as odontodysplasia and umbilical hernias, meningomyelocele, meningoencephalocele, multiple hamartomas and intracranial malformations, spinal dysraphism, and trisomy 13-15.[7,8]

Management is reassurance and counseling. Persistent and prominent cases can be managed with an intense pulsed dye laser.

b. **Port wine stain (Lateral telangiectatic nevus):**

Port wine stain (PWS), a common congenital vascular malformation, usually affects 0.3-0.5% of all newborns.[9] The terminology port wine birthmarks, as opposed to PWS, is being advocated by dermatologists across the globe.

PWS is caused by abnormally dilated capillaries in the dermis, with pathogenesis involving a variety of factors, including somatic genetic mutations, abnormal vasculogenesis, and dysregulation of VEGF (vascular endothelial growth factor) signaling pathways. Recent studies have identified several genes, such as *GNAQ* and *GNA11*, which play an essential role in the development of PWS via angiopoietin-2 activation. GNA11 results in a larger capillary malformation and glaucoma but has less severe neurologic symptoms. A distinguishing feature in this phenotype is diffuse, reticulated capillary malformations of the trunk and limbs with associated hyper- or hypotrophy.[10,11]

PWS is typically present at birth as well-defined segmental pink to red macules with clear midline demarcation, which, over time, tend to darken, resembling the port wine color [Figure 2]. They may thicken or develop nodularity over time. The location, size, and distribution of PWS can vary widely among individuals. Four types of PWS are defined in the literature, namely pink, purple, thickened, and nodular. Associated complications include glaucoma (in periocular PWS), Sturge–Weber syndrome (PWS on V1 and V2 dermatomes of the trigeminal nerve), and pyogenic granuloma (PWS on V2 dermatome).[12,13]

PWS is primarily diagnosed based on clinical examination. The dermatoscopy of PWS helps correlate with age, location, subtype, prior treatment, and response to pulsed dye laser therapy.[14] Linear vessels are the most common dermosocopic finding [Figure 3]. Other dermoscopic features include sausage-like vessels, reticular vessels, whitish veil, and dots and globules. Whitish veil and sausage vessels are more common in thickened PWS, while mixed vessels are common in purple PWS. The frequency of white circles and white veil is significantly higher in the treated group as compared to the non-treated group.[14] Histopathologically, PWS is characterized by the dilatation of capillaries in the papillary and reticular dermis along with an increased number of normal-looking capillaries [Figure 4]. As the disease progresses from pink PWS to purple, thickened, and nodular PWS, the vascular composition, diameter of vessels, depth, and difficulty in treating increase.[15]

To objectively visualize and evaluate subsurface structures, various new technologies have been developed. These include high-frequency ultrasound (HFUS), laser Doppler flowmetry (LDF), laser speckle contrast imaging (LSCI), reflectance confocal microscopy (RCM), a cross-polarized diffuse reflectance imaging system (CDR), spatial frequency domain imaging (SFDI) and optical coherence tomography (OCT). HFUS depicts hypoechoic homogenous signals in superficial to deep dermis but no subcutis involvement. Depth (0.2-3.7 mm, with a mean of 1.0 mm) and vascular assessment also help in identifying different subtypes of PWS. HFUS helps differentiate PWS from hemangiomas or AVM at birth, which are pink in color and show hyperechoic shadows on ultrasound.[16] LSCI provides a two-dimensional real-time image of perfusion in biological surfaces, which is higher in PWS compared to normal skin. The

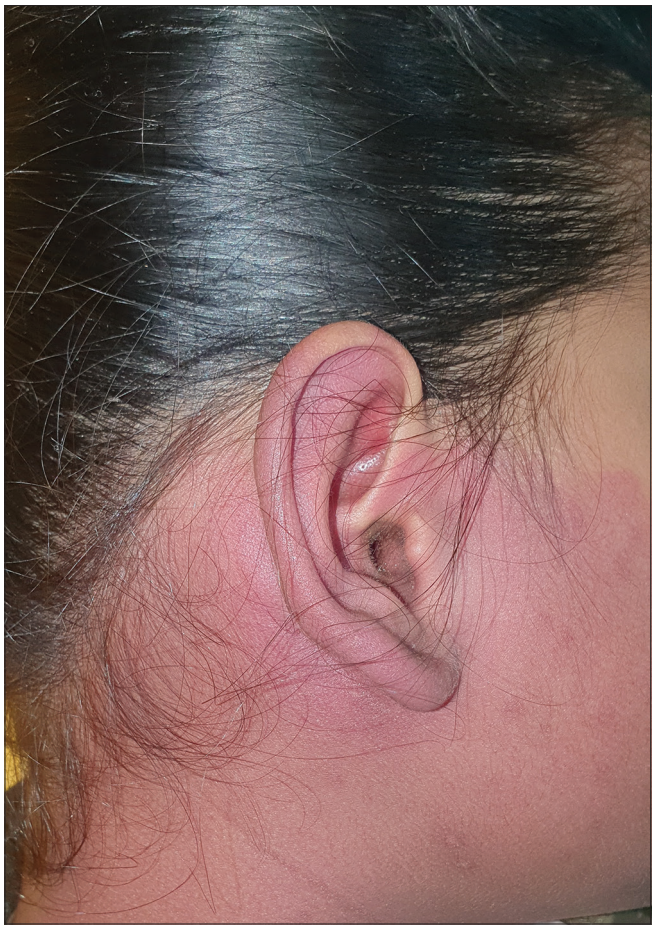

Figure 2: Port wine stain: dusky erythematous plaque over the lateral aspect of face and neck

response to pulsed dyed laser therapy can be assessed using LSCI. RCM provides cellular information of the skin comparable to histopathology analysis. In PWS, varying vessel morphology has been detected at different depths, with an increase in mean density and diameter of vessel with progressive increase in depth up to 300 um. OCT is a non-invasive method that allows for 3D visualization of PWS lesions with real-time angiography. It can assess the depth of vessels with good resolution of up to 0.5 mm and vessel wall morphology. In a study, the median diameter of hemangioma in comparison with PWS was 50-70 um and 70-100 um, respectively, with PWS vessels being thicker with higher density of vessels. Neonatal MRI is commonly employed to identify which infants with a facial port wine (PW) birthmark might develop brain involvement in Sturge-Weber syndrome (SWS). Regrettably, early MRIs often yield negative results, providing false reassurance. In contrast, electroencephalography (EEG) serves as a non-invasive neuroimaging technique that can be repeatedly used with minimal risk and without the need for sedation. EEG abnormalities have long been observed in SWS. In symptomatic individuals, routine visual inspection frequently reveals reduced

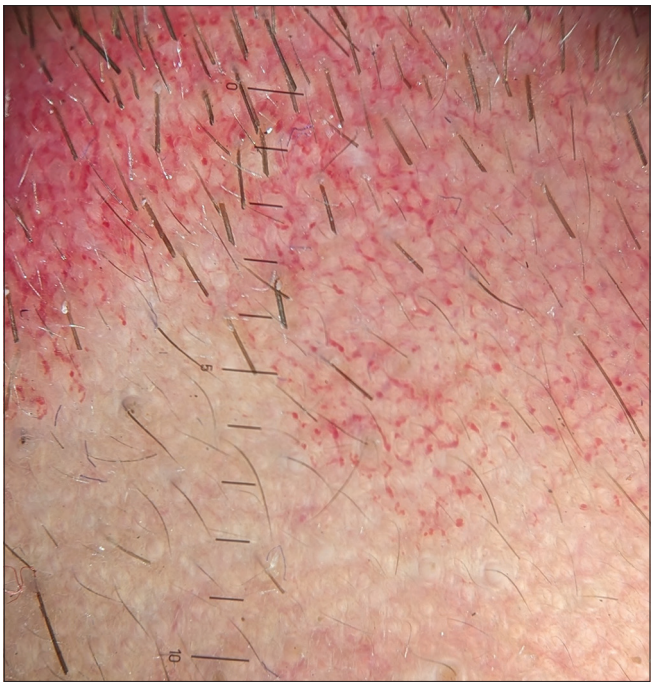

Figure 3: Dermoscopy of port wine stain showing broken network of thin vessels and dots (Dermlite 4, Polarised, 10x)

EEG signal amplitude on the side of the brain affected by SWS, typically matching the side of the PW birthmark.[16,17]

Several treatment modalities are available for PWS, including laser therapy, surgical excision, and topical agents (rapamycin, axitinib, imiquimod, endothelin receptor antagonist, timolol, oxymetazoline, and artificial red blood cells).[18] Laser treatment with pulsed dye laser (PDL) is the gold standard, offering effective lightening, or complete clearance of PWS lesions. The efficacy is highest if the treatment is started during infancy.[19] The risk factors associated with PDL-resistant PWS include age (>1 year), size (>40 cm^2), central face location, thicker, or nodular lesions, vessel depth (>400 micron), vessel diameter (>20 micron), number of treatment session (>5).[20] A split-face trial comparing PDL versus broadband intense pulse light (IPL) in 20 patients revealed that both therapies lighten PWS; however, the median clinical improvement (65% versus 30%) and proportion of patients achieving good to excellent improvement (75% versus 30%) were much higher in PDL group.[20] Combination therapies such as PDL with imiquimod and rapamycin have shown promising results in improving treatment outcomes.[21,22]

Photodynamic therapy (PDT) is yet another two-step treatment method for PWS that acts via free-radical damage to the endothelial cells. It has site-specific action, with damage being limited only to photoilluminated areas post-exposure to a photosensitizer.[23] Hematoporphyrin monomethyl

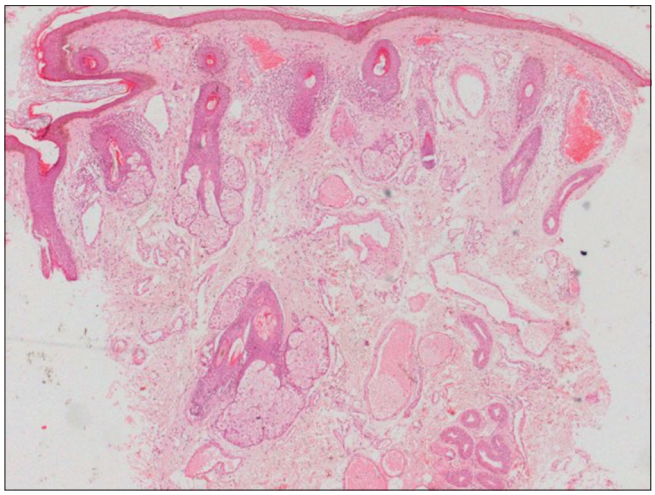

Figure 4: Port wine stain showing multiple dilated capillaries in upper and mid dermis (H and E, 40x)

ether (HMME) is a newly authorized photosensitizer for the treatment of PWS in China, which is currently gaining prominence. In a retrospective study, 72 patients received HMME-PDT therapy, of which 47 showed fair response, 13 showed good efficacy and 7 had an excellent response. The response was higher in patients with pink, purple type as opposed to hypertrophic or nodular type.[24,25]

Another treatment modality gaining prominence is cosmetic camouflage and cosmetic tattooing. This treatment option is favorable for patients unwilling to laser treatment or patients resistant to conventional therapy. A new modality named site-specific pharmaco-laser therapy (SSPLT) combines conventional laser therapy with thermosensitive drug delivery systems that encapsulate prothrombotic and antifibrinolytic drugs focusing on luminal occlusion by thrombus formation in the affected vessels.[26]

Psychosocial Impact and Patient Support: Living with PWS can have substantial psychosocial implications, including negative self-esteem, social stigmatization, and emotional distress. Especially patients with facial PWS are more prone to worsening lesions with age, adding to the adaptation process during the initial childhood years.[27] A multidisciplinary approach involving dermatologists, psychologists, and support groups is crucial in providing holistic care to patients and family members.[28]

Acquired PWS: Acquired PWS is a rare vascular lesion that is morphologically similar to congenital PWS. The main causative agents described are trauma (Fegeler syndrome), hormonal changes, chronic sun exposure, obstruction of the peritoneo-venous shunt, frostbite injury, and acoustic neuroma. The underlying pathogenesis is proposed to be due to the loss of sympathetic function and subsequent unregulated blood flow in cutaneous blood vessels, leading to ectasia.[29] PWS secondary to spinal root compression and herpes zoster have also been described, adding to the neural damage theory of pathogenesis.[30]

c. **Cutis marmorata telangiectasia congenita:**

Cutis marmorata telangiectasia congenita (CMTC), a rare congenital vascular disorder is characterized by the presence of persistent cutis marmorata (a mottled or marbled appearance of the skin) and telangiectasia (dilated superficial blood vessels), usually on the extremities. CMTC presents as a distinctive reticular or marbled pattern of the skin at birth, which becomes more prominent in response to cold temperatures. Telangiectatic vessels may be present within the affected areas. It has a reported incidence of 0.3-0.5 per 10,000 live births.[31] CMTC can have varying degrees of severity, ranging from isolated cutaneous involvement to systemic complications. In a large review, of 485 patients with CMTC, 4.5% of patients had generalized CMTC, whereas 26.9% had CMTC involving the face. Up to 42% of CMTCs have underlying anomalies, namely body asymmetry (37.7%), neurological defects (10.1%; seizures and developmental delay), and ophthalmic complications (9.9%; congenital glaucoma).[31]

Pathogenesis involves abnormalities in embryonic blood vessel development and maturation. In a subset of patients, mutation in *RASA1* gene was seen, suggesting a probable genetic basis.[32] Recently, *GNA11* mutation found in affected skin indicates that CMTC is possibly a post-zygotic mosaic condition.[33] Diagnostic criteria were put forth by Kienast and Heoger with three major criteria (congenital reticulate erythema, unresponsiveness to local warming, and absence of venectasia) and two out of five minor criteria (fading of erythema within 2 years, PWS outside CMTC area, telangiectasia, ulceration, and atrophy) required to fulfill the diagnosis.[34] Cutaneous atrophy, ulceration, and subsequent scarring are also described in CMTC. Generalized CMTC or CMTC localized to face can have a higher incidence of congenital glaucoma.[34]

Management of CMTC focuses on symptomatic relief and addressing potential complications. Management strategies include protection from cold, which can exacerbate the cutaneous manifestations, and diligent monitoring for associated complications, such as limb length discrepancies or developmental delays. In most cases, CMTC is a self-limiting disorder that gradually improves over time, with the resolution of cutaneous findings. Cosmetic interventions, such as PDL or IPL laser therapy or camouflage techniques, may be considered in some cases to improve the appearance of affected skin.[35] Regular follow-up evaluations are necessary to monitor for potential complications.

Venous malformations

a. **Venous malformation (VM)**

VM are slow-flow vascular anomalies whose incidence is 1 to 5 VM per 10000 live births.[36] Somatic activating

mutations in *TEK/TIE2* gene are responsible for up to 60% of sporadic unifocal VMs, and 20% of sporadic VMs are due to somatic mutations in the *PIK3CA* gene.[37]

Clinical features: Unifocal and sporadic VM account for 90% of cases with an initial presentation at birth. The lesions tend to become more prominent with an increase in age. Head and neck are the most common sites, followed by trunk and extremities.[38] They occur as bluish to purple, soft, compressible lesions without any thrill or bruit [Figure 5]. Pain and swelling occur secondary to thrombosis, resulting in phlebolith, which is characteristic of long-standing VM. Inherited forms include the cutaneomucosal VM and glomuvenous malformation, which are generally multifocal. A table differentiating the features of the two entities has been put forth in Table 2.

Investigations: A high or elevated D-dimer is an important specific biomarker for the diagnosis of VMs. It is a marker of ongoing localized intravascular coagulopathy observed in 40% of all VMs. Increased D-dimer levels help differentiate VM from glomuvenous malformation and LM. It also distinguishes slow-flow Klippel–Trenaunay syndrome from fast-flow Parkes–Weber syndrome.[39] Histopathologically, enlarged venous channels which are lined by a single layer of normal flattened endothelial cells surrounded by sparse, irregularly distributed smooth muscle cells, are seen. Lumens of vessels are either empty or contain blood or organized thrombi, which calcify later, causing phleboliths. Masson's phenomenon (papillary endothelial hyperplasia) is also seen. IHC staining shows CD31 positivity, WT1 negativity (verrucous VM), and D2-40 and PROX-1 negativity (LM).[40]

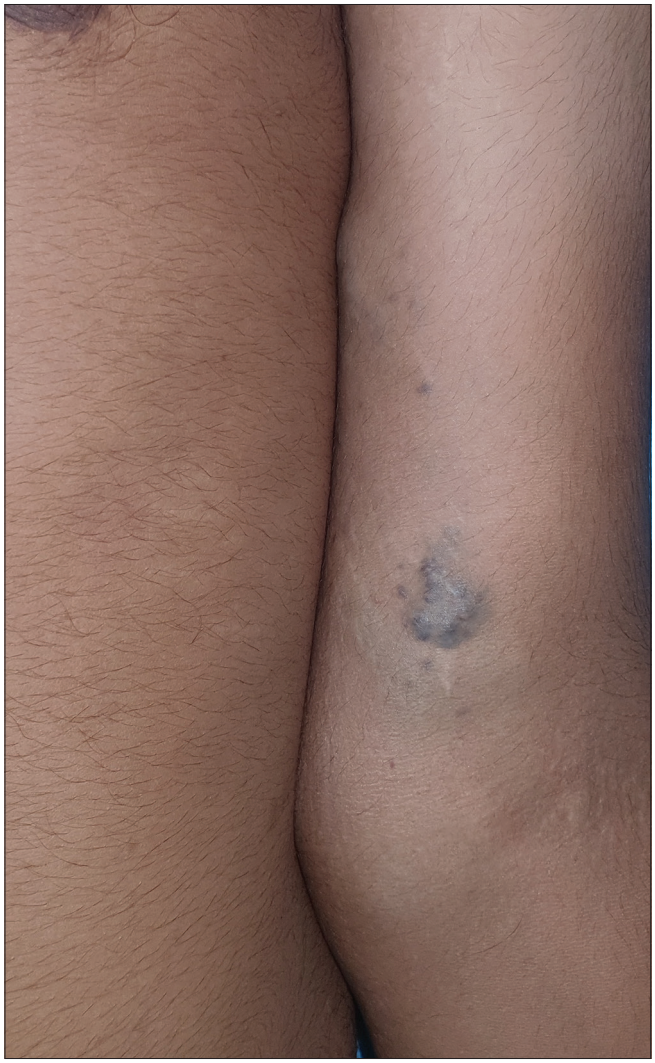

Figure 5: Venous malformation: Bluish soft painless compressible swellings over the left arm

Duplex ultrasound is the first-line modality used to confirm slow flow malformation, to identify the feeder's vessel, and to rule out arterial component. It appears as hypoechoic or heterogenous structure which is easily compressible. MRI helps in the pretherapeutic evaluation of VMs by providing information regarding the anatomic relation of VM with underlying organs, bones, or muscles. On T2- weighted images, hyperintense channels containing septations are seen. X-rays help to look for and confirm the presence of phleboliths while CT may be helpful in the case of intraosseous VM.

Treatment: The management of VMs depends on various factors such as size, location, and extent of the disease. The aesthetic outcome also plays a role in deciding the approach to managing VMs.[41] In small VMs wherein excision is possible without any functional impairment, surgical removal is the first line. Percutaneous sclerotherapy, however, remains the gold standard therapy used alone or in combination with excision, as it has shown reduced chances of recurrence overall. In complex cases, a multidisciplinary approach involving dermatologists, radiologists, and surgeons should be undertaken. Targeted therapy with sirolimus has gained prominence since the finding of TEK/TIE2 mutations, and trials have shown good efficacy and safety of this modality.[42]

Localized intravascular coagulation (LIC): Unlike disseminated intravascular coagulation, LIC refers to activity limited to the vascular malformation which is observed in up to 58% of VMs.[43] It is typically characterized by increased D-dimer levels along with FDPs (fibrin degradation products), low levels of fibrinogen, antithrombin III, Factor V, Factor VIII, and Factor XIII. Due to the chronicity of this state, microthrombosis tends to occur, leading to pain and phlebolith formation over time. Surgical resection, embolization, sclerotherapy, infection, trauma, or drugs are known precipitants of Disseminated intravascular coagulation (DIC) occurring in cases of VM with LIC. The underlying pathogenesis is believed to be due to abnormal function and structure of endothelial cells and blood stasis. Treatment includes the use of low

molecular weight heparin therapy as it lowers pain, reduces complication risk, and controls the deranged laboratory parameters. Individuals diagnosed with confirmed thromboembolism are advised to consider lifelong preventive anticoagulation. The reasons for treatment are debatable, and some suggest that preventive treatment via subcutaneous injections should be considered 10 days before and 20 days after surgical procedures. The process of LIC does not involve platelets, so the application of aspirin does no better and raises major bleeding during surgery.[43]

b. **Glomuvenous malformation:**

Glomuvenous malformation (GVM) is a rare vascular disorder that is characterized by the presence of abnormal glomus cells within the venous channels. Earlier, this entity was confused with VM, but now it is considered a separate entity [Table 2].[44] The exact pathogenesis of GVM is not completely known yet. However, it is believed to result from abnormal proliferation and migration of glomus cells, which are specialized perivascular cells involved in thermoregulation. Mutations in novel factor glomulin (gene localized to chromosome 1p21–22) are responsible for GVM.[45]

GVM typically presents as a painless, soft, and compressible mass on limbs, trunk, and head and neck regions. The lesion may have a bluish or purplish discoloration and can be associated with temperature sensitivity or hypersensitivity. Symptoms such as pain, cold intolerance, or localized sweating disturbances may be present in some cases[46] [Figure 6]. Diagnosis of GVM is usually based on clinical examination and imaging studies. Dermoscopy features vary according to morphology, with plaque-type showing multiple bluish-white to bluish-red structureless areas. Ultrasonography and magnetic resonance imaging (MRI) are essential tools for evaluating the characteristics and extent of the lesion. Histopathological examination, which shows at least two to three layers of glomus cells (bland round-to-oval nuclei, pale eosinophilic cytoplasm, and clearly defined cell margins) in distended vein-like structures, including immunohistochemistry for glomus markers such as smooth muscle actin and calponin, can provide definitive confirmation of the diagnosis.[47]

The management of GVM aims to alleviate symptoms, minimize functional impairment, and improve cosmetic appearance. Treatment options for mild cases include conservative measures, such as compression garments and pain management. In more severe or symptomatic cases, interventional procedures, including embolization and surgical resection, may be considered. However, complete excision of GVM can be challenging due to the extensive involvement of glomus cells within the venous channels.

c. **Blue rubber bleb nevus syndrome:**

Blue rubber bleb nevus (BRBN) syndrome is a rare vascular anomaly that is characterized by the presence of multiple cutaneous and visceral (commonly gastrointestinal) venous malformations. Genetic basis is identified due to the presence of somatic mutations in the *TIE2* gene (*TEK* gene) in some cases. These mutations affect the signaling pathway involved in angiogenesis and vascular stability. However, the majority of cases are sporadic, and the underlying cause in these instances remains unknown.[48] Cutaneous lesions appear as blue or purple soft nodules or blebs, primarily affecting the

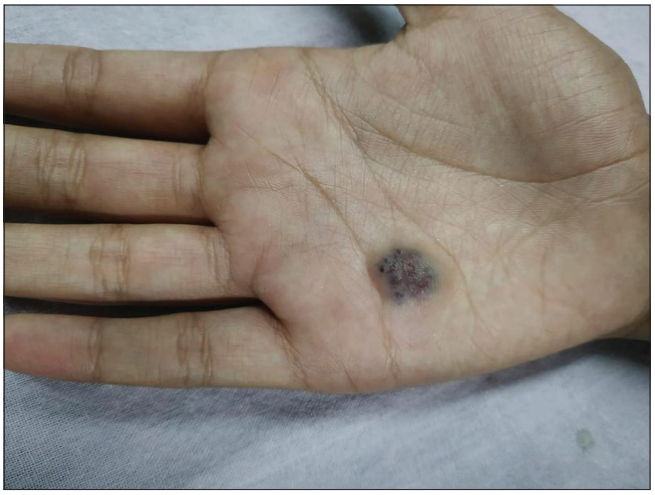

Figure 6: Glomuvenous malformation: Single soft tender bluish swelling present since birth

Table 2: Comparison of Cutaneomucosal VM with GVM

	Cutaneomucosal venous malformation	Glomuvenous malformation
Color	Various hues of blue	Pink in infants to deep blue to deep purple in children and adults
Extension	Skin, oral mucosa, and can involve skeletal tissue	Skin and subcutis but rarely involve mucosa or underlying muscle
Most common location	Cervicofacial area and extremities	Extremities
Morphology	Typically, hemispherical	Raised with a cobblestone appearance
Compressibility	Soft and easily compressible	Not compressible
Pain	Noticed after activity or change in temperature	Noted on compression
Presence of phlebolith	Yes	No
Elastic compressive therapy	Advocated	Relative contraindication as it increases the pain
Extensive lesions	Associated with localized intravascular coagulopathy	Not common

skin of the trunk and limbs [Figure 7]. Gastrointestinal involvement can lead to recurrent gastrointestinal bleeding, which may present as melena, hematochezia, or iron-deficiency anemia. The liver, lungs, ophthalmic, and central nervous system are also involved. Association with migraine headaches represents a sign of central nervous system involvement and must always be kept in mind.[49]

Dermoscopic features of lesions with exophytic, verrucous surfaces include red-purple nodules with lacunae, divided by white linear structures and arborizing venous patterns or vessel dilations. Doppler ultrasonography, CT, and MRI can demonstrate the extent of venous malformations. Capsule endoscopy and colonoscopy are performed to identify and evaluate gastrointestinal lesions. Histopathological examination of the lesions reveals dilated thin-walled veins with no evidence of endothelial proliferation.

Treatment options include endoscopic interventions, such as sclerotherapy or electrocoagulation, for gastrointestinal bleeding. Blood transfusion and iron supplementation are often necessary to manage anemia. Surgical resection or embolization may be considered for localized or refractory lesions. In cases where surgical excision is not possible, oral sirolimus therapy has been successfully tried with trough levels of 10-15 ng/ml. Long-term treatments for as long as nine years have been given with good efficacy and minimal side effects in BRBN syndrome.[50,51] Complications of BRBN syndrome include localized intravascular coagulopathy with high D-dimer and low fibrinogen levels. MRI brain screening should be routinely performed as these patients can have cerebral VM as well.[52]

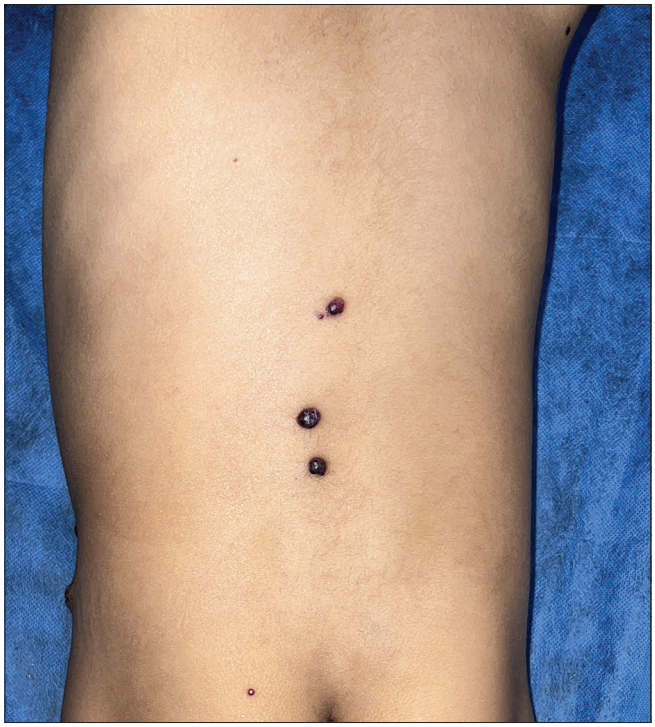

Figure 7: Blue rubber bleb syndrome: Multiple soft bluish nodules over the trunk

d. **Verrucous venous malformation:**

Verrucous venous malformation (VVM) is a rare vascular anomaly that is characterized by the presence of enlarged, dilated, and tortuous veins with an overlying verrucous or papillomatous epidermal growth. Previously, it was called as verrucous hemangioma, which was a misnomer given that it presents at birth and increases in size proportionate to a person's growth. The underlying pathogenesis is poorly understood. Recently, a somatic mutation in the *MAP3K3* gene has been linked to VVM.[53] They usually present at birth or a few days later as flat, soft, bluish, completely compressible masses which, over the years, enlarge, changing color to brownish black and developing thick keratotic surfaces [Figure 8]. Further warty hyperkeratosis occurs as a result of infection or trauma, which is commonly known to occur in VVM. A variant known as subcutaneous VVM, presenting as swelling without clinically apparent epidermal features, has also been described. On histopathology, blood-filled channels resembling veins and capillaries infiltrate the adipose tissue to form aggregates of nodules with fibrosis. Diagnosis is confirmed by GLUT-1 (25%-75% immunopositive channels); D2-40 (1%-25% channels); and Prox-1 (1%-50% of channels) on IHC.[54]

The clinical mimics include angiokeratoma and LMs, which are frequently misdiagnosed. Predominant dermoscopic features include red to reddish-purple dots, globules, and structureless areas. Other features described are rosettes, shiny white structureless areas, lines, linear irregular crypts, and comedo-like openings [Figure 9].[55] Histopathology remains the gold standard for diagnosis. [Figure 10] GLUT-1 (weak correlation) and WT-1(strong correlation) positivity on IHC are strong indicators of VVM diagnosis. Deep tissue involvement helps to differentiate it from angiokeratoma, where the latter is predominantly confined to the papillary dermis.[56]

MRI is a mandatory investigation required to delineate deep tissue involvement. They show an intermediate signal on T1-weighted images, while T2-weighted and Short tau inversion recovery (STIR) sequences are hyperintense. In contrast, the lesions homogenously enhance. MRI is helpful in differentiating VVM from VM, LM, and arteriovenous malformation. The presence of phlebolith and small foci of dark signal in all MRI sequences point toward VM, as other features are similar to VVM.[57]

For localized lesions, surgical excision is the first line of management. However, recurrence is the rule in VVM. The combination with PDL offers additional

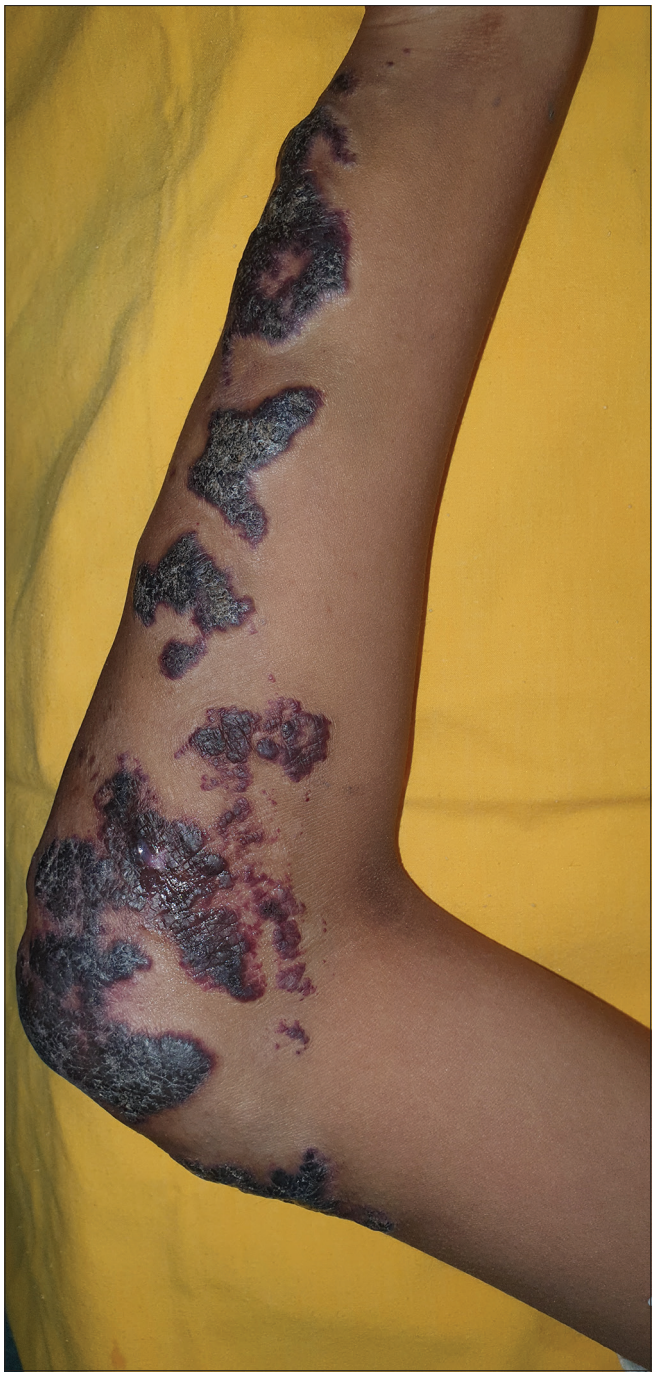

Figure 8: Verrucous venous malformation: Dusky erythematous hyperkeratotic plaques in a linear distribution

benefits. Other therapies tried are topical corticosteroids, cryotherapy, and radiofrequency ablation. Oral sirolimus, via its inhibitory action on the mammalian target of rapamycin, has shown great promise in managing VVM unresponsive to conventional modalities.[58]

Arterial malformations

Arterial malformations are classified under high-flow malformations. They are further divided into arteriovenous malformations, arteriovenous fistulas (AVF), and capillary malformation–arteriovenous malformation.

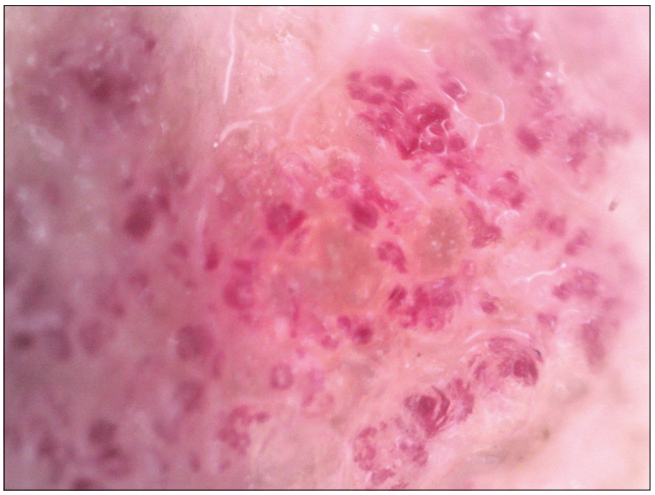

Figure 9: Dermoscopy of verrucous venous malformation showing clustered dots and globules with loop, comma-shaped vessels, circumferential white lines (200x)

a. **Arteriovenous malformations (AVM):**
AVM occur due to persistence of arteriovenous channels in the primitive retiform plexus. The intervening capillaries are absent and the dysmorphic arteries and veins are directly connected to one another. Nidus, a characteristic feature of AVM, is a central mass of low resistance, which is connected to afferent arteries and efferent veins. It is believed that the cells in this region initiate molecular signals for the involvement of new vessels thus having a crucial role. AVMs can be either soft tissue or bony.
Bleeding is the most common complication.[59] Features of soft tissue and bony AVM are summarized in Table 3. *Schobinger R et al.* postulated a staging system for AVM [summarized in Table 4].[60]
Imaging: Ultrasonography (USG) is the first-line imaging technique for diagnosis, which shows high-flow lesions with difficult-to-trace arterial and venous sides. For soft tissue involvement, MRI determines the diagnosis and the extent of the lesions, and the lesion appears as a tangle of vessels with flow voids on both T1W and T2W sequences. CT plays a vital role in bony AVM to determine the extent of bone and teeth involvement. The gold standard modality in diagnosing AVM is angiography. It gives information about feeding arteries and draining veins. It is both diagnostic and therapeutic (embolization). CT or MR angiography yields superior results compared to USG.[59,61]
Management: Destruction of Nidus remains a vital step in the treatment of AVM because of its role in the expansion. Management can be curative or palliative, depending on the stage of AVM. Nonsurgical methods include endovascular transcatheterization followed by injection of n-butyl cyanoacrylate (NBCA) or absolute ethanol. Absolute ethanol is the most powerful sclerosant and acts by damaging the endothelial layer and partially to complete demolition of the nidus. Complications

include local or distant nerve damage, pulmonary thromboembolism, and cardiovascular collapse. Onyx (ethylene-vinyl alcohol copolymer) is the safest alternative for absolute ethanol. NBCA acts by obliterating the feeding vessels and should not be used as a curative method. Preoperative embolization using angiography is usually performed 24-48 hours before surgery.

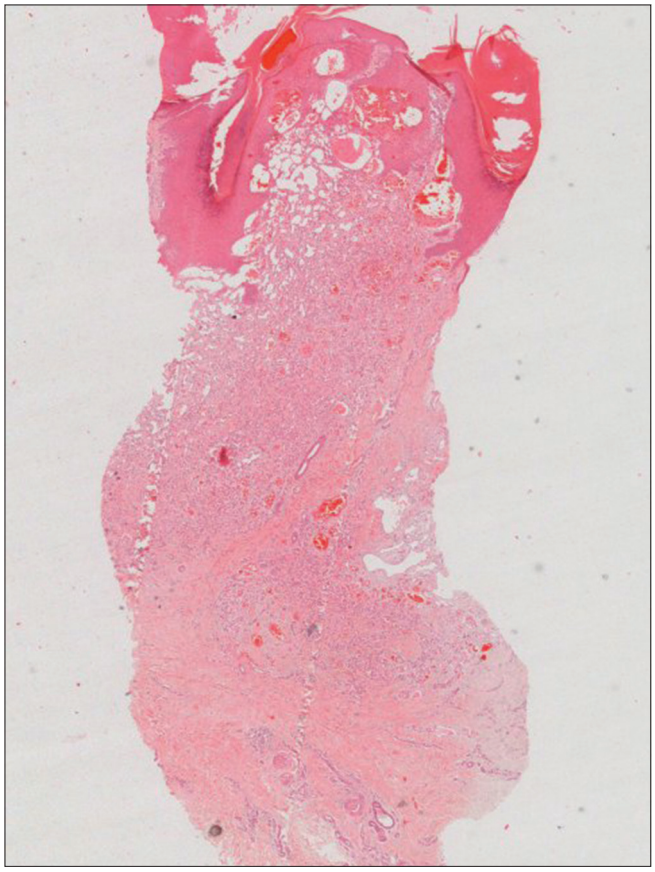

Figure 10: Histopathology of verrucous venous malformation showing epidermal acanthosis, papillomatosis, and dilated and congested blood vessels in the dermis (H and E, 40x)

Surgical management in the case of AVM depends on the risk-to-benefit ratio and should be performed with extensive care by an experienced surgeon.[3] McCarthy C *et al*. reported a case of giant chest wall AVM, which presented with a single mass over the anterior left side of the upper chest and significant bleeding. They successfully removed the AVM en-bloc following an embolization 48 hours before the surgery.[62]

Syndromes associated:

i. Stewart–Bluefarb syndrome (SBS) is a rare condition that is characterized by the presence of acroangiodermatitis along with an underlying AVM. Early suspicion and detection are crucial in these cases for better prognosis. Cutaneous features include violaceous to brown macules, papules, plaques, or nodules that can become verrucous or even ulcerate [Figure 11]. Parsi K *et al*. reported five cases of SBS, of which three cases had AVM of lower limbs (great toe, ankle, and foot), and two cases showed arteriovenous fistula of calf and ankle (one congenital and one acquired non-traumatic). Diagnosis and treatment remain the same as that of AVM.[63]
ii. Cobbs syndrome is a rare condition characterized by spinal AVM along with cutaneous features like capillary malformations (PWS) distributed in the particular dermatome. A few cases may also have dilated veins with palpable thrill, mostly involving the trunk. Neurological symptoms like numbing and paresthesia will be limited to a dermatome. Imaging techniques (CT, MRI) remain the same. Initially, laminectomy followed by decompression is the treatment of choice. Combined therapy of oral corticosteroids with endovascular embolization has shown good results.[64]
iii. Hereditary hemorrhagic telangiectasia (HHT**),** also called as Osler-Weber-Rendu disease, is an autosomal dominant vascular disease. It is characterized by mucocutaneous telangiectasias and AVMs in the liver, the lungs, and the nervous system. Clinical diagnosis

Table 3: Features of soft tissue AVM and Bony AVM

Soft tissue AVM	Bony AVM
Indolent, slowly growing mass, pulsatile and slightly compressible on palpation, rarely painful, reddish-bluish discolouration when skin or mucosa infiltration occurs	Two-thirds of patients show mandibular AVMs
Becomes apparent in 10-20 years of life	Triad involves tooth mobility, gingival bleeding, and radiographic evidence of a hypodense mass (pathognomic of AVM)
Male > Female	
Bruit is present	No sexual preponderance
Not replenished in supine position like venous malformations	

Table 4: *Schobinger R et al*. staging for AVM

Stages	Features
Stage 1—Quiescent/Dormant phase	Macular or slightly infiltrated (resembling port wine stain)
Stage 2—Expansion phase (Begins during adolescence, induced by puberty, trauma, and pregnancy)	Warm masses with throbbing and thrills over dilated draining veins
Stage 3—Destructive phase	Stage 2 + Necrosis, hemorrhage, ulceration, and lytic lesions of bone
Stage 4	Stage 2±3 Cardiac decompensation

can be made by using Curaçao criteria (telangiectasia, epistaxis, visceral involvement, and family history), and molecular diagnosis is established based on genetic analysis of the ENG, SMAD4, GDF2, and ACVRL1 genes. A multidisciplinary approach is required for the management of these cases, which can provide normal life expectancy to patients. Bevacizumab, an anti-VEGF antibody, is found to be effective in cases having bleeding complications and severe liver damage with cardiac repercussions. Tyrosine kinase inhibitors are currently being investigated for management.[65]

b. **Capillary Malformation—Arterial Venous Malformation (CM-AVM):**
CM-AVM syndrome generally presents with multiple small capillary malformations (mostly over the face and limbs) along with associated internal AVM/AVF of skin, bone, muscle, brain, etc., It is subdivided into two types based on pathogenicity: CM-AVM 1 (RASA1 on chr 5) and CM-AVM 2 (EPHB4 on chr 7). A variant of CM-AVM with limb hypertrophy due to underlying AVM/AVF is Parkes–Weber syndrome. CM-AVM 1 and 2 are congenital and present early in childhood, and the differences are the presence of AVM/AVF is more in CM-AVM 1, whereas the presence of telangiectasias and epistaxis is more common with CM-AVM 2 (resembling HHT). Cutaneous manifestations include multifocal, atypical pink-to-reddish brown, small, and multiple round-to-oval lesions. Congenital cardiac malformations like septal defects, Tetralogy of Fallot, and valve anomalies may be associated. Due to underlying pathology in the RAS-MAPK pathway (RASA1 mutation), CM-AVMs are considered under RASopathies. Management requires a multidisciplinary approach; CMs and telangiectasias are of cosmetic concern, whereas AVM/AVF requires prompt assessment and appropriate treatment.[66-68]

c. **Arteriovenous fistulas (AVF):**
AVF are either congenital or acquired. Acquired causes of AVF include injury piercing the skin like gunshot or stab wounds or created by the surgeon in hemodialysis patients. They may involve any organ like lungs, liver, brain, kidney, etc., AVFs are never usually seen presenting alone, and they are mostly associated with syndromes discussed below.

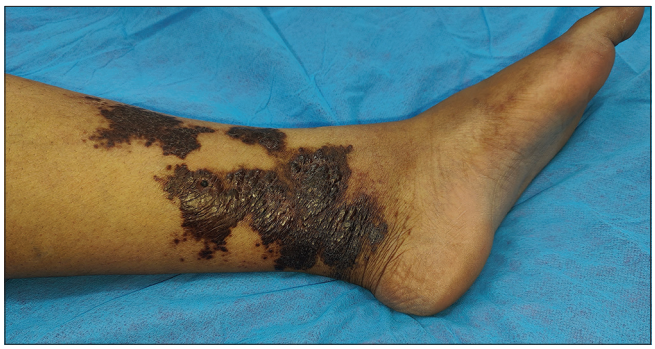

Figure 11: Stewart–Bluefarb syndrome presenting as dusky erythematous plaques over the lower limb in patient with underlying arteriovenous malformation

Lymphatic malformations (LM)

LMs were earlier named as "lymphangiomas" and "cystic hygromas." These arise due to embryological disturbances in the development of lymphatic channels. They are further classified as macrocystic LM (>2 cm), microcystic LM (<2 cm), and mixed type [Table 5 and Figure 12].[69]

Imaging: In macrocystic LMs, USG shows anechoic or heterogeneous cystic lesions with fine septa dividing into compartments, which can later become iso- or hyperechoic, with a liquid–liquid level in some cases of intracystic bleeding due to rupture of small vessels of the septa. Microcystic LMs on color Doppler USG show echogenic infiltration without hypervascularization. The gold standard modality to know the depth and extent of lesions is MRI; they show a high T2 signal with minimal enhancement, whereas T1 signal is variable. Few cases of microcystic LMs show diffuse enhancement of the cystic walls, and such cases are prone to recurrence after surgery or sclerotherapy. MR angiography has no role in diagnosing LMs.

Biopsy shows cystic lymphatic spaces with flattened epithelium, and markers like podoplanin, VEGFR-3, and CD34 are expressed by the lymphatic vessels. Fine needle aspiration can sometimes be performed, showing citrine-rich fluid with lymphocytes.[61,69]

Complications:

- Cervicofacial LMs—Airway obstruction, speech development, difficulty with feeding, progressive overgrowth, and distortion of the mandible.
- Orbit LMs: Ocular pain and swelling, congenital cataract, diplopia, strabismus, and acute proptosis.
- Recurrent potentially life-threatening infections.

Treatment:[70] Sclerotherapy is the first line of treatment in many cases, especially in macrocystic LMs that cause discomfort. Sclerosants used are sodium tetradecyl sulfate, OK-432, sodium morrhuate, polidocanol, bleomycin,

Table 5: Macrocystic LM versus Microcystic LM

Microcystic LM	Macrocystic LM
Usually presents above the mylohyoid muscle involving oral cavity, tongue, parotid, and submandibular gland[12]	Usually seen in areas where loose connective tissue is abundant like axilla, groin, cervical triangles (below the mylohyoid muscle)[12]
Presents as a plaque with tiny, clear, and firm vesicles giving an impression of brawny edema[12]	Presents as large, compressible, or non-compressible, smooth translucent masses under normal skin[12]
Also known as Lymphangioma circumscriptum	Hemorrhage inside the mass cause sudden swelling, with the mass becoming tender, firm, and purplish to yellow color
	Also known as cystic hygroma

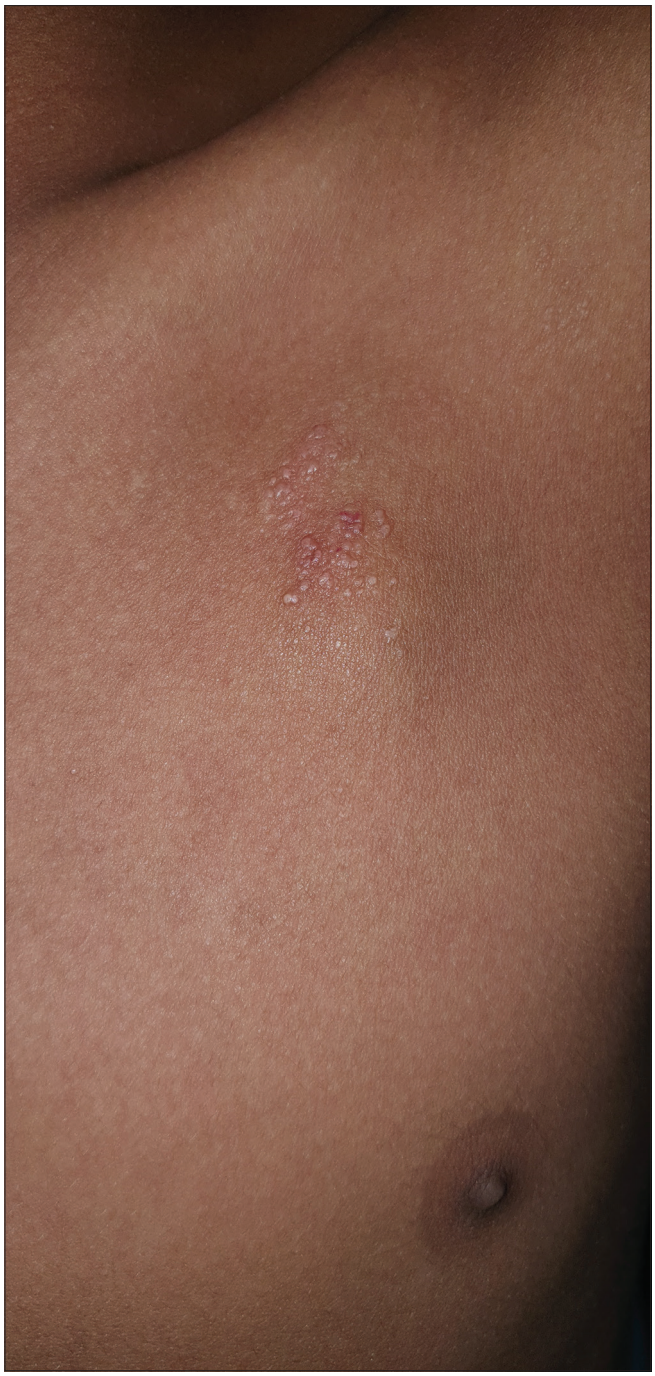

Figure 12: Lymphatic malformation: Grouped clear fluid-filled vesicles over the chest

absolute ethanol, and doxycycline. They are injected after aspirating 30-50% of the content. The effect is observed in 4-6 weeks and can be repeated with a 3-6 months gap.

Physiotherapy: It is not a definite curative mode but improves the quality of life for a brief period. It includes compression and lymphatic drainage.

Physical therapy: Includes electrocoagulation, radiofrequency ablation, and fractional CO_2 laser. It is mainly useful for superficial destruction, prevents bleeding, and reduces redness. Fractional CO_2 laser is found to be effective in cutaneous lymphangiectasias. Savas JA *et al*. have identified 16 studies with 28 patients of cutaneous lymphangiectasias, out of which 8 patients were disease-free from 4 months to 3 years, 10 patients had partial recurrence and 2 had complete recurrence.[71]

Medical therapy: Sirolimus acts by inhibiting lymphangiogenesis via PI3K/AKT/mTOR signaling pathway. It is effective in almost 90% of the cases for reducing the symptoms and partially reducing the volume. Treatment duration is long and drug interactions should be monitored regularly.[72] Sildenafil (a potent selective PDE 5 inhibitor) is found to be effective in few case series and is kept as a last resort.[73] Bevacizumab is a monoclonal antibody against VEGF-A, which also has an effect on lymphangiogenesis. No definitive evidence, but clinical trials are being conducted for systemic use as well as a sclerosant.[74] Alpelisib, a new molecule, is a targeted therapy that has direct inhibitory effect on PIK3. It is under clinical trial, and a pilot study has reported its effectiveness in syndromic associations (CLOVES, Klippel–Trenaunay).[75]

Syndromic vascular malformations

The remaining syndromic malformations have been depicted in table [Supplementary Table 1].

Recent updates in treatment of vascular malformations

There has been a growing interest in the role of RAS/RAF/MEK Kinase pathway in the pathogenesis of vascular malformations over the last decade, and trametinib, an oral inhibitor of kinase activity of MEK1 and MEK2 has shown its efficacy in vascular anomalies with mutation in RAS/RAF/MEK pathway.

a. MEK inhibitor in slow flow malformations:

In a murine model developed from cells of a patient having kaposiform lymphangiomatosis (KLA)/generalized lymphatic anomaly, it was seen that it contained proliferative lymphatic cells with high levels of protein kinase B and extracellular signal-regulated kinases phosphorylation. Combined treatment with rapamycin (blocks phosphorylation of protein kinase B (PKB)) and trametinib (blocks extracellular signal regulated kinase (ERK) phosphorylation) reduced the viability of these lymphatic cells. Prospective research with combined modality may help in such patients.[95]

In a report of a patient with complex lymphatic anomaly with activating ARAF mutation, trametinib was seen to induce near-complete resolution with a significant reduction in symptoms.[96] Another patient with KLA having a point mutation of Casitas B-lineage lymphoma *(CBL)* proto-oncogene, a negative regulator of RAS signaling, and sustained activation of RAS/

MEK signaling, dramatically responded to low dose trametinib therapy of 0.5 mg daily.[97]

b. MEK inhibitors in fast flow malformations:
Somatic activating KRAS mutation in brain AVM leads to increased ERK activity in endothelial cells, thereby enhancing angiogenesis and migratory behavior.[98]
Recently, off-label treatment of extracranial AVMs with trametinib has been tried successfully in an 11-year-old girl with a large AVM on her back having a somatic in-frame deletion of MAP2k1 gene. The treatment was started at 0.5 mg once daily, followed by 0.5 mg twice daily, with a significant reduction in volume of AVM and symptoms. Currently, a phase 2 trial named Trametinib in AV malformations (fast flow) (TRAMAV) is ongoing, evaluating the role of trametinib in refractory AVM.[99]

Conclusion

In conclusion, vascular malformations encompass a diverse group of congenital anomalies affecting blood vessels, with variations in their types, locations, and clinical manifestations. Accurate diagnosis and appropriate management are crucial for optimizing patient outcomes. A multidisciplinary approach involving specialists from various medical disciplines is often necessary to provide comprehensive care. Advances in diagnostic techniques and treatment modalities have improved our understanding and ability to manage vascular malformations effectively. However, further research is needed to enhance our knowledge of their underlying mechanisms, develop targeted therapies, and improve long-term outcomes for affected individuals. Through ongoing research and collaboration, we can strive to provide better diagnostic tools, refine treatment strategies, and ultimately improve the quality of life for individuals living with vascular malformations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Syndromic vascular malformations

Syndrome with genetic mutation	Clinical features	Diagnosis	Treatment	Recent updates
STURGE–WEBER SYNDROME Genetic mutation—GNAQ gene, GNA11 gene[76]	ROACH SCALE CLASSIFICATION (Type I: facial + leptomeningeal malformations; may have glaucoma (classic SWS). Type II: facial capillary malformation alone; may have glaucoma. Type III: isolated leptomeningeal angiomatosis; usually no glaucoma) Cutaneous features: -Capillary malformations are the most common, especially over the sensory distribution of trigeminal nerve (V1 involvement is high risk), bony or soft tissue overgrowth (especially of maxillary bone and upper lip) - Risk factors for CNS involvement- Extensive bilateral involvement, Hemifacial, and forehead involvement, median port wine birthmark, >50% of contiguous hemi forehead involvement. -Angiomatous nodules, pyogenic granuloma over skin or mucosa can be seen, dermal melanocytosis is also seen. -SWS associated with GNA11 mutation—different clinical presentation like pale pink reticulated capillary malformation, pigmentary changes (dermal melanocytosis, nevus anemicus, café-au-lait macules), mild neurological features with limb hyper/hypotrophy, renal anomalies, and hypertension. -Malignant transformation has been reported to be common, being basal cell carcinoma. Neurological features: -Seizures (due to cortical irritability caused by cerebral vascular malformations) -Leptomeningeal angiomatosis (unilateral, posterior, ipsilateral to port wine stain) -Migraine-like headaches -Stroke/transient or permanent hemiparesis -Hypoperfusion of cerebral hemispheres, chronic hypoxia leading to atrophy and calcifications (occipital lobe common) -Cognitive impairment, attention, emotional, and behavioral problems.	-Gadolinium-enhanced MRI is the main imaging method used to detect leptomeningeal enhancement, abnormal venous drainage, cortical atrophy, and hypermyelination. - Susceptibility-weighted imaging (SWI) and contrast-enhanced FLAIR (fluid-attenuated inversion recovery) are required to complement the T1-weighted MRI findings. -Neuroimaging in child less than 1 year is controversial and is mainly required when there is drug-resistant epilepsy to know the extent of involvement. - PET scan is useful to monitor disease progression. -EEG (Electroencephalography) is a minimally invasive and cost-effective modality to know cortical affection and epilepsy. - Biomarkers: Angiogeneic factors in urine like matrix metalloproteinases (MMP), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (b-FGF) to track the progression of the disease. Out of which, MMP-2,9 are useful for disease progression and b-FGF levels for judging the efficacy of neurological treatment.[77]	For Port wine stains:[78] -Pulsed dye laser (PDL) -Alexandrite laser is the next alternative -Intense pulse light lasers (IPL) and long pulse Nd: YAG lasers are used in cases of PDL resistance. -Fractionated Ablative devices like CO_2, Erbium: Glass, Erbium: YAG lasers -Adjuvants like topical imiquimod, topical rapamycin have been tried along with PDL in laser-resistant cases. - Other treatment modalities include surgical resection, photodynamic therapy, and corrective cover-up product use. - Interval of laser therapy ranges from 2 weeks to 3 months. Targeted therapy:[18] -Sirolimus is found to be effective in the regression of vascular malformations; however, it has no direct signaling against the GNAQ gene -Rapamycin (0.8 mg/m^2/dose) along with oral aspirin (10mg/kg/day) for early onset seizures showed beneficial results in a 3-month-old infant. -Rapamycin showed beneficial effects on overgrowth. -Antiepileptic medications remain the mainstay of treatment (levetiracetam, low-dose aspirin, oxcarbazepine, and phenobarbitone)	-Recently, area of highest risk has been described as forehead, area lateral and inferior to outer canthus of eye including upper eyelid to top of ears (developed from neural crest cells migrated from prosencephalon, leptomeninges, and eyes are also derived from prosencephalon).[76] -R.He *et al*. reported a case of Sturge–Webber and Klippel-Trenaunay overlap syndrome with features of both. On genetic analysis, the patient had both somatic mosaic GNAQ and KRAS mutation.[79]

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Supplementary Table 1: Contd...

Syndrome with genetic mutation	Clinical features	Diagnosis	Treatment	Recent updates
	Ocular features: -Ipsilateral glaucoma (abnormal angle development, poor drainage, raised episcleral venous pressure) -Choroidal hemorrhage (tomato ketchup fundus) -Other features like Iris heterochromia, ocular melanocytosis, iris mamillations, hemiretinal occlusion, cilioretinal occlusion. -Risk factors for glaucoma in relation to port wine stain-extensive, involving frontal and large malar area, lower lid involvement, right and bilateral involvement, male (<4-year-old patients). Other manifestations: -Hypothalamic pituitary compromise -Gingival hyperplasia (disease associated or anticonvulsants induced)	- Fundus fluorescein angiography, B-scan ultrasound, OCT, indocyanine green chorioangiography, and MR to confirm the choroidal hemorrhages.	- Low-dose aspirin (3-5mg/kg/day) is found to be safe even in pediatric population. -Cannabidiol (2-25mg/kg/day) is effective in controlling refractory epilepsy cases. - For diffuse choroidal hemorrhage causing vision loss-external beam radiotherapy, proton beam radiotherapy, stereotactic radiotherapy, and plaque brachytherapy. Photodynamic therapy with verteporfin has recently been found to be effective. For circumscribed Choroidal hemorrhage, argon lasers are useful.	
PROTEUS SYNDROME Genetic mutation—Overexpression of AKT1 gene[80]	- Asymmetric progressive disproportionate overgrowth -Skull abnormalities, pigmented naevi, lung cysts, and intra-abdominal lipomas -Cutaneous changes like palmar and plantar cerebroid thickening	Histopathology shows asymmetric overgrowth of soft tissue, adipose tissue, bone, and vascular malformations		Miransertib (AKT1 inhibitor) at a dose of 5mg/kg/m^2 is found to be effective[81]
Phakomatosis pigmentovascularis Genetic mutation: GNA11 mutation	- Applied to a group of phenotypes that consist of different pigmentary and vascular lesions that coexist in the same individual. -Five types Ia/b- Epidermal naevus + PWS IIa/b- Phacomatosis cesioflammea- dermal melanocytosis + PWS (nevus anemicus, hypotrichosis, lipohypoplasia, hypoplastic nails IIIa/b- Phacomatosis spilorosea/melanorosea- nevus spilus (macular) + nevus roseus (light red pink CM) IV a/b—Phacomatosis melanovascularis—Café-au-lait macules + CM, sometimes features of II + III or II + V Va/b- Phacomatosis cesiomarmorata—Dermal melanocytosis + cutis marmorata telangiectasia congenita			Recent updated classification-[82] I. Phacomatosis cesioflammea II. Phacomatosis cesiomarmorata III. Phacomatosis spilorosea IV. Phacomatosis melanorosea V. Phacomatosis cesioflammeamarmorata VI. Phacomatosis melanocesioflammea

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Supplementary Table 1: Contd...

Syndrome with genetic mutation	Clinical features	Diagnosis	Treatment	Recent updates
BONNET–DECHAUME–BLANC SYNDROME (Wyburn– Mason syndrome)[83]	A neurocutaneous syndrome characterized by multiple AVMs involving face and brain (choroid plexus, chiasma, thalamus) leading to hemiparesis/hemiplegia, seizures, decreased visual acuity, blindness, recurrent epistaxis, nasal obstruction, and gingival hemorrhage. Cutaneous lesions are mostly small facial angiomas in the trigeminal distribution	Imaging by MRI Brain and CT Brain	similar to management of AVMs	
SOLAMEN SYNDROME Genetic mutation: mosaic PTEN wild-type allelic loss[80]	-Development of progressive proportionate segmental overgrowth with soft tissue hypertrophy, macrocephaly, hypertrophic, hamartomatous, neoplastic lesions involving skin, genital mucosa, GIT, thyroid, and breast. - Multifocal, intramuscular, fast flow lesions associated with ectopic fat and focal segmental dilatation of draining veins.	Histopathology is suggestive of lipomatosis or angiolipoma without bony involvement.	Multidisciplinary approach involving orthopedic and laser therapy.	
GORHAM–STOUT DISEASE (Vanishing bone disease)[84]	Lymphatic malformations involving bones making them osteolytic, mostly involving maxillofacial, femur, upper extremities. Involvement of thoracic bone can be associated with pulmonary lymphangiectasias.	Heffez *et al.* gave 8 diagnostic criteria-[81] (1) positive biopsy findings (angiomatous tissue) (2) absence of cellular atypia; (3) minimal or no osteoclastic response and absence of dystrophic calcifications; (4) evidence of local bone progressive resorption; (5) non-ulcerative, non-expansive lesion; (6) absence of visceral involvement; (7) osteolytic radiographic pattern; (8) absence of other etiologies (metabolic, hereditary, neoplastic, immunologic infections) -Blood investigations—only raised Alkaline phosphatase -Plain X-ray shows radiolucent foci in the intramedullary or subcortical regions -MRI and CT have variable findings.	Medicine therapy- Bisphosphonates showed good results due to their anti-osteolytic activity. Others like Vit D, a-2b IFN, calcium, adrenal extracts, and androgens have been tried. Radiation- In long-standing symptomatic cases, radiation with surgery is the treatment of choice. Risks of occurrence of secondary malignancies and growth restriction in children are seen with high dose therapy. Surgical therapy- Resection and reconstruction with bone grafts.	

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Syndrome with genetic mutation	Clinical features	Diagnosis	Treatment	Recent updates
FAST FLOW–PARKES–WEBER SYNDROME Genetic mutation: RASA 1 gene[86]	-It is clinically similar to KTS, except that it is associated with fast-flow lesions, whereas KTS is associated with slow flow. -Capillary AVM causing pink skin -Hypertrophy of soft tissue or bone of the affected limb -cardiac dysfunction due to many low-resistance high-flow shunts (can present as high output cardiac failure)	X-ray to confirm the hypertrophy. MR Angiography/ CT Angiography to identify high-flow AVMs. Angiography shows pale AVF like stains in the periarticular region (specific to PWS)	Small AVM can be left untreated. Embolization can be tried. Surgical resection is difficult due to the extensive involvement of soft tissues and bone. Limb amputation is preferred in large AVMs. Regular imaging follow-up is required to see the progression. Symptomatic management of cardiac failure	
SLOW FLOW – I. MAFUCCI SYNDROME Genetic mutation: IDH 1 gene[87]	-Very rare condition characterized by multiple enchondromas, vascular malformations like phleboliths, hemangiomas (bluish subcutaneous nodules), and lymphangiomas mostly involving extremities and rarely face. - 52-57% malignant transformation, 30% are chondrosarcoma -bony lesions occur in the metaphysis of short tubular bones of hands and feet	Imaging shows round calcifications in soft tissues (phleboliths), multiple osteolytic lesions	Symptomatic management and early detection to prevent complications. Surgical resections are the treatment of choice in enchondromas and large malformations. Regular follow-up due to high chances of malignant transformation	Shen *et al*. reported a successful surgical resection with sclerotherapy in a facial vascular malformation in Mafucci syndrome.[88]
II. CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies) Genetic mutation: Somatic gain of function mutation in PIK3CA gene[86,89]	One of the conditions of PIK3CA-related overgrowth spectrum (PROS) -Low-flow (venous, lymphatic) malformations are more common, but spinal and paraspinal high-flow malformations can be seen -Capillary malformations with port wine stain appear over the trunk and extremities and overlap with lipomatous overgrowth -Extravascular features include: Linear epidermal nevi, lipomas, and hamartomas Thoracic lipomatous hyperplasia Hand and/or foot overgrowth Macrodactyly Sandal-gap toe Scoliosis, spina bifida, and pectus deformity Wilms tumor association is seen.	Sequential analysis of DNA from fresh tissue samples shows a heterozygous mosaic gain of function mutation of PIK3CA gene. Imaging techniques like MRI and CT for skeletal and vascular anomalies	Sirolimus has shown beneficial outcomes. -Surgical resection or scleroembolization for large vascular anomalies	Targeted therapy with Alpelisib (specific inhibitor of the p110a subunit of PI3K), (50mg once daily for 2-18 years old, dose can be increased to 125 mg once daily for >6 years old. 250 mg once daily can be given for >18 years old). It is found to be efficacious and safer compared to sirolimus.[90]

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Supplementary Table 1: Contd...

Syndrome with genetic mutation	Clinical features	Diagnosis	Treatment	Recent updates
III. KLIPPEL-TRENAUNAY SYNDROME (KTS)[85,90,91] Genetic mutation: PIKC3A mutation	-Triad of port-wine stains, varicosities, bone and soft tissue hypertrophy (unilateral) - low-flow venous or lymphatic vascular Malformations and geographic vascular malformations are common, and arteriovenous can occur. It can involve visceral organs like spleen, pleura, liver, colon, and bladder. -Large lateral embryonic draining vein of Servelle seen in an enlarged lower extremity (pathognomonic) - Craniofacial involvement → deviated nasal septum, nasal obstruction, oral, and nasal mucosa having angiomatous malformations jaw enlargement, facial asymmetry, premature tooth eruption, hemangiomas of lips and tongue -CNS abnormalities - hemorrhage, hemimegalencephaly, hydrocephalus, infarction, and seizures - Other features like superficial thrombophlebitis, deep vein thrombosis, pulmonary embolism, oligodactyly, syndactyly, macrodactyly, polydactyly, hip dysplasia, hypospadias, paresthesia thrombosis, ulceration, stasis dermatitis, hypertrichoosis, hyperhidrosis, decalcification of involved bones, and spina bifida. -Complications like GI bleeding, venous insufficiency, recurrent cellulitis and ulcerations, lymphedema, protein losing enteropathy is also described.	Conventional radiography of affected and contralateral limb to screen for true limb discrepancy (osseous hypertrophy) - Contrast-enhanced MRI/ MR Angiography is used to evaluate the vascular malformations. MR Venography will check for deep venous system involvement, if any.	Conservative management- Elastic compression stockings for varicosities over limbs, conventioanl scleroembolization for vascular anomalies, antibiotics, analgesics for cellulitis. -Surgical intervention in case of large vascular malformations and limb amputation if overgrowth is severe. -Laser therapy for Port wine stains	-Pang HQ *et al*. reported a case of prenatal ultrasonographic diagnosis of KTS[92] -Inverse KTS where there is hypotrophy or shortening of affected limb, pathogenesis is unknown. Probable hypothesis is the post-zygotic recombination of "minus," "plus," alleles.[93] -Onoda *et al*. reported lymphaticovenular anastomosis for a case of KTS with recurrent cellulitis at seven sites which showed excellent response.[94]

KTS - Klippel Trenaunay syndrome