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ARTERIOVENOUS MALFORMATIONS – DIAGNOSIS AND TREATMENT

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Introduction

Vascular malformations (VM) remain one of the most difficult diagnostic and therapeutic enigmas in modern medicine due to their extremely variable clinical presentation, ranging from asymptomatic birthmarks to life-threatening conditions. The incidence of VM is 1.5% in the general population. These malformations are localized errors of angiogenic development. Most vascular malformations are mixed, and several are associated with developmental abnormalities (e.g., Klippel-Trenaunay syndrome and Parkes-Weber syndrome). The International Society for the Study of Vascular Anomalies recently adopted a classification scheme that clearly separated vascular tumors (hemangiomas of different types), which result from active cell proliferation, from vascular malformations, which are inborn defects in vascular morphogenesis. While the majority of VM are sporadic, autosomal dominance has been described (Table 1). These two types of lesions have different clinical behavior and require different diagnostic and therapeutic strategies. The majority of VM (approximately 65%) are predominantly related to venous malformations. The Hamburg Classification of vascular malformations uses criteria that take into account the underlying anatomical, histological, pathophysiological, and hemodynamic status of each malformation (Table 2). Venous malformations are differentiated into truncular and extratruncular forms, with the truncular forms (38%) being obstructions or dilations and the extratruncular forms (62%) being limited or infiltrating[1] The prevalence of deep venous anomalies associated with VM is approximately 47%.[2]

Clinical Assessment

Patients with VM are generally asymptomatic and often only have a cutaneous or mucosal birthmark. The most frequent clinical sign is skin discoloration, and the most frequent symptom is pain. Patients seeking treatment at a VM treatment clinic often present a complex picture, including atypical varicose veins, limb edema or overgrowth, port wine stains, or digital anomalies. There is often a palpable mass that is pulsatile. Bleeding or lymph leakage from vascular malformations is not uncommon. Symptoms and signs of chronic venous insufficiency may also be present. Venous malformations are known to be occasionally painful because of thrombotic episodes inside the lesion, and coagulation disorders are present in up to 58% of the patients.[3] The diagnosis of a vascular malformation is now achieved with a combination of noninvasive imaging studies. Selective invasive studies are generally reserved as a road map for treatment.

Imaging

Duplex ultrasound can document the structure and hemodynamic characteristics of the arterial and venous circulations feeding the vascular malformations. Inflation of a cuff proximal to a high-flow fistula will result in an increase in systolic blood pressure and a drop in pulse rate. Ultrasound can provide information on the structural and hemodynamic characteristics of a vascular malformation. Quantification of vascular malformations at the time of diagnosis, during assessments of diseases progress, and post-interventionally, using both the resistance index of Pourcelot and measurement of the vascular blood flow velocities, are particularly appropriate for longitudinal follow-up.[4]

CONDITION	GENE ABNORMALITY
Familial Mucocutaneous VM	Angiopoietin receptor TIE2/TEK on chromosome 9p21
Glomuvenous VM	Glomulin on short arm of chromosome 1
Capillary Malformations	RASA1 on chromosome 5q
Hereditary hemorrhagic telangiectasia	Abnormalities in TGF- genes
Congenial lymphedema	VEGFR-3 on chromosome 5q35.3

Table 1. Known Genetic Associations with AVMs

Hamburg Classsification

TYPES

Predominantly arterial defects
Predominantly venous defects=
Predominantly arteriovenous (AV) shunting defects
Predominantly lymphatic defects
Combined vascular defects

EMBRYOLOGICAL SUBTYPES

Extratruncular forms	Truncular forms
Infiltrating, diffuse	Aplasia or obstruction
Limited, localized	Hypoplasia, aplasia, hyperplasia
	Stenosis, membrane, congenital spur
	Dilation
	Localized (aneurysm)
	Diffuse (ectasia)

Table 2. The Hamburg Classification uses criteria that take into account the underlying anatomical, histological, pathophysiological, and hemodynamic status of each vascular malformation.

Cross-sectional imaging with computed tomography angiography (CTA) or magnetic resonance angiography (MRA) provides accurate determination of the size, feeding vessels, and involvement of the adjacent tissue associated with a vascular malformation. Vascular malformations can also be classified into high-flow and low-flow malformations. Vascular malformations have the ability to cross multiple tissue boundaries. Not only is subcutaneous tissue often involved, but multiple muscle groups, tendons, bone cortex, and bone marrow are also not uncommonly violated. Magnetic resonance imaging (MRI) can characterize the flow pattern of these malformations to guide treatment towards transarterial embolization for vascular malformations and percutaneous embolization for low-flow malformations; it also is essential to define the anatomic extent and involvement of various tissue layers (providing a distinct advantage over ultrasound) and to correlate treatable components of the malformation with patient symptoms.[5,6] Skin burns in patients with venous malformations treated with alcohol embolization (vide infra) are associated with the length of skin involvement and with the absence of deeper tissue involvement as depicted on MR imaging.[7] Contrast arteriography and venography are reserved for documenting the feeding vessels prior to possible percutaneous intervention. Shunting is best documented with a technetium-99m labeled human albumin study. Less than 3% of the agent should pass through a normal capillary bed.

Management

There are absolute and relative indications for the treatment of VM.[8] The absolute indications include hemorrhage, ischemia, refractory ulcers, and congestive heart failure. Relative indications include pain, claudication, functional impairment, limb asymmetry, and cosmesis. Treatment strategies have to be set up separately for the "primary malformation" itself and for their "secondary disorders" in the vascular system and/or skeleton and soft tissue. Vascular malformations should be treated in a multidisciplinary clinic comprising vascular interventionalists, plastic surgeons,

orthopedic surgeons, and physical therapists.[9, 10] Many vascular malformations can be managed conservatively with compressive therapy, wound management, and orthotics. When intervention is undertaken, the principle of nodus ablation is clear, particularly when a patient suffers clinical complications from the VM. If the vascular malformation remains connected to the bloodstream by a drainage vein during nidus opacification, flow control is necessary to achieve complete nidus ablation.

Percutaneous Therapy:

Percutaneous embolization has emerged as a primary therapy for VM.[11] Embolization can be achieved with polyvinyl alcohol (PVA) particles (100-500µm), absolute alcohol, coils, gelfoam, and cyanoacrylate adhesives. Each is appropriate for a different part of the circulation in the vascular malformation.[12, 13] Particles and liquid occlusive agents induce occlusion at both the arteriolar level and the capillary bed. Coils will occlude small to medium arteries. Embolization can achieve 80% occlusion. Complications associated with embolization include access site complications, tissue necrosis, pulmonary Embolization, and distal embolization outside the VM. Percutaneous transcatheter or direct puncture sclerotherapy with absolute ethanol is frequently used for predominantly venous malformations. It is very painful and often requires general anesthesia. Absolute ethanol sclerotherapy achieves excellent results in the infiltrating type of the extratruncular forms of vascular malformation.[14] The success of sclerotherapy has been reported to range from 74-91%. Absolute alcohol therapy should be used with caution (maximum dose 1 ml/kg body weight) as it is associated with significant side effects (tissue necrosis, skin sloughing, pulmonary hypertension, deep vein thrombosis, and nerve injury) in 10 to 30% of cases.[15, 16, 17] Using a modified angiographic classification for peripheral arteriovenous malformations (AVMs), AVMs of the trunk and extremities were categorized according to the angiographic morphology of the nidus: type I (arteriovenous fistulae), type II (arteriolovenous fistulae), type IIIa (arteriolovenulous fistulae with nondilated fistula), and type IIIb (arteriolovenulous fistulae with dilated fistula). Ethanol embolization was most effective for type II (100%) and more effective for type IIIb (83%) than for type IIIa or mixed types (< 50%). Despite the use of the transarterial approach, direct puncture and transvenous approaches were more relevant for treating type II AVMs. Only the transarterial approach was used for treating type IIIa; both direct puncture and transarterial approaches were used for treating the other types.[18]

Sotradecol and polidocanol foams (maximum volume 10 ml) have also been used as sclerotherapy agents.[19] Use of foam permits small volumes to be used and is associated with less pain and fewer significant side effects. Although initial experience with liquid agents relied on arterial injection, direct percutaneous injection is now the preferred approach for venous malformations and has a high reported success rate.[20] Cyanoacrylate embolotherapy alone or in combination with surgical resection of the vascular malformations provide excellent long-term palliation in patients with upper-extremity vascular malformations.[21] An example of a lower extremity AVM treated with cyanoacrylate embolotherapy alone is shown in Figures 1-3.

Laser Therapy:

Laser therapy is frequently used to treat cutaneous capillary malformations. Initially, laser therapy was associated with scarring in 5-24% of patients, but the introduction of yellow light lasers has reduced this

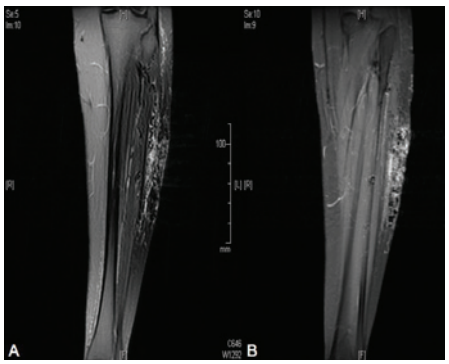

Figure 1. MRI of a left lateral AVM of the calf that has ulcerated to the skin. Patient presented with pain and bleeding.

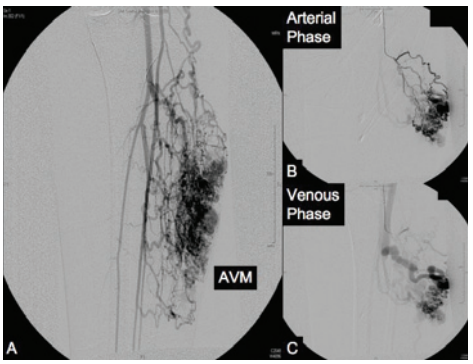

Figure 2. Contrast angiogram of the left lateral AVM of the calf with a full view of the AVM (A) and images of the arterial (B) and venous (C) phases of the filling of the AVM.

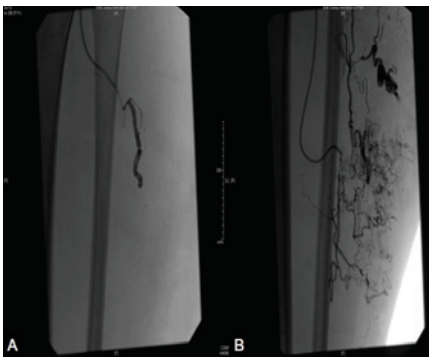

Figure 3. Contrast angiogram showing (A) injection of glue into the AVM and (B) the final result with the majority of AVM vessels opacified with radiopaque glue.

problem. The best results are achieved with a flash-lamp-pumped pulsed dye laser (585 nm).

Surgical Therapy:

Surgical therapy utilizes different tactics and techniques based on the pathologic form and the type of malformation and can include: (1) surgery to reduce the hemodynamic activity of the malformation (venous hypertension), (2) surgery to eliminate the lesion, and (3) reconstructive surgery.[22] Surgical therapy must be fully integrated with the embolo/sclerotherapy, and active incorporation of the preoperative and/or postoperative embolo/sclerotherapy substantially improves the overall results of the therapy. Non- to poor surgical candidates should be considered for embolo/sclerotherapy as the primary mode of therapy. Percutaneous injection of Sotradecol within two days of surgery is shown to cause thrombosis of the vascular lesions, facilitating surgical identification, dissection, and resection with minimal blood loss. Surgical excision of AVM is rarely curative and should be performed after embolization, as a failed surgery markedly reduced the success of percutaneous therapy. Various combinations of the embolo/sclerotherapy and conventional surgical therapy are properly implemented to treat different types of malformation: absolute ethanol sclerotherapy for the venous malformation, absolute ethanol and/or N-butyl cyanoacrylate and/or coil for the vascular malformations, and OK-432 for lymphatic malformation,[23] as major embolo/scleroagents. Extreme lesions with a completely nonfunctional limb status should be considered for early amputation and subsequent proper rehabilitation instead of continuing with nonproductive embolo/sclerotherapies. Multiple operative procedures are often required to achieve palliation.

Clinical Syndromes

Capillary Malformations:

These are composed of dilated capillary to venular-sized vessels and often signal an underlying structural abnormality (e.g., Sturge-Weber Syndrome). MRI is therefore appropriate to ensure that no other defects are detected. Capillary malformations respond well to laser therapy.

Lymphatic Malformations:

These lesions can be macro- or microcystic in nature and occur most commonly in the axilla, cervicofacial, mediastinal, retroperitoneum buttock, and anogenital areas. MRI remains the best imaging modality. Sclerotherapy with doxycycline, OK-432, and sodium tetradecyl sulfate (STS) is the modality most often used, frequently followed by staged excision.

Venous Malformations:

These are composed of thin-walled dilated channels that can occur as localized lesions or as a generalized problem. Most are solitary. MRI is the test of choice. Patients presenting with a large venous malformation may have an associated intravascular coagulopathy that should be screened for prior to any intervention. Treatment is indicated for appearance, pain, or functional problems. Sclerotherapy is the first-line treatment of choice for venous malformations; however, in small isolated lesions, excision is curative.

Arteriovenous Malformations:

These are generally capillary venous malformations and more commonly found in the intracranial as opposed to the extracranial circulation. They are fast-flow lesions that can be imaged with duplex ultrasound or MR angiogram. Embolization 72 hours prior to surgical intervention is the norm. However, sclerotherapy is used when the filling vessels cannot be cannulated. Serial embolizations for palliation are also undertaken if surgery will be maiming in nature.

Parkes-Weber Syndrome:

Parkes-Weber syndrome is a "haemolymphatic malformation" using the Hamburg classification. It is a capillary arteriovenous malformation that affects the lower limb more often than the upper limb. On MRI, soft tissue overgrowth is noted in the muscle and boney compartments with generalized arterial and venous dilatations. Treatment is tailored to symptoms.

Klippel-Trenaunay Syndrome:

Klippel-Trenaunay syndrome (KTS) is a complex congenital anomaly featuring two or more of the following: (1) capillary malformations (port-wine stains), (2) soft tissue or bony hypertrophy (or both), and (3) varicose veins or venous malformations. Venous disease in limbs with KTS is a major source of morbidity in affected patients. Limbs with KTS are characterized by complex reflux patterns, severe valvular incompetence, calf muscle pump impairment, and venous hypertension.[24] Imaging shows variable findings in the venous circulation and microcytic features in the lymphatic circulation. The management of patients with KTS continues to be primarily nonoperative, but those patients with patent deep veins can be considered for excision of symptomatic varicose veins and VMs. Although the recurrence rate is high, clinical improvement is significant, and reoperations can be performed if needed. Occasionally, deep vein reconstruction, excision of persistent sciatic veins, or subfascial endoscopic perforator surgery is indicated.[25]

Conclusion

Vascular malformations remain a unique area for therapy and intervention. Their care should be performed within a multidisciplinary environment where there is access to imaging, interventional, and surgical expertise.

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