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REVIEW

Pediatric Vascular Malformations: Pathophysiology, Diagnosis, and the Role of Interventional Radiology

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Abstract The Mulliken and Glowacki classification (1982) differentiated vascular anomalies into two groups based on their endothelial characteristics: hemangiomas and vascular malformations. Vascular anomalies are localized defects of the vasculature that affect a limited number of vessels in a restricted area of the body. These defects are secondary to errors in vascular morphogenesis. Depending on the type of vessel involved, the vascular malformation group was subdivided into high-flow (such as arteriovenous malformation and arteriovenous fistula) and low-flow lesions (such as venous and lymphatic malformations). Depending on the type of lesion, the location and degree of involvement and the clinical effect, different types of treatment would be required. For the purpose of this review, we concentrate solely on vascular malformations: the clinical features, genetics, diagnosis, and current treatment options.

Keywords Pediatric · Paediatric interventions · Embolization/embolisation · Embolotherapy · Sclerotherapy · Vascular malformations

Introduction

The Mulliken and Glowacki classification (1982) differentiated vascular anomalies into two groups based on their endothelial characteristics: hemangiomas and vascular malformations. The vascular malformation group was subdivided into lesions consisting of capillary, arterial, venous, lymphatic, and fistulous networks [1]. For the purpose of this review, we concentrate solely on vascular malformations: the clinical features, genetics, diagnosis, and current treatment options.

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Low Flow Vascular Malformations

Lymphatic Malformations

Definition

Lymphatic malformations (LMs) are congenital anomalies composed of dilated lymphatic channels that result from the defective embryological development of the primordial lymphatic channels. They are filled with a proteinaceous fluid and generally do not have connections to the normal lymphatic system. Lesions can be macrocystic, microcystic or mixed.

Genetics

Multiple genes have been described in the process of lymphangiogenesis including, VEGFR3, VEGFC and Ang2, Lyve1, Nrp2, podoplanin [2]. Developmental defects during embryonic lymphangiogenesis result in lymphatic malformations [3, 4].

Clinical Features

Lymphatic malformations appear as soft, nonpulsatile masses with normal overlying skin present at birth or early childhood (Fig. 1A). Prenatal ultrasound can detect macrocystic lesions during the late first trimester. LMs not diagnosed prenatally are generally evident at birth or

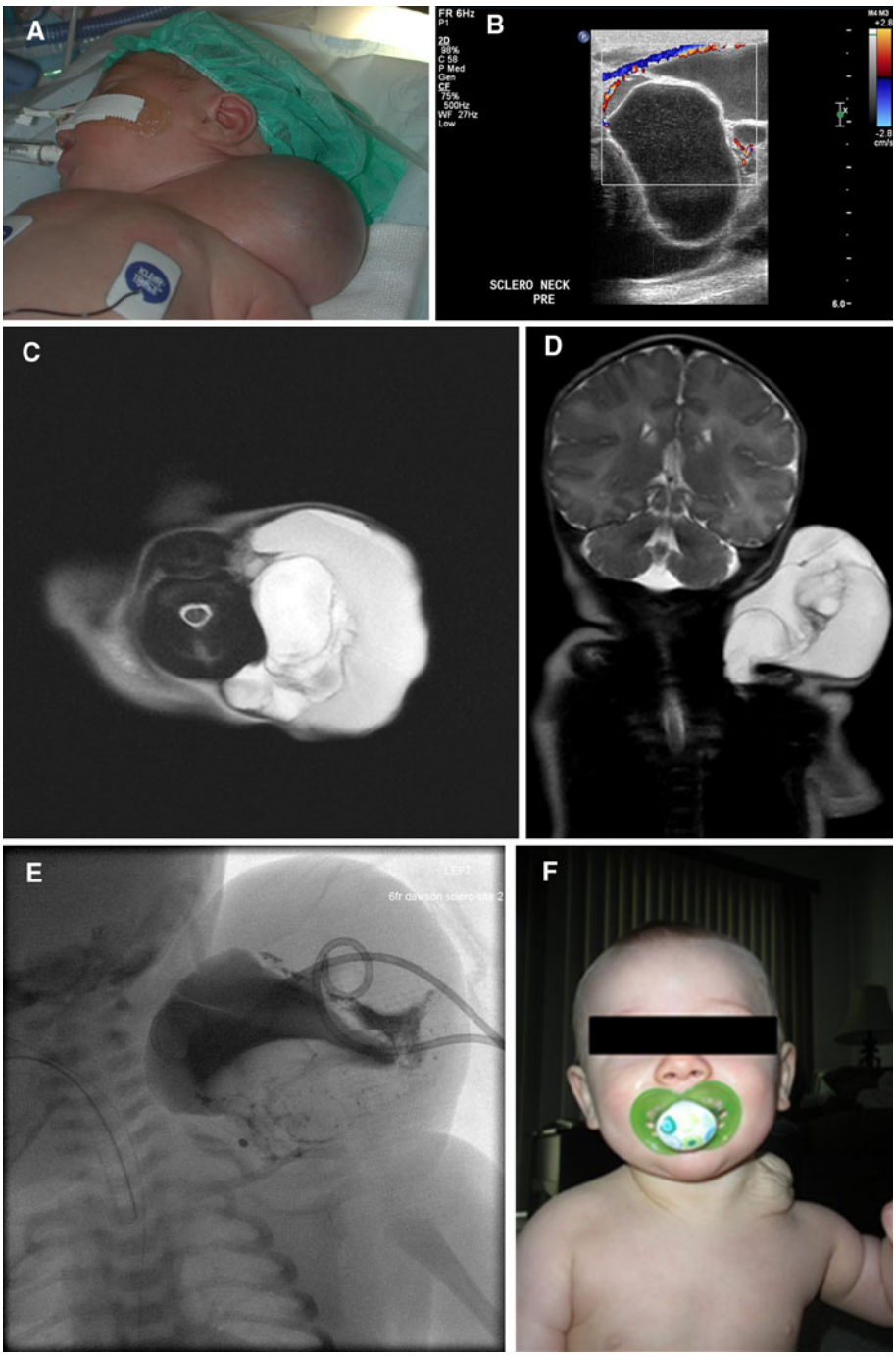

Fig. 1 Patient with lymphatic malformation of the left side of the neck. **A** Neonate with large lymphatic malformation extending from the left side of the neck, intubated for sclerotherapy treatment. **B** Axial ultrasound image of the lymphatic malformation demonstrates a predominantly macrocystic lesion. **C** and **D** Axial and coronal T2-weighted magnetic resonance images of the lymphatic malformation shows a predominantly macrocystic lesion without airway compression. **E** Fluoroscopic image during doxycycline sclerotherapy demonstrates two pigtail catheters positioned in noncommunicating components of the macrocystic lymphatic malformation. **F** Eight months after sclerotherapy demonstrating almost complete clinical resolution of the macrocystic lymphatic malformation

before age 2 years. LMs occur in the head and neck in 48%, trunk and extremities 42%, and intrathoracic or intra-abdominal viscera in 10% [5]. They can be associated with overlying angiokeratomas, which at intervals may bleed or become infected.

Macrocystic LMs are generally defined as lesions that contain cyst spaces > 2 cm and microcystic as cysts < 2 cm. LMs can be solitary or multifocal, slow growing, and rarely involuting. They can rapidly enlarge due to hemorrhage or infection leading to potential compression of structures, such as the airway or the optic nerve in the case of orbital lesions. In these instances, urgent therapy is required to decompress the lesion.

Radiological Features

Ultrasound Macrocystic LMs appear on gray scale as anechoic cavities with possible internal septa and debris

(Fig. 1B). Microcystic lesions have small cavities resulting in innumerable reflective interfaces and hyperechoic appearance, giving the lesion a more solid appearance [6]. Ultrasound (US) is an excellent imaging modality for assessment of superficial lesions to monitor size and extent pretreatment. US is limited in assessing the extent of the lesion in relation to the airway and osseous involvement.

Computed Tomography LMs appear as fluid-filled, low-attenuation masses, occasionally with fluid-fluid levels that can represent acute or subacute bleeding. Peripheral contrast enhancement of the walls may occur [7]. The internal septa are generally not well seen. The role of CT in these lesions should generally be reserved for acute lesion enlargement and secondary compression.

Magnetic Resonance Imaging Lymphatic malformations appear as multicystic masses that insinuate between tissue planes. These lesions demonstrate predominantly fluid-type characteristics on all MRI sequences (low signal on T1 and high signal on T2 sequences) with varying degrees of septation and fatty elements (Figs. 1C and D) [8]. The presence of hemorrhage within the cystic spaces may alter the imaging appearance somewhat. Minimal enhancement is seen, and this is usually visualized in the area of prominent septa formation. Macrocystic and microcystic components are easily differentiated, unlike CT imaging. Microcysytic lesions demonstrate intermediate signal intensity on T1 and T2 spin echo sequences [2].

MRI is an excellent modality to assess lesion extent in terms of tissue planes, airway compression, mediastinal extension, and potential solid organ and bone involvement. It also is the modality of choice for orbital lesions and optic nerve assessment.

Treatment

Despite the high rates of recurrence/residual disease (25–52%) and complication rates of 12.5–44%, surgical excision has been historically considered the main treatment of choice for lymphatic malformations [9].

To date, there have been no prospective, randomized trials comparing the sclerotherapy agents currently in use. Different sclerosing agents have been used effectively, including doxycycline, Ethibloc, absolute alcohol, sodium tetradecyl sulphate, OK 432, and bleomycin [9–14]. Percutaneous sclerotherapy has been proven to be an effective treatment using these agents with excellent response rates ranging between 20–64%.

In addition overall complication rates are reported in a number of series to range from 2–22% and include skin ulceration requiring skin grafting, loss of vision resulting from an infected corneal ulcer, scarring, airway obstruction, and nerve damage [11, 14, 15].

The technique of sclerotherapy for lymphatic malformations is generally performed with US guidance, which provides good visualization of the lesion during access and reduces the number of puncture attempts required. Contrast is injected under fluoroscopic guidance to identify and quantify the cystic component of the lesion (Fig. 1E).

Larger macrocystic lesions are generally treated using catheter access to allow adequate drainage of the cyst contents and replacement with sclerotherapy agent. In patients with large head and neck lesions with the potential for compression, the procedure is generally performed with general anesthesia and the child remains intubated and monitored in the intensive care unit during the course of the therapy. Smaller macrocystic lesions can be treated with aspiration and sclerotherapy without catheter drainage [14]. In general, macrocystic lesions are more responsive to any sclerotherapy agent than microcystic or mixed lesions with reported response rates of 88–100% using agents, such as ethanol, doxycycline, OK432, and sodium tetradecyl sulphate [12, 14, 16].

Microcystic lesions are a challenge to treat and generally require multiple therapies. Agents, such as sodium tetradecyl foam, doxycycline (bland or foam), and bleomycin, have been directly injected into these lesions with response rates reported between 55.7 and 100% [11, 14, 17]. Response rates for OK432 in microcystic disease also have been reported as 68% compared with 90–100% with single cyst and macrocystic disease [12].

Due to the high incidence of spontaneous infection together with an increased risk on accessing the lesion, prophylactic antibiotics have been recommended immediately before sclerotherapy of lymphatic malformations [5, 10, 11].

Doxycycline Doxycycline can be injected directly into the lesion or via a catheter and is generally instilled at a concentration of 10 mg/ml for 1–3 treatments for consecutive days with an instillation time of 1–6 h. Absolute ethanol has been used in the same mechanism. Doxycycline tends to have less neurotoxic effects and local skin risks, such as blistering and skin necrosis, than ethanol [14, 15].

The dose of doxycycline can range from 150 mg to 1,000 mg depending on the size of the lesion being treated. In our own institution, we performed a review of a 7-year period (2003–2009) of 17 children (7 girls; mean age, 4 months; range, 5 days–13 months) who underwent doxycycline sclerotherapy for large congenital head and neck lymphatic malformations. There were four major immediate complications: hemolytic anemia in one infant required blood transfusion and a hypoglycemic event with metabolic acidosis in three neonates (300 mg doxycycline, all

with complete recovery). Based on these findings, our practice in neonates is to administer a maximum dose of 150 mg of doxycycline in any single session because higher doses are more likely to result in the side effects described above. Blood glucose monitoring is performed 2 hourly postprocedure in neonates, and in addition an IV dextrose solution can be administered to prevent hypoglycemia.

STS Foam Catheter-directed therapy using a combination of sodium tetradecyl sulphate foam succeeded by instillation of absolute ethanol has been reported with excellent response rates of up to 100% as determined by radiologic (US and MRI) and clinical resolution [10, 11].

Alcoholic Solution of Zein Alcoholic Solution of Zein (Ethibloc) a combination of zein (corn protein), sodium diatrizoate, and oleum in ethanol is not currently approved in the United States. Dubois et al. reported >95% regression in 64% of lesions and >50% in the remainder of both macrocystic and microcystic lesions. The most frequent complication was soft tissue leakage of the sclerotherapy agent in 70% cases without sequelae [13].

OK432 OK432 (Picibanil) is an attenuated strain of *Streptococcus pyogenes*, which was first reported by Ogita et al. in 1987 [18]. A review of the literature by Poldervaart et al. demonstrate that the best efficacy for this agent is for macrocystic lesions with excellent response rates of 88%, i.e., lesion regression >90%. Microcystic lesions, however, demonstrated excellent response rates in only 27%, good in 33%, and poor in 40%. Adverse effects were mild, such as fever, lethargy, and local inflammation manifesting as local pain, redness, and swelling and only occurred in 5–8% [16]. Severe delayed swelling can occur, leading to airway obstruction [16].

Bleomycin Bleomycin is an antineoplastic drug that has been in use since at least 1972 [19]. The biggest concern in the use of bleomycin, although rare, is pulmonary toxicity. In a study retrospective review by Blum et al. of bleomycin as a chemotherapy treatment for various tumors in a cohort of 808 patients, there was an overall 10% incidence of definite to questionable pulmonary toxicity with an overall definite rate of 1.1% resulting in death in 0.84% patients. There was a strong correlation between the risk of death from pulmonary toxicity and total doses of >450 mg; the most common dose regimen was 15 mg/m^2 twice per week. Bleomycin is generally injected into the interstitial tissues with more superficial lesions treated using a more dilute injection in the subdermal plane.

A review of the literature by Acevedo et al., including case reports and cohort studies for sclerotherapy of lymphatic malformations, described excellent response rates with bleomycin in 35.2%, good in 37.1%, fair/poor in 18.4% and no response in 11.6% [20]. Muir et al. [21] reported response rates of 82–88% for lymphatic malformations in a 15-year review of the literature from 1987–1998. In this series, complications were mild, such as fever, redness, and swelling.

Laser Therapy The role of laser therapy for lymphatic malformations is generally reserved for the associated superficial cutaneous/mucosal vesicles. In addition, microcystic lesions of the tongue and oral cavity have been treated with the carbon dioxide laser and the Nd:YAG with some success [22, 23].

Radiofrequency Ablation Grimmer et al. reported a response rate of up to 62% when radiofrequency ablation was used in 11 patients with microcystic lesions of the lips, tongue, floor of mouth, or buccal mucosa. Improvement in bleeding, pain, infection, and vesicle formation was noted [24].

Due to the high incidence of spontaneous infection together with an increased risk upon accessing the lesion, prophylactic antibiotics have been recommended immediately before sclerotherapy of lymphatic malformations [5, 10, 11].

Venous Malformations

Clinically venous malformations (VM) are present at birth, although not always apparent and tend to grow steadily in proportion to the somatic growth of the child, especially during puberty and pregnancy. Overall, these congenital lesions affect boys and girls equally with a reported incidence of 1–2 per 10,000 births and a prevalence of 1% [25].

Genetics

Most venous malformations (95%) are sporadic but a genetic TIE2 mutation has been described in some hereditary cutaneomucosal venous malformations; the most common is the glomuvenous malformation [26].

Clinical Features

Venous malformations can occur anywhere in the body but are most frequently seen in the head and neck (40%), extremities (40%), and trunk (20%). Most present as solitary lesions. They entail the whole spectrum of a solitary

relatively small, well-circumscribed, superficial lesion to large, infiltrative lesions involving multiple soft-tissue planes [5].

Superficial lesions are soft and compressible; the lesion can easily be "emptied." They are nonpulsatile and have no bruit in contrast to the arteriovenous malformations. The mass may have a light blue to deep purple color and can be associated with telangiectasias, varicosities, or ecchymosis. Lesions can increase in size with activity, Valsalva (crying in children), tourniquet, or dependent posture. Patients will typically present with swelling and pain, which is secondary to thrombosis of a portion of the lesion due to the extreme slow flow in these dilated vein-like channels. The severity of the patient's symptoms will depend on the lesion size, location, and proximity to vital structures.

Venous malformations are usually isolated findings; however, they may be associated with syndromes, such as:

- Klippel Trenaunay (KT) syndrome
- Blue Rubber Bleb Nevus syndrome (BRBN)
- Mucocutaneous Familial Venous Malformation
- Glomuvenous Malformation
- Maffucci's syndrome
- Proteus syndrome
- Bannayan—Riley—Ruvalcaba syndrome
- CLOVE/S syndrome

Elevated D-dimers have been determined to be highly specific for venous malformations and can help to distinguish VMs from LMs and slow-flow KT syndrome from high-flow Parkes-Weber syndrome [27].

Radiological Features

Ultrasound On gray-scale imaging, venous malformations can appear as hypoechoic or heterogenous lesions with anechoic structures visible in <50% of cases [28] (Fig. 2A, B). In addition the Doppler flow is generally monophasic low velocity flow, and in some cases flow is only discernible with compression and release of the lesion [29].

Computed Tomography On nonenhanced CT, venous malformations are hypoattenuating or heterogeneous depending on the degree of fatty infiltration. The presence of dystrophic calcifications within the lesion and involvement of adjacent bony structures can be well characterized.

After contrast administration, gradual peripheral enhancement is noted [29]. The relationship of these vascular lesions to muscle groups, fascial planes, tendons, and neurovascular structures can be more accurately defined with MR imaging.

Magnetic Resonance Imaging Venous malformations appear typically as isointense or hypointense lesions on T1-weighted images but could be hyperintense depending on the presence of intralesional fat. Heterogeneous intensity can occur as a result of differential signal intensity between regions of hemorrhage and thrombosis. Punctuate areas of low signal voids are seen in the presence of phleboliths.

In T2-weighted or inversion recovery sequences, VMs demonstrate high-signal intensity, and this sequence is the best sequence to determine the full extent of the lesion and its relationship to adjacent vital structures (Figs. 3A, B; 4A and B). Gradient echo sequences reveal areas of low signal corresponding to calcification or hemosiderin or thrombosis. T1-weighted postcontrast imaging demonstrates homogenous or heterogeneous enhancement, and dynamic contrast-enhanced MR imaging has increased the specificity of venous malformation diagnosis [30, 31].

MR imaging can be useful to predict the possibility of complications post sclerotherapy. Fayad et al. identified a positive correlation between the risk of skin burns post sclerotherapy and the length of skin involvement of the lesion combined with the absence of deeper tissue involvement [32].

Diagnostic Venography Contrast venography is a helpful tool in the anatomic characterization of venous malformations. It may be performed for treatment planning to confirm the patency of a normal deep venous system, especially in the lower extremity, and to fully assess the

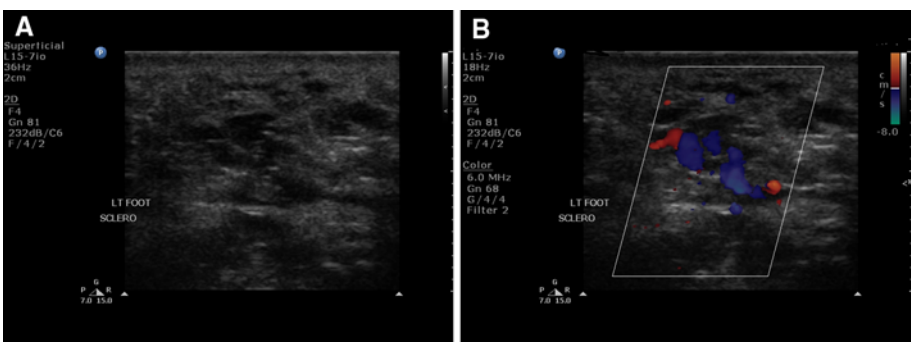

Fig. 2 Patient with venous malformation on the sole of the foot. **A** Ultrasound image shows multiple tubular hypoechoic structures. **B** Doppler image demonstrates flow in the hypoechoic structures consistent with the venous malformation

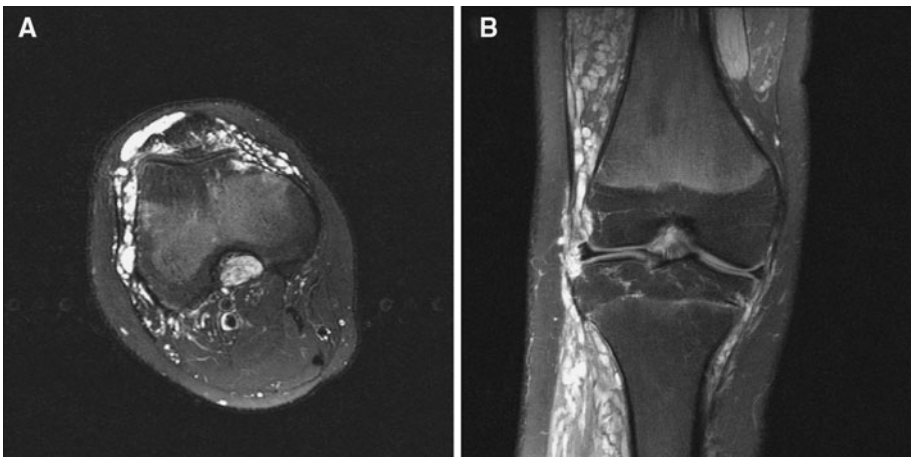

Fig. 3 Patient with venous malformation of the right knee. **A** and **B** Axial and coronal fat sat T2-weighted images of the right knee demonstrates multiple dilated venous channels in the subcutaneous and deeper soft tissues in the anteromedial aspect of the right knee

extent of the venous malformation and draining venous channels. Venography is performed once the lesion is accessed at the time of the procedure to determine the volume of contrast needed to fill the malformation before egress into draining veins. This allows the operator to determine the amount of sclerosant that can be safely injected.

Based on the pattern of venous drainage channels and their differential response to treatment and rates of complications, Dubois et al. and Puig et al. divided VMs into four types: [2, 33, 34].

- Type I: Isolated malformation without discernible venous drainage.
- Type II: Lesion draining into normal veins.
- Type II: Lesion draining into dysplastic veins.
- Type IV: Lesions consist primarily of venous ectasia.

Types I and II (to a lesser extent) respond best to sclerotherapy with higher control rates and a lower number of sessions of treatment to achieve control. Higher rates of complications are attributed to types III and IV [34].

Treatment

Sclerotherapy In general, venous malformations are treated percutaneously with sclerosing agents. The most common agents described in the literature include ethanol, sodium tetradecyl sulphate foam, Ethibloc, polidocanol and more recently bleomycin [21, 33, 35–37].

Sclerotherapy is generally performed using a percutaneous approach with the aid of US and fluoroscopic guidance (Fig. 4C and D).

More recently with the advent of cone beam CT capabilities in the IR suite multiplanar imaging can be performed to evaluate the anatomical distribution of the administered sclerotherapy agent and compare distribution to the preprocedure imaging (Fig. 4E and F) [38].

Venography may be performed at that time to delineate the size of the lesion, and the presence of outflow veins. In addition, the presence of a normal deep venous system can also be defined at that time. Fluoroscopy is used to monitor the sclerosant injection in order to decrease the risk of extravasation or undesired egress of the sclerosing agent into deep veins thereby lowering the risk of complications. A tourniquet, blood pressure cuff, or manual compression may be required to reduce egress of sclerotherapy agent into the outflow vein. An additional two needle access technique also can be used to allow decompression of the lesion through the second needle access and reduce overfilling.

Burrows et al. recommends the placement of a peripheral IV in the affected limb. This has a dual purpose in that heparinized saline can be perfused through the deep veins during sclerotherapy to reduce the risk of secondary thrombosis and confirmation of deep vein patency can be performed at the beginning and end of the sclerotherapy treatment [39]. Care should be taken to visualize the overlying skin for ischemic change. Any pallor or duskiness of the overlying tissues should signify cessation of the injection. Cold saline compresses may then help improve perfusion. Ethanol should be avoided in regions adjacent to nerves such as the facial nerve for parotid lesions or the sympathetic plexus in cervical lesions [39].

Adjunctive techniques, such as coil or tissue adhesive embolization or laser ablation, may be helpful in selected cases, such as in children in whom rapid venous outflow is demonstrated or in those individuals with large varices or persistent lateral veins, such as in KT syndrome. In addition anastomoses with the normal deep veins also can be occluded with coils or NBCA before the injection of the sclerotherapy agent [39].

There have been no prospective randomized trials for sclerotherapy agents for venous malformations. The most common agents used appear to be ethanol and sodium

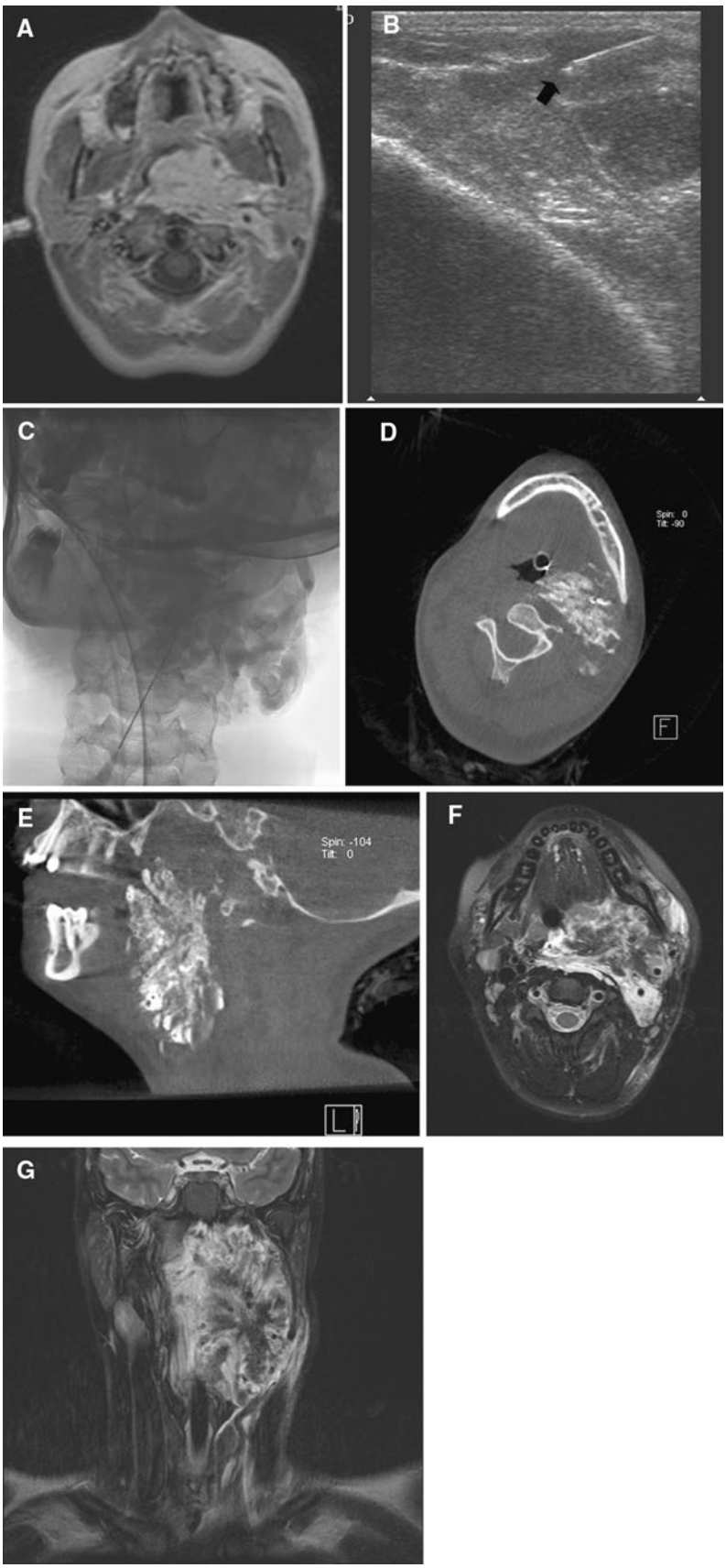

Fig. 4 Patient with venous malformation of the left neck. **A** Axial T1-weighted image post-Gadolinium demonstrates an enhancing soft-tissue lesion occupying the left retrolaryngeal area consistent with a venous malformation. There is significant airway compression. **B** Ultrasound-guided access of the lesion for sclerotherapy. Evidence of the needle advancing into one of the vascular channels (*black arrow*). **C** Fluoroscopic image during sclerotherapy demonstrates intralesional opacification with sodium tetradecyl foam. **D** and **E** Axial and sagittal plane cone beam CT image obtained after sclerotherapy demonstrates complete opacification of the lesion with the sclerosing agent and no soft-tissue extravasation. **F** and **G** Axial and coronal fat sat T2-weighted images before extubation demonstrates intralesional hypointensity consistent with thrombus formation after sclerotherapy

tetradecyl sulphate foam. Response rates of between greater than 90% have been described with 3% STS foam sclerotherapy in a small series after a mean of four treatment sessions. Complications included pain, blistering and skin erosions in this series [40]. In another series lower rates of treatment success were noted with lower extremity VM's and in particular those with an intra-articular component [41].

Ethanol is probably the most common agent used for sclerotherapy for venous malformation but also the most toxic. Response rates of up to 98% and no recurrences at 18 month follow-up have been described but after multiple treatment sessions with a mean of four procedures [35]. Predictors of response to ethanol sclerotherapy have been identified as no or delayed visualization of an outflow vein on venography, well defined margin on MRI and female gender [42].

When administering absolute ethanol the volume used is the most reliable predictor of serum ethanol level and Mason et al demonstrated that a level of >1 ml/kg may put patients at increased risk of respiratory depression, cardiac arrhythmias, seizures and rhabdomyolysis [43]. As a result 0.5 mg/kg maximum dose per single session is recommended when appropriate especially in pediatric patients.

Mason et al. also identified a positive relationship between the use of alcohol and sodium tetradecyl sulphate and abnormalities of the coagulation profile such as a decrease in platelets and fibrinogen, an increase in prothrombin time and a positive D-dimer profile. This results in a potential increase in bleeding risk in patients undergoing preoperative sclerotherapy [44].

Polidocanol 3%, which is milder and may be more suitable for superficial lesions, has been shown to have good success on MR imaging follow-up in a small series of patients [45].

Other agents such as Alcoholic Solution of Zein have been shown to have excellent response rates in 74% cases, with complete cure in 50%, using sclerotherapy alone or in conjunction with surgery [33].

Bleomycin used via a percutaneous approach in a moderate series of VM patients demonstrated complete resolution in 32% patients and significant improvement in 52% patients with no serious side effects [21].

NBCA has a limited role in the treatment of venous anomalies because it forms a hard mass and is slowly absorbed. Burrows et al. recommend its use for preoperative intra-articular venous malformation treatment diluted to 1:6 with oily contrast medium to increase distribution in the lesion [39].

Endovenous diode laser therapy has been reported in a small series of venous malformations to have a good response with 14-month follow-up [46]. Success rates of 95–100% have been reported with endovenous laser ablation of the saphenous vein [47, 48]. This has been a useful alternative therapy for treatment of the large marginal vein in Klippel–Trenaunay syndrome, although there are no reports to date in the literature.

With the advent of retrievable filters the use of prophylactic IVC filtration has been used preoperatively for vein ligation/stripping in KT patients particularly those with a history of deep venous thrombosis or thromboembolism [49]. There are several reports of successful retrievable IVC filter placement and removal in children in the literature, some as young as 2 years with caval diameters as low as 9 mm [50, 51].

The most common complications observed after sclerotherapy of venous malformations are: skin erythema, blistering, skin breakdown, bleeding, necrosis, and hemoglobinuria. Less frequently, thrombophlebitis, thromboembolism, and cardiovascular complications can occur. Hemoglobinuria occurs secondary to hemolysis and can be conservatively treated with IV fluid replacement until urinary clearance. Adequate hydration is advised before the procedure.

Different rates of complications have been associated with each type of sclerosing agent. In most of the series, the use of ethanol revealed a higher percentage of minor and major complications in approximately 12% of the sessions and 27.9% of the patients [35]. The use of sodium tetradecyl sulphate has reported lower total complication rates ranging from 0 to 9.6% [36].

In patients with extensive venous malformations in whom a low fibrinogen is present, the use of low molecular weight heparin is recommended for 2 weeks pretreatment and possible cryoprecipitate transfusion if still low on the day of the procedure. This therapy will reduce the consumptive coagulopathy of the extensive VM and potentially lower the recanalization rate [39].

High Flow Vascular Malformations

Arteriovenous Malformations

Definition

Arteriovenous malformations consist of multiple dysplastic arteries that drain or shunt directly into arterialized veins creating a vascular nidus without an intervening normal capillary network.

Genetics

AVMs are generally sporadic and genetic predisposition is unlikely. Recently, an association between atypical capillary malformations and high flow lesions, such as AVMs,

Table 1 Clinical staging system of arteriovenous malformations based on Schobinger

Stage I	Quiescence	Cutaneous blush, skin warmth, arteriovenous shunt on Doppler ultrasound
Stage II	Expansion	Darkening blush, lesion shows pulsation, thrill and bruit
Stage III	Destruction	Steal, distal ischemia, pain, dystrophic skin changes, ulceration, necrosis, soft tissue, and bony changes
Stage IV	Decompensation	High-output cardiac failure

AV fistula, and Parkes-Weber syndrome, have been described and associated with RASA-1 mutations [52]. This new association has been termed CM/AVM or capillary malformation-arteriovenous malformation.

Phosphatase and tensin homologue (PTEN) is a tumor-suppressor gene located on chromosome 10q mutations of which are associated with syndromes, such as Bannayan–Riley–Ruvalcaba syndrome and Cowden syndrome. There are numerous reports in the literature of PTEN mutations associated with cerebral and peripheral AVMs and screening is recommended [53–55].

Mutations in endoglin and activin receptor-like kinase 1 (ALK1) are associated with hereditary hemorrhagic telangiectasia (HHT), which can manifest as AVMs in the lungs, liver, gastrointestinal tract, and brain [56].

Clinical Features

AVMs can be detected at birth in 40% of the cases and most commonly occur in the extremities and pelvis [5]. These lesions are characterized by high-flow physiology and an aggressive clinical course.

AVMs are generally latent during infancy and childhood and expand during adolescence as a warm, pink patch in the skin with an underlying thrill or bruit. Later cutaneous features may include ischemic changes, ulceration, pain, and intermittent bleeding. The hormonal changes of puberty or local trauma seem to trigger expansion.

In 1990, the Schobinger clinical staging system, documenting the natural history of AVMs, was introduced at the International Workshop for the Study of Vascular Anomalies in Amsterdam (Table 1).

Radiological Features

Ultrasound High-flow AVMs are seen as lesions with multiple internal, well-defined anechoic structures. On conventional US and color Doppler, both feeding and draining vascular flow patterns can be identified. Spectral waveforms of feeding arteries indicate low peripheral resistance and dilated draining veins show pulsatile flow, suggesting the presence of direct AV communications without an intervening capillary bed. The nidus of the AVM is characterized by a "mosaic" pattern of Doppler signals with a mixture of red and blue color patterns in the anechoic structures as well as coarse "rumbling" acoustic Doppler representation.

Computed Tomography On contrast-enhanced CT, AVMs demonstrate multiple enlarged feeding arteries with rapid contrast shunting into enlarged draining veins without intervening tissue enhancement. For the purposes of radiation reduction, CT ideally should be reserved for acute imaging purposes, such as acute bleeding or adjacent structure compression, e.g., airway.

Magnetic Resonance Imaging MRI allows better assessment of the lesion with respect to adjacent structures, such as muscle and fascial planes, involvement of bony structures, and provides better detail in confined locations, such as the orbit.

AVMs demonstrate multiple hypertrophied arteries and dilated venous spaces connected by linear or focal shunting seen as low signal on T1- and T2-weighted spin echo sequences. AVMs exhibit a characteristic lack of soft tissue component or identifiable soft tissue mass. On T1- and T2-weighted sequences, vessels exhibit signal voids and increased signal is noted on gradient echo and angiographic sequences. In addition, gadolinium enhancement delineates feeding arteries and draining veins well [6].

MRA using phase-contrast and time of flight (TOF) techniques can successfully identify abnormal arteries and veins. Phase-contrast MRA is usually sufficient to identify whether a lesion is high flow and treatable by embolization. Dynamic contrast opacification of the lesion can be performed using time-resolved MR sequences, but spatial resolution tends to be compromised [6, 57].

Angiography Angiography is recommended only when the MRI/MRA examination is equivocal or if vascular intervention is considered. It is rarely used for diagnostic purposes alone.

The classic angiographic appearance of AVMs demonstrates multiple hypertrophied feeding arteries rapidly shunting into engorged dilated draining veins via a nidus. The nidus is defined as the point at which arterial structures first opacify the venous drainage (Fig. 5A, B, C). No soft-tissue enhancement is seen in AVMs, unlike vascular tumors and hemangiomas. Direct arteriovenous fistulous components and intralesional aneurysms also may be identified.

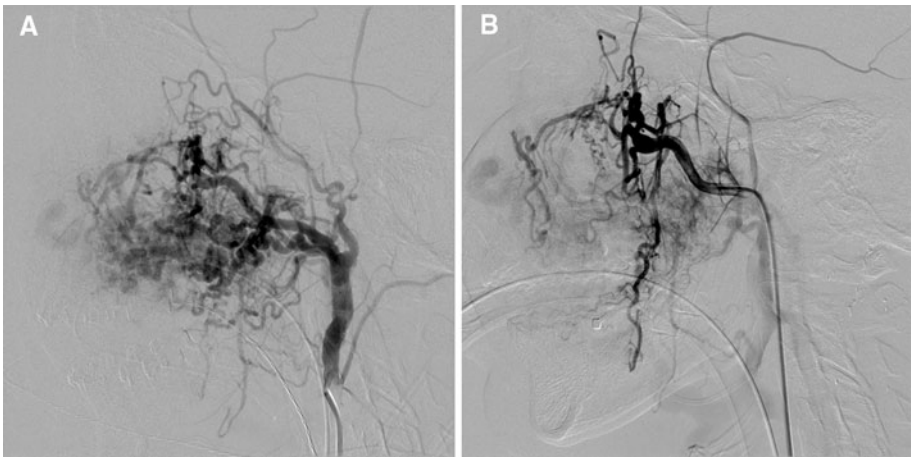

Fig. 5 Patient with arteriovenous malformation of the right cheek. **A** Lateral angiogram of right cheek arteriovenous malformation demonstrates multiple tortuous channels arising from multiple branches of the external carotid artery with early venous drainage. **B** Lateral view of right cheek arteriovenous malformation after alcohol injection demonstrates significant obliteration of the nidus

Cho et al. proposes an angiographic classification of AVMs based on nidal morphology with implications for therapeutic approach and outcomes [58].

- Type I: arteriovenous fistulae
- Type II: arteriolovenous fistulae
- Type IIIa: arteriolovenulous fistulae with nondilated fistula
- Type IIIb: arteriolovenulous fistulae with dilated fistula

Treatment

Arterial malformations are the most problematic and symptomatic of the vascular malformation group. Because of their size and location, most arterial malformations are inoperable or require extensive, potentially disfiguring, resection or even amputation. Transcatheter and percutaneous nidal embolization often is the first therapeutic option and is an effective approach that can be used as a palliative procedure or as an adjunct to a surgical resection.

Transcatheter Embolization

In the treatment of an AVM, the main goal is to obtain complete eradication of the nidus [59]. The nidus is the causative factor that leads to high-flow shunting between the arterial and the venous system. Surgical ligation or embolization of the supplying artery or arteries with mechanical agents, such as coils, can achieve only temporary control. Interruption of the proximal supplying vessels inevitably results in the development of a collateral arterial supply and an inability to access the feeding vessels for endovascular intervention. The use of particulate agents, such as polyvinyl alcohol particles (PVA), should be reserved for preoperative embolization because recanalization rates are high [60].

To achieve this goal, selective nidal access for embolic agent delivery must be obtained. In this way, the nidus is maximally exposed to the effects of the chosen agent, minimizing local and systemic complications.

To achieve more nidal-specific access, three routes can be used [5, 58].

- The sclerosant can be delivered transarterially in close proximity to the nidus, using a superselective microcatheter technique. This allows maximal dose administration to the nidus with minimal dilution and maximal protection against nontarget embolization.
- Direct percutaneous puncture into the nidus.
- Retrograde sclerosant administration via a transvenous approach, with the assistance of a balloon occlusion device [61].

Flow reduction techniques, increase concentration, and dwell time allow greater control of distribution of embolic agent within the nidus. Temporary flow arrest can be obtained by [5]:

- Use of balloon occlusion catheters at the arterial inflow or venous outflow during embolization [61].
- Tourniquets or pneumatic cuffs can be inflated upstream or downstream of the lesion if in an extremity [61].
- Permanent occlusion can be performed using coils or cyanoacrylate adhesives to collateral venous pathways. Large coils can be placed within the collateral or main venous drainage to assist flow reduction [61].

Whatever technique is used, injection of the embolization agent is preceded by contrast injection into the vascular distribution to be embolized to determine the volume and flow rate of the malformation.

Ethanol is the embolization agent most frequently used and tends to be the most effective. In a large patient series,

success rates of up to 68% have been published with multiple treatment sessions required and complications noted in 52% patients (major in 12% patients) [62]. Response rates of up to 82% have been reported with extremity bone AVMS with a similar complication profile [63]. Based on the classification by Cho et al., ethanol embolization was most effective with type II and type IIIb AVMs. A combination of transarterial, transvenous, and percutaneous approaches was performed with the transarterial approach used exclusively in type IIIa. Type II lesions were more effectively treated with the transvenous and direct puncture techniques in this series [58] (Figs. 6, 7).

The maximum recommended volume is 1.0 ml/kg, but Mason et al. recommend that this should probably be reduced to 0.5 ml/kg due to the overall increased serum levels of alcohol recorded posttreatment of vascular anomalies and potential negative systemic effects [43]. Rapid systemic mixing of alcohol and blood, especially in large volumes (>1 ml/kg), can result in pulmonary vasospasm, cardiac arrhythmia, and electromechanical disassociation. Coagulation disturbances also have been described with higher dose ethanol use [43, 44]. In patients with large AVMs, pulmonary artery and peripheral arterial monitoring has been recommended [64]. Mild increases in pulmonary and peripheral artery pressure have been demonstrated with ethanol injection even under general anesthesia, concluded to be due to a pain response causing sympathetic stimulation [65]. Shin et al., in a retrospective review of absolute ethanol use in soft tissue AVMs, concluded that dose limitations of <0.5–1 mg/kg and a maximum dose per injection of 10 ml does not cause an overall increase in pulmonary artery pressures in multisession therapies [62].

The most common complications reported with ethanol include skin and peripheral nerve injury and less common complications related to systemic effects are cardiopulmonary collapse, renal failure, and adjacent or end organ damage [58, 62–64]. Use of ethanol in superficial

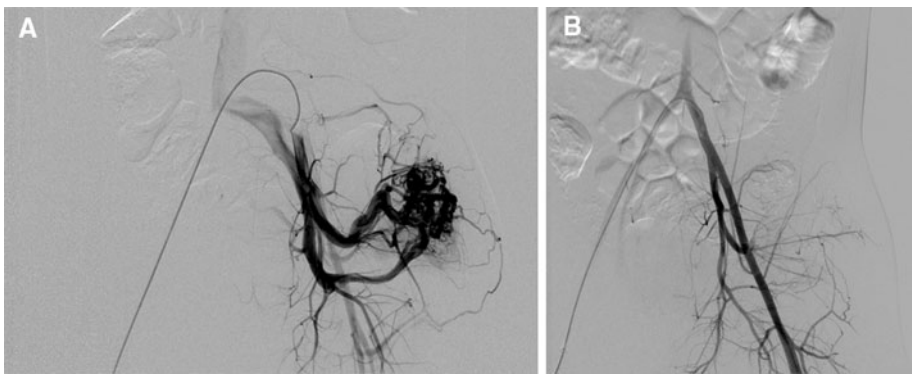

Fig. 6 Patient with arteriovenous malformation of the left thigh. **A** AP angiogram of left common iliac artery demonstrates an arteriovenous malformation arising from gluteal branches of the left internal iliac artery with an arterial nidus and early venous drainage. **B** Subtraction angiography after glue embolization confirms nonopacification of the arterial nidus and early draining veins of the arteriovenous malformation

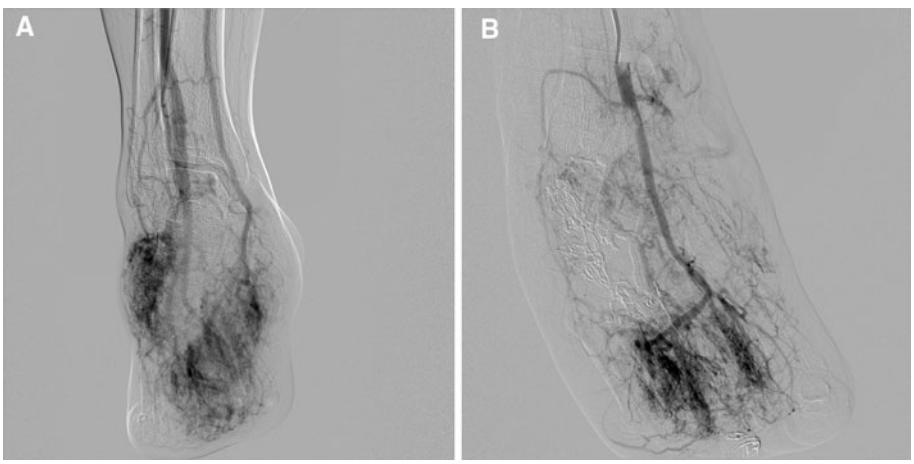

Fig. 7 Patient with grade III arteriovenous malformations of the right foot with clinical evidence of ulceration. **A** AP angiogram of the right foot demonstrates a diffuse AVM of the right foot with early venous drainage. **B** After staged Onyx embolization, there is significant reduction in nidal opacification on the lateral aspect of the foot at the site of known ulceration. After this treatment, the toes have been preserved and the ulcer subsequently healed

cutaneous lesions can result in skin depigmentation, necrosis, nerve damage, and altered sensation and in extreme circumstances skin sloughing requiring skin grafting. Care should be taken when using ethanol in regions adjacent to nerves, such as the facial nerve, although use in this area is not contraindicated.

Other embolic materials include N-Butyl-2-cyonoacrylate (NBCA) (Histoacryl; B. Braun, Melsungen, Germany) and ethylene-vinyl alcohol (Onyx, Liquid embolic system; Micro Therapeutics, Inc, Irvine, CA) [66–69]. The majority of the published literature describes the use of these agents for embolization of cerebral AVMs, but there are scant reports of their use in peripheral high flow lesions [70–73].

N-Butyl-2-cyonoacrylate belongs to the group of cyanoacrylates or adhesives glues. When the cyanoacrylates are exposed to anions, such as the hydroxyl groups present in the blood, they polymerize, causing histotoxicity and an acute fibrotic inflammatory reaction that progresses over several weeks as a foreign body giant cell granulomatous reaction. The disadvantages of this material include, recanalization of the AVM nidus [74], inadvertent pulmonary embolism [75], catheter adhesion [70], and formation of subcutaneous or intramuscular glue masses that can subsequently be a source of infection or tissue erosion or muscular dysfunction [64]. In a large series of cerebral AVM embolizations, complications were identified with NBCA in 14% patients, and 65% of those complications were significant. Risk factors identified included small and large lesions, complex lesions, deep venous drainage, and location in the eloquent cortex [68]. NBCA may have role in preoperative embolization of lesions for resection but in infiltrating-type AVMs surgical resection is associated with a high morbidity [59].

Ethylene vinyl alcohol copolymer (Onyx) is a nonadhesive liquid embolic agent. It is dissolved in dimethyl sulfoxide (DMSO) and micronized tantalum powder is added for radiographic visualization. The viscosity of this mixture is low, decreasing the risk of catheter adhesion. On contact with blood DMSO diffuses rapidly, leaving the EVAL–metrizamide mixture as a spongy mass that acts as a purely mechanical obstruction, without adherence to the vascular wall [67]. Care must be taken when surgical resection is undertaken after Onyx embolization to avoid the use of monopolar diathermy due to the risk of combustion of the Onyx material [76]. The published literature reports rates for cerebral AVM lesion obliteration up to 24.4%, average lesion volume reduction of 70% with 3.8% morbidity and 2.5% mortality [68, 69]. In a small pediatric series of cerebral AVMs embolized with Onyx 18, average lesion size reduction was noted to be 60% with low transient morbidity [77].

Conclusions

Vascular malformations are highly complex lesions that can pose a challenge both diagnostically and therapeutically and require a highly specialized multidisciplinary team approach. The genetics of vascular malformations continues to evolve, providing insight into the potential for some lesions to be inherited, thereby requiring families to have genetic counseling. Interventional radiology can play a vital role in vascular malformation therapy as the sole therapy of choice or as an adjunct to surgery.

There are currently a wide variety of embolosclerotherapy agents being used to treat vascular malformations, but to date there are no published, randomized, control trials comparing the therapeutic efficacy of these agents. Further work needs to be accomplished in this area to streamline the future therapeutic pathway for each type of vascular malformation.

Conflict of interest The authors declare that they have no conflict of interest.

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