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Diagnosis and Management of Extracranial Vascular Malformations in Children: Arteriovenous Malformations, Venous Malformations, and Lymphatic Malformations

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Introduction

Vascular malformations are congenital abnormalities resulting from dysregulated vascular development during embryogenesis.[1-3] Importantly, vascular malformations, as described by the International Society for the Study of Vascular Anomalies (ISSVA) classification,[4] are distinct entities from vascular tumors, such as hemangiomas.

Vascular malformations are typically classified as either high-flow or low-flow malformations. Congenital high-flow vascular malformations consist of arteriovenous malformations (AVMs) and arteriovenous fistulas. Congenital low-flow vascular malformations consist of venous malformations (VMs) and lymphatic malformations (LMs). In recent years, both percutaneous and endovascular procedures performed by pediatric interventional radiologists (IRs) have become first-line therapy for children suffering from these lesions. As such, it is essential for pediatric IRs to possess foundational knowledge about the etiology, clinical presentation, diagnostic work-up, clinical management, and procedural management of patients with vascular malformations. In addition to the technical aspects of therapeutic interventions, a firm grasp on a wide array of medications (predominantly acting as sclerosants) is necessary to optimally treat different malformations in varying anatomic locations.

The purpose of this manuscript is to describe the typical clinical presentation and therapeutic management of patients with congenital extracranial vascular malformations, with a focus on the role of interventional radiology in the care of these patients.

High-Flow Vascular Malformations

AVMs

AVMs are congenital lesions (Figs. 1 and 2) that involve dysplastic arteries with abnormal connection to draining veins that bypass normal capillary beds.[5,6] Less than half of these lesions are noticeable at birth; however, they grow with the child over time and often present in adolescence. Most commonly, AVMs present with a pulsatile mass, pain, ulceration, bone edema, and/or arterial steal symptoms. AVMs most commonly involve the extremities, pelvis, and head/neck.[7-9]

These lesions have traditionally been clinically classified via the Schobinger clinical classification (Table 1).[7] However, an angiographic classification has more recently been developed by Park et al (Table 2).[5] Regardless of classification, AVMs are nearly universally challenging to treat. In fact, total cure is rarely achieved in these patients, and discussion of symptom palliation is necessary prior to initiation of treatment.

Historically, surgical resection was the only available treatment options for these patients. However, due to the high morbidity from surgery and the very high rate of recurrence, surgery is now rarely pursued as first-line treatment.[1] Instead, angiography and endovascular therapy have become the gold standard for diagnosis, classification, and treatment.

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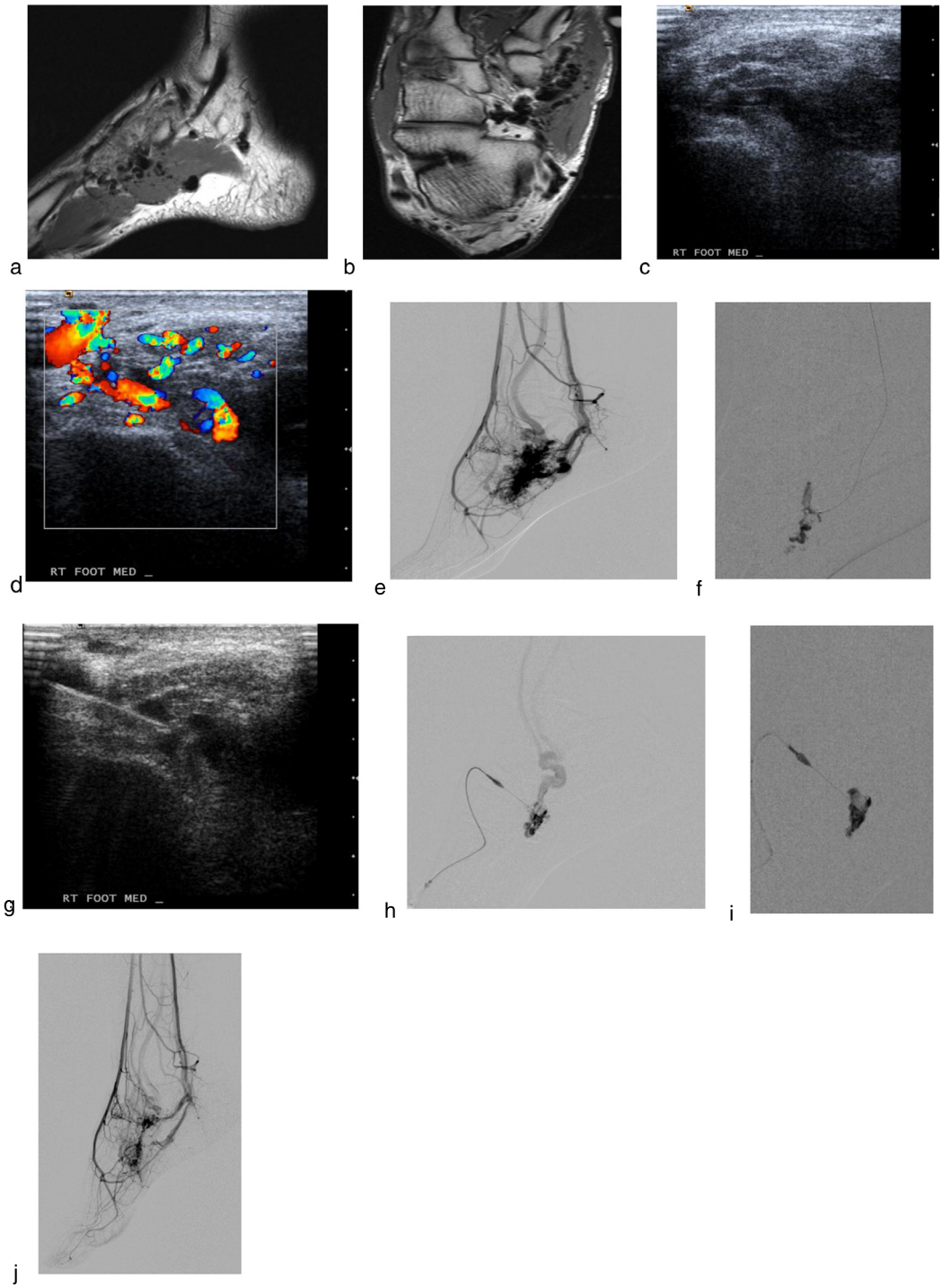

Figure 1 17-year-old male with medial right foot AVM. Transarterial glue embolization was performed via a microcatheter, and percutaneous glue embolization of venous outflow via direct puncture was also performed. Sagittal (a) and axial (b) magnetic resonance T1 images demonstrate enlarged, tortuous vessels in the medial aspect of the right foot. Grayscale (c) and color-flow (d) ultrasound images of the AVM. Digital subtraction angiography of the ankle and foot (e) shows increased vascularity in the midfoot, with nidus and early contrast opacification of a large draining vein. Transarterial glue embolization was performed via a microcatheter (f). Grayscale ultrasound shows percutaneous needle access of a large draining vein in the foot (g). Digital subtraction intralesional venography via the percutaneous access (h) shows a portion of the nidus and draining veins. Glue embolization was performed through this access using negative roadmap fluoroscopy (i). Postembolization digital subtraction angiography of the left ankle and foot (j) shows decreased vascularity of the AVM with decreased visualization of the nidus and early draining veins.

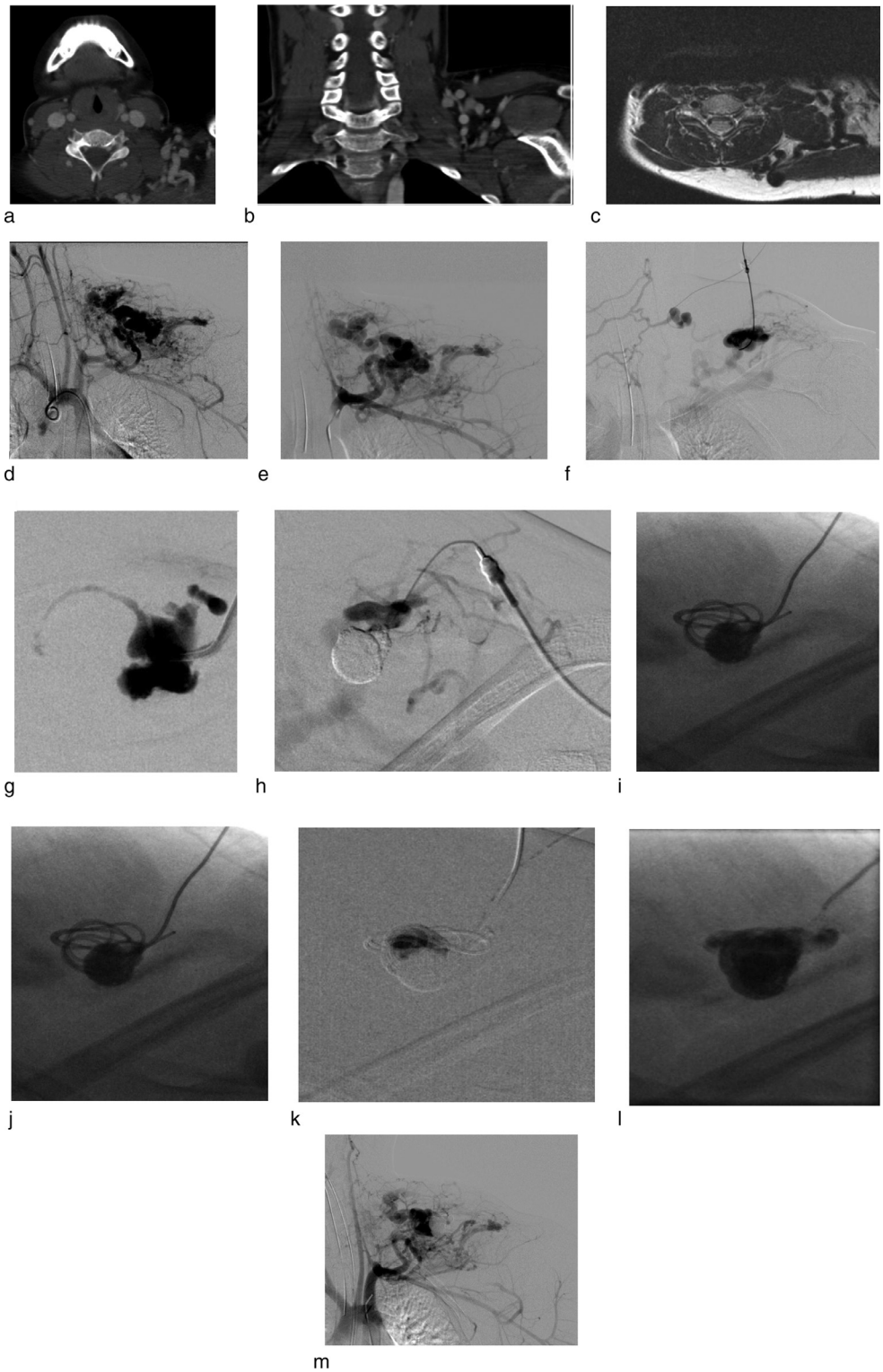

Figure 2 13-year-old male with left supraclavicular AVM. Percutaneous glue embolization of venous outflow was performed via direct injection and also using temporary wire placement as a scaffold for glue. CTA axial (a) and coronal (b) images and axial T1 magnetic resonance (c) image demonstrate enlarged and tortuous vessels in the left supraclavicular region, compatible with AVM. Digital subtraction aortogram (d) and left subclavian arteriogram (e) show left supraclavicular AVM with numerous enlarged draining veins. Ultrasound-guided percutaneous needle access (not shown) of 2 suprascapular draining veins was obtained using 21-gauge EchoTip needles. The needles were exchanged over 0.018 inch nitinol wires for 4 French micropuncture sheaths. Digital subtraction venography via access 1 (f) was performed, followed by glue embolization under negative roadmap fluoroscopic technique (g). Digital subtraction venography via access 2 (h) was performed, followed by temporary deployment of a decored 0.035 inch Bentson wire (i) into the draining vein to serve as a scaffold for glue embolization (j). The wire was then removed (k). Postembolization digital subtraction left subclavian arteriogram showed decreased vascularity of the AVM, with decreased opacification of the nidus and draining veins.

Table 1 Schobinger Clinical Classification of AVMs

Stage	Clinical Findings
Stage 1 (quiescence)	Skin warmth, discoloration
Stage 2 (expansion)	Enlargement, pulsation, bruit
Stage 3 (destruction)	Pain, ulceration, bleeding
Stage 4 (decompensation)	High-output cardiac failure due to volume overload

Table 2 Anatomic AVM Classification Proposed by Park Et Al

Type	Anatomic Description
Type I	An AVM with no more than 3 separate arteries shunting to a single vein
Type II	An AVM with multiple arterioles shunting into a single draining vein
Type IIIa	Multiple small arteriovenous fistulas
Type IIIb	Multiple hypertrophied and dilated arteriovenous fistulas that appear as a complex network

Multiple modalities can be utilized to diagnose AVMs. Ultrasound shows multiple hypoechoic channels with low-resistance arterial waveform throughout with no associated soft-tissue mass. MRI with time-resolved gradient echo imaging will show a rapidly enhancing nidus with early draining veins. The veins draining extremity AVMs are typically asymmetrically enlarged compared to the same veins in the contralateral limbs. On physical exam, if the AVM is superficial enough, a palpable thrill is often present. Additional physical exam findings sometimes present include a palpable mass, overlying skin discoloration (often red/purple), limb overgrowth (either syndromic or from hyperemia), and distal ischemia (if steal is present). AVMs are sometimes, but not always, painful when palpated. Superficial AVMs, particularly those that involve mucosa and surfaces of the head/neck (lip, oral mucosa, external auditory canal, etc.), can present with bleeding. Of note, overgrowth syndromes associated with AVMs are further detailed elsewhere in this issue.[10]

Although there have been a number of recent advances related to the discovery of genetic mutations associated with AVMs,[6,11] a causative mutation is yet to be discovered, and no medical therapy is currently available. Consequently, catheter-directed endovascular therapy remains the most viable and efficacious option for these patients.

Angiographically, the nidus of the AVM is the point at which abnormal arteries connect with draining veins (often multiple). In the majority of cases, AVMs have many arterial "feeders" and many draining veins. Importantly, AVMs do not have an associated enhancing mass, such as what is seen in vascular tumors. This is an important distinguishing characteristic. When pursuing endovascular embolization from an arterial approach, selective microcatheter technique is nearly universally required and recommended. The authors recommend use of very small microcatheters (often 1.7F or smaller) to position the catheter tip within (or just beyond) the nidus.

Dehydrated alcohol (EtOH) is the most commonly used embolic for treatment of AVMs.[5] Alcohol is cytotoxic and causes near-immediate thrombosis and death of endothelial cells leading to fibrinoid necrosis.[12] The advantage of EtOH as compared to other embolics, in the setting of AVMs, is thought to be due to its ability to abolish endothelial excretion of angiogenic growth factors by destroying endothelial cells. This is in contradistinction with other embolics, which instead induce a state of "ischemia" in the endothelial cells which theoretically leads to increased excretion of angiogenic growth factors. In fact, multiple reports have shown aggressive growth and worsening symptoms following proximal embolization of arterial feeders in AVMs with noncytotoxic embolics, such as coils.[1,7,13]

Prior to embolizing with EtOH, test injections are performed with contrast to assess volume and rate of injection. Care is taken to angiographically assess for opacification of normal blood vessels and other risks for nontarget embolization. Once deemed safe, EtOH is injected in a similar volume and rate of the previous "simulated" contrast injection. More rapid injection of EtOH leads to increase endothelial death with less thrombosis, whereas slower injections promote more thrombosis with less endothelial necrosis.[12] Multiple injections are commonly performed when treating AVMs. The maximum dose of EtOH per session has been reported between 0.5 mL/kg and 1 mL/kg[1,5,13]; however, the authors prefer to conservatively never exceed 0.5 mL/kg per session. Additionally, a single injection of EtOH should not exceed 0.1 mL/kg. These dose limits are to help prevent EtOH toxicity and severe pulmonary edema, which had been previously reported prior to these dose limits being widely adopted.[13] In fact, prior studies have shown that adhering to these dose limits does not significantly increase pulmonary arterial pressures during multiple treatment sessions.[8,14] Importantly, EtOH causes moderate to severe pain. Thus, the authors recommend that these procedures be performed under general anesthesia.

There are a number of different approaches that can be utilized when treating AVMs. As described, the transarterial route is commonly used to access the AVM nidus. Direct puncture into the nidus is also feasible for superficial AVMs. Additionally, retrograde transvenous access via the draining veins can also be utilized for access and for occlusion of venous outflow.[1,13] Any of these methods in isolation or combination can be used based on the morphology of the AVM. Additionally, flow modulation of embolic can be achieved with occlusion balloons and/or micro-occlusion balloons either in the arterial "feeders" or venous outflow. However, flow modulation can be very challenging in complex AVMs with multiple arterial "feeders" and venous outflow routes. Additionally, achieving stasis with EtOH with flow modulation, due to its lack of viscosity, increases the risk of extravascular and parenchymal structures adjacent to the AVM. The rate at which this type of damage occurs under various degrees of flow modulation is unknown.

There are a number of complications that can occur when using EtOH to embolize AVMs. The complications are not uncommon, either. In fact, multiple authors cite greater than 10% major complication rate when using EtOH as an

embolic agent for vascular malformations.[14,15] These complications include permanent neuropathy, compartment syndrome, arterial thrombosis, and permanent skin injury. When dose limits are not adhered to, systemic complications, such as pulmonary edema and renal failure, have been reported.[8] These are important considerations to discuss with patients during initial clinical encounters and the consent process.

Multiple reports have described use of alternative embolics when treating AVMs. The 2 most common alternative embolics used for AVM embolization are *n*-butyl-2-cyanoacrylate (*n*-BCA glue; DePuy Synthes, Raynham, MA) and ethylene vinyl alcohol suspended in dimethyl sulfoxide.[2,16] The latter embolic is otherwise known as the Onyx liquid embolic system (Medtronic, Dublin, Ireland). The majority of the existing literature related to these alternative embolics is related to embolization of intracranial CNS AVMs, although a few case series describing their use in extracranial AVMs exist.[17] Of note, there is currently no FDA indication for use of Onyx for peripheral AVMs. When using liquid embolics for treatment of AVMs, it is important for the operator to consider subsequent care for the patient. For example, superficial AVMs will be hard and palpable following embolization with glue or Onyx. Superficial lesions embolized with Onyx may show skin discoloration/darkening. Also, if no surgical resection is planned, the lack of endothelial destruction—either from incomplete penetration into the nidus or from endothelial ischemia, not death (as Onyx causes mechanical obstruction without adherence to the vascular wall)—may lead to aggressive growth and/or likely recurrence.[8,13] Prior reports have shown excellent initial response to Onyx embolization. However recurrence rates were >30%.[7,8,18] Additionally, glue has been shown to be naturally resorbed by the body in prior reports, which may lead to increased risk of nidal recanalization.[13,18] Thus, for extracranial AVMs, at the authors' institutions, use of transarterial glue and Onyx are typically reserved for embolization prior to surgical resection, except in unique circumstances. Overall, however, there is little evidence to support or refute the efficacy of these embolics for treatment of AVMs.

Although further comprehensive description of the use of glue and Onyx is beyond the scope of this article, 2 important points should be considered when using Onyx: (1) Onyx can only be used with dimethyl sulfoxide compatible catheters, and (2) when pursuing surgical resection following Onyx embolization, surgeons should be warned that contact of unipolar cautery with Onyx will cause sparking and possible combustion. This phenomenon does not occur with bipolar cautery.

More recently, interstitial (eg, extravascular) bleomycin injection has been shown to reduce the size of Schobinger stage I and II extracranial AVMs.[7] Although little is understood about the mechanism of interstitial instillation of bleomycin, this suggests that vascular remodeling stemming from pericytes may play a role in the growth of AVMs.[19] More research is necessary to understand the mechanism of action and efficacy of interstitial bleomycin in treatment of extracranial AVMs. See discussion below on low-flow vascular malformations for further description of bleomycin as a sclerosing agent.

Beyond procedural specifics, comprehensive clinical management of patients with AVMs is paramount for successful treatment. It is important to set realistic expectations at the initial clinic encounter. Importantly, IRs should be clear with patients that: (1) complete cure is unlikely, (2) the goal is to palliate and relieve clinical symptoms, and (3) multiple treatments will likely be required to achieve clinical improvement. At the authors' institutions, initial treatment sessions are ideally pursued 4-6 weeks apart until clinical improvement is achieved. Clinical follow-up, at least annually, should occur to assess for need for additional embolization procedures.

Arteriovenous Fistulas

True congenital (not iatrogenic) extracranial arteriovenous fistulas are quite rare, and consist of a direct connection between a single artery and a single dominant draining vein, with bypass of the capillary bed. Although the collective experience with these entities is limited, successful embolization is typically achieved with mechanical occlusion using coils and/or plugs.[1] These lesions tend to be much easier to treat and manage than congenital AVMs.

Low-Flow Vascular Malformations

VMs

VMs are congenital lesions (Figs. 3 and 4) that result from somatic mutations leading to dysplastic development of veins.[3,20,21] This dysplasia results in venous stasis, engorgement, and pain. These lesions are the most common type of vascular malformation, are present at birth, demonstrate growth commensurate with the young child, and are hormonally responsive tending to grow more rapidly during puberty and pregnancy.[2,3] This natural history is important, as VMs are often misdiagnosed as hemangiomas of infancy (HOIs). However, HOIs are not present at birth, but rather appear shortly after birth and then grow rapidly during the first few months of life before commonly involuting.[22,23] HOIs are true vascular tumors with hyperchromatic/hypermitotic nuclei, which differs from VMs.[22]

VMs can be present anywhere in the body, and are most common in the head/neck and extremities. They are commonly trans-spatial in the head/neck, and can be intraosseous and intra-articular in the extremities.[21] Although commonly localized, VMs can also be diffuse and involve entire limbs. Of note, VMs in the setting of overgrowth syndromes are discussed elsewhere in this issue.[10] Thus, this section will focus on typical presentation, diagnosis, and treatment of isolated, nonsyndromic VMs.

Clinical Presentation and Work-Up of VMs

Patients with VMs most commonly present with pain and swelling, although thrombophlebitis and coagulopathies are also commonly seen.[3,24] A typical history is one in which the patient describes worsening pain and swelling either at the

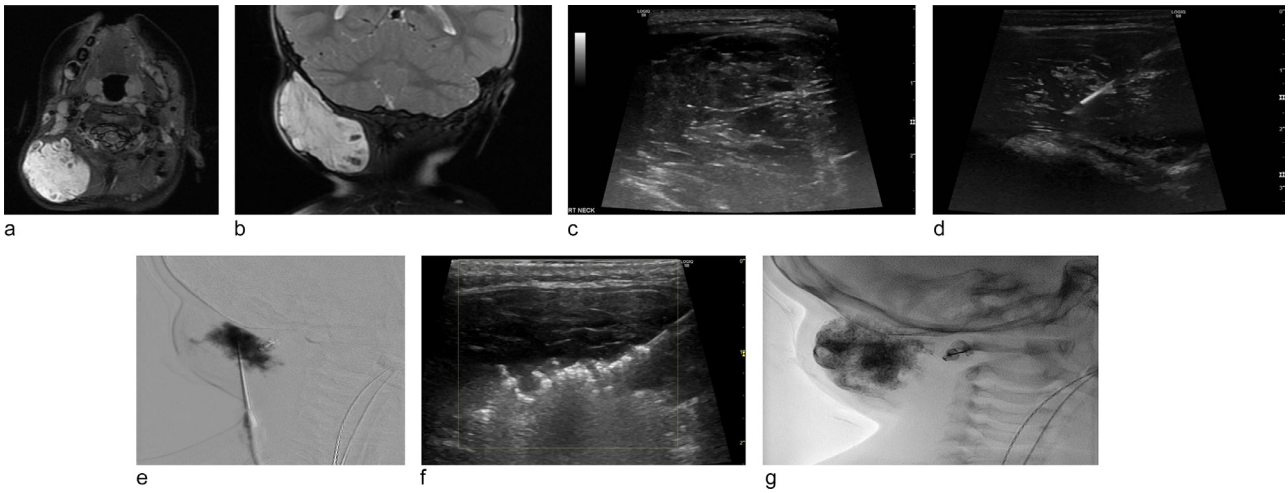

Figure 3 3-year-old female with VM of the right neck. Sclerotherapy was performed with STS foam. Axial STIR (a) and coronal T2 (b) magnetic resonance images of the right neck show lobular increased signal of the VM with scattered hypointense foci compatible with phleboliths. Grayscale ultrasound demonstrates dilated venous channels within the malformation (c) and ultrasound-guided placement of a 21-gauge EchoTip needle into one of these channels (d). Intralesional venography using negative roadmap fluoroscopy (e) shows opacification of a portion of the VM without evidence of extravasation or visualization of large draining veins. Grayscale ultrasound shows echogenic foam being injected into the malformation (f). Postsclerotherapy spot fluoroscopic image (g) demonstrates contrast opacification of the treated lesion.

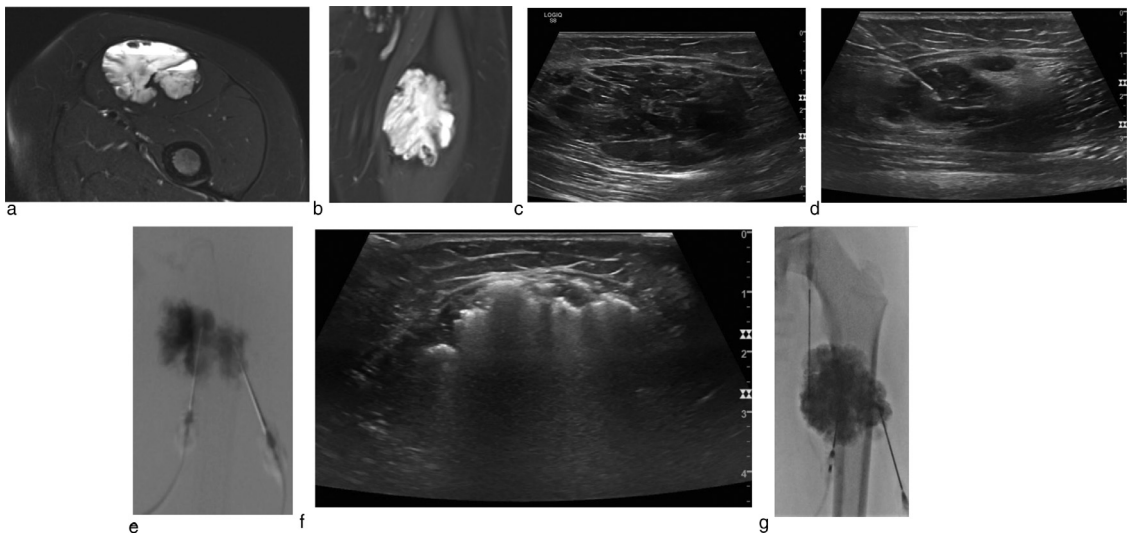

Figure 4 5-year-old female with intramuscular VM of the left thigh. Sclerotherapy was performed with STS foam. Axial STIR (a) and coronal FSEIR (b) magnetic resonance images of the left thigh show increased signal of the intramuscular VM. Note the fluid levels on the axial image as well as scattered hypointense foci compatible with phleboliths. Grayscale ultrasound demonstrates dilated venous channels within the malformation (c) and ultrasound-guided placement of a 21-gauge EchoTip needle into one of these channels (d). Intralesional venography via this needle and another needle placed more laterally within the malformation (placement not shown) using negative roadmap fluoroscopy (e) shows opacification of the malformation without evidence of extravasation or visualization of large draining veins. Postsclerotherapy grayscale ultrasound shows echogenic foam distributed throughout the malformation (f). Postsclerotherapy spot fluoroscopic image (g) demonstrates contrast opacification of the treated lesion. (Note that a third access into the malformation had been obtained to facilitate treatment of the entire lesion.)

end of the day or after vigorous activity. On physical exam, these lesions are soft, compressible, and often associated with blue/purplish discoloration of the skin.[25] Unless thrombophlebitis is present, these lesions are typically not painful to palpation. When thrombophlebitis and/or venous engorgement is/are present, the overlying skin may be warm/red and painful to touch. When present, phleboliths may also be palpable. On ultrasound, VMs have innumerable, dysmorphic compressible channels without an associated soft tissue mass. In many instances, flow through these lesions is so slow that color Doppler interrogation may not show color signal unless compressed. Phleboliths may be

visible on radiographs. On MRI, VMs are hyperintense on T2, irregular in shape, often with dark T2 phleboliths present within the malformation.[26] Following contrast, these lesions enhance inhomogeneously due to the extremely slow flow in some of these lesions and depending on how delayed the postcontrast images are obtained. In certain instances, incomplete enhancement of the mass may indicate a lymphatic component, such as that seen in true, mixed veno-LMs. However, in the authors' collective experience, true, mixed veno-LMs are very rare. Importantly, evaluation of the deep venous system is essential on preprocedure imaging. According to prior reports, up to 8% of people will not have normal deep veins,[27,28] although this reported incidence is higher than that observed by the authors. In certain instances, if venous drainage from an extremity flows through a VM and there is no deep venous system, embolization/sclerotherapy of the VM may be contraindicated so as to avoid venous hypertension and post-thrombotic syndrome.

Additionally, the initial work-up for patients with VMs should include coagulation profile, including d-dimer and fibrinogen levels. In a subset of patients, increased d-dimer and decreased fibrinogen may be observed—an entity referred to as localized intravascular coagulation in the setting of VMs—which may warrant anticoagulation managed by a pediatric hematologist.[29]

Procedural Technique and Outcomes for VMs

Percutaneous treatment via embolization/sclerotherapy has emerged as first-line treatment for VMs. Previously, many of these lesions were surgically excised. But as with AVMs (discussed above), the high rate of recurrence in combination with high morbidity in many instances, has rendered surgical excision a secondary therapeutic option. EtOH was historically the most common sclerosant used to treat VMs percutaneously. However, high complication rates, severe pain, and volume limitations (see discussion about EtOH dose above) have led to markedly decreased use in VMs (despite ardent proponents for its continued use).[15] Instead, Sotradecol (sodium tetradecyl sulfate; Mylan Pharma Group Ltd, Casla, Ireland), an anionic surfactant detergent, has emerged as the most widely used embolic/sclerosant for treatment of VMs.[2,3,24,30] Sotradecol (STS) comes in both 3% and 1% solutions, although use of the 1% solution is limited to very superficial VMs, with the 3% solution being more commonly used. Prior authors have suggested limiting 3% STS dosage to 20 mL or 0.5 mL/kg per session.[3]

Technically, ultrasound is used to percutaneously access the channels of the VM with either an angiocatheter, 21-G needle, or butterfly needle (23-G or smaller). Diagnostic venography is performed to assess for venous outflow and confirm intravascular location. Based on the outflow pattern, a number of maneuvers can be performed to decrease outflow and keep the embolic foam within the malformation, as egress of foam into normal veins increases the risk of DVT. These maneuvers include external compression, use of a tourniquet, and/or use of an occlusion balloon. Additionally, slow injection of STS embolic foam often occludes venous outflow channels, thus mitigating the need for additional outflow occlusion maneuvers. Once outflow is sufficiently mitigated, STS is injected under fluoroscopic roadmapping guidance and/or ultrasound guidance as a foam solution. The most commonly reported composition is 3 parts air, 2 parts STS, and 1 part ethiodized oil.[31] However, other mixtures/configurations of STS foam have also been used.[31] Additionally, some operators have reported using albumin or contrast rather than ethiodized oil.[1,2] However, these do not create a foam that is as stable as that made with ethiodized oil, thus STS falls more quickly out of solution. STS is injected as a foam in order to slow transit through the malformation as well as increase contact with the endothelium in the nondependent portion of the dysmorphic veins. Importantly, STS will not sufficiently treat VMs if it does not physically contact endothelial cells. Often, multiple access sites are necessary to sufficiently fill the VM with adequate sclerosant. Care is taken to mitigate outflow until STS has caused sufficient thrombosis so as to keep sclerosant from leaching into the normal, systemic venous system. STS has been associated with a number of complications. Skin injury is the most common and is nearly always self-limited.[1,3] Other reported complications include DVT, neuropathy, hemoglobinuria, and fever—although these are relatively rare.[1] Reported complication and complication rates in the literature are largely poorly defined with wide ranges. However, in the authors' experience, transient skin injury, such as skin blisters, occurs in approximately 3%-5% of VMs when treated with STS. Other complications, listed above, are exceedingly rare (<0.5%) and depend largely on the location and size of the VM.

Multiple treatment sessions are often required when using STS as the primary sclerosant for treatment of VMs. Treatments are spaced 6-8 weeks apart and are performed until symptoms improve and are no longer burdensome. Despite the need for multiple treatments, a recent analysis suggested that sclerotherapy for VMs was cost-effective for improving quality-of-life metrics for patients with moderate to severe pain receiving 1-3 treatments.[32] However, this study utilized EtOH and polidocanol as sclerosants and only enrolled 31 patients over a 15-month span. This study is also limited in that it did not show a statistically significant improvement in quality-of-life at 12-month follow-up and no patients had greater than 12-month follow-up. Consequently, the evidence from this study is limited in its applicability to current practice. Ultimately, very little evidence exists that describes the efficacy of sclerotherapy for VMs as it relates to quality of life.[33] More research is sorely needed in this regard.

Similarly, the literature assessing overall success rate of percutaneous sclerotherapy is limited to predominantly single-center cohorts with highly variable methods for reporting complications and procedural techniques. Even the definition of "success" has been irregularly reported and remains highly debated at international meetings. In the authors' opinion, "success" is defined clinically (not by imaging) and is the point at which symptoms have ceased or are so minimal so as to not impose any significant morbidity on the patient. By this definition, the authors report success rates of 90%-95% at their respective institutions. Clearly, multi-institutional studies are necessary as well as clearer definitions of outcome measures. Fortunately, multiple efforts are underway to improve the research around treatment of VMs and other vascular anomalies.[34]

Patients should be followed-up by an IR in clinic approximately 6-8 weeks after their final sclerotherapy so as to assess

effectiveness of treatment. Regardless of symptom cessation, patients should be reminded that VMs often recur during puberty and pregnancy. If symptoms recur, new baseline imaging can be obtained, and sclerotherapy can be reattempted.

Numerous other embolics (other than STS and EtOH) have also been employed in the treatment of VMs. Polidocanol, a foam sclerosant, has been used by other operators in a similar manner to that of STS. However, a recent histologic analysis demonstrated that STS induced greater endothelial cell damage and media thickness injury than polidocanol, leading to lower risk of recanalization of treated vessels.[30] In fact, polidocanol showed no media thickness damage in this analysis. Thus, despite polidocanol making a more stable foam (and potentially remaining in the vessel longer than STS foam), the increased cellular damage induced by STS is advantageous and preferred.

Bleomycin, a cytostatic antibiotic derivative commonly used as a chemotherapeutic, has more recently emerged as a therapeutic embolic/sclerosant for VMs, specifically in situations in which limiting inflammation is warranted, such as when treating VMs near the orbit or airway.[34] The exact mechanism of sclerosis induced by bleomycin has not been clearly elucidated. Recent evidence has shown the bleomycin disrupts endothelial cross-linkage junction cells as well as induces endothelial mesenchymal transition, leading to fibroblast-like transformation in both VMs and LMs.[35] When used in VMs, many operators create a "bleo-foam" solution in an effort to slow transit time of bleomycin through the VM, although little is known about the amount of time needed for bleomycin to induce sclerosis of VM endothelial cells. The authors create "bleo-foam" by reconstituting 15U of bleomycin in 2.5 mL of normal saline, and then mixing with 2.5 mL of 25% albumin and 5 mL of air. When this foam is used, operators can monitor intravascular dispersion sonographically, or add a small volume of contrast if fluoroscopic dispersion is preferred. The most feared risk of bleomycin is pulmonary fibrosis. Thus, the maximum dose for each session is 15 U or 0.5-1 U/kg.[3,35] Lifetime dose limits are reported between 150 U and 450 U. The reported risk of pulmonary fibrosis varies. Specifically, some authors have reported the risk of pulmonary fibrosis to be 3%-5% with a lifetime dose of less than 450 U of bleomycin, while others have reported an 8% risk of pulmonary fibrosis with a cumulative dose of 300 U.[7] When adhering to the dose limits listed above (15 U or 0.5-1 U/kg per session), there has only been a single case report of acute lung toxicity in a patient receiving bleomycin for treatment of a vascular malformation.[36] Based on the currently available evidence, the authors currently use 150 U as their maximum lifetime dose for their patients. Other risks of bleomycin include self-limited hyperflagellate pigmentation and permanent skin pigmentation related to adhesive.[35] Recently published patient-reported outcomes following sclerotherapy of low-flow vascular malformations showed that approximately 50% of patients report improvement in clinical symptoms following bleomycin sclerotherapy.[34] While this outcome is less than desirable, a recent meta-analysis demonstrated that bleomycin has a more favorable safety profile than other sclerosants.[37] As the use of bleomycin as an embolic/sclerosant for low-flow VMs continues to increase, additional studies should aim to answer many of the unknowns delineated above.

Additionally, there are reports of using *n*-BCA glue to embolize VMs prior to surgical excision. Although this technique has been implemented at only a few institutions, early results are promising.[38]

Genetics and Future of Medical Management of VMs

To this point, no medical cure has been discovered for VMs. Recently however, a mutation in an endothelial cell tyrosine kinase receptor (TIE2/TEK) has been elucidated in greater than 50% of sporadic VMs.[39] Although beyond the scope of this manuscript, this cellular signaling pathway may reveal targets for future medical treatments of VMs.[40]

LMs

LMs are low-flow vascular malformations (Figs. 5 and 6) that are caused by dysregulated embryogenesis of lymphatic channels resulting in cyst-like morphologies that often do not connect to normal lymphatic channels.[1-3] Notably, "lymphangioma" and "cystic hygroma" are histologically inaccurate identifiers for these lesions and no longer preferred. LMs are congenital and commonly visible at birth. Larger lesions are often detected on prenatal imaging. Smaller more conspicuous lesions may not present until later, but still often present during the first 2 years of life. In general, LMs present earlier than VMs.

LMs may be macrocystic, microcystic, or combined macro- and microcystic. In general, macrocysts are defined as cysts larger than 1-2 cm. LMs can occur anywhere on the body, but are most common in the head/neck. As such, presence of these lesions often necessitates evaluation for airway obstruction and oropharyngeal dysfunction, sometimes requiring tracheostomy and enteral feeding assistance (nasogastric tube or percutaneous gastrostomy).[25,41-43]

Clinical Presentation and Work-Up of LMs

LMs typically present as soft, bulging masses. These lesions can change dramatically in size over hours to days if intralesional hemorrhage or inflammation (often in the context of infection anywhere in the body, including URI or otitis media) occurs. Hemorrhage within macrocysts and/or multiple microcysts can cause overlying redness and increase the risk of infection and subsequent cellulitis, which is a primary reason for treating LMs. Typically, these lesions are painful during episodes of acute enlargement, which can last 10-14 days. After acute hemorrhage or inflammation resolve, LMs can dramatically decrease in size. In fact, it is not unusual to see a patient in clinic, schedule their sclerotherapy, only to have the patient arrive with an LM that is difficult to detect. LMs otherwise grow with the child overtime and in general do not regress. In sporadic, nonsyndromic LMs, coagulopathies are not present and a work-up is usually not warranted.

Ultrasound shows multiple cystic lesions with no internal flow on Doppler interrogation.[26] Doppler signal may be detected in the intervening septae. Microcystic LMs can

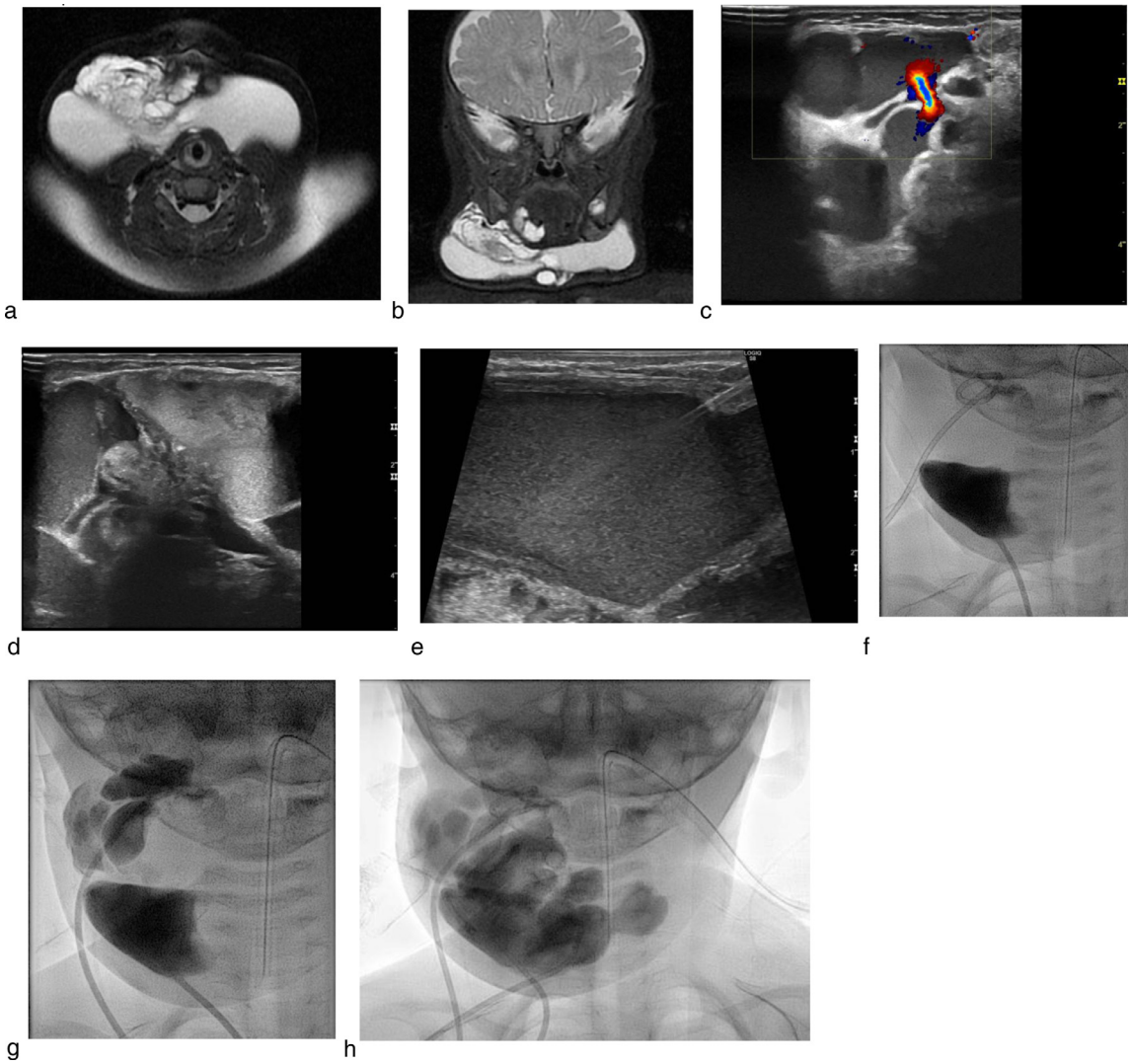

Figure 5 8-month-old female with large macrocystic LM of the anterior neck. Drains were placed and serial sclerotherapy with doxycycline was performed over 3 days. Axial T2 fat-sat (a) and coronal STIR (b) magnetic resonance images show multicystic lesion in the neck compatible with macrocystic LM. Color flow (c) and grayscale (d) ultrasound images show multiple macrocysts, some of which contain echogenic fluid that likely reflects prior hemorrhage. Grayscale ultrasound image shows 6.5 French pigtail drainage catheter placement into a large macrocyst (e). Fluoroscopic images (f and e) after intralesional contrast injection through the percutaneous drains show appropriate position of the drains within the cysts without evidence of extravasation. Spot fluoroscopic image after sclerotherapy demonstrates appropriate opacification of the macrocystic LM without evidence of extravasation. (Note that a third drain had been placed in order to facilitate treatment of the entire lesion.)

sometimes be difficult to detect with ultrasound and appear more-mass like or like thickened echogenic tissue. Internal proteinaceous debris and hematocrit levels may be visible. On MRI, LMs have increased signal on T2-weighted sequences and show only septal enhancement on postcontrast images. LMs commonly violate fascial plains and have difficult-to-define margins.[26] As with ultrasound, dependent proteinaceous material and/or hematocrit may be detectable on MRI.

Procedural Technique and Outcomes for LMs

Similar to the other vascular malformations described in this manuscript, surgical excision of these lesions has become a secondary option with percutaneous management emerging as primary therapy. Sclerotherapy is typically performed with ultrasound and/or fluoroscopic guidance. Depending on the size of the LM being treated, access into the LMs can obtained with an angiocatheter, needle, or pigtail drain. Prior to instillation of the sclerosant, fluid is aspirated. During the patient's first treatment, fluid is always sent for cytology, as rare cystic tumors can mimic LMs. Next, cystography is performed to ensure no connection with the systemic venous system (so as to limit large systemic doses of medications). Next, approximately 50%-75% of the aspirated volume is replaced/instilled with sclerosant. If the lesion is large enough to place an indwelling drain, prior published reports have shown efficacy with multiday doxycycline (the preferred

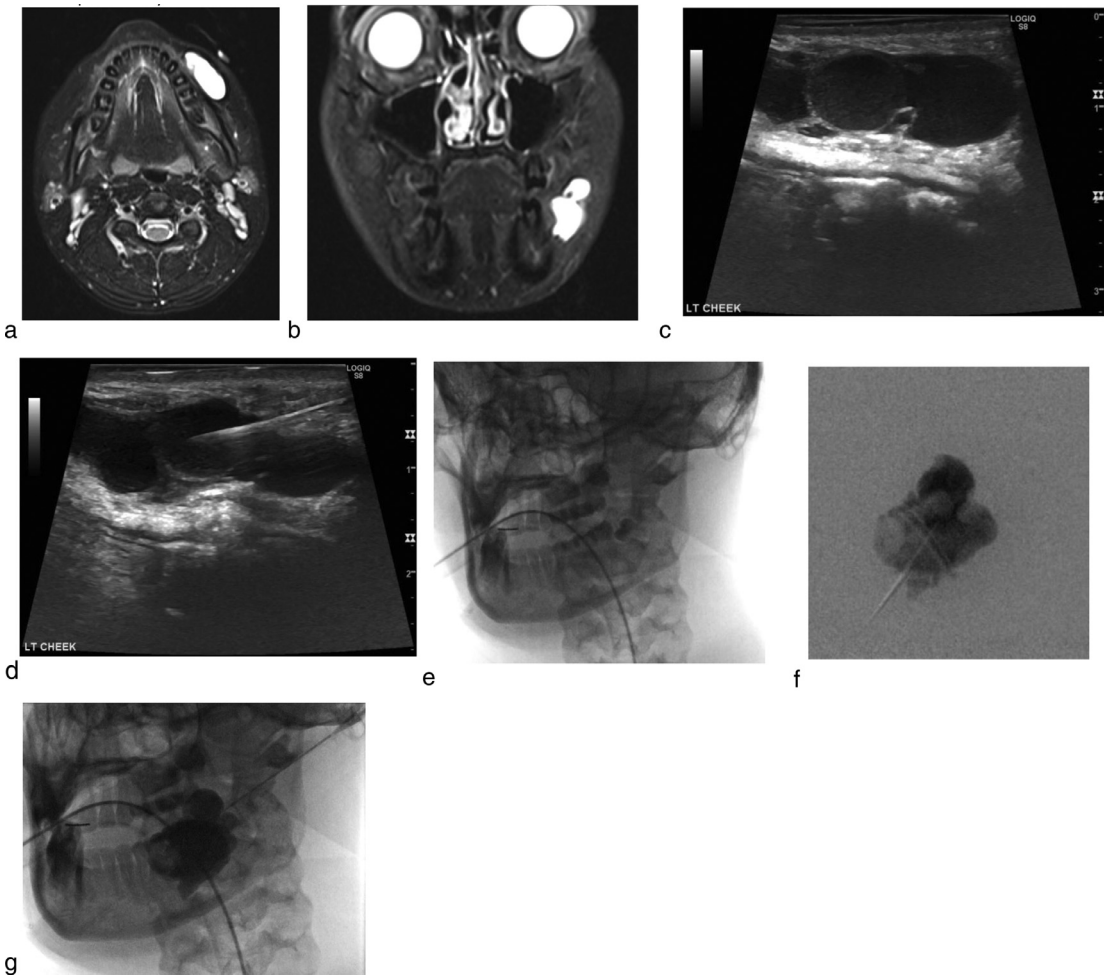

Figure 6 14-year-old female with macrocystic LM of the left cheek overlying the mandible. Sclerotherapy was performed with doxycycline. Axial T2 fat-sat (a) and coronal STIR (b) magnetic resonance images show multicystic lesion in the left cheek compatible with macrocystic LM. Grayscale ultrasound images show multiple superficial macrocysts (c) and ultrasound-guided placement of a 21-gauge EchoTip needle into the lesion (d). Scout fluoroscopic image prior to sclerotherapy (e) was obtained. Intralesional injection of contrast using negative roadmap fluoroscopic technique (g) demonstrates filling of the macrocysts without evidence of extravasation. Postsclerotherapy spot fluoroscopic image (g) shows opacification of multiple macrocysts in the left cheek.

sclerosant for large macrocystic lesions) injections in which doxycycline is allowed to dwell for 4 hours on day 1 and day 2.[44] On day 3, doxycycline is injected and the drain is removed.[44] Other institutions allow doxycycline to dwell for 45-60 minutes before being aspirated with subsequent removal of the drain. If the lesion is too small for drain placement, the sclerosant is left within the lesion. There are no head-to-head trials demonstrating superior efficacy of any method of treatment.

Doxycycline has emerged as an excellent sclerosant for macrocystic LMs.[2,3,44,45] Commonly used as an antibiotic, doxycycline is generally easy to obtain, relatively cheap, and has an excellent safety profile. Large doses of doxycycline also allow for treatment of very large LMs, which require physical contact with lymphatic endothelial cells. The exact sclerosing mechanism of doxycycline has not been entirely elucidated. Side effects of doxycycline include skin injury (if extravasation occur), as well as hemolytic anemia and metabolic acidosis in neonates.[2] Because of the potential for the latter complications, some authors report implementation of dose limits. At the authors' institutions, the following doxycycline dose limits are adhered to: 150 mg per session for neonates, 300 mg per session for infants less than 12 months old, 1200 mg per session in all other patients. Doxycycline is typically reconstituted in sterile water at either 10 mg/mL or 20 mg/mL concentrations, depending on the desired volume. Doxycycline has shown excellent efficacy, with clinical success rates of >90%.[1,46,47]

Other sclerosants have been reported to be efficacious for the treatment of LMs. Bleomycin is specifically efficacious in microcystic LMs.[35] However, because of its dose limits (described above), its use is limited in large, macrocystic LMs. One advantage of bleomycin is that it induces markedly less inflammation than doxycycline, and can be used in locations where decreased inflammation is warranted, such as periorbital locations or in the tongue or other lesions that may potentially affect the airway.[35]

OK-432 is a biologic product of Streptococcus Group A that has been used to successfully treat LMs.[48] However, due to the

common requirement of an institutional IRB and similar efficacy to doxycycline, OK-432 is less commonly utilized currently.

As with VMs, multiple treatments are commonly required to treat LMs based on the size of the lesion. When multiple treatments are necessary, these are often spaced 6-8 weeks apart. Also, these patients should be followed up in clinic at least following the final sclerotherapy treatment so as to accurately report clinical success and recurrence.

Because LMs tend to not be as hormonally responsive as VMs, recurrence rates are lower (although poorly reported). If symptoms recur, repeat sclerotherapy can be performed.

Multidisciplinary Management of LMs

LMs result from somatic mutations in the PIK3CA pathway.[49] Consequently, sirolimus—an mTOR inhibitor—has recently been discovered as an efficacious medical therapy for LMs.[50] Although an extensive review of this medication and cell-signaling pathway are beyond the scope of this manuscript, it is important for IRs to have baseline knowledge of this pathway.[49] Much remains unknown about recurrence of LMs after cessation and/or tapering of sirolimus therapy, long-term effects from the medication, or appropriate dosing for LM therapy. Despite many unknowns, a recent review of the available literature concluded that sirolimus might be effective in treating LMs and called for future randomized, controlled studies.[51] Sirolimus has immune-suppressing qualities and causes other side effects, such as hyperlipidemia and mouth sores.[50,51] Consequently, use of this medication is often reserved for very complex/diffuse LMs and for microcystic LMs that do not respond to sclerotherapy and should be managed by pediatric hematologists.

In addition to medical management, surgical management of large, complex LMs is also often necessary to accompany percutaneous sclerotherapy and/or medical management.[42] Specifically, massive head/neck LMs and superficial extremity LMs have residual fibrotic scar tissue that may require surgical resection after the cystic spaces have been embolized/obliterated. Microcystic lesions that do not respond well to sclerotherapy can often be surgically excised.[35] Also, as mentioned above, airway and enteric feeding management often requires surgical management during the early phases of treatment.

This variety of available, and often complimentary and necessary, therapeutic options for these patients underscores the need for multidisciplinary vascular anomalies clinics with multispecialty expertise in these congenital vascular lesions.

Conclusion

Pediatric IRs now play a primary role caring for patients with vascular malformations. In order to adequately serve patients in this role, having a firm grasp on the clinical presentation, diagnostic work-up, therapeutic management, cellular physiology, and pharmacologic mechanism of action of sclerosants/embolics is essential. Pediatric IRs should also be eager to seek multidisciplinary collaboration when caring for patients with vascular malformations, as patients and their families benefit from coordinated care.

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