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Lymphatic Malformations: An Overview of Pathology, Imaging, and Treatment

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A B S T R A C T

Lymphatic malformations are an overall rare, slow-flowing vascular anomaly consisting of microcysts and macrocysts, along with a dilated lymphatic system, that do not communicate with the normal lymphatic drainage system. Treatment goals prioritize regaining control of the presenting symptoms and decreasing the overall size of the anomaly. With studies indicating a conservative, less-invasive approach with sclerotherapy producing similar success rates as surgical resection, it is now seen as a mainstay treatment option. The purpose of this article is to discuss the presentation, pathology, indications, treatment options, including discussion of various sclerosants and outcome goals of lymphatic malformations.

Introduction

Lymphatic malformations (LMs) are benign, slow-flowing vascular anomalies made of a dilated lymphatic system and cysts that do not directly communicate with the normal lymphatic drainage system. LMs encompass a large variety of possible abnormalities. The incidence is estimated at one of 2000-4000 live births, with no difference in race or sex (Acord et al., 2016). They are more often seen in the head and neck (45-52%), which are considered lymphatic-rich regions, in addition to being found in the mediastinum, axilla, retroperitoneum, and groin. LMs are thought to be secondary to abnormal development of the lymphatics and the lymphatic jugular sacs during embryonic development that results in a failure to drain into the normal system (Elluru et al., 2014). Currently, there is little known information in regard to the genetics of LMs as most appear in those patients with no other syndrome manifestations. Turner Syndrome, Proteus Syndrome, Klippel-Trenaunay-Weber syndrome, and CLOVES syndrome are seen in a minority of patients with LMs (Bagrodia et al., 2015). Most LMs present before age two and grow proportionally as the child grows (Acord et al., 2016).

Presentation and pathology

Classification, clinical presentation, and treatment planning for the malformation depends on the size of the cysts and are described as macrocystic (cysts >1 cm), microcystic (cysts <1 cm), and combined or mixed (Shiels, 2012). Macrocystic malformations often involve the anterior and posterior cervical triangles (Elluru et al., 2014), are large, and depending on location, may transilluminate (Acord et al., 2016), may be compressible or noncompressible, and are typically smooth. The overlying skin may be normal in color, or if there is intralesional hemorrhage, a blue hue may be present. If erythema and warmth are present, a localized or intralesional infection may be present as well (Acord et al., 2016; Elluru et al., 2014). Large macrocystic malformations can also be seen on in utero ultrasound as early as the second trimester.

Microcystic malformations may be found infiltrating numerous subcutaneous and muscular tissues, and often present as firm, clear, tiny vesicles. Most often, microcystic malformations involve the oropharynx, oral cavity, parotid gland, tongue, submandibular gland, and pre-epiglottic spaces. Combined or mixed malformations commonly occur below the head and neck (Elluru et al., 2014).

Histologically, LMs primarily comprised protein-rich and eosinophilic fluid–filled vascular spaces. There is also a flattened, single layer endothelium that lines the walls of the channels. The vessel walls can have variable thickness and abnormal smooth muscle tissue. Lymphocyte collections are seen throughout the connective tissue (Elluru et al., 2014). Shiels describes a fourth LM classification, solid, that histologically contains fibrous tissue and

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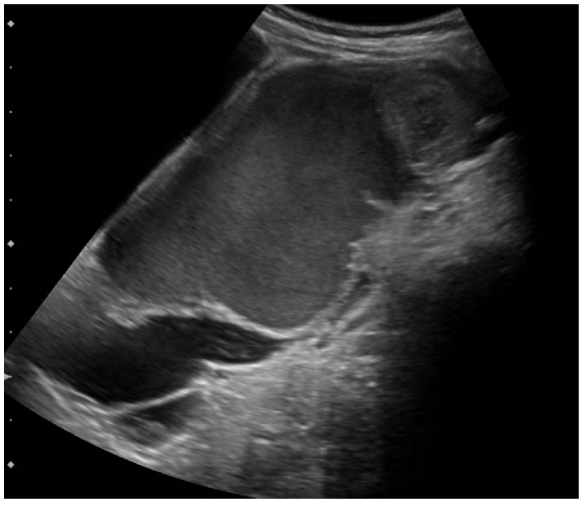

Figure 1. Transverse image of an abdominal macrocystic lymphatic malformation showing septation and debris after intralesional hemorrhage.

smooth muscle, along with microscopic cysts not discernible with current imaging modalities. He reports this classification is important for planning and managing expectations of these patients, along with their referring physicians, as treatment may include nonsurgical ablation or surgical resection (Shiels, 2012).

Diagnostic imaging

For those smaller more superficial malformations, ultrasound can be useful for detailing the size, extent, and components. Typical macrocystic malformations are compressible, predominantly anechoic cysts with thin septations. If hemorrhage or infection has occurred, debris may be present, and layer dependently within the cyst (Figures 1 and 2). There should be no internal vascularity present, despite blood vessels being detectible in the septa and walls of the malformation. Microcystic malformations typically appear solid and hyperechoic in nature (Figure 3) (Acord et al., 2016).

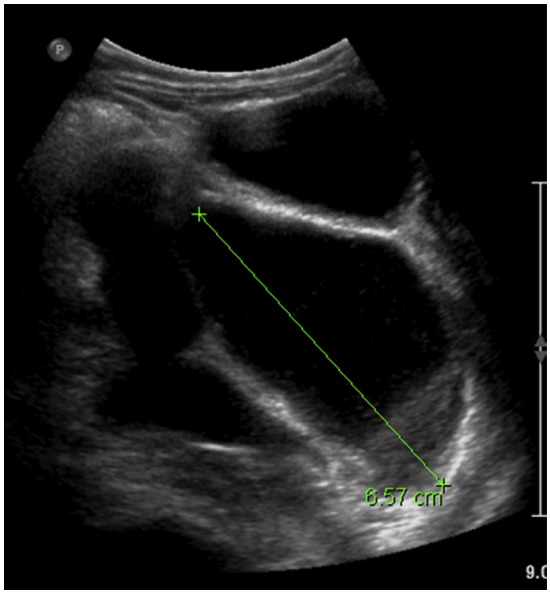

Figure 2. Layering debris at inferior aspect of a macrocyst.

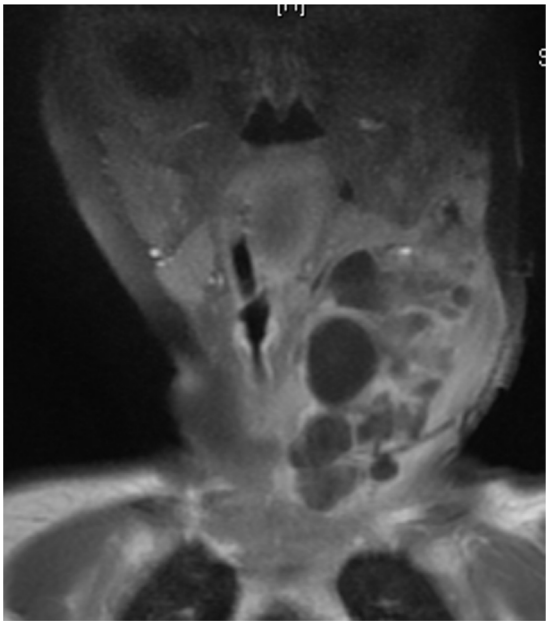

Figure 3. T1 coronal image of left neck combined LM. Note the multiple septations seen. LM, lymphatic malformation.

As stated previously, microcystic malformations can infiltrate subcutaneous and muscular tissues, thus, magnetic resonance imaging (MRI) is the imaging modality of choice to assess the extent of the malformation (Shiels, 2012). Typical MRI findings for LMs include no flow voids, no filling defects, infiltrations of soft tissue planes, and the malformation follows fluid signals on all MRI sequences. T1-weighted images may show hyperintensity in the setting of intralesional hemorrhage. Septation enhancement and interstitial fatty elements may also be visualized (Figures 3 and 4) (Acord et al., 2016).

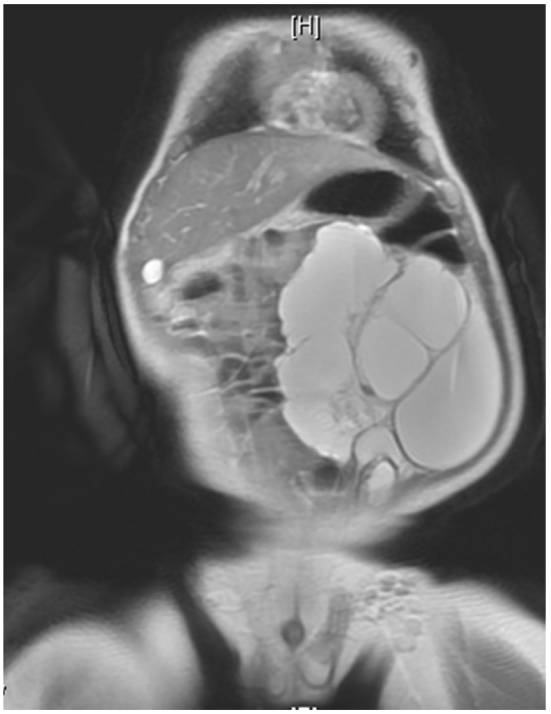

Figure 4. Multiple septations seen in a left-sided abdominal macrocystic LM. LM, lymphatic malformation.

Indications and treatment

The overarching goal of treatment is not cure, but improvement of function, reduction of complications, and cosmetic enhancement. Any newborn with a malformation involving critical structures should undergo emergent treatment, especially in the setting where infection or hemorrhage could result in threat to life or vision. Other indications for more urgent treatment include those malformations in the digestive tract and mouth, along with those that cause physical debilitation, pain, or disfigurement (Acord et al., 2016).

Historically, surgical resection was the treatment of choice regardless of the recurrence rate and associated complications including scarring, lymphatic leak, nerve damage, and incomplete resection (15-53%) (Shiels, 2012). Gilony et al. (2012) published a retrospective review of patients with LMs who underwent treatment, dividing them into three categories: observation, sclerotherapy, and surgery. They concluded that 45% of the malformations deemed observable, spontaneously regressed. Ninety-five percent of patients in the sclerotherapy arm had an excellent or fair response, with only one patient requiring surgical resection after failure. Sixty-seven percent of the surgical arm patients had complete resolution, 20% had incomplete removal and fair cosmetic results, and 13% with poor cosmetic results. These findings indicate the feasibility of all treatment courses, and that a large percentage of malformations do well during an initial observation period before selecting a treatment modality (Gilony, 2012). With data also suggesting that a more conservative approach is feasible, sclerotherapy is now considered first-line treatment (Shiels, 2012).

Sclerotherapy is typically performed under general anesthesia, but the consideration for moderate sedation, or local anesthesia, could be considered for those older patients with superficial malformations or for those malformations distal to critical structures (Acord et al., 2016). Under ultrasound guidance, the microcystic malformations are accessed with a small gauge needle, followed by aspiration of the contents, and then installation of a sclerosant. In those cysts that do not communicate, multiple needle access sites may be necessary. Fluoroscopy during injection may be used to visualize extravasation and to monitor for adequate treatment (Acord et al., 2016). Macrocystic malformations are directly accessed using ultrasound guidance and 5-8Fr pigtail catheters. The macrocysts are decompressed via the pigtail catheter and then injected with the sclerosant. Sclerosant fill volume is typically 50-75% of the aspirated contents during decompression of the cyst (Acord et al., 2016; Shiels, 2012). Shiels reports using short dwell time, catheter-based, dual-drug technique, which provided a 100% ablation of head, neck, trunk, and extremity macrocystic malformations >10 mm (Shiels, 2012).

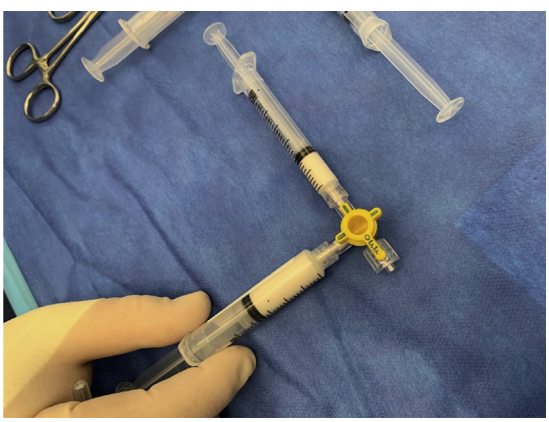

Figure 5. Bleomycin and albumin mixed and agitated to create foam before injection.

Available Sclerosants

Absolute ethanol was found to have a varied response rate of 84-100% with complication rates as high as 61%. Complications included, but were not limited to, local skin complications (necrosis and ulcerations), along with nerve injury. Absolute ethanol works by altering cellular proteins, resulting in damaged vascular endothelium and destruction of the lumen (Horbach et al., 2016).

Bleomycin is an antineoplastic agent that inhibits DNA synthesis but has also been found to produce an inflammatory response on the endothelial cell wall. If bleomycin is selected as the preferred agent, repeated injections have been required, but a favorable response (70-100%) has been reported. Complications associated with bleomycin use include localized pain, swelling, and skin discoloration but were all reported as transient and minimal (Horbach et al., 2016). Bleomycin is reported to produce less swelling than other sclerosants, including doxycycline, and is considered a more desirable choice for treatment of head and neck malformations (Elluru et al., 2014). Pulmonary toxicity has been reported with bleomycin of greater than 400 units lifetime dose, which far exceeds usual sclerotherapy dosage. It should be noted that the usual dosing of bleomycin is based on the size of the cysts being injected. Mixing bleomycin with albumin to form a foam, or reconstitution with contrast media, allows for increased visibility during fluoroscopy-guided injections (Figure 5) (Acord et al., 2016).

Sodium tetradecyl sulfate, also known as STS (Sotradecol), is an anionic detergent that removes lipoproteins of the cell membrane, which promotes permeability of the membrane to exposure of a second sclerosing agent, ultimately increasing treatment success (Acord et al., 2016; Shiels, 2012). Horbach et al. (2016) report one study with acceptable outcomes with STS single-agent therapy in 12 children, but it is typically used as a first agent in dual-drug therapy.

Doxycycline is a well-known, readily available tetracycline antibiotic that is also commonly used during sclerotherapy of LMs. The mechanism of action is unknown, but success with its use has been attributed to inhibition of cell proliferation and suppression of

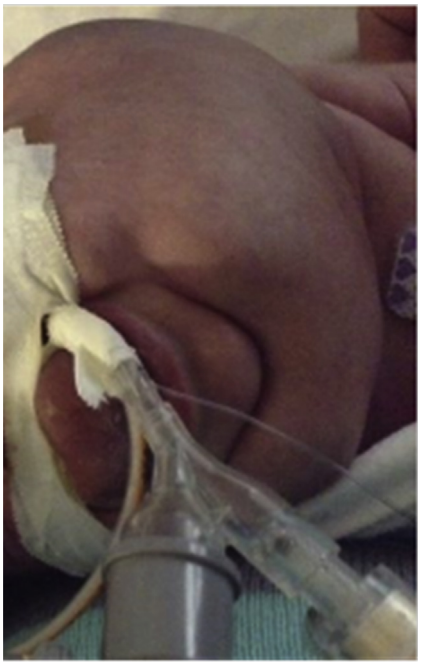

Figure 6. Frontal view of left and right neck LM. LM, lymphatic malformation.

vascular endothelial growth causing fibrin and collagen deposition that forms adhesions and fibrosis of the malformations. It is generally well tolerated with minimal, if any, side effects and a response rate of 67-100% (Horbach et al., 2016). Given this preparation of doxycycline is administered locally and not systemically, the classically known side effects, especially teeth discoloration, are not seen. Doxycycline is frequently reconstituted to a foam using albumin to aid in lesion coverage and penetration (Acord et al., 2016).

Shiels (2012) described his dual-drug treatment technique by "washing" the macrocystic malformations first with 3% STS, which is allowed to dwell for 2 minutes and then removing the STS and injecting 98% absolute ethanol at half the cyst volume. The absolute ethanol is then allowed to dwell for 15 minutes, followed by aspiration, and suction drainage for approximately 3 days. This dual-drug treatment regimen is often performed on an outpatient basis (Shiels, 2012).

Complications and Limitations of Treatment

Many of the sclerotherapy complications are associated with localized pain and sclerosant extravasation into the surrounding soft tissues. The overall rate of complications is estimated at 3-22%, with the most common issues described as skin blistering, breakdown, or necrosis. All of these issues are most commonly seen with absolute ethanol therapy or STS. In the rare instance of large extravasation, the patient can be placed at risk for nerve injury, permanent numbness, and other conditions associated with the sequelae of compartment syndrome. When using STS, providers should be aware of the small risk of hemoglobinuria from red blood cell hemolysis, but this is relatively easily treated with hydration therapy (Acord et al., 2016). Management of these complications includes conservative close follow-up and supportive care. Severe skin necrosis, blistering, and ulcerations may require consultation with wound management teams or plastic surgery (Acord et al., 2016).

Although most LMs are managed on an outpatient basis, providers should also consider any potential critical structure compromise because of postprocedural swelling. This swelling can be minimized by the choice of the sclerosant, aspiration of cyst contents before sclerosant injection, and the volume of the sclerosant used. Postprocedural assessment should be made in the Post Anesthesia Care Unit or outpatient care areas for any obstructive upper airway concerns, dysphagia, or feeding issues that may lead to dehydration before discharging the patient home. For those instances of large macrocystic malformations involving the head and neck, maintaining a patent airway preprocedure, intraprocedure, and postprocedure is vital. These unique patients could require management and coordination with the intensive care teams.

As discussed, sclerotherapy has now become a first-line mainstay treatment for LMs, but limitations and drawbacks must also be considered. Discussion of response times, requirement of multiple procedures scheduled weeks apart, and both anesthesia and radiation exposures are important aspects while formulating a treatment plan. Regardless of the success of the sclerotherapy, residual solid tissue may or may not cause cosmetic deformities, and surgical resection may still be required (Acord et al., 2016; Elluru et al., 2014).

Additional treatment options

Radiofrequency ablation (RFA), or laser therapy, has been described as a possible therapeutic option. RFA is performed under direct ultrasound image guidance after a percutaneous probe is advanced into the malformation (Acord et al., 2016). It can be delivered in a high-frequency mode, allowing for deep tissue destruction, with no affect to adjoining mucosa and structures. A low-frequency mode requires transmission of energy through a medium that removes superficial layers, resulting in minimal damage to adjacent structures and nearby tissues. The size of the malformation is decreased secondary to fibrosis formation (Bagrodia et al., 2015).

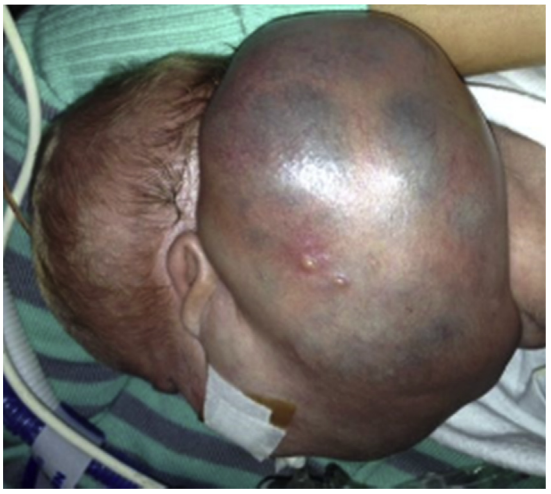

Figure 7. Right side lying view of the large left neck LM. LM, lymphatic malformation.

Sirolimus (Rapamune), an oral immunosuppressant antiproliferative drug, has recently been shown to be effective in those large, more vascular malformations that have been refractory to other treatment options. Small case series and reports have shown a decrease in size of the malformation or all together resolution. Utilization of sirolimus requires close consultation with providers experienced in the management of the medication, as it has a narrow therapeutic window requiring regular monitoring and dose titrations. Associated risks with the use of sirolimus most notably include immunosuppression along with a potential for pulmonary toxicity, metabolic abnormalities, and secondary neoplasm (Acord et al., 2016).

Case study

The following case study represents a rather complex scenario in which a multidisciplinary and multimodal approach was necessary to achieve best outcomes and the goal of gaining control of and improving symptoms associated with a large neck LM.

This case describes a young male patient with past medical history including prematurity and delivery via EXIT, or ex utero intrapartum treatment, procedure with immediate intubation due to a large neck LM with possible airway involvement (Figures 6 and 7). MRI was performed shortly after delivery, which revealed a massive cystic lesion on both sides of the neck, left greater than right. The right-sided lesion primarily consisted of dominant macrocysts measuring approximately 4.1 cm. The left-sided lesion extended from the posterior cervical to the anterior cervical level into the retropharyngeal space at the upper cervical level with small cysts along the tongue base (Figure 8).

Initially, the patient presented to interventional radiology (IR) for placement of drains into the macrocysts to allow for decompression. A total of five drains were placed into the malformation (Figure 9) and he underwent his first sclerotherapy procedure during the first week of life, which included injection of 3% STS into drains 2 through 5. The STS was allowed to dwell within the cysts for 5 minutes, was then aspirated, and followed by injection of

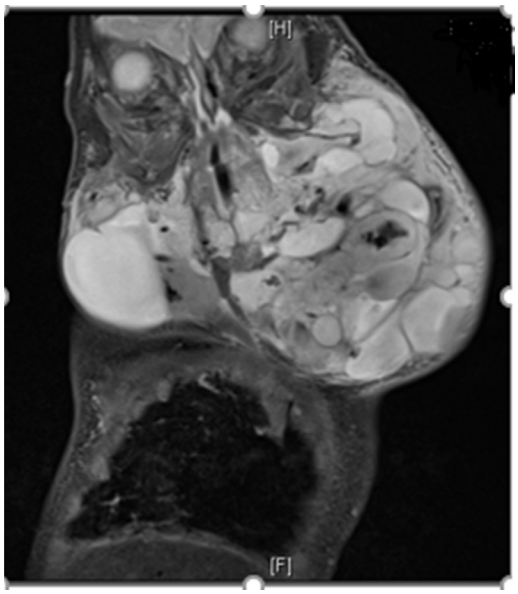

Figure 8. Coronal MR image of the large left and right neck LM. LM, lymphatic malformation.

absolute ethanol. After allowing the absolute ethanol to dwell for 5 minutes, it too was then aspirated. Drain 1 was not injected with the sclerosants because of preprocedure extravasation of contrast into the adjacent soft tissue structures. The drains were reconnected to bulb suction for continued decompression and were removed 2 days later.

A second stage of planned sclerotherapy was performed approximately 2 weeks later. There was improvement seen particularly on the right side before this procedure, but persistent left neck enlargement was seen. During this second sclerotherapy, again five pigtail drains were placed into the left-sided macrocystics and fluid was aspirated from each. The initial sclerotherapy agent was 3% STS that was injected into each drain, allowed to dwell for 5 minutes and then aspirated. This was followed by similar steps using absolute ethanol. The drains were then placed to bulb suction

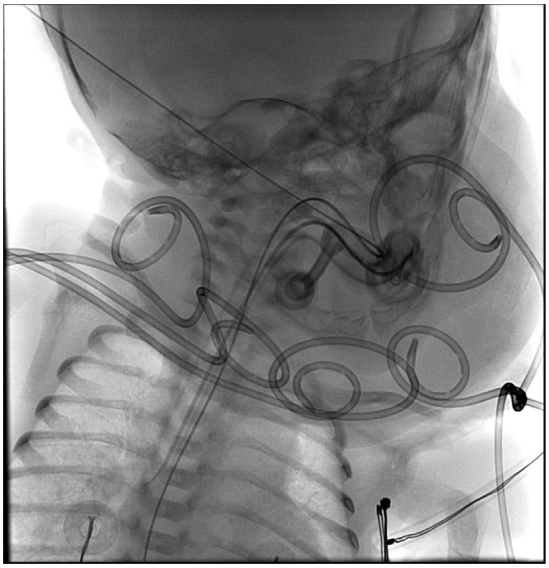

Figure 9. Fluoroscopic image of drain placement.

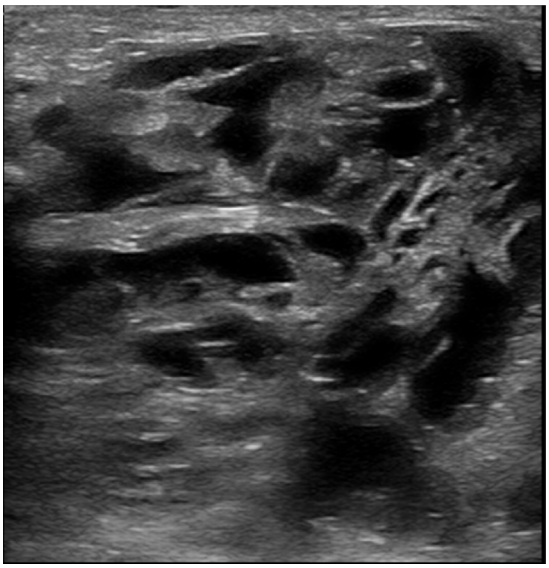

Figure 10. Left anterior neck longitudinal view ultrasound. Note multiple scattered microcysts.

for continued decompression over the next 48 hours. In addition to the drain placement, smaller cysts were punctured with a 21-gauge needle, aspirated, and then injected with doxycycline foam.

Improvement was again seen before a third-staged sclerotherapy to the extent that the macrocysts were not large enough to allow drains to dwell. During this session, multiple cysts were targeted and injected with small aliquots of doxycycline foam.

Despite the improvements seen between each of the sclerotherapy treatments, the malformation remained large enough that he required a 15% mass debulking and tracheostomy placement. He was then started on sirolimus, with no obvious enlargement or worsening of the neck swelling.

After his initial prolonged hospitalization, he did functionally well at home until he presented to IR approximately 1 year later for tongue swelling and protrusion. During this outpatient visit, his tongue was mildly protuberant and enlarged, but despite its size, he was able to nearly completely retract it into this mouth. There was fullness to the floor of his mouth and chin with bulkiness along both sides of the anterior neck. An ultrasound was performed during this visit that revealed small scattered cysts and echogenic mass–like tissue hypertrophy (Figure 10). A large left lateral neck cyst with internal swirling contents was also visualized. Case management was discussed extensively with the family, including continued close observation vs multiple bleomycin injections into the tongue to aid in bulk reduction.

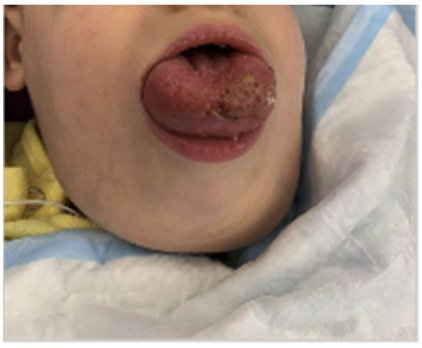

Figure 11. Note significant reduction in bulk size of both the right and left neck. Obvious tongue protrusion and fullness.

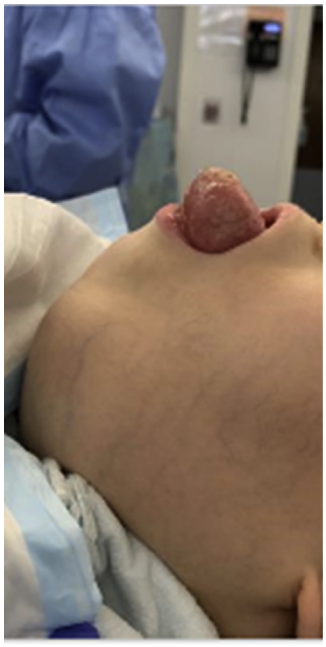

Figure 12. Lateral view shows extent of tongue protrusion and bulk.

The patient returned for his first outpatient bleomycin injections 1 month later. A preprocedure ultrasound demonstrated numerous enlarged lymphatic channels throughout the anterior tongue. Using direct ultrasound visualization, these areas were targeted with a 25-gauge needle, injected with bleomycin foam, and the foam was seen to flow freely throughout the lymphatic compartments. A second-stage procedure was completed approximately 4 months later, and a third procedure 6 months after that. This patient will continue to be seen in IR for intermittent bleomycin sclerotherapy treatments to further aid in bulk reduction of the tongue and improvement of functionality (Figures 11 and 12).

Follow-up and expected outcomes

As with many other complex medical conditions, a multidisciplinary approach is essential. It is also imperative to inform patients that the goal of sclerotherapy is to gain control of their symptoms, knowing that regrowth and recurrence is seen (Elluru et al., 2014). Patients are typically seen every 6-12 weeks to reassess their treatment response. A positive response is seen most importantly with improvement of pretreatment symptoms, along with a decrease in the malformation size. Each follow-up appointment should include documentation of the malformation size by using ultrasound visualization. During these appointments, ongoing treatments should be discussed. On average, 2-3 sessions are required to see a clinical response (Acord et al., 2016).

Conclusion

Appropriate diagnosis and treatment planning for LMs, regardless of their classification, is essential to achieving best outcomes. Understanding that the main goal of sclerotherapy, to gain control of and vicariously improve presenting symptoms, is necessary for managing patient expectations. Each patient, and their specific malformation, should be treated as a unique case because of the lack of universally accepted treatment guidelines. The treatment regimen and sclerosant selection should be based on the experience and comfort of the treating team. Objective monitoring of the treatment goals is of the utmost importance to ensure efficacy and satisfaction.

References

Acord, M., Srinivasan, A.S., & Cahill, A.M. (2016). Percutaneous treatment of lymphatic malformations. *Techniques in Vascular and Interventional Radiology, 19*, 305-311.

Bagrodia, N., Defnet, A.M., & Kandel, J.J. (2015). Management of lymphatic malformations in children. *Current Opinion in Pediatrics, 27*, 356-363.

Elluru, R.G., Balakrishnan, K., & Padua, H.M. (2014). Lymphatic malformations: diagnosis and management. *Seminars in Pediatric Surgery, 23*, 178-185.

Gilony, D., Scwartz, M., Shpitzer, T., Feinmesser, R., Kornreich, L., & Raveh, E. (2012). Treatment of lymphatic malformations: a more conservative approach. *Journal of Pediatric Surgery, 47*, 1837-1842.

Horbach, S.E.R., Lokhorst, M.M., Saeed, P., de Gouyon Matignon de Pontouraude, C.M.F., Rothova, A., & van der Horst, C.M.A.M. (2016). Sclerotherapy for low-flow vascular malformations of the head and neck: a systematic review of sclerosing agents. *Journal of Plastic, Reconstructive & Aesthetic Surgery, 69*, 295-304.

Shiels, W.E. (2012). Lymphatic malformation: radiologic-pathologic-therapeutic correlation and management implications. *Journal of the American Osteopathic College of Radiology, 1*, 2-8.