Pathology and clinical presentation

Lymphatic malformation (LM, previously known as lymphangioma) is a common vascular malformation and represents a disturbance in the development of the lymphatic ductal system. The pathology of LM is central to understanding the science and design of effective therapeutic interventional procedures. Pathologically, LM is a complex of multiple cysts lined with lymphatic vascular endothelium (Fig. 1). The supporting matrix of the LM is a combination of fibrous tissue and smooth muscle with small feeding vessels and aggregates of lymphocytes in the interweaving septations. The cystic spaces may or may not communicate and contain serous or hemorrhagic fluid. Lesions can be classified as macrocystic (>1 cm), microcystic (< 1cm), or mixed (combined microcystic and macrocystic). Microcystic LM may infiltrate multiple soft tissue planes, including skin. Pathologically, the solid matrix elements of LM may be a minor component (predominantly cystic as defined with diagnostic imaging studies) or large volume percentage of an LM (few cysts defined with imaging studies). When macrocystic disease predominates, pathologists refer to these as cavernous lesions or the typical “Cystic Hygroma”. Histologically, solid elements of LM not only contain fibrous tissue and smooth muscle, but also contain microscopic cystic spaces that are not resolved with current diagnostic imaging studies (US, CT, MR). This understanding of the histologic composition of solid LM tissue is critical to therapeutic planning and outcomes expectations, and thus, important in patient care plans and communication. As a result, the author includes “solid LM” as a fourth classification category, as this is readily understood by patients undergoing treatment that may target ablation of cystic spaces and leave residual solid LM tissue, as well as referring physicians (particularly surgeons), for future treatment decisions that include surgical resection or non-surgical ablation techniques (e.g. radiofrequency ablation).

Lymphatic malformations represent approximately 5% of all benign masses and may present at any age. More than half are recognized at birth and 90 percent before 2 years of age. Occasionally, LM may first manifest with a visible mass in early or late adulthood. A LM that is diagnosed at birth usually presents as a soft, spongy, non-tender mass. In older children and adults, a LM may present with rapid development of a firm painful mass, occurring as a result of hemorrhage into previously undiagnosed LM locules. LM is most frequently diagnosed in the head and neck, but can present in numerous

Figure 1. Pathology of lymphatic malformation. High power image of LM demonstrating multiple cysts lined by flat vascular endothelium (arrows), as well as solid elements of fibrous tissue and smooth muscle (arrowheads). Cysts in the solid matrix (curved arrows) may be so small as to be non-discriminable with diagnostic imaging modalities.
Lymphatic Malformations, Shiels

locations, to include the orbit, mediastinum, retroperitoneum, chest, abdomen, extremities, scrotum and penis. LM in the orbit may lead to severe disability, acute bradycardia, visual loss, or complete blindness. Microcystic LM that infiltrates skin may manifest as cutaneous vesicles (cutaneous LM or “lymphangioma circumscripta”) with chronic drainage of serous fluid.

Diagnostic Imaging Evaluation

Diagnostic imaging is best performed with a combination of MRI and sonography. MR is the imaging modality of choice for global assessment of the extent of a LM. MR demonstrates LM extension in areas invisible to sonography, such as LM behind airway and boney structures. MRI and sonography demonstrate LM to be a multiloculated cystic mass with variable appearance of the cyst fluid depending on the presence or absence of intracystic hemorrhage. Sonography may be the sole diagnostic imaging modality if the lesion is well localized in a superficial location, also providing definition of microcystic and solid elements, distinct from macrocystic elements. The definition of LM with MRI and sonography demonstrates cystic spaces without fast (high) flowing fluid (arterial blood flow), thus LM is characterized as a “low flow” vascular malformation.

Treatment of Lymphatic Malformation

Surgical resection has been considered standard treatment for these lesions, despite recurrences in 15 to 53 percent of reported clinical series. Significant complications in up to one-third of cases, including nerve paralysis, have been reported following operative resection. Surgical literature studies recognize the benefit of an interdisciplinary approach to treatment, often including percutaneous treatment as the first line therapy prior to surgical debulking and/or resection.

Radiological therapy is focused on selective ablation of vascular endothelium that lines LM cysts. Interventional radiological therapy has been attempted around the world over the past two decades using intralesional sclerotherapy with single agents including bleomycin, doxycycline, ethanol, Ethibloc™, OK-432, and sodium tetradecyl sulfate, with excellent response in only 20 to 67 percent of patients. A recent literature analysis of various sclerosant agents reported LM treatment requiring one to 23 treatment sessions with complete ablation of LM in 20 percent and good response in 51 percent of patients. Previously, complications from sclerotherapy have been observed in 22 to 46 percent of patients, including nerve damage, persistent pain, skin ulceration, fever, airway obstruction, and myoglobinuria.

New dual-drug treatment regimens (detergent followed by ethanol, short dwell time) with improved outcomes and fewer complications have been reported. The scientific rationale for dual-drug therapy is based on the cellular level of action of detergent as an agent of “poration” that removes lipoproteins and opens cell membrane pores, enhancing ethanol permeability for intracellular destructive action.

Percutaneous treatment is divided into two therapeutic regimens, one for macrocystic disease and one for microcystic disease. Percutaneous LM therapy reports vary, with the majority grading response either on gross cosmetic patient appearance or degree of shrinkage of LM cysts. Alternative outcomes measure reporting uses simple presence or absence of cysts (successful complete ablation as the treatment goal) for LM in a broad spectrum of locations including the head, neck, trunk, extremities, and orbit.

Macrozystic LM Treatment

Macrozyst (>1cm) access is most frequently performed with ultrasound guidance and placement of either a 5-8F pigtail catheter in each cyst or needle/angiocatheter cyst puncture for individual cyst treatment. Macrozyst treatment with simple needle puncture, aspiration, and injection (sclerosant not aspirated following injection) has been most frequently reported with OK-432, bleomycin, and doxycycline (10 mg/ml). Results with both “injection only” techniques are similar for doxycycline, OK-432, and bleomycin,
with good-to-excellent results reported in 80-90% of patients.\textsuperscript{6,9,16,18-19}

Two series reports of catheter-based doxycycline therapy studies report similar 3-day treatment techniques, injecting doxycycline (10 mg/ml) into individual cysts and maintaining the doxycycline 4-6 hours, then aspirating, and repeating these treatments, as inpatients, daily for 3 days (each day with sedation or general anesthesia). In these series, treatment outcome of good-to-excellent was reported in 65 and 90%, respectively, with average number of treatment sessions of 3.6 and 2.9 (range 1-10 treatment sessions).\textsuperscript{16,17} Minor complications in these two series were reported as 10 and 14%, respectively, and included hemolytic anemia, hypoglycemia, metabolic acidosis, transient hypotension, skin blistering, and hair loss.\textsuperscript{16,17} In the same series, major complications were reported with a frequency of 2 and 14%, including Horner’s syndrome, facial nerve palsy, and phrenic nerve palsy.\textsuperscript{16,17} Complications with bleomycin therapy include skin blisters, pulmonary fibrosis (acute and chronic), and flagellate hyperpigmentation.\textsuperscript{18-22}

Macrocystic LM treatment using a short dwell time, catheter based, dual-drug technique resulted in 100% ablation of macrocysts has been reported in the head and neck, as well as trunk and extremities.\textsuperscript{3-4} In these two reports, 100% of macrocysts were ablated with mean number of treatment sessions of 1.1 and 1.3, respectively.\textsuperscript{3-4} Infection was the only complication (6 and 13%, prior to routine use of peri-procedural antibiotic administration) with the short dwell time, catheter based, dual-drug technique.\textsuperscript{3-4} In both series, no major complications occurred (no nerve injury, including treatments involving the brachial plexus, face, orbit, and neck). The dual-drug catheter based technique includes 5-8F pigtail catheters placed in cysts larger than 10 mm (Fig. 2-5). Following complete drainage of the macrocysts and contrast cystogram definition, macrocysts are treated with a dual-drug system, each drug with short dwell time treatment. Cyst lining cells are first washed with detergent (sodium tetradecyl sulfate, 3%) maintained in the cyst for 2 minutes prior to aspiration. The detergent removes cell membrane lipoproteins, thus increasing membrane permeability for intracellular delivery of ethanol for protein denaturation and cell death. Following detergent aspiration, 98% ethanol (50% cyst volume) is injected and maintained for 15 minutes. Following aspiration of the ethanol, macrocysts are placed to suction drainage for 3 days prior to catheter removal. The dual-drug catheter based treatment is routinely performed as an outpatient.\textsuperscript{3-4} Patients with 5F pigtail catheters (including orbit, head, and neck) reported no pain from the indwelling catheter (Fig. 2 and 3).\textsuperscript{3-4} Furthermore, the dual-drug macrocystic therapy can be performed without sedation using intracystic local anesthetic in older children and adults (Fig. 5).\textsuperscript{3-4}

\textbf{Figure 2.} Macrocystic lymphatic malformation of the orbit in a 13-year old boy with proptosis, pain, and bradycardia. Axial T2 image (A) demonstrates a retrobulbar lymphatic malformation of the left orbit (arrows). Note the stretched optic nerve (arrowhead) encased by the LM. A pontine cavernous malformation is noted. B shows a 5F drainage catheter (arrow) in position for drainage and ablation. A contrast cystogram (C) defines the cystic mass (arrowhead) prior to ablation. Axial T2 image (D) 2 years following treatment demonstrates normal globe, optic nerve, and orbital contents. The patient has normal vision following sclerotherapy. \textit{Images reprinted with permissions Pediatric Directions 2011; Vol. 38, NCH}
Figure 3. Macrocystic and microcystic lymphatic malformation of the orbit in 6-year-old girl. Clinical photo of a 6-year-old girl (A) demonstrates severe proptosis and ecchymosis due to a massive intraorbital LM. Coronal T2 image (B) reveals a left orbital mixed macro-and microcystic LM (arrow) encasing the optic nerve (arrowhead). Coronal T2 image (C) defines microcystic elements of the LM (arrow). Contrast cystogram image (D) shows a 5F drainage catheter with contrast for drainage and ablation of the macrocystic element (arrowhead). Image during US guided microcyst treatment (E) with 25G needle (arrowhead) in the leftmost of 2 microcysts, containing echogenic doxycycline foam (curved arrow). Straight arrow indicates the adjacent microcyst that will be treated next with echogenic doxycycline foam. Clinical photograph 10 months following treatment (F) demonstrates resolution of proptosis and visual acuity improvement to 20/100. Images reprinted with permissions Pediatric Directions 2011; Vol. 38, NCH

Figure 4. Mixed (macrocystic and microcystic) lymphatic malformation of the neck, retropharynx, and mediastinum. Clinical photograph of 13-month-old girl (A) with a massive LM of the left neck. Coronal T2 image (B) demonstrates the LM (arrows) extending from the neck into the superior mediastinum. Axial T2 image (C) shows the LM (arrows) encasing the carotid sheath and extending into the retropharynx. Contrast cystogram (D) during macrocystic LM (arrow) ablation treatment. Axial T2 image 4 years following treatment (E) demonstrates no macrocysts or microcysts, and small amount of fibrofatty tissue (arrows) remaining after cyst ablation. Photograph at age 5 (F) shows no visible mass effect or scar in the left neck. The scar (arrow) on front of the neck is from the plastic tracheostomy frame skin abrasions. Images reprinted with permissions Pediatric Directions 2011; Vol. 38, NCH
Figure 5. Macrocystic LM in the neck of a 47-year-old woman treated with a single session of outpatient percutaneous sclerotherapy performed under local anesthesia. US image (A) demonstrates the large macrocystic LM (arrows) of the left neck prior to treatment. Contrast cystogram (B) defines the left neck macrocystic LM (arrow) during dual-drug treatment. US image 6 months following treatment (C) demonstrates normal neck soft tissues (arrow on normal carotid artery) and no evidence of cysts or scar from treatment. Images reprinted with permissions Pediatric Directions 2011; Vol. 38, NCH

Microcystic LM Treatment

Percutaneous treatment of microcystic LM (includes those with purely microcystic or mixed LM) using liquid doxycycline, OK-432, and bleomycin yields good-to-excellent results in 60-63% of patients in recent reports.15,16,18-19 A new protein foam formulation of doxycycline (5 mg/ml) has been developed for treatment of microcystic LM (Fig. 3).23 Treatment of microcystic LM involves aspiration of each individual microcyst and injection of doxycycline foam, the foam changing the color of the microcyst on ultrasound from black to white, defining treated from untreated microcysts. This study reports safe and successful treatment of over 1200 LM microcysts as small as 1 mm in the eye, head, neck, trunk, and extremities, with successful microcyst LM ablation in 93% of patients following 3 treatment sessions (including sessions with simultaneous macrocystic treatment).23 The use of stable protein microfoam for bleomycin injection has also been reported for safe and accurate treatment of microcystic LM.24

Figure 6. Six-year-old girl with right forearm microcystic LM. US image (A) demonstrates a mixed solid and microcystic LM with arrows on the small microcysts treated with doxycycline foam. US image of the LM (B) (margins outlined with curved arrows) with arrow on a moderate-sized microcyst treated with doxycycline foam. US images image of the LM (C) following doxycycline microcystic sclerotherapy. Curved arrows outline the residual solid LM tissue with lack of discernible microcysts. Surgical resection of residual solid LM mass was performed following sclerotherapy of definable microcysts. Histology (D) demonstrates microscopic cysts (arrows) that remain following sclerotherapy, adjacent to fibrous (arrowheads) and adipose (curved arrows) LM matrix. Fluoroscopic image during lymphocele therapy (E) with arrow indicating a large lymphocele that was successfully treated over a 3 week period (dual drug sclerotherapy every 3 days).
Limitations and surgical planning

New techniques and drug combinations discussed above offer patients and physicians options for LM cyst ablation with success rates approaching 100%. Following sclerotherapy, small amounts of residual solid LM fibrofatty tissue may not result in cosmetic deformity and may not require surgical resection (Fig. 4). Annual surveillance of patients with residual LM solid tissue may reveal new microcysts that mature into definable cysts (with diagnostic imaging studies) and may be treated with intermittent sessions of microcystic therapy. In the setting of significant solid LM tissue, there is potential for both residual cosmetic mass effect and development of new cysts from the solid tissue that contains microscopic LM cysts (not large enough to be defined with diagnostic imaging modalities) following percutaneous sclerotherapy (Fig. 6). Multidisciplinary planning should include discussion of need and choice of timing for debulking surgery, either before or following sclerotherapy.

Two primary issues are important for both surgeons and radiologists on the Vascular Anomalies team to consider in these planning discussions. When doxycycline sclerotherapy is performed prior to debulking surgery, surgeons must be prepared to encounter significant scar tissue encasing nerves, blood vessels, and other vital structures. This potential for encasing scar tissue may drive a decision for debulking surgery prior to sclerotherapy (to treat residual or recurrent cysts). The second issue for planning is the post-operative tissue bed and the potential for lymphocele development (and need for subsequent percutaneous treatment). If an LM lies superficially, surgical resection may result in tenuous blood supply to the overlying skin that may be compromised or lost with lymphocele sclerotherapy. Furthermore, patients with post-operative lymphoceles should be prepared for the significant time commitment required for multi-session sclerotherapy of the lymphocele over a 2-week period. These issues are best discussed with the patient/family, the surgeon, and interventional radiologist prior to initiation of treatment.

Solid LM with microscopic cysts, especially LMs infiltrating skin and oral mucosa, present a unique challenge for surgeons and radiologists. Since sclerotherapy is best directed at cysts defined with high-resolution ultrasound, solid LM tissue is not well treated with current sclerotherapy techniques. Radiofrequency ablation (RFA) offers an alternative treatment for solid LM with recurrent mucosal and lingual vesicles, as well as lingual microcystic LM that results in an enlarged tongue. The author has utilized RFA successfully for reduction of mass effect and treatment of cutaneous vesicles. Patient care plans with RFA must include clear expectations and a treatment plan for the RFA burn site.

Summary

Treatment of LM involves a multidisciplinary vascular anomalies team approach, with an expanding clinical armamentarium that offers patients excellent treatment options and hope for superb clinical results. In this multidisciplinary team, the interventional radiologist plays a critical role in the provision of innovative and excellent patient care.

References