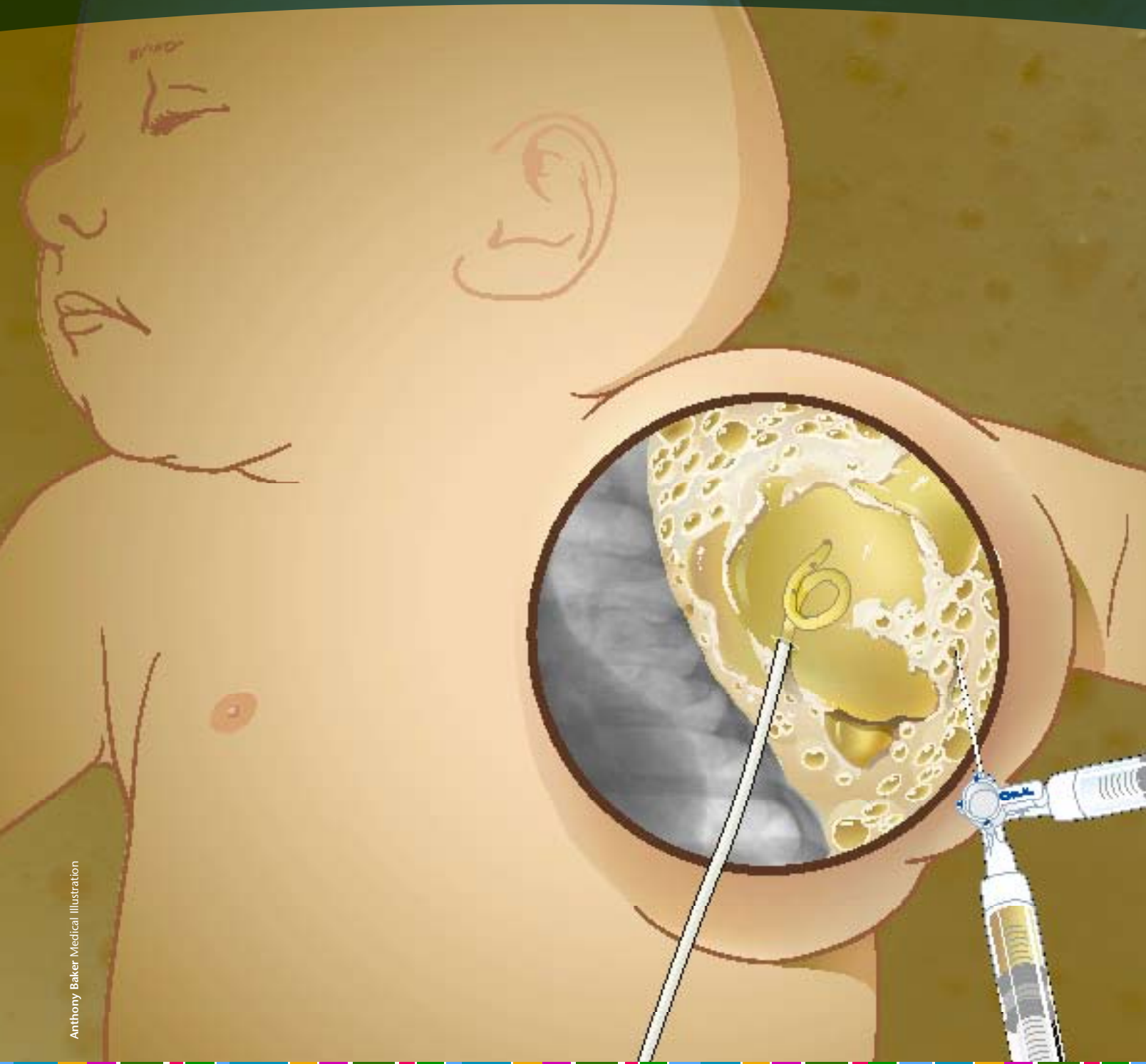


Lymphatic Malformation Treatment: Defining State-of-the-Art

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Anthony Baker Medical Illustration

Lymphatic Malformation Treatment
at Nationwide Children's Hospital

As a world center of excellence in radiology, the interventional radiology team at Nationwide Children's Hospital has pioneered numerous minimally invasive treatments for children and adults. This article will focus on new treatments developed and used at Nationwide Children's Hospital for lymphatic malformations (previously termed lymphangioma), in diverse areas from head to toe. Pediatric surgeons, otolaryngologists, ophthalmologists, oculoplastic surgeons, neurosurgeons, urologists and other surgeons now offer their patients these minimally invasive treatments as alternatives to more extensive and potentially deforming surgical procedures. The case studies in this article illustrate the dramatic impact these treatments can make in a patient's life.

Lymphatic malformations (LM)

Lymphatic malformations (LM) are common vascular malformations in infants and children, which account for about five percent of all benign tumors. More than half are recognized at birth and 90 percent before 2 years of age. Occasionally, lymphatic malformations 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 soft or firm non-tender mass, occurring as a result of hemorrhage into previously undiagnosed LM locules. Less frequently, LM presents with infection of the mass or pain. LM is most frequently diagnosed in the head and neck, but can present in numerous locations to include the orbit, mediastinum, retroperitoneum, chest, abdomen, extremities, scrotum and penis.

The pathology of LM is central to understanding imaging findings with various modalities, as well as designing effective therapeutic interventional radiological techniques. Pathologically, LM is a complex of multiple cysts lined with lymphatic vascular endothelium. 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, microcystic or mixed. When macrocystic disease predominates, pathologists refer to these as cavernous lesions, or the typical "cystic hygroma."

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. For the first time, recurrence of cystic hygroma is non-existent and serious surgical complications can be avoided with definitive interventional radiological procedures developed at Nationwide Children's Hospital.

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. It demonstrates LM extension in areas invisible to sonography, such as LM behind airway and boney structures. Sonography may be the sole

diagnostic imaging modality if the lesion is well localized in a superficial location. 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. The masses contain sparse blood vessels that supply the supporting stroma of the LM. Sonography during a preoperative consultation facilitates pre-procedural mapping, as well as effective parent/patient education.

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 varying agents including bleomycin, doxycycline, ethanol, Ethibloc™, OK-432, and sodium tetradecyl sulfate, with excellent response in only 20 to 64 percent of patients.

A recent literature analysis of multiple 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. 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. Prior to therapeutic discoveries at Nationwide Children's, there was no percutaneous therapeutic regimen consistently delivering outcomes of 80 percent or greater success.

PERCUTANEOUS THERAPY OF LYMPHATIC MALFORMATION

Patients who have undergone treatment for LM at Nationwide Children's, range in age from 2-months to 51 years of age. Locations of percutaneous treatment for LM include the neck, head, orbit, ear, arm, leg, axilla, chest wall, abdomen, scrotum, and penis. Most procedures are performed as definitive first-line therapy, with occasional patients referred after surgical debulking or following surgical recurrence. Procedures are performed in the interventional radiology suite under deep intravenous anesthesia or general anesthesia. Treatment is divided into two therapeutic regimens, one for macrocystic disease and one for microcystic disease.

Macrocystic LM Treatment

Macrocyst (>1 cm) access is most frequently performed with ultrasound guidance and placement of a coaxial 5F pigtail catheter system. Massive lesions may accept larger catheters such as 8 to 10 French size. In multilocular lesions, each macrocyst is treated with separate catheter placement. This technique of individual targeted cyst ablation has proven to be technically interesting with up to five catheters placed in a single child's parotid LM and eight catheters placed in an abdominal LM. Following complete drainage of the macrocysts, contrast cystogram with fluoroscopy is performed to document the native cyst volume, containment of contrast without extravasation, and complete evacuation of contrast with aspiration. Following contrast aspiration, the macrocysts are treated with dual-drug chemoablation, developed

at Nationwide Children's, using 50% original volume sequential intracystic injections of sodium tetradecyl sulfate (STS) 3% (2 minute dwell time) followed by aspiration and injection of ethanol 98% solution (dwell time 15 minutes). The synergistic drug combination has for the first time resulted in outcomes of macrocyst ablation of greater than 95 percent success. The key to therapeutic success is cell membrane pretreatment with detergent (STS), which effectively removes cell membrane lipoproteins, thus increasing membrane permeability for intracellular delivery of ethanol for protein denaturation and cell death. Following aspiration of the ethanol, catheters are connected to suction drainage for three days prior to catheter removal. This treatment is effective greater than 95 percent of the time, with the majority of patients (85 percent) responding in a single treatment. *(See title illustration on page 14 which demonstrates the use of a pigtail catheter to ablate a cyst, and the injection of solution to ablate any residual microcysts.)*

Microcystic LM Treatment

Microcysts (0.5-10mm) are treated with needle puncture, individual cyst drainage, and injection of Doxycycline solution. Nationwide Children's Radiology team is the first in the world to develop a method and drug delivery system that allows 50 or more microcysts to be sequentially treated in a single treatment session. In this regime each microcyst is individually aspirated and doxycycline is delivered in an emulsified form that is sonographically visible and allows differentiation from treated and untreated cysts.

Successful treatment is defined at Nationwide Children's as complete cyst ablation documented by sonography or MR imaging, unlike other centers that grade success based on external cosmetic appearance of residual mass effect. Radiological follow-up is performed at one month and annually thereafter, with high-resolution sonography for focal lesions and MRI for lesions not accessible to sonographic examination. Ultrasound examination performed one month following sclerotherapy will demonstrate complete ablation of the treated cysts in greater than 95 percent of cases, without imaging evidence of scar formation or tissue retraction.

Massive LMs have been successfully treated in the neck, chest, abdomen, and mesentery without complications. In the treatment of large cysts there is a 15 percent incidence of repeat hemorrhage in cysts following sclerotherapy. Following repeat hemorrhage, a second treatment has been effective for ablation in 100 percent of cases. In our patients, no cases of neuropathy, unexpected skin necrosis, or myoglobinuria have been encountered with sclerotherapy.

In LM that involves the cutaneous epidermis, sclerotherapy targets the LM and involved skin to provide a clean tissue bed for successful skin grafting. Orbital LMs are treated with access from either the inferior or superior eyelid crease, or eyebrow, with no resultant cosmetic deformity. Massive orbital LMs that envelope the optic nerve 360 degrees are successfully treated without visual loss or extraocular muscle

Case Study 1: LM of the Neck, Shoulder and Chest

In the first few hours of life, Hayden underwent a CT scan that clearly illustrated for the pediatric surgeon in Kentucky the extent of the mass, previously seen on a prenatal ultrasound. The mass involved the left neck, shoulder and the entire length of the left chest wall. Surgical mapping indicated extensive surgical resection involving major nerves and vital structures, resulting in an up to 50 percent chance of recurrence.

After consultation with The Lymphatic Malformation Center at Nationwide Children's, the surgeon decided against operative resection and transferred Hayden to Nationwide Children's for definitive interventional radiological treatment. Following the five hour trip from southern Kentucky, Hayden, age 6 months, underwent his first two-hour procedure that ablated more than 95 percent of the lymphatic malformation, through a 2 mm opening in the skin. Hayden came back six months later to complete his second procedure which only took 60 minutes, and was released to go home with only a Spiderman bandaid for a dressing, and no remaining cysts for treatment.

LYMPHATIC MALFORMATION OF THE CHEST, SHOULDER, AND NECK



Figure 1A



Figure 1B

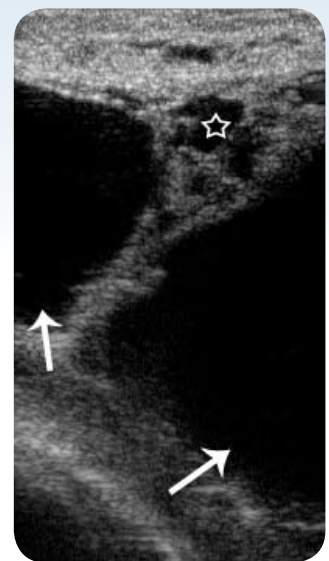


Figure 1C

Figure 1A: CT scan of 6-month-old male with large left chest, shoulder, and neck LM.

Figure 1B: 5F drainage catheters and contrast placed in the dominant chest lobule during primary percutaneous therapy that ablated the LM macrocysts in a single treatment.

Figure 1C: Ultrasound image with macrocysts (arrows) and microcysts (star) successfully treated in the first session.

continued on back page

injury. Patients treated at Nationwide Children's from states other than Ohio undergo clinical follow-up with their local referring physicians and send imaging studies electronically for Nationwide Children's radiologists to review for telephonic follow-up and future treatment decision-making.

LYMPHATIC MALFORMATION OF THE ABDOMEN

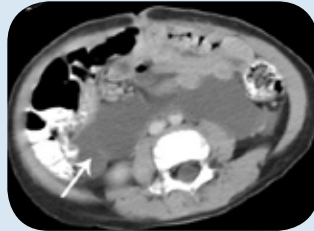
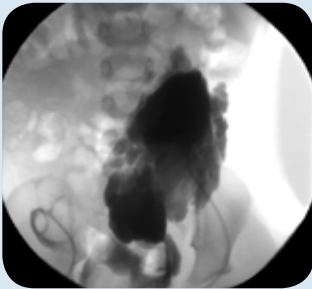


Figure 3B

Figure 3A

2-year-old male with massive intraabdominal LM, which recurred following three attempts at surgical resection.

Figure 3A: Contrast cystogram of one of three large abdominal LM locules during successful ablation procedure.

Figure 3B: CT scan demonstrating the intraabdominal LM (arrows)

Due to the success of percutaneous sclerotherapy, the Nationwide Children's Lymphatic Malformation Center team of radiologists and surgeons have designed treatment pathways that determine when surgery is best for treatment, and if so, prior to or after interventional radiological therapy. In this pathway, surgery is best for solid LM or debulking massive LMs in very small children (due to large volume spontaneous intracystic hemorrhage that could produce significant anemia during a course of staged percutaneous interventional radiological ablation procedures). Once debulked, percutaneous techniques are then used for definitive therapy of residual or recurrent LM.

Because LM percutaneous ablation is a unique minimally invasive procedure used to treat LMs that effect people at any age, Nationwide Children's Radiology Department patient population has grown to include adults as well as children. If you have questions about this procedure, or would like more information, contact Dr. William Shiels at William.Shiels@NationwideChildrens.org.

Bio:

William E. Shiels II, DO, is the chairman, Department of Radiology, Nationwide Children's Hospital and president of The Children's Radiological Institute. Dr. Shiels is a clinical professor of Radiology, Pediatrics, and Biomedical Engineering at The Ohio State University College of Medicine. Dr. Shiels is a clinical professor of Radiology at The University of Toledo Medical College and Visiting Scientist at the Armed Forces Institute of Pathology, Washington, DC. References for this article are available upon request at www.NationwideChildrens.org/PediatricDirections.

Case Study 2: Orbital LM

Jordan, age 13, dreamed of being able to do simple things that his friends enjoyed, such as running track, playing baseball, and rollerblading, to name a few. Since the age of 3, Jordan had undergone treatment for a left orbital lymphatic malformation. Each intervention provided little success at relieving his proptosis or recurrent symptoms. By age 13, when his LM flared up it sent him to the hospital with a severe headache, visual loss and bradycardia. Surgeons operated to attempt removal of the mass, drained the cystic spaces and consulted with experts around the country for other surgical options. One leading east coast pediatric teaching center suggested that if additional treatment were attempted, they anticipated Jordan would have a three to four month inpatient stay, and the high risk of recurrence.

Before proceeding with additional surgical options, Jordan's oculoplastic surgeon in Kansas placed his case on the Internet, for fellow oculoplastic surgical opinions around the country. Dr. Kenneth Cahill, Oculoplastic Surgeon at Grant Medical Center and Nationwide Children's Hospital, read the e-mail and recommended that Jordan come to Nationwide Children's for treatment. Following Dr. Cahill's recommendation, Jordan's surgeon followed up with his family who opted to make the trip and bring their son to Nationwide Children's. Jordan needed just one interventional radiology procedure, with a 23-hour inpatient stay.

As a result of the procedure, Jordan no longer has proptosis, and has no recurrence of his bradycardia. At age 13, Jordan is realizing his dream of enjoying the simple things. Now his biggest physical complaint is sore leg muscles from running track.

LYMPHATIC MALFORMATION OF THE ORBIT

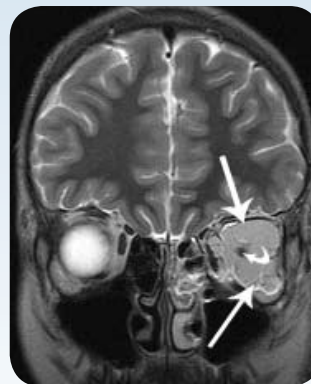


Figure 2A

Figure 2A: MRI of 13-year-old male with proptosis due to retrobulbar lymphatic malformation (straight arrows). Note the optic nerve (curved arrow) that is encased by the LM.



Figure 2B

Figure 2B: 5F drainage catheter in position for drainage and ablation.



Figure 2C

Figure 2C: Contrast cystogram defining the orbital cystic mass prior to ablation.