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Lymphatic Interventions

Techniques in Vascular and Interventional Radiology

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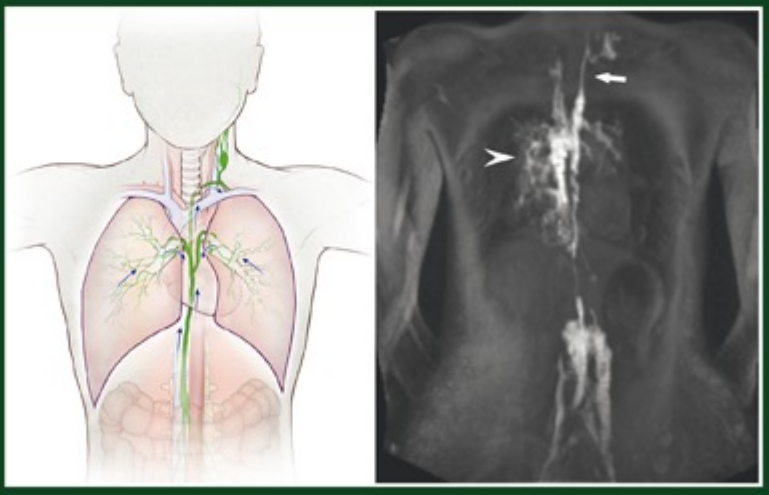

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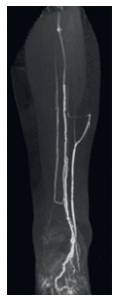

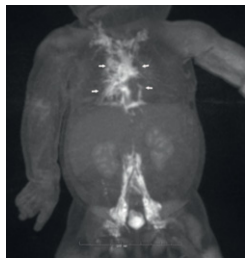

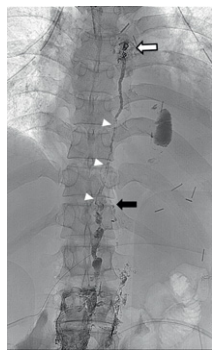

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Techniques in Vascular and Interventional Radiology

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Introduction

It has been 20 years since one of the founders of interventional radiology, Constantine Cope, introduced the first lymphatic interventional procedure, thoracic duct embolization, a concept that was all but inconceivable during that time.[1] I remember being completely stunned reading about a procedure that sounded like science fiction. The thoracic duct embolization became a gold standard in the treatment of chylothorax 20 years later in the most academic and private institutions around the globe. More importantly, it opened the door for a completely new type of treatment—image guided lymphatic interventions, providing the patient with new innovative treatment approaches.

Overall, 60% of the human body consists of water and represents a collection of colloid and crystalloid solutions with different concentrations of electrolytes, proteins, fats, and sugars. The vast majority of body resources are dedicated to maintaining this gentle balance, and the lymphatic system is in the center of this. Fascination with this fluid has been occupying the minds of intellectuals for many generations, and extensive research has been conducted to understand the anatomy of the lymphatic system, which early on was proven to be extremely complex.[2] Ernest Starling was the first to describe the mechanism of lymph production by introducing the "Starling equation" at the end of the 19th century.[3] This knowledge inspired multiple investigators to look deeper in understanding the role of lymph in the fluid metabolism. Lymphatic flow research exploded and immense progress has been made in the understanding of the complex interface of the vascular and lymphatic systems.[4,5] In spite of the significant progress in the lymphatic research, the clinical application of this knowledge has been limited, primarily owing to the extreme complexity of lymphatic anatomy, difficulties in its imaging, and lack of intervention options.

The imaging of the lymphatic system lagged behind vascular imaging, primarily due to difficulties in delivering contrast material into the lymphatic vessels. Until recently, there were only 2 methods: direct cannulation of the lymphatic vessels (pedal lymphangiography) and interstitial injection of the contrast agents that are absorbed into the lymphatic system (lymphoscintigraphy and lower extremities magnetic resonance [MR] lymphangiography). Pedal lymphangiography was first described by Hernani Monteiro at the University of Porto in 1931, but it was the contribution of John Bernard Kinmonth, with direct injection of radiopaque contrast into pedal lymphatic vessels, that promoted clinical utilization of the technique to study lymphatic disorders.[6] Pedal lymphangiography, however, is technically tedious, associated with a significant number of complications and is limited in its ability to image the central lymphatic system. Lymphoscintigraphy, on the contrary, delivers poor anatomical resolution, however, can provide important information regarding lymphodynamics. Lower extremity MR lymphangiogram has been developed over the last decade and has proven to be valuable in patients with lymphedema of lower and upper extremities.[7]

The introduction of the intranodal lymphangiogram, as an alternative to pedal lymphangiography, changed the field of the lymphatic interventions.[8,9] Based on simple ultrasound-guided needle placement into inguinal node, followed by injection of iodinated contrast, the technique has been adopted with enthusiasm worldwide and brought the lymphatic intervention procedures out of the shadow of a few academic centers into the community.[10] Intranodal lymphangiogram is an excellent modality for guiding the interventions; however, due to physical properties of the oil-based contrast agent, imaging of the central lymphatic system remained inadequate. Application of the intranodal injection technique as a way to deliver gadolinium-based contrast agents into the lymphatic system for MR imaging gave birth to dynamic contrast-enhanced MR lymphangiography.[11,12] Dynamic contrast-enhanced MR lymphangiography became an instant hit in our institutions owing to its exceptional ability to visualize the central lymphatic system. This technique already allowed discovery of the cause of plastic bronchitis, a deadly complication of Fontan surgery in patients with single ventricle, as well as the cause of adult lymphatic plastic bronchitis and neonatal chylothorax, and allowed the development of the concept of abnormal pulmonary lymphatic flow known as "Pulmonary Lymphatic Perfusion Syndrome."[13,14]

Since the original description by Constantine Cope, lymphatic embolization techniques evolved over the years. Many creative physicians tried to introduce new interventional

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approaches to the lymphatic system, including retrograde transvenous thoracic duct, computed tomography-guided approaches, and interstitial injection of N-BCA glue into lymph nodes and lymphatic tissue.[15,16] The last technique, however, holds its own merit as an innovative approach that can be applied in other areas rich in lymphatic vessels, such as in liver and retroperitoneal lymphatics.[17]

With all the recent progress in lymphatic imaging and interventions, there is still a lot unknown and a lot of place for more progress. Two main lymphatic systems, liver and intestinal, which generate approximately 80% of the lymphatic fluid in the body, remain practically unexplored due to the absence of an appropriate imaging technique. The importance of the liver lymphatic system in heart failure and liver cirrhosis in development of abdominal ascites has been established many years ago.[4,5] Liver lymphangiogram and liver lymphatic embolization, the techniques we are exploring at the moment for patients with protein-losing enteropathy, hold some promise to be the first modality to help us get insight into understanding of these systems.

Lymphatic imaging and interventions research and further development of the treatment options can be the next frontier for interventionalists that can significantly change the way we practice medicine.

Maxim Itkin, MD
Guest Editor

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Techniques in Vascular and Interventional Radiology

Lymphatic Anatomy

Michael C. Hsu, MD,[*] and Maxim Itkin, MD, FSIR[†,*]

Recent development of new lymphatic imaging and intervention techniques, such as intranodal lymphangiogram, dynamic contrast enhanced magnetic resonance lymphangiography and lymphatic embolization, have resulted in the resurgence of interest in the lymphatic anatomy. The lymphatic system is a continuous maze of interlacing vessels and lymph nodes and is extremely complex and variable. This presents a significant challenge for interpretation of imaging and performance of interventions on this system. There is an embryological reason for this complexity and variability; the lymphatic system sprouts off of primordia from several locations in the body, which later fuse together at different stages of development of the embryo. The lymphatic system can be divided in three distinct parts: soft tissue lymphatics, intestinal lymphatics, and liver lymphatics. Liver and intestinal lymphatics generate approximately 80% of the body lymph and are functionally the most important parts of the lymphatic system. However, their normal anatomy and pathological changes are relatively unknown. In this chapter we will explore the anatomy of these three systems relevant to lymphatic imaging and interventions.
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KEYWORDS Lymphatic, Anatomy, Embryology

Compared with vascular, the lymphatic system anatomy is extremely complex and variable. Most of the lymphatic vessels are very small and together with lymphnodes they create a maze of interlacing vessels. For that reason, classical anatomical research methods, such as continuous dissection and corrosion casting, are hindered. In spite of that, since Greek times scientists and physicians have tried to explore the structure and function of these small vessels filled with colorless and milky fluid. However, not until the Renaissance era, in 1552, is Eustachius credited as being the first to discover and name this milky colored duct "Vena albathoracis" after observing it during a horse dissection. However, it was GasparoAselli (1581-1626), a professor of anatomy and surgery in Pavia, who was the first to observe "lacteal vessels," while dissecting a dog after a heavy meal, tracing them from the gut to the mesentery. Later, Bartholinus (1653) understood the connection between different parts of the lymphatic system and Rudbeck during the same time first described the lymphatic vessels on the liver surface. The famous French anatomist Rouviere published the most extensive anatomical description of the lymphatic system in 1938.

The lymphatic system consists of at least the following 3 distinct parts: soft tissue lymphatic system, intestinal lymphatic system, and liver lymphatic system.[1-4] All 3 systems communicate with each other and eventually coalesce together at the level of the cisterna chyli and continue in the thorax as the thoracic duct (TD). As an analogy, the thoracic duct represents the trunk of an inverted lymphatic tree a simple approximation represents a reverse tree where the thoracic duct represents the trunk. The terminal drainage of lymphatic fluid is the venous system via lympho-venous connections. The main lympho-venous connection is between the thoracic duct and junction of the left subclavian and internal jugular veins (Fig. 1). While multiple other normal lympho-venous connections exist in the body (Fig. 2), it should be noted that functional or anatomic occlusion of downstream lymphatic vessels can result in opening of new, pathologic lympho-venous connections, which can become clinically relevant[5].

The core function of the lymphatic system is collection of excess interstitial fluid from the soft tissues with eventual return to the venous system. However, the

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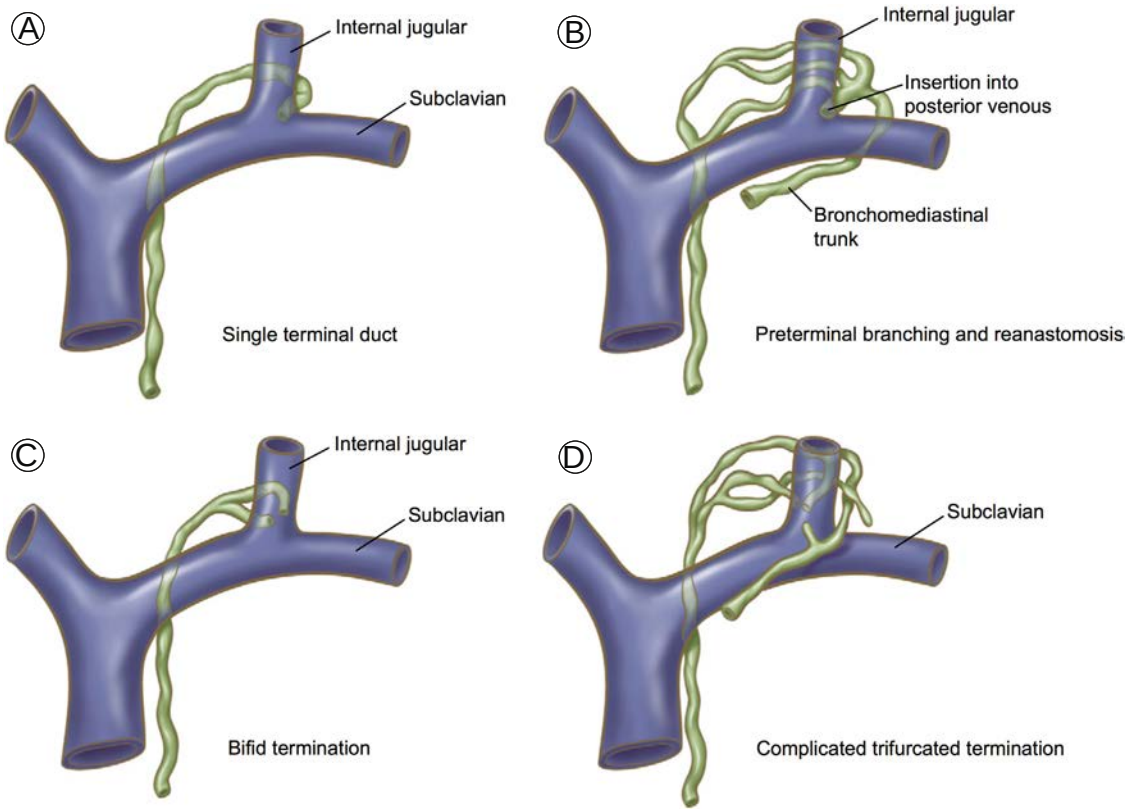

Figure 1 Illustration of variations in termination of the thoracic duct: (A) typical termination of the thoracic duct (single terminal duct), (B) preterminal branching and reanastomosis of the thoracic duct, (C) bifid termination, and (D) complicated trifurcated termination. (Reprinted with permission from Hematti and Mehran.[18]) (Color version of figure is available online.)

lymphatics also These three systems not only drain different part of the body, but perform other important functions in addition to removal of the excessive interstitial fluid. The intestinal lymphatics system actively participates in absorption of dietary fats, and and the liver lymphatics system delivers liver-producedhepatic proteins into the systemic circulation. The clinical presentation of lymphatic flow abnormalities in these lymphatic systems is completely highly different variable, and rangesincluding from lymphedema due tofrom soft tissue lymphatic obstruction of the soft tissue lymphatic toand liver lymphorrhea and chylous ascites from lymphatic leakage, such as liver lymphorea and chylous leaks.

The core function of the lymphatic system is collecting the residual interstitial fluid from the soft tissue and delivering it back into veins through lympho-venous connections. The main lympho-venous connection is between the thoracic duct and junction of the left subclavian and jugular veins (Fig. 1). However, there are multiple other lympho-venous connections at different levels of the body (Fig. 2).[5] More importantly, functional or anatomical occlusion of the lymphatic vessels downstream can result in opening of new lympho-venous connections, resulting in changes that can become relevant under some clinical scenarios.

The imaging anatomy of extremity, pelvic, lumbar, and central (cisterna chyli and thoracic duct) lymphatic systems is well known and has been described based ondemonstrated with conventional lymphangiogram and, more recently, lower extremity Magnetic resonance lymphangiography[6-8]. Traditionally, abdominal and pelvic lymphatic anatomy has been more extensively studied with lymphangiograms to delineate lymph node involvement in the setting of malignancy. While radiologists often neglected this system. it is more recently gaining more attention as intranodal lymphangiogram and glue embolization are becoming new diagnostic and treatment options for patients with chylous ascites and lymphocele (Hur S, Shin JH, Lee IJ, et al. Early experience in the management of postoperative lymphatic leakage using lipiodol lymphangiography and adjunctive glue embolization. J Vasc Interv Radiol 27:1177–1186.e1, 2016; Baek Y, Won JH, Chang SJ, et al. Lymphatic embolization for the treatment of pelvic lymphoceles: preliminary experience in five patients. J Vasc Interv Radiol 27:1170–1176, 2016). Despite these advances, the anatomy of the liver and intestinal lymphatics remain relatively unknown, due to absence of clinical imaging techniques. Since they combine to produce approximately 80% of the body's lymph, understanding the anatomy and pathology of these two particular systems is far more important than any other lymphatic system. Furthermore, lymphatic flow in these systems can increase tenfold during certain pathological conditions, significantly affecting fluid exchange

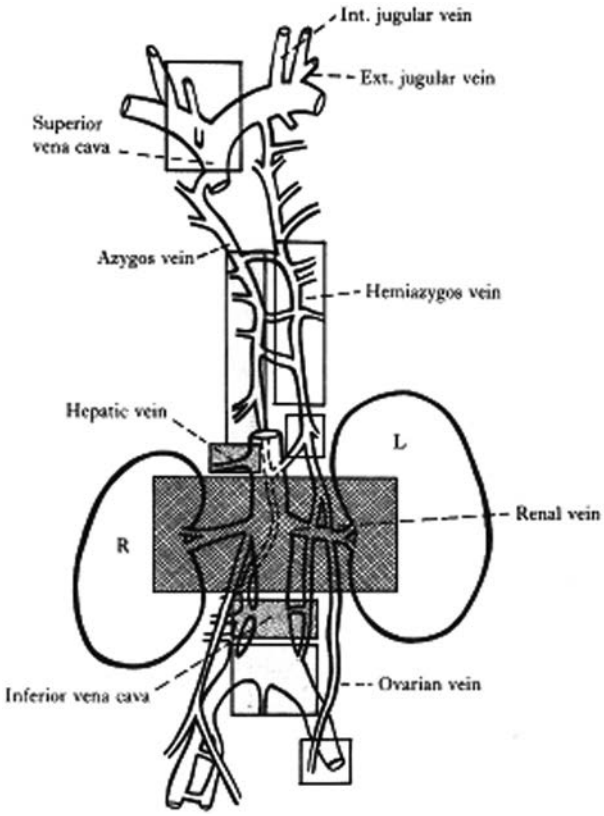

Figure 2 Sites of lymphovenous communications and their frequency in mammals. The degree of the frequency is indicated by the density of shading. (Reprinted with permission from Threefoot.[5])

(Dumont AE, Witte MH. Significance of excess lymph in the thoracic duct in patients with hepatic cirrhosis. Am J Surg 1966;112:401–406; van der Putte SC, van Limborgh J. The embryonic development of the main lymphatics in man. Acta Morphol Neerl Scand 1980;18:323–335)[9-12]

The objective of this article is to provide readers with an update on lymphatic anatomy.

Cisterna Chyli and TD Anatomy

The TD is the largest and longest lymphatic duct in the body and can reach up to 45 cm in length. It represents the terminal part of the lymphatic system and drains lymph from 80%-90% of the body, except right hemithorax, right head and neck, and right arm. For the lymph from these parts of the body drains into the right lymphatic duct. The TD drains into the junction of the left internal jugular and subclavian veins whereas the right lymphatic duct empties into the junction of the right subclavian and right internal jugular veins.

There are significant variations in the anatomy of the TD due to complex embryological development.[13,14] The lymphatic system primordia sprout off the veins as separate lymphatic sacs that form initially in the jugular-axillary area and then in the retroperitoneum, mediastinum, and pelvis. All of the primordial lymph sacs fuse together at different stages of development of the embryo and lose their connection with veins, with the exception of 2-3 connections between jugular-axillary lymph sacs and venous angles. At the age of 56 days, right and left TDs are developed and then the right TD elongates and fuses with jugular-axillary lymphatic sacs, whereas the left TD superiorly ends blindly. The number and level of the anastomoses between the 2 TDs has been shown to be variable in older embryos.[13]

The TD usually starts with the cisterna chyli, which is typically located at the level of L1-L2 as a fusiform dilatation. It is located behind the lower part of the right crural pillar and between the aorta and inferior vena cava (IVC). The cisterna chyli is formed by the confluence of the left lumbar trunk and intestinal trunk and, rarely, right lumbar trunk, with significant variability is observed in these relationships (Fig. 3).[15]

The TD crosses from the retroperitoneum into the mediastinum in the space between the aorta and azygos vein, through the aortic hiatus.[16] Ascending through the mediastinum it accepts paired intercostal lymphatic ducts from lower 6-7 intercostal spaces as well as lymphatic ducts from multiple mediastinal structures.[17] In its classic presentation, the TD ascends in the posterior mediastinum to the right of the midline, and at the level of T5 the duct crosses midline and ascends toward the thoracic inlet along the left edge of the esophagus.[18] Although often a single channel, the TD was found to have multiple channels in 40%-60% of cases.[14,19,20] The distal TD ascends 2-3 cm above the clavicle then courses posterior the internal jugular vein, curving inferiorly to drain into the junction of the left internal jugular and subclavian veins. The termination of the distal TD in the venous system is highly variable and has been the subject of multiple anatomical and radiological studies (Fig. 1).[21-24]

As mentioned earlier, variability of the course of the TD is significant and multiple classification schemes were proposed. Most of them are based on the embryological development of the TD as a pair of the left and right duct that are connected with a network of the lymphatic vessels (Fig. 4).[14,18,25]

Liver Lymphatic Anatomy

Hepatic lymph originates in the perisinusoidal space of Disse and Mall (Fig. 5).[26] The perisinusoidal space is the site of exchange of materials between blood and hepatocytes which contains interstitial fluid (mostly plasma) and migrating cells. Excess interstitial fluid that remains in the perisinusoidal space passes through channels between hepatocytes and through the space along the initial segment of the hepatic sinusoids to enter the connective tissue along the portal tract ultimately draining into lymphatic vessels around portal vein branches.

Normal liver lymphatics are not visualized in cross-sectional studies because of their small size. However under certain conditions, such as congestion in patients

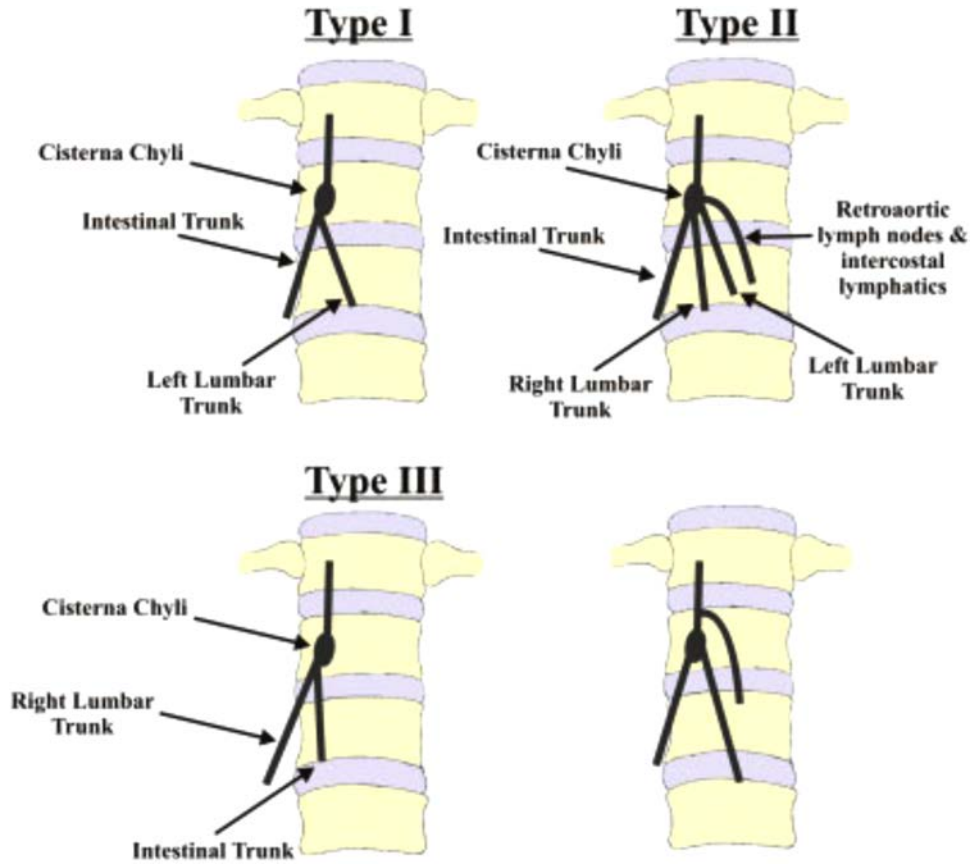

Figure 3 Schematic representation of the lymphatic origin of the cisterna chyli. The most common configuration (45%) was a single cisterna chyli formed by left lumbar trunk and intestinal trunk (Type 1). In 30% of cases, lumbar trunks, intestinal trunk, and other lymphatic join cisterna chyli directly (Type II) and 20% of cases cisterna chyli is formed by union of right lumbar trunk and intestinal trunk (Type III). In 5% of the cases the anatomy cannot be classified. (Reprinted with permission from Loukas et al.[15]) (Color version of figure is available online.)

with liver cirrhosis or following liver transplantation, they manifest as a periportal thickening on computed tomography or ultrasonography.[27] The classification of the liver lymphatic ducts is based on location within the liver and flow direction. Lymphatic ducts are divided into deep lymphatics, which follow portal and hepatic veins tracts, and superficial lymphatics which are located on the surface of the liver (Fig. 6). The deep lymphatic system drains into periportal lymphatic ducts where 12-15 separate lymphatic ducts run alongside the hepatic artery and then drain into lateral to the superior pancreatic lymph nodes and to the lateral aortic group. Other ducts connect to the celiac lymph nodes and then into the TD. They also communicate with intestinal lymphatic ducts that then jointly drain into the TD. It is possible that because of these complex communications, ascites in patients with liver cirrhosis can sometimes be chylous.[28] The other group of deep lymph vessels accompanies the hepatic veins and continues in the wall of the IVC (Fig. 6A). The superficial lymphatics from the convex surface of the liver drain directly into mediastinal and peripancreatic lymphatic vessels and lymph nodes through hepatic ligaments and diaphragmatic openings around the IVC (Fig. 6B). Superficial lymphatics from the concave surface of the liver drain to the liver/hilar lymph nodes and from the right hepatic lobe to the right periaortic lymph nodes.[29]

Pathological retrograde flow in the liver lymphatic vessels has been described while performing lymphangiogram.[30] In our practice we observed retrograde flow primarily in patients with increased lymphatic flow in the lumbar lymphatic ducts.

Inguinal Lymphatics

Located inferior to the inguinal ligament, the inguinal lymph nodes serve an important relay in the lymphatic system from the lower limb as well as filtering lymphatic drainage originating from the groin, penile, vulvar, and rectal areas (Fig. 7). The lymphatic system of the inguinal region is divided into superficial and deep inguinal lymph nodes by the fascia lata. The superficial inguinal lymph nodes, which range in number from 4-25, are bounded superiorly by the inguinal ligament, laterally by the sartorius muscle, medially by adductor longus, and are located superficial to the fascia lata and cribiform fascia, which separates them from the femoral neurovascular bundle and deep inguinal lymph nodes.[31]

The superficial inguinal lymph nodes are further subdivided based on relative location to the saphenofemoral junction (Fig. 7A). The *superior group* is distributed parallel

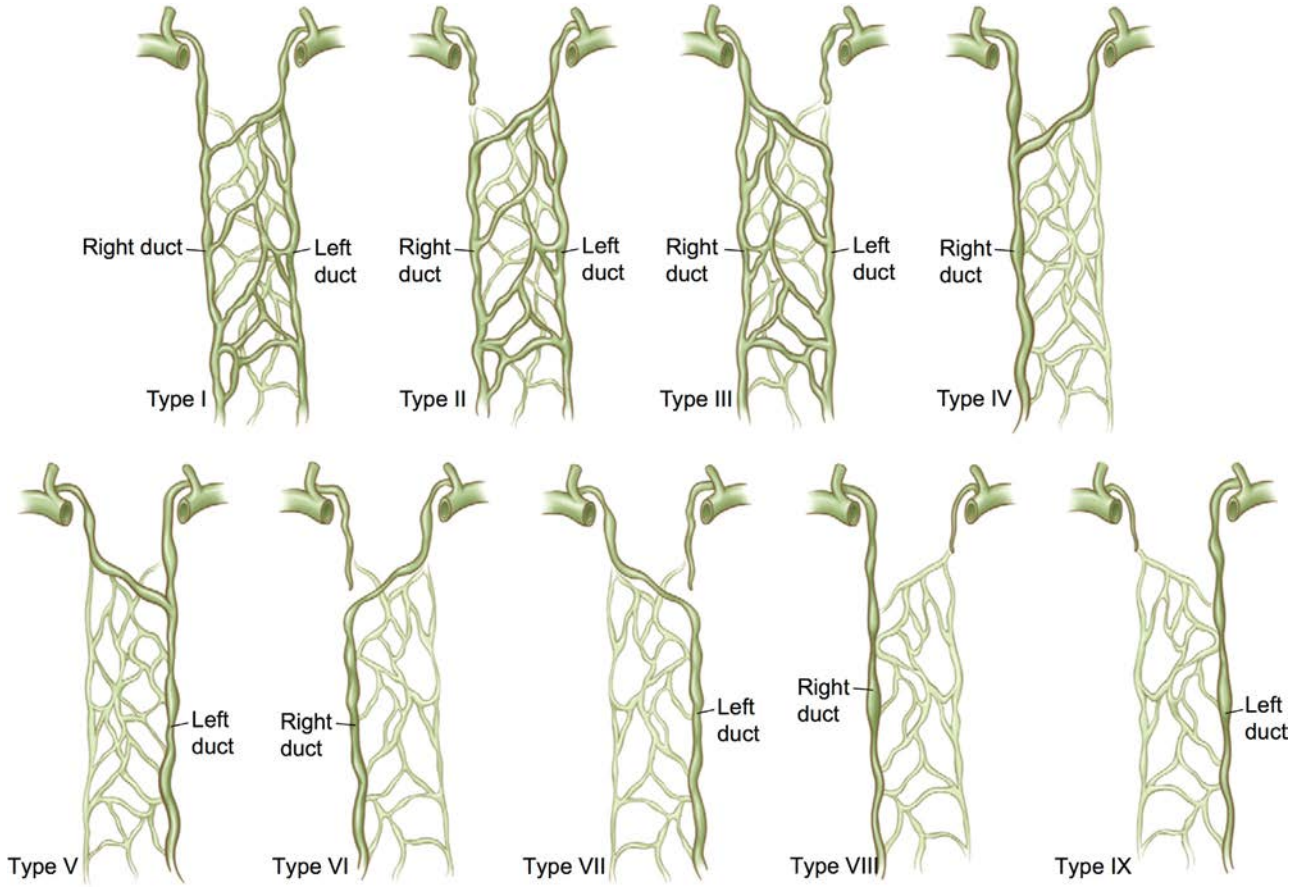

Figure 4 Nine types of the thoracic duct anatomy based on Davis.[25] The most common types are Types VI and II. (Reprinted with permission from Hematti and Mehran.[18]) (Color version of figure is available online.)

but inferior to the inguinal ligament, whereas the *inferior group* is distributed vertically along the terminus of the great saphenous vein. The *superomedial group* is associated with the superficial epigastric and external pudendal vessels. These lymph nodes receive afferent drainage from the hypogastric abdominal wall below the umbilicus, medial gluteal region, and external genitalia, including the skin of the penis, scrotum, vulva, distal vagina, and inferior anal canal/perianal region.[31,32] The *superolateral group* is associated with the superior circumflex iliac vessels with afferents originating from the integument of the lateral gluteal region, lower back, adjacent lateral anterior abdominal wall below the umbilicus, and posterior aspect of the upper thigh.[31-35]

The *inferomedial* and *inferolateral groups* receive superficial lymphatic drainage of the lower limb, except the lateral foot and posterolateral calf, mainly via the medial

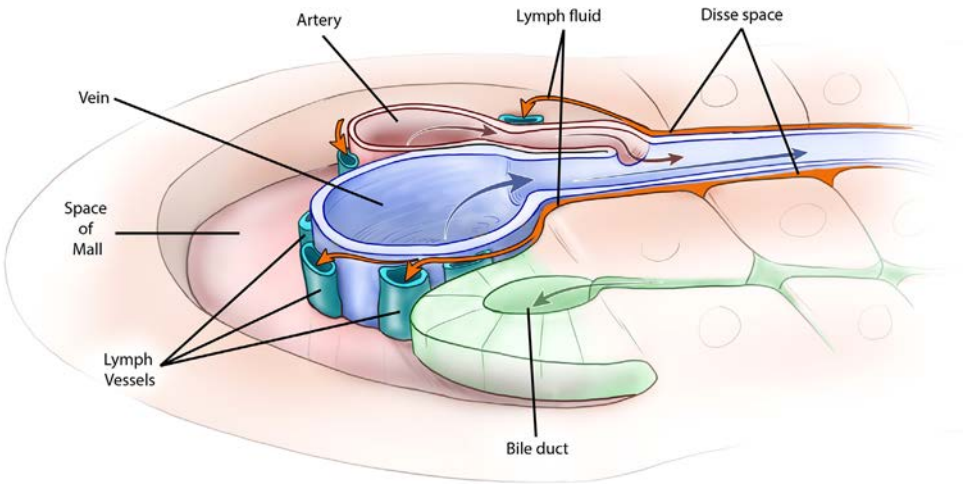

Figure 5 Schematic diagram of the microanatomy of the hepatic lymphatic vascular system. (Printed with permission from The Children's Hospital of Philadelphia. © 2016. All Rights Reserved.) (Color version of figure is available online.)

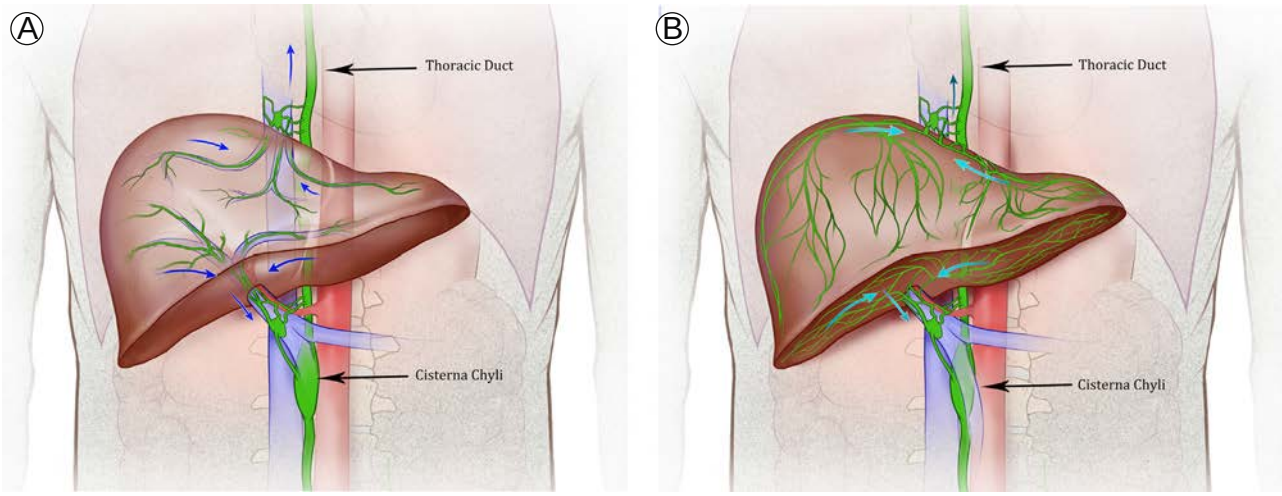

Figure 6 Schematic diagram of the deep (A) and superficial (B) lymphatic system of the liver. (Printed with permission from The Children's Hospital of Philadelphia. © 2016. All Rights Reserved.) (Color version of figure is available online.)

superficial lymphatic pathway with some contribution from the lateral superficial lymphatic pathway.[34]

The efferent lymphatic vessels from the 4 subgroups travel to the deep inguinal lymph nodes either through the saphenous opening or directly through the cribiform fascia, which creates its fenestrated appearance. In some people, the 4 subgroups converge toward a central lymph node or group of small lymph nodes, when present, located within the saphenous opening before reaching the deep inguinal lymph nodes.[31,32] Additionally, some efferents from the inferior group of the superficial inguinal lymph nodes course directly into the pelvis through the femoral ring along the medial aspect of the common femoral artery to the external iliac chain, particularly the lateral and intermediate lacunar lymph nodes.[32,36]

The *deep inguinal lymph nodes* are comprised of 1-3 lymph nodes located along the medial side of the femoral vein deep to the fascia lata. This system receives afferent

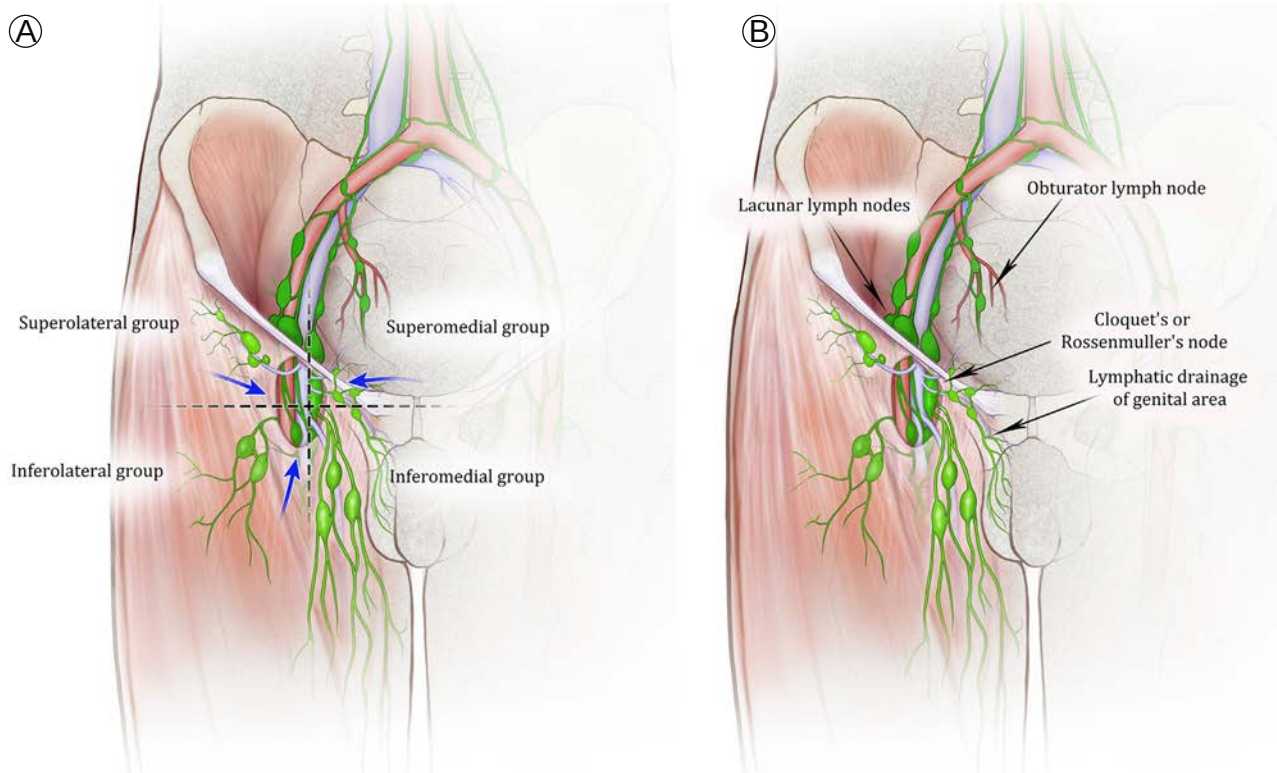

Figure 7 Schematic representation of the inguinal and pelvic lymph nodes: (A) Lymph flow direction in inguinal area and 4 superficial lymph nodes groups and (B) lymph nodes of the inguinal and pelvic areas. (Printed with permission from The Children's Hospital of Philadelphia. © 2016. All Rights Reserved.) (Color version of figure is available online.)

drainage from the deep lymphatic network of the lower limb coursing with the femoral vessels, the superficial inguinal lymph nodes, and the glans of the penis and clitoris. The efferent lymphatics from this system drain into the *lacunar external iliac nodes*. When all 3 lymph nodes are present, there is typically 1 inferior lymph node located inferior to the saphenofemoral junction, 1 superior lymph node located medially within the femoral ring, and 1 lateral lymph node lateral to the femoral ring. Although the lateral deep inguinal lymph node is most commonly absent, the superior lymph node located in the femoral ring is most commonly present and is referred to as *Cloquet's or Rossenmuller's* node. Often protruding into the pelvis, this node is particularly important as it is thought to link the inguinal lymph nodes with the iliac and obturator lymph nodes located superior to the inguinal ligament.

Iliac Lymphatics

The external iliac lymph node chain is typically comprised of 9-10 lymph nodes forming 3 distinct chains of approximately 3 nodes each, called the lateral, middle/intermediate, and medial chains. The lateral chain often has the largest nodes and is located lateral to the external iliac artery but medial to the psoas muscle. The most inferior node in this particular chain, named the *lateral lacunar lymph node*, is located deep to the inguinal ligament and crosses the femoral septum near the origin of the deep inferior epigastric and deep circumflex iliac arteries. This lymph node receives afferent drainage from the corresponding lymph node groups along these vessels. The middle, or intermediate, lymph node chain lies medial to the external iliac artery and anterior to the external iliac vein. The inferior node, often referred to as the *intermediate lacunar node*, is often absent. The middle node is always present and located midway between the inguinal ligament and common iliac artery bifurcation, whereas the superior node is located at the common iliac artery bifurcation and is covered by the ureter. Finally, the medial external iliac lymph node chain is medial to the external iliac vein. Again, *the medial lacunar lymph* node is the most inferior node in this chain and is located posterior to the femoral septum, contacting Cloquet's deep inguinal lymph node. The middle node in this chain, sometimes referred to as the *obturator node*, lies superior to the inguinal ligament adjacent to the obturator internus muscle and receives drainage from Cloquet's node. Generally, the external iliac lymph node system receives afferent drainage from the superficial and deep inguinal lymph nodes that drain first into the lacunar lymph nodes, as well as drainage from the subumbilical abdominal wall. The efferent lymphatic vessels from the external iliac system drain into the inferior lymph nodes of the common iliac lymph node chain. It should be noted that there are interchain anastomotic channels connecting medial to intermediate chain, and intermediate chain to lateral chain with efferent flow terminating in the lateral common iliac chain.

The common iliac lymph node chains normally extend from the aortic bifurcation at L4 to the common iliac bifurcation at S2. Analogous to the external iliac lymphatic system, the common iliac lymph nodes have lateral, middle/intermediate, and medial lymph node chains that drain afferents from the respective external iliac chain with a total of about 4-7 lymph nodes. The lateral chain is located lateral to the common iliac artery. The middle, or intermediate, chain travels along the posteromedial aspect of the common iliac artery and also receive afferent drainage from the internal iliac lymph nodes. Finally the medial chain courses medially to the common iliac artery and terminates at the aortic bifurcation to form an inverted "V" configuration.

Lateral Aortic Lymphatics

The efferent drainage from the common iliac lymph node chains enter the right and left lateral aortic nodes via ascending lymphatic trunks. The left lateral aortic lymph node chain is oriented craniocaudally along the left side of the abdominal aorta, lies on the vertebral attachments of the psoas muscle, and is crossed anteriorly by the left renal vasculature. The right lateral aortic lymph node chain has varying locations with respect to the IVC, including precaval (anterior), postcaval (posterior), laterocaval (lateral), and aortocaval (medial). The efferent lymphatics from both lateral aortic lymph node chains form the right and left lumbar trunks which eventually terminate to form the inferolateral corners of the cisterna chyli.

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Techniques in Vascular and Interventional Radiology

Novel Lymphatic Imaging Techniques

Yoav Dori, MD, PhD

The lymphatic system plays an important role in immune regulation, transport of metabolites, and fluid balance. The key circulatory role of the lymphatic system is to transport fluid from tissue back into the venous system via lymphovenous connections. Despite the centuries-old recognition of this key role, there has been poor understanding of lymphatic flow pathophysiology because of a lack of a simple reliable noninvasive clinical lymphatic imaging method. This lack of clinical imaging has limited the treatment options for patients with lymphatic flow disorders. Recent development of noncontrast magnetic resonance (MR) lymphangiogram and dynamic contrast MR lymphangiography make it possible to visualize central lymphatic anatomy and flow dynamics with high spatial and temporal resolution. Dynamic contrast MR lymphangiography has provided insight into understanding the pathophysiology of several pulmonary lymphatic flow disorders and provides guidance for interventional procedures. Another important development has been intranodal lymphangiogram, which has now replaced pedal lymphangiogram as the main lymphatic interventional modality, and which provides quick and reliable access to the central lymphatic ducts for interventional procedures. These new techniques have led to a resurgence in interest in the lymphatic system and the development of new treatments for patients with lymphatic flow disorders.
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KEYWORDS Lymphangiography, Dynamic contrast MR lymphangiography, Lymphatic flow disorders, Pulmonary lymphatic perfusion syndrome, Lymphatic leaks

Pedal and Intranodal Lymphangiography

Lymphatic flow disorders can involve peripheral lymphatic channels or the central lymphatic system, which includes the thoracic duct (TD), cisterna chyli, and their tributaries. Traditionally, the main imaging technique for central lymphatic for diagnosis and interventional lymphatic procedures has been pedal lymphangiography (PL). This technique involved exposure of small lymphatic ducts in the dorsum of the foot, which were then cannulated, followed by injection of an oily contrast agent (Lipiodol, Guerbet LLC, Bloomington, IN) that would track its way up the legs and into the central lymphatic ducts.[1] PL is invasive, time consuming, and challenging, which made it a significant barrier for most practitioners. Intranodal lymphangiography has now replaced PL as the new method for central lymphangiography.[2,3] This technique involves cannulation of lymph nodes in the groin with thin needles followed by injection of an oily contrast agent that is allowed to proceed up the central lymphatic conducting vessels. Intranodal lymphangiography is faster, less complicated, and has a higher success rate than PL, making it feasible to perform lymphatic procedures in most centers.

Noncontrast Magnetic Resonance Lymphangiography

Noncontrast T2-weighted magnetic resonance (MR) lymphangiography has been described as a noninvasive MR technique that depicts central and peripheral lymphatic system with good spatial resolution.[4-8] T2 imaging exploits the differences in T2-weighted signal intensity between fluid-filled structures and adjacent soft tissue so that slow-moving nonbloody fluids produce high T2 signal. This technique is able to visualize parts of the anatomy of the peripheral lymphatic system in patients with lymphedema, and with lymphatic malformations, as well as segments of the central lymphatic anatomy, including the TD in disease states such as liver cirrhosis.[7,9-11] This technique has also

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been used to demonstrate patterns of abnormal lymphatic anatomy in patients with single ventricle physiology.[12] The main limitations to noncontrast T2 imaging are that it does not provide information about lymphatic flow and the lack of a contrast agent makes it difficult to visualize small lymphatic ducts. Consequently, its use in diagnostic and interventional lymphangiography is limited.

Pedal Lymphoscintigraphy

Intradermal pedal lymphoscintigraphy has been used as a screening tool for disorders of both the central and peripheral lymphatic systems. In addition to anatomical information, lymphoscintigraphy is able to demonstrate regions of abnormal lymphatic perfusion. This additional flow information is key for an understanding of the pathophysiology of certain lymphatic flow disorders.[13,14] Improved anatomical localization with SPECT-CT has overcome the relatively poor spatial resolution inherent to scintigraphy. Despite this improved anatomical localization with SPECT-CT, the spatial resolution of this modality is not conducive to guiding lymphatic interventional procedures (PL is further discussed in a later section of this issue).

Dynamic Contrast-Enhanced MR Lymphangiography

There are 2 types of contrast MR lymphatic imaging techniques: and they are imaging of the extremities and imaging of the central lymphatic system. Multiple techniques have been described for extremity imaging including gadolinium injected intradermally or subcutaneously. Intradermal injected gadolinium-based contrast material has been shown to be absorbed readily into the lymphatic vessels. This technique has been used to delineate lymphatic abnormalities in patients with lymphedema as well as to demonstrate the central lymphatic anatomy in animal models.[10,15-17] However, intradermal contrast injection does not provide sufficient information for imaging of the central lymphatic channels because of dilution of the contrast material leading to poor enhancement of deeper structures.

Dynamic contrast MR lymphangiography (DCMRL) is a new technique, which alleviates this dilution problem by bypassing the lower extremity lymphatics leading to fast and reliable enhancement of the central lymphatic ducts. In addition, this technique shows both static anatomy as well as dynamic flow with good temporal and spatial resolution.[18-20] This new modality is quickly becoming the modality of choice for both diagnostic purposes as well as for preprocedural interventional planning. DCMRL is a safe procedure that can be performed in any age group in all patient populations as long as the patient does not have a contraindication for an MR imaging (MRI) study.

Current indications for DCMRL include as follows:

(1) Nontraumatic lymphatic leak such as chylothorax, chylous ascites, chylopericardium, or chylurea.
(2) Complicated traumatic lymphatic leaks where the source of the leak cannot be visualized with conventional lymphangiography.
(3) Suspected lymphatic complications of lymphatic disorders such as Kaposiform lymphangiomatosis, generalized lymphatic anomaly, Gorham disease.
(4) Plastic bronchitis or other unspecified pulmonary disease of unclear etiology where the lymphatic system could be suspected to play a role in the disease process.
(5) Congenital lymphatic flow disorders such as congenital lymphatic dysplasia, neonatal chylothorax, and neonatal chylous ascites.
(6) Suspected secondary lymphatic flow abnormalities, such as ascites or chylothorax, due to systemic disease such as heart failure or liver cirrhosis.

Absolute contraindications to DCRML are the same as for any conventional MRI and include presence of some implantable electric and electronic devices such as pacemakers with epicardial leads. Relative contraindications include correctable coagulopathy and claustrophobia.

DCMRL Technique

Lymph node access, which requires proper needle placement, is done using ultrasound and fluoroscopy guidance. Consequently, DCMRL procedures are started in a fluoroscopy suite or in a suite with available ultrasound and c-ARM. After properly positioning the patient on the table, an inguinal lymph node is directly accessed under ultrasound guidance with a 25-gauge spinal needle connected to a 3 mL syringe via a short connector tubing (BD Medical, Franklin Lakes, NJ)[3] (Fig. 1). The needle tip is

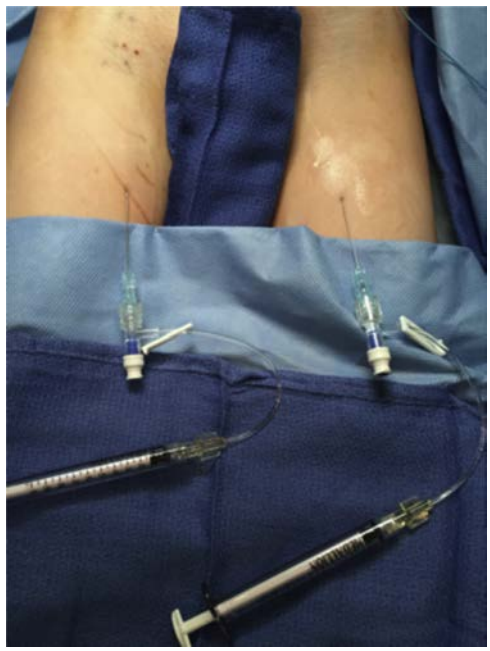

Figure 1 A 25-gauge 3.5 cm spinal needles placed in bilateral inguinal LN's before DCMRL. (Color version of figure is available online.)

Figure 2 XMR suite with patient transferred from Miyabi table into the MRI scanner. (Color version of figure is available online.)

positioned in the hilum of the lymph node and position is confirmed with either injection of a small amount of iodinated contrast agent or a few drops of the oil base contrast agent Lipiodol (Ethiodol; Savage Laboratories, Melville, NY). If the lymph node or its efferent lymphatics are not clearly identified or extravasation is observed, the position of the needle is adjusted until good efferent lymphatic vessel is seen. Once the position is confirmed, the needle is secured with Tegaderm (3M, St Paul, MN), a lymph node in the opposite groin is accessed similarly, and the patient is transferred to the MRI scanner for imaging. Because of the tenuous needle position and inability to confirm needle position inside the MRI scanner, movement of the patient while transferring from the fluoroscopy suite to the MRI machine needs to be done with as a little disturbance as possible. In our institution we use an XMR suite that couples MR scanner with a catheterization laboratory (Siemens, Erlangen, Germany) where a Miyabi sliding table connects both modalities (Fig. 2). However, a detachable MRI compatible table that can be moved into the fluoroscopy suite can be used as well.

DCMRL Protocol

Any 1.5 T or 3 T MRI scanner is suitable for DCMRL imaging. A volume of 0.1 mmoL/kg of undiluted contrast or contrast diluted 1:1 with normal saline is injected by hand into each lymph node at a rate of 0.5-1 mL/min. We use Gadovist (Bayer Healthcare Pharmaceuticals Inc, Wayne, NJ) with good success. One minute after the initiation of the injection, scanning is initiated. For dynamic imaging a contrast-enhanced time resolved MR angiography sequence is used. Typical scanning parameters are as follows: matrix 320 × 240, field of view 300-450 mm, repetition time 3 msec, time to echo 1 msec, flip angle 25°, slice thickness 1.2 mm, isotropic voxel size 1.2 mm × 1.2 mm × 1.2 mm, and scan time per 3D volume of 3-6 seconds with a total scan time ≈ 15 minutes. Typical time course of contrast is shown in Figure 3. At the end we obtain static high resolution MR angiography. A navigated 3D-spoiled gradient echo sequence with inversion recovery works well with the following scanning: matrix 320 × 240, field of view 300-450, repetition time 300, time to echo 1.5, flip angle 20, slice thickness 1.2, and isotropic voxel size 1.2 × 1.2 × 1.2. Scan time for this sequence varies between 1 and 2 minute Other contrast-enhanced sequences are also possible.

Uses of MR Lymphangiography

There are many applications of DCMRL including the assessment of the anatomy of the central lymphatic system before surgery, identification of lymphatic leaks, and determination of the etiology of lymphatic flow disorders in order to help plan interventional lymphatic procedures.

Traumatic Lymphatic Leaks

Lymphatic leaks can be divided into 2 broad categories as traumatic and nontraumatic leaks. Posttraumatic chylous leaks can result as a complication of surgeries such as cardiothoracic and neck surgery leading to chylothorax or oncological surgeries leading to chylothorax or chylous ascites.[21] Percutaneous treatment of traumatic chylous leaks has become the main treatment choice for these patients with a very high cure rate especially when imaging is able to demonstrate the leak source.[21] In patients with traumatic chylothorax, DCMRL can help in identifying the source of the leak and assist in planning interventions by

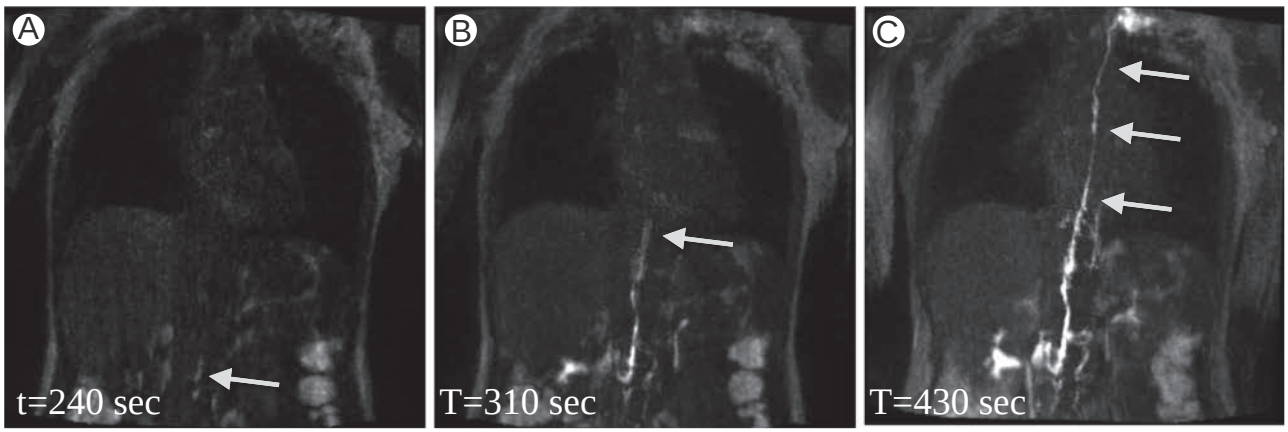

Figure 3 Time course from beginning of injection of contrast in the central lymphatic ducts in a normal person. At 240 second (A) contrast first appears in the cysterna chyli (arrow). At 310 second contrast has reached the level of the diaphragm (arrow) (B). Complete visualization of the TD is seen in 430 second post injection (arrows) (C).

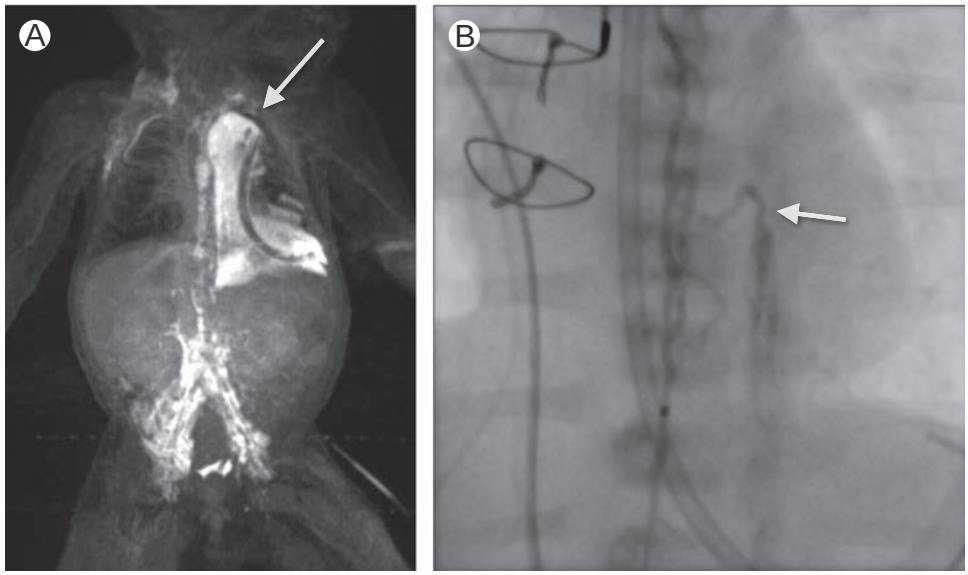

Figure 4 Postsurgical traumatic chylothorax. (A) MIP of DCMRL demonstrates clear filling of the left lung (arrow). (B) Contrast lymphangiogram confirms leak from accessory lymphatic duct at the level of the midthorax (arrow).

identifying the underlying lymphatic anatomy and potential therapeutic targets (Fig. 4). In patients with traumatic chylous ascites, leaks can originate from trauma to peripheral lymphatic ducts such as mesenteric or liver ducts, which would not be visualized by DCMRL. However, when the leak originates in the central lymphatic ducts or their tributaries DCMRL can reveal the location of the leak and provide a possible therapeutic target (Fig. 5).

Nontraumatic Lymphatic Leaks

Nontraumatic lymphatic leaks are a heterogeneous group of diseases with multiple etiologies including idiopathic leaks, leaks due to primary lymphatic disorders such as Gorham disease, generalized lymphatic anomaly, Kaposiform lymphangiomatosis, lymphangioleiomyomatosis and blood cancers, malignancies, etc.[1,22,23] The mechanism of leak in this population is variable and depends on the etiology. Oncological processes and primary lymphatic disorders can obstruct or erode lymphatic channels leading to the leak (Fig. 6). In other instances leaks can originate from lymphatic masses or malformations that appear to generate a large amount of lymphatic fluid, which can cause seeping from or rupture of lymphatic ducts. Because of the variability in mechanisms and etiology of leak in this population the treatment of these disorders is more challenging. Consequently, understanding of the underlying lymphatic anatomy and flow patterns and identifying a possible leak source using

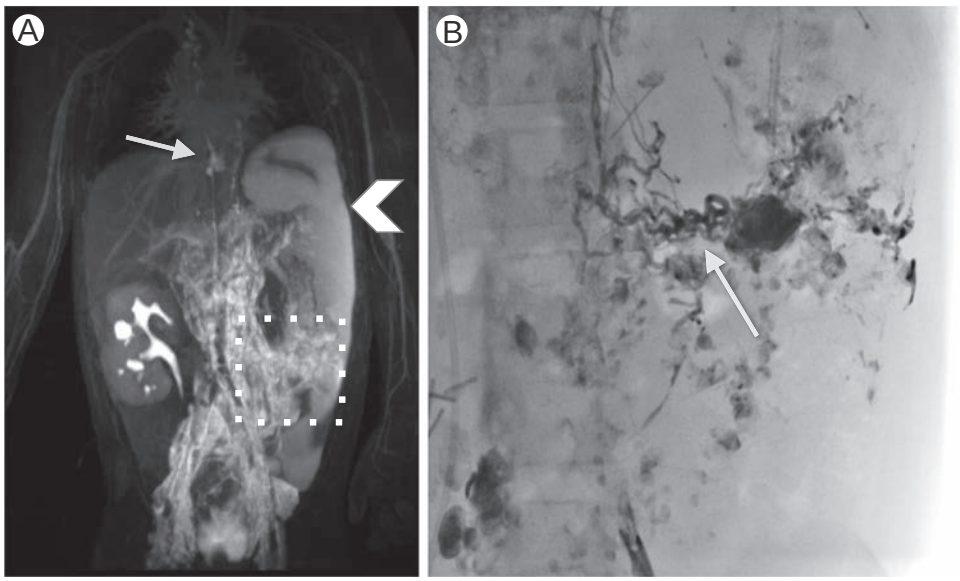

Figure 5 Postsurgical traumatic chylous ascites. (A) MIP of DCMRL demonstrates occlusion of the TD (arrow) with abnormal retrograde perfusion of the mesentery (box) and clear spillage of contrast into the peritoneum (arrow head). (B) Contrast lymphangiogram confirmed the leak source from abnormal mesenteric lymphatic ducts, which were glue embolized with resolution of the leak (arrow).

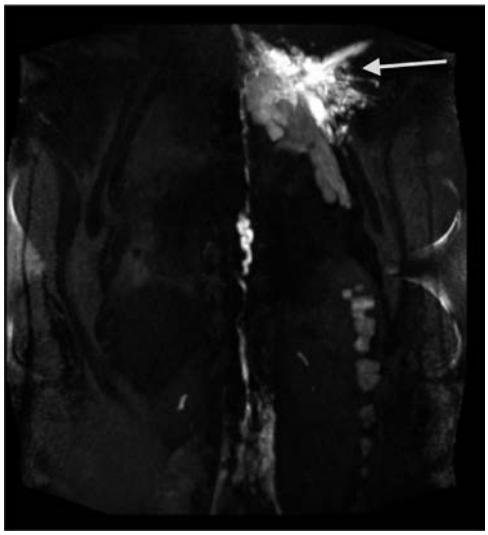

Figure 6 MIP of DCMRL of a nontraumatic chylothorax in patient with Gorham disease. The source of the leak is an abnormal lymphatic network in the left shoulder (arrow).

DCRML is essential for procedure planning and interventional success.[23]

Lymphatic Conduction Disorders

One group of poorly understood lymphatic diseases where DCRML is key in diagnosis and treatment are lymphatic conduction disorders. The etiology of these disorders is not fully understood but they likely result from a combination of congenital lymphatic anatomical variant and abnormal in utero formation of lymphatic ducts or valves that present clinically in response to increased lymphatic flow load such as in the setting of heart failure or liver cirrhosis. Normally, intranodal injection of MRI contrast agent should enhance the lumbar lymphatic channels, cisterna chyli, and TD and flow should propagate from lumbar lymphatics to the TD toward lymphovenous connection between the TD and right subclavian vein. More peripheral lymphatic channels should not enhance if the lymphatic valves are maintaining unidirectional flow. In patients with conduction abnormalities, unidirectional lymphatic flow is not preserved; instead a typical finding on DCMRL is abnormal retrograde lymphatic perfusion. This retrograde flow can present in one or more organs such as lungs, liver, kidneys, and intestinal mesentery (Fig. 7). When this abnormal tissue lymphatic perfusion causes symptoms, treatment might be necessary, and thorough understanding of the patient lymphatic anatomy and lymphatic perfusion patterns is essential for planning and successful intervention. Any attempt to treat these patients without this knowledge can result in irreversible worsening of the disease leading to significant morbidity and mortality.

Plastic Bronchitis and Pulmonary Lymphatic Perfusion Syndrome

One example of a lymphatic conduction disorder, which requires thorough anatomical understanding before treatment is plastic bronchitis. Plastic bronchitis is a relatively rare disorder of abnormal pulmonary perfusion usually secondary to elevated central venous pressure but can also occur in the setting of other diseases or can be idiopathic (Fig. 8).[24,25] The disease is caused by exudation of proteinaceous material and cells in the airways leading to branching cast formation. Embolization of the TD and retrograde pulmonary lymphatic channels responsible for the abnormal flow has been shown to be effective in treating this disease.

Another example of a conduction disorder with pulmonary lymphatic perfusion syndrome (PLPS) is characterized by a narrow or occluded distal TD, a massively dilated and tortuous TD proximal to the narrow region, and unilateral or bilateral PLPS supplied from one or multiple dilated lymphatic ducts originating from the TD (Fig. 9). Embolization of the TD in patients with these character-

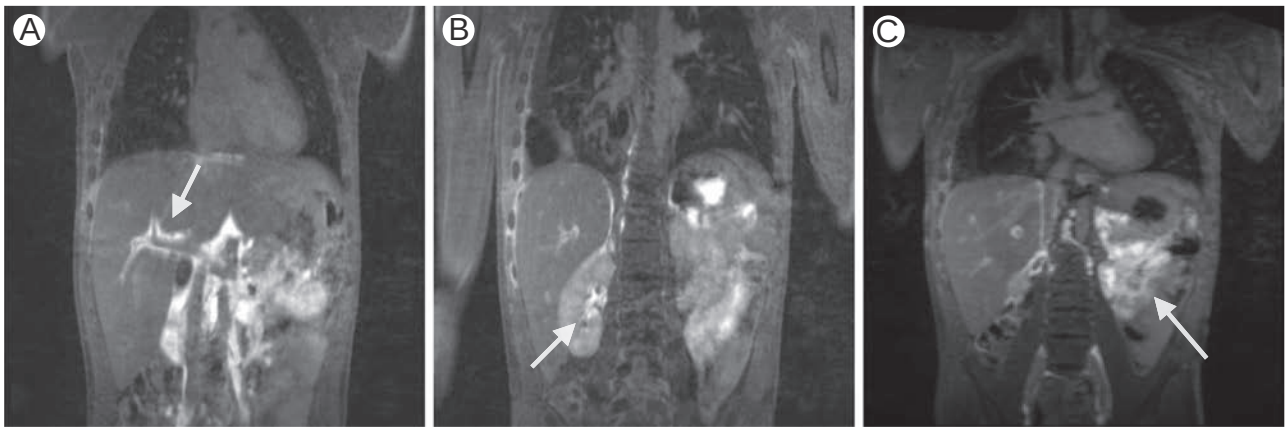

Figure 7 Single slice of DCMRL in a patients with an ill-defined lymphatic conduction disorder. (A) Retrograde flow into the liver parenchyma and periportal lymphatics is seen (arrow). (B) Retrograde flow into the right renal chalychs was demonstrated (arrow). This was not seen into the left kidney (arrow). (C) There is filling of small bowl loops and enhancement of multiple loops of the small intesting due to retrograde mesenteric flow (arrow).

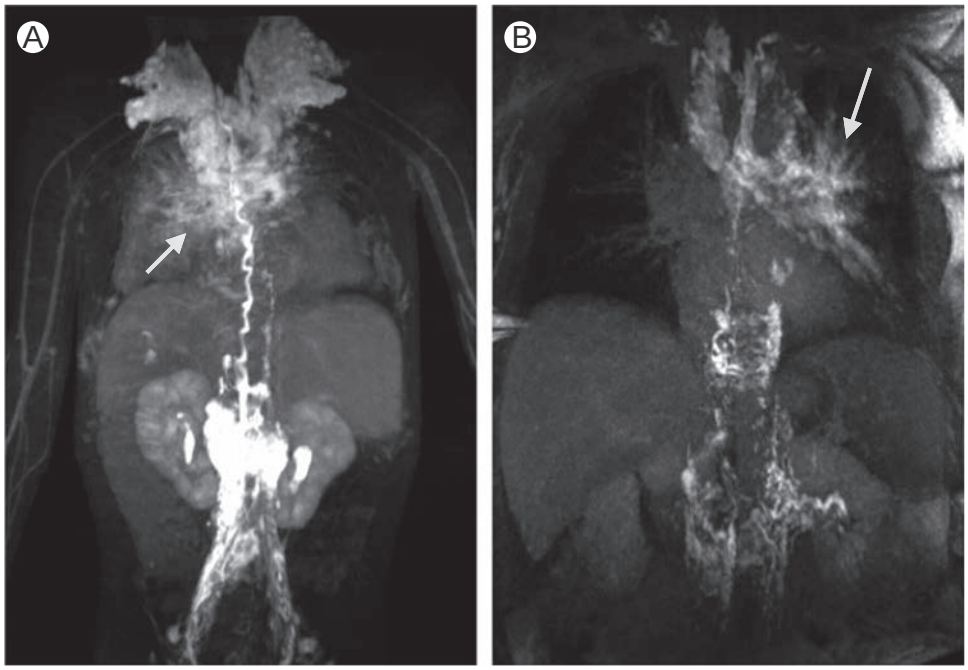

Figure 8 MIP of DCMRL in patient with type 2 PB due to heart disease (A) and patient with type 2 idiopathic PB (B). In both abnormal pulmonary perfusion is seen (arrows).

istic findings and chylothorax or chylous pericardium has been found to be curative. In neonates DCMRL can help distinguish between 2 conduction disorders, neonatal chylothorax, and congenital lymphatic dysplasia (CLD). Neonatal chylothorax is characterized by PLPS on DCMRL, whereas in CLD the perfusion is more diffuse and often involves more than 1 organ system including the lung, mesentery, or dermis. Distinguishing between these 2 disorders is essential because neonatal chylothorax has a good minimally invasive treatment option and good prognosis, whereas CLD is difficult to treat and has a poorer prognosis.[26]

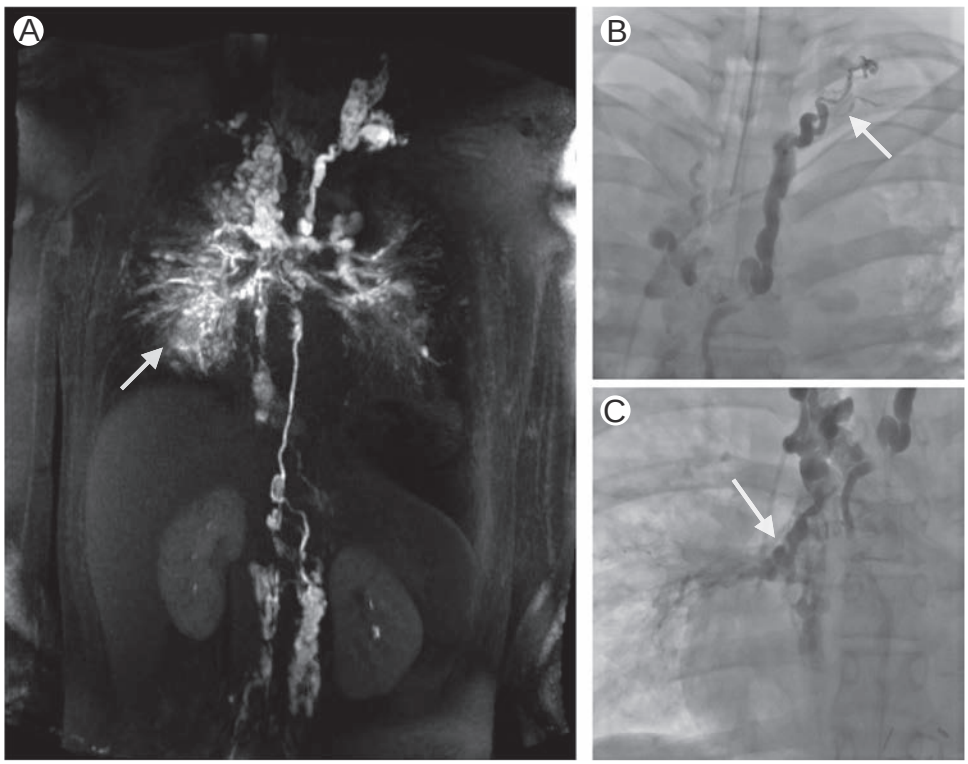

Figure 9 MIP of DCMRL (A) of patient with dilated tortuous TD, distal duct narrowing (arrow), and PLPS (arrow head). (B) Conventional lymphangiogram at the distal duct better demonstrating the narrow regions (arrow). (C) The origin of the abnormal pulmonary flow is seen (arrow).

Complications

DCMRL has no significant risk for complications other than a small risk for infection from the needle access, localized pain that can occur during the needle stick or contrast injection, and contrast reaction. Extravasation of contrast into soft tissue can occur but has not resulted in significant adverse consequences, such as tissue damage, other than resulting in an unsuccessful study due to loss of contrast.

Limitations of DCMRL

DCMRL is able to detect subtle flow abnormalities but the technique has a few potential pitfalls that need to be considered. DCMRL is excellent at demonstrating the anatomy and flow in the central lymphatic ducts but is limited in areas where the flow is diminished or the lymphatic channels are not connected to the central lymphatic system. Furthermore, flow abnormalities can be subtle when the lymphatic leak is small or the abnormal perfusion pattern is subtle. It is possible that this imaging modality would not be able to demonstrate the abnormalities, leading to a false negative study. A negative study can also occur if there are lymphovenous anastomoses proximal to cisterna chyli or if there is a significant susceptibility artifact at the region of interest from devices or wires. Intranodal lymphangiography is often needed to supplement MR lymphangiogram if the DCMRL is negative and there remains a high suspicion for abnormal flow originating from the central lymphatic ducts or there is contraindication to MRI.

Summary

Imaging is the key first step in the diagnosis of lymphatic flow disorders and for lymphatic interventional planning. New imaging modalities, including intranodal lymphangiography and DCMRL, have been developed making it feasible to quickly, reliably, and minimally invasively image the central lymphatic system anatomy and flow. Intranodal lymphangiography has now replaced PL as the main method for conventional lymphangiography, and DCMRL is a new minimally invasive safe lymphatic imaging technique that poses low risk to patients and should be used as the principle method for central lymphatic imaging for both diagnostic purposes as well as for preprocedural interventional planning. These new techniques have led to a resurgence in interest in the lymphatic system and the development of new treatments for patients with lymphatic flow disorders.

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Techniques in Vascular and Interventional Radiology

Peripheral Magnetic Resonance Lymphangiography: Techniques and Applications

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Peripheral lymphedema is a chronic progressive and debilitating disorder that results from abnormal lymphatic drainage. Advances in microsurgical techniques have led to the development of new treatment options for lymphedema that benefit from preoperative imaging to select the most appropriate surgical repair. Magnetic resonance (MR) lymphangiography is a noninvasive imaging modality capable of providing high-resolution 3D images of the lower extremities to define the severity and extent of lymphedema and depict individual lymphatic channels. The MR examination consists of 2 primary sequences. The first is a 3D heavily T2-weighted sequence to depict the severity and extent of the lymphedema. The second is a fat-suppressed 3D spoiled gradient-echo sequence performed after the intracutaneous injection of an extracellular gadolinium-based MR contrast agent. As venous enhancement almost always occurs, one of the interpretative challenges is differentiating enhancing lymphatic channels from superficial veins. MR techniques that can help with venous contamination include the addition of a contrast-enhanced MR venogram to the examination protocol, or the use of an iron-based blood-pool contrast agent to selectively suppress venous enhancement.

KEYWORDS Lymphatics, Lymphedema, Lymphatic Surgery, Lymphangiography, Magnetic Resonance Lymphangiography

Peripheral Lymphedema

Peripheral lymphedema is a chronic progressive disorder caused by altered lymphatic drainage that leads to the accumulation of fluid, cells, and proteins in the extracellular space of the involved extremity. In early stages, lymphedema presents as soft pitting edema of the involved extremity (Fig. 1). In chronic disease, the prolonged interstitial exposure to proteins, debris, and elevated pressure results in hyperproliferative and inflammatory soft tissue changes that lead to skin thickening, fat deposition, fibrosis, and disfigurement (Fig. 2).[1]

Lymphedema is classified as either primary or secondary. Primary disease results from a congenital malformation, aplasia, or hypoplasia of lymphatic channels, whereas secondary disease results from the destruction or obstruction of normally formed lymphatics owing to surgery, radiation, trauma, tumoral blockage, or infection.[2] The most common cause of secondary lymphedema worldwide is infection with *Wucherreria bancrofti*.[1] In developed countries, however, peripheral lymphedema is most commonly the result of treatment of malignancy[1] with rates of occurrence of postoperative lymphedema reported as high as 67% depending on the surgical procedure.[2]

Clinical Evaluation

In most cases, the diagnosis of lymphedema is made from the history and physical examination. Patients subjectively

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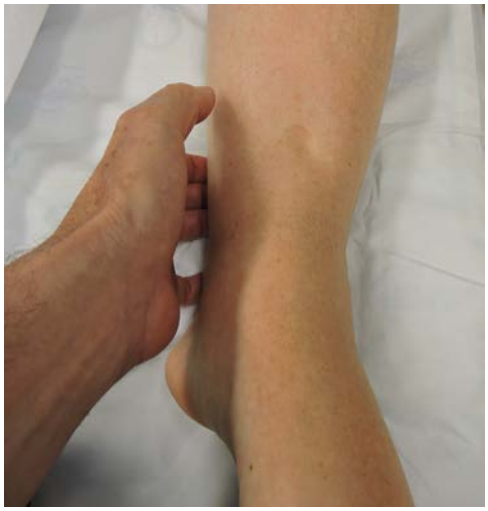

Figure 1 This is a 54-year-old woman patient with lymphedema of her left leg after pelvic surgery and radiation for carcinoma of the uterus. The right leg was not involved. This patient demonstrates pitting edema. She underwent treatment with LVA and showed moderate improvement 1 year postoperatively. LVA, lymphaticovenular bypass. (Color version of figure is available online.)

describe a sensation of heaviness or tightness, as well as decreased range of motion of the lymphedematous extremity. On physical examination, the limbs are evaluated for adipose tissue hypertrophy, fibrosis, skin changes, and the presence and type of edema.[3] Based on the history and physical examination findings, the disease can be clinically staged based on guidelines from the International Society of Lymphology Lymphedema (Table 1).[4]

In the clinic, peripheral lymphedema can be objectively assessed with circumference or volume measurements. Limb circumference measurements are done with a flexible measuring tape at specified locations along the length of the extremity.[5] Limb volume can then be calculated based on the summation of disks.[6] Based on limb volume, the disease is considered mild when the volume difference between the lymphedematous limb and the unaffected limb is less than 20%, moderate for a volume differences between 20% and 40%, and severe when the volume difference is more than 40%.[3] Volumetric measurements can also be made using water displacement, where the extremity is immersed in a container of water, and the volume of displaced water represents the volume of the submerged limb. Water displacement can be cumbersome, and the technique is not able to detect localized changes in limb volume.[7] Although these 2 measurement techniques are the most commonly used, they have the disadvantage of high interreader and intrareader measurement variability.[7] A third alternative is perometry, which consists of an optoelectronic device that uses infrared light to image the external surface of an extremity to calculate limb volume. Although perometry has a high accuracy and reproducibility, the device is not widely available.[8] An important limitation of all circumference and volume techniques is that they are not able to differentiate lymphedema from other causes of increased limb size.[7,9]

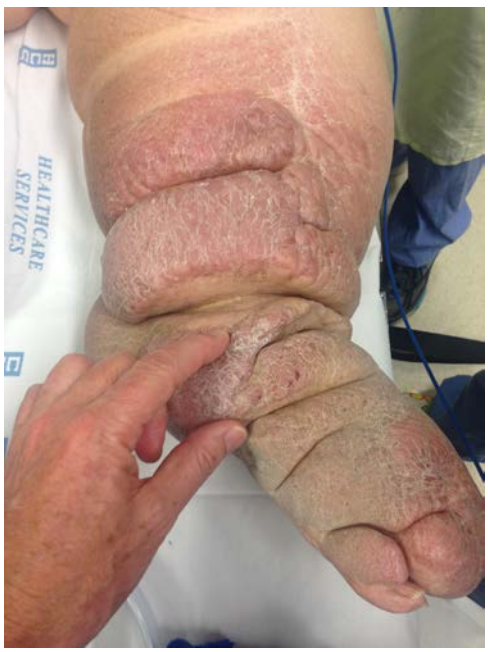

Figure 2 This is a 62-year-old woman patient who presented with severe, chronic lymphedema of her left leg. This presented spontaneously when she was 37 years old, and gradually worsened over time. Note, the severe trophic skin changes. She did not exhibit any pitting. This patient underwent an excision procedure. (Color version of figure is available online.)

Lymphedema Imaging

Imaging can be helpful when the diagnosis is unclear, when anatomical information is needed to plan surgical interventions, and to assess the response to treatment.[4] Clinically available imaging techniques used in patients suspected of having peripheral lymphedema include bioelectric impedance spectroscopy, nuclear medicine lymphoscintigraphy, indocyanine green lymphography (ICGL), and magnetic resonance lymphangiography (MRL).[2] Bioelectric impedance spectroscopy is an emerging technique that uses electrical resistance to measure the amount of extracellular fluid in an extremity.[10] The technique is sensitive and reproducible, and is increasingly being used for the early detection of lymphedema.[2] Currently, nuclear medicine lymphoscintigraphy is the most commonly performed imaging test to provide evidence of abnormal lymphatic flow for the diagnosis of lymphedema.[2,11] With lymphoscintigraphy, a radiotracer is injected intracutaneously into the hand or foot, and the uptake of the tracer into the lymphatic circulation is imaged using a gamma camera. Lymphatic dysfunction is seen as delayed, asymmetric, or absent visualization of regional lymph nodes, asymmetric visualization of lymphatic channels, or dermal backflow.[11] ICGL can be used to stage the severity of disease[12] and for preoperative and intraoperative planning.[13] With this technique, fluorescent indocyanine green is injected intracutaneously into the

Table 1 Clinical Staging of Lymphedema

Stage	Clinical Description
0—Latent or subclinical lymphedema	Reduced lymphatic transport that results in the accumulation of interstitial lymph fluid that is not clinically evident. Subjective symptoms can be present.
I—Reversible lymphedema	Soft, pitting edema without fibrosis. Prolonged limb elevation leads to resolution of limb swelling
II—Irreversible lymphedema	Fibrosis decreases tissue compliance. Nonpitting edema can occur. Limb elevation does not resolve limb swelling.
III—Lymphostatic elephantaiasis	Increased, now severe soft tissue hypertrophy and fibrosis with skin changes. Nonpitting edema.

hand or foot, and a photoelectric device is used to image the indocyanine green fluorescence within the superficial lymphatic channels and at sites of dermal backflow.[14] MRL is a relatively new imaging application that provides high-resolution volumetric datasets to evaluate the presence and severity of peripheral lymphedema, image individual superficial lymphatic channels, and define the status of the subcutaneous soft tissues.[15–18]

Indications for MRL

Currently, MRL is used to (1) provide the anatomical and morphologic information needed for surgical planning, and (2) support the diagnosis of lymphedema when the physical examination and other initial studies are equivocal.[19] Surgical treatment of peripheral lymphedema is considered in patients who are refractory to conservative management. Several different surgical treatment options are available, broadly characterized as excision or liposuction for soft tissue debulking, lymphaticovenular bypass (LVA) to redirect obstructed lymphatic drainage to the venous circulation, and vascularized lymph node transfer to promote lymphangiogenesis.[1,2,7] As nuclear medicine lymphoscintigraphy cannot depict individual lymphatic channels[16] and ICGL has a limited penetration depth of approximately 2 cm,[20] our microsurgeons use MRL as the primary preoperative imaging modality owing to its ability to depict and define the status of individual lymphatic channels regardless of depth and the status of the subcutaneous soft tissues (Fig. 3).[21] When no functioning superficial lymphatic channels are depicted with MRL, the patient is no longer considered a candidate for reconstruction with lymphaticovenular bypass and becomes a potential candidate for excisional debulking or liposuction. The absence of functioning lymphatics is often associated with chronic-phase disease, where there is fibrosis and fatty hypertrophy, features that can also be identified on MRL (Fig. 4). If the patient has had prior lymphadenectomy, vascularized lymph node transfer can be attempted to try to induce regeneration of lymphatics in that region.

MR Imaging

MRL is a minimally invasive technique for imaging the superficial lymphatics and sites of dermal backflow in patients with peripheral lymphedema. MRL examinations can be performed using either 1.5 T or 3.0 T imaging platforms, and require the intracutaneous injection of an extracellular gadolinium-based MR contrast to allow uptake of the contrast agent by the lymphatic circulation.[15]

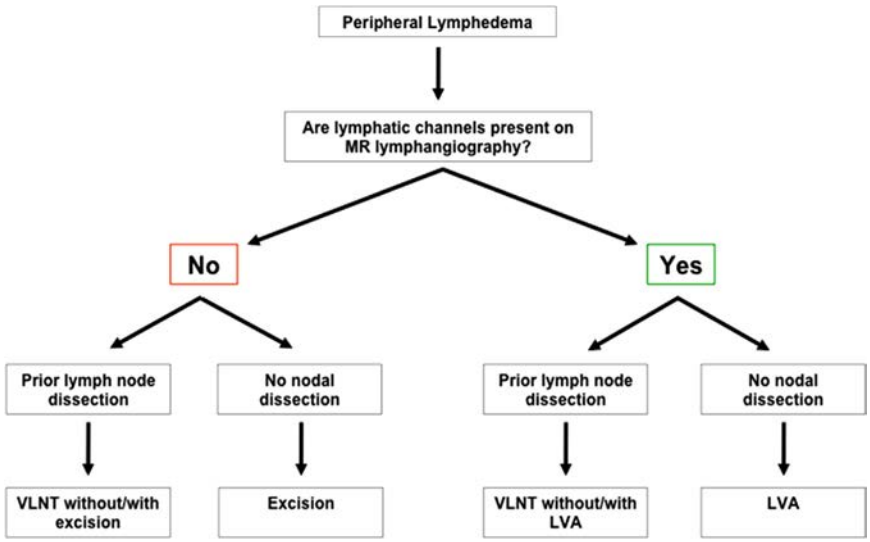

Figure 3 Surgical treatment selection algorithm based on MRL. LVA, lymphaticovenular bypass; VLNT, vascularized lymph node transfer. (Adapted with permission from Neligan et al.[21]) (Color version of figure is available online.)

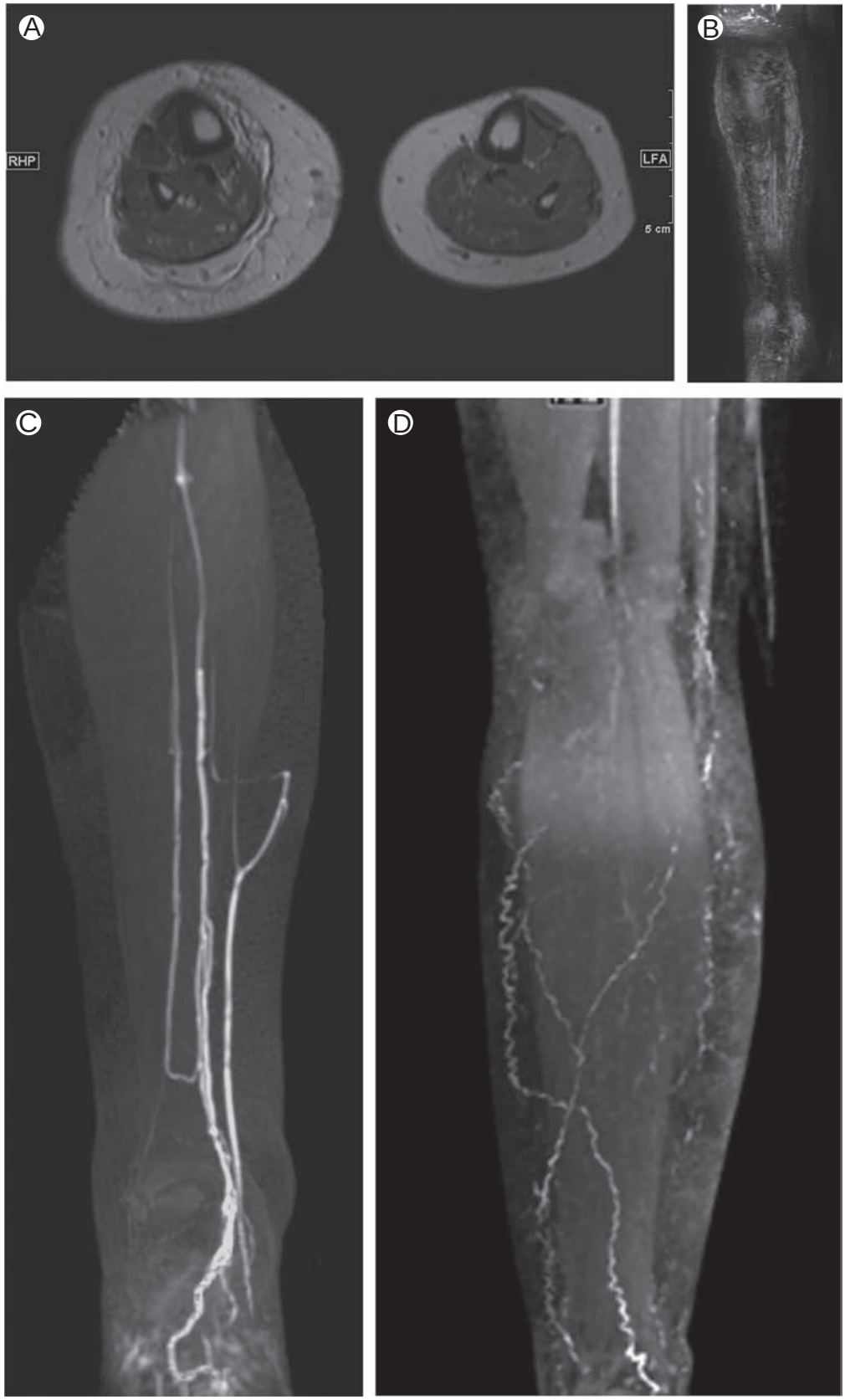

Figure 4 (A-C) MR lymphangiography for surgical treatment planning. A 65-year-old male patient with chronic right lower extremity lymphedema being evaluated for surgical treatment. Axial T2-weighted image (A) shows severe fatty hypertrophy and fibrosis of the right lower extremity. Coronal MIP of the T2-weighted image of the right calf (B) demonstrating moderate lymphedema (bright areas). Coronal MIP of contrast-enhanced MRL of the right calf (C) reveals only venous enhancement, but not enhancing lymphatic channels. The absence of lymphatic channels on MRL makes this patient a poor candidate for lymphaticovenular bypass (LVA). Compare this with a left lower extremity coronal MIP in a 24 year-old male patient with longstanding primary lymphedema (D), nicely demonstrating a large number of "corkscrew" lymphatics. This was performed using ferumoxytol for venous suppression.[32] MIP, maximum intensity projection; MRL, MR lymphangiography.

Table 2 Equipment Needed for MR Lymphangiography

Patient preparation	Sterile skin preparation (hibiclens) 5mL syringe(s) (1 per foot) 26-gauge needle(s) (1 per syringe)
MR contrast	4 mL of an extracellular gadolinium-based contrast agent per extremity (e.g. gadobenate dimeglumine, MultiHance) 1 mL of 1% lidocaine
MR imaging	1.5 or 3.0 T scanner platform long z-coverage phased-array surface coil or peripheral vascular coil 3D heavily T2-weighted TSE sequence Dynamic fat-suppressed 3D SPGR sequence (6 dynamic phases at 10 min intervals)
Examination interpretation	3D image postprocessing software for interactive MIP and MPR creation (e.g. GE Advanced Windows Workstation)

TSE, turbo spin echo.

The equipment needed for an MRL examination is listed in Table 2.

For lower extremity MRL examinations, patients are placed supine and feet first on the scanner table. This permits access to the feet from the far side of the gantry for the intracutaneous contrast injection that is done part way through the examination. Coil placement and scan orientation would depends on whether a unilateral or bilateral lower extremity scan is requested. The largest available *z*-axis phased-array surface coils are selected and positioned to cover the lower extremities from the midfoot to the groin. If a large field-of-view coil is available, the study can be prescribed as a 3-station exam. If only a single station surface coil is available, a 2-station examination is performed[22] where the coil is positioned to include the lower legs from the midfoot to the knees, and then the positioning is changed to incorporate the thighs from the knees to the groin. As inhomogeneous fat suppression may result in artifacts that can mask enhancing lymphatics[16], the patient is offset laterally on the scanner table for a unilateral examination to place the leg as close to the magnet isocenter as possible. This improves shimming and uniformity of fat suppression.

There are 2 primary sequence components of our MRL examination as follows: (1) a heavily T2-weighted 3D turbo spin echo (TSE) with spectral fat suppression, to determine the severity and extent of edema; and (2) a dynamic fat-suppressed T1-weighted 3D spoiled gradient-echo (SPGR) (either a single-echo 3D T1w gradient-echo (GRE) with spectral fat suppression or dual-echo 3D T1w GRE with Dixon reconstruction) before and after intracutaneous contrast injection to visualize enhancing lymphatic channels and sites of dermal backflow. Prescribing high-resolution near-isotropic source datasets is important to enable interactive use of image post-processing algorithms such as the 3D cursor, multiplanar reformations (MPR), and maximum intensity projection (MIP) reconstructions to facilitate examination interpretation.[16,30] Typical MRL examination sequence parameters used are presented in Table 3.[15] Although these are based on the vendor platform available at our institutions, these can be used to guide protocol development on other platforms. Currently, we

Table 3 Examples of MRL Sequence Parameters Used at Our Institution at 1.5 T and 3.0 T

	3D T2w TSE	Single-Echo 3D T1w GRE (1.5 T)	Dual-Echo 3D T1w GRE (3.0 T)
Sequence	3D Multishot TSE	3D T1-TFE	3D T1-mFFE
Orientation	Sagittal	Sagittal	Sagittal
Partial Fourier factor	0.8	0.85 × 0.675	0.85 × 0.85
Fat suppression	SPIR	SPIR	Dual-echo Dixon
Field-of-view (mm^3)	380 × 312 × 150	485 × 162 × 100	360 × 221 × 147
Voxel size (mm^3)	1.7 × 1.7 × 3.0	1.3 × 1.3 × 1.0	1.2 × 1.2 × 1.6 mm^3
TR (ms)	2500	7.2	6.2
TE (ms)	350	3.3	1.5/2.8
ETL	90		
Flip angle (deg.)	90	30	20
SENSE factor	2		
Scan time (min:s)	3:47 per station	1:27 per dynamic	1:25 per dynamic

Note—These sequence parameters are used with a Philips Achieva 1.5 T and Ingenia 3 T and can form the starting point for performing the examination on other vendor platforms. ETL, echo train length; SENSE, SENSitivity Encoding; SPIR, spectral presaturation with inversion recovery; TE, echo time; TR, repetition time; TSE, turbo spin echo. (Adapted with permission from Mitsumori et al.[15])

perform a minimum of 6 dynamic phase acquisitions at 10-minute intervals (0-10-20-30-40-50 minutes). For the lower extremity examination using a single station coil, the distal-most station is imaged at the first 4 time points, after which the coil is moved to the upper leg for the last 2 time points. This can be modified based on the progression and cranial extent of the lymphatic enhancement observed in the lower station. With full field-of-view coil arrays, the distal-most station of the lower extremity is imaged at the first 4 time points, with all of the stations imaged for the latter 2 time points.

The low molecular weight of extracellular gadolinium-based MR contrast agents allows these agents to be taken up by the lymphatic circulation after intracutaneous injection.[1,21] We use gadobenate dimeglumine (Gd-BOPTA, MultiHance) as the extracellular MR contrast agent for our MRL examinations owing to the agent's higher relaxivity, potential for weak protein binding, thermal stability, and absence of reported complications after intracutaneous injection.[23,24] We believe these features are beneficial for imaging the small- and low-volume superficial lymphatic channels. Other extracellular MR contrast agents have also been safely used for MRL—gadopentate dimeglumine (Gd-DTPA, Magnevist),[16,18] gadoterate meglumine (Gd-DOTA, Dotarem),[25] gadoteridol (Gd-HPDO3A, Prohance),[17,26,27] and gadodiamide (Gd-DTPA-BMA, Omniscan).[22,28] As patients often feel mild-to-moderate pain during the intracutaneous injection, we use small gauge needles and mix a local anesthetic with the MR contrast agent before the intracutaneous injection.[29]

The contrast material is typically prepared during patient positioning and precontrast scan acquisition. The intracutaneous injection consists of a solution of 10 mL contrast (gadobenate dimeglumine, MultiHance, Bracco), with 1 mL of 1% lidocaine and 1 mL of sodium bicarbonate.[30] The contrast mixture is drawn into 1 or 2 syringes of 5 mL depending on whether a unilateral or bilateral lower extremity examination is being performed. After the T2-weighted sequence has been completed, the precontrast 3D SPGR (time point 0 minutes) is obtained. The patient is then moved into the gantry until the feet can be comfortably reached from the far side of the scanner gantry. The skin of the dorsal foot or feet is sterilely prepped, and then 1 mL of the contrast mixture is injected intracutaneously into each of the 4 interdigital web spaces of the foot using a 25 or 26-gauge needle. The injection sites are then massaged for 60 seconds to facilitate lymphatic uptake.[11,22] The patient is returned to magnet isocenter, and the 5 postcontrast dynamic 3D SPGR phases are completed. At this time, the extent of lymphatic enhancement is assessed, and if progressive enhancement is seen additional phases are obtained to completely image the extent of lymphatic enhancement.[15]

Examination Interpretation

The objectives of MRL are as follows: (1) Define the severity and extent of lymphedema; and (2) Depict the presence, number, course, and location of enhancing lymphatic channels. For examination interpretation, we review source images on an independent 3D workstation to allow the real-time creation of 3D postprocessed images. This allows creation of interactive MPR, MIP reconstructions, volume rendering, and use of the 3D cursor to characterize and localize structures of interest on different image reconstructions. Screen capturing composite post-processed images helps to create a summary of examination findings to communicate spatial and depth information to the surgeon that can be viewed before and in the operating room.[15]

To characterize the degree of peripheral lymphedema, multiplanar reformats of heavily T2-weighted 3D volumetric datasets are viewed along with full-volume MIP reconstruction of the extremity. In the report, we describe the location and extent of edema, and qualitatively grade edema severity as none, mild, moderate, or severe. Evaluation of the superficial lymphatics is performed using the dynamic contrast-enhanced 3D T1w GRE sequence. On dynamic postcontrast images, lymphatics typically appear as twisting, beaded, irregular, and discontinuous enhancing channels that progressively enhance with time.[22,30] As part of the examination interpretation, full-volume MIPs are created for each of the 6 dynamic phases to highlight temporal progression and select the phase with the greatest degree and extent of lymphatic channel enhancement. Interactive examination review is then performed using the image data from the phase with the greatest degree of lymphatic enhancement. In the examination report, we describe the: (1) presence and pattern of lymphatic drainage; (2) number, course, depth, and size of enhancing lymphatic channels; and (3) presence, location, and size of any sites of dermal backflow.[15]

Overcoming Challenges

As venous contamination almost universally occurs after the intracutaneous injection of an extracellular Gadolinium-based MR contrast agent, one of the interpretative challenges with MRL is differentiating enhancing lymphatic channels from enhancing superficial veins (Figs. 4C and 5A). Although morphologic differences and the time course of enhancement can be used to differentiate lymphatics from superficial veins,[15] interpretation requires interactive review of multiple phases of the dynamic MRL acquisition to assess the location of an enhancing structure and visualize how the degree of enhancement changes with time (Fig. 6). Thus examination interpretation can be tedious, and even with interactive image interpretation, there are still cases where it remains challenging to decide if a particular enhancing structure is a lymphatic channel or vein. We have found 2 different MR techniques useful to help with venous contamination; the incorporation of a delayed MR venogram to demonstrate the location and course of the superficial veins[31] and the intravenous administration of an iron-oxide blood-pool MR contrast agent

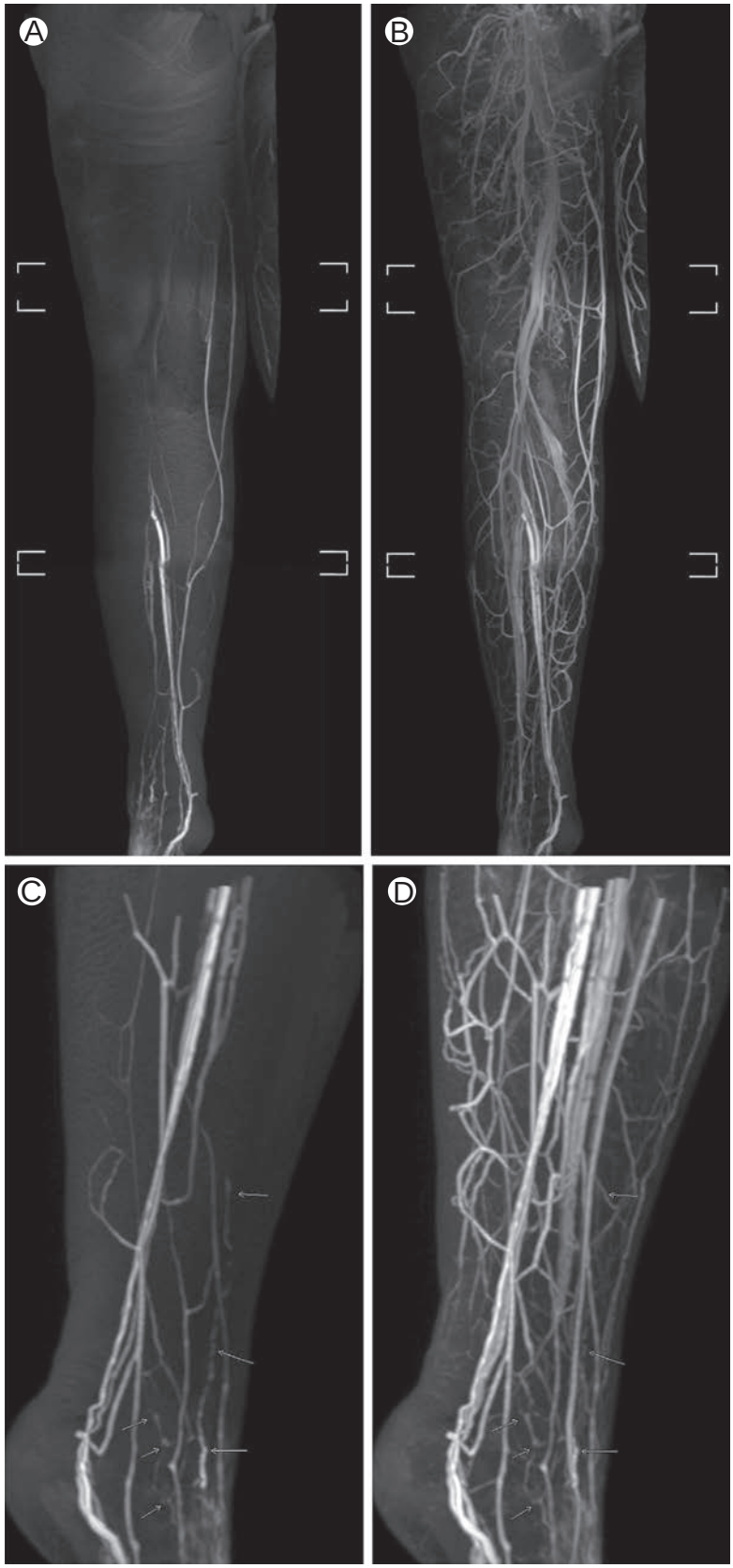

Figure 5 A 75-year-old female patient with prior pelvic lymph node dissection. Three station coronal fused MIP of the contrast-enhanced MRL of the right leg (A) demonstrates venous contamination, but it is unclear if any of the enhancing structures reflect lymphatics. Repeat scanning (MR venogram) was then performed after intravenous injection of 0.1 mmol/kg gadobenate dimeglumine ((B) - coronal MIP). Simultaneous interactive review of the MRL and MR venogram images helps to differentiate lymphatics from veins. Magnified sagittal MIP (C) of the right foot demonstrates probable lymphatic channels (arrows). Comparing the appearance on MRL with the MR venogram (D) demonstrates that these structures do not change after intravenous contrast administration, indicating that they are not veins.

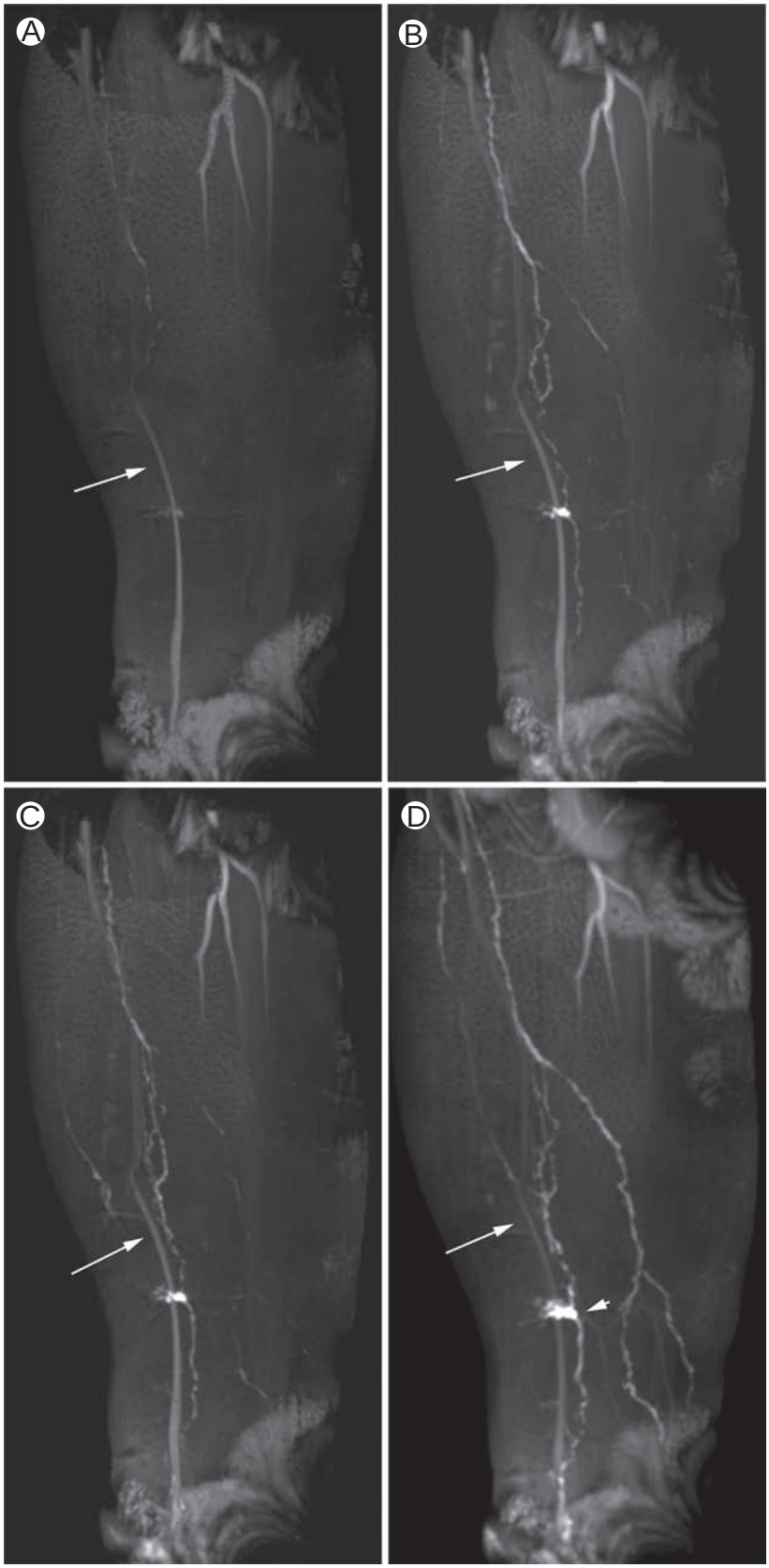

Figure 6 A 34-year-old male patient with secondary lymphedema. Coronal MIP of 4 phases of the dynamic contrast-enhanced MRL of the right calf performed at 5 (A), 10 (B), 20 (C), and 40 minutes (D). Note, venous enhancement (arrows) decreases with time whereas lymphatic enhancement progresses with time. The region of blush (arrowhead in D) represents a site of a prior LVA, not communicating with but overlapping the visualized vein. The arterial trifurcation enhancement is secondary to inflow. LVA, lymphaticovenular bypass.

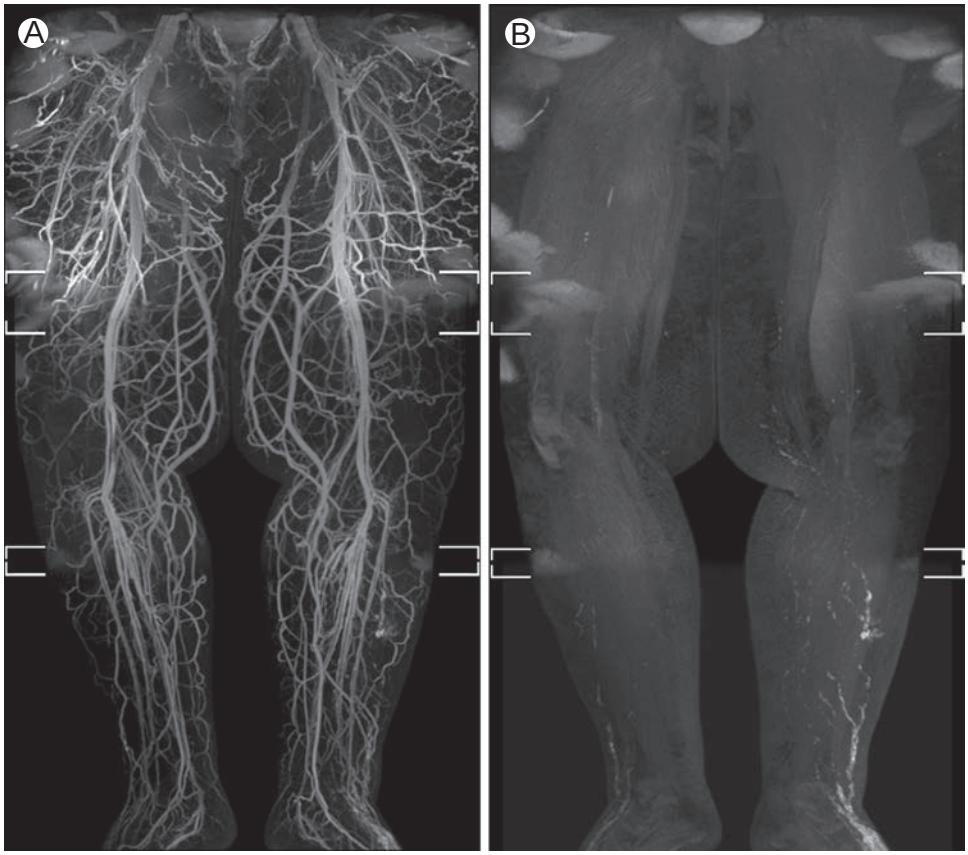

Figure 7 Venous signal suppression with Ferumoxytol. A 52-year-old male patient with secondary lymphedema. Bilateral lower extremity MRL using ferumoxytol to suppress veins through its T2* shortening blood-pool effect. Coronal fused 3-station MIP of the MRL (A) shows both enhancing veins and lymphatics in the lateral left lower leg. Note, the lymphatics are difficult to visualize owing to the extensive venous enhancement. Coronal fused MIP after the Dixon echo times were increased to 5.8/6.9 ms (B) demonstrates venous signal suppression, producing a lymphatic only image, where the lymphatic channels in the left lower leg are now clearly seen.

(Ferumoxytol; Feraheme, Advanced Magnetics, Cambridge, MA) to remove venous signal secondary to T2* suppression (Fig. 4D).[32]

After the first few clinical MRL examinations, we added a delayed MR venogram to our base MRL protocol to depict the location of superficial enhancing veins. For the MR venogram, we use the same fat-suppressed T1-weighted 3D SPGR sequence prescribed for the lymphangiogram, and acquire a single phase acquisition 180 seconds after a single dose (0.1 mmol/kg) intravenous injection of the same Gd-based MR contrast agent used for the lymphangiogram. Because the acquisition is performed as a dynamic acquisition, interactive viewing on an image postprocessing workstation enables the colocalization between the lymphangiogram and the venogram to help differentiate lymphatic channels from veins (Fig. 5).

More recently, our institution began using an iron-based blood-pool agent (Ferumoxytol) that is injected intravenously either before gadolinium injection or any time deemed necessary during the examination, and can be used to suppress venous signal to create a "lymphatic only" image (Fig. 7). Ferumoxytol is a carbohydrate-coated ultrasmall iron-oxide particle that is Food and Drug Administration approved for therapeutic iron supplementation, but is increasingly used as an off-label agent for MR angiography in patients with contraindications to gadolinium-based MR contrast. Ferumoxytol is a blood-pool agent, having an intravascular half-life of 15 hours.[33] A recent study has shown that the T2* effects of the ultrasmall iron-oxide particle can be used to provide venous signal suppression for MRL.[32]

Recognizing and Treating Complications

In addition to the contraindications and risks of any contrast-enhanced MRI examination,[34,35] patients undergoing MRL can experience mild-to-moderate pain and swelling at the sites of the intracutaneous contrast injections.[15] Although only small volumes (4 mL) of extracellular gadolinium-based contrast are administered into each foot for the exam, the risk of tissue injury is higher in these patients due to both their abnormal lymphatic drainage and the location of the injections in the foot. When patients complain of significant pain and swelling,

we treat the symptomatic site similar to contrast extravasation that can occur with intravenous contrast injections.[35]

(1) Obtain baseline vitals.
(2) Assess for compartment syndrome, skin ulceration, and tissue necrosis.
(3) Elevate affected extremity.
(4) Cold compress to help alleviate pain at the injection site.
(5) Monitor, release if signs and symptoms have improved, and no new symptoms have developed.
(6) Provide the patient with instructions to seek additional medical care for worsening symptoms, skin ulceration, development of neurologic, or circulatory symptoms.
(7) Surgical consultation obtained for severe extravasation injury. (Progressive swelling or pain, altered tissue perfusion, change in sensation, skin ulceration, or blistering.)
(8) Notify referring physician.
(9) Document in the medical record.

Conclusion

Peripheral lymphedema is a chronic progressive and debilitating disease that in the United States is most commonly related with the treatment of malignancy. Advances in microsurgical techniques have led to the recent development of several new long-term treatment options for the disease. MRL is an imaging technique that can characterize the severity of peripheral lymphedema, depict the anatomy of enhancing superficial lymphatic channels, and define the status of the soft tissues of the swollen lower extremity. Currently, MRL is used for preoperative planning to better individualize treatment and to confirm the diagnosis in equivocal cases.

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Techniques in Vascular and Interventional Radiology

Lymphoscintigraphy for Imaging of the Lymphatic Flow Disorders

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Lymphoscintigraphy has introduced with the great advantage for diagnostic imaging of the lymphatic flow disorders. Lymphoscintigraphy can be performed in patients of any age, including neonates, and even in patient in critical conditions. The procedure is quite simple, and it needs only subcutaneous injection of small amounts of radiotracers. From subcutaneous tissue the radiotracer is taken by the lymphatic vessels and gives off energy in the form of gamma radiation detected by a gamma camera. Radiotracers rarely cause the allergic reaction and can be administered to the patients with allergy to iodine contrast media. Comparing with the Lipiodol, radiotracers cannot cause pulmonary embolism; therefore, it is safe for the patients with respiratory dysfunction. The objective of this article is to describe the indication, technique, equipment, pitfalls, safety, and effectiveness of lymphoscintigraphy for imaging of the lymphatic flow disorders.
Tech Vasc Interventional Rad 19:273-276

KEYWORDS Lymphoscintigraphy, Tc-99m albumin, Lymphatic flow, Lymphedema, Lympatic leakage, Chylothrax

Introduction

Lymphoscintigraphy has been initially described by Threefoot et al[1] in 1963, and it has introduced with the great advantage for diagnostic imaging of the lymphatic flow disorders since then[2-5]. The traditional imaging for the lymphatic imaging has been lympangiography[6-10]. Lympangiography is performed by injection of iodized oil directly into the lymphatic vessels and needs the specialized technique and time.

Lymphoscintigraphy could reflect the physiological lymphatic flow using small amounts of radioactive materials called radiotracers that are typically injected subcutaneously and get into the lymphatic flow. Radiotracers behave the same flow as lymphatic fluid because it has the water-soluble nature unlike lipiodol which is oil-soluble material used for lymphangiography. Comparing with the lipiodol, radiotracers cannot cause pulmonary embolism; therefore, it is safe for the patients even with respiratory dysfunction (Fig).

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Clinical Evaluation of the Patient

There are 2 main groups of clinical presentation of the patients with lymphatic pathology: symptoms that are associated with lymphatic obstruction and presenting with lymphedema and symptoms that are associated with lymphatic leaks, presenting as chylothorax or chylous ascites. The main clinical presentation of chylothorax and chylous includes dyspnea or tachycardia caused by pleural effusion, distention of the abdomen by ascites. Patients with lymphatic obstruction show unilateral or bilateral swelling of lower or upper extremities. Loss of the lymphatic fluid can result in malnutrition or immunodeficiency or both. Lymphedema may present months to years after surgery because of gradual deterioration in intrinsic contractile force of lymphatic wall and lymphatic valves incompetence.

On physical examination, we check vital sign, body weight, height, and examine the lungs and the abdomen. We also record medical history, especially of surgical, previous intervention, cancer that was treated with chemotherapy, venous ligation, or repeated infection.

Typical laboratory data include complete blood count, C-reactive protein, blood level of total protein, and albumin level. The lymphatic fluid collected during

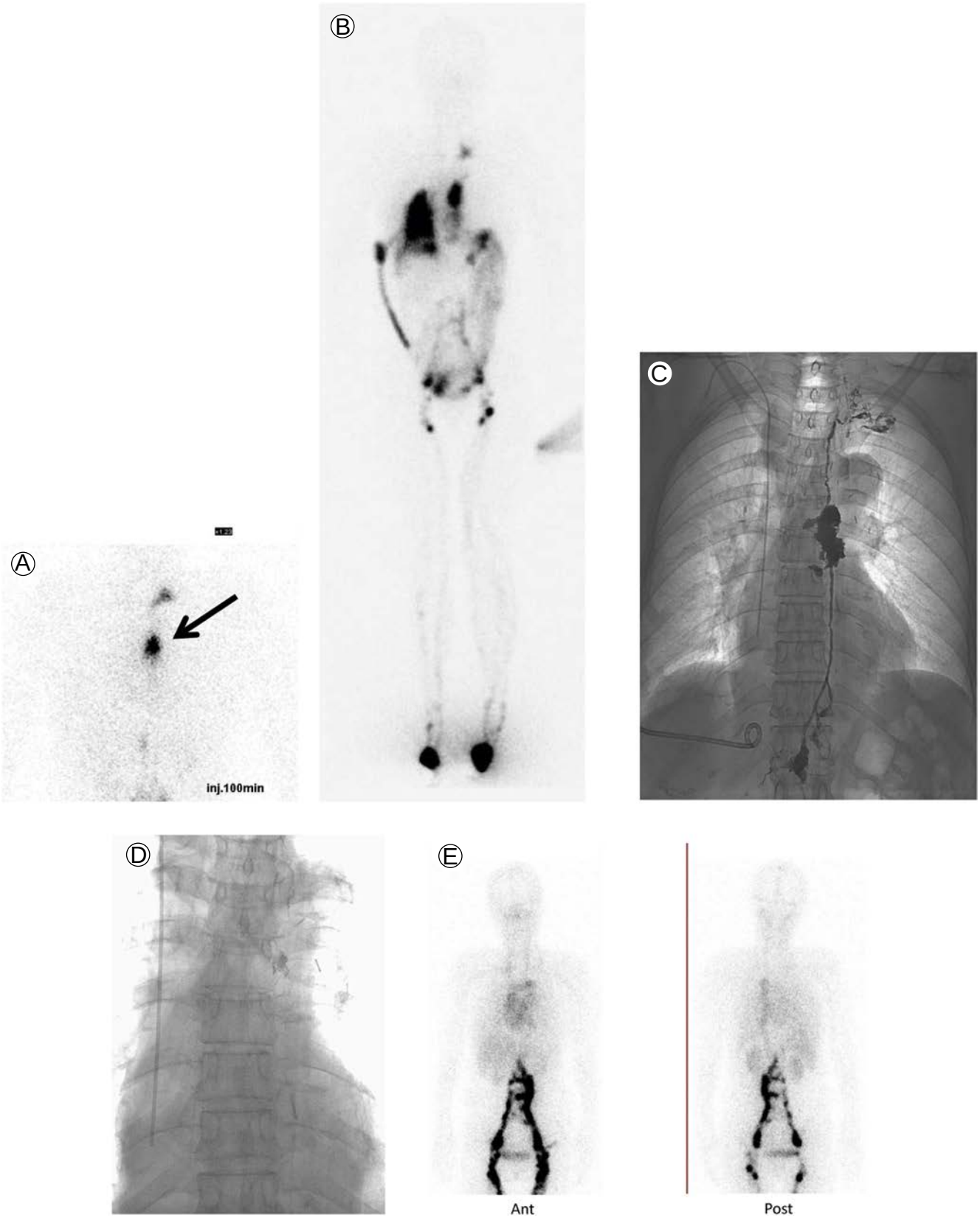

Figure A 61-year-old Japanese woman presented with severe chylothorax 8 days after esophagectomy for esophageal cancer. Lymphoscintigraphy was taken in the active stage of onset. (A) Anterior view of the thorax in initial lymphoscintigraphy shows massive lymphatic leakage into the mediastinum [Arrow] 100 min after injection. (B) Whole body anterior view after 3 hours injection demonstrates extensive pooling in the right thoracic cavity and also spot findings in the left. (C) The lymphatic leakage was treated by thoracic duct embolizatrion (TDE) using NBCA (Histoacryl B; B. Braum, Melsugen, Germany) following lymphangiograpgy. (D) Postprocedural chest-X-ray shows the presence of NBCA at the site. (E)Lymphoscintigraphy demonstrates the cessation of the leakage of the lymphatic flow, which is well consistent with the clinical course after TDE.

paracentesis or thoracentesis is examined visually for characteristic color ("milky") of chyle as well as for cell count with differential and total protein level. The ratio of the total protein level and lymph cell count of the fluid and blood is calculated.

Lymphoscintigrapgy has the advantage of being relatively minimally invasive and requiring minimal cooperation from the patient; thus, it is a method of choice for the neonates and intensive care patients.

Indications for the Lymphoscintigraphy

The indication for lymphoscintigraphy includes primary lymphatic dysplasia, secondary lymphatic dysplasia, primary lymphedema, congenital lymphedema, lymphedema precox, secondary lymphedema, and chylous leaks (chylous ascites and chylothorax).

When To Do It? When Not To?

The main indication for lymphoscintigraphy is for diagnosis of the of lymphatic flow disorders. We use lymphoscintigraphy not only for establishing the initial diagnosis but also for monitoring the outcome of the treatment and disease progression.

Extra precautions needs to be taken by pregnant or breastfeeding female patients.

Also if the patient cannot be maintained the certain position even during the one single shooting, then another examination could be considered. Even though this test is well tolerated by the patients, it requires to be stationary for short period of time, so if patient cannot stay still, another test needs to be administered.

Lymphoscintigraphy Equipment

The small amount of radiotracers, which is Tc-99 albumin solution, is injected subcutaneously. Radiotracer is absorbed into the lymphatic capillaries and then carried into the lymphatic circulation. Radiotracer gives off energy in the form of gamma rays that acquired by a gamma camera. The manipulation of the images is then performed using a dedicated computerized workstation. Radiotracers rarely cause the allergic reaction, can be administered to the patients with allergy to iodine contrast media and never cause pulmonary embolism; therefore, it is safe for the patients with pulmonary dysfunction.

Procedural Steps

(1) The dose of Tc-99 albumin solution is 500 μCi (18.5 MBq): 92%-98% of albumin, tightly bound to Tc-99m. Injection volume is 0.05 mL; >98% of albumin macromolecules (molecular weight of 60 kDa).
(2) Tc-99 albumin solution is injected subcutaneously, 261 raising a wheal in first interdigital web space of both extremities (feet or hands).
(3) Imaging should be taken immediately after injection, 10-40 minutes and 3-5 hours using parall-hole collimator passing over patient.

Overcoming Technical Challenges

Lymphoscintigraphy has low spatial resolution, which can improve with the fusion with computed tomography and single-photon emission computed tomography.

Owing to relatively low spatial resolution, lymphoscintigraphy is limited for detection of the small lymphatic leaks in small vessels.

In addition, precise detection of the lymph leaks into the free third space like peritoneal cavity or thoracic cavity is hindered by quick dilution of the water-soluble radiotracer once it leaks into the fluid collection.

Injection of the radiotracer into extremities can demonstrate only the peripheral lymphatic flow. If it needs to evaluate the lymphatic flow of solid organ like liver or digestive system, radiotracers should be injected directly into the digestive system so as to put it to the right lymphatic flow, which is the same mechanism as lymphangiography[11,12].

Common Trouble Spots

One of the main advantages of lymphoscintigraphy is that it can be performed both before and after the event and for that reason can capture the diagnostic event over the long stretch of time. However, due to practical reasons, the image acquisition is done not continuously but at certain points, so it is possible that if the diagnostic event happened in between the acquisition, it can be missed. The specific study protocol (length of the study and frequency of acquisition) depends on clinical scenario and anatomical region. On average, the length of the study is approximately 4 hours if the lymphatic flow is within normal range. Lymphocyntigraphy can be safely repeated in case patient condition worsens or clinical follow-up is needed.

Lymphoscintigraphy has a high, close to 100%, technical success rate. Administration of the radiotracer does not require specialized skills or equipment such as in intranodal lymphangiogram or pedal lymphangiogram[6-9]. Injection of the tracer in the skin at any location such as extremity or even neck is technically simple, requiring minimal skills.

Lymphoscintigraphy is less cost-effective than magnetic resonance imaging or computed tomography.

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Techniques in Vascular and Interventional Radiology

Lymphangiography for Thoracic Duct Interventions

Michael S. Stecker, MD, and Chieh-Min Fan, MD

Lymph leaks resulting in chylous pleural effusions can be life-threatening. Minimally invasive thoracic duct embolization and disruption have been gaining acceptance as first-line treatment for these leaks. This review discusses the techniques for both pedal and intranodal lymphangiography in detail. It also discusses the use of lymphangiography as a means of targeting a retroperitoneal lymphatic to facilitate thoracic duct interventions for chyle leaks. Finally, outcomes and adverse events pertaining to these thoracic duct interventions are discussed.
Tech Vasc Interventional Rad 19:277-285

KEYWORDS Thoracic duct, Chyle leak, Lymphatic embolization

Noninvasive computed tomography and magnetic resonance imaging has largely replaced lymphangiography for evaluation of lymphatic abnormalities. The ability to perform lymphangiography has largely become an obsolete art, but in recent years there has been a small resurgence of its use for lymphatic targeting for interventional procedures.

Thoracic duct embolization and disruption for traumatic chylous pleural effusions has been gaining acceptance and use as first-line therapy for chylous leaks. These leaks are life-threatening and those demonstrated on lymphangiography are unlikely to close without intervention.[1] The technique has also been employed for nontraumatic chyle leaks. This review describes the technique for lower extremity and abdominal lymphangiography as well as for thoracic duct embolization and disruption.

Clinical Evaluation of the Patient

Indications

In our practice, the usual patient referred for a thoracic duct intervention has undergone recent thoracic surgery complicated by chylothorax. However, nearly every patient referred with a chyle leak is considered for treatment. These patients generally have a pleural fluid output of at least 500 mL/d, pleural fluid triglyceride level of at least 110 mg/dL, and presence of chylomicrons in the pleural fluid. These numbers are not absolutes, as patients who are not taking any nutrition enterally, with or without administration of total parenteral nutrition, and those on a low-fat diet may not meet these criteria, but still may be considered for treatment.

Contraindications

Allergy to any of the agents discussed below would contraindicate performance of lymphangiography. Other contraindications to lymphangiography that may be considered include right-to-left cardiac shunts and severe pulmonary disease, primarily because iodinated oil contrast agent eventually drains into the systemic venous circulation. In addition, radiation to the lungs and mediastinum may predispose to cerebral embolization of iodinated oil contrast agent.[2]

There are very few absolute contraindications to thoracic duct interventions, such as uncorrectable coagulopathy or presence of a lesion that should not be traversed along any potential percutaneous path from the anterior abdomen to the retroperitoneum (eg, abdominal aortic aneurysm). Review of existing or preprocedural cross-sectional imaging is very useful to evaluate for such entities.

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Equipment and Agents

Lymphatic Indicator Dyes

Lymphatic indicator dyes are used to identify intradermal lymphatic vessels for targeting during pedal cutdown. Isosulfan blue 1% (Mylan, Rockford, IL) is currently the preferred dye. Others, such as methylene blue (American Regent, Shirley, NY), have also been used in the past.[3]

Iodinated Oil Contrast Agents

Oil-based contrast agents are used for lymphangiography as they stay within the lymphatic system, as opposed to water-based agents that easily leak out. Lipiodol (Guerbet LLC, Bloomington, IN) is the sole iodinated oil contrast material that is available. Caution should be taken when cracking the neck of the glass vial; and because of the high viscosity, a large needle (at least 18 gauge) is needed to aspirate the contents into a polycarbonate syringe.

The dose of iodinated oil contrast agent has been recommended to be limited to 20 mL per procedure in adults to minimize the risk of complications from pulmonary artery oil embolization.[4,5] More has been used without noted adverse events, probably because of the combination of leakage from the thoracic duct injury and subsequent occlusion of the thoracic duct preventing remaining oil from entering the systemic circulation.[3] Nonetheless, the infusion should be stopped as soon as possible.

Embolization Glue

Most interventional radiologists interested in incorporating lymphatic interventions into their practice will already be familiar with use of n-butyl cyanoacrylate (n-BCA) glue (TRUFILL, Codman Neurovascular, Raynham, MA). However, a description of our technique is included here. New sterile gloves are donned before handling any materials pertaining to the glue to avoid contamination with ions that could cause the glue to begin to polymerize prematurely. The entire 1 g of glue is carefully removed from its tube and the iodinated oil drawn up into a polycarbonate syringe. They are thoroughly mixed in a sterile shot glass in a 1:1 to 1:2 ratio by volume of glue to oil, and approximately half the vial tantalum powder is added to increase the radiopacity. The mixture is drawn up into a 3-mL polycarbonate syringe through a large-bore needle. The glue is not mixed until after coil embolization is completed.

Lymphangiography Needle

When using the pedal approach, a lymphangiography needle is required. The only one of which we are aware is the lymphangiography catheter with 30-gauge needle (Cook, Bloomington, IN). It is an approximately 1-cm, 30-gauge needle with a slender 60-cm degradation-resistant tubing attached. It has a female luer lock connector hub at the opposite end (Fig. 1). It is prepared by flushing with normal saline via a 3-mL syringe, which is left attached for subsequent testing after lymphatic cannulation.

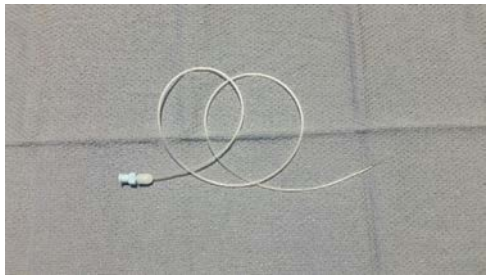

Figure 1 Lymphangiography needle. A 30-gauge needle with 60-cm extension tubing. (Color version of figure is available online.)

Nodal Access System

When using the intranodal approach, a different system is needed, as the lymphangiography needle is far too short.[6] It is very helpful to completely assemble one needle-syringe system for each side, and prime them, before making the nodal punctures (Fig. 2). To construct a needle-syringe system, the trocar is removed from a 25-gauge, 3.5-in. spinal needle. Use of a 25-gauge or smaller needle limits the rate of injection and therefore reduces the risk of extravasation and needle dislodgement.[6] The male end of a 6-in. connector tube with approximately a 0.2-mL volume is attached to the luer lock hub of the needle. The female end of the connector tube is connected to a 3-mL polycarbonate syringe filled with iodinated oil contrast agent. The contrast agent is gently injected to remove the air from the system and prime the tubing.

Thoracic Duct Access System

Any "non-vascular" access kit used for accessing the renal or biliary system can be used. It should have a 15- or 20-cm long 21-gauge trocar needle for ductal puncture. It should also include a triaxial catheter system with a metal stiffener and an inner 2.5-3.0-Fr catheter that mates to an 0.018-in. wire. The outer catheter is too large and can be discarded.

Thoracic Duct Embolization Catheters

Although many different microcatheters have been employed for thoracic duct embolization, our group

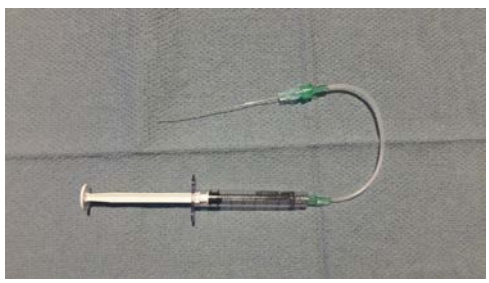

Figure 2 Intranodal needle-syringe access system. The 25-gauge spinal needle is connected to a short connector tube and a 3-mL polycarbonate syringe. (Color version of figure is available online.)

prefers the 3-Fr, 80-cm SlipCath (Cook), as it is inexpensive, less floppy than others used for transarterial embolization, and has a more manageable working length. With this catheter, a 0.025-in. Bentson wire works very well as a cost-effective coil pusher.

Lymphangiography Contrast Infusion Devices

Because of the viscosity of the iodinated oil contrast agents used in lymphangiography, it is very helpful to have a mechanical device to perform the infusion, although it can be done manually. If one has access to a lymphangiography pump (Cordis, Johnson and Johnson, Miami Lakes, FL),[7] that is probably preferred, although this device is no longer commercially available. Another device that has been used is a Harvard Pump (Harvard Apparatus, Holliston, MA).[7] Caution should be taken, though, as these devices may not be approved by the Food and Drug Administration for human use, and we have not been able to use them in our practice. We have used several medication infusion pumps, but they tend to repeatedly alarm and stop injecting because of the high pressure needed to infuse oil.

Currently, when using the pedal technique, we use an angiographic power-injector (Mark V Plus, Medrad, Indianola, PA) with a conversion device (Fig. 3) that we were able to obtain directly from the manufacturer. For safety, this dedicated injector is only used for lymphangiography with the injection rate set on "milliliters per hour," and not for other angiographic procedures, as a "milliliters per second" setting that was not noted would easily rupture the cannulated pedal lymphatic. The conversion device keeps the activation button depressed on the injector's hand control for the entire duration of the infusion, which can be several hours. The hub of the lymphangiography needle can be connected directly to the injector syringe. We have not had problems with degradation and leaking of the needle hub by the oil contrast agent, but some prefer to use a metal stopcock between the injector syringe and needle hub to further reduce the risk, as this cannot be easily remedied.

Imaging of the Lymphatic System

Patient Positioning

It should be ensured that when the patient is positioned supine on the fluoroscopy table they are as comfortable as possible, as even in skilled hands and with straightforward anatomy these procedures can take upward of 2 hours for successful completion. A small wedge under the patient's upper back and head can increase comfort without compromising positioning. In particular, when using the pedal approach, one should make sure that the patient's feet are in a position that would minimize motion; our group prefers to let them dangle over the bottom edge of the fluoroscopy table rather than rest on top of it. This also decreases external rotation of the leg, making it easier to work on the dorsum of the foot. Most patients will have a chest tube in place; it should be ensured that it will not get dislodged during the procedure, and it should be excluded from the prepared field. Anesthesiologist consultation is obtained for patients who may have difficulty holding still.

Scout Images

Scout radiographs of the abdomen and chest, including obliques in the abdomen, are taken before commencing, because early iodinated oil contrast agent opacification of lymphatic channels may be a subtle finding. Images of the lower extremities can also be obtained, but they are generally not needed.

Lymphangiography Spot Images

Serial imaging is performed from the access site(s) to the abdomen, using fluoroscopy to monitor progression.

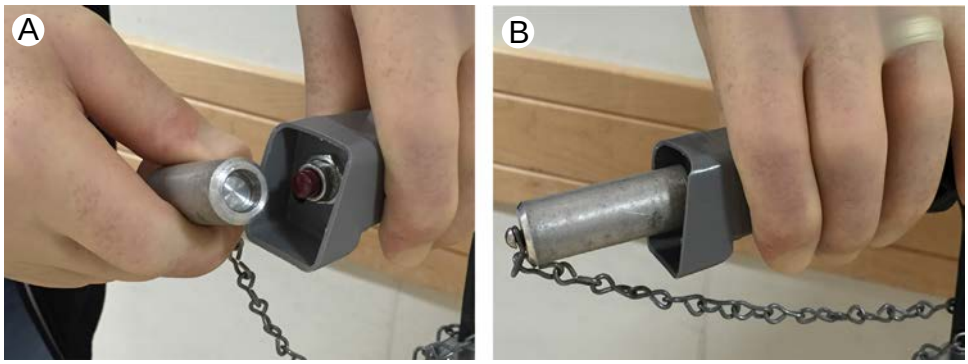

Figure 3 Lymphangiography injector device. The device consists of an aluminum cylinder that is internally threaded at one end. The other end has a chain to fasten it to the injector so it does not become misplaced. The internally threaded end precisely matches the external threads on the push-button switch that also allow the locking nut to keep the switch fastened in the injector handle (A). The device is carefully screwed onto the switch via the mating threads until the flat inner surface contacts the top of the button and depresses it, turning the injector on (B). If the infusion needs to be interrupted, the device is slightly loosened until the injector turns off. (Color version of figure is available online.)

Images should overlap to ensure imaging of the entire lymphatic system. With pedal access it begins at the ankle, and with intranodal technique it begins at the hips. Shorter intervals between imaging can be used in the leg and thigh (10-20 minutes). Longer intervals (20-45 minutes) can be used through the pelvis where progression is slowed owing to traversal of numerous iliac chain lymph nodes. Shorter intervals may again be used in the abdomen (15-30 minutes). Massage of the medial leg and thigh may help to push oil centrally if progression is slow, particularly when infusing from the foot.[8] Spot images are also taken showing the level of ductal access and to document the position of coils when performing an intervention.

Thoracic Duct Imaging

During interventions, after catheterization of the thoracic duct is achieved, a PA digital subtraction lymphangiogram is performed at 1 or 2 frames per second. It is centered over the chest and upper abdomen to show the thoracic duct from the cisterna (or catheterized large retroperitoneal duct) to the flow into left subclavian vein. It can be easily performed by hand injection of less than 10 mL of water-soluble contrast agent and allows evaluation of the size and course of the thoracic duct, and the presence and location of a leak, an obstruction, or both (Fig 4).

Additionally, after embolization of the thoracic duct with coils, a digital subtraction lymphangiogram may be helpful to assess for any residual or collateral flow or both before injection of glue to complete the embolization.

Lymphangiography Access Techniques

Lymphangiography via a pedal cutdown has been the most common technique until fairly recently when the intranodal technique has had increasing preference. Intranodal lymphangiography is less technically demanding than pedal lymphangiography, it does not require a dedicated injector or specific access needle, and is less subject to needle dislodgement. In the distant past, it was largely abandoned for diagnostic lymphography due to rupture of the injected node resulting in extravasation, which obscured anatomical details and the potential for oil to enter the venous system through the resulting lymphovenous communication.[9] Today, these risks are mitigated, as noted earlier, by use of high-resistance needles for slow infusion. In one small study, the intranodal technique saved an average of approximately 50 minutes for completion of lymphangiography and performance of thoracic duct catheterization, compared with pedal lymphangiography.[6] Although ultrasonography has been shown to be useful for successful lymph node puncture, including small and deep nodes,[10] small nodes may severely reduce the success of this technique.[6] Reviewing prior computed tomography or magnetic resonance cross-sectional imaging for adequate-sized inguinal nodes is helpful, as is immediate preprocedural ultrasonography of the inguinal regions.[6] Thus, both pedal and intranodal techniques are described here.

Pedal Lymphangiography

Pedal lymphangiography may be performed bilaterally or unilaterally, in which case the right side is preferred as the lymphatics on that side are more likely than those on the

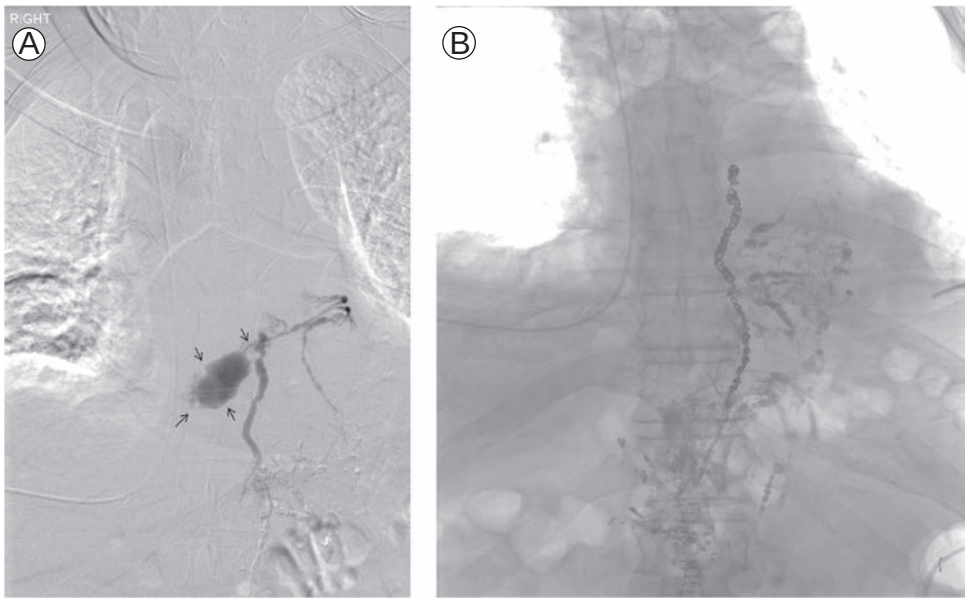

Figure 4 Thoracic duct leak. Patient who underwent esophagectomy for esophageal carcinoma and developed a high-output chylous pleural effusion. Image from a DSA lymphangiogram of the chest shows occlusion of the mid thoracic duct (A). At that level there is a large leak (arrow) adjacent to the right chest tube. This was treated with coil and glue embolization (B). DSA, digital subtraction angiography.

left to fill retroperitoneal ducts away from the aorta.[1] A unilateral approach may decrease the amount of iodinated oil used.[8]

Prophylactic intravenous antibiotics active against skin flora, such as cefazolin or clindamycin, are administered. The feet are thoroughly cleansed with isopropyl alcohol, particularly between the toes. A total of 1 mL of an indicator dye is then slowly injected intradermally with a 27-gauge tuberculin syringe in the first and third web spaces. Caution must be taken to avoid dye leakage which is easily spread onto the foot and could obscure visualization of dermal lymphatics. Some advocate mixing 1% lidocaine with the indicator dye.[7] We have used Gebauer's Ethyl Chloride medium jet spray (Gebauer Company, Cleveland, OH) to numb the skin before injection with good effect, but extreme caution must be maintained with its use and storage, as it is extremely flammable.

The feet are then prepared and draped in a sterile fashion with clear chlorhexidine gluconate and isopropyl alcohol solution (ChloraPrep One-Step, CareFusion, Leakwood, KS) to about half way up the lower leg; many such prep sticks include a dye to better allow one to see exactly where the solution has been applied, but this would interfere with visualization of the indicator dye once it is taken up. A large subcutaneous wheal of lidocaine 1%, which makes dissection easier, is created over a longitudinally running blue streak in the dorsum of the foot, roughly overlying the first metatarsal.

A careful skin incision is then made with a 15 blade scalpel, recalling that the lymph vessels run just under the dermis, and transecting one may severely compromise the ability to access one with a needle due to spillage. Both transverse and longitudinal incisions have been used. Transverse orientation may demonstrate more lymphatics to choose from for cannulation, but only allows viewing a very short lymphatic segment and goes across the skin dermatomes which may be more difficult to heal. The longitudinal incision is our group's preference and allows isolation of a much longer segment of pedal lymphatic. The incision should be as limited in length as possible, but long enough to allow adequate access of the vessel, keeping in mind that a short incision can always be lengthened if needed.

Blunt dissection with a fine curved surgical clamp is then used to identify and free up the lymphatic. It is very carefully skeletonized by removing the tiny pieces of loosely adherent fatty tissue. The vessel is isolated proximally and distally with 4-0 silk ties secured to the skin by one-fourth-in. Steri-Strips (3M Health Care, St. Paul, MN), and a third tie is left in a loose overhand knot around the upper third of the lymphatic. A right-angled clamp is helpful to go under the lymphatic vessel to pass ties. The trimmed backing paper from the Steri-Strips, shiny side up, helps support the lymphatic once isolated.[11]

The lymphatic is then cannulated with a lymphangiography needle prepared as noted earlier. Better skeletonization makes this cannulation easier. Some find that a magnification lamp or surgical loupes allow enhanced visualization of these small ducts. It has been suggested that slightly blunting the needle tip, such as gently running it across a sterile cloth towel, can prevent it from "double walling" the lymphatic.[11] In addition, some prefer to put a short piece of Steri-Strip around the base of the needle as a handle.[11] The previously noted third tie is then carefully slid caudally and tightened to secure the tip of the needle in the lymphatic. DeBakey-type forceps are helpful for grasping the tie to snug the knot down without disrupting the needle.

The proximal isolating tie is then released and the access is gently tested with saline. The lymph vessel should plump up and the blue indicator dye should be flushed out. There should be minimal leaking around the needle at the lymphatic cannulation site, although a small amount of leakage is tolerable. If there is too much leaking, rather than loosening the suture and reaccessing the lymphatic, it is usually more successful to place another loose tie around the lymphatic (just proximal to the one securing the needle), carefully advance the needle another half to one millimeter further and into the center of the lymphatic lumen, and subsequently tighten this fourth silk tie. Some tension on the initial tie securing the needle can help stabilize the vessel when readvancing the needle. This may be repeated several times if needed.

The luer lock of the needle is connected to the infusion device which must be positioned very close to the foot. Iodinated oil contrast agent injection is then commenced at a rate of 8-12 mL/h per side.[8,12] There will be a meniscus seen in the tubing of the lymphangiography needle designating the transition from priming saline to iodinated oil contrast agent. Just after the meniscus reaches the needle, brief fluoroscopy over the foot and ankle should be used to confirm that contrast agent is progressing in the lymphatics (Fig. 5). The vessel and needle are gently covered with a damp gauze to keep the vessel from desiccating during the infusion.

The contrast agent is followed fluoroscopically, and intermittent images obtained, as detailed earlier. Placing the patient in reverse Trendelenburg position may help progression of oil contrast agent,[7] as may antegrade massage of the medial thigh to manually "milk" the lymph.[8] Use of general endotracheal anesthesia may slow progression of oil contrast agent because of increased intrathoracic pressure.

If an adequate target duct has not been demonstrated after injection of 15-20 mL of the iodinated oil contrast agent, the contrast column can be propelled further with use of saline.[7] The injection is temporarily suspended, the lymphangiography needle is disconnected from the injector, and the syringe containing the iodinated oil contrast agent is removed from the infusion device. It is refilled with up to 20 mL of normal saline and replaced on the injector. Infusion is then resumed at the previous rate.

At the end of the procedure, the needle is removed from the lymphatic, and all of the suture material must also be removed. The free ends of the silk ties are carefully clipped close to the knot and all knots untied. Gerald-type forceps are useful to untie the knots to avoid injuring the lymphatic, which could result in lymph leak. Vertical mattress skin stitches using 2-0 polypropylene allow for

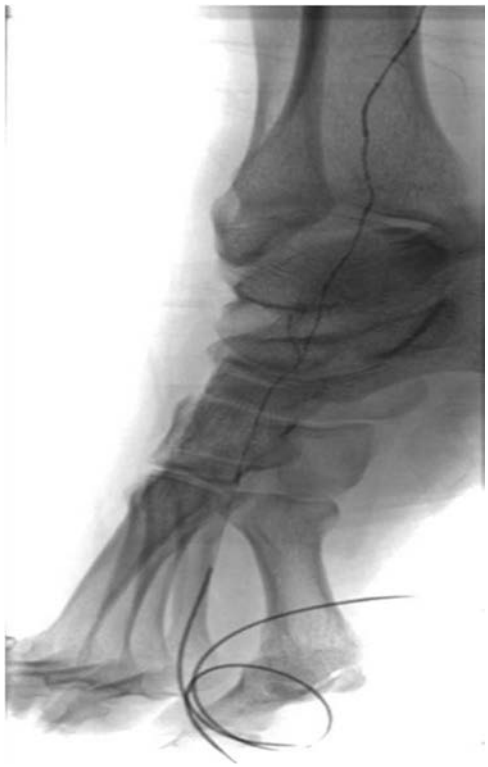

Figure 5 Initial pedal lymphangiogram. The needle tip is seen just at the proximal end of the first metatarsal and the connecting tubing is by the first toe. A pedal lymphatic filled with iodinated oil contrast agent is seen coursing along the medial foot, ankle, and lower leg.

minimal tension on the wound and good tissue eversion. Care should be taken to avoid the previously accessed lymphatic. The wound is covered with antibiotic ointment, with dry sterile gauze, and with clear film dressing. Stitches are removed in 7-10 days.

Intranodal Lymphangiography

The inguinal regions are sterilely prepared and draped with chlorhexidine gluconate and isopropyl alcohol solution. A bilateral approach is universally used for this technique. The needle-syringe systems are assembled and primed as described earlier. Using real-time ultrasound guidance with a high frequency linear vascular-type transducer in a longitudinal orientation, a lymph node in one groin is punctured with the spinal needle (Fig. 6A); local anesthesia is not needed because of the diminutive size of the access needle. A very shallow angle is used to allow better anchoring of the spinal needle in the skin and subcutaneous tissues to reduce the risk of dislodgement, and the skin puncture site is at least 2 cm away from the ultrasound probe. A controlled "jab" helps penetrate the lymph node capsule. Positioning the needle tip at the junction of the lymph node cortex and medulla has been recommended to reduce extravasation; positioning in the hilum could result in iodinated oil contrast agent injection into the lymph node's vein.[6] One author advocates for testing the nodal cannulation with a small injection of saline or water-soluble contrast agent and observation under ultrasonography or fluoroscopy, respectively, looking for swelling of the node, visualization of microbubbles flowing into the medulla and absence of perinodal leakage.[10] We prefer to test the nodal access with gentle injection of the iodinated oil contrast agent that has been primed in the system under fluoroscopic monitoring, looking for opacification of efferent lymphatics (Fig. 6B). One must avoid through-and-through nodal puncture or puncture of a lymph node more than once because of the potential for contrast extravasation and reduced efficiency of progression of the intralymphatic contrast column.

Hand injection of iodinated oil contrast agent is then commenced under intermittent fluoroscopic observation. It should be injected at a rate of approximately 1 mL/5 min.[6] If there is good intralymphatic contrast flow, the contralateral side should be accessed with the same technique. The needle tip may be repositioned very carefully if contrast progression ceases or if there is increasing perinodal leakage; the side that seems to flow better initially may not continue to be so as time progresses, so one must be patient and continue with bilateral injections.

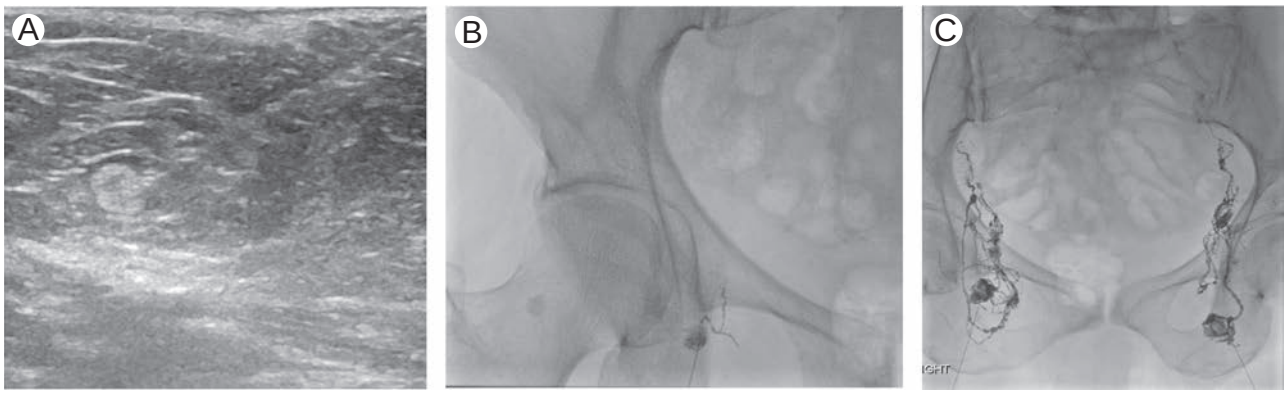

Figure 6 Initial intranodal lymphangiogram. Longitudinal ultrasound image demonstrating the course of the access needle with the tip in an inguinal lymph node, at the junction of the cortex and medulla (A). Initial image showing iodinated oil contrast agent filling a right inguinal lymph node, and the contrast agent beginning to exit the efferent lymphatic (B). Later image after a left-sided lymph node was subsequently accessed, with progression of contrast agent along the iliac lymphatics bilaterally (C).

Reaching the retroperitoneum generally requires injection of a total of 3-6 mL of oil-based contrast agent on each side. After that, saline can be substituted and injected at the same rate (although it will infuse easier) to push the contrast column further. Caution must be taken to not to disturb the needle when changing syringes. Furthermore, the oil may degrade the connector tube hubs, and the tubing may need to be very carefully replaced to resolve leakage. Overtightening connections may predispose to hub cracks and subsequent leakage.

At the completion of the procedure, the needles can be removed, and owing to the very small size punctures dressings do not need to be placed.

Thoracic Duct Interventions

Direct Thoracic Ductography

When using the pedal technique, once there is adequate opacification of a retroperitoneal lymphatic or the cysterna chyli, the abdomen is prepped and draped in a sterile fashion with chlorhexidine gluconate and isopropyl alcohol solution. When using the intranodal technique, it is usually more efficient to drape the abdomen and groin regions at the same time. Prophylactic intravenous antibiotics to cover gastrointestinal flora, such as levofloxacin or a second- or third-generation cephalosporin, are administered.

The image intensifier is angled at approximately 15°-20° left posterior oblique and as craniocaudal as possible, and centered on the target duct. Local anesthetic is administered and a skin nick made with a 11 blade scalpel. A "down the barrel" technique is used by advancing the access needle parallel to the axis of the image intensifier and toward the target lymphatic until it is near the duct.

The image intensifier is then angled away (right posterior oblique) as the needle tip approaches the spine and the duct is "speared" against the anterior vertebral body, which helps puncture the lymphatic. The trocar is removed while holding the needle cannula in position to prevent it from recoiling and dislodging, and probing is performed with a stiff, hydrophilic-tipped 0.018-in. guidewire, such as a V18 Control Wire (Boston Scientific, Natick, MA). If the tip of the wire does not begin to advance straight up the duct easily, it is pulled back into the needle. The needle is then withdrawn a fraction of a millimeter and the duct similarly probed again. This process is repeated until either the wire advances into the lymphatic duct, or the needle tip is no longer in proximity to the target, in which case another puncture attempt is made. The needle is exchanged for the inner catheter with stiffening cannula from the access kit, and once the tip of the system reaches the duct, the catheter is advanced off the stiffener, over the wire, and into the duct. Digital subtraction thoracic ductography can then be performed as discussed previously.

When using the pedal approach, the iodinated oil contrast agent infusion should be stopped as soon as possible once catheterization of the thoracic duct has been achieved.[8]

Thoracic Duct Embolization

Once the decision is made to embolize the thoracic duct, the nonvascular access inner catheter is exchanged for a microcatheter over the stiff 0.018-in. guidewire. The catheter is advanced up to and, when possible, above the leak. The duct is then embolized with multiple 0.018-in. coils from above the leak to approximately 2-3 cm above ductal entry site. Owing to the long length of duct that usually needs to be filled with coils, we prefer Nester coils (Cook), as they are relatively inexpensive, come in multiple diameters and are 14 cm long. We tend to embolize as much duct as possible, because underembolization could result in clinical failure of the procedure and reintervention is much more challenging.

The embolization is completed with n-BCA glue, mixed as described earlier. Caution must be taken at this point while mixing the glue such that the short segment of catheter still in the duct does not become dislodged. The microcatheter hub is rinsed with 5% dextrose solution and then the catheter gently flushed with only 1-2 mL of 5% dextrose solution to remove any ions from the dead space of the catheter, but not such that ions are flushed out of the lymphatic system where they will be needed for glue polymerization. The glue is then carefully injected under fluoroscopic observation. Care must be taken to ensure that the glue stays within the lymphatic system. Once all of the glue is injected, the catheter is quickly withdrawn while being aspirated with the syringe. The skin access site is covered with a small gauze dressing.

Thoracic Duct Disruption

This term is commonly employed when discussing lymphatic interventions, although it is a misnomer as it is actually the retroperitoneal lymphatics that are disrupted and macerated, rather than the thoracic duct itself. If the thoracic duct cannot be successfully catheterized after numerous attempts, there will usually be some iodinated oil contrast agent seen leaking into the retroperitoneum. Any remaining ducts that are seen, are safely located for needle puncture, may be repeatedly punctured to cause maximal leakage. It is hypothesized that the viscosity of the iodinated oil contrast agent, the lymph leak from the punctures, and the small retroperitoneal hematoma may diminish lymph flow enough that the leak in the chest closes.[13] Additionally, the iodinated oil contrast agent in the lymphatic system alone may be sufficient to resolve a leak.[14,15]

Outcomes of Thoracic Duct Interventions

The technical success of catheterizing the thoracic duct has been reported as 67%.[7] The clinical success rate of thoracic duct embolization, with resolution of a traumatic lymph leak, has been reported as high as 90%.[7] Success is higher when glue is used either by itself or in conjunction with coils (91%), compared with using coils alone (84%).[7] Others have

found a lower clinical success rate of 72%, but that study included both traumatic and nontraumatic lymph leaks.[3]

Thoracic duct disruption is not as successful as embolization. Clinical success rates of 55%[3] and 72%[7] have been reported. Repeat procedures, both embolization and disruption, may be successful after initial failures.[3,7]

Treatment of nontraumatic chyle leaks is less successful than traumatic leaks, with an overall clinical success of between 13%[3] and 53%.[15] In these patients, a pre-embolization lymphangiogram demonstrating occlusion of the thoracic duct, compared to a normal appearance, failure to opacify the thoracic duct, or demonstration of extravasation from the thoracic duct, has correlated with a greater clinical success rate.[15]

Overall, on an intention-to-treat basis (ie, including all presenting patients), success of these interventions is between 62% and 71% for treatment of traumatic high-output chyle leaks.[3,7] Predictors of clinical success include traumatic compared with nontraumatic etiology, and pneumonectomy compared with other types of surgery as the precipitating event.[3] In addition, one study showed that patients with clinical successes had mean pleural effusion output of less than 1000 mL/d both preprocedure and postprocedure, and they also had a greater pleural effusion output percentage decrease from preintervention to postintervention than clinical failures.[3]

These techniques have even been used successfully in children.[10]

Adverse Events

Lymphangiography

Hypersensitivity may occur with indicator dyes as well as with iodinated oil contrast agents.[2] Mild adverse events have included pulse rate elevation, fever, shivering, generalized aches, nausea, and vomiting.[2,5] Infection or delayed healing of a foot wound may require local wound care or antibiotics or both.[3,5,7,15] Leg swelling may be self-limited,[7] but there have also been instances of thromboembolism that have been attributed to prolonged immobilization of the limb during the study.[5] As previously noted, oil embolization to the lungs can be a serious complication resulting in hemoptysis, which may be related to both mechanical obstruction and chemical toxicity.[4,5] Severe complications including cerebral embolization and death have been described.[2] Complications relating to iodinated oil contrast agent in the inguinal regions have not been reported to our knowledge.

Thoracic Duct Interventions

Various adverse events have been reported with thoracic duct interventions. Perihepatic hematoma that resolved without treatment has been reported,[3] as has bile leak requiring stent placement.[16] There have been aortic punctures without observed sequelae.[17] Guidewire fragments may be sheared off in the retroperitoneum, but do not require aggressive measures for removal.[3] Care must be taken to avoid glue tracking completely through the column of coils and causing nontarget embolization into the lungs[3,7,15] (Fig. 7), or leaking out the ductal entry site and into adjacent vessels, such as the inferior vena cava or the portal venous system[3] (Fig. 8), which may have been transgressed during the access of the retroperitoneal lymphatic. Finally, aspiration requiring intubation has been reported,[16] although any adverse events related to procedural sedation may occur, as with any other complex procedure.[3]

A recent retrospective review of patients who had undergone thoracic duct embolization showed that there also appear to be long-term risks. Overall, there was a 14.3% rate of long-term complications that were probably related to the procedure.[18] These adverse events were

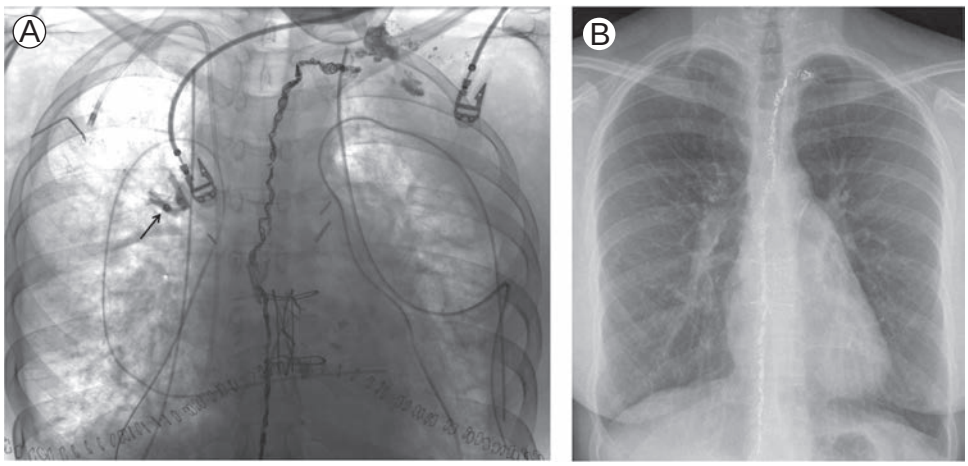

Figure 7 Patient with cystic fibrosis who underwent bilateral lung transplantation and subsequently developed increasing right chylous pleural effusion. Postembolization image of the chest shows coils throughout the thoracic duct and n-BCA glue filling within their open spaces (A). Nontarget embolization of glue that leaked through the coils, into the left subclavian vein, and finally was trapped in right upper lobe pulmonary artery branches has a crown-like appearance (arrow). Subsequent chest radiograph obtained approximately 2.5 years later for unrelated reasons shows coils along the course of the thoracic duct and resorption of the right upper lobe glue (B).

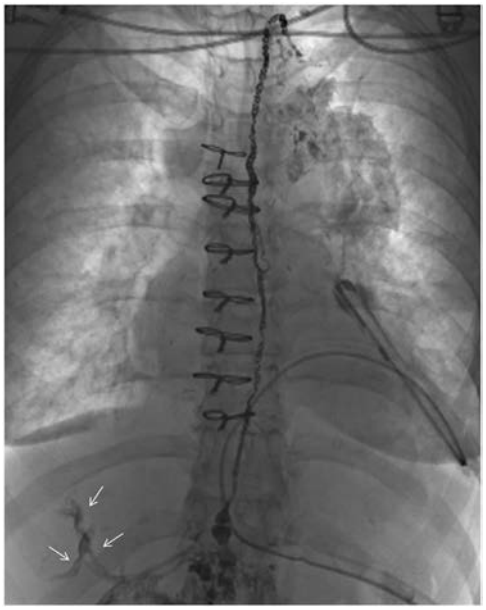

Figure 8 Patient who developed high-output chylous pleural effusion after undergoing 3-vessel coronary artery bypass grafting. Postembolization image of the chest and upper abdomen shows coils and glue in the thoracic duct. The cisterna chyli is seen over the lowermost thoracic vertebral body. Arrows show a cast of n-BCA glue in the portal venous system. The patient was asymptomatic and liver function tests remained normal.

lower extremity swelling (8%) and chronic diarrhea (8%), although the symptoms were generally described as mild and not disabling.[18]

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Techniques in Vascular and Interventional Radiology

Nontraumatic Chylothorax: Diagnostic Algorithm and Treatment Options

Gregory Nadolski, MD

Nontraumatic chylothorax is a relatively rare condition in which the intestinal lymph (chyle) leaks into the pleural cavity. Nontraumatic chylothorax is more difficult to treat than the more common traumatic chylothorax because the site of chylous leak may occur in less predictable locations. In the past, patients with nontraumatic chylothoraces were offered traditional fluoroscopically guided lymphangiography and thoracic duct embolization similar to traumatic chylothorax. However, the observation that thoracic duct embolization outcomes for nontraumatic chylothorax differed based on the imaging findings during lymphangiography has led to the development of a treatment algorithm, which incorporates noninvasive diagnostic studies, such as magnetic resonance lymphangiography. The development of this systematic approach allows better delineation of the source of the chylous leak and selection of the appropriate method of embolization. In this article, we will review the etiologies of nontraumatic chylothorax, the diagnostic work-up for managing this condition, and the treatment algorithm to care for these patients.

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KEYWORDS chylothorax, thoracic duct embolization, chylous effusion

Diagnosis and Etiology

Nontraumatic chylothorax is a relatively rare condition in which the intestinal lymph (chyle) leaks into the pleural cavity. In general, the diagnosis of a chylothorax is made by the presence of milky colored fluid after thoracentesis or postsurgical with laboratory analysis of the fluid revealing a triglyceride count more than 200 mg/dL in patients on regular diet. Additionally, the presence of chylomicrons is traditionally considered to be the gold standard for diagnosis of chylous effusion, however this test may not be readily available in all institutions. Lastly, others rely on a cell count and differential demonstrating fluid rich in lymphocytes (>70%) to supports the diagnosis of chylous leak although no agreed on threshold exists in the literature.

The etiologies of the nontraumatic chylothorax include malignancy,[1] congenital or idiopathic disorders of the lymphatic system, systemic diseases (eg, systemic lupus erythematosus and Behçet's disease) and infection (eg, tuberculosis).[2] Malignancy, specifically lymphoma, is responsible for most cases of nontraumatic chylothorax.[1,3,4] In these cases, the tumorous invasion of posterior mediastinal or retroperitoneal lymph nodes can either obstruct lymphatic flow resulting in high pressure in small lymphatic channels causing a spontaneous rupture or directly erode into these small lymphatic channels leading to a leak.

Disorders primarily resulting in abnormal lymphatic channels or masses such as Gorham's disease, generalized lymphatic anomaly, Kaposiform lymphangiomatosis, and lymphangiomatosis may present as nontraumatic chylothorax.[5] The mechanism of leak in this population can be variable. Leaks may originate from lymphatic masses or malformations that appear to generate a large amount of lymphatic fluid, which can cause seeping from or rupture of lymphatic ducts (Fig. 1). Similar to malignancy, these masses may obstruct the normal pattern of lymphatic flow resulting in the spontaneous leak of chyle from small lymphatic channels.

For both disorders resulting in abnormal lymphatic vessel or masses and malignancy, the site of leak may be from lymphatic channels in the retroperitoneum.

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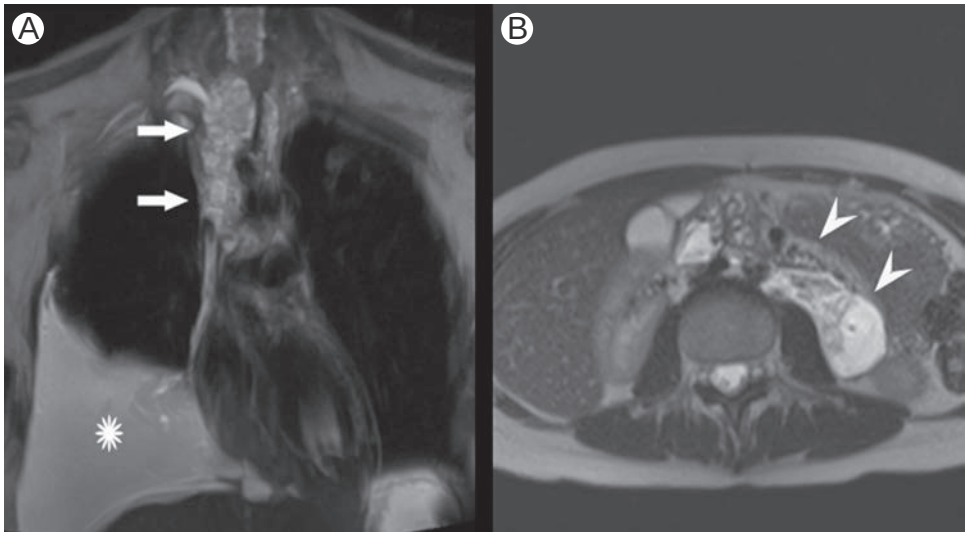

Figure 1 Coronal (A) and axial (B) heavy T2 images of the chest in a patient with lymphangiomatosis and left chylothorax (white star). There are multiple retroperitoneal (white arrowhead) and mediastinum (white arrows) lymphatic masses.

The chyle is drawn into the pleural space by the negative intrathoracic pressure through small, otherwise asymptomatic fenestrations in the diaphragm. Patients with leaks from retroperitoneal lymphatics may present as isolated chylothorax or combined with chylous ascites. The potential for nontraumatic chylothorax to originate from a retroperitoneal leak is rationale for using diagnostic imaging with dynamic contrast enhanced magnetic resonance (MR) lymphangiography (DCMRL), which would be discussed in detail in a separate article in this edition.[6-8]

Another group of conditions, which may present with nontraumatic chylothorax where preintervention imaging is critical to confirming the diagnosis and developing a treatment strategy, are lymphatic conduction disorders. The etiology of these conditions is not understood but they may result primarily from abnormal formation of lymphatic ducts or their valves or may occur secondarily from increased lymphatic volume or flow in the setting of heart failure or cirrhosis. Normally, lower extremity lymph and chyle should flow from the extremities, liver, and intestine to the central retroperitoneal lymphatics and cysterna chyli before entering the thoracic duct (TD) and returning to the venous circulation. In patients with conduction disorders, this unidirectional pattern of lymphatic flow is disrupted and often reversed (Fig. 2). If this reversal of flow results in retrograde flow into the lungs, patients can develop plastic bronchitis pulmonary lymphatic perfusion syndrome.[9] Embolization of the lymphatic channels responsible for the abnormal flow has been shown to be effective in treating these diseases. These diseases and their characteristic imaging findings would be discussed in greater detail in the article on dynamic contrast enhanced MR lymphangiography and pulmonary lymphatic perfusion syndrome.

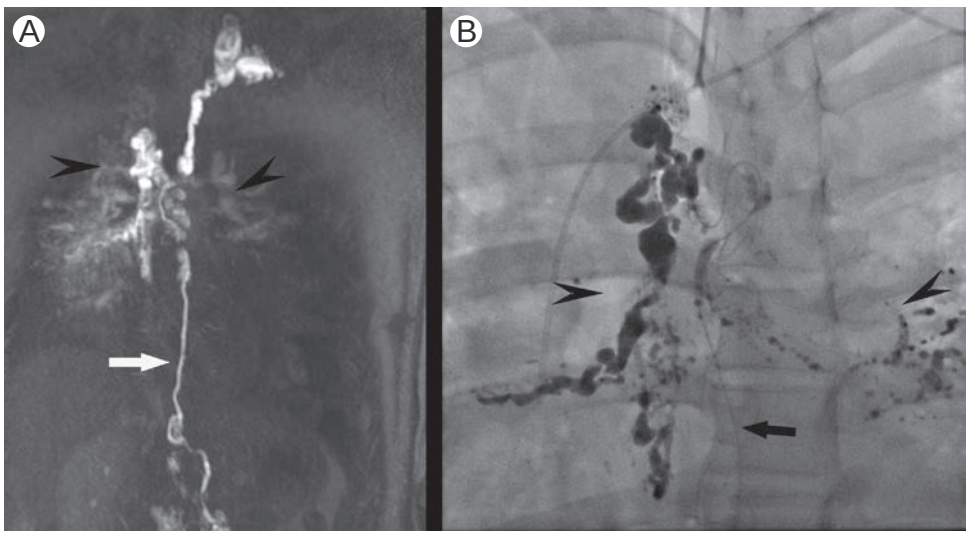

Figure 2 (A) DCMRL and (B) fluoroscopy image of the thoracic duct injection through the microcatheter (black arrow) in a patient with idiopathic chylothorax, demonstrating retrograde flow in the pulmonary lymphatic vessels (black arrowheads).

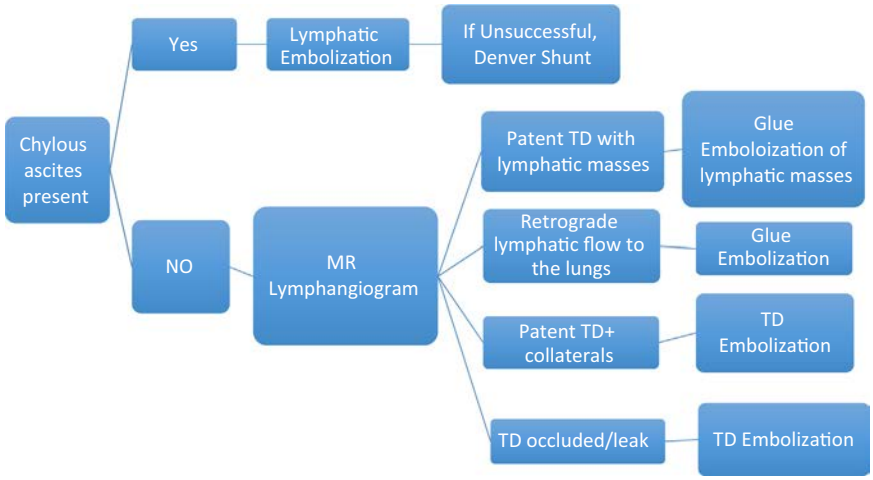

Figure 3 Diagram of the treatment algorithm for nontraumatic chylothorax. TD, thoracic duct; LM, lymphatic malformation. (Color version of figure is available online.)

Management

Traditionally, nontraumatic chylothorax has been managed conservatively just like traumatic chylothorax. This initially begins with diet modification (low fat diet, nil per os).[10-12] Thoracentesis, pleurodesis, and surgical management (TD ligation or tube drainage) have been performed for cases failing conservative management.[13,14] However, with the minimally invasive nature of the TD embolization (TDE) combined with its capability to identify the location of the chyle leak and variation in TD anatomy, TDE is becoming a more commonly offered intervention for chylothorax.[15]

Given the high degree of variability in mechanisms and etiology of nontraumatic leaks, the treatment of these disorders is more challenging than traumatic leaks. Consequently, thorough understanding of the underlying lymphatic anatomy and flow patterns and identifying a possible leak source with imaging is often essential for planning an intervention and for interventional success.[16] This need for preintervention assessment of the lymphatic system has led to the development of MR lymphangiography techniques to classify the etiology of the chylothorax as well as the site of the leak.[6-8]

As stated above, several disorders that originate as chylous ascites may present as chylothorax. Thus, the first step in our diagnostic algorithm for patients with nontraumatic chylothorax is to evaluate for chylous ascites (Fig. 3). If ascites is present, the fluid should be sampled and tested for chylomicrons, triglycerides, cell count with differential to confirm it is chylous. Once confirmed, the treatment strategy should conform to the diagnostic algorithm for chylous ascites as described in a separate article in this edition. The clinical significance of chylous ascites being the source of a chylothorax is that conventional embolization of the TD in these patients almost uniformly results in worsening ascites and effusion due blockage of the normal outflow pathway of the lymphatic system and increased pressure and leakage out the site of leak.

As a next step in the algorithm, MR lymphangiography is performed. The heavily T2 weighted sequences of an MR lymphangiogram can ascertain whether lymphatic masses are present either within the pleural cavity or along the abdominopelvic lymph node chain (Fig. 1). DCMRL images demonstrate the flow pattern of the lymph from the abdomen toward chest, assess the patency of the TD and establish the lymphatic anatomy. The treatment of the patient varies based on the magnetic resonance imaging findings as demonstrated in the diagnostic algorithm (Fig. 3).

Interventional Treatment Planning

Treatment planning is primarily based on results of MR imaging. There are 3 MR findings that are taken into consideration. If the leakage of the contrast from the TD or abnormal pulmonary lymphatic flow is observed, embolization of the TD is indicated. If the lymphatic flow from the abdomen into the lungs is conducted through the retroperitoneal lymphatic pathways, direct percutaneous access and embolization of these pathways keeping TD patent. If lymphatic masses in the retroperitoneum are observed, again direct percutaneous access and embolization of the masses with glue should be performed to permit the TD to remain patent.

Lymphatic Interventions

At the time of intervention, intranodal lymphangiography is used to opacify the lymphatic system using real-time ultrasound guidance to access inguinal lymph nodes with a 25-G spinal needle (BD, Franklin Lakes, NJ). To minimize needle movement, the needle is preassembled before nodal access as follows: the stylet is removed, the needle is attached to a 3-mL polycarbonate syringe (MeritMedical, South Jordan, UT) using a short extension

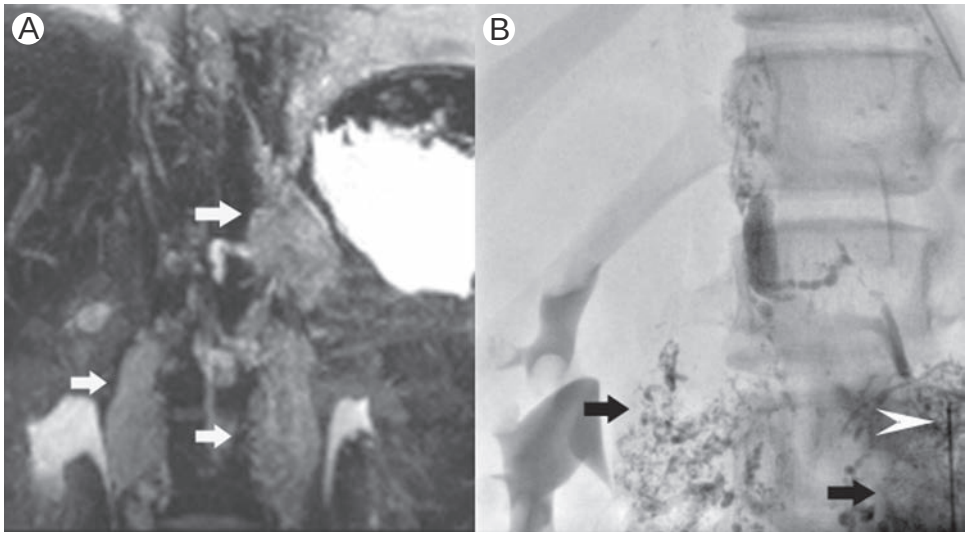

Figure 4 (A) Heavy T2 imaging of the retroperitoneal masses (white arrows) that are the source of the leak in the patient with idiopathic chylopericardium. (B) Fluoroscopic image of the injection of this retroperitoneal mass (black arrows) with N-butyl cyanoacrylate glue through 22 G needle inserted transabdominally (white arrow head).

tubing used for an intravenous angiocatheter, and flushed with oil-based contrast agent (Ethiodol, Savage Laboratories, Melville, NY). The needle tip is positioned in the transitional zone between the cortex and hilum of the lymph node using a shallow angle to create a relatively long subcutaneous tract to assist in stabilizing the needle. Under fluoroscopic guidance, contrast is injected by hand at a rate of about 0.5 mL per 5 minutes. After the initial injection of contrast confirms proper position of the needle within the lymph node and visualization of the efferent lymphatics, the polycarbonate syringe can be removed and further injection of contrast can be performed using an angioplasty balloon inflation device preloaded with 10 mL of lipiodol. The inflation handle can be tightened to administer a pressure of around 3 atm to propagate the contrast into the lymphatic system. A total volume of approximately 6-12 mL of lipiodol can be injected into each lymph. Infusion of contrast was terminated once the contrast opacified the lymphatics at approximately the L3 level. If at the end of the contrast injection the cysterna chyli was not visualized, the initial bolus was followed by injection of normal saline at 1 mL per 5 minutes to facilitate propagation of the contrast.[16,17] The lymphatic system is accessed and the TD cannulated as previously described.[18] At this point, additional non–oil based iodinated contrast may be injected to detail the flow and anatomy of the TD and any anomalies in the thorax.

For patients with lymphatic masses and a patent TD, TDE will not resolve the chylous leak similar to those patients with chylous ascites presenting with chylothorax. As these lymphatic masses result in over production of lymph, their presence in the thorax cavity may allow weeping of excess lymph into the pleural space or they may spontaneously leak into the pleural space through a small defect in one of their many malformed lymphatic channels. Thus, the treatment of choice in this clinical scenario is direct injection of the lymphatic masses. Initially, the masses can be accessed with a 21 or 22 G needle under fluoroscopic guidance (Fig. 4). Oil or water-based iodinated contrast is injected to confirm placement in the lymphatic mass. Subsequently, the lymphatic network in the mass can be occluded with N-butyl cyanoacrylate glue (TrueFill; Cordis, Miami Lakes, FL) diluted with ethiodol in a ratio dependent on the size of the lymphatic mass but generally ranging between 1:1 and 1:3 (glue:ethiodol) or obliterated using a liquid scleroscent such as 3% sodium tetradecyl sulfate foam or absolute ethanol.

For patients with a patent TD with abnormal collaterals or lymphatic vessel malformations or aberrant flow pattern toward the lungs, traditional TDE can be performed to exclude the site of leak. In these patients, platinum based microcoils are delivered through a 3 Fr microcatheter, Rapidtransit (Cordis Hialeah, FL), proximal to the abnormality followed by injection of N-butyl cyanoacrylate glue (TrueFill; Cordis, Miami Lakes, FL) diluted with ethiodol 1:1. Conventional TDE is also the treatment of choice for patients with occluded TDs with leaks occurring less than the level of occlusion. In prior studies, this was found to be the etiology of over half of all nontraumatic chylothoraces and embolization has shown to be effective in nearly 90% of patients.[5]

Follow-Up and Outcomes

After TDE or embolization of lymphatic masses, the output from pleural drainage tubes should be monitored daily. Once output has decreased less than 200 mL in a 24-hour period (or by about half in patients with low volume leaks), the patient can be returned to a fat containing diet to increase chyle flow through the lymphatic system allowing confirmation of adequate embolization. If output from the chest tubes remains low after resuming normal

diet, the chest tubes can be removed. In patients without a chest tube, follow-up chest radiographs can be used to monitor the success of the treatment. If embolization was technically successful, but failed clinically, repeat embolization can be performed during the same hospitalization.

Generally, the clinical success of treating nontraumatic chylothorax is not as high as traumatic leaks largely because of difficulty in identifying the site of leak. The largest published series on treating adults with nontraumatic chylothorax was published before the advent of intranodal lymphangiography and DCMRL and only included 34 patients.[5] In this series, TD catheterization was performed in only 70% of cases. In the remaining cases, the TD could not be catheterized (12%) or was not attempted because of nonvisualization of the cisterna chyli (18%). Overall, the intention to treat cure rate was 53% ($N = 18$ of 34). In the group in which the TDE was technically successful ($N = 24$), the cure rate was 68% ($N = 16$). As the main challenge in treating nontraumatic chylothorax is identifying the cause and site of the chyle leak, the poorer results in this series likely reflects early experience with TDE for nontraumatic chylothorax and inadequate imaging from that time period. The study, done using pedal lymphangiography, only was able to identify the cause of the leak in 65% of patients ($N = 22$ of 34). Although the intention to treat success rate was only 52% in this study, the result compared favorably with a previous study by Maldonado et al[19] who reported an overall success rate of 27% using a combined approach of conservative and surgical management for nontraumatic chylothorax. Lastly, when the site of leak could be identified and embolization the technical success rate increased to 67%. Future studies using the current algorithm for managing nontraumatic chylothorax with current imaging techniques would likely demonstrate an improved success rate similar that seen with traumatic leaks.

In summary, nontraumatic chylothorax is a relatively rare condition, which is more difficult to treat than traumatic chylothorax because the site of chylous leak may occur in less predictable locations and from a myriad of disease processes directly or indirectly affecting the lymphatic system. The experience with offering traditional TDE to nontraumatic chylothoraces led to the observation that TDE outcomes for nontraumatic chylothorax differed based on the imaging findings during lymphangiography resulting in a treatment algorithm, which incorporates noninvasive diagnostic studies, particularly MR lymphangiography to better delineate the source of the chylous leak and selection of the appropriate method of embolization. The development of this treatment algorithm and advances in MR lymphangiography would likely result in improved outcomes for treatment of nontraumatic chylothoraces in the future.

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Techniques in Vascular and Interventional Radiology

Percutaneous Treatment of Chylous Ascites

Jinoo Kim, MD, PhD, and Je Hwan Won, MD

Chylous ascites occurs as a result of lymphatic leakage, which contains high concentration of triglycerides. The leakage is caused by various benign or malignant etiologies ranging from congenital lymphatic abnormality to trauma. Lymphangiography has been shown to be effective in the diagnosis of lymphatic leakage and has also been reported to have therapeutic outcome. The development of intranodal technique for lymphangiography has recently made the procedure more widespread. As an adjunctive procedure, percutaneous embolization may be performed which involves use of embolic agents such as N-butyl cyanoacrylate and coil to occlude the leak. Embolization in the lymphatic system was first made popular by the introduction of thoracic duct embolization by Cope et al and has recently led to the development of various techniques for percutaneous embolization. This article reviews the options and techniques for percutaneous treatment of lymphatic leaks in patients presenting with chylous ascites.
Tech Vasc Interventional Rad 19:291-298

KEYWORDS Lymphatic system, Lymphangiography, Chyle, Embolization, Cn-butyl-2-cyanoacrylate

Introduction

Chylous ascites is a condition characterized by accumulation of triglyceride-rich fluid in the peritoneum and results from various etiologies that cause disruption of the lymphatic system.[1,2] Reported causes include congenital lymphatic abnormalities, inflammatory conditions, liver cirrhosis, malignancies, trauma, and iatrogenic injury during surgery.[3-7] The definition for chylous ascites varies among the literature. Although some authors define chylous fluid as that with "milky" appearance and triglyceride content above 110 mg/dL, others use a higher threshold value of 200 mg/mL.[1,5,8] Not only does chylous ascites cause mechanical symptoms related to abdominal distension it also may lead to malnutrition and complications in the immune system that is linked with morbidity and mortality.[9] Initially, conservative treatment is attempted with high-protein, low-fat diet with medium-chain triglycerides and, when needed, absolute fasting with total parenteral nutrition and intravenous administration of octreotide.[9,10] Surgery such as lymphatic duct ligation or peritoneovenous shunting is reserved for patients that fail conservative management and is associated with perioperative morbidity especially owing to the poor condition of such patients.[2,9] In contrast, lymphangiography and percutaneous embolization is less invasive.[11-13] Lymphangiography alone has been reported to have therapeutic effect in 56%-86% of patients with lymphatic leaks.[13-17] Lymphatic embolization was first described by Cope et al where the thoracic duct was catheterized and subsequently embolized to treat chylothorax.[18,19] Thereafter, there have been accumulating reports on the subject of lymphatic embolization describing the techniques and outcome of the procedure.[20-25]

Clinical evaluation

At our institution, most cases of chylous ascites that are referred for lymphatic intervention largely comprise patients who have undergone extensive lymph node dissection during surgery for malignancies in the esophagus, stomach or pelvis. The reported incidence of lymphatic leak attributed to retroperitoneal lymph node dissection reaches up to 4%.[10,26] A large proportion of the patients have had surgical drains placed in the surgical field at the time of surgery, whereas the remaining few are referred beforehand for percutaneous placement of drainage catheters to alleviate symptoms related to abdominal

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distension. Although, the indication for lymphatic intervention varies according to the discretion of the referring surgeon, our patients generally suit one of the following criteria: drainage of 1000 mL/d for >5 days or persistent drainage lasting more than 1-2 weeks despite conservative treatment. The long duration of hospitalization resulting from conservative treatment that may last from weeks up to months after surgery, together with improved outcomes after lymphatic intervention during the recent years have resulted in a generally low threshold for converting from conservative treatment to percutaneous lymphatic intervention.

Currently, there is no guideline which states absolute indications or contraindications to lymphangiography and adjunctive embolization. Ahead of the procedure, the patients are informed of how the procedure is carried out and what to expect with respect to outcome. While obtaining informed consent, they are also informed of complications reported in the literature including allergic reaction to Lipiodol, pulmonary oil embolism and, in rare patients with right-to-left cardiac shunts, embolism to the brain.[14] At our institution, we do not routinely screen the patients for underlying cardiac disease. Furthermore, questioning each patient if they have history of allergy to ethiodized oil is not practical because they are very unlikely to have been exposed to such agent in the past. Lastly, the patients are informed of chronic complications that may result from embolization of the thoracic duct or cisterna chyli such as swelling of the abdomen, lower extremities, and chronic diarrhea.[27] The patients are given time to consider the benefits of the procedure over the consequences of prolonged, refractory chylous ascites that may lead to malnourishment and problems in the immune system.[1] To prevent loss of compliance during the period of treatment, the patients should be informed that repeated intervention may be required on some occasions to cure lymphatic leaks.

Equipment and Technique

Intranodal injection of Lipiodol (Guerbet, Aulnay-sous-Bois, France) is the sole technique used at our institution to obtain a lymphangiogram. All procedures are performed under guidance of ultrasound and fluoroscopy. With the patient in supine position on the fluoroscopy unit, cutaneous disinfection is performed from the level of the xiphoid process to that of the upper thigh. The groin and thigh regions are scanned with a linear transducer on both sides to determine the most accessible lymph node. Although larger lymph nodes are readily identified and tend to be easier to target under ultrasound guidance, smaller ones that are not hyperplastic are also accessible with a fine needle. The needle used is a 25-gauge metallic spinal needle that is not damaged by Lipiodol during injection as seen with some needles that have plastic components. The main advantage of using such a fine needle is that it penetrates the lymph node easily rather than pushing it away and that it prevents forceful injection of Lipiodol when injected manually. An additional advantage is that the patients mostly do not experience pain when the needle is introduced. After removal of the stylet of the needle, it is pre-assembled with a short connecting tube that is also stable in Lipiodol before puncturing the lymph node. Once the needle and connecting tube is assembled, the lymph node of interest is targeted with the needle under ultrasound guidance. A shallow angle of needle entry ensures secure positioning of the needle that is less prone to getting dislodged as compared to when the angle of entry is steep. The tip of the needle can be placed anywhere within the lymph node to inject Lipiodol. Some authors have suggested that the junction of the hilum and cortex should be targeted to achieve success.[28,29] Although this is also true in our experience, lymphangiography was nevertheless successful in any location regardless of whether the cortex or hilum was punctured. However, because of abundant fat within the hilum, a higher rate of extravasation was demonstrated when the needle tip was positioned at the center of the lymph node. Lipiodol injection was performed manually using a 3-mL syringe and controlled injection was performed allowing 3 mL of Lipiodol to be injected over a time of 6 minutes (0.5 mL/min). This rate is a little faster than that described in an earlier study by Kariya et al[28] where the injection rate was either 1 mL/3 min. The rate ranges between 0.2 and 0.4 mL/min in other reports.[14,29] A successful injection is demonstrated by a "blush" or "reticular" appearance of the cortex with opacification of the efferent ducts on fluoroscopy. Meanwhile, a globular collection of Lipiodol suggests extravasation into the fatty hilum or perinodal soft tissue. In the presence of extravasation, if some of the Lipiodol is seen to opacify the efferent ducts, Lipiodol injection is continued under close monitoring. However, if no efferent ducts are seen, Lipiodol injection is discontinued and another lymph node is sought. If a lymphaticovenous shunt is seen, caution must be taken not to allow excessive shunting of Lipiodol into the systemic venous circulation that may consequently result in pulmonary oil embolism.[28] The maximum dose of Lipiodol should not exceed 20 mL owing to risk of pulmonary embolism.[11] Fluoroscopy is used intermittently to avoid excessive radiation to the patient and operator. Lipiodol injection is continued until the Lipiodol reaches the ascending lumbar trunk. Usually, at this stage, Lipiodol injection can be withheld while waiting for the Lipiodol in the ascending lumbar trunk to slowly flow upwards to opacify the cistern chyli and thoracic duct. Lymphangiography has been reported to successfully demonstrate leaks in up to 86% of patients with lymphatic disruption.[13-15,17] Recently, we have started to make use of cone-beam CT that is available on our fluoroscopy equipment in cases where the leak is not clearly demonstrated on fluoroscopy. When the leak is identified, either one of the following choices can be made: (1) expect for therapeutic effect of lymphangiography alone (Figs. 1 and 2); (2) perform adjunctive percutaneous embolization. The latter is performed when therapeutic lymphangiography fails or in the face of high-out leaks exceeding 1000 mL/d. When the

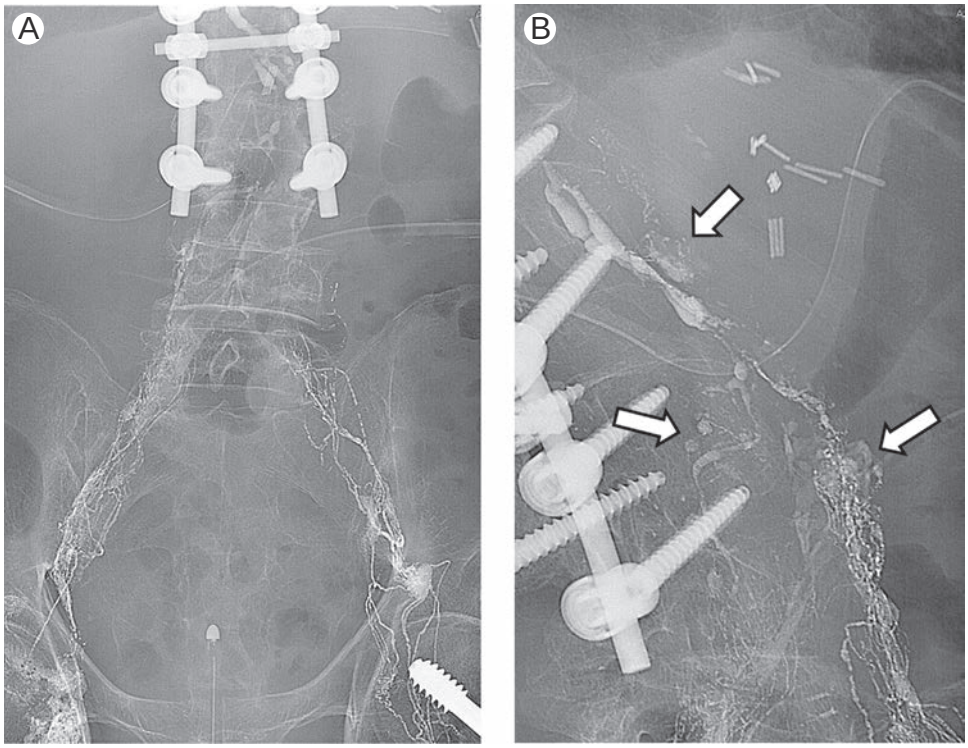

Figure 1 A 68-year-old male patient who developed high-output chylous ascites after esophageal surgery. (A) Intranodal lymphangiography was performed through lymph nodes in bilateral upper thigh regions to assess for lymphatic leakage. (B) Multiple leaks (arrows) were identified in the retroperitoneum on spot radiography. Therapeutic effect of lymphangiography was expected and therefore no further procedure was carried out. The surgical drains were successfully removed 4 days later.

leakage is identified in the lower thoracic duct or cisterna chyli, the conventional technique for thoracic duct embolization is performed by percutaneously accessing the ascending lumbar trunk or the cistern chyli itself using a fine needle, passing a 0.014- or 0.018-in guide wire through the needle and into the thoracic duct and then coaxially delivering a microcatheter over the guide wire to perform transcatheter embolization of the leaking duct (Fig. 3). The embolic agent of choice is glue, a mixture of N-butyl cyanoacrylate (NBCA; B. Braun, Melsungen, Germany) and Lipiodol usually mixed at 1:1 ratio. A coil may be placed before injection of glue to stabilize the cast and prevent it from being washed out. Unlike leaks in the thoracic duct or cistern chyli, leakage below this level is technically more challenging to treat. This may be a reason for the scarcity of reports that describe treatment of lymphatic leaks in the retroperitoneum, mesentery, or pelvis, which contrasts to the relative abundance of articles in the English literature on thoracic duct embolization. Some authors have described techniques where the leakage itself was percutaneously targeted using a fine needle under fluoroscopy or CT guidance and was subsequently embolized by injecting glue.[21,30,31] We use the same technique when lymphangiography reveals a collection (or a "sac") of extravasated Lipiodol that appears feasible for percutaneous access. A 21-guage needle is used to puncture the lymphatic sac after which glue is injected. The glue can be injected directly through the needle or through a microcatheter (Fig. 4) that has replaced the

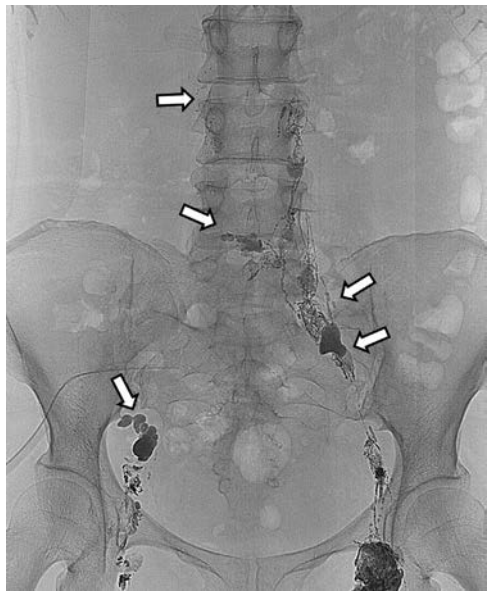

Figure 2 A 52-year-old female patient who developed chylous ascites after undergoing extensive lymph node dissection in the pelvis and para-aortic nodal stations during surgery for endometrial cancer. Intranodal lymphangiography demonstrates typical features of multilevel leakage along the bilateral iliac and retroperitoneal lymph node chains occurring after extensive lymph node dissection. Therapeutic effect was achieved by lymphangiography only and the drains were successfully removed 2 days later.

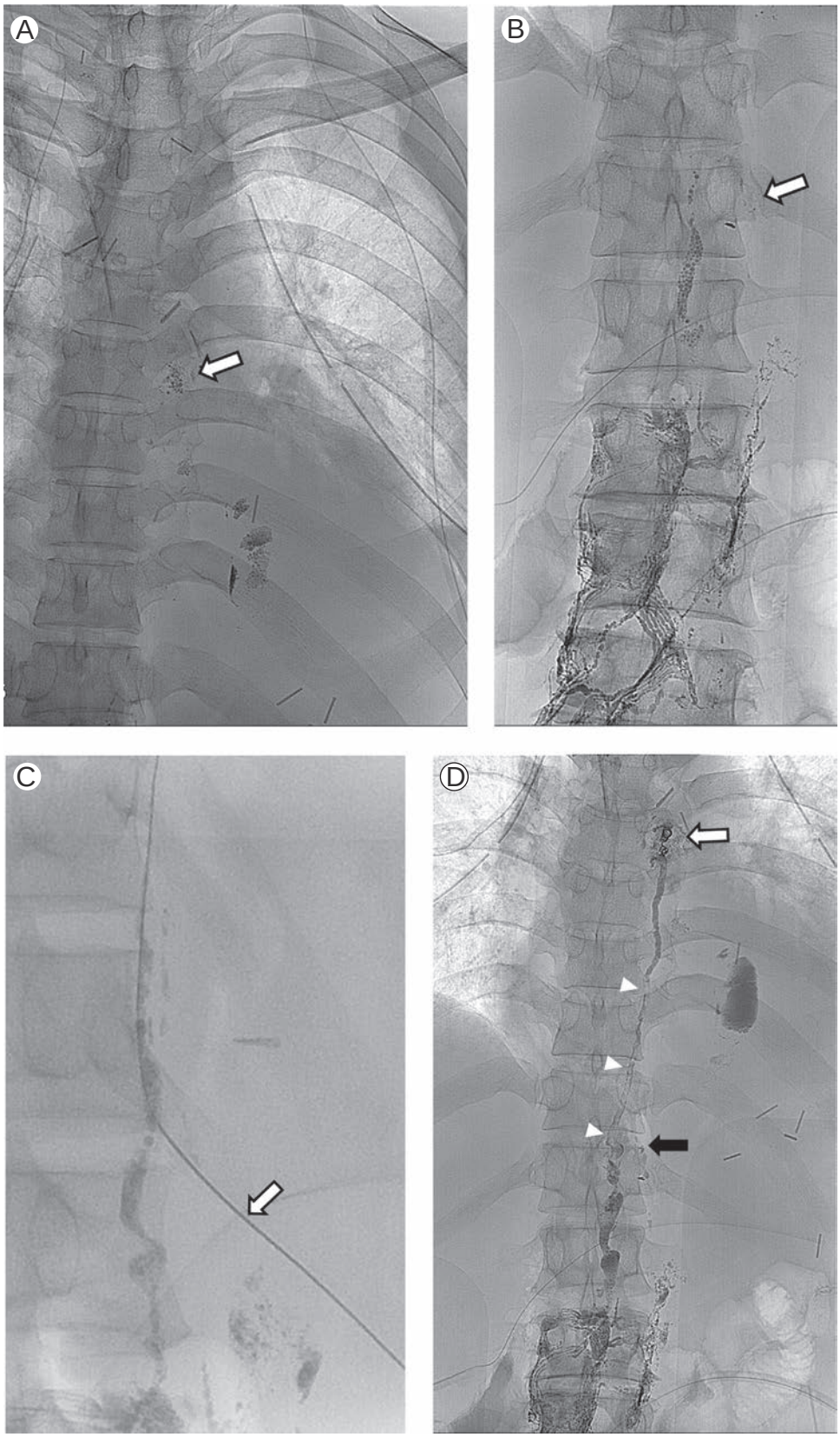

Figure 3 A 59-year-old male patient who developed chylothorax (1800 mL/d) and chylous ascites (800 mL/d) after surgery for esophageal cancer. (A and B) Lymphangiography revealed leaks in the upper and lower thoracic duct (arrows). (C) The lymphatic duct was percutaneously accessed below the level of the leakage using a 22-gauge needle (arrow) and 0.014-in guide wire. Thereafter, a microcatheter (not shown) was advanced over the wire into the thoracic duct. (D) After placing a pushable coil (white arrow) at the leaking point in the upper thoracic duct, 1:1 glue mixture (seen as a linear filling defect within the thoracic duct and indicated by white arrowheads) was injected simultaneously as the microcatheter was caudally withdrawn (black arrow indicating the most caudal level of glue embolization where there was retroperitoneal leakage). Both chylothorax and chylous ascites resolved after the procedure.

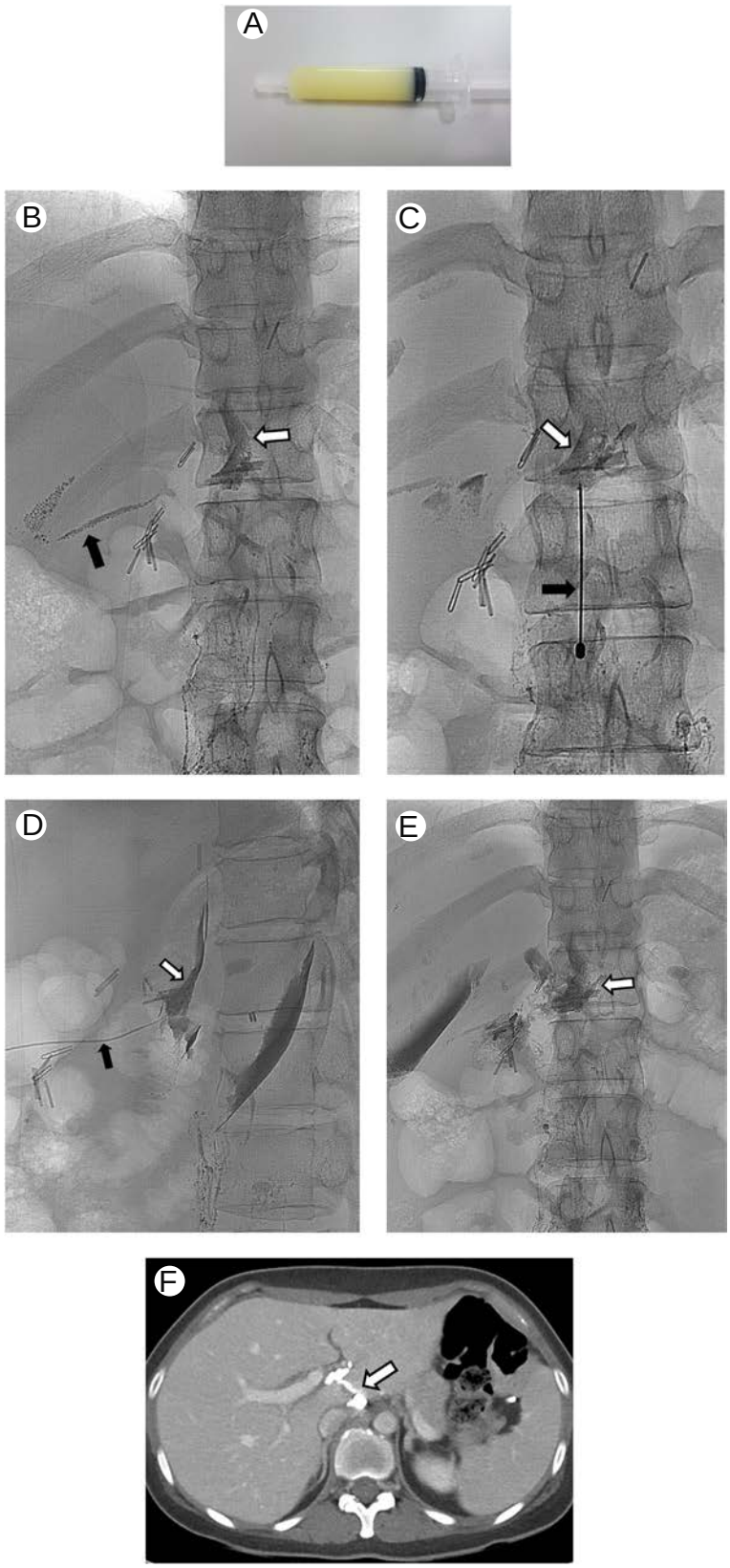

Figure 4 A 31-year-old female patient who developed abdominal distension after surgery for advanced gastric cancer. (A) Percutaneous drainage was performed to evacuate the intraperitoneal fluid which was found to have "milky" appearance. (B) Intranodal lymphangiography revealed a leak (white arrow) at the level of the thoracolumbar junction and the extravasated Lipiodol (black arrow) was seen to flow toward the perihepatic space. (C) A 21-gauge needle (black arrow) was used to percutaneously access the site of the leak (white arrow). (D) After inserting a 0.016-in guide wire (not shown) though the needle, the needle was exchanged for a 2.4-Fr microcatheter (black arrow) in a coaxial fashion after which NBCA-Lipiodol mixture of 1:1 ratio was injected into the leak (white arrow). (E) A glue cast (white arrow) is seen on spot radiography that was acquired immediately after embolization. (F) CT performed 2 months after embolization shows trace of embolic material (white arrow) at the prior leakage site. The perioneal cavity is free from chylous ascites.

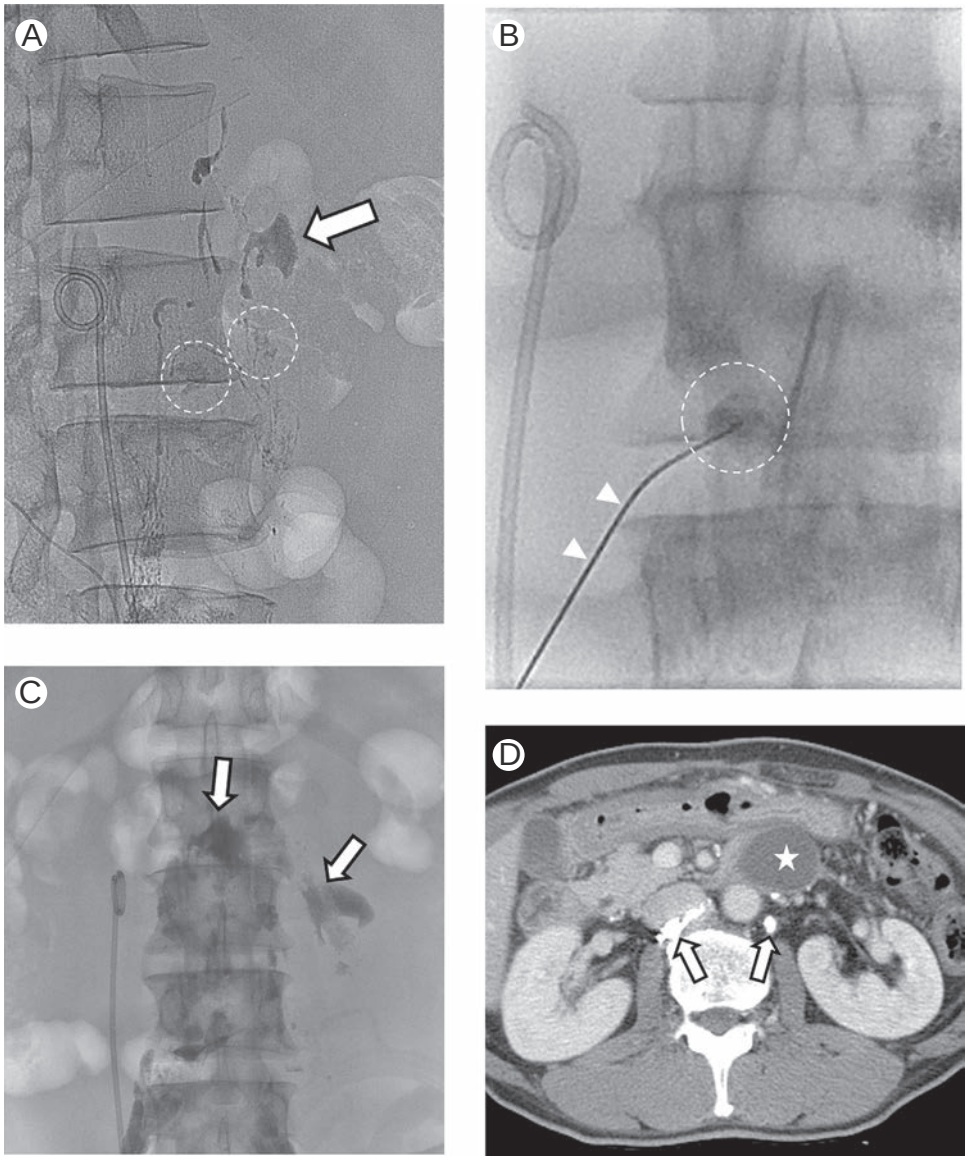

Figure 5 A 47-year-old male patient who developed chylous ascites after surgery for rectosigmoid cancer. (A) Leakage (arrow) was identified at the site of para-aortic lymphadenectomy. White circle outlines the location of a lymph node just below the level of the leak. (B) The lymph node was targeted with a 22-gauge needle (arrowheads) which was intentionally bent just proximal to the tip for directional control within the peritoneum. NBCA and Lipiodol mixture of 1:6 was injected into the lymph node until the glue cast flowed into the leak. (C) Spot radiography taken on the following day shows the glue cast (arrows) in the retroperitoneum. (D) CT acquired seven months later demonstrated an asymptomatic lymphocele (starred) but the peritoneum was free from chylous ascites. Note the remnant cast of glue (arrows) in the retroperitoneum.

needle over a guide wire in coaxial fashion. Gradual refinements have been made over time regarding the ratio of NBCA and Lipiodol mixture used for embolization in which the mixture has become more concentrated. Currently, we use NBCA and Lipiodol mixture of 1:1. As the glue is injected directly through the needle, premature polymerization does not occur even without the use of dextrose-5-water. Such concentrated mixture of glue is less prone to being washed out. As with thoracic duct embolization, adjunctive use of pushable or detachable coils is an option, which may provide a matrix for the glue to adhere. During injection of glue, it is important to exclude presence of any lymphaticovenous anastomoses that may result in migration of glue from the lymphatic duct to the systemic venous circulation and consequently result in pulmonary embolism of the polymerized cast.

As an alternative technique for embolization, we perform intranodal injection of glue (Fig. 5), which has previously been described by Baek et al.[32,33] for the treatment of lymphatic injury related to pelvic lymphadenectomy. To prevent extensive embolization of collateral flow, a lymph node that is located just caudal to the leakage site is punctured with a fine needle. After test injection with Lipiodol to confirm the position of the needle within the lymph node, intranodal glue injection is performed until the cast reaches the site of disruption. The concentration of glue varies from 1:4 to 1:8 depending on the size of the lymphatic vessels and distance from the

lymph node to the leak. Flushing with dextrose-5-water is usually not required because the lymph node and ducts have already become saturated with Lipiodol during lymphangiography which consequently alleviates the concern for premature polymerization. Intranodal glue injection is an attractive embolization technique for leaks that occur in the ascending lumbar and pelvic lymphatic chains where, unlike in thoracic duct embolization, direct access into the lymphatic duct is often technically infeasible.

Overcoming Technical Challenges

Technical challenges in successful lymphatic intervention are 2-fold. The first challenge is to acquire a complete lymphangiogram that demonstrates the site of chylous leakage. The transit time from injection of Lipiodol to opacification of the central lymphatic system varies among patients. It takes more time and effort to acquire a complete lymphangiogram in some patients than in others. To reduce the transit time, we routinely take a few measures. First, we perform Lipiodol injection on both sides to reduce procedure time. Second, as soon as a lymph node located at a higher station (either in the pelvis or lower lumbar level) is opacified after intranodal Lipiodol injection in the groin, the higher lymph node is punctured with another needle and the Lipiodol is propagated from this level. By actively moving up through the nodal stations, stagnant lymphatic vessels can be bypassed to allow a faster procedure. The second challenge in lymphatic intervention is percutaneous targeting of the lymphatic duct or site of leakage with a fine needle. In patients who have markedly distended abdomen owing to large amount of ascites or those who are obese, we use a 20-gauge needle that is stiffer and allows more directional control than the 22-gauge needle. Thus far, we have had no complications related to transperitoneal puncture. Furthermore, the tip of the needle can be gently bent to provide directional control while it is advanced through the peritoneal space. The bent tip also helps to direct the guide wire cranial or caudal to the site of needle penetration depending on the level of the leak.

Outcomes and Complications

Complication following lymphangiography is rare. The overall morbidity and mortality related to lymphangiography has been reported to be lower than 5%.[34] The most notable complication is pulmonary oil embolism which was found to be directly related to the volume of Lipiodol injected. A threshold limit of 10 mL per extremity or 1 mL/10 kg/extremity for a maximum dose of 7 mL/extremity has been suggested in the literature.[12] Furthermore, the presence of lymphaticovenous anastomoses may allow significant amount of Lipiodol to be shunted into the systemic venous system to result in pulmonary embolism.[28] The reported complication of lower extremity edema for pedal lymphangiography is no longer an issue which the current trend in intranodal technique.

With respect to percutaneous embolization using a fine needle, there are no reported complications related to transperitoneal puncture. Instead, complications may arise from migration of glue into the systemic venous system via lymphaticovenous shunting and therefore the glue should be closely monitored under fluoroscopy while it is injected. Complications such as abdominal swelling, lower extremity swelling, and chronic diarrhea have been reported after thoracic duct embolization but there is no such data for procedures that are performed in the lower levels.[27]

Postprocedural Care and Follow-Up

The most common complaint after the procedure is pain in the groin or pelvis after the procedure.[11] The pain is usually transient and resolves over a few hours of observation or conservative management. The amount of drainage is monitored and documented to determine the outcome of the procedure. A successful procedure is rewarded by markedly decreased amount of drainage and conversion of "milky" fluid to clear fluid. There is a lack of data regarding the cutoff value of drainage according to which the decision for drain removal can be made. In the study by Kawasaki et al, the criterion for successful treatment was a daily output of less than 200 mL that is nonchylous.[15] At our institution, surgical drains in patients who have undergone gynecologic surgery are routinely removed when the amount of output decreases below 300 mL/d and there have been no related complications.[35] In those who undergo lymphatic intervention, we currently keep to a cutoff range of 200-300 mL/d or lower. Any amount below this range is successfully controlled conservatively and we have not experienced any case of recurrent ascites after drain removal. Repeated intervention is considered for patients who either have drainage above this amount or show evidence of chyle in the drained fluid.

Although imaging is not routinely performed because of cost issues, we perform follow-up radiography of the chest and abdomen only when therapeutic lymphangiography has been performed without adjunctive embolization. Cross-sectional imaging studies are only considered in patients who have refractory chylous ascites of despite intervention.

Conclusions

Chylous ascites can be managed by therapeutic effects of lymphangiography alone or with adjunctive embolization techniques that include direct percutaneous injection of glue into the leakage site or into a nearby lymph node. Refinements are still needed regarding the technique of

embolization and further investigations are warranted in the future to assess the outcome of such techniques.

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ELSEVIER

Techniques in Vascular and Interventional Radiology

Interventional Treatment of Pulmonary Lymphatic Anomalies

Maxim Itkin, MD, FSIR

Pulmonary lymphatic diseases have been recognized for many years and have been referred as pulmonary lymphangiectasia, pulmonary lymphangiomatosis, plastic bronchitis, and idiopathic chylothorax or chylopericardium. The lymphatic etiology of these conditions has been determined by detection of cystic lymphatic structures on biopsy or postmortem examination. Development of new imaging techniques such as dynamic contrast–enhanced magnetic resonance lymphangiography has allowed better understanding of pathophysiology of these conditions. Dynamic contrast–enhanced magnetic resonance lymphangiography demonstrated that the common denominator of these disorders is an abnormal pulmonary lymphatic flow from the thoracic duct toward pulmonary parenchyma. This abnormal lymphatic flow propagates into mediastinum, lung parenchyma, pleural surfaces, and bronchial submucosa and has been termed as pulmonary lymphatic perfusion syndrome (PLPS). Known clinical presentation of PLPS includes spontaneous chylothorax or pericardium, neonatal chylous effusions, and plastic bronchitis. PLPS has been observed in all age groups and can be considered as a congenital anatomical lymphatic variant. The onset of the clinical symptoms can be provoked by increase of the lymphatic flow owing to elevated central venous pressure that results in lymphatic distention, trauma, and severe upper respiratory infection. Reported treatment of PLPS is obliteration of these abnormal lymphatic pathways by percutaneous embolization, a technique similar to thoracic duct embolization in chylothorax.

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KEYWORDS Pulmonary lymphatic disorders, Lymphatic embolization, Magnetic resonance

Background

Pathologic changes of the lymphatic system of the lungs has been known since an 1895 report by Virchow,[1] who described lymphatic cysts in the lung of a child on postmortem examination. Since then, similar postmortem findings were reported by multiple authors.[2,3] With the development of the first lymphatic imaging modality, pedal lymphangiography, several authors reported the phenomenon of lymph flowing from the thoracic duct toward lung parenchyma calling it "lymphatic reflux."[4] However, the understanding of the extent of abnormal pulmonary lymphatic flow has been limited owing to the difficulty of high viscosity Lipiodol (Guerbet LLC, Bloomington, IN) oil–based contrast agent to propagate into small lymphatic vessels. Recent development of the dynamic contrast–enhanced magnetic resonance (MR) lymphangiography (DCMRL) allowed better visualization of the lymphatic vessels owing to more distal propagation of less viscous gadolinium imaging agents and higher tissue contrast resolution of the MR. DCMRL let us better understanding the extent of the abnormal pulmonary lymphatic flow.[5] This improved visualization of the anatomical distribution of pulmonary lymphatic flow allowed the identification of lymphatic enhancement of the mediastinal and lung tissues that we termed "Pulmonary Lymphatic Perfusion Syndrome (PLPS)" (Fig. 1).[6]

Pathophysiological Mechanism

Overall, 90%-80% of the lymph in the body is generated below the diaphragm in the abdomen primarily in the liver and intestine.[7] The lymphatics from the liver, intestine,

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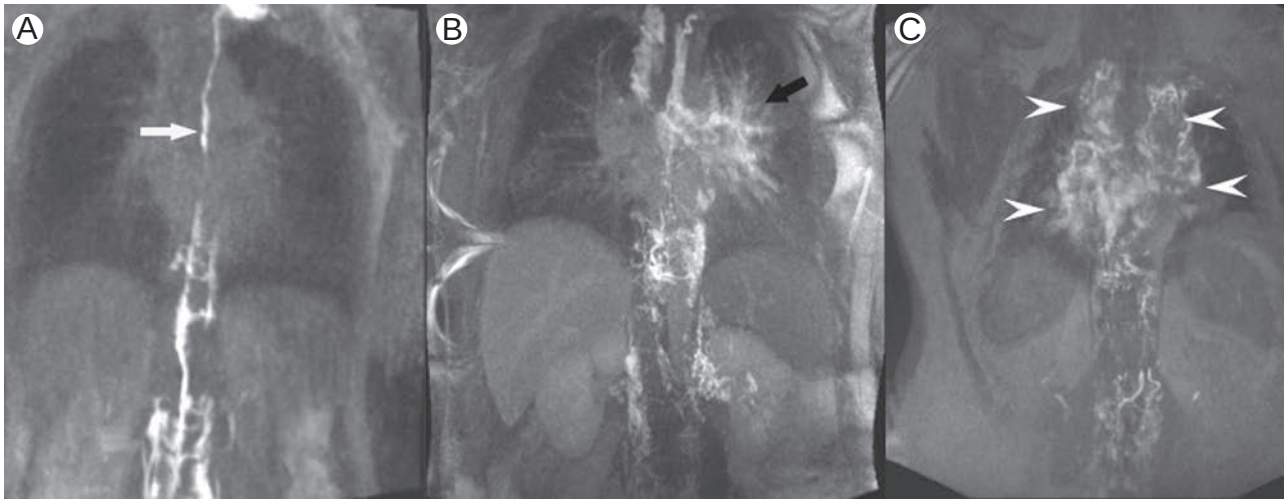

Figure 1 DCMRL imaging of the patients with plastic bronchitis. (A) Normal TD (white arrow) with no pulmonary lymphatic flow in patient 6; (B) abnormal TD with abnormal pulmonary lymphatic flow toward left hilum and lung in patient 3 (black arrow); and (C) bilateral abnormal pulmonary perfusion in patient 5 (black arrowhead). (*Copyright*: American Thoracic Society). Permission to reprint requested 10-4-16. TD, thoracic duct.

and soft tissue then converge together in the cisterna chyli that conducts lymph further into the thoracic duct that in turn discharges the lymph into the venous system in the area of the junction of left jugular and subclavian veins. Traversing through the mediastinum, the thoracic duct accepts lymphatic contributories from the mediastinal organs, such as heart, esophagus, and lungs. In patients with PLPS, part of the lymph flows retrograde from the thoracic duct toward lung parenchyma, mediastinum through the aberrant lymphatic vessels (Fig. 2). We hypothesize that these vessels are collaterals and developed as a decompression mechanism to in utero occlusion or stenosis or compression of the downstream parts of the thoracic lymphatic system (Fig. 3). We hypothesized that these lymphatic collaterals are often not clinically significant if their course is deep in the soft tissue; however, they can become symptomatic if they abut serous and mucosal surfaces such as pleura, pericardia, and bronchi where under certain circumstances they can start to leak in these compartments.[8] The commencement of the symptoms can be provoked by: (1) silent trauma that would result in rupture of these lymphatic vessels causing chylothorax or chylopericardioum; (2) severe upper respiratory infection, which can cause injury of the bronchial lining causing lymphatic plastic bronchitis in adult patients[9]; and (3) overdistention of the lymphatic vessels owing to increase of lymphatic production in patients with congenital cardiac diseases causing plastic bronchitis or chylothorax.[6]

Clinical Presentation of Pulmonary Lymphatic Perfusion Syndrome

Clinically PLPS can present at any age starting from newborns (neonatal chylothorax) to older adults as chylothorax or plastic bronchitis.

Neonatal Chylothorax

Neonatal chylothorax is a condition that is often diagnosed on prenatal ultrasound as a pleural effusion. Moreover, 90% of all pleural effusions in utero are chylothorax.[10] To prevent the underdevelopment of the lung parenchyma owing to its compression by pleural effusion, the drainage of the pleural space is performed by placing a thoracoamniotic shunt.[11] In our practice, all newborns with neonatal chylothorax undergo DCMRL. Typical findings on DCMRL are complete occlusion of the midthoracic duct and the development of abnormal pulmonary lymphatic flow (Fig. 4A). It is very important to differentiate isolated chylothorax from chylothorax that presents with chylous ascites and tissue edema. The latter condition is called congenital lymphatic dysplasia and is caused by general dysplasia of the lymphatic system and is one of the most difficult neonatal conditions to treat.[12]

Immediately after the DCMRL, we perform intranodal lymphangiography using a technique described previously by Nadolski et al.[13] The findings on the intranodal lymphangiography correlate well with the findings on DCMRL and include complete occlusion of the thoracic duct in middle mediastinum and retrograde flow of the contrast in the lung parenchyma (Fig. 4B).

The rate of the chylothorax leak in these patients is often very slow, in the range of tens of milliliters a day, and for that reason lymphangiography that uses a small amount of oil-based contrast lipiodol is often curative owing to its well-known embolization effect.[14,15] The amount of lipiodol that is used during lymphangiography, however, has to be less than 0.25 mL/kg[16] because larger doses can embolize non-target lymphatic vessels resulting in generalized edema.

Idiopathic Chylothorax or Chylopericardium

We defined idiopathic chylothorax or chyloperiradium as a condition with no identifiable cause, such as remote trauma, systemic diseases, and malignancies.

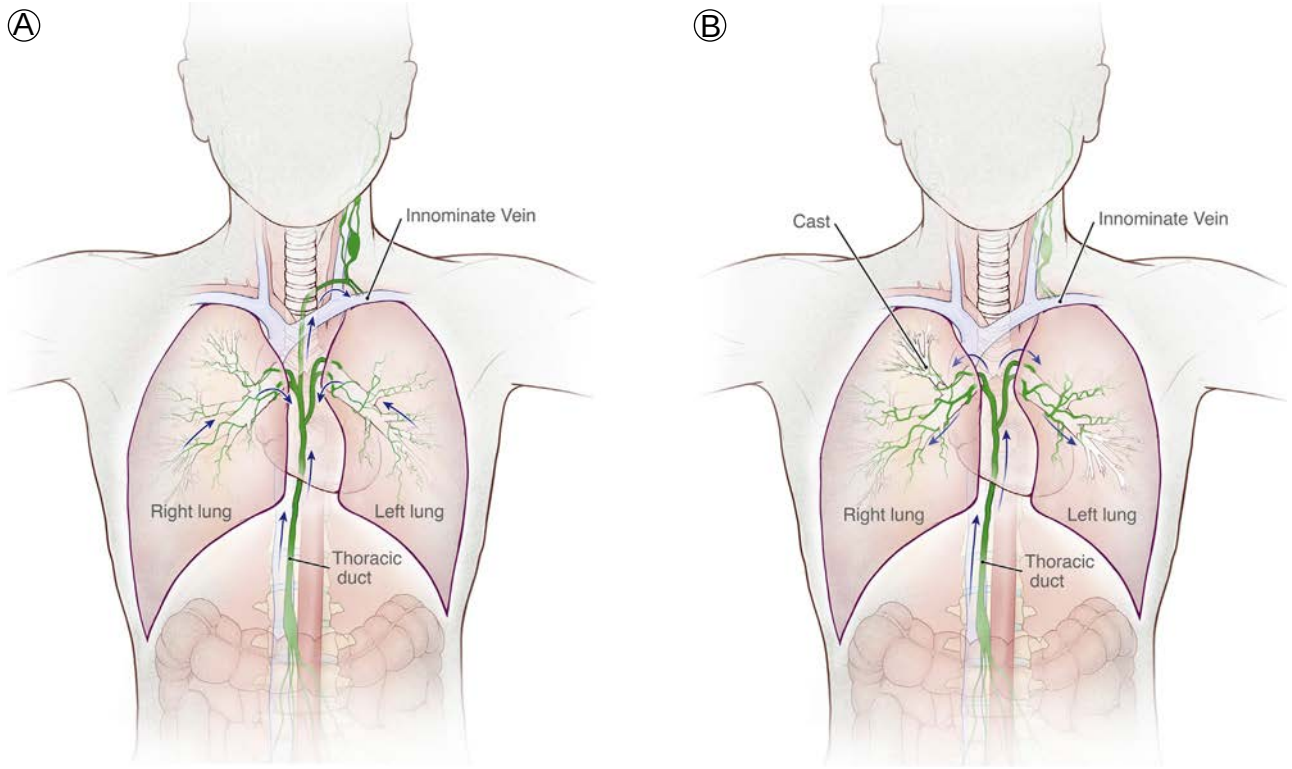

Figure 2 (A) Schematic representation of the normal pulmonary lymphatic flow from pulmonary parenchyma toward thoracic duct. Thoracic duct empties in the left subclavian vein. (B) Schematic representation of the abnormal pulmonary lymphatic flow in plastic bronchitis from the thoracic duct toward lung parenchyma. (C) There is occlusion of the upper part of the thoracic duct. (Printed with permission from the Children's Hospital of Philadelphia © 2016. All Rights Reserved.) (Color version of figure is available online.)

Idiopathic chylothorax can present at any age and equally between the sexes.[17] In the past the understanding of the pathophysiological mechanisms of idiopathic chylothorax was not clear owing to absence of robust lymphatic imaging modalities. DCMRL provided with insight into the understanding of the cause of the idiopathic chylothorax. One of the main causes of idiopathic chylothorax or chylopericardium is the PLPS. More detailed description of the diagnostic and treatment algorithm of nonidiopathic chylothorax can be found in another part of this techniques in vascular and interventional radiology (TVIR) issue.

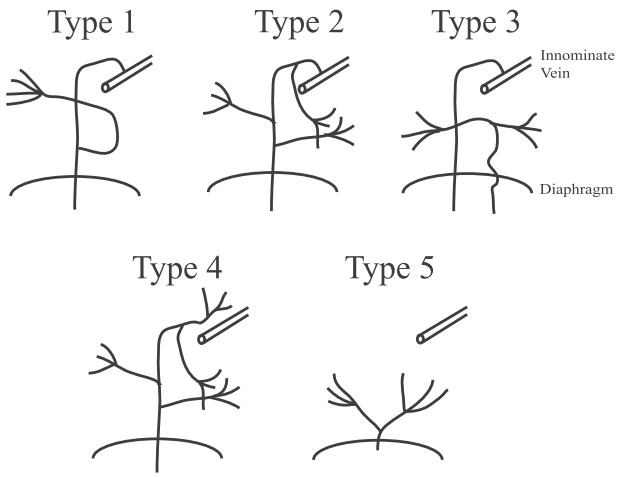

Figure 3 Schematic drawing of the 5 PB types. PB indicates plastic bronchitis. (Reprinted with permission from Dori et al.[6])

Clinical history usually reveals that these patients had prolonged pulmonary symptoms, such as unexplained prolong productive cough, in some cases resembling symptoms of plastic bronchitis or frequent pulmonary infections or both. The diagnostic workup in these patients starts with DCMRL that usually demonstrates typical PLPS findings such as occlusion or stenosis of the upper part of the thoracic duct with retrograde flow of the contrast toward lung parenchyma (Fig. 5).

The interventional treatment of patients with idiopathic chylothorax and PLPS is similar to the technique of embolization of the thoracic duct in patients with traumatic chylothorax. The main goal is to occlude the thoracic duct below the take of the lymphatic vessels that carry the lymphatic flow toward pulmonary parenchyma.

Plastic Bronchitis

Plastic bronchitis is a condition in which children or adults expectorate casts of their bronchial tree (Fig. 6). It is most commonly associated with congenital heart diseases such as in children with a single ventricle who underwent Fontan palliative procedure. In these children blood from superior vena cava and inferior vena cava flows passively into the pulmonary veins, causing significant elevation of the central vein pressure and as a result increased lymph production.[6] Plastic bronchitis can also present as a

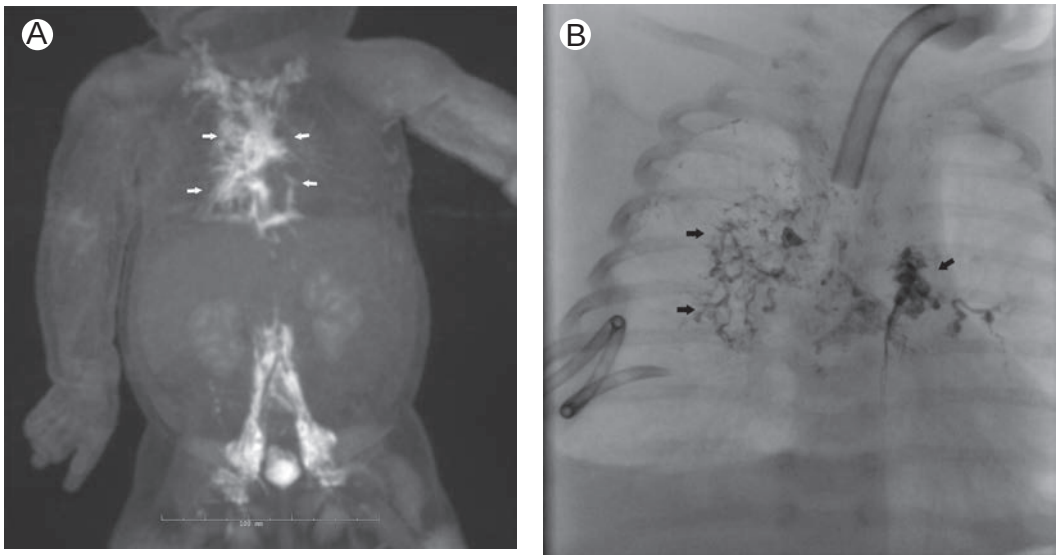

Figure 4 (A) DCMRL of the patient with neonatal chylothorax, demonstrating abnormal pulmonary lymphatic flow toward lung parenchyma (black arrows). (B) Fluoroscopy image of the chest again demonstrating abnormal flow of the lipiodol injected through groin lymph nodes toward lung parenchyma (black arrows).

lymphatic plastic bronchitis in adult patients (Itkin, in press).

In all patients with plastic bronchitis regardless of cause, the underlying pathology is PLPS and is very similar to the lymphagiographic picture of patients with idiopathic chylothorax[6]. The main difference, however, is that the abnormal lymphatic perfusion occurs in the bronchial mucosa, where the lymph "seeps" into the lumen of the bronchi and then dries up to form the cast of the lung. When injecting the color indicator (methylene blue or lymphazurin 1%) through the catheter positioned in the thoracic duct while performing the bronchoscopy, we can visualize these submucosal vessels.

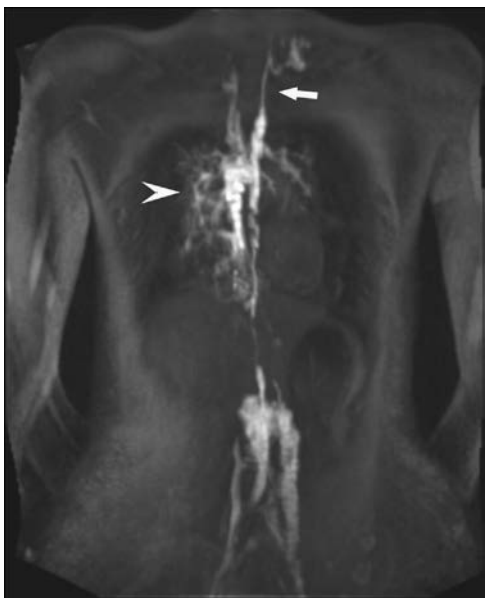

Figure 5 DCMRL of the patient with idiopathic chylothorax, demonstrating narrowing of the upper part of the thoracic duct (white arrow), and retrograde flow of the contrast in the pulmonary parenchyma (white arrowhead).

Percutaneous embolization of these abnormal pulmonary lymphatic vessels results in alleviation of the symptoms of plastic bronchitis in close to 100% of the patients with minimal complications.[6]

DCMRL Findings in PLPS

In our institution all patients with clinically suspected PLPS undergo DCMRL unless there are contraindications to MR, such as presence of certain type of pacemaker, defibrillators, claustrophobia, etc. We use Dotarem (Guerbet LLC, Bloomington, IN) contrast agent in patients with impaired renal function. DCMRL is usually performed under anesthesia or deep sedation in pediatric patients and with local anesthesia in adults. The description of the DCMRL technique can be found in the other chapter in this issue of TVIR. DCMRL can be performed at the same time as embolization treatment or at a separate setting.

DCMRL allows establishment of the diagnosis of PLPS and demonstrates the anatomy of the central lymphatic system. The most common unifying finding on PLPS is

Figure 6 Picture of the patient bronchial cast. (Color version of figure is available online.)

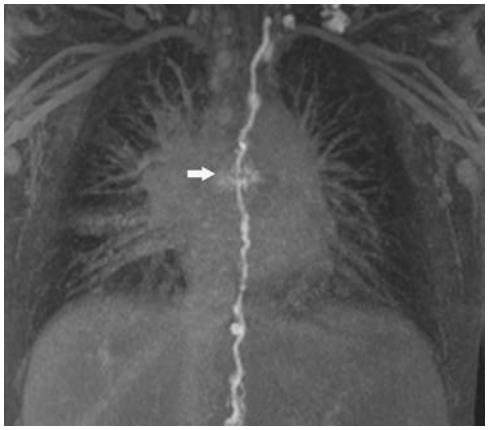

Figure 7 DCMRL of the patient with plastic bronchitis, demonstrating subtle abnormal mediastinal lymphatic perfusion (white arrow).

presence of the lymphatic enhancement on the mediastinum and lung parenchyma. The extent of the lymphatic perfusion can range from subtle enhancement around thoracic duct (Fig. 7) to extensive perfusion of the mediastinum and lung parenchyma (Fig. 1B and C). From our experience DCMRL is much more sensitive in identification of the PLPS than direct injection of the thoracic duct with contrast. DCMRL also helps to plan the treatment procedure by identifying the anatomical elements of the lymphatic system and their relationship to the abnormally perfused lung. Typical anatomical findings that are relevant to the procedure are single vs double thoracic duct, presence of the cisternae chyle, presence of intramediastinal communication between different branches of the thoracic duct, absence or narrowing of the distal part of the thoracic duct, and relationship of each component of the central lymphatic system to the abnormally perfused area (Fig. 3). Identification of distended cisterna chyle and thoracic duct in some cases allowed us to access the central lymphatic system without help of intranodal lymphangiography, based on the DCMRL findings.

Embolization Technique

The embolization technique in patients with PLPS is very similar to the standard thoracic duct embolization as described in this issue of TVIR with the exception of patients with congenital heart disease. Presence of the right-to-left shunt in these patients can result in crossing of the lipiodol systemic embolization with oily contrast.[18]

To prevent this complication in all patients with congenital heart disorders, we perform right heart catheterization and embolization of all veno-veno collaterals. In case of large Fontan fenestration, which is a connection between Fontan circuit and single atrium, we place a temporary occlusion balloon. During the procedure, we opt to use water-soluble agent as often as possible. Owing to significant dilation of the lymphatic system in patients with right-sided heart failure it is possible to access cisterna chyli based on landmarks provided by DCMRL without use of intranodal lymphangiography.

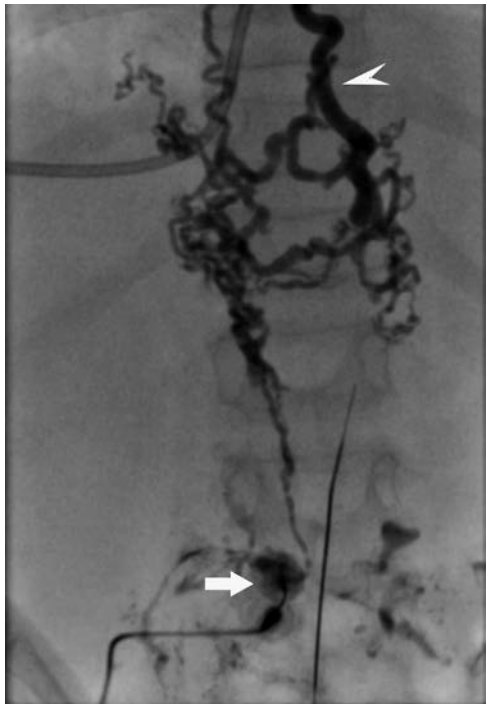

Figure 8 Fluoroscopic image of the embolization of the thoracic duct (white arrowhead) in neonate with chylothorax by injecting N-BCA glue thorough needle positioned in retroperitoneal lymph node (white arrow).

In patients without left-to-right shunt, the embolization starts with intranodal lymphangiography. In patients with neonatal chylothorax, delivery of the lipiodol contrast material into the lymphatic system can be curative and alleviate the need to perform catheterization and embolization of the thoracic duct (Fig. 4B).

Catheterization of the thoracic duct in neonates can be challenging owing to its small size. In this case it is possible to perform the embolization of the thoracic duct by injecting the N-BCA glue through the needle with its tip positioned in the retroperitoneal lymph node (Fig. 8).

Selective catheterization of the branch of the thoracic duct that leads to the pathologically perfused area is possible; however, we found that most of the time complete embolization of the thoracic duct is the only curative option. The lymphatic embolization technique is very similar to the embolization technique of the thoracic duct. If the thoracic duct is patent, a nest of coils is deployed in the thoracic duct proximal to the area of the abnormal perfusion, to create a matrix for glue polymerization, and to prevent spillage of the contrast into draining vein. If the thoracic duct is occluded and there is no connection with vein, N-BCA glue diluted 1:2 with lipiodol can be injected directly below the area of the abnormal flow.

Conclusion

Development of DCMRL allowed us to understand the underlying pathology of several pulmonary conditions by demonstrating abnormal pulmonary lymphatic flow from

the thoracic duct toward pulmonary parenchyma, which we termed PLPS. Percutaneous embolization of these abnormal pulmonary lymphatic vessels has been proven to be successful treatment of these conditions with minimal complication rate. We believe that PLPS is a congenital anatomical lymphatic variant that can present clinically under certain conditions. It is possible that other poorly understood lung conditions and even pulmonary symptoms in some patients with heart failure could be explained by PLPS. Wider acceptance and use of DCMRL and percutaneous embolization techniques can further expand our knowledge and treatment options for these pulmonary conditions.

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ELSEVIER

Techniques in Vascular and Interventional Radiology

Percutaneous Treatment of Lymphatic Malformations

Michael Acord, MD, Abhay S. Srinivasan, MD, and Anne Marie Cahill, MD

Lymphatic malformations are slow-flow vascular anomalies composed of dilated lymphatic channels and cysts of varying sizes. Percutaneous treatments, particularly sclerotherapy, play an important role in the treatment of these lesions, often obviating the need for surgical intervention. Owing to the complex nature of these lesions, a multidisciplinary approach should be used to guide diagnosis and management. This submission focuses on the workup and treatment of pediatric lymphatic malformations at our institution, with a focus on sclerotherapy. Therapeutic outcomes and the management of postprocedural complications are also discussed.

KEYWORDS Sclerotherapy, Lymphatic malformations, Pediatric

Background

Lymphatic malformations (LMs) are slow-flow vascular anomalies composed of dilated lymphatic channels and cysts. LMs do not demonstrate discrete communications with the normal lymphatic or venous systems. Depending on cyst size, they are classified as macrocystic, microcystic, or combined lesions (Fig. 1). Although there is no consensus definition or size cutoff of macrocystic vs microcystic LMs, the term macrocystic is generally reserved for lesions that are easily amenable to aspiration, which is usually 1-2 cm.[1,2] LMs are often transspatial in nature and can range in size from localized to diffusely infiltrating. Recent studies estimate the incidence to be 1/2000-4000 live births, without significant difference in sex.[3] Owing to the complexity of these lesions, our institution favors a multidisciplinary approach to clinical evaluation and treatment.

Clinical Evaluation

Presentation and Clinical Assessment

Clinical presentation depends primarily on the size and location of the malformation. Although LMs may involve any part of the body, most (48%-75%) are found in the cervicofacial region and 20%-42% are found in the extremities.[4,5] If large enough, lesions may be detected as early as the first trimester on prenatal ultrasound or prenatal magnetic resonance imaging (MRI). Those not identified prenatally would usually present shortly after birth as a soft tissue mass. The vast majority of the lesions present before the age of 2 years.[6]

Like other vascular malformations, LMs are congenital and grow proportionally with the child. If the lesions are small, patients may not present to the clinic until later in childhood when a lesion-related complication, such as infection or spontaneous hemorrhage, brings it to attention. Rarely, lesions would return to their prior size after resolution of the insult, going unnoticed until a repeat complication. LMs that are near joints may cause difficulty in ambulation, noticeable when the child is learning to walk or crawl.

As with other vascular malformations, management is best addressed in the setting of a vascular anomalies clinic, which is commonly staffed by interventional radiology and plastic surgery, with support from services such as dermatology, otorhinolaryngology, general surgery, ophthalmology, and oncology. On physical examination, LMs are solitary or multifocal soft masses with normal overlying skin. There are cases, however, where involvement of the dermal lymphatics results in the formation of dermal vesicles or angiokeratomas, which themselves may ooze blood-stained lymphatic fluid for a prolonged period or become superinfected (Fig. 2A). The skin may show a bluish discoloration if hemorrhage is present or show warmth in cases of infection

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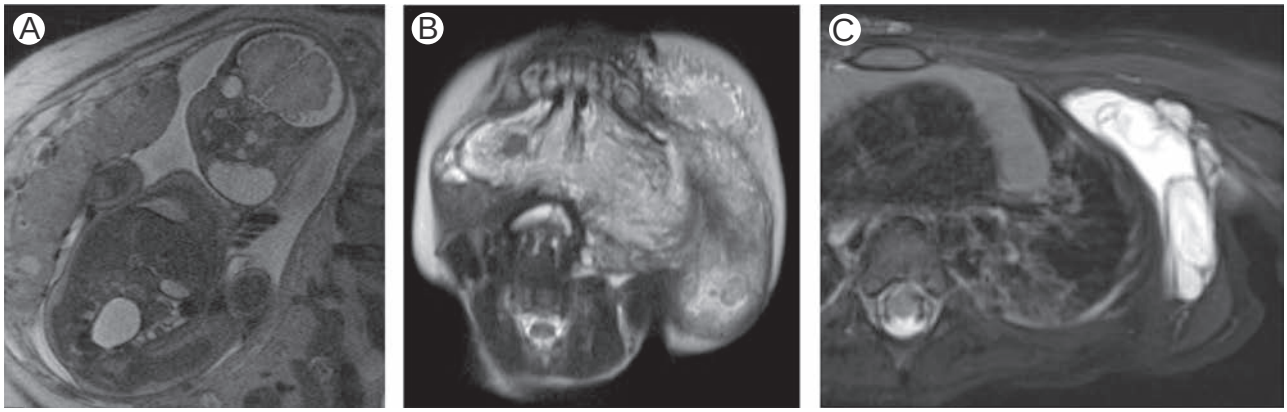

Figure 1 T2-weighted images showing different types of lymphatic malformations. (A) Prenatal MRI shows a macrocystic malformation involving neck. (B) A 3-month-old male with a cervical microcystic LM extending into the floor of the mouth. (C) A 10-month-old male with a left axillary mixed LM.

(Fig. 2B). LMs do not have a palpable pulse or thrill to suggest a high-flow component. Macrocystic LMs may transilluminate with a flashlight. Physical examination of the LM should primarily focus on identifying the location, extent and the relationship of the lesion to nearby structures. Pretreatment clinical photographs should also be obtained to document a baseline appearance of the lesion.

Imaging Assessment

Ultrasound is useful in the workup and to monitor treatment effect of LMs, particularly for smaller superficial lesions. Therefore, the baseline ultrasound should detail the extent, components and size of the lesion. The appearance of LMs on ultrasound depends on the cyst size. Macrocystic lesions appear as compressible, predominantly anechoic cysts with thin septations. Debris, which may result from hemorrhage or infection, may layer dependently within the cavities. Although blood vessels are detectible in cyst walls and septa, there should be no internal vascularity. In contrast, microcystic lesions consist of tiny cavities that produce a hyperechoic, solid appearance.

Most of our patients undergo an MRI study before treatment. MRI not only clarifies the diagnosis but also provides a better assessment of the extent of the lesion, therefore providing guidance for treatment. On MRI, LMs may transgress soft tissue planes and should follow fluid signal on all sequences in uncomplicated lesions. Fluid-protein levels may also be present. Hyperintensity on T1-weighted images may be seen in the setting of hemorrhage. The lesion should not contain flow voids, and there should be no filling defects to suggest the presence of a thrombus or phlebolith. There may be varying degrees of interstitial fatty elements as well as enhancement of septations. When LMs are predominantly microcystic they can have the appearance of a solid lesion and may mimic a tumor. A venous malformation can coexist with lymphatic components in a subset of patients, yielding the term "venolymphatic" malformation.

It is imperative to consider other differential diagnoses before initiating therapy. Mimickers of LMs in the young child include complex neoplasms such as teratomas, lipoblastomas, and rhabdomyosarcomas. These lesions are expected to show more solid and enhancing components. Nonneoplastic mimickers include cystic lesions such as dermoids or epidermoids and ciliated cysts.[7] Most of these lesions can be differentiated based on clinical history, location, and appropriate imaging. In difficult cases, percutaneous biopsy should be considered for definitive diagnosis.

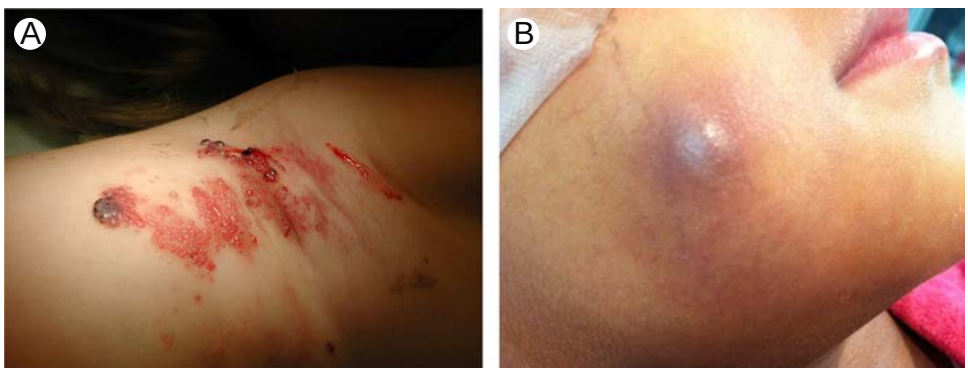

Figure 2 (A) Dermal vesicles (angiokeratomas) overlying a lymphatic malformation, which have become infected. (B) Bluish discoloration overlying a LM as a consequence of internal hemorrhage. (Color version of figure is available online.)

Treatment

Indications

Newborn patients with LMs involving critical structures, such as the airway or the retro-orbital region, should undergo semiurgent treatment. Without treatment, spontaneous hemorrhage or infection can result in an immediate threat to life or vision. Lesions that surround the digestive tract or floor of the mouth may inhibit feeding or speech and should also be treated. Additional indications for intervention include lesions that cause pain, physical debilitation, or disfigurement.

Historically, surgery was the mainstay of treatment, despite the high recurrence rate and a reported complication rate—including incomplete resection, incisional scarring, lymphatic leak, and local nerve damage–of 12.5%-44%.[6,8,9] Sclerotherapy has demonstrated similar outcomes to primary surgery after 1 year, without differences in resource utilization.[10] This suggests a percutaneous approach is appropriate to treat symptomatic lesions and for asymptomatic lesions that cannot be managed with a conservative "watch-and-wait" approach.[11] Given the straightforward percutaneous technique, relative decrease in morbidity, and nonsuperiority of surgery in the literature, it is appropriate to treat macrocystic lesions with sclerotherapy.[12] Microcystic and mixed lesions are more difficult to treat with sclerotherapy alone and often require a combined approach and repeat sclerotherapy sessions.[5,13] Nonetheless, sclerotherapy is often the initial treatment modality for these lesions as well. Surgery, therefore, is reserved for cases of sclerotherapy failure or when urgent intervention is needed.

The goal of treatment should not be cure but rather to improve function, decrease the risk of complications and preserve or improve cosmesis. At the outset, the desired goal should be clearly delineated with the patient and family so that realistic expectations are set.

Preprocedure

We perform most of the sclerotherapy procedures under general anesthesia. Moderate sedation or local anesthesia may be used for superficial lesions in older patients or for lesions distant from critical structures. Patients with cervicofacial LMs are always intubated for airway protection.

When treating larger LMs or small retrobulbar lesions, we administer systemic steroids, such as standard dosing of (intravenous [IV]) dexamethasone, to reduce the degree of posttreatment swelling and pain. There is no consensus on the administration of prophylactic IV antibiotics, though, some advocate their use when treating macrocystic lesions.[14] In our practice, IV antibiotics are used in areas difficult to prepare with sterile technique, such as the tongue and floor of mouth.

Technique

Using a high-megahertz linear probe, superficial lesions are initially evaluated with ultrasound to identify the morphology of the lesion and to define suitable access sites for therapy. MRI, when available, is also appropriate for guidance if the lesions are deep seated, although this is not a focus in the current article.[15] Under imaging guidance, microcystic and small macrocystic lesions are accessed directly with a small (18-22 gauge) needle, aspirated and injected with the desired sclerosant. If multiple cysts are traversed in a single puncture, the sclerosant is administered as the needle is slowly withdrawn. Additionally, side-holes can be manually made, if a sheathed needle is used, to allow better flow of fluid and penetration of smaller cavities. For most lesions, doxycycline or sodium tetradecyl sulfate (STS), in liquid or foam consistency, are injected at the preference of the operator. In critical regions such as the tongue, floor of mouth or orbit, bleomycin may be considered. Details on these agents are discussed below.

Many of the cysts would not communicate with one another and multiple sites of access may be necessary for complete treatment. Injection is performed under fluoroscopy to monitor for extravasation into normal soft tissues and to ensure adequate treatment of the lesion (Fig. 3). If a foam mixture is used, injection can also be monitored under ultrasound with intermittent use of fluoroscopy. As some mixed lesions, referred to as venolympathic malformations, will communicate with the venous system, attention should be given to the presence of venous egress.

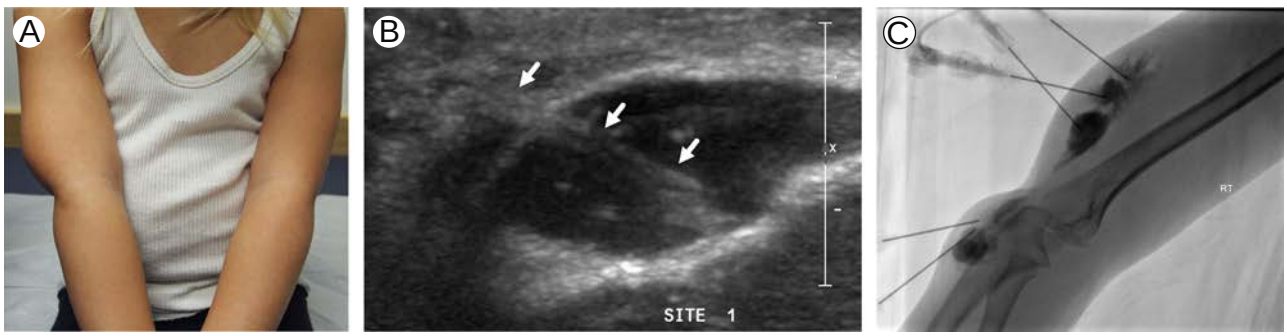

Figure 3 A 3-year-old female with a right arm LM. (A) Clinical photograph shows bulging of the lateral right arm. (B) Doxycycline sclerotherapy was performed after accessing the cysts under ultrasound (arrows). (C) Most of the cysts were noncommunicating and multiple sites of injection were required. (Color version of figure is available online.)

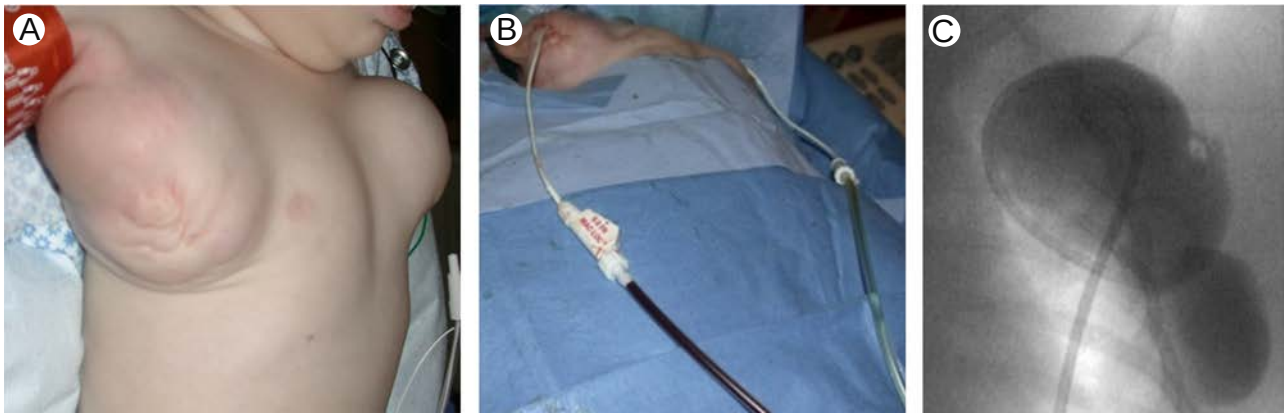

Figure 4 (A) Infant with bilateral macrocystic malformations. (B) These were treated with catheter-based sclerotherapy. Note different appearance of drainage from each lesion. (C) Fluoroscopy confirmed distribution of sclerosant and position of the catheter. (Color version of figure is available online.)

If contrast media is seen entering the venous system, an alternate treatment plan may be necessary, such as altering the choice or composition of sclerosant or occluding the outflow tract. The skin should also be monitored closely and any change in skin color is an indication for immediate cessation of treatment. Applying cold, sterile saline to induce cutaneous vasoconstriction can help minimize skin damage. After needle removal, light pressure is applied to prevent leakage of the sclerosant.

Larger macrocystic lesions are directly accessed with small-bore (5-6 Fr) catheters and the sclerosant is injected after cyst decompression (Fig. 4). Typically, the volume injected measures between 50% and 75% of the volume aspirated so as to avoid overfilling, leakage and cyst rupture. Sclerosant is allowed to dwell within the lesion for up to 6 hours, after which the catheter is attached to bulb suction. Multi-day catheter injections may be repeated for up to 72 hours and the catheter can be left in place until the output falls below 10% of the original lesion volume. Repeat instillations may be performed as an outpatient or, in extensive lesions, at the inpatient bedside under ultrasound guidance. At our institution, the preferred sclerotherapy agent for these larger lesions is doxycycline.

Improving Treatment Coverage

One challenge in sclerotherapy is insuring that treatment covers the entire lesion. To confirm proper distribution of the sclerosant, we routinely use low-dose C-arm computed tomography (CT). Using a syngoDynaCT (Artis Zee VC14H; Siemens Healthcare, Forchheim, Germany), 3-dimensional volumetric images are obtained in the interventional radiology suite. These images are obtained after sclerotherapy and are used to ensure adequate coverage of the lesion and to evaluate for soft tissue extravasation. In cases of drain placement, the C-arm CT can be used to confirm an intralesional location of the catheter.

A recent technical advancement is the development of X-ray-MRI fusion, which allows overlaying an MRI data set on top of live fluoroscopic images. A blocked-radiation C-arm CT scan is performed to calibrate the C-arm to the patient table and geometric space. Automatic registration between the MRI data set and this blank spin is then performed using *syngo*InSpace 3-D/3-D fusion software (Siemens), after which real-time fluoroscopic overlay can proceed (Fig. 5).[16] This technology provides real-time visualization of lesion filling and often obviates the need for the postprocedure C-arm CT.

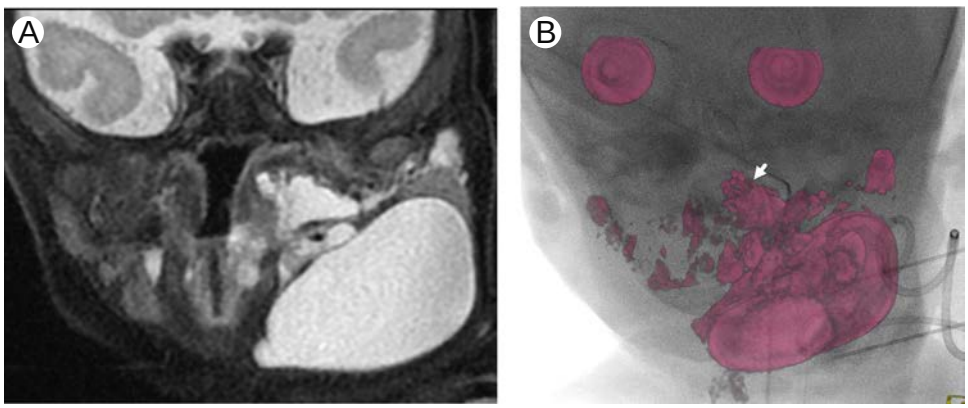

Figure 5 MRI fusion. (A) T2-weighted MRI of a 0-day-old male with a LM surrounding the airway. (B) MRI fusion was critical in insuring doxycycline reached components adjacent to the trachea, arrow. Note 2 drains and multiple access sites used during treatment. (Color version of figure is available online.)

Postprocedure

A loose sterile dressing is applied to all puncture sites. For neonates who receive large doses of doxycycline (>150 mg), our practice is routine monitoring for hypoglycemia and metabolic acidosis, both of which have been shown to occur sporadically in neonates less than 10 kg.[17]

Due to the risk of increased airway compression, patients who undergo drain placement for large cervicofacial malformations adjacent to the airway remain intubated for the duration of therapy. Subsequent catheter instillations are then performed with ultrasound in the intensive care unit. These patients are extubated after the final instillation is complete and the cysts are decompressed.

We observe patients with larger lesions in the hospital overnight. Inpatient pain control regimens include morphine sulfate and IV nonsteroidal anti-inflammatory agents. These patients are discharged the following day if their pain is controlled and there are no additional complications. Patients with smaller lesions are treated as outpatients and discharged with an oral analgesic. Telephone follow-up is performed within 24 hours and again within 1 week to assess pain management and to evaluate for complications.

Sclerosants

Many types of sclerosants have been reported in the literature. There are, however, no randomized controlled trials comparing different agents currently in use, which include doxycycline, bleomycin, STS, absolute ethanol, betadine, sodium morrhuate, pingyangmycin, OK-432, and alcoholic solution of Zein. The choice of sclerosant depends on operator experience and lesion location. Some agents are preferred based on cost or owing to the degree of inflammation they produce. Agents routinely used at our institution are discussed below.

Doxycycline

Doxycline powder (APP Pharmaceuticals, LCC Schaumburg, IL) is a readily available antibiotic that is commonly used for sclerosis in LMs as well as in other medical interventions. This has largely replaced ethanol as a sclerosant given its greater safety profile and decreased risk of neurolysis.[13] The usual concentration is 10 mg/mL, which is created by mixing doxycycline powder with a 4:1 ratio of Omnipaque-300 (GE Healthcare Canada, Mississauga, Canada) to normal saline. For microcystic lesions and to improve lesion penetration, a doxycycline foam consistency can be created by mixing it with albumin or aerated saline through a 3-way stopcock. At least 30 agitations are usually necessary to create a homogenous, well-suspended mixture. The total dose can range up to 1000 mg depending on the size of the lesion. In our anecdotal experience with hypoglycemia and metabolic acidosis in neonates, we currently limit the total dose in of doxycycline in neonates less than 3 kg to 150 mg per session in larger lesions.

Sodium Tetradecyl Sulfate

A 3% STS (Sotradecol; AngioDynamics, Queensbury, NY) is a detergent that is used for sclerotherapy. STS can be used in liquid form or as a foam consistency. This sclerosant has been reported to cause less swelling than ethanol and is nonneurolytic.[2,18] To create a foam consistency, our preference is a 1:1:3 ratio of STS to Ethoidized oil (Ethiodol; Savage Laboratories, Melville, NY) to air mixed with a compatible stopcock. STS may also increase treatment success when used as a combined agent, possibly because it improves penetration of the sclerosant through the LM membrane. In these cases—so-called lesion washing—nondilute STS is allowed to dwell in the lesion for 2 minutes, after which it is drained and the second agent is administered.[14]

Bleomycin

Bleomycin is an antineoplastic drug that tends to produce a less robust inflammatory reaction and soft tissue edema than doxycycline. As such, this is a useful agent in superficial LMs in anatomically sensitive regions, such as on the soles of the feet, or those adjacent to critical structures, particularly the orbit, tongue, floor of mouth, or in the airway. Bleomycin can be reconstituted with contrast media to increase visibility or administered as a foamed form by mixing with albumin. Mild flu-like symptoms have been reported after bleomycin use. Pulmonary toxicity is a general concern when using bleomycin, although it is usually reported with greater than 400 units lifetime dose, far above the usual dose for LM treatment.

Complications of Sclerotherapy

Complications of sclerotherapy are primarily related to pain and local extravasation, with an overall complication rate reported between 3% and 22%.[5,13] Common risks include skin necrosis, blistering and breakdown, all of which are more common with ethanol or STS. Skin breakdown can lead to cellulitis, requiring antibiotics, or scarring. In patients undergoing catheter-based therapy, their lesions may become superinfected. Cervicofacial lesions may result in complications such as phrenic or recurrent laryngeal nerve injury, Horner syndrome or aspiration, all of which tend to be self-limited. In other cases of nerve injury, a dose of tapered steroids may be necessary.

Extensive treatment of a lesion or a large volume of extravasation can place the patient at risk for compartment syndrome, nerve injury and permanent numbness. There is also a small risk of hemoglobinuria from hemolysis when using STS, leading to renal impairment that usually resolves with hydration.[2] The risk of embolic phenomenon is more commonly seen when treating venous malformations.

Management of Complications

Mild skin changes, such as redness and swelling, are managed conservatively with close follow-up and

supportive care. These patients can be seen in clinic as necessary to monitor skin recovery. Patients with skin ulceration are treated in collaboration with the division of plastic surgery and, rarely, skin grafting may be required. Cellulitis and cyst infection leading to abscess are not common but may require intravenous antibiotics and drainage. More severe complications such as airway compromise, visual impairment, and compartment syndrome will require urgent surgical consultation and corrective intervention.

Alternative Treatment Options

While sclerotherapy is the preferred and most pervasive treatment modality, laser therapy, and radiofrequency ablation (RFA) have also been described as therapeutic options. Laser therapy is reserved for superficial cutaneous or mucosal lesions.[19] RFA has shown promise in treating microcystic malformations, which are difficult to fully penetrate with sclerotherapy, as well as submucosal lesions.[20] This heat-based therapy is applied with a percutaneous probe under image guidance and destroys the LM, producing fibrosis. When a lesion is close to the skin surface, cooling packs can be used to decrease the risk of skin necrosis. Often, a multimodality approach is used for complex lesions where larger cysts are first treated with sclerotherapy and the residual component is treated with RFA.[21]

When sclerotherapy, ablation or surgery are not viable options for providing control in recalcitrant or diffuse vascular malformations, Sirolimus, a chemotherapeutic agent initially used as a transplant immunosuppressant, has recently shown efficacy in treatment.[22,23] Sirolimus is an oral antiangiogenic, antiproliferative drug that is involved in the mammalian target of rapamycin (mTOR) molecular pathway. Although robust clinical trials are lacking, case reports and small case series have demonstrated a decrease in lesion size or resolution using siroliums.[22,24] Lesion response has been described to improve with increasing lymphatic components of the malformation, even in conjunction with sclerotherapy or after percutaneous treatment has been exhausted (Fig. 6). At our institution, an oncologist, who is a member of the vascular anomalies team, administers Sirolimus. Administration of this drug requires thorough consultation, as treatment is long term and requires both strict compliance and regular serum monitoring to titrate dose. Risks include immunosuppression, with a potential for secondary neoplasm, pulmonary toxicity and metabolic abnormalities.

Clinical Follow-up and Expected Outcomes

Patients are typically followed up in the interventional radiology clinic 6-12 weeks following sclerotherapy to assess treatment response. Response to therapy is measured by the decrease in lesion size and, more importantly, in the improvement of symptoms. Change in size is assessed and documented with an ultrasound performed in the clinic. At this visit, the need for further treatment is assessed.

Often, only focal lesions respond completely to a single session of sclerotherapy and, on average, 2-3 sessions are needed to achieve an adequate clinical result. Macrocystic lesions respond better to treatment, with reports reaching 100% success vs 86% and 43% for microcystic and mixed lesions, respectively.[13] Using multiple treatment sessions with single agent doxycycline therapy, 86% of patients may achieve a 95% or greater reduction in LM size no matter the type.[5] Finally, a systematic literature review of

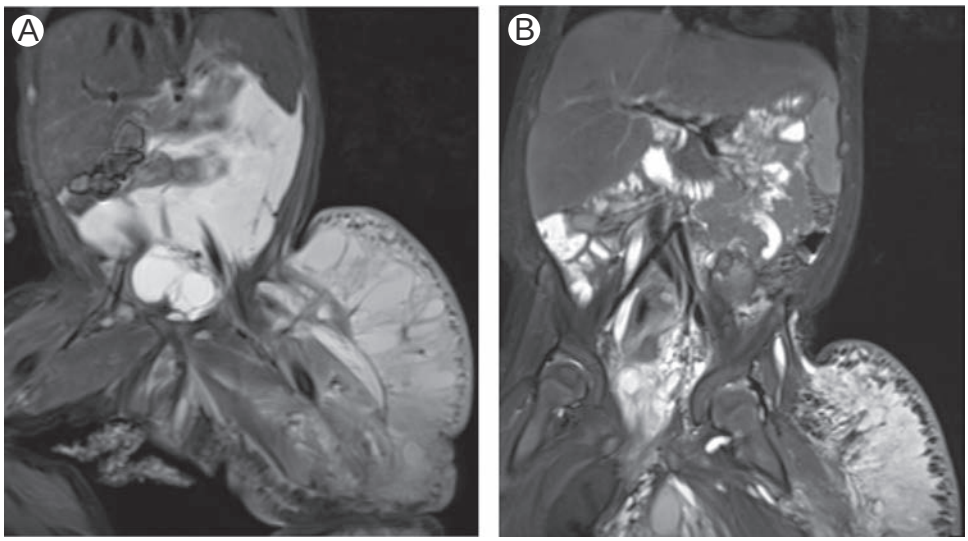

Figure 6 Rapamycin treatment. (A) T2-weighted MRI of a 3-week-old female with extensive LM involving the left lower extremity and abdomen. Owing to the extensive nature, the lesion was treated with rapamycin alone. (B) T2-weighted MRI obtained 9 months after treatment shows near resolution of the intra-abdominal component and decrease in size of the microcystic soft tissue components.

sclerosing agents used in the treatment of cervicofacial malformations found a mean complete response of 39%-79% and an overall response of 71%-100%.[25]

Lesions may reoccur regardless of the choice of sclerosant. The rate of recurrence is not well reported in the literature, although, the recurrence of a macrocystic malformation after successful sclerotherapy is uncommon. Patients are usually amenable to repeat sclerotherapy or alternative percutaneous treatments. A subset of patients may require surgical resection, particularly if the lesion becomes fibrotic or microcystic after sclerotherapy. Sirolimus may also be considered for extensive and symptomatic lesions.

Conclusion

LMs are complex lesions that require a multidisciplinary approach to both diagnosis and management. Percutaneous sclerotherapy is now a mainstay of treatment in all types of lesions, which can be approached using a multitude of sclerotherapy agents. Complications are low for sclerotherapy and can be minimized by diligent planning and rigorous technique. New medications and adjunctive modalities are on the horizon and present ongoing opportunities for research. Patients and their family should be made aware of the goals of therapy and potential for multiple sclerotherapy sessions.

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