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Lymphatic Intervention, the Frontline of Modern Lymphatic Medicine: Part II. Classification and Treatment of the Lymphatic Disorders

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Lymphatic disorders encompass a broad spectrum of diseases involving the lymphatic system, ranging from traumatic lymphatic leaks to lymphatic malformations. Lymphatic disorders can be categorized into traumatic and non-traumatic disorders according to their etiology. These two categories may be further divided into subgroups depending on the anatomical location of the lymphatic pathology and their association with clinical syndromes. Thoracic duct embolization was a milestone in the field of lymphatic intervention that encouraged the application of percutaneous embolization techniques to treat leaks and reflux disorders in the lymphatic system. Additional access routes for embolization, including retrograde thoracic duct and transhepatic lymphatic access, have also been developed. This article comprehensively reviews a variety of options for the treatment of lymphatic disorders, from conservative management to the most recent embolization techniques.

Keywords: *Lymph; Lymphatic; Intervention; Lymphangiography; Radiology*

INTRODUCTION

Recent advances in lymphatic imaging, outlined in Part 1, have enhanced our understanding of lymphatic disorders. Novel imaging modalities have aided in the classification of lymphatic disorders, which, in turn, will potentially help with treatment planning. While conservative management and surgery retain their role in the treatment of lymphoceles and lymphatic leaks, percutaneous procedures, ranging from drainage and sclerotherapy to transcatheter embolization, have proven to be comparable in terms of treatment outcomes. In particular, the introduction of thoracic duct embolization (TDE) has paved the way for the development of various percutaneous techniques to embolize the lymphatic ducts associated with leaking lymph or lymphatic reflux. This article covers various strategies for managing lymphatic disorders, ranging from traditional percutaneous modalities, such as sclerotherapy, to embolization techniques that have recently been described in the literature.

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Classification of Lymphatic Disorders from the Perspective of Lymphatic Intervention

Numerous attempts have been made to categorize lymphatic disorders into subsets that would allow a better understanding of such heterogeneous groups of diseases. Based on the frequent finding of lymphatic disorders associated with vascular anomalies, the International Society for the Study of Vascular Anomalies (ISSVA) perceives lymphatic disorders as part of the latter spectrum. It proposes a classification that incorporates both vascular anomalies and lymphatic disorders [1]. The components were categorized according to their histological and genetic features, after which revisions to the classification were

made each time new scientific discoveries were made. Lymphatic disease occurs in various forms (ranging from cystic lymphatic malformations to channel-type lymphatic malformations), and is associated with a variety of clinical manifestations (ranging from Gorham-Stout disease [GSD] to primary lymphedema). Except for a few lymphatic disorders that demonstrate characteristic clinical and histologic features (such as GSD), most lymphatic disorders associated with lymphatic leaks have been classified as channel-type lymphatic malformations. Not only does this category encompass a large variety of lymphatic disorders, but the discrimination of lymphangioma from lymphangiectasia or vice versa is not always possible. Due to these limitations, the ISSVA classification often fails to function as a practical guide for the management of complicated lymphatic disorders. In search of a practical classification that could be integrated into clinical practice, Hillard proposed an alternative classification (which was later revised to become what is known as the "modified Hillard classification") that takes into account both histologic and clinical features of lymphatic disorders [2,3]. To date, there remains a lack of consensus regarding the classification of lymphatic disorders. One explanation is that the imaging of the lymphatic system has been limited in the past. Without imaging, the understanding of the distribution of the disease and flow dynamics of the lymph is limited. Many lymphatic disorders are associated with abnormal lymphatic flow and involve a large body size. Therefore, localized diagnostic procedures, such as tissue sampling for histological and genetic analysis, fail to reveal the anatomical distribution and physiological aspects of these disorders. In this regard, it can be claimed that advancements in the field of radiology have led to a better understanding of lymphatic disorders and stimulated investigators to seek new classifications. An example is pulmonary lymphatic perfusion syndrome (PLPS), which was recently introduced by Itkin et al. [4] based on the discovery of abnormal lymphatic flow observed on dynamic contrast-enhanced MR lymphangiography (DCMRL) [4,5]. A major advantage of such classification is that it is based on the anatomical distribution of the disease, and the flow of lymph is that it can be put to practical use when treating lymphatic disorders. Herein, we propose a new classification in which various lymphatic disorders are categorized according to symptoms (lymphatic leak and lymphedema), etiology (traumatic and non-traumatic), origin of fluid (chylous, non-chylous, and hepatic), anatomical location (chylothorax, chylous ascites, chyluria, and cutaneous lymphorrhea), and syndromes associated with lymphatic abnormalities (GSD, Noonan syndrome, generalized lymphatic anomaly [GLA], Kaposiform lymphangiomatosis [KLA], and lymphangioleiomyomatosis).

A review of the literature revealed numerous synonyms for identical clinical conditions. This may be attributed to the low incidence of lymphatic disorders, some of which are rare. The accumulation of scientific information is restricted by the inconsistent use of terminology, which, in turn, creates a vicious cycle in which a consensus for uniform terminology and classification cannot be reached. Efforts should be made to develop a systematic classification system that is practical and appealing to physicians worldwide.

Traumatic Lymphatic Disorders

Lymphoceles

Pelvic Lymphocele

Pelvic lymphocele has been reported to develop in up to 20% of patients who undergo pelvic surgery that involves lymph node dissection [6]. Most lymphoceles are asymptomatic and, therefore, do not necessarily require treatment. However, those associated with clinical symptoms should be further assessed using ultrasonography or CT (Fig. 1). While percutaneous drainage is sufficient in most patients with lymphoceles, some may require further management through sclerotherapy or lymphatic embolization due to rapid re-filling of the sac. Only one study compared the outcomes of sclerotherapy and lymphatic embolization, and the authors reported superior results for the latter. However, in addition to the retrospective, non-randomized nature of this study, there were many limitations, including the fact that the two procedures were performed during different periods (lymphatic embolization was introduced later in their practice) [7]. Sclerotherapy is a well-established procedure that is safe and effective in preventing re-expansion of lymphocele after drainage. Although the lymphocele is essentially a pseudocyst, meaning that there is no fluid-secreting epithelium lining the wall, it is postulated that sclerotherapy causes adhesion not only within the lymphocele cavity but also at the site of the leaking lymphatic channel to which the lymphocele is attached. Sclerotherapy is a minimally invasive procedure with a shallow learning curve and is

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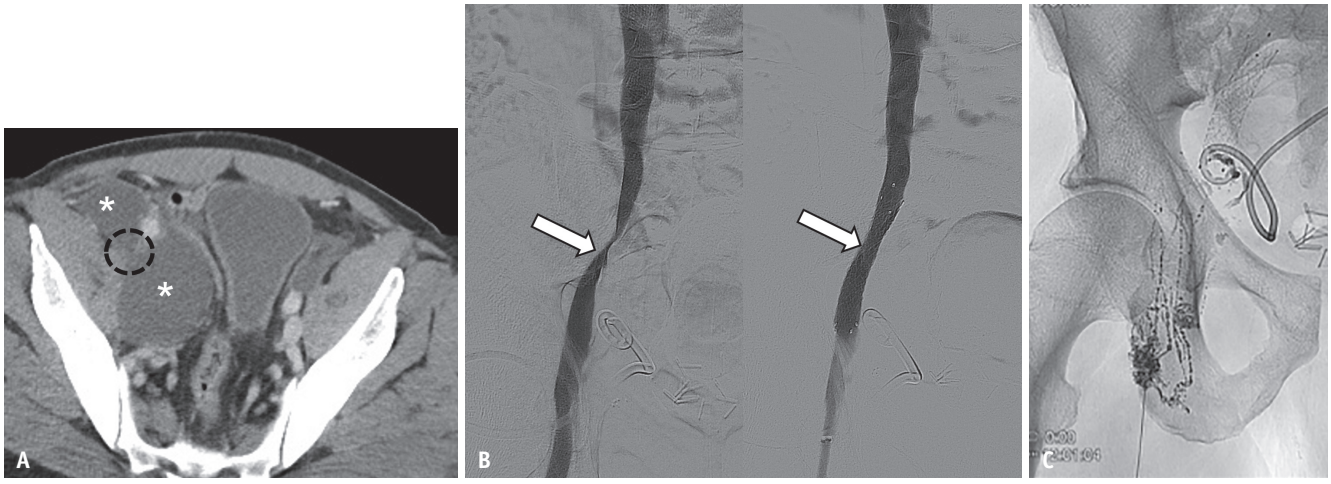

Fig. 1. A 57-year-old male patient developed a pelvic lymphocele after undergoing prostatectomy with lymph node dissection for prostate cancer.
A. Initial CT showing compression of the right iliac vein (within the dashed circle) by lymphoceles (asterisks) located anteriorly and posteriorly. The patient developed ipsilateral iliofemoral deep venous thrombosis, prompting treatment of pelvic lymphoceles. **B.** Digital subtraction angiogram showing restored patency of the right iliofemoral vein (arrows) after manual aspiration thrombectomy, iliac vein stenting, and percutaneous sclerotherapy of the lymphocele. **C.** The patient underwent intranodal lymphangiography and lymphatic embolization due to re-expansion of the lymphocele with recurrent thrombosis of the femoral vein. A follow-up CT scan (not shown) acquired 8 months later showed a patent iliofemoral vein without a recurrent lymphocele.

therefore easily reproducible. Lymphatic embolization can be reserved for recalcitrant lymphoceles that do not respond to sclerotherapy.

Inguinal Lymphocele or Lymphorrhea

Lymphoceles may develop after catheterization or surgical procedures in the groin. Earlier reports have described successful outcomes after pedal lymphangiography [8]. Following the introduction of intranodal lymphangiography, there have been reports on the technique of lymph node embolization (LNE), for which glue mixture is injected directly through lymph nodes of the groin or thigh to treat inguinal lymphocele or lymphorrhea [9]. Lymph nodes close to and preferably below the leak were accessed for lymphangiography. Once the leak was visualized, glue was injected through the same lymph node (Fig. 2). Alternative access routes, such as popliteal lymph node access or pedal access, may be sought when inguinal lymphangiography does not reveal any leak.

Retroperitoneal Lymphocele

As with any lymphocele, percutaneous drainage followed by sclerotherapy is the ideal approach for its management. However, sclerotherapy is unsuitable for cases in which the lymphocele cavity is not confined, particularly those associated with lymphatic ascites. Lymphoceles in the retroperitoneum may be categorized as chylous or non-chylous. Non-chylous lymphoceles in the retroperitoneum develop anywhere along the line of lymphatic flow from the pelvis to the lumbar trunk. In this case, lymphatic inflow can be interrupted by percutaneous embolization techniques, such as LNE. Meanwhile, chylous leaks identified at locations around the cisterna chyli or nearby tributaries, as well as those in the para-aortic lymph node stations, may be treated by lymphopseudoaneurysm embolization (Fig. 3). However, it should be kept in mind that not all chylous leaks are identified on inguinal lymphangiography because of the direction of lymphatic flow from the mesenteric lymphatic system to the central conducting lymphatics. When inguinal lymphangiography fails to reveal the leak site, the lymphocele may be filled with water-soluble contrast media to identify the communicating channel between the lymphopseudoaneurysm and the disrupted lymphatic duct. When the inflow duct is identified, a microcatheter can be retrogradely advanced into the lymphatic duct, followed by glue embolization, with or without the use of coils. Although reports on this technique are limited, the results published thus far are promising [10].

Chylothorax and Chylous Lymphorrhea from Neck Surgery Site

Any surgical procedure performed along the course of the thoracic duct or its tributaries may be complicated by chyle

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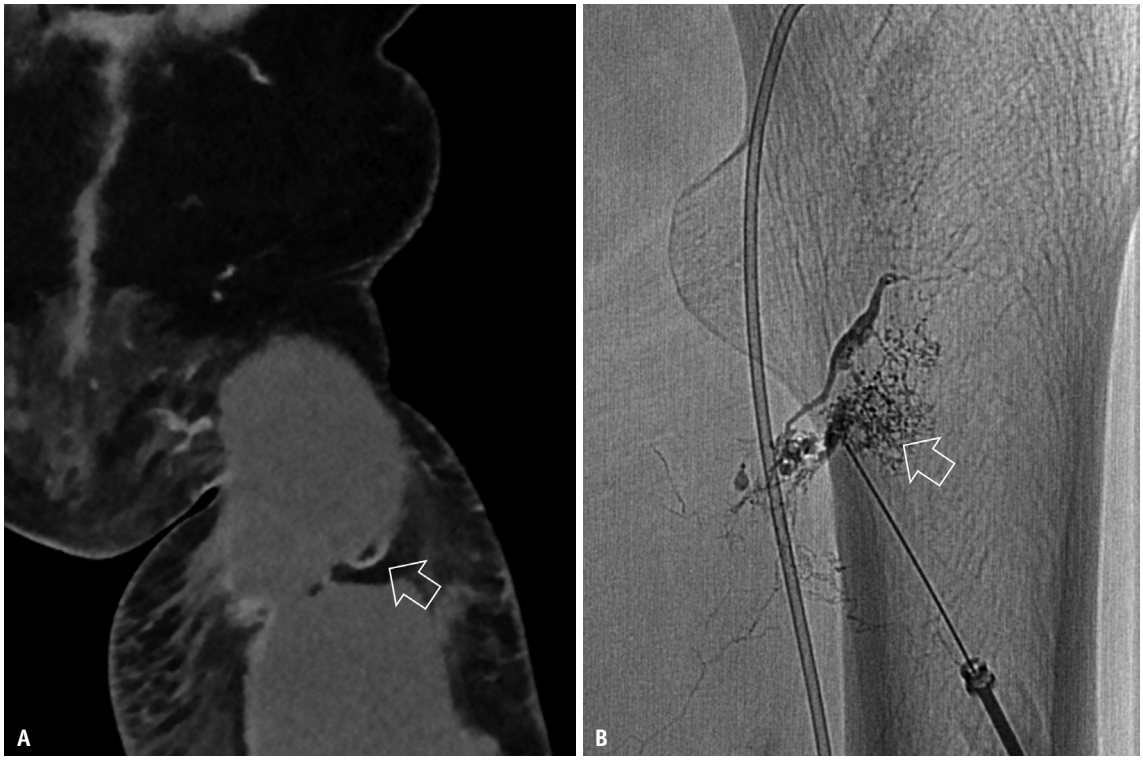

Fig. 2. A 67-year-old female with inguinal lymphocele after groin lymph node dissection for vulvar cancer.
A. A fractured inguinal lymph node (arrow) is observed next to a large inguinal lymphocele. **B.** The lymph node (arrow) was accessed under ultrasound guidance and lymph node embolization was performed by injecting diluted glue (N-butyl cyanoacrylate:Lipiodol = 1:3 mixture).

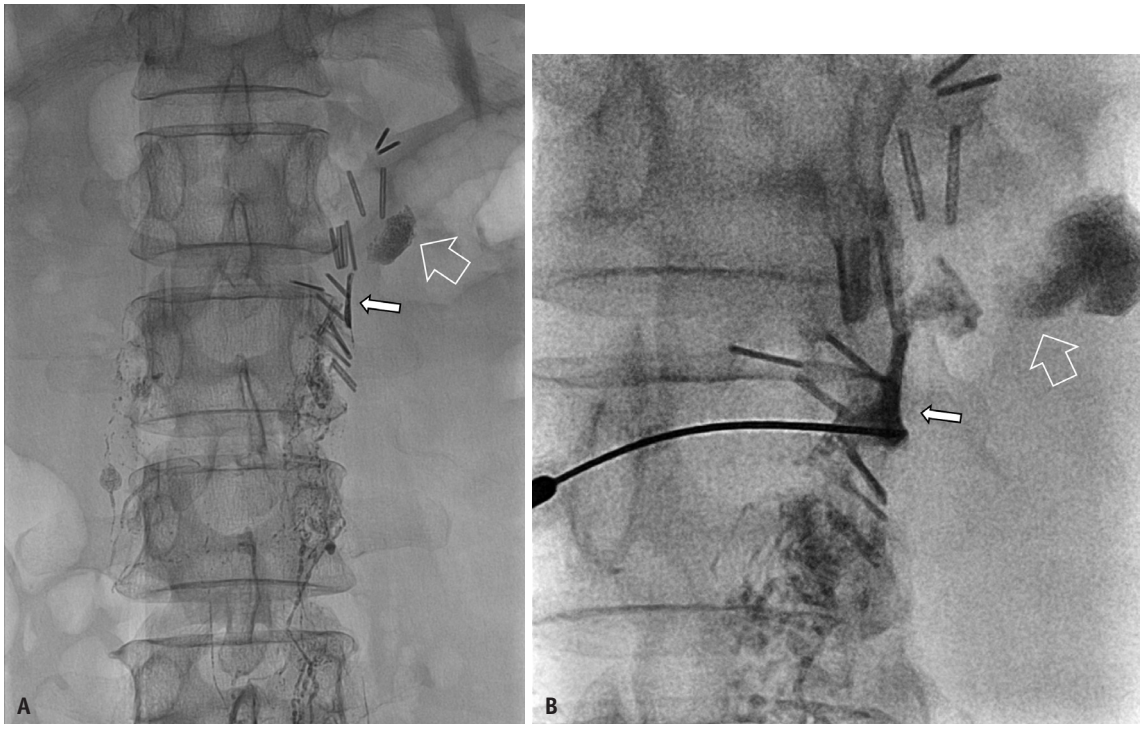

Fig. 3. A 57-year-old female with chylous ascites after left-sided nephrectomy for living donor kidney transplantation.
A. A slit-like lymphopseudoaneurysm is opacified with Lipiodol (arrow). Extravasated Lipiodol is identified as a collection of Lipiodol droplets in the gravity-dependent portion of the retroperitoneal lymphocele (open arrow). **B.** The lymphopseudoaneurysm (arrow) is directly accessed with a needle under fluoroscopic guidance. Dense glue (N-butyl cyanoacrylate:Lipiodol = 1:2 mixture) was injected until it filled the lymphopseudoaneurysm (open arrow).

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leakage. Depending on the anatomical location of the leak, the patient may present with chylothorax, chylopericardium, or chyle leakage from the surgical wound in the neck. Common surgical procedures associated with chylous leaks include head and neck, esophageal, and lung surgeries.

The incidence of postoperative chylothorax varies among reports ranging from 1%–9% [11,12]. Without appropriate management, the consequences of chylothorax may be more severe than those of lymphatic leaks. The thoracic duct serves as the final pathway of the lymph, before it drains into the systemic vein. Therefore, spillage into potentially large spaces, such as the pleural cavity, results in rapid accumulation of lymph outside the thoracic duct. The negative pressure created within the thorax during the inspiratory phase of the respiratory cycle also contributes to the development of a chylothorax.

Surgical ligation of the thoracic duct or pleurodesis may be attempted, in addition to the conservative management described in the previous section. More recently, TDE has been widely considered a safe alternative to surgery because the latter is associated with perioperative morbidity and mortality. In one systematic study, the technical success rate of thoracic duct catheterization was 63.1%, while the clinical success rate among those in whom the thoracic duct was successfully catheterized was 92.4% [13]. This result reflects that the clinical outcome of TDE is highly dependent on technical expertise in the catheterization of the thoracic duct. Centers with more experience in the procedure exhibiting higher rates of clinical success than others, efforts should be made to achieve consistent outcomes across institutions. Furthermore, retrograde techniques to access the thoracic duct should be considered in cases in which conventional means of thoracic duct catheterization are unsuccessful.

The following should be considered if chylothorax does not respond to TDE: 1) anatomical variation of the thoracic duct or presence of patent collateral pathways, 2) overdilution of glue mixture or other technical reasons for incomplete embolization, and 3) the thoracic duct may not be the source of chyle leak. Selective embolization of the leaking side branch may be considered when the leak originates from a side branch of the thoracic duct [14]. Although the effectiveness of this technique is yet to be evaluated, it addresses the potential complications of TDE, such as lymphedema or abdominal pain.

Chylous Ascites

While TDE is a well-established procedure, there is no standard technique for treating chylous ascites due to the heterogeneity in its etiology and the source of the lymphatic leak. In a report by Nadolski et al. [15], lymphangiography revealed leaks in only 55% of patients with chylous ascites. The remaining 45% were observed for spontaneous resolution or therapeutic effect of Lipiodol (Guerbet), among which only 21% responded.

From a radiological perspective, the most significant limitation of current imaging modalities, such as Lipiodol lymphangiography and nuclear scintigraphy, is that these studies only show the course of lymph flow from the lower extremities to the thoracic duct. Theoretically, leaks occurring outside this axis are unlikely to be revealed using these imaging modalities. A report described a case in which this limitation was overcome by occluding the lower thoracic duct with an occlusion balloon, thereby allowing for reflux of contrast media into the mesenteric lymphatic system where the leak had developed [16].

Percutaneous embolization of lymphatic leak that is demonstrated on lymphangiography can be accomplished by various techniques, including glue injection into lymphopseudoaneurysm, retrograde lymphatic duct catheterization through direct lymphopseudoaneurysm access, upstream LNE, and direct catheterization of leaking duct (Fig. 4). Examples of these techniques have been previously reported [10,17]. When lymphangiography fails to reveal a leak, mesenteric lymphangiography may be considered. Mesenteric lymphangiography is a surgical procedure that may be reserved for debilitating chylous ascites that fail to respond to all means of conservative treatment and percutaneous procedures [18]. Although the safety and efficacy of mesenteric lymphangiography and embolization need further validation, such a technique is significant in that it provides another option for the treatment of chylous ascites, particularly those originating from the mesenteric lymphatics.

Liver Lymphorrhea

Liver lymph constitutes a large proportion of the lymph produced in the human body, the amount of which is comparable to that of chylous lymph. However, unlike chylous lymph, the liver lymph is a clear fluid, making liver lymphorrhea challenging to diagnose. Ascites resulting from liver lymph leakage may be underdiagnosed for this reason. Surgery involving the liver or porta hepatis may result in

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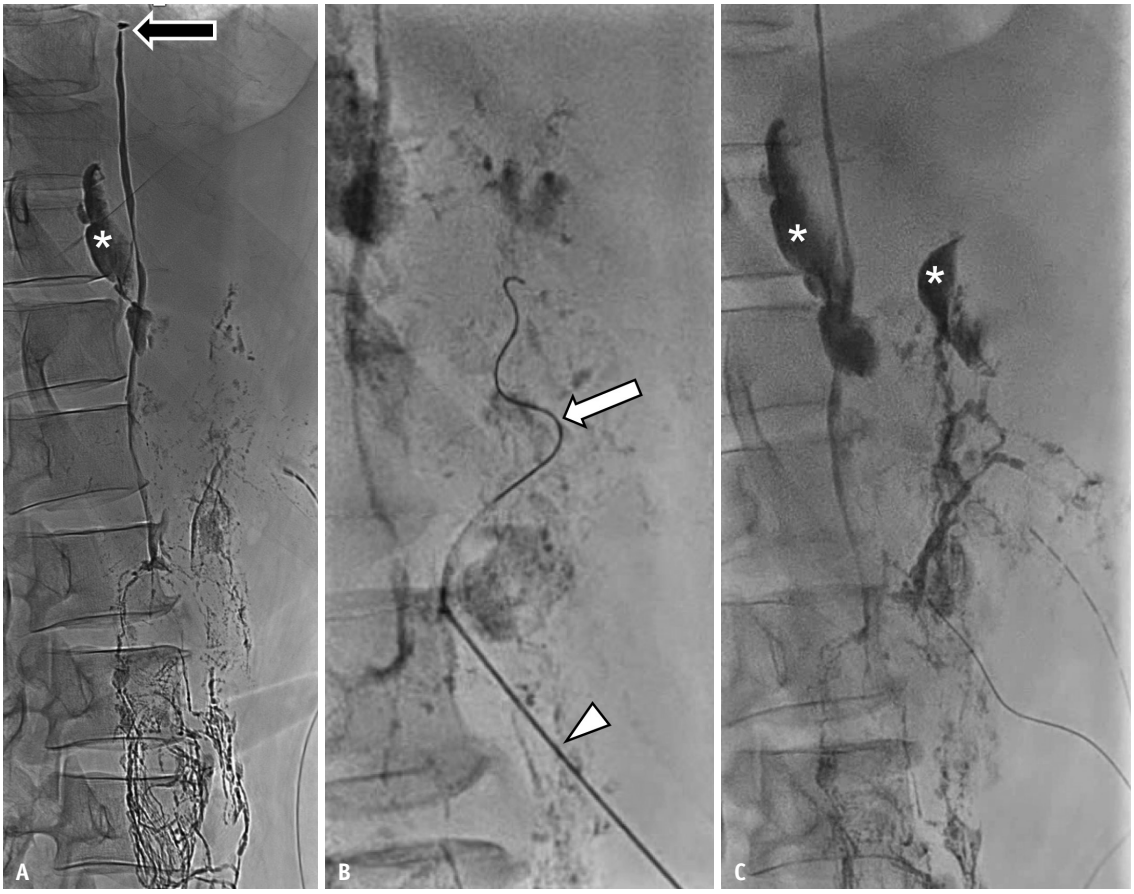

Fig. 4. A 55-year-old male presented with postoperative chylous ascites after undergoing Ivor-Lewis operation with thoracic duct ligation for esophageal cancer.
A. Lipiodol stagnation is seen at the level of the thoracic duct ligation (arrow). Lipiodol is observed to reflux into the mesenteric lymphatic system and extravasate (asterisk) into the peritoneal space. **B.** The mesenteric lymphatic trunk is percutaneously accessed using a fine needle (arrowhead). A co-axial microcatheter system (arrow) is advanced into the mesenteric lymphatic system. **C.** Selective embolization of the leaking mesenteric ducts was performed using a glue mixture. Note extravasation (asterisks) of the glue mixture in the peripheral mesenteric ducts. The chyle leak was successfully managed after a single procedure, and the patient remained free from ascites for more than 6 months.

leakage of liver lymph into the peritoneal space. Previous reports have described the feasibility of transhepatic lymphangiography and embolization for the management of liver lymphorrhea [19].

Non-Traumatic Lymphatic Disorders

Recent advances in lymphatic imaging, including DCMRL, have provided new insight into a variety of non-traumatic lymphatic disorders, including non-traumatic chylothorax [20], plastic bronchitis [4], non-traumatic chylous ascites, chyluria [21], protein-losing enteropathy (PLE) [22,23], and primary chylous reflux disease of genitalia (lymph scrotum) [24]. Attempts have been made to treat these disorders using percutaneous interventional techniques with some success.

Lymphedema

Lymphedema is defined as the accumulation of protein-rich lymph within the interstitial space due to the failure of the lymphatic system to conduct lymph back into blood circulation. Traditionally, primary lymphedema has been classified based on the age of onset of lymphatic disorders into congenital lymphedema, lymphedema precox, and lymphedema tarda [25,26]. It is a chronic condition characterized by swelling of the affected limbs with subsequent fibrosis, inflammation, and increased risk of infection [26].

Methods of imaging patients with primary lymphedema which have been described include conventional Lipiodol lymphangiography, lymphoscintigraphy, non-contrast MR lymphangiography, DCMRL, and Indocyanine Green (ICG) lymphography.

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Lipiodol lymphangiography is no longer used to assess lower limb lymphedema, given its invasiveness and potential complications. Intranodal Lipiodol lymphangiography can provide good anatomical information on central lymphatics and flow dynamics, as described in the previous section.

Lymphoscintigraphy helps assess functional lymph flow and identify abnormalities even in patients with mild lymphedema. Interstitial injection of a radiolabelled tracer is performed, which is selectively absorbed by the lymphatic vessels, enabling visualization using a gamma camera. Dynamic imaging and transit time were used to quantitatively measure the lymph flow. Lymphatic drainage within the entire limb and uptake in regional lymph nodes can be determined. However, the spatial resolution of lymphoscintigraphy is poor [27-29].

Non-contrast MR lymphangiography demonstrates lymphedema as a combination of fluid infiltration of subcutaneous fat and epifascial fluid collection. The fluid infiltration of subcutaneous fat commonly exhibits a honeycomb pattern in the trabecular structure with enlarged fat pockets surrounded by lines that correspond to fluid, fibrous tissue, or both [30]. The severity of lymphedema can be assessed by the extent of subcutaneous infiltration of lymphedema, increase in dimensions of subcutaneous fat and thickness of epifascial fluid collection, presence of 'honeycombing', thickening of the dermis, involvement of muscular compartments, number of lymph nodes present, and the presence or absence of lymphatic trunks and dilated lymphatic vessels [30]. For example, a correlation can be made between imaging findings of aplastic and hyperplastic patterns of inguinal lymphatic vessels, which are related to more severe lymphedema, and hypoplastic and normal patterns of these lymphatic vessels, which are related to milder lymphedema.

DCMRL, compared to non-contrast MR lymphangiography, allows the functional assessment of lymph flow and nodal uptake. Thus, the spatial resolution is significantly improved. However, intranodal versus pedal DCMRL is superior in imaging central lymphatics, as injection from the feet results in poorer quality enhancement of pelvic lymphatic vessels and increased incidence of venous contamination. Studies have shown that the correlation between DCMRL and lymphoscintigraphy is good for demonstrating delayed and diffuse lymphatic drainage in peripheral lymphedema [31].

Another method of imaging primary lymphedema is the use of near-infrared fluorescence lymphatic imaging or ICG lymphography. This allows the identification of superficial lymphatic vessels, which can be very useful in identifying lymphatic vessels perioperatively and is of particular use when performing surgical lymphovenous anastomoses. Previous studies have demonstrated the ability to identify different lymphatic flow patterns. However, ICG lymphography is limited by its small field of view and limited penetration depth [32].

Various imaging methods allow for the identification of fluid or assessment of the extent of lymphedema (with MRI); identification of anatomical abnormalities of the central lymphatics, including the presence or absence of the thoracic duct and variations in anatomy (with conventional Lipiodol lymphangiography and DCMRL), and abnormal lymphatic flow, such as intercostal lymphatic flow and dermal backflow (with DCMRL and conventional Lipiodol lymphangiography) [33].

The identification of these abnormalities can be useful in managing therapy in these patients. Potential interventions for anatomical abnormalities include TDE and lymphovenous anastomosis. In patients without anatomical abnormalities, conservative management with diet and limited Lipiodol intervention can provide a good clinical response, thus guiding treatment [34].

Noonan Syndrome

Named after Jacqueline Noonan, a pediatric cardiologist, Noonan syndrome is a genetic disorder characterized by unusual facial features, small stature, and thoracic deformities. It affects approximately one in 1000 to 2500 live births and has recently been associated with genetic mutations that affect the Ras/Mitogen-activated protein kinase (MAPK) signaling pathway in 60% of patients. Aside from cardiac anomalies, about 20% of patients develop lymphatic abnormalities. Noonan syndrome contributes to a large percentage of patients with nontraumatic lymphatic disorders. Manifestations included hydrops, chylothorax, pulmonary lymphangiectasia, mesenteric lymphangiectasia, and scrotal lymphangiectasia. Depending on the clinical presentation, some symptoms may respond to lymphatic intervention.

Primary Chylous Reflux Disease of Genitalia and Leg Lymphedema

The combination of lymph overproduction and insufficiency of lymphatic valves in the mesenteric lymphatics may result in reflux of lymph into the groin

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and legs, causing lymphedema and chylous lymphorrhea in the scrotum, labia, and thighs. Such symptoms are exacerbated in the erect position because of the effects of gravity. Although these are common manifestations of Noonan syndrome, they are not exclusive. While nuclear scintigraphy has long been considered the best imaging modality to diagnose abnormal lymph flow, lymphatic reflux has often been misinterpreted as lymphatic obstruction due to disturbances in antegrade flow. Meanwhile, inguinal lymphangiography using Lipiodol readily shows reflux or to-and-fro motion in pathologic lymphatic vessels. Similar features can be identified in DCMRL. Once chylous reflux is diagnosed, lymphatic embolization may be performed to prevent reflux (Fig. 5). Recent reports have described the successful outcome of lymphatic embolization in treating lymphedema associated with lymphatic reflux [24].

Generalized Lymphatic Anomaly, Kaposiform Lymphatic Anomaly, Gorham-Stout Disease [35]

GLA is a rare disorder characterized by extensive proliferation of lymphatic channels in the lungs, mediastinum, spleen, and other organs (Fig. 6). Synonyms for GLA include systemic congenital lymphangiomatosis, disseminated lymphangiomatosis, and multifocal infiltrative lymphangiomatosis. KLA is a severe form of GLA that is histologically characterized by pattern-less clusters (hence, the word "kaposiform") of spindle lymphatic endothelial cells. Blood cells were also found in the lymph nodes. KLA is associated with localized intravascular coagulopathy, which is attributed to its poor prognosis. GSD is a lymphatic disorder accompanied by bone osteolysis adjacent to anomalous lymphatic channels. GSD is also considered a "vanishing bone disease" because of the radiological features of radiolucencies in the affected bones on plain radiography. It is not always possible to discriminate between lymphatic disorders. Interventional treatment focuses on the clinical manifestation of lymphatic leakage, more specifically, on the anatomical origin of the leak.

Central Conducting Lymphatic Anomaly (Channel Type Lymphatic Malformation)

Central conducting lymphatic anomaly (or channel-type lymphatic malformation) is a group of disorders commonly referred to as lymphangiectasia. It is classified as a separate entity from the GLA, KLA, and GSD in the ISSVA classification. Central conducting lymphatic anomalies may be associated with lymphatic leakage in any part of the body, and are presumed to be the underlying cause of most

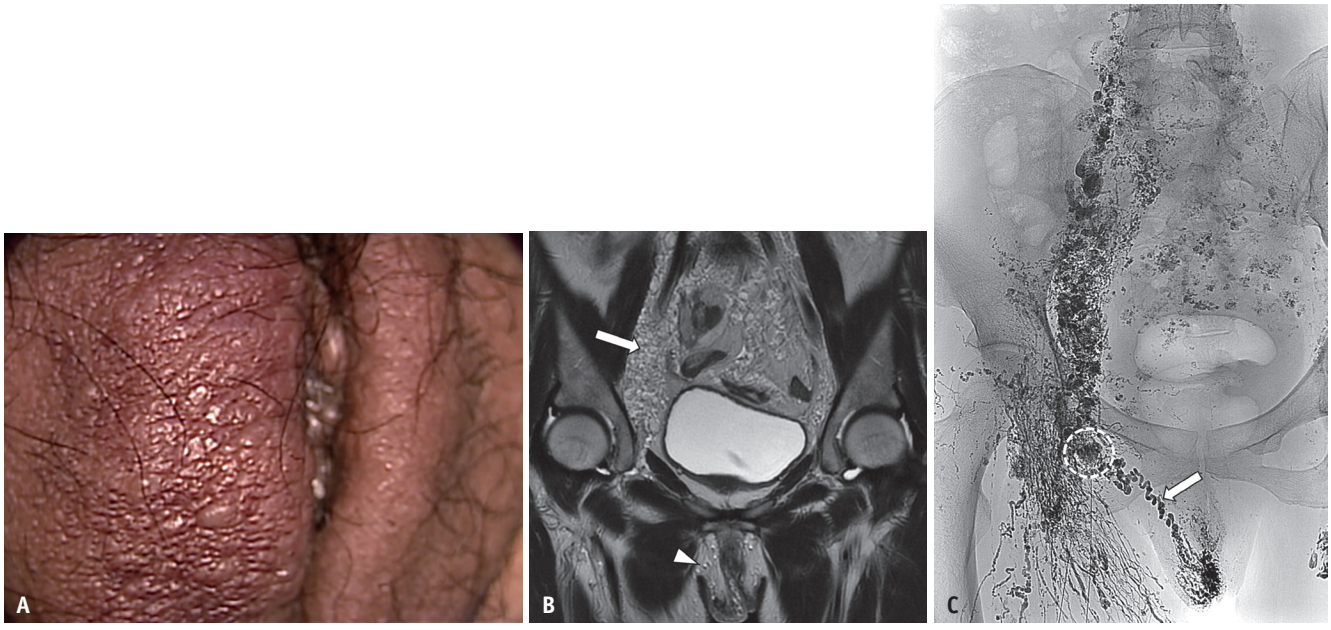

Fig. 5. A 46-year-old female presented with idiopathic labial swelling and chylous discharge.
A. Gross appearance of the swollen labia, predominantly on the right side. **B.** T2-weighted MR imaging reveals extensive distribution of high signal intensity, tubular structures (arrow) in the pelvic cavity, suggestive of ectatic lymphatic channels. Similar structures are also observed in the labium (arrowhead). **C.** Intranodal Lipiodol lymphangiography performed in the right thigh showed ectatic lymphatic channels in the pelvis, with abnormal reflux of Lipiodol into the labium and thigh. An inguinal lymph node (dashed circle) connected to the ectatic lymphatic channel (arrow) in the right labium is selectively embolized using a glue mixture.

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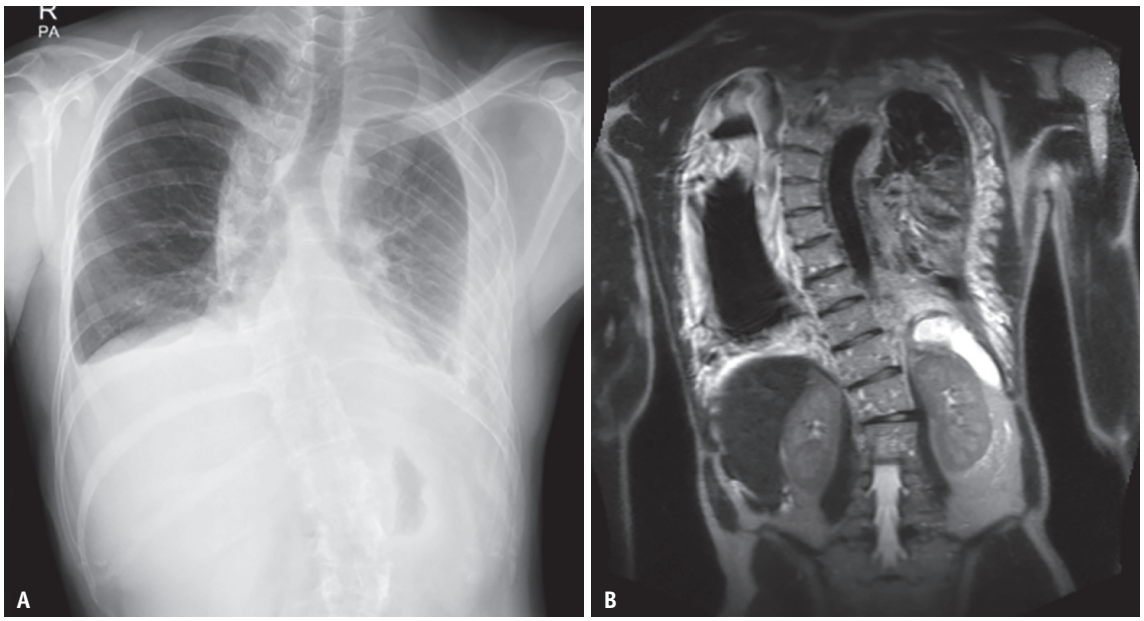

Fig. 6. A 29-year-old male diagnosed with Gorham–Stout disease presented with dyspnea associated with massive chylous effusion.
A. Chest radiography reveals a deformed thoracic cage and spine with osteolytic changes in the left ribs. A large pleural effusion is noted on both sides. **B.** T2-weighted MR images shows high signal intensity in the left thoracic cage, reflecting the presence of abnormal lymphatic tissue in the ribs, intercostal muscles, and subpleural soft tissues. These findings are consistent with those of Gorham disease.

non-traumatic chylothorax or chylous ascites (Fig. 7).

Protein-Losing Enteropathy

PLE refers to a condition in which there is an excessive loss of serum protein from the gastrointestinal system. While the liver possesses the potential to increase the synthesis of plasma proteins when required, in PLE, the amount of protein lost through the gastrointestinal mucosa exceeds that produced by the liver. Various underlying conditions have been associated with PLE, which either affect the integrity of the gastrointestinal mucosa or increase pressure in the lymphatic network beneath the mucosal lining. The latter may result from etiologies such as bowel lymphangiectasis, mesenteric lymphatic obstruction caused by tumors or sclerosing mesenteritis, and pre- or post-sinusoidal portal hypertension.

PLE is a well-known complication of the Fontan procedure [36,37]. Hepatoduodenal lymphatic connections, combined with elevated central venous pressure resulting from the Fontan operation, are postulated to play a role in the development of PLE. This is based on the finding by Ernest Starling, in which elevated central venous pressure was associated with liver congestion and a subsequent increase in the flow of liver lymph [38]. Increased flow of liver lymph is thought to compete with intestinal lymphatic

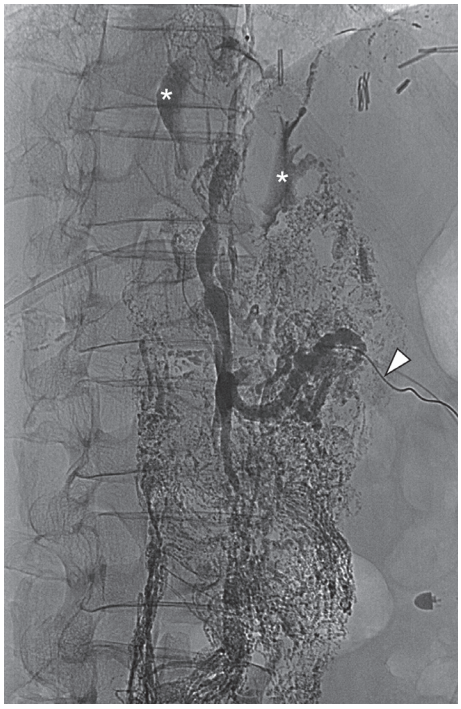

Fig. 7. A 65-year-old male patient presented with chylous ascites after esophageal surgery. Diffuse lymphatic ectasia is seen around the central conducting lymphatic ducts and mesenteric trunk. These features were most likely to be present before surgery and are suggestive of central conducting lymphatic anomaly. The ectatic mesenteric trunk was percutaneously accessed with a co-axial microcatheter system (arrowhead) for glue embolization of mesenteric leaks (asterisks).

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drainage within the hepatoduodenal lymphatic connections, resulting in dilatation of the hepatoduodenal lymphatic ducts and intestinal lacteals [39]. This predisposes protein-rich lymph from the liver to leakage into the intestinal lumen.

An earlier report described a technique involving percutaneous transhepatic injection of isosulfan blue dye into the liver lymphatics, which was allowed to flow with lymph through the dilated hepatoduodenal lymphatic connection [23]. Details on the techniques of liver lymphangiography and transhepatic lymphatic embolization are described in Part 1. Although there have been reports on the successful outcome of lymphangiography and embolization for PLE, various challenges remain in the treatment of PLE in post-Fontan patients. Similarly, challenges remain in the treatment of PLE unrelated to the Fontan operation owing to the diversity in the underlying etiology and extent of disease in the gastrointestinal tract.

Pulmonary Lymphatic Perfusion Syndrome (Neonatal Chylothorax, Idiopathic Chylothorax and Chylopericardium, and Plastic Bronchitis)

PLPS encompasses a spectrum of disorders that result in lymph reflux from the thoracic duct towards the mediastinum and lung parenchyma. PLPS may manifest as idiopathic chylothorax or chylopericardium, neonatal chylothorax, or plastic bronchitis following cardiothoracic surgery or secondary to inflammatory conditions (Fig. 8)

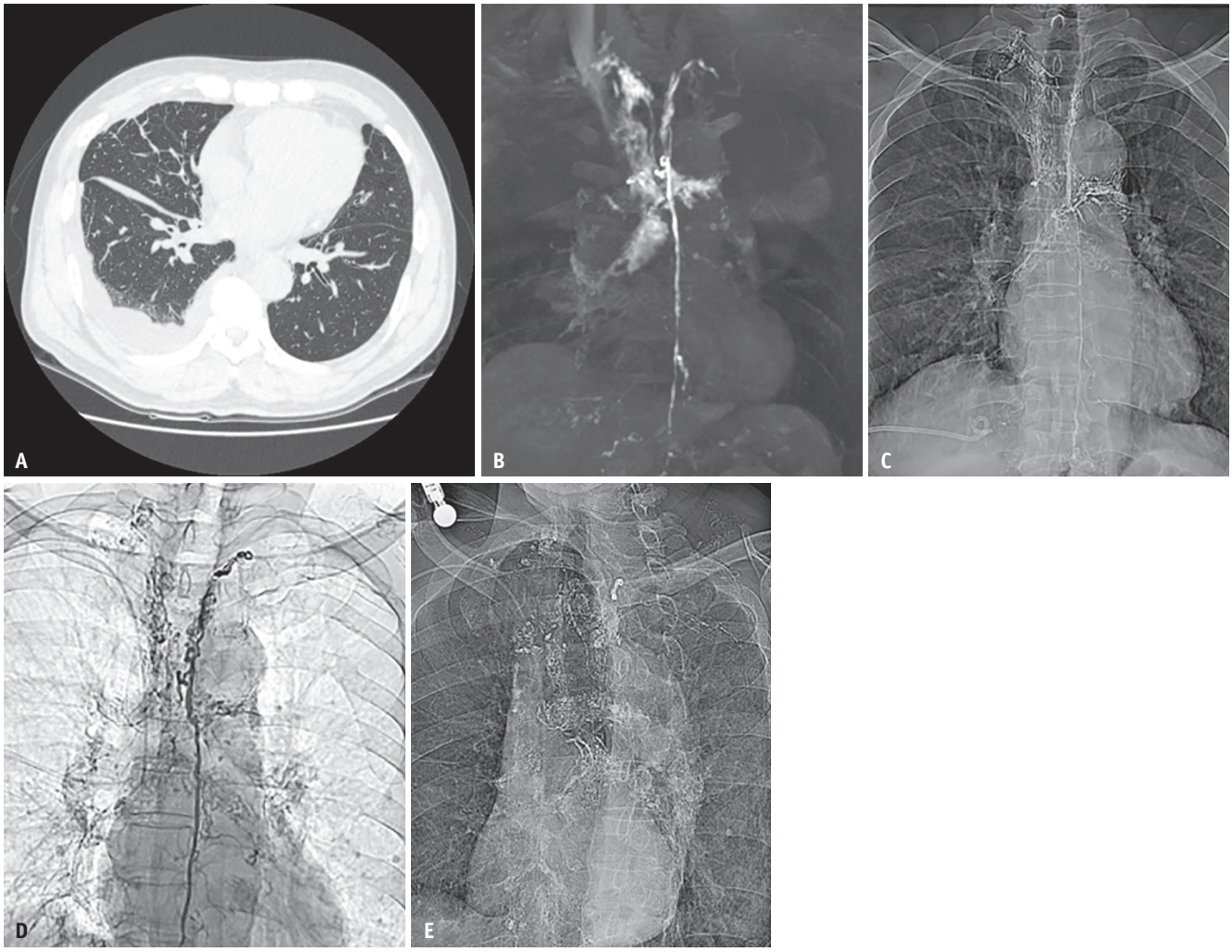

Fig. 8. A 64-year-old male patient with idiopathic chylothorax.
A. Chest CT reveals interlobular septal thickening in the right lung with pleural effusion. **B.** Dynamic contrast enhanced MR lymphangiography demonstrates abnormal lymphatic perfusion from the thoracic duct to mediastinal and hilar tissues. **C.** Findings of abnormal lymphatic perfusion is well correlated on Lipiodol lymphangiography. **D, E.** The thoracic duct and its tributaries were embolized using detachable coils and diluted glue mixture (N-butyl cyanoacrylate:Lipiodol = 1:6).

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[4,5,40,41]. PLPS may go undetected until later in life, when the patient develops symptoms secondary to elevated central venous pressure, trauma, or infection. DCMRL allows for an understanding of the thoracic duct anatomy and provides information on the direction of lymph flow. TDE may be considered based on DCMRL findings.

It should be noted that idiopathic chylothorax should be differentiated from the secondary accumulation of chyle in the pleural space in chylous ascites. The chyle from the peritoneum can pass freely from the peritoneal cavity into the pleural space through diaphragmatic fenestrations [40]. Negative pressure in the thoracic cage causes a pressure gradient between the two spaces, which drives the lymph across the diaphragm. In such a clinical setting, TDE would result in the aggravation of chylous ascites because the outflow of lymph via the thoracic duct is compromised (Fig. 9). The treatment strategy should be based on the origin of chyle leak.

Treatment of Lymphatic Disorders

Conservative and Medical Treatment

There are two components of the conservative treatment of lymphatic leaks: percutaneous drainage of fluid collections and strategies to decrease lymphatic flow into dead spaces. The former step helps decompress the region of interest, thereby relieving the surrounding organs from extrinsic compression and also lowers the risk of secondary infection in lymph collections. The amount of daily drainage should be monitored to determine trends in lymphatic output. The decision for additional interventional treatment or removal of the drainage catheter was based on these results. A sudden decrease in the amount of drainage may not necessarily mean that the leak has been resolved. Before considering catheter removal, the function of the catheter should be checked, and if available, ultrasound or CT should be used to exclude the possibility of a dysfunctional catheter. A strategy to decrease chyle production helps promote healing at the leak

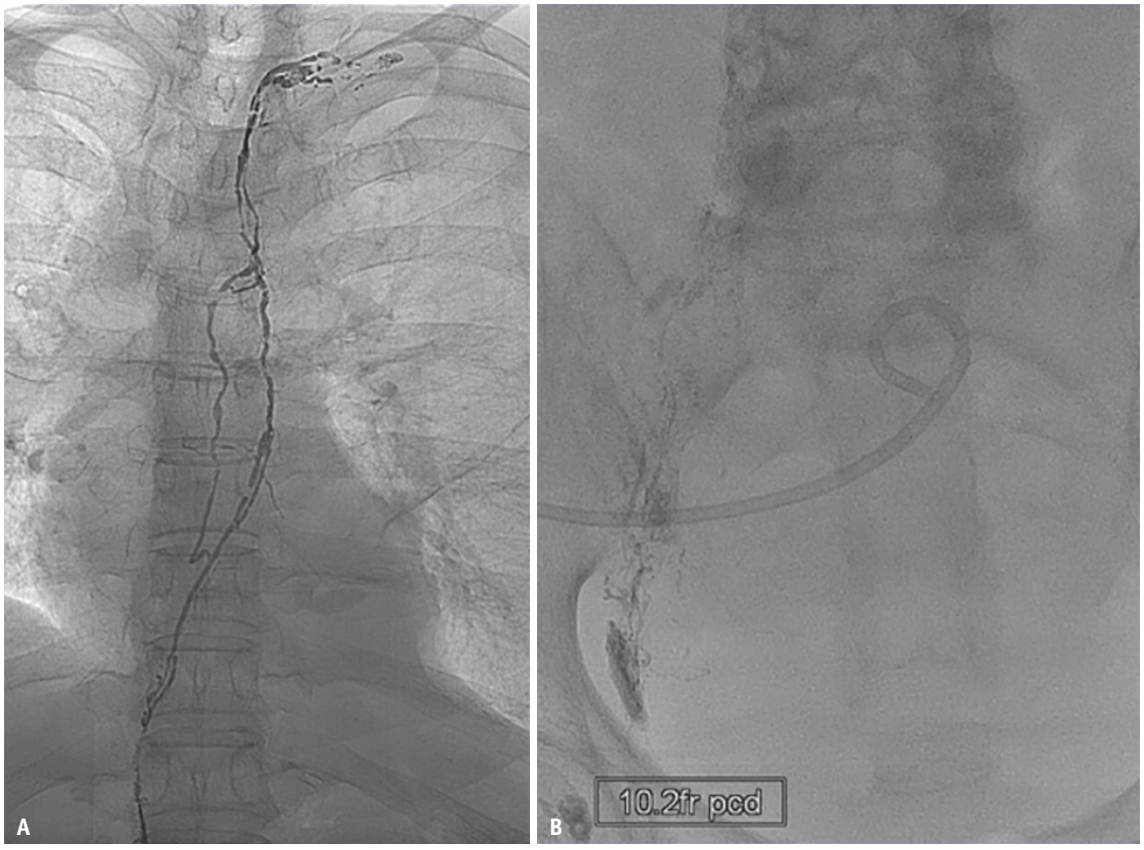

Fig. 9. A 72-year-old female with idiopathic chylothorax.
A. Intranodal lymphangiography demonstrates a patent thoracic duct without evidence of lymphatic leakage or obstruction. Thoracic duct embolization (data not shown) was performed despite the absence of abnormal findings. **B.** The patient returned with worsened chylothorax and the onset of chylous ascites. A pigtail drainage catheter was placed into the peritoneal cavity for abdominal decompression.

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site. This includes diet modification, such as a low-fat diet, substitution of dietary fats with medium-chain fatty acids, fasting with the provision of total parental nutrition, and administration of octreotide [42,43].

In recent studies, new therapeutic agenets that target the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) or Ras/MAPK signalling pathways have been shown to significantly improve symptoms if used in patients with corresponding genetic abnormalities. The mTOR inhibitor sirolimus is thought to act on lymphatic tissues within lesions of some complex non-traumatic lymphatic disorders such as GLA, KLA, or GSD by decreasing lymphatic endothelial cell activity and hence regulating the production and leakage of lymph [35]. MEK inhibitors showed a promising greatly improves symptoms that are related to severe lymphatic abnormality in Noonan syndrome by complete remodeling of central lymphatic system [44,45].

Surgical Treatment

Thoracic duct ligation is a well-known surgical procedure in which the thoracic duct is sutured below the leak site. Another surgical strategy is to deviate the flow of the lymph into the systemic vein by creating a lymphovenous shunt for lymphatic edema of the lower extremity secondary to lymphatic occlusion. For uncomplicated lymphoceles, surgical deroofing of these pseudocysts may be sufficient to decompress the space-occupying lesions. Other surgical techniques include lymph node transplantation and ablative surgery. The technical details of these surgical techniques are beyond the scope of the present study.

Interventional Treatment

Lymphocele Sclerotherapy

Sclerotherapy has long been considered the gold standard treatment for lymphocele. In contrast to true cysts, lymphoceles are pseudocysts without an endothelial lining. In true cysts, the sclerosant comes into contact with the epithelial cells that procedure the fluid. In lymphoceles, where the fluid originates from a leaking lymphatic vessel, the sclerosant administered into the cavity is thought to come in contact with the leaking lymphatic vessel and incite an inflammatory response, resulting in occlusion of the disrupted lymphatic vessel [46]. The sclerosant also causes adhesion between the pseudocyst walls, thereby reducing the potential dead space [7].

Despite its long history, there is still a consensus regarding the technical details of sclerotherapy. The choice and dose of sclerosant are inconsistent among institutions. Commonly used sclerosants are concentrated (99%) alcohol (otherwise known as “pure” ethanol), betadine (povidone-iodine), doxycycline, and bleomycin among others [47]. Alcohol is readily available in most institutions and is associated with minimal side effects when used with caution. The protocol for alcohol sclerotherapy at our institution is described below.

Before sclerotherapy, a drainage catheter was percutaneously placed into the fluid cavity to decompress the lymphocele. Evacuation of fluid also prevents the sclerosant from diluting inside the cavity. The daily output should be monitored and documented over the first few days. Larger tubes (10–12 French or larger) are less prone to clogging than smaller tubes. Once the daily amount of drainage became consistent, an ultrasound scan was performed to check for collapse of the lymphocele cavity. Under fluoroscopy, water-soluble contrast media are introduced into the lymphocele through the catheter to determine the estimated volume of the cavity. If the cavity was large, the contrast medium was diluted with normal saline to increase the total volume of the contrast solution). The contrast solution was then evacuated through the catheter and alcohol was administered. The amount of alcohol used was equal to the amount of aspirated contrast solution, but should not exceed 100 mL in a single session to avoid the risk of alcohol intoxication. The patient was instructed to change positions (turning 90° clockwise or anti-clockwise) every 5 minutes so that each side of the pseudocyst wall came into contact with the sclerosant. It generally takes 20 minutes for the patient to complete the cycle, which includes supine and prone positions and both lateral decubitus positions. Treatment is generally considered successful when the volume of daily drainage does not exceed 10 mL, at which point the tube can be removed. Repeated sessions of sclerotherapy should be considered if the amount exceeds the threshold. There is no limit to the number of repeated sessions; therefore, some institutions perform repeated procedures every 1–2 days until the target is reached.

The main advantage of sclerotherapy is that it is easy to perform, without the need for sophisticated equipment other than a drainage catheter. However, this is not indicated in patients with fluid collection that is not confined by a pseudomembrane. Furthermore,

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large lymphoceles may not respond to sclerotherapy [7]. Lymphatic embolization techniques have recently been applied to overcome such difficulties in treating challenging lesions.

Lipiodol as an Embolic Agent

In addition to its use as a contrast medium for lymphangiography, Lipiodol has been shown to play a therapeutic role in preventing chylous leaks [48]. However, the underlying mechanisms are poorly understood. Reports of worsening lymphedema after pedal lymphangiography indicate the possibility of an embolic effect of Lipiodol itself due to its viscous nature [49]. Another plausible explanation is that extravasated Lipiodol may incite an inflammatory response at the leakage site, subsequently leading to granulomatous tissue formation that occludes the leak. This mechanism has been described in reports on dacryocystography using Lipiodol [50]. The reported clinical success of Lipiodol lymphangiography ranges from 35%–89% [9,51-56]. Such variation in outcomes can be attributed to multiple factors, including heterogeneity in the etiology of the lymphatic leak and the amount of leakage. For example, successful outcomes are more consistent for the treatment of neonatal chylothorax than other forms of idiopathic chylous effusions [4,57-59]. Regarding drainage output, studies have reported higher rates of treatment failure in patients with high-output leaks [60].

However, the true role of Lipiodol in the cessation of lymphatic leak remains controversial owing to the retrospective nature of the reports on the subject. Not only does the definition of clinical success vary among these reports, but the time to recovery (the interval between lymphangiography and defined clinical success) is also inconsistent. Under such circumstances, it is impossible to determine whether lymphangiography alone contributes to the resolution of the lymphatic leak. In the future, prospective and randomized controlled studies that seek to objectively compare the clinical outcomes of lymphangiography alone and lymphangiography with adjunctive embolization are warranted. Such studies will help to make standardized decisions on whether to perform adjunctive embolization after lymphangiography.

Thoracic Duct Embolization

The TDE was developed by Constantine Cope, who first experimented with his new technique in porcine models. In 1998, Cope reported the successful outcome of TDE in five patients with chylothorax. Since then, numerous publications have been published on this subject. Cope's report on TDE has served as the basis for a variety of embolization procedures performed in the lymphatic system. In Cope's original description of TDE, a needle was passed through the peritoneum to reach the retroperitoneal lymphatic duct. This approach does not consider anatomical structures along the path of the needle. When there is a concern, the operator may perform cross-sectional imaging before transperitoneal access to minimize the chance of penetrating high-risk structures, such as an abdominal aortic aneurysm or hypervascular mass. Due to the high likelihood that the needle will penetrate one or more segments of the bowel, it is recommended that the patient fast overnight. Fasting also helps reduce chyle production, which, in turn, decreases lymph flow in the thoracic duct. Slow-flowing Lipiodol in the thoracic duct is easier to trace than it is rapidly washed out. Therefore, the prophylactic administration of intravenous antibiotics should be considered. TDE is a three-step process involving lymphangiography, thoracic duct catheterization, and embolization in sequence.

Step 1: Lymphangiography

Both pedal and intranodal lymphangiography should be performed to reveal the anatomy of the central conducting system prior to TDE. A study comparing the two techniques during the TDE process unsurprisingly demonstrated shorter procedure times for the latter [61]. Furthermore, with intranodal lymphangiography, the thoracic duct may be filled with a higher concentration of Lipiodol, allowing for better visualization during catheterization. Bolus chasing with normal saline or application of pneumatic pumps around the legs may be considered to speed up the process of lymphangiography [62].

Step 2: Thoracic Duct Catheterization (Fig. 10)

As soon as the cisterna chyli and thoracic duct are opacified by Lipiodol, a fine needle (such as a Chiba needle measuring 15–21 cm in length) is used to puncture any prominent retroperitoneal lymphatic duct (usually the cisterna chyli or its tributaries). Some favor access to the lumbar trunk below the cistern chyli to prevent iatrogenic chyle leak from the cisterna chyli or the lower thoracic duct. The technical success rate of thoracic duct access is estimated to be approximately 63.1% but varies widely across reports, presumably owing to different levels of

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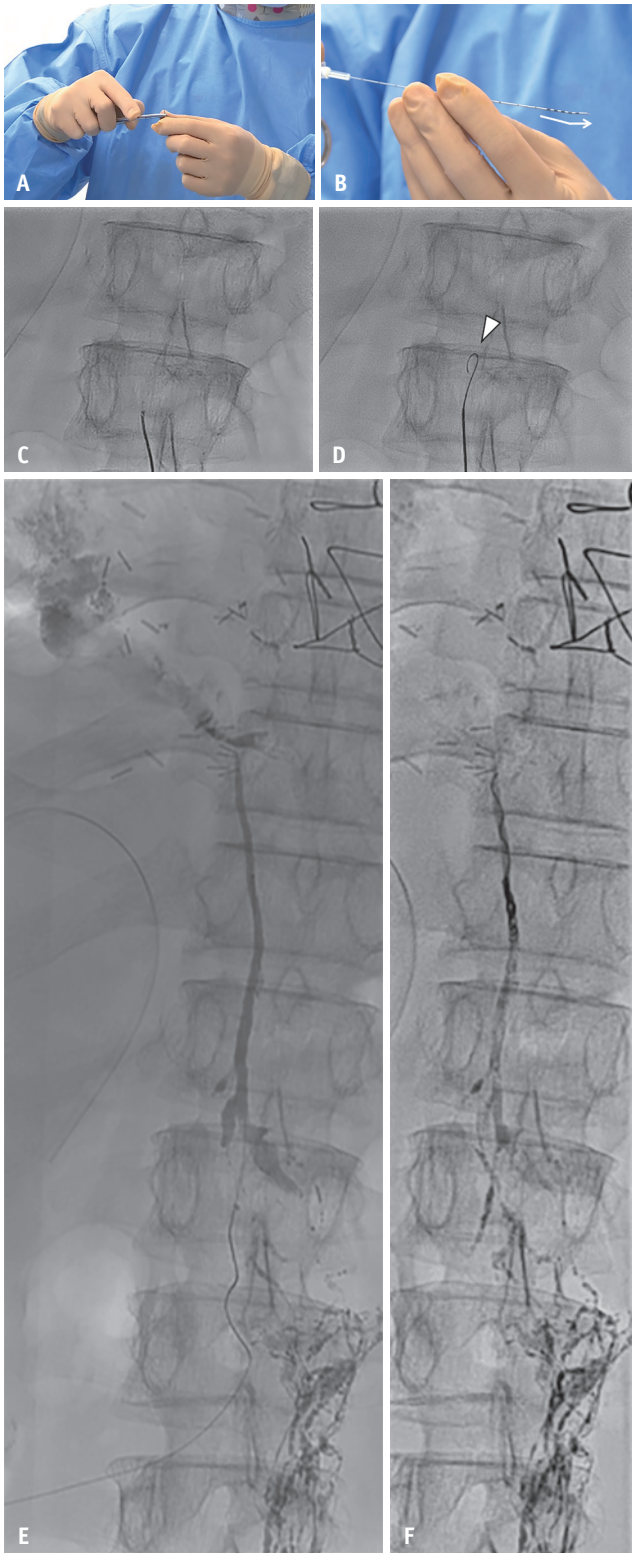

Fig. 10. A 46-year-old male with chylothorax after thymectomy and pleural metastectomy for thymoma (the same patient as in Fig. 3 of Part 1).
A, B. A gentle curve is made near the tip of a 21-gauge Chiba needle to allow steerability during transperitoneal access. **C.** The curved needle tip is slowly navigated towards the target duct by rotating the needle shaft. **D.** The looped configuration (arrowhead) of the guidewire suggests that the distal end of the guidewire is in the lymphatic lumen rather than in the retroperitoneal soft tissue. **E, F.** A thoracic ductogram using a water-soluble contrast medium demonstrates the anatomy of the thoracic duct and the site of leakage.

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experience [13]. Even though the penetration of bowel structures, solid organs, or major vessels is inevitable, TDE is considered safe [63]. Following a successful puncture, a guidewire was passed through the needle and directed into the upper thoracic duct. Thereafter, the needle was removed, and a 2–3 F microcatheter was delivered coaxially over the guide wire.

Step 3: Embolization

Once the thoracic duct is accessed, contrast medium can be injected directly into the thoracic duct through the microcatheter. The contrast media used at this stage may either be Lipiodol or water-soluble, depending on the operator's preference. The latter provides an option for digital subtraction imaging. Once the leak is detected, the coils are deployed in the thoracic duct, followed by the injection of the glue mixture. A widely used glue mixture is created by diluting N-butyl cyanoacrylate (NBCA) with Lipiodol. Lipiodol delays the polymerization of NBCA and makes the mixture radiopaque, allowing for visualization under fluoroscopy. It is important to note that NBCA polymerizes at a slower rate in lymph than in blood [64]. The authors prefer to use concentrated glue mixtures (glue-to-Lipiodol ratio of 1:1 or 1:2) to prevent inadvertent migration of glue into the systemic vein and subsequently into the pulmonary arteries. Before injecting NBCA, the microcatheter was flushed with a small amount (just enough to fill the dead space of the microcatheter) of dextrose-5-water. Then, the glue mixture was injected while slowly pulling back on the microcatheter until the cast covered both the proximal and distal segments around the leak site.

In their first report, Cope et al. [65] reported successful outcomes in 74% of 42 patients. Meanwhile, Itkin et al. [66] reported an overall success rate of 71% in a group of 109 patients who underwent thoracic duct intervention (including 16% in the study group that underwent thoracic duct disruption [TDD]) on an intent-to-treat basis, among which clinical success was reported in 90% of patients who underwent TDE. A recent meta-analysis pooled results from cohorts that included a minimum of ten patients and reported pooled technical success and clinical success rates of 63.1% and 79.4% for TDE [13]. These results are expected to improve with the use of newer techniques for thoracic duct cannulation.

Retrograde Thoracic Duct Catheterization

Transvenous retrograde thoracic duct catheterization was first described in 2008 by Mittleider et al. [67] in an attempt to treat chylous ascites. It starts with venous access, usually through the femoral or brachial vein. A curved angiographic catheter and co-axial microcatheter system are used to engage the terminal part of the thoracic duct, which typically joins at an angle formed by the confluence of the left internal jugular and subclavian veins [68]. If performed during or immediately after intranodal lymphangiography, the presence of Lipiodol in the terminal thoracic duct serves as an anatomical landmark for retrograde catheterization (Fig. 11). This process may be technically challenging owing to the anatomy of the terminal thoracic duct. Furthermore, the varying anatomy of the thoracic duct further limits the application of this technique. Ultrasound or MR lymphangiography may help determine the location and anatomy of the terminal thoracic duct before retrograde thoracic duct catheterization.

An alternative technique for retrograde thoracic duct catheterization is direct puncture of the cervical portion of the thoracic duct. When this is preceded by intranodal lymphangiography, stagnant Lipiodol in the uppermost portion of the thoracic duct is an ideal target under

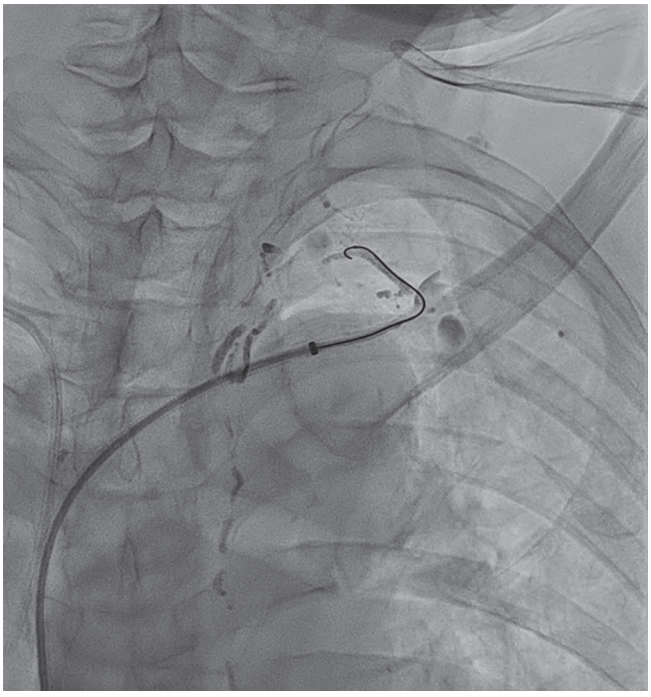

Fig. 11. A 74-year-old female with idiopathic chylothorax and immunoglobulin G4-related mesenteritis. An angiographic catheter is placed near the venous angle following intranodal lymphangiography. Lipiodol stagnation is observed in the terminal thoracic duct, revealing the location of the venous angle. A microcatheter and co-axial guide wire are navigated retrogradely across numerous valves in the distal thoracic duct.

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fluoroscopy. Without preceding lymphangiography, the cervical portion of the thoracic duct can be identified and accessed under ultrasound guidance [21,69]. The terminal thoracic duct typically courses between the left internal jugular and vertebral veins to join the confluence of the internal jugular and subclavian veins (Fig. 12). Valves are frequently identified on ultrasonography, most of which are located at the point where the thoracic duct drains into the systemic vein. Intermittent bursts of echogenic "speckles" are seen as lymph passes in sync with the valvular motion.

Once the terminal thoracic duct is identified on fluoroscopy or ultrasonography, the most superficial segment of the thoracic duct is punctured with a 21-gauge needle. A guidewire is then navigated into the lower thoracic duct under fluoroscopic guidance (Fig. 13).

In any of the techniques described above, the guidewire must be retrogradely navigated from the terminal duct to the lowermost segment of the thoracic duct. Retrograde guidewire navigation is often challenged by the presence of numerous valves along the course of the thoracic duct.

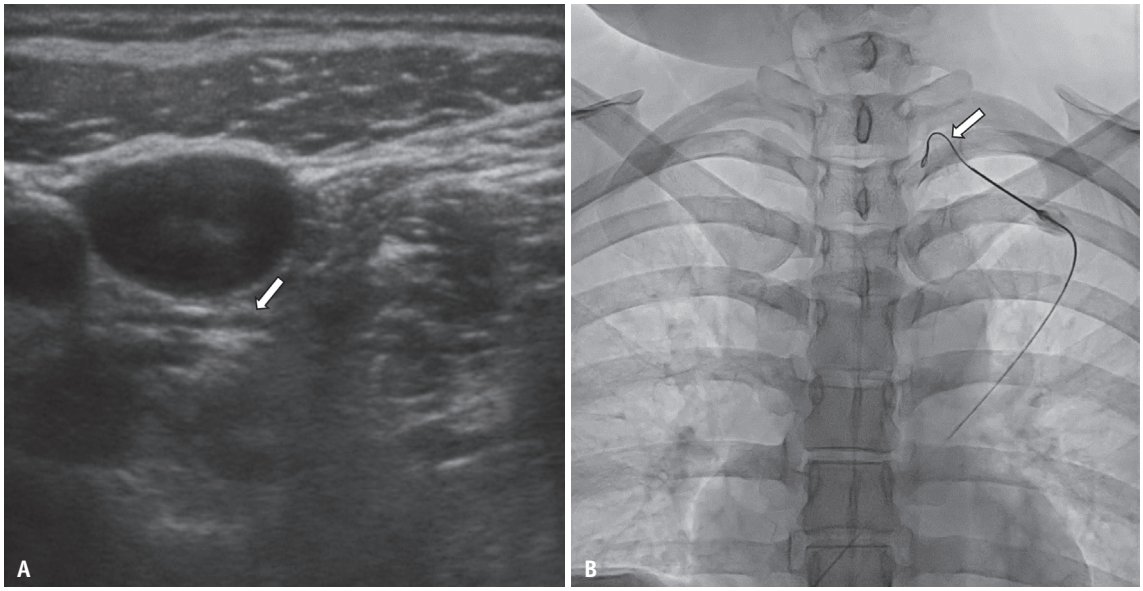

Fig. 12. A 26-year-old female presented with a 9-year-history of chyluria.
A. The terminal portion of the thoracic duct is seen behind the left internal jugular vein on ultrasound (arrow). **B.** The guidewire is retrogradely advanced into the thoracic duct (arrow) after ultrasound-guided access to the terminal thoracic duct.

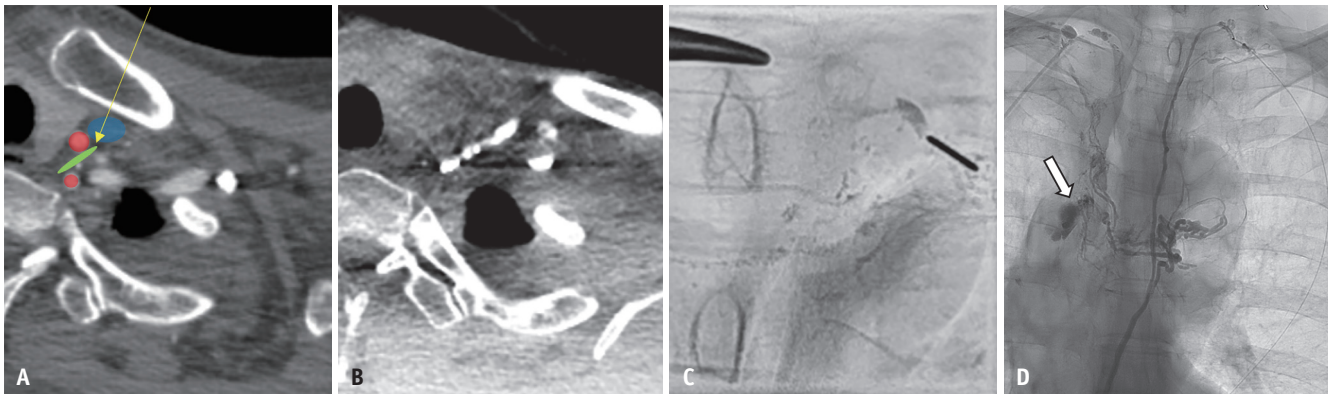

Fig. 13. A 70-year-old male with right chylothorax after right upper lobectomy for non-small cell lung cancer.
A, B. The anatomical relationship between the thoracic duct and surrounding vessels (red circle: common carotid artery, vertebral artery, blue ellipse: internal jugular vein) can be appreciated by simultaneously reviewing contrast-enhanced CT acquired prior to lymphangiography and cone-beam CT during lymphangiography. Arrow shows the expected approach course of the needle to the terminal thoracic duct. **C.** Stagnated Lipiodol reveals the location of the terminal thoracic duct, which can be percutaneously accessed using a fine needle. Fluoroscopic guidance in the left anterior oblique projection allows for a safe needle trajectory because the thoracic duct courses anteriorly towards the venous angle as it passes through the space between the carotid and vertebral arteries. **D.** Thoracic ductogram using water-soluble contrast reveals leakage from the right pulmonary hilum (arrow). A communicating channel between the right lymphatic and thoracic ducts is noted.

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Careful manipulation of the guidewire and microcatheter is required to catheterize the lower part of the thoracic duct without causing iatrogenic injury.

The publication of retrograde thoracic duct access is limited to brief reports on small retrospective cohorts. Nevertheless, the technique of retrograde thoracic duct access provides the interventionist with an alternative strategy that should make antegrade thoracic duct access unsuitable or unsuccessful. A recent study had reported a technical success rate of 93% for thoracic duct catheterization when antegrade access was complemented by retrograde access [14]. Recently, retrograde thoracic duct access has been applied in advanced imaging and embolization techniques, including balloon-occluded retrograde transcatheter MR lymphangiography and balloon-occluded retrograde abdominal lymphangiography and embolization [16].

Thoracic Duct Disruption

Cope first reported TDD for the treatment of chylothorax following his publication on TDE [20,65,70,71]. It was not intended as a first-line procedure, but rather as a technique to bail out from an unsuccessful TDE procedure. When thoracic duct catheterization was unsuccessful, the lower thoracic duct was repeatedly punctured with a needle. The resulting hematoma and tissue scarring at the needling site have been proposed as the reasons for the successful outcome. Itkin et al. [66] reported a success rate of 72% after TDD for chylothorax. However, considering that some leaks respond to lymphangiography alone, it is unclear if and to what extent TDD contributes to cessation of thoracic duct leakage. A systematic review of thoracic duct interventions revealed a lower rate of clinical success with TDD than with TDE [13]. With recent advances in intranodal lymphangiography and techniques for retrograde thoracic duct catheterization, the role of TDD in the treatment of chylothorax is gradually fading.

Lymph Node Embolization

LNE is a form of lymphatic embolization in which glue is directly injected into lymph nodes. This technique is useful for treating leaks from small lymphatic vessels that cannot be catheterized. As with TDE, intranodal lymphangiography is first performed to delineate lymphatic structures and identify the leak site. Thereafter, one or more lymph nodes close to the level of the leak were punctured for glue injection. Based on the direction of lymph flow, the lymph node chosen for this purpose is usually located just below the leak. The glue injected into this lymph node initially fills the interstitium of the lymph node and then spreads through efferent vessels towards the leak (Fig. 14) [9,72,73]. Regarding the concentration of the glue mixture, NBCA was diluted with Lipiodol at a ratio of 1:2 and 1:4. This should be determined based on the distance of the leak from the access lymph node and the extent of interstitial lymphatics that must be filled before the glue mixture reaches the target leak. To prevent premature polymerization, it is important to flush the needle and lymphatic channels with dextrose-5-water before injecting the glue mixture. In terms of the efficacy of this technique, the evidence level is low owing to the lack of large-scale, controlled studies. Clinical failures may result from a complex network of collaterals or multiple leakage sites that may not be evident on lymphangiography. Therefore, repeated embolization sessions should be considered.

Transhepatic Lymphatic Embolization

The deep lymphatic system of the liver may serve as an

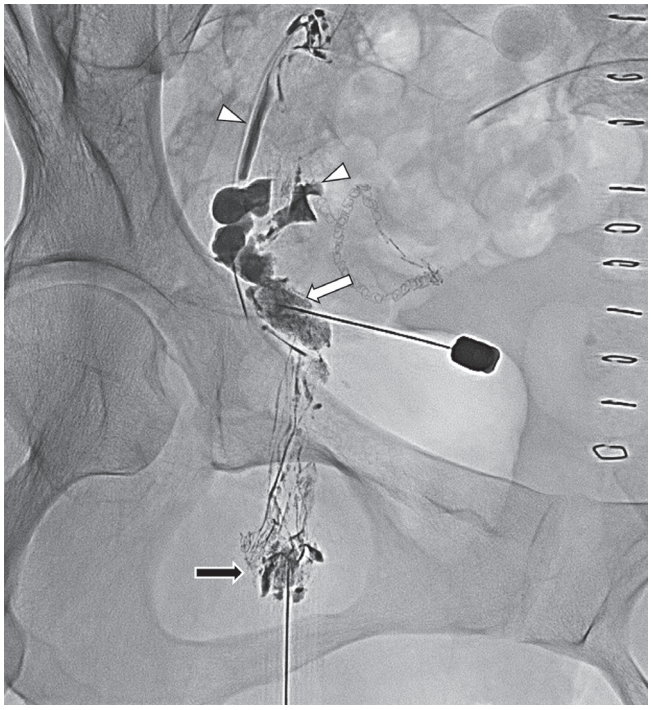

Fig. 14. A 43-year-old female developed postoperative, non-chylous lymphatic leak after debulking surgery for ovarian cancer. Lipiodol lymphangiography performed through a lymph node (black arrow) in the right thigh reveals a leak above the external iliac lymph node (white arrow). Extravasated Lipiodol (arrowheads) is seen between bowel structures and the surgical drain. The external iliac lymph node below the leak was separately accessed with a fine needle for glue injection.

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access for lymphangiography and lymphatic embolization. This technique was first reported by Guez et al. [74] in 2013, when the authors described the successful treatment of hepatic lymphorrhea. Onyx is the embolic agent of choice. Another report published in 2019 described the same technique used to treat PLE related to the Fontan operation in a patient with underlying congenital heart disease [23]. NBCA was used for embolization.

The procedure starts with percutaneous puncture of the liver through the intercostal or subcostal space. A fine needle (between 21- and 25-gauge) was directed towards the periportal sheath under ultrasound guidance (Fig. 15). Once in position, water-soluble contrast media are carefully injected under real-time fluoroscopy to opacify the chain of lymphatic structures around the portal vein. Injection should be performed slowly until deep lymphatic vessels in the hepatoduodenal ligament and outflow are demonstrated. Fluoroscopic images should be reviewed to identify extravasation of contrast medium into the peritoneum or bowel. This was followed by the injection of the glue mixture through the same needle (Fig. 15). The injection should be performed forcefully and steadily, and the needle tip must be stable throughout the injection process. An alternative technique involves endoscopic guidance, in which the mucosal side of the lymphatic leak is directly punctured through a duodenoscope followed by glue injection.

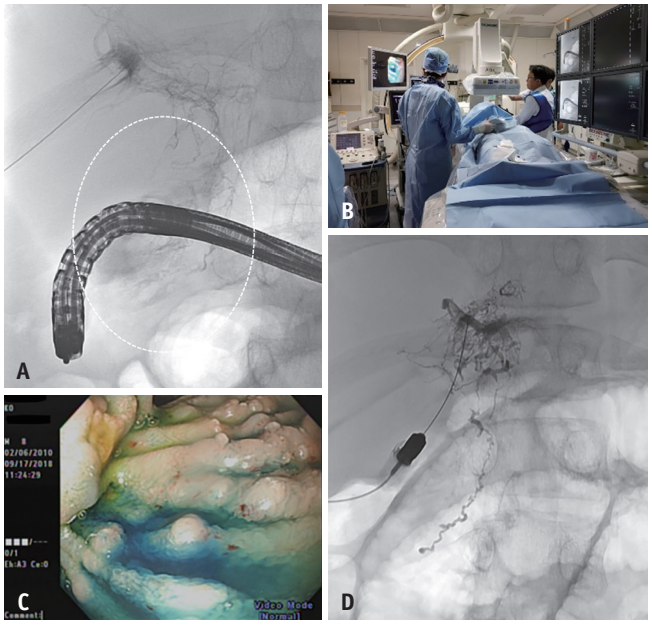

Fig. 15. A 17-year-old male with protein-losing enteropathy following Fontan operation.
A. Liver lymphangiography using water-soluble contrast media shows abnormal lymph flow along the hepatoduodenal ligament to the duodenum (dashed circle). The endoscopy probe is positioned in the duodenum during liver lymphangiography to identify lymphatic leakage in the duodenum. **B, C.** Endoscopic image shows isosulfan blue dye injected through the liver lymphatics seeping out of the duodenal mucosa. The diagnosis of protein-losing enteropathy was based on these findings. **D.** Diluted glue (N-butyl cyanoacrylate:Lipiodol = 1:5 mixture) was injected through a needle into the periportal lymphatic vessels to occlude abnormal lymphatic perfusion to the duodenum.

Post-embolization CT may reveal periportal edema, suggesting an alteration in the lymphatic circulation. However, these features are transient and do not affect liver function or other clinical parameters. Although no complications have been reported thus far, transhepatic lymphatic embolization is a relatively novel procedure for which isolated case reports or retrospective studies with small cohorts constitute most of the literature.

Lymphopseudoaneurysm Embolization

The term lymphopseudoaneurysm was first used by Hur et al. [9], who described a small pool of extravasated lymphatic fluid confined by the surrounding tissue. Ascites is usually associated with ascites in the abdomen. Although the ideal approach would be to interrupt lymphatic inflow of the lymphopseudoaneurysm, catheterization of lymphatic channels below the cisterna chyli or lumbar trunk is technically challenging. Therefore, lymphopseudoaneurysms may be the only target amenable to direct needle access. Most of the earlier case reports on percutaneous embolization of intra-abdominal leaks described the process of direct sac puncture [75-77]. Unlike lymphoceles, sclerotherapy is not indicated in lymphopseudoaneurysm since there is a lack of a mature wall found in the former. Instead, the glue mixture can be injected into the small confinement of the lymphopseudoaneurysm to act as a plug to stop the lymphatic leak (Fig. 16). This concept is similar to that of percutaneous thrombin injection for femoral artery pseudoaneurysms. Once lymphopseudoaneurysm is revealed on intranodal lymphangiography, it is directly punctured with a fine needle under fluoroscopic guidance. A concentrated glue mixture (minimally diluted with Lipiodol at a ratio of 1:1 or 1:2) was injected into the sac. Because of the need to fill the sac for a successful outcome, the procedure should only be considered in small lymphopseudoaneurysm. Meanwhile, for larger fluid collections, the inflow of lymph should be interrupted to stop the lymphopseudoaneurysm from filling. This can be achieved by either targeting the inflow channel below the leak [9,78] or using a microcatheter to navigate from the

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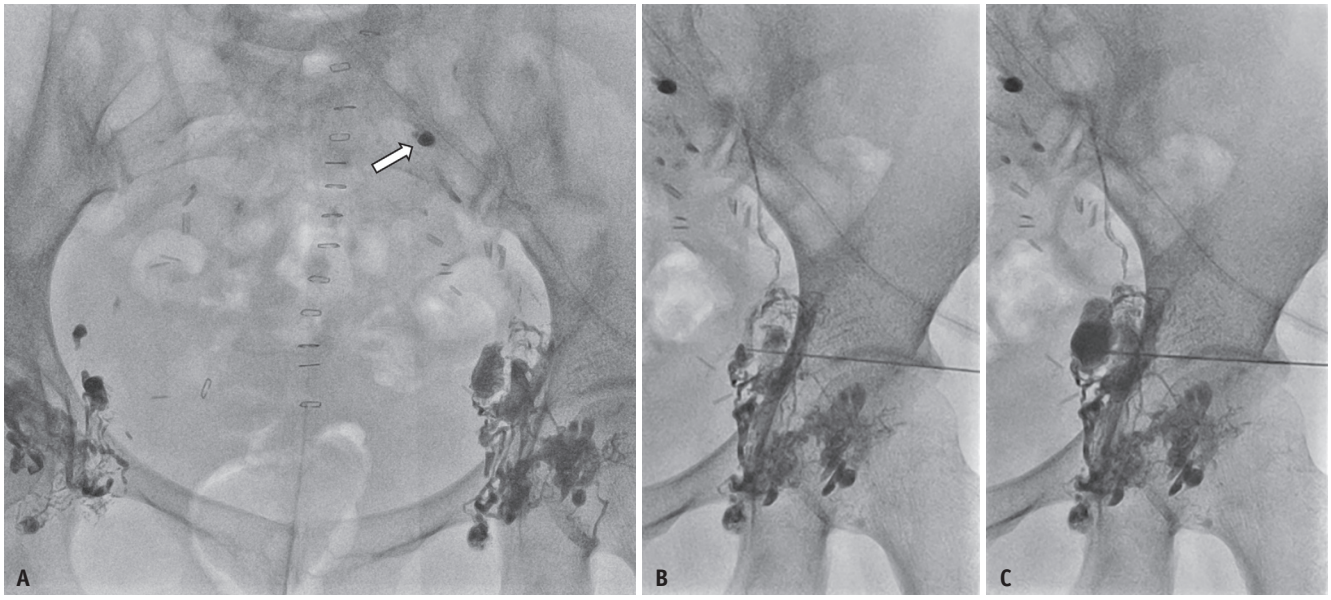

Fig. 16. A 56-year-old female with lymphatic ascites after radical surgery for cervical cancer.
A. Intranodal lymphangiography reveals a lymphopseudoaneurysm in the left iliac lymphatic chain. Lipiodol droplets (arrow) are noted in the iliac vein, resulting from the shunting of Lipiodol through a pre-existing lymphovenous shunt. Lymph node embolization may lead to inadvertent glue migration into the systemic venous system, and subsequently into the pulmonary arteries. **B.** The lymphopseudoaneurysm is directly accessed with a fine needle under fluoroscopic guidance. Successful access was confirmed by aspirating the Lipiodol content in the lymphopseudoaneurysm. **C.** Concentrated glue (N-butyl cyanoacrylate:Lipiodol = 1:1 mixture) was injected through the needle until it filled the lymphopseudoaneurysm.

lymphopseudoaneurysm into the inflow channel [10,17]. In theory, strategies that interrupt lymphatic inflow should be more effective than lymphopseudoaneurysm embolization. However, this theory should be tested in the future through well-constructed prospective investigations.

Complications of Lymphatic Intervention

In 1968, a survey investigating complications arising from 32000 cases of pedal lymphangiography reported 104 cases of pulmonary complications (excluding asymptomatic cases of Lipiodol pulmonary embolism), 97 cases of hypersensitivity reactions associated with the use of blue dye or Lipiodol, nine cases of cerebral complications, six cases of hypotension, and 18 deaths [79]. After the introduction of intranodal lymphangiography in 2011, complications arising from pedal procedures such as dye-related hypersensitivity and surgical wounds were no longer an issue. Intranodal injection may be complicated by extravasation of Lipiodol in the perinodal soft tissues, but this has never been associated with significant adverse effects. The only significant complication related to intranodal lymphangiography was associated with Lipiodol, which contains iodine. As with many of the widely used agents, iodine-based, water-soluble contrast agents, hypersensitivity reactions, and hypothyroidism are listed among the adverse effects of Lipiodol.

Lipiodol in the lymphatic system flows with the lymph and drains into the central venous system. Lipiodol reaches the lungs in small amounts and rarely causes severe symptoms. It is uncertain how much Lipiodol is retained in the lymphatic system and what proportion of it flows into the systemic vein. Previous publications have reported significant pulmonary complications (such as lipoid pneumonia, pulmonary edema, hemoptysis, and pulmonary infarction) when > 20 mL of Lipiodol was used [79-83]. Therefore, it is recommended that the total dose of Lipiodol should be maintained below this amount. Unfortunately, when such pulmonary complications occur, patients are most likely to recover with conservative management.

Cerebral oil embolism has also been reported to occur within minutes to hours following lymphangiography. The clinical manifestations include convulsions, delirium, lethargy, and altered consciousness. The diagnosis is based on imaging features of cerebral infarction on CT or MRI. Since it is not possible to trace the movement of Lipiodol from the lymphatic system to the cerebral vascular system during the procedure, it remains to be elucidated how Lipiodol reaches cerebral circulation. The

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presence of right-to-left shunts in the heart and pulmonary arteriovenous malformations has been proposed as a plausible explanation. Another explanation is that excessive amounts of Lipiodol in the lungs may flow through the lung capillaries and into the pulmonary vein to reach the systemic arterial system. Once in the brain, Lipiodol has the potential to occlude vessels, destroy the blood-brain barrier, or have a direct cytotoxic effect in the brain.

More rarely, there have been reports of oil embolization in the liver and kidney, which are postulated to occur only in the presence of abnormal pathologies such as tumors that allow Lipiodol to shunt into these systems [84]. The examiner should always be aware of possible lymphovenous shunts through which large amounts of Lipiodol may preferentially flow into the systemic vein before filling the lymphatic system. Lipiodol flow should be observed under real-time fluoroscopy during the injection. Access through another lymph node should be sought if excessive shunting is observed. For safety, the total dose of Lipiodol per session should be limited to 20 mL in adults and 0.25 mL/kg in pediatric subjects [85,86].

Penetration of abdominal organs is unavoidable when performing transperitoneal embolization. Fortunately, bleeding or infection rarely occurs with fine needles such as the 21-gauge Chiba needle. Safety precautions include preprocedural assessment with CT to rule out the presence of unexpected anatomy or pathology that may increase the risk of bleeding. Despite the low incidence of complications from transperitoneal needle access, the authors preferred to avoid needle paths that may cross the aorta or colon. If penetration of the colon cannot be avoided, empirical antibiotic therapy may help prevent abdominal infection [87]. In any case, the patient should fast before the procedure to clear the gastrointestinal system. One complication to note is bile peritonitis resulting from gallbladder penetration [63,87,88]. Therefore, it is recommended that the gallbladder be avoided when performing transperitoneal access, especially when distended.

Lymphedema is uncommon after embolization owing to the presence of multiple collateral pathways. When they develop, they are often transient. A previous surgery that compromises lymphatic drainage may predispose patients to lymphedema. Furthermore, extensive embolization may result in lymphedema. One study reported a complication rate of 14.3% after TDE, including transient abdominal pain, chronic diarrhea, peripheral lymphedema, and PLE [89]. Complications of TDE may be conservatively managed by fasting and restricting the fatty diet until sufficient collateral pathways develop. Despite the general notion that thoracic duct interruption (including surgical ligation and embolization) is safe, the thoracic duct represents the most important final pathway of the lymph to the systemic venous system. If in any doubt, selective embolization of pathologic side branch vessels may be considered [14]. With leg edema resulting from lymphatic embolization, conservative treatment, including massage therapy, compression stockings, and lifestyle modifications, may improve the patient's symptoms. Recently developed surgical techniques, including lymphovenous shunt creation and lymph node transplantation, are still being investigated.

CONCLUSION

Significant strides have been made over recent years in the field of lymphatic imaging and percutaneous treatment. New tools and techniques should be utilized because of their utmost potential in diagnosing and classifying lymphatic disorders. Such efforts will not only help improve our general understanding of lymphatic disorders but will also help in developing a common treatment strategy. Techniques for intranodal lymphangiography and TDE are the foundation of numerous embolization techniques developed in recent years to address lymphatic leaks and reflux disorders. Additional routes for percutaneous access to the lymphatic system, including the terminal thoracic duct and liver, have helped expand the indications for lymphatic embolization. Ongoing research, technical refinements, and the development of new techniques are anticipated in the future.

Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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