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Techniques in Vascular and Interventional Radiology

# Complex Lymphatic Anomalies and Therapeutic Options

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**Complex lymphatic anomalies include a variety of disorders with overlapping clinical, histological and imaging features. The often-confusing nomenclature used for lymphatic anomalies limits timely diagnosis and treatment. The updated 2018 classification of the International Society for the Study of Vascular Anomalies divides lymphatic anomalies into several subsets.[1] Newer imaging techniques including intranodal and magnetic resonance lymphangiography have improved our understanding of anatomy and function of the lymphatic system. Advances in medical, interventional, and surgical treatments have opened a realm of new therapeutic options for patients with complex lymphatic disorders.**


**KEYWORDS** Lymphatic, lymphangiography, lymphatic leak, lymphatic flow

## Introduction

The principal function of the lymphatic system is to drain interstitial fluid from soft tissues and return it to the circulation.[1,2] The system initially develops as blind ending sacs, which coalesce to form a delicate plexus of vessels. These peripheral lymphatics drain into filtering nodes and then into central lymphatic channels, including the cisterna chyli. Chyle is a mixture of lymph and chylomicrons absorbed from the intestine. This mixes with clear lymph from the pelvis and lower extremities and empties into the thoracic duct. The thoracic duct drains lymph from the entire body, except for the right upper extremity and chest, and the right side of the head and neck, which drain via the right lymphatic duct.

Obstruction or dysfunction of the lymphatic system can result in expansion of the interstitial spaces with lymph, leading to lymphedema, or leakage from the central channels, manifesting as pleural effusions and ascites. Depending on the site of obstruction, the fluid may be clear lymph or chylous. Chylous leaks imply leakage from the thoracic duct but may also be seen caudal to the cisternal chyli as a result of chylous reflux.[3] The type of fluid leak can be confirmed by aspiration. A high lymphocyte count will be seen in both, while milky white fluid with a high triglyceride level is consistent with chyle.

In the updated 2018 International Society for the Study of Vascular Anomalies classification,[4] lymphatic malformations (LM) are subdivided into common (cystic) LM or a variety of other conditions, including generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA), Gorham-Stout disease (GSD), channel-type LM (synonymous with central conducting lymphatic anomaly (CCLA)), lymphedema, and "others."

### Gorham-Stout Disease

Initially described by Jackson in 1838 as "disappearing bone syndrome," GSD is a disorder of progressive osteolysis.[5] Possible hypotheses include bone loss secondary to proliferation of thin walled sinusoidal lymphatic channels or periosseous expansion of lymphatic channels leading to progressive loss of cortical bone.[3] The disease can be rapidly progressive but can also spontaneously stabilize. GSD is typically regional in distribution, involving adjacent bones, and is much more common in the axial skeleton.[5] Associated lymphatic leaks can also be seen. Pleural effusions can develop due to involvement of the thoracic bones, or be iatrogenic, such as after biopsy of an involved rib. The diagnosis of GSD is usually established by imaging. The key imaging feature is

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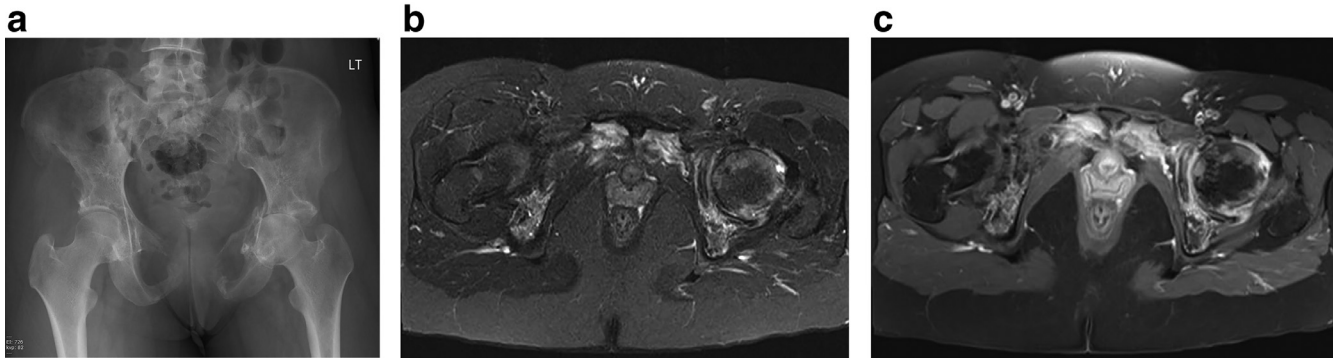


**Figure 1** Nineteen-year-old female with Gorham-Stout disease. (a) AP radiograph of the pelvis. There is resorption of the superior and inferior pubic rami bilaterally, with erosive changes also seen in the acetabula and right iliac wing (b) axial T2 fat-saturated (FS) MRI sequence. High signal is seen in the soft tissue surrounding the area of osteolysis, (c) postgadolinium T1 FS MRI. Avid enhancement is seen in the areas of osseous and soft tissue abnormality.

cortical bone loss, and serial studies can demonstrate progression of osteolysis (Fig. 1). Periosseous infiltrative soft tissue is seen in the majority of patients,[5] which is bright on fluid-weighted magnetic resonance imaging (MRI) sequences with intense enhancement after administration of contrast.

The mainstay of treatment of GSD is medical therapy, with the aim to stabilize disease and minimize complications. The most described regimen is interferon-alfa 2a or 2b, often in combination with bisphosphonates, but there has been recent encouraging data with the use of sirolimus.[6-8] Interventional treatment is currently limited to procedures to alleviate symptoms or complications, most commonly pleural and peritoneal drainage and pleurodesis.

## Generalized Lymphatic Anomaly

Formerly termed as "lymphangiomatosis," GLA is a multifocal lymphatic disorder.[5] Osseous disease is commonly seen, with focal lytic lesions in multiple bones, typically without a sclerotic margin (Fig. 2). In contrast to GSD, there is no infiltrative periosseous soft tissue mass, loss of cortical bone or progressive osteolysis.[5] The number of bones involved in GLA are greater, and are often noncontiguous or remote. Visceral organ involvement, particularly splenic cysts, and macrocystic LM, are more common in GLA than GSD. The ribs are the most common site of involvement in GLA, followed by the spine. Biopsy of ribs should be avoided as it can lead to refractory iatrogenic pleural effusion.[3] Lesions are also commonly seen in the appendicular skeleton. The natural history of the disease is variable, but there are commonly long periods of stability. Vertebral compression fractures are sometimes seen due to weakening of the involved bone, but other sites of pathologic fracture are uncommon. The osseous changes are best appreciated on computed tomography, but MRI is required for accurate assessment of bone marrow changes and soft tissue involvement.[5]

Primary therapy for GLA has been interferon with or without bisphosphonates, but there have also been recent reports of response to sirolimus.[8,9] Interventional treatment is aimed at providing symptomatic relief, with drainage, pleurodesis, and sclerotherapy. Shunting of ascites into the venous circulation (eg, Denver shunt) is temporizing, with high likelihood of the shunt clogging, and with associated risk of bacteremia/septicemia. A case report of a modified Denver shunt procedure describes connecting a large lymphatic cyst with the peritoneal cavity, resulting in resolution of lymphorrhea.[10]

Many conditions with diffuse lymphatic disease have been termed as GLA, but the increased use of lymphangiography has led to recategorization of some of these as CCLAs or KLA.

## Central Conducting Lymphatic Anomalies

CCLA is characterized by distension of central lymphatic channels secondary to dysmotility or distal obstruction.[3] The ensuing lymphatic hypertension can result in leakage from lymphatic channels. The fluid is most commonly chylous, reflecting disruption of channels superior to the cisterna chyli. The inadequate clearing of lymph results in reflux, which may also manifest as pulmonary lymphangiectasia, protein-losing enteropathy, cutaneous vesicles, or superficial

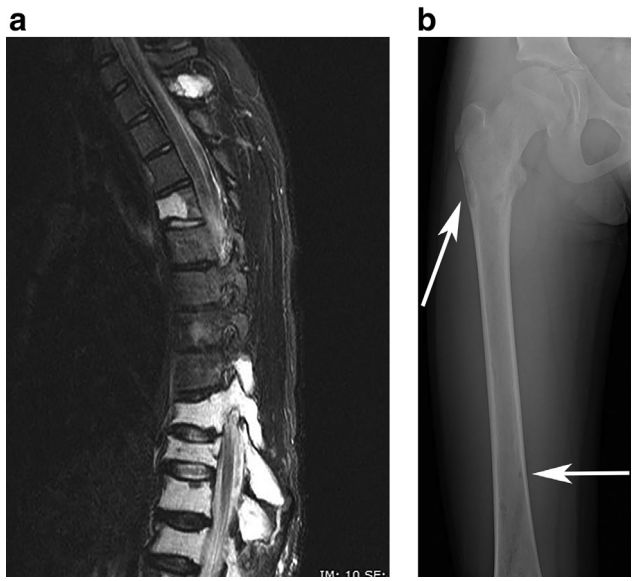


**Figure 2** Ten-year-old girl with generalized lymphatic anomaly. (a) Sagittal STIR MRI of the spine. Multiple thoracic and lumber vertebrae are involved, some with associated compression fractures. (b) X-ray of the right femur. Multiple discrete lytic lesions are seen in the right femur (arrows) with preservation of the surrounding cortex.

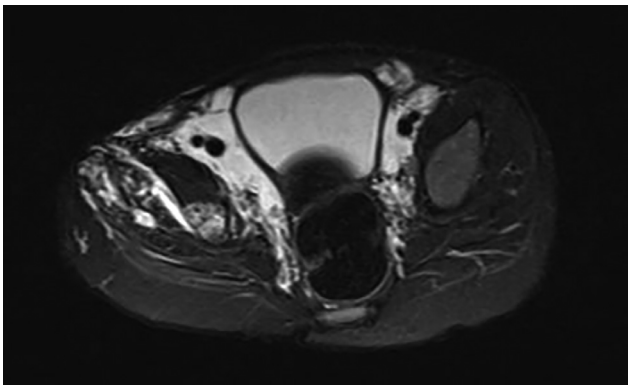

**Figure 3** Three-year-old boy with CCLA. Axial T2 fat-saturated MRI sequence. Perivascular high-signal soft tissue is seen in the pelvis, with infiltration of the surrounding muscles and soft tissue on the right.

chylous leaks.[3,11] Osseous changes are also be seen in CCLA due to reflux of chyle into bone. In contrast to GLA, the bone is more diffusely involved, with an almost permeative appearance due to dilated intraosseous channels.[9]

The diagnosis may be suggested on MRI by the presence of congested-appearing high-signal tissue on fluid-weighted sequences around the iliac vessels and aorta (Fig. 3). However, the diagnosis is best established by conventional or MR lymphangiography. The lymphangiogram may demonstrate global dysmotility of the lymphatic channels reflecting a more functional etiology, or obstruction/abnormal anatomy of the terminal portion of the thoracic duct.[12] Differentiating a functional disorder from a primarily obstructive one is essential as the latter condition may be amenable to microsurgical reimplantation of the terminal thoracic duct into another intrathoracic-valved vein.[13] If a focal leak is identified on lymphangiography, it can potentially be treated by direct puncture and embolization.

## Kaposiform Lymphangiomatosis

KLA is a complex lymphatic anomaly that exhibits features of both neoplasia and malformation.[14] It has overlapping clinical and imaging features with CCLA and GLA, but can be differentiated histologically.[15] The histopathology demonstrates a combination of malformed lymphatic channels with focal areas of proliferative spindle cells. Sequencing of the tissue has recently identified a somatic activating NRAS variant, as seen in a growing group of vascular tumors and malformations.[16] Clinically, thrombocytopenia, hemoptysis, and the presence of hemorrhagic pleural effusions should suggest this diagnosis.

On imaging, as in CCLA, there is dilated/congested perivascular soft tissue that is hyperintense on fluid-weighted MRI sequences. Chylothorax and splenic cysts are also seen. However, thoracic involvement in KLA is much more extensive, with mediastinal disease seen in almost all patients.[15] Soft tissue that is hyperintense on fluid-weighted MRI sequences is seen in the mediastinum, extending to the hila and along the bronchovascular bundles. After administration of gadolinium, there is enhancement of this soft tissue, which helps to differentiate it from CCLA (Fig. 4). The

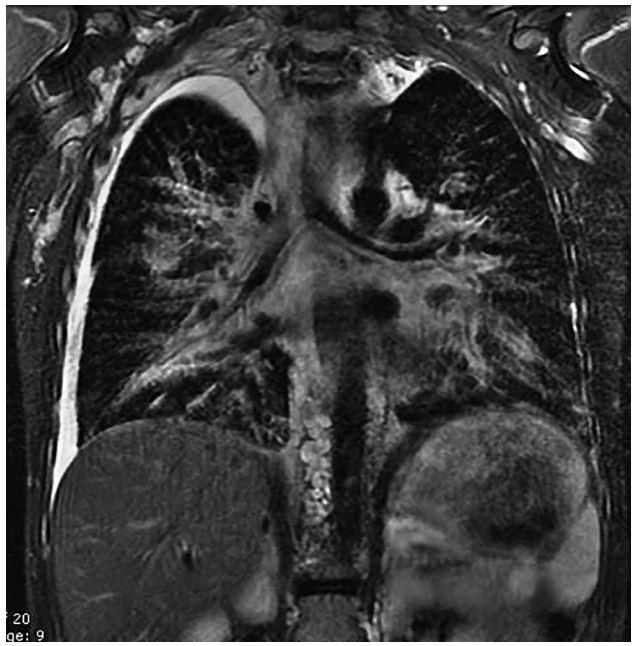

**Figure 4** Fourteen-year-old girl with KLA. Coronal T2 image of the chest. Hyperintense soft tissue is seen in the mediastinum extending along the bronchovascular bundles. There are bilateral pleural effusions and a tortuous dilated thoracic duct.

lymphangiographic findings of KLA are very similar to CCLA, with abnormal contour of the thoracic duct, dilated central channels, and evidence of reflux.

The osseous imaging appearances of KLA overlap with that of GLA and CCLA, with multiple noncontiguous lytic lesions sparing the cortex. The vertebral bodies are the most common sites of bony involvement. In contrast to GLA, infiltrative periosseous soft tissue is commonly seen in KLA.[15]

The natural history of the disease reflects its aggressive nature, with a 5-year survival rate of 50%. However, early evidence suggests that the outlook is significantly improved with the use of sirolimus, with most patients achieving disease stability.[17] Currently, interventional and surgical treatments are largely palliative. Drainage, pleurodesis, or sclerotherapy can be performed for symptom control. Symptoms related to reflux may be improved by embolization and surgical diversion.

## Lymphangiography Technique

### Preprocedural

The indication for the procedure and all cross-sectional imaging should be reviewed. In our practice, the majority of the procedures are performed for evaluation of CCLA/KLA, with the remainder for assessment and treatment of spontaneous or iatrogenic lymphatic leaks. Any prior history of surgical or interventional procedures should be noted. There are very few absolute contraindications to conventional lymphangiography, beyond allergies to any of the agents to be used.[18] Patients with suspected right to left cardiac shunt should have an echocardiogram performed, and if proven, ethiodized oil should not be used as a contrast agent due to risk of systemic arterial embolization.[12] If thoracic duct embolization is planned, preprocedure antibiotics should be administered.

If there is suspected venous obstruction of the thoracic duct, bilateral upper extremity intravenous catheters are placed.

## Procedure Technique

Bilateral inguinal regions and upper thighs are prepped. The left upper chest and neck are also prepped to allow sonographic evaluation of the terminal portion of the thoracic duct. If there is potential for cannulation of the thoracic duct, the entire abdomen should be prepped. Tubes and catheters overlapping the expected course of the thoracic duct are removed. Spot images of the chest, abdomen, and pelvis are taken.

In cases of suspected venous obstruction, central venography is performed via simultaneous injection into bilateral upper extremities.

Using a high-frequency transducer, inguinal lymph nodes are accessed along the long axis bilaterally (Fig. 5). A 22-25 gauge hypodermic needle connected to a 3 mL syringe via a short extension tubing and primed with contrast is used. The needle should be advanced to at least the junction of the node cortex and medulla. Some authors caution against advancing into the hilum to avoid contrast injection into the lymph node vein, but secure access in the node is paramount. Care should be taken to avoid through and through puncture, as this will invariably lead to extravasation. The needle and tubing are secured with steri-strips. Fluoroscopy is then used to confirm intranodal positioning, as evidenced by filling of efferent lymphatic channels. If there is evidence of extravasation, the site should be abandoned, and a different node accessed.

A slow rate of injection is essential to avoid extravasation. The exact rate is determined by the size of the node but should average around 1 mL every 5-10 minutes. Some authors prefer to use a variety of injector devices to ensure a steady rate of injection.[18] We use an upper dose limit of 0.25 mL/kg of ethiodized oil, with the total dose limit not to exceed 10 mL.

Intermittent fluoroscopy is then used to confirm progression of contrast. If the maximum dose of iodized oil has been used, the contrast can be flushed forward with saline. This may also expedite the flow of ethiodized oil. Fluoroscopy cine clips should be stored to document the dynamic flow of contrast, with occasional spot images.

If there is stasis of contrast in the abdomen and pelvis with lack of opacification of the thoracic duct, abdominal massage can be used to propagate contrast. Fluoroscopy of the chest should be performed during the massage to document filling and emptying of the thoracic duct. Particular attention should be directed to the terminal portion of the thoracic

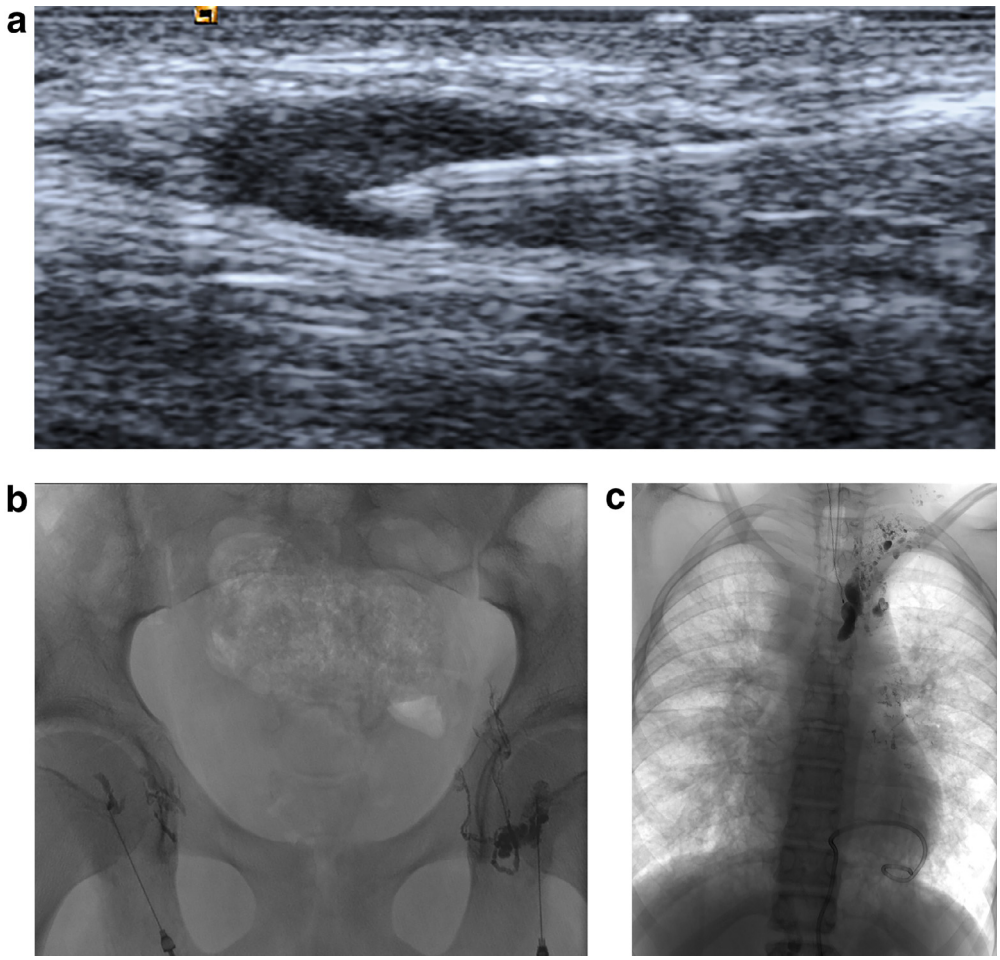


**Figure 5** Fourteen-year-old with CCLA. (a) A superficial inguinal lymph node is accessed using a 25-gauge hypodermic needle. (b) Opacification of efferent lymphatic channels is seen bilaterally, (c) There is an aperistaltic, dilated thoracic duct with reflux into pulmonary, pericardial, and supraclavicular lymphatic channels.

duct. Note should be made of signs of ectasia, reflux, crossing, collateralization, lymphaticovenous shunts, obstruction, leak, slow flow, poor peristalsis of thoracic duct, and drainage via the cervical potion.

Sonography of the terminal portion of the thoracic duct via a supraclavicular approach can be very useful in demonstrating poor emptying and reflux. The echogenic ethiodized oil is readily identified emptying at the venous angle between the left internal jugular and subclavian veins.

The needles are removed at the end of the procedure. No dressings are required and there are no postprocedure restrictions.

If direct thoracic duct access is planned, the image intensifier should be angled at 15°-20° craniocaudal to provide an end-on view. A 21-gauge needle is then advanced into the cisterna chyli or another targeted duct. Curving the needle can sometimes be helpful in ensuring a shallower access into the channel. Preloading the needle with a stiff 0.018" guidewire can reduce the possibility of losing access during attempted guidewire placement. We typically use a V18 Control guidewire (Boston Scientific, Natick, MA) for this purpose. If the duct cannot be accessed, repeat punctures can be made or another site selected. In the case of chylous leaks, thoracic duct disruption alone may be enough to terminate leakage. If the leak is in the pelvis or retroperitoneum, embolization can also be attempted by direct injection of glue (diluted to 1:3 or 1:4) into the lymph nodes.[19]

Once the guidewire has been advanced into the thoracic duct, the needle is exchanged for a microcatheter. Water-soluble contrast is injected to confirm access. If a leak is identified, the duct can be embolized using coils. We most commonly use Interlock 0.018" coils for this purpose (Boston Scientific, Natick, MA). The embolization can then be completed with injection of *n*-butyl cyanoacrylate diluted into a 1:1 or a 1:2 mixture with lipiodol. If embolizing with *n*-butyl cyanoacrylate glue only, care should be taken not to dilute the glue further as the polymerization in chyle is much slower than in blood, leading to risk of venous embolization. The catheter is then removed rapidly while aspirating.

### Adverse Events

Complications of lymphangiography alone are uncommon. Hypersensitivity reactions can occur to any of the agents used in the study. In the absence of an intracardiac right to left shunt, cerebral embolization of ethiodized oil is rare. Oil embolization to the lungs can in rare instances result in hemoptysis.[12,18,20] Potential complications of thoracic duct access include hematoma and bile leaks. Attempted thoracic duct embolization can be associated with nontarget embolization of glue and shearing of the guidewire or catheter.

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