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LYMPHATIC SYSTEM: A FORGOTTEN AREA?

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Development of new methods of visualization of the lymphatic system and in the treatment of several pathologies associated with impaired lymph flow. The lymphatic system is an integral part of the circulation. One of the main functions of the lymphatic system is to transport residual interstitial fluid from the tissue back to the venous system. Despite growing recognition of the role of the lymphatic system in many disease processes, the techniques for imaging and interventions on the lymphatic system have lagged behind the well-developed methods for imaging and interventions on the cardiovascular systems. This is primarily due to small size and variability in anatomy of the lymphatic vessels, and difficulty of introducing contrast into lymphatic ducts. Due to lack of imaging and intervention options, the flow function of the lymphatic system was relatively ignored over the last few decades. Recently, there has been resurgence in the interest in the flow function of the interventions on the lymphatic system with the development of percutaneous minimally invasive techniques, such as thoracic duct embolization, to treat life threatening lymphatic leaks. Our group recently introduced two new methods of lymphatic imaging: intranodal lymphangiography and dynamic contrast MR lymphangiography. These methods have allowed further understanding of lymphatic anatomy, pathophysiology, lymphodynamics, as well as provided guidance for novel minimally invasive lymphatic interventions. Using new techniques, the group discovered the causes and then developed treatments for several fatal conditions effecting single ventricle patients including plastic bronchitis and protein losing enteropathy. Treatment for other conditions has evolved as well including congenital lymphodysplasia, chylothorax, and chylous ascites. The study of the liver lymphatic system has been little explored despite its significant relevance as exemplified in ascites formation in association with cirrhosis, one of the most recognized clinical manifestations of lymphatic vascular system disorders. Liver lymphangiogram is an additional minimally invasive technique that allows visualization of the liver lymphatics. Embolization of the liver lymphatic system has been proven to be curative for liver lymphorrhea. Due to the lack of the imaging ability of the lymphatic system the understanding of these relationships lacked. Intranodal lymphangiogram, and liver lymphangiograms are one of the first steps in attempt to understand these relationships. Embolization of the lymphatic system provides the opportunity to treat the abnormal lymphatic flows in conditions such as pulmonary lymphatic perfusion syndrome, liver cirrhosis, cardiac failure.

Key words: lymphatic system, imaging, interventions, lymphatic ducts, minimally invasive techniques, lymphangiography, MR, plastic bronchitis, enteropathy, liver lymphorrhea.

NEW LYMPHATIC IMAGING MODALITIES

Intranodal lymphangiogram

Pedal lymphangiogram has been the mainstay for lymphatic imaging over the last few decades. However, dissection and cannulation of pedal lymphatic vessels require a degree of expertise that may not be available in all contemporary radiology departments. Pedal lymphangiogram equipment, such as a lymphangiogram pump, is not currently manufactured and cannot be found in some radiology departments. Even after successful placement of lymphangiogram needles, minimal movement of the patient can dislodge the needles.

Given the technically challenging nature of pedal lymphangiogram, Nadolski et al described an alternati-

ve lymphatic imaging technique – Intranodal Lymphangiogram [1]. The authors showed that there is an easier and more practical way to opacify central lymphatic channels leading to the cisterna chili. Simple ultrasound-guided puncture of a readily accessible lymph node in the groin can be used to opacify the lymphatic system. This task is well within the skill set of most interventionalists trained today. Moreover, the new technique appears to be safer and faster than the older method. A shallow angle for puncture was used to create a long subcutaneous tract to assist in stabilizing the needle. The needle tip was positioned in the center of the node. Under fluoroscopic guidance, lipiodol (Guerbet LLC, Bloomington, IN) was injected at approximate rate of 2 mL per 5 minutes by hand. Initial injection was ob-

served under fluoroscopy to confirm proper positioning of the needle. A lymph node in the contralateral groin was accessed using the above-described technique. A total volume of approximately 3–6 mL of lipiodol was injected into each lymph node.

Dynamic Contrast Enhanced MR Lymphangiogram (DCRML)

One of the main obstacles in contrast enhanced lymphatic imaging is the difficulty of introducing the contrast agent into the lymphatic vessels [1]. Dori et al recently described the MR imaging method that utilizes intranodal lymphangiogram for delivery gadolinium contrast material for dynamic imaging of the lymphatic system [2]. The main technical challenge however is need to introduce the needles in the inguinal lymph nodes outside the MR machine using US guidance and then transport the patient into MR suite. XMR suite couples an MR scanner with a catheterization lab (Siemens, Erlangen, Germany) and ultimately built for this purpose. In this set up the needles are introduced in the cath lab and then the patient is transferred to MR on the same table, thus minimizing the chance of the dislodgement of the needles. DCRML allows almost complete visualization of the lymphatic system including the dynamic component and distribution of the lymphatic flows. Using DCRML allowed us to understand pathophysiology of condition such plastic bronchitis, idiopathic chylothorax and pulmonary lymphangiomatosis.

Below is the short description of the technique.

Using ultrasound guidance, bilateral inguinal lymph nodes (LN) were directly accessed with 25-gauge spinal needles attached to a short connector tubing (BD Medical, Franklin Lakes, New Jersey), similar to the method described by Nadolski et al [1]. A small amount of Lipiodol (Guerbet LLC; Bloomington, IN) or Omnipaque (GE Healthcare, Mickleton, NJ) was injected under fluoroscopic guidance to confirm the correct position of the needles inside the lymph nodes. After stabilizing the needle, the patients were transferred into the MRI suite. MR was performed on a 1.5 T Siemens Magnetom Avanto scanner (Siemens, Erlangen, Germany). MR lymphangiogram imaging technique was performed as described in details by Doriet al [3]. It included T2W sequence for identification of the lymphatic masses. T2W imaging was followed by injection of 2–8 cc of undiluted gadopentetate dimeglumine (Magnevist, Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ) and dynamic imaging using syngo time-resolved angiography with stochastic trajectories [TWIST] sequence. A delayed imaging using high-resolution navigator gated 3D flash IR sequence was then used to determine final details of contrast distribution in the lymphatic system. In all patients the scan area covered the neck, chest, and abdomen as caudally as feasible. Volume rendering and

further processing of the 3D volume, MIP and coronary reconstructions were performed on a Syngo InSpace Dynamic workstation (Siemens, Erlangen, Germany).

NEW INTERVENTIONAL TECHNIQUES ON THE CENTRAL LYMPHATIC SYSTEM

Thoracic Duct Embolization

TDE is the brainchild of one of the fathers of Interventional Radiology, Dr. Constantine Cope. An experienced lymphangiographer and interventional radiologist, Cope envisioned TDE as a minimally invasive alternative to TD ligation as a treatment of chylothorax [4, 5]. The treatment consists of lymphangiography followed by transabdominal catheterization of the CC or its tributaries and embolization of the TD/CC proximal to the leak or occlusion. This technique became the main approach for treatment of chylothorax including patients with idiopathic chylothorax. Below is a short description of the technique: Initially, the lymphographic dye progresses slowly through the network of pelvic and retroperitoneal lymphatic vessels to approximately the L1–L2 level. At this level, the lymphatic ducts quickly lose their definition and clarity, an indicator of lymph inflow from intestinal and hepatic lymphatics. To prevent chyle leakage from an access point in the CC, we recommend accessing the TD below this inflow point, through one of the lumbar lymphatic ducts (preferably the right). Even though it is more challenging to cannulate a lumbar lymphatic duct due to its small size, this difficulty is offset by its more constant and defined appearance during lymphangiography. When a target duct is identified, cannulation is performed using 21- or 22-gauge 15- to 20-cm Chiba needle (Cook Inc., Bloomington, IN) and fluoroscopic guidance. After identification of the cause of chyle leakage (extravasation or obstruction), embolization of the TD is performed proximally. First, coils are placed to provide a matrix for glue polymerization. Next, a maximum of 0.2 mL of D5W is used to flush the catheter to prevent intracatheter glue polymerization diluted 1:1 in Ethiodol is the used for embolization (Fig. 1).

PULMONARY LYMPHATIC PERFUSION SYNDROME

Pathological changes of the pulmonary lymphatic system of the lungs have been known since 1895 reported by Virchow, who described lymphatic cysts in the lung of the child on postmortem examination. Since then similar postmortem findings were reported by multiple author [6, 7]. With the development of first lymphatic imaging modality, pedal lymphangiogram, several authors described the phenomenon of lymph flowing from the thoracic duct toward lung parenchyma and termed it «lymphatic reflux» [8]. The understanding of the ex-



Fig. 1. Fluoroscopic image of thoracic duct embolization, demonstrating contrast extravasation (black arrow) from thoracic duct (black arrowhead)

tent of abnormal pulmonary lymphatic flow has been limited due to difficulty of high viscosity of oil based contrast agent (Lipiodol) to propagate into small lymphatic vessels. Recent development of the Dynamic Contrast Enhanced MR Lymphangiogram (DCMRL) allowed better visualization of the lymphatic vessels due to better distribution of the less viscous gadolinium imaging agents and higher tissue contrast resolution of the MR, thus allowing to better understand the extent of the abnormal lymphatic flow [3]. This improved distribution of contrast into soft tissue allow us to observe that contrast not only flows retrograde in the lymphatic vessels, but penetrates deeper in the soft tissue, creating the visual impression of lymphatic enhancement of the tissues that we termed «Pulmonary Lymphatic Perfusion Syndrome (PLPS)» (Fig. 2) [2].

PATHOPHYSIOLOGICAL MECHANISM

From eight to ninety percent of the lymph in the body is generated below the diaphragm in the abdomen primarily in the liver and intestine [9]. The lymphatics from the liver, intestine and soft tissue then converge together in the cisterna chyli that conducts the lymph further into thoracic duct that in turn discharges the lymph into venous system in the area of the junction of left jugular and subclavian vein. Traversing through the mediastinum, thoracic duct accepts lymphatic tributaries from the mediastinal organs, such as heart, esophagus and lungs. In the patients with PLPS, part of the lymph, flows retrograde from the thoracic duct toward lung parenchyma, mediastinum through the aberrant lymphatic vessels. We hypothesize that these vessels developed as a decompression mechanism to in utero occlusion/stenosis/compression of the downstream parts of the thoracic lymphatic system (Fig. 3).



Fig. 2. DCRML imaging of the patients with PB: a – normal TD (white arrow) with no pulmonary lymphatic flow in Patient 6; b – abnormal TD with abnormal pulmonary lymphatic flow toward left hilum and lung in Patient 3 (black arrow); c – bilateral abnormal pulmonary perfusion in Patient 5 (black arrowhead)

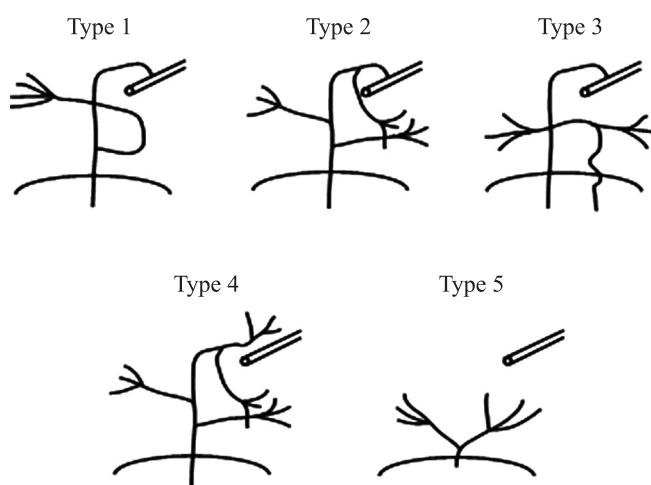


Fig. 3. Five types of the pulmonary lymphatic perfusion syndrome [2]

It is possible that majority of these anatomical variants don't present clinically. The clinical presentation happens when these lymphatic vessels abut serous and mucosal surfaces such as pleural (chylothorax), pericardial (chylopericardium) and bronchi (plastic bronchitis and chyloptosis) [10]. The beginning of the symptoms can be provoked by silent trauma that would result in rupture of these lymphatic vessels; a severe upper respiratory infection, that can cause the injury of the bronchial lining and cause lymphatic plastic bronchitis in adult patients (Itkin in press). In patients with congenital cardiac diseases with significant right sided heart failure, the increase of the lymphatic production can result in overdistention of the lymphatic vessels and result in plastic bronchitis or chylothorax [2].

CLINICAL PRESENTATION OF THE PLPS

Clinical presentation of PLPS encompasses the range of the ages starting from newborns (neonatal chylothorax) to older adults as chylothorax or plastic bronchitis.

Neonatal chylothorax

Neonatal chylothorax is the condition that is most often diagnosed in utero by US as a pleural effusion and 90% of all pleural effusions in utero are chylothorax [11]. To prevent the underdevelopment of the lung parenchyma by pleural effusion the drainage of the pleural space is performed by placing the thoracoamniotic shunts [12].

In our practice all newborns with neonatal chylothorax are undergo DCRML. Typical findings on DCRML are complete occlusion of the midthoracic duct and development of abnormal pulmonary lymphatic flow. It is very important to differentiate isolated chylothorax and chylothorax that present with chylous ascites and tissue edema. The latter condition is called congenital

lymphatic dysplasia and is caused by general dysplasia of the lymphatic system and is one of the most difficult neonatal conditions to treat.

We usually perform intranodal lymphangiogram immediately following the MR lymphangiogram. The lymphangiogram in these children is performed using intranodal lymphangiogram technique that is previously described [1]. However, it is very important to not inject too much contrast material, because the same way as it close the leaks it can block the lymphatic vessels resulting in generalized edema. Typical findings on the lymphangiogram is occlusion are collaborate with the findings on the DCRML are complete occlusion of the thoracic duct in middle mediastinum and retrograde flow of the contrast in the lung parenchyma.

The rate of the chylothorax leak in these patients is often very slow within tens of the milliliters and for that reason lymphangiogram is both diagnostic and curative and in most cases there is no need to perform thoracic duct embolization [13].

Idiopathic chylothorax/chylopericardium

We define the idiopathic chylothorax/chylopericardium as a condition in which the patient presents with chylothorax/chylopericardium while not suffering any other conditions, such as remote trauma, systemic diseases and malignancies.

It can present in any age and split equal between the sexes. In the past the understanding of the cause of the chylothorax was not clear and pedal lymphangiogram was one of the main diagnostic modalities. Since the development of the DCRML provide us with insight in the understanding of the cause of the idiopathic chylothorax.

Careful clinical history in these patients usually discovers that these patients had past history of pulmonary diseases, such as unexplained chronic productive cough. In some cases, past clinical symptoms resemble symptoms of plastic bronchitis. The diagnostic workup in this patients starts with DCRML where the typical PLPS findings such as occlusion/stenosis of the upper part of the thoracic duct with retrograde flow of the contrast toward lung parenchyma.

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

Plastic bronchitis

Plastic bronchitis is a condition in which children or adults expectorate cast of their lungs.

It is most commonly associated with congenital heart diseases such as in children with single ventricle who underwent Fontan palliative procedure. In these

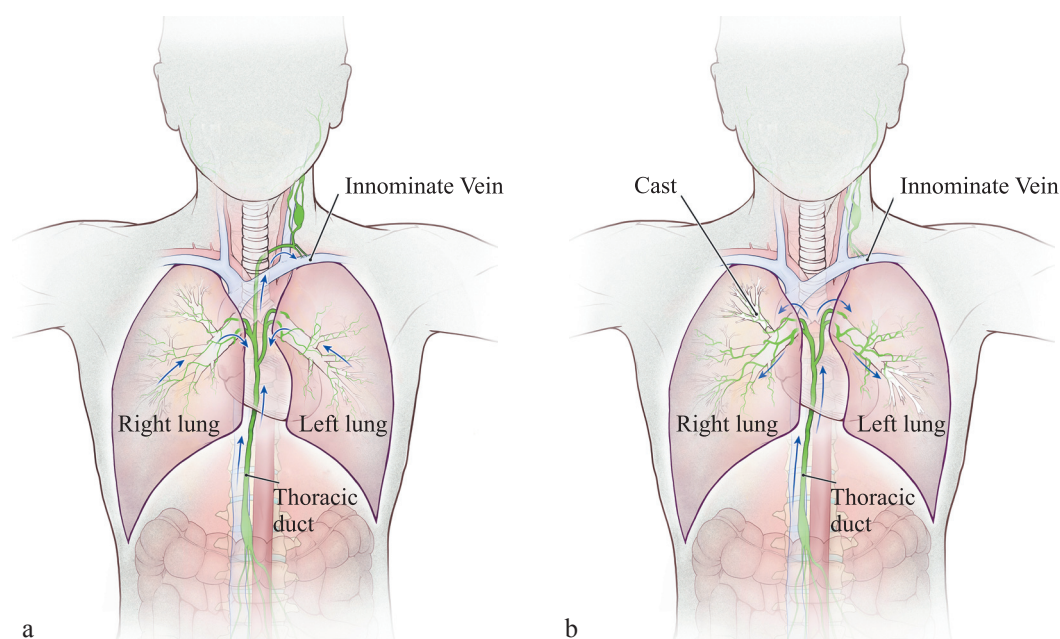


Fig. 4. Schematic representation of the normal lymphatic flow in the chest (a) and reversed flow in pulmonary lymphatic perfusion (b)

children the flow from the SVC and IVC flows passively into the pulmonary veins that causing significant elevation of the central vein pressure.

However, in all patients with plastic bronchitis regardless of cardiac or non-cardiac cause, the underline anatomical variant is the same and consists of PLPS, abnormal pulmonary lymphatic flow toward the lung parenchyma (Fig. 4) [2]. The only main difference from the patients with idiopathic chylothorax is that the abnormal lymphatic perfusion occurs in the bronchial mucosa, where the lymph «seeps» into the lumen of the bronchi and then dries up to form the cast of the lung. When injecting of the color indicator (methylene blue or Lymphazurin 1%) through the catheter positioned in the thoracic duct, while performing the bronchoscopy we can visualize these submucosal vessels. Plastic bronchitis occurs more often in patients with severe right heart failure because elevated central venous pressure results in turn resulted in increased production of the lymph due to congestion of organs, primarily liver.

Percutaneous embolization of these abnormal pulmonary lymphatic vessels using above described thoracic duct embolization technique results in alleviation of the symptoms of plastic bronchitis in close to 100% of the patients with minimal complications [2].

Liver Lymphangiogram and Liver lymphatic embolization

Liver lymphangiogram is a relatively unknown technique that was described first in 1963 by Moreno et al [12] as a part of the liver hemodynamical evaluation in patients with liver cirrhosis. Technically, it was performed by deposition of the contrast in the liver paren-

chyma. Liver lymphangiogram has been reported to be used to understand the contribution of changes of liver lymph flow to the symptoms of portal hypertension, to demonstrate the role of liver lymphatic outflow in liver metastasis, and for the diagnosis of liver lymphorrhea [9]. Liver lymphangiography is technically challenging in patients with normal liver because liver lymphatics are small and difficult to access. However, in patients with liver cirrhosis and CHF liver lymphatics are dilated making them easier to access [7, 9].

Description of the technique

Initially the access to liver parenchyma was performed using 21-gauge Chiba needle (Cook, Bloomington, IN) placed into the liver parenchyma. Using US guidance the needle was advanced in close proximity to the portal vein. Embolization of the liver lymphatics was performed by either injecting lipiodol or n-BCA glue diluted with lipiodol 1:6 through the needle. To prevent early polymerization of the glue in the liver parenchyma, the needle was flushed with 5% Dextrose solution.

Pathological conditions

Increase of venous pressure in patients with Fontan circulation results increase in the liver lymphatic production 10-fold, a phenomenon first described by Ernest Starling in 1894 [16–18]. Increase in liver lymphatic flow causes overdilatation of these abnormal lymphatics, with subsequent rupture and leakage of the lymph into the intestinal lumen that can potentially result in protein losing enteropathy that is a common complication of the patient with significant right heart failure.



Fig. 5. Fluoroscopic image of the liver lymphangiogram of the patient with right heart failure and significant ascites demonstrating the needle (black arrow) positioned in the liver lymphatic ducts. Abnormal distribution of the liver lymphatic flow in the mesentery (black stars)

This lymphatic congestion and distention can potentially be responsible for creation of the ascites in liver cirrhosis and CHF. Embolization of these liver lymphatic ducts can significantly improve the patient symptoms (Fig. 5).

CONCLUSION

Lymphatic system is the integral part of the circulation. The interaction between the lymphatic system and vascular system is intimate, reciprocal and continuing. Due to the lack of the imaging ability of the lymphatic system the understanding of these relationships lacked. Intranodal lymphangiogram, DCRML and liver lymphangiograms are one of the first steps in attempt to understand these relationships.

Embolization of the lymphatic system provides the opportunity to treat the abnormal lymphatic flows in conditions such as Pulmonary Lymphatic Perfusion Syndrome. Better cognition of liver lymphatic system in pathological conditions such as CHF and liver cirrhosis would allow future understanding the contribution of the liver lymphatic system to explanation of the symptoms in these patients. Embolization of the disturbance lymphatic vessels can help to develop new therapeutic approaches in a number diseases.

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