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EDITORIAL

Clinical approach for pulmonary lymphatic disorders

Chalisa Thamkittikun, Prakarn Tovichien

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Abstract

In this editorial, we discuss the clinical implications of the article "Lymphatic plastic bronchitis and primary chylothorax: A study based on computed tomography lymphangiography" published by Li *et al*. Pulmonary lymphatic disorders involve abnormalities in the lymphatic tissues within the thoracic cavity. Specifically, pulmonary lymphatic perfusion syndrome describes a condition where the flow of lymphatic fluid in the lungs is redirected towards abnormally widened lymphatic vessels. Clinically, individuals with this syndrome may experience symptoms such as chyloptysis, plastic bronchitis (PB), chylothorax, chylopericardium, and interstitial lung disease. These disorders can be caused by various factors, including PB, chylothorax, and complex lymphatic malformations. Advancements in lymphatic imaging techniques, such as intranodal lymphangiography, computed tomography lymphangiography, and dynamic contrast-enhanced magnetic resonance lymphangiography, have enabled the detection of abnormal lymphatic flow. This has enhanced our understanding of the pathophysiology of these conditions. Additionally, innovative minimally invasive treatments, such as thoracic duct embolization, selective embolization of lymphatic channels, and surgical procedures aim to improve clinical condition of patients and address their dietary needs.

Key Words: Chylothorax; Dynamic contrast-enhanced magnetic resonance lymphangiography; Plastic bronchitis; Pulmonary lymphatic disorder; Pulmonary lymphatic perfusion syndrome

Core Tip: The pulmonary lymphatic perfusion syndrome likely stems from an inherent variation in the lymphatic system, leading to various pulmonary lymphatic disorders. Clinically, it manifests as conditions such as plastic bronchitis, chylothorax, and interstitial lung disease. Recent advancements in dynamic contrast-enhanced magnetic resonance lymphangiography have improved our understanding of these pathophysiologies and contributed to the development of interventional therapies.

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INTRODUCTION

Pulmonary lymphatic disorders (PLD) encompass various conditions characterized by abnormalities in the lymphatic tissue within the thoracic cavity. PLD often involves anatomical variations, blockages in the upstream anatomy, problems with lymphatic conduction, leaks, and excessive lymphatic production due to congenital heart diseases, liver disorders, and genetic syndromes such as Noonan syndrome, Turner syndrome, Down syndrome, and lymphatic malformations[1].

Pulmonary lymphatic perfusion syndrome occurs when lymphatic fluid in the lungs diverts towards overly expanded lymphatic vessels from the thoracic duct (TD). Instead of following its typical path into the TD, the flow heads towards the mediastinum and lung tissue. This syndrome can occur at any age and might present as chyloptysis, plastic bronchitis (PB), and chylothorax. Possible triggers include infections, trauma, or increased central venous pressure, especially in individuals with cavo-pulmonary shunts like those in Fontan palliation[2].

The pulmonary lymphatic system is crucial for maintaining respiratory function and immune balance. It comprises flexible channels lined with endothelial cells that extend throughout the respiratory system, connecting with the bronchovascular bundle. Lymphatic flow begins at capillaries, then progresses through vessels, nodes, trunks, and ducts before draining into the venous system *via* the TD. One-way valves in collecting vessels promote lymph movement and prevent backward flow[3]. The central lymphatic system consists mainly of the cisterna chyli and the TD. Disruptions in lymphatic flow can lead to abnormal leakage of fluid into the airways or lung interstitium, while lymphatic dilation may compress nearby tissues.

CLINICAL PRESENTATION

In addition to common clinical symptoms like coughing, breathing difficulties, wheezing, and chest discomfort, PLD presents pulmonary lymphatic perfusion syndrome, which encompasses chyloptysis, PB, chylothorax, interstitial lung disease, and compression of the mediastinum or lungs. The specific symptoms experienced depend on the proximity of abnormal lymphatic vessels to lung structures, such as the bronchial mucosa or serous membranes (pleural and pericardial). In many PLD cases, this abnormal lymphatic perfusion can involve multiple surfaces, resulting in a combination of symptoms like PB and chylothorax. These pathological processes can also lead to respiratory failure.

IMAGING FINDINGS

Common radiological findings in PLD include fluid accumulation in pleural or pericardial spaces, increased interstitial markings, ground glass opacities, and the presence of mass in the mediastinum and lungs[4]. Advances in lymphatic imaging techniques like intranodal lymphangiography (IL), computed tomography lymphangiography (CTL), and dynamic contrast-enhanced magnetic resonance lymphangiograms (DCMRL) have significantly improved our ability to visualize the central lymphatic system in patients with PLD. Meanwhile magnetic resonance imaging (MRI) offers the advantage of measuring lymphatic dysfunction and characterizing diseases without exposing patients to high doses of ionizing radiation, compared to other methods[5]. These procedures involve injecting contrast agents into the inguinal lymph nodes: Oil-based contrast for IL and gadolinium-based contrast for DCMRL. IL provides real-time guidance during interventional procedures such as catheterization of the TD and TD lymphangiography (TDL), while DCMRL offers precise spatial and anatomical details. DCMRL, conducted before intervention, is crucial for identifying leaks and planning TD embolization. Initially, 25G needles are inserted into inguinal lymph nodes under ultrasound guidance, typically outside the MRI suite. After confirming positioning within the lymphatic system using ultrasound or iodinated contrast, the patient is transferred to the MRI table for imaging. Throughout this process, images are taken while injecting a gadolinium-based contrast agent at controlled rates of 0.5-1.0 mL/seconds, utilizing MR angiography sequences[6]. DCMRL provides both spatial and temporal resolution without radiation exposure and avoids using oil-based contrast in patients with right-to-left shunts. While both DCMRL and TDL offer excellent visualization of the central lymphatic anatomy, TDL specifically evaluates the patency of the TD and the TD-venous junction.

The primary imaging indicator in all PLD cases is the presence of abnormal pulmonary lymphatic flow (PLF). PLF is identified when there is evidence of enhanced pulmonary lymphatic activity outside of the TD, which is considered abnormal. The origin of PLF is categorized as: (1) Hilar PLF, arising from the perihilar region; (2) Suprahilar PLF, originating above the mid-trachea; and (3) Diaphragmatic PLF, starting at or just above the diaphragm. This abnormal PLF can arise from either the TD or lymphatic pathways extending from the retroperitoneum into the mediastinum and lung tissue[6].

The reverse flow of contrast within a lymphatic vessel is termed chylolymphatic reflux. Branches displaying chylolymphatic reflux are named based on lymphatic nodal stations identified through anatomical dissection by Riquet *et al*[7] Cine images are reviewed to evaluate the patency of the TD. Upon accessing it, direct injection of contrast into the duct typically results in rapid movement of the contrast through the TD and into the left subclavian vein. If contrast fails to enter the subclavian vein at the venous angle after repeated direct injections, this indicates occlusion or absence of the TD. In cases of TD occlusion or absence, the location is noted based on the nearest landmark, such as the terminal TD/venous angle, the hilum, or the diaphragm. The TD and chylolymphatic reflux branches were categorized according to a previously established pulmonary lymphatic perfusion classification in a pediatric population[8]: Type 1 denotes a patent TD with abnormal flow in one branch; type 2 indicates a patent TD with abnormal flow in multiple branches; type 3 describes a double TD with one TD supplying the lungs; type 4 specifies complete occlusion of the TD with flow in multiple branches; and type 5 refers to the absence of any identifiable anatomical TD with perfusion of the lungs.

Image findings of PLF show consistency across different types of PLD, including neonatal chylothorax, PB, and adult idiopathic chylothorax. This suggests that abnormal PLF could be a congenital variation in the lymphatic system, appearing clinically at different stages of life and under specific conditions. While some triggers, like increased lymphatic flow in individuals with congenital heart conditions, are well understood, identifying triggers in other cases can be challenging.

Li *et al*[4] found that CTL effectively reveals the characteristics of lymphatic PB and non-traumatic chylothorax, establishing it as a valuable diagnostic tool for these conditions. Meanwhile, O'Leary *et al*[9] observed that both DCMRL and TD lymphangiography showed similar results in patients with lymphatic PB and/or non-traumatic chylothorax, indicating a common underlying cause. This supports the idea that clinical presentation depends on the proximity of abnormal lymphatic vessels to the bronchial mucosa, leading to PB, or to the pleural cavity, resulting in chylothorax.

PULMONARY LYMPHATIC PERFUSION SYNDROME

Pulmonary lymphatic perfusion syndrome describes the deviation of pulmonary lymphatic flow towards unusually dilated lymphatic vessels from the TD. Rather than following its typical course into the TD, this abnormal flow heads towards the mediastinum and lung tissue. It can manifest at any age and may result in conditions such as PB, chyloptysis, or chylothorax. Possible triggers include infections, trauma, or elevated central venous pressure, especially in individuals with cavo-pulmonary shunts like those in Fontan palliation.

PB

PB is characterized by airway obstruction resulting from the formation of bronchial casts within the air passages[6]. Clinically, it is characterized by the expulsion of these casts through coughing and nonspecific respiratory symptoms. Severe cases can progress to respiratory failure due to the blockage of the airways. Although PB primarily affects individuals with congenital heart conditions, it has also been observed in patients without prior heart ailments. Those who have undergone Fontan palliation may develop this complication due to changes in hemodynamics or lymphatic injury during the procedure.

PB has two main causes: Lymphatic and eosinophilic[10]. The lymphatic origin of PB has long been suspected due to the presence of lymphangiectasia observed in bronchial biopsies[11]. Evidence supporting the lymphatic basis for PB includes documented resolution of PB following TD ligation in a case report[12]. However, it was only with the introduction of DCMRL that abnormal PLF from the TD to the lung parenchyma was definitively demonstrated, confirming this pathophysiological mechanism[13]. These casts form due to lymph leakage into the airways, caused by the swelling of peribronchial lymphatics due to excessive pulmonary lymph production or overflow[6]. Elevated pressure in the pulmonary artery, resulting from high blood flow from the cavo-pulmonary shunt, contributes to damage to the alveolar-capillary barrier[14].

DCMRL and TDL showed similar findings for both cardiac and non-cardiac PB cases. Introducing a color indicator, usually methylene blue, into the TD also reveals abnormal perfusion in the bronchial submucosa, further supporting the abnormal submucosal lymphatic perfusion mechanism. Treatment for PB commonly involves selectively embolizing abnormal lymphatic vessels, with reported success rates of over 90% in both cardiac and non-cardiac PB cases[8,13].

Chyloptysis

Chyloptysis occurs when there's an abnormal connection between the bronchial tree and lymphatic channels or a bronchopleural fistula in chylothorax cases[15]. While symptoms make it easy to diagnose in adults, it's often overlooked in children without imaging. Chyloptysis can result from swollen and congested peribronchial pulmonary lymphatics, causing them to burst into the bronchial passage[16]. DCMRL demonstrates abnormal pooling of lymph in the lung tissue, indicating issues with pulmonary lymphatic perfusion.

Chylothorax

Chylothorax is common among individuals with congenital heart disease and can result from various causes, including trauma, surgical procedures, or non-traumatic factors like elevated central venous pressures or central venous thrombosis, which impede lymphatic flow[6]. Post-surgical chylothorax often occurs due to injury to the TD or its tributaries[17] following procedures such as esophageal surgery, cavo-pulmonary anastomosis (Glenn and Fontan surgeries), heart transplantation, repair of transposition of the great arteries, and vascular ring repairs[18-20]. Congenital chylothorax may arise from obstructions, hypoplasia, or valvular incompetence of the TD, or from conditions like lymphangiectasia, lymphangiomatosis, or lymphatic dysplasia[18,21]. Non-traumatic chylothorax can be caused by the invasion or compression of the TD by conditions such as lymphoma and thoracic malignancies, or by lymphatic dysfunction following radiation therapy or tuberculosis[18]. Chylous effusions can exacerbate a child's health condition by leading to malnutrition, immunodeficiency, coagulopathy, electrolyte imbalances, and respiratory insufficiency.

The diagnosis of chylothorax is confirmed by thoracentesis, which detects an exudative pleural effusion profile showing elevated lymphocytes and triglyceride levels[18]. Recent studies have used DCMRL to investigate the causes of post-surgical chylothorax[20]. This research revealed that abnormal PLF was the primary factor in 9 out of 25 patients, while surgical trauma to the TD was found in only 3 cases. The imaging findings of abnormal PLF closely resembled those observed in cardiac PB, with some children also presenting concurrent PB. Moreover, there is substantial evidence indicating that prolonged post-surgical chylothorax increases the risk of developing PB[22]. Notably, TD embolization proved effective in both TD injury and PLF cases, leading to complete remission. Additionally, the study identified central lymphatic flow disorders (CLFD) as another cause of chylothorax, occurring in nine out of 25 patients. The imaging and clinical findings in post-cardiac surgery chylothorax closely resembled those of CLFD, with all affected children under one year of age. However, TD embolization in this patient group was unsuccessful, resulting in high mortality rates. Lympho-venous anastomosis resolved chylothorax in only one patient. This underscores the importance of DCMRL imaging in understanding the disease mechanism.

The main treatments typically begin with draining excess pleural fluid using chest tubes and making dietary changes. Once chylothorax is confirmed, a suitable fat-modified diet is started for 24-72 hours. This fat-modified diet restricts long-chain triglycerides, alters the type of fat, and promotes medium-chain triglycerides. For neonates and infants, use a medium-chain triglyceride-based infant formula or defatted human milk. For children and adolescents, fat modification ranges from less than 10 g total fat/day to less than 30% of daily calories from fat. When total fat is reduced or changed, other calories need to be optimized to ensure proper nutrition. If the patient cannot have a fat-modified diet at diagnosis, start nil per os (NPO) with total parenteral nutrition (TPN). Intravenous lipid emulsions should be given while NPO, as they go directly into the bloodstream, bypass the lymphatic system, and provide essential fats and calories.

After 24–72 hours on a fat-modified diet, classify "high-volume chylothorax" as more than 20 mL/kg/day of chest tube output and "low-volume chylothorax" as 20 mL/kg/day or less. If chest tube output stays above 20 mL/kg/day after 24–72 hours on a fat-modified diet, start NPO with TPN and monitor output daily to determine eligibility for low-output management. If chest tube output is 10 mL/kg/day or more after 7 days of NPO, consider surgical and lymphatic evaluation for refractory chylothorax. If chest tube output is below 10 mL/kg/day at any time, switch to low-volume management and resume or start a fat-modified diet.

The fat-modified diet should be continued for four to five days if chest tube output stays at 20 mL/kg/day or less after the initial 24–72 hour trial or if it drops below 10 mL/kg/day in high-volume patients. If chest tube output is between 10 and 20 mL/kg/day after 4–5 days on a fat-modified diet, or more than 20 mL/kg/day at any time, switch to high-volume management. Continue a fat-modified diet for 2–4 weeks from when it is started or resumed after NPO. Prolonged oral diets providing less than 10% of calories from long-chain triglycerides for more than 1-3 weeks put children at risk for essential fatty acid deficiency. Nutrition optimization during dietary fat restriction may include more meals, snacks, and oral supplements throughout the day to help meet nutrition goals.

Biochemical monitoring, including a basic metabolic panel, phosphorus, albumin, and immunoglobulin levels, along with routine physical exams and tracking of somatic growth, is warranted for anyone on a fat-modified diet for more than two weeks. Large-volume output from chylothorax can cause high-protein losses, resulting in low albumin levels, and excessive loss of fat, electrolytes, immunoglobulins, and other protein-bound minerals like zinc, copper, and selenium[23,24]. If these initial approaches don't work, doctors might consider more invasive procedures such as TD embolization or ligation and pleurodesis[25]. Patients with abnormal PLF or TD trauma can be effectively treated with TD embolization or ligation, while those with CLFD require conservative management unless there is an obstructed TD, in which case surgical anastomosis may be necessary.

CLFD

CLFD, also known as congenital lymphatic dysplasia, can arise during fetal development or at birth. Anomalies or reduced flow within the central lymphatic system can result in fluid accumulation in various parts of the body. This condition typically presents with a combination of symptoms, including chylothorax, generalized swelling, and chylous ascites[26]. Infants affected by CLFD may display nutmeg lung and body wall edema before and after birth. Unfortunately, individuals with CLFD face a mortality rate ranging from 69% to 75%[5]. This condition is often linked with Noonan syndrome, Turner syndrome, or Down syndrome[27,28].

During pregnancy, fetal MRI has shown pulmonary lymphangiectasia in CLFD. This condition appears as a diverse lung signal with slender T2 hyperintense branching tubular structures extending from the hilum to the lung periphery [29]. The most precise diagnosis is made using DCMRL after accessing lymph nodes, revealing dermal backflow of lymphatic contrast agent alongside abnormal multicompartmental lymphatic flow. In such instances, DCMRL has indicated a lack of contrast propagation from the retroperitoneal lymph nodes through the central lymphatic system/TD,

along with dermal backflow of contrast along the abdominal wall[30]. This suggests likely alterations in the anatomy/flow of the central lymphatic system without sufficient collateralization. If a TD cannot be identified, a pressurized conventional lymphangiogram should be performed at the anatomical origin of the TD at the level of T12-L1 to try to fill any obstructed TD portion.

If a distal obstruction of the TD is found, surgical lympho-venous anastomosis might be considered[31]. However, when the TD is dysplastic or aplastic, interventions such as embolization are ineffective due to blockage rather than leakage. In such cases, pharmacological treatments like the somatostatin analog octreotide, Sirolimus (an MTOR inhibitor) and Trametinib (MEK inhibitor), have been tried with some effectiveness. These drugs work by inhibiting the RAS pathway, but their use is still in its early stages. Currently, there is no clear way to predict how patients will respond to these medications, and the long-term prognosis and potential complications remain uncertain[32].

Complex lymphatic anomalies

Complex lymphatic malformations (LM), also known as lymphatic anomalies, encompass a variety of conditions that affect the lymphatic system in different organs such as the lungs, spleen, liver, bones, and intestines. The International Society for the Study of Vascular Anomalies identifies three distinct entities within this spectrum: Generalized Lymphatic Anomaly (GLA), Kaposiform Lymphangiomatosis (KLA), and Gorham-Stout Disease (GSD)[33]. These conditions display varying degrees of phenotypic expression, and the proliferation of lymphatic tissue in specific organs contributes to morbidity. Bone involvement is prevalent in all three diseases, with KLA and GLA typically sparing the cortex, while GSD affects the cortex, thereby increasing the risk of fractures[34]. KLA, a subset of GLA, presents with the aforementioned lymphatic anomalies, in addition to thrombocytopenia, severe coagulopathy, chronic DIC, and distinctive lymphatic endothelial spindle cells observed on tissue biopsy. Patients with KLA often have a poorer prognosis and frequently exhibit hemorrhagic effusions rather than pure chylous effusions[35].

Lymphatic malformations (LM) impact several organ systems, but their effect on the lungs notably escalates morbidity and mortality. In a study involving 85 LM patients, Ozeki *et al*[36] reported a 20% mortality rate, all of whom had pulmonary complications, whereas those without such issues experienced long-term survival. The research also underscored a significantly worse prognosis for individuals with KLA in comparison to those with GLA and GSD. Hence, addressing respiratory complications in these cases should be a paramount focus for both research and treatment efforts.

Radiological findings on individuals with LM reveal various abnormalities, including pleural effusions, thickening of the pulmonary interstitium and/or perivascular interlobular septa, ground glass/alveolar opacities, and mediastinal masses[37]. A recent study examined DCMRL findings in 16 LM patients with pulmonary involvement[5]. Among them, aberrant PLF originating from the TD, retroperitoneum, or both was found in 14 out of 16 cases. Additionally, nine patients exhibited a tortuous dilated TD, indicating increased lymphatic flow. The contrast enhancement observed in the lung tissue supports the idea that abnormal PLF from the TD or retroperitoneum causes dilation of interstitial lymphatic ducts, contributing to the observed thickening on imaging. Over time, this dilation may surpass the capacity of pulmonary interstitial lymphatics, leading to leakage into nearby compartments. This sequence of events serves as a core mechanism behind the development of alveolar ground glass opacification, pleural effusions, and interstitial lung disease in affected individuals.

The management of pulmonary symptoms in LM patients typically involves several strategies, including drainage to alleviate chylothorax and breathing difficulties, dietary adjustments, and considering pleurodesis[36]. Patients with complex LM often have heightened levels of MTOR and VEGF in their abnormal lymphatic channels. Sirolimus, which decreases the expression of both VEGF and MTOR, has shown effectiveness in specific cases[38]. A study examined the effectiveness of lymphatic embolization in individuals with pulmonary symptoms linked to LM. Among the seven patients studied, significant pulmonary insufficiency resulting from interstitial lung disease and/or pleural effusion was evident. Following embolization, all patients experienced improvement in pulmonary function. Proactive embolization of these anomalous lymphatic pathways offers a promising approach to maintaining respiratory function and extending life expectancy.

PERCUTANEOUS LYMPHATIC INTERVENTION

Advancements in interventional and surgical techniques, such as TD embolization, interstitial embolization, and lymphovenous anastomosis, have revolutionized the treatment of conditions associated with lymphatic abnormalities. These methods primarily address issues like chylothorax and lymphatic flow disorders. Lymphatic embolization procedures involve several steps. Initially, IL is performed to visualize the lymphatic system by injecting an oil-based contrast material (Lipiodol) into the inguinal lymph node under ultrasound and fluoroscopy guidance[39]. Access to the lymphatic system is then established either by catheterizing the major lymphatic ducts such as the TD or by inserting small needles into the surrounding tissue. Once access is achieved, contrast material is injected to visualize the lymphatic structure and detect abnormalities. Subsequently, abnormal flow is embolized by injecting a mixture of N-butyl cyanoacrylate glue diluted with Lipiodol until flow cessation is achieved.

CONCLUSION

Pulmonary lymphatic perfusion syndrome likely originates from a congenital variation in the lymphatic system,

persisting across various clinical scenarios and giving rise to a range of PLDs. Clinically, it presents as conditions such as PB, chylothorax, and interstitial lung disease. Recent advancements in lymphatic imaging have significantly deepened our understanding of these pathophysiologies and facilitated the development of interventional treatments. Lymphatic embolization has emerged as a promising treatment option with minimal complication rates.

FOOTNOTES

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