Nonmalignant Adult Thoracic Lymphatic Disorders

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KEYWORDS

• Lymphangioma • Lymphangiomatosis • Lymphangiectasia • Generalize lymphatic anomaly (GLA) • Gorham-Stout disease (GSD) • Kaposiform lymphangiomatosis (KL) • Pulmonary lymphangiectasia • Yellow nail syndrome

KEY POINTS

- The thoracic lymphatic disorders typically present with symptoms of cough, shortness of breath, chyloptysis, or expectoration of branching casts.
- Typical pulmonary manifestations of the thoracic lymphatic disorders include chylous effusions, peribronchiolar interstitial infiltrates, and mediastinal masses.
- The emergence of sophisticated imaging techniques that characterize abnormal lymphatic flow promises to improve the classification and therapeutic approaches to the thoracic lymphatic disorders.

INTRODUCTION

Primary lymphatic anomalies comprise a bewildering array of congenital and acquired conditions that can affect every organ system containing lymphatic channels, generally considered to be all tissues except brain and bone marrow. Lymphatic anomalies usually come to medical attention during childhood or early adulthood, but can also present later in life. For the purpose of this article, the discussion focuses on the lymphatic disorders that involve thoracic structures, either primarily or as part of a more global lymphatic disease process, and which preferentially affect older children and adults.

The pulmonary lymphatics are a network of vessels that function to transport cells and fluids from the periphery of the lung to the central lymphatic conduits, in order to regulate tissue pressure and facilitate regional immune responses. The peripheral lymphatic vessels converge on the larger conduits coursing on the surface of major airways in the hila and mediastinum and ultimately drain into the right lymphatic duct and thoracic duct (TD). The right lymphatic duct inserts into the subclavian vein in the neck and drains the right upper lobe. The TD inserts into the left innominate vein at the junction with the internal jugular vein and drains the left lung, right middle and lower lobes of the right lung, as well as all structures below the diaphragm (Fig. 1). A broad discussion of lymphatic anatomy is beyond the scope of this article, but it is important to note that intestinal lymph (chyle) that contains chylomicrons (dietary fats) enters the TD at the level of cisterna chyli in the upper abdomen and is transported to the venous system in the neck. The primary route thorough which chylous fluid reaches the pleural space or other thoracic structures in subjects with chylous effusions, therefore, is either through (1) reflux from an obstructed or pressure-overloaded

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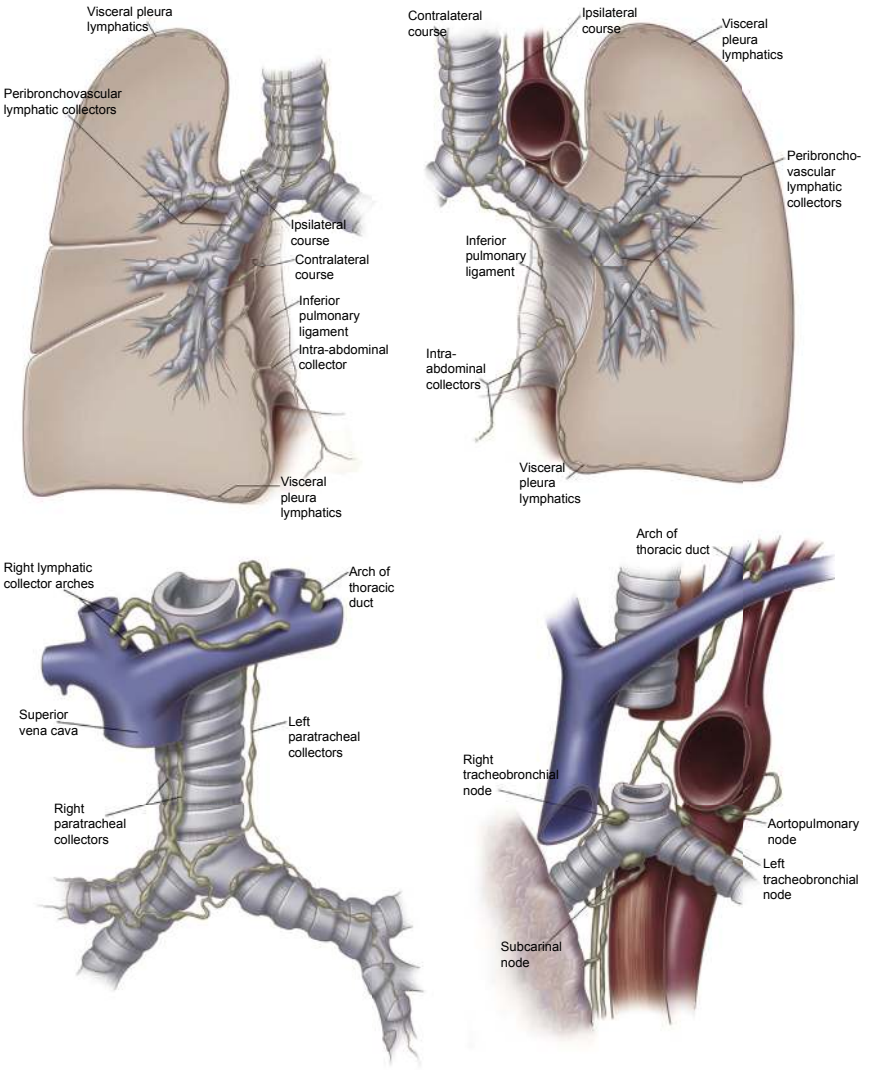

Fig. 1. Schematic representation of pulmonary lymphatic anatomy. (*Adapted from* Riquet M. Bronchial arteries and lymphatics of the lung. Thorac Surg Clin 2007;17:619–38; with permission.)

TD into the pulmonary lymphatic stream, or (2) through a pathologic connection between chylous lymphatics and the pleural space, airways, or lung parenchyma, as can occur following surgery or trauma or as part of a pathologic process. Other thoracic chylous complications that can result from these 2 processes include chylous congestion in the lung parenchyma,[1] plastic bronchitis (PB; expectoration of branching casts),[2] chylopericardium, and chyloptysis.

The thoracic lymphatic disorders (TLD) comprise a group of diseases that are variably associated with mediastinal or pulmonary masses, interstitial infiltrates, airway disorders including chyloptysis, PB, pleural effusions that are often chylous, and repeated pulmonary infections and bronchiectasis (eg, yellow nail syndrome, YNS). Extrapulmonary manifestations of the TLDs can include lymphatic leaks in various distributions (eg, chylous ascites), protein-losing enteropathy, recurrent fevers and prostration, lymphatic obstruction resulting in lymphedema of extremities, coagulopathy, and bony lesions. The TLDs often present in protean manner and can be congenital or acquired, localized or systemic. Attempts to classify these disorders have generally been based on defining commonalities of a limited number of cases or the consensus of experts.[3–6] Most of the published classification systems use inconsistent terminology and lack clear diagnostic, clinical, laboratory, or imaging standards. The TLDs are often grouped based on symptoms, age of presentation, histologic appearance, associated illnesses, or secondary imaging

findings rather than on unifying pathologic processes.

Common terms that have been used to describe primary lymphatic disorders include lymphangioma, lymphangiectasia, lymphangiomatosis, primary lymphedema,[7] pulmonary lymphangiectasia (PL),[8–10] intrathoracic lymphangiomatosis,[11] thoracic lymphangiomatosis,[12] diffuse pulmonary lymphangiomatosis,[13] and mediastinal lymphangiomatosis.[14] The mode of clinical presentation is often added to modify these disease classifications, using terms idiopathic, congenital, neonatal, or acquired to describe chylothorax, chylous ascites, or chylopericardium.[15–18]

In particular, the terms lymphangioma and lymphangiectasia have been used interchangeably to describe a heterogeneous group of disorders associated with excess lymphatic tissue. Although both conditions are very similar histologically,[6,19] by definition lymphangiomas are sequestered from the main lymphatic system, and lymphangiectasias are connected to it. The primary means to differentiate between these 2 disorders clinically is with imaging capable of revealing lymphatic flow. Revealing lymphatic flow was formerly accomplished with pedal lymphangiogram and lymphoscintigraphy,[20,21] which have been reported to demonstrate pathologic lymphatic flow ("lymphatic reflux") in lymphangiectasia despite its limitations in anatomic definition.[22–24] Over the last few decades, however, these procedures have been less frequently performed and the expertise required to execute them has been lost to many radiology departments. Intranodal lymphangiogram (IL)[25] and dynamic contrast-enhanced magnetic resonance lymphangiogram (DCMRL)[26,27] are new imaging techniques that can better define lymphatic anatomy and lymphatic flow. These approaches have opened new vistas in the understanding the importance of lymphatic flow in primary lymphatic disorders[26,27] and will likely lead to more rational approaches to classification.

The International Society for the Study of Vascular Anomalies (ISSVA) approved new guidelines for classification of the lymphatic disorders at the 20th ISSVA Workshop in Melbourne, Australia in 2014. Disorders of the pulmonary lymphatic system include macrocystic, microcystic, and mixed lymphatic malformations, generalized lymphatic anomalies (GLA, also previously known as diffuse lymphangiomatosis), lymphatic malformations in Gorham-Stout disease (GSD), channel-type lymphatic malformations, and primary lymphedema. Not mentioned in the ISSVA classification are disorders associated with combinations of lymphatic and other tissue anomalies, including lymphangioleiomyomatosis (LAM), or YNS. The disorders we have chosen to discuss below are a subset of TLDs that might conceivably present with pulmonary infiltrates, thoracic masses, or chylous leaks in an adult pulmonary clinic, including lymphangioma (a term that has now been replaced with microcystic or macrocystic lymphatic malformation), diffuse pulmonary lymphangiomatosis (DPL; a term that is obsolete but without an accepted replacement, here called primary pulmonary lymphatic anomaly [PPLA]), GLA with pulmonary involvement, a new subtype of GLA called Kaposiform lymphangiomatosis (KLA), lymphatic malformation in GSD, PB, and YNS. Disorders that are exclusively found in neonates primarily, are malignant, or which do not typically involve thorax, such as congenital chylothorax, primary lymphedema, Kaposi sarcoma, or lymphangiosarcoma, are not discussed in this article. An overriding theme in this review is the importance of lymphatic imaging in classifying and treating these disorders.

THORACIC LYMPHANGIOMAS (MICROCYSTIC AND MACROCYSTIC LYMPHATIC MALFORMATIONS)

Lymphangiomas are focal proliferations of well-differentiated lymphatic tissue that present as multicystic or sponge-like accumulations.[19,28] In many cases, they represent embryologic remnants of lymphatic tissues. Acquired or secondary lymphangiomas can occur at the site of radiation, trauma, or infection. Cystic lymphangiomas (also known as cystic hygromas or cystic hydromas) can occur anywhere but are most common in the armpit and the neck. In the thorax, they manifest as masses in the mediastinum,[29,30] pleura,[31,32] or intrapulmonary[33] distributions (**Fig. 2**). Mediastinal lymphangiomas are equally distributed between the anterior, posterior, and medial mediastinal compartments and often envelop and displace mediastinal vessels. Thoracic lymphangiomas are usually detected as nodules or cystic masses on chest radiographs. MRI is the most useful diagnostic modality, because it accurately predicts intraoperative findings, and heavy T2 weighting brightly elucidates tumor boundaries. Histologically, lymphangiomas are composed of an increased number dilated lymphatic channels and are filled with proteinaceous fluid. Although most lymphangiomas occur in the first 2 years of life, 40% of 151 lymphangiomas reviewed in consultation by the Air Force Institute of Pathology were from patients who were older than 16 years of age.[34] Clinically, intrathoracic lymphangiomas

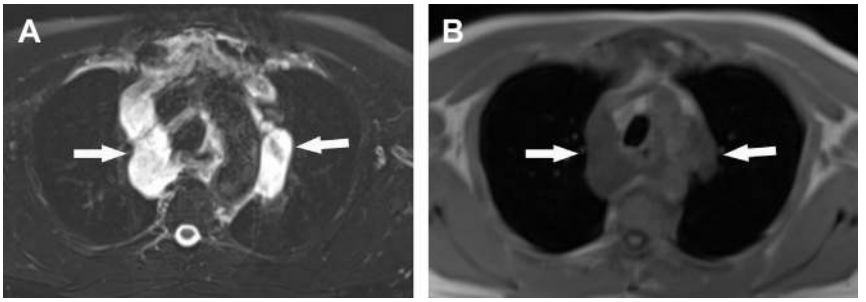

Fig. 2. MRI features of patient with mediastinal lymphangioma (*arrows*). (*A*) Axial T2-weighted MRI shows high signal pretracheal and paratracheal masses. The high signal is due to high water content in lymphangiomas. (*B*) The signal on T1-weighted image is similar to smooth muscle.

can present as incidental findings or associated with symptoms of organ compression, such as cough, dyspnea, stridor, or Horner syndrome. Because they are often isolated from the main lymphatic system, intrathoracic lymphangiomas are typically not associated with chylous pleural effusions. Surgical resection of mediastinal lymphangiomas has been successfully performed to relieve compression on adjacent organs.[35,36] Recently, a high prevalence of PIK3CA mutations have been reported in patients with lymphatic malformations and malformative syndromes.[37]

LYMPHANGIOLEIOMYOMATOSIS

LAM, also known as lymphangiomyomatosis, is a rare cystic lung disease that occurs most commonly in women.[38] Recent research from multiple laboratories has revealed that LAM is a progressive, low-grade metastasizing neoplasm associated with smooth muscle-like cell infiltration of the lung interstitium and cystic remodeling of the pulmonary parenchyma.[39,40] Cystic changes consistent with LAM occur in both men and women with tuberous sclerosis complex,[41] associated with germ-line mutations in either TSC1 or TSC2.[42] Sporadic LAM occurs in patients who do not have TSC, has been reported only in women, and is driven by somatic mutations in TSC2.[43,44] Although the source of LAM cells that infiltrate the lung is unknown, available evidence suggests that the disease spreads primarily through lymphatic channels.[45,46] Lymph node involvement is greatest in low abdominal and pelvic locations and decreases in a gradient-like fashion to the thoracic mediastinum, suggestive of an origin in the pelvis.[47] The uterus is a prime candidate for the source of LAM cells, a notion that is supported by the estrogen and progesterone receptor positivity of the neoplastic cells and multiple case reports of uterine involvement in LAM.[48–51]

Lymphatic manifestations of LAM include TD wall invasion, mediastinal lymphangioleiomyoma formation, and chylous fluid collections in the peritoneal, pleural, and pericardial spaces. Abnormal communications between lymphatic channels and hollow viscera can result in protein-losing enteropathy, chyluria, chyloptysis, chylocolporrhea (chylometrorrhea), chyle leak from the umbilicus, chylous pulmonary congestion, and lower extremity lymphedema. LAM lesions express lymphangiogenic growth factors, vascular endothelial growth factor (VEGF)-C and VEGF-D,[45] growth factor receptors, VEGFR-2 and VEGFR-3 (Flt-4), and markers LYVE-1 and podoplanin, and are laced with chaotic lymphatic channels.[52] Serum VEGF-D is elevated in 70% of patients with LAM and is a clinically useful diagnostic and prognostic biomarker.[53–56] Molecular targeted therapy with sirolimus is antilymphangiogenic and is effective at stabilizing lung function and for the lymphatic and chylous complications of LAM,[51,57] although little is known about the optimal dose and duration of the drug. Other approaches to control chylous pleural effusions include pleurodesis, TD embolization, and TD ligation. Patients with problematic or refractory chylous fluid collections and leaks should undergo imaging with IL[25] or DCMRL[26,27] to identify the source of the leak (**Fig. 3**). As an example of the importance of understanding underlying pathologic lymphatic anatomy and flow before intervening, chylous pleural effusions requiring repeated taps may be revealed by IL or DCMRL to arise from lymphatic leakage into the abdomen rather than into the chest. Because in those cases the thoracic effusion arises from chylous ascites that is drawn into the chest by negative pleural pressures generated during respiration, TD ligation would be contraindicated. In this situation, embolization, pleurodesis, or sirolimus treatment would be preferred approaches.

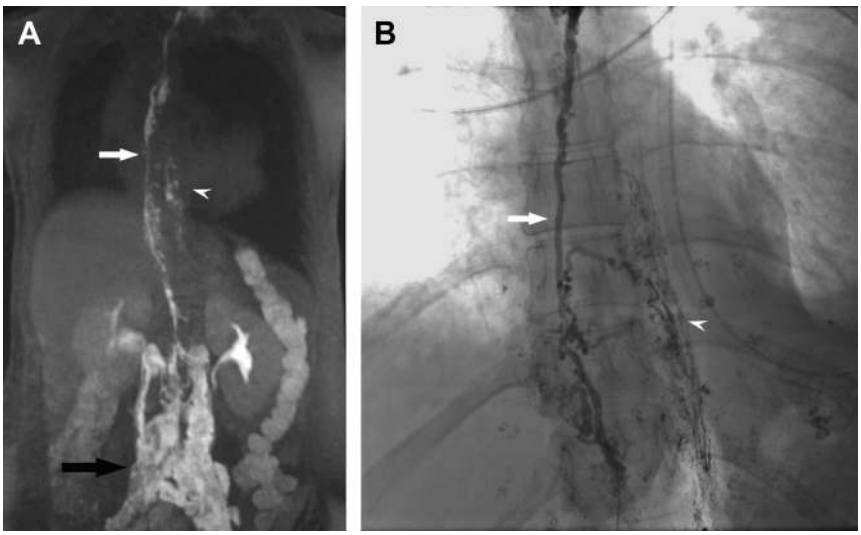

Fig. 3. (*A*) DCMRL imaging of a patient with LAM, demonstrating large retroperitoneal masses (*black arrow*), prominent TD (*white arrow*), and abnormal branching of the lymphatic vessels from TD, resulting in development of chylothorax (*arrowhead*). (*B*) Corresponding fluoroscopy image of the TD of the same patient, following injection of contrast material through the microcatheter positioned in the proximal part of TD. Injection confirms mild dilation of the TD (*white arrow*) and abnormal branching of the lymphatic vessels from the TD, resulting in development of chylothorax (*arrowhead*).

PRIMARY PULMONARY LYMPHATIC ANOMALY

In rare cases, especially in children, primary lymphatic anomalies may be entirely restricted to the thoracic cavity. These disorders have been reported in the literature as DPL,[13,19] pulmonary lymphangiectasis,[58] intrathoracic lymphangiomatosis,[11] thoracic lymphangiomatosis,[59] and diffuse pulmonary angiomatosis.[60] Tazelaar and colleagues[13] originally proposed the term "diffuse pulmonary lymphangiomatosis," but the most recent ISSVA guidelines support the use of the suffix "-oma" only in cases where the lymphatic abnormality is known to be neoplastic. Indeed, most lymphatic disorders discussed here are likely due to persistence or duplication of well-differentiated lymphatics rather than clonal tumor growth. Tazelaar also proposed that DPL be distinguished from PL, which he thought should be restricted to the very rare congenital or secondary cause cases where pulmonary lymphatics are dilated but not increased in number. In the new classification of vascular malformations, the ISSVA avoids using the term lymphangiomatosis and describes 2 distinct lymphatic malformation conditions[4]: GLA, and GSD. Because the ISSVA group does not appear to have directly addressed the nomenclature for the organ-restricted disorder formerly known as DPL, the term PPLA is used here. On gross examination, the lung parenchyma in cases of PPLA does not reveal any discrete nodules or masses. At low power, the lung may reveal spongiform expansion of interlobular septa, but no true cysts. Histologically, PPLA is associated with extensively anastomosing, variably sized, endothelial cell-lined spaces distributed along lymphatic routes throughout the lung. According to Tazelaar and colleagues,[13] compared with PL, there is a prominence of collagen and spindle-shaped cells surrounding endothelial lined channels. Compared with LAM, although hemosiderin-laden macrophages can be prominent in either, the surrounding lung parenchyma is usually normal in PPLA. Chest radiographs and computed tomography (CT) scans reveal alveolar and interstitial infiltrates, and pulmonary function tests often reveal a restrictive abnormality.[61] PPLA can be confused with LAM because of the presence of vimentin and desmin–positive spindle cell smooth muscle infiltrates and chylous accumulations, but PPLA is generally not associated with cystic change in the pulmonary parenchyma or with positivity for HMB-45. There are no known treatments for PPLA, but if proven to be a true lymphangiectasia, it is possible that the disorder could be treated by interruption of caudal lymphatic flow, such as TD ligation or TD embolization.

GENERALIZED LYMPHATIC ANOMALY WITH PULMONARY INVOLVEMENT

GLA may affect the skin, superficial soft tissue, abdominal and thoracic viscera, and bone.[62] GLA

has been described in all ages, from birth to age 80. Thoracic involvement is common and often includes mediastinal lymphangioma, chylothorax, chylopericardium, chyloptysis, or PB, and interstitial changes that are often most prominent along bronchovascular bundles. Extrapulmonary features can include chylous ascites, protein-losing enteropathy, peripheral lymphedema, lymphopenia, hemihypertrophy, and disseminated intravascular coagulopathy. Bony involvement is common in GLA. When present, GLA tends to spare the cortex and to follow a more stable course than GSD.[63] Single or multiple lymphangiomyomas can be found within the mediastinum, diffusely infiltrating mediastinal fat, or adherent to the pleura or chest wall. Lymphangiography reveals multiple lesions of the TD, dilated lymphatic channels, and lymphangiomas throughout the bones and lungs. Bilateral interstitial infiltrates or pericardial and pleural effusions are often present on the chest radiograph. Pulmonary function tests may reveal a restrictive pattern, but mixed patterns are also found. CT scans of the thorax reveal diffuse thickening of intralobular septa and bronchovascular bundles with extensive involvement of mediastinal fat and perihilar regions. Histopathology demonstrates anastomosing endothelial-lined spaces along pulmonary lymphatic routes. Heavy T2-weighted MRI may reveal lymphatic anomalies in the thorax and abdomen, and IL[25] or DCMRL[26,27] can be used to define abnormal lymphatic low. A recent phase II trial demonstrated that sirolimus resulted in at least partial responses in 100% of patients with GLA.[64]

GORHAM-STOUT DISEASE

GSD, also called vanishing bone disease, is associated with abdominal and thoracic visceral lymphatic involvement, effusions, and destructive bony disease (**Fig. 4**).[65] In contrast to GLA, GSD involves the bone cortex and can result in progressive osteolysis.[63] Tissue samples are positive for lymphatic endothelial cell markers, suggesting that GSD is primarily a disease of disordered lymphangiogenesis.[66] Current treatments for GSD are primarily symptomatic and supportive and include control of mass effect using sclerotherapy,[67] and conservative and surgical treatment of chylous leaks. In a recent phase II trial of sirolimus treatment, 3 of 3 patients with GSD had partial responses.[64]

KAPOSIFORM LYMPHANGIOMATOSIS

KLA is a newly characterized entity that was initially described as a subtype of GLA but is now

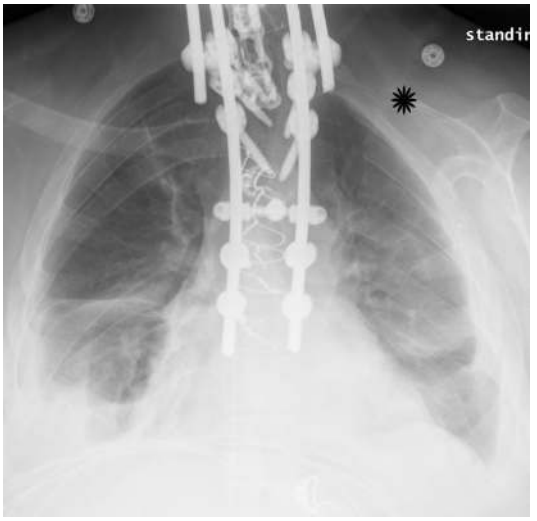

Fig. 4. Chest radiograph of an 11-year-old patient with GSD. Note the absence of the left clavicle (*black star*) due to osteolysis.

pathologically differentiated from that disorder by the presence of clusters or sheets of spindle-shaped lymphatic endothelial cells infiltrating malformed lymphatic channels.[68] It is important to distinguish KLA from PPLA or GLA because it tends to follow a more aggressive course, at least in children. Characteristic hematological abnormalities that occur in KLA can be helpful in that regard, including elevated fibrin split products and D-dimer, low fibrinogen and platelet count. Hemorrhagic complications also occur, including bloody effusions and expectorations. As with GLA, dilated, malformed lymphatic channels are lined by a single layer of endothelial cells in KLA. However, in KLA, foci of pattern-less clusters of intralymphatic or perilymphatic podoplanin, PROX1, and LYVE-1-positive spindled cells are found associated with platelet microthrombi, extravasated red blood cells, hemosiderin, and fibrosis without significant atypia or mitoses. It is not known whether spindled cells are clonal/neoplastic or reactive. Although the disease typically presents in early childhood, later onset has also been reported.[69] The most common manifestations of KLA are respiratory symptoms, including cough, shortness of breath and hemoptysis (50%), hemostatic abnormalities (50%), enlarging, palpable masses (35%),[68] mediastinal masses, interstitial infiltrates (**Fig. 5**), and effusions, which can be chylous or hemorrhagic. Dilated, blood-filled lymphatic channels may be visualized on the pleural surface during video-assisted thoracoscopic surgery. Hemorrhagic lesions have also been seen on peritoneal and pericardial surfaces. Progressive interstitial lung disease and chylous

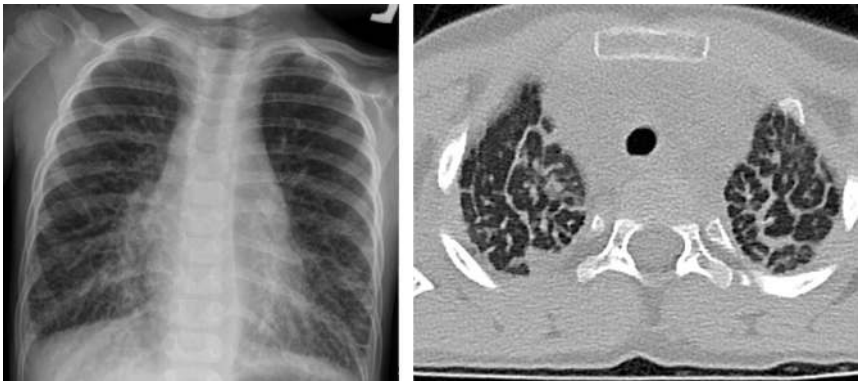

Fig. 5. Chest radiograph and chest CT of a patient with KLA shows increased interstitial markings.

pleural effusions can lead to respiratory failure. Vincristine and sirolimus treatment have been reported in KLA.[70,71] In a recent phase II sirolimus trial, 5 of 7 patients with KLA had a partial response and 1 had stable disease.[64]

CHYLOPTYSIS AND PLASTIC BRONCHITIS

PB describes a heterogenous group of allergic, immunologic, infectious, cardiac, neoplastic, and lymphatic disorders that are associated with expectoration of bronchial casts.[72] PB as it has been defined is not a single disease with a unifying mechanism that explains cast formation in all conditions. Indeed, it is not clear that PB is always associated with bronchitis, defined as disruption, dysfunction, or inflammation of bronchial mucosa. In most cases of true PB, the bronchial system may be serving as no more than a mold for congealing bronchial contents. This finding is certainly true in the most common form of PB, which follows cardiac surgery for congenital heart disease, especially the Fontan procedure. In these cases, abnormal pulmonary lymphatic flow (**Fig. 6**) results in leakage of proteinaceous and lipid-rich fluids into the bronchial tree.[73] Recently, heavy T2-weighted MRI has revealed that occult lymphatic anomalies that represent developmental remnants or subclinical GLA are present in adults who present with expectoration of large multiantennary, branching casts.[2] IL[25] and DCMRL[26,27] have been used to more precisely image the leaks, and in the small number of patients who have been treated to date, embolization of the TD has

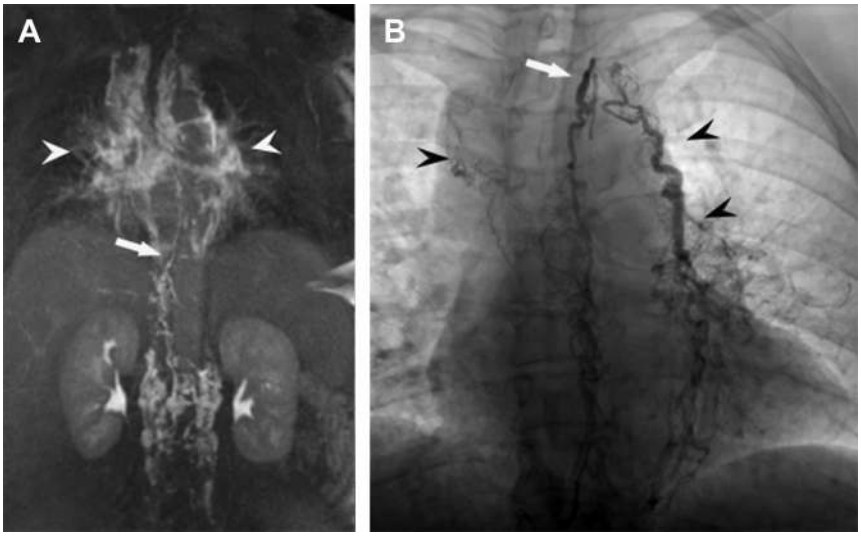

Fig. 6. (*A*) DCMRL in patient with idiopathic PB demonstrating small TD (*white arrow*) and abnormal pulmonary lymphatic perfusion in the mediastinum and lung hila (*white arrowheads*). (*B*) Corresponding fluoroscopy image of the TD of the same patient, following injection of contrast material through the microcatheter positioned in the proximal part of TD, demonstrating occlusion of the distal part of the TD (*white arrow*) and retrograde flow of the contrast in the mediastinal lymphatic ducts (*black arrowheads*).

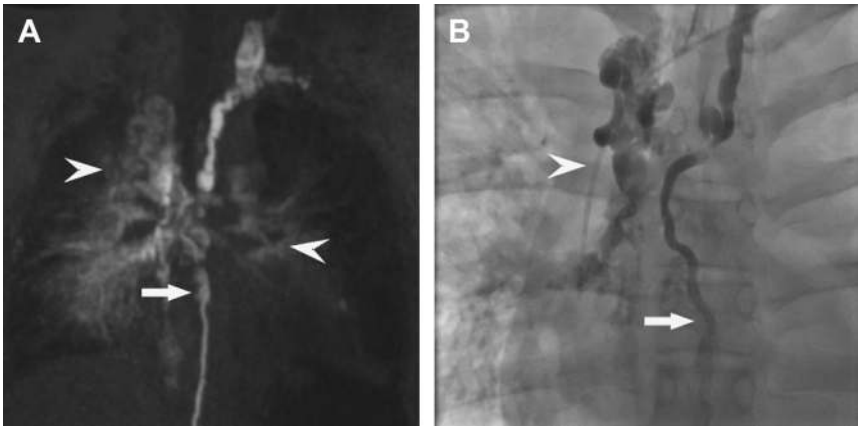

Fig. 7. (*A*) DCMRL in a patient with pulmonary lymphangiectasia demonstrating dilated TD (*white arrow*) and abnormal pulmonary lymphatic perfusion in the lung hilum (*white arrowheads*). (*B*) Corresponding fluoroscopy image of the TD of the same patient, following injection of contrast material through the microcatheter positioned in proximal part of TD, confirms the dilation of the TD (*white arrow*) and retrograde flow of the contrast in the mediastinal lymphatic ducts (*white arrowhead*).

been highly successful in controlling cast formation (Maxim Itkin, Francis X. McCormack, Yoav Dori, unpublished data, 2016). The authors submit that lymphatic causes should be considered in all patients who present with expectoration of complex, multiantennary branching casts. Heavy T2-weighted MRI, and, as appropriate, IL and/or DCMRL may be useful for identifying pathogenic lymphatic tissue and lymphatic flow. Cannulation of the TD followed by embolization should be considered in those patients who are shown to have leakage of lymphatic fluid into the airway.[27] Therapeutic interventions with medium-chain triglyceride-enriched low-fat diets, intratracheal heparin, inhaled tissue plasminogen activator, and steroids have also been reported and have met with variable success.[74–77]

PULMONARY LYMPHANGIECTASIA

PL describes pathologic dilation of lymphatic vessels in the lungs. Both primary and secondary forms have been described. The former primarily occurs in neonates due to failure of pulmonary interstitial tissues to regress and is typically fatal, and the secondary forms are usually due to processes that impair lymphatic flow or increase lymph production. The ISSVA defined isolated lymphangiectasia as a lymphatic conductive disorder,[4] highlighting that the ectatic lymphatic vessels are connected to the main lymphatic system. As a result, a common presentation of thoracic lymphangiectasia is chylous effusion. The cause of lymphangiectasia is unknown, but may be due to congenital occlusion of parts of the central lymphatic system, such as the TD, absence of the lymphatic valves, or lymphatic fluid overproduction that results in overdistention and overgrowth of the lymphatic vessels.[78]

The clinical presentation of PL includes respiratory symptoms of wheezing, chronic cough or chest pain, bilateral interstitial infiltrates, restrictive pulmonary physiology, and pericardial and pleural effusions.[13]

The diagnosis of PL is based on dilated lymphatic vessels in perivascular and peribronchial distributions on pathologic analysis, patchy ground glass opacification and thickening of the interlobular septa on CT,[61] or reflux of contrast into the lung parenchyma on lymphangiogram.[79]

Occlusion and narrowing of the upper part of the TD with retrograde pulmonary lymphatic flow occurs in patients with idiopathic chylopericardium and chylothorax on DCMRL and IL (**Fig. 7**). For that reason, the authors recommend DCMRL and IL as the first imaging modalities for a patient presenting with idiopathic chylothorax/chylopericardium with and without lung disease.

Treatments that have been attempted for PL include thoracentesis, dietary modification, pleurodesis, octreotide, and interruption of cranial thoracic lymphatic flow (TD embolization, TD ligation).[80] Prognosis is usually good in cases where chylothorax and chylopericardium can be controlled.

THE YELLOW NAIL SYNDROME

Of all the TLDs, the YNS is one of the most likely to present in adulthood, at a median age of 40 to 50 years.[81,82] The YNS was first described by

White and Samman in 1964,[83] now defined as the triad of yellow dystrophic fingernails (86%), pleural effusion (36%), and idiopathic lymphedema (80%). Only 20% to 30% of cases have all 3 manifestations, and the presence of any 2 is generally considered to be diagnostic. More than 60% of patients develop sinopulmonary manifestations other than pleural effusion, which can include chronic cough, repeated infection, rhinosinusitis, recurrent pneumonia, bronchiectasis, and sinusitis. Whether YNS represents a genetic or acquired disorder remains controversial.[84,85] Wells described an extended family with 8 affected members.[86] The proband developed lower extremity lymphedema as well as edema in the vocal cords, genitalia, hands, and face. Although cases of YNS have occurred in patients with connective tissue disease, neoplasms, immunodeficiencies, and endocrine disorders, it is unclear if these disorders play a direct role in disease pathogenesis or simply represent chance associations. In the largest retrospective study of YNS to date, 9 of 150 patients were found to have a family history of lymphedema or YNS.[81] Two reports of infants born with hydrops and chylothorax to mothers with YNS suggest a heritable cause in some cases.[87,88] Mutations in the FOXC2 gene have been described in patients with the lymphedema-distichiasis (LD) syndrome, some of whom also have yellow nails, leading Finegold and colleagues[89] to conclude that there is phenotypic overlap between LD and YNS. A subsequent analysis of 4 families with YNS revealed no evidence of FOXC2 mutations, however.[90] It is important to note that although nail changes and yellowing occur in other forms of lymphedema, the nail manifestations of YNS are quite distinctive and include marked thickening, very slow growth, excessive side-to-side curvature, loss of lunulae and cuticles, and detachment from the nail bed (onycholysis).[91] It is interesting that the nail changes in YNS can spontaneously regress. The male:female ratio of affected patients is 1.2/1. Pulmonary effusions are bilateral in 68% of cases and are most commonly lymphocytic exudates.[81] Chylothorax is documented in a minority of cases in retrospective series (~20%), but it is unclear if the diagnosis was rigorously pursued in all cases. Pleural effusions routinely reoccur despite repeated taps, but pleurodesis is effective in more than 80% of cases. Pericardial effusions have also been described, and in some cases, have required pericardiectomy. Nail matrix biopsies reveal ectatic endothelial lined channels and dense stromal fibrosis, and pleural biopsies demonstrate dilated lymphatics associated with lymphocytic pleuritis and moderate fibrosis. Lymphangiograms and lymphoscintigraphy often reveal hypoplasia of lymphatics. There is no effective treatment for YNS, but octreotide therapy has been attempted in some cases.[92,93]

SUMMARY AND FUTURE DIRECTIONS

There has been an explosion in molecular understanding of lymphatic development in the last 2 decades, yielding powerful new markers to probe disease pathogenesis in the TLD.[94] More detailed histopathologic and immunohistochemical characterization using these tools is defining subsets of GLA that exhibit more aggressive behavior. Improved imaging of the lymphatic system (eg, DCMRL) promises to rapidly enhance the understanding of the pathogenesis of TLD. Genetic analyses are revealing the genetic basis of lymphatic malformation and primary lymphedema disorders. Recent trials of the antilymphangiogenic drug sirolimus have revealed stabilizing effects on lung function, reversal of chylous effusions, shrinkage of lymphatic masses, and promising benefits in many of the complex vascular anomalies described here. Lymphatic biomarkers that are useful diagnostically and correlate with disease progression have been reported. Recent technical advances have resulted in novel approaches to controlling lymphatic leaks. Powerful new approaches to molecular and genetic characterization promise to shed new light on disease pathogenesis and uncover novel therapeutic targets.

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