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Pulmonary Lymphangiomatosis

Melissa N. Satria, Gustavo Pacheco-Rodriguez, Ph.D., and Joel Moss, M.D., Ph.D.

Abstract

Lymphangiomatosis is a rare disease characterized by diffuse infiltration of lymphangiomas in the lung, bone, and other tissues. Due to its rarity, the spectrum of lymphangiomatosis is beginning to be elucidated based on case reports. The limited pathological, radiological, and clinical studies have shed light on this disease. Treatments have been tested in unblinded manner with promising results; however, further understanding of the pathogenesis of disease, as well as its natural history, is needed to facilitate drug development.

Introduction

Lymphangiomatosis is a rare disease characterized by diffuse infiltration of lymphangiomas in the lung, bone and other organs. Within the thorax, lymphangiomas may be found in the mediastinum, heart, thoracic duct, lung, and pleura.[1] Lung involvement is a leading cause of death. Lymphangiomatosis can present with single organ (eg, diffuse pulmonary lymphangiomatosis) or multiple organ involvement.[1,2] The disease is believed to be congenital with no sex predilection and can present in infancy as well as in adulthood, although the majority of cases are diagnosed in childhood.[3–5] It has been postulated that the disease results from abnormal lymphatic development. Hamartomata may result from proliferation of abnormal smooth muscle-like spindle cells.[6] Diffuse pulmonary lymphangiomatosis is difficult to diagnose due to its presentation with nonspecific symptoms such as wheezing, cough, dyspnea, hemoptysis, and chest pain, and is commonly misdiagnosed as asthma or other respiratory diseases.[7] However, pulmonary function tests, radiographic findings, clinical presentation, and pathological studies have aided in its diagnosis. Among the manifestations of lymphangiomatosis that facilitate its diagnosis are bone lesions in conjunction with chylothorax. It is noteworthy that most of the information obtained about this disease is based on case reports. Despite the lack of controlled clinical trials in lymphangiomatosis, there are case reports of potential treatments, which require further validation. It should be noted that lymphangiomatosis can be described as generalized, diffuse pulmonary, intra-thoracic, and cystic disease, depending on the extent of the affected tissue.

Natural History

Diffuse pulmonary lymphangiomatosis has a poor prognosis and is characterized by slow progressive growth of lymphatics commonly with chylous effusions, and may be associated with lytic bone lesions and mediastinal compression.[8] Other manifestations include cervical lymphangioma, pericardial effusions, chyloptysis, hemoptysis, protein-wasting enteropathy, lymphedema, and splenic lesions.[1,4,9] Lymphangiomas can be associated with the lung parenchyma, pleura, mediastinum, and chest wall. The disease is often misdiagnosed due to nonspecific symptoms (eg, chest pain, chest tightness, shortness of breath, dyspnea, wheezing). Interestingly, patients with lymphangiomatosis with either bone or soft tissue involvement have a better prognosis than those with bone and soft tissue involvement.[1] Lymphangiomatosis with bone involvement, also known as Gorham-Stout disease, can occur without lung involvement.[10] Children less than 16 years old have a higher mortality rate (~40%) than adults (0%).[4,11] Primary causes of death are respiratory failure, infections, and accumulation of chylous fluid.

Pathology and Histology

The presence of lymphangiomas (ie, proliferative differentiated lymphatic tissue) characterize lymphangiomatosis.[1] However, diffuse pulmonary lymphangiomatosis may present as a form of lymphangiectasia, which is characterized pathologically as dilations of lymphatics without proliferation and without an anastomosing pattern.[1] Pathologically, lymphangiomatosis is characterized by benign-appearing lymphatic vessels, thickened by a layer of normal-appearing flat endothelial cells, with varying amounts of collagen, and edema, and anastomosing spaces filled with eosinophilic material or chyle.[1,6,7,12] Further, hemosiderin-laden macrophages are frequently present within the lung parenchyma.

Spindle cells can be found arranged in poorly delineated fascicles.[13] The spindle cells vary in their positivity to antibodies, which react with antigens commonly found in smooth muscle cells (eg, vimentin, desmin, alpha smooth muscle

Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

actin). Progesterone receptor has been found in a few cases; most of the spindle cells are not reactive to antibodies that recognize the estrogen receptor. Due to the presence of proliferative spindle cells, similar to those found in lymphangioleimyomatosis (LAM), reactivity with the monoclonal antibody HMB45, which recognizes the melanosomal protein gp100 present in LAM, is often tested.[14] Reactivity to HMB45 has not been found in diffuse pulmonary lymphangiomatosis.[3] The lymphatic channels in lymphangiomatosis are lined with endothelial cells that react with anti-CD31 antibodies, which recognize the platelet-endothelial cell adhesion molecule 1 (PECAM1/CD31). These endothelial cells contain CD31 and von Willebrand factor VIII-related (FVIIIr) antigen, and react with the lectin *Ulex europaeus* I.[7,13,15] Bone biopsies can reveal lesions, which are associated with osteolysis.[8] Reaction with anti-CD31 antibodies has been used to detect lymphatic endothelial cells; however, lymphatic channels are more specifically identified by the presence of podoplanin, a transmembrane protein regulated by the lymphatic transcription factor PROX1,[16] and recognized with the antibody D2-40. Thus, spindle cells in lymphangiomatosis appear to express smooth muscle actin, other smooth muscle cell proteins, and CD31; they appear to lack estrogen receptor, pmel17/gp100 (reactivity to HMB-45 antibodies), and S-100 protein.[3,13]

Diagnostic Methods

Diagnosis of lymphangiomatosis is based on compilation of radiographic scans, clinical presentation, and pulmonary function tests. Other useful diagnostic methods include bone and lung biopsy, lymphangiography, fiberoptic bronchoscopy, lymphoscintigraphy, and echocardiograms.[9] Lymphoangiography is an effective method of differentiating lymphangiomas from other forms of angiomas, as well as providing detailed images of the lymphatics.[1,17] This method uses oil-based dyes injected into the lymphatics, which can cause pulmonary complications (eg, allergic reaction, fever, infection, and inflammation of lymphatic vessels).[11,18] Alternatively, lymphoscintigraphy is a quick, minimally invasive method to follow disease progression and guide therapy.[11] It can define direction of lymphatic flow and help to differentiate between normal and abnormal lymphatic vessels.

Imaging

Computed tomography (CT), ultrasound, magnetic resonance imaging (MRI), and sonographic imaging provide effective assessment and diagnosis of lymphangiomatosis. Imaging reveals the behavior, location, and severity of disease. CT scans can quantify pulmonary interstitial, septal, and mesenteric thickening, mediastinum tumors, pleural effusions, ground glass opacities, and cystic bone lesions.[7,9] Diffuse fluid infiltration of mediastinal soft tissue and pleural effusions are two of the most universal characteristics seen in CT scans. Both CT and MRI imaging detect lesions in the bone and soft tissue. Lesions are defined by thickened cystic walls; those in bone appear translucent.[8] Chest radiographs often reveal porous soap bubble or honeycomb texture in bone due to osseous expansion, periosteal reaction, and cortical invasion.[8] Bone lesions can be present in ribs, humerus, cervical, femur, and other long bones.[10]

Pulmonary Function Tests (PFTs)

PFTs can reveal a mixed restrictive and obstructive pattern based on abnormalities in forced expiratory volume in one second (FEV_1), FEV_1/FVC (forced vital capacity) ratio, total lung capacity (TLC), residual volume (RV), and RV/TLC ratio.[7]

Comparison of Histopathology of Lymphangiomatosis and Lymphangioleiomyomatosis (LAM)

Lymphangiomatosis and LAM are both tumors involving the lymphatic system, but the two diseases differ significantly in pathogenesis and natural history. Lymphangiomatosis shows a characteristic proliferation, dilation, and thickening of lymphatic vessels,[6,19] with collagen, muscle fibers, and spindle-shaped cells surrounding the lymphatic vessels.[1] Macrophages may be found within the lung parenchyma. The cystic lesions characteristic of LAM lungs are not apparent in lymphagiomatosis.[3] The smooth muscle-like spindle cells in LAM react with HMB45, whereas in lymphangiomatosis, the spindle cells are HMB45-negative.[3,20] Lymphangiomatosis occurs in both males and females,[1,4] in contrast to the marked female predominance of LAM.[1,14]

Treatment

Due to the rarity and lack of knowledge of lymphangiomatosis, it has been difficult to establish a treatment. The treatments available are palliative and aimed at managing chylous fluid accumulations and proliferation of lymphatics and alleviate symptoms that come with compression of adjacent organs. Although surgical resection is advised in some cases, it may be unsuccessful due to difficulty of differentiating and separating affected lymphatic tissue from normal tissue and the potential risk of recurrence.[1] Conservative treatment options such as total parenteral nutrition (TPN), medium chain triglyceride (MCTG), and high protein diet appear to be ineffective.[11,21] Other options described in multiple case reports with good results (eg, Refs. 4, 22, 23) include sclerotherapy with doxycycline, pleural and pericardial drainage, pleurectomy, radiation, chemotherapy, and embolization of lesions. Sclerotherapy aids in relief from lymphedema and lymph accumulation; yet, due to pain associated with the procedure, patients often opt out of it.[1] Interferon α-2b therapy has recently been tested with significant improvements in clinical and radiological findings,[21] although there have been reports of unfavorable outcomes. Interferon appears to suppress tumor cell division and boost the immune system and does not have any life-threatening side effects.[24] Recently, it has been shown that propranolol, a nonselective beta-blocker, may be effective in treatment of diffuse lymphangiomatosis by reducing the levels of vascular endothelial growth factor (VEGF) and the amount of chylous effusions.[25]

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Address correspondence to:
Joel Moss, M.D., Ph.D.
Cardiovascular and Pulmonary Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Building 10/Room 6D05
9000 Rockville Pike
Bethesda, MD 20892-1590

E-mail: mossj@nhlbi.nih.gov