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Case Report

Pulmonary Lymphangiomyomatosis Masquerading as Progressive Mediastinal Lymphadenopathy

*Gregory Fishberger[5], Farah Khali[1,2], Andrew Kuykendall[5], Holly R May[1], Prudence V. Smith[1,2], Jose Silva-Morales[1,6], Joseph R. Garrett[1], Carla C. Moodie[1], and Eric M. Toloza[1,3,4]**

[1]Department of Thoracic Oncology, Moffitt Cancer Center, Tampa, FL, USA

[2]Department of Pathology, Moffitt Cancer Center, Tampa, FL, USA

[3]Department of Surgery, University of South Florida Health Morsani College of Medicine, Tampa, FL, USA

[4]Department of Oncologic Sciences, University of South Florida Health Morsani College of Medicine, Tampa, FL, USA

[5]University of South Florida Health, Morsani College of Medicine, Tampa, FL, USA

[6]San Juan Bautista School of Medicine, Caguas, PR, USA

Abstract

Introduction: Mediastinal lymphadenopathy is usually diagnosed by Computerized Tomography (CT) scan and has a broad differential diagnosis, including primary or metastatic neoplasia, acute infection, sarcoidosis, and chronic infection, such as Histoplasmosis or tuberculosis. Various mimickers of lymphadenopathy have been described, and their identification is vital to establish an accurate diagnosis, to minimize unnecessary diagnostic workup, and to provide appropriate therapy.

Case presentation: We present a 46-year-old woman with history of pregnancy-associated chylothorax requiring pleuro-peritoneal shunt 19 years previously. More recently, she presented 3 months prior with back pain, exertional dyspnea, and left supraclavicular lymphadenopathy, without fever or night sweats. Her dyspnea worsened and serial CT scans noted progressively enlarging mediastinal Lymph Nodes (LNs). Positron Emission Tomography (PET)-CT scan was compared to a PET-CT scan 5 years earlier and revealed extensive mediastinal lymphadenopathy as well as prevascular, para-aortic, and retroperitoneal soft tissue masses, with minimal to low fluorodeoxyglucose activity. Left supraclavicular LN biopsy revealed prominent smooth muscle with staining for desmin and smooth muscle actin, indicating a likely lymphangioma. She was referred for surgical evaluation of her mediastinal LNs. She underwent left video-assisted thoracoscopy, with extensive pleurolysis and pleural and posterior mediastinal biopsies. The presumed extensive posterior mediastinal LNs were found to be actually loculations of chylous fluid. Pleural and mediastinal biopsies were consistent with pulmonary lymphangiomyomatosis. She had no perioperative complications and was discharged to home on postoperative day #2. She was treated with daily oral pazopanib, a tyrosine kinase and angiogenesis inhibitor. She is alive 4-1/2 years later off pazopanib, with radiographically stable disease.

Discussion: Lymphangiomyomatosis (LAM) is an uncommon gender-restricted disease characterized by progressive dyspnea on exertion, recurrent pneumothoraces, lymphadenopathy, chylous effusions, abdominal tumors, and characteristic thin-walled cysts on High Resolution CT (HRCT). In our case, loculated chylous lakes mimicked a finding of progressive mediastinal lymphadenopathy, which, in addition to our patient's gender, age, and lack of smoking history, weight loss, or infectious symptoms, resulted in initial suspicion for lymphoma. However, history of chylous effusion during child-bearing age resulted in concern for LAM. Surgical biopsy proved useful to confirm diagnosis in this atypical case.

Conclusion: Pulmonary LAM is rare, with classic presenting features occurring in a characteristic patient population. With nonspecific imaging features, maintaining high clinical suspicion is important to establish an accurate diagnosis.

Keywords: Pulmonary; Lymphangiomyomatosis; Mediastinal; Lymphadenopathy

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***Corresponding author:** Eric M Toloza, MD, Ph.D, Department of Thoracic Oncology, Moffitt Cancer Center, 12902 USF Magnolia Drive, Suite CSB-6 (ThorProg), Tampa, FL 33612, USA, Tel: +1-813-745-7282; Fax: +1-813-449-8446; E-mail: eric.toloza@moffitt.org

Introduction

Mediastinal lymphadenopathy is usually diagnosed by Computerized Tomography (CT) scan and has a broad differential diagnosis, including primary or metastatic neoplasia, acute infection, sarcoidosis, and chronic infection, such as Histoplasmosis or tuberculosis. Various mimickers of lymphadenopathy have been described, and their identification is vital in order to establish an accurate diagnosis, to minimize unnecessary diagnostic workup, and to provide appropriate therapy.

Case Presentation

We present a 46-year-old woman with history of pregnancy-associated chylothorax requiring pleuro-peritoneal shunt 19 years previously (Figure 1). More recently, she presented 3 months prior with back pain, exertional dyspnea, and left supraclavicular

lymphadenopathy, without fever or night sweats. Her dyspnea worsened, and serial CT scans noted progressively enlarging Lymph Nodes (LNs) particularly in the left lower cervical and supraclavicular regions and throughout the mediastinum. Positron Emission Tomography (PET)-CT scan was compared to a PET-CT scan 5 years earlier and was interpreted as revealing increased size of extensive mediastinal lymphadenopathy, prevascular, para-aortic, and retroperitoneal soft tissue masses, and loculated left pleural effusion, with minimal to low Fluoro-Deoxyglucose (FDG) activity and maximum standardized uptake values (maxSUV) of 2.7-3.4 (Figure 2). These radiologic findings were concerning for a low FDG-avid malignancy, such as lymphoma.

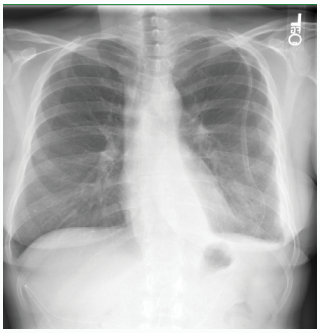

Figure 1: Chest radiograph showing fluid accumulation within the left pleural space as well as a pleuro-peritoneal shunt that extends inferiorly into the perihepatic region.

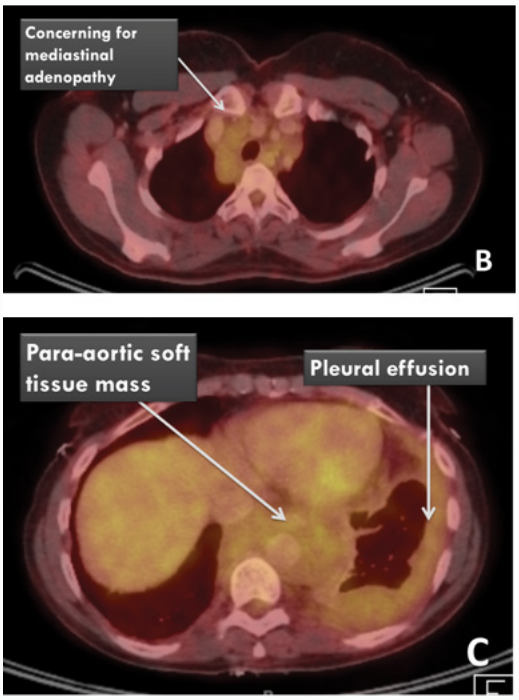

Figure 2: Fused axial Positron-Emission Tomography (PET) and Computerized Tomography (CT) images demonstrating diffuse increased Fluoro-Deoxyglucose (FDG) uptake throughout the mediastinum, corresponding to a large confluent soft tissue mass, interpreted as extensive mediastinal lymphadenopathy, particularly in the right anterior mediastinum, with maximum standardized uptake value (maxSUV) of 3.2 (upper panel), and in the posterior mediastinum around the descending aorta, with maxSUV of 3.4, as well as a moderate-sized loculated left-sided pleural effusion, with diffuse increased FDG uptake and maxSUV of 2.7 (lower panel).

Left supraclavicular LN biopsy revealed prominent smooth muscle with staining for desmin and smooth muscle actin, indicating a likely lymphangioma. Histologic sections showed a vascular neoplasm in connective tissue demonstrating multiple small endothelial-lined spaces, which were devoid of red cells (Figure 3, upper panels). Lymphoid aggregates were noted focally within the lesion. Definitive features of a lymph node were not seen. Within the mass surrounding these vascular spaces were haphazard arrangements of smooth muscle. Immunohistochemistry stains showed endothelial cells to be positive for CD31 and smooth muscle adjacent to the vascular channels to be positive for smooth-muscle actin and desmin. An HMB-45 stain was negative. The histologic and immunophenotype were compatible with the diagnosis of lymphangioma.

She was referred for surgical evaluation of her mediastinal LNs. She underwent left video-assisted thoracoscopy, with extensive pleurolysis and pleural and posterior mediastinal biopsies. The presumed extensive posterior mediastinal LNs were found to be actually loculations of chylous fluid.

Left pleural and posterior mediastinal biopsies revealed vascular lesions with features most compatible with pulmonary lymphangiomyomatosis. Histologic sections of the posterior mediastinal mass biopsies showed background of collagenous tissue in which there was scattered, somewhat haphazardly arranged smooth muscle surrounding compressed and open vascular spaces (Figure 3, lower panels). A small area showed features suggestive of a lymphangioma, with apparent interconnecting vascular channels separated by the collagenous tissue. Most lumens were empty, but others contained either proteinaceous material alone or proteinaceous material together with a few red blood cells. The endothelial cells were more widely spaced than surrounding blood vessels, compatible with lymphatic vessels. No luminal lymphocytes were noted. Rare small arteries and veins were present. Immunohistochemical stains revealed these vessels to be lined by CD31-positive endothelial cells (Figure 4, upper left panel). A D2-40 stain faintly marked a subset of endothelial cells. Immunostains for actin and desmin confirmed the presence of smooth muscle adjacent to these lymphatic spaces (Figure 4, upper right panel). The Masson trichrome stain revealed some fibrosis as well. An elastic stain (Van Giasson) was negative in the lymphatic

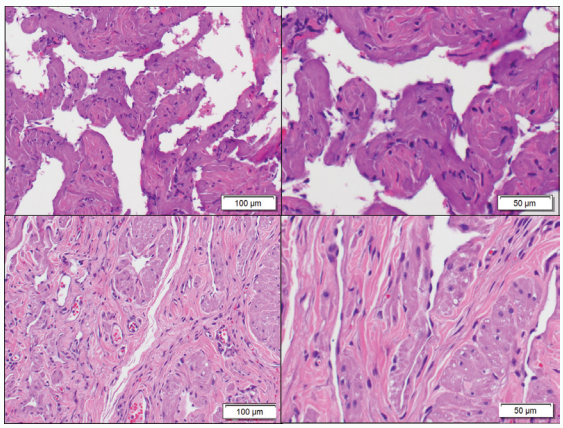

Figure 3: Photomicrographs of lymphangioma (Hematoxylin & Eosin [H&E] stained) showing interconnecting vascular channels at low power (upper left panel) and at high power (upper right panel) and of Lymphangiomyomatosis (LAM; H&E stained) showing collagenous tissue with haphazardly arranged smooth muscle surrounding compressed and open vascular spaces at low power (lower left panel) and at high power (lower right panel).

vessels (Figure 4, lower left panel). An S-100 stain was negative for neural tissue, and an HMB-45 stain was focally positive in some areas of adjacent muscle (Figure 4, lower right panel). The histologic findings together with the clinical history were compatible with the diagnosis of Lymphangiomyomatosis (LAM).

She had no perioperative complications and was discharged to home on postoperative day #2. She was treated with daily oral pazopanib, a tyrosine kinase and angiogenesis inhibitor.

Discussion

Lymphangiomyomatosis (LAM), also known as lymphangioleiomyomatosis, is an uncommon gender-restricted disease characterized by progressive dyspnea on exertion, recurrent pneumothoraces, lymphadenopathy, chylous effusions, abdominal tumors, and characteristic thin-walled cysts on High-Resolution CT (HRCT) [1]. In our case, loculated chylous lakes mimicked a finding of progressive mediastinal lymphadenopathy, which, in addition to our patient's gender, age, and lack of smoking history, weight loss, or infectious symptoms, resulted in initial suspicion for lymphoma. However, history of chylous effusion during child-bearing age resulted in concern for LAM. Surgical biopsy proved useful to confirm diagnosis in this atypical case.

The subclasses of LAM include LAM occurring with tuberous sclerosing complex (LAM-TSC) and sporadic LAM. Sporadic LAM affects approximately 3.3 to 7.4 women per million worldwide in mostly menopausal women, while LAM presents in about 30% of women with inherited TSC [2]. The root cause of LAM in both instances can be attributed to mutations in either the *TSC1* or *TSC2* genes for the *TSC1* case and in *TSC2* for the sporadic case [3]. The *TSC1* and *TSC2* genes code for the hamartin and tuberin proteins, respectively [4]. Hamartin and tuberin proteins form a tumor suppressor complex that regulates the mTOR signaling pathway [5]. Loss of *TSC1* or *TSC2* leads to unrestricted LAM cell growth [6].

While not inherently oncogenic, LAM cells function similarly to metastatic cells, as they develop from an extrapulmonary source and invade the lung parenchyma [7]. Cyst formation and chylous effusions result from pulmonary LAM lesions that recruit lymphatic endothelial cells through the secretion of vascular endothelial growth factor-D (VEGF-D) [8]. The lung parenchymal destruction mediated by LAM cells in their metastasis and progression leads to decreased diffusion capacity, pulmonary cystic dilation, and pneumothorax, which all negatively impact pulmonary function [9].

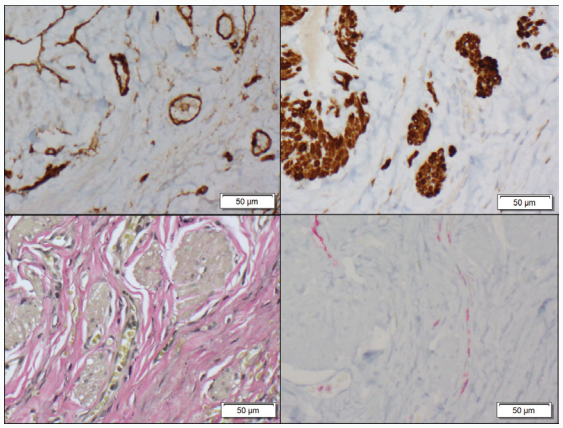

Figure 4: Photomicrographs of Lymphangiomyomatosis (LAM) with CD31 Immunohistochemical (IHC) stain highlighting endothelial cells lining the lymphatic spaces (upper left panel), desmin IHC stain confirming presence of smooth muscle adjacent to lymphatic spaces (upper right panel), elastic IHC stain negative within lymphatic walls (lower left panel), and HMB-45 IHC stain focally positive in vascular cells.

LAM cells, which drive pathogenesis, are epithelioid and smooth muscle-like, which express estrogen and progesterone receptors [10], indicating that disease progression is exacerbated in pregnancy and hormone-based contraceptives. Estrogen has been identified as a potential key driver via both genomic and non-genomic pathways, in part through driving mTOR signaling [11]. Furthermore, estradiol upregulates c-myc activity leading to an increase in expression of proliferative genes [12]. Consequently, pregnant women with LAM experience higher rates of pneumothorax, and women diagnosed with LAM before pregnancy face decreased lung function following pregnancy [13]. However, clinicians may advise patients with milder disease that pregnancy can be tolerated and that they will likely give birth to a heathy child [14]. Ultimately, expression of estrogen and progesterone hormone receptors on LAM cells provides insight into the prevalence of the disease in women.

Due to the symptomatic impact of early pulmonary LAM on lung function, LAM may be misdiagnosed as interstitial lung disease, COPD, or asthma [15]. Reported symptoms of LAM that overlap with the aforementioned conditions include shortness of breath, wheezing, and chest pain [16]. As a result, delayed diagnosis of LAM may occur, such as in a case report published by Khaddour et al. [17], in which a 32-year-old female, who was three months postpartum, presented with symptoms of intermittent dyspnea and was prescribed a bronchodilator. Following another pregnancy, her symptoms worsened without improvement from the inhaler, and her chest x-ray was normal. An HRCT scan revealed cystic spaces, characteristic of LAM. Typically, chest radiographs and CT scans taken during disease progression reveals bilateral round-shaped symmetric opacities, with a honeycomb appearance distributed throughout the lungs [18]. Pleural effusion, pneumothorax, and chylothorax may be visualized [13].

Distinguishing mediastinal or hilar lymphadenopathy from LAM is essential in coordinating a treatment plan. Cystic dilation of lymph nodes in lymphangioma due to lymphatic blockage produces a benign fluid-filled lesion that has the potential to directly impact the airway or lung parenchyma by the lesion's sheer size [19,20]. Cystic lymph node dilation in the context of lymphatic blockage may present with similar clinical complications to LAM, including chylothorax and pulmonary parenchymal compression [21]. Furthermore, both pathologies demonstrate a lack of focal density within fluid-filled cystic lesions [9,19]. However, analysis of the cellular content of a LAM lesion will reveal smooth muscle spindle cells [16]. Our pathology report cites mostly empty lumens, with some lumens containing proteinaceous material but never luminal lymphocytes.

Alternatively, the patient's history raised concern for mediastinal lymphoma, which could develop as part of systemic lymphomas (Hodgkin lymphoma and non-Hodgkin lymphoma), but can be the primary lesion in 10% of lymphoma cases [22]. Lymphoma may also present with dyspnea, pleural effusions (including chylothorax), and chest wall invasion [23]. In our case, the patient experienced exertional dyspnea and a five-year history of mediastinal lymphadenopathy and prevascular, para-aortic, and retroperitoneal soft tissues masses. Our patient's presentation and radiological findings, thus, overlapped with those for lymphoma. That the patient's PET scan revealed minimal

to low FDG activity was beneficial as indicating that the lymphatic lesions were not highly metabolically active and likely not malignant.

Spirometry testing demonstrates that airflow obstructive changes, as measured by Forced Expiratory Volume in 1 second (FEV1), is highly common in LAM, being reduced in 57% to 60% of patients [24,25], and progressive declines in FEV1 can be used as a measure of LAM progression [9]. An increase in pulmonary residual volumes is thought to be an early indicator of LAM, and hyperinflation is present in 6% of cases [24]. Reduced diffusion capacity of the lung to Carbon Monoxide (DLCO) is also an early indicator of LAM. Ultimately, abnormal DLCO is commonly observed, with decreased DLCO in greater than 60% of patients [26].

Diagnostic tissue biopsy is considered to be highly reliable for LAM identification [15]. Histopathology typically reveals a diffuse emphysema-like honeycomb cystic appearance sectioned by thick septa [27]. LAM is characterized by both cuboidal epithelioid cells and spindle-shaped epithelioid cells [28]. Spindle cells are located more in the center of the lesion, and epithelioid cells are present towards the rim of the lesion [14]. LAM cells stain positive for smooth muscle actin and the intermediate-filament proteins desmin and vimentin, as well as for estrogen and progesterone receptors [29]. Of note, hormone receptors are not present in the neighboring healthy tissue. Cuboidal LAM cells react with the monoclonal antibody HMB-45 that targets pre-melanosomal protein gp100 [30].

Perhaps one of the most important clinical indicators of LAM is elevated serum VEGF-D levels (>800 pg/mL) in women [31]. VEGF-D functions as a ligand to the VEGFR-3 receptor [32]. VEGF-D is secreted by LAM cells and acts on local endothelial cells by initiating angiogenesis and lymphangiogenesis [8]. A positive correlation exists between serum levels of VEGF-D and disease severity, particularly in the context of decreased pulmonary function tests [33].

Thus, diagnosing LAM is fairly difficult given the low disease prevalence and lack of familiarity of the disease among practitioners [2]. While symptomatic and epidemiological data is useful in raising suspicion for LAM, imaging, pulmonary function tests, histopathology, and serum VEGF-D levels have proven to be highly effective in confirming the diagnosis.

Treatment of LAM remains fairly limited. For severe cases of the disease, in which patients are experiencing respiratory failure, lung transplantation is a valid treatment option [34]. However, given the metastatic nature of the disease and the genetic component, LAM may recur in lung allografts, albeit at rates often <10% [35]. Symptomatic treatment consists of bronchodilator use, as well as pleurodesis for pneumothorax incidents [16].

The current FDA approved treatment indicates the use of an mTOR pathway inhibitor, rapamycin [36]. The drug was approved for LAM in May 2015 and is the sole FDA approved pharmaceutical treatment option for LAM. Rapamycin has generated significant interest due to speculation that the drug could improve longevity in healthy individuals, have an antiproliferative effect in cancer cells, and may even be useful in the treatment of SARS-CoV2 [37-39]. Rapamycin functions as an immunosuppressive medication and further reduces VEGF-D levels, improves quality of life, and stabilizes lung function [40]. Given rapamycin's role as an immunosuppressant [41], there is understandable concern regarding the flare or the emergence of previously undiagnosed diseases. In the context of respiratory infections, the use of mTOR inhibitors does not increase their incidence and may exert a protective effect [42]. The reason for this phenomenon is not well-understood and requires further study.

Pazopanib, a multi-target receptor tyrosine kinase inhibitor of KIT, PDGF, and VEGF receptors 1, 2, and 3, has been considered as a therapeutic option for treating LAM. Spencer et al. [43] published a case report describing a 33-year-old female diagnosed with LAM with pulmonary nodules, hepatic lesions, and splenic lesions. Treatment of the patient with 800 mg of oral pazopanib daily, under the initial suspicion of a low-grade angiosarcoma or a metastatic splenic littoral cell tumor, improved the patient's condition by stabilizing the growth of the hepatic and splenic lesions [43].

In our case, the patient was treated with oral pazopanib. Given the successful treatment of LAM with pazopanib by Spencer et al. [43] and the involvement of VEGFR3 and mTOR in lymphangiogenesis [44,45], we believed that the treatment of our patient with pazopanib is justified and contributed to her clinical outcome. To avoid the potential for VEGFR3 and mTOR mediated drug resistance, dual therapy with pazopanib and rapamycin could be used to treat LAM. The drug combination has been utilized for the treatment of soft tissue sarcoma and prevented pazopanib resistance [46]. Future studies should aim to assess the safety and efficacy of pazopanib-rapamycin use in the treatment of LAM.

Conclusion

Pulmonary LAM is rare, with classic presenting features occurring in a characteristic patient population. However, given the overlap of nonspecific pathophysiologic and imaging features among unrelated conditions, maintaining high clinical suspicion is important in order to establish an accurate diagnosis.

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Informed consent

A.K. is currently an assistant member of the Department of Malignant Hematology at the Moffitt Cancer Center in Tampa, FL, USA.

Permission was obtained from the patient for publication of this case report and any accompanying images for education purposes as part of our institutional surgical informed consent. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict-of-Interest (COI) Disclosures

None of the authors have any COI to disclose.

Provenance and Peer Review

Not commissioned, externally peer-reviewed.

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