Pulmonary Lymphangioleiomyomatosis: A Case Report and Literature Review

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Abstract

Pulmonary lymphangioleiomyomatosis (LAM) is a rare lung disease characterized by diffuse cystic changes caused by a destructive proliferation of smooth muscle-like cells or LAM cells. It is a part of the perivascular epithelioid cell family of tumors. LAM may be associated with the genetic disorder tuberous sclerosis complex or may occur sporadically. Individuals affected by LAM are typically females of child-bearing age who present with recurrent spontaneous pneumothorax. The microscopic findings can be subtle and careful examination is needed to identify the neoplastic cells of LAM. Immunohistochemical markers in cases of LAM demonstrate a characteristic co-expression of myogenic and melanocytic markers. We report a case of a 41-year-old woman who presented with multiple episodes of spontaneous pneumothorax and microscopic findings characteristic of LAM.

Keywords

Pulmonary lymphangioleiomyomatosis, spontaneous pneumothorax, tuberous sclerosis

Abbreviations

AML = Angiomyolipoma
BHD = Birt-Hogg-Dubé syndrome
BML = Benign metastasizing leiomyoma
COPD = Chronic obstructive pulmonary disease
CT = Computed tomography
DIP = Diffuse interstitial pneumonia
ER = Estrogen receptor
FDA = US Food and Drug Administration
HP = Hypersensitivity pneumonitis
ILD = Interstitial lung disease
IPF = Idiopathic pulmonary fibrosis
LAM = Lymphangioleiomyomatosis
MiTF = Micropthalmia transcription factor
mTOR = Mechanistic target of rapamycin signaling pathway
PEComatous tumors = Perivascular epithelioid cell family of tumors
PLCH = Pulmonary Langerhans cell histiocytosis
PR = Progesterone receptor
RB-ILD = Respiratory bronchiolitis-associated interstitial lung disease
S-LAM = Sporadic LAM
TSC = Tuberous sclerosis complex
TSC-LAM = TSC-associated LAM

Introduction

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease characterized by diffuse cystic changes in the lungs resulting from destructive proliferation of smooth muscle-like or LAM cells. LAM was formerly categorized as an interstitial lung disease (ILD) due to its diffuse nature. However, genetic studies later indicated that the process was best considered as a low-grade destructive neoplasm.[1] The neoplastic cells in LAM originate from perivascular epithelioid cells, which make LAM a part of the perivascular epithelioid cell family of tumors (PEComatous tumors), which include angiomyolipoma (AML), clear cell "sugar" tumor of the lungs and extrapulmonary sites, clear cell myomelanocytic tumor of the falciform ligament, and rare clear cell tumors of other anatomic sites.[2] While the true origin of the LAM cell is undetermined, there are 2 plausible hypotheses. The first theory proposes that LAM cells are either of airway or vascular origin. Another model suggests that LAM cells originate from AML in the kidney and are transported to the lungs by means of neoplastic dissemination.[3]

LAM exists in 2 main forms, the first is associated with the genetic disorder tuberous sclerosis complex (TSC-LAM), and the second is sporadic form (S-LAM). Overall, the majority of patients with LAM are sporadic (85%).[2] TSC-LAM is found in 26%-49% of females with TSC[4,5] and 10% of males with TSC,[5] while S-LAM occurs primarily in women with a single exceptional case report of S-LAM in a male patient.[6] Both TSC-LAM and S-LAM are associated with a mutation in either the *TSC1* or *TSC2* gene, causing a loss of function in the corresponding gene products, namely hamartin (*TSC1*) and tuberin (*TSC2*).[7]

We report a case of a middle-aged woman who presented with recurrent spontaneous pneumothorax. The microscopic findings are typical for pulmonary LAM.

Case Report

Clinical History

The patient is a 41-year-old woman with a medical history of hypertension and dyslipidemia. She presented to the emergency department at another institution with sudden shortness of breath and left sided pleuritic chest pain. The diagnosis of left pneumothorax was made and a chest tube placed. Prior to this admission, she experienced multiple episodes of spontaneous pneumothorax over the past 17 years, which resolved without intervention. She reported smoking tobacco, less than 2 cigarettes per day for the past 21 years. Computed tomography (CT) scan of the chest revealed multiple, thin-walled cysts in both lungs of variable dimension. As the pneumothorax persisted despite chest tube placement for 1 week, she was transferred to our institution for surgical management.

The patient underwent left parietal pleurectomy and doxycycline pleurodesis. Given the clinical suspicion for ILD, wedge resection biopsy of the lingual and left lower lobes was performed. Intraoperatively, diffuse cysts and blebs were described in the upper, middle, and lower lobes.

Pathology

The histologic sections of the pulmonary wedge resection exhibited numerous cysts and bleb formations corresponding to the intraoperative findings. There were multiple foci of smooth muscle-like, spindle cell proliferations (Figure 1). These foci were located at the periphery of the cysts and around bronchioles (Figure 2). The neoplastic cells demonstrated a distinct morphology, similar to that of smooth muscle cells of the airway but more corpulent with larger nuclei and higher nuclear to cytoplasmic ratios (Figure 3). There was no significant atypia or increased mitotic activity. Chronic inflammation and pleural fibrosis were also noted. Immunohistochemical staining revealed that the neoplastic cells were positive for HMB-45 and caldesmon (Figure 4). The overall morphologic and immunophenotypic features supported the diagnosis of pulmonary LAM.

Progression

During postoperative period, the chest tube was removed and the patient recovered appropriately. She was discharged without noted postoperative complications. The patient was seen by her pulmonologist 6 months after the operation. Her clinical status was stable. She reported no shortness of breath or chest tightness. Based on the LAM diagnosis, she was started on sirolimus therapy with suggested follow up at 6-month intervals.

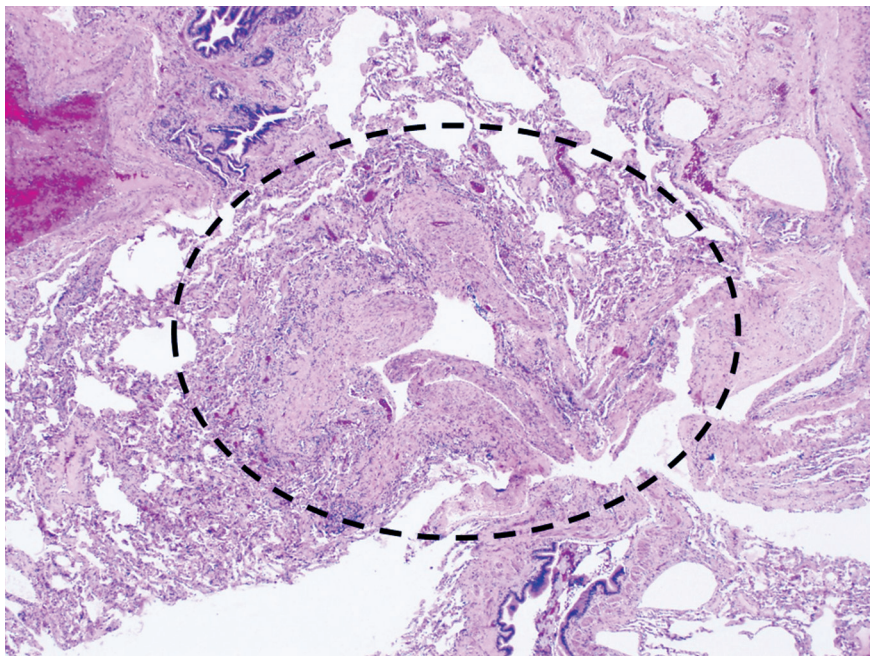

Figure 1. Low power view of the lung shows a nodule of lymphangioleiomyomatosis (dotted circle). The nodule is composed of smooth muscle-like neoplastic cells (hematoxylin-eosin, original magnification 40x).

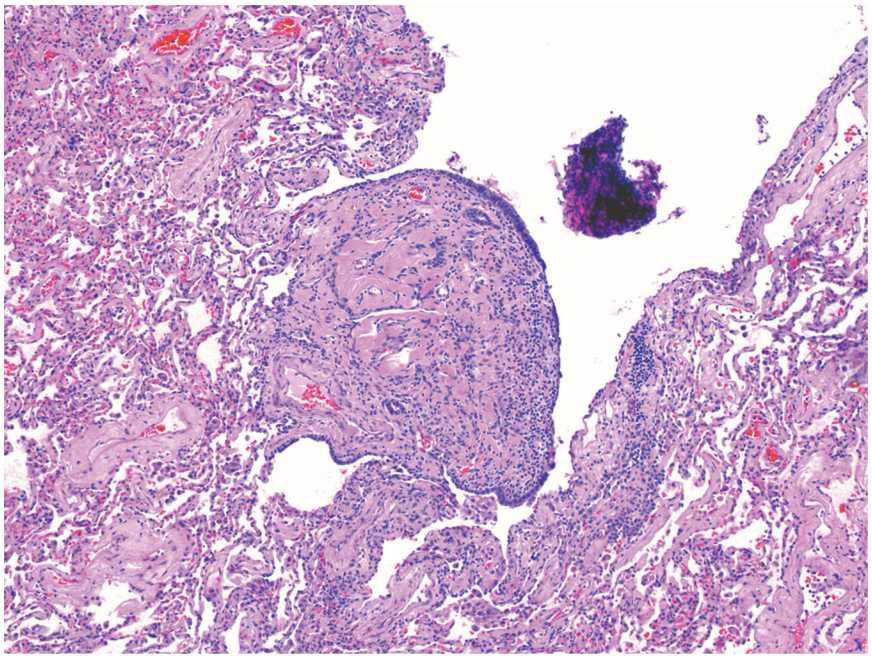

Figure 2. Nodule of lymphangioleiomyomatosis located at the periphery of a cystic lung lesion. An associated chronic inflammatory cell infiltrate is present (hematoxylin-eosin, original magnification 100x).

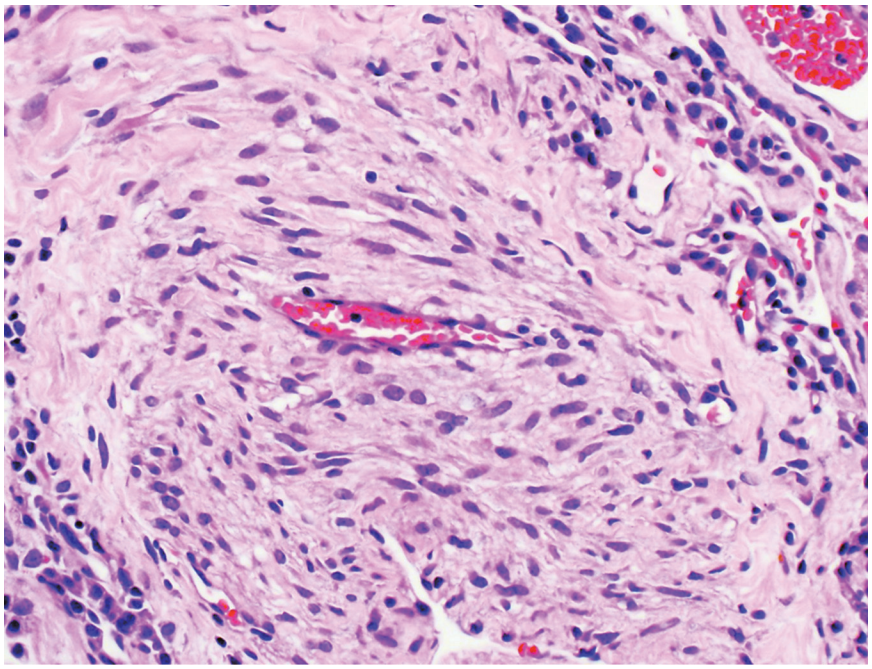

Figure 3. High power view of a lymphangioleiomyomatosis nodule encasing a vessel. The neoplastic cells are spindle-shaped to epithelioid with brightly eosinophilic cytoplasm and mildly pleomorphic nuclei with fine chromatin. Chronic inflammatory cells are seen in the adjacent lung parenchyma (hematoxylin-eosin, original magnification 400x).

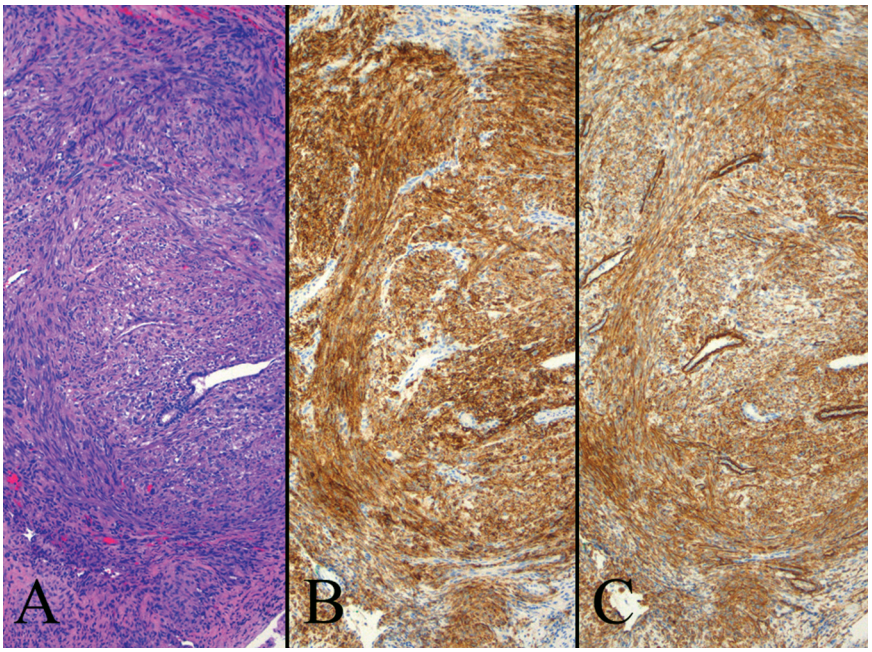

Figure 4. Immunohistochemical studies reveal the neoplastic cells are positive for HMB45 (figure 4B) and caldesmon (figure 4C). In figure 4C, caldesmon also highlights entrapped small airways (A. hematoxylin-eosin, B. HMB45, C. caldesmon, original magnification 100x).

Discussion

Patients with LAM are typically females of child-bearing age, with a mean age of 35 years.[7] The most common clinical presentation is dyspnea on exertion (>70%).[7] Recurrent pneumothorax is also a common presentation, as seen in the current case. Pneumothorax is the first presentation in 40% of patients and will occur in 66% of patients over the course of the disease.[8] Other less common presentations include chest pain, cough, hemoptysis, wheezing, chylothorax, and chylous ascites.[9] Apart from pneumothorax, chest X-ray may be unremarkable in early stages of the disease. In later stages, interstitial reticular opacities can be observed on chest X-ray, with predominant involvement of the lower lung zones.[9] CT scan is more sensitive and demonstrates the characteristic finding of numerous 2-5-mm thin-walled cysts throughout the lungs bilaterally.[9] In severe cases, cysts range from 6-12 mm in size and replace nearly all of the normal lung parenchyma.

Lungs involved by LAM have a cystic, honeycomb appearance, with cysts uniformly distributed throughout the lung parenchyma. Microscopic examination reveals a proliferation of plump spindle-shaped cells with pale eosinophilic cytoplasm. The architectural pattern is variable, with growth in nests, clusters, or as nodules, as seen in the present case. The neoplastic cells in LAM are broadly classified as spindle-shaped or epithelioid.[2] The spindle-shaped cells are usually located in the central regions of the nodules, whereas epithelioid cells exist in the periphery. The tumor cell nuclei are oval to cigar shaped, with fine or vesicular chromatin. Mitotic figures are rare. LAM cells are generally found at the edges of the cysts and along the alveolar walls, pulmonary blood vessels, lymphatics, and bronchioles. Some cases are subtle, necessitating a concerted effort to definitively identify LAM cells. The subtle changes in early stages of the disease can lead to misinterpretation as emphysema or even normal lung tissue.[2] Pneumocyte type 2 hyperplasia or micronodular pneumocyte hyperplasia can be seen, which may be particularly evident in cases of TSC-LAM.[10]

Immunohistochemical analysis is essential to definitively identify the neoplastic cells of LAM and distinguish LAM cells from non-neoplastic smooth muscle cells. While LAM cells consistently stain for myogenic markers such as smooth muscle actin and desmin, the characteristic immunophenotype is a co-expression of smooth muscle and melanocytic markers, including HMB-45, melan-A, and micropthalmia transcription factor (MiTF). This pattern of co-expression is also seen in other tumors of the PEComatous family. Currently, staining with HMB-45 is considered the gold standard for the identification of LAM cells.[11] However, as HMB-45 expression may be focal, the specimen should be sampled thoroughly for microscopic examination and subsequent immunohistochemical analysis. Recently, beta-catenin has been identified as another potential marker for LAM. One study shows that beta-catenin has higher immunoreactivity to LAM cell than HMB-45.[12]

The differential diagnosis includes other ILDs that present with cystic changes. Patients with chronic obstructive pulmonary disease (COPD) or emphysema may also present with recurrent pneumothorax and multiple lung cysts on imaging. The pathologist should ensure that LAM cells are not present in such cases. Smoking related-ILDs should also be considered, including pulmonary Langerhans cell histiocytosis (PLCH), diffuse interstitial pneumonia (DIP), and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).[13] Other ILDs may exhibit a cystic component secondary to a dominant disease pattern, as may be seen in idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis (HP), and sarcoidosis.[13] Certain infections also result in diffuse cystic changes in the lungs. A minority of individuals with *Pneumocystis jiroveci* infection (10%-34%) present with multiple lung cysts, referred to as pneumatoceles.[14] Other microorganisms that can cause pneumatoceles include *Staphylococcus* species, *Coccidioides* species, and parasitic infection caused by the lung fluke, *Paragonimus westermani*.[13] Birt-Hogg-Dubé (BHD) syndrome may also mimic pulmonary LAM, with a similar clinical presentation (young female with recurrent pneumothorax); however, the cysts in BHD are surrounded by normal lung parenchyma without evidence of a proliferative neoplastic cell population or significant inflammation.[15]

Benign metastasizing leiomyoma (BML) is another neoplastic disease with clinical and pathologic features that overlap with LAM. Clinically, both processes affect middle-aged females and present with variable respiratory signs and symptoms. Histologically, LAM and BML are similarly comprised of low-grade spindle cell proliferations. However, the smooth muscle cells in BML usually forms small nodules with entrapped pnuemocytes, whereas the LAM cells are located in the expanded interstitium. The imaging study in BML typically shows multiple nodular infiltrates rather than the cysts expected in LAM, cystic changes in a case of BML have been described.[16] In addition, estrogen receptor (ER) and progesterone receptor (PR) are positive in both entities.[17] As such, melanocytic inmmunohistochemical markers, such as HMB-45 remain important in the pathologic distinction between BML and LAM.

The United Kingdom's national LAM database showed that 55% of patients developed Medical Research Council grade 3 dyspnea (breathlessness while walking on level ground) at 10 years after the onset of symptoms, while 10% were housebound due to dyspnea.[18] Survival rates at 5 and 10 years from the time of lung biopsy are 85.1% and 71.1%, respectively.[19] The higher percentage of lung tissue involved by cystic changes and the infiltration of LAM cells at the time of biopsy negatively impact survival.[19] Cigarette smoking is also a significant risk factor in disease progression.[18] Overall, TSC-LAM tends to demonstrate a milder course of disease progression compared to S-LAM.[8]

Since the neoplastic cells in LAM commonly express ER and PR, hormonal manipulation was historically considered a mainstay of treatment. There are studies demonstrating reductions in mortality in LAM cases treated with hormonal therapy.[20] However, randomized controlled trials evaluating the utility of hormonal agents in LAM are lacking.[8] A quarter of patients with LAM respond to inhaled bronchodilators and thus the agents are often administered in patients with airflow obstruction.[8]

Both TSC-LAM and S-LAM are associated with either *TSC1* or *TSC2* mutations, which cause continuous activation of the mechanistic target of rapamycin (mTOR) signaling pathway. The mTOR pathway activation leads to increased protein translation and proliferation, with reduced autophagy.[21] This underlying mechanism of tumorigenesis prompted a clinical trial of the mTOR inhibitor, sirolimus, in the treatment of LAM. Sirolimus has been shown to improve lung function and quality of life in people with LAM compared to placebo.[22] Accordingly, in 2015, the United States Food and Drug Administration (FDA) approved sirolimus (Rapamune®) for the treatment of LAM.[23] Lung transplantation is also an accepted therapy for end-stage LAM.[24] LAM patients who receive a lung transplant demonstrate superior results compared to patients transplanted for other indications, with rare instances of recurrence.[8]

Conclusion

Pulmonary LAM is a rare lung neoplastic process with microscopic findings that are often subtle. When faced with recurrent pneumothorax in a middle-aged woman, LAM should be considered in the differential diagnosis. The characteristic co-expression of myogenic and melanocytic immunohistochemical markers is a useful diagnostic feature. Since FDA-approved therapy is available, prompt diagnosis is crucial.

Conflict of Interest

None of the authors identify any conflict of interest.

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