Case Report

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TANAFFOS

From Cystic Lung Lesions to Pulmonary Lymphangioleiomyomatosis: A Case-Based Diagnostic and Therapeutic Approach

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Background: Lymphangioleiomyomatosis (LAM) is a rare, progressive cystic lung disease that primarily affects women of reproductive age. It arises from abnormal proliferation of smooth muscle-like cells, resulting in cystic lung remodeling, impaired airflow, and recurrent pneumothorax. Serum vascular endothelial growth factor D (VEGF-D) can support diagnosis, but normal levels do not exclude the disease.

Case Presentation: We describe a 37-year-old woman with six months of progressive dyspnea and hypoxia (SaO_2: 86%). High-resolution CT revealed diffuse, thin-walled cystic lesions. VEGF-D levels were within the normal range. Pulmonary function tests showed moderate obstructive impairment (FEV_1 61%, FEV_1/FVC: 64%) and reduced diffusing capacity (DLCO: 45%). Transbronchial lung biopsy confirmed LAM with HMB-45 positivity. Sirolimus therapy was initiated in response to symptomatic impairment.

Conclusion: This case shows that normal VEGF-D levels do not rule out LAM. Histopathologic confirmation remains essential when clinical and imaging findings are suggestive. Timely diagnosis enables initiation of mTOR inhibitor therapy, which can help stabilize lung function, manage cystic lesions, and inform decisions about further interventions, including lung transplantation.

Keywords: LAM; Lung lymphangioleiomyomatosis; PEComa; Cystic lung lesion; Serum vascular endothelial growth factor D

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare, progressive, cystic, and nodular lung disease caused by abnormal proliferation of perivascular and peribronchial smooth muscle cells in women of reproductive age. Previously classified as an interstitial lung disease (ILD) because of its diffuse nature, LAM is now categorized as a low-grade, destructive, metastatic lung tumor (Perivascular Epithelioid Cell Tumor: PEComa) in the latest World Health Organization (WHO) classification of lung tumors (1,2).

The infiltration and proliferation of LAM cells, consisting of two types (3): spindle-shaped myofibroblast-like cells and polygonal epithelioid cells, lead to:

1. Pulmonary vein obstruction, increased pulmonary venous pressure, and ultimately hemoptysis (1-5).

2. Enlargement of hilar and mediastinal lymph nodes and extrathoracic lymphadenopathy, leading to dilation of lymphatic vessels in the lungs, thoracic duct, and abdomen, which can cause chylothorax and chyloperitoneum.

3. Bronchial obstruction, dilation of air spaces, and the formation of cystic parenchymal lung lesions, whose destruction results in spontaneous pneumothorax (PTX) in LAM patients (1,3,6-8).

CASE SUMMARIES

A 37-year-old woman with no significant medical history presented with progressive dyspnea over six months and hypoxia (SaO_2: 86%). She initially consulted a cardiologist, who detected a pulmonary artery pressure (PAP) of 60 mmHg on echocardiography and referred her to a pulmonologist. Laboratory tests for antinuclear antibody (ANA), thyroid-stimulating hormone (TSH), and human immunodeficiency virus (HIV) were negative. A mild reticular pattern was observed on chest X-ray (CXR), prompting a high-resolution computed tomography (HRCT), which revealed diffuse thin-walled cystic lesions, raising suspicion of LAM (Figure 1).

Figure 1. Lung HRCT scan without contrast with diffuse, small, thin-walled lesions

Due to the absence of evidence for chylothorax, angiomyolipoma (AML), and tuberous sclerosis (TS) in association with cystic lesions on HRCT, serum levels of vascular endothelial growth factor D (VEGF-D) were measured according to the diagnostic algorithm, which yielded negative results (Figure 2).

LAM should be considered in the differential diagnosis of thin-walled, multicystic lung disease. In patients with characteristic CT findings, a clinical diagnosis is supported by the presence of tuberous sclerosis complex (TSC), chylothorax, lymphangiomyoma, or AML. If these features are absent, a VEGF-D level >800 pg/ml is diagnostic. In cases with negative VEGF-D, TBB, pleural fluid cytology, or fine-needle biopsy of abdominal or thoracic masses may provide a non-surgical diagnosis. If inconclusive, VATS (Video-assisted thoracoscopic surgery) biopsy can help differentiate LAM from other conditions such as emphysema, Langerhans cell histiocytosis, and lymphocytic interstitial pneumonitis or follicular bronchiolitis (9).

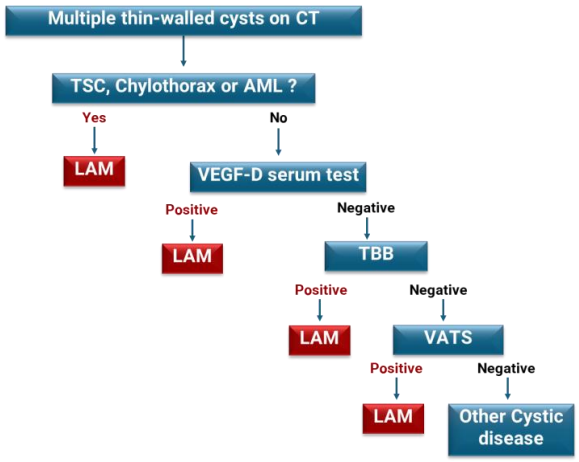

Figure 2. The diagnostic algorithm for a patient with suspicious pulmonary cystic lesions suggestive of LAM, adapted from the Murray book (9)

Consequently, for definitive diagnosis, bronchoscopy with transbronchial biopsy (TBB) was performed. Immunohistochemical (IHC) analysis of the biopsy sample showed HMB-45 staining of the cytoplasm in smooth muscle cells (Figure 3). Following the confirmed diagnosis of LAM and the presence of medical treatment indications, sirolimus therapy was initiated.

FEV1/FVC: 64 TLC: 140

FEV1: 61% RV: 245

FVC: 82% DLCO: 45%

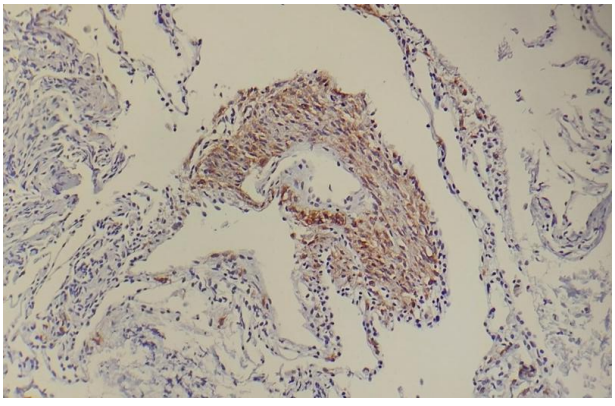

Figure 3. A transbronchial biopsy sample from the patient, obtained via bronchoscopy and stained with IHC using HMB-45, demonstrating brown-stained cytoplasm in smooth muscle cells

DISCUSSION

Lymphangioleiomyomatosis (LAM) is a low-grade, metastatic pulmonary cancer that affects women of reproductive age, with an incidence of approximately 1 in 1,000,000 in Europe and the United States. However, it is likely underdiagnosed because early stages are often asymptomatic and its clinical presentation resembles other pulmonary diseases. These factors have led to frequent misdiagnosis as obstructive or restrictive lung diseases, resulting in inappropriate treatments (1,2). Additionally, delayed diagnosis not only postpones treatment but also obscures the true prevalence of the disease (10-14).

LAM exists in two forms: sporadic LAM (LAM-S), accounting for 60% of cases, which presents at a younger age with fewer systemic complications, and LAM associated with tuberous sclerosis (LAM-TS), a congenital form that manifests later in life and is associated with more severe neurological and renal complications than pulmonary involvement (8). The underlying cause is a mutation in the TSC1 or TSC2 genes (3), leading to dysregulation of the mammalian target of rapamycin (mTOR) signaling pathway (7).

The clinical manifestations of LAM are diverse, with progressive dyspnea and recurrent pneumothorax (PTX) being the most common symptoms. Other symptoms include chest pain, cough, hemoptysis, chylothorax, ascites, and pericardial effusion (2,3,10,15-17). Notably, 50% of LAM patients present with spontaneous PTX (18-20), which is attributed to the proliferation of smooth muscle cells in vessel and bronchial walls, airway narrowing, alveolar damage, and cystic lesion formation with subsequent rupture (16).

Angiomyolipoma (AML) is observed in more than 90% of LAM-TS cases and 30-50% of LAM-S cases (19-21). LAM cells express high levels of estrogen and progesterone receptors (ER, PR), explaining the hormonal dependence of the disease (4,5). Estrogen receptor activation has been identified as a major factor in LAM progression in the lungs, explaining the worsening of LAM during pregnancy (7). Researchers suggest that estrogen plays a crucial role in LAM cell proliferation, migration, and metastasis. A study by Yu et al. (22) demonstrated that anti-estrogen therapy with tamoxifen reduced LAM cell growth. However, other studies reported that tamoxifen promoted AML cell growth, and letrozole worsened LAM symptoms. Due to these controversial findings, anti-hormonal therapy is not recommended for LAM treatment.

Radiologic and Pulmonary Function Findings

Chest X-rays (CXR) reveal mild reticular patterns in 80% of LAM patients. High-resolution CT (HRCT) shows multiple thin-walled cystic lesions, typically 2-5 mm in diameter, surrounded by normal lung parenchyma. As the disease progresses, cysts enlarge to over 1 cm. Small pleural-based nodules (1-3 mm), indicative of type II pneumocyte hyperplasia, may also be seen on HRCT (1,2).

Pulmonary function tests (PFTs) are often normal in early disease but progressively show airflow obstruction (↓FEV1) and reduced diffusing capacity (↓DLCO) (11). In some cases, both obstructive and restrictive patterns—similar to sarcoidosis, hypersensitivity pneumonitis (HP), pulmonary Langerhans cell histiocytosis (PLCH), and respiratory bronchiolitis-associated ILD (RB-ILD)—are observed.

LAM and Air Travel Risks

LAM patients have a threefold increased risk of PTX during air travel due to atmospheric pressure changes and the likelihood of subpleural cyst rupture (10). Therefore, pleurodesis is recommended to prevent PTX recurrence (10,16,17). Importantly, pleurodesis does not contraindicate lung transplantation in LAM patients who may require it in the future (16).

Diagnostic Approach

As described by Murray, if HRCT findings are consistent with LAM, the presence of at least one of the following—AML, TS, or chylothorax—confirms the diagnosis, and no further evaluation is needed. If none of these are present, vascular endothelial growth factor D (VEGF-D) levels should be measured, and a level above 800 pg/mL is diagnostic for LAM. If VEGF-D is inconclusive, as in our patient, a lung biopsy via video-

assisted thoracoscopic surgery (VATS) or open lung surgery is required for confirmation. Histopathologic examination with immunohistochemical (IHC) staining for HMB-45 and microphthalmia-associated transcription factor (MiTF) confirms the diagnosis of LAM (13,14,23).

Differential Diagnosis

The first step in differentiating LAM is distinguishing true cystic lesions with well-defined walls from lucent lesions without clear walls, such as emphysema. Other pulmonary cystic diseases that must be considered include (24,25):

- Pulmonary langerhans cell histiocytosis (PLCH)
- Lymphocytic interstitial pneumonitis (LIP)
- Pneumocystis jiroveci pneumonia (PJP)
- Bacterial and fungal infections (e.g., *Staphylococcus, Coccidioidomycosis, Paragonimus westermani*).

LIP is more common in children, typically presenting with pleural and pericardial effusions without HMB-45 positivity. PLCH affects male smokers aged 20-40 years and exhibits bizarre-shaped cystic lesions, whereas LAM cysts are uniform, small, and diffusely distributed throughout the lungs (8).

Supportive Care and Treatment

Supportive treatment for LAM patients with airflow obstruction includes inhaled bronchodilators. Oxygen therapy is recommended for hypoxic patients with dyspnea to maintain SaO_2>90% (26). All LAM patients should receive influenza and pneumococcal vaccinations. Additionally, patients on sirolimus therapy should receive the recombinant shingles vaccine to prevent herpes zoster reactivation. mTOR inhibitors such as everolimus and sirolimus are effective in the treatment of renal and pulmonary LAM by inhibiting T-cell proliferation (27-30).

The American Thoracic Society (ATS) and Japanese Respiratory Society (JRS) have defined the indications for initiating sirolimus therapy as follows: decline in FEV_1 below 70% of the predicted value, symptomatic chylous effusion, rapid decline in pulmonary function with an annual FEV_1 reduction of more than 90 cc, and signs indicating high disease burden such as hypoxia, air trapping, and decreased DLCO (31).

The effects and benefits of sirolimus include reduction in the size of pulmonary cysts, AML, lymphangioleiomyomas, and chylous effusions (32-34), improvement in pulmonary function with increased FEV_1 and FVC and decreased RV, and reduction in serum VEGF-D levels, which serves as both a diagnostic and prognostic marker.

The adverse effects of sirolimus include mucositis and oral ulcers, hypercholesterolemia, pneumonia, pyelonephritis, diarrhea, edema, and cellulitis (35). The recommended daily dose of sirolimus is 2 mg, achieving a serum concentration of 5–15 ng/mL (36). To evaluate the efficacy of sirolimus and ensure FEV_1 stability, spirometry with bronchodilator testing is performed every 3 months after initiating sirolimus for one year. Blood cell counts, liver and kidney function tests, urinalysis, and lipid panels are performed monthly for the first 3 months and then every 3 months thereafter (37). Due to the risk of bronchial anastomotic dehiscence after lung transplantation while on sirolimus (38), sirolimus is discontinued 6 weeks before transplantation (39).

Inhibition of Rho-GTPase with statins or inhibition of STAT3-JAK with interferon-gamma has also shown effectiveness (26). In any case, lung transplantation remains the definitive treatment for LAM, increasing patient survival rates to 79% at 1 year, 74% at 2 years, 64% at 5 years, and 52% at 10 years (40).

Indications for lung transplantation

1. FEV_1 <30% of the predicted value
2. Reduced quality of life, such as disability due to dyspnea or inability to maintain SaO_2 despite supplemental O_2 therapy (10).

CONCLUSION

LAM is a rare cystic lung disease occurring in women of reproductive age, characterized by dyspnea and recurrent PTX. The challenging diagnosis of LAM leads to delays in treatment initiation and worsens prognosis. The definitive treatment is lung transplantation, and if

transplantation is not immediately performed, mTOR inhibitors such as sirolimus can be used with blood level monitoring.

Consent to participate

Written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for the publication of any identifiable data included in this article.

Competing interests

The authors declare no competing interests.

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