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(CASE REPORT)

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Sporadic lymphangioleiomyomatosis in a 33-year-old female with no association with tuberous sclerosis complex: Case report and a brief literature review

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Abstract

Lymphangioleiomyomatosis (LAM) is an uncommon, low-grade neoplastic cystic lung illness that mostly affects women of reproductive age and may manifest randomly or in conjunction with tuberous sclerosis complex (TSC). This case details a 33-year-old nonsmoker female who had two previous spontaneous pneumothoraces without clinical signs of TSC, as well as an 18-month history of worsening exertional dyspnea and a nonproductive cough that were first treated as asthma. Spirometry showed a mild obstructive pattern and decreased diffusing capacity, whereas high-resolution computed CT showed widespread thin-walled lung cysts with undamaged intervening parenchyma. A diagnosis of sporadic LAM was supported by a significantly elevated serum vascular endothelial growth factor-D (VEGF-D) level (1,200 pg/mL). A transbronchial biopsy showed bland spindle cells that were positive for melan-A, HMB-45, and smooth muscle actin, consistent with perivascular epithelioid cells (LAM cells) origin. Sporadic illness was confirmed by next-generation sequencing, which found a somatic TSC2 frameshift mutation without germline change.

In addition to immunization and pneumothorax precautions, the patient was given sirolimus and inhaled tiotropium. She had very mild side effects during the 18-month follow-up, including increased exercise tolerance, a stable cystic load, improved FEV1, and lowered VEGF-D levels. This case demonstrates the effectiveness of mTOR inhibition in halting disease progression and underscores the utility of a noninvasive, biomarker- and imaging-based diagnostic strategy for sporadic LAM.

Keywords: Lymphangioleiomyomatosis; Perivascular epithelioid cells; Perivascular epithelioid cell tumor; Tuberous sclerosis complex; High-resolution chest CT; Vascular endothelial growth factor-D

1. Introduction

Perivascular epithelioid cells (LAM cells) are abnormal, smooth-muscle-like cells that drive Lymphangioleiomyomatosis (LAM), a rare progressive disease affecting the lungs, lymphatics, and kidneys. They belong to the PEComa (perivascular epithelioid cell tumor) family and are characterized by the co-expression of muscle and melanocytic markers. [1]

LAM is a rare, progressive disease characterized by cystic destruction of the lungs, milky fluid buildup around the lungs (chylothorax), and benign abdominal tumors. It affects up to 40% of women with tuberous sclerosis complex (TSC). [2] Sporadic cases of LAM also occur and are not as commonly associated with abdominal tumors. The pathophysiology of tuberous sclerosis-associated LAM is a loss-of-function mutation in TSC2. This mutation fails to suppress mTORC1

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signaling, resulting in uncontrolled smooth muscle cell growth. This mutation rarely occurs in the sporadic form of LAM. [3]

Patients with LAM usually present clinically with progressive exertional dyspnea. In smokers, this can lead to the misdiagnosis of COPD and delay the actual diagnosis of LAM by 3-5 years. [4] A hallmark presentation is recurrent pneumothorax in women aged 30 to 40 years. Chylothorax is also a common presentation in about 20% of patients. [4] Diagnostic characteristics of LAM include the presence of TSC or angiomyolipomas (AMLs) in a woman with characteristic diffuse thin-walled cystic changes on a high-resolution chest computed tomography scan. [2] A definitive diagnosis is made using a thoracoscopic biopsy because half of the women with LAM do not have AMLs. Serum VEGF-D is also a clinically useful diagnostic test that can distinguish sporadic LAM from other cystic and chylous lung diseases. [1] VEGF-D induces lymphangiogenesis and promotes the spread of tumor cells to lymph nodes. The use of VEGF reduces the need for lung biopsy because of the high specificity for accurately determining the presence and severity of LAM. [2]

Currently, sirolimus appears to be the most effective treatment for LAM, but the patient would need to be managed carefully because lung function declines upon discontinuation of the drug. [5]

We report this case to highlight the indolent course of LAM and the delay in diagnosis in a woman previously diagnosed with asthma and no history of tuberous sclerosis. The patient presented with progressive dyspnea on exertion and intermittent nonproductive cough and spontaneous pneumothoraces over the prior three years. This case underscores the importance of maintaining a high index of suspicion for LAM in women presenting with recurrent pneumothorax and diffuse cystic lung disease.

2. Case Presentation

2.1. Clinical Presentation

A 33-year-old female nonsmoker presented with an 18-month history of progressive dyspnea on exertion and intermittent nonproductive cough. She had experienced two spontaneous pneumothoraxes over the prior three years, each managed conservatively with chest tube drainage. Her symptoms recently worsened, limiting her to walking one block on level ground, which prompted her current evaluation. She denied hemoptysis, fever, or weight loss. Previous management had included inhaled bronchodilators for presumed asthma, with no symptomatic benefit. There was no history of TSC or known family history of pulmonary disease. She sought medical attention due to declining functional capacity and fear of recurrent pneumothorax.

2.2. Physical Examination, Labs, Imaging, and Differential Diagnosis

Physical examination revealed a thin female in no acute distress. Chest auscultation showed clear breath sounds without wheezes or crackles. No clubbing, cyanosis, or lymphadenopathy was present. Personal history was negative for seizures, renal angiomyolipomas, or skin lesions. Family history was unremarkable for TSC or cystic lung disease. Lab work, including complete blood count, basic metabolic panel, and autoimmune serologies (ANA, RF, anti-CCP, ANCA), was unremarkable. High-resolution chest CT (HRCT) demonstrated multiple thin-walled cysts diffusely distributed throughout both lungs, predominantly in the mid and lower lung zones, with normal intervening parenchyma. No chylous effusions were seen. Spirometry showed a moderate obstructive pattern (FEV1/FVC 65%, FEV1 55% predicted) with mildly reduced diffusing capacity of the lungs for carbon monoxide (DLCO) (50% predicted). Clinical differential diagnosis included pulmonary Langerhans cell histiocytosis (PLCH), Birt-Hogg-Dubé syndrome, and lymphoid interstitial pneumonia. Radiologic differential centered on LAM versus pulmonary Langerhans cell histiocytosis (PLCH), though the absence of upper-zone predominance and nodules favored LAM.

2.3. Multidisciplinary Tumor Board Discussion and Management Decisions

The tumor board, including pulmonology, thoracic radiology, and pathology, focused on confirming the diagnosis of sporadic LAM given the patient's age, sex, cystic HRCT pattern, and absence of TSC stigmata. The team debated whether to pursue a transbronchial lung biopsy or serum vascular endothelial growth factor-D (VEGF-D) testing as the next diagnostic step.

Given the moderate disease severity and the patient's preference to avoid an invasive biopsy, consensus favored obtaining serum VEGF-D levels. The board also discussed initiating sirolimus therapy if VEGF-D was elevated above 800 pg/mL, given evidence of progression. Recommended next steps included serum VEGF-D assay, baseline renal ultrasound to exclude occult AMLs, and pulmonary rehabilitation.

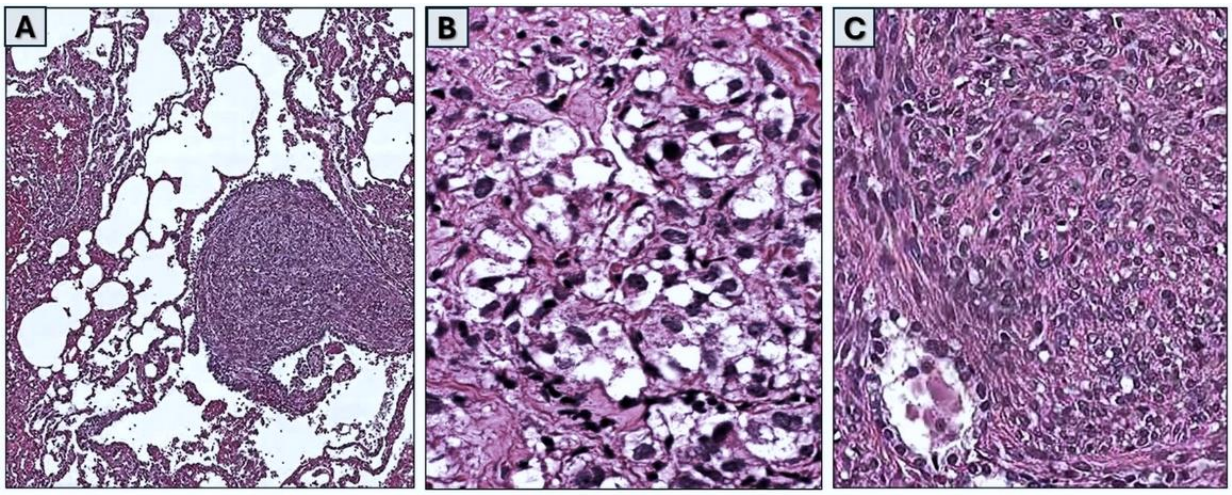
2.4. Special Studies, Pathology, and Molecular Testing

Serum VEGF-D returned markedly elevated to 1,200 pg/mL, establishing a diagnosis of sporadic LAM without the need for tissue biopsy. However, given the moderate disease and planned sirolimus therapy, bronchoscopy with transbronchial biopsy was performed to exclude infection and confirm typical histology.

On microscopic examination, the lung tissue was broken by scattered, thin-walled, round air cysts of various sizes. Cellular bundles abnormally thickened the walls of the cysts and the surrounding small airways. Two main types of abnormal cells were identified: one was long, thin spindle cells in the centers of the cell clusters, proliferating along alveolar septa and lymphatics. The other type of cells were plump, round epithelial cells with clear pink centers on the outer edges. Immunohistochemistry (IHC) revealed positive staining for smooth muscle actin (SMA), HMB-45, and melan-A (MART-1), and negative staining for cytokeratin and S-100. These findings confirmed that the LAM cells were of perivascular epithelioid cell (PEComa) origin. Molecular studies using next-generation sequencing of biopsy tissue identified an activating mutation in TSC2 (c.2026delC, frameshift), with no germline TSC1 or TSC2 mutations detected in peripheral blood, confirming sporadic disease.

2.5. Treatment, Outcome, and Follow-Up at 18 Months

The patient started on sirolimus (2 mg daily, adjusted to a trough level of 5-10 ng/mL) and inhaled tiotropium for symptom control. She underwent pneumococcal and influenza vaccination and was counseled on air travel and pneumothorax precautions. At 18-month follow-up, she reported significant improvement in exercise tolerance, able to walk four to five blocks without stopping. Repeat HRCT showed no new cyst formation or progression of existing cysts, and stable mild bilateral disease. Spirometry demonstrated improvement in FEV1 (65% predicted) and stable DLCO (52% predicted). Serum VEGF-D decreased to 750 pg/mL. She experienced mild oral ulcers and hypercholesterolemia, managed with topical mouthwash and atorvastatin. No pneumothoraces occurred. Renal ultrasound remained normal. She continues sirolimus with annual HRCT, pulmonary function tests, and VEGF-D monitoring.



1A: Low power view showing lung tissue, broken by scattered, thin-walled, round air cysts and cell clusters of various sizes (H&E X20); 1B: High power view showing clear plump, round epithelioid cells with clear pink centers on the outer edges of the aggregates (H&E X60); 1C: High power view showing thin spindle cells in the center of the cell clusters proliferating along alveolar septa and lymphatics (H&E X40)

Figure 1 Microscopic features of lymphangioleiomyomatosis

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification):

LAM is a rare, progressive multisystem disease characterized by the proliferation of abnormal smooth muscle–like LAM cells. The disease was first described in 1918 by René Lutembacher in a woman with TSC, with the first report of sporadic LAM published by von Stössel in 1937. [6] According to the World Health Organization (WHO), LAM is classified as a low-grade metastasizing PEComa. [7, 8]

LAM occurs either sporadically (sporadic LAM [S-LAM]) or in association with TSC, an autosomal dominant multisystem disorder caused by pathogenic variants in the TSC1 or TSC2 genes. While TSC-associated LAM may occur in both men

and women, sporadic LAM almost exclusively affects women of reproductive age, with a mean age at diagnosis in the third to fourth decades of life. [9] The estimated annual incidence is 0.23–0.31 cases per million women, with a prevalence of approximately 3.4–7.8 cases per million women worldwide. [6,9,10]

The pathogenesis of LAM is driven by loss of function of the TSC1 or, more commonly, TSC2 tumor suppressor genes, resulting in constitutive activation of the mammalian target of rapamycin (mTOR) signaling pathway and uncontrolled proliferation of LAM cells. In sporadic LAM, patients generally lack germline TSC1/TSC2 mutations, whereas affected tissues frequently harbor somatic "two-hit" mutations, particularly involving TSC2, supporting a neoplastic mechanism of disease. [6] Disease progression also appears to be influenced by estrogen, as LAM cells express estrogen receptors and pulmonary manifestations may worsen during pregnancy or following exogenous estrogen exposure. [7,9]

LAM primarily affects the lungs but may also involve the lymphatic system and kidneys, where ALMs are a characteristic extrapulmonary manifestation. Progressive cystic destruction of the pulmonary parenchyma leads to declining lung function and clinical manifestations including exertional dyspnea, recurrent spontaneous pneumothorax, chylous pleural effusions, and, less commonly, lymphangiomyomas. [8,9] HRCT, demonstrating diffuse, bilateral, thin-walled pulmonary cysts, remains the cornerstone of diagnosis and, when combined with characteristic extrapulmonary features or elevated VEGF-D levels, may establish the diagnosis without the need for lung biopsy. [8]. Distinguishing sporadic LAM from TSC-associated LAM has important implications for genetic evaluation, surveillance for extrapulmonary manifestations, and long-term management

3.2. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, lab, diagnosis, management and outcome)

The presentation of this case closely mirrored established patterns in the literature while highlighting critical diagnostic challenges in sporadic LAM. Consistent with recent case series, the patient initially experienced recurrent spontaneous pneumothoraces and progressive exertional dyspnea, which were mistakenly attributed to asthma due to a moderate obstructive pattern on spirometry. [11,12] This misdiagnosis is frequently reported in young women with LAM, leading to significant delays in appropriate management. [4]

The use of serum VEGF-D in this case aligned with current diagnostic guidelines, which state that a level exceeding 800 pg/mL, in the presence of characteristic cystic changes on high-resolution computed tomography, is diagnostic of LAM, often circumventing the need for surgical lung biopsy. [13] However, unlike many cases where the diagnosis relies solely on serology, a transbronchial biopsy was performed here, successfully identifying the classic perivascular epithelioid cell proliferation and activating somatic mutation in TSC2 (c.2026delC). [15]

The patient's robust clinical and functional response to the mTOR inhibitor sirolimus further corroborated findings from the landmark MILES trial, reinforcing the efficacy of targeted therapy in stabilizing lung function and reducing symptoms in moderate-to-severe sporadic LAM. [5]

4. What Have We Learned from This Case?

This case underscored several critical clinical insights for the management of young women presenting with recurrent pneumothorax and obstructive lung disease. A key diagnostic lesson was the necessity of maintaining a high index of suspicion for rare cystic lung diseases when patients with presumed asthma fail to respond to standard bronchodilator therapy, especially in the context of recurrent pneumothoraces. [5,11] Clinicians should recognize persistent exertional dyspnea and spontaneous pneumothorax in a young, non-smoking female as significant red flags warranting prompt high-resolution chest imaging.

This case reinforced the utility of serum VEGF-D as a highly specific, noninvasive diagnostic biomarker that can streamline the diagnostic pathway and reduce the reliance on invasive surgical biopsies. [13,14] The successful identification of a somatic TSC2 mutation via transbronchial biopsy also highlighted the evolving role of precision medicine and molecular diagnostics in confirming sporadic LAM.

For long-term management, the prompt initiation of sirolimus demonstrated significant clinical benefit, emphasizing the importance of early targeted intervention to stabilize pulmonary function and prevent further cystic destruction. [5] Ultimately, this case challenged the routine acceptance of common obstructive diagnoses in atypical demographics and reinforced the value of a multidisciplinary approach in managing complex, rare pulmonary disorders.

Abbreviations

- Lymphangioleiomyomatosis (LAM);
- Perivascular epithelioid cells (LAM cells);
- perivascular epithelioid cell tumor (PEComa);
- Tuberous sclerosis complex (TSC);
- Angiomyolipomas (AMLs);
- High-resolution chest CT (HRCT);
- Vascular endothelial growth factor-D (VEGF-D); Immunohistochemistry (IHC)

5. Conclusion

This case report highlighted the successful diagnosis and management of sporadic lymphangioleiomyomatosis in a young woman initially misdiagnosed with treatment-resistant asthma. By detailing the clinical progression from recurrent pneumothoraces to the definitive diagnosis, with elevated serum VEGF-D and a transbronchial biopsy revealing a somatic TSC2 mutation, this report provides valuable evidence for the clinical utility of noninvasive biomarkers and targeted molecular testing.

We presented this case to emphasize the critical need for early recognition of LAM in young females with unexplained obstructive lung disease and to demonstrate the profound clinical impact of early intervention with mTOR inhibitors like sirolimus. Ultimately, this case served as an important reminder to the medical community to broaden the differential diagnosis in atypical presentations of common respiratory symptoms, thereby reducing diagnostic delays and improving patient outcomes in rare cystic lung diseases.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

This work did not involve any studies on human or animal subjects performed by the authors. It was a retrospective review of archival pathology material collected during routine clinical care, and all data were fully de-identified before analysis.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

Informed consent for the publication of this case was obtained from the patient.

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