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A Rare Case of Progressive Dyspnea-Lymphangioleiomyomatosis

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Abstract

This report details the diagnosis and management of a 60-year-old postmenopausal woman presenting with a 3-year history of progressive exertional dyspnea. High-resolution computed tomography (HRCT) revealed diffuse, thin-walled cystic lung lesions. Serum vascular endothelial growth factor-D (VEGF-D) was below the diagnostic threshold (800 pg/mL), and no other non-invasive confirmatory features, such as tuberous sclerosis complex, renal angiomyolipoma, chylous effusion, or lymphangioleiomyoma, were present; therefore, a video-assisted thoracoscopic surgery (VATS)-guided surgical lung biopsy was pursued. Histopathology confirmed the diagnosis of lymphangioleiomyomatosis (LAM) through the identification of proliferating spindle-shaped cells within cyst walls that stained positive for HMB-45, smooth muscle actin (SMA), and estrogen receptors. The patient was treated with sirolimus (titrated to a target trough of 5 - 15 ng/mL), resulting in stabilized lung function and the ability to discontinue supplemental oxygen after 12 months. The case underscores the importance of considering LAM in the differential diagnosis of diffuse cystic lung disease in women of all ages, including those who are postmenopausal.

Keywords

Lymphangioleiomyomatosis, Dyspnea, HRCT

1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare, progressive, low-grade neoplastic lung disease caused by the proliferation of perivascular epithelioid cells (LAM cells) [1]. Similar to smooth muscle-like cells, LAM cells proliferate and destroy lung parenchyma. The disease is predominantly seen among females of reproductive age, with a mean age of diagnosis of approximately 35 years [1]. It involves

multiple systems and can lead to angiomyolipomas, cystic lesions of the axial lymph nodes, and gradually worsening dyspnea. It can also be associated with the tuberous sclerosis complex (TSC-LAM form). LAM cells characteristically express vascular endothelial growth factor (VEGF-C and VEGF-D), which is frequently used as a diagnostic biomarker [1] [2]. Sporadic LAM has an estimated prevalence of approximately 3.4 - 7.8 per million women, though this is likely an underestimate due to underdiagnosis and diagnostic delay [1].

LAM cell growth results in bronchiolar obstruction and cyst formation, which ultimately induce excessive distension and lung parenchyma destruction, potentially resulting in pneumothorax. Imaging, such as high-resolution computed tomography (HRCT), reveals lung cysts with thin walls surrounded by normal parenchyma [1]. Although pulmonary function tests are typically performed to establish a baseline, they usually reveal obstructive characteristics and a markedly reduced diffusion capacity for carbon monoxide (DLCO), which is reduced in approximately 90% of patients [1]. A lung biopsy that histologically reveals lung cysts and LAM cells positive for smooth muscle actin (SMA), estrogen receptors, and Human Melanoma Black-45 (HMB-45) can confirm the diagnosis when non-invasive criteria are not met [1]. Abdominopelvic imaging is recommended at diagnosis to evaluate for renal angiomyolipomas and retroperitoneal lymphadenopathy, as identification of these entities can obviate the need for biopsy [1].

LAM cells exhibit worsening proliferation when exposed to estrogen surges during pregnancy, menstruation, and oral contraceptive use [1]. Although lung function decline in LAM is more rapid in premenopausal women and slows after menopause, the disease may present or progress after menopause [1]. Such presentations in postmenopausal women are uncommon and may reflect delayed diagnosis rather than late-onset disease, as the slower rate of decline in lung function observed after menopause may contribute to diagnostic delay [1] [3].

2. Case Presentation

A 60-year-old female presented to the pulmonology clinic for evaluation of progressive dyspnea. She had been referred for a 3-year history of gradually worsening exertional dyspnea, initially noticed with exertion, which had progressed to limit activities of daily living. For the last 2 weeks, she had required 2L supplemental oxygen at home after pulse oximetry at the primary care office revealed oxygen saturation of 82% on room air.

She had no history of smoking. She denied any history of lung disease before the onset of this disease. She had never had exposure to silica, asbestos, or coal dust. She denied exposure to tuberculosis or travel outside the country. She did not have any exposure to caves or animals. There was no pertinent family history of pulmonary diseases.

On examination, the patient appeared comfortable at rest on 2 liters per minute of supplemental oxygen via nasal cannula. Vital signs revealed blood pressure 128/76 mmHg, heart rate 78 beats per minute, respiratory rate 18 breaths per mi-

nute, temperature 36.8˚C (98.2˚F), and oxygen saturation 94% on 2L supplemental oxygen (88% on room air). Body mass index was 24.5 kg/m^2.

Physical examination demonstrated clear lung fields bilaterally without wheezes, crackles, or rhonchi. Dermatologic examination revealed no facial angiofibromas, periungual fibromas, or hypomelanotic macules. The rest of the physical exam was non-contributory. Initial spirometry revealed an obstructive pattern with FEV_1 56% predicted and FVC 88% predicted, with a ratio of 0.63 and no bronchodilator response. The patient had markedly reduced diffusion capacity with DLCO of 50% predicted. Arterial blood gas showed pCO_2 36 mmHg, pO_2 58 mmHg, and oxygen saturation 88%.

Alpha-1 antitrypsin level was 142 mg/dL with the MM genotype (normal). Antinuclear antibody, rheumatoid factor, anti-SSA/SSB antibodies, angiotensin-converting enzyme level, and total eosinophil count were unremarkable. HRCT revealed bilateral, diffuse, uniform thin-walled cystic lesions present throughout all lung zones with normal-appearing intervening lung parenchyma.

Serum VEGF-D was measured at 420 pg/mL, which was below the diagnostic threshold of ≥800 pg/mL and therefore non-diagnostic. Contrast-enhanced abdominopelvic CT was performed to screen for renal angiomyolipomas and retroperitoneal lymphangioleiomyomas; no angiomyolipomas, lymphangioleiomyomas, or lymphadenopathy were identified. A detailed history and physical examination for features of tuberous sclerosis complex (TSC) was performed, including assessment for dermatologic stigmata (facial angiofibromas, shagreen patches, periungual fibromas, hypomelanotic macules), neurologic features, and retinal hamartomas; no features of TSC were identified. No chylous effusions were present.

Given the characteristic HRCT findings in the absence of any non-invasive confirmatory features (no TSC, no angiomyolipomas, non-diagnostic VEGF-D, no chylous effusion, no lymphangioleiomyoma), a video-assisted thoracoscopic surgery (VATS)-guided surgical lung biopsy of the right middle lobe was pursued for definitive diagnosis, consistent with ATS/JRS guideline recommendations. Histopathology demonstrated proliferation of spindle-shaped and epithelioid LAM cells within the walls of cystic spaces and along small airways, with a bland appearance and few mitoses. Immunohistochemistry was positive for HMB-45, smooth muscle actin (SMA), and estrogen receptors, confirming the diagnosis of lymphangioleiomyomatosis.

The patient was started on sirolimus 2 mg daily, with dose titration guided by whole blood trough concentrations targeting 5 - 15 ng/mL, consistent with FDA-approved dosing for LAM. Trough levels were measured at 10 - 20 days and subsequently every 3 months once a stable dose was achieved. The patient was counseled to avoid estrogen-containing medications.

At 12-month follow-up, the maintenance sirolimus dose was 2 mg daily with a trough level of 7.1 ng/mL. Lung function slightly improved with FEV_1 of 60% predicted and diffusion capacity of 54% predicted. The patient had improvement in

subjective dyspnea and resting oxygen saturation had improved to 93% on room air (from 88% at baseline), meeting criteria for discontinuation of supplemental oxygen.

Adverse effects during the treatment period included mild oral mucositis in the first 3 months, which resolved spontaneously, and mild hyperlipidemia managed with dietary modification; no serious adverse events occurred. Pulmonary function testing was scheduled every 6 months for ongoing monitoring, and abdominopelvic imaging was planned annually to screen for the development of angiomyolipomas.

3. Discussion

This case illustrates the diagnosis and management of sporadic lymphangioleiomyomatosis (LAM) in a postmenopausal woman, a presentation that, while atypical in terms of age, highlights the importance of considering LAM in the differential diagnosis of diffuse cystic lung disease regardless of patient demographics.

The diagnosis of LAM can be established through several pathways. The ATS/JRS clinical practice guidelines recommend that a diagnosis of LAM can be made without biopsy when characteristic HRCT findings (bilateral, diffuse, round, thin-walled cysts in an otherwise normal lung parenchyma) are present in combination with any of the following: tuberous sclerosis complex, renal angiomyolipoma, elevated serum VEGF-D (≥800 pg/mL), chylous effusion, lymphangioleiomyoma, or cystic lymphangioleiomyomas confirmed by biopsy at another site [1]. A serum VEGF-D concentration of >800 pg/mL in the presence of characteristic cysts on CT is associated with a sensitivity of approximately 60% - 70% and specificity of nearly 100% for distinguishing LAM from other cystic lung diseases; however, approximately 30% of patients with LAM have VEGF-D levels below this threshold, and a negative result does not exclude the diagnosis [2] [3]. In this patient, serum VEGF-D was 420 pg/mL (non-diagnostic), no TSC features were identified on detailed clinical evaluation, abdominopelvic CT showed no angiomyolipomas or lymphangioleiomyomas, and no chylous effusions were present. Therefore, a VATS-guided surgical lung biopsy was required for definitive diagnosis before initiation of pharmacotherapy, consistent with guideline recommendations that a definite diagnosis should be established before starting mTOR inhibitor therapy [1].

The histopathologic hallmark of LAM is the proliferation of abnormal smooth muscle-like LAM cells that have a spindle-shaped or epithelioid morphology with few mitoses and a bland appearance [1] [4]. These cells stain positive for smooth muscle markers (including smooth muscle actin), the melanocytic marker HMB-45, and estrogen/progesterone receptors, an immunohistochemical profile characteristic of perivascular epithelioid cell tumors (PEComas) [1] [4]. In this case, the biopsy demonstrated proliferating spindle-shaped cells within cyst walls positive for HMB-45, SMA, and estrogen receptors, confirming the diagnosis.

The differential diagnosis of diffuse cystic lung disease on HRCT is broad and includes pulmonary Langerhans cell histiocytosis (PLCH), lymphocytic intersti-

tial pneumonia (LIP), and emphysema [1]. Several features help distinguish LAM from these entities. LAM cysts are characteristically round, thin-walled, uniform in size, and diffusely distributed throughout all lung zones, without sparing the costophrenic angles, in contrast to PLCH, where cysts are irregular in shape, spare the costophrenic angles, and are associated with nodules [1]. Birt-Hogg-Dubé syndrome produces cysts that are predominantly basilar and medial, often lenticular in shape, and is associated with renal tumors and skin fibrofolliculomas [1]. The absence of smoking history in this patient helped exclude PLCH and emphysema, while the normal alpha-1 antitrypsin level and genotype excluded.

The age of presentation in this case, 60 years, is notably older than the typical age at diagnosis for sporadic LAM, which is usually in the third to fourth decade [1]. However, LAM in postmenopausal women has been increasingly recognized, and the 3-year history of progressive symptoms suggests that disease onset may have occurred in the late perimenopausal period. Although LAM predominantly affects premenopausal women, it can present or progress after menopause, and age alone should not exclude the diagnosis [1] [3]. The slower rate of decline in lung function observed in postmenopausal women compared to premenopausal women may contribute to delayed diagnosis in this population [1].

The pathogenesis of LAM involves dysregulation of the mechanistic target of rapamycin (mTOR) signaling pathway. LAM cells harbor inactivating mutations in the TSC1 or TSC2 tumor suppressor genes, leading to constitutive activation of the mTOR complex 1 (mTORC1), which promotes cell growth, proliferation, and survival [1]. This molecular understanding provided the rationale for the use of mTOR inhibitors in LAM treatment.

The landmark Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) trial, a randomized, double-blind, placebo-controlled study of 89 patients with LAM and $FEV_1 \leq 70\%$ predicted, demonstrated that sirolimus stabilized lung function (FEV_1 change of $+1 \pm 2$ mL/month vs. -12 ± 2 mL/month for placebo; $p < 0.001$), improved quality of life, and reduced serum VEGF-D levels [5] [6]. In the MILES trial, sirolimus was initiated at 2 mg daily and titrated to maintain a blood trough of 5 - 15 ng/mL, with a mean sirolimus trough concentration of 7.2 ng/mL [1].

However, lung function decline resumed after discontinuation of sirolimus, suggesting that ongoing therapy is necessary to maintain benefit [5] [6]. Long-term observational data have demonstrated sustained efficacy over 5 years, with 59% of patients maintaining a positive response and an acceptable safety profile [3] [7]. A large registry study of 574 patients demonstrated that sirolimus therapy was associated with an 85% reduction in the 8-year risk of death (HR 0.149; 95% CI 0.075 - 0.299) [8]. Based on these results, the ATS/JRS guidelines conditionally recommend sirolimus for patients with LAM who have $FEV_1 \leq 70\%$ predicted, chylous complications, rapidly declining lung function (FEV_1 decline ≥ 90 mL/year), or other measures suggesting substantial disease burden, such as abnormal diffusion capacity or the need for supplemental oxygen [1].

Additional management considerations for LAM include avoidance of estro-

gen-containing medications (oral contraceptives, hormone replacement therapy), as estrogen promotes LAM cell proliferation [1]. Pneumothorax is a common complication, occurring in approximately 505 - 80% of LAM patients over their lifetime, and early definitive treatment (pleurodesis) should be considered after the first pneumothorax given the high recurrence rate [1]. Importantly, prior pleurodesis is not a contraindication to future lung transplantation, which remains an option for patients with progressive disease refractory to medical therapy [1]. Screening for renal angiomyolipomas with abdominal imaging is recommended at diagnosis and periodically thereafter, even in sporadic LAM, as angiomyolipomas are found in approximately 30% - 40% of sporadic LAM patients [1].

This case highlights several important clinical learning points. First, LAM should be considered in the differential diagnosis of diffuse cystic lung disease in women of any age, including postmenopausal women. Second, when characteristic HRCT findings are present but non-invasive confirmatory criteria are not met (no TSC, no angiomyolipomas, non-diagnostic VEGF-D), surgical lung biopsy remains necessary for definitive diagnosis before initiating mTOR inhibitor therapy. Third, sirolimus is the standard of care for LAM patients with declining or abnormal lung function, with evidence of stabilization and modest improvement in pulmonary function. Fourth, long-term monitoring of lung function, renal imaging, and sirolimus drug levels and adverse effects is essential.

This is a single case report and therefore cannot distinguish between delayed recognition and true late-onset disease in this postmenopausal patient. The practical implication for clinicians is that LAM should remain in the differential diagnosis of diffuse cystic lung disease in women, regardless of menopausal status, and a low threshold for HRCT and further workup should be maintained even in older women presenting with unexplained obstructive lung disease and cystic changes.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

AI-Assisted Tool Disclosure

AI was used to assist with the language polishing of this manuscript, improving its fluency and clarity of expression.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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