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Case Report

Concurrent Pulmonary and Extra-Pulmonary Lymphangioleiomyomatosis: A Case Report

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Abstract:

This retrospective study reports a case of a 37-year-old female patient initially diagnosed with benign leiomyoma based on a pelvic mass, later confirmed as lymphangioleiomyomatosis (LAM) involving both the lungs and the left broad ligament. The patient had been misdiagnosed with pneumothorax due to pulmonary cystic lesions, leading to a diagnostic delay of 60 months. Combining this patient's diagnostic and therapeutic course, we systematically analyze the clinical characteristics and treatment advances in pulmonary LAM (PLAM). We focus on the current status and future directions of mTOR inhibitors, novel targeted agents, and personalized treatment strategies, aiming to provide insights for clinical practice.

Keywords: lymphangioleiomyomatosis; histopathology; immunohistochemical phenotype; misdiagnosis

Introduction

Lymphangioleiomyomatosis (LAM) is a rare systemic neoplastic disease belonging to the perivascular epithelioid cell tumor (PEComa) family, with an incidence of approximately one per million. It predominantly affects women of childbearing age. Over 90% of cases involve the lungs, manifesting as progressive pulmonary cystic changes, pneumothorax, and chylothorax, ultimately leading to respiratory failure. Extrapulmonary LAM (e.g., retroperitoneal, pelvic) occurs in less than 10% of cases and is highly prone to misdiagnosis. The pathogenesis of LAM is associated with mutations in the TSC1/TSC2 genes or sporadic abnormal activation of the mTOR pathway; however, no cure currently exists. This report presents a case of combined pulmonary and extrapulmonary lymphangioleiomyomatosis and discusses diagnostic and therapeutic advances.

Case Report

A 37-year old female was admitted to our hospital's gynecology department in 2018 with mild abdominal distension and pain for 2 months and a newly discovered pelvic mass for half a month. The chest CT scan at the hospital indicated diffuse lesions in both lungs (Figure 1). Gynecological ultrasound revealed a cystic mass (61x45mm) in the left adnexal region and pelvic fluid. Routine blood tests and vaginal infection panels were normal. The tumor marker CA125 was elevated at 45.4 ng/ml, while CEA, AFP, and CA199 were normal. Repeat ultrasound showed "Cystic mass in left adnexa: Hydrosalpinx? (84x49mm), Pelvic fluid." Exploratory laparotomy and mass excision were performed. Intraoperatively, the uterus and bilateral adnexa appeared normal, but the left broad ligament was enlarged (approx. 6x5x4 cm), cystic, and adherent to the bowel via membranous adhesions. Postoperative pathology was reported as "leiomyoma"(Figure 2). Forty days postoperatively, the patient developed ascites. Chylous fluid was drained via culdocentesis (Figure 3). Ascites analysis showed a positive Rivalta test, +++ red blood cells, and LDH 162 U/L. Reviewing her history, she had undergone resection for "pulmonary cysts" at another hospital in 2013, which was misdiagnosed as pneumothorax pathology.

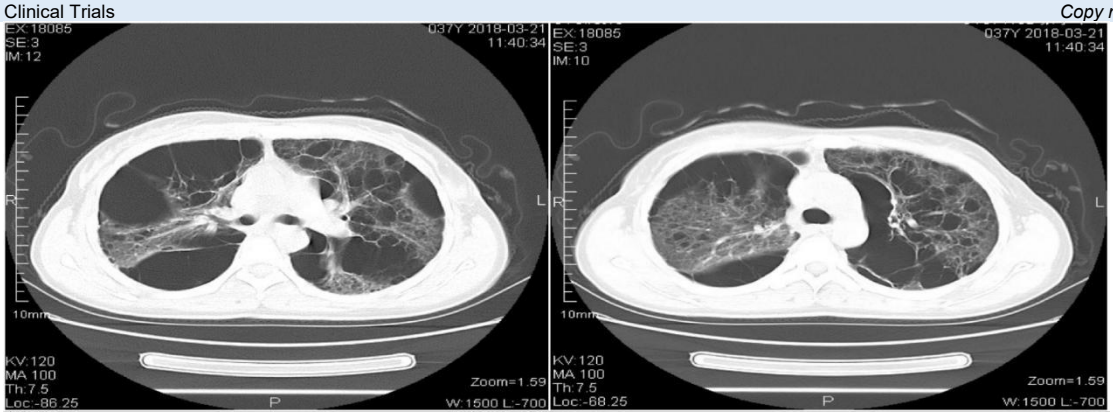
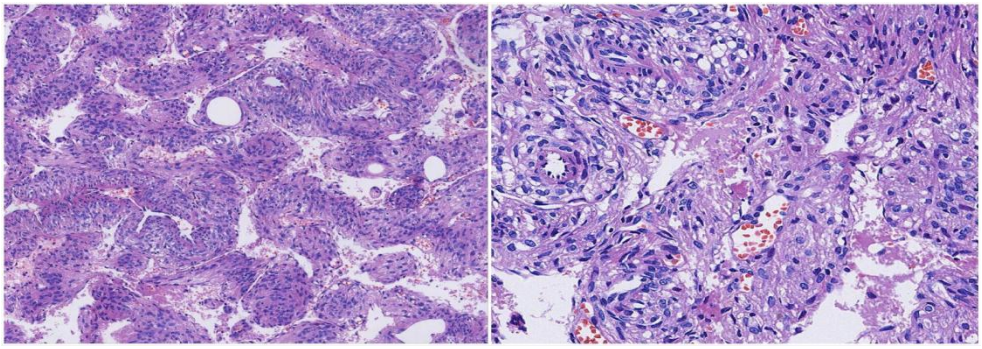


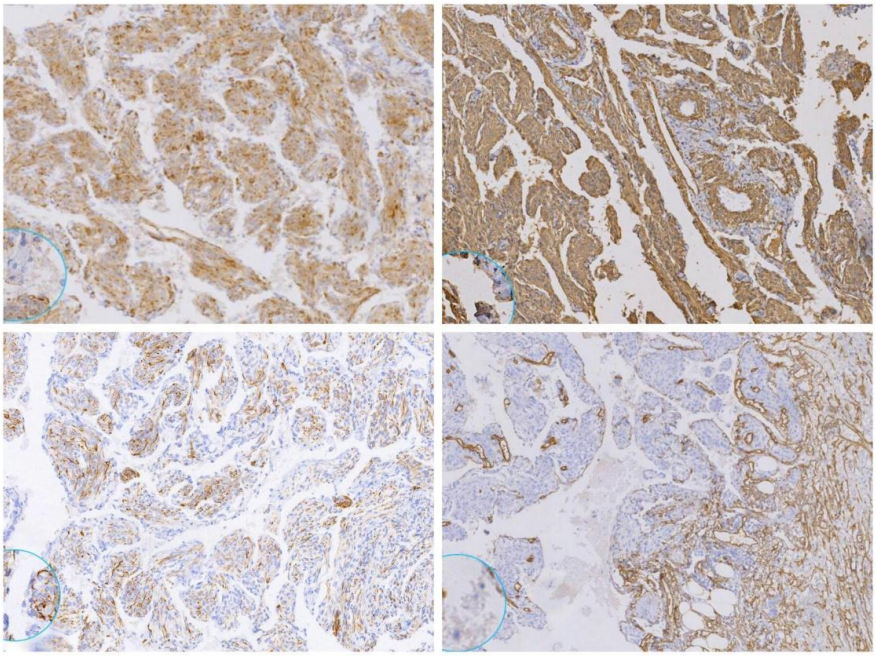
Figure 2: Postoperative pathological section of the left broad ligament

Chest CT at hospital :
"1. Diffuse, multiple, variably sized cystic lucencies in both lungs, with thickened lung interstitium and multiple linear opacities. No significant pleur al effusion."



HE×40 HE×100

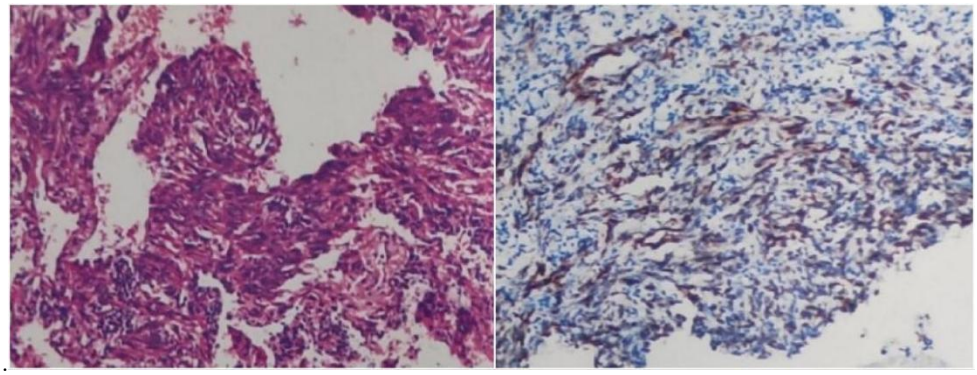
Hematoxylin and Eosin (H&E) staining revealed spindleshaped cells arranged in bundles, with bland morphology, interspersed with dilated vascular stru ctures.



External hospital immunohistochemistry (IHC, ×40) consultation on broad ligament specimen：SMA（+++）、Des（+）、S-100（+）、HMB45（++）、MelanA（-）、Ki67（+5%）、CD10（-）、CD34（+）、D2-40（+）、ER（-），Findings consistent with LAM.

Figure 3： Image of chylous fluid drained via culdocentesis.

Figure 4: Review of 2013 lung tissue the Original misdiagnosis (pneumothorax cyst wall) was revised to LAM.



HE×100 IHC HMB45+×100

Figure5: Variably sized alveolar spaces, some fused. Focal hemorrhage in some alveoli. Focal interstitial fibrosis and smooth muscle hyperplasia. IHC: HMB45 (+), ER (-), PR (+), Desmin (+), CK7 (epithelial +), SMA (+). Supportive of pulmonary LAM.

Based on imaging, histopathology, and IHC, a definitive diagnosis of LAM (Figure 4)

Involving both lungs and the left broad ligament was made, with a diagnostic delay of 60 months. Analysis of Misdiagnosis Causes:

1. Nonspecificity of pulmonary lesions: Cystic changes in LAM are easily misdiagnosed as pneumothorax, emphysema, or bullae. The 2013 misdiagnosis occurred due to lack of supportive IHC (HMB45/D2-40).
2. Occult nature of extra-pulmonary LAM:Pelvic LAM is rare and often initially classified as benign leiomyoma, requiring IHC for differentiation.
3. Nsufficient pathological awareness: Lack of familiarity with the immunophenotype of PEComa family tumors at primary care hospitals led to omission of key markers.

Postdischarge, the patient underwent cervical cancer screening in 2020 showing HPV types 52, 53, 66, 81 positive and TCT indicating LSIL. Colposcopy with biopsy confirmed CIN1. Pelvic ultrasound showed a left mixed echoic area (56x40mm), an anechoic area (53x27mm), and pelvic fluid (48mm). Repeat biopsies confirmed CIN1. After anti-HPV treatment, persistent HPV 52, 53, 59 and LSIL on TCT led to cervical conization at our hospital. Regular follow-up continued without specific LAM medication.

Discussion

Pulmonary LAM (PLAM) is a slow-progressing, low grade metastatic tumor primarily affecting women. It is characterized by infiltration of abnormal smooth musclelike cells into the lung parenchyma, causing cystic destruction. The origin of LAM cells remains unclear; they harborTSCgene mutations leading to mTOR pathway hyperactivation, dysregulated cell proliferation, impaired lymphangiogenesis, and disordered lung remodeling/respiratory failure. The metastatic potential of LAM and its possible origins (uterus, renal angiomyolipomas, or unknown sites) are widely accepted[1]. LAM is classified as sporadic (SLAM) or associated with tuberous sclerosis complex (TSC-LAM)[2].

PLAM typically presents with cough, dyspnea, wheezing, spontaneous pneumothorax, and occasionally hemoptysis, chest pain, or chylous effusions[3]. TSC patients may exhibit characteristic skin lesions. HRCT is highly diagnostic, showing bilateral, diffuse, thin-walled cysts. Pulmonary function tests usually show obstruction; our case exhibited restriction.

International guidelines emphasize histopathology as key for diagnosis. Microscopically, LAM shows clusters of epithelioid and spindle cells with clear cytoplasm, irregular vascular channels, and positive IHC for smooth muscle markers (SMA, H-Caldesmon), HMB45, and lymphatic markers (D2-40, CD34) in channel-lining cells.

Despite the similar immunophenotype of LAM cells, the clinical presentation, behavior, and histologic features of extrapulmonary LAM are not the same as those of pulmonary LAM[4]. Although LAM predominantly involves the parenchyma of the lymph nodes, in some cases it may also extend into the subperipheral sinus and extranodal lymphatic vessels or soft tissues. Histologically, LAM involving extra-nodal soft tissues can resemble intraventricular smooth muscle neoplasia and angiogenic smooth muscle tumor-type misshapen tumors, as all three diseases exhibit benign spindle cell hyperplasia with smooth muscle differentiation. Smooth muscle tumors are mostly composed of well-differentiated smooth muscle cells arranged in bundles without the epithelioid morphology of LAM cells, and the

characteristic markers SMA, desmin, and H-caldesmon are positive HMB-45 negative, ER/PR can be positive, and the presence of large dilated veins around them facilitates the diagnosis of intraventricular smooth muscle neoplasia. The histologic features of angiosmooth muscle tumor-type malignant tumors are the partial replacement of normal nodular parenchyma by hyperplastic smooth muscle cells and disorganized vasculature. The presence of irregularly distributed thick-walled blood vessels in the dense fibrocollagenous mesenchyme supports the diagnosis of angiogenic smooth muscle tumors.

In addition, extrapulmonary LAM may be associated with various manifestations of PEComa family tumors or tuberous sclerosis (TSC). Of note, it is unclear whether all patients with extrapulmonary LAM also have pulmonary LAM or are at risk of developing pulmonary LAM. Therefore, the potential relationship between LAM and TSC needs to be of particular concern in patients with clinically occult LAM involving the pelvic lymph nodes, which is incidentally detected during surgical staging of uterine and ovarian malignancies, and long-term follow-up is recommended.

Searching the relevant literature at home and abroad, more and more cases about extrapulmonary PLM have been reported, and endometrial carcinoma combined with pelvic lymph node LAM has rarely been reported[5]. One potential mechanism of LAM cell proliferation may be related to sex hormones, which may be induced by the alteration of the hormonal milieu of patients with gynecological malignancies. It has been noted that estrogen accelerates the rate of proliferation of TSC2 mutants with their tumor cell genes, thereby stimulating LAM proliferation[6]. Endometrioid carcinoma induces a hyperestrogenic state. Given that endometrioid carcinoma and LAM typically exhibit strong immunoreactivity to hormone receptors, sex hormones are thought to play a role in the pathogenesis of both diseases. Some researchers have hypothesized that significant expression of ER and PR may correlate with the severity of pulmonary LAM in pregnant women[7]. In this study, two TSC patients with pulmonary LAM exhibited strong immunoreactivity to hormone receptors and metastatic cancer cells from the endometrium and ovaries were detected in lymph nodes affected by the LAM lesions.Frequent pelvic lymph node involvement in LAM and its gynecological identification suggest that alterations in the hormonal milieu may contribute to the pathogenesis of LAM. Further studies are needed to elucidate the relationship between sex hormone levels and the development of LAM.

Therapeutic Advances in LAM

1.Traditional Treatment Strategies

mTOR inhibitors form the therapeutic cornerstone for LAM. The representative drug Sirolimus (Rapamycin) inhibits the mTORC1 complex, blocking cell proliferation, angiogenesis, and lymphatic leakage. The MILES trial confirmed that Sirolimus stabilizes lung function (reducing annual FEV1 decline by 50%), shrinks renal angiomyolipomas (AMLs), and reduces chylothorax/chylous ascites recurrence (response rate >70%). For symptomatic chylous fluid accumulation, Sirolimus is recommended before invasive procedures. Clinically, low-dose regimens are preferred due to its dose-response reversal effect: efficacy increases with dose within a threshold but decreases beyond it. Limitations include long-term use requirements and side effects like oral ulcers, hyperlipidemia, and immunosuppression. For Sirolimus-intolerant patients, Everolimus serves as an alternative with a similar mechanism but higher bioavailability (30-hour half-life).

2.Surgical Management :

For earlystage LAM patients presenting with pneumothorax, conservative management may be considered. However, in acute pneumothorax, chest tu be placement is the standard intervention. Pleurodesis can be subsequently performed to reduce recurrence[8]. When cystic changes are confined to a s ingle lobe or segment, focal lobectomy or segmentectomy may be indicated to prevent LAM cell dissemination. Lung transplantation remains rare for LAM but is an effective option for endstage disease, offering improved qua lity of life and survival[9].

Prognosis

A comprehensive review by Jaiswal et al. underscores that patients exhibiting nodal lymphangioleiomyomatosis (LAM) lesions measuring at least 10 mm invariably present with either concurrent pulmonary LAM or subsequently develop pulmonary involvement. Consequently, it is reasonable to postulate that larger LAM lesions, extensive nodal involvement (defined as ≥90% infiltration of nodal areas), or a combination of both factors may serve as predictors for the progression to pulmonary LAM or other neoplasms within the perivascular epithelioid cell tumor (PEComa) family. Given the locally destructive nature of pulmonary LAM and its established correlation with respiratory failure, the implementation of systematic screening protocols for early detection of sizable nodal LAM lesions holds significant potential to improve patient prognosis through facilitating timely clinical intervention. Furthermore, vascular endothelial growth factor D (VEGF-D)—a well-validated diagnostic biomarker for LAM—plays a pivotal role in the tumor's metastatic mechanisms. Serum VEGF-D levels demonstrate a direct correlation with disease progression in affected individuals, suggesting its utility as a prognostic indicator for survival outcomes. Additionally, VEGF-D concentrations exhibit a strong association with overall disease severity, substantiating its role as a biomarker for stratifying the extent of pathological involvement and clinical aggressiveness in LAM.

Emerging Insights

The mechanisms regulating LAM metastasis remain unclear. While extracellular vesicles (EVs) have been reported to regulate cancer metastasis, their role in LAM has not been investigated. Research by Kalvala et al. indicates that EV biogenesis is increased in LAM, and LAM-derived EVs are enriched with cargo such as lung-homing integrins, metalloproteinases, and cancer stem cell markers. LAM-EVs enhance LAM cell migration and invasion through the ITG α6/β1–c-Src–FAK–AKT axis. The metastatic (hybrid) phenotype of LAM metastatic cells, crucial for metastasis, is regulated by EVs originating from either the primary tumor or metastatic LAM cells. This regulation occurs through distinct mechanisms: shuttling ATP synthesis to cellular pseudopods or activating integrin adhesion complexes. In a LAM mouse model, LAM-EVs increase pulmonary metastatic burden via mechanisms involving remodeling of the lung extracellular matrix. Collectively, these data provide evidence for the role of EVs in promoting LAM pulmonary metastasis and identify novel EV-dependent mechanisms regulating the metastable phenotype of tumor cells. This highlights LAM-EVs as promising new therapeutic targets for LAM treatment[10].

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