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A RARE CASE OF 64 YEAR POSTMENOPAUSAL WOMAN WITH LYMPHANGIOLEIOMYOMATOSIS

Medicine

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ABSTRACT

Background and Aims: Lymphangioleiomyomatosis (LAM) is a rare lung disease characterized by the abnormal growth of smooth muscle cells, mainly affecting women of reproductive age. This study presents a unique case of a 64-year-old postmenopausal woman diagnosed with LAM, emphasizing the diagnostic challenges and management in this demographic. **Methods:** A 64-year-old female presented with vomiting, abdominal pain, and dyspnea. Diagnostic investigations included blood tests, chest X-ray, HRCT, and lung biopsy. The diagnosis of LAM was confirmed based on HRCT findings and histopathology. Patient consent and ethical approval were obtained. **Results:** HRCT showed multiple diffuse cysts in both lungs. The patient had elevated ESR and CRP levels. Pulmonary function tests revealed obstructive patterns. Treatment involved sirolimus, oxygen therapy, and anti-rheumatic drugs, leading to clinical stabilization. **Conclusion:** LAM should be considered in postmenopausal women presenting with cystic lung disease. Early diagnosis and treatment with mTOR inhibitors can help manage disease progression.

KEYWORDS

Lymphangioleiomyomatosis; Postmenopausal; HRCT; Sirolimus; Pulmonary function.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare condition that primarily impacts the lungs, marked by the infiltration and unusual growth of smooth muscle cells, particularly in the lung parenchyma, lymphatic system, and pulmonary vasculature. This abnormal growth leads to lung tissue damage and the formation of multiple cysts. LAM is categorized into two major forms: sporadic LAM and LAM associated with tuberous sclerosis complex (TSC). The latter is linked to mutations in the **TSC1** and **TSC2** genes.[1-3]

LAM predominantly affects women of reproductive age and typically manifests with symptoms such as progressive shortness of breath, chest discomfort, persistent coughing, or coughing up blood (hemoptysis). Besides pulmonary involvement, LAM can present with extrapulmonary symptoms, including benign renal tumors (angiomyolipomas), chylous ascites, and lymphatic abnormalities like abdominal lymphadenopathy.[2,3]

In this study, we present a unique case of a 64-year-old female patient diagnosed with LAM, which is particularly noteworthy due to the patient's age at presentation, as LAM is rarely seen in postmenopausal women. This atypical age at presentation contributes to the possibility of misdiagnosis. The case also highlights the coexistence of autoimmune disorders, like rheumatoid arthritis, and the severity of symptoms that necessitated advanced medical interventions, including high-flow oxygen therapy and interventional treatments like ICD insertion for pneumothorax.

Case Report

History: A 64-year-old female presented to the outpatient department (OPD) with complaints of recurrent vomiting for the past 15 days, fever for the last 12 days, abdominal pain for 10 days, and shortness of breath on exertion for the past 10 days. She had a significant history of tobacco smoking for 25 years and was diagnosed with rheumatoid arthritis five years prior, for which she had been receiving Disease-Modifying Anti-Rheumatic Drugs (DMARDs) treatment from a local practitioner.

While her medical background includes several conditions, such as rheumatoid arthritis, these were not directly related to the current diagnosis of Lymphangioleiomyomatosis (LAM). Her smoking history may have aggravated her respiratory symptoms, but it is not directly associated with the cause of LAM. Additionally, her past surgical history includes a hysterectomy, though this also bears no known connection to LAM. There was no family history of tuberous sclerosis or other lung cystic diseases that could predispose her to LAM.

On examination during admission, the patient was conscious and alert with a SpO2 of 94% on room air, breathing spontaneously. She showed signs of dehydration, was febrile to the touch, and had abdominal distension. The physical examination revealed hepatosplenomegaly. No notable skin lesions, lymphadenopathy, or other abnormal systemic findings were present.

Investigations: A complete set of investigations was performed, including blood count, renal and liver function tests, blood gas analysis, urine and blood cultures, CRP, ESR, procalcitonin levels, and tests for infections like dengue and scrub typhus. Radiological tests included chest X-ray, abdominal ultrasound (USG), and a high-resolution computed tomography (HRCT) scan of the thorax.

The patient was found to have moderate microcytic hypochromic anemia with hemoglobin levels of 8.14 g/dL. Her liver and kidney function tests were within normal ranges. The chest X-ray revealed ill-defined opacities, and the abdominal USG showed multiple nodules in the liver, hepatosplenomegaly, and a prominent common bile duct (CBD). Typhi dot test results were positive for both IgM and IgG antibodies. Further tests showed an elevated ESR of 38 mm/hour and a CRP level of 47.36 mg/dL. Cardiac evaluations, including ECG, 2D-ECHO, and NT-ProBNP, were within normal limits.

The urine culture detected **E. coli** with significant coliform counts (>105 CFU), but subsequent cultures were sterile after 5 days of incubation. An upper GI endoscopy performed due to recurrent vomiting revealed Grade B esophagitis with gastritis, although testing for Helicobacter pylori (RUT) was negative. A D2 biopsy identified mild to moderate chronic inflammation with partial villous atrophy, leading to a suspicion of celiac disease. Anti-TTG testing was performed but returned normal results.

Radiological Findings: The HRCT scan of the thorax revealed multiple diffuse, variable, smooth-walled cysts in both lung fields, along with mediastinal lymphadenopathy and paraseptal emphysematous areas. These findings strongly indicated Lymphangioleiomyomatosis (LAM).

Further diagnostic investigations were conducted to explore the etiology of the patient's condition. A contrast-enhanced CT (CECT) of the abdomen revealed hepatosplenomegaly, along with multiple subcentimetric nodular lesions in the liver and spleen, and periportal lymphadenopathy. These findings pointed towards a granulomatous condition.

To rule out tuberculosis (TB) and sarcoidosis, tests such as IGRA (Interferon-Gamma Release Assay), serum angiotensin-converting enzyme (ACE) levels, and calcium levels were performed. Both sputum and bronchoalveolar lavage (BAL) samples were collected. The ACE levels were within normal limits (44.5 nmol/mL/min), which reduced the likelihood of sarcoidosis. BAL culture results

showed no bacterial growth, the PCR for TB was negative, and no fungal elements were found in the KOH mount. IGRA test results were negative as well, effectively ruling out tuberculosis. The BAL biopsy revealed signs indicative of Interstitial Lung Disease (ILD).

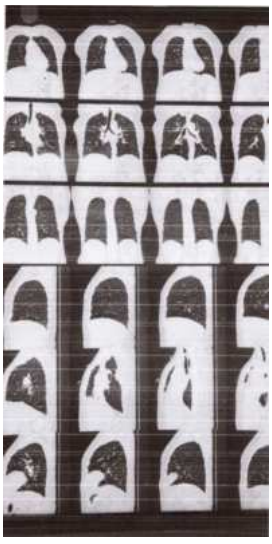

Fig 1: HRCT Chest (Coronal Section)

Fig 2: HRCT Chest (Sagittal Section)

Despite treatment for typhoid and a urinary tract infection (UTI), the patient continued to experience a fever. Therefore, further investigations were conducted for autoimmune markers, including ANA, ANCA, and anti-CCP, even though the patient already had a known history of rheumatoid arthritis. The rheumatoid factor was elevated (80 U/mL), and anti-CCP levels exceeded 200 U/mL. ANA was positive (1+), but ANCA returned negative results. To eliminate any possibility of malignancy, tests for tumor markers such as CA-19.9, CA-125, AFP, and CEA were performed, all of which were within normal ranges, dismissing the suspicion of underlying cancer.

A pulmonary function test (PFT) showed obstructive patterns with a FEV1/FVC ratio below 70%, accompanied by reduced DLCO (diffusion capacity). On the 11th day of admission, the patient's chest X-ray revealed a right-sided pneumothorax, prompting the insertion of an intercostal drain (ICD). Continuous monitoring with high-flow oxygen therapy was initiated.

This case was notable due to the rarity of LAM in a postmenopausal woman with no family history or clinical features of tuberous sclerosis, such as epilepsy, angiofibromas, or ash leaf macules. Most importantly, the patient was no longer in her reproductive years, which makes the diagnosis of LAM even more unusual.

Provisional Diagnosis: The initial diagnosis considered Lymphangioleiomyomatosis (LAM), with evidence of lower respiratory tract infection (LRTI) and suspected rheumatoid arthritis-induced ILD.

LAM is a rare bilateral cystic lung disease affecting the lung parenchyma, vasculature, and lymphatic system. Differential diagnoses in such cases may include conditions like Langerhans cell histiocytosis (LCH), Birt-Hogg-Dubé syndrome, lymphoid interstitial pneumonia (LIP), and amyloidosis. The test results suggested LAM but were not definitive in isolation, requiring a comprehensive approach that included ruling out other potential causes.

In this case, the HRCT findings, showing multiple diffuse smooth-walled cysts in both lung fields, effectively ruled out rheumatoid arthritis-associated ILD (RA-ILD), which typically shows a UIP pattern with honeycombing.

The patient was advised to undergo a VEGF-D test (not available at the current facility), and the HRCT was re-evaluated by radiologists, confirming the diagnosis of LAM. A lung biopsy showed moderate lymphocytic infiltration with mild fibrosis, further supporting the diagnosis of ILD and conclusively LAM.

Final Diagnosis: Lymphangioleiomyomatosis (LAM) confirmed through HRCT thorax review, lung biopsy, and clinical findings.

Treatment: The patient was started on sirolimus for LAM, along with supportive care including supplemental oxygen, IV fluids, and antibiotics (ceftriaxone) to address the typhoid infection. Once cultures returned negative for any ongoing infection, the antibiotics were discontinued. The patient also received disease-modifying anti-rheumatic drugs (DMARDs), such as hydroxychloroquine, for her rheumatoid arthritis. Nintedanib was introduced to prevent the progression of pulmonary fibrosis.

DISCUSSION

Our patient embodies a rare case of Lymphangioleiomyomatosis (LAM) in a postmenopausal age group. Pathologically, this condition is characterized by an irregular proliferation of smooth muscle cells in the lung parenchyma, lymphatics, and airway walls, leading to the formation of multiple lung cysts.[4,5,6] The origin of LAM cells remains undetermined, and two theories have been proposed. The first theory postulates that LAM cells may have an airway or vascular origin, while the second suggests that LAM cells originate from angiomyolipomas in the kidneys and are transported to the lungs through dissemination.[10,11,12,13,14]

The progression of this disease involves the destruction of the lungs through infiltration and proliferation of LAM cells. In LAM, these cells express smooth muscle proteins like actin and desmin, as well as melanocytic markers like HMB-45, Melan-A, and MART-1, which indicates a perivascular epithelioid cell (PEC) origin. However, in this case, these theories were deemed inappropriate as the LAM cells were diffusely distributed in the lungs without organized nodules or angiogenesis. Lymphangioleiomyomatosis not only destroys the lung parenchyma but also infiltrates the axial lymphatic system, affecting hilar lymph nodes, extra-thoracic lymph nodes, and mediastinal ganglia.[7]

As LAM progresses, it causes airway obstruction, mimicking symptoms seen in other obstructive lung diseases.[8] In severe LAM, there is a decline to less than 40% of the predicted values for DLCO and FEV1, often necessitating long-term oxygen therapy or even lung transplantation. The prevalence of LAM is approximately 1 to 2.6 cases per 100,000 females. The true incidence is difficult to determine due to the subtle and gradual progression of LAM and the absence of specific diagnostic tests.

Clinically, LAM presents as progressive dyspnea, often misdiagnosed as an airway disorder, and these patients are frequently treated with bronchodilators.[5] Other clinical manifestations include spontaneous pneumothorax (57%), hemoptysis (32%), abdominal angiomyolipomas (32%), lymphangioleiomyomas (29%), and pleural effusions (12%). Less common manifestations occur in the later stages of LAM, including abdominal hemorrhage originating from renal angiomyolipomas, chylous effusions into pleural and abdominal cavities such as chylothorax, chylous ascites, chyluria, and chyloptysis.[9]

The invasion of irregular smooth muscle cells into the pulmonary

venous vasculature leads to venous obstruction, causing pulmonary venous hypertension and deposition of hemosiderin in the lung parenchyma, resulting in hemoptysis.[6,9] Radiological findings vary with the progression and severity of LAM. The typical chest X-ray of LAM shows hyperinflated lungs due to the obstructive nature of the disease, while HRCT demonstrates diffuse, variable smooth-walled cysts in both lung fields. Ground glass appearances may also be seen due to hemosiderosis.[11,12]

Pulmonary function testing (PFT) often shows obstructive or mixed patterns, with reduced FEV1 due to restricted airflow. Residual volume (RV), total lung capacity (TLC), and RV/TLC ratios increase due to air trapping.[12] This is generally due to increased airway resistance and reduced lung elasticity. Approximately 20% of patients experience improvement with bronchodilators.[13] While resting PFTs may appear nearly normal, abnormalities in gas exchange and ventilation are often seen during exercise testing. Nonetheless, LAM's progression is tracked using diffusion capacity and FEV1 measurements.[14]

LAM should always be considered when evaluating female patients with these symptoms. While a high-resolution CT scan can contribute to the diagnostic process, tissue biopsy is required in most instances. The confirmation of the diagnosis relies on immunochemical stains for smooth muscle cell markers such as actin, desmin, or HMB-45, with HMB-45 being the gold standard for confirming LAM.

Bronchodilators are an essential component of supportive treatment for LAM patients with dyspnea. Depending on disease severity, some patients may benefit from immunomodulatory therapy, such as mTOR inhibitors like sirolimus or everolimus. These therapies stabilize the patient's condition and offer a 10-year transplant-free survival rate of 86%, with a median transplant-free survival period of 29 years from symptom onset.[15,16] In advanced cases, lung transplantation remains the ultimate cure.

Recommendations

This case highlights the importance of including LAM in the differential diagnosis for cystic lung diseases, even in atypical cases. Clinicians should maintain a high index of suspicion for LAM in women presenting with unexplained cystic lung disease. Comprehensive diagnostic testing, including HRCT and immunohistochemical markers like HMB-45, is critical for confirming the diagnosis. Early and accurate diagnosis allows for effective management and improved outcomes, especially with newer treatment options like sirolimus that have demonstrated efficacy in slowing disease progression.

CONCLUSION

LAM typically affects women of reproductive age but may occasionally present in postmenopausal women, as demonstrated in this case. While diagnosing cystic lung diseases, particularly in women, LAM should be considered as a potential diagnosis. Due to its gradual progression and misdiagnosis as obstructive airway diseases, early identification and management are crucial. Treatment options include mTOR inhibitors and, in severe cases, lung transplantation for patients who experience advanced disease progression.

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