

Pulmonary Lymphangiomyomatosis: A Rare Cause of Cystic Lung Disease – A Case Report

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ABSTRACT

Lymphangioleiomyomatosis in sporadic form is a rare and progressive lung disease that primarily affects women, especially during the reproductive phase. We report a case of a 66-year-old patient who consulted for exertional dyspnea. The thoracoabdominopelvic CT scan revealed several pulmonary cystic lesions and renal angiomyolipomas, allowing the diagnosis of lymphangioleiomyomatosis. The diagnosis of lymphangioleiomyomatosis should be considered in young women presenting with spontaneous pneumothorax, unexplained dyspnea, or angiomyolipoma. While a definitive diagnosis can be confirmed through a lung biopsy, current guidelines allow for non-invasive methods based on characteristic imaging findings and clinical features.

KEYWORDS

Lymphangioleiomyomatosis; Orphan disease; Cystic lung; Angiomyolipoma; mTOR inhibitors; Sirolimus

INTRODUCTION

Sporadic lymphangioleiomyomatosis (LAM) is an uncommon pulmonary orphan disease in young women, characterized by numerous cystic parenchymal destructions that can progress to chronic lung failure. Although earlier reports suggested a median survival of about 10 years from symptom onset, recent advances in treatment, particularly the use of mTOR inhibitors, have improved outcomes. Survival now varies significantly depending on the individual and the use of these therapies, which can slow disease progression and improve lung function [1, 2]. While LAM primarily affects women during their reproductive years, it can occasionally develop or be diagnosed after menopause. It is estimated that around 10-15% of sporadic LAM cases occur in postmenopausal women [3], as it did with our patient. It can present with symptoms such as

dyspnea, recurrent pneumothorax, and cough. Although lung biopsy is a gold standard, current diagnostic criteria, such as those established by the European Respiratory Society (ERS), often allow for a definitive diagnosis without histological confirmation, especially in the presence of characteristic imaging and clinical features [4].

CASE PRESENTATION

A 66-year-old woman, followed for hypertension under monotherapy and having no history of hormone replacement therapy or oral contraceptive use, presented for stage III of Modified Medical Research Council score mMRC) dyspnea that has progressively aggravated, coupled with a productive cough bringing back mucopurulent sputum.

The clinical general examination of admission found a conscious patient, febrile at 39° Celsius, polypneic at 20 cycles per minute, arterial pressure at 140/75 mmHg, and blood oxygen saturation at 90% on ambient air adjusted under 2 l of O₂, while the pulmonary examination revealed diffuse bilateral sibilant crackles. The rest of the exam was unremarkable.

The diagnosis of LAM was suggested by the chest CT scan, initially motivated by a search for thromboembolic disease, with evidence of multiple cystic lesions of diffuse distribution in both pulmonary hemifields of variable size and shape with very thin walls from 2 to 5 mm (Figure 1).

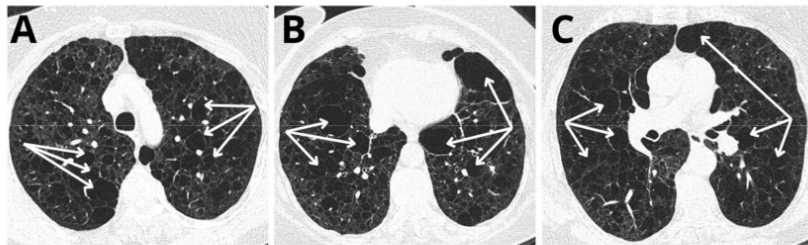


FIGURE 1: Thoracic CT axial parenchymal sections (A,B,C) showing thin-walled cystic images of diffuse distribution in both pulmonary hemifields of variable size and shape (white arrows).

The complementary assessment confirms the diagnosis by the identification of renal angiomyolipomas on the abdominal floor (Figure 2).

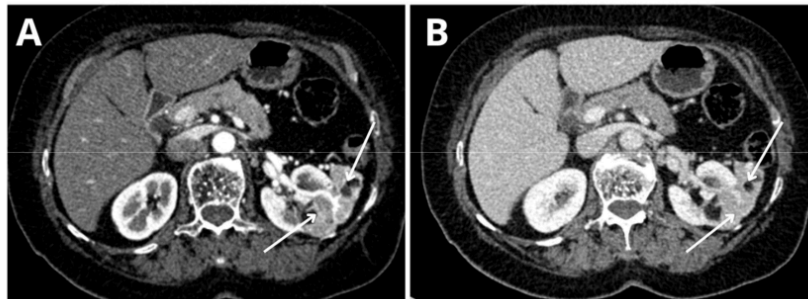


FIGURE 2: Axial arterial phase (A) and axial portal venous phase (B) sections of abdominal CT showing a hypervascular left renal mass containing a fatty contingent measuring 63x37mm related to an angiomyolipoma (white arrows).

The patient was treated with bi-antibiotic therapy with good clinical and biological improvement. A spirometry was performed, revealing an obstructive syndrome with a tiffeneau coefficient (FEV1/FVC) at 41% reversible after short-acting beta-2 agonist and a forced expiratory volume per second (FEV1) at 0.60 L/s (26%). A transthoracic echocardiography (TTE) showed mildly dilated right cavities without pulmonary arterial hypertension.

The file was discussed in a multidisciplinary consultation meeting; the decision was to undergo treatment with sirolimus.

DISCUSSION

Pulmonary lymphangioleiomyomatosis (LAM) is a rare lung disease that can occur sporadically or as part of a genetic disease: tuberous sclerosis complex (TSC). The sporadic form of LAM affects 1/400,000 adult women [4]. It is encountered almost exclusively in women of childbearing age but can occasionally occur after menopause. During TSC, LAM is present on chest CT in 30 to 40% of women [1, 5, 6, 7]. In our patient, the diagnosis was revealed after menopause.

Histologically, LAM is defined by abnormal and diffuse proliferation of perivascular epithelioid cells and smooth muscle cells in the lymphatic and pulmonary vein walls of peribronchiolar, perivascular, and subpleural topography, leading to the formation of nodules, cystic masses of the lymphatic tract, and cystic destruction of the lung parenchyma [8, 9].

The pathophysiology involves the mutation of two tumor suppressor genes: TSC1 and TSC2, respectively coding for the proteins hamartin and tuberin which control the activity of an intracellular enzyme called mTor involved in the regulation of cell growth. TSC2 mutations are more prevalent than TSC1 mutations, making up the bulk of sporadic LAM (S-LAM) and about 60% of LAM associated with TSC (TSC-LAM) [10, 11, 12, 13]. In our case, the patient was not tested for TSC mutations, the diagnosis of S-LAM was made based on clinical and imaging findings, and no additional features suggestive of a tuberous sclerosis complex were identified.

Several data suggest hormone dependence of LAM due to exacerbations observed during pregnancy and when taking oral contraceptives. However, the results of studies evaluating the efficacy of medical or surgical anti-estrogen treatment are often contradictory and very difficult to assess in the long term. One study had reported the beneficial effects of tamoxifen, but many subsequent works have contradicted these results [14, 15, 16, 17, 18, 19].

LAM is underdiagnosed. It is frequently mistaken with other lung illnesses due to the similarity of the first symptoms, such as restrictive or obstructive lung disease. Clinically, it can manifest as progressive dyspnea (70%), recurrent pneumothorax (40%), cough (39%), and chylothorax (13%). Hemoptysis and chyloptysis are rarer and appear later [20, 21, 22, 23].

Extra-respiratory expectation is mainly represented by renal angiomyolipomas, which are often asymptomatic but can be complicated by hemorrhagic rupture if larger than 4 cm in diameter. Abdominal lymphadenopathy is common, usually asymptomatic, although it can induce chylous ascites in 4 to 20% of cases during the course of the disease. Pulmonary arterial hypertension is an uncommon and late-onset complication in LAM [3, 23, 24, 25].

In Boehler's study of 32 LAM patients, dyspnea was the main symptom (94%), followed by pneumothorax (78%), and cough (41%) [26]. In the Urban series, which studied 69 cases of LAM, dyspnea was present in 71% of cases,

pneumothorax revealed the diagnosis in 52% of cases, cough represents 32% of symptoms, followed by chylothorax in 20% [23].

Thoracic computed tomography in high resolution and thin sections is the reference radiological examination, allowing for the identification of multiple cystic images (>10) that are rounded, regular, and disseminated throughout the lung parenchyma, with no predominance or sparing of pulmonary territories. Their diameter varies from 2 mm to 30 mm, and their wall is thin, generally measuring less than 2 mm. The demonstration of a chylothorax, a renal angiomyolipoma or lymphangioleiomyomas reinforces the diagnostic probability. The diagnosis is based on a range of clinical, radiological, and biological arguments according to the recommendations of the European respiratory society (Table 1). Typical forms do not require histological confirmation for diagnosis [4].

TABLE 1: ERS Lymphangioleiomyomatosis guidelines, 2010.

| Category | Criteria |
|--------------|---|
| Definite LAM | 1. Characteristic or compatible lung HRCT and lung biopsy fitting the pathological criteria for LAM; or 2. Characteristic CT scan and at least one of the following: * Renal Angiomyolipoma * Chylous effusion (pleural or ascites) * Lymphangioleiomyoma or lymph-node involved by LAM * Definite or probable TSC |
| Probable LAM | 1. Characteristic HRCT and compatible clinical history; or 2. Compatible HRCT and at least one of the following: * Renal Angiomyolipoma (kidney) * Thoracic or abdominal chylous effusion |
| Possible LAM | Characteristic or compatible HRCT |

HRCT: high resolution computed tomography

In our case, the diagnosis was retained on the typical CT appearance and the presence of a renal angiomyolipoma.

Pulmonary function tests show an obstructive syndrome (FEV1/VC < 70% of theoretical) of varying intensity, sometimes partially reversible after

administration of short-acting beta-2 agonists. Expiratory air trapping (RV/TLC > 30%) and thoracic distension (TLC > 120%) are frequently observed. The primary sign of the disease is an alteration in the diffusing capacity of the lungs for carbon monoxide (DLCO), reflecting the extent of cystic parenchymal destruction. During evolution, the FEV1 and the DLCO decrease, with a variable rate of decline from one patient to another [3, 23, 27, 28, 29].

Treatment is mainly symptomatic and is based on inhaled bronchodilators in patients with reversible bronchial obstruction. Although bronchiolar inflammation is seen in certain patients, the efficacy of inhaled steroids in LAM has not been tested [4]. Pneumothorax recurrences are more common after conservative treatment with chest drainage than after pleurodesis. The management of chylothorax can consist of the following: evacuating puncture, pleural drainage, or pleural talc [24, 30].

Regarding hormone treatment, there have been no randomized controlled studies on the effect of progestins in LAM, only observational studies with uncertain outcomes. This treatment is not routinely recommended [4].

mTOR inhibitors such as sirolimus and everolimus have shown a beneficial effect on the decline in lung function and on the reduction in the size of angiomyolipomas. In Bissler's trial evaluating the efficacy of sirolimus on 25 patients with LAM, the FEV1 increased by 118 +/- 330 ml, and the FVC increased by 390 +/- 570 ml. At 24 months, five patients had a persistent reduction in angiomyolipoma volume of 30% or more [31]. One year after sirolimus discontinuation, FEV1 was 62 +/- 411 mL above baseline, and FVC was 346 +/- 712 mL above baseline. In Goldberg's series of 25 women with lymphangioleiomyomatosis treated with everolimus, FVC remained stable, while FEV increased from baseline after 26 weeks of treatment, and the walking distance from 6 min improved by 47 m [32]. Lung transplantation is the last resort at the stage of end-stage lung failure with resting hypoxemia, class III or IV NYHA dyspnea, and severe impairment of lung functions, before the age of 60-65 years and in the absence of significant comorbidities or contraindications [4].

CONCLUSION

Lymphangioleiomyomatosis is a rare and progressive disorder that primarily affects women of childbearing age. Its prognosis is conditioned by respiratory involvement, as progressive lung function decline can result in respiratory failure, which is a major cause of morbidity and mortality in these patients. The diagnosis is based on characteristic clinical and radiological findings, in line with the European Respiratory Society guidelines, which allow for non-invasive diagnosis in typical cases. This approach is particularly relevant given the risk of cyst rupture in the pleura, which can lead to pneumothorax, a common complication in LAM patients. Recent breakthroughs in the pathogenesis of LAM, notably the role of mutations in TSC genes, have led to significant improvements to treatment options. The use of mTOR inhibitors, such as sirolimus, has shown promise in slowing disease progression and stabilizing lung function, offering new hope for patients with LAM.

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