

Lymphangioleiomyomatosis – case series

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Abstract

English:

We describe a series of five cases of sporadic lymphangioleiomyomatosis (LAM) diagnosed in a 2-year period and followed for at least 6 months. All cases describe women aged between 37 years and 67 years (median at 44), mostly non-smokers, either with symptomatic presentations, complications at debut or incidental imagistic diagnosis. The cystic lesions were unanimous, but two cases had atypical patterns. Spirometric parameters were normal in two cases, the rest presenting obstruction with hyperinflation ± bronchodilator positive response. The diffusing capacity of lung for carbon monoxide (DLCO) varied between 79.8% and 29.5%. Two cases had histopathological confirmation, one of which was really unexpected considering its imagistic pattern. The therapeutic intervention consisted of sirolimus and/or bronchodilator. The evolution was stationary for four cases and unfavourable for one. This case series ranges from textbook to atypical LAM and has the aim to raise awareness regarding this rare disease.

Keywords

lymphangioleiomyomatosis • LAM • case series • VEGF-d

Limfangiomatoza - serie de cazuri

Rezumat

Romanian:

Descriem o serie de cinci cazuri de limfangioleiomiomatoză (LAM) sporadică diagnosticate într-o perioadă de doi ani și urmărite timp de cel puțin șase luni. Toate cazurile sunt reprezentate de femei cu vârste cuprinse între 37 și 67 de ani (vârsta medie de 44 ani), în mare parte nefumătoare, fie cu prezentări simptomatice, complicații la debut sau diagnostic imagistic incidental. Leziunile chistice au fost unanime, dar două cazuri au avut modele atipice. Parametrii spirometrici au fost normali în două cazuri, restul prezentând obstrucție cu hiperinflație ± răspuns pozitiv la bronhodilatator. Difuziunea alveolo-capilară a monoxidului de carbon (DLCO) a variat între 79,8% și 29,5%. Două cazuri au avut confirmare histopatologică, unul dintre acestea fiind cu adevărat neașteptat având în vedere modelul său imagistic. Intervenția terapeutică a constat în sirolimus și/sau bronhodilatator. Evoluția a fost staționară pentru patru cazuri și nefavorabilă pentru unul. Această serie de cazuri variază de la LAM tipic până la atipic și are scopul de a crește gradul de conștientizare cu privire la această boală rară.

Cuvinte-cheie

limfangioleiomiomatoza • LAM • serie de cazuri • VEGF-d

Introduction

Lymphangioleiomyomatosis (LAM) is a multi-system cystic disease caused by the abnormal proliferation of atypical smooth muscle cells and chaotic lymphatic channel development. It mainly affects the lungs by forming pulmonary cystic lesions, and sometimes, lymphatic cysts

can also appear. The pathogenic substrate resides in mutations of the tuberous sclerosis complex (TSC) genes, mainly with a decrease in hamartin and tuberlin synthesis, suppressor proteins of the mTOR pathway (1). A seven-country study conducted in the USA identified a prevalence

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of LAM of 3.4 to 7.8/million women (2). In the TSC population, 1%–3% of patients develop the condition (3). The highest prevalence is in pre-menopausal women in their forties but it ranges from teenagers to even 80 years, contrary to the traditional belief that it is a condition of younger females (4). LAM should be considered in any woman presenting with progressive shortness of breath, obstructive ventilatory dysfunction and chylous pleural effusion or recurrent pneumothorax. Characteristic thoracic computed tomography (CT) scans open the road for the diagnosis, completed by transbronchial, thoracoscopic or open lung biopsy. In appropriate clinical settings where the biopsy is unavailable, imagistic evidence of characteristic lung cysts, angiomyolipomas, chylous effusion, TSC or Vascular Endothelial Growth Factor D (VEGF-D) serum levels sustain the diagnosis of LAM (5). The follow-up for these patients is based on functional testing, with interesting data showing a correlation between VEGF-d levels, DLCO and CT scan lesions severity. Pulmonary function decline, once inevitably leading to lung transplantation, is nowadays managed with mTORC1 inhibitors – sirolimus and everolimus. These molecules are the gold standard therapy in LAM cases with lung function decline, symptomatic chylous effusions, lymphangioleiomyomas or large angiomyolipomas.

Clinical problems, differential diagnosis, results of clinical findings

M.I., a 46-year-old non-smoker female who presented with progressive shortness of breath during the last 5 years can now barely climb a flight of stairs. She also coughs with minimal expectoration in the morning during the changes in weather. She has a spirometry report with partially reversible obstructive airflow limitation and administers combination therapy with inhaled corticosteroid and long-acting beta-agonist (ICS/LABA), without much improvement. She had an abdomino-thoracic CT (Figure 1) that describes diffuse cystic thin-walled lesions replacing most of the pulmonary parenchyma, one mediastinal and several para-reno-aortic fluid collections (not shown).

The physical findings at the time she presented to our clinic were scarce and consisted of clubbing and low-breath sounds. The resting oxygen saturation was 95% and during the six-minutes-walk test (6MWT), it dropped to 77% after 85% of the predicted distance. We performed complex lung function testing and objectified severe air trapping – a residual volume (RV) at 239% of predicted and severely impaired gas exchange with DLCO 25.7%. We also recommended VEGF-d serum testing, which resulted positive (1402 pg/mL). She started the therapy with sirolimus which stopped the progression of her disease and at 6 months follow-up visit,

we proposed to start the procedures for pulmonary transplant evaluation.

E.I., a dyspneic 67-year-old female, has been carrying the COPD diagnosis for several years even though she was a non-smoker and had no exposures. At our first evaluation, she had bilateral basal crackles and the functional evaluation showed severe obstructive dysfunction with FEV1 28%, and DLCO 30% as predicted. Her basal SpO₂ was 90% at rest and her tolerance to effort was low as it reached 76% during the 6MWT after 150 m. The thoracic imaging was highly suggestive for LAM (Figure 2), and the abdominal ultrasonography identified a renal cyst. The patient did not pursue further diagnosis investigation, because her pulmonary function degraded and she was prescribed sirolimus. After 1 year, she is clinically and functionally stationary with no complications so far.

F.R., a 37-year-old asymptomatic ex-smoker female came to our hospital for incidental pulmonary cystic lesions (Figure 3),

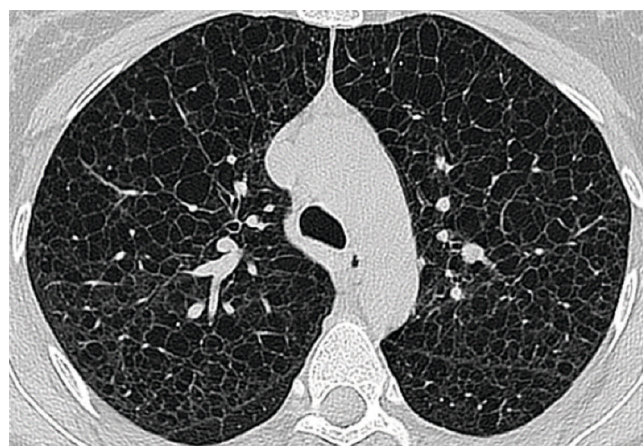


Figure 1. Thoracic CT transversal section showing multiple thin-walled cystic lesions replacing the normal lung parenchyma in a LAM patient. LAM, lymphangioleiomyomatosis.

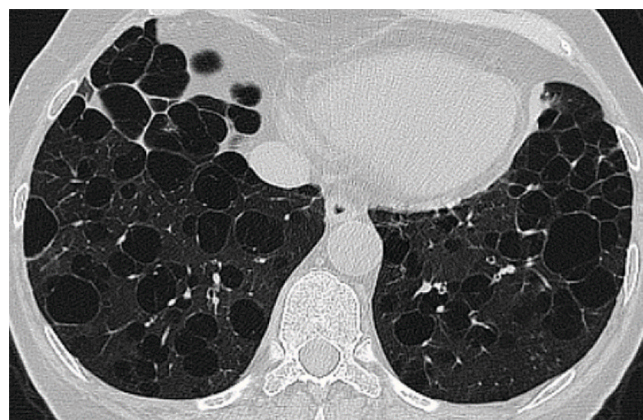


Figure 2. Thoracic CT of a 67-year-old non-smoker female presenting with bilateral basal crackles and chronic respiratory failure.



Figure 3. Lung cysts in a patient with a history of colon cancer and Hodgkin lymphoma. The biopsy through video-assisted thoracoscopic surgery revealed a histopathological diagnosis of LAM. LAM, lymphangioleiomyomatosis.

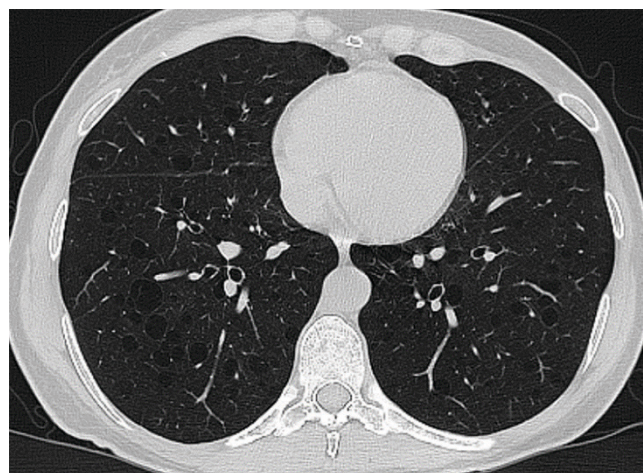


Figure 4. Cystic lesions of a patient with biopsy confirmed LAM after two spontaneous pneumothoraces. LAM, lymphangioleiomyomatosis.

which were discovered during the oncological follow-up after being diagnosed with colon cancer. She also had a childhood history of Hodgkin lymphoma and so the probability of malignant pulmonary lesions was high and hence a lung biopsy was performed. The histologic diagnosis was LAM. Her clinical examination and lung function were normal and so we recommended periodical monitoring. During the 1-year follow-up visit, the patient was under sirolimus treatment, with no progression of the lung lesions.

T.I., a never smoker 41-year-old female had a history of repeated spontaneous pneumothoraces for 6 years (2015 and 2021). She had no prior predisposing factor and no diagnosed respiratory condition. At the moment of the second pneumothorax, a surgical lung biopsy was performed and the result was suggestive for LAM. What is interesting about this case is the absence of the architectural distortion of the lung (Figure 4). This patient's thoracic imagistic studies identified less than 10 cystic lesions which were enough for her to suffer two pneumothoraces. Her lung function and clinical exam were normal. So, we opted for periodical monitoring, including via serological VEGF-d testing that was positive at diagnosis. Her evolution is favourable without new complications so far.

S.I., a 44-year-old non-smoker female presented with shortness of breath that got aggravated during the previous year. The clinical examination was normal, without desaturation at the 6MWT, but the complex lung function tests objectified distal obstruction with hyperinflation (RV 213%) and mild reduction of DLCO to 73% as predicted. The thoracic CT identified cystic lesions (Figure 5), in this clinical context. Moreover, after finding out that the patient was following hormonal therapy and had two in-vitro fertilization (IVF) pregnancies, the likelihood of LAM was high. She refused the lung biopsy.

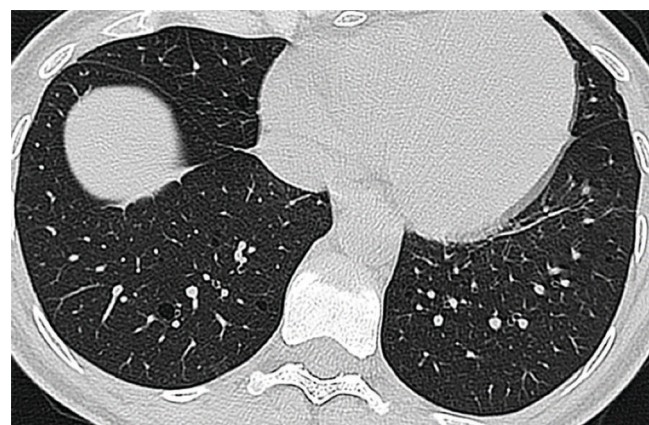


Figure 5. Lung cysts in a young woman under hormonal therapy with two IVF pregnancies. IVF, in-vitro fertilization.

She was recommended VEGF-d serology with periodical monitoring, and is stable so far at 1 year.

Discussions

We presented the cases of five female patients who were diagnosed with a rare disease in a short period of time. Even if our hospital cannot compete with the experience of other centres that gather cohorts of hundreds of patients, we consider that sharing our experience is important. It should be kept in mind that labelling the tomographic cystic lesions of a young non-smoker female as 'emphysema' can delay the diagnosis and cost her a great amount of lung function and years of life. E.I was diagnosed with COPD for several years based on the spirometric obstructive syndrome, and interpreting her lesions as emphysema would have

been a great mistake. The differential diagnosis was the main actor in F.R.'s scenario, as she had a high pre-test probability for lung metastases. Such a rare disease should situate at the end of the differential diagnoses list, after cancer, Langerhans cell histiocytosis, Sjögren syndrome, amyloidosis, *Pneumocystis jirovecii* pneumonia or Birt-Hogg-Dubé syndrome (6). We presented a spectrum of imagistic patterns from architectural cystic distortion to several scattered small cysts. The hallmark feature of LAM on high-resolution chest CT is the bilateral cystic lesion with a thin well-defined wall between 0.1 mm and 2 mm and size ranging from 2 mm to 40 mm, without lobar predominance (7). This being said, we can only emphasize the particularity of the case of T.I. and her paucity of lesions, yet enough to cause a repeated pneumothorax. The pneumothorax manifests in about one-third of cases of sporadic LAM and affects 50%–60% of these patients (1), some of them requiring pleurodesis. Another particular case is the case of S.I., the woman with a history of two IVF pregnancies and hormonal therapy. The literature describes important pathogenic links between female sex hormones and LAM, reflected in the intersexual difference in prevalence of the disease and its evolution throughout the menstrual cycle and after menopause (8). We also think that the case of M.I. was particular because of the severity of the lesions in a young woman. In her situation, the lung biopsy was not even debated due to the easy access to the VEGF-d serology and the identification of cystic mediastinal and abdominal lesions described on the abdomino-thoracic CT. We need to reiterate the utility of VEGF-d serology in the context of typical pulmonary lesions, given the availability of any biologic marker compared to surgical procedures.

Conclusions

We presented a case series of five patients with a wide spectrum of pulmonary lesions and different approaches, aiming to popularize this rare cystic disease that any physician should keep in his differential diagnosis.

Funding

None.

Authors contributions

All authors have contributed equally to this work.

Conflict of interest

The authors declare no conflict of interest.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

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