Pulmonary lymphangioleiomyomatosis
A diagnostic challenge in a developing country

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Abstract

Lymphangioleiomyomatosis (LAM) is a rare, progressive neoplastic disease that almost exclusively affects women of reproductive age. The annual incidence is five to nine cases per million women, representing an uncommon cause of pleural effusion. It is characterized by thin-walled pulmonary cysts, chylous pulmonary effusion, and kidney lymphangioleiomyomatosis and angiomyolipomas, which eventually progresses to respiratory failure. It may present sporadically (SLAM) or be associated with the tuberous sclerosis complex (TSC-LAM) (1). We report the case of a previously healthy 39-year-old female who presented with a complaint of dyspnea and chronic progressive cough. Her radiological tests showed right pleural effusion and interstitial lung disease, meriting complex invasive diagnostic tests to obtain a definitive diagnosis. However, despite obtaining an accurate diagnosis, her disease course was unfavorable. In conclusion, pulmonary lymphangioleiomyomatosis is an extremely rare neoplastic disorder whose complex diagnostic approach requires a high investigative capacity. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.3130).**

Keywords: *lymphangioleiomyomatosis, pleural effusion, radiology, pulmonology, chyle*

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Introduction

Lymphangioleiomyomatosis (LAM) is a rare, slowly progressive systemic disease associated with cystic lung destruction, abdominal tumors, and the accumulation of chyle due to infiltration of immature neoplastic smooth muscle cells known as "LAM cells." The reported global incidence ranges from five to nine cases per million women (1). Typically, it presents with progressive dyspnea, spontaneous pneumothorax and, in 20% of cases, as chylous pleural effusion in women of reproductive age (2). Its diagnosis requires a high index of suspicion, as the progressive dyspnea presentation is vague, with multiple differential diagnoses, delaying diagnosis by up to five years.

A LAM diagnosis is complex and involves high-resolution computed tomography (HRCT) of the chest, an abdominal-pelvic CT looking for angiomyolipomas or lymphangioleiomyomas, and serum levels of vascular endothelial growth factor D (VEGF-D). In some cases, a lung biopsy is required to confirm the diagnosis (3). Treatment is also complex, has changed over the last decades, and is hard to obtain in some countries.

The importance of this case lies in the fact that, as an uncommon disease with a nonspecific presentation, it is rarely suspected, which reduces quality of life and delays the diagnosis until the onset of pulmonary complications that require multidisciplinary treatment. Therefore, a high index of suspicion should be maintained, as the disease may have a favorable course if it is diagnosed early. We present the case of a 39-year-old woman who consulted our service due to chylothorax and whose diagnostic approach led to the histopathological documentation of pulmonary lymphangioleiomyomatosis, despite the financial limitations of our healthcare system.

Case presentation

We present the case of a 39-year-old female patient who was a homemaker from Tegucigalpa, Honduras, with no relevant medical history, nulliparous, and with no history of smoking. She presented to the hospital complaining of four months of progressive dyspnea and a dry cough that did not improve with short-action bronchodilators; she denied fever, trauma or pleuritic pain.

On examination, her blood pressure was 110/80 mmHg, heart rate was 95/min, respiratory rate was 31/min, and temperature was 36.6 degrees Celsius. She was alert, oriented and cooperative, but with halting speech due to her dyspnea. Physical examination showed no jugular distention or lymph node enlargement. Her heart exam was within normal limits. However, her lung exam revealed asymmetric right lung expansion, dullness in the posterior lower third, and decreased ipsilateral breath sounds. Her abdomen was nonpainful on palpation, and her extremities were symmetrical, with no edema.

A chest x-ray showed homogenous radio-opacity in the right lower third, compatible with pleural effusion (Figure 1A). Her initial blood chemistry was normal, as was her

electrocardiogram. She was admitted for a work-up of the pleural effusion, and thoracocentesis was performed, obtaining a thick, milky fluid (Figure 1B). The cytochemical analysis of the pleural fluid reported the following: protein 4.45 g/dL, lactate dehydrogenase 455 U/L, glucose 96 mg/dL, and 1,050 cells per mm^3, with a 95% predominance of lymphocytes. Triglyceride and cholesterol levels in the fluid were reported as 597 mg/dL and 101 mg/dL, respectively, compatible with chylothorax. Pleural fluid cytology did not show LAM cells.

She underwent thoracic and abdominal ultrasound, revealing approximately 2,000 mL of free pleural fluid and a right ovarian cyst, with no reports of angiomyolipomas in the rest of the abdominal cavity. A pleural catheter was placed to drain the pleural effusion and relieve her dyspnea, draining more than 5,000 mL. An HRCT was also performed, showing a fine, bilateral interstitial reticular pattern, compatible with septal thickening, and multiple, bilateral, round, thin-walled pulmonary cysts, measuring 5-15 mm (Figure 2).

Since serum VEFG-D is not available at our institution, a pulmonary biopsy was performed to reach the definitive diagnosis. It is worth mentioning that pulmonary function tests could not be performed, as they were not available at the time.

An open lung biopsy was performed, confirming the diagnosis of pulmonary lymphangioleiomyomatosis (Figure 3). The patient had a sluggish postoperative course, which prolonged ventilatory support for several days, and developed a spontaneous pneumothorax that required pleurodesis twice.

Since mTOR inhibitors are not available in Honduras, they had to be ordered, and the patient was discharged in a stable condition to await this pharmacological treatment. Three months after discharge, the patient was readmitted to the hospital in respiratory failure secondary to bilateral pneumothorax, and died.

Discussion

Pulmonary LAM is a very rare idiopathic interstitial disease that involves the lungs and affects five to nine per million women of reproductive age. However, its true prevalence is underestimated, as most studies are retrospective. Although most cases occur in women, cases of LAM have been reported in men (1). Three clinical variants have been described: S-LAM, S-LAM with renal angiolipomas, and LAM associated with tuberous sclerosis complex (TSC-LAM). Lymphangioleiomyomatosis occurs in 30% of women with tuberous sclerosis, due to *TSC1* and *TSC2* gene mutations. These genes participate in tumor suppression through the mTOR molecular pathway, regulating cellular growth, motility and survival, favoring the formation of smooth muscle neoplastic cells in the blood stream and lymph vessels, which, when deposited in the lung tissue, cause parenchymal destruction (4, 5).

Lymphangioleiomyomatosis classically presents with progressive dyspnea, pneumothorax, chylothorax and hemoptysis in women of reproductive age. In most patients, the initial symptoms are dyspnea or pneumothorax. Dyspnea may be mistakenly diagnosed as asthma or chronic obstructive pulmonary disease (COPD), as one third will have reversible obstruction on spirometry, delaying the diagnosis of LAM. Spontaneous pneumothorax occurs in 33%, and chylothorax in 10-30%. Atypical manifestations like kidney angiolipomas occur in 30% of S-LAM cases and 80% of TSC-LAM cases. Furthermore, up to 25% of cases may have chest pain, cough, hemoptysis and chyloptysis (6-10).

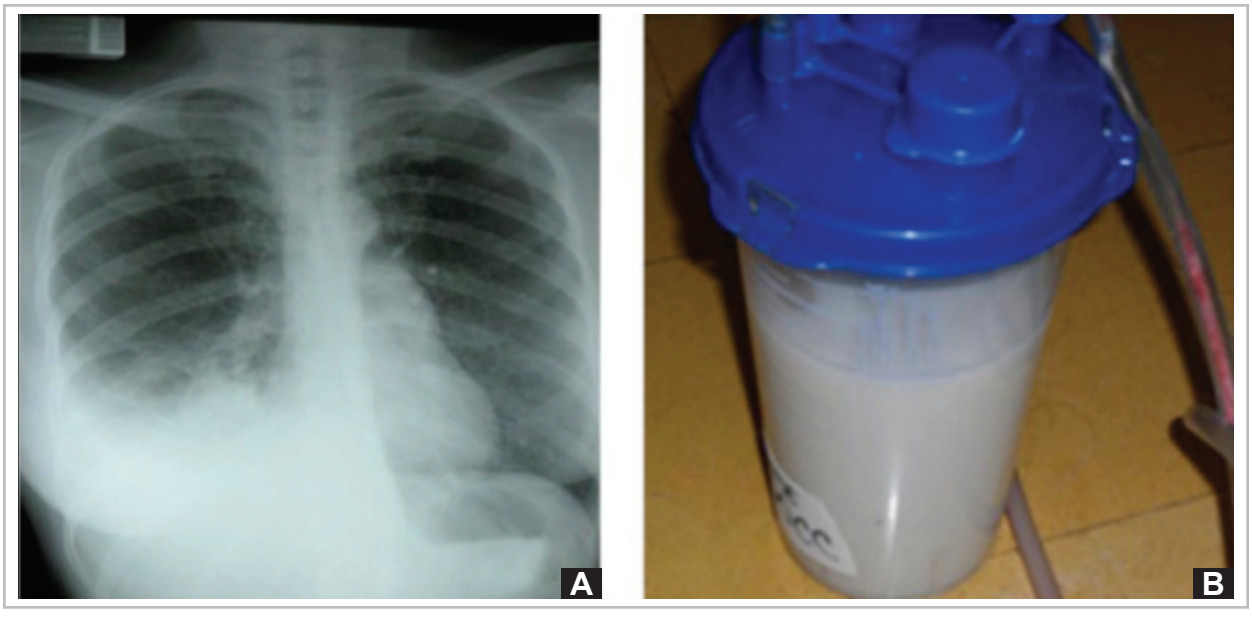

Figure 1. *(A) chest x-ray showing pleural effusion. (B) chylothorax.*

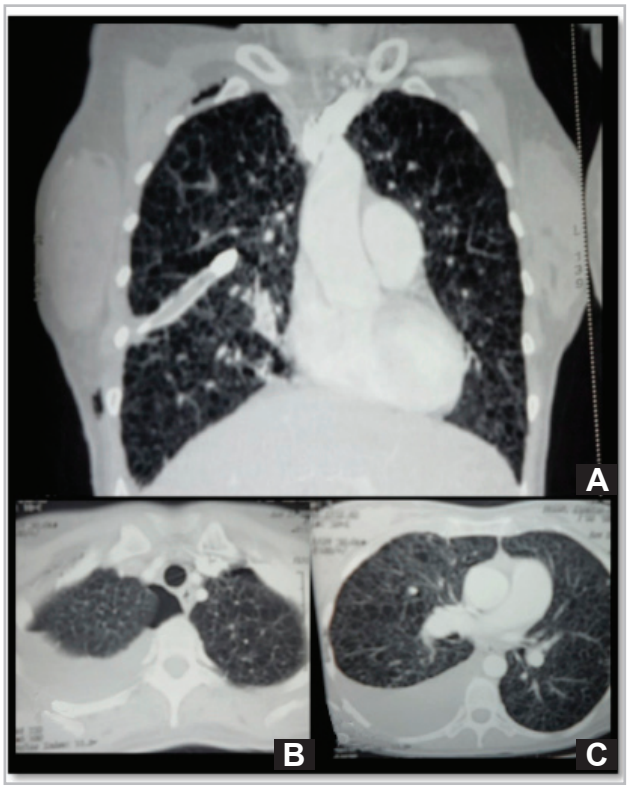

Figure 2. *A: chest CT showing multiple pulmonary cysts and a fine reticular pattern. B, C: pulmonary cysts, bilateral interstitial pattern with pleural effusion and right pneumothorax.*

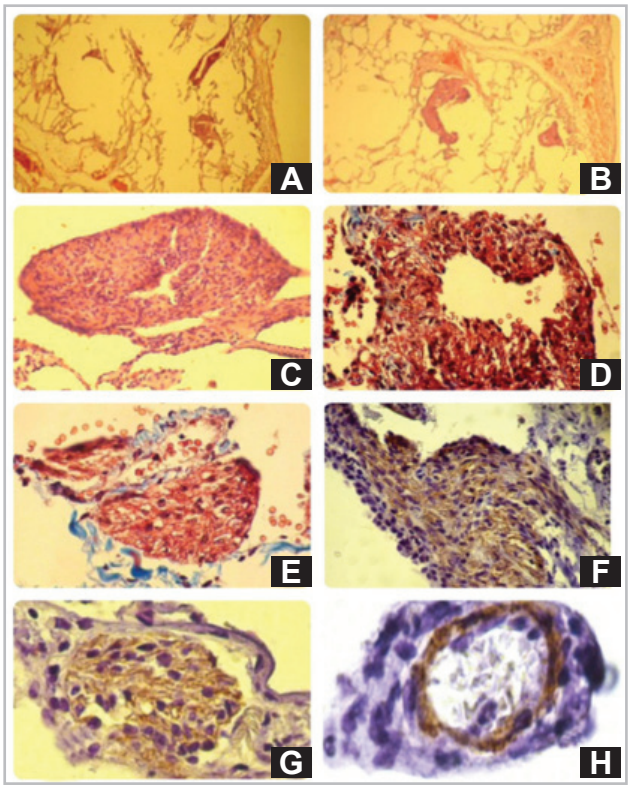

Figure 3. *A, B, D: hematoxylin and eosin, showing cysts with smooth muscle cell proliferation in blood and lymph vessel walls. 40x. C: Masson's trichrome stain, smooth muscle proliferation around the lymph vessel lumen. 1,000x. E: smooth muscle cells occluding the lymph vessel. F: immunohistochemistry showing positive smooth muscle-specific actin in the cytoplasm. G: positive HMB-45 in the smooth muscle cells. H: the CD34 receptor highlights the endothelial cells. 1,000x.*

Currently, LAM diagnosis requires an HRCT showing diffuse, bilateral thin-walled cysts, without lobar predominance. Other radiological findings may include reticular opacities, increased attenuation, and pulmonary nodules. High-resolution computed tomography has a high sensitivity and specificity for diagnosing LAM; however, it does not confirm the diagnosis. Serum VEGF-D levels are needed for confirmation. The diagnosis is confirmed when the VEGF-D is higher than 800 pg/mL (11-13). In cases where tests are inconclusive or not available, a lung biopsy may be considered to differentiate between LAM and other differential diagnoses like Langerhans disease, Sjögren's syndrome, follicular bronchiolitis, lymphoid interstitial pneumonitis, hypersensitivity pneumonitis, amyloidosis and Birt-Hogg-Dubé syndrome. Lung biopsy has almost 100% sensitivity when pulmonary cysts with LAM cells are found, identified through HMB-45-positive immunohistochemistry (14, 15).

The treatment for LAM consists of managing the mechanical complications and using mTOR inhibitors to stop its progression. Some cases will require lung transplantation. The American Thoracic Society and Japanese Respiratory Society recommend using sirolimus or everolimus for patients with LAM who have any of the following criteria: a forced expiratory volume in one second (FEV-1) less than 70%, chylothorax, a ≥90 mL reduction in FEV-1 per year, diffusion capacity impairment, air trapping, hyperinflation, and the use of supplementary oxygen. Bronchodilators may be used when there is evidence of reversible obstruction on spirometry, while hormonal contraceptives are contraindicated (16). Due to the recurrence of pneumothorax, pleurodesis is recommended after the first episode, reducing recurrence from 70-30%.

Chylothorax should initially be treated conservatively with sirolimus but, in cases with no improvement, invasive procedures may be used, such as thoracic duct ligation or permanent pleural catheters (14). Lung transplantation is recommended in terminal cases or when there is no response to pharmacological therapy. In the United States, 10-year survival in these patients is 55%. Sirolimus can prevent the recurrence of complications like chylothorax; however, it has been associated with an increased risk of bronchial anastomosis dehiscence (2, 3, 17).

In conclusion, many advances have been achieved over the last few decades. Non-invasive diagnostic tests like VEFG-D have reduced the morbidity and mortality associated with lung biopsies, and pharmacological therapies like sirolimus have proven to be effective. However, questions remain regarding the optimal dose, the effectiveness of combination therapies and new tests that can predict early pharmacological failure. Some developing countries do not have access to tests like VEFG-D levels, and therefore lung

biopsies must still be used in these cases. These countries also lack access to mTOR inhibitors, and therefore these patients suffer the natural course of LAM, which eventually ends in respiratory failure.

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