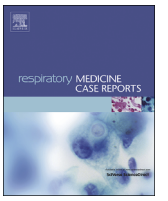
Respiratory Medicine Case Reports 52 (2024) 102128

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Tuberous sclerosis-associated pulmonary lymphangioleiomyomatosis: The role of pulmonary rehabilitation - A case report

Flor Castro-Rodriguez [a], Yakdiel Rodriguez-Gallo [b, *]

[a] Department of Critical Care Medicine, National Hospital of El Salvador, Avenida la Revolución 222, Ex-Cifo., CP 01101, San Salvador, El Salvador
[b] Faculty of Biomedicine, Don Bosco University, Calle a Plan del Pino Km 1 1/2, Soyapango, 1874, El Salvador

ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Lymphangioleiomyomatosis
Pulmonary rehabilitation
TSC-LAM
S-LAM
Klebsiella pneumonia

ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare lung disease that primarily affects women. A patient with a medical history of Tuberous Sclerosis-Associated Lymphangioleiomyomatosis (TSC-LAM), a prior thyroidectomy for thyroid cancer, chronic hypertension, and a previous pulmonary thromboembolism was admitted to the hospital. Following the stabilization of her clinical condition, diaphragmatic exercises and incentive spirometers were implemented. This intervention significantly enhanced her respiratory status, prevented the need for invasive mechanical ventilation, and expediting pulmonary functional recovery. While further studies are needed, pulmonary rehabilitation has the potential to influence the clinical course of TSC-LAM patients in the ICU by improving respiratory capacity and reducing hospitalization time.

1. Introduction

Tuberous Sclerosis-Associated Pulmonary Lymphangioleiomyomatosis (TSC-LAM) is a rare condition characterized by the formation of benign tumors in multiple organs, especially in the lungs. This condition can occur sporadically (S-LAM) or in association with tuberous sclerosis complex (TSC-LAM) [1]. Despite the European Respiratory Society acknowledging pulmonary rehabilitation as a means to manage dyspnea in LAM [2], there is a shortage of literature specifically addressing physiotherapy approaches for LAM patients. Pulmonary rehabilitation has demonstrated a positive impact on the quality of life for individuals with chronic respiratory diseases. Although it is usually implemented post-hospital discharge [3], the available literature on this topic remains limited [4]. We present a case in which a patient received pulmonary rehabilitation therapy in the Intensive Care Unit (ICU), leading to a rapid recovery and improvement over time.

2. Case presentation

A woman in her 30s presented at the emergency unit with dyspnea and subcostal retractions. Upon admission, her vital signs were as follows: blood pressure of 130/70, heart rate of 110, respiratory rate of 30, and oxygen saturation of 74 %. Physical examination revealed crackles in the pulmonary fields, predominantly at the posterior left base. Additionally, a pericardial friction rub was noted, with no apparent electrocardiographic changes. Furthermore, findings from the physical examination included angiofibromas on the face and neck.

* Corresponding author.
E-mail address: yakdiel.rodriguez@udb.edu.sv (Y. Rodriguez-Gallo).

https://doi.org/10.1016/j.rmcr.2024.102128
Received 31 May 2024; Received in revised form 30 September 2024; Accepted 2 October 2024
Available online 5 October 2024

The patient received a TSC-LAM diagnosis six years ago and has been on continuous treatment, managed with prednisone 50mg (one tablet orally each day) and budesonide/formoterol (2 puffs every 12 hours). In the same year, she underwent a thyroidectomy due to a history of thyroid cancer and manages this with levothyroxine (one tablet orally each day) for hypothyroidism, along with secondary post-surgical hypoparathyroidism. Two years after the TSC-LAM diagnosis, she developed and received treatment for chronic arterial hypertension, managed with irbesartan 300 mg (one tablet orally each day), plus amlodipine 5 mg (one tablet orally each day). One year before the current presentation, she experienced a pulmonary thromboembolism, which is being treated with rivaroxaban (one tablet orally each day) and gabapentin (one tablet orally each day). Her gynecological and obstetric history includes zero pregnancies and zero vaginal deliveries, with a history of dysmenorrhea and menarche at 13 years old. Additionally, it's noteworthy that she had been hospitalized just a week earlier due to an ulcer related to deep venous insufficiency.

Laboratory test results revealed a leukogram with neutrophilia greater than 90 %, hyperfibrinogenemia, elevated D-dimer, and elevated ProBNP. Consequently, the patient was transferred to the Intensive Care Unit (ICU). A high-flow nasal cannula was placed at a flow rate of 60 L/minute with an FiO2 of 100 %, resulting in improved oxygen saturation (93 %), and a gradual reduction of subcostal retractions and dyspnea. Bronchodilators and steroids were prescribed, and Piperacillin/Tazobactam (4.5 g IV every 6 hours) was initiated due to suspected pneumonia. A high-resolution computed tomography (HRCT) scan was performed, which showed generalized thickening of interstitial septa, panlobular emphysema, and a subpleural basal left bulla (Fig. 1a, left). Moreover, the presence of pericardial effusion was detected (Fig. 1b, right), and it was treated with diuretics.

On the third day, *Klebsiella pneumoniae* ESBL+ was detected in a bronchial secretion culture (MALDI-TOF MS Biotyper), necessitating a switch to Meropenem (1 g intravenous (for 3 hours) every 8 hours). On that same day, pulmonary rehabilitation was initiated with diaphragmatic exercises. No inspiratory exercises with CPAP (continuous positive airway pressure) were performed due to the presence of a posterior giant bulla. On the fourth day, the patient was successfully transitioned to a Venturi mask (50 %). On the tenth day, a thoraco-abdominal CT scan was conducted, detecting renal cysts with hematic and perirenal fat remnants, resembling a cobweb-like appearance in both kidneys. An infiltrative-appearing lymphadenopathy at the aorto-caval interface was also identified (Fig. 1c).

Respiratory exercises were initiated in conjunction with the antibiotic treatment. These exercises started on the third day, and this program was implemented for the patient. Initially, it was administered once daily for a maximum of 20 minutes, adjusted according to the patient's tolerance and clinical advancement. Subsequently, the frequency of these exercises was gradually increased to twice daily, with a maximum duration of 45 minutes. Following improvement in the acute phase, the practice was restricted to a maximum of two sessions per day, each lasting 5 minutes for each type of exercise.

The initial exercise centered on thoracic expansion, guiding the patient to inhale deeply while applying moderate pressure with their hands to expand the thoracic area. This procedure was supplemented by a brief pause in maximal inspiration, succeeded by a gradual exhalation. The second exercise, conducted in a supine position, emphasized abdominal breathing. The patient took a deep breath through the nose, allowing the abdomen to press against the hand, and exhaled through pursed lips. The third exercise, referred to as pursed-lip breathing, entailed a gradual nasal inhalation with the mouth closed, succeeded by exhalation through partially closed lips, maintaining a duration ratio of twice the inspiration. The fourth exercise, diaphragmatic breathing, was conducted while seated. The patient inhaled deeply through the nose with a closed mouth, followed by a slow and gentle exhalation through slightly parted lips, allowing the abdominal muscles to return to their initial position. The fifth exercise, aimed at lung expansion, required the patient to inhale deeply while applying pressure to the chest with their hands, followed by a controlled exhalation. At the end of exhalation, a gentle vibration was applied over the area. The sixth exercise, focusing on effective and controlled coughing, involved a deep breath followed by controlled exhalation, incorporating short and forceful coughs. The seventh exercise integrated the use of an upright incentive spirometer. The patient sealed their lips around the mouthpiece, took a deep breath, raising the marker to its upper limit, maintaining it there for as long as possible before releasing the mouthpiece and exhaling. Coughing was recommended after each session of this exercise.

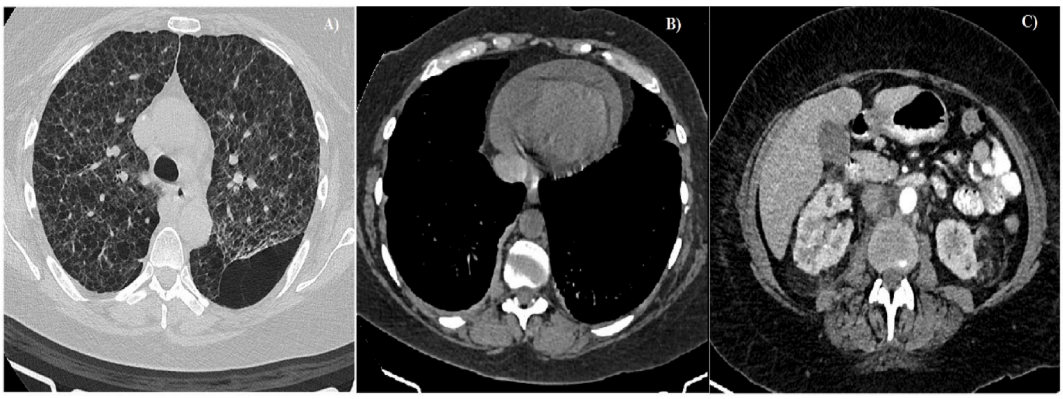


Fig. 1. a) HRCT shows septal thickening, panlobular emphysema and a subpleural basal left bulla. b) Tomographic scan revealing the presence of pericardial effusion. c) Renal cysts with hematuria remnants are observed in the middle third of both the right and left kidneys. An adenopathy is observed at the aorto-caval region.

After 21 days in the ICU, the patient moved to intermediate care for one day and then to internal medicine. Upon discharge, she received prescriptions for oral and inhaled medications along with diaphragmatic exercises.

3. Discussion

In patients with acute LAM caused by infections, it is essential to detect and treat infections early due to the high risk of developing acute respiratory failure and requiring mechanical ventilation. Consequently, timely treatment of infections plays a fundamental role in this population. Chylothorax or pneumothorax complicating LAM requires surgical intervention, whereas lung transplantation becomes imperative in cases of advanced-stage LAM [5]. The main treatment for LAM is mTORC1 inhibition with medications such as sirolimus, which stabilizes lung function and reduces the size of lung destruction, lymphangioleiomyomas (LLM), angiomyolipomas (AML), chylous effusions, and giant cell astrocytomas [6,7].

We conducted a search on PubMed (Medline) for the past 20 years (until March 16, 2024), focusing on reviews and original research papers related to lymphangioleiomyomatosis, published in English. We employed the terms "lymphangioleiomyomatosis," "LAM," and "lymphangiomyomatosis" in combination with "tuberous sclerosis complex," "TSC-LAM," "pulmonary rehabilitation," " exercise," and "physiotherapy." A total of 18 papers meeting the criteria were identified. Most of these studies focus on exercise in the context of assessing functional capacity (13 papers). An example is the study conducted by Medeiros et al. [8], which addresses the evaluation of sleep desaturation in patients with LAM and its correlation with various functional parameters. Furthermore, Zafar et al. [9] conducted low-intensity and progressive exercise echocardiograms on patients using an incremental protocol with a supine ergometer. This form of exercise echocardiography was employed to assess exercise-induced pulmonary hypertension, intracardiac shunts, and pulmonary vascular shunts in dyspneic patients. The document emphasizes the unexpected occurrence of intrapulmonary arteriovenous shunts (IPAVS) in this patient group and underscores the need for further studies to comprehend the implications of these findings on desaturation, dyspnea, and exercise limitation. Additionally, Taveira-DaSilva et al. [10] noted that the risk of pneumothorax associated with pulmonary function tests (PFT) or cardiopulmonary exercise tests (CPET) in patients with lymphangioleiomyomatosis (LAM) is low. The study involved 691 patients. The research concludes that, although the risk is low, efforts associated with these tests may lead to pneumothorax, especially in patients with cystic lung diseases like LAM.

Other papers focus on cardiopulmonary rehabilitation programs in stable patients. Initially, five studies met the criteria, and two were selected to avoid duplicative information (Table 1). Aerobic and strength training exercises are commonly used as physiotherapy modalities in the rehabilitation of individuals with pulmonary disease [11]. No documented cases have been found where individualized pulmonary rehabilitation was implemented in the ICU for patients with TSC-LAM.

Although there is no specific cardiopulmonary rehabilitation guideline for LAM, the European Respiratory Society asserts that the benefits of rehabilitation in COPD can be extrapolated to LAM [16]. There is a scarcity of literature specifically addressing physiotherapy approaches for LAM patients. The trend is towards using remote technology, as well as the Internet of Things (IoT), to develop supervised home exercise programs for patients with pulmonary diseases [17].

The main difference in this case, compared to interstitial lung disease (ILD) and COPD, was the early initiation of exercises, which were implemented during the first days of antibiotic treatment. The antibiotic regimen was not completed before starting; only hemodynamic stability and the absence of accessory muscle use during exercises were considered. Additionally, unlike ILD and COPD, no inspiratory exercises were performed with CPAP or an incentive spirometer [18,19]. This decision was based on the individualization of the case, considering the weakened alveolar walls due to LAM and the patient's history of spontaneous pneumothorax. The program was adjusted according to the disease's pathophysiology.

The analysis of the reviewed studies indicates that a cardiopulmonary rehabilitation program for individuals with LAM, incorporating aerobic exercises and strength training, leads to improved pulmonary function, enhanced exercise tolerance, decreased dyspnea, and contributes to an overall improvement in quality of life.

Table 1
Reports on the rehabilitation of Pulmonary Lymphangioleiomyomatosis.

Author, (year).	Country	Number of patients	Type of exercise	Main outcomes
Child et al. [4] 2023	United States of America	15	Aerobic and strength training	The program improved submaximal exercise capacity, muscular endurance, fatigue, and health-related quality of life in patients with LAM. The program achieved high adherence, acceptability, and patient satisfaction, and no adverse events related to the study or changes in systemic inflammation or cardiac wall stress biomarkers were observed.
Medeiros et al. [5] 2022	Brazil [12]	40	Aerobic and muscle strength training sessions	The analyzed studies suggest that a cardiopulmonary rehabilitation program, encompassing both aerobic and strength training, stands out as the primary physiotherapeutic approach capable of improving lung function and exercise tolerance in individuals with LAM.
	United States of America [13]	1	Supervised aerobic exercise training	
	China [14]	26	24-week program of yoga class training	
	Germany [15]	58	Endurance and strength training	

4. Conclusion

In summary, for patients with TSC-LAM, starting pulmonary rehabilitation early in the ICU, once the clinical condition stabilizes, should lead to a quicker improvement in respiratory function compared to delayed implementation. However, further research on this topic is needed. Respiratory muscle exercises and strengthening of the thoracic cavity contribute to improving ventilatory function. Additionally, the early application of rehabilitation has been observed to correlate with a reduction in hospitalization days and the need for supplemental oxygen.

Funding

No funding from an external source supported the publication of this case report.

CRediT authorship contribution statement

Flor Castro-Rodriguez: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Yakdiel Rodriguez-Gallo:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We extend our gratitude to the Hospital Nacional El Salvador for its support, and to the patient for providing her consent.

References

[1] A.M. O'Mahony, E. Lynn, D.J. Murphy, A. Fabre, C. McCarthy, Lymphangioleiomyomatosis: a clinical review, Breathe 16 (2020) 200007, https://doi.org/10.1183/20734735.0007-2020.
[2] N. Carvajal Tello, A. Segura Ordoñez, A.J. Arias Balanta, Pulmonary rehabilitation in the in-hospital and outpatient phases, Rehabilitacion 54 (2020) 191–199, https://doi.org/10.1016/j.rh.2020.02.008.
[3] K.-F. Xu, X. Tian, J.H. Ryu, Recent advances in the management of lymphangioleiomyomatosis, F1000Res 7 (2018) https://doi.org/10.12688/f1000research.14564.1, F1000 Faculty Rev-758.
[4] C.E. Child, M.L. Kelly, H. Sizelove, M. Garvin, J. Guilliams, P. Kim, H.D. Cai, S. Luo, K.J. McQuade, E.R. Swenson, A.T. Wise, Y.T. Lynch, L.A. Ho, M.B. Brown, A remote monitoring-enabled home exercise prescription for patients with interstitial lung disease at risk for exercise-induced desaturation, Respir. Med. 218 (2023) 107397, https://doi.org/10.1016/j.rmed.2023.107397.
[5] V.M.G.D. Medeiros, J. Gonçalves De Lima, C. Rosa, J. Rega, M.F.F. Mediano, L.F. Rodrigues Junior, Physiotherapy in lymphangioleiomyomatosis: a systematic review, Ann. Med. 54 (2022) 2732–2739, https://doi.org/10.1080/07853890.2022.2128401.
[6] A.M. Taveira-DaSilva, J. Moss, Lymphangioleiomyomatosis, in: S.M. Janes (Ed.), Encyclopedia of Respiratory Medicine, second ed., Academic Press, Oxford, 2022, pp. 447–465, https://doi.org/10.1016/B978-0-12-801238-3.11475-8.
[7] C.D. Burger, Efficacy and safety of sirolimus in lymphangioleiomyomatosis, N. Engl. J. Med. 365 (2011) 271–272; author reply 272, https://doi.org/10.1056/nejmc1106358.
[8] P. Medeiros, G. Lorenzi-Filho, S.P. Pimenta, R.A. Kairalla, C.R.R. Carvalho, Sleep desaturation and its relationship to lung function, exercise and quality of life in LAM, Respir. Med. 106 (2012) 420–428, https://doi.org/10.1016/j.rmed.2011.12.008.
[9] M.A. Zafar, F.X. McCormack, S. Rahman, C. Tencza, K.A. Wikenheiser-Brokamp, L.R. Young, Y. Shizukuda, J.M. Elwing, Pulmonary vascular shunts in exercise-intolerant patients with lymphangioleiomyomatosis, Am. J. Respir. Crit. Care Med. 188 (2013) 1167–1170, https://doi.org/10.1164/rccm.201304-0618LE.
[10] A.M. Taveira-DaSilva, P. Julien-Williams, A.M. Jones, J. Moss, Incidence of pneumothorax in patients with lymphangioleiomyomatosis undergoing pulmonary function and exercise testing, Chest 150 (2016) e5–e8, https://doi.org/10.1016/j.chest.2015.10.071.
[11] T. Troosters, W. Janssens, H. Demeyer, R.A. Rabinovich, Pulmonary rehabilitation and physical interventions, Eur. Respir. Rev. 32 (2023), https://doi.org/10.1183/16000617.0222-2022.
[12] M.S. Araujo, B.G. Baldi, C.S. Freitas, A.L. Albuquerque, C.C.M. da Silva, R.A. Kairalla, C.R. Carvalho, C.R. Carvalho, Pulmonary rehabilitation in lymphangioleiomyomatosis: a controlled clinical trial, Eur. Respir. J. 47 (2016) 1452–1460, https://doi.org/10.1183/13993003.01683-2015.
[13] T.W. Lowder, High-intensity exercise improves pulmonary function and exercise tolerance in a patient with TSC-LAM, Adv Respir Med 88 (2020) 356–359, https://doi.org/10.5603/ARM.a2020.0129.
[14] X. Li, W. Xu, L. Zhang, Y. Zu, Y. Li, Y. Yang, Y. Xiang, Y. Xiang, L. Chen, W. Liu, L. Chen, K.-F. Xu, Effects of yoga on exercise capacity in patients with lymphangioleiomyomatosis: a nonrandomized controlled study, Orphanet J. Rare Dis. 15 (2020) 72, https://doi.org/10.1186/s13023-020-1344-6.
[15] R. Gloeckl, C. Nell, T. Schneeberger, I. Jarosch, M. Boensch, H. Watz, H. Wirtz, T. Welte, K. Kenn, A.R. Koczulla, Benefits of pulmonary rehabilitation in patients with advanced lymphangioleiomyomatosis (LAM) compared with COPD - a retrospective analysis, Orphanet J. Rare Dis. 15 (2020) 255, https://doi.org/10.1186/s13023-020-01540-3.
[16] S.R. Johnson, J.-F. Cordier, R. Lazor, V. Cottin, U. Costabel, S. Harari, M. Reynaud-Gaubert, A. Boehler, M. Brauner, H. Popper, European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis, ERJ 35 (2010) 14–26, https://doi.org/10.1183/09031936.00076209.
[17] A. Sarmento, K. King, D.C. Sanchez-Ramirez, Using remote technology to engage patients with interstitial lung diseases in a home exercise program: a pilot study, Life 14 (2024) 265, https://doi.org/10.3390/life14020265.
[18] A.A. El-Koa, H.A. Eid, S.R. Abd Elrahman, M.M. El Kalashy, Value of incentive spirometry in routine management of COPD patients and its effect on diaphragmatic function, Egypt J Bronchol 17 (2023) 8, https://doi.org/10.1186/s43168-023-00185-7.
[19] Outcome of pulmonary rehabilitation in patients with COPD: comparison between patients receiving exercise training and those receiving exercise training and CPAP, Egypt. J. Chest Dis. Tuberc. 66 (2017) 609–616, https://doi.org/10.1016/j.ejcdt.2017.10.005.