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Case Report

Pulmonary lymphangiomyomatosis (LAM): A literature overview and case report ^{☆,☆☆}

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ABSTRACT

Lymphangiomyomatosis is a rare multisystem disease associated with genetic mutations. The disease usually occurs in women of childbearing age and is characterized by infiltration of immature smooth muscle cells into the lungs, airways, and axial lymphatic systems of the chest and abdomen. The disease often destroys lung parenchyma and produces air cysts. Lymphangiomyomatosis cell infiltration of the lymphatic axis can affect hilar lymph nodes, mediastinal ganglia, and extrathoracic lymph nodes. The disease can cause lymphatic dilation in the lungs and thoracic ducts, causing chylous effusion into the pleural or abdominal cavities. Invasion of cells into the walls of pulmonary veins can lead to venous obstruction and pulmonary venous hypertension with hemoptysis. Most patients present with cough, dyspnea, pneumothorax, hemoptysis, and abnormal lung function. Definitive diagnosis is usually based on histopathology and immunohistochemistry. We present a case of LAM in a 36-year-old female patient who was confirmed by specimens obtained from pneumothorax surgery and positive immunohistochemical staining with HMB-45.

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Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease characterized by progressive proliferation of perivascular LAM cells (PECs), bronchioles, and lymphatics in the chest and abdomen. In the new World Health Organization (WHO) classification of lung tumors, LAM is considered a low-grade, destructive metastatic cancer and PEC tumor (PEComa) [1,2]. The disease usually occurs in women of childbearing age. One of the greatest challenges in the diagnosis and treatment of LAM is the origin of LAM cells; furthermore, the mechanism of sexual dimorphism in LAM remains unresolved and is not well understood. Infiltrative LAM leads to bronchial obstruction, destruction of lung tissue, and the formation of isolated pulmonary cysts. LAM may be associated with renal artery leiomyoma (present in 15% of cases). The proliferation of LAM cells in the lymphatic system can lead to enlarged lymph nodes in hilar, mediastinal, and extrathoracic regions, sometimes dilating lymphatic vessels in the lungs and thoracic duct and leading to chylous pleural or abdominal effusion. The proliferation of LAM cells in pulmonary veins can cause venous obstruction and lead to pulmonary hypertension, which can present as hemoptysis [1-5].

The pathogenesis of LAM explains its imaging features. Obstruction of the bronchioles creates air cysts and excessive distension of the cysts combined with destruction of the cyst wall or pneumothorax. Most LAMs are found to be due to recurrent pneumothorax of unknown etiology [1,3,6-8].

Conventional radiographic manifestations of LAM include reticular, mesh-nodular, nodular, and honeycomb patterns. More than 50% of patients have radiographic evidence of pneumothorax at the time of initial presentation. Lung volume may be increased, and radiographs often do not reveal the presence of diffuse pulmonary cysts [2].

On high-resolution computer tomography (HRCT), patients with characteristic LAM show multiple, thin-walled pneumococcal cysts surrounded by relatively normal lung parenchyma; the diameter of the cysts ranges from 2 mm to 5 cm, or larger. Cyst size tends to increase with disease progression: in patients with mild disease, the cysts are usually less than 5 mm in diameter, whereas in patients with severe disease, the cysts tend to be more than 1 cm in diameter. The walls of the pulmonary cysts are usually thin and easily discernible, although they can sometimes be up to 4 mm thick. Pulmonary cysts are usually round, and irregular shapes, such as those found in patients with LCH, are uncommon. Very small (1-3 mm) nodules may also be present and represent proliferation of type II pleural cells [1,2].

Definitive diagnosis of LAM is usually based on pathologic results and immunohistochemical staining of lung biopsy specimens obtained through the chest wall or during endoscopic surgery for pneumothorax. Currently, the technique used to quantify lymphatic growth factors in the blood using VEGF-C and VEGF-D is also recommended to confirm the diagnosis of LAM [9].

We present a case of LAM with a full, classic clinical and epidemiologic history, that was confirmed by thoracoscopic lung biopsy and immunohistochemical staining that was positive for HMB-45.

Case report

A 36-year-old female patient was admitted to the hospital due to chest pain. The disease had progressed 7 days before admission, when the patient presented with right chest pain and shortness of breath, and without fever or cough. The patient had been examined and treated at a provincial hospital with slow improvement before being transferred to the National Lung Hospital (NLH) for treatment.

Before the current hospital admission, the patient had a history of 2 previous admissions for pneumothorax: the first, a right-sided pneumothorax in 2018 that resolved with medical treatment; and the second, a left-sided pneumothorax in 2019 that was treated with laparoscopic surgery at Thanh Hoa Lung Hospital. The patient also reported infrequent, small-volume hemoptysis.

*Examination on admission to the NLH: The patient was awake, accessible, SpO₂ 97%, breathing spontaneously, with constant pain in the right chest, no cough, no fever, regular heart, right lung auscultation revealed hypoventilation and unknown rales. Physical examination of other organ systems, especially the endocrine and genitourinary systems, revealed no abnormalities. On admission, laboratory results for complete blood count, blood chemistry, and urine were all within normal ranges. Microbiological tests for tuberculosis and non-tuberculous bacteria were negative.

The patient underwent routine chest X-ray imaging. Detailed images and interpretations are shown in Fig. 1.

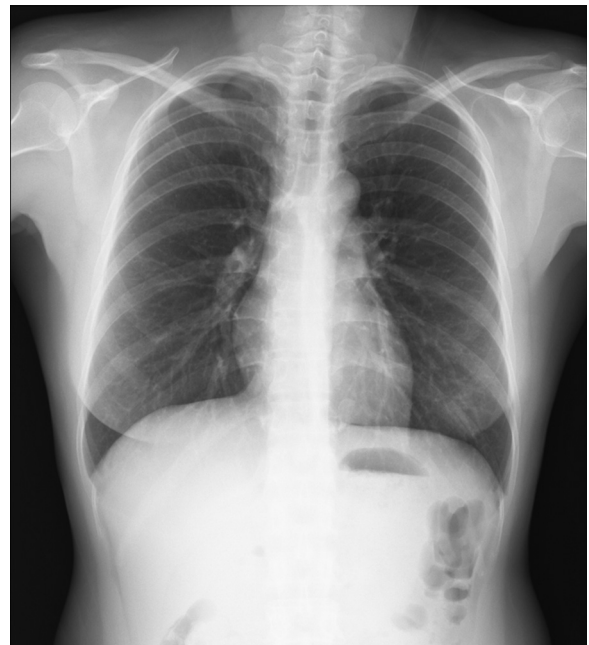


Fig. 1 – Chest X-ray radiograph of the patient at the first examination at NLH (note that the patient underwent surgery for pneumothorax 1 year prior). The main sign is increased chest volume (hypertension of the lungs) and the parenchymal structure is similar in lung regions. In addition, no parenchymal abnormalities are seen.

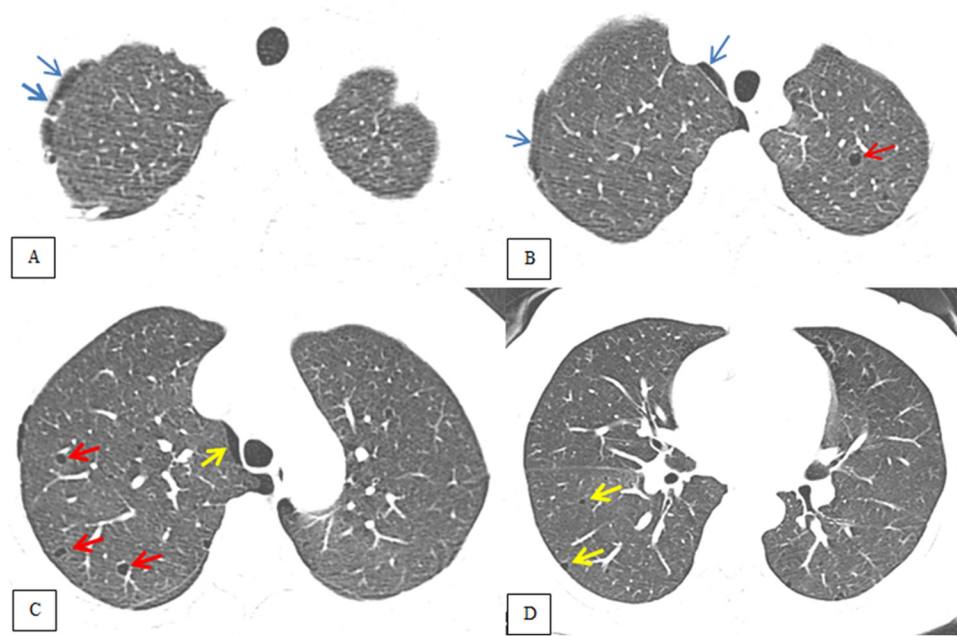


Fig. 2 – Chest CT image of the patient's lungs at 4 different levels. (A) The right-sided, low-grade pneumothorax appears, to be localized (green arrows). (B) Lower view shows right-sided pneumothorax (green arrows) and the presence of a 5-mm-diameter, thin-walled air cyst in the upper lobe of left lung. (C) A lower section shows pneumothorax (yellow arrow) and multiple small air cysts (red arrows). (D) Subsection of the carina shows no right-sided pneumothorax and few small air cysts (yellow arrows) (Color version of the figure is available online.)

Due to a history of surgery for pneumothorax 1 year prior, the patient underwent a CT scan of the chest. The results are shown in detail in Fig. 2.

The patient also underwent basic examinations: abdominal ultrasound did not detect any abnormalities; respiratory function test: the 6-minute walk test resulted in 67.46%; the bronchial recovery test was negative; the diffusing capacity for carbon monoxide (DLCO) (the ability to diffuse air across the alveolar capillary membrane) was within normal limits; and electrocardiography revealed sinus rhythm, a heart rate of 70, and a medial axis. The patient was diagnosed after laparoscopic surgery to treat the right-sided pneumothorax. Follow-up and specialist consultation was required to determine the cause of bilateral pneumothorax.

After 1 week, the patient had a complete blood count: white blood cell (WBC) counts $12 \times 10^3/\mu\text{L}$ (82% neutrophils [increased] and 11.7% lymphocytes [decreased]); red blood cell count $3.9 \times 10^6/\mu\text{L}$; platelet count $275 \times 10^3/\mu\text{L}$. The patient was treated with antibiotics, which improved her condition, and further monitored before a definitive diagnosis was made.

After 13 days, the patient presented with dyspnea, and left-sided chest pain. The patient underwent a chest X-ray and was diagnosed with left-sided pneumothorax. Details are shown in Fig. 3.

The patient underwent a CT scan of the chest. The detailed results are shown in Fig. 4.

Due to the large degree of the left pneumothorax, drainage of the pneumothorax did not improve the condition and the patient underwent thoracoscopic surgery. During laparoscopic surgery, a parenchymal biopsy was obtained. The

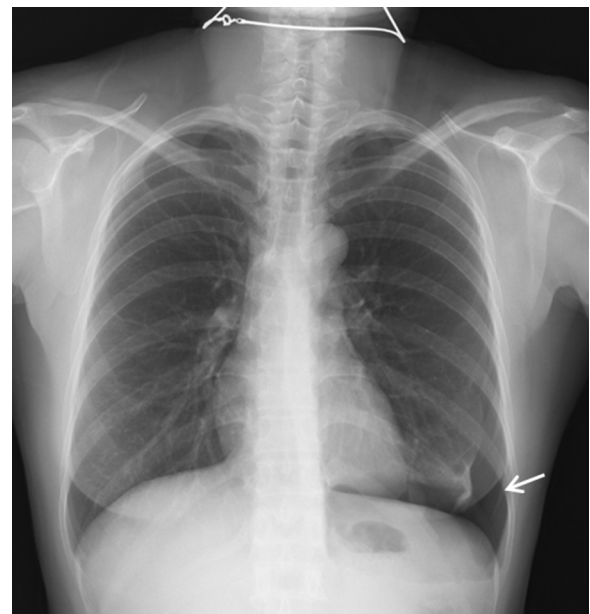


Fig. 3 – Chest X-ray taken 13 days after admission. X-ray shows increased chest volume and left-sided pneumothorax (white arrow). Note that the parenchymal structure is uniform in all regions.

results of the histopathological and immunohistochemical analyses are presented in the following section.

The patient was stable 10 days after surgery and was discharged home for follow-up, received comprehensive medical advice, and was scheduled re-examination.

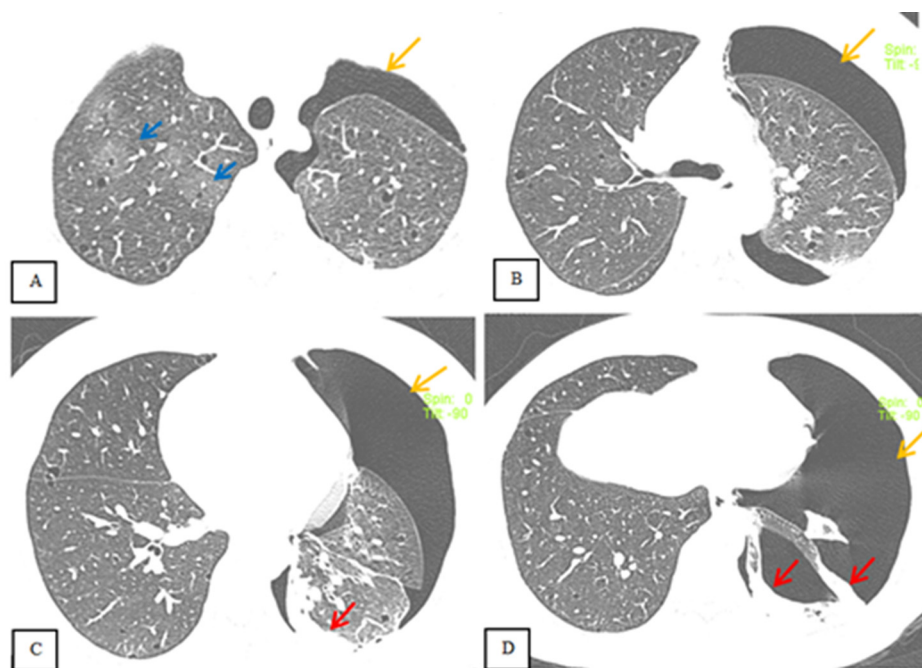


Fig. 4 – Chest CT taken 13 days after admission. (A) A left pneumothorax (yellow arrow) is visible, with no air in the right pleural space, and small air cysts in the parenchyma of the right upper lobe in the area of ground-glass opacity (GGO) (blue arrow). (B, C, D) Severe left pneumothorax (yellow arrow) is visible with passive atelectasis (red arrow). Many small air cysts remain scattered throughout the lung parenchyma (A, B, C, D) (Color version of the figure is available online.)

After 3 months, the patient presented with chest pain, dyspnea, and scattered hemoptysis. The patient returned to the hospital and a chest X-ray was performed. The results showed right pneumothorax and suspected left pneumothorax. Details are shown in Fig. 5.

The patient underwent a chest CT scan and the detailed results are shown in Fig. 6.

The patient was consulted and decided to undergo a third laparoscopic surgery to treat the right pneumothorax. Stitching of the perforated air cysts causing the pneumothorax and negative pressure drainage of the right pleural cavity after surgery was performed by the surgeons. The operation was successful. The patient was treated with antibiotics after surgery and the drainage tube was removed after 13 days. Details of the follow-up are demonstrated through a series of chest radiographs shown in Fig. 7.

The patient was discharged from the hospital and was re-examined after 1 month. The patient had a follow-up visit after 1 month, where the doctor requested another chest CT scan. The detailed results are shown in Fig. 8.

After re-examination, the patient was assessed for stable disease. Treatment with drugs to inhibit lymphatic growth was advised by doctors but could not be implemented (the drugs were expensive and not available in Vietnam). Currently, due to complications associated with the development of the COVID-19 pandemic, the patient has been unable to return for follow-up examination; however, the patient has been contacted via telephone, and reports leading a normal life.

In both surgeries, a lung biopsy of the affected area was obtained, and the results of histopathological and immuno-

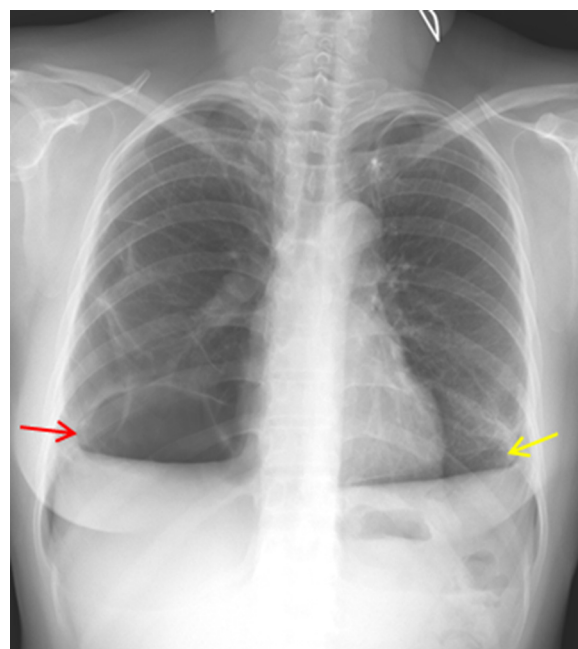


Fig. 5 – Chest X-ray 3 months after laparoscopic surgery for left pneumothorax. Right pneumothorax (red arrow) and a suspected left pneumothorax (yellow arrow) are visible (Color version of the figure is available online.)

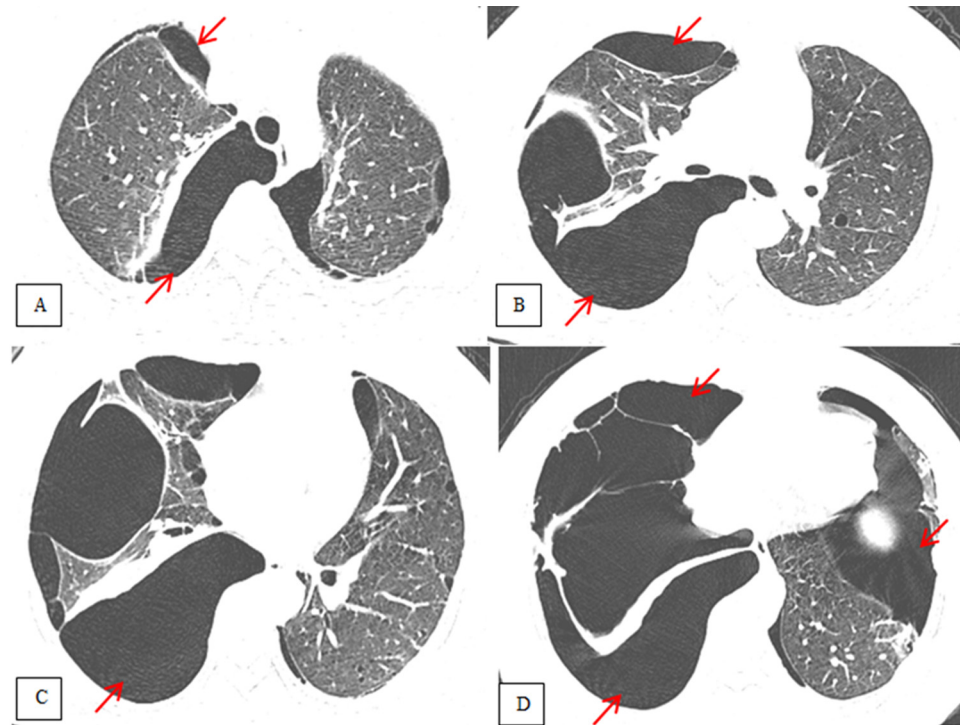


Fig. 6 – Chest CT 3 months after laparoscopic surgery for left pneumothorax. (A–C) Bilateral pneumothorax; the right side is more severe than the left (red arrows) (Color version of the figure is available online.)

histochemical analysis showed typical features of LAM. The details of the analyses are shown in Fig 9.

*Diagnosis confirmed case: Pulmonary Lymphangi-oleiomyomatosis.

Discussion

Pulmonary LAM is a low-grade malignancy of the lungs found in women of reproductive age. Very few cases have been reported in postmenopausal women or in men with scleroderma. Approximately 1% of patients with scleroderma have LAM-like changes in their lungs. The disease is very rare, only seen in 1-2.6/100,000 women [2]. LAM cells express estrogen and progesterone receptors, and lung function declines during periods of high circulating estrogen levels. Many studies have found that estrogen is an important driver of LAM cell proliferation, migration, and metastasis. LAM exists in 2 main forms: the first is related to hereditary multiple sclerosis complex (TSC-LAM) and the second is the sporadic form (S-LAM) [9]; most patients with LAM have the S-LAM form (85%) [2]. The true origin of LAM cells remains unknown, and there are currently 2 theories that are considered reasonable: the first theory proposes that LAM cells have airway or vascular origin, while the second theory suggests that LAM cells originate from AML in the kidney and are transported to the lung via neoplastic dissemination [10–14]. The disease progresses, with destruction of lung tissue by proliferation of rhombus cells and epithelial cells with the phenotype of perivascular cells, also known as PECs. Due to the co-expression of smooth

muscle proteins (actin and desmin) and melanocyte markers (HMB-45, Melan-A, and MART-1), LAM cells are thought to be of perivascular epithelial cell origin, although this is still unclear. Initially, these cells were thought to be of airway or vascular smooth muscle origin, but this hypothesis was inappropriate as LAM cells appeared diffusely in both lungs and were unevenly distributed in the nodules, with no angiogenesis organized classes. Another theory is that LAM cells form from hemangiomas and migrate to the lungs. This cell is also found in the blood and urine of patients with LAM. In addition to damaging the lungs, it also travels through the bloodstream, and lymphatics to secondary sites. This observation is supported by the recurrence of LAM nodules in the lungs of LAM lung transplant patients that are confirmed to be similar to the patient's original LAM cells. The actual incidence of LAM may be higher than reported due to incorrect diagnoses combined with multiple underlying diseases in these patients [13,15–18].

Currently, the development of testing techniques for lymphatic growth factors VEGF-C and VEGF-D is fostering hope for the diagnosis of LAM without the need of a lung biopsy. Elevated serum VEGF-D in 70% of patients with LAM is a clinically useful diagnostic and prognostic biomarker. Furthermore, sirolimus, a therapeutic drug that inhibits VEGF-D and anti-lymphocyte proliferation, is highly effective in stabilizing lung function, and minimizing complications in LAM cases [9,10,19,20].

LAM in the lungs often presents with the clinical features of dyspnea on exertion and recurrent pneumothorax. Some less common symptoms, such as chest pain, dry cough, hemoptysis, ascites, and chylous effusion, or manifestations such as sepsis, hematuria, pericardial effusion, and lymphedema,

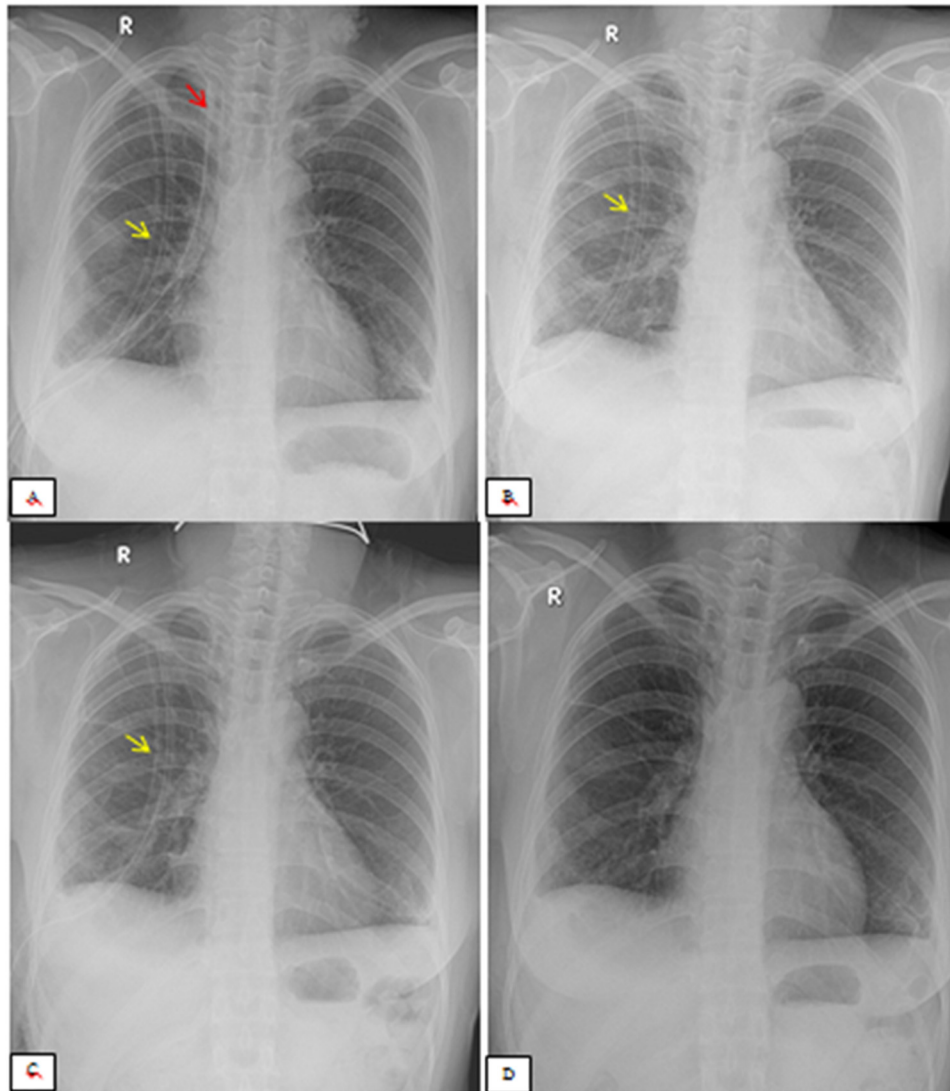


Fig. 7 – A series of postoperative follow-up X-ray radiograph (for 13 days). (A) Two drainage tubes (red arrow) and the mediastinal pleural space and right posterior pleural space (yellow arrow) are visible. (B) The pleural-mediastinal drainage tube was withdrawn after 3 days. (C) The right pleural drainage tube remains in place, behind (yellow arrow). (D) On day 13 after surgery, the drainage tube has been removed, and no air is visible in the bilateral pleural spaces (Color version of the figure is available online.)

have also been described; these symptoms worsen during pregnancy. Spontaneous pneumothorax is a common feature that often suggests LAM. LAM should be considered in women with dyspnea due to pneumothorax, hemoptysis, and chest radiograph abnormalities. On conventional radiographs, 80% of patients with LAM show a mild reticular pattern; in patients with advanced disease, a pattern of multiple pulmonary cysts mimicking honeycomb may be seen. The lungs often appear abnormal, with the basal region appearing structurally similar to the apical region. As with histiocytosis, lung mass often appears increased despite the presence of a meshwork structure. Pleural abnormalities may precede, accompany, or evolve after the lung disease is recognized. Approximately 50% of patients have a pneumothorax at the time of presentation, and unilateral or bilateral pleural effusions are present in 10%-20%

of cases. Approximately 10%-25% of patients have normal radiographs at the time of examination despite the presence of multiple pulmonary cysts [21-23].

On HRCT, patients with TSC-LAM and S-LAM show the characteristic feature of numerous isolated, thin-walled, rounded pulmonary cysts. These cysts are usually 2-5 mm in diameter but can be larger; their size tends to increase with disease progression. In critically ill patients, >80% of the lung parenchyma is involved, and most of the cysts are larger than 1 cm in diameter. The walls of the cyst are usually thin and light. Irregular cyst shapes, as seen in patients with LCH, are uncommon. The cysts are usually widely distributed throughout the lung, from apex to base, and no longer have the same lung area as LCH [22-24]. The presence of diffuse pulmonary involvement is seen even in LAM patients with mild disease.

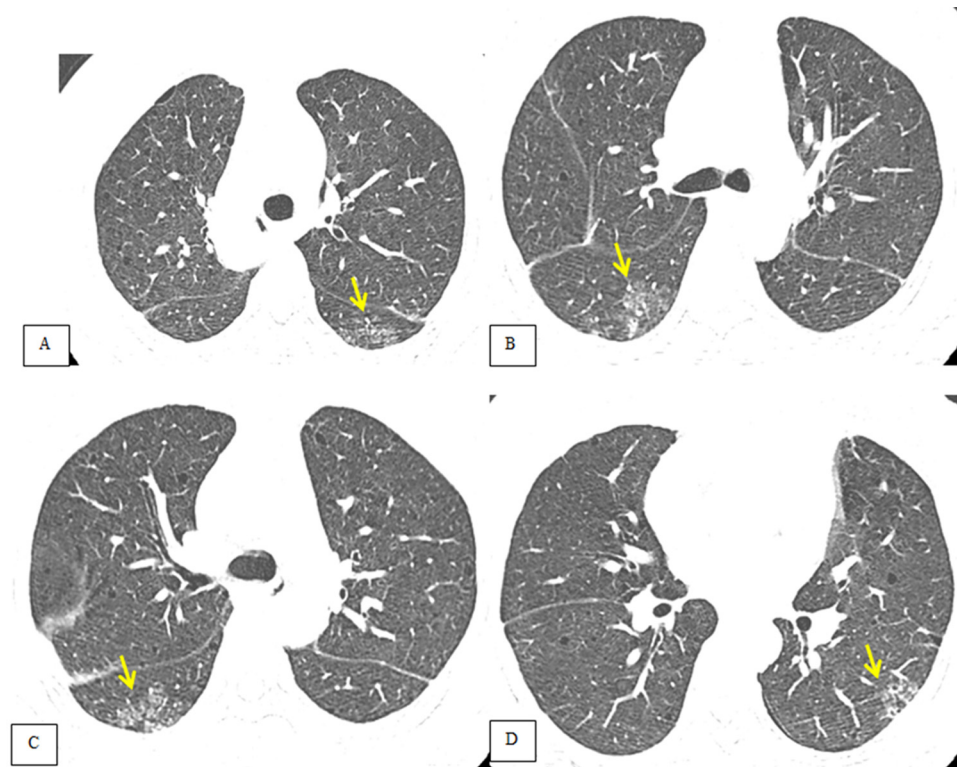


Fig. 8 – Chest CT of the patient taken 1 month after discharge. A–D: Bilateral pneumothorax is no longer visible. Nodular infiltrates are seen in segment VI of both lungs (yellow arrow). Small air cocoons persist but are inconspicuous (Color version of the figure is available online.)

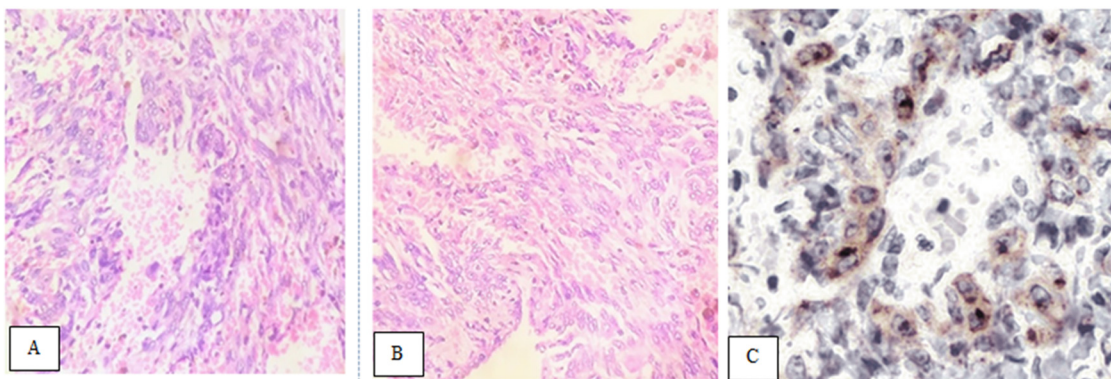


Fig. 9 – Microscopic examination of lung lesion biopsies obtained through laparoscopic surgery. (A) Histopathological examination of the first surgical specimen. (B) Histopathological examination of the second surgical specimen. Hematoxylin and eosin (HE) staining shows proliferation of LAM cell nodules with central spindle characteristics and peripheral epithelial cells (HE x 200). Histopathological lesions show that the lung parenchyma has dilated alveoli, the interstitial tissue, the alveolar wall contains proliferated rhombus cells, the nuclei are oval-shaped and regular, benign, and without mitotic nuclei. The cells are arranged in clusters and scattered in the dilated alveolar regions. Histopathological diagnosis: lesions consistent with pulmonary lymphangioma (LAM). (C) Immunohistochemical staining with HMB-45 was positive in epithelial cells (IHCS x 400).

In most patients, the internodal lung parenchyma appears normal on HRCT; however, in some cases, a slight increase in interstitial thickening, interlobular septal thickening, or irregular areas of opacity are also seen. Later in the disease course, areas of pulmonary hemorrhage can be seen [25,26].

Some patients with TSC-LAM have nodular hyperplasia represented by small pulmonary nodules, 1–8 mm in diameter, with a random distribution, which is not seen in patients with S-LAM. In many cases, a specific CT diagnosis can be made when diffuse, thin-walled, rounded cysts are identified

in women of childbearing age. On HRCT, as well as on chest radiographs, pneumothorax may be associated with cysts in patients with LAM. Other features of LAM include pleural effusion, hilar lymph nodes, mediastinum, and recurrence. Renal vascular lipomas are also visible when cut through the upper abdomen. These symptoms are present in >90% of patients with TSC-LAM and in 30%-50% of patients with S-LAM [22-24].

Sathirareuangchai et al. reported a case of a 41-year-old female patient who experienced multiple episodes of spontaneous pneumothorax that resolved with medical therapy or spontaneously before LAM was detected. The patient had smoked at least 2 cigarettes per day for 21 years. Chest CT revealed multiple thin-walled cysts of varying sizes in both lungs and the pneumothorax persisted despite having a drainage tube in place for 1 week. The patient underwent laparoscopic surgery for pneumothorax, parenchymal resection of the lingual lobe for diagnosis, and the left pleural adhesions were treated with doxycycline. Histopathological analysis of the wedge-shaped pneumonectomy showed numerous cysts, including water-filled cysts, which corresponded to the intraoperative findings. There were many foci of spindle-shaped, smooth muscle-like proliferations; the foci were located in the peripheries of the cysts and around the bronchioles. The neoplastic cells were morphologically distinct and appeared similar to airway smooth muscle cells, but with more numerous corpuscles with larger nuclei, and a higher nuclear-to-cytoplasm ratio. There was no abnormal expression of increased mitotic activity. Chronic inflammation and pleural fibrosis were also noted. Immunohistochemical staining revealed neoplastic cells positive for HMB-45 and caldesmon. The overall morphologic and immunophenotypic features supported the diagnosis of pulmonary LAM. The patient was treated with sirolimus and scheduled for a follow-up visit after 6 months. Compared with our case, the age of detection was earlier (36 years old), and the patient had only had 2 prior episodes of pneumothorax before LAM was diagnosed. Immunohistochemical staining showing HMB-45-positive LAM cells was also used in our case to obtain a definitive diagnosis [4].

Of note during the third surgery in our case, although the patient had bilateral pneumothorax, we only treated the right pneumothorax. During the postoperative follow-up, the left pleural air pocket was spontaneously, and completely absorbed. Currently, although receiving no specific treatment, our patient is leading a normal life. This observation is consistent with the literature and case reports [4]. LAM can stabilize and regress spontaneously over a certain amount of time; this might explain why LAM is slow to diagnose and often creates diagnostic confusion at primary health care levels.

LAM can cause damage to both lungs. Extrapulmonary involvement may occur in the pelvis, mediastinum, and may be associated with renal lipoma [3]. In our case, we completed a thorough screening of the whole body by CT scan, and only found a single lesion in the lung.

Regarding the anatomic characteristics of LAM, the macroscopic image shows a cystic, honeycomb shape. The cysts are usually evenly distributed throughout the lung and may contain air or fluid (serous or chylous). The lungs increase in size in the presence of severe emphysema. The cysts range in size

from 0.5 to 2 cm and can be more than 10 cm in diameter. Microscopically, the early stages of LAM cell infiltration are easily missed, with biopsies showing only emphysema or normal lung tissue. In later stages, the presence of characteristic LAM cells can be observed in clusters or small foci adjacent to the cysts, along the alveoli, pulmonary vasculature, lymphatic vessels, and bronchioles. The cells typically have a low mitotic index. LAM was formerly classified as an interstitial lung disease (ILD) due to its diffuse nature; however, later genetic studies showed that this disease is more appropriately described as a destructive, low-grade cancer. The neoplastic cells in LAMs originate from perivascular epithelial cells, making LAMs part of the family of perivascular epithelial cell tumors (PEComas) that also includes angiomas (AML) [25]. LAM cells that infiltrate the bronchial wall and distal vessels can cause airway obstruction, air trapping, air bubble formation, pneumothorax, hemoptysis, and foci of hematoma. The close relationship between LAM cells and lymphatic vessels is believed to be the cause of chylous effusion. The formation of cysts causes loss of the normal alveolar structure of the lung. The cyst wall contains LAM cells and is lined by alveoli and bronchial epithelial plaques. LAM cells proliferate heterogeneously and are morphologically classified into 2 types: epithelial cells and rhombus cells. The rhombus cells are usually centrally located, while the epithelial cells are found at the peripheries of LAM nodules. These 2 cell types are thought to represent alternative phenotypes and differentiate into these phenotypes under the control of undetermined stimuli [27]. In our case, the microscopic results of 2 lung biopsies obtained during laparoscopic surgery were consistent with the aforementioned features.

In terms of immunohistochemistry, LAM cells express smooth muscle actin and desmin proteins and melanocyte markers (HMB-45, HMSA-1, Melan-A, MART-1, and weakly, microsignature transcription factor). These features indicate that the tumor cells belong to the group of perivascular epithelial cells. The intensity of HMB-45 positivity is simultaneously associated with cell proliferation. Rhombus cells are weakly positive for HMB-45, and the positive index for the cell proliferation marker is higher. Epithelial cells are strongly positive for HMB-45 and their cell division index is lower [22]. These data suggest that rhombus cells are more proliferative in the proliferative phase while epithelial cells are present in a more mature state. Matsui et al. also reported the expression of ER and PR in LAM epithelial cells in 5 of 10 hormone-naïve patients [27]; however, in patients who had been treated with Progesterone and Tamoxifen, no expression of ER or PR was observed. Therefore, ER and PR are selectively expressed on LAM epithelial cells and can be regulated by hormone therapy. Rhombus and epithelial LAM cells were found to be positive for CD1a and cathepsin K, providing useful new evidence for differentiating pulmonary LAM from renal angiomas [22,27-29].

The differential diagnosis of LAM includes other ILDs that present with cystic lung changes. Patients with chronic obstructive pulmonary disease (COPD) or emphysema may also present with recurrent pneumothorax and multiple pulmonary cysts on imaging, but they lack the presence of LAM cells in their alveoli, which needs to be confirmed by a pathologist. Smoking-related ILDs should also be considered,

including Langerhans cell lung disease (positive for CD1a, S100, and langerin), diffuse interstitial pneumonia (DIP), respiratory bronchiolitis caused by interstitial lung disease (RB-ILD), idiopathic pulmonary fibrosis (IPF), eosinophilic hypersensitivity pneumonia (HP), and sarcoidosis. Lymphoid proliferative pneumonia (LIP) has many similarities to LAM, but the disease is more common in children and in both sexes, the lesions often contain interstitial infiltrate, and pleural effusion and pericarditis are often present. Histologically, the alveolar lumen is lined by a contiguous endothelium along the pulmonary, pleural, and mediastinal lymph glands. Compared with LAM, there is less smooth muscle proliferation, no alveolar dilation, and negative staining for HMB-45. Some infections also lead to diffuse cystic changes in the lungs. A small number of individuals infected with *Pneumocystis jirovecii* (10%-34%) have multiple lung cysts. Other microorganisms that can cause pulmonary cysts include *Staphylococcus* species, *Coccidioides* species, and parasitic infections caused by the lung fluke *Paragonimus westermani*. Birt-Hogg-Dubé syndrome (BHD) can also mimic pulmonary LAM, with a similar clinical presentation of young women with recurrent pneumothorax; however, the cysts in BHD are surrounded by normal lung parenchyma without evidence of proliferative cancer cell populations or significant inflammation [4].

Because LAM is a disease of premenopausal women, it can be aggravated during pregnancy or after estrogen use. Due to the expression of ER and PR by the tumor cells, several hormonal therapies have been proposed, such as bilateral oophorectomy, gonadotropin-releasing hormone agonists, tamoxifen, or progesterone. Schiavina et al., who treated 36 LAM patients with hormone therapy for 20 years, reported reduced mortality and improved quality of life. The 5-year survival rate in the study was 97%, the 10-year survival rate was 90%, and the 25-year survival rate was 71%. However, hormone therapy remains controversial. Inhaled bronchodilators provide symptomatic relief in patients with obstructive airway disease. Lung transplantation is an approved treatment for LAM in end-stage lung disease, with 1-, 2-, 5-, and 10-year survival rates of 79.6%, 74.4%, 64.7%, and 52.4%, respectively [9]. Research into the medical genetics of TSC and the biological pathways involved in LAM offers potential treatment options for patients with LAM using a new immunosuppressant of the macrolide class (rapamycin). Inhibition of Rho GTPase by a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) or inhibition of the JAK-STAT3 pathway by interferon gamma may also represent potential therapeutics for LAM [30].

According to the natural progression of LAM, patients will develop restrictive ventilation disorders causing respiratory failure, and arrhythmia. However, the rate of disease progression varies among patients, and there are no established clinical or subclinical prognostic factors. The 5-year survival rate for LAM ranges from 50%-97% [30]. This variation is due to the large number of LAM patients who were studied since childhood and is also related to different clinical features and therapeutic approaches [2,30,31].

In our case, from history to clinical diagnosis, imaging and pathology involved multi-specialty coordination, the histopathological images with characteristics of LAM cells were typical, their distribution was consistent with small cystic

lesions on chest CT, and additional immunohistochemical staining was performed to reveal HMB-45 positivity. Therefore, this case is complete, with sufficient evidence to confirm the diagnosis. Currently, the patient is in a temporary stable stage, and she is being closely monitored by our hospital and continues to receive advice on preventing complications and appropriate management.

Conclusion

The case of LAM we introduce belongs to the group of rare diseases, quite consistent with the literature. Unexplained recurrent pneumothorax, shortness of breath, and hemoptysis are notable signs in this disease. The cystic lesion in this patient was still at a mild stage, but there was a bilateral pneumothorax, and a rather complicated course. The patient is unlikely to receive specific treatment but is currently in a stable phase consistent with the known features of the disease, with self-limited, transient stages of progression and remission. Current diagnostic methods still rely on lung biopsy, histopathology, and immunohistochemistry. We hope that in the near future, quantitative blood tests for growth factors VEGF-C, and VEGF-D will be common. Then the disease can be diagnosed more easily and in larger numbers.

Authors' contributions

Cung-Van C and Nguyen MD contributed equally to this article as co-first authors. All authors read and approved final version of this manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of patient information in this article.

Informed consent

Informed consent for patient information to be published in this article was obtained.

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