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Case Report

Sporadic Lymphangioleiomyomatosis Disease: A Case Report

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Abstract

Pulmonary Lymphangioleiomyomatosis (LAM) is a rare disease of the lung and lymphatic system that primarily affects women of childbearing age. LAM is a progressive disease with a terrible prognosis, which worsens over time and is extremely difficult to treat. In this study, we discuss the case of a 31-year-old woman with LAM who was initially misdiagnosed with leiomyoma and the way that led to a true diagnosis and effective treatment. Following a precise diagnosis based on comprehensive clinical data and particular immunohistochemical tests, sirolimus treatment was initiated, and the patient entirely responded to the treatment. This case report demonstrated that LAM is an uncommon condition that is challenging to diagnose, which causes its treatment to be delayed.

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Keywords ● Lymphangioleiomyomatosis ● Lung ● Rare diseases ● Pneumothorax

What's Known

- Pulmonary Lymphangioleiomyomatosis (LAM) is a rare disease of the lung and lymphatic system that primarily affects women of childbearing age. The disease is distinguished by extensive nodular infiltration of the lungs, which is accompanied by the proliferation of smooth muscle-like cells. Shortness of breath and pneumothorax are the most typical clinical manifestations of this disease.

What's New

- Lymphangioleiomyomatosis is difficult to diagnose and should be considered in the differential diagnosis, especially in women of childbearing age. A comprehensive clinical history is required for an accurate pathology diagnosis. Moreover, the histopathological and immunohistochemical investigation revealed that HMB-45, desmin, and ER were positive, while CD31, CD34, and CD10 were negative.

Introduction

Pulmonary Lymphangioleiomyomatosis (LAM) is a rare pulmonary disease that primarily affects women of childbearing age. Since LAM affects less than one in a million people, it rarely receives an early diagnosis. Although it has been considered a disease with a poor prognosis, recent therapies such as sirolimus are considered promising, especially if prescribed soon. When making early clinical impressions and recommending a pathologist, certain radiologic aspects can greatly assist the clinician. If the pathologist is provided with rich clinical and paraclinical data and a plausible diagnosis, they will sign out truthfully.[1]

The disease is distinguished by extensive nodular infiltration of the lungs, which is followed by the proliferation of smooth muscle-like cells (SMLC).[1] Pneumothorax and shortness of breath are the most frequent clinical symptoms of this condition. Chylothorax and bloody sputum are also possible. LAM is a progressive disease that worsens over time and has a poor prognosis. Mutations in the tuberous sclerosis complex-1 (TSC-1) and tuberous sclerosis complex-2 (TSC-2) genes contribute to LAM development. The disease is caused by the proliferation of SMLCs over time, particularly in the lungs, lymphatic system, and pleurae. This abnormal growth causes the lung to develop holes or cysts. Many of the symptoms of LAM are similar to those of other lung diseases, making diagnosis challenging. These clinical manifestations are caused by SMLCs aberrant growth, which causes damage to the lung parenchyma, constriction of the airways, and lymphatic obstruction.

An abdominal computed tomography (CT) scan may reveal angiomyolipoma-related kidney lesions. Although a mixed obstructive and restrictive pattern may be detected, pulmonary function tests clearly demonstrate a progressive obstructive ventilatory deficit.[2] Clinically, sporadic (S-LAM) and tuberous sclerosis complex associated (TSC-LAM) are two types of LAM.

TSC-LAM is an autosomal dominant neoplastic disease that affects adult female patients more frequently.[3] This is a case study of a well-known but uncommon condition. This study aimed to describe a rare condition to help in early diagnosis and distinguish it from similar diseases. Therefore, appropriate treatments could be initiated as soon as possible.

Case Presentation

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (code: IR.SUMS.REC.1401.234). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

On 21 January 2021, a 31-year-old woman was admitted to the General Hospital, Bushehr, Iran. She had been experiencing shortness of breath for several weeks and had no history of smoking. Additionally, there was no family history of any pulmonary disease. During the initial examination, ascites and a small amount of pleural effusion were discovered. Thoracentesis was performed, and some milky-colored fluid was sent for microscopic examination, analysis, and culture. The laboratory results indicated an exudative fluid with a negative culture and cytologic evaluation, in favor of a nonmalignant and noninfectious condition. Some milky ascitic fluid was also extracted, and its analysis likewise produced no conclusive diagnosis. Abdominopelvic ultrasonography revealed a solid mass containing cystic areas in the pelvis and adjacent to the left ovary. There was also a substantial amount of ascites. Pleural effusion was seen on chest imaging in both pleural compartments. In this case, a mass in the pelvis was found during the initial investigations, which underwent surgery and was totally excised. The surgical specimen was sent to pathologists without sufficient clinical information. Following histopathologic examination and immunohistochemistry (IHC) study, it was diagnosed as leiomyoma, which was negative for CD31, CD34, and CD 10, low for KI67, and positive for smooth muscle actin (SMA), desmin and estrogen receptor (ER). However, this impression could not explain the entire scenario of the disease. As a result of the request for a review of the embedded mass tissue in light of new clinical data, the pathologic report was revised to LAM based on histopathologic morphology, and a relevant IHC that was positive for HMB-45, desmin, and ER, low for KI67, and negative for CD31, CD34, and CD10.

Although the patient was discharged, her symptoms persisted and were managed with repeated pleural and abdominal taps. Finally, a pleural catheter was inserted, and milky fluid was continuously drained from it.

Eventually, she was visited by an internist-pulmonologist, who evaluated a high-resolution CT scan (HRCT) of her chest, which revealed diffuse bilateral thin wall cystic lesions, tiny nodules, some parenchymal interstitial edema, and bilateral pleural effusion (figures 1-3). Spirometry was performed, and the results indicated an obstructive pattern with forced expiratory volume 1 sec/forced vital capacity (FEV1/FVC)=59% before and 71% after bronchodilator treatment, indicating the presence of a reversible obstructive component. Repeated thoracocentesis revealed a TG level of 240 mg/dL, which is high and within the range of chylothorax. This implied that the ascitic fluid

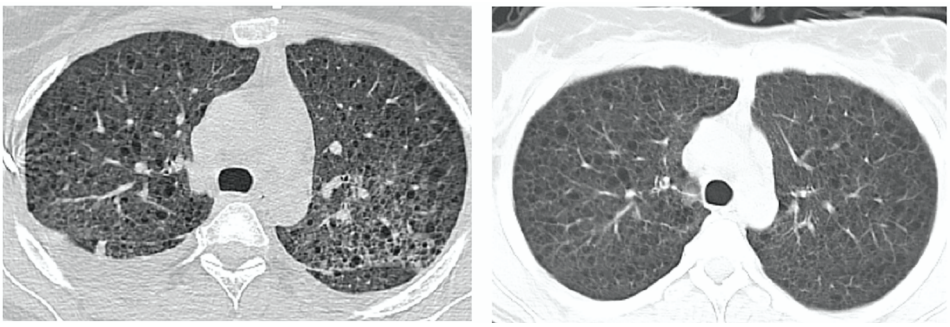

Figure 1: In the Left figure, axial HRCT (high-resolution CT scan) at the upper lung level reveals multiple thin wall gas-filled cystic lesions in both lungs. The intervening lung parenchyma appears hazy, and the main fissures and interlobular septa are slightly apparent, suggestive of interstitial pulmonary edema (left is more than right side (L>R). Bilateral pleural effusion is seen (proved to be chylous). The right image shows follow-up a few months after treatment with sirolimus. Although the pulmonary edema and pleural effusion are being resolved, the cystic lesions persist.

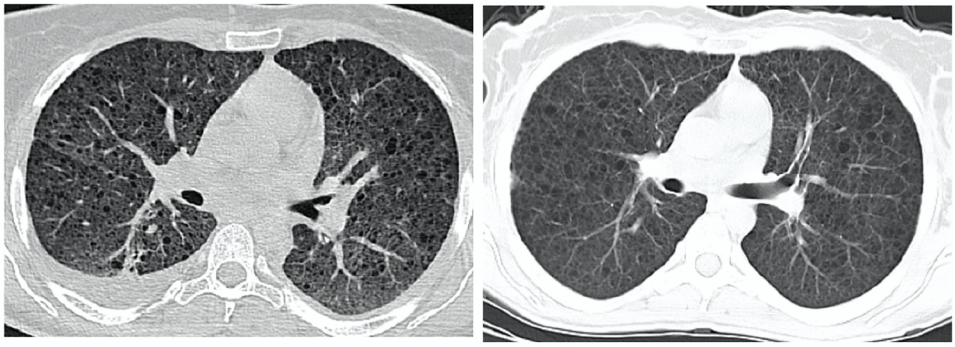

Figure 2: This figure shows axial HRCT (high-resolution CT scan), sub-carinal level in the acute phase, and follow-up on the left and right, respectively. The findings are the same as those shown in figure 1.

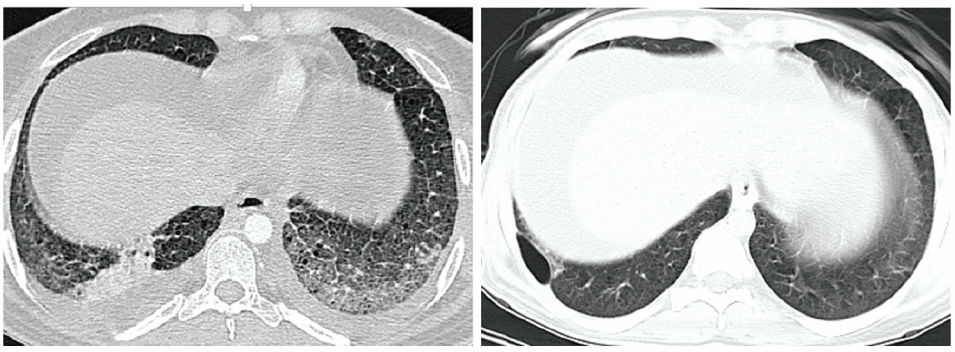

Figure 3: The Left figure shows HRCT (high-resolution CT scan) at the lung base level. The same findings are seen here. The presence of pulmonary edema is evident. Patchy consolidation on right is suggestive of atelectasis. The right figure shows the follow-up, several months following treatment. No pleural effusion, pulmonary edema, or atelectasis are present. A tiny loculated pneumothorax on right implies previous complications and adhesions.

was of the same type and was a chylous ascites. A consultation with a dermatologist was also done, who noted diffuse acne over the face, and upper trunk but no indication of any additional lesions, such as angiofibroma, shagreen patches, hypopigmented macules, etc.

A combination of Interstitial cystic lung disease as seen in the chest HRCT as well as an obstructive pattern of spirometry, chylothorax, and chylous ascites suggested LAM as the most likely diagnosis. Thus, we asked pathologists to review the specimens, and they confirmed LAM through histopathology and IHC study. Histologic examination showed spindle smooth muscle-like proliferation similar to leiomyoma with slit-like vascular gaps and some lymphoid aggregates, which were overlooked during the initial pathological examination. In addition to positive SMA and desmin markers, the IHC study revealed positive human melanoma black 45 (HMB-45), which was diagnostic for lymph angioleiomyoma (figures 4 and 5).

After starting sirolimus, the patient's clinical condition improved significantly. Then, after about six months, dyspnea and the ascites both disappeared. A subsequent HRCT demonstrated that pleural effusion and interstitial edema faded, however, the cysts persisted, necessitating further HRCTs for monitoring them in the upcoming months.

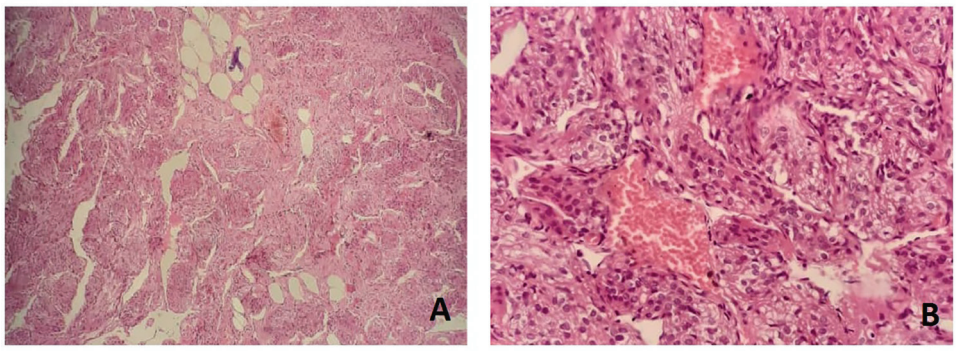

Figure 4: Histological findings show the proliferation of spindle cells with slit-like gaps between them. (A): low power (hematoxylin & eosin stain, ×40), (B): mid-power (hematoxylin & eosin stain, ×200).

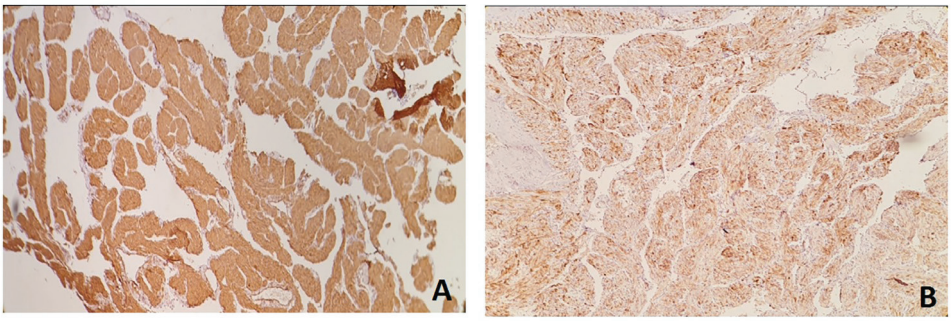

Figure 5: Immunohistochemistry (IHC) study showed positive smooth muscle actin (SMA) in (A) and HMB45^{+} in (B).

Discussion

The present case was diagnosed in a 31-year-old woman. The disease is distinguished by the aberrant proliferation of smooth muscle-like cells, particularly in the lung parenchyma and airway walls, as well as lymph nodes.[4] Similar to other obstructive lung diseases, the condition progresses to constriction and obstruction of the airways, and eventually, to alveolar destruction and cystic disease in the lungs and lymphatic system.[5]

According to the dermatologist, the skin lesions seen in this patient were acne rather than angiofibroma, as seen in tuberous sclerosis. Moreover, no further skin lesions characteristic of tuberous sclerosis were observed, and there was no history of CNS involvement or clinical signs and symptoms. Therefore, the type of LAM, in this case, was sporadic (S-LAM) with no associated tuberous sclerosis.

Primary symptoms of the disease include activity-induced dyspnea (shortness of breath) and spontaneous pneumothorax (lung collapse) in 49% and 46% of patients, respectively.[3] These clinical manifestations are caused by lung parenchymal damage, the constriction of the airways, and lymphatic obstruction caused by the abnormal proliferation of smooth muscle-like cells.[6] Obstruction of arteries, lymphatics, and airways leads to the accumulation of chylous pleural fluid, hemoptysis, airflow obstruction, and pneumothorax.[7]

In many aspects, LAM cells act like metastatic tumor cells. These cells seem to have migrated to the lungs from an extrapulmonary source. The inactivation of the tumor suppressor TSC-2 is associated with abnormal proliferation, differentiation, migration, and invasion of LAM cells in the lungs. The cellular and molecular mechanisms of neoplastic transformation and destruction of the lung parenchyma by LAM cells still remain unknown.[8]

Typically, diagnosis is delayed for five to six years. This condition is often misdiagnosed as asthma or chronic obstructive pulmonary disease.[9] In this study, the disease was not diagnosed until about six months after the initial visits.

LAM may also be associated with fluid-filled hypodense masses in the retroperitoneal portions of the abdomen and pelvis, which are seen in approximately 30% of LAM patients. Typically, no intervention is required. A biopsy or resection may result in a long-term leak.[10]

Radiographic findings vary depending on the severity and development of the disease. CT scan also shows diffuse thin wall cysts in the lung parenchyma. A ground-glass appearance due to hemosiderin deposition might also be noticed.[11] In this case, a preliminary CT scan of the lungs revealed diffuse and bilateral thin-wall gas-filled cystic lesions. The intervening lung parenchyma appeared hazy, with conspicuous main fissures and interlobular septa, indicating interstitial pulmonary edema.

In most cases, clinical and radiological findings are insufficient to make a conclusive diagnosis. Thus, a biopsy is required. Video-assisted pulmonary thoracoscopy is the most definitive procedure, and the diagnosis is confirmed with the distinctive immunohistochemical staining, that is specific for smooth muscle cells such as actin, desmin, or HMB-45. Additionally, the cytology of chylous ascites, abdominal nodules, or lymph nodes can also be used to make a diagnosis.[12] In this case, the histopathologic examination and IHC study confirmed the clinical impression.

In addition, it seemed that the initial clinicians failed to diagnose the disease, because it was so rare. Besides, they lacked sufficient knowledge about it, and they disregarded the pulmonary and radiologic findings, which were a golden key for the diagnosis of this rare disease, and could be avoided, if a radiologist had been consulted earlier. The pathologists were also unable to diagnose the true nature of the disease due to its rarity and the lack of clinical data provision. Indeed, it is suggested that clinicians and

para-clinicians including pathologists and radiologists establish a close communication and exchange data to reach the right diagnosis, especially in complicated and rare conditions such as ours. This is the magical takeaway lesson of this study: It is not necessary or possible to know everything about all diseases, especially rare ones. However, teamworking and data exchange can get us there. Fortunately, the patient was eventually visited by a pulmonologist who was knowledgeable about this rare disease and proposed his clinical impression, which was confirmed by the pathologist after reviewing the previous specimen.

Given that both LAM and metastasizing leiomyoma affect young women, it is crucial to distinguish between the two conditions. Moreover, there are other similarities between metastasizing leiomyoma and LAM, such as smooth muscle proliferation, pulmonary location, and hormonal reliance as indicated by progression during child-bearing years.[13] Pitts and colleagues mentioned the radiological, microscopic, and particular distinctions between metastasizing leiomyoma (ML) and LAM, which is summarized in the following:

Well-circumscribed solitary or multiple pulmonary nodules with a diameter of a few millimeters to several centimeters are seen bilaterally throughout the normal interstitium as part of the radiologic appearance of ML. Microscopic features are similar to those of primary pulmonary leiomyoma, with glandular structures resembling entrapped epithelium. Special studies include Estrogen RC$^+$, Progesterone RC$^+$, and HMB-45$^+$.[13]

Radiologic appearance in LAM includes an interstitial pattern (which could be reticular, reticulonodular, military, or honeycomb), hyperinflation, and thin-walled cysts. Pneumothorax, pleural effusion, or chylothorax might be present. A high-resolution CT scan reveals several thin-walled cysts throughout the normal lung, with no preference for a zone. Microscopic features include disorganized, spindle-shaped atypical smooth muscle; such as cells that proliferate in lymphatics, alveoli, respiratory bronchioles, tiny arteries, cystic spaces, and centrilobular emphysema. Desmin$^+$, vimentin$^+$, actin$^+$, and fibroblast antibodies are among the special studies, and certain cells are HMB-45$^+$, estrogen RC$^+$, and progesterone RC$^+$.[13]

Some studies reported that somatic mutations in the TSC-2 gene occured in angiomyolipomas and pulmonary LAM cells of women with sporadic LAM, which strongly supported the direct involvement of TSC-2 in the pathogenesis of this disease. Unfortunately, no mutation analysis studies were conducted in the present study.

Conclusion

LAM is a rare disease that affects women of childbearing age. The disease is challenging to diagnose and is usually diagnosed late. In women of childbearing age, LAM should be considered in the differential diagnosis of cystic pulmonary disease and spontaneous pneumothorax. Radiologic findings of this rare disease are pathognomonic enough to help with its early diagnosis and treatment.

Acknowledgment

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Authors' Contribution

Y.N and M.Sh: Data collection, data interpretation, and revised the manuscript, M.M, and M.Kh: contributed to the conception of the work and drafted the manuscript. A.M: participated in the interpretation of clinical results and helped to write the draft of the manuscript. M.B and R.R: re-evaluated the clinical data and revised the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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