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LYMPHANGIOLEIOMYOMATOSIS: A LITERATURE OVERVIEW

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Abstract: Lymphangioleiomyomatosis is a rare multisystem disease associated with genetic mutations. The disease usually occurs in women of reproductive age and is characterized by infiltration of immature smooth muscle cells into the lungs, airways, and axial lymphatic systems of the thorax and abdomen. The disease often destroys the lung parenchyma and produces air cysts. Cellular infiltration of lymphangioleiomyomatosis into the lymphatic axis can affect hilar lymph nodes, mediastinal nodes, and extrathoracic lymph nodes. The disease can cause lymphatic dilation in the lungs and thoracic ducts, causing chylous effusion in the pleural or abdominal cavities. Invasion of cells in the walls of pulmonary veins can lead to venous obstruction and pulmonary venous hypertension with hemoptysis. Most patients have cough, dyspnea, pneumothorax, hemoptysis, and abnormal lung function. Definitive diagnosis is usually based on histopathology and immunohistochemistry. We expect that, in the near future, quantitative blood tests for the growth factors VEGF-C and VEGF-D will become commonplace. Then the disease can be diagnosed more easily and in greater numbers.
Keywords: Pulmonary lymphangioleiomyomatosis, LAM, Computed tomography.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare disease with diffuse cystic pulmonary degeneration and multisystemic involvement, affecting mainly women of reproductive age, but rarely appearing in male patients[1]. Currently, it is estimated that LAM affects more than 7.8 per million women,[2] but the prevalence of LAM in males is non-existent. Two subtypes have been identified: sporadic (S-LAM) and tuberous sclerosis complex (TSC-LAM) that are associated with LAM. Occurrence of patients

with TSC-LAM is caused by mutations in the TSC1 or TSC2 genes [3]. LAM occurs more often in patients with S-LAM, and patients with S-LAM can be caused by mutations in the TSC2 gene.[4] Mutations in these genes result in dysregulation of the mammalian target of the mTOR pathway of rapamycin[5].

LAM is a chronic progressive disorder. Clinical manifestations include dyspnea, cough, hemoptysis and pause, with pulmonary complications such as pneumothorax and chylothorax. Cases of asymptomatic patients incidentally detected with severe pulmonary involvement have also been reported in men and women[6,7]. TSC is an autosomal dominant disease that affects multiple organ systems, including the central nervous system, skin, eye, kidney and lung. As the disease progresses, patients with TSC may develop disease with LAM[8]. The lowest prevalence of 13% of men with TSC had cystic lung changes consistent with LAM compared to 42% of female patients with TSC[9]. Therefore, cystic changes in the lungs of patients with TSC must be immediately screened for LAM disease. S-LAM is another form of LAM disease that is common in the general population. According to accidental findings on computed tomography (CT) of the abdomen or lungs, 12% of patients with S-LAM have cystic changes in the lung or abdomen[10]. Thus, patients with S-LAM are often accidentally found in extrapulmonary organs. Previous studies that compared patients with TSC-LAM and S-LAM did not find differences in pulmonary manifestations [11.] Published data from the LAM Registry of the National Heart, Lung, and Blood Institute (NHLBI) showed that TSC-LAM was lighter. However, no differences were observed in the evolution to death between these groups[12]. LAM in men was first described in 1986 by Fairfax[13]. Subsequently, several rare reports of misdiagnosis of LAM disease were recorded in men[14, 15]. Unfortunately, when misdiagnosed, this condition can result in respiratory failure. In the early stages of the disease, patients do not seek medical attention or may be neglected by medical professionals, resulting in poor outcomes.

Studies on single-cell analysis have shown that a unique population of LAMCORE cells has been identified in the lung and uterus of patients with LAM, sharing close transcriptomic identity, and they believe that the uterus may be the origin of the cells that drive LAM in the lungs[16].

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

Definitive diagnosis of LAM is usually based on pathological findings 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.

MATERIAL AND METHODS

A review of the current literature was carried out. The following databases were consulted: MEDLINE (PubMed); Base; Web of Science, Google Scholar. Conference abstracts/papers have been deleted from Embase. No other limits were applied. All retrieved records

were organized using Endnote citation management software version 20. To remove duplicates, literature review citation screening and review software was used.

The search strategy was designed to capture the theme in current reviews on Pulmonary lymphangioleiomyomatosis (LAM). Searches were complemented by hand searching and retrieving any additional articles that met the eligibility criteria that were cited in our reference lists.

DEVELOPMENT

The clinical spectrum of LAM is wide, involving multiple systems, including lungs, lymphatic vessels, kidneys and liver, and this condition is especially rare in men. Frequent cases of misdiagnosis can pose a serious threat to public health. 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, seen in only 1-2.6/100,000 women[2]. LAM cells express estrogen and progesterone receptors, and lung function declines during periods of high levels of circulating estrogen. 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 the multiple sclerosis hereditary 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 currently there are 2 theories considered reasonable: the first theory proposes that LAM cells originate in the airways or vascular, while the second theory suggests that LAM cells originate from the AML in the kidney and are transported to the lung via neoplastic dissemination[10,11,12,13,14]. The disease progresses, with destruction of the lung tissue by the proliferation of diamond cells and epithelial cells with a perivascular cell phenotype, also known as EPCs. 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 believed to be of perivascular epithelial origin, although this is not yet confirmed. Of course. 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 organized classes of angiogenesis. 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[13,15,16,17,18].

Currently, the development of testing techniques for the lymphatic growth factors VEGF-C and VEGF-D is providing hope for diagnosing LAM without the need for 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 cases of LAM[9,10,19,20].

LAM in the lungs usually 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 have also been described; these symptoms worsen during pregnancy. Spontaneous pneumothorax is a common feature that often suggests LAM. LAM must be considered in women with dyspnea due to pneumothorax, hemoptysis, and chest X-ray abnormalities. On conventional radiographs, 80% of patients with LAM show a mild reticular pattern; in patients with advanced disease, a pattern of multiple lung cysts mimicking honeycomb may be seen. Lungs often appear abnormal, with the basal region looking structurally similar to the apical region. As with histiocytosis, the lung mass often appears enlarged despite the presence of a mesh structure. Pleural abnormalities may precede, accompany, or evolve after lung disease is recognized. Approximately 50% of patients present with pneumothorax at the time of presentation, and unilateral or bilateral pleural effusions are present in 10% to 20% of cases. Approximately 10% to 25% of patients have normal radiographs at the time of examination, despite the presence of multiple pulmonary cysts[21,22,23].

On HRCT, patients with TSC-LAM and S-LAM have the characteristic appearance of numerous, isolated, thin-walled, rounded lung cysts. These cysts are usually 2-5 mm in diameter but can be larger; its size tends to increase with the progression of the disease. In critically ill patients, >80% of the lung parenchyma is involved, and most cysts are greater than 1 cm in diameter. The cyst walls are usually thin and light. Irregular cyst shapes, as seen in patients with LCH, are uncommon. Cysts are generally widely distributed throughout the lung, from apex to base, and no longer have the same lung area as LCH[22,23,24]. The presence of diffuse pulmonary involvement is observed even in LAM patients with mild disease. 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 is also observed. Later in the course of the disease, areas of pulmonary hemorrhage can be observed[25,26]. Some patients with TSC-LAM have nodular hyperplasia represented by small pulmonary nodules, 1-8 mm in diameter, with random distribution, which is not observed 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 reproductive age. On HRCT, as well as on chest X-rays, 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 in the upper abdomen. These symptoms are present in >90% of patients with TSC-LAM and in 30%-50% of patients with S-LAM[22,23,24].

Sathirareuangchai et al. reported the case of a 41-year-old patient who had multiple episodes of spontaneous pneumothorax that resolved with medical therapy or spontaneously before detection of LAM. The patient had been smoking at least 2 cigarettes a day for 21 years. Chest CT scan revealed multiple thin-walled cysts of varying sizes in both lungs and the pneumothorax persisted despite a 1-week drainage tube being placed. 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 fusiform

smooth muscle-like proliferations; the foci were located on the periphery 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 nucleus-to-cytoplasm ratio. There was no abnormal expression of increased mitotic activity. Chronic inflammation and pleural fibrosis have also been observed. Immunohistochemical staining revealed neoplastic cells positive for HMB-45 and caldesmon. General morphological 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 to our case, the age of detection was earlier (36 years) and the patient had only 2 previous episodes of pneumothorax before the diagnosis of LAM[4].

LAM may spontaneously stabilize and regress over a period of time; this may explain why LAM is slow to diagnose and often creates diagnostic confusion at primary health care levels. LAM can damage both lungs. Extrapulmonary involvement can occur in the pelvis, mediastinum and may be associated with renal lipoma[3].

Regarding the anatomical characteristics of LAM, the macroscopic image shows a cystic honeycomb shape. 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. Cysts range in size from 0.5 to 2 cm and can be over 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. Cells normally have a low mitotic rate. LAM was formerly classified as an interstitial lung disease (ILD) due to its diffuse nature; however, later genetic studies have shown that this disease is more accurately described as a low-grade destructive cancer. 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. Cyst formation causes loss of the lung's normal alveolar structure. 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. Diamond cells are usually located centrally, while epithelial cells are found at the periphery of LAM nodules. It is believed that these 2 cell types represent alternative phenotypes and differentiate in these phenotypes under the control of undetermined stimuli[27].

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, microsurgical transcription factor). These characteristics indicate that 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 score for the cell proliferation marker is higher. Epithelial cells are strongly positive for HMB-45 and their cell division rate is lower[22].

These data suggest that diamond cells are more proliferative in the proliferative phase, whereas epithelial cells are present in a more mature state. Matsui et al. also reported ER and PR expression in LAM epithelial cells in 5 of 10 hormone-naive patients[27]; however, in patients treated with Progesterterol and Tamoxifen, no ER or RP expression was observed. Therefore, ER and PR are selectively expressed in LAM epithelial cells and can be regulated by hormone therapy. Diamond and epithelial LAM cells were found to be positive for CD1a and cathepsin K, providing useful new evidence to differentiate pulmonary LAM from renal angiomas[22,27,28,29].

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 have recurrent pneumothorax and multiple lung cysts on imaging but lack the presence of LAM cells in their alveoli, which needs to be confirmed by a pathologist. Smoking-related ILDs must also be considered, including Langerhans cell lung disease (CD1a, S100, and Langerin positive), diffuse interstitial pneumonia (DIP), respiratory bronchiolitis caused by interstitial lung disease (RB-ILD), idiopathic pulmonary fibrosis (IPF), eosinophilic hypersensitivity (PH) pneumonia, and sarcoidosis. Lymphoid proliferative pneumonia (LIP) has many similarities to LAM, but the disease is more common in children and in both sexes, lesions often contain interstitial infiltrate, and pleural effusion and pericarditis are often present. Histologically, the alveolar lumen is lined by contiguous endothelium along the pulmonary, pleural, and mediastinal lymph nodes. 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 lung cysts include Staphylococcus species, Coccidioides species, and parasitic infections caused by the lung parasite Paragonimus westermani. Birt-Hogg-Dubé syndrome (BHD) can also mimic pulmonary LAM, with a similar clinical presentation to young women with recurrent pneumothorax; however, cysts in BHD are surrounded by normal lung parenchyma, with no evidence of proliferative populations of cancer cells or significant inflammation[4].

As 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 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%[9]. Research on the medical genetics of TSC and the biological pathways involved in LAM offer potential treatment options for patients with LAM using a new immunosuppressant from the macrolide class (rapamycin). The inhibition of Rho GTPase by a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) or the inhibition of the JAK-STAT3 pathway by interferon gamma may also represent a potential therapy for LAM[30].

According to the natural evolution of LAM,

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

FINAL CONSIDERATIONS

The present study of LAM that we present 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. Current diagnostic methods still depend on lung biopsy, histopathology and immunohistochemistry. We expect that, in the near future, quantitative blood tests for the growth factors VEGF-C and VEGF-D will become commonplace. Then the disease can be diagnosed more easily and in greater numbers.

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