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*review*

# Lymphangioleiomyomatosis

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***Background.*** *Lymphangioleiomyomatosis is a rare disease of unknown origin, which affects women in their reproductive period. It is characterised by non-neoplastic proliferation of atypical smooth muscle cells in the lung parenchyma, lymphatic vessels and mediastinal and abdominal lymph nodes. The most common presenting symptoms are spontaneous pneumothorax, dyspnea, hemoptysis and chylothorax.*
***Conclusions.*** *High-resolution computed tomography (HRCT) and open lung biopsy followed by the immunohistologic studies are two diagnostic procedures with which diagnosis can be confirmed. Various treatment modalities are applied, particularly hormonal therapy, though their efficacy remain unknown. The prognosis of patients is bad.*

*Key words: lymphangiomyomatosis – diagnosis – therapy*

## Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease of unknown origin which occurs exclusively in women. It is characterised by non-neoplastic proliferation of atypical smooth muscle cells in the lung parenchyma and thoracic and abdominal lymph nodes and lymphatic vessels. This leads to progressive loss of lung function and, ultimately, death. The disease was first mentioned in medical literature in 1937, and until today, not much has been known about its aetiology and treatment efficacy. The incidence varies from country to country and it seems to be increasing in recent years, which is probably due to a more extensive use of, and easier accessibility to the high-resolution computed tomography (HRCT) that is essential in LAM diagnosing.[1] According to some estimates, there are around 300 cases of LAM in the USA, whereas exact data for Slovenia are not available. In the last 20 years, 2 cases have been diagnosed at the Clinical Department of Pulmonary Diseases and Allergology at Golnik, Slovenia.[2]

The first study in which the data on a greater number of patients was gathered, was the study by Cornog and Enterline which was published in 1966. They examined 20 patients with the disease that is today known as LAM and was earlier referred to as lymphangioma, lymphangiomyoma, lymphangiopericytoma, leiomyomatosys, lymphangious malformation and intrathoracic angiomatous hyperplasia. In these first reports arguments were made in favour of the malignant charac-

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ter of the disease because of the diffuse and extensive infiltration of smooth muscle cells into the soft tissue, lymphatic vessels and lymph nodes in the thorax and abdomen. Cornog and Enterline supported the view that the disease could not be regarded as malignant because of a well organised structure of lung lesions and absence of mitotic overactivity, cell atypia and distant metastases.[3]

Several authors also suggest that LAM may be a form of tuberous sclerosis complex (TSC). TSC is an autosomally inherited form of congenital hamartomatosis, which usually affects the skin and central nervous system. It is characterised by mental retardation, epileptic attacks and angiofibromas on the face. The incidence of the disease is similar in both sexes. In contrast to epileptic attacks, the TSC pulmonary lesions develop only in adults and are detected in only 0,1-2-3 % of all patients, of whom 84 % are women. Histologically, TSC pulmonary lesions are similar to that of LAM lesions.[4] Nevertheless, the relation between TSC and LAM has not been definitely confirmed.[5]

## Clinical features

LAM usually affects women aged 30 to 40 years although several patients have been diagnosed as having LAM after menopause. The initial and typical signs and symptoms are advancing dyspnea on exertion, cough, hemoptysis and recurrent pneumothorax. Other signs and symptoms that develop later in the course of the disease are persistent dry cough, chest pain, chylous pleural effusion and chylous ascites. The interrupted lymphatic flow may result in the chylous ascites, chyloptysis, chyluria, chylous pericardial effusion and oedema of the lower extremities. The physical examination may reveal crackles and wheezing, clubbing and signs and symptoms of pneumothorax, pleural effusion and ascites.[6] The rate of the disease progress varies from case to case and the survival usually ranges from 10 to 20 years from the diagnosis.[2]

LAM may develop or progress considerably during pregnancy. Yet, so far, it has not been made clear whether the symptoms and signs of LAM are only detected earlier due to hemodynamic and ventilatory changes associated with pregnancy. The application of exogenous estrogens is another cause that can induce the disease or worsen the clinical picture.[7]

Renal angiomyolipoma is a rare hamartomatous tumour, composed of smooth muscle cells, blood vessels and adipose tissue. It rarely occurs autonomously, but may develop in relation to TSC and is also frequent in the patients with LAM. Usually these tumours are asymptomatic, though they may be characterised by palpable mass and pain in the lumbar region or hematuria.[8]

## Histopathology

Histopathologic characteristics of LAM are diffuse cystic changes in the lung related to the proliferation of the atypical smooth muscle cells, also termed as LAM cells. The proliferation can occur in all structures of the lung. The proliferation of LAM cells in the wall of bronchioles may result in the obstruction of small airways and formation of the air-filled parenchymal cysts. The rupture of the cysts located on the surface of the lung can lead to pneumothorax. Involvement of the venules and arterioles may result in partial or total occlusion of these vessels and subsequent pulmonary venous hypertension. Hemoptysis may be due to ruptures of the small blood vessels and minor bloodshedings into alveolar spaces. Obstruction of lymphatic channels may disrupt normal lymph flow and cause chylous pleural effusions or chyloptysis. Sometimes pleura is also involved.[9]

Pulmonary emphysema additionally impairs the pulmonary function. So far, it has not

been clarified how the emphysema develops. Some authors believe that it is a result of the respiratory tract obstruction whereas others support the theory that it may be due to disintegration of the elastic tissue caused by degranulation of the elastase- filled granules which were found in the cytoplasm of LAM cells.[10]

The thoracic duct may be considerably enlarged and divided into multiple microscopic channels with poor passage by the network of smooth muscle fibbers. Pathologic changes may be observed in the intra- and extrathoracic lymph nodes. Involved nodes appear grossly spongy and resilient. Microscopic examination shows progressive replacement of the lymphatic tissue with atypical LAM cells.[11]

Other associated abnormalities include renal angiomyolipomas and abdominal or pelvic masses, which may be cystical and histologically appear as cords of smooth muscle cells and a network of lymphatic channels.[12]

Many authors have reported the presence of oestrogen and progesterone receptors in the cytosol of LAM cells. In healthy subjects these receptors were found in the myometrium, but not in the smooth muscle cells in the colon, bladder and lung. As the normal lung tissue does not display any of these receptors, most probably the hormones affect LAM tissue. However, the mechanism of this process remains unclear.[13]

Monoclonal antibody HMB-45, that recognises antigens in the cytoplasm of melanoma cell lines, specifically binds to the LAM cells, too. As in the normal lung parenchyma or in the case of interstitial lung disease this type of binding does not occur, immunohistochemical staining with HMB-45 may be a very effective diagnostic method, particularly when only a transbronchial biopsy specimen is available. HMB-45 reactivity has also been documented in retroperitoneal LAM and in renal angiomyolipomas.[14,15]

Multifocal micronodular pneumocyte hyperplasia, clear-cell tumours of the lung and non-caseating granulomas have also been noted in patients with LAM.[16]

## Diagnosis

Due to the rarity of LAM and because of the frequent non-specific nature of the clinical symptoms and signs and findings on the chest radiograph, many cases of LAM are initially misdiagnosed as more common diseases, such as asthma or chronic obstructive pulmonary disease. In most cases, patients are seeing the doctor and complaining about non-specific chest pain or dyspnea on exertion as a complication of spontaneous pneumothorax. Such clinical picture is present in number of other lung diseases, so it is not a surprise that the first diagnosis is usually incorrect in almost all cases. LAM should be included in differential diagnosis, when a young female patient presents with dyspnea, recurrent pneumothorax or chylothorax.[17]

### *Diagnostic imaging methods*

In the initial stages of the disease, the changes in the lung are so discrete that they are seen only on CT image. At this stage chest X-ray (CXR) is usually misleading. In later stages of the disease, the CXR shows a generalised, symmetric reticular or reticulonodular interstitial infiltrate in the lung parenchyma as a consequence of the smooth muscle cell proliferation in the walls of lymphatic and small blood vessels. At the beginning the infiltration is limited to the base of the lung, in later stages it is found throughout the lung parenchyma. However, these findings are non-specific and may be detected in patients with other interstitial lung diseases, as well. The lung volume in LAM is usually not changed, but due to the pulmonary emphysema, the CXR may also show evidence of hyperinflation.[18-20]

The obstruction of lymphatic vessels is seen as septal or Kerley's B lines and a rough re-

ticular pattern. In the terminal stage of the disease honeycombing, pneumothorax or pleural effusion may be seen.[20]

HRCT is a highly sensitive method for the detection of the disease in its early stages as the changes in the lung parenchyma are present long before they are seen on CXR. HRCT scans reveal the diffuse cystic changes that account for the reticulation seen on CXR. The cysts are air-filled, have thin walls and are scattered all over the lung parenchyma. Their size ranges from 2 to 60 mm and are usually round, but may be polygonal or bizarrely shaped. The surrounding parenchyma is usually normal. With the progress of the disease, the cysts are growing in size and number. Though cysts are typical for LAM, they are not pathognomic, since they may be detected also in histiocytosis X.[18-20]

In order to detect or confirm renal angiomyolipomas and enlarged retroperitoneal, paraaortic and pelvic lymph nodes it is advisable to perform ultrasonography or computed tomography of the entire abdomen.[12] Lymphangiography may detect abnormal filling and cystic changes in the involved lymph nodes.[21] Abnormal pulmonary blood flow may be detected on nuclear perfusion scan.[22]

*Lung function tests*

The pulmonary physiologic features of patients with LAM are variable and depend on the severity of the disease. They include obstructive, restrictive or mixed patterns. The diffusing capacity for carbon monoxide (DLCO) is reduced in most patients, resulting in some degree of blood hypoxia. Total lung capacity and residual volume are usually increased.[6]

*Lung biopsy*

A definitive diagnosis of LAM usually requires an open lung biopsy and the judgement of the experienced pathologist. Occasionally, transbronchial lung biopsy or even cytological analysis of pleural fluid is sufficient. In case of the extrapulmonary tissues involvement, many authors recommend biopsy of the involved structures. Whenever lung biopsy cannot be performed, the diagnosis can be established with a fair degree of certainty when characteristic HRCT findings are seen along with renal angiomyolipoma.[23,24]

## Therapy

Because of the rarity of the disease and the variable clinical course little data is available on different therapeutic strategies and their success. Given the occurrence of the disease in women in child-bearing years, reports of worsening of the clinical picture following administration of exogenous estrogens, and the presence of oestrogen and progesterone receptors in the proliferating LAM cells, hormonal manipulation would seem to be appropriate for therapy. Several techniques of hormonal blockage have been proposed: ovariectomy, progesterone, tamoxifen or other antiestrogen agents, luteinizing hormone releasing hormone (LHRH) agonists or radioablation of the ovaries. In some cases various combinations of these treatments have been attempted. Responses to such treatments have been variable, and no deffinitive conclusions should be drawn from these reports.[25-28]

In addition to hormonal medications intended to interrupt the proliferation of LAM cells, various interventions aimed at preventing or treating the complications of LAM, such as pneumotorax and pleural or peritoneal fluid collections, have been advised, too. The repetitive drainage of chylous pleural fluid collections may be hazardous due to the loss of proteins. Chemical or surgical pleurodesis has been performed with variable success in preventing recurrent pneumothorax or pleural effusion. The ligation or irradiation of the thoracic duct may prevent the depositi-

on of chylous pleural effusion. Recently, the option of the lung transplantation is considered in the patients with heavily impaired lung functions in the end-stage lung disease related to LAM.[29,30] A few cases of recurrence were reported in the patients who have undergone the lung transplantation. Interestingly, in some of these cases, the donor lungs were also from males, which raises the possibility of some kind of so far unknown circulating mitogen in the pathogenesis of the disease.[31]

## Conclusion

Because LAM is the disease with low incidence and because little is known about its aetiology, it should be included in the differential diagnosis in women in child-bearing years presenting with clinical signs and symptoms of dyspnea, hemoptysis and recurrent spontaneous pneumothorax. HRCT and open lung biopsy followed by the immunohistologic studies are two diagnostic procedures with which diagnosis can be confirmed. More studies have to be performed, to understand the mechanisms of the disease better, for up to date, the treatment of the disease has been rather ineffective and its prognosis is bad.

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