Archives of the Balkan Medical Union
vol. 50, no. 4, pp. 548-552
December 2015

REVIEW

LYMPHANGIOLEIOMYOMATOS IS AN UPDATE

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Summary

During the last 5 years there have been important advances in understanding the disease and lymphangioleiomyomatosis (LAM) treatment, even if there have been difficulties regarding clinical research in this area. The results of research studies on LAM were influenced by the small number of cases and slow evolution in time. LAM is a rare disease, with a chronic course, that occurs in women during the fertile period. The etiology is unknown. The disease is caused by the nonmalignant proliferation in lymphatic vessel walls, blood vessels and small airways by the smooth muscle like cells (LAM cells) and by epithelioid cell proliferation around bronchovascular structures. Patients become symptomatic after a long period of evolution. The case is discovered on the occurrence of pneumothorax or chylothorax or after investigating progressive dyspnea on effort in women. During the evolution there is a functional decline in FEV1 (flow expiratory volume in one second) and DLCO (diffusing capacity for carbon monoxide). The presence of bilateral multiple thin wall cysts is considered a specific feature of HRCT. LAM may evolve independently (sporadic LAM) or may accompany the genetic disease tuberous sclerosis complex (TSCLAM). In LAM pathogenesis, dysregulation of the kinase mammalian target of rapamycin (mTOR0 signaling plays an important role, as a result of mutation in TSC1 (hamartin) level and TSC2 gene (tuberin). More and more studies have proven the efficacy of specific inhibitors of mTOR such as rapamycin (Sirolimus). Lung transplantation remains indication for LAM.
Key words: lymphangioleiomyomatosis, LAM, pneumothorax, chylothorax, VEGFD, specific inhibitors of mTOR, rapamycin (Sirolimus)

Résumé

La lymphangioléiomyomatose - mise au point

Pendant les 5 dernières années, il y a eu des progrès importants dans la compréhension de la maladie et le traitement de la lymphangioléiomyomatose (LAM) même si il y a eu des difficultés en termes de recherche clinique dans ce domaine. Les résultats des études de recherche en matière de LAM ont été influencés par le nombre reduit des cas et la lente évolution dans le temps. LAM est rare, avec une évolution chronique, qui survient chez les femmes fertiles. LAM est causée par des proliférations benignes des cellules musculaires lisses (cellules LAM) dans les parois des vaisseaux lymphatiques, les vaisseaux sanguins et les petites voies respiratoires, et aussi la prolifération cellulaire épithélioïde autour des structures bronchovasculaires. L'étiologie est inconnue. La maladie devient symptômatique après une longue période d'évolution. La découverte des cas se fait quand un pneumothorax ou chylothorax apparaît, ou à l'occasion d'une enquête sur la dyspnée d'effort qui se trouve chez une jeune femme. Pendant l'evolution fonctionnelle on trouve diminués le FEV1 et DLCO. De multiples kystes bilatéraux à parois minces sont spécifiques sur HRCT. LAM peut évoluer indépendamment (LAM sporadique) ou associée à la sclérose tubéreuse de Bourneville, maladie génétique complexe (TSC-LAM). Dans la pathogenèse de LAM un rôle important joue la kinase cible mammalienne de la rapamycine dysrégulation (mTOR) de signalisation, due à une mutation dans le TSC1 (hamartine) et les gènes de TSC2 (de tubérine). De plus en plus d'études ont prouvé l'efficacité des inhibiteurs spécifiques de mTOR comme la rapamycine (sirolimus). Le transplant pulmonaire reste une indication pour LAM.
Mots clés: lymphangioleiomyomatose, LAM, pneumothorax, chylothorax, VEGF D, des inhibiteurs spécifiques de mTOR, Rapamicine

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Definition

Lymphangioleiomyomatosis LAM is a rare but progressive pulmonary disease, of unknown etiology that occurs in women during their fertile period. It appears due to non malignant proliferation of smooth muscle like cells (LAM cells) in lymphatic vessel walls, blood vessels and small airways and by epithelioid cell proliferation around bronchovascular structures (1,2). LAM may evolve independently (sporadic LAM) or may accompany the genetic disease tuberous sclerosis complex (TSCLAM). Angiomyolipomas, a fat and smooth muscle tumor of kidney, occur in 80% of patients with TSCLAM and 30% of patients with SLAM (3). The first important information about the disease were brought by Cornog and Enterline, in 1966, in patients presented with dyspnea, cystic pulmonary parenchymal disease with or without chylous pleural effusion and sometimes associated mediastinal or abdominal tumor formations. Although cases have been described under other names, lymphangiomyoma, lymphangioma, lymphangioperycitoma or leiomyomatosis, the authors notified the smooth muscle fiber damage, similar to TSC lesions and suggested genetic involvement. TSC is an autosomal inherited disorder that associates mental retardation, central nervous system, skin, or ocular manifestations (2,3).

Epidemiology

Lymphangioleiomyomatosis (LAM) is a rare disease, developing in about 5 persons per 1 million (4,5). It affects childbearing age women, rarely has been described in menopausal women, some of whom were under hormone replacement therapy (1,2). The average age is between 30 and 40 years (but it can vary between 18-76 years of age) (2). The frequency is highest in Caucasian women (6). The incidence of sporadic LAM form is estimated at 1 in 400,000 adult women and 30-40% in women presenting tuberous sclerosis who develop LAM (1,2,7,8). Most patients have mutations in genes of tuberous sclerosis complex (TSC): TSC1 or TSC2 genes in somatic cells (1,2,6).

Pathogenesis

The etiology is unknown. The central key in pathogenesis is dysregulation of mTOR signaling as a result of a mutation occurring at TSC1 (hamartin) and TSC2 gene (tuberin) responsible for repressing the kinase mammalian target of rapamycin (mTOR).

Loss of TSC gene function constitutively activates the mammalian target of rapamycin (mTOR) signaling pathway, which regulates multiple cellular functions, including growth, motility, and survival (4). LAM cells also express two lymphatic growth factors receptors, VEGFR2 and VEGFR-3/Flt4. Vascular endothelial growth factors C (VEGF C) and D (VEGFD) are ligands for these receptors, which induce formation and dissemination, via local lymphangiogenesis, of the LAM cells to lymph nodes in mouse models and in humans (8,9). There are few studies, which had the aim to establish the diagnostic usefulness of a serum VEGFD level test for LAM (9,10). They found that the serum VEGFD value discriminated LAM from other cystic lung disease and from healthy volunteers (9,10).

Pathology

Pathologic lesions are caused by the nonmalignant proliferation in lymphatic vessel walls, blood vessels and small airways by the smooth muscle like cells (LAM cells) contributing to the formation of cysts. A mechanism "ballvalve" like obstruction leads to distention of the terminal airspaces (11). Degradation of elastic fiber by the release of proteolytic enzymes appears to be also involved (12,13). LAM cells may infiltrate lung, pleura, and axial lymphatics of the thorax, abdomen and pelvis. This is a cause of occlusion of lymphatics resulting in chylothorax and chylous ascites and mediastinal, abdominal or pelvic lymphadenopathy (13).

Clinical diagnostic criteria

Symptoms depend on when the diagnosis is made. As evolution is longer, symptoms are more frequent and more severe. The most common symptoms in women are progressive effort dyspnea (found in 42% of cases at presentation and 87% of cases during disease course), recurrent pneumothorax (43% at presentation, 65% during disease course) and the emergence of pleural or abdominal chylous effusions (10% chylothorax, chyloperitoneum) (1,4,15). Over half of patients associated cough, sometimes productive. Chest pain, microhemoptysis, chylous ascites may appear during evolution (2). Physical examination may be normal or reveals hyperinflation, decreased or absent breath, endexpiratory crackles and brhonchi, pleural effusion or ascites. Clubbing is uncommon. Pneumothorax may recur (75%) (2,16), may be bilateral and is a medical emergency that patients should be informed about. As the disease progresses, onset of clinical signs such as respiratory failure, decreased exercise tolerance and impaired quality of life of patients appear. St. George's Respiratory Questionnaire (SGRQ), a respiratory specific HRQL instrument that was designed for asthma and COPD, proved to be an instrument capable to monitor longitudinal changes in LAM, correlating FEV1, DLCO or walking distance in the 6 minute walk test (17). In a variable percentage, according to studies, LAM can be associated with renal angiomyolipomas, which are benign masses containing blood vessels, fat and muscle tissue (3357%). They are asymptomatic or can cause back pain, hematuria or palpable tumor mass (11,17). Also, LAM patients present a higher risk for meningiomas (2). Therefore, their screening should include abdominopelvic CT and cerebral RM (2).

Investigations

The standard chest XRay can be normal or can highlight reticular opacities, cystic images, diffuse hyperinflation, emphysema, pneumothorax or pleural effusion (18). High resolution computed tomography (HRCT) has a critical role in diagnostic algorithm. Round, thin wall cysts (0,12 mm), randomly distributed throughout the lung parenchyma, with 240 mm diameter are present in

100% of patients (4). At least 10 lung cysts are needed to support diagnosis (1,6).

Pneumothorax, pleural effusion or mediastinal lymphadenopathy could be found since the beginning or may appear during the evolution of the disease. Enlarged thoracic duct needs to be checked on HRCT (4). Identification of renal angiomyolipoma, retroperitoneal or pelvic leiomyoma and lymphangioma at abdominopelvic level by ultrasound and abdominal CT is important to confirm a positive diagnosis (14).

Anatomopathological diagnostic criteria

In patients with compatible symptoms and typical aspect on HRCT, the anatomo-pathological confirmation through biopsy could be avoided, especially when other features, supportive for LAM, are present: chylous collection, renal angiomyolipoma, TSC (19). When biopsy is required, video assisted thorascopic surgery (VATS) is better than transbronchial lung biopsy for obtaining an adequate tissue sample. These may have incidents or risks like prolonged air leak, pain, death (10). Lesions that are characteristic of LAM are cysts in the lung parenchyma and multifocal nodular proliferation of smooth muscle fibers and perivascular epithelioid cells. The presence of renal angiomyolipoma, retroperitoneal or pelvic or mediastinal leiomyoma lymphangioma, is specific, too (20).

Immunohistochemical stains, necessary when diagnostis is not clear, are positive with melanocytic markers (HMB45) and muscle markers (smooth muscle actin filaments) (4). LAM nodule can also be found, with high proliferative capacity spindle-shape LAM cells at the center and epitheloid-type cells capacity with greater reactivity to HMB45 at periphery (21,22). The presence of estrogen and progesterone receptor can support diagnosis (22,23).

Pulmonary function tests (PFTs) include spirometry, plethysmography, and diffusing capacity for carbon monoxide (DLCO). Initial normal debits and volumes are found (57% of cases), but they may occur during the evolution of disease airflow obstruction (34%) or in mixed dysfunction (9%) (3,4). Reversibility to bronchodilator inhaler was observed in 30% of patients (3). The rate of FEV1 decreases was 75 to 118 ml per year (25-27). Plethysmography identified hyperinflation (rise of total lung capacity and residual volume). DLCO is low, sometimes severely decreased4, 6minutes' walk test and cardiopulmonary effort test are used to monitor effort tolerance (3). Blood gases may reveal hypoxemia and hypercapnia in advanced stages (3).

When TSC is associated, dermatological (using Woods light) exam is needed to identify hypomelanotic patches (4).

The positive diagnosis can be significantly delayed due to nonspecific symptoms, lesions on chest radiographs and rarity of the disease. Suspicion usually arises when a young woman has pneumothorax or chylothorax or when a HRCT is performed to discover the etiology of dispneea (1,2,3,4). Lung biopsy remains the gold standard of diagnosis (1,2,3,4). LAM diagnosis is confirmed by highlighting the proliferation of smooth muscle fibers and positive IHC tests for HMB45 or actin. Lung biopsy may be performed transbronchially (positivity in 60% of cases) (27) or surgically (by minimal thoracotomy or videoassisted thoracoscopy). Sometimes mediastinal lymph node biopsy or extrathoracic tumor formations can be diagnosed (2). Diagnosis of probability can be sustained on HRCT only, with patients presenting multiple thinwalled lung cysts (> 10) who associate chylothorax renal angioleiomyoma or chyloperitoneum. In this case lung biopsy is not necessary (1,4,11).

Lisa R.Young at. all showed increased level of VEGF in 78% of patients with SLAM, respectively in 96% of women with TSCLAM. The 600 pg/mL levels is "highly likely" for LAM and VEGFD could be considered as a biomarker of diagnosis when higher than 800 mcg/L and typical cystic change on HRCT scan appears. This could avoid biopsy in 70% of patients. However the normal level (1/3 of cases) doesn`t exclude the diagnosis (10,30).

Differential diagnosis

In the absence of specific symptoms and HRST, LAM may be mislabeled as asthma or emphysema with or without alpha-1 antitrypsin deficiency (cysts without walls), delaying the diagnosis with 34 years (29). The young age, careful anamnesis, smoking history, and variability of symptoms are helpful for positive diagnosis. Primary spontaneous pneumothorax in a woman should be investigated to exclude a present feature of early disease of LAM. Langerhans cell histiocytosis is another cystic disease which should be considered in a differential diagnosis. An experimented evaluation of the type of lesions on HRCT, presence of Langerhans cells CD1 positive in bronchoalveolar lavage, smoking and sex related feature are clues for positive diagnosis (6).

Unusually, type IV radiological sarcoidosis (increased angiotensin converting enzyme, lymphocytosis with CD4 / CD8 grown ratio in LBA), hypersensitivity pneumonia in chronic form, peripheral hypereosinophilic syndrome, chronic intravenous drug consumption (cysts in the upper and peripheral lobes), Sjögren syndrome, systemic lupus erythematosus, other connective tissue diseases are other forms of diffuse interstitial lung disease are to be considered for differential diagnosis (1,3,6,10). BirtHoggDubé disease, (caused by follicle gene mutation) which is associated with renal cancer, skin fibrofolliculoma, spontaneous pneumothorax, cystic lung disease and tuberous sclerosis associated with skin manifestations, seizures, other benign extrapulmonary tumors must be excluded by other specific investigations (neurological, dermatological exams, abdominal CT, cerebral IMR) (3,4,6).

Management and treatment

During the last 5 years there have been important advances in understanding the disease and lymphangioleiomyomatosis treatment, even if there have been difficulties regarding clinical research in this area. The results of research studies on LAM were influenced by the low number of cases geographically dispersed, slow moving disease, absence of surrogate biomarkers and unclear remission definition (30).

Currently the most important treatment appears to be inhibitors of mTOR. Rapamycin (Sirolimus) is an inhibitor of the proliferation of smooth muscle cells by inhibiting the mTOR complex. Since1999, Sirolimus has been used as an immunosuppressive agent to prevent organ rejection in patients receiving kidney transplant (5).

A randomized study on 89 patients with LAM studied the Sirolimus effect for an initial dose of 2 mg/day to obtain a plasma between 515 ng/ml for 12 months versus placebo. Sirolimustreated group showed that the decline in FEV1 has stopped. It was also observed an increase in quality of life, an increase in FVC (Forced Vital Capacity) and FRC (Functional Residual Capacity) and decreased VEGF (6,31). The commonly reported side effects were nausea, mouth and lip ulcers, diarrhea, chest or abdominal pain, sore throat, leg swelling, upper respiratory tract infection, headache, dizziness, muscle pain and elevated cholesterol (5,31).

Treatment should be conducted in specialized centers. It is better to use the lowest effective dose because the therapy may need to be lifelong, it is important to avoid interruptions, to be aware of interactions with the antibiotics used for infections, continue to administer Sirolimus one week before and after for surgery and interrupt it on the day of the transplant (30).

For LAM treatment, Rapamune (Sirolimus) was approved by 'Japanese FDA' on July 4th, 2014 and on May 28th, 2015 by U.S. Food and Drug Administration (5,30).

Lung transplantation

LAM has lung transplantation indication in patients under 65 years old, evolving with respiratory failure, and in those belonging to severity Class IIIIV NYHA. Only 1.1% of lung transplants are performed for LAM (32). Post transplant survival is 86% at one year and 65% at 5 years (33). Cases of relapsed AML of the transplanted lung after unipulmonary transplant were described (34). LAM TCS or the presence of angiolipoma are not a contraindication for transplant, but patients must be carefully monitored before (33,35).

Inhaled bronchodilator treatment Beta 2 type

Inhaled bronchodilator treatment Beta 2 type - adrenergic or anticholinergic agonists can be used in case of severe obstruction highlighted on spirometry or of important functional decline rate, as long as they have a favorable response (20% of patients). Inhaled corticosteroids are not indicated (36).

Pneumothorax treatment

Is a surgical emergency; it is caused by significant morbidity with a high rate of recurrence (36). Pleurodesis is indicated since the first pneumothorax episode. Pleurectomy can be considered, too. In case of lung transplantation special attention should be paid to increased bleeding risk (2).

Chylothorax treatment

Low fat diet, substitution of medium chain triglycerides and pleurodesis type surgical procedures, evacuation of chylous collections, or sometimes ligation of the thoracic duct are indicated (4,37).

Angiomyolipoma treatment

Small angiomyolipoma do not require treatment but they should be monitored by ultrasound at least once every two years. Angiomyolipoma with sizes bigger than 4 cm, or those presenting aneurysms over 5 mm should be monitored twice a year. In case of bleeding embolization or surgically excised with conservation of renal tissue is needed (1,4).

Hormone treatment

Hormone treatment, surgical or chemical castration including, long used are no longer recommended because they have not proven effective. Patients with accelerated decline in lung function should receive progesterone or gonadotrophin releasing hormone agonist (GnRH) (6). Women with LAM are advised to avoid pregnancy due to the risk of disease progression using mechanical methods to avoid hormonal treatmentsestrogen containing medication including oral contraceptives and hormone replacement therapy (1).

Quitting smoking, annual influenza and pneumococcal vaccination taking into consideration pulmonary rehabilitation, chronic oxygen therapy and osteoporosis treatment, when needed, represent general advice (1). Airplane flight was considered to increase the risk of pneumothorax so air transport is discouraged especially in patients with a history of pneumothorax or extensive subpleural cystic lesions (2,6). Patients should be educated on the risks of pneumothorax or other complications to recognize symptoms and require medical help in an emergency. LAM Foundations provide valuable support in this respect.

Evolution and Prognosis

The prognosis remains reserved, the disease progressing to chronic respiratory failure and death. Over time, studies have shown an increase in survival from 47 years to 8-10 years for 71-90% of patients 4,3840. Longer survivals of 20-30 years are described 3840. Some predictors of survival were described: younger age of onset, lung severe functional impairment and nodular and cystic lesions expansion 4,40. Evolution is encumbered by the increased degree of dyspnea, FEV 1 (70120 ml/year) decrease, 1 or more episodes of pneumothorax in 2/3 of patients and chylous pleural effusion in 1020% 4,4143. Patients who associate angiolipoma may occasionally have renal hemorrhage (14). LAM evolution in LAMTSC patients appears to be mild. Functional monitoring up to 36 months in the first year of diagnosis and then up to 312 months depending on the severity of the disease is proposed (1). VEGFD could be also considered as a prognostic biomarker (high VEGFD correlates with lung function decline in untreated patients) and predictive biomarker (high VEGFD correlates with treatment response)(10).

CONCLUSIONS

Much progress in understanding the etiology and evolution of the disease and LAM therapy has been made. Correct clinical, imaging and serological evaluation (VEGFD) can lead to a diagnosis of certainty in 2/3 of the cases avoiding biopsy. Rapamycin appears to be a treatment that can influence the evolution of the disease. Further research is envisaged to prevent progression to symptomatic disease, stabilization of the disease, discovery of surrogate biologic markers for diagnosis and also new effective drugs. Reference centers to continue monitoring the treatment of such cases as well as a LAM National Registry should be established in Romania.

REFERENCES

1. Johnson SR, Cordie JF, Lazor R, et all. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J 2010; 35: 14–26.
2. Sullivan EJ. Lymphangioleiomyomatosis: a review. Chest 1998; 114:1689-1703.
3. Ryu JH, Moss J, Beck GJ, et al. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. Am J Respir Crit Care Med 2006; 173:105.
4. Johnson SR. Lymphangioleiomyomatosis. In Costabel U, du Bois RM, Egan JJ: Diffuse Parenchimal Lung Diseases. Prog Respir Res. Basel, KZargener, 2007, vol 36, pp 275-284
5. FDA approves Rapamune to treat LAM, a very rare lung disease. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm448523.htm
6. Toma C. Limfangioleiomiomatoza. In Strambu I, Tudorache V. Ghid de diagnostic si tratament al pneumopatiilor interstitiale difuze, 2015.
7. Franz DN, Brody A, Meyer C, et al. Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. Am J Respir Crit Care Med. 2001;164(4): 661-668.
8. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med. 2006;355(13):1345-1356.
9. Seyama K, Kumasaka T, Souma S, et al. Vascular endothelial growth factor-D is increased in serum of patients with lymphangioleiomyomatosis. Lymphat Res Biol. 2006;4(3):143-152.
10. Young LR, Van Dyce R, Gulleman PM et al. Serum Vascular Endothelial Growth Factor-D Prospectively Distinguishes Lymphangioleiomyomatosis From Other Diseases, CHEST 2010; 138(3):674–681
11. King TE. Pulmonary lymfpangioleiomyomatosis. http://www.uptodate.com/contents/pulmonary-lymphangioleiomyomatosis
12. Fukuda Y, Kawamoto M, Yamamoto A et al. Role of elastic fiber degranulation in emphysema –like lesions of pulmonary lymphangioleiomyomatosis. Hum Pathol 1990, 21: 1252-1261
13. Zhe X, Yang Y, Schuger L. Imbalance plasminogen system in lymfpangioleiomyomatosis: potential role of serum responce factor. Am Jrespir Cell Mol Biol2005: 32:28-34
14. Avila NA, Kelly JA, Chu SC. Lymfpangioleiomyomatosis abdominopelvic CT and US finding. Radiology 2000; 216:147-53
15. Moss J, Avila NA, Barnes PM, et al. Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med 2001; 164:669.
16. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, et al. Maximal oxygen uptake and severity of disease in lymphangioleiomyomatosis. Am J Respir Crit Care Med 2003; 168: 1427–1431.
17. Swigris JJ, Hye- Seung Lee, Cohen M. St George`s Respiratory Questionnarie has Longitudinal Construct Validity in Lymphangioleiomyomatosis. CHEST 2013; 143(6):1671–1678.
18. Crausman RS, Lynch DA, Mortenson RL, King TE Jr, Irvin CG, Hale VA, Newell JD Jr. Quantitative CT predicts the severity of physiologic dysfunction in patients with lymphangioleiomyomatosis. Chest. 1996;109(1):131.
19. McCormack FX. Lymphangioleiomyomatosis: a clinical update. Chest. 2008; 133(2) : 507-516.
20. Torres VE, Björnsson J, King BF, et al. Extrapulmonary lymphangioleiomyomatosis and lymphangiomatous cysts in tuberous sclerosis complex. Mayo Clin Proc. 1995;70(7):641.
21. Matsumoto Y, Horiba K, Usuki J et al. Markers of cell proliferation and expression of melanosomal antigen in lymfangioleiomyomatosis of the lung. Am J Surg Pathol 1993; 17:1092-1102
22. MatsuiK,TakedaK,YuZX,etal. Downregulation of estrogen and progesterone receptors in the abnormal smooth muscle cells in pulmonary lymphangioleiomyomatosis following therapy. An immunohistochemical study. Am J Respir Crit Care Med 2000; 161: 1002–1009.
23. Glassberg MK, Elliot SJ, Fritz J, et al. Activation of the estrogen receptor contributes to the progression of pulmonary lymphangioleiomyomatosis via MMP-induced cell invasiveness. J Clin Endocrinol Metab 2008; 93: 1625–1633.
24. Ryu JH, Moss J, Beck GJ, et al. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. Am J Respir Crit Care Med 2006; 173:105.

NHLBI Workshop Summary. Report of workshop on lymphangioleiomyomatosis. National Heart, Lung, and Blood Institute. Am J Respir Crit Care Med 1999; 159:679.

25. Johnson S. Rare diseases. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. Thorax 1999; 54:254.
26. Corrin B, Liebow AA, Friedman PJ. Pulmonary lymphangiomyomatosis. A review. Am J Pathol 1975; 79:348.
27. Meraj R, Wikenheiser-Brokamp KA, Young LR, et al. Utility of transbronchial biopsy in the diagnosis of lymphangioleiomyomatosis. Front Med. 2012 Dec; 6(4):395-405
28. Glasgow CG, Avila NA, LinJP, et al. Serum vascular endothelial growth factor D levels in patients with lymphangioleiomyomatosis reflect lymphatic involvement. Chest 2009; 135:1293.
29. Cophen MM, Pollock-BarZiv S, Johnson SR. Emerging clinical picture of lymphangio-leiomyomatosis Thorax 2005;60: 875-879.
30. McCormack FX. Clinical Trials and State of the Art. ERS 2014: presentation Munich.
31. McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleio-myomatosis. N Engl J Med. 2011;364(17):1595
32. Benden C, Rea F, Behr J, et al. Lung transplantation for lymphangioleiomyomatosis: the European experience. J Heart Lung Transplant 2009; 28:1.
33. Pechet TT, Meyers BF, Guthrie TJ, et al. Lung transplantation for lymphangioleiomyomatosis. J Heart Lung Transplant. 2004; 23(3):301
34. Nine JS, Yousem SA, Paradis IL, Keenan R, Griffith BP. Lymphangioleiomyomatosis: recurrence after lung transplantation. J Heart Lung Transplant. 1994;13(4):714.
35. Reynaud-Gaubert M, Mornex JF, Mal H, et al. Lung transplantation for lymphangioleiomyomatosis: the French experience. Transplantation 2008; 86: 515–520.
36. Martignoni G, Pea M, Reghellin D, Gobbo S, Zamboni G, Chilosi M, Bonetti F. Molecular pathology of lymphangioleiomyomatosis and other perivascular epithelioid cell tumors. Arch Pathol Lab Med. 2010 Jan;134(1):33-40.
37. TaveiraDaSilva AM, Jones AM, Julien Williams P, et al. Effect of Fasting on the Size of Lymphangioleiomyomas in Patients with Lymphangioleiomyomatosis. Chest 2015; Jun 11. doi: 10.1378/chest.15-0456
38. Kitaichi M, Nishimura K, Itoh H, Izumi T. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. Am J Respir Crit Care Med 1995; 151:527.
39. Urban T, Lazor R, Lacronique J, et al. Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine (Baltimore). 1999;78(5):321
40. Carrington CB, Cugell DW, Gaensler EA, et al. Lymphangioleiomyomatosis. Physiologic-pathologic-radiologic correlations. Am Rev Respir Dis 1977; 116: 977–995.
41. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. Thorax 2000; 55: 1052–1057.
42. Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. Am J Respir Crit Care Med 1999; 160: 628–633.
43. Taveira-DaSilva AM, Stylianou MP, HedinCJ, et al. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. Chest 2004;126:1867-1874.