Aleksandra Sobiborowicz[1,2], Anna M. Czarnecka[1,3], Anna Szumera-Ciećkiewicz[4,5], Piotr Rutkowski[1], Tomasz Świtaj[1]

[1]Department of Soft Tissue/Bone, Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Medical Faculty, Medical University of Warsaw, Warsaw, Poland
[3]Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[4]Pathology Laboratory, Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[5]Department of Diagnostic Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

Diagnosis and treatment of lymphangioleiomyomatosis (LAM) from the PEComa group

Address for correspondence:

Dr n. med. Tomasz Świtaj

Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy w Warszawie ul. Roentgena 5, 02–781 Warszawa

Tel.: 22 546 20 31; faks: 22 643 93 75

e-mail: tomasz.switaj@pib-nio.pl

ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare, proliferative lung disease, leading to progressive damage of their structure and is a member of the PEComa neoplasm family (perivascular epithelioid cell tumors). In the patients, solid-cystic masses described as lymphangioleiomyoma or extrapulmonary LAM (E-LAM) can occur. E-LAM foci have been described in the mediastinum, supraclavicular lymph nodes, the liver, walls of the small and large intestine, the pancreas, mesentery. E-LAM masses can attain very large sizes — tumors 15–22 cm long have been described. On the basis of positive results of clinical trials sirolimus, a drug from the group of mTOR kinase inhibitors, was registered by the Food and Drug Administration (FDA) in May 2015 as the first and currently only drug for systemic LAM therapy. Sirolimus use is recommended in patients with LAM, accompanied by rapidly progressing deterioration of respiratory system function or $FEV_1 \leq 70\%$ predicted value and in patients with pleural lymph exudate before applying invasive methods of treatment.

Key words: lymphangioleiomyomatosis, sirolimus

Oncol Clin Pract 2021; 17, 1: 28–41

Introduction

Lymphangioleiomyomatosis (LAM) is a rare, proliferative lung disease leading to progressive damage to their structure with the formation of numerous small cysts and lymph accumulation in the pleural cavity [1]. At its basis is the multifocal proliferation of smooth muscle cells and perivascular epithelioid cells, (PECs); in LAM they are also designated LAM cells in the lung interstitium and is therefore included in the family of PEComa type neoplasms (perivascular epithelioid cell tumors) [2]. The PEComa group also includes angiomyolipoma (AML), clear-cell sugar tumor (CCST) — pulmonary and extrapulmonary forms (primary extrapulmonary sugar tumor, PEST), clear-cell myomelanocytic tumor (CCMMT) and primary cutaneous PEComa, CCCMT — cutaneous clear cell myomelanocytic tumor and PEComa NOS (not otherwise specified) [3]. Pulmonary *LAM* (P-LAM) occurs in two clinical forms: associated with tuberous sclerosis [Bourneville-Pringle disease, tuberous sclerosis complex (TSC)] — a genetic syndrome caused by inactivating germline mutations in the *TSC1* and *TSC2* genes, characterized by the occurrence of many tumors of the hamartoma type, perturbations of the nervous system, including epileptic seizures, autism and intellectual disability of various degrees [4], and as a sporadic form — sporadic LAM (S-LAM), in women with no predisposing factors [5]. In addition to pulmonary manifestation of LAM, in these patients, numerous irregularities are observed in the lymph system outside the chest such as perturbations of the patency of the thoracic duct, lymph exudate in the retro-orbital space and pelvis, or lymphadenopathy [5]. Moreover, in rare cases, there is a proliferation of pathological lymph vessels infiltrated by LAM cells, leading to an obstruction of their lumen and accumulation of lymph resulting in the formation of solid-cystic masses described as lymphangioleiomyoma or extrapulmonary LAM (E-LAM) [6].

Frequency of occurrence

The frequency of occurrence of lung LAM differs depending on the clinical type — pulmonary LAM is found in 30–50% women and approximately 10% men with tuberous sclerosis [7, 8], whereas the sporadic form occurs in one woman out of 200–400 thousand [5, 7]. Lymphangioleiomyomatosis concerns almost exclusively women of reproductive age — the median age at diagnosis is in the range of 35–41 years [9– 12]. Pleural LAM is rarely diagnosed in postmenopausal patients – of note here is the often occurring information about the use of hormonal replacement therapy [12, 13]. Single cases have been described of the occurrence of the disease in children and men without predisposing genetic factors [14– 16]. Extrapulmonary perturbations within the lymphatic system are found often in patients with the pulmonary LAM form — perturbations in the patency of the thoracic duct are found in over 70%, lymph exudate in the retroperitoneal space is observed in 30% of the cases [17]. Lymphangioleiomyoma is less common — in 10–21% of patients with pulmonary S-LAM [12, 17– 19] and is often accompanied by a swelling of lymph nodes within the abdominal cavity, ascites and a broadening of the thoracic duct [18]. It seems that the frequency of occurrence of lymphangioleiomyoma in patients with the pulmonary form of LAM increases with the severity of its course [18], but they are not more common in patients with tuberous sclerosis — in a retrospective analysis from the Mayo Clinic, among 403 patients with TSC, E-LAM occurred in only 3 [20]. In the analysis of autopsy material or material obtained from gynecological surgery in 10 female patients with the pulmonary form of LAM, the presence of small LAM foci in the uterus, adnexa or broad ligament of the uterus was observed in as many as 90% , and in 80% — the occupation of the lymph nodes in the retroperitoneal space [21]. It is not clear whether the presence of E-LAM foci predisposes to the development of the pulmonary form of LAM. In a large retrospective analysis of material obtained from 1732 patients without a history of LAM (median age 56 years), who underwent gynecological surgery with lymphadenectomy, extrapulmonary LAM foci were found in 8 patients [22]. In one of them a pulmonary form of LAM was diagnosed, 7 years after the gynecological surgery whereas the remaining women did not have a LAM relapse in any form (median observation 26 months) [22]. In a similar analysis among 19 patients in whom asymptomatic extrapulmonary LAM had been detected occupying the uterus and pelvical and paraortal lymph nodes during an average 33 month observation none developed the pulmonary form [23]. Besides the description of cases concerning women with LAM foci in paraaortal and pelvical lymph nodes, in whom pulmonary LAM did not occur nor tuberous sclerosis [24, 25], descriptions are also available in which extrapulmonary LAM was the first symptom of the development of the pulmonary LAM form, which if it occurs is most commonly diagnosed within about 2 years from the diagnosis of the extrapulmonary form [6, 26–31].

Anatomy and clinical picture

Pulmonary LAM leads to progressive destruction of the lung parenchyma and its replacement by numerous small cysts, causing a progressive respiratory deficiency [7]. In the course of LAM exercise tolerance is progressively limited as well as everyday physical activity to a degree greater than in for example chronic obstructive pulmonary disease [32]. Among the most common early symptoms of the disease are: dyspnea, persistent coughing and hemoptysis [7, 11, 12]. Dyspnea at rest and the need for oxygen therapy appears in most patients within 10 years from the diagnosis [33]. The course of the disease is complicated by recurring pneumothorax, occurring in about 5% of the patients per year from the moment of diagnosis; additionally, in about one-half of the cases they are the first symptom of developing LAM [3, 12, 34]. Moreover, because of the perturbation of lymphatic vessel patency, there are lymph exudates in the pleural cavity causing an intensified dyspnea and chest pain [35]. LAM is also a rare cause of occurrence of pulmonary hypertension (about 7.6% patients LAM) [9].

Lymphangioleiomyoma is most commonly localized in the retroperitoneal space and the uterus and in surrounding lymph nodes [6, 24, 27]. Moreover, E-LAM foci developing in the mediastinum [36], supraclavicular lymph nodes [37, 38], liver [39], walls of the small and large intestine [40, 41], pancreas [26, 42], mesentery [43] have been described. E-LAM masses can reach very large sizes — cases of tumors with the greatest length 15–22 cm have been described [18, 44–46] — and can extend along lymph vessels — coming from the retroperitoneal space to the chest [19], and further even along the neck along with the sternocleidomastoid muscle [47].

The symptoms of lymphangioleiomyoma presence occur in about 55–60% patients [6, 18] and the most commonly are: pain in the vicinity of the tumor [26, 29, 46] and bleeding from the reproductive system in the case of LAM localized in the uterus [24, 48, 49]. Symptoms associated with the pressure of the tumor mass on neighboring organs are also frequently observed: dyspepsia, bloating and symptoms of obstruction of the alimentary tract [46], hydronephrosis or edema and paresthesia of the lower extremities [46, 50]. Lymphangioleiomyoma localized in the mediastinum may cause Horner syndrome, lymph exudates to the pleural cavity and heart rhythm perturbations [6, 18]. If LAM cells infiltrate the ureters, chyluria occurs [51], whereas the occupation of Vater's papilla may lead to cholestasis [45]. In the case of large lymphangioleiomyomas, ascites

linked to a large lymph volume may be observed [6] or bleeding from the tumor to the abdominal cavity [52]. Symptoms due to pressure on neighboring organs such as: bloating, pain in the vicinity of the tumor, pollakiuria, edema and paresthesia of the lower extremities or constipation are more intense during the day [18]. This is associated with an increase in tumor volume during the day due to greater flow of lymph through the abdominal cavity and the pelvis after meals and during daily activity, and an increase in hydrostatic pressure in the erect position [18, 27]. The increase in volume during the day is 140% on average [18]. Changes in lymphangioleiomyoma volume during the menstrual cycle have also been described [53].

Diagnosis

According to the recommendations of the European Pulmonological Society, the gold standard in LAM diagnosis is a lung biopsy and high-resolution computer tomography of the chest [7]. Characteristics additionally favoring this diagnosis are: angiomyolipoma currently/in the patient's history, lymph exudates within the chest and abdominal cavity, tuberous sclerosis, the presence of lymphangioleiomyoma or microscopically detected occupation of lymph nodes by LAM cells [7]. In the recommendations of the American Thoracic Society/Japanese Respiratory Society from 2017, the following are also included among these properties: plasma concentration of vascular epithelial growth factor D (VEGF-D) ≥ 800 pg/mL and the presence of LAM cells in a cytological examination of the lymph exudates in the pleural cavity [54]. Because LAM is exceedingly rare in males, the final diagnosis should be made in each case on the basis of a typical result of a lung biopsy [7]. A transbronchial biopsy has been shown to be a relatively safe method in the group of LAM patients [55].

High-resolution computer tomography is the examination of choice both in the diagnostic process as well as to observe disease progression [7]. Among typical radiological changes observed in all patients are numerous, small round cysts in the lung (2–5 mm diameter), equally distributed within the lung parenchyma [11]. Because of the frequent co-occurrence of LAM and renal angiomyolipoma computer tomography with an abdominal cavity and pelvic contrast is recommended, and in the case of contraindications for contrast use — a magnetic resonance analysis [7].

Lymphangioleiomyoma in computer tomography most commonly takes the form of well-defined, solid-cystic lesions, with walls of different thickness and numerous septs [26, 27, 46]. Less commonly a solid or only cyst-like character is observed [27]. The lesion is generally delimited but a few lymphangioleiomyomas with an in-

filtrating type of growth are observed [18]. Solid tumors have a density similar to the liver (59–71 HU), cyst-like lesions a lower one (3–25 HU), corresponding to lymph accumulation [18]. The cyst walls may become more pronounced after contrast [17]. Lymphangioleiomyoma under magnetic resonance shows differentiated values of signal both in T1 and in T2 exposure [38, 44, 49, 50]. In PET a small uptake of glucose is observed [26]. In ultrasound E-LAM can give the appearance of an isoechogenic, hypo- and hyperechogenic lesion, not permitting its differentiation from ovarian neoplasms or lymphomas [27]. However, changes in the structure during the day are characteristic: solid changes in the morning hours, can in the evening have a solid-cystic character and change their echogenicity [27]. Moreover, lymphangioleiomyomas have been found to increase their volume during the day which differentiates them from other neoplastic lesions localized in the retroperitoneal space and the pelvis [27].

LAM is also associated with an increased risk of meningioma development, therefore in the case of symptoms from the central nervous system magnetic resonance of the head is justified [7]. Patients with LAM should also be under the care of a genetic counselling facility — TSC is characterized by a broad range of phenotypes and poorly clinically expressed characteristics of this syndrome may lead to incorrect classification of the case as sporadic [7].

Morphology

The typical appearance for LAM encompasses the occurrence of numerous cysts in the parenchymal tissue of the lungs and multifocal proliferation of immature smooth myocytes and perivascular epitheliod cells (PECs), known in the case of lymphangioleiomyoma as LAM cells [7]. Foci of proliferation for LAM cells and myocytes are most commonly located around lymph vessels, interlobar septae and the pleura [3]. Within LAM cysts smaller fusiform cells are localized more centrally, whereas epithelioid cells with abundant cytoplasm are localized mainly at the periphery [56]. Cytological atypia and division patterns are generally not present [57].

On the basis of the intensity of two morphological changes typical for LAM: the occurrence of cysts and intensification of LAM cell proliferation within lung biopsy material, Matsui et al. (2001), elaborated a division into III histologic severity grades (LHS, histologic severity of LAM) [34]. The percentage of lung tissue occupied by the described lesions viewed under a small magnification was qualified as follows: LHS1 < 25%; LHS-2: 25–50% and LHS-3 > 50% [34]. The authors also showed a strong correlation of the grade of LHS severity with 10-year overall survival, which was: 100%,
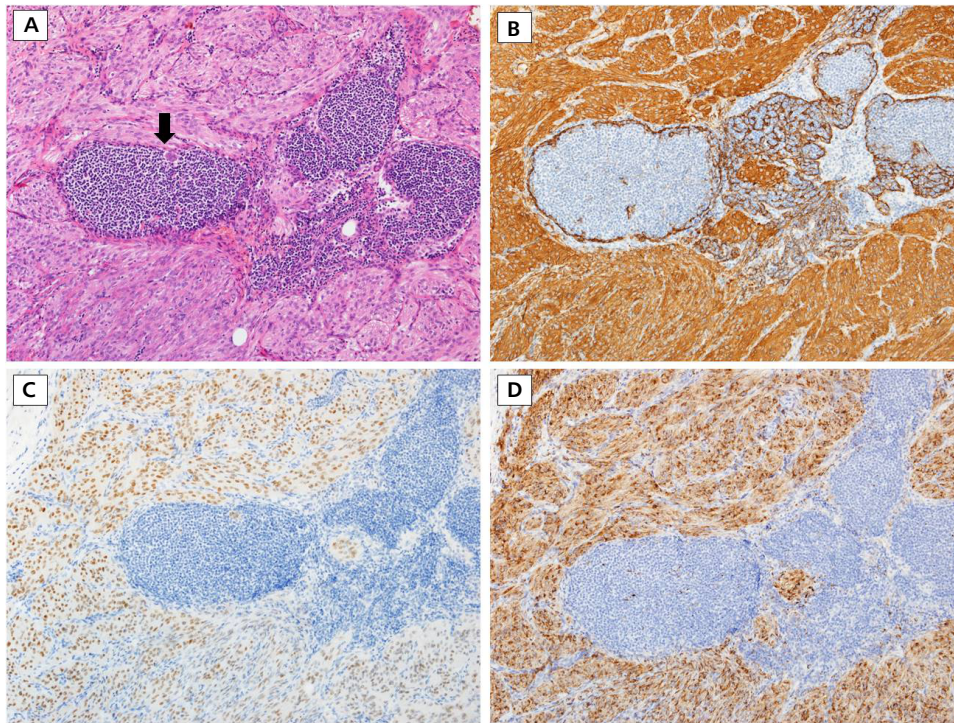
Figure 1A–D. Retroperitoneal LAM with infiltration of lymph node — in the order of staining HE, SMA, HMB-45, progesterone receptors [100×]

74.4% and 52.4%, respectively in w LHS-1, LHS-2 and LHS-3 [34]. LHS is currently an acknowledged prognostic factor in pulmonary LAM [58].

Lymphangioleiomyoma is generally described as lesions well delimited from surrounding tissues [21, 26], with the presence of a fibrous capsule [57]. Infiltration of LAM cells beyond the capsule is rare [6]. LAM foci in the uterus are an exception, they are frequently poorly separated from unaffected smooth uterine muscle coat [21, 24]. Differential diagnosis of E-LAM within the uterus encompasses myoma, leiomyosarcoma, endometrial stromal sarcoma or paraganglioma [48]. Lymphangioleiomyomas similarly as the pulmonary form is composed of fusiform and epithelioid LAM cells with round and oval nuclei with an abundant slightly acidophilic cytoplasm [6, 24, 50]. These cells form nests — resembling the so-called „zellballen" described in phaeochromocytomas [26], separated by slot-like vessels with thin walls lined with endothelial cells [50], which may undergo hyalinization [21, 24, 26]. Typically necrosis and blood extravasation to the tumor are not observed [6, 21, 26, 46]. In most cases the mitotic activity is low [6, 21], in some cases, up to 4 figures for 10 visual fields were observed [24, 37]. A fairly common finding are small clusters of reactive lymphocytes, resembling lymph nodules [6].

LAM cells are characterized by the simultaneous expression of melanocyte (HMB-45, Melan A, MART1) and smooth muscle (SMA, desmin, actin) markers (Fig. 1) [59, 60]. The expression of HMB-45 is observed in all cases, and the percentage of cells showing the expression of this marker is variable — it is in general 20–40% and concerns predominantly epithelioid cells [11, 56, 60, 61]. In almost all cases the expression of the estrogen (ER) and progesterone (PR) receptor also occurs — mainly within fusiform cells [56], and in general PR expression is stronger [62]. Other markers useful in the differential diagnosis are β-catenin and E-cadherin and cathepsin K, whose expression has been observed in all analyzed cases [56, 63, 64]. The co-occurrence of the expression of lymph vessel endothelium markers is also characteristic: podoplanin (D2-40), PROXI, VEGFR-3 and LYVEI, which occurs both in cells lining lymph vessels and in the LAM cells themselves [56]. Among less typical markers is the epithelial growth factor receptor (EGFR), whose expression was observed in about one-half of cases [56]. Kobayashi et al. (2018) have also demonstrated the cytoplasmic expression of EGFR/ErbB-1 and HER4/ErbB-4 in LAM cells [65]. Maisel et al. (2018) described the strong expression of the programmed death-ligand 1 (PD-L1) in preparations from lung biopsies from 6 patients with LAM, which was greater in preparations from pulmonary nodules than in tissue from healthy lungs [66]. They also found the presence of T lymphocytes showing the expression of programmed death-ligand 1 (PD-1) receptor, infiltrating

LAM foci [66]. In the case of lymphangioleiomyoma, LAM cells show the expression of a similar marker profile: HMB45 — particularly in epithelial cells [6], Melan A, calponin, SMA, desmin, nuclear expression of ER and PR [6, 24, 46, 50]; moreover expression of β-catenin [35], E-cadherin [67], MiiTF [25] and in the lymph vessel endothelium: CD34, podoplanin, CD31, and VEGFr-3 [21, 24, 26, 43].

Genetics

Similarly, as other proliferative diseases from the PEComa family, lymphangioleiomyoma has a higher frequency of occurrence in patients with tuberous sclerosis — characterized by the presence of germline inactivating mutations and loss of heterozygosity (LOH) in the 16p13.3 region, in the *TSC2* locus, encoding the tuberin protein and in the 9q34 region, locus *TSC1*, encoding the hamartin protein [8, 68]. Tuberin has an inhibiting action on the signalling protein Rheb — a homolog of the Ras protein (Ras homolog enriched in the brain — Rheb), which in turn is a known activator of the mTOR serine-threonine kinase [69]. Hamartin forms a complex with tuberin, stabilizing it and protecting it from degradation in proteosomes [70]. Excessive activation of the Rheb protein due to the loss of function of one of these two proteins leads to activation of the mTORC1 pathway, increased synthesis of proliferation stimulating proteins and angiogenesis resulting in the presence of numerous tumors of the PEComa type in patients with tuberous sclerosis [69]. The pulmonary form of LAM is found in approximately 30–50% women and in approximately 10% men with tuberous sclerosis, these are more commonly patients with mutations within *TSC2* [8, 71]. Similarly, somatic inactivating mutations and loss of heterozygosity in the *TSC1* and *TSC2* genes are observed in LAM cells obtained from patients with the sporadic LAM form though as this form is rare there are no analyses of large groups of patients [72]. Badri et al. (2013) analyzed material obtained from 10 patients with sporadic LAM, showing that in as many as 8 of them LAM cells showed perturbations within the *TSC2* locus, moreover, in 4 of them complete loss of tuberin occurred because of loss of heterozygosity and a mutation in the second allele (3 cases) and two inactivating mutations in both alleles simultaneously in one case [73]. In the paper by Fujita et al. (2015), inactivating somatic *TSC1*/*TSC2* mutations were detected in LAM cells in 6 out of 9 patients with LAM [74]. Among other genetic changes observed in patients with lymphangioleiomyoma are: germline mutations within *BARD1*, *BLM* and *BRCA2* [14] and *EGFR* amplification [56], however, their role in LAM pathogenesis has not been fully analyzed.

Evaluation of the stage of the pulmonary form of LAM and factors affecting the severity of its progression

Among analyses of the functioning of the respiratory system whose results correlate with the irregularities observed in radiological and histopathological analyses and which change with disease progression are: analysis of the coefficient of lung transfer for carbon monoxide (TLco) and a spirometric analysis — especially the measurement of the forced expiratory volume in 1 second (FEV$_1$) [58]. In the first evaluation of the degree of progression of the disease TLco and spirometric analysis with a bronchodilatory test are recommended [7]. Moreover, in patients from whom a lung biopsy was obtained a histological evaluation of the progression in the LHS scale, which was described earlier, is performed [58]. FEV$_1$ and TLco measurements should be repeated every 3–6 months in order to evaluate the progression of the disease and the response to treatment and in the case of stable results, the control analyses can be reduced to annual ones [7]. In patients in the initial stage of the disease in general deviations are not observed in gasometric blood analysis, it is used as an indication of indications for oxygen therapy and lung transplantation in patients with advanced disease [7]. An exercise test and a 6-minute marching test (6MWT) find application in the evaluation of the effect of the disease on general performance and response to treatment [58]. The pulmonary LAM form is characterized by a milder course in patients with tuberous sclerosis, in comparison to the sporadic form [7, 58]. Moreover, patients in whom the first LAM symptoms are hemoptysis and dyspnea have a worse disease than those in whom LAM was diagnosed because of pneumothorax, which may be associated with the delay in diagnosis in the first group [58]. A tendency of LAM to progress more slowly in post-menopausal women has been indicated [75]; in the analysis by Gupta et al. (2019) the change in FEV$_1$ in pre-menopausal women was on the average –118 mL/year, whereas in postmenopausal women it was –74 mL/year (p = 0.003) [76]. A recently described prognostic factor in lymphangioleiomyoma is the plasma level of vascular endothelial growth factor D (VEGF-D), which is much higher in patients than in the healthy population, especially in patients with tuberous sclerosis [77]. A high level of VEGF-D (over 800 pg/mL) was correlated with a more rapid rate of deterioration of FEV$_1$ values [78] and the presence of lymph exudates to the pleural cavity and the number of pulmonary cysts [77]. Other markers which have been associated with the severity of the course of pulmonary LAM are: the concentration of extracellular matrix metalloproteinases (MMP) in urine [58], the plasma concentration of vitamin D binding protein (VTDB) [79, 80], VEGF-3 receptor and chemokine CCL21 [81]

or the expression of the receptor of the human epithelial growth factor 3 (HER3) w LAM cells [61].

Pulmonary LAM treatment

Respiratory rehabilitation encompassing aerobic exercises and exercises for strengthening the breathing muscles exerts a proven, favorable effect on the evaluation of life quality, the 6MWT result, the feeling of dyspnea and the level of everyday activity of LAM patients [82]. By analogy to the procedure in chronic obstructive pulmonary disease, it is recommended that LAM patients be covered by prophylactic vaccinations against pneumonia diplococcus and influenza and because of the frequent occurrence of osteoporosis, patients with LAM should undergo periodic densitometric analyses [7]. LAM is associated with an increased risk of pneumothorax, which occurs in about one-half of patients at the moment of diagnosis and in over 60% of patients in the course of the disease, with a tendency to frequent recurrences [7]. Factors additionally increasing the risk of pneumothorax are pregnancy and flying [7, 83]. Pleurodesis is effective in preventing recurring pneumothorax; the analysis by Gonano et al. (2018) of a group of 145 patients indicated that pleurodesis prevented its occurrence with a probability of 82%, 68% and 59% after one, 5 and 10 years, respectively after the procedure in comparison with 55%, 46% and 39% among patients who did not undergo the procedure (p = 0.026) [83]. In the case of abundant lymph exudates to the pleural cavity a diet low in fat is recommended, and if clinical symptoms occur (dyspnea, coughing, chest pain) — traditionally draining of the pleural cavity through thoracentesis is applied [7], however, in the light of new evidence before starting treatment by invasive methods an attempt to control the symptoms by systemic treatment with sirolimus is recommended [5, 35, 84]. In advanced stages of LAM, in patients considered to be class III–IV on the NYHA scale with hypoxemia at rest, lung transplantation can be applied [7]. Average time from diagnosis to the transplantation varies in papers from various centers in the range of 4–5 years [85, 86]. In a large retrospective analysis of data concerning the course of the disease in 138 patients with LAM who had undergone a lung transplantation 1-year, 5-year and 10-year overall survival after the procedure were: 94%, 73% and 56%, respectively, and the causes of death were most commonly: bronchiolitis obliterans and chronic transplant rejection [87]. Such parameters as the presence of lung hypertension and the 6MWT distance before the procedure, the patient's age, time of organ ischemia during the procedure or transplantation of one or both lungs did not affect overall survival after the procedure [87]. In the analysis by Reynaud-Gaubert et al.

(2008), summing up the results of lung transplantation of several French transplantation centers 1-year, 5-year and 10-year overall survival after the procedure were 79.6%, 74.4% and 64.7%, respectively [85]. Baldi et al. (2017) obtained similar results in an analysis encompassing 11 patients with LAM, the probability of surviving one, three and five years after lung transplantation was 90%, 90% and 75%, respectively [86]. There are rare descriptions of patients with a LAM recurrence in the transplanted lung [85, 88].

In recent years a breakthrough has occurred in systemic lymphangioleiomyomatosis treatment, which for many years was resistant to anti-estrogen therapy (removal of ovaries, use of medroxyprogesterone or selective estrogen receptor modulators) whose efficacy had finally not been proven [89]. No efficacy was demonstrated for treating LAM using doxycycline [5] or an aromatase inhibitor — letrozole [90]. On the basis of positive results of clinical trials, sirolimus, a drug from the group of mTOR kinase inhibitors was registered by the Food and Drug Administration (FDA) in May 2015 as the first and currently the only drug for systemic LAM treatment [5]. According to the guidelines of the American Thoracic Society/Japanese Respiratory Society, sirolimus is indicated in patients with LAM, accompanied by a rapidly deteriorating function of the respiratory system or $FEV_1 \leq 70\%$ wn. and in patients with symptomatic pleural lymph exudates, before using invasive treatment methods [5]. Clinical trials concerning the use of mTOR inhibitors (sirolimus, everolimus) in treating lymphangioleiomyomatosis are summarized in Table 1 — without taking retrospective analyses into consideration.

A randomized, multicenter, placebo-controlled, double-blind phase III clinical trial MILES (Multicenter International Lymphangioleiomyomatosis Efficacy And Safety Of Sirolimus), is so far the largest clinical trial concerning the use of sirolimus in LAM [91]. 89 patients were randomly divided into 43 receiving placebo and 46 sirolimus p.o. at an initial dose of 2 mg/d, and then established to maintain the serum concentration of the drug at a level of 5 to 15 ng/mL [91]; this dosage was accepted as a standard in successive trials [84, 92, 93]. After 12 months of treatment in the group receiving sirolimus FEV_1 stabilization was observed ($+1 \pm 2$ mL/month) with worsening FEV_1 at 12 ± 2 mL/month in the placebo group (p < 0.001). In the treatment group improvement was also observed in forced vital capacity (FVC), exercise tolerance, evaluation of the quality of life and a decrease in the serum concentration of VEGF-D in comparison with the placebo group. After finishing taking sirolimus, FEV_1 decreased at the same rate in both groups, which suggests that sirolimus therapy does not stop the progression of the disease when therapy is terminated, but also does not speed up this process [94].

Table 1. Clinical trials concerning the use of mTOR inhibitors mTOR (S-sirolimus, E-everolimus) in LAM

Author, year	Trial type	N	Age-years	TSC %	Drug	Drug concentration/dose	Length	FEV$_1$ changes	Other effects
Bissler et al. 2008 *[105]	Single center, open	25 (18 LAM)	–	66.7	S	10–15 ng/mL	12 months + 12 months observation	At the end of treatment: +118 ± 330 mL vs. wp / At the end of observation: + 62 ± 411 mL vs. wp	↑FVC, ↓AML volume
Dabora et al. 2011 *[106]	Multicenter, open	36 (21 LAM)	34	100	S	9–15 ng/mL	52 weeks	No changes vs. wp	↓AML volume, ↓VEGF–D, ↓number of skin changes
Davies et al. 2011 *[107]	Multicenter, open	16	–	33	S	3–10 ng/mL	24 months	–76 ± 52 mL/r	↓AML volume, ↓FVC, ↓Dlco
McCormack et al. 2011 *[91]	Multicenter, randomized, double blind, placebo control	89	45.4	9	S	5–15 ng/mL	12 months + 12 months observation	Sirolimus: +1 ± 2 mL/month placebo: –12 ± 2 mL/month	↑FVC, ↑QoL, ↓VEGF–D, ↓FRC
Neurohr et al. 2011 [93]	Single center, open/observational	10	42.4	20	S	5–10 ng/mL	12.1 ± 2.81 months	After 6 months: + 345 ± 58 mL	↑ FVC, ↑Dlco, ↑6MWD
Taveira-DaSilva et al. 2011 [84]	Single center, open/observational	19	41	0	S	5–15 ng/mL	2.5 years	Before treatment: –2.8% ± 0.8% wn/r sirolimus: + 1.8% ± 0.5% wn/time of observation	↑FVC, ↑ΔDLco, ↓chylothorax
Bissler et al. 2013*[108]	Multicenter, randomized, double-blind, placebo-control	118 (29 LAM)	31	96	E	10 mg/d	E: average 38 weeks placebo: average 34 weeks	Everolimus: –1% wp placebo: –4% wp	↓AML volume, ↓ number of skin changes
Yao et al. 2014 [109]	Single center, open	38	40.9	13	S	8.0 ± 2.5 ng/mL	Average 40.8 months	Before treatment: –2.3 ± 0.1% wn/r sirolimus: +1 ± 0.3% wn/r	↑DLco
Goldberg et al. 2015* [110]	Multicenter, open	24	42.5	5	E	10 mg/d	26 weeks	+ 114 mL (95% CI: 11–217)	↑ 6MWD, ↓VEGF–D
Takada et al. 2016* [92]	Multicenter, open	63	41.5	3.2	S	5–15 ng/mL	24 months	FEV$_1$ ↓ / FEV$_1$↑ in the group with chylothorax in history	–
Bee et al. 2018* [111]	Prospective, cohort	47	43.6	19	S	1–2 mg/d	Average 35.8 months	In the whole group: +11 mL/r (od +254 do –148 mL/r) / In a group of 21 patients in whom Δ FEV$_1$ before the trial was known: –150 mL/r before vs. +35 mL/r during	–
Taveira-DaSilva et al. 2018 [112]	Single center, open	25	40,6	8	S	5–15 ng/mL	54 ± 19.2 months	Before treatment: –7.4% ± 1.4% wn/r sirolimus: –0.3% ± 0.5% wn/r	↓ AML diameter, ↓VEGF–D, ↓Dlco, ↓chylothorax

BP — blood pressure; DLCO — lung diffusion capacity for carbon dioxide; DN — adverse effects; DDO — lower respiratory tract; DO — respiratory tract; GDO — upper respiratory tract; FEV$_1$ — first second forced vital capacity; FVC — forced vital capacity; OO — peripheral edema; N — number of trial participants; TC — total cholesterol; TG — triglycerides; WBC — white blood count; ZUM — infection of the urinary tract; wn — predicted value; wp — initial value; *trial included in meta-analysis by Gao et al. (2018) [98]

In the MILES trial, VEGF-D serum concentration was indicated as a negative prognostic factor but at the same time as a positive predictive factor for response to sirolimus treatment [95]. A higher VEGF-D level at the beginning of the trial was associated with a better response to treatment in the group receiving sirolimus (improvement in FEV_1 and FVC values), but at the same time a more rapid decrease in the value of these parameters in the placebo group [95]. In the last performed analyses a positive effect of sirolimus on burdensome LAM complications such as lymph exudates to the pleural cavity and recurring pneumothorax was also observed. In the trial by Zhou et al. (2018) in 5 analyzed patients with recurring pneumothorax in spite of pleurodesis, taking sirolimus in doses ensuring the maintenance of the drug concentration in serum at a level 3–10 ng/mL, no recurrences of pneumothorax were observed during the whole time of treatment [96]. However, interruption of therapy or a decrease of the blood concentration of the drug below 3 ng/mL resulted in recurrence of pneumothorax in 2 patients during 2 and 3 year-long observation [96]. In an observational trial by Taveira-DaSilva et al. (2011) planned to evaluate the benefit of using sirolimus in patients with a severe course of LAM and abundant lymph exudates in the pleural cavity in all 12 patients a complete or almost complete reduction of the volume of the accumulating liquid took place which allowed draining of the pleural cavity to be stopped in 2 of them [84]. In two retrospective analyses the effectiveness of sirolimus at a lower dose (target drug concentration in serum below 5 ng/m) in comparison with a standard dose (drug concentration in serum 5–15 ng/mL on the basis of the MILES trial), was evaluated, yielding contradictory results [10, 97]. Ando et al. (2013) showed an improvement in the function of the respiratory system and withdrawal of lymph exudates in patients treated with low doses, to a degree comparable with the results of trials using the higher dose [10]. However, Yoon et al. (2018) showed lower effectiveness of lower doses of sirolimus, whose use at the same time did not lead to a decreased frequency of undesirable adverse effects [97]. In a meta-analysis by Gao et al. (2018), encompassing 7 clinical trials concerning the use of sirolimus in LAM, a significant improvement of FEV_1 and FVC was confirmed in treated patients – the weighted average of differences was: 0.15 l (95% CI: 0.08–0.22, $p < 0.01$, $I_2 = 0\%$) for FEV_1 and 0.22 l (95%: 0.11–0.32, $p < 0.01$, $I_2 = 0\%$) for FVC [98]. However, no improvement of the 6-minute walk test nor the diffusion capacity of the lungs for carbon dioxide was observed. The accumulated frequency of occurrence of adverse events was: 50% for stomatitis, 40% for hyperlipidemia, 23% for headaches, 20% for bone marrow suppression and 19% for diarrhea [98]. Among frequently mentioned adverse effects of sirolimus are also respiratory tract

infections, but sirolimus was not shown to increase their frequency with respect to the population of patients with LAM not using systemic therapy [99].

Sirolimus is currently the only drug whose use in LAM is recommended in the guidelines of the American Thoracic Society/Japanese Respiratory Society, in the light of the lack of convincing evidence for the effectiveness of other substances [5]. Preclinical and clinical trials are also being conducted on autophagy inhibitors [100], statins [101], hydroxychloroquine [102], a synthetic flavonoid — Proxison — an antioxidant normalizing mitochondrial metabolism, which showed synergy with sirolimus in inhibiting LAM cell growth *in vitro* [103], drugs targeting signal pathways connected with the receptor for vascular endothelial growth factor — VEGFR [104] or PD-1 inhibitors, prolonging survival in mouse models of LAM [66].

Treatment and prognosis in E-LAM

Lymphangioleiomyomas, even though they attain large sizes and are often non-resectable [29, 45], in general, have a mild clinical course. In a retrospective analysis by Matsui et al. (2001) among 17 patients with E-LAM, only one died because of an aggressive course of a simultaneously occurring pulmonary LAM form, all the others were alive at the moment of publishing the results with an average observation time of 5.5 years [6]. Radical resection allows long-term control of the disease [16, 24, 39, 40, 42, 50], also when laparoscopic techniques are used [43, 113]. There are reports in the literature about local recurrence after E-LAM resection [37, 114], which can, however, be treated with good effects by a repeated resection [115]. Long survival times were also observed in the case of non-resectable disease; the case of an 11-year old girl has been described in whom a non-radically excised mesenterial lymphangioleiomyoma did not undergo progression in spite of lack of treatment for 10 years [116] and a 47-year old woman with uterine E-LAM and metastases to the lungs and ovary who remained in good overall status for 12 years of observation [117]. Because of the lack of unified methods of lymphangioleiomyoma treatment and their relatively mild clinical course, screening of patients with the pulmonary form of LAM for E-LAM is not recommended, if they do not have any clinical symptoms [7]. If cumbersome clinical symptoms occur such as pain in tumor progression, constipation or edema of the lower extremities, attempts to treat are undertaken similar to the pulmonary form of LAM — by hormone therapy [12] and mTOR inhibitors [118] and radiotherapy for the area of the occupied lymph nodes [119]. Radzikowska et al. (2016) performed a retrospective analysis of the effectiveness of sirolimus in 14 patients with pulmonary LAM (including one with TSC) and lymphangioleiomyoma of the retroperitoneal tract [118]. During 10 months of therapy with sirolimus (at

Table 2. E-LAM cases treated with mTOR inhibitors — sirolimus and everolimus available in the literature

Author	Age	TSC	Pulmonary LAM	Localization	Max. tumor diameter	Symptoms from tumor	Drug: Dose	Best response	Time of observation	Progression
Chen et al. 2009 [88]	23	no	yes	PZ	–	–	Sirolimus; 1 mg/d	–	36 months	No
Possekel et al. 2009 [41]	23	no	no	Numerous in liver, mesentery, wall of small and large intestine	10 cm	A feeling of incomplete elimination, stomach pain	Sirolimus; 1.5 Mg/d	PR	3 months	No
Rosenberg et al. 2013 [121]	41	no	yes	PZ	16.5 cm	Stomach pain, early feeling of satiety	Sirolimus; –	PR	9 months	No
Freitas et al. 2015 [122]	26	no	yes	PZ, abdominal lymph nodes	–	–	Sirolimus; 2 mg/d	PR	12 months	No
	37	no	later	PZ	18 cm	Pain in the vicinity of tumor	Sirolimus; 2 mg/d	PR	6 months	No
Hecimovic et al. 2015 [123]	44	no	yes	PZ	7cm	–	Sirolimus; 2–3 mg/d	PR	10 months	No
	33	no	later	PZ, pelvis	10 cm	–	Sirolimus; 1 mg/d	PR (almost CR)	9 months	No
	34	no	later	PZ	8 cm	Stomach pain, increase in stomach diameter, ascites, hemoptysis	Sirolimus; 2 mg/d	PR	3 months	No
Cabeza et al. 2016 [124]	53	no	yes	Numerous in PZ	6.8 cm	Stomach pain	Sirolimus; 2 mg/d	PR (almost CR)	12 months	No
Harrari et al. 2016 [125]	39	no	no	Numerous in PZ	–	–	Sirolimus; 2 Mg/d	PR	18 months	No
Ito et al. 2016 [126]	39	no	yes	PZ, pelvis	6.2 cm;	Edema of lower extremity	Sirolimus; 1mg/d for 2 weeks then 2 mg/d	PR (almost CR)	18 months	No
Wahid et al. 2016 [127]	37	yes	no	pelvis	15.3 cm	Back ache, fainting	Everolimus; 10mg/d	PR	12 months	No
	45	no	no	PZ	8.5 cm	Feeling of satiety, pain in vicinity of tumor	Everolimus; 10mg/d	CR	18 months	No
Lecuelle et al. 2019 [128]	35	no	yes	PZ	8.5 cm	–	Sirolimus; 5mg/d	CR	30 months	No
Ussavarungsi et al. 2019 [129]	26	no	yes	PZ	26 cm	–	Sirolimus; 1 mg/d	SD	14 months	No

CR — complete response; d — day; max. — maximal; PD— disease progression; PR— partial response; PZ — retroperitoneal space

Table 3. E-LAM cases with the use of hormone therapy available in the literature

Author	Age	TSC	Pulmonary LAM	Localization	Max. tumor diameter	Symptoms from tumor	Drug; Dose	Best response	Time of observation	Progression	Drug; Dose
Klein et al. 1992 [130]	36	No	Yes	Mediastinum lymph nodes, pz and pelvis	Numerous — max 5 cm	None	Oophorectomy + ifn-α2b (for 3 months) + t tamoxifen	3×10^6 j. 3×/ week + 20 mg/d	CR	18 months	No
de Groot et al. 2008 [45]	23	No	Later	Pz	16 Cm	Pain in the vicinity of tumor	Goserelin + tamoxifen	3.6 mg/month + 40 mg/d	PD	–	–
							Goserelin + medroxyprogesterone + thalidomide	3.6 mg/month + 500 mg/d + 50 mg/d	PD	-	-
							Goserelin + ifn-α2b	3.6 mg/m + 3×10^6 j. 3×/week	SD	9 years	No
Yamashita et al. 2011 [131]	30	No	No	Pelvis	-	Recurring stomach pains during menstruation	Leuprorelin	1.88 mg/ month	SD	6 months	No
Szpurek et al. 2014 [117]	47	No	No	Uterus, metastases to ovary and lungs	-	Brak	Tamoxifen	–	SD	5 months	Yes
Basnet et al. 2015 [132]	24	No	No	Pz, pelvis, mesentery	Numerous, approx. 3 Cm	Pain in vicinity of tumor	Medroxyprogesterone	150 mg i.m; 2 doses given with a 3 month interval	PR	6 months	Yes
Yoshizawa et al. 2019 [133]	36	Yes	No	Uterus	-	Stomach pain	Leuprorelin	–	PD	–	–

CR — complete response; d — day; IFN-α2b — interferon α2b; j. — unit; max. — maximum; PD — disease progression; PR — partial response; PZ — retroperitoneal space

a dose of 1−5 mg/d, in order to attain blood concentration of the drug at a level of 5−15 ng/mL), besides improvement of respiratory tract ailments, a significant decrease was observed in the volume of the lesions in comparison to the initial value ($1603.85 \pm 2437.56\,cm^3$ vs. $198.01 \pm 315.43\,cm^3$; $p = 0.00026$), and total withdrawal of lymph from the retroperitoneal space and pleura in 13 of then [118]. In the analysis by Mohammadieh et al. (2013), encompassing 5 patients with lymphangioleiomyoma of the abdominal cavity, the effectiveness of everolimus (at a dose 1−1.5 mg/d; in two divided doses) was evaluated [120]. After 6 months of therapy in 4 out of 5 patients a partial or complete response was observed and withdrawal of the ascites [120]. The descriptions in the literature of cases treated with mTOR inhibitors and hormone therapy in E-LAM are presented in Table 2 and Table 3, respectively. It is worth stressing that among the cases presented in Table 2 (mTOR inhibitors), disease progression did not occur in any of the cases during the administration of a drug from this group.

Summary

Lymphangioleiomyomatosis is a member of the PEComa (perivascular epithelioid cell tumors) family [2]. In patients with the pulmonary form of LAM, LAM foci have been described in the uterus, adnexa or broad ligament of the uterus and there is the frequent occupation of lymph nodes in the extraperitoneal space [21]. Lymphangioleiomyoma in computer tomography, in general, has the form of a well-separated solid-cystic lesion, with walls of different thickness and numerous septae [26, 27, 46]. Solid or cystic character is less common [27]. The lesion is generally well separated, but a few lymphangioleiomyomas with infiltrating growth are also observed [18]. Sirolimus is currently the only drug whose use in LAM is recommended by international recommendations [5]. The randomized, multicenter, placebo-controlled, double-blind clinical phase III MILES trial (Multicenter International Lymphangioleiomyomatosis Efficacy And Safety Of Sirolimus), is so far the largest clinical trial concerning the use of sirolimus in LAM [91]. Preclinical and clinical trials also encompass autophagy inhibitors [100], statins [101], hydroxychloroquine [102], anti-VEGFR drugs [104] and PD-1 inhibitors [66].

Conflict of interest

The authors report no conflicts of interest.

References

1. Klimczak A, Pękul M, Wiater K, et al. PEComa — grupa rzadkich nowotworów pochodzenia mezenchymalnego. NOWOTWORY Journal of Oncology. 2011; 61(1): 52–56.

2. Martignoni G, Pea M, Reghellin D, et al. Molecular pathology of lymphangioleiomyomatosis and other perivascular epithelioid cell tumors. Arch Pathol Lab Med. 2010; 134(1): 33–40, doi: 10.1043/2008-0542-RAR1.1, indexed in Pubmed: 20073603.

3. Thway K, Fisher C. PEComa: morphology and genetics of a complex tumor family. Ann Diagn Pathol. 2015; 19(5): 359–368, doi: 10.1016/j.anndiagpath.2015.06.003, indexed in Pubmed: 26144278.

4. Słowińska M, Jóźwiak S, Peron A, et al. Early diagnosis of tuberous sclerosis complex: a race against time. How to make the diagnosis before seizures? Orphanet J Rare Dis. 2018; 13(1): 25, doi: 10.1186/s13023-018-0764-z, indexed in Pubmed: 29378663.

5. McCormack F, Gupta N, Finlay G, et al. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management. American Journal of Respiratory and Critical Care Medicine. 2016; 194(6): 748–761, doi: 10.1164/rccm.201607-1384st.

6. Matsui K, Tatsuguchi A, Valencia J, et al. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. Hum Pathol. 2000; 31(10): 1242–1248, doi: 10.1053/hupa.2000.18500, indexed in Pubmed: 11070117.

7. Johnson SR, Cordier JF, Lazor R, et al. Review Panel of the ERS LAM Task Force. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J. 2010; 35(1): 14–26, doi: 10.1183/09031936.00076209, indexed in Pubmed: 20044458.

8. Muzykewicz DA, Sharma A, Muse V, et al. TSC1 and TSC2 mutations in patients with lymphangioleiomyomatosis and tuberous sclerosis complex. J Med Genet. 2009; 46(7): 465–468, doi: 10.1136/jmg.2008.065342, indexed in Pubmed: 19419980.

9. Freitas CSG, Baldi BG, Jardim C, et al. Pulmonary hypertension in lymphangioleiomyomatosis: prevalence, severity and the role of carbon monoxide diffusion capacity as a screening method. Orphanet J Rare Dis. 2017; 12(1): 74, doi: 10.1186/s13023-017-0626-0, indexed in Pubmed: 28427470.

10. Ando K, Kurihara M, Kataoka H, et al. Efficacy and safety of low-dose sirolimus for treatment of lymphangioleiomyomatosis. Respir Investig. 2013; 51(3): 175–183, doi: 10.1016/j.resinv.2013.03.002, indexed in Pubmed: 23978644.

11. Chu SC, Horiba K, Usuki J, et al. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest. 1999; 115(4): 1041–1052, doi: 10.1378/chest.115.4.1041, indexed in Pubmed: 10208206.

12. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. Thorax. 2000; 55(12): 1052–1057, doi: 10.1136/thorax.55.12.1052, indexed in Pubmed: 11083892.

13. Kebria M, Black D, Borelli C, et al. Primary retroperitoneal lymphangioleiomyomatosis in a postmenopausal woman: a case report and review of the literature. Int J Gynecol Cancer. 2007; 17(2): 528–532, doi: 10.1111/j.1525-1438.2007.00785.x, indexed in Pubmed: 17362325.

14. Liu Yi, Guo Z, Zhao C, et al. Lymphangioleiomyomatosis: a case report and review of diagnosis and treatment. Onco Targets Ther. 2018; 11: 5339–5347, doi: 10.2147/OTT.S161360, indexed in Pubmed: 30214240.

15. Takia L, Jat KR, Mandal A, et al. Lymphangioleiomyomatosis (LAM) presenting as recurrent pneumothorax in an infant with tuberous sclerosis: treated successfully with sirolimus. BMJ Case Rep. 2018; 2018, doi: 10.1136/bcr-2018-226244, indexed in Pubmed: 30413450.

16. Fiore MG, Sanguedolce F, Lolli I, et al. Abdominal lymphangioleiomyomatosis in a man with Klinefelter syndrome: the first reported case. Ann Diagn Pathol. 2005; 9(2): 96–100, doi: 10.1016/j.anndiagpath.2004.12.007, indexed in Pubmed: 15806517.

17. Zhang C, Chen X, Wen T, et al. Computed tomography lymphangiography findings in 27 cases of lymphangioleiomyomatosis. Acta Radiol. 2017; 58(11): 1342–1348, doi: 10.1177/0284185116688381, indexed in Pubmed: 28132530.

18. Avila NA, Bechtle J, Dwyer AJ, et al. Lymphangioleiomyomatosis: CT of diurnal variation of lymphangioleiomyomas. Radiology. 2001; 221(2): 415–421, doi: 10.1148/radiol.2212001448, indexed in Pubmed: 11687685.

19. Avila NA, Kelly JA, Chu SC, et al. Lymphangioleiomyomatosis: abdominopelvic CT and US findings. Radiology. 2000; 216(1): 147–153, doi: 10.1148/radiology.216.1.r00jl42147, indexed in Pubmed: 10887241.

20. Torres VE, Björnsson J, King BF, et al. Extrapulmonary lymphangioleiomyomatosis and lymphangiomatous cysts in tuberous sclerosis complex. Mayo Clin Proc. 1995; 70(7): 641–648, doi: 10.4065/70.7.641, indexed in Pubmed: 7791386.

21. Hayashi T, Kumasaka T, Mitani K, et al. Prevalence of uterine and adnexal involvement in pulmonary lymphangioleiomyomatosis: a clinicopathologic study of 10 patients. Am J Surg Pathol. 2011; 35(12): 1776–1785, doi: 10.1097/PAS.0b013e318235edbd, indexed in Pubmed: 22020043.

22. Kuno I, Yoshida H, Shimizu H, et al. Incidental lymphangioleiomyomatosis in the lymph nodes of gynecologic surgical specimens. Eur J Obstet Gynecol Reprod Biol. 2018; 231: 93–97, doi: 10.1016/j.ejogrb.2018.10.027, indexed in Pubmed: 30336310.

23. Schoolmeester JK, Park KJ. Incidental nodal lymphangioleiomyomatosis is not a harbinger of pulmonary lymphangioleiomyomatosis: a study of 19 cases with evaluation of diagnostic immunohistochemistry. Am J Surg Pathol. 2015; 39(10): 1404–1410, doi: 10.1097/PAS.0000000000000470, indexed in Pubmed: 26135558.

24. Ando H, Ogawa M, Watanabe Y, et al. Lymphangioleiomyoma of the uterus and pelvic lymph nodes: a report of 3 cases, including the potentially earliest manifestation of extrapulmonary lymphangioleiomyomatosis. Int J Gynecol Pathol. 2020; 39(3): 227–232, doi: 10.1097/PGP.0000000000000589, indexed in Pubmed: 30789500.

25. Rabban JT, Firetag B, Sangoi AR, et al. Incidental pelvic and para-aortic lymph node lymphangioleiomyomatosis detected during surgical staging of pelvic cancer in women without symptomatic pulmonary lymphangioleiomyomatosis or tuberous sclerosis complex. Am J Surg Pathol. 2015; 39(8): 1015–1025, doi: 10.1097/PAS.0000000000000416, indexed in Pubmed: 25786086.

26. Abdelkader A, Lam CA, Shahir KS, et al. Retroperitoneal lymphangioleiomyoma with lymph node involvement: A pathologic-radiologic correlation of a rare form of myomelanocytic tumor. Ann Diagn Pathol. 2017; 27: 69–73, doi: 10.1016/j.anndiagpath.2017.01.008, indexed in Pubmed: 28325364.

27. Avila NA, Dwyer AJ, Murphy-Johnson DV, et al. Sonography of lymphangioleiomyoma in lymphangioleiomyomatosis: demonstration of diurnal variation in lesion size. AJR Am J Roentgenol. 2005; 184(2): 459–464, doi: 10.2214/ajr.184.2.01840459, indexed in Pubmed: 15671364.

28. Ernst JC, Sohaey R, Cary JM. Pelvic lymphangioleiomyomatosis. Atypical precursor to pulmonary disease. Chest. 1994; 106(4): 1267–1269, doi: 10.1378/chest.106.4.1267, indexed in Pubmed: 7924509.

29. Kim HS, Park MI, Suh KS. Lymphangiomyomatosis arising in the pelvic cavity: a case report. J Korean Med Sci. 2005; 20(5): 904–907, doi: 10.3346/jkms.2005.20.5.904, indexed in Pubmed: 16224174.

30. Lam B, Ooi GC, Wong MP, et al. Extrapulmonary presentation of asymptomatic pulmonary lymphangioleiomyomatosis. Respirology. 2003; 8(4): 544–547, doi: 10.1046/j.1440-1843.2003.00498.x, indexed in Pubmed: 14708559.

31. Lu HC, Wang J, Tsang YM, et al. Lymphangioleiomyomatosis initially presenting with abdominal pain: a case report. Clin Imaging. 2003; 27(3): 166–170, doi: 10.1016/s0899-7071(01)00349-7, indexed in Pubmed: 12727053.

32. Bahmer T, Watz H, Waschki B, et al. Reduced physical activity in lymphangioleiomyomatosis compared with COPD and healthy controls: disease-specific impact and clinical correlates. Thorax. 2016; 71(7): 662–663, doi: 10.1136/thoraxjnl-2015-207852, indexed in Pubmed: 26968971.

33. Johnson SR, Whale CI, Hubbard RB, et al. Survival and disease progression in UK patients with lymphangioleiomyomatosis. Thorax. 2004; 59(9): 800–803, doi: 10.1136/thx.2004.023283, indexed in Pubmed: 15333859.

34. Matsui K, Beasley MB, Nelson WK, et al. Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. Am J Surg Pathol. 2001; 25(4): 479–484, doi: 10.1097/00000478-200104000-00007, indexed in Pubmed: 11257622.

35. Lama A, Ferreiro L, Golpe A, et al. Characteristics of patients with lymphangioleiomyomatosis and pleural effusion: a systematic review. Respiration. 2016; 91(3): 256–264, doi: 10.1159/000444264, indexed in Pubmed: 26938102.

36. Pontes M, Barbosa C, Coelho ML, et al. Probable initial pulmonary lymphangioleiomyomatosis and mediastinal lymphangioleiomyoma. Rev Port Pneumol. 2014; 20(2): 101–106, doi: 10.1016/j.rppneu.2013.06.007, indexed in Pubmed: 24268918.

37. Derweduwen AM, Verbeken E, Stas M, et al. Extrapulmonary lymphangioleiomyomatosis: a wolf in sheep's clothing. Thorax. 2013; 68(1): 111–113, doi: 10.1136/thoraxjnl-2012-201973, indexed in Pubmed: 22863757.

38. Kamitani T, Yabuuchi H, Soeda H, et al. A case of lymphangioleiomyomatosis affecting the supraclavicular lymph nodes. J Comput Assist Tomogr. 2006; 30(2): 279–282, doi: 10.1097/00004728-200603000-00022, indexed in Pubmed: 16628048.

39. Fu W, Li Y, Li H, et al. Solitary extrapulmonary lymphangioleiomyomatosis of the liver: A case report and literature review. Exp Ther Med. 2016; 12(3): 1499–1502, doi: 10.3892/etm.2016.3502, indexed in Pubmed: 27588070.

40. Goh SG, Ho JM, Chuah KL, et al. Leiomyomatosis-like lymphangioleiomyomatosis of the colon in a female with tuberous sclerosis. Mod Pathol. 2001; 14(11): 1141–1146, doi: 10.1038/modpathol.3880449, indexed in Pubmed: 11706076.

41. Possekel AK, Katenkamp D, Brambs HJ, et al. Lymphangioleiomyomatosis: solitary abdominal manifestation (2009: 9b). Eur Radiol. 2009; 19(12): 3015–3018, doi: 10.1007/s00330-008-1275-4, indexed in Pubmed: 19921526.

42. Singh M, Saroha V, Wadhwa R, et al. Solitary lymphangioleiomyoma of pancreas mimicking pancreatic pseudocyst — a case report. J Gastrointest Cancer. 2012; 43(2): 336–339, doi: 10.1007/s12029-010-9183-7, indexed in Pubmed: 20602180.

43. Jun Y, Jang S, Han H, et al. Extrapulmonary lymphangioleiomyoma presenting as a mesenteric cystic mass. Basic and Applied Pathology. 2011; 4(2): 63–65, doi: 10.1111/j.1755-9294.2011.01097.x.

44. Ascher KB. Glassberg Csete MK. Lymhangioleiomyomatosis (LAM) of the Uterus: Risk of Pulmonary LAM? D32 ILD: CASE REPORTS II. American Thoracic Society International Conference Abstracts: American Thoracic Society. 2018: A6507–A.

45. de Groot JWB, Vecht J, van den Bergen HA, et al. Extrapulmonary lymphangioleiomyomatosis: an unusual cause of biliary tract obstruction. Neth J Med. 2008; 66(1): 31–34, indexed in Pubmed: 18219066.

46. Atallah D, Checrallah A, Rouzier R, et al. Retroperitoneal lymphangioleiomyoma mimicking ovarian tumor emerging after tamoxifen therapy. Obstet Gynecol. 2006; 108(3 Pt 2): 762–764, doi: 10.1097/01.AOG.0000192548.92503.ab, indexed in Pubmed: 17018494.

47. Favoreel N, Van Meerbeeck SF, Gosselin R. Extrapulmonary manifestation of lymphangioleiomyomatosis. JBR-BTR. 2015; 98(1): 53, doi: 10.5334/jbr-btr.759, indexed in Pubmed: 26223072.

48. Grant L, Chipwete S, Soo Hoo S, et al. Extrapulmonary uterine lymphangioleiomyomatosis (LAM) and dysfunctional uterine bleeding: the first presentation of LAM in a tuberous sclerosis complex patient. BMJ Case Rep. 2019; 12(2), doi: 10.1136/bcr-2018-226358, indexed in Pubmed: 30804158.

49. Han JM, Lee KH, Kim SJ, et al. A case of lymphangioleiomyomatosis originated in the pelvic cavity. J Gynecol Oncol. 2008; 19(3): 195–198, doi: 10.3802/jgo.2008.19.3.195, indexed in Pubmed: 19471572.

50. Jaiswal VR, Baird J, Fleming J, et al. Localized retroperitoneal lymphangioleiomyomatosis mimicking malignancy. A case report and review of the literature. Arch Pathol Lab Med. 2003; 127(7): 879–882, indexed in Pubmed: 12823048.

51. Gray S, Carrington C, Cornog J. Lymphangiomyomatosis: Report of a case with ureteral involvement and chyluria. Cancer. 1975; 35(2): 490–498.

52. Longacre TA, Hendrickson MR, Kapp DS, et al. Lymphangioleiomyomatosis of the uterus simulating high-stage endometrial stromal sarcoma. Gynecol Oncol. 1996; 63(3): 404–410, doi: 10.1006/gyno.1996.0344, indexed in Pubmed: 8946880.

53. Sandrini A, Silverstone E, Yates DH. Menstrual cycle variation of retroperitoneal lymphangioleiomyomas in lymphangioleiomyomatosis. Intern Med J. 2011; 41(12): 832–835, doi: 10.1111/j.1445-5994.2011.02593.x, indexed in Pubmed: 22151950.

54. Gupta N, Finlay GA, Kotloff RM, et al. ATS Assembly on Clinical Problems. Lymphangioleiomyomatosis Diagnosis and Management: High-Resolution Chest Computed Tomography, Transbronchial Lung Biopsy, and Pleural Disease Management. An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2017; 196(10): 1337–1348, doi: 10.1164/rccm.201709-1965ST, indexed in Pubmed: 29140122.

55. Koba T, Arai T, Kitaichi M, et al. Efficacy and safety of transbronchial lung biopsy for the diagnosis of lymphangioleiomyomatosis: A report of 24 consecutive patients. Respirology. 2018; 23(3): 331–338, doi: 10.1111/resp.13190, indexed in Pubmed: 28960664.

56. Grzegorek I, Lenze D, Chabowski M, et al. Immunohistochemical evaluation of pulmonary lymphangioleiomyomatosis. Anticancer Res. 2015; 35(6): 3353–3360, indexed in Pubmed: 26026095.

57. Matsui K, Tatsuguchi A, Valencia J, et al. Lymphangioleiomyomatosis (LAM): a review of clinical and morphological features. J Nippon Med Sch. 2000; 67(5): 311–329, doi: 10.1272/jnms.67.311, indexed in Pubmed: 11031360.

58. Taveira-DaSilva AM, Pacheco-Rodriguez G, Moss J. The natural history of lymphangioleiomyomatosis: markers of severity, rate of progression and prognosis. Lymphat Res Biol. 2010; 8(1): 9–19, doi: 10.1089/lrb.2009.0024, indexed in Pubmed: 20235883.

59. Zhe X, Schuger L. Combined smooth muscle and melanocytic differentiation in lymphangioleiomyomatosis. J Histochem Cytochem. 2004; 52(12): 1537–1542, doi: 10.1369/jhc.4A6438.2004, indexed in Pubmed: 15557209.

60. Zhang X, Travis WD. Pulmonary lymphangioleiomyomatosis. Arch Pathol Lab Med. 2010; 134(12): 1823–1828, doi: 10.1043/2009-0576-RS.1, indexed in Pubmed: 21128782.

61. Davis JM, Hyjek E, Husain AN, et al. Lymphatic endothelial differentiation in pulmonary lymphangioleiomyomatosis cells. J Histochem Cytochem. 2013; 61(8): 580–590, doi: 10.1369/0022155413489311, indexed in Pubmed: 23609227.

62. Gao L, Yue MM, Davis J, et al. In pulmonary lymphangioleiomyomatosis expression of progesterone receptor is frequently higher than that of estrogen receptor. Virchows Arch. 2014; 464(4): 495–503, doi: 10.1007/s00428-014-1559-9, indexed in Pubmed: 24570392.

63. Flavin R, Cook J, Fiorentino M, et al. β-Catenin Is a Useful Adjunct Immunohistochemical Marker for the Diagnosis of Pulmonary Lymphangioleiomyomatosis. American Journal of Clinical Pathology. 2011; 135(5): 776–782, doi: 10.1309/ajcppc9ex1zhmrma.

64. Dongre A, Clements D, Fisher AJ, et al. Cathepsin k in lymphangioleiomyomatosis: LAM cell-fibroblast interactions enhance protease activity by extracellular acidification. Am J Pathol. 2017; 187(8): 1750–1762, doi: 10.1016/j.ajpath.2017.04.014, indexed in Pubmed: 28623674.

65. Kobayashi K, Miki Y, Saito R, et al. Roles of human epidermal growth factor receptor family in pulmonary lymphangioleiomyomatosis. Hum Pathol. 2018; 81: 121–130, doi: 10.1016/j.humpath.2018.07.002, indexed in Pubmed: 30030119.

66. Maisel K, Merrilees MJ, Atochina-Vasserman EN, et al. Immune checkpoint ligand PD-L1 is upregulated in pulmonary lymphangioleiomyomatosis. Am J Respir Cell Mol Biol. 2018; 59(6): 723–732, doi: 10.1165/rcmb.2018-0123OC, indexed in Pubmed: 30095976.

67. Uehara K, Kawakami F, Hirose T, et al. Clinicopathological analysis of clinically occult extrapulmonary lymphangioleiomyomatosis in intra-pelvic and para-aortic lymph nodes associated with pelvic malignant tumors: A study of nine patients. Pathol Int. 2019; 69(1): 29–36, doi: 10.1111/pin.12749, indexed in Pubmed: 30688413.

68. Smolarek TA, Wessner LL, McCormack FX, et al. Evidence that lymphangiomyomatosis is caused by TSC2 mutations: chromosome 16p13 loss of heterozygosity in angiomyolipomas and lymph nodes from women with lymphangiomyomatosis. Am J Hum Genet. 1998; 62(4): 810–815, doi: 10.1086/301804, indexed in Pubmed: 9529362.

69. Kristof AS, You Z, Han YS, et al. mTOR signaling in lymphangioleiomyomatosis. Lymphat Res Biol. 2010; 8(1): 33–42, doi: 10.1089/lrb.2009.0019, indexed in Pubmed: 20235885.

70. Huang J, Manning BD. The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. Biochem J. 2008; 412(2): 179–190, doi: 10.1042/BJ20080281, indexed in Pubmed: 18466115.

71. Strizheva GD, Carsillo T, Kruger WD, et al. The spectrum of mutations in TSC1 and TSC2 in women with tuberous sclerosis and lymphangiomyomatosis. Am J Respir Crit Care Med. 2001; 163(1): 253–258, doi: 10.1164/ajrccm.163.1.2005004, indexed in Pubmed: 11208653.

72. Murphy SJ, Terra SB, Harris FR, et al. Genomic rearrangements in sporadic lymphangioleiomyomatosis: an evolving genetic story. Mod Pathol. 2017; 30(9): 1223–1233, doi: 10.1038/modpathol.2017.52, indexed in Pubmed: 28643793.

73. Badri K, Gao L, Hyjek E, et al. Exonic mutations ofTSC2/TSC1Are common but not seen in all sporadic pulmonary lymphangioleiomyomatosis. American Journal of Respiratory and Critical Care Medicine. 2013; 187(6): 663–665, doi: 10.1164/ajrccm.187.6.663.

74. Fujita A, Ando K, Kobayashi E, et al. Detection of low-prevalence somatic TSC2 mutations in sporadic pulmonary lymphangioleiomyomatosis tissues by deep sequencing. Hum Genet. 2016; 135(1): 61–68, doi: 10.1007/s00439-015-1611-0, indexed in Pubmed: 26563443.

75. Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. Am J Respir Crit Care Med. 1999; 160(2): 628–633, doi: 10.1164/ajrccm.160.2.9901027, indexed in Pubmed: 10430739.

76. Gupta N, Lee HS, Ryu JH, et al. NHLBI LAM Registry Group. The NHLBI LAM registry: prognostic physiologic and radiologic biomarkers emerge from a 15-year prospective longitudinal analysis. Chest. 2019; 155(2): 288–296, doi: 10.1016/j.chest.2018.06.016, indexed in Pubmed: 29940164.

77. Amaral AF, de Oliveira MR, Dias OM, et al. Tuberous Sclerosis, Lymphangioleiomyomatosis and Angiomyolipoma Study Group, Universidade de Sao Paulo, Brazil. Concentration of Serum Vascular Endothelial Growth Factor (VEGF-D) and Its Correlation with Functional and Clinical Parameters in Patients with Lymphangioleiomyomatosis from a Brazilian Reference Center. Lung. 2019; 197(2): 139–146, doi: 10.1007/s00408-018-00191-3, indexed in Pubmed: 30623243.

78. Radzikowska E, Jaguś P, Sobiecka M, et al. Correlation of serum vascular endothelial growth factor-D concentration with clinical presentation and course of lymphangioleiomyomatosis. Respir Med. 2015; 109(11): 1469–1475, doi: 10.1016/j.rmed.2015.09.005, indexed in Pubmed: 26386638.

79. Miller S, Coveney C, Johnson J, et al. The vitamin D binding protein axis modifies disease severity in lymphangioleiomyomatosis. Eur Respir J. 2018; 52(5), doi: 10.1183/13993003.00951-2018, indexed in Pubmed: 30093573.

80. Liu HJ, Henske EP. Vitamin D binding protein: a new biomarker of disease severity in lymphangioleiomyomatosis. Eur Respir J. 2018; 52(5), doi: 10.1183/13993003.01886-2018, indexed in Pubmed: 30385604.

81. Lamattina AM, Taveira-Dasilva A, Goldberg HJ, et al. Circulating Biomarkers From the Phase 1 Trial of Sirolimus and Autophagy Inhibition for Patients With Lymphangioleiomyomatosis. Chest. 2018; 154(5): 1070–1082, doi: 10.1016/j.chest.2018.08.1029, indexed in Pubmed: 30144422.

82. Araujo MS, Baldi BG, Freitas CSG, et al. Pulmonary rehabilitation in lymphangioleiomyomatosis: a controlled clinical trial. Eur Respir J. 2016; 47(5): 1452–1460, doi: 10.1183/13993003.01683-2015, indexed in Pubmed: 26917604.

83. Gonano C, Pasquier J, Daccord C, et al. Air travel and incidence of pneumothorax in lymphangioleiomyomatosis. Orphanet J Rare Dis. 2018; 13(1): 222, doi: 10.1186/s13023-018-0964-6, indexed in Pubmed: 30545392.

84. Taveira-DaSilva AM, Hathaway O, Stylianou M, et al. Changes in lung function and chylous effusions in patients with lymphangioleiomyomatosis treated with sirolimus. Ann Intern Med. 2011; 154(12): 797–805, doi: 10.7326/0003-4819-154-12-201106210-00007, indexed in Pubmed: 21690594.

85. Reynaud-Gaubert M, Mornex JF, Mal H, et al. Lung transplantation for lymphangioleiomyomatosis: the French experience. Transplantation. 2008; 86(4): 515–520, doi: 10.1097/TP.0b013e31817c15df, indexed in Pubmed: 18724219.

86. Baldi BG, Samano MN, Campos SV, et al. Experience of lung transplantation in patients with lymphangioleiomyomatosis at a brazilian reference centre. Lung. 2017; 195(6): 699–705, doi: 10.1007/s00408-017-0045-y, indexed in Pubmed: 28823029.

87. Khawar MU, Yazdani D, Zhu Z, et al. Clinical outcomes and survival following lung transplantation in patients with lymphangioleiomyomatosis. J Heart Lung Transplant. 2019; 38(9): 949–955, doi: 10.1016/j.healun.2019.06.015, indexed in Pubmed: 31303421.

88. Chen F, Omasa M, Kondo N, et al. Sirolimus treatment for recurrent lymphangioleiomyomatosis after lung transplantation. Ann Thorac Surg. 2009; 87(1): e6–e7, doi: 10.1016/j.athoracsur.2008.07.107, indexed in Pubmed: 19101258.

89. Sobiecka M. Limfangioleiomiomatoza. Postępy Nauk Medycznych. 2011; 4: 295–302.

90. Lu C, Lee HS, Pappas GP, et al. Trial of an Aromatase Inhibitor in Lymphangioleiomyomatosis Group. A Phase II Clinical Trial of an Aromatase Inhibitor for Postmenopausal Women with Lymphangioleiomyomatosis. Ann Am Thorac Soc. 2017; 14(6): 919–928, doi: 10.1513/AnnalsATS.201610-824OC, indexed in Pubmed: 28570161.

91. McCormack FX, Inoue Y, Moss J, et al. National Institutes of Health Rare Lung Diseases Consortium, MILES Trial Group. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011; 364(17): 1595–1606, doi: 10.1056/NEJMoa1100391, indexed in Pubmed: 21410393.

92. Takada T, Mikami A, Kitamura N, et al. Efficacy and safety of long-term sirolimus therapy for Asian patients with lymphangioleiomyomatosis. Ann Am Thorac Soc. 2016; 13(11): 1912–1922, doi: 10.1513/AnnalsATS.201605-335OC, indexed in Pubmed: 27513278.

93. Neurohr C, Hoffmann AL, Huppmann P, et al. Is sirolimus a therapeutic option for patients with progressive pulmonary lymphangioleiomyomatosis? Respir Res. 2011; 12: 66, doi: 10.1186/1465-9921-12-66, indexed in Pubmed: 21600034.

94. Kida Y, Burger CD. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011; 365(3): 271–272, doi: 10.1056/NEJMc1106358, indexed in Pubmed: 21774717.

95. Young L, Lee HS, Inoue Y, et al. MILES Trial Group. Serum VEGF-D a concentration as a biomarker of lymphangioleiomyomatosis severity and treatment response: a prospective analysis of the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial. Lancet Respir Med. 2013; 1(6): 445–452, doi: 10.1016/S2213-2600(13)70090-0, indexed in Pubmed: 24159565.

96. Zhou Li, Ouyang R, Luo H, et al. Efficacy of sirolimus for the prevention of recurrent pneumothorax in patients with lymphangioleiomyomatosis: a case series. Orphanet J Rare Dis. 2018; 13(1), doi: 10.1186/s13023-018-0915-2.

97. Yoon HY, Hwang JJ, Kim DS, et al. Efficacy and safety of low-dose sirolimus in lymphangioleiomyomatosis. Orphanet J Rare Dis. 2018; 13(1): 204, doi: 10.1186/s13023-018-0946-8, indexed in Pubmed: 30428897.

98. Gao N, Zhang T, Ji J, et al. The efficacy and adverse events of mTOR inhibitors in lymphangioleiomyomatosis: systematic review

and meta-analysis. Orphanet J Rare Dis. 2018; 13(1): 134, doi: 10.1186/s13023-018-0874-7, indexed in Pubmed: 30107845.

99. Courtwright AM, Goldberg HJ, Henske EP, et al. The effect of mTOR inhibitors on respiratory infections in lymphangioleiomyomatosis. Eur Respir Rev. 2017; 26(143), doi: 10.1183/16000617.0004-2016, indexed in Pubmed: 28096282.

100. Parkhitko A, Myachina F, Morrison TA, et al. Tumorigenesis in tuberous sclerosis complex is autophagy and p62/sequestosome 1 (SQSTM1)-dependent. Proc Natl Acad Sci U S A. 2011; 108(30): 12455–12460, doi: 10.1073/pnas.1104361108, indexed in Pubmed: 21746920.

101. Taveira-DaSilva AM, Jones AM, Julien-Williams PA, et al. Retrospective review of combined sirolimus and simvastatin therapy in lymphangioleiomyomatosis. Chest. 2015; 147(1): 180–187, doi: 10.1378/chest.14-0758, indexed in Pubmed: 25167325.

102. El-Chemaly S, Taveira-Dasilva A, Goldberg HJ, et al. Sirolimus and Autophagy Inhibition in Lymphangioleiomyomatosis: Results of a Phase I Clinical Trial. Chest. 2017; 151(6): 1302–1310, doi: 10.1016/j.chest.2017.01.033, indexed in Pubmed: 28192114.

103. Abdelwahab EMM, Pal S, Kvell K, et al. Mitochondrial dysfunction is a key determinant of the rare disease lymphangioleiomyomatosis and provides a novel therapeutic target. Oncogene. 2019; 38(16): 3093–3101, doi: 10.1038/s41388-018-0625-1, indexed in Pubmed: 30573768.

104. Atochina-Vasserman EN, Abramova E, James ML, et al. Pharmacological targeting of VEGFR signaling with axitinib inhibits Tsc2-null lesion growth in the mouse model of lymphangioleiomyomatosis. Am J Physiol Lung Cell Mol Physiol. 2015; 309(12): L1447–L1454, doi: 10.1152/ajplung.00262.2015, indexed in Pubmed: 26432869.

105. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med. 2008; 358(2): 140–151, doi: 10.1056/NEJMoa063564, indexed in Pubmed: 18184959.

106. Dabora SL, Franz DN, Ashwal S, et al. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: kidney angiomyolipomas and other tumors regress and VEGF-D levels decrease. PLoS One. 2011; 6(9): e23379, doi: 10.1371/journal.pone.0023379, indexed in Pubmed: 21915260.

107. Davies DM, de Vries PJ, Johnson SR, et al. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangioleiomyomatosis: a phase 2 trial. Clin Cancer Res. 2011; 17(12): 4071–4081, doi: 10.1158/1078-0432.CCR-11-0445, indexed in Pubmed: 21525172.

108. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2013; 381(9869): 817–824, doi: 10.1016/S0140-6736(12)61767-X, indexed in Pubmed: 23312829.

109. Yao J, Taveira-DaSilva AM, Jones AM, et al. Sustained effects of sirolimus on lung function and cystic lung lesions in lymphangioleiomyomatosis. Am J Respir Crit Care Med. 2014; 190(11): 1273–1282, doi: 10.1164/rccm.201405-0918OC, indexed in Pubmed: 25329516.

110. Goldberg HJ, Harari S, Cottin V, et al. Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study. Eur Respir J. 2015; 46(3): 783–794, doi: 10.1183/09031936.00210714, indexed in Pubmed: 26113676.

111. Bee J, Fuller S, Miller S, et al. Lung function response and side effects to rapamycin for lymphangioleiomyomatosis: a prospective national cohort study. Thorax. 2018; 73(4): 369–375, doi: 10.1136/thoraxjnl-2017-210872, indexed in Pubmed: 28993539.

112. Taveira-DaSilva AM, Jones AM, Julien-Williams P, et al. Long-Term effect of sirolimus on serum vascular endothelial growth factor d levels in patients with lymphangioleiomyomatosis. Chest. 2018; 153(1): 124–132, doi: 10.1016/j.chest.2017.05.012, indexed in Pubmed: 28533049.

113. Ding Y, Yan S, Tian Y, et al. Primary abdominal lymphangioleiomyomatosis: report of a case. World J Surg Oncol. 2015; 13: 93, doi: 10.1186/s12957-015-0512-y, indexed in Pubmed: 25888993.

114. Słodkowska J, Patera J, Breborowicz J, et al. Extrapulmonary lymphangioleiomyomatosis presented as the asymptomatic retroperitoneal tumours — two cases report. Pol J Pathol. 2006; 57(4): 205–207, indexed in Pubmed: 17285764.

115. Bhattacharyya A, Balogh K. Retroperitoneal lymphangioleiomyomatosis a 36-year benign course in a postmenopausal woman. Cancer. 1985;

56(5): 1144–1146, doi: 10.1002/1097-0142(19850901)56:5<1144::aid-cncr2820560531>3.0.co;2-f.

116. Mboyo A, Flurin V, Foulet-Roge A, et al. Conservative treatment of a mesenteric lymphangiomyomatosis in an 11-year-old girl with a long follow-up period. J Pediatr Surg. 2004; 39(10): 1586–1589, doi: 10.1016/j.jpedsurg.2004.06.034, indexed in Pubmed: 15486914.

117. Szpurek D, Szubert S, Zielinski P, et al. Malignant presentation of uterine lymphangioleiomyomatosis. Taiwan J Obstet Gynecol. 2015; 54(5): 603–607, doi: 10.1016/j.tjog.2015.08.015, indexed in Pubmed: 26522119.

118. Radzikowska E, Przerwa KB, SkroAska P. Lymphangioma in patients with pulmonary lymphangioleiomyomatosis: results of sirolimus treatment. Journal of Cancer Science & Therapy. 2016; 8(9), doi: 10.4172/1948-5956.1000419.

119. Tümay LV, Güner OS, Zorluoğlu A. An extrapulmonary manifestation of lymphangioleiomyomatosis: A rare case report. Int J Surg Case Rep. 2017; 41: 315–318, doi: 10.1016/j.ijscr.2017.10.057, indexed in Pubmed: 29132117.

120. Mohammadieh AM, Bowler SD, Silverstone EJ, et al. Everolimus treatment of abdominal lymphangioleiomyoma in five women with sporadic lymphangioleiomyomatosis. Med J Aust. 2013; 199(2): 121–123, doi: 10.5694/mja12.11567, indexed in Pubmed: 23879512.

121. Rozenberg D, Thenganatt J. Dramatic response to sirolimus in lymphangioleiomyomatosis. Can Respir J. 2013; 20(6): 413–414, doi: 10.1155/2013/120376, indexed in Pubmed: 24137571.

122. Freitas CS, Baldi BG, Araújo MS, et al. Use of sirolimus in the treatment of lymphangioleiomyomatosis: favorable responses in patients with different extrapulmonary manifestations. J Bras Pneumol. 2015; 41(3): 275–280, doi: 10.1590/S1806-37132015000004553, indexed in Pubmed: 26176526.

123. Hecimovic A, Jakopovic M, Pavlisa G, et al. Successful treatment of pulmonary and lymphatic manifestations of lymphangioleiomyomatosis with sirolimus. Lymphology. 2015; 48(2): 97–102, indexed in Pubmed: 26714374.

124. Cabeza L, Ruiz-Cobos M, Casanova Á. Resolution of thoracic and abdominal lymphangioleiomyomas in a patient with lymphangioleiomyomatosis treated with sirolimus. Archivos de Bronconeumología (English Edition). 2016; 52(6): 329–330, doi: 10.1016/j.arbr.2016.04.002.

125. Harari S, Spagnolo P, Cocconcelli E, et al. Recent advances in the pathobiology and clinical management of lymphangioleiomyomatosis. Curr Opin Pulm Med. 2018; 24(5): 469–476, doi: 10.1097/MCP.0000000000000502, indexed in Pubmed: 29927757.

126. Ito T, Suno M, Sakamoto K, et al. Therapeutic effect of sirolimus for lymphangioleiomyomatosis remaining in the abdominopelvic region after lung transplantation: a case report. Transplant Proc. 2016; 48(1): 271–274, doi: 10.1016/j.transproceed.2015.12.021, indexed in Pubmed: 26915883.

127. Wahid S, Chiang PC, Luo HL, et al. Pelvic lymphangioleiomyomatosis treated successfully with everolimus: Two case reports with literature review. Medicine (Baltimore). 2017; 96(10): e4562, doi: 10.1097/MD.0000000000004562, indexed in Pubmed: 28272193.

128. Lecuelle D, Basille D, Renard C, et al. Highly effective sirolimus therapy for abdominal lymphangioleiomyoma. Respir Med Res. 2019; 75: 32–34, doi: 10.1016/j.resmer.2019.02.002, indexed in Pubmed: 31262426.

129. Ussavarungsi K, Laroia AT, Burger CD. Low-dose sirolimus in retroperitoneal lymphangioleiomyomas. Lung India. 2019; 36(4): 349–352, doi: 10.4103/lungindia.lungindia_433_18, indexed in Pubmed: 31290423.

130. Klein M, Krieger O, Ruckser R, et al. Treatment of lymphangioleiomyomatosis by ovariectomy, interferon alpha 2b and tamoxifen — a case report. Arch Gynecol Obstet. 1992; 252(2): 99–102, doi: 10.1007/BF02389635, indexed in Pubmed: 1471918.

131. Yamashita S, Nakamura K, Shinozaki H, et al. Lymphangioleiomyomatosis suspected to be a gynecologic disease. J Obstet Gynaecol Res. 2011; 37(3): 267–269, doi: 10.1111/j.1447-0756.2010.01368.x, indexed in Pubmed: 21314806.

132. Basnet A, Shaaban H, Kessler W. A case of recurrent retroperitoneal lymphangioleiomyomatosis treated with progesterone therapy. Urol Ann. 2015; 7(1): 127–128, doi: 10.4103/0974-7796.148664, indexed in Pubmed: 25657565.

133. Yoshizawa H, Kawai S, Hirota Y, et al. A case of uterine lymphangioleiomyomatosis in a young woman that was identified via peritonitis. J Obstet Gynaecol Res. 2019; 45(2): 482–486, doi: 10.1111/jog.13822, indexed in Pubmed: 30338891.