Lymphangioleiomyomatosis (LAM) is a diffuse cystic lung disease. There are two main types of LAM: sporadic, and LAM associated with the tuberous sclerosis complex (TSC), which is caused by mutations in the TSC1 and TSC2 genes. LAM is characterised by cystic lung disease resulting in progressive dyspnoea, renal angiomyolipomas and lymphatic complications. Pneumothorax occurs frequently (70%) and definitive management with pleurodesis is recommended as the risk of recurrence is high. Characteristic thin-walled cysts are seen on computed tomography and the presence of elevated serum levels of a vascular endothelial growth factor-D has good diagnostic specificity. Currently, no single clinical or serological factor has been shown to predict prognosis. However, over the past decade, significant advances in our understanding of the pathophysiology of LAM has led to improved recognition of this rare disease and identification of treatment options. Mechanistic target of rapamycin inhibitors slow the rate of lung function decline and can resolve chylous effusion and regress angiomyolipomas. Life expectancy in patients with LAM is favourable, with a mean transplant-free survival >20 years from the time of diagnosis. Continued advances in understanding the molecular basis of LAM will lead to improved therapeutic targets and the development of more robust prognostic indicators.

Educational aims

- To illustrate the clinical features, common presentations and radiological features of LAM
- To outline the diagnostic approach to LAM, including the role of VEGF-D
- To review the current prognostic indicators in LAM, and outline the impact of lung function, hormonal status, VEGF-D and clinical presentation on outcome
- To inform clinicians on the management options for LAM both pharmacological and nonpharmacological
**Pathophysiology**

LAM is a complex disorder where the pathophysiology is only partially understood, with increasing knowledge emerging as to the underlying molecular drivers of disease. Briefly, smooth muscle-like neoplastic cells from an unknown origin circulate in blood and lymphatic vessels, and deposit in the lungs, causing parenchymal destruction and cystic disease [1, 7, 13]. Mutations in the tumour suppressor genes TSC1 and TSC2 lead to inappropriate signalling through the mTOR pathway, and occur in both S-LAM and TSC-LAM [4, 14] (figure 1). These pathways play a role in regulation of cellular functions including growth, motility and survival. LAM cells also express lymphan giogenic growth factors (vascular endothelial growth factor (VEGF)-C and VEGF-D), which are involved in the metastatic spread of LAM cells [15, 16], and breakdown of the extracellular matrix by matrix metalloproteinases (MMPs) possibly contributes to cyst formation; MMP-2 and MMP-9 have been found in tissue in cystic areas in the lung [17, 18]. Female sex hormones are also implicated in the pathogenesis of LAM, demonstrated by predominance of LAM in females and exacerbations of LAM during exposures to surges in female sex hormones, i.e. pregnancy, hormonal contraception and during menstruation; and the observation that in the post-menopausal period, patients with LAM often experience stabilisation of their disease [19].

**Clinical features**

LAM should be considered in females of reproductive age with unexplained dyspnoea and strongly considered in those with a primary spontaneous pneumothorax. However, as dyspnoea is common to a range of respiratory conditions, patients with LAM are often mislabelled as having asthma, emphysema or COPD. Additionally, one-third of women with LAM have reversible airflow obstruction, contributing to diagnostic delays [20]. The appearance of diffuse pulmonary cysts indicates possible LAM (figure 2) but many conditions can mimic LAM, including pulmonary Langerhans cell histiocytosis (LCH), emphysema, follicular bronchiolitis, lym phoid interstitial pneumonia, Birt–Hogg–Dubé syndrome (BHD), light chain deposition disease and advanced interstitial lung disease. A thorough smoking and occupational history should be recorded in all patients. The physical examination is often normal but wheeze, crackles, abdominal masses or features suggestive of TSC may be present, depending on the clinical presentation. Careful clinical examination to uncover cutaneous signs of TSC (facial angiofibromas, shagreen patch, periungual fibromas and retinal astrocytoma) [5], features of BHD (facial acrochordons and trichodiscomas) [21] and signs of connective tissue disease (mechanic’s hands, Raynaud phenomenon
Lymphangioleiomyomatosis (LAM) and nail changes) is recommended. In LAM, two-thirds of patients present with progressive dyspnoea [9], while respiratory symptoms such as cough, infection and chest pain occur in 25% [9, 22–24]. Haemoptysis, chyloptysis (due to reflux of chyle from the axial lymphatics into the pulmonary lymphatic circuit) and fatigue are also seen to varying degrees [9, 25].

**Figure 1** mTOR signalling pathways and sites of action of mTOR inhibitors. Two different complexes contain mTOR: mTORC1 (acutely sensitive to rapamycin) and mTORC2 (inhibited by rapamycin after prolonged exposure). The tuberin–hamartin complex acts as a regulator of protein synthesis and cell growth. Upstream signals such as growth factors, energy state and amino acids (AA) serve to regulate mTOR. The complex maintains Rheb (Ras homologue enriched in brain) in the guanosine diphosphate (GDP)-loaded state, thereby inhibiting mTORC1 function. Activation of mTORC1 leads to phosphorylation of S6 kinase 1 (S6K1), which is required for ribosome assembly and protein synthesis. Activation of mTORC2 results in phosphorylation of Akt, further promoting mTOR activity by inhibition of tuberin–hamartin. When activated, mTORC1 blocks further phosphorylation of Akt via a negative feedback loop. AMPK: AMP-dependent protein kinase; Raptor: regulatory associated protein of TOR; mLST8: mammalian lethal with SEC13 protein 8; PRR5: proline-rich protein 5; Rictor: rapamycin-insensitive companion of TOR; mSIN1: mammalian stress-activated protein kinase-interacting protein 1; 4E-BP1: factor 4E-binding protein 1.
One third of patients will present with a pneumothorax [9] and the incidence of pneumothorax in LAM is 1000 times higher than in the general female population [26]. Furthermore, 50–80% of patients will experience a pneumothorax during the course of the disease. Relapses are frequent [9, 22, 24, 26, 27], with the mean number of cumulative pneumothoraces found in one population study to be four [9].

Pleural effusion

Pleural effusion complicates the clinical course in 10–30% of LAM patients [3, 9, 22, 28]. Chylous effusions (chylothorax) predominate, caused by the disruption or blockage of the thoracic duct or one of its branches by neoplastic LAM cells or transdiaphragmatic flow from chylous ascites [29]. These are mostly unilateral (76%) and right sided (63.2%), but bilateral effusions can occur [29]. Biochemically, effusions are characterised by exudative fluid that is lymphocytic and with higher levels of proteins than lactate dehydrogenase. Hallmarks of chylous effusions (high triglyceride, cholesterol and chylomicrons) are seen [29]. Effusions in LAM have a variable clinical course and can be stable over time [29, 30].

Renal AMLs

AMLs occur in 30% of patients with S-LAM and up to 80% of those with TSC-LAM. In S-LAM, AMLs are usually unilateral and asymptomatic. If bilateral, they are usually associated with TSC. Haemorrhage secondary to an AML is the presenting complaint in a small subset of LAM patients [27] and when symptomatic, patients report a palpable mass or abdominal pain [9, 31]. AMLs are identified on noncontrast computed tomography (CT) of the abdomen. Biopsy is rarely necessary as the benign tumour contains smooth muscle, blood vessels and fat, and it is the presence of fat that gives a characteristic CT appearance. Sporadic renal AMLs can be associated with previously undiagnosed LAM in 10% of patients and clinicians should have a low threshold for scanning such patients [32] (figure 3).
high-resolution computed tomography (HRCT) performed for another indication. For patients with TSC and those with lymphatic abnormalities or AMLs, careful evaluation to exclude LAM is needed. Certain blood work, including α₁-antitrypsin and connective tissue disease screen (anti-Ro/La, anti-cyclic citrullinated peptide, rheumatoid factor and antinuclear antibody), will help identify other causes of cystic lung disease but to make a confident diagnosis of LAM by the least invasive means, a stepwise approach is suggested, using a combination of clinical, radiological and serological tests [36] (figure 4).

### Pulmonary function

Pulmonary function tests (PFTs) are nonspecific in LAM but are useful to establish the baseline severity of pulmonary disease and to facilitate monitoring over time [20]. Common features include airflow obstruction (25–66%), restrictive/mixed (<25%) and no abnormality in up to 60%. Diffusing capacity of the lung for carbon monoxide ($D_L(CO)$) is reduced in up to 90% of cases [9, 24] and is a more useful indicator of possible LAM if present in isolation in a young patient. Reversible airflow obstruction is present in 30% of patients and is related to prognosis [20, 22, 37].

### Radiology

A chest radiograph is not diagnostic for LAM. Early in the clinical course, chest radiographs are often normal or show nonspecific features of pleural involvement. Later, reticular or nodular opacities, hyperinflation, pneumothorax or lymphadenopathy may occur [9, 38]. HRCT of the thorax is the modality of choice [14, 36], demonstrating thin-walled cysts; characteristically, these cysts are diffuse, round, well defined, devoid of internal structure, often bilateral and without lobar predominance [8, 36, 39, 40] (figure 2). Features on CT may also be used to differentiate LAM from other causes of cystic lung disease, such as LCH or emphysema [36, 39]. Despite demonstrating high sensitivity and specificity for the diagnosis of LAM [41], use of HRCT alone is not considered diagnostic [14, 36]. By current guidelines [8, 36], a definitive diagnosis of LAM can be made based on the presence of multiple characteristic cysts on lung HRCT and any of the following: kidney AML, thoracic or abdominal chylous effusion, lymphangioleiomyomas or lymph nodes involved in LAM, TSC, and elevated VEGF-D (>800 pg·mL⁻¹) (figure 4).

### Vascular endothelial growth factor-D

VEGF-D is a growth factor that binds to VEGF receptor 3 and has been shown to be elevated in 70% of patients with LAM, especially those with lymphatic involvement [16, 42]. Current guidelines advocate measuring serum VEGF-D in all suspected LAM patients [36]. When present at levels >800 pg·mL⁻¹ in the presence of characteristic lung cysts on HRCT, it is associated with a specificity that approaches 100% for the diagnosis of LAM [36, 42]. Moreover, VEGF-D can reliably distinguish LAM from other causes of cystic lung disease [16, 42].
Lung biopsy

Integration of clinical, radiological and serological data has led to a reduction in biopsy rate of 60–80% [16]. Biopsies should be considered in cases where a definitive diagnosis is required, if still disputed despite the aforementioned investigations [36]. The decision to proceed with biopsy should be made in an institute familiar with the care and management of LAM patients, and take into account the benefit and risk of securing a diagnosis. In patients with mild disease and minimal symptoms, a probable clinical diagnosis of LAM with serial monitoring may be sufficient if a definitive diagnosis of LAM would not change management [36]. Histologically, the hallmark features of pulmonary LAM are lung cysts and LAM cells, which are positive for oestrogen receptors and an immunopositive reaction to the Human Melanoma Black (HMB)-45 antibody [38] (figure 5). Previously, a surgical lung biopsy (SLB) was considered the gold standard but more recently, emphasis has been placed on obtaining a diagnosis through less invasive means. Transbronchial lung biopsy has an estimated yield >50% for the diagnosis of LAM and markers of LAM severity such as abnormal $D_{LCO}$ are associated with an increased diagnostic yield [43]. As yet, the true rate of complications is unknown as there have been no prospective studies. Retrospective case reports and cases series provide limited evidence [36] and as such, SLB remains the gold standard. SLB is associated with a high diagnostic yield (nearly 100%) but is associated with significant morbidity and mortality [36].

Other investigations

Abdominal–pelvic imaging should be performed to assess for AMLs, which are found in 33% of those with S-LAM. This can be achieved via CT or magnetic
resonance imaging (MRI) [8]. This imaging may also uncover lymphangioliomyomas, abdominal or retroperitoneal lymphadenopathy, or other lymphatic manifestations [27, 34].

Natural history

LAM is diagnosed usually in the third or fourth decade of life; however, many patients are symptomatic for up to 2 years prior to their diagnosis [9]. The clinical manifestations and rate of progression of lung disease vary considerably between individuals. Observational data pre-sirolimus therapy show patients develop progressive airflow obstruction but the rate of decline in lung function (forced expiratory volume in 1 s (FEV₁)) is variable, ranging from 40 to 120 mL·year⁻¹ [19, 27, 44, 45], but rapid deterioration in lung function can also occur [24, 44]. LAM is a progressive disease with no cure, although treatments such as sirolimus have resulted in slowing the rate of FEV₁ decline and respiratory impairment [45]. Along with progressive dyspnoea and FEV₁ decline, some patients will experience respiratory (pneumothorax), chylos and nonrespiratory complications as mentioned previously. The estimated 10-year survival rates are variable, but exceed 90% and are more favourable than previously believed [19, 22]. Median transplant-free survival is >20 years with 15-year and 20-year transplant-free survival rates of 75% and 64%, respectively [19, 22]. Some patients progress to respiratory failure, although given the variability of the clinical course, it is difficult to predict accurately when and if this will occur. To further characterise patients who may deteriorate quicker or benefit from intervention, research has focused on potential prognostic factors [14].

Prognostic factors

No single clinical or serological factor has been shown to predict prognosis. However, certain factors or biomarkers are associated with an accelerated decline in lung function and other factors are also thought to be protective. These are summarised in table 1. Dyspnoea on exertion as the presenting symptom has previously been shown to be associated with increased mortality in LAM [47]. Conversely, patients presenting with a pneumothorax were previously thought to have a more favourable prognosis [25]. However, subsequent studies have not shown any association between pneumothorax and long-term outcomes [19, 46]. Previously, it was thought that patients with TSC-LAM had a milder disease course [9]. However, studies have demonstrated no difference in the rate of lung function decline in patients with S-LAM versus TSC-LAM [19, 37, 50] and when compared, S-LAM is not associated with poorer outcomes (death/transplant) [19].

| Table 1 Prognostic factors in LAM |
|-------------------------------------|
| **Favourable prognosis** | **Poor prognosis** |
| Older age at diagnosis [46] | Progressive dyspnoea at presentation [47] |
| Post-menopausal status [19] | Pre-menopausal status [19, 37, 44, 45] |
| FEV₁ >70% pred at diagnosis [19] | FEV₁ <70% pred at diagnosis [20, 48] |
| Reversible airflow obstruction [19, 49] | Use of supplementary oxygen [19, 46] |
| VEGF-D: high levels (>800 ng·mL⁻¹) [18] | |

Hormonal status and pregnancy

Several studies have shown that pre-menopausal women demonstrate a faster rate of decline in lung function compared to post-menopausal [20, 44, 45]. In the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial, pre-menopausal women in the placebo group declined five-fold faster than postmenopausal patients [37]. Recently, it was demonstrated that post-menopausal participants had slower decline in FEV₁ (74 versus 118 mL·year⁻¹) and this rate of decline decreased with increasing age at diagnosis [19]. An earlier study also showed increasing age was associated with less risk of mortality [46]. Patients with LAM are at increased risk of pneumothorax, chylothorax and loss of lung function during pregnancy [8]. Women should be counselled on the risks of pregnancy but unfortunately, no known factors that reliably predict risk exist. Exogenous oestrogens have been associated with exacerbations of LAM [51]. Exposure to these agents should be minimised and if possible avoided, and oestrogen-containing contraceptives should be prescribed only with caution. Progesterone use is also associated with poorer outcomes, with limited retrospective studies showing greater decline in DLCO in patients treated with progesterone [20] and an increased risk of death [46].

Pulmonary function as prognostic indicator

Abnormal pulmonary function at presentation (FEV₁ <70% predicted) is a negative prognostic factor [20, 48]. The rate of decline in FEV₁ is inversely correlated with the initial DLCO and age (lower decline in patients with higher DLCO). The National Heart, Lung and Blood Institute (NHLBI) LAM registry provides evidence that better baseline lung function (FEV₁) is associated with better overall outcome [19]. Abnormal gas exchange requiring use of supplementary oxygen is also associated with poorer prognosis [46]. There is evidence that reversible airflow obstruction may predict disease progression [49]. In the recent NHLBI LAM registry longitudinal study, bronchodilator responsiveness was associated with an increased risk of progression to death or transplant [19], but in analysis of the
**Management of renal AMLs**

Although the majority of AMLs are incidental findings and do not result in symptoms, it is recommended that all patients have cross-sectional imaging at time of diagnosis of LAM and in those with tumours <3 cm, to have surveillance imaging every 1–2 years. In patients with larger tumours or in those who are symptomatic (bleeding, haematuria, aneurysmal dilatation or pain), MRI is recommended with either selective embolisation or nephron-sparing surgery recommended where required [58]. AMLs have been shown to regress with the use of mTOR inhibitors but increase again when therapy is discontinued [59].

**Management of chylothorax**

Chylothorax management must be individualised in LAM and invasive treatment should only be
Lymphangioleiomyomatosis

considered after a trial of sirolimus, which can lead to a complete resolution of the effusion [30]. Usually, several months of treatment will be required, with a risk of re-accumulation after cessation of treatment. Pleurodesis with or without thoracic duct ligation can be effective where medical management or observation is insufficient [30] and in patients that cannot tolerate mTOR inhibitors, or where invasive intervention is required intermittent drainage or indwelling catheters may be considered.

Contraception and hormone replacement

Hormonal therapy is not recommended in patients with LAM as the disease is known to worsen with exposure to oestrogen and improves in the post-menopausal period [19]. Oestrogen-based contraceptives are contraindicated [14] and patients are advised to use barrier methods, a copper coil intrauterine device or progesterone-only therapy with caution [52]. If patients are receiving oestrogen-containing products at the time of diagnosis, this should be discontinued.

Pregnancy

Patients with LAM are less likely to plan pregnancy compared to women without LAM, citing advanced disease and advice from professionals as reasons for avoiding pregnancy [60]. It has been suggested that women with LAM are less fertile and have fewer children than the general population [60, 61]. Those who do achieve pregnancy have a higher risk of pregnancy complications including pneumothorax, chylous effusions, worsening dyspnoea or bleeding from AMLs [13, 60, 62, 63]. LAM can present for the first time in pregnancy with pneumothorax or increased dyspnoea [9, 64]. It is unclear whether this is due to progression of disease caused by hormonal changes in pregnancy or whether there is an unmasking of the disease due to the physiological changes experienced with pregnancy [65]. Those with advanced LAM should be advised to avoid pregnancy and to commence sirolimus rather than delay [66]. The safety of sirolimus in pregnancy is unclear.

Lung transplantation

Once a fatal disease with lung transplantation as the only treatment option, mTOR inhibitors have been shown to slow loss of lung function in LAM [67]. However, patients with advanced LAM and respiratory failure may ultimately require lung transplantation, and patients with LAM undergoing lung transplantation have better outcomes than transplantation for other lung diseases [68, 69]. In those who are to undergo transplantation, sirolimus can help optimise their condition prior to transplantation, and post-transplantation, use of sirolimus can prevent recurrence of complications such as chylous effusions [70–72].

Future Directions

While significant progress has been made in LAM, there remains much to learn regarding the pathogenic mechanisms and natural history of disease. It remains unclear when is the best time to commence mTOR therapy and trials are ongoing to determine their utility in milder disease. While VEGF–D is an excellent diagnostic and prognostic biomarker, it is normal in ~30% of patients; hence, other measures are needed. These include alternative blood-based biomarkers [73] and improved use of CT imaging technology to determine progressive disease in those with normal spirometry [74, 75]. Recent studies have identified that that LAM cells probably originate in the uterus and specific proteins associated with this may be novel biomarkers [76]. These continued advances in understanding the molecular pathogenesis will potentially identify better therapeutic options and reveal more robust clinically meaningful biomarkers.

Key points

- LAM is a rare diffuse cystic lung disease, characterised by proliferation, metastatic spread and infiltration of tissues (most commonly lung parenchyma) by abnormal smooth muscle-like LAM cells.
- Formation of diffuse, thin-walled cysts results in dyspnoea, pneumothorax and progressive decline in lung function, and can lead to respiratory failure.
- Vascular endothelial growth factor (VEGF)-D is a useful diagnostic biomarker, elevated in 70% of patients with LAM, and should be measured in all suspected cases of LAM.
- Biopsy should be reserved for cases where VEGF-D levels are normal and there is no evidence of other manifestations of LAM.
- Mechanistic target of rapamycin inhibitor therapy is highly effective in LAM and slows the rate of lung function decline.
Lymphangioleiomyomatosis

Affiliations
Anne M. O’Mahony1,5, Evelyn Lynn1,5, David J. Murphy2, Aurelie Fabre3,4, Cormac McCarthy1,4
1Dept of Respiratory Medicine, St Vincent’s University Hospital, Dublin, Ireland. 2Dept of Radiology, St Vincent’s University Hospital, Dublin, Ireland. 3Dept of Histopathology, St Vincent’s University Hospital, Dublin, Ireland. 4School of Medicine, University College Dublin, Dublin, Ireland. 5These authors contributed equally.

Conflict of interest
None declared

References
1. McCormack FX, Travis WD, Colby TV, et al. Lymphangioleiomyomatosis: calling it what it is: a low-grade, destructive, metastasizing neoplasm. Am J Respir Crit Care Med 2012; 186: 1210–1212.
2. McCormack FX. Lymphangioleiomyomatosis: a clinical update. Chest 2008; 133: 507–516.
3. Johnson SR. Lymphangioleiomyomatosis. Eur Respir J 2006; 27: 1056–1065.
4. Gupta N, Vassallo R, Wikenheiser-Brokamp KA, et al. Diffuse cystic lung disease. Part I. Am J Respir Crit Care Med 2015; 191: 1354–1366.
5. 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: 669–671.
6. Cudzilo CJ, Szczesniak RD, Brody AS, et al. Lymphangioleiomyomatosis screening in women with tuberous sclerosis. Chest 2013; 144: 578–585.
7. Henske EP, McCormack FX. Lymphangioleiomyomatosis – a wolf in sheep’s clothing. J Clin Invest 2012; 122: 3807–3816.
8. Johnson SR, Cordier JF, Lazor R, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J 2010; 35: 14–26.
9. Ryu JH, Moss J, Beck GJ, et al. Clinical course and progression in UK patients with lymphangioleiomyomatosis. Thorax 2004; 59: 800–803.
10. Taylor JR, Ryu J, Colby TV, et al. Lymphangioleiomyomatosis. N Engl J Med 1990; 332: 1254–1260.
11. Cohen MM, Pollock-BaiZiv S, Johnson SR. Emerging clinical picture of lymphangioleiomyomatosis. Thorax 2005; 60: 875–879.
12. Concono C, Pasquier J, Daccord C, et al. Air travel and incidence of pneumothorax in lymphangioleiomyomatosis. Orphanet J Rare Dis 2018; 13: 222.
13. Baldo BG, Fréitas CS, Araujo MS, et al. Clinical course and characterisation of lymphangioleiomyomatosis in a Brazilian reference centre. Sarcoïdosis Vasc Diffuse Lung Dis 2014; 31: 129–135.
14. Johnson SR, Lazor CH, Hubbard RB, et al. Survival and disease progression in UK patients with lymphangioleiomyomatosis. Thorax 2004; 59: 800–803.
15. Baldo BG, Fréitas CS, Araujo MS, et al. Clinical course and characterisation of lymphangioleiomyomatosis in a Brazilian reference centre. Sarcoïdosis Vasc Diffuse Lung Dis 2014; 31: 129–135.
16. Sjölin T, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. Thorax 2000; 55: 1052–1057.
17. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. Thorax 2000; 55: 1052–1057.
18. McCormack FX, Gupta N, Finlay GR, et al. Official American Thoracic Society/Japanese Respiratory Society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. Am J Respir Crit Care Med 2016; 194: 748–761.
19. Hirose M, Matsumuro A, Arai T, et al. Serum vascular endothelial growth factor-D as a diagnostic and therapeutic biomarker for lymphangioleiomyomatosis. PLoS One 2019; 14: e0212776.
20. Young LR, Vandyke R, Gullemann PM, et al. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioleiomyomatosis from other diseases. Chest 2010; 138: 674–681.
21. Taveira-DaSilva AM, Moss J. Clinical features, epidemiology, and therapy of lymphangioleiomyomatosis. Clin Epidemiol 2015; 7: 249–257.
22. Young L, Lee HS, Inoue Y, et al. 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: 445–452.
23. Gupta N, Lee HS, Ryu JH, et al. The NHLBI LAM registry: prognostic physiologic and radiologic biomarkers emerge from a 15-year prospective longitudinal analysis. Chest 2019; 155: 288–296.
24. Taveira-DaSilva AM, Stylianou MP, Hedin C, et al. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. Chest 2004; 126: 1867–1874.
25. Gupta N, Vassallo R, Wikenheiser-Brokamp KA, et al. Diffuse cystic lung disease. Part II. Am J Respir Crit Care Med 2015; 192: 17–29.
26. Johnson SR, Whale CI, Hubbard RB, et al. Survival and disease progression in patients with lymphangioleiomyomatosis. Thorax 2004; 59: 800–803.
27. 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 (GERMO*P’). Medicine (Baltimore) 1999; 78: 321–337.
28. Gupta R, Kitachi M, Inoue Y, et al. Lymphatic manifestations of lymphangioleiomyomatosis. Lymphology 2014; 47: 106–117.
29. Lama A, Ferreiro L, Golpe A, et al. Characteristics of patients with lymphangioleiomyomatosis and pleural effusion: a systematic review. Respir Med 2016; 91: 256–264.
30. Ryu JH, Doerr CH, Fisher SD, et al. Chylothorax in lymphangioleiomyomatosis. Chest 2003; 123: 623–627.
31. Bernstein SM, Newell JD, Jr., Adamczyk D, et al. How common are renal angiomyolipomas in patients with pulmonary lymphangioleiomyomatosis? Am J Respir Crit Care Med 1995; 152: 2138–2143.
32. Ryu JH, Hartman TE, Torres VE, et al. Frequency of undiagnosed cystic lung disease in patients with sporadic renal angiomyolipomas. Chest 2012; 141: 163–168.
33. Derweduwen AM, Verbeken EJ, Stas M, et al. Extrapulmonary lymphangioleiomyomatosis: a wolf in sheep’s clothing. Thorax 2013; 68: 111–113.
34. Chu SC, Horiba K, Usuki J, et al. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999; 115: 1041–1052.
35. Avila NA, Kelly JA, Chu SC, et al. Lymphangioleiomyomatosis: abdominopelvic CT and US findings. Radiology 2000; 216: 147–153.
36 Gupta N, Finlay GA, Kotloff RM, et al. 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: 1337–1348.

37 Gupta N, Lee HS, Young LR, et al. Analysis of the MILES cohort reveals determinants of disease progression and treatment response in lymphangioleiomyomatosis. Eur Respir J 2019; 53: 1802066.

38 Kallassian KG, Doyle R, Kao P, et al. Lymphangioleiomyomatosis: new insights. Am J Respir Crit Care Med 1997; 155: 1183–1186.

39 Seaman DM, Meyer CA, Gilman MD, et al. Diffuse cystic lung disease at high-resolution CT. AJR Am J Roentgenol 2011; 196: 1305–1311.

40 Tobino K, Jokhoh T, Fujimoto K, et al. Computed tomographic features of lymphangioleiomyomatosis: evaluation in 138 patients. Eur Radiol 2015; 24: 534–541.

41 Gupta N, Meraj R, Tanase D, et al. Accuracy of chest high-resolution computed tomography in diagnosing diffuse cystic lung diseases. Eur Respir J 2015; 46: 1196–1199.

42 Young LR, Inoue Y, McCormack FX. Diagnostic potential of serum VEGF-D for lymphangioleiomyomatosis. N Engl J Med 2008; 359: 199–200.

43 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: 331–338.

44 Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progestrone treatment. Am J Respir Crit Care Med 1999; 160: 628–633.

45 McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011; 364: 1595–1606.

46 Oprescu N, McCormack FX, Byrnes S, et al. Clinical predictors of mortality and cause of death in lymphangioleiomyomatosis: a population-based registry. Lung 2013; 191: 35–42.

47 Hayashida M, Seyama K, Inoue Y, et al. The epidemiology of lymphangioleiomyomatosis in Japan: a nationwide cross-sectional study of presenting features and prognostic factors. Respir Care 2007; 12: 523–530.

48 Hayashida M, Yasuo M, Hanaoka M, et al. Reductions in pulmonary function detected in patients with lymphangioleiomyomatosis: an analysis of the Japanese National Research Project on Intractable Diseases database. Respir Invest 2016; 54: 193–200.

49 Taveira-DaSilva AM, Steagall WK, Rabel A, et al. Reversible airflow obstruction in lymphangioleiomyomatosis. Chest 2009; 136: 1596–1603.

50 Taveira-DaSilva AM, Jones AM, Julien-Williams P, et al. Severity and outcome of cystic lung disease in women with tuberous sclerosis complex. Eur Respir J 2015; 45: 171–180.

51 Yano S. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous oestrogen used for infertility treatment. Thorax 2002; 57: 1085–1086.

52 Feemster LC, Lyons PG, Chatterjee RS, et al. Summary for clinicians: lymphangioleiomyomatosis diagnosis and management clinical practice guideline. Am Am Thorac Soc 2017; 14: 1073–1075.

53 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: 1273–1282.

54 Taveira-DaSilva AM, Hedin C, Stylianou MP, et al. Reversible airflow obstruction, proliferation of abnormal smooth muscle cells, and impairment of gas exchange as predictors of outcome in lymphangioleiomyomatosis. Am J Respir Crit Care Med 2001; 164: 1072–1076.

55 Le K, Steagall WK, Stylianou M, et al. Effect of beta-agonists on LAM progression and treatment. Proc Natl Acad Sci USA 2018; 115: E944–E953.

56 Cooley J, Lee YGC, Gupta N. Spontaneous pneumothorax in diffuse cystic lung diseases. Curr Opin Pulm Med 2017; 23: 322–333.

57 Weil D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015; 34: 1–15.

58 Johnson SR, Taveira-DaSilva AM, Moss J. Lymphangioleiomyomatosis. Clin Chest Med 2016; 37: 389–403.

59 Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008, 358: 140–151.

60 Cohen MM, Freyer AM, Johnson SR. Pregnancy experiences among women with lymphangioleiomyomatosis. Respir Med 2009, 103: 766–772.

61 Wahedna I, Cooper S, Williams J, et al. Relation of pulmonary lymphangio-leiomyomatosis to use of the oral contraceptive pill and fertility in the UK: a national case control study. Thorax 1994; 49: 910–914.

62 Brunelli A, Catalini G, Fianchini A. Pregnancy exacerbating unsuspected mediastinal lymphangioleiomyomatosis and chylothorax. Int J Gynaeol Obstet 1996; 52: 289–290.

63 Hughes E, Hodder RV. Pulmonary lymphangioleiomyomatosis complicating pregnancy. A case report. J Reprod Med 1987, 32: 553–557.

64 Mitra S, Gosal AG, Bhattacharya P. Pregnancy unmasking lymphangioleiomyomatosis. J Assoc Physicians India 2004, 52: 828–830.

65 Sullivan EJ. Lymphangioleiomyomatosis: a review. Chest 1998, 114: 1689–1703.

66 Taveira-DaSilva AM, Moss J. Management of lymphangioleiomyomatosis. F1000Prime Rep 2014, 6: 116.

67 Ando K, Okada Y, Akiba M, et al. Lung transplantation for lymphangioleiomyomatosis in Japan. PLoS One 2016; 11: e0146749.

68 Boehler A, Speich R, Russi EW, et al. Lung transplantation for lymphangioleiomyomatosis. N Engl J Med 1996; 335: 1275–1280.

69 Machuca TN, Losso MJ, Camargo SM, et al. Lung transplantation for lymphangioleiomyomatosis: single-center Brazilian experience with no chylothorax. Transplant Proc 2011; 43: 236–238.

70 Ohara T, Oto T, Miyoshi K, et al. Sirolimus ameliorated post lung transplant chylothorax in lymphangioleiomyomatosis. Ann Thorac Surg 2008; 86: e7–e8.

71 Hussein M, Aljehani YM, Nizami I, et al. Successful management of bilateral refractory chylothorax after double lung transplantation for lymphangioleiomyomatosis. Ann Thorac Med 2014; 9: 124–126.

72 Morton JM, McLean C, Booth SS, et al. Regression of pulmonary lymphangioleiomyomatosis (PLAM)-associated retroperitoneal angiomyolipoma post-lung transplantation with rapamycin treatment. J Heart Lung Transplant 2008; 27: 462–465.

73 Miller S, Coveney C, Johnson J, et al. The vitamin D binding protein axis modifies disease severity in lymphangioleiomyomatosis. Eur Respir J 2018; 52: 1800951.

74 Schmittorst VJ, Altes TA, Young LR, et al. Automated algorithm for quantifying the extent of cystic change on volumetric chest CT: initial results in lymphangioleiomyomatosis. AJR Am J Roentgenol 2009, 192: 1037–1044.

75 Yao J, Taveira-DaSilva AM, Colby TV, et al. CT grading of lung disease in lymphangioleiomyomatosis. AJR Am J Roentgenol 2012; 199: 787–793.

76 Guo M, Yu JJ, Perl AK, et al. Identification of the lymphangioleiomyomatosis cell and its uterine origin. bioRxiv 2019; pre-print [https://doi.org/10.1101/784199].