Characteristics of Patients with Lymphangioleiomyomatosis and Pleural Effusion: A Systematic Review

Adriana Lama^a Lucía Ferreiro^{a, b} Antonio Golpe^{a, b} Francisco Gude^{d, e}
José M. Álvarez-Dobaño^{a, b} Francisco J. González-Barcala^{a, b} María E. Toubes^a
Esther San José^{b, c} Nuria Rodríguez-Núñez^a Luis Valdés^{a, b}

^aServicio de Neumología, Complejo Hospitalario Clínico-Universitario de Santiago, ^bGrupo Interdisciplinar de Investigación en Neumología, Instituto de Investigaciones Sanitarias de Santiago (IDIS), ^cServicio de Análisis Clínicos, Complejo Hospitalario Clínico-Universitario de Santiago, ^dUnidad de Epidemiología Clínica, Complejo Hospitalario Clínico-Universitario de Santiago, and ^eGrupo Epidemiología de Enfermedades Frecuentes, Instituto de Investigaciones Sanitarias de Santiago (IDIS), Santiago de Compostela, Spain

Key Words

Chylothorax · Pleurectomy/decortication ·
Lymphangioleiomyomatosis · Pleural effusion ·
Pleural fluid · Sirolimus · Tuberous sclerosis complex

Abstract

The characteristics of patients with lymphangioleiomyomatosis (LAM) are poorly defined, as they may present with or without pleural effusion (PE). We performed a systematic review across four electronic databases searching for studies reporting clinical findings, PE characteristics, and the most effective treatment of LAM. Case descriptions and retrospective studies were included, unrestricted by year of publication. The review consisted of 94 studies (199 patients) spanning a period of nearly 55 years. The median age was 38 years (range: 1 month to 69 years), and 79.7% were between 21 and 50 years old. All cases had dyspnea, 95% had a cough, and 87.5% had chest pain. PE was exudative chylothorax, usually unilateral (76%) and right-sided, predominantly lym-

phocytic, and with proportionately higher levels of proteins than lactate dehydrogenase. Sirolimus was effective in all cases, completely in 87%, and partially in 13%, although the number of patients receiving sirolimus was small. The present study confirmed that LAM and PE mainly occur in women of childbearing age (third to fifth decade of life). PE was usually unilateral and presented as a lymphocyte-predominant chylous exudate. The most effective treatment for PE seems to be sirolimus, although studies with larger series are needed to confirm this.

© 2016 S. Karger AG, Basel

Introduction

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease that almost exclusively affects women of childbearing age. It is characterized by abnormal proliferation of smooth muscle cells in different regions of the lung. This myeloproliferative process is often associated

with diffuse cystic changes in the lung parenchyma, with the possible appearance of pneumothorax, and the disruption or obstruction of the thoracic duct or one of its branches, causing chylous pleural effusion (PE) [1]. LAM can occur sporadically (noninherited form) or be associated with the tuberous sclerosis complex (TSC), a hereditary neurocutaneous syndrome (autosomal dominant) characterized by the formation of hamartomas in multiple organs including the skin, eyes, central nervous system, abdominal organs (especially the kidney), and lungs. About a quarter (26%) of women with TSC present with evidence of LAM [2].

Most patients have a sporadic form of the disease (sporadic LAM) that is not associated with germline mutations of TSC genes. However, they may present with some of the extrapulmonary manifestations found in TSC (renal angiomyolipoma, lymphadenopathy, and abdominal lymphangiomyoma) but not with others (eye, skin, or central nervous system involvement), which are necessary to establish the diagnosis of TSC [3]. While LAM, diagnosed by biopsy, may occur in some men with TSC [4], pulmonary involvement in patients with sporadic LAM has almost exclusively been reported in women [2].

The diagnosis of definite LAM may be made in the presence of a characteristic CT scan and a transbronchial, thoracoscopic, or open lung biopsy showing the characteristic histological features of LAM and reactivity with monoclonal antibody (human melanin black antibody-45). Alternatively, the presence of a characteristic lung CT and angiomyolipomas, chylous effusions, lymphangioleiomyoma, or TSC are sufficient to establish the diagnosis [5, 6].

About 55% of patients with sporadic LAM or TSC-LAM have a pneumothorax during the course of the disease and 21–28% have a PE [1, 7]. However, the characteristics of these patients are not well established since no large studies have been performed. Using a systematic review, our aim was to describe the characteristics of patients with LAM or TSC-LAM and PE, to analyze the characteristics of the pleural fluid (PF) and to evaluate the most effective treatment options of the recurrent PE that occurs in these cases.

Material and Methods

The method employed was that outlined in the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [8]: in the absence of large studies which could provide answers to the study questions, the material comprised cases previously described in the literature.

Selection Criteria

All cases that described LAM or tuberous sclerosis and PE at any age published in any format were eligible for inclusion, except abstracts of papers presented at conferences, editorials, reviews, or letters to the editor that did not document any new case.

Sources of Information

The search strategy included several databases with no restriction on year of publication, although the full text of the study had to be in English, French, or Spanish. The literature search included the following electronic databases (online): MEDLINE (through PubMed), Embase, Scopus and Web of Science. The searches were carried out between 1 October and 30 November 2014. The following search terms were used, adapted for each database: pleural effusion AND lymphangioleiomyomatosis OR lymphangiomyomatosis OR tuberous sclerosis.

In addition to the electronic databases, reference lists from the included articles were manually searched. Any studies fulfilling the above criteria were included, and then each article was independently screened and assessed to identify those that were considered potentially relevant. Studies were reviewed in three stages based on the title, the abstract, and then the full text with consensus sought at each stage of the review.

Data Collection Process

The data from the selected studies were extracted in electronic form (Microsoft Excel 2010, Microsoft Corp., USA). The information extracted included the following: authors, year of publication, number of cases in the series, age at diagnosis and at the time PE appeared, gender, type of disease (LAM or TSC-LAM), smoking history and family disease, dyspnea, hemoptysis, chest pain, chyloptysis, number of previous pneumothorax events, pneumothorax concurrent with PE, pneumothorax laterality, PE size and laterality, high-resolution computed tomography of the chest findings, presence of abdominal lymph nodes and renal angiomyolipoma, PF appearance, transudate or exudate characteristics, number of nucleated cells, lymphocyte count expressed as a percentage, segmented cells and eosinophils, PF values of total protein, lactate dehydrogenase, albumin, cholesterol, triglycerides, chylomicrons, glucose, pH, adenosine deaminase, results of culture, cytology, pleural biopsy and lung biopsy, ascites (documenting whether it was chylous), treatment received and response, and complications and deaths recorded.

Methodological Quality of Individual Studies

Because most of the articles included in the review were single case reports, study type, internal validity, generalizability, heterogeneity, or accuracy were not evaluated.

Outcomes of Interest

Outcomes of interest were the demographic characteristics of patients, family history, biochemical, microbiological and cytological characteristics of the PE, and the response to various treatments.

Statistical Analysis

Due to the wide heterogeneity and descriptive nature of the studies, simple descriptive statistics (proportion, median, and range) of each outcome of interest were calculated.

Fig. 1. PRISMA flowchart of evidence synthesis.

Fig. 2. Age group distribution of patients with LAM and PE.

Results

Ninety-four studies involving 199 patients were selected for review, spanning a period of nearly 55 years. Figure 1 presents a flowchart showing the complete breakdown

Table 1. Demographic and clinical findings of patients with LAM and PE

Median age ¹ , years	38
Males/females	3/186
Smokers or ex-smokers/nonsmokers	5/29 (14.7)
Dyspnea, yes/no	76/0 (100)
Cough, yes/no	38/2 (95)
Chest pain, yes/no	28/4 (87.5)
Chyloptysis, yes/no	6/10 (37.5)
Hemoptysis, yes/no	17/4 (81)
Prior pneumothorax, yes/no	16/37 (30.2)
Simultaneous pneumothorax, yes/no	15/52 (22.4)
Prior or simultaneous pneumothorax, yes/no	28/47 (37.3)
Ascites, yes/no	44/25 (63.8)
Abdominal lymphadenopathy, yes/no	48/15 (76.2)
Renal angiomyolipoma, yes/no	20/13 (60.6)
LAM/STC/LAM-STC	178/7/14
Family history, yes/no	1/16 (5.9)

Values in parentheses represent percentage. ¹ Range: 1 month to 69 years.

of the steps used in the identification of appropriate studies [9–102]. They correspond to isolated case reports (between 1 and 4 per article) and 12 retrospective series [16, 25, 38, 43, 55, 57, 63, 67, 68, 86, 95, 100].

Demographic and Clinical Characteristics

Clinical and demographic characteristics of the 199 patients included in the study are shown in table 1, and their age group distribution is shown in figure 2. The median age was 38 years (range: 1 month to 69 years). The disease occurred mainly during the reproductive age (21–50 years; 106/133, 79.7%). Age was not available for 66 patients. Gender was not available for 10 patients. Of the final study population, 186/189 (98.4%) were women. Only 3 patients were male (2 TSC [37, 77] and 1 lymph-angiomyomatosis [62]; ratio 62/1).

Pleural Effusion

PE was unilateral in 95 patients (76%), right-sided in 60 (63.2%), and left-sided in 35 (36.8%). In 30 patients, PE was bilateral (24%). In 74 cases the authors did not specify whether it was unilateral or bilateral. Of the 158 cases of patients with PE and descriptions of its appearance, 155 (98.1%) were chylous, 1 opaque fluid (triglycerides: 3,898 mg/dl) [80], and 2 serous-hematic [21, 48], although in a subsequent thoracentesis in 1 of them, the PF was described as ‘pink creamy’ [21]. Triglyceride levels were not specified in serous-hematic cases.

Table 2. Descriptive analysis of the parameters determined in pleural fluid

Parameter	n	Values ¹	Range	Comments
Nucleated cells, cells/mm ³	5	2,900	2,100–7,000	
Differential count, % lymphocytes	6	94	74–97	Predominantly lymphocytes: 100% (6/6 cases)
Proteins, g/dl	20	4.7	2.5–8	95% of cases (19/20) ≥3 g/dl
LDH, IU/l	7	360	142–474	Low values: only 1 case with values >400 U/l [86]
Cholesterol, mg/dl	14	91	29–199	2 cases with cholesterol values ≤30 mg/dl [45, 80]
Triglycerides, mg/dl	20	1,606	190–4,600	High values: all levels >110 mg/dl
Chylomicrons, yes/no	3	3/0		
Glucose, mg/dl	8	99.5	91–144	High values
pH	4	7.46	7.42–9	No case with low pH; 1 case with high values [74]

LDH = Lactate dehydrogenase. ¹ Values are given as median or number.

Biochemical characteristics and cellular differentiation of PF are described in only a few cases (table 2). The question of whether the PE was transudate or exudate was only addressed in 14 cases, and all corresponded to the latter. PF triglyceride levels were reported in 20 cases [23, 25, 29, 32, 37, 45, 47, 49, 60, 63, 74, 77, 81–84, 87, 88, 91, 101], and all had values higher than 110 mg/dl (range 190–4,600 mg/dl). The presence of chylomicrons was only specified in 3 cases [46, 83, 101]. The PF culture was negative in the 16 cases where this was reported [10, 21, 30, 33, 37, 39, 45, 46, 49, 62, 65, 74, 80, 81, 83, 93], as was cytology for malignancy in the 25 cases where this parameter was described [11, 12, 16, 21, 22, 27, 30, 35, 37, 39, 40, 45, 46, 48, 50, 58, 60, 62, 71, 72, 74, 81, 87, 93, 99]. Pleural biopsy results were provided for 7 patients: in 3 cases the results were considered normal [21, 40, 66]; 1 showed a discrete mesothelial reaction [13]; in another, the histopathological examination of the pleura showed aggregates of nodular smooth muscle cells [22], and in 2 cases the postmortem study showed dilated lymph nodes in 1 case [16] and firm, white pleural thickening containing cystic cavities in the other [18].

Treatment of PE

Many different therapeutic measures have been used to treat PE and its symptoms, with widely varying rates of success. Table 3 shows a summary of the most common measures (favorable: total or partial control of PE or its symptoms; unfavorable: no control of PE, recurrence, or symptoms). The most widely used treatment option was repeat thoracentesis (62 times), but the overall success rate was low (7/62, 11.3%) [18, 21, 37, 42, 48, 83]. Pleurodesis was the second most commonly used treatment option, with favorable outcome in 56.8% (25/44) [15, 16, 23,

24, 27, 29, 53, 56, 58, 61, 65, 66, 71–73, 85, 88, 101, 102]. The largest rate of favorable results was obtained with sirolimus (23/23 patients, 100%) [79, 86, 89–91, 94, 95] and pleurectomy/decortication (9/11 cases, 81.8%) [10, 13, 24, 45, 57, 62, 63]. Medroxyprogesterone was used in 23 patients, either alone (6 cases [35, 40, 45, 49, 63, 74]) or in combination with other treatments [29, 33, 39, 41, 42, 46, 48, 57, 61, 63, 66, 79] (thoracentesis, chest tube pleurodesis, pleurectomy, and oophorectomy) with favorable results [33, 40, 42, 45, 48, 49, 57, 63, 66, 74] in 13 cases (56.5%). Lung transplantation (unilateral or bilateral) was performed in 7 patients with poor response in all cases [44, 52, 79, 94, 101], although in 1 case the disease took 5 years to reappear [79]. In another case, chylothorax appeared after bilateral lung transplant [76]. PE was not treated in 7 cases [16, 20, 28, 44, 57, 69], and the choice of treatment was not specified in another 75 patients with PE.

Discussion

Publications on LAM and PE involve isolated case reports and some small series, so key issues such as clinical course, characteristics of PE, or the most effective treatments are not well known. These questions were addressed using a systematic review of the literature relating to this disease.

Although LAM and PE can occur at any age, the largest number of cases (79.7%, 106/133) occurred during the reproductive age (21–50 years) (fig. 2). Most series of LAM with PE reflect the fact that it almost exclusively affects women, although some case reports involving men were found [37, 62, 77]. Two of them [37, 77] were in fact

Table 3. Established treatments for the control of PE associated with LAM

Treatment	n	Favorable ¹	Unfavorable ¹	Unknown
Therapeutic thoracentesis ²	62	7 (11.3)	53 (85.5)	2 (3.2)
Pleurodesis ³	44	25 (56.8)	15 (34.1)	4 (9.1)
Thoracic drainage ⁴	32	8 (25)	23 (71.9)	1 (3.1)
Decortication/pleurectomy ⁵	11	9 (81.8)	2 (18.2)	
Thoracotomy + thoracic duct ligation	20	12 (60)	7 (35)	1 (5)
Sirolimus	23	23 (100) ⁶	0 (0)	
Medroxyprogesterone ⁷	23	13 (56.5)	9 (39.1)	1 (4.4)
Lung transplant	7	0 (0)	7 (100)	

Values represent the patient number with the percentage given in parentheses. ¹ Favorable: full or partial control of PE or its symptoms; unfavorable: no control of PE or its symptoms, or recurrence. ² Includes once-only evacuating thoracentesis, repeated thoracentesis, thoracentesis plus a free- or low-fat diet, thoracentesis plus treatment with medroxyprogesterone, octreotide, tamoxifen, or luteinizing hormone. ³ Includes pleurodesis with bleomycin, doxycycline, talc, povidone iodine, nitrogen mustard, OK-432, KE OK-432 (0.1 mg dehydrated preparation of *Streptococcus pyogenes*), mechanical pleurodesis, and pleurodesis plus thoracic duct ligation. ⁴ Chest drainage plus diet, tamoxifen, sirolimus, progesterone, octreotide, or antibiotics. ⁵ Includes pleurectomy alone and pleurectomy plus thoracic duct ligation, progesterone, or radiotherapy. ⁶ Partial resolution in 2 cases, and PE in 1 other case was stabilized. ⁷ Alone or combined with other treatments (thoracentesis, chest drainage, pleurodesis, pleurectomy, and oophorectomy).

cases of TSC without characteristics of LAM. However, these studies were included because there is disagreement about whether LAM and TSC lung lesions represent opposite ends of a continuum or whether LAM is a distinct entity. The third case corresponded to LAM with bilateral chylothorax [62], a characteristic already reported (LAM in a man) [4] but without PE. The typical patient, thus, would be a woman (98.4% of cases) aged 21–50 years (79.7%), nonsmoker (85.3%), presenting with dyspnea (100%), cough (95%), chest pain (87.5%), hemoptysis (81%), abdominal lymphadenopathy (76.2%), ascites (63.8%), renal angiomyolipoma (60.6%), and no family history (94.4%). Conversely, the presence of simultaneous or prior chyloptysis and pneumothorax is less frequent (37.5 and 37.3%, respectively) (table 1). The frequency of these characteristics is not always similar to that of patients with LAM, so those with PE have more frequently dyspnea (100 vs. 73%), cough (95 vs. 30.9%), chyloptysis (37.5 vs. 7%), hemoptysis (81 vs. 30.4%), ascites (63.8 vs. 4.3%), and renal angiomyolipoma (60.6 vs. 37.8%) and are less frequently smokers (14.7 vs. 39.6%) or have prior or simultaneous pneumothorax (37.3 vs. 55.5%) [1].

PE occurred in roughly a quarter (21–28%) of LAM cases during the course of the disease [7], more frequently in sporadic LAM than in TSC-LAM [1]. Three mechanisms may be involved in the development of chylothorax

in LAM: (1) chyle leaking from the thoracic duct or its tributary branches due to proximal lymphatic obstruction or direct involvement; (2) chyle oozing from pleural lymphatics or collateral vessels, and (3) a transdiaphragmatic flow occurring from chylous ascites [63]. In our series, 98.1% (154/157) of the cases in which PE was described were chylous; in 2 cases the PF was described as opaque fluid (triglycerides: 3,893 mg/dl) [81] and as creamy pink at the second thoracentesis (no triglyceride data) [21], suggesting that they were also chylothorax, and only 1 case with PE was not (serous-hematic appearance). However, it is possible that PE was more likely due to hemoperitoneum than LAM in that patient [48]. It therefore appears that PE secondary to LAM is indicated by exudative chylothorax (triglycerides >110 mg/dl in all cases described), usually unilateral, mainly right-sided, and predominantly lymphocytic with higher levels of proteins than lactate dehydrogenase (table 2). This characteristic PF analysis is representative of an increased capillary permeability or lymphatic dysregulation rather than pleural space inflammation. Measurements of pH and glucose can be useful to rule out other diseases but not to confirm the diagnosis. Cytology and culture of PE were negative in all cases. In 44 of 69 patients (63.8%) in whom ascites was described, PE was accompanied by this condition [9, 11, 16–18, 24, 26, 28, 30, 39, 48, 52, 55, 58, 63–65, 68, 73, 75, 76, 78, 82, 84–86, 88, 95], and in 97.3%

(36/37) of the cases it was chylous. The only case of non-chylous ascites corresponded to the already mentioned patient that had a hemiperitoneum and a serous-hematic PE [48]. It is possible that in these cases the source of chylothorax was more likely due to the passage of fluid from the abdominal cavity than to the pulmonary involvement of the disease. Although this is the normal behavior of PE, there are exceptions, such as observing a predominance of eosinophils [21], values of protein and cholesterol that could suggest the existence of a transudate [45, 81, 87], or a pH outside the normal range [74]. The pleural biopsy findings are nonspecific; therefore, it seems to be an unnecessary test for the diagnosis of LAM [99].

The optimal method of managing chylothorax in LAM has not seemed clear. There is no agreement on the management of chylothorax in LAM. Experts believe that treatment should be identified based on the size of the PE, its recurrence, the respiratory status of the patient, and existing comorbidities [6]. The most frequently used treatments are therapeutic thoracentesis (62 patients) and pleurodesis (44 patients), with a favorable response in 11.3% [18, 21, 37, 42, 48, 83] and 56.8% [15, 16, 24, 27, 29, 53, 56, 57, 61, 63, 65, 66, 71–73, 85, 88, 101], respectively. However, the best response is obtained with sirolimus (100%). This drug (rapamycin), by binding to the protein FKBPI2, inhibits the pathway of the mammalian target of rapamycin, a protein that regulates the growth, proliferation, motility, and cell survival, and the addition of protein synthesis and transcription. Sirolimus has been shown to improve lung function [103] and the resolution of chylous effusions in all patients with LAM, although in some only partially [86, 95]. Therefore, some authors considered it the standard treatment for LAM [5]. Other treatment modalities have been decortication/pleurectomy (11 patients), chest tube (32 patients), ligation of the thoracic duct (20 patients), and medroxyprogesterone (23 patients) with favorable responses in 9 (81.8%) patients [10, 13, 45, 57, 63], 8 (25%) patients [30, 33, 57, 63, 87], 12 (60%) patients [10, 12, 15, 24, 27, 57, 70, 73, 93, 96, 99], and 13 (56.5%) patients [33, 40, 42, 45, 48, 49, 57, 63, 66, 74], respectively. However, these, possibly very optimistic, results should be interpreted with caution, since in the majority of these studies they were associated with various treatments, and sometimes it is difficult to know which treatment led to the favorable outcome. Furthermore, the follow-up period was generally short in the majority of cases. Lung transplant does not appear to be useful, since there were no favorable outcomes in any of the cases, although a temporary remission of 5 years in the disease was observed

in 1 case [79]. Furthermore, in a series of 13 patients (only 3 chylothorax), all had posttransplant complications [52], and in another patient, chylothorax appeared after a double lung transplant [76]. Treatments with luteinizing hormone [58], triptorelin [60], tamoxifen [84], octreotide [87, 94], or chylovenous shunt [39, 76] seem rather anecdotal since the number of cases in which they have been used is very small, and in general results have not been good. Spontaneous improvement of chylothorax has also been described [31].

Our review has some limitations. The most important is the reliance on descriptions of case reports instead of case series or comparative trials. Therefore, the evaluation of the quality of the reported literature could limit internal validity, generalizability, and accuracy. In addition, some articles highlight the clinical characteristics of the patients, while others stress diagnostic and therapeutic aspects. Due to the heterogeneity of the reported information, it is not possible to provide the details required, making it difficult to correctly classify some effusions or evaluate the response to a particular treatment. As in all rare diseases, the publication bias would be another limitation to consider since the successfully treated cases or atypical cases are more likely to get published. Finally, the significant variation in the diagnosis and treatment of this disease throughout the period studied (with the inclusion of cases where no CT was available and the disease had not been described well in the literature) has contributed to increasing the complexity of this review.

In summary, patients with LAM and PE are generally women of childbearing age in whom dyspnea is always present. The symptoms and physical examination data are similar to those of any patient with LAM, whether PE is present or not, although its frequency may be different. The PE is usually unilateral, normally on the right side, behaves as paucicellular chylothorax and is exudative lymphocyte-predominant. Finally, the most effective treatment seems to be the sirolimus, although larger studies are needed to confirm this.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest to disclose. This work was performed without funding.

References

- Ryu JH, Moss J, Beck GJ, Lee JC, Brown KK, Chapman JT, et al: Characteristics of 230 patients at enrollment. The NHLBI Lymphangioma Registry. *Am J Respir Crit Care Med* 2006;173:105–111.
- Costello LC, Hartman TE, Ryu JH: High frequency of pulmonary lymphangiomyomatosis in adult women with tuberous sclerosis complex. *Mayo Clin Proc* 2000;75:591–594.
- Roach ES, DiMario FJ, Kandt RS, Northrup H: Tuberous sclerosis consensus conference: recommendations for diagnostic evaluation. *J Child Neurol* 1999;14:402–407.
- Aubry MC, Myers JL, Ryu JH, Petri-Henske E, Jalal SM, Tazelaar HD: Pulmonary lymphangiomyomatosis and micronodular pneumocyte hyperplasia in a male patient with tuberous sclerosis complex. *Am J Respir Crit Care Med* 2000;162:749–752.
- Taveira-DaSilva AM, Moss J: Clinical features, epidemiology, and therapy of lymphangiomyomatosis. *Clin Epidemiol* 2015;7:249–257.
- Johnson SR, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, et al: European Respiratory Society guidelines for the diagnosis and management of lymphangiomyomatosis. *Eur Respir J* 2010;35:14–26.
- Johnson SR: Lymphangiomyomatosis. *Eur Respir J* 2006;27:1056–1065.
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- Heppleston AG: The pathology of honeycomb lung. *Thorax* 1956;11:77–93.
- Laipply TC, Sherrick JC: Intrathoracic angiomatous hyperplasia associated with chronic chylothorax. *Lab Invest* 1958;7:387–400.
- Inglis K: The nature and origin of smooth-muscle-like neoplastic tissue in the lungs and corresponding lymph nodes in a case of so-called ‘honeycomb lungs’. *Arch De Vecchi Anat Patol* 1960;31:179–209.
- Correll N, Fischer C: Lymphangioma of the thoracic duct. *JAMA* 1962;182:1136.
- Justin Besancon L, Pequignot H, Galey JJ, Renault P, Even P: Acquired diffuse pulmonary lymphangiectasis with respiratory insufficiency and chylothorax. *Sem Hop* 1963;39:1179–1190.
- Pachter MR, Lattes R: Mesenchymal tumors of the mediastinum. III. Tumors of lymph vascular origin. *Cancer* 1963;16:108–117.
- Rienhoff WF 3rd, Shelley WM, Cornell WP: Lymphangiomatous malformation of thoracic duct associated with chylous pleural effusion. *Ann Surg* 1964;159:180–184.
- Cornog JL Jr, Enterline HT: Lymphangioma, a benign lesion of chyliferous lymphatics synonymous with lymphangiopericytoma. *Cancer* 1966;19:1909–1930.
- Frack MD, Simon L, Dawson BH: The lymphangiomyomatosis syndrome. *Cancer* 1968;22:428–437.
- Collard M, Fievez M, Godart S, Toussaint JP: The contribution of lymphangiography in the study of diffuse lymphangiomyomatosis. Report of a case with anatomic observations. *Am J Roentgenol Radium Ther Nucl Med* 1968;102:466–470.
- Pamukcoglu T: Lymphangiomyoma of the thoracic duct with honeycomb lungs. *Am Rev Respir Dis* 1968;97:295–301.
- Bush JK, McLean RL, Sieker HO: Diffuse lung disease due to lymphangiomyoma. *Am J Med* 1969;46:645–654.
- Broughton RB: Pulmonary tuberous sclerosis presenting with pleural effusion. *Br Med J* 1970;1:477–478.
- Wolff M: Lymphangiomyoma: clinicopathologic study and ultrastructural confirmation of its histogenesis. *Cancer* 1973;31:988–1007.
- Lieberman J, Agliozzo CM: Intrapleural nitrogen mustard for treating chylous effusion of pulmonary lymphangiomyomatosis. *Cancer* 1974;33:1505–1511.
- Silverstein EF, Ellis K, Wolff M, Jaretzki A 3rd: Pulmonary lymphangiomyomatosis. *Am J Roentgenol Radium Ther Nucl Med* 1974;120:832–850.
- Corrin B, Liebow AA, Friedman PJ: Pulmonary lymphangiomyomatosis. A review. *Am J Pathol* 1975;79:348–382.
- Shuman RL, Engelman R, Kittle CF: Pulmonary lymphangiomyomatosis. *Ann Thorac Surg* 1979;27:70–75.
- Berger JL, Shaff MI: Pulmonary lymphangiomyomatosis. *J Comput Assist Tomogr* 1981;5:565–567.
- Svensen TL, Viskum K, Hansborg N, Thorpe SM, Nielsen NC: Pulmonary lymphangiomyomatosis: a case of progesterone receptor positive lymphangiomyomatosis treated with medroxyprogesterone, oophorectomy and tamoxifen. *Br J Dis Chest* 1984;78:264–271.
- Sobonya RE, Quan SF, Fleishman JS: Pulmonary lymphangiomyomatosis: quantitative analysis of lesions producing airflow limitation. *Hum Pathol* 1985;16:1122–1128.
- Adamson D, Heinrichs WL, Raybin DM, Raffin TA: Successful treatment of pulmonary lymphangiomyomatosis with oophorectomy and progesterone. *Am Rev Respir Dis* 1985;132:916–921.
- Merchant RN, Pearson MG, Rankin RN, Morgan WK: Computerized tomography in the diagnosis of lymphangiomyomatosis. *Am Rev Respir Dis* 1985;131:295–297.
- Bertolani M, Romagnoli R, Barbolini G: Diagnostic approach to pulmonary lymphangiomyomatosis. Case report. *Eur J Radiol* 1987;7:60–62.
- Murray DP, O’Sullivan DJ: Pulmonary tuberous sclerosis responds to progesterone treatment. *Ir J Med Sci* 1988;157:196–197.
- Rodríguez Vela L, Ariño I, Liédana JM, Horndler C, Roncalés A, Rioja C, Rioja LA: Bilateral angiolipomas of the kidney in Bourneville’s tuberous sclerosis. *Arch Esp Urol* 1989;42:423–431.
- Swank DW, Hepper NG, Folkert KE, Colby TV: Intrathoracic lymphangioma mimicking lymphangiomyomatosis in a young woman. *Mayo Clin Proc* 1989;64:1264–1268.
- Sherrier RH, Chiles C, Roggli V: Pulmonary lymphangiomyomatosis: CT findings. *AJR Am J Roentgenol* 1989;153:937–940.
- Foresti V, Casati O, Zubani R, Villa A: Chylous pleural effusion in tuberous sclerosis. *Respiration* 1990;57:398–401.
- Taylor JR, Ryu J, Colby TV, Raffin TA: Lymphangiomyomatosis. Clinical course in 32 patients. *N Engl J Med* 1990;323:1254–1260.
- Hede J, Jurik AG: Lymphangiomyomatosis. Diagnostic imaging approach to a rare disease in women. *Röfo* 1991;155:582–584.
- Spencer JA, Smith MJ, Golding SJ: Lymphangiomyomatosis with unusual calcific retroperitoneal lymphangioma: CT findings. *Eur J Radiol* 1992;14:192–194.
- Woodring JH, Howard RS 2nd, Johnson MV: Massive low-attenuation mediastinal, retroperitoneal, and pelvic lymphadenopathy on CT from lymphangiomyomatosis. Case report. *Clin Imaging* 1994;18:7–11.
- Ernst JC, Sohaey R, Cary JM: Pelvic lymphangiomyomatosis. Atypical precursor to pulmonary disease. *Chest* 1994;106:1267–1269.
- Kitaichi M, Nishimura K, Itoh H, Izumi T: Pulmonary lymphangiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. *Am J Respir Crit Care Med* 1995;151:527–533.
- Khan SU, Mehta AC: Chyloptyses found in a patient with lymphangiomyomatosis. *Chest* 1995;108:1775.
- Druelle S, Aubry P, Levi-Valensi P: Pulmonary lymphangiomyomatosis: a 3-year follow-up of medroxyprogesterone acetate therapy. Apropos of a case. *Rev Pneumol Clin* 1995;51:284–287.
- Zanella A, Toppan P, Nitti D, Lise M: Pulmonary lymphangiomyomatosis: a case report in postmenopausal woman treated with pleurodesis and progesterone (medroxyprogesterone acetate). *Tumori* 1996;82:96–98.
- Dweik RA, Arroliga AC: A 36-year-old woman with progressive shortness of breath and chylous pleural effusion. *Cleve Clin J Med* 1996;63:129–131.
- Longacre TA, Hendrickson MR, Kapp DS, Teng NN: Lymphangiomyomatosis of the uterus simulating high-stage endometrial stromal sarcoma. *Gynecol Oncol* 1996;63:404–410.

- 49 Jounieaux V, Druelle S, Mayeux I, Grimault E, Charet JC: Progesterone treatment in chylothorax associated with pulmonary tuberous sclerosis. *Eur Respir J* 1996;9:2423–2425.
- 50 Itami M, Teshima S, Asakuma Y, Chino H, Aoyama K, Fukushima N: Pulmonary lymphangiomyomatosis diagnosed by effusion cytology. A case report. *Acta Cytol* 1997;41:522–528.
- 51 Matthews LM: Fine needle aspiration diagnosis of lymphangiomyomatosis. A case report. *Acta Cytol* 1999;43:1155–1158.
- 52 Collins J, Müller NL, Kazerooni EA, Mc Adams HP, Leung AN, Love RB: Lung transplantation for lymphangiomyomatosis: role of imaging in the assessment of complications related to the underlying disease. *Radiology* 1999;210:325–332.
- 53 Cope C, Salem R, Kaiser LR: Management of chylothorax by percutaneous catheterization and embolization of the thoracic duct: prospective trial. *J Vasc Interv Radiol* 1999;10:1248–1254.
- 54 Kirchner J, Stein A, Viel K, Dietrich CF, Thahammer A, Schneider M, et al: Pulmonary lymphangiomyomatosis: high-resolution CT findings. *Eur Radiol* 1999;9:49–54.
- 55 Chu SC, Horiba K, Usuki J, Avila NA, Chen CC, Travis WD, et al: Comprehensive evaluation of 35 patients with lymphangiomyomatosis. *Chest* 1999;115:1041–1052.
- 56 Kun KY, Tang R, Tai CM, Ng TK: Tuberous sclerosis in a Chinese baby presented with a pleural effusion and cardiac tumour during prenatal period. *J Obstet Gynaecol* 1999;19:429–430.
- 57 Johnson SR, Tattersfield AE: Clinical experience of lymphangiomyomatosis in the UK. *Thorax* 2000;55:1052–1057.
- 58 Yamauchi M, Nakahara H, Uyama K, Tsujimoto A, Tamai M, Aozasa K: Cytologic finding of chyloascites in lymphangiomyomatosis. A case report. *Acta Cytol* 2000;44:1081–1084.
- 59 Matsui K, Tatsuguchi A, Valencia J, Yu Zx, Bechtle J, Beasley MB, et al: Extrapulmonary lymphangiomyomatosis (LAM): clinicopathologic features in 22 cases. *Hum Pathol* 2000;31:1242–1248.
- 60 López-García F, Romero-Sanz V, Carratalá-Torregrosa JA, Andrada-Becerra E, Shum-Funk C, Martín-Hidalgo A: Pulmonary lymphangiomyomatosis. Description and course of 2 cases. *An Med Interna* 2000;17:599–602.
- 61 Morimoto N, Hirasaki S, Kamei T, Horiike A, Miyatake H, Ogita Y, et al: Pulmonary lymphangiomyomatosis (LAM) developing chylothorax. *Intern Med* 2000;39:738–741.
- 62 Kaptanoglu M, Hatipoglu A, Kutluay L, Gunay L, Dogan K: Bilateral chylothorax caused by pleuropulmonary lymphangiomyomatosis: a challenging problem in thoracic surgery. *Scand Cardiovasc J* 2001;35:151–154.
- 63 Ryu JH, Doerr CH, Fisher SD, Olson EJ, Sahn SA: Chylothorax in lymphangiomyomatosis. *Chest* 2003;123:623–627.
- 64 Cowen EW, Rabel A, Nava V, Turner M, Moss J: Eruptive linear papules on the abdomen of a woman with ascites. *J Am Acad Dermatol* 2004;51:75–78.
- 65 Bearz A, Rupolo M, Canzonieri V, Balestreri L, La Mura N, Berretta M, et al: Lymphangiomyomatosis: a case report and review of the literature. *Tumori* 2004;90:528–531.
- 66 Bhat MA, Bhat GM: Pulmonary lymphangiomyomatosis: a rare presentation. *Indian J Chest Dis Allied Sci* 2004;46:209–211.
- 67 Abbott GF, Rosado-de-Christenson ML, Frazier AA, Franks TJ, Pugatch RD, Galvin JR: From the archives of the AFIP: lymphangiomyomatosis: radiologic-pathologic correlation. *Radiographics* 2005;25:803–828.
- 68 Kumasaka T, Seyama K, Mitani K, Souma S, Kashiwagi S, Hebisawa A, et al: Lymphangiogenesis-mediated shedding of LAM cell clusters as a mechanism for dissemination in lymphangiomyomatosis. *Am J Surg Pathol* 2005;29:1356–1366.
- 69 Kishi K, Homma S, Miyamoto A, Kurosaki A, Motoi N, Kohno T, et al: Rounded atelectasis associated with pulmonary lymphangiomyomatosis. *Intern Med* 2005;44:625–627.
- 70 Christodoulou M, Ris HB, Pezzetta E: Video-assisted right supradiaphragmatic thoracic duct ligation for non-traumatic recurrent chylothorax. *Eur J Cardiothorac Surg* 2006;29:810–814.
- 71 Tynski Z, Eisenberg R: Cytologic findings of lymphangiomyomatosis in pleural effusion: a case report. *Acta Cytol* 2007;51:578–580.
- 72 Hiram M, Atsuta R, Mitani K, Kumasaka T, Gunji Y, Sasaki S, et al: Lymphangiomyomatosis diagnosed by immunocytochemical and genetic analysis of lymphangiomyomatosis cell clusters found in chylous pleural effusion. *Intern Med* 2007;46:1593–1596.
- 73 Kaya S, Dursunoglu N: Non-malignant thoracic pathologies of the women of reproductive age. Can we suggest to collect them under the same heading? *Maturitas* 2007;58:316–318.
- 74 Shawki HB, Muhammed SM, Reda AN, Abdulla TS, Ardan DM: Pulmonary lymphangiomyomatosis. *Saudi Med J* 2007;28:131–134.
- 75 De Lima AS, Martynychen MG, Florêncio RT, Rabello LM, de Barros JA, Escuiato DL: Pulmonary lymphangiomyomatosis: a report of two cases. *J Bras Pneumol* 2007;33:229–233.
- 76 Fremont RD, Milstone AP, Light RW, Ninan M: Chylothoraces after lung transplantation for lymphangiomyomatosis: review of the literature and utilization of a pleurovenous shunt. *J Heart Lung Transplant* 2007;26:953–955.
- 77 Warth A, Herpel E, Schmähl A, Hoffmann H, Herth FJ, Schirmacher P, et al: Mediastinal angiolipomas in a male patient affected by tuberous sclerosis. *Eur Respir J* 2008;31:678–680.
- 78 Ohara T, Oto T, Miyoshi K, Tao H, Yamane M, Toyooka S, et al: Sirolimus ameliorated post lung transplant chylothorax in lymphangiomyomatosis. *Ann Thorac Surg* 2008;86:e7–e8.
- 79 Sugimoto R, Nakao A, Yamane M, Toyooka S, Okazaki M, Aoe M, et al: Sirolimus amelioration of clinical symptoms of recurrent lymphangiomyomatosis after living-donor lobar lung transplantation. *J Heart Lung Transplant* 2008;27:921–924.
- 80 Billings ME, Mulligan M, Raghu G: Acute constrictive pericarditis after lung transplantation for lymphangiomyomatosis. *J Heart Lung Transplant* 2009;28:110–113.
- 81 Malinowska-Kolodziej I, Finlay G, Campbell G, Garcia-Moliner ML, Weinstein B, Dougherty CA, et al: Lymphangiomyomatosis: cause of a malignant chylous pleural effusion. *J Clin Oncol* 2010;28:4–6.
- 82 Takagi Y, Sato T, Morio Y, Kumasaka T, Mitani K, Miyamoto H, et al: A pleuro-peritoneal communication through the diaphragm affected with lymphangiomyomatosis. *Intern Med* 2010;49:439–445.
- 83 Befort P, Corne P, Bourdin A, Bommart S, Jonquet O: Pleural effusion, cystic pulmonary disease and renal mass. *Rev Mal Respir* 2010;27:497–499.
- 84 Bisceglia M, D'Alessandro V, Simeone A, Ben-Dor D, Pasquinelli G: Selected case from the Arkadi M. Rywlin International Pathology Slide Seminar: sporadic lymphangiomyomatosis. *Adv Anat Pathol* 2010;17:445–452.
- 85 Dursunoglu N, Ors S, Gunay S, Bir F, Başer S, Ozkurt S, et al: A young lady with severe dyspnea in postpartum period after long term infertility treatment. *Turk Toraks Dergisi* 2011;12:127–129.
- 86 Taveira-DaSilva AM, Hathaway O, Stylianou M, Moss J: Changes in lung function and chylous effusions in patients with lymphangiomyomatosis treated with sirolimus. *Ann Intern Med* 2011;154:797–805.
- 87 Min HK, Jung JI, Song JS, Park CK, Kim YK, Kang JY: A 29-year-old woman with an intractable postoperative pleural effusion and pulmonary parenchymal opacification. *Chest* 2012;142:791–796.
- 88 Palmeiro R, Arosa V, Cuerda C, Bretón I, Camblor M, Rodríguez MC, et al: Persistent chylothorax in patient with lymphangiomyomatosis. *Nutr Hosp* 2012;27:940–942.
- 89 Moua T, Olson EJ, Jean HCS, Ryu JH: Resolution of chylous pulmonary congestion and respiratory failure in lymphangiomyomatosis with sirolimus therapy. *Am J Respir Crit Care Med* 2012;186:389–390.
- 90 Chachaj A, Drozd K, Chabowski M, Dziegiel P, Grzegorek I, Wojnar A, et al: Chyloperitoneum, chylothorax and lower extremity lymphedema in woman with sporadic lymphangiomyomatosis successfully treated with sirolimus: a case report. *Lymphology* 2012;45:53–57.

- 91 Rozenberg D, Thenganatt J: Dramatic response to sirolimus in lymphangioleiomyomatosis. *Can Respir J* 2013;20:413–414.
- 92 Ansótegui-Barrera E, Mancheño-Franch N, Peñalver-Cuesta JC, Vera-Sempere F, Padilla-Alarcón J: Lung transplantation in sporadic lymphangioleiomyomatosis: study of 7 cases. *Med Clin (Barc)* 2013;141:349–352.
- 93 Sharp C, Meller M, Moody A, Hands G: A hormonal effusion? *Thorax* 2013;68:697–698.
- 94 Barrera P, Simons SO, Luijk B, Wessels MJ, Heijdra YF: Efficacy of sirolimus therapy for chylous effusions in lymphangioleiomyomatosis. *Ann Am Thorac Soc* 2013;10:408–409.
- 95 Ando K, Kurihara M, Kataoka H, Ueyama M, Togo S, Sato T, et al: Efficacy and safety of low-dose sirolimus for treatment of lymphangioleiomyomatosis. *Respir Investig* 2013;51:175–183.
- 96 Csiszkó A, Herr G, Sz Kiss S, Hallay J, Gyöngyösi Z, Szentkereszty Z: VATS therapy of chylothorax caused by leiomyomatosis complicated with tuberous sclerosis complex. *J Minim Access Surg* 2013;9:84–86.
- 97 Fan D, Ding L, Liu H, Wang J, Ran W, Li Y, et al: Effusion cytology: an effective method for the diagnosis of pulmonary lymphangioleiomyomatosis. *J Thorac Dis* 2014;6:54–57.
- 98 Khoja AM, Duggal D, Keni A, Patel CS, Chavan R: Palliative management of lymphangioleiomyomatosis: using video-assisted thoracoscopic surgery. *J Bronchol Interv Pulmonol* 2014;21:54–57.
- 99 Liu M, Wu B, Cui Y, Chang D, Zhang S, Gong M: Surgical treatment of chylothorax caused by lymphangioleiomyomatosis. *J Thorac Dis* 2014;6:11–14.
- 100 Cai X, Pacheco-Rodriguez G, Haughey M, Samsel L, Xu S, Wu HP, et al: Sirolimus decreases circulating lymphangioleiomyomatosis cells in patients with lymphangioleiomyomatosis. *Chest* 2014;145:108–112.
- 101 Hussein M, Aljehani YM, Nizami I, Saleh W: Successful management of bilateral refractory chylothorax after double lung transplantation for lymphangioleiomyomatosis. *Ann Thorac Med* 2014;9:124–126.
- 102 Kinoshita Y, Sakamoto A, Hidaka K: Recovery of chylous pulmonary congestion in tuberous sclerosis complex-associated lymphangioleiomyomatosis. *BMJ Case Rep* 2014, DOI: 10.1136/bcr-2014-205701.
- 103 McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, et al: Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med* 2011;364:1595–1606.

Erratum

Table 6b in the paper by Slebos D-J et al. entitled ‘Bronchoscopic coil treatment for patients with severe emphysema: a meta-analysis’ [*Respiration* 2015;90:136–145] should read:

Table 6. Minimal clinically important difference
b Number of patients who reached both MCIDs at the 6-month or the 12-month follow-up

	$\Delta FEV_1 > 0.1$ liters		$\Delta SGRQ$ score > -4 points		$\Delta 6MWD > 26$ m	
	6-m FU	12-m FU	6-m FU	12-m FU	6-m FU	12-m FU
$\Delta RV > 0.4$ liters	37 (31)	26 (28)	47 (38)	24 (26)	41 (34)	24 (26)
$\Delta FEV_1 > 0.1$ liters			32 (26)	20 (22)	35 (30)	25 (27)
$\Delta SGRQ$ total score > -4 points					54 (45)	38 (41)

Data are presented as n (%). Numbers in square brackets behind variables in table 6a are references supporting the MCID cutoffs. 6-/12-m FU = 6-/12-month follow-up; TLC = total lung capacity.