Respiratory Medicine 168 (2020) 105993

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Short communication

Natural history of incidental sporadic and tuberous sclerosis complex associated lymphangioleiomyomatosis

Fabiano Di Marco [a,b,*], Silvia Terraneo [a,c], Olívia Meira Dias [d], Gianluca Imeri [a,b], Stefano Centanni [a,c], Rocco Francesco Rinaldo [a,c], Lisa Giuliani [a,c], Elena Lesma [a], Giuseppina Palumbo [a,c], Mark Wanderley [e], Carlos Roberto Ribeiro Carvalho [d], Bruno Guedes Baldi [d]

[a] Department of Health Sciences, Università Degli Studi di Milano, Milan, Italy
[b] Respiratory Unit, ASST – Papa Giovanni XXIII Hospital, Bergamo, Italy
[c] Respiratory Unit, ASST Santi Paolo e Carlo, Milan, Italy
[d] Divisao de Pneumologia, Instituto Do Coracao (InCor), Hospital Das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil
[e] Departamento de Radiologia, Hospital Das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

ARTICLE INFO

Keywords:
Lymphangioleiomyomatosis
Tuberous sclerosis complex
Natural history

ABSTRACT

Lymphangioleiomyiomatosis (LAM) is a rare disease affecting women in childbearing age. A sporadic form (S-LAM) affecting previously healthy women, and a form associated with Tuberous Sclerosis Complex (TSC-LAM) are described. Some data suggested that TSC-LAM could be a milder disease compared to S-LAM. To investigate whether the different disease behavior is real or due to overdiagnosis of screened TSC women, we compared the natural history of S-LAM and TSC-LAM in patients with incidental diagnosis. Clinical, and functional data from 52 patients (23 with S-LAM and 29 with TSC-LAM) were analysed. At diagnosis functional impairment was mild without differences between groups [FEV1 % pred was 97% (88-105) and 94% (82-106) in TSC-LAM and S-LAM, respectively, p = 0.125]. Patients with S-LAM had less renal angiomyolipoma, and lower VEGF-D serum levels than TSC-LAM. There was no difference in the baseline extent of pulmonary cysts on CT scan and no difference in yearly rate of functional decline between TSC-LAM, and S-LAM patients [e.g. yearly rate of decline of FEV1 % pred was −0.51 (−1.59–2.24) and −0.90 (−1.92–-0.42) in TSC-LAM and S-LAM, respectively, p = 0.265]. In conclusion, the natural history of TSC-LAM and S-LAM, when a potential selection bias due to screening in the latter group is balanced, is similar. Our study suggests that the prevalence of S-LAM can be significantly underestimated due to a tendency to diagnosis more frequently patients with more severe impairment, without identifying several ones with asymptomatic disease.

1. Introduction

Lymphangioleiomyiomatosis (LAM) is a rare disease affecting mostly women in childbearing age [1,2].

A sporadic form (S-LAM), and a form affecting female patients with Tuberous Sclerosis Complex (TSC-LAM) [3] are described. The reported prevalence of LAM in women with TSC is up to 49% in recent publications [4–6], and the estimated number of TSC-LAM patients exceeds the sporadic LAM group; however, the majority of patients who require medical intervention for LAM have the sporadic form of the disease [7]. Previous data showed that TSC-LAM patients have better lung function, and a milder radiological involvement when compared to S-LAM [8,9], leading to a hypothesis that TSC-LAM patients could have milder disease. However, systematic screening for LAM using computed tomography of the lungs in TSC patients could lead to a pre-clinic identification of the disease. Furthermore, complications due to extrapulmonary manifestations in TSC patients (e.g. abdominal bleeding due to angiomyolipoma, intellectual disability) could potentially require complementary exams leading to identification of pulmonary involvement.

* Corresponding author. Papa Giovanni XXIII Hospital, Piazza OMS, 1 – 24127, Bergamo, Italy.
E-mail addresses: fabiano.dimarco@unimi.it (F. Di Marco), silvia.terraneo@asst-santipaolocarlo.it (S. Terraneo), meiradias@yahoo.com.br (O.M. Dias), gianluca.imeri@gmail.com (G. Imeri), stefano.centanni@unimi.it (S. Centanni), rocco.rinaldo@unimi.it (R.F. Rinaldo), lisa.giuliani@unimi.it (L. Giuliani), elena.lesma@unimi.it (E. Lesma), palumbo.g.gp@gmail.com (G. Palumbo), mark.wanderley@gmail.com (M. Wanderley), crrcarvalho@uol.com.br (C.R. Ribeiro Carvalho), bruno.guedes2@terra.com.br (B. Guedes Baldi).

https://doi.org/10.1016/j.rmed.2020.105993
Received 7 November 2019; Received in revised form 28 March 2020; Accepted 23 April 2020
Available online 28 April 2020

List of abbreviations

DLCO	carbon monoxide diffusing capacity
FEV1	forced expiratory volume, 1st second
FVC	forced vital capacity
KCO	Krogh factor for carbon monoxide
LAM	Lymphangioleiomyiomatosis
S-LAM	sporadic Lymphangioleiomyiomatosis
TSC	Tuberous Sclerosis Complex
TSC-LAM	Tuberous Sclerosis Complex associated LAM
VA	alveolar volume
VEGF-D:	vascular endothelial growth factor, D-isoform

Additionally, recently published data from the National Heart, Lung and Blood Institute (NHLBI) LAM Registry confirmed a higher severity of S-LAM compared to TSC-LAM at diagnosis, but did not identify significant differences in the rate of functional decline [10] nor in the progression to death or lung transplant [10] between these groups. Finally, an intrinsic difference in the natural history of these two LAM subgroups cannot be ruled out.

To investigate whether the different disease behaviour is real or due to overdiagnosis of screened TSC women, we performed a study to evaluate the natural history of S-LAM and TSC-LAM by comparing functional, and radiological data over time in these two populations with an incidental LAM diagnosis (i.e. by screening asymptomatic women with TSC, or incidentally discovering through imaging performed for indications other than respiratory or extrapulmonary symptoms possibly due to S-LAM).

2. Methods

We performed a retrospective multicentric study in two centres (San Paolo Hospital, Milan, Italy, and Heart Institute (InCor), Hospital das Clinicas, Sao Paulo, Brazil) from 1995 to 2017. The diagnosis of both LAM and TSC were based on the previously published guidelines [11–13]. At study recruitment, the Pulmonary Clinic of San Paolo Hospital, Italy followed 71 adult patients (50 TSC-LAM, and 21 S-LAM), while the Heart Institute Sao Paulo, Brazil followed 105 patients (32 TSC-LAM, and 73 S-LAM). The local ethical committees approved this study. We re-evaluated the clinical history of each patient, and selected all cases with an incidental diagnosis of LAM, which was defined by the finding of cystic lung lesions in the upper slices of abdominal CT scans or chest CT scans performed for reasons other than pulmonary or extrapulmonary symptoms possibly due to LAM, and by screening asymptomatic women with TSC. We compared clinical and functional data (forced expiratory volume in the first second, FEV1, forced vital capacity, FVC, and carbon monoxide diffusing capacity, DLCO) from patients with at least two spirometries at different times (at least 4 months apart). Quantification of the volume of the cystic lesions, total lung volume, and the ratio of the abnormal cyst volume to the total lung volume were obtained automatically by densitovolumetry using a computer program (Advantage Workstation Thoracic VCAR software; GE Medical Systems, Milwaukee, WS, USA). The volume of the cystic lesions was obtained by selecting pixels between −1000 and −950 HU on soft tissue filter images [14]. Serum levels of VEGF-D were measured.

Data are reported as the mean ± SD for variables with normal distribution, as the median (25th–75th percentiles) for variables with non-normal distribution, or as numbers (percentiles). The Mann−Whitney *U* test was used to compare continuous variables, whereas categorical variables were compared using the Fisher's exact or Chi-square tests. The estimated yearly rate of decline (slope) was calculated from simple linear regression using the percentage of predicted of functional parameters.

3. Results

Demographic, clinical and functional data from 52 patients (23 with S-LAM and 29 with TSC-LAM) were analysed (35 from the Brazilian group, 23 with S-LAM and 12 with TSC-LAM, and 17 from the Italian group, all affected with TSC-LAM) and are described in Table 1. Genetics data were available for 23 patients: 7 (12%) patients showed a mutation in TSC1 gene, 10 patients (17%) showed a mutation in TSC2 gene and in 6 (10%) patients an atypical mutation was found. The median age in the whole population was 39 years (31-46), with no difference between the groups. The reason for performing CT scans included chest pain without evidence of pneumothorax or pleural effusion (4 patients), fever (7 patients), abdominal pain without evidence of abdominal manifestation of LAM (14 patients), or screening in 27 patients with TSC. Brazilian patients were followed for an average time of 61 ± 50 months, while Italian patients were followed for 52 ± 21 months (p = 0.359), with a cumulative average follow up time of 58 ± 43 months. During follow up period, twelve patients were treated with mTOR inhibitors (six with TSC-LAM and six with S-LAM, p = 0.746): a patient was treated with everolimus, and 11 with sirolimus. There were no differences in demographics, clinical features and functional data between Italian and Brazilian patients with TSC-LAM (data not showed).

Brazilian patients underwent on average 5.1 ± 3.0 respiratory function tests while Italian patients underwent 4.4 ± 2.3 respiratory function tests (p = 0.339) during the follow-up period. Functional impairment at baseline was mild without significant differences between the groups. Patients with TSC-LAM had a higher percentage of renal angiomyolipoma, and higher VEGF-D serum levels at diagnosis than those with S-LAM. There was no difference in the baseline extent of pulmonary cysts on CT scan when comparing S-LAM and TSC-LAM patients (Table 1).

Figure shows the variations of lung function parameters in both groups during follow-up. As noted, there was no functional difference in yearly rate of decline when comparing TSC-LAM and S-LAM groups, including FEV1 % pred [-0.51 (−1.59−2.24) and −0.90 (−1.92−-0.42), respectively, p = 0.265], FVC [-0.76 (−3.70−1.04) and −0.56 (−1.92−-0.42), respectively, p = 0.719] and DLCO [-0.37 (−3.96−1.91) and −0.42 (−2.54−2.25), respectively, p = 0.712] (Fig. 1).

4. Discussion

This is the first study aimed at comparing the natural history of S-

Table 1
Baseline and follow-up data of the whole study sample.

	TSC-LAM (n = 29)	S-LAM (n = 23)	P
Baseline data			
Age, yrs	37 (27–46)	43 (35–49)	0.125
Renal AML presence, %	72	39	<0.05
Abdominal lymphangioleiomyoma, %	1 (3.4%)	4 (17.4%)	0.157
FEV1, % pred	97 (88–105)	94 (82–106)	0.552
FVC, % pred	95 (80–107)	95 (83–103)	0.885
DLCO, % pred	81 (74–92)	88 (71–99)	0.605
Cystic lesions extent at CT, %	3.7 (0.2–11.1)	7.0 (1.8–10.3)	0.524
VEGF-D, pg/mL**	1355 (633–2853)	726 (263–1098)	<0.05
Follow-up data			
Pneumothorax during follow-up, %	4 (13.8%)	3 (13%)	1.000
Chylothorax during follow-up, %	0	1 (4.3%)	0.442
Use of mTOR inhibitors, %	21	26	0.746

Data are expressed as median (IQR: interquartile range); p < 0,05 in bold. *results available for 10 TSC-LAM and 18 S-LAM patients; **results available for 24 TSC-LAM and 20 S-LAM patients. AML: angiomyolipoma; CT: computed tomography; FVC: forced vital capacity; mTOR: mechanistic target of rapamycin; VEGF-D: vascular endothelial growth factor D.

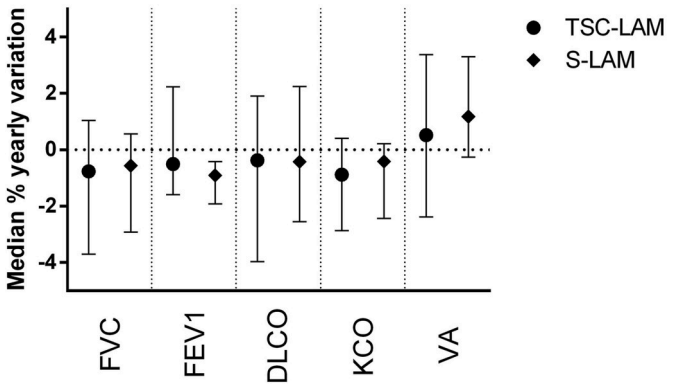

Figure 1. Yearly variation of lung function parameters in TSC-LAM and S-LAM patients.
FEV1: forced expiratory volume, 1st second; FVC: forced vital capacity; DLCO: carbon monoxide diffusing capacity; KCO: Krogh factor for carbon monoxide (DLCO/VA): DLCO divided by VA (DLCO/VA); S-LAM: sporadic LAM; TSC-LAM: LAM associated with Tuberous Sclerosis Complex; VA: alveolar volume. P-values for FVC, FEV1, DLCO, KCO, VA percent predicted (0.719, 0.265, 0.712, 0.780, and 0.506 respectively).

LAM, and TSC-LAM in patients with incidental LAM diagnoses. We found that, the natural history of TSC-LAM and S-LAM, when a potential selection bias due to screening in the latter group is balanced, is similar.

A previous study that compared the yearly variation in functional parameters between lung-function matched TSC-LAM and S-LAM patients also showed that there was no difference between the groups. However, the authors did not assessed exclusively asymptomatic patients [9]. In the (NHLBI) LAM Registry, there was no difference in the rate of decline of FEV1 between these groups [10]. The absence of difference in functional decline between TSC-LAM and S-LAM groups in our study was probably not related to sirolimus because the prevalence of the use of this drug was not different between the groups.

The results of our study suggest that the prevalence of S-LAM can be significantly underestimated due to a tendency to diagnosis more frequently patients with more severe impairment, without identifying several ones with asymptomatic disease. This hypothesis is reinforced by the fact that 24% of our patients with sporadic LAM were asymptomatic, with an incidental diagnosis. In this context, it is likely that there are other asymptomatic patients with undiagnosed LAM in the general population.

The main limitations of this study include the number of patients, due to the rare nature of the disease, and the comparison of two potentially different populations, the first comprised only of TSC-LAM patients (Italian cohort), and the second (Brazilian cohort) with different ethnic origin. However, there is no evidence of different natural histories of LAM due to different ethnic origins.

5. Conclusions

In conclusion, our study demonstrates that the natural history of TSC-LAM and S-LAM, when a potential selection bias due to screening in the latter group is balanced, is similar, and that the prevalence of S-LAM is probably underestimated.

Ethics approval

Comitato Etico Interaziendale Milano Area A.

Committee for Ethics in Research of the University of Sao Paulo Medical School.

Consent for publication

All patients or relatives when requested, gave the consent to data collection and analysis.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy, and since patients did not consent to have their full transcripts made publicly available but are available from the corresponding author on reasonable requested.

Funding

Not founded.

Author's contributions

FDM, ST, GI had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: FDM, ST, OMD, BGB; Acquisition of data: FDM, ST, OMD, RR,GI, LG, GP, MW; Analysis and interpretation of data: FDM, ST, GI, BGB; Drafting of the manuscript: FDM, ST, OMD, BGB; Critical revision of the manuscript for important intellectual content: SC, EL, CRRC; Statistical analysis: FDM, ST, GI. All authors reviewed and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Fabiano Di Marco: Conceptualization, Investigation, Data curation, Methodology, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Silvia Terraneo:** Conceptualization, Investigation, Data curation, Methodology, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Olívia Meira Dias:** Conceptualization, Investigation, Data curation, Methodology, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Gianluca Imeri:** Conceptualization, Investigation, Data curation, Methodology, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Stefano Centanni:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Rocco Francesco Rinaldo:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Lisa Giuliani:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Elena Lesma:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Giuseppina Palumbo:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Mark Wanderley:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Carlos Roberto Ribeiro Carvalho:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Bruno Guedes Baldi:** Conceptualization, Investigation, Data curation, Methodology, Formal analysis, Validation, Writing - original draft, Writing - review & editing.

Acknowledgements

The authors would like to thank Associazione Sclerosi Tuberosa (AST) and Associazione Italiana Linfangioleiomiomatosi (AILAM Onlus) for the constant motivation to improve research in this field.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.105993.

References

[1] E.P. Henske, F.X. McCormack, Lymphangioleiomyomatosis - a wolf in sheep's clothing, J. Clin. Invest. 122 (2012) 3807–3816, https://doi.org/10.1172/JCI58709.

[2] S.R. Johnson, Lymphangioleiomyomatosis, Eur. Respir. J. 27 (2006) 1056–1065, https://doi.org/10.1183/09031936.06.00113303.

[3] P. Curatolo, R. Bombardieri, S. Jozwiak, Tuberous sclerosis, Lancet 372 (2008) 657–668, https://doi.org/10.1016/S0140-6736(08)61279-9.

[4] L.C. Costello, T.E. Hartman, J.H. Ryu, High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex, Mayo Clin. Proc. 75 (2000) 591–594, https://doi.org/10.4065/75.6.591.

[5] F. Di Marco, S. Terraneo, G. Imeri, G. Palumbo, F. La Briola, S. Tresoldi, A. Volpi, L. Gualandri, F. Ghelma, R.M. Alfano, E. Montanari, A. Gorio, E. Lesma, A. Peron, M.P. Canevini, S. Centanni, Women with TSC: relationship between clinical, lung function and radiological features in a genotyped population investigated for lymphangioleiomyomatosis, PloS One 11 (2016), e0155331, https://doi.org/10.1371/journal.pone.0155331.

[6] J.H. Ryu, J. Moss, G.J. Beck, J.C. Lee, K.K. Brown, J.T. Chapman, G.a. Finlay, E. J. Olson, S.J. Ruoss, J.R. Maurer, T.a. Raffin, H.H. Peavy, K. McCarthy, A. Taveira-DaSilva, F.X. McCormack, N.a. Avila, R.M. DeCastro, S.S. Jacobs, M. Stylianou, B. L. Fanburg, The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment, Am. J. Respir. Crit. Care Med. 173 (2006) 105–111, https://doi.org/10.1164/rccm.200409-1298OC.

[7] E.C. Harknett, W.Y.C. Chang, S. Byrnes, J. Johnson, R. Lazor, M.M. Cohen, B. Gray, S. Geiling, H. Telford, A.E. Tattersfield, R.B. Hubbard, S.R. Johnson, Use of variability in national and regional data to estimate the prevalence of lymphangioleiomyomatosis, QJM 104 (2011) 971–979, https://doi.org/10.1093/qjmed/hcr116.

[8] N.A. Avila, A.J. Dwyer, A. Rabel, J. Moss, Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis: comparison of CT features, Radiology 242 (2007) 277–285, https://doi.org/10.1148/radiol.2421051767.

[9] A.M. Taveira-DaSilva, A.M. Jones, P. Julien-Williams, J. Yao, M. Stylianou, J. Moss, Severity and outcome of cystic lung disease in women with tuberous sclerosis complex, Eur. Respir. J. 45 (2015) 171–180, https://doi.org/10.1183/09031936.00088314.

[10] N. Gupta, H.-S. Lee, J.H. Ryu, A.M. Taveira-DaSilva, G.J. Beck, J.-C. Lee, K. McCarthy, G.A. Finlay, K.K. Brown, S.J. Ruoss, N.A. Avila, J. Moss, F. X. McCormack, The NHLBI LAM registry: prognostic physiologic and radiologic biomarkers emerge from a 15-year prospective longitudinal analysis, Chest (2018), https://doi.org/10.1016/j.chest.2018.06.016.

[11] S.R. Johnson, J.F. Cordier, R. Lazor, V. Cottin, U. Costabel, S. Harari, M. Reynaud-Gaubert, A. Boehler, M. Brauner, H. Popper, F. Bonetti, C. Kingswood, European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis, Eur. Respir. J. 35 (2010) 14–26, https://doi.org/10.1183/09031936.00076209.

[12] F.X. McCormack, N. Gupta, G.R. Finlay, L.R. Young, A.M. Taveira-DaSilva, C. G. Glasgow, W.K. Steagall, S.R. Johnson, S.A. Sahn, J.H. Ryu, C. Strange, K. Seyama, E.J. Sullivan, R.M. Kotloff, G.P. Downey, J.T. Chapman, M.K. Han, J. M. D'Armiento, Y. Inoue, E.P. Henske, J.J. Bissler, T.V. Colby, B.W. Kinder, K. A. Wikenheiser-Brokamp, K.K. Brown, J.F. Cordier, C. Meyer, V. Cottin, J. L. Brozek, K. Smith, K.C. Wilson, J. Moss, Official American thoracic society/Japanese respiratory society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management, Am. J. Respir. Crit. Care Med. 194 (2016) 748–761, https://doi.org/10.1164/rccm.201607-1384ST.

[13] H. Northrup, D.A. Krueger, Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 iinternational tuberous sclerosis complex consensus conference, Pediatr. Neurol. 49 (2013) 243–254, https://doi.org/10.1016/j.pediatrneurol.2013.08.001.

[14] B.G. Baldi, M.S. Araujo, C.S.G. Freitas, G.B. da Silva Teles, R.A. Kairalla, O.M. Dias, D.A.S. Pereira, S.P. Pimenta, C.R.R. Carvalho, Evaluation of the extent of pulmonary cysts and their association with functional variables and serum markers in lymphangioleiomyomatosis (LAM), Lung (2014), https://doi.org/10.1007/s00408-014-9641-2.