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Characterization of lymphangioleiomyomatosis patients with discordance between spirometric and diffusion measurements of pulmonary function

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Abstract. *Background:* A subset of lymphangioleiomyomatosis (LAM) patients present with normal FEV1 and FVC but with reduced DLCO. Patients with an isolated reduction in DLCO in other diseases appear to be at higher risk for pulmonary hypertension and worse survival but this has not been previously described in LAM patients. *Objective:* To characterize the prevalence and clinical progression of LAM patients who present with discordantly low DLCO. *Methods:* This was a retrospective cohort study of LAM patients in two centers in the United States and Brazil. Discordant DLCO was defined as FEV1 >80% predicted, FVC >80% predicted, and DLCO<80% predicted. We compared the rate of decline in pulmonary function, pulmonary artery to aorta (PA-A) ratio, and VEGF-D levels in patients with concordant and discordant DLCO. *Results:* The overall prevalence of discordant DLCO was 26.0%. Patients with discordant DLCO did not have a higher rate of yearly decline in FEV1 (-1.0±0.6 vs -1.0±0.6, p=0.50), FVC (-1.0±0.7 vs -0.3±0.8, p=0.54), or DLCO (-2.2±0.9 vs -1.6±0.6, p=0.79). They did not have higher rates of PA-A ratio>1 (23.3% vs 20.1%, p=1.00). Patients with discordant DLCO did not have higher levels of VEGF-D (1214±1256 pg/mL vs 1706±1214 pg/mL, p=0.07). *Conclusions:* LAM patients who present with a discordantly low DLCO do not appear to have different rates of decline in pulmonary function. Additional biological and radiographic markers are needed to more fully characterize this population. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 206-212)*

Key words: DLCO, FEV1, lymphangioleiomyomatosis, pulmonary artery to aorta ratio, VEGF

Introduction

Pulmonary lymphangioleiomyomatosis (LAM) is an interstitial lung disease characterized by abnormal smooth muscle cell proliferation and cystic destruction of the lungs. Some patients with LAM are diagnosed because of screening programs in tuberous sclerosis populations or because of incidental findings on chest imaging; others because of symptoms including dyspnea, recurrent pneumothorax/chylothorax, hemoptysis, or symptoms related to renal angiomyolipomas. Depending on the timing of diagnosis, patients may have varying degrees of pulmonary impairment at presentation, ranging from near normal, to severely reduced pulmonary function tests (PFTs) (1).

A subset of LAM patients present with normal FEV1 and forced vital capacity (FVC) but with

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reduced diffusion capacity of the lungs for carbon monoxide (DLCO). The clinical significance of this finding is unclear although patients with an isolated reduction in DCLO in other diseases such as systemic sclerosis appear to be at higher risk for pulmonary hypertension (PH) and reduced survival (2). Possible mechanisms for a discordantly low DLCO in LAM patients include concurrent PH from reduced pulmonary vascular capacitance or from LAM cell invasion and vascular remodeling of the pulmonary arterial walls (3-53, 45). Alternatively, patients with discordantly low DLCO may have LAM-associated intrapulmonary shunts whereby increased nitric oxide synthase III by LAM cells results in pulmonary vasodilation and shunting (6, 7). This process would be similar to patients with hepatopulmonary syndrome, which has also been characterized by discordantly low DLCO (8).

Regardless of etiology, there are limited data on the prevalence of discordant DLCO among LAM patients or on disease progression in this population. We do not know to what extent a discordant DLCO corresponds to measures of PH, such as pulmonary artery to aorta (PA-A) ratio on chest computed tomography (CT), or to disease burden, as measured by vascular endothelial growth factor-D (VEGF-D) levels (9, 10). Given that treatment with the mammalian/mechanistic target of rapamycin (mTOR) inhibitor rapamycin does not seem to prevent decline in DLCO as significantly as FEV1, characterizing patients with discordant DLCO may also help identify a population at risk for disease progression despite treatment (11).

The purpose of this study was to identify the prevalence of discordantly low DLCO in LAM patients at the time of first complete PFTs and to determine whether discordance is associated with decline in PFTs, PA-A ratio, and VEGF-D levels compared to LAM patients with concordant DLCO.

Materials and methods

This was a two site retrospective cohort study of patients with sporadic or tuberous sclerosis complex (TSC)-associated LAM followed at Brigham and Women's Hospital (BWH) in the United States and the University of Sao Paulo (USP) in Brazil from 1992-2016 (BWH dates) and 2006-2016 (USP dates). Patients were diagnosed with LAM based on European Respiratory Society (ERS) guidelines (12), including by lung biopsy, the presence of lung cysts plus TSC plus renal or abdominal angiomyolipomas, lung cysts plus VEGF-D >800 picograms per milliliter (pg/mL) (when available), or lung cysts plus chylothorax. For each patient, we recorded sporadic or TSC-LAM, method of diagnosis, history of pneumothorax, chylothorax, or pleurodesis, smoking history, age at lung function tests, length of available follow-up time, and treatment with mTOR inhibitors, if any.

Pulmonary function tests were performed according to American Thoracic Society/ERS standards with reference values for percent predicted FEV1, FVC, and DLCO specific to the Brazilian and United States populations, respectively (13,14). The same reference values were used for the percent predicted calculations for each test at each site. Patients were considered to have discordant DLCO if they had a FEV1 >80% predicted, a forced vital capacity FVC >80% predicted, and a DLCO <80% predicted. They were considered to have a very discordant DLCO if they had a FEV1 >80% predicted, FVC>80% predicted, and a DLCO <65% predicted.

To assess the yearly rate of decline in DLCO, we included patients with three or more complete set of PFTs performed over more than one year. We calculated rate of yearly change in patients with discordant and very discordant versus non-discordant DLCO. To assess whether discordant DLCO was associated with concurrent PH, we selected PA-A ratio as our measure of PH. PA-A ratio has a specificity of between 72-92% for PH in patients with interstitial lung disease and a positive predictive value between 73-96% (9). PA-A ratio has the additional advantage of being available at the time of diagnosis for most patients given the role of CT in identifying imaging characteristics consistent with LAM. We measured PA-A ratio at the level of the PA bifurcation as previously described (15). We excluded patients whose first available CT was not within one year of their initial set of PFTs.

To assess whether discordant DLCO was associated with differences in VEGF-D levels, we included patients who had a VEGF-D level within one year of their initial PFTs. We further divided patents into those with and without a VEGF-D level >800 pg/mL, the threshold of diagnostic specificity for LAM (16).

Statistical analysis

Data are presented descriptively. We used t-tests (for normally distributed) and Wilcoxon rank sum (for non-normally distributed) to compare continuous variables and Fisher exact tests to compare categorical variables. All analyses were performed using Stata (Version 14, Stata Corp, College Station, Texas). The Institutional Review Boards at BWH and at USP approved this study.

Results

Of the 89 patients in the BWH cohort, 7 (7.9%) were excluded from the full cohort because they did not have documented PFT data available. Among the 82 included patients, 27 (32.9%) had a discordant DLCO and 9 (11.0%) had a very discordant DLCO. All 72 patients in the USP cohort had PFTs, 13 (18.0%) of whom had a discordant DLCO and 4 (5.5%) of whom had a very discordant DLCO. The overall prevalence of discordant DLCO was 26.0%. There was no significant difference in initial FEV1, FVC, or DLCO in the two cohorts. Other clinical characteristics of the study cohort are listed in Table 1.

There was no difference between patients with and without discordant DLCO in smoking status (18.5% vs 26.5%, p=0.23), diagnosis of sporadic LAM (77.5% vs 69.0%, p=0.42), history of pneumothorax (40.0% vs 48.9%, p=0.36) or chylothorax (12.5% vs 13.3%, p=1.00), or age (42.9±10.8 vs 42.2±11.1, p=0.72). There was no difference in treatment with mTOR inhibitors between the two groups (30.0% vs 37.7%, p=0.44) or in the duration of follow-up time (median 3.4 vs 4.5 years, p=0.55 by Wilcoxon rank-sum). In the BWH cohort there was no difference in need for supplemental oxygen at rest

Table 1. Full cohort characteristics

	BWH	USP	Combined
Age	44.3±11.1	40.0±10.0	42.4±11.0
Length of follow-up, median (IQR)*	5.6 (3.3-7.6)	2.0 (1.0-5.0)	4.0 (2.0-7.4)
S-LAM	57 (70.4%)	52 (72.2%)	109 (71.2%)
TSC-LAM	24 (29.6%)	20 (27.8%)	44 (28.8%)
Method of diagnosis			
Lung biopsy	37 (45.6%)	27 (51.4%)	62 (41.8%)
Lung cysts plus TSC plus abdominal or renal angiomyolipoma	20 (24.7%)	17 (23.6%)	37 (24.2%)
Lung cysts plus abdominal or renal angiomyolipoma	21 (25.9%)	12 (16.7%)	33 (21.6%)
Lung cysts plus chylothorax	1 (1.2%)	5 (6.9%)	6 (3.9%)
Lung cysts plus increased levels of VEGF-D	2 (2.5%)	1 (1.4%)	3 (2.0%)
History of pneumothorax	32 (39.5%)	39 (54.2%)	71 (46.4%)
History of chylothorax	9 (11.1%)	11 (15.3%)	20 (13.1%)
History of pleurodesis	30 (37.0%)	27 (37.5%)	57 (37.2%)
Former smoker	25 (30.9%)	11 (15.3%)	36 (23.2%)
mTOR treatment	33 (40.2%)	22 (30.5%)	55 (35.7%)
Initial percent predicted FEV1	82.5±23.6	74.6±25.0	78.8±24.5
Initial percent predicted FVC	94.0±18.2	87.3±17.1	90.9±17.9
Initial percent predicted DLCO	68.4±23.4	69.1±27.1	68.7±25.1
PA-A ratio	0.90±0.13	0.90±0.11	0.90±0.12
PA-A ratio >1	15 (29.4%)	12 (16.7%)	27 (21.9%)
VEGF-D level, median (IQR)*	1427 (564-2833)	816 (337-1038)	964 (502-1618)
VEGF-D >800	23 (63.9%)	16 (51.6%)	39 (58.2%)

Reported as means and standard errors unless otherwise noted. *P<0.05
DLCO=diffusion capacity of the lung for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; mTOR=mammalian target of rapamycin; PA-A=pulmonary artery to aorta; S-LAM=sporadic lymphangioleiomyomatosis; TSC-LAM=tuberous sclerosis complex lymphangioleiomyomatosis; VEGF-D=vascular endothelial growth factor-D

at the time of initial PFTs (3.7% vs 7.1%, p=1.00). In the USP cohort, there was no difference in six minute walk test (522.3±92.5 vs 460.9±124.0, p=0.10). Data on six minute walk was not consistently available in the BWH cohort.

In the BWH cohort, 48 (58.5%) of the included patients had three or more complete PFTs available and performed over more than one year. Patients with discordant DLCO were not more likely to have longitudinal PFTs available (55.6% vs 58.9%, p=0.81). There was a significant difference in FEV1 and FVC between patients with concordant and discordant DLCO on initial PFTs but not in DLCO. There was no difference in the change in percent predicted FEV1, FVC, or DLCO per year between the two groups (Figure 1, Table 2). Patients with discordant DLCO did not have lower DLCO at the time of the last available PFTs compared to those without discordant DLCO (Table 2).

All patients in the USP cohort and 51 (62.2%) patients in the BWH cohort had a chest CT within 1 year of their initial PFTs and available for review. A PA-A ratio>1 was not more common in patients with discordant DLCO in the individual or combined cohorts (23.3% vs 20.1%, p=1.00) (Table 3). Nor was a PA-A ratio>1 more common in patients with very discordant DLCO (21.9% vs 22.2%, p=1.00 for the combined cohorts).

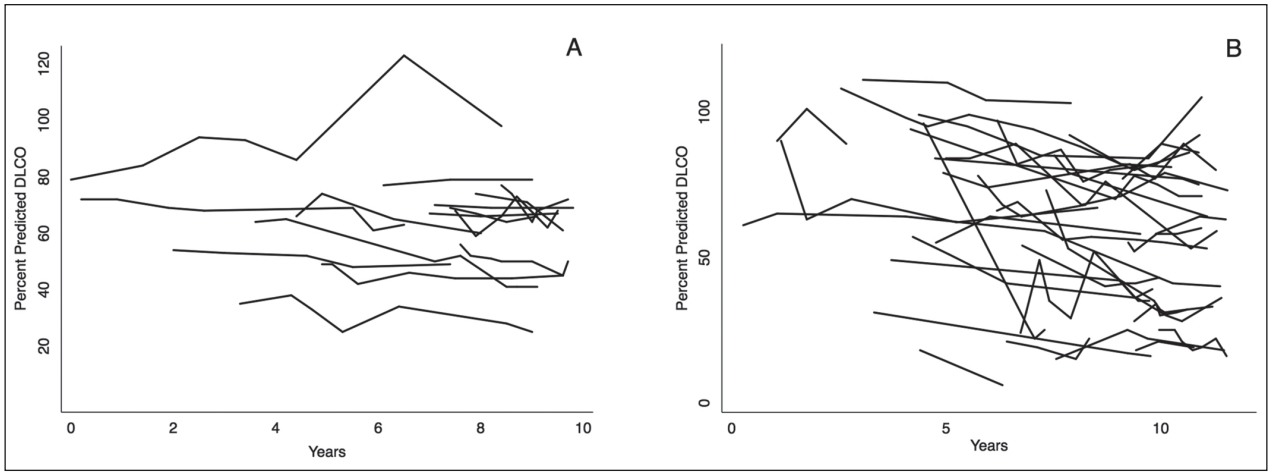

Fig. 1. Change in percent predicted diffusion capacity of the lung for carbon monoxide (DLCO) over time in patients with concordant (A) and discordant (B) DLCO on initial pulmonary function tests. There was no significant difference in mean yearly change between the two groups (-2.2±0.9 versus -1.6±0.6, p=0.79). Brigham and Women's Hospital cohort only

Table 2. Initial, final, and change per year in pulmonary function tests in patients with concordant and discordant diffusion capacity of the lungs for carbon monoxide in Brigham and Women's Hospital cohort

	Concordant DLCO (n=33)	Discordant DLCO (n=15)	p value
Initial percent predicted FEV1	73.4±4.0	98.9±4.3	<0.001
Initial percent predicted FVC	86.0±3.1	103.3±3.5	0.002
Initial percent predicted DLCO	67.3±5.0	65.1±3.1	0.78
Change in percent predicted FEV1 per year	-1.0±0.6	-1.8±0.9	0.50
Change in percent predicted FVC per year	-1.0±0.7	0.3±0.8	0.54
Change in percent predicted DLCO per year	-2.2±0.9	-1.6±0.6	0.79
Follow-up time (years)	5.3±0.7	3.9±0.5	0.17
Final percent predicted FEV1	70.0±4.6	93.5±4.5	0.003
Final percent predicted FVC	82.1±3.4	104.5±3.7	<0.001
Final percent predicted DLCO	55.1±4.8	60.9±4.3	0.46

Reported as means and standard errors
DLCO=diffusion capacity of the lung for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; PFTs=pulmonary function tests

Table 3. Difference in pulmonary artery to aorta ratio in patients with discordant, very discordant, and non-discordant DLCO

	Brigham and Women's Hospital			University of Sao Paolo			Combined		
	Non-discordant DLCO (n=35)	Discordant DLCO (n=16)	p value	Non-discordant DLCO (n=59)	Discordant DLCO (n=13)	p value	Non-discordant DLCO (n=94)	Discordant DLCO (n=29)	p value
PA-A ratio >1, n (%)	10 (28.6%)	5 (31.3%)	1.00	11 (18.6%)	1 (7.7%)	0.68	21 (22.3%)	6 (20.1%)	1.00
	Non-very discordant DLCO (n=46)	Very discordant DLCO (n=5)	p value	Non-very discordant DLCO (n=68)	Very discordant DLCO (n=4)	p value	Non-very discordant DLCO (n=114)	Very discordant DLCO (n=9)	p value
PA-A ratio >1, n (%)	13 (28.3%)	2 (40.0%)	0.62	12 (17.6%)	0 (0.0%)	1.00	25 (21.9%)	2 (22.2%)	1.00

DLCO=diffusion capacity of the lungs for carbon monoxide; PA-A=pulmonary artery to aorta

Table 4. Difference in vascular endothelial growth factor-D in patients with discordant, very discordant, and non-discordant DLCO

	Brigham and Women's Hospital			University of Sao Paolo			Combined		
	Non-discordant DLCO (n=21)	Discordant DLCO (n=15)	p value	Non-discordant DLCO (n=28)	Discordant DLCO (n=3)	p value	Non-discordant DLCO (n=49)	Discordant DLCO (n=18)	p value
VEGF-D, mean±SD	1740±1664	1885±1246	0.78	807±436	819±437	0.73	1214±1256	1706±1214	0.07
VEGF-D >800, n (%)	12 (57.1%)	11 (73.3%)	0.48	14 (50.0%)	2 (66.7%)	1.00	26 (53.1%)	13 (72.2%)	0.17
	Non-very discordant DLCO (n=31)	Very discordant DLCO (n=5)	p value	Non-very discordant DLCO (n=30)	Very discordant DLCO (n=1)	p value	Non-very discordant DLCO (n=61)	Very discordant DLCO (n=6)	p value
VEGF-D, mean±SD	1709±1543	2366±1010	0.37	1258±508	—	—	1266±1253	2158±1037	0.03
VEGF-D >800, n (%)	18 (58.1%)	5 (100.0%)	0.13	15 (50.0%)	1 (100.0%)	—	33 (54.1%)	6 (100.0%)	0.04

DLCO=diffusion capacity of the lungs for carbon monoxide; SD=standard deviation; VEGF-D=vascular endothelial growth factor-D

31 (43.0%) patients in the USP cohort and 36 (43.9%) patients in the BWH cohort had an available VEGF-D level within one year of their initial PFTs. In the combined cohort there was a trend toward higher VEGF-D levels in patients with discordant DLCO (Table 4). Patients with a very discordant DLCO had higher VEGF-D levels (Table 4). This relationship did not change in significance after excluding the 15 patients who were being treated with mTOR inhibitors at the time that VEGF-D level was measured. In neither the individual nor combined cohorts did patients with discordant DLCO have higher rates of VEGF-D levels >800 pg/mL even after excluding patients treated with mTOR inhibitors. Patients with a very discordant DLCO had higher rates of VEGF-D levels >800 pg/mL in the combined cohort even after excluding patients treated with mTOR inhibitors.

Discussion

Some patients with LAM present with normal spirometric function but an isolated impairment in DLCO. The prevalence of this finding has not been described in large cohorts and it is unknown whether discordantly low DLCO is related to concurrent PH. Our primary findings were that: 1) a discordantly low DLCO is not uncommon in LAM patients with a prevalence ranging from 18-33%; 2) patients with discordantly low DLCO have the same rate of decline in PFTs as patients with concordant DLCO and do not appear to differ significantly with regard to LAM clinical characteristics; 3) patients with discordantly low DLCO do not have higher rates of PA-A>1; and 4) patients with very discordant DLCO have higher VEGF-D with a trend toward higher VEGF-D in patients with discordant DLCO.

To our knowledge, this is the first study in LAM patients to focus specifically on discordant DLCO. Isolated reductions in DLCO, however, have been reported in patients with other interstitial lung diseases. For example, Steen et al found that 19% of patients with systemic sclerosis had an isolated reduction in DLCO at presentation (3). These patients were at higher risk for developing PH, particularly those with an initial DLCO <55% predicted. Small cohort studies of patients with rheumatoid arthritis-associated interstitial lung disease, Sjogren's disease, and systemic lupus erythematosis have identified a prevalence of discordantly low DLCO ranging from 20.0-31.4% (17-1917, 18, 19). Authors in these studies hypothesized that discordant reduction in DLCO may be related to concurrent PH, although this was not directly assessed.

We did not find that LAM patients with discordantly low DLCO had increased rates of PA-A >1, our marker for PH. There are several possible explanations for this observation. Although PA-A ratio >1 is relatively specific for mean PA pressure >25 mmHg it has not previously been validated in LAM. Given that patients with other obstructive lung diseases and a PA-A ratios >1 have mPA pressure of 31±10 mmHg, there is no specific reason not to expect a correlation in LAM (20). It may be that more time is needed for PH to emerge in a way that begins to differentiate the two populations. For example, Cottin et al. found that the mean onset of PH in LAM patients was 9 years after initial diagnosis and that two of the four patients with mPAP>35 had normal FEV1 (5). In contrast, the average follow-up time for patients with discordant DLCO in our cohort was 3.9 years. It may be that serial CT measurements would reveal increasing numbers of patients with PA-A>1 in that population.

The rate of decline in FEV1and DLCO was similar in our cohort as has been previously described in LAM (21). As has also been reported, approximately 5% of patients had a more rapid decline in FEV1 and DLCO (22). The sample size was insufficient to assess whether this was more common in patients with discordant DLCO. Finally, patients with discordant DLCO did not have higher levels of VEGF-D, even after excluding patients receiving inhibitors of the mTOR pathway, which lowers VEGF-D levels (23). This is consistent with the small literature on VEGF and systemic lupus erythematosus where VEGF levels have not been associated with discordantly low DLCO (24). Together with the fact that patients with discordant DLCO did not have high rates of VEGF-D >800 pg/mL, this suggests that discordance is not simply a function of LAM cell disease burden (10). However, the fact that patients with very discordant DLCO had higher levels of VEGF-D may indicate a connection with LAM cell burden at the extremes. Recent evidence demonstrates that activating mutations in VEGF-D can result in aberrant pulmonary vasculature through enhanced signaling via VEGFR-2 (25). Whether increased levels of VEGF-D can result in similar changes to the pulmonary vasculature remains to be investigated. This should be treated as hypothesis generating given the small numbers of patients in the very discordant DLCO population.

As in other areas of LAM research, novel biomarkers may help better identify and characterize the pathogenesis of DLCO discordance. One candidate is endostatin, which is associated with lymphangiogenesis and has shown to be elevated in patients with pulmonary arterial hypertension but not in controls (26, 27). Serial measurements of endostatin could help establish a connection between DLCO discordance and PH and serve as a prognostic measure, as in pulmonary arterial hypertension (25). Alternatively, additional radiographic assessments such as ultrashort echo-time magnetic resonance imaging (UTE MRI) may help identify a cystic destruction pattern that is associated with discordant DLCO. For example, if peripheral capillary destruction and subsequent centralization of blood flow is a primary driver of isolated low DLCO, this could be identified as low signal intensity on UTE MRI (28). Finally, if the mechanism of discordant DLCO is related to intrapulmonary shunt, then further characterization with contrast-enhanced echocardiography may be beneficial (7).

Our study has several limitations. First, because this was a retrospective cohort, we were limited to previously collected data. As a result, multiple patients in the BWH and USP cohorts lacked data on PA-A ratio and VEGF-D levels. Second, patients were not routinely screened for PH with cardiac catheterization so we do not have direct assessment of pulmonary pressures. Prospective research involving the correlation of cardiac catheterization with PA-A ratio and echocardiographic findings of PH is necessary to fully characterize the role of PA-A ratios in this population. Finally, we did not include

information on specific clinical outcomes such as functional status, oxygen dependence, or time to transplantation or death. As patients with discordantly low DLCO are better characterized these data will be important to establish the clinical significance of an isolated low DLCO at initial LAM diagnosis.

Conclusion

Patients with LAM who present with discordantly low DLCO do not appear to have a more rapid decline in their pulmonary function nor are they more likely to have a PA-A ratio>1 on CT near the time of diagnosis. VEGF-D levels are higher in patients with very discordant DLCO. Additional biomarkers as well as longitudinal follow-up data, including serial assessments for PH, are necessary to more fully characterize this population and to assess their risk for adverse clinical outcomes.

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