Effect of non-uniform cyst distribution in lymphangioleiomyomatosis on pulmonary function: a cross-sectional study

To the Editor:

Lymphangioleiomyomatosis (LAM) is a rare multi-system lung disease that may involve the kidneys (e.g. angiomyolipomas; AML) and lymphatics (e.g. lymphangioleiomyomas, chylous effusions). LAM occurs with increased frequency in patients with tuberous sclerosis complex (TSC), an autosomal-dominant neurocutaneous disorder, associated with mutations in the TSC1 and TSC2 genes [1, 2]. LAM predominantly affects women of childbearing age, although it is found as well in post-menopausal women. Patients with LAM develop cysts throughout their lungs, leading to a reduction of pulmonary function, e.g. forced expiratory volume in 1 s (FEV1) or diffusion capacity of the lung for carbon monoxide (DLCO) [2]. Although LAM has been described as a diffuse cystic lung disease with a homogeneous distribution [2, 3], we report here that LAM patients have more cystic disease in the middle regions of the lung with effects predominately on FEV1 [2].

The entire study population consisted of 113 LAM patients. Of this population, nine patients were excluded due to lack of visible cysts, unavailable pulmonary function test results, and blurry computed tomography (CT) scans. The mean±sd age of the study participants (n=104) at the time of the scans was 49.8±10.2 years. Of these 104 LAM patients, 81 individuals were Caucasian, with 77 being non-Hispanic and four of Hispanic descent. There were eight non-Hispanic Asian Americans, seven non-Hispanic African Americans, one non-Hispanic Pacific Islander, three multiracial non-Hispanic patients, one multiracial patient of Hispanic descent and three of unknown racial origin. In this population, AMLs were documented in 58 patients, lymphangioleiomyomas in 77 patients, history of pneumothorax in 34 patients, and chylothorax in 39 patients. Patients were diagnosed with LAM based on lung biopsy, or CT and the presence of renal angiomyolipomas, vascular endothelial growth factor-D (VEGF-D) >800 pg·mL\(^{-1}\) and/or a diagnosis of TSC [2, 4]. All patients provided written informed consent, and chest CT scans were obtained in LAM patients (n=104, all-female, age 49.7±11.2 years) enrolled consecutively in a clinical study at the National Institutes of Health (NHLBI protocol 95-H-0186).

On some of the acquired CT scans, we noted on review that the lung involvement was more visible in the middle half of the lungs than in the top and bottom quarters. Thus, we hypothesised that the volume occupied by the cysts is more in the middle half of the lung compared to the rest of the lung. To test our hypothesis, we used the US Food and Drug Administration-approved software provided by the vendor of the CT scanner and measured the regional percentage of the parenchymal volume occupied by cysts, or cyst score. To avoid the effect of anatomical variation on our lung volume measurements, we divided the lung based on its vertical length, measured by the number of slices covering the entire lung volume. We measured the full length of the lung and divided it to four equal regions. The cyst score was determined for the total lung, top quarter, middle half and the bottom quarter (figure 1a). Wilcoxon signed-rank test was used to assess the uniformity of cyst distribution. We performed principal component analysis among the local cyst scores and multiple linear regression analysis for the correlation between these components and lung function tests, e.g. percent of predicted FEV1, FEV1 to forced vital capacity ratio (FEV1/FVC), and percent of predicted DLCO.

The average cyst scores of full lungs, top quarter, middle half and the bottom quarter were measured to be 9.89%, 7.73%, 10.87% and 8.31%, respectively. The cyst scores (percent of lung occupied by cysts) [5] of

Cysts in LAM patients tend to be more concentrated in the middle half of the lungs. FEV1 but not DLCO is influenced by cyst distribution. https://bit.ly/3p8z9CF

the top and bottom quarters of the lungs were significantly lower than that of the full-lung (p<0.001 and p=0.037), whereas that of the middle half was significantly greater than that of the full-lung (p<0.001) (figure 1b).

Multiple linear regression analysis showed that FEV1 and FEV1/FVC are predicted by a combination of the full-lung cyst score (p<0.001) and the difference between the mid-half and the rest of the lung (p<0.001 and R2=0.57). For patients with the same full-lung cyst scores, those with higher middle lung involvement had a lower FEV1 and FEV1/FVC (p<0.001). DLCO was predicted by the full-lung cyst score (R2=0.52) and was not significantly correlated with the cyst distribution (p=0.54).

In the present study of lung high-resolution CT (HRCT) scans and pulmonary function, we observed that the two middle quartiles of the lung were found to be significantly more populated by cysts than the upper or lower quartiles. Further, involvement of middle region of the lung with cysts was most likely to have significant effects on FEV1, with no significant effects on DLCO. LAM is thought to have lymphatic origins, with an increase in lymphatic biomarkers, such as the lymphangiogenesis marker, VEGF-D [4, 6–8], invasion of the axial lymphatics and associated lymph nodes with LAM cells [9], and the presence in chylous effusions of LAM cell clusters [10], which are LAM cells encircled with lymphatic endothelial cells [10, 11]. However, there is no clear explanation for why LAM cysts populate preferentially the middle half of the lung. Of interest, the preferential location of cysts in the middle of the lung, does not correlate with the preferential location of lymphatics in the lung bases.

Patients with LAM present with both abnormal FEV1 and DLCO [12], in some cases, with predominant effects on one or the other of the pulmonary functions [2]. In these cases, differential effects on HRCT are seen [13, 14], as shown in the present report. These data suggest that there are different mechanisms for the pathogenesis of LAM, with differential effects on cyst formation. This study supports the model that LAM is a heterogenous disease with different subtypes related to cyst location and resulting effects on pulmonary function.

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