Pulmonary lymphangioleiomyomatosis: Analysis of disease manifestation by region-based quantification of lung parenchyma

Poster No.: C-2112  
Congress: ECR 2014  
Type: Scientific Exhibit  
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Keywords: Respiratory system, Lung, Thorax, CT, Computer Applications-3D, Genetic defects  
DOI: 10.1594/ecr2014/C-2112

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Lymphangioleiomyomatosis (LAM) is a rare idiopathic multisystem disorder first described in 1937 by von Stossel et al. (1,2). It has an estimated incidence ranging between 1 and 2.6 cases per 1000,000 patients (3,4) and affects almost exclusively women of reproductive age (5,6,7). LAM occurs sporadically in patients with no evidence of genetic disease and in about one third of women with tuberous sclerosis complex (TSC), an autosomal dominant disease characterized by hamartomas involving multiple organs (8-10). Both diseases are caused by mutations in one of the two tumor suppressor genes tuberin (TSC2) and hamartin (TSC1) (11, 12). The pathology of LAM is characterized by the nonneoplastic proliferation of atypical smooth muscle cells in the walls of airways, venules and lymphatic vessels of the lung, resulting in hurdle and thickening of interstitial tissue and in small airway obstruction leading to air trapping, dyspnea and eventual respiratory failure (13,14). Disease severity and progression are evaluated with pulmonary function and gas exchange testing as well as imaging findings.

To date, there is no effective therapy for LAM, but there are case studies and clinical trials that showed disease stabilization by progesterone and oophorectomy in a small number of patients. Newer drugs for the treatment of LAM, under which in some studies an improvement of pulmonary symptoms could be detected, are sirolimus (rapamycin) and doxyclin. In the advanced stage of the disease lung transplantation is still the best therapy (15,16). The aim of this study was to evaluate the typical distribution of cystic defects in LAM with quantitative volumetric chest computed tomography (CT). Of special interest was the distribution between the central lung areas and the subpleural space.
Methods and materials

We cross-referenced the database of the Department of Pulmonology at the Charité university hospital, Berlin - a referral center for the treatment of LAM - with the radiology information system (RIS) to identify all patients with confirmed LAM who had undergone CT imaging of the lung at our institution. A total of 20 patients with confirmed diagnosis of LAM and had been examined by CT imaging between 2002 and 2013 were identified. All patients were women. The average age at time of presentation was 40.4 years (range: 21 - 62 years). Patients with concomitant lung pathologies were excluded. The diagnosis of LAM was confirmed in each case by histopathology from resected or biopsied tissue samples and examined by an experienced pulmonary pathologist.

CT studies were performed on multivolume CT scanners (different vendors: Toshiba Aquilion ONE 320-slice, Toshiba Aquilion 64, Toshiba Aquilion 16, Philips Mx8000IDT 16, General Electric Light Speed VCT 64, General Electric Light Speed Power 16, General Electric Light Speed Ultra 8). Slice thickness was 0.5 - 7.0 mm (0.5 mm (N=5); 0.625 mm (N=1); 1.0 mm (N=5), 1.250 mm (N=3), 2.0 mm (N=2), 5.0 mm (N=3), 7.0 mm (N=1)).

Scans were obtained in deep inspiration with or without intravenous contrast medium.

Analysis of region-based quantification of lung parenchyma was performed by the PULMO 3D software (v3.42, Fraunhofer MEVIS, Bremen, Germany). This software package enables the segmentation of lung areas with a density of -950 and lower to identify cystic lung areas and to determine the ratio of normal and emphysematous lung parenchyma (i.e. emphysema score).

We used this software to obtain region-based quantification of lung parenchyma. As the regional distribution of the cysts in the lungs was of interest, we divided each lung into three horizontal stacks (upper, middle and lower thirds) with identical number of slices. In addition, we defined a "peel" of the lung comprising of a 2 cm subpleural space and a "core" for the remaining inner lung area (Fig.1). The PULMO software enables the automatic segmentation between core and peel based on the selected diameter of the peel.

In order to show differences between different lung areas a statistical analysis was performed using the Wilcoxon test. A p-value of < 0.05 was considered significant.

Statistical analysis was performed with IBM SPSS Statistics 19.0.0.
Fig. 1: To obtain region based quantification between central and peripheral lung areas the lung was automatically segmented using the PULMO software based on the selected diameter of the "peel" (purple lines). Fig 1A shows a slice before and Fig. 1B after segmentation based on a density of HU -950 or lower.

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Results

Total lung volume ranged from 1.610 liters to 6.163 liters. Cystic changes accounted for 0.1 to 39.1% of the total lung volume with a median of 18.2%. Lower thirds of lung parenchyma showed significantly less cystic changes than upper or middle lung areas and also in comparison to upper and middle lung areas combined (lower third: median 13.37, upper and middle thirds: median 19.01; p = 0.001) (Fig 2, 3). Disease manifestation in the central lung was significantly higher than in peripheral areas (peel median: 15.1%, core median: 20.5%; p = 0.001, Fig. 3). There was no difference in the localization of cystic lesions considering the distribution between central and peripheral lung areas between mild and severe cases of LAM (p = 1.0).
Fig. 2: 3D visualization of cystic changes due to LAM in a 30 years-old patient by the PULMO 3D software (A). For comparison the coronal reformatted CT of the same patient (B). Cystic changes in this patient accounted for 11% of total lung volume. The preponderance of cystic changes in the upper lung fields can be appreciated.

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Fig. 3: Histogram showing the distribution of lung densities for the whole lung (left dotted line), the upper lung field (purple line), middle lung field (blue line), and lower lung field (green line). For the upper lung field voxels exhibit lower densities consistent with the overall observation that cysts in LAM are predominantly located in upper lung fields.

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Fig. 4: 3D images of a 21 years-old woman with LAM. This transparent view shows the preferred location of the cysts more in the central lung areas (core) compared to the periphery (peel).

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Conclusion

The distribution of cystic lesions in LAM was shown to be significantly more pronounced in the central lung areas compared to the subpleural space. There is a significant preponderance of cystic changes in the apical and intermediate lung zones compared to the lung bases.
References