European Journal of Radiology 84 (2015) 732–737

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

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

D. Theilig[a,*,1], F. Doellinger[a,1], J.M. Kuhnigk[b], B. Temmesfeld-Wollbrueck[c], R.H. Huebner[c], N. Schreiter[a], A. Poellinger[a]

[a] Charité, Universitätsmedizin Berlin, Department of Radiology, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
[b] Fraunhofer MEVIS, Universitaetsallee 29, 28359 Bremen, Germany
[c] Charité, Department of Pneumology, Augustenburger Platz 1, 13353 Berlin, Germany

ARTICLE INFO

Article history:
Received 23 August 2014
Received in revised form
18 December 2014
Accepted 24 December 2014

Keywords:
Thoracic imaging
Quantitative methods
Computed tomography
Lymphangioleiomyomatosis

ABSTRACT

Purpose: Lymphangioleiomyomatosis (LAM) is characterized by proliferation of smooth muscle tissue that causes bronchial obstruction and secondary cystic destruction of lung parenchyma. The aim of this study was to evaluate the typical distribution of cystic defects in LAM with quantitative volumetric chest computed tomography (CT).

Materials and methods: CT examinations of 20 patients with confirmed LAM were evaluated with region-based quantification of lung parenchyma. Additionally, 10 consecutive patients were identified who had recently undergone CT imaging of the lung at our institution, in which no pathologies of the lung were found, to serve as a control group. Each lung was divided into three regions (upper, middle and lower thirds) with identical number of slices. In addition, we defined a "peel" and "core" of the lung comprising the 2 cm subpleural space and the remaining inner lung area. Computerized detection of lung volume and relative emphysema was performed with the PULMO 3D software (v3.42, Fraunhofer MEVIS, Bremen, Germany). This software package enables the quantification of emphysematous lung parenchyma by calculating the pixel index, which is defined as the ratio of lung voxels with a density <−950 HU to the total number of voxels in the lung.

Results: Cystic changes accounted for 0.1–39.1% of the total lung volume in patients with LAM. Disease manifestation in the central lung was significantly higher than in peripheral areas (peel median: 15.1%, core median: 20.5%; $p = 0.001$). Lower thirds of lung parenchyma showed significantly less cystic changes than upper and middle lung areas combined (lower third: median 13.4, upper and middle thirds: median 19.0, $p = 0.001$).

Conclusion: The distribution of cystic lesions in LAM is significantly more pronounced in the central lung compared to peripheral areas. There is a significant predominance of cystic changes in apical and intermediate lung zones compared to the lung bases.

1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare idiopathic multisystem disorder with progressive cystic destruction of the lungs. It has an estimated prevalence of about 1 in 1,000,000 people and affects almost exclusively women of reproductive age [1]. LAM occurs sporadically in patients with no evidence of genetic disease and in about one third of women with tuberous sclerosis complex (TSC) [2,3]. The pathology of LAM is characterized by proliferation of atypical smooth muscle cells in the walls of airways, venules and lymphatics leading to air trapping and formation of cysts in the lung [4]. The often predominant pulmonary symptoms comprise dyspnea, pneurothorax, chylous pleural effusions, haemoptysis and eventual respiratory failure [1]. Extrapulmonary manifestations of LAM include lymphadenopathy, lymphangioleiomyomas, angiomyoliomas and chylous abdominal collections [1,5]. Disease severity and progression are evaluated with pulmonary function and gas exchange testing such as FEV_1 and diffusing capacity of the lung for carbon monoxide as well as imaging findings. There have also been attempts to capture the progress of the disease with a questionnaire exploring symptoms, activity and impact of the

* Corresponding author at: Charité, Universitätsmedizin Berlin, Department of Radiology, Charité Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel.: +49 30 450 657263; fax: +49 30 450 7557137.
E-mail address: dorothea.theilig@charite.de (D. Theilig).
[1] D. Theilig and F. Doellinger are equally contributing First Authors.

http://dx.doi.org/10.1016/j.ejrad.2014.12.019
0720-048X/

disease on central aspects of life [6]. 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 [7]. Newer drugs for the treatment of LAM, under which in some studies an improvement of pulmonary symptoms could be detected, are sirolimus (rapamycin) [8,9] and doxycyclin [10,11]. In the advanced stage of the disease lung transplantation is still considered the best therapy [7]. Pathogenesis of LAM remains unclear. As recurrence of the disease after lung transplantation has been observed a metastatic mechanism has been proposed [12,13]. Since LAM occurs mainly in women of reproductive age and some of the smooth muscle cells were shown to express estrogen and progesterone receptors one of the exiting hypothesis for the pathogenesis of LAM is that of a low grade metastatic disease of the uterus [14,15].

High resolution computed tomography (HRCT) plays a pivotal role in diagnosing LAM as can be seen in the current European Respiratory Society guidelines to diagnose LAM published by Johnson et al. [16] and detailed in Section 2.

Furthermore lung screening with HRCT is recommended by the European Respiratory Society for females with TSC at the age of 18 years and if negative again at the age of 30–40 years, for females with TSC in the presence of otherwise unexplained respiratory symptoms and for patients with unilateral angiomyolipoma but no clinical features of TSC and no pulmonary symptoms [16].

Characteristic features of LAM in HRCT are described as follows by Johnson et al.: "Multiple thin-walled round well-defined air-filled cysts with preserved or increased lung volume with no other significant pulmonary involvement specifically no interstitial lung disease with the exception of possible features of multifocal micronodular pneumocyte hyperplasia in patients with TSC" [16]. Typical cyst size is reported to range from 2 to 5 mm in diameter but some may become as large as 25 mm in diameter [17]. However, in the literature the description of the cyst distribution within the lungs of patients with LAM varies from even distribution [17,18] to relative sparing of the apices in patients with mild disease [19] to predominant involvement of upper or lower lung zones [20]. Given the clinical relevance of HRCT in diagnosing LAM pointed out above elucidating the actual distribution pattern of cysts in LAM is of clinical significance. A more specific characteristic appearance of LAM in HRCT may obviate the need for biopsy in more cases and it would help to identify LAM earlier on. Early diagnosis in turn will be beneficiary to patients for they will be able to receive education on the symptoms of pneumothorax, be advised to avoid estrogen containing treatments and smoking, get prophylactic vaccination against influenza and pneumococcus as well as being monitored for progression of the disease at an earlier stage and possibly offered to participate in clinical studies [16]. Hence, the aim of this study was to evaluate the typical distribution of cystic defects in LAM in a more objective way by using quantitative volumetric chest computed tomography described in Section 2 rather then using visual scoring systems and consensus methods employed in most existing studies with a similar objective. Of special interest was the distribution in the cranio-caudal orientation and between central lung areas and the subpleural space.

2. Materials and methods

We cross-referenced the database of the department of pulmonology at the Charité University Hospital, Berlin 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 who 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 in order to eliminate confounding due to other conditions with an increased amount of low density voxels such as emphysem. Only patients with definite LAM according to the current European Respiratory Society guidelines to diagnose LAM published by Johnson et al. [16] were included. These guidelines are as follows:

"Definite LAM:

1) Characteristic or compatible lung HRCT, and lung biopsy fitting the pathological criteria for LAM; or
2) Characteristic lung HRCT and any of the following: angiomyolipoma (kidney); thoracic or abdominal chylous effusionc; lymphangioleiomyoma or lymph-node involved by LAM; and definite or probable TSC.

Probable LAM:

1) Characteristic HRCT and compatible clinical history; or
2) Compatible HRCT and any of the following: angiomyolipoma (kidney); and thoracic or abdominal chylous effusions.

Possible LAM: characteristic or compatible HRCT" [16].

We also identified 10 consecutive patients who had recently undergone CT imaging of the lung at our institution, in which no pathologies of the lung were found, to serve as a control group.

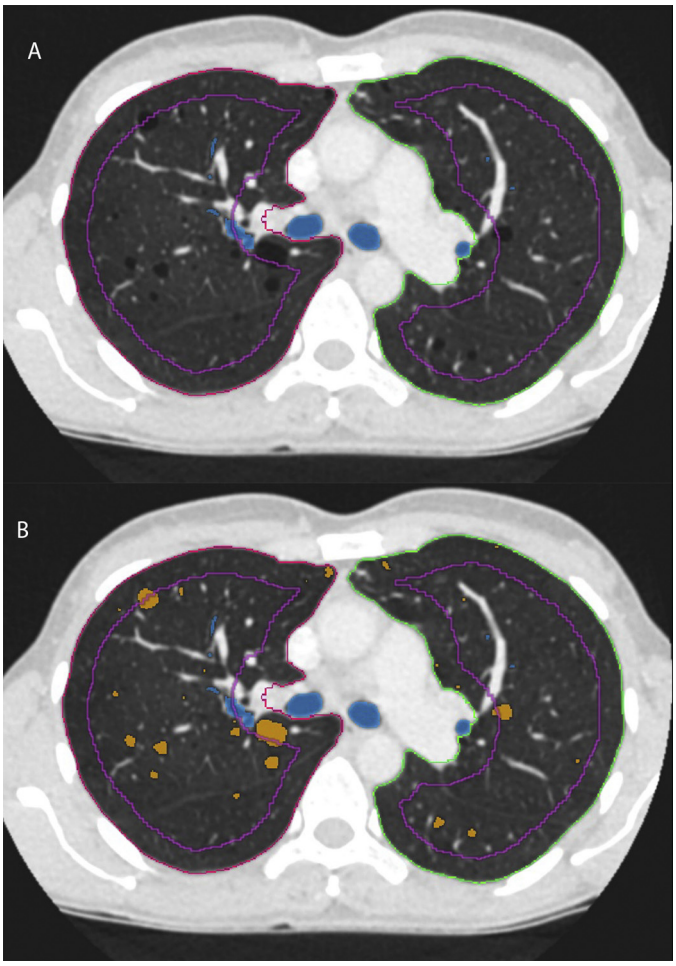

Fig. 1. In order to analyze the relative distribution of cystic changes the lung was segmented into an inner lung area defined as "core" and an outer area defined as "peel" comprising the 2 cm subpleural space.