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Cystic lung disease is not uncommon in men with tuberous sclerosis complex

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KEYWORDS
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Summary
Objective: To assess the frequency of cystic lung disease suggestive of pulmonary lymphangiomyomatosis in men with tuberous sclerosis complex.
Patients and methods: Retrospective review of CT scans of the chest and abdomen on 29 men with tuberous sclerosis complex encountered during a 13-year period, 1998 to 2010.
Results: Cystic lung disease (defined as $\geq$4 cysts) was seen in 11 of 29 men (38%) with tuberous sclerosis complex. The mean age of those with cystic lung disease was 46.3 $\pm$ 19.1 years. None of the patients had experienced pneumothorax or chylothorax and none had undergone a lung biopsy for evaluation of cystic lung disease. Lymphangiomyomatosis had been diagnosed in two of 11 patients with cystic lung disease. Renal angiomyolipomas were demonstrated in 14 of 25 patients (56%) with renal imaging available; all 14 had multiple bilateral renal involvement. In this limited cohort of patients, the presence of cystic lung disease did not correlate with age, smoking exposure or the presence of renal AMLs.
Conclusion: We conclude that tuberous sclerosis complex -related lymphangiomyomatosis may not be rare in men but is milder in severity.

Introduction

Tuberous sclerosis complex (TSC) is an inheritable disorder (autosomal dominant) characterized by multisystem hamartomas.[1–3] The prevalence of TSC is estimated to be nearly 1 per 10,000 persons.[1] Males and females are affected equally. Approximately 60% of TSC patients have no prior family history of disease and appear to represent

Abbreviations: AML, angiomyolipoma; D_{LCO}, Single breath diffusing capacity of the lung for carbon monoxide; HRCT, high-resolution CT; LAM, lymphangiomyomatosis; TSC, tuberous sclerosis complex; US, ultrasonography.

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new mutations.[1] TSC is associated with highly variable expressivity and the clinical features are age-dependent.[1,4]

Pulmonary involvement in TSC manifests mainly as pulmonary lymphangiomyomatosis (LAM) or micronodular pneumocyte hyperplasia.[5–9] LAM occurring in patients with TSC is associated with diffuse cystic lung lesions as depicted on high-resolution CT (HRCT) scanning of the chest and appears identical to sporadic LAM.[10] In both instances, LAM is characterized histologically by infiltration and proliferation of atypical smooth muscle-like cells ("LAM cells") in the lung.[11,12] Pneumothorax and chylothorax are well-recognized complications of LAM in both groups but TSC stigmata such as central nervous system, retinal, and skin lesions are not seen in patients with sporadic LAM.[11,12]

Sporadic LAM has been shown to affect almost exclusively women.[11,12] Similarly, TSC-LAM has also been thought to occur mostly in women and only rarely in men with TSC but lung involvement in men with TSC has not been adequately explored.[6–9,13] In this study, we assessed the frequency of cystic lung disease suggestive of LAM in men with TSC by retrospectively studying CT scans available in such patients seen at our medical centers.

Patients and methods

A computer-assisted search of medical records was conducted to identify men (aged 18 years or older) with TSC seen at Mayo Clinic, Rochester, MN and Jacksonville, FL during a 13-year-period between Jan. 1, 1998 and Dec. 31, 2010. Approval was obtained from the Mayo Foundation Institutional Review Board prior to beginning the study.

All subjects included in this study fulfilled the current consensus criteria for definite TSC.[3] We identified those who had undergone a CT scan of the chest and also included those who had undergone CT scan of the abdomen on which the lung parenchyma could be adequately evaluated with views of the lung extending above the dome of the diaphragm as previously described.[14] Of 44 men with TSC identified, CT scan of the chest or abdomen was available in 29 patients (66%) and included 17 with CT chest and 23 with CT abdomen (11 had both CT chest and abdomen).

The CT scans were reviewed by two of the authors (JHR, AGS) independently to identify cystic lesions (defined as round lucency with a definable thin wall) in the lung. The number and sizes of the cysts in the lung were noted. Differences in interpretation were settled by consensus. As previously described, the presence of 4 or more cysts in the lungs was designated to be abnormal.[14] Medical records of these patients were reviewed to extract data regarding age, sex, smoking history, clinical presentation, imaging studies, biopsy procedures, and diagnoses.

Statistical analysis

Subjects with lung cysts versus those without lung cysts were compared using the two-sample rank sum test for continuous variables and the chi-square (exact) test for categorical variables. In all cases p-values <0.05 were considered statistically significant.

Results

The mean age of the 29 men with TSC was 34.9 $\pm$ 16.8 years (Table 1). More than one-half were nonsmokers. TSC mutation analysis had been performed in 6 patients with mutation detected in TSC1 gene in 2 patients and TSC2 gene in 4 patients. Twenty five patients (86%) had undergone a CT abdomen or ultrasonography of the kidneys; 14 of these patients (56% of those with kidney imaging) had renal angiomyolipomas (AMLs). The indication for performing abdominal imaging was to assess for the presence of renal AMLs in all patients. All of those with renal AMLs had multiple tumors and bilateral involvement. Indications for chest CT included abnormal chest radiography (6 patients), cough (2 patients), dyspnea (2 patients), chest pain (2 patients), staging of suspected renal neoplasm (2 patients), weight loss (1 patient), and assessment for possible LAM (2 patients). Chest radiographic abnormalities that led to chest CT included increased interstitial markings (3 patients), lung nodule (2 patients), and focal infiltrate (1 patient).

Among 29 men with TSC, 11 (38%) had cystic lung disease (defined as $\geq$4 cysts) demonstrated on CT chest or abdomen (Table 2). The cystic lung lesions were identified by CT chest in 8 patients and by CT abdomen in the remaining 3

Table 1 Demographic and clinical characteristics of 29 men with TSC.

Characteristic	With cysts(n = 11)	Without cysts(n = 18)	All(n = 29)
Age, yr, median (range)	41 (25–76)	36 (18–74)	38 (18–76)
Ethnicity, no. (%)			
Caucasian	10 (91)	17 (94)	27 (93)
Hispanic	1 (9)	1 (6)	2 (7)
Smoking status, no. (%)			
Never	5 (45)	13 (72)	18 (62)
Previous	3 (27)	5 (28)	8 (28)
Current	3 (27)	0 (0)	3 (10)
Renal AMLs, no. (%)			
Present	6 (55)	8 (44)	14 (48)
Absent	2 (18)	9 (50)	11 (38)
Unknown	3 (27)	1 (6)	4 (14)

AML = angiomyolipoma; TSC = tuberous sclerosis complex.