Pulmonary Cysts Consistent With Lymphangioleiomyomatosis Are Common in Women With Tuberous Sclerosis*

Genetic and Radiographic Analysis

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CHEST 2002; 121:61S

Abstract

Lymphangioleiomyomatosis (LAM) and multifocal micronodular pneumocyte hyperplasia produce cystic and nodular disease, respectively, in the lungs of patients with tuberous sclerosis (TSC). The objective of this study was to prospectively characterize the prevalence, clinical presentation, and genetic basis of lung disease in TSC. CT scanning of the chest on 23 asymptomatic women with TSC identified cystic or nodular changes in 52%. Cystic pulmonary parenchymal changes consistent with LAM were found in nine patients (39%). These patients tended to be older than cyst-negative patients (31.9 ± 7.6 years vs 24.8 ± 11.6 years, p = 0.09), and there was no correlation between presence of cysts and tobacco use, age at menarche, history of pregnancy, or use of estrogen-containing medications. Three of the cyst-positive patients had a prior history of pneumothorax. Pulmonary function studies revealed evidence of gas trapping but normal spirometric indexes in the cyst-positive group. All 9 cyst-positive patients had angiomylipomas, which were larger (p < 0.05) and more frequently required intervention (p = 0.08) than cyst-negative patients (6.5 vs 14 patients with angiomylipomas, p < 0.05). Ten patients (43%) had pulmonary parenchymal nodules. Pulmonary nodules were more common in women with cysts (78% vs 21%, p < 0.05). TSC2 mutations were identified in all cyst-positive patients who were tested (n = 8), while both TSC1 and TSC2 mutations were identified in patients with nodular disease. Correlation of the mutational and radiographic data revealed one pair of sisters who were discordant for cystic disease, two mother-daughter pairs who were discordant for nodular disease, and no clear association between cyst development and a specific mutational type. This prospective analysis demonstrates that cystic and nodular pulmonary changes consistent with LAM and multifocal nodular pneumocyte hyperplasia are common in women with TSC.

Microsatellite Mutational Analysis of Endothelial Cells Within Plexiform Lesions From Patients With Familial, Pediatric, and Sporadic Pulmonary Hypertension*

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CHEST 2002; 121:61S

Abstract

Severe pulmonary hypertension (PH) is characterized by elevated pulmonary artery pressures leading to right-heart failure, yet the pathogeneses of familial PH, pediatric PH, and sporadic PH (SPH) are poorly understood. We previously demonstrated monoclonal proliferation of endothelial cells (ECs) within plexiform lesions in primary SPH, and we showed that plexiform ECs display dysregulated gene expression compared to normal pulmonary ECs arranged in monolayers. We posited that mutations in genes controlling EC growth and death might drive monoclonal EC growth in plexiform lesions. Using polymerase chain reaction, we found microsatellite instability within the hMSH2 mismatch repair gene and frameshift mutation within the transforming growth factor-β receptor type II (TGF-β RIi) and Bax genes. Specifically, we show genetic instability in 13 patients with primary SPH (6 of 19 lesions TGF-β RIi; 4 of 19 lesions Bax) and in 1 patient with primary pediatric PH (2 of 5 lesions hMSH2), but not in 5 patients with familial PH (0 of 16 lesions) nor in 10 normal lungs. EC monoclonality, when performed, correlated tightly with occurrence of mutation (three of three primary SPH patients). Immunohistochemistry revealed absence of TGF-β RIi, hMSH2, and hMLH1 expression in plexiform lesion ECs of SPH tissues compared to ECs in normal pulmonary arteries from both normal and PH patients. To our knowledge, this is the first report of mutation within ECs outside the setting of neoplasia. Our observations may assist in subclassification of PH patients as well as point to future novel therapeutic interventions.

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