Characteristics and Disease Activity of Early Interstitial Lung Disease in Subjects With True Parenchymal Abnormalities in the Posterior Subpleural Aspect of the Lung*

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Study objectives: **To evaluate characteristics or disease activity of early interstitial lung disease (ILD) in subjects with true parenchymal abnormalities in the posterior subpleural aspect of the lung.**

Patients and methods: **This study enrolled 14 subjects with dependent densities that disappeared on helical CT obtained with the subject prone (control group) and 7 subjects with true parenchymal abnormalities that remained unchanged on prone CT image but were not detectable on chest radiographs (true abnormalities group). Pulmonary function tests and serum markers for idiopathic lung fibrosis as KL-6, surfactant protein D (SP-D), and surfactant protein A (SP-A) in the two groups were evaluated.**

Results: **In the true abnormalities group, curvilinear subpleural lines or thickened interlobular and intralobular lines were observed more frequently in the lower lung fields. Diffusing capacities of the lung for carbon monoxide (15.3 ± 3.5 mL/min/mm Hg vs 18.8 ± 3.7 mL/min/mm Hg, p = 0.0493) were lower, and KL-6 (607 ± 297 U/mL vs 318 ± 143 U/mL, p = 0.0090), SP-A (59 ± 24 ng/mL vs 34 ± 12 ng/mL, p = 0.0207), and SP-D (112 ± 54 ng/mL vs 42 ± 24 ng/mL, p = 0.0028) were higher in the true abnormalities group than in the control group (± SD).**

Conclusion: **True parenchymal abnormalities in the posterior subpleural aspect of the lung may indicate early ILD activity.** ***(CHEST 2006; 129:402–406)***

Key words: annual health examinations; curvilinear subpleural lines; KL-6; subpleural ground-glass opacities; surfactant protein A; surfactant protein D; thickened interlobular and intralobular lines

Abbreviations: DLCO = diffusing capacity of lung for carbon monoxide; %DLCO = ratio of diffusing capacity of lung for carbon monoxide to predicted diffusing capacity of lung for carbon monoxide; FEV_1% = ratio of FEV_1 to FVC; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LDH = lactate dehydrogenase; SP-A = surfactant protein A; SP-D = surfactant protein D; TLC = total lung capacity; VC = vital capacity; %VC = ratio of vital capacity to predicted vital capacity

We have occasionally encountered asymptomatic subjects with parenchymal abnormalities in the posterior subpleural aspect of the lung that were visualized on helical CT but were not detectable on chest radiographs. Although one problem is that these opacities closely mimic the appearance of one of the idiopathic interstitial pneumonias,[1–3] most of them are gravity-related physiologic phenomena because these opacities disappear on helical CT obtained with the subject prone, resulting in a "dependent density" as described by Webb et al.[1] However, true parenchymal abnormalities that did not disappear on prone CT image are suspected of early interstitial lung disease (ILD) including idiopathic pulmonary fibrosis (IPF). This disease is characterized on high-resolution CT by the presence of reticulation or honeycombing involving predomi-

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nantly the subpleural lung lesions and the lower lung fields,[4–7] but there has not been any report on the appearance of early ILD not detectable on chest radiographs. In addition, it is not clear whether or not these parenchymal abnormalities in the posterior subpleural aspect of the lung have characteristics or disease activity for ILD. The purpose for this study was to evaluate pulmonary function tests and serum-sensitive markers for IPF in subjects with dependent densities that disappear on prone CT imaging and in subjects with true parenchymal abnormalities that remain unchanged on prone CT imaging.

Materials and Methods

During the 4-year period from April 1, 1999, to March 31, 2003, helical CT screening was performed as an optional test in 1,385 subjects who received annual health examinations. This screening was done at the end of two breath holds and on supine imaging (ProSeed Accell CT system; GE Yokokawa Medical System; Tokyo, Japan), and examination parameters were 120 kilovolts, 140 mA, 10-mm collimation, and 10 mm-per-rotation table speed. All evaluations in the present study were made at the same window setting (1,500 Hounsfield units, − 600 Hounsfield units). The CT images were assessed independently by both a radiologist and a chest specialist without reference to clinical data.

The study was approved by the institutional review board, and all patients completed informed consent forms. One hundred seven subjects (8%) had parenchymal abnormalities in the posterior subpleural aspect of the lung and were advised to receive additional CT scans in a prone position. Eighty-eight subjects underwent prone image CT scans (same parameters on supine image), but the other 19 subjects refused to undergo the test. In 78 subjects, the opacities disappeared on prone image helical CT and were diagnosed as dependent densities. Ten subjects had true parenchymal abnormalities that did not disappear on prone CT image. Three of them were excluded from this study because they had the appearance of honeycombing detectable on chest radiography. Twenty-one subjects underwent an additional high-resolution CT and blood examinations and pulmonary function tests. Patients were classified into two groups: patients with dependent density that disappeared on prone CT imaging (n = 14, control group); and patients with true parenchymal abnormalities that remained unchanged on prone CT imaging (n = 7, true abnormalities group).

The classification of Aberle et al[2] was used to evaluate the radiologic findings of parenchymal abnormalities in the posterior subpleural aspect of the lung on helical CT. This classification consists of the following: (1) curvilinear subpleural lines, defined as linear densities within 1 cm of the pleura and parallel to the inner chest wall; (2) thickened interlobular and intralobular lines, defined as single or branching lines 1 to 2 cm in length, seen in the subpleural parenchyma, extending peripherally toward the pleural surface; (3) subpleural dependent density, defined as broad bands of featureless increased density marginated the dependent lung, varying in width from 2 to 20 mm and sufficiently opaque to obscure the morphologic structure of the underlying parenchyma; (4) parenchymal lines, defined as linear, nontapering densities 2 to 5 cm in length extended through the lung to contact the pleural surface; and (5) honeycombing, defined as small cyst-like spaces with thick walls were seen, most commonly in the subpleural regions of the lung. The term *subpleural dependent density* was not used in this study because this phrase is a generic term for gravity-related parenchymal abnormalities; instead, the expression *subpleural ground-glass opacities* was used. To evaluate the predominant distribution of parenchymal abnormalities on supine CT image, four levels of helical CT were stratified, as follows: apex levels (a horizontal level appeared adjacent to the upper margin of the aortic arch) representative of upper lung fields of the lung; hilum (a horizontal level appeared adjacent to the upper margin of trunk of the right pulmonary artery); heart (a horizontal → appeared adjacent to the right inferior pulmonary vein connecting to the left atrium) levels representative of middle lung fields; and basal levels (a horizontal level appeared adjacent to he upper margin of spleen) representative of lower lung fields.

A hematologic analysis was performed (Sysmex SE-9000; Sysmex; Kobe, Japan), as was biochemical analysis (TBA-80FR NEO2; Toshiba Medical; Tokyo, Japan). Measurements of serum KL-6, surfactant protein A (SP-A), and surfactant protein D (SP-D) were performed using an electrochemiluminescence immunoassay kit (Sanko Junyaku; Kobe, Japan; reference range < 500 U/mL), an enzyme-linked immunoassay kit (Sysmex; reference range < 43.8 ng/mL), and an enzyme-linked immunoassay kit (Yamasa Shoyu; Chiba, Japan; reference range < 110 ng/mL) following the instructions of the manufacturer. Respiratory function measurements in all subjects were made (CHESTAC-33 spirometer; Chest; Tokyo, Japan). Measurements of vital capacity (VC); ratio of VC to predicted vital capacity (%VC); FVC; FEV_1; ratio of FEV_1 to FVC (FEV_1%); total lung capacity (TLC); ratio of residual volume (RV) to TLC; diffusing capacity of lung for carbon monoxide (DLCO); and ratio of DLCO to predicted DLCO (%DLCO) were based on two satisfactory maximal forced expiratory maneuvers performed with the subjects in a standing position.

Statistical analysis was performed on a personal computer using statistical software (Stat View J 5.0; SAS Institute; Cary, CA). Differences between two independent samples were tested using the Mann-Whitney *U* test. Analysis of categorical data was

Table 1—*Radiologic Findings of Parenchymal Abnormalities on Supine CT Imaging in the Control Group and the True Abnormalities Group

Variables	Control Group (n = 14)	True Abnormalities Group (n = 7)
Location		
Right	0	0
Left	3 (21)	0 (0)
Bilateral	11 (79)	7 (100)
Distribution at CT levels		
Apex	0	0
Hilum	6 (43)	5 (71)
Heart	14 (100)	7 (100)
Basal	1 (7)	7 (100)†
Parenchymal abnormalities on supine CT imaging		
Curvilinear subpleural lines	4 (30)	5 (71)
Thickened interlobular and intralobular lines	3 (21)	6 (86)†
Subpleural ground-glass opacities	13 (93)	7 (100)
Parenchymal bands	0	0
Honeycombing	0	0

*Data are presented as No. (%).

†$p < 0.05$ vs control group by Fisher exact probability test.