Disease Activity of Idiopathic Pulmonary Fibrosis*
— Value of High Resolution CT —

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Introduction

Idiopathic pulmonary fibrosis (IPF) has characteristic clinical and pathologic features. In patients with uniform intra-alveolar cellularity, the process is often referred to as desquamative interstitial pneumonia. When alveolar septal fibrosis predominate, the process is known as usual interstitial pneumonia. Recently most investigators believe that desquamative interstitial pneumonia is the early stage and usual interstitial pneumonia is the late stage of the same disease process (1). The long-term survival and the best response to treatment with corticosteroids is found in patients with marked disease activity and little fibrosis (2,3). Since disease activity is reflected by interstitial and intra-alveolar cellularity, activity of idiopathic pulmonary fibrosis might result in opacification of air spaces on CT scans (4).

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Several modalities were used for evaluation of the disease activity of idiopathic pulmonary fibrosis, which included the open lung biopsy, transbronchial lung biopsy, bronchoalveolar lavage (BAL) and Gallium-67 scanning (5,7). Nowadays, high resolution CT (HRCT) was increasingly used for evaluation of disease activity. We estimated the capability of HRCT in accessing disease activity and compared the capability of HRCT with BAL and pathologic score using the improvement of diffusion lung capacity of carbon-monoxide after corticosteroids treatment as a parameter.

Materials and Methods

We reviewed the HRCT scans and the follow-up data of percentage of predicted value of diffusion lung capacity of carbon-monoxide (DLCO/VA) in 15 patients who were diagnosed as idiopathic pulmonary fibrosis from 1987 to 1989 at the Seoul National University Hospital. Nine of 15 patients had suffered open lung or transbronchial lung biopsy. Twelve of 15 patients had done BAL. The age of these patients was ranging from 50 to 81 years (mean = 62.6). The interval between HRCT and initial pretreatment DLCO/VA was within four weeks (4.5±16.7 days) and the duration of DLCO/VA follow up interval was ranged from 1 to 20 months (4.5±4.7 months). Bronchoscopic examination for BAL and transbronchial lung biopsy and open lung biopsy were done within one week from HRCT. All 15 patients were treated with corticosteroid after the diagnosis (Prednisolone 1mg/Kg/day).

Activity score on HRCT

HRCT scanning was performed on a CT/T 9800 scanner (General Electric Medical Systems, Milwaukie). In all patients, 1.5mm collimation scans with bone algorithm (140KVP, 170mA, 3 or 2 sec) were obtained at the level of the aortic arch, tracheal carina, left atrium and diaphragmatic dome. Images were photographed at window levels that were appropriate for the lung parenchyma (Level = - 400, Window = 1500). The HRCT scans were assessed independently by two observers who were blinded of clinical and pathological data. We evaluated only

Fig. 1. Correlation between disease activity from HRCT score(a), lymphocytosis in BAL fluid (b) and Pathologic score (c) and improvement of DLCO/VA (%) after steroid treatment. The activity score of HRCT had more correlation with the improvement of DLCO/VA after steroid treatment than others.

*DLCO/VA (%) = The percentage of predicted value of diffusion lung capacity
*DLCO/VA (%) Imp. = Improvement of DLCO/VA (%).
right lung because there were blurring of image in left side lung by cardiac motion. Homogeneous air-space opacification or ground glass area were regarded as active (4). Visual estimation was used in assessing the percentage of active area in each slice, ranging from 0% to 100% with 10% interval. The sum of the active area in proportion to the whole lung of each slice was calculated as a percent.

**Disease activity in BAL**

BAL was performed through two or more segmental bronchus using flexible fiberscope. Bronchoalveolar lavage fluid was analyzed for differential count. The percentage of lymphocyte in lavage fluid is known to reflect the disease activity (6,8). We compared the percent of lymphocyte in lavage fluid with the DLCO/VA improvement after corticosteroids treatment.

**Pathologic score for disease activity**

The pathologic score of disease activity was determined with a slight modification of the method described by Watters et al. (4,6,8). Cellular activity was graded from 0 to 24 by using six categories: alveolar desquamation, that is, intraalveolar histiocytes (0-6); alveolar septal inflammation (0-6); granulation tissue in alveoli and alveolar ducts (0-3); obstructive pneumonitis (0-3); lymphoid nodules.

**Fig. 2.** HRCT scan of right lung at the level of the left atrium. Ill-defined patchy area (arrowheads) suggests active alveolitis area and honeycombed area (arrows) suggests established fibrosis area. Note the lesions are distributed subpleurally.

**Fig. 3.** HRCT scan of the right lung at the level of the left atrium. (a) There is ill defined opaque density involving whole lung field, sparing only a small portion of anterior and paraspinal area. 85% of active score was given and DLCO/VA score was 50% at that time. (b) Follow-up scan after corticosteroid treatment for three months since (a). Ill-defined opaque densities that had been noted on pre-treatment HRCT scan was nearly disappeared, and DLCO/VA score was improved up to 80%. Subjective symptom of dyspnea also improved remarkably.

**Fig. 4.** HRCT scan of the right lung at the level of the tracheal carina. Lesions are composed mostly of honeycombing with interlacing small area of ill-defined opaque area (arrows). Bronchovascular arrangements has severely distorted by fibrosis. Activity score was estimated as 30.04%. This patient did not show any clinical improvement after corticosteroid treatment for three months. DLCO/VA decreased from 44% to 36%.
Response of DLCO to Corticosteroids treatment

Single-breath carbon monoxide diffusing capacity were measured, and expressed as DLCO/VA. The difference between the value of pre-and post-corticosteroids treatment was calculated.

Statistical Analysis

Inter-observer difference for the activity score of HRCT was assessed with paired T-test (9). The HRCT scores of both observers for each patient were averaged for analysis. The HRCT scores, the percentage of lymphocyte in BAL, and the pathologic activity score were compared with the improvement of DLCO/VA using the Spearman rank correlation coefficient (9).

Results

There was no significant difference in estimating the visual HRCT scores of active area between two observers (p>0.05). Activity score of HRCT scan correlated significantly with improvement of DLCO/VA after corticosteroids treatment (r=0.608, p=0.006) (Fig. 1a). The improvement of DLCO/VA after corticosteroids treatment tended to increase in accordance with the increase of pathologic activity score (r=0.284, p=0.213) and lymphocytosis in BAL fluid (r=0.263, p=0.217) (Fig. 1b, 1c), but were statistically not significant.

Discussion

IPF is a progressive, generally fatal disease characterized by an interstitial and intra-alveolar inflammatory process with interstitial fibrosis. Current concepts of the pathogenesis of IPF are that the fibrosis is preceded by an inflammatory cellular infiltration. Early disease is characterized by minimal fibrosis and an active cellular response, whereas advanced disease is characterized by severe fibrosis and minimal cellularity (4,10,11). When there is marked disease activity seen pathologically, this results in patchy predominantly peripheral opacification of air spaces (Fig. 2). This is presumably due to alveolar septal inflammation and filling of air spaces by mononuclear cells (4). In follow-up HRCT scan after corticosteroids treatment, the opacification of air space disappeared (Fig. 3), but the honeycomb change with septal fibrosis persisted (Fig. 4). Correlative studies have shown that the prognosis and response to therapy in IPF is determined by the degree of cellularity (1,9).

The carbon-monoxide diffusing capacity is reduced early in the course of the interstitial lung disease and may be low even when the lung volumes are mal (12,14). Impairment in gas exchange has been shown to correlate better with the extent of interstitial fibrosis and alveolar cellular infiltration as assessed pathologically than the static lung volumes or expiratory flows (15,16). Thus, we used DLCO/VA as a parameter of improvement in IPF patients.

Although the results of this study are encouraging, there are some possible limitations. Ground glass opacity in HRCT scan can also be visualized by respiratory motion, thus resulting in overestimation of active area. However, by recognizing the motion artifact from double lined interlobar fissure or bronchovascular bundle, we can compromise and reasonably can adjust visual estimation. Calculation of active area by visual estimation looks arbitrary and anecdotal. However, we believe visual estimation works well as were supported by the fact that there was no statistically significant difference between the two independent readers.

Better correlation of HRCT with the improvement of DLCO after corticosteroid treatment than histopathologic examination is believed due to overall assessment of the lung by HRCT while histopathologic examination is limited to a specific small focus.

Our data indicates that HRCT can provide quantitative assessment of disease activity in IPF better than BAL and histopathologic examination and as HRCT can repeatedly be done non-invasively, we believe the use of HRCT in the evaluation of IPF should be in a main stream.

REFERENCES

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