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Hideo Yamanouchi* Yuji Ohtsuki† Jiro Fujita‡
Shuji Bandoh** Takeo Yoshinouchi†† Toshihiko Ishida‡‡

*Kochi Medical School,
†Kochi Medical School,
‡Kagawa Medical University,
**Kagawa Medical University,
††Nagoya City University,
‡‡Kagawa Medical University,

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Hideo Yamanouchi, Yuji Ohtsuki, Jiro Fujita, Shuji Bandoh, Takeo Yoshinouchi, and Toshihiko Ishida

Abstract

Leu-7 positive lymphocytes, including natural killer cells, play an important role in the immune system's surveillance function to prevent the development of cancer. The incidence of lung cancer is significantly high in patients with end-stage pulmonary fibrosis. We hypothesized that the number of Leu-7 positive cells may be decreased in areas of severe pulmonary fibrosis. To demonstrate this, Leu-7 positive cells were immunohistochemically stained in 41 lung specimens obtained from patients with idiopathic pulmonary fibrosis and pulmonary fibrosis associated with collagen vascular disorders. The number of Leu-7 positive cells was evaluated according to the pathological findings. In pathologically normal lung, Leu-7 positive cells were mostly found within the capillaries of the septa and rarely in the alveolar space or the stroma. The number of Leu-7 positive cells was 0.69 +/- 0.15 in areas of advanced fibrosis (n = 41), 2.39 +/- 0.60 in areas that had newly developeing fibrosis (n = 41), 1.14 +/- 0.57 in bronchiolitis obliterans organizing pneumonia (n = 9), and 1.35 +/- 0.87 in diffuse alveolar damage (DAD) (n = 11). The number of Leu-7 positive cells in areas of newly developing fibrosis (2.39 +/- 0.60) was significantly higher than that in areas of established fibrosis (0.69 +/- 0.15, $P < 0.05$). Our present study demonstrates a significant decrease in the number of Leu-7 positive cells in areas of advanced fibrosis. This evidence may partly explain the high incidence of lung cancer associated with pulmonary fibrosis.

KEYWORDS: Leu-7 positive cells, natural killer cells, idiopathic pulmonary fibrosis, lung cancer

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Original Article

The Distribution and Number of Leu-7 (CD57) Positive Cells in Lung Tissue from Patients with Pulmonary Fibrosis

Hideo Yamanouchi[a,b*], Yuji Ohtsuki[a], Jiro Fujita[b*], Shuji Bandoh[b], Takeo Yoshinouchi[c], and Toshihiko Ishida[b]

[a]Department of Pathology II, Kochi Medical School, Kochi 783-8505, Japan,
[b]First Department of Internal Medicine, Kagawa Medical University, Kagawa 761-0793, Japan, and
[c]Department of Internal Medicine, Nagoya City University, Nagoya 467-8602, Japan

Leu-7 positive lymphocytes, including natural killer cells, play an important role in the immune system's surveillance function to prevent the development of cancer. The incidence of lung cancer is significantly high in patients with end-stage pulmonary fibrosis. We hypothesized that the number of Leu-7 positive cells may be decreased in areas of severe pulmonary fibrosis. To demonstrate this, Leu-7 positive cells were immunohistochemically stained in 41 lung specimens obtained from patients with idiopathic pulmonary fibrosis and pulmonary fibrosis associated with collagen vascular disorders. The number of Leu-7 positive cells was evaluated according to the pathological findings. In pathologically normal lung, Leu-7 positive cells were mostly found within the capillaries of the septa and rarely in the alveolar space or the stroma. The number of Leu-7 positive cells was 0.69 ± 0.15 in areas of advanced fibrosis ($n = 41$), 2.39 ± 0.60 in areas that had newly developeing fibrosis ($n = 41$), 1.14 ± 0.57 in bronchiolitis obliterans organizing pneumonia ($n = 9$), and 1.35 ± 0.87 in diffuse alveolar damage (DAD) ($n = 11$). The number of Leu-7 positive cells in areas of newly developing fibrosis (2.39 ± 0.60) was significantly higher than that in areas of established fibrosis (0.69 ± 0.15, $P < 0.05$). Our present study demonstrates a significant decrease in the number of Leu-7 positive cells in areas of advanced fibrosis. This evidence may partly explain the high incidence of lung cancer associated with pulmonary fibrosis.

Key words: Leu-7 positive cells, natural killer cells, idiopathic pulmonary fibrosis, lung cancer

The anti-Leu-7 antibody reacts with CD57-positive lymphocytes, including large granular lymphocytes: showing natural killer (NK) activity in the peripheral blood [1]. CD-57 positive cells are detected in the normal pulmonary tissues of rats [2, 3]. Recently, we demonstrated that the number of Leu-7-positive cells decreased in the lung in cases involving emphysematous bulla or subpleural bleb; the results suggested that a weakness in local immune system's surveillance function is related to a high incidence of lung cancer associated with bullous diseases [4].

Several conditions resulting in chronic interstitial fibrosis of the lungs are associated with a later development of cancer [5-10]. Such conditions include idiopathic pulmonary fibrosis (IPF), pulmonary fibrosis associated with progressive systemic sclerosis (PSS), and pulmonary fibrosis in patients with rheumatoid arthritis (RA) [5-10]. It has been reported that the incidence of lung

Received June 27, 2001; accepted November 27, 2001.
*Corresponding author. Phone: +81-87-891-2145; Fax: +81-87-891-2147
E-mail: jiro@kms.ac.jp (J. Fujita)

cancer in patients with chronic interstitial fibrosis varies from 9.8 to 17% [8, 10]. In addition, many reports have documented the association of lung cancer with IPF, especially in areas of advanced fibrosis [11–14]. In addition, Raeburn and Spencer have reported observing a relationship between the site of many peripheral lung cancers and areas of previous scarring (lung scar cancers) [11].

However, the precise properties of fibrosis that hypothetically can lead to the development of carcinoma are unknown. Considering these previous studies, we immunohistochemically evaluated the distribution and number of Leu-7-positive cells in samples of tissue from patients with pulmonary fibrosis from the viewpoint of the local immune surveillance system.

Materials and Methods

Samples. Forty-one lung specimens were obtained from 13 patients histologically diagnosed with IPF (usual interstitial pneumonia [UIP]). The median age was 74 and there were 4 females and 9 males. Seven samples were obtained by open lung biopsy and 6 were obtained by autopsy. Fifteen patients with pulmonary fibrosis associated with RA were included (median age, 70; 6 females and 9 males; 6 samples were obtained by open lung biopsy and 9 by autopsy). Six patients with pulmonary fibrosis associated with dermatomyositis (DM) were included (median age, 50; 5 females and 1 male; 3 samples were obtained by open lung biopsy and 3 by autopsy). Seven patients with pulmonary fibrosis associated with PSS were included (median age, 56; 6 females and 1 male; 3 samples were obtained by open lung biopsy and 4 by autopsy). In total, 19 lung specimens were obtained by open lung biopsy, and 22 were obtained by autopsy. As a control, we also evaluated 10 autopsied cases that showed no history or evidence of pulmonary fibrosis (median age, 62; 3 females and 7 males).

Pathological findings. The pathological findings were classified into one of four categories: i) advanced fibrosis, ii) newly developing fibrosis, iii) bronchiolitis obliterans organizing pneumonia (BOOP) pattern, and iv) diffuse alveolar damage (DAD) pattern. Advanced fibrosis was defined as areas showing severe structural destruction, increased collagen with partial hyalinization, no myofibroblasts, and less inflammatory cell infiltration. Newly developing fibrosis was defined as areas showing mild unclear: comparison is not explicit. less structural destruction, mixoid change, mild collagen increase, some myofibroblasts, and abundant inflammatory cell infiltration.

Immunohistochemistry. Three-micrometer-thick sections were deparaffinized in lemosol, dehydrated, and placed in methanol containing 5% hydrogen peroxide for 5 min at room temperature. Samples were incubated with goat serum for 10 min. Subsequently, incubation with monoclonal antibody to Leu-7 antigen (Becton-Dickinson, 1:30 dilution) was carried out for 60 min at room temperature. The slides were then washed and incubated with biotinylated goat anti-mouse immunoglobulin antibody, and incubated with avidin-biotin-peroxidase complex for 8 min using a DAKO LSAB Kit. Afterwards, chromogen 3, 3-diaminobenzidine tetrahydrochloride was applied for 3 min and counterstaining was carried out with Mayer's hematoxylin for 10 sec. Positive cells were counted and the data were was presented as an average number in 100 high-power ($\times$ 200) fields.

Statistical analysis. Results are expressed as mean values $\pm$ standard error of the mean. Comparisons of values between groups were analyzed with the Mann-Whitney U test. Comparison between newly developing and advanced fibrosis in the same specimens were analyzed with the Wilcoxon signed-ranks test. A P value of less than 0.05 was considered to be significant.

Results

In non-affected areas of lung that appeared pathologically normal areas of lung, Leu-7 positive cells were mostly found within the capillaries of the septa, but rarely in the alveolar space or the stroma (Fig. 1). In the capillaries, these cells were attached to the endothelial cells. Positive reaction of the plasma membrane was lacked at the sites where Leu-7 positive cells were attached to the endothelial cells.

In samples from patients with interstitial lung diseases, free Leu-7 positive cells were also observed in the alveolar spaces, within areas of fibrosis, and in vessels. In addition, the distribution of Leu-7 positive cells was less uniform in affected areas of the lung than in the apparently normal parts of the lung. Interestingly, few Leu-7 positive cells were observed in areas of advanced fibrosis (Fig. 2). In contrast, a relatively high number of Leu-7 positive cells was observed in the capillary, in the alveolar space, and in the stroma in areas of newly developing

fibrosis (Fig. 3A); sometimes such cells were observed in a cluster (Fig. 3B). Leu-7 positive cells were also frequently observed in lymphoid follicles, especially in cases of rheumatoid arthritis (data not shown). However, we excluded these latter cells from the data analysis.

In areas of advanced fibrosis, the number of Leu-7 positive cells was 0.76 ± 0.26 in UIP ($n = 13$), 0.71 ± 0.26 in RA ($n = 15$), 0.21 ± 0.09 in DM ($n = 6$), and 0.96 ± 0.42 in PSS ($n = 7$), respectively (Fig. 4). No significant differences were observed between groups. In normal lung tissue, Leu-7 positive cells were observed only in the alveolar septa (0.58 ± 0.28).

In areas of newly developing fibrosis, the number of Leu-7 positive cells was 3.80 ± 1.52 in UIP ($n = 13$), 1.85 ± 0.77 in RA ($n = 15$), 0.57 ± 0.25 in DM ($n = 6$), and 2.52 ± 1.11 in PSS ($n = 7$), (Fig. 5). No significant differences were observed between groups.

In each case, the number of Leu-7 positive cells was

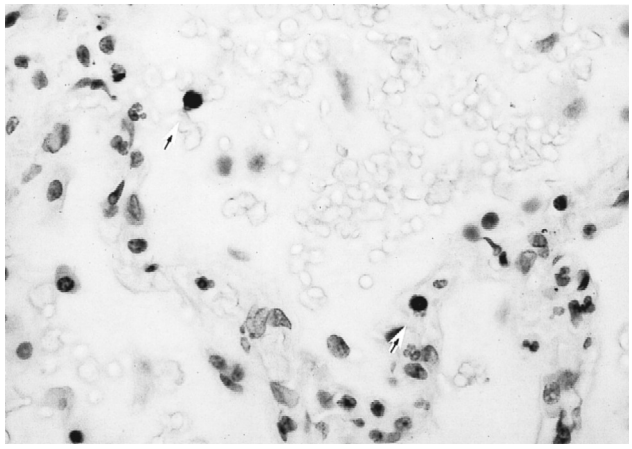


Fig. 1 Most of the Leu-7-positive cells in apparently normal areas of a diseased lung are detected in the capillaries and also in the alveolar space (arrows) in a patient with rheumatoid arthritis. Avidin-biotin peroxidase complex method (× 860).

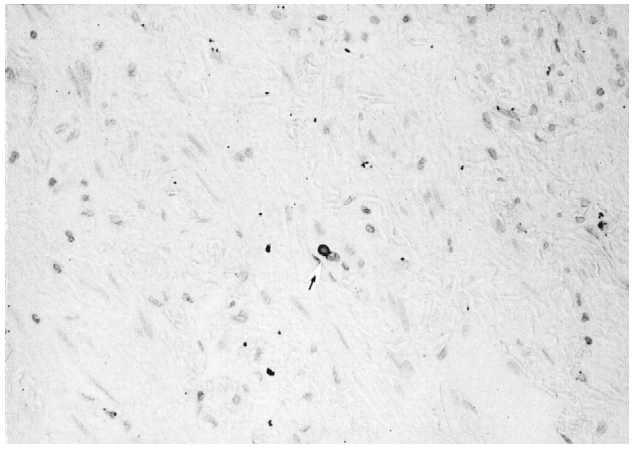
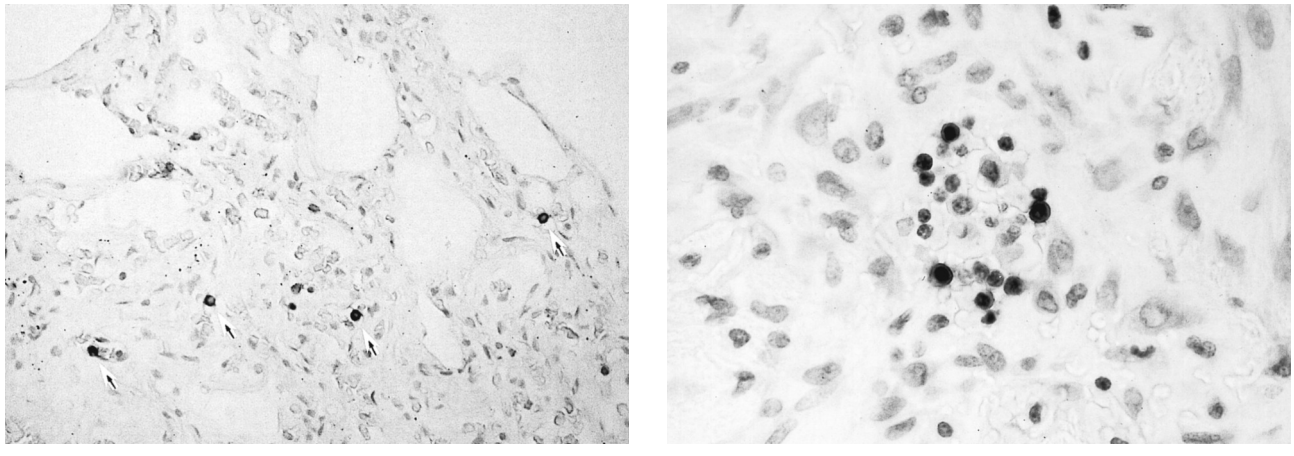


Fig. 2 Few Leu-7-positive cells (arrows) are observed in areas of advanced fibrosis in a patient with usual interstitial pneumonia. Avidin-biotin peroxidase complex method (× 430).



A B

Fig. 3 A, a relatively high number of Leu-7-positive cells (arrows) are observed in areas involving newly developing fibrosis in a patient with usual interstitial pneumonia. Avidin-biotin peroxidase complex method (× 430). B, these Leu-7-positive cells were present in sporadic clusters in areas of newly developing fibrosis in a patient with rheumatoid arthritis. Avidin-biotin peroxidase complex method (× 860).

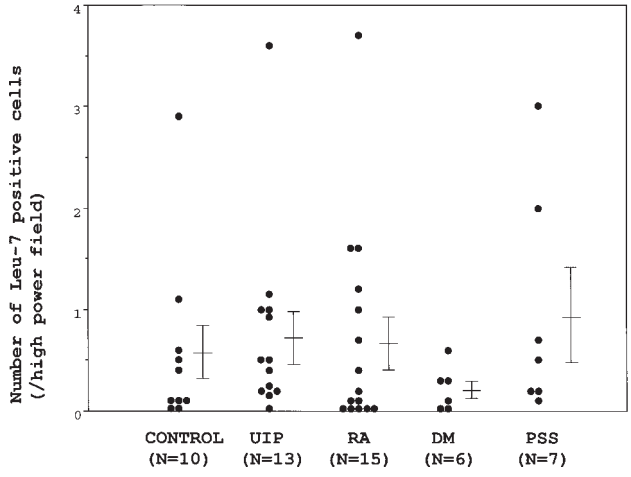


Fig. 4 The number of Leu-7 positive cells in areas of advanced fibrosis in lung specimens obtained from patients with idiopathic pulmonary fibrosis (IPF), pulmonary fibrosis associated with rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), and dermatomyositis (DM). A bar represents mean ± standard error. There were no significant differences between groups.

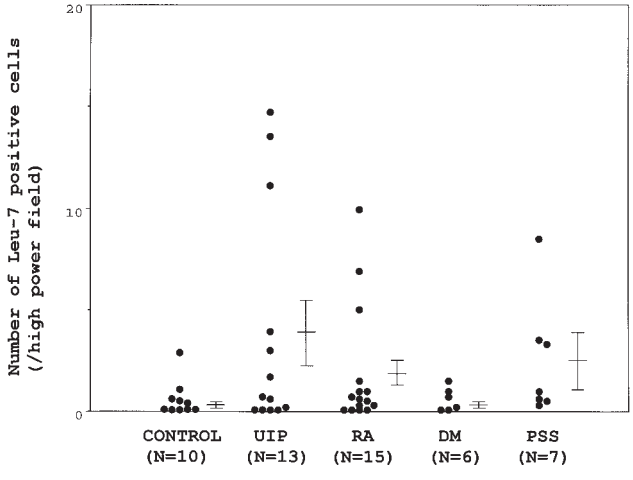


Fig. 5 The number of Leu-7 positive cells in areas of newly developing fibrosis in lung specimens obtained from patients with idiopathic pulmonary fibrosis (IPF), pulmonary fibrosis associated with rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), and dermatomyositis (DM). A bar represents mean ± standard error. There were no significant differences between groups.

evaluated according to the pathological findings. The number of Leu-7 positive cells was 0.69 ± 0.15 in areas of advanced fibrosis (n = 41), 2.39 ± 0.60 in areas of newly developing fibrosis (n = 41), 1.14 ± 0.57 in cases with the BOOP pattern (n = 9; 5 patients with RA, 3 DM, and 1 PSS), and 1.35 ± 0.87 in cases with the DAD

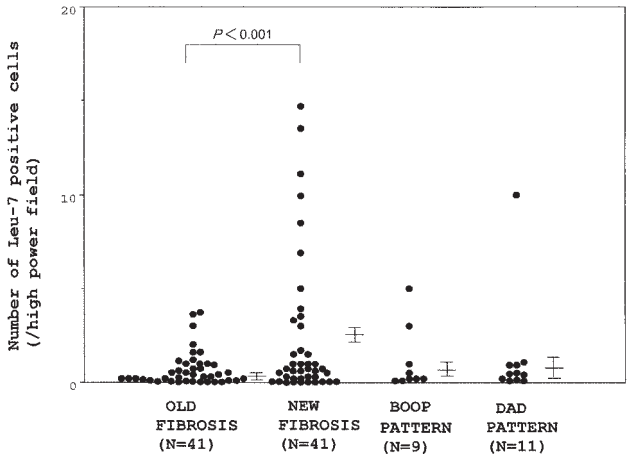


Fig. 6 The number of Leu-7 positive cells according to the histological findings. Histological findings are classified as follows: advanced fibrosis, newly developing fibrosis, BOOP pattern, and DAD pattern. The number of Leu-7-positive cells in areas of advanced fibrosis is significantly lower than that in areas of newly developing fibrosis ($P < 0.001$).

pattern (n = 11; 4 from patients with UIP, 4 RA, 2 DM, and 1 PSS) (Fig. 6). The number of Leu-7-positive cells in areas of newly developing fibrosis (2.39 ± 0.60) was relatively high compared with that in areas of advanced fibrosis (0.69 ± 0.15, Fig. 6). In all 41 lung tissue samples, it was possible to evaluate the number of Leu-7 positive cells in areas of advanced fibrosis and newly developing fibrosis in the same tissue specimen. The number of Leu-7-positive cells in areas of advanced fibrosis was significantly lower than that in areas of newly developing fibrosis ($P < 0.001$, Wilcoxon signed-ranks test, Fig. 6). In the areas demonstrating both DAD and BOOP patterns, the number of Leu-7 positive cells was relatively low. In addition, Leu-7 positive cells were distributed mostly among the affected areas in tissue showing advanced fibrosis, the DAD pattern, and the BOOP pattern.

We also separately evaluated Leu-7 positive cells in areas of newly developing fibrosis and in areas of advanced fibrosis in patients with UIP and in patients with pulmonary fibrosis associated with collagen vascular diseases. In 13 patients with UIP, the number of Leu-7-positive cells in areas of advanced fibrosis (0.76 ± 0.26) was significantly lower than that in areas of newly developing fibrosis (3.80 ± 1.52, $P < 0.05$, Wilcoxon signed-ranks test). In 28 patients with pulmonary fibrosis associated with collagen vascular diseases, the number of

Leu-7 positive cells in areas of advanced fibrosis (0.66 ± 0.18) was also significantly lower than that observed in areas of newly developing fibrosis (1.74 ± 0.50, $P < 0.001$, Wilcoxon signed-ranks test).

In 22 autopsied lung tissues, it was possible to evaluate number of Leu-7-positive cells in areas of advanced fibrosis, in areas of newly developing fibrosis, and in areas of relatively normal alveoli in the same lung (Fig. 7). The number of Leu-7 positive cells in areas of newly developing fibrosis (2.74 ± 0.94) was significantly higher than that in areas of old fibrosis (0.77 ± 0.23, $P < 0.01$, Wilcoxon signed-ranks test) and than that in areas of relatively normal lung (0.98 ± 0.24, $P < 0.01$, Wilcoxon signed-ranks test). There was no significant difference in the number of Leu-7-positive cells observed in areas of advanced fibrosis and in areas of relatively normal alveoli. In areas of relatively normal alveoli, Leu-7-positive cells were typically found within the capillaries of the septa. In contrast, in areas involving advanced fibrosis, Leu-7-positive cells were only distributed within areas of fibrosis. In areas of newly developing fibrosis, a relatively high number of Leu-7-positive cells was observed in the capillary, in the alveolar space, and in the stroma.

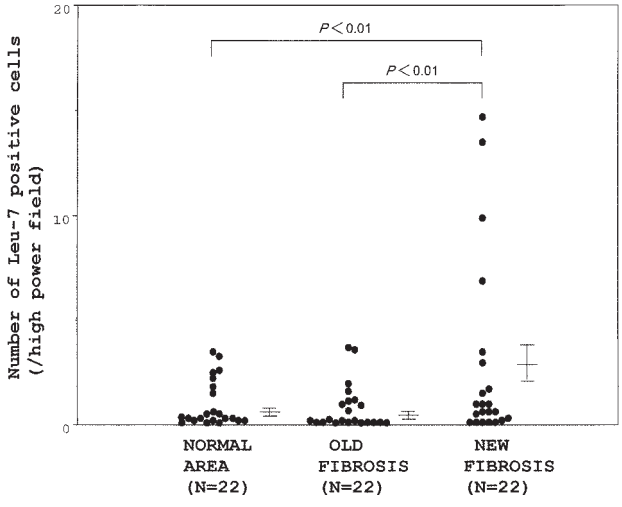


Fig. 7 The number of Leu-7-positive cells in areas of advanced fibrosis, in areas of newly developing fibrosis, and in areas of relatively normal alveoli in 22 autopsied lung samples. The number of Leu-7-positive cells in areas of newly developing fibrosis is significantly higher than that in areas of advanced fibrosis and than that in areas of relatively normal lung ($P < 0.01$).

Discussion

In the present study, we present the distribution and number of Leu-7-positive cells observed in lung samples from patients with pulmonary fibrosis. We demonstrate that the number of Leu-7-positive cells in areas of advanced fibrosis was significantly lower than that in areas of newly developing fibrosis.

Several conditions resulting in chronic interstitial fibrosis of the lungs, such as IPF and pulmonary fibrosis associated with collagen vascular diseases, are complicated with the development of lung cancer [5–10]. Many reports have documented the association of lung cancer with IPF [5–15]. Nagai *et al.* have reported that most tumors (87.9%) in 31 patients with lung cancer associated with IPF, including squamous cell carcinoma have been observed in the peripheral region of the lung [14]. In addition, according to Mizushima *et al.*, in patients with multiple lung cancers or single lung cancer associated with IPF, most tumors were observed in the peripheral regions of the lung (98% in patients with multiple lung cancers and 91% in patients with single lung cancer) [13]. Furthermore, Haddad *et al.* have reported that areas of atypical epithelial proliferation were seen in the terminal air spaces in 8 cases of idiopathic diffuse interstitial pulmonary fibrosis; in three of these cases, lung cancer had developed in the bed of an advanced fibrosis [12]. Lee *et al.* have also reported that lung cancer developed mostly (65.6%) in the peripheral portion of the lung, where advanced fibrosis predominated [15]. They also suggested that the occurrence of lung cancer is related to diffuse fibrosis of the lung [15].

The precise properties of fibrosis that hypothetically lead to the development of a carcinoma are unknown. Many factors are involved in the development of lung cancer in patients with pulmonary fibrosis. One possibility that has been suggested is that scarring causes lymphatic obstruction, resulting in a local increase in potentially carcinogenic particulate material [15]. However, there have been no reports evaluating local immune surveillance in patients with pulmonary fibrosis.

Anti-Leu-7 antibody reacts with CD57-positive cells, including large granular lymphocytes responsible for most NK activity [1] and NK cells are thought to play an important role in the defense against cancer [1, 3]. In addition to their well-described cytotoxicity with respect to a number of tumor cells [16], NK cells exert a number of other important effects on cell-mediated immune

responses [17–20]. For example, cells with an NK phenotype have been shown to exert immunosuppressive actions *in vivo* and *in vitro* [18, 19]. Interestingly, it has been demonstrated that dendritic cells expressing antigens are rapidly lysed by NK cells [19]. These properties are likely to play an important role in the progression of an inflammatory response, especially in the lung, which is an organ that expresses a high level of NK cell activity [20].

Denis has reported that lung NK cells exert a suppressive influence on the development of cellular infiltrates and tissue damaging reactions that occur after instillation with the thermophilic actinomycete *Faeni rectivirgula* [17]. The same study also suggested that this effect was either the result of the suppressive activity of NK cells, or else it could have resulted from either NK cell ability to lyse actinomycete-laden macrophages, thereby preventing these cells from secreting sustained monokine levels that would otherwise be expected to enhance the granulomatous reaction [17].

However, there have been few reports which have evaluated Leu-7 cells in cases involving interstitial lung disease [21, 22]. Ishida *et al.* reported that the number of Leu-7-positive cells in peripheral blood is increased in cases of interstitial lung disease associated with Sjogren's syndrome [21]. In addition, Costabel *et al.* have reported that the number of Leu-7-positive cells was increased in bronchoalveolar lavage fluid as compared to that in a control group, in a study of asbestosis and mixed dust pneumoconiosis [22]. However, the distribution of Leu-7-positive cells in the lung tissues was not studied in those reports.

In the present study, the distribution and number of human Leu-7-positive cells was evaluated. We demonstrated that Leu-7-positive cells were significantly decreased in areas of advanced fibrosis. In addition, although Leu-7-positive cells were mostly found within the capillaries of the septa in unaffected areas of lung, Leu-7-positive cells were distributed only among the affected areas in areas of advanced fibrosis, and in areas demonstrating the DAD or BOOP patterns. Since NK cells in the lung are believed to play an immunosuppressive role [17–19], it can be speculated that Leu-7-positive cells detach from capillaries and infiltrate into fibrotic areas in order to play a role in the local immune system's surveillance function, thereby influencing the pathogenesis of fibrotic lung diseases.

In addition, it is supposed that Leu-7-positive cells attached to the endothelium can directly attack abnormal epithelial cells, because epithelial cells exist very closely to capillaries. Since lung cancer appears to be more likely to develop in beds of advanced fibrosis [11], this weakness in the local immune system's surveillance function might be related to the occurrence of lung cancer.

In conclusion, our present study demonstrates a significant decrease in the number of Leu-7-positive cells in areas of advanced fibrosis. Abnormalities involving both number and distribution of Leu-7-positive cells could be related to the immune system's surveillance function of alveoli in interstitial lung diseases.

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