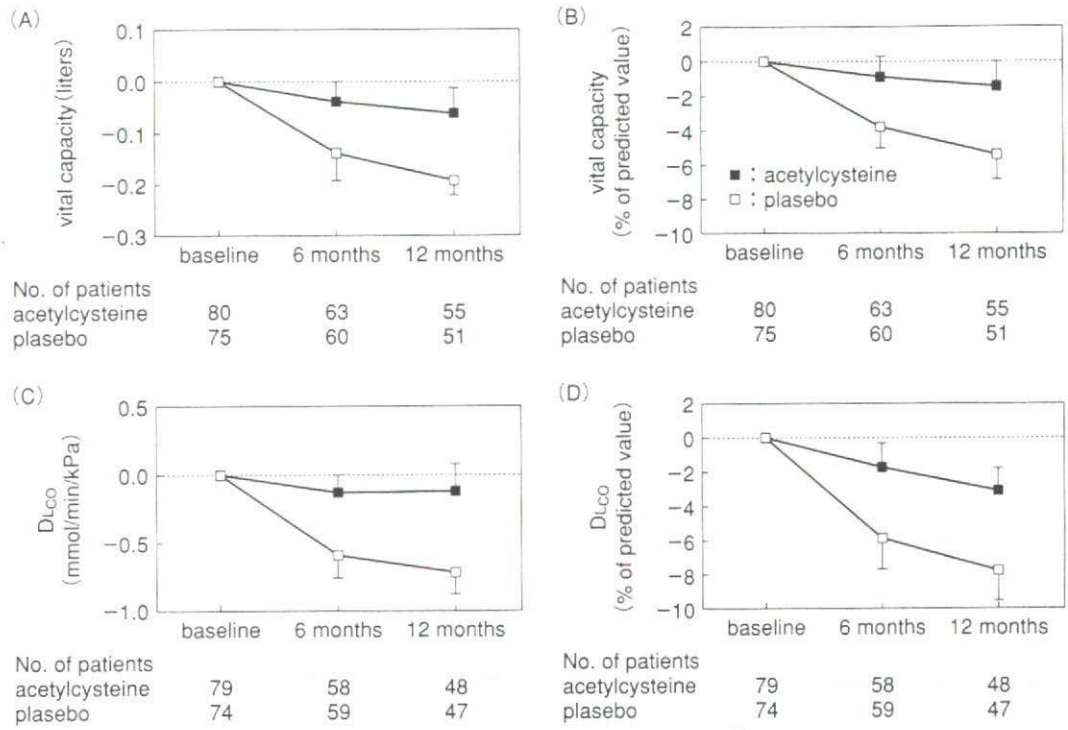

図 1　NAC療法によるVCとD_{LCO}の変化[8]

VC および D_{LCO}の絶対値と%予測値の 6 カ月後および 12 カ月後の基礎値からの変化．NAC 群ではプラセボ群と比較して有意な変化を認めていない．

が，GSH の前駆体であり，細胞内 GSH 増加作用を有するうえ，それ自体にも antioxidant 作用がある薬剤である．さらに，NAC は NF-κB の活性化を抑制し，サイトカインや接着分子の発現を抑制することも報告されている[5]．ヨーロッパでは古くから NAC の経口薬が慢性気管支炎の急性増悪率を減少させる効果があることが多施設共同研究の結果，報告され，市販されている[6]．NAC の経口によって，IPF 患者の気管支肺胞洗浄液中の GSH 濃度が増加することも報告されている．

NAC内服による臨床試験

このような背景から NAC 内服が IPF の治療法として有用である可能性が考えられ，1997 年にドイツのグループより，NAC の経口大量投与(1,800 mg/day)が 20 症例の IPF および膠原病に伴う線維化肺の肺機能や運動負荷時の血液ガス改善に有用であるとの報告がはじめてなされた[7]．20 例のうち 13 例はステロイドや免疫抑制剤が併用されていた．NAC 投与前 4 カ月程度の観察期間では VC や拡散能，PaO_2を合わせて算出した lung function index が 72%の症例で低下したが，NAC 投与後の 3 カ月間では 78%の症例で増加に転じた．この結果を受けてヨーロッパでは IPF の NAC 内服による治療に関する randomized controlled trial(RCT)である IFIGENIA Study が行われた．

IFIGENIA Study[8]では IPF 症例 155 例を対象に，プレドニン＋アザチオプリン併用のうえに NAC (1,800 mg/day)経口またはプラセボが加えられ，1 年間の経過観察が行われた．NAC 群 57 例，プラセボ群 51 例が 1 年間の試験を完了し，NAC 群ではプラセボ群と比較して，肺拡散能力(D_{LCO})と肺活量(VC)の悪化の有意な減少が認められた(図 1)．その差は VC で 0.18 l(9%)，D_{LCO}で 0.75 mmol/min/kPa(24%)であった．死亡率は，NAC で 9%，プラセボで 11%と差がなかった．また，NAC 群で有意に骨髄抑制が少なかった以外は副作用に差はなかった．この結果から，おそらく NAC 経口薬は IPF の治療薬として適応拡大が承認され，臨床使用されるものと思われる．

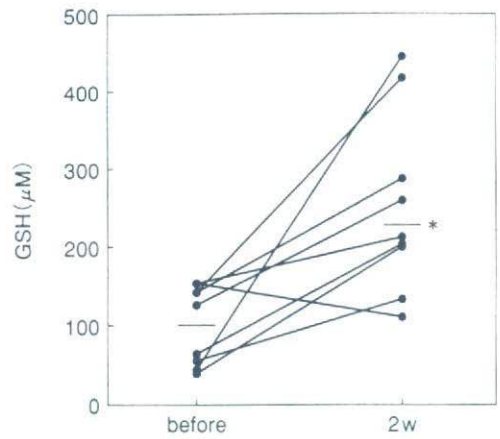

図 2　IPF症例におけるNAC吸入による喀痰中GSH濃度の変化[9]
*：$p<0.01$.

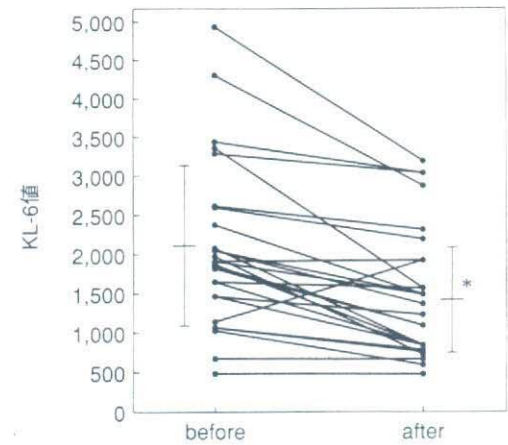

図 3　IPF症例におけるNAC吸入前および3カ月後の血清中KL-6値の変化[12]
*：$p<0.01$.

IPFに対するNAC吸入療法

著者らは NAC 経口薬の trial がはじめて報告される以前より NAC 療法の可能性に関心をもち研究を行っていたが，わが国においては NAC は吸入剤のみが去痰薬として使用可能であったため，IPF に対する NAC 吸入療法の可能性を探ってきた．まず，マウスブレオマイシンモデルを用いて NAC 吸入の有用性を証明した[4]．つぎに，1 日 2 回の NAC 吸入によって，IPF 症例の気道で減少した GSH が補充できることを確認した(図 2)[9]．

さらに，有用性および安全性を知るためオープン臨床試験を行った[10,11]．肺炎など感染症による増悪期あるいは急性悪化期にある症例は除き，ステロイドや免疫抑制剤など他の治療薬を使用していない症例を対象とした．NAC は 1 A 352.4 mg を生理食塩水で 5〜10 ml とし，1 日 2 回超音波ネブライザーで吸入した．吸入開始後 3〜6 カ月の時点における短期効果では 28 例中約半数の症例で労作時呼吸困難，咳嗽など自覚症状の改善を認め，一部の症例では画像所見や肺機能所見の改善も認められた．1 年以上治療を継続しえた症例の長期効果においても臨床症状の改善は 27.8%に認められ，44.5%に臨床的有用性ありと判定された．最長 53 カ月の長期使用においても特別な副作用は認めず，安全性も確認された．間接的所見ではあるが，多くの症例で間質性肺炎の活動性マーカーである KL-6 値が NAC 吸入によって有意に低下をみた(図 3)[12]．このことは NAC の薬剤としての効果を反映しており，画像所見や肺機能所見に改善がみられない症例においても線維化の進行を抑制している可能性は十分に考えられるものと思われた．

IPF治療法としてのNACの可能性

IPF の病態にオキシダントが大きく関与することは明らかであり，抗酸化薬治療は理論的に期待でき，IFIGENIA Study の結果からも，NAC によって呼吸機能低下の進行を抑制できる可能性が示唆された．海外ではまもなく NAC 経口薬の臨床使用が開始されると思われる．一方，著者らが考案した NAC 吸入療法も，古くから喀痰融解剤として用いられてきた薬剤であり，その安全性は確立されているうえ，去痰剤としての作用も期待できること，経口投与では気道におけるグルタチオン濃度は上昇するが，NAC 自体は気道には到達しないといわれており，吸入療法のほうが NAC 自体を炎症の場に直接作用させ，さらに GSH の補充も行われる点から，より効率のよい投与法と考えられる．IPF に対して確立した治療法のない現状では，NAC 吸入療法は副作用もない点から試みられるべき選択肢のひとつと考えられる．

現在，わが国でも NAC 吸入療法の多施設臨床試験が厚生労働省研究班によって開始されており，今後の症例の集積による有用性の解析が期待される．

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Gefitinib Prevents Bleomycin-induced Lung Fibrosis in Mice

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Rationale: Transforming growth factor-α and epidermal growth factor (EGF), the ligands for EGF receptor (EGFR), stimulate fibroblast proliferation and play an important role in the pathogenesis of pulmonary fibrosis. Therefore, inhibition of the EGFR signal by an EGFR tyrosine kinase inhibitor (EGFR-TKI) may prevent pulmonary fibrosis. However, there is a possibility that blocking the EGFR signal may inhibit epithelial cell repair, thereby exaggerating lung fibrosis.
Objective: To investigate the effect of EGFR-TK inhibition on lung fibrosis.
Methods: We looked at the effects of the EGFR-TKIs gefitinib (20, 90, 200 mg/kg) and AG1478 (12 mg/kg) on a bleomycin-induced lung fibrosis model in mice.
Measurements and Main Results: Gefitinib prevented lung fibrosis at all three doses. Furthermore, in those mice that did not receive bleomycin treatment, gefitinib at 200 mg/kg did not induce lung fibrosis. Immunohistochemistry revealed that phosphorylation of EGFR in lung mesenchymal cells induced by bleomycin was inhibited by gefitinib. AG1478 also attenuated the lung fibrosis. *In vitro* studies further demonstrated that the addition of gefitinib or AG1478 suppressed the EGFR ligand–induced proliferation of lung fibroblasts.
Conclusions: These findings suggest that, in the preclinical setting, EGFR-TKIs may have a protective effect on lung fibrosis induced by bleomycin. Because these molecular targeted drugs may have differing effects depending on species and individuals, a cautious interpretation is warranted.

Keywords: epidermal growth factor; EGF receptor tyrosine kinase inhibitor; fibroblasts; interstitial lung disease; molecular targeted drug

Molecular targeted drugs have been attracting a great deal of attention as novel cancer therapies, with the goal of inhibition of cancer cell proliferation by the suppression of growth signals through growth factor receptor tyrosine kinase inhibition (1, 2). Growth factor receptors are located not only in cancer cells but also in normal cells, playing a role in cell proliferation. The main pathologic feature of idiopathic pulmonary fibrosis is proliferation of fibroblasts stimulated with various growth factors. Therefore, inhibition of growth factor receptor signaling in fibroblasts may be useful in the treatment of fibrosis. Growth factors in fibroblasts include transforming growth factor-α (TGF-α) and epidermal growth factor (EGF) as well as TGF-β, platelet-derived growth factor, and insulin-like growth factor-1. There are many reports indicating that TGF-α and EGF, ligands for EGF receptor (EGFR), play an important role in the pathogenesis of pulmonary fibrosis. TGF-α was increased in the bronchoalveolar lavage of patients with idiopathic pulmonary fibrosis and was immunolocalized to type II epithelial cells, fibroblasts, and the vascular endothelium (3). Expression of TGF-α and EGFR mRNA was also increased in fibrotic lung tissue after bleomycin-induced lung injury in rats (4). Furthermore, conditional expression of TGF-α caused pulmonary fibrosis in transgenic mice (5), whereas TGF-α deficiency reduced pulmonary fibrosis in TGF-α knockout mice (6). An *in vitro* study also showed that the ligands stimulated fibroblast proliferation (7). Therefore, blocking EGFR-mediated signaling by EGFR tyrosine kinase inhibitors (EGFR-TKIs) could be useful in the treatment of pulmonary fibrosis. In fact, the EGFR-TKI AG1478 reduced the pulmonary fibrosis induced by vanodium pentoxide in rats (8).

However, interstitial pneumonia and acute lung injury have been reported in approximately 5.8% of Japanese patients (with a mortality rate of 2.3%) treated with another EGFR-TKI, gefitinib (9–12), which is already used clinically for lung cancer therapy (2, 13). It is unclear whether the injury is caused by the inhibition of EGFR signaling or by another mechanism possibly not related to gefitinib. In addition, interstitial lung disease (ILD) is a condition that may be associated with lung cancer itself (14). In a study using a murine model of bleomycin-induced pulmonary fibrosis, gefitinib at a dose of 200 mg/kg (a dose close to the maximum tolerated dose and the highest dose used in xenograft models [15]) augmented the lung fibrosis (16). Therefore, in this study, we looked at the inhibitory effect of three doses of gefitinib on bleomycin-induced lung fibrosis; considering that the minimum inhibitory concentration for transplanted tumors in nude mice is 12.5 mg/kg (15), we chose 20 mg/kg as a probable effective dose for EGFR-TK inhibition, 200 mg/kg as a dose 10 times that of the effective dose, and 90 mg/kg as an intermediate dose. The effect of gefitinib was also compared with AG1478 in the same experimental system.

Some of the results of these studies have been previously reported in the form of an abstract (17).

METHODS

Additional details are provided in the online supplement.

Fibroblast Proliferation Assay

Proliferation of human fetal lung fibroblasts (HFL-1) in response to TGF-α and EGF was determined by 5-bromo-2′-deoxyuridine (BrdU) incorporation using a cell proliferation ELISA kit (Roche Diagnostics Corporation, Indianapolis, IN). Gefitinib (10^{-6} M; AstraZeneca, Osaka, Japan), AG1478 (10^{-6}M; Calbiochem, La Jolla, CA), or vehicle was added to the cultures 30 min before addition of the growth factors.

Animal Treatment

Bleomycin (3 mg/kg; Nippon Kayaku Co., Tokyo, Japan) was intratracheally administered in 60 μl saline to the male C57BL/6 mice (8–10 wk old; Japan Clea, Tokyo, Japan). On Days 3, 7, and 14 after bleomycin treatment, the animals were killed and the lungs were removed en bloc. Animals were allocated to seven groups, as follows: (*1*) intratracheal saline + vehicle givenally, (*2*) intratracheal saline + 200 mg/kg of oral gefitinib, (*3*) intratracheal bleomycin + oral vehicle, (*4*) intratracheal

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bleomycin + 20 mg/kg of oral gefitinib, (5) intratracheal bleomycin + 90 mg/kg of oral gefitinib, (6) intratracheal bleomycin + 200 mg/kg of oral gefitinib, (7) intratracheal bleomycin + 12 mg/kg of intraperitoneal AG1478. Gefitinib suspension in 1% Tween 80 (0.2 ml) was given daily by gavage from Day 1 to Day 13; AG1478 was given intraperitoneally at a daily dose of 12 mg/kg in dimethyl sulfoxide solution from Day 1 to Day 13. For the saline and the bleomycin control groups (groups 1 and 3), a daily dose of vehicle (1% Tween 80 solution) was given orally. All experiments were performed in accordance with National Institutes of Health guidelines and protocols approved by the Dokkyo Medical University School of Medicine Subcommittee on Research Animal Care.

Histologic Evaluation

The right lung was fixed in 10% buffered formalin, and stained with hematoxylin and eosin and Masson's trichrome. Histologic grading of fibrosis was performed by three experienced histopathologists using a blinded semiquantitative scoring system for extent and severity of fibrosis in lung parenchyma based on previous studies (18, 19) with modifications. Severity of fibrosis was scored according to the method of Ashcroft and colleagues (20), with minor modifications as follows: The area of the fibrosis field for each grade and the ratio to the entire field of the section were calculated using a film scanner and the NIH Image software (National Institutes of Health, Bethesda, MD). The sum of the product of ratio multiplied by the grade was used as the score for each section. The mean score of the four sections was considered as the fibrosis score for the animal.

Collagen Assay

The left lung was homogenized and the collagen content determined using the Sircol Collagen Assay kit (Biocolor Ltd., Belfast, Northern Ireland) (21).

Immunohistochemistry

Lung tissues were prepared according to the Amex method (22). Sections taken from paraffin-embedded samples were immunostained for EGFR and phosphorylated EGFR by the labeled streptavidin-biotin (LSAB) method using a Dako LSAB+/HRP kit (Dako-Cytomation, Glostrup, Denmark) (23). To evaluate fibroblast proliferation and expression of EGFR on fibroblasts, lungs were double-immunostained for fibroblast-specific marker S100A4 (24) and EGFR. For the representative samples, immunofluorescent double-staining for S100A4 and EGFR was also performed. For a semiquantitative analysis of receptor expression, more than 500 cells per immunostained section were observed to count positive cells. The labeling index was calculated as follows: labeling index (%) = positive cells/all counted cells × 100.

Statistical Analysis

Data are expressed as means ± SEM. Statistical significance was determined by one-way analysis of variance or *t* test. p values less than 0.05 were considered significant.

RESULTS

In Vitro Cell Proliferation Assay

We examined the effect of gefitinib and AG1478 on EGF ligand–induced HFL-1 cell proliferation *in vitro*. TGF-α and EGF stimulated proliferation of the cells. The addition of gefitinib or AG1478 significantly inhibited the growth of the cells induced by TGF-α or EGF in a dose-dependent manner (Figures 1 and 2).

Bleomycin-induced Pulmonary Fibrosis

Histologic examination of mouse lung revealed that bleomycin induced marked inflammatory cell infiltration with fibrosis in the lungs (Figure 3). The fibrosis score for mice given gefitinib 200 mg/kg without bleomycin treatment showed no significant change. In bleomycin-treated mice, gefitinib at doses of 20, 90, and 200 mg/kg significantly prevented the bleomycin-induced lung fibrosis (Figures 3 and 4). There was no significant difference in the inhibitory effect of the inhibiters at any dose. AG1478

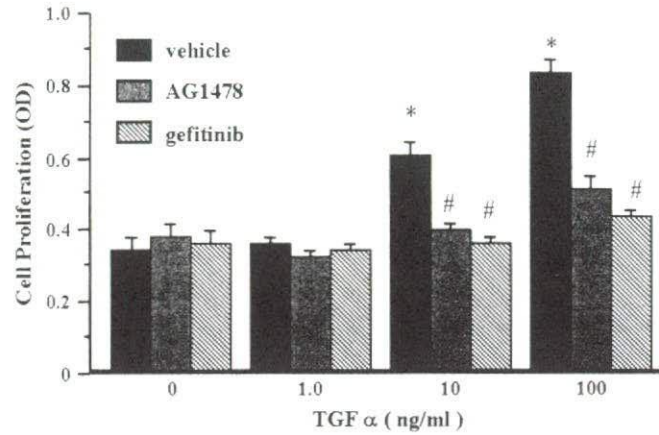

Figure 1. Gefitinib and AG1478 inhibited *in vitro* transforming growth factor (TGF)-α–stimulated fibroblast proliferation. Cell proliferation was determined by 5-bromo-2′-deoxyuridine (BrdU) incorporation. BrdU absorbance (OD) was measured at 450 nm with 690 nm as reference wavelength. (n = 6 in each group; *p < 0.01 vs. TGF-α, 0 ng/ml; #p < 0.01 vs. vehicle.)

also attenuated the lung fibrosis (Figures 3 and 4). The two EGFR-TKIs also significantly reduced the bleomycin-induced lung collagen accumulation (Figure 5).

Gefitinib Inhibited Bleomycin-induced Phosphorylation of EGFR

Immunohistologic examination was conducted to confirm changes of EGFR and phosphorylated EGFR expression in the lung during the bleomycin-induced fibrosis process and to confirm that phosphorylation of EGFR could be inhibited by gefitinib. EGFR expression in the lung of the control group was positive in about 15% of cells, mainly epithelial cells and interstitial cells. The expression was not augmented by bleomycin, and a slight decrease in labeling index was observed after 14 d (Figure 6). On the other hand, phosphorylated EGFR expression was significantly increased 3 d after bleomycin treatment in the epithelial cells of fibrotic lung tissue and in interstitial fibroblast-like cells, compared with the control. Gefitinib significantly reduced this

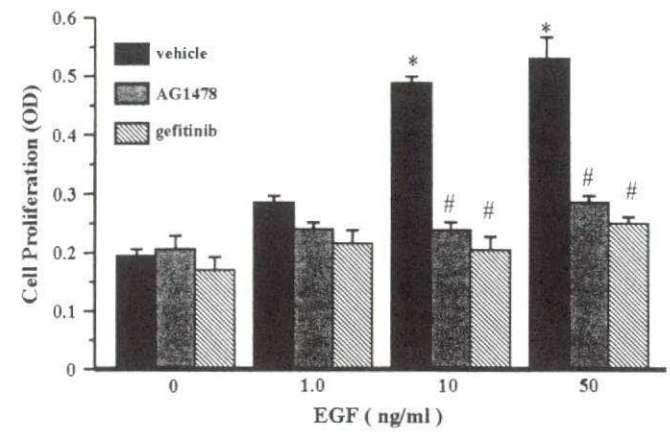

Figure 2. Gefitinib and AG1478 inhibited *in vitro* epidermal growth factor (EGF)–stimulated fibroblast proliferation. Cell proliferation was determined by BrdU incorporation. (n = 6 in each group; *p < 0.01 vs. EGF, 0 ng/ml; #p < 0.01 vs. vehicle.)

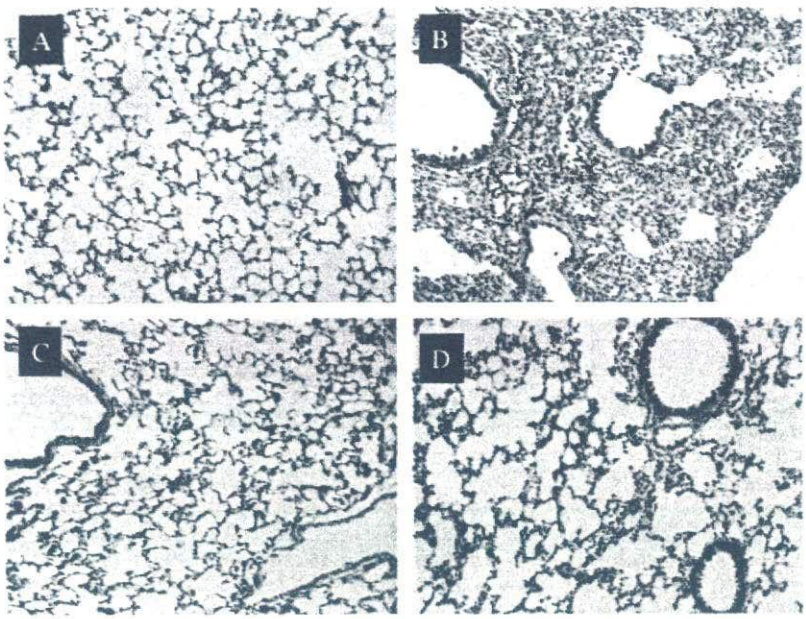

Figure 3. Representative pathologic findings of lung tissue by Masson's trichrome stain obtained 14 d after bleomycin instillation. (*A*) Vehicle given orally with saline instillation. (*B*) Vehicle given orally with bleomycin instillation. (*C*) Gefitnib 200 mg/kg given orally with bleomycin instillation. (*D*) Intraperitoneal AG1478 with bleomycin instillation. Mice were given orally the vehicle alone or gefitinib (200 mg/kg) 1 h before and on Days 1–13 after an intratracheal injection of bleomycin (3 mg/kg). AG1478 (12 mg/kg) was injected intraperitoneally 1 h before bleomycin instillation and on Days 1–13. Original magnification, ×100.

expression (Figures 7 and 8). There was a decreasing tendency of phosphorylated EGFR expression with time; however, even on Day 7, gefitinib significantly reduced the phosphorylation compared with the bleomycin control group (Figure 8).

Fibroblast Proliferation and EGFR Expression on Fibroblasts *In Vivo*

To determine whether the bleomycin treatment induces fibroblast proliferation and whether EGFR is expressed in fibroblasts cells *in vivo*, lungs were double-immunostained for fibroblast-specific marker S100A4 and EGFR. The number of S100A4-positive cells was significantly increased with time at Days 3, 7, and 14 in the bleomycin group as compared with the control group (Figure 9). Gefitinib treatment at doses of 20 and 200 mg/kg significantly attenuated the bleomycin-induced increase in S100A4-positive cell number (Figure 9). Double-inmmunostaining clearly revealed that EGFR is expressed on the S100A4-positive fibroblasts (Figures 10 and 11). The percentage of EGFR-positive cells in S100A4-positive cells (EGFR labeling index) was about 10% in the control untreated lungs (Figure 12). Bleomycin treatment slightly increased this index up to 16% on Day 3, but the index was not altered on Days 7 and 14 (Figure 12).

DISCUSSION

In those mice that had not received bleomycin treatment to induce lung fibrosis, no changes to the lung were observed after the administration of gefitinib, even at the high dose of 200 mg/kg, which was close to the maximum tolerated dose and the highest dose used in xenograft models (15). Gefitinib at each of the dose levels—20, 90 and 200 mg/kg—significantly prevented the lung

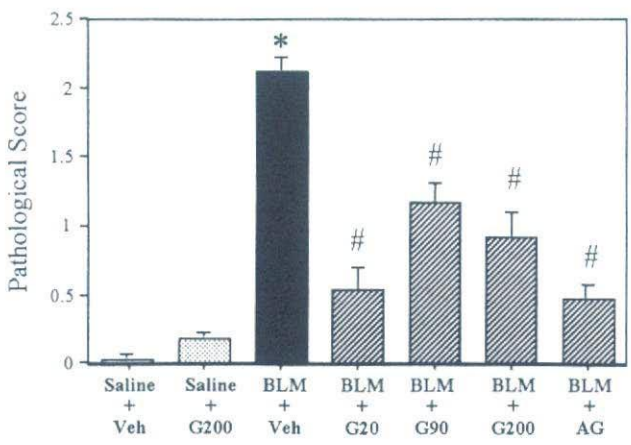

Figure 4. Fibrosis scoring based on severity and area of fibrosis. The fibrosis score for gefitinib 200 mg/kg without bleomycin showed no significant change. Gefitinib at doses of 20, 90, and 200 mg/kg significantly prevented the bleomycin-induced lung fibrosis. AG1478 also prevented the fibrosis. (n = 6–8 in each group; *$p < 0.001$ vs. saline + vehicle, #$p < 0.001$ vs. bleomycin + vehicle.) AG = AG1478 12.5 mg/kg; BLM = bleomycin; G20 = gefitinib 20 mg/kg; G90 = gefitinib 90 mg/kg; G200 = gefitinib 200 mg/kg; Veh = vehicle.

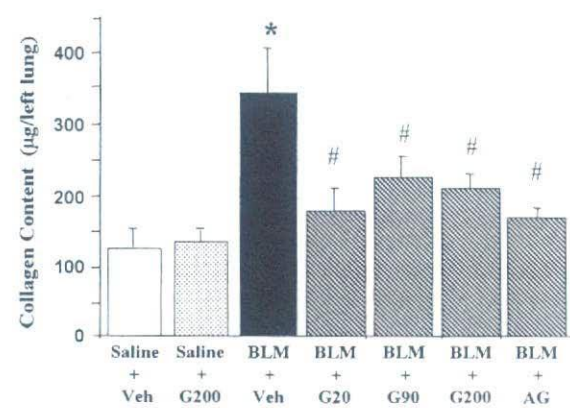

Figure 5. Collagen content in lung tissues. Bleomycin augmented the lung collagen content. Gefitinib at doses of 20, 90, and 200 mg/kg significantly prevented the increased collagen content. AG1478 also prevented the collagen content. (n = 6–8 in each group; *$p < 0.001$ vs. saline + vehicle, #$p < 0.001$ vs. bleomycin + vehicle.) AG = AG1478 12.5 mg/kg; BLM = bleomycin; G20 = gefitinib 20 mg/kg; G90 = gefitinib 90 mg/kg; G200 = gefitinib 200 mg/kg; Veh = vehicle.

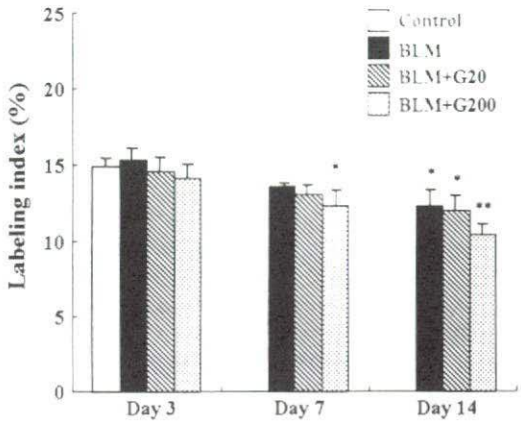

Figure 6. Immunohistochemical labeling index of EGFR expression on lung tissues after the intratracheal instillation of bleomycin. (n = 3–6; *p < 0.05, ** p < 0.01 vs. control.) BLM = bleomycin; G20 = gefitinib 20 mg/kg; G200 = gefitinib 200 mg/kg.

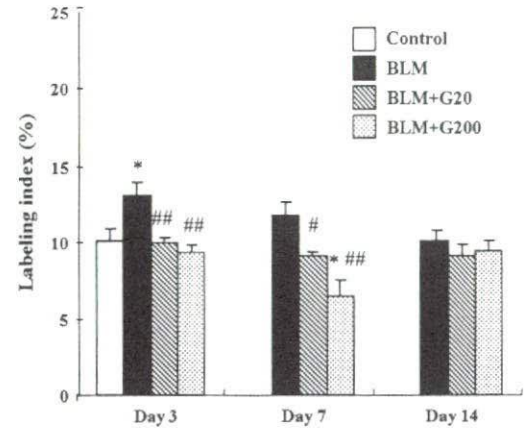

Figure 7. Immunohistochemical labeling index of phosphorylated EGFR expression on lung tissues after the intratracheal instillation of bleomycin. (n = 3–6; *p < 0.05 vs. control, #p < 0.05 vs. bleomycin, **p < 0.02 vs. bleomycin.) BLM = bleomycin; G20 = gefitinib 20 mg/kg; G200 = gefitinib 200 mg/kg.

fibrosis induced by intratracheal bleomycin. The fibrosis was effectively reduced by gefitinib 20 mg/kg, which was about twice the growth-inhibitory dose (12.5 mg/kg) used on transplanted tumors in nude mice (15). A similar suppression effect was observed at a dose of 200 mg/kg, 10 times the low dose and close to the maximum tolerated dose, without aggravation of fibrosis. AG1478 also significantly attenuated the fibrosis, indicating that EGFR-TK inhibition itself had a protective effect on lung fibrosis in a mouse bleomycin-induced pulmonary fibrosis model.

Immunohistochemical staining revealed that gefitinib treatment significantly decreased fibroblast proliferation induced by bleomycin *in vivo* and that EGFR was expressed on fibroblasts almost constantly. Meanwhile, EGFR phosphorylation of the lungs was induced by bleomycin early on Day 3, which, however, was suppressed by gefitinib. This evidence was considered to support the *in vitro* observation that the EGFR-TKIs prevented the fibroblast proliferation induced by EGF ligands, as well as the *in vivo* observation that the EGFR-TKIs inhibited the bleomycin-induced lung fibrosis.

EGFR is also expressed and phosphorylated in alveolar or airway epithelial cells, and therefore, gefitinib is considered to have had effects on those cells. It has been suggested that epithelial injury and delay of its repair could play an important role in the fibrogenesis process (25, 26). Therefore, inhibition of epithelial regeneration by an EGFR-TKI might promote fibrogenesis. Moreover, blocking of EGFR could induce epithelial apoptosis (27). In the present study, although we did not directly examine whether or not retardation of epithelial repair or promotion of apoptosis was induced, fibrogenesis was clearly reduced as a result, indicating that inhibition of fibroblast migration and proliferation could result in prevention of fibrosis even in a retarded condition of epithelial regeneration.

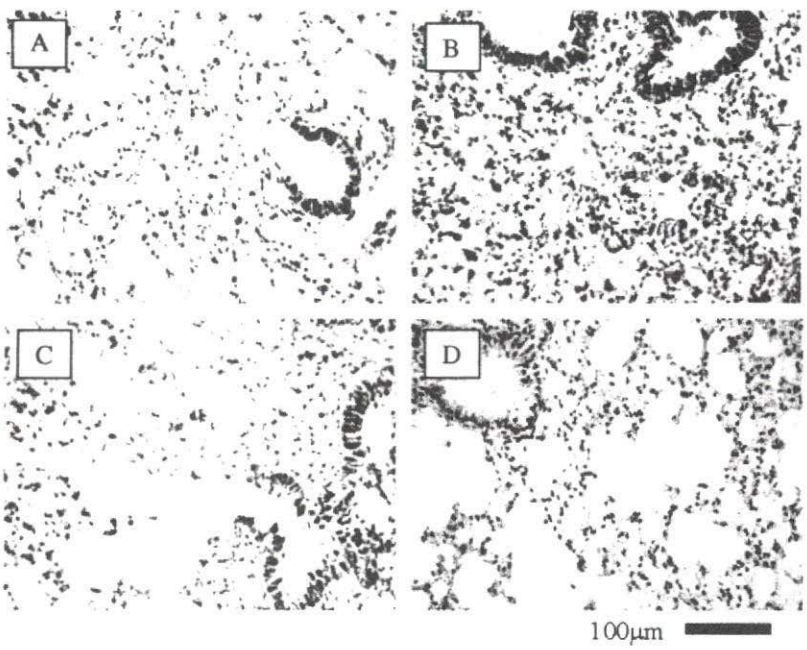

Figure 8. Representative findings on immunohistochemical staining for phosphorylated EGFR. Lung tissues were obtained from mice 7 d after intratracheal instillation of bleomycin. Control mice were given a saline instillation (*A*). Mice were treated with orally given vehicle (*B*) or gefitinib (200 mg/kg; *C*) after bleomycin instillation. There was no specific staining in preparations incubated with control IgG (*D*).

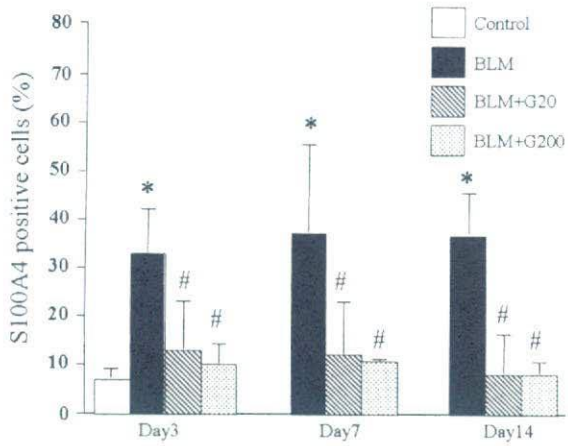

Figure 9. Number of S100A4-positive cells in the lung tissues after the intratracheal instillation of bleomycin. Quantification was performed by counting the numbers of positive cells/mm² in a minimum of three randomly chosen microscopic fields. (n = 3–6; *$p < 0.01$ vs. control, #$p < 0.01$ vs. bleomycin). BLM = bleomycin; G20 = gefitinib 20 mg/kg; G200 = gefitinib 200 mg/kg.

EGFR is expressed by many cell types in the lung, including the epithelium, smooth muscle cells, endothelium, and fibroblasts (28). Ligands for the EGFR found in the lung include TGF-α, EGF, amphiregulin, and heparin-binding EGF. Some studies demonstrated that the ligands were abundantly localized in the lung due to elevated production in pathologic lung fibrosis (3, 4). Expression of EGFR was also increased (4). Pulmonary fibrosis by bleomycin in TGF-α–knockout mice was reduced compared with wild-type mice (6), whereas the fibrosis was induced in TGF-α transgenic mice (5). Those findings suggested that EGFR and its ligands were significantly involved in pathology of lung fibrosis, and therefore blocking of both signal transductions could be a useful treatment for pulmonary fibrosis. In fact, the EGFR-TKI AG1478 reduced the pulmonary fibrosis induced by vanadium pentoxide in rats (8). The results of our study are thus consistent with those of a sequence of studies.

Suzuki and colleagues reported that gefitinib augmented bleomycin-induced pulmonary fibrosis in mice (16). Their study used 200 mg/kg (a subtoxic dose) of gefitinib; therefore, in this study, three doses were chosen: 200 mg/kg as a high dose, 20 mg/kg as enough to inhibit EGFR, and 90 mg/kg as an intermediate dose. Fibrosis was significantly reduced in all three dose groups without any aggravation due to the drug. There were no significant differences between the experimental methods, except for the difference in strains used: ICR and C57BL/6 mice, in which exposure for gefitinib showed little difference between the two strains based on the observed maximum serum concentration (Cmax), the area under the serum concentration—time curve from 0 to 24 h ($AUC_{0\text{-}24}$), and the terminal half-life of gefitinib (AstraZeneca, unpublished data). The reason for the discrepancy between the results is not known.

ILD is a condition considered to be associated with lung cancer (14). Since gefitinib was clinically introduced as an anticancer drug for lung tumors, interstitial pneumonia or acute lung injury have been seen in patients treated with gefitinib (9–12). The incidence of interstitial pneumonia is about 5% in Japanese patients, which is higher than the incidence reported globally of 0.8% (29). There are no large differences in the incidence of interstitial pneumonia between gefitinib and new-generation cytotoxic anticancer agents such as paclitaxel, docetaxel, irinotecan, vinorelbine, gemcitabine, and amrubicin, according to the reported incidences of interstitial pneumonia (0.1–6.2%) in the late phase 2 trials in Japan (data from the package inserts of the agents). As for possible mechanisms of pathogenesis, pharmacology of EGFR-TKIs, drug toxicity independent of pharmacology, and immunoreaction have been postulated. The results of this study reveal that neither universal effects induced by the drug itself at a high dose nor repair inhibition triggered by inflammation in the host could have contributed to the development of ILD.

In clinical studies with gefitinib in patients with lung cancer, a greater antitumor effect was observed in adenocarcinomas, females, and nonsmokers (11, 12), and an ethnic difference was evident, with a greater antitumor effect seen in Japanese populations than in non-Japanese populations (30). Also, mutation of the EGFR gene has been known to be involved as a determinant

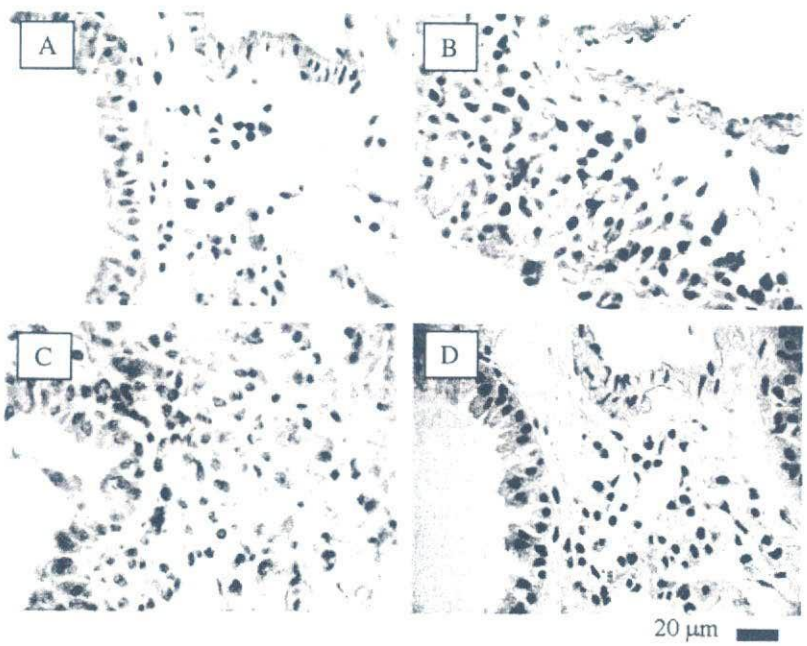

Figure 10. Representative findings on double immunohistochemical staining for fibroblast-specific marker S100A4 (*gray/black*) and EGFR (*pink/red*). Lung tissues were obtained from mice 14 d after intratracheal instillation of bleomycin. Control mice were given a saline instillation (*A*). Mice were treated with orally given vehicle (*B*) or gefitinib (200 mg/kg; *C*) after bleomycin instillation. There was no specific staining in preparations incubated with control IgG (*D*).

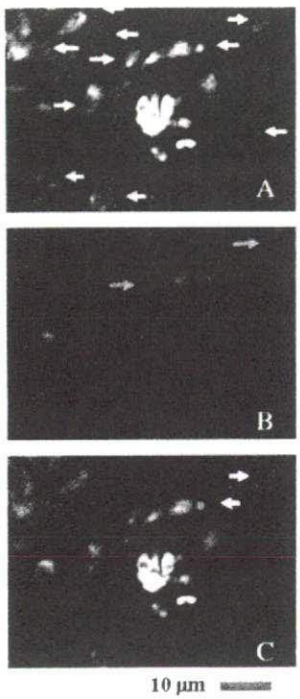

Figure 11. Representative findings on double immunofluorescence staining for fibroblast-specific marker S100A4 and EGFR. Lung tissues were obtained from mice 14 d after intratracheal instillation of bleomycin. (*A*) Samples were stained with anti-S100A4 antibody (*green*). (*B*) Samples were stained with anti-EGFR antibody (*red*). (*C*) Double-immunofluorescence staining of S100A4 and EGFR (*yellow*). *Arrows* indicate positive-staining cells.

of response to gefitinib therapy (31–33): gefitinib was more effective in patients with mutations on exon 18, 19, and 21 of the EGFR gene. There was a higher rate of mutation-positive patients in the groups that exhibited a greater clinical effect with gefitinib, such as nonsmokers or Japanese patients (32, 34). On the contrary, reports of lung injury in association with gefitinib therapy were also higher in Japanese populations than in non-Japanese populations. This suggested the potential involvement of genetic factors, although this has not been demonstrated (10). Smoking and underlying pulmonary fibrosis have been identified as risk factors for interstitial pneumonia and acute lung injury (11). Although it is possible that gefitinib could induce unbalanced repair after lung injury and thereby could result in lung fibrosis, our results have shown that no lung fibrosis was observed with gefitinib itself, even at a high dose, and that gefitinib reduced rather than increased the bleomycin-induced lung fibrosis.

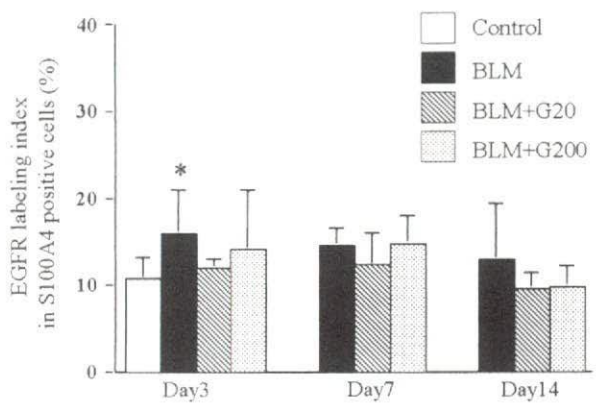

Figure 12. EGFR labeling index in S100A4-positive cells on lung tissues after the intratracheal instillation of bleomycin. (n = 3–6, *p < 0.05 vs. control.) BLM = bleomycin; G20 = gefitinib 20 mg/kg; G200 = gefitinib 200 mg/kg.

The present study demonstrated that EGFR-TKIs, such as gefitinib and AG1478, attenuated bleomycin-induced lung fibrosis in mice, possibly by inhibiting growth signaling in fibroblasts. This suggests that EGFR-TKIs might be useful for the treatment of pulmonary fibrosis, although many issues remain to be resolved. Moreover, imatinib, which is a platelet-derived growth factor (a growth factor in fibroblasts) receptor TKI, has been shown to suppress bleomycin-induced lung fibrosis (35–37), and its clinical use has been discussed. However, because interstitial pneumonia has been also reported as a complication of imatinib (38), the mechanism of pathogenesis should be clarified.

Although the mechanism of induction of clinical interstitial pneumonia and lung injury could not be explained in this study, one hypothesis could be that blocking EGFR could alter the balance between repair and fibrosis after lung injury in a negative direction by genetic factors in particular individuals, leading to the induction of fibrosis. Pathologic elucidation using genetic analysis in lung fibrosis cases is necessary to improve understanding.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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≪特発性間質性肺炎の治療最前線≫
特発性間質性肺炎に対する治療法の概要
――現在の治療法とその限界

石井芳樹*

要旨

- 特発性間質性肺炎の現状における治療法は，ステロイドとその他の免疫抑制薬に限られる．
- その効果は，病型によって異なるため正しい診断が重要である．
- 特発性肺線維症(IPF)は，慢性進行性で予後不良な疾患であるが，有効な治療法は確立されていない．ステロイド単独による治療効果は薄く，cyclophosphamide や azathioprine，cyclosporin などが併用されるが，その効果も限られる．
- 病理所見に基づき正しく診断された症例を対象とした大規模多施設共同臨床試験は，ほとんど行われていないため，エビデンスとなるデータはきわめて少ない．
- これらの治療は日和見感染症など副作用も多く，新しい治療法の開発が期待される．

はじめに

特発性間質性肺炎(idiopathic interstitial pneumonias：IIPs)には，特発性肺線維症(IPF)，非特異的間質性肺炎(NSIP)，急性間質性肺炎(AIP)，特発性器質化肺炎(COP)，剥離性間質性肺炎(DIP)，呼吸細気管支炎を伴う間質性肺炎(RB-ILD)，リンパ球性間質性肺炎(LIP)といった，七つの異なる病態が含まれる．

現状での IIPs の治療法はステロイドとその他の免疫抑制薬であるが，治療反応性は病理組織パターンによって異なる．IIPs の中でも IPF，fibrotic NSIP や AIP は治療反応性が乏しい．それに対して cellular NSIP や DIP は，ステロイドに対する反応性が良好である．したがって，まず IIPs の病型を正しく診断することが重要となる．

日常臨床でもっとも問題となるのは，組織学的に NSIP なのか，通常型間質性肺炎(UIP)なのかということである．この鑑別は，多くの場合 HRCT によって判定できるが，10～30% 程度は診断に間違いが生じる可能性が報告されている[1,2]．正確な診断には，外科的肺生検が必要となるが，この場合も，採取した場所によって診断が異なる場合も存在するし，分類不能な場合(unclassifiable interstitial pneumonia)もあるので，外科的肺生検が行われたからといって絶対的診断が確定するわけではない[3]．また，肺病変先行型の膠原病肺や慢性過敏性肺炎など，鑑別が困難な症例が含まれる可能性も考慮する必要がある．この辺の問題点を理解したうえで，治療の適応を考えなければならない．

治療に関しては，2000 年に ATS/ERS(American Thoracic Society/European Respiratory Society)のステートメント[4]が発表され，2004 年には日本呼吸器学会の手引き[5]が出されているが，EBM に基づいた治療成績の報告がほとんどないため，強く推奨できる治療法は確立されていない．したがって，治療に反応する可能性と治療に伴う副作用などのデメリットを，それぞれの症例にお

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いてよく考慮したうえで，治療を行う必要がある．

特発性肺線維症(IPF)の治療○

1．ステロイド

ステロイドが単独使用でIPFの治療に有用であるかどうかの成績はいくつか報告されてきたが，有効であったという報告のほとんどは，1994年にNSIPの概念が提唱される以前のものであるため，NSIP症例が含まれていたことにより有効性が高く出た可能性があり，評価が困難であった．NSIPの概念が認識された以降の新しい診断基準を用いた成績では，有効性は8～17%と低い[6]．

最近，肺線維化は慢性炎症自体に起因するものではなく，上皮傷害の治癒過程の問題であると考えられており，ステロイドのような抗炎症薬では線維化を抑制できないものと考えられている．分子生物学的にも，ステロイドは線維化に関わるサイトカインであるPDGFやTGF-βを抑制しないこと，IPF肺組織ではステロイド受容体の発現が低下していることなどが知られており，IPFにステロイドが効果を示さないことを裏付けている．

したがって，原則的にIPF/UIP症例には，ステロイド単剤では使用しない．しかし，日常臨床では，IPF/UIPの診断が100%正しいという確証はなく，HRCTでスリガラス陰影(ground-glass opacity：GGO)が多いとか気管支肺胞洗浄(bronchoalveolar lavage：BAL)液でリンパ球が多いなど，NSIPや慢性過敏性肺炎(chronic HP)も完全には否定できない場合などは，ステロイドを試みて反応性をみてもよいと思われる．

ステロイドは，減量による急性増悪のリスクを避けるため，ATS/ERSのステートメントに示されているような，急激な減量は行わない．prednisoloneの投与は，0.5 mg/kg/dayで4週間，その後2～4週に5 mg減量し，5～10 mg/dayまたは，20 mg/day隔日で維持する方法と，はじめからprednisolone 20 mg/day隔日投与で維持する方法のどちらかを選ぶ．免疫抑制薬の併用を原則とし，cyclophosphamide 1～2 mg/kg/day，あるいは，azathioprine 2～3 mg/day，または，cyclosporin 3 mg/kg/dayで併用する．

2．cyclophosphamide

アルキル化薬であり，細胞周期非特異的にDNA合成を阻害して，Tリンパ球よりもBリンパ球を抑制する．IPFに対するステロイドとの併用療法については，エビデンスによる裏付けは乏しく，保険適用もないが，免疫抑制薬の中ではもっとも多く使用されてきた．1989年のJohnsonらの報告[7]では，ステロイド単独群(prednisolone 20～60 mg/day隔日)22例とステロイド(prednisolone 20 mg/day隔日)＋cyclophosphamide(100～200 mg/day)併用群21例を比較している．いずれの群も治療抵抗性であったが，併用群のほうが予後良好であった．

現在の診断基準を用いた研究では，2004年にCollardら[8]が報告しており，82例のステロイド(prednisolone 0.5～1.0 mg/kg/day)＋cyclophosphamide(2 mg/kg/day)併用群に対して，年齢とFVC%をマッチさせた無治療群82例をretrospectiveに比較したが，生存率に有意な差はみられなかった．このような状況から，ステロイドとcyclophosphamideの併用を積極的に推奨する根拠はきわめて乏しいが，IPFがきわめて予後不良な疾患であることに鑑みると，日和見感染症併発などのリスクを考慮したうえで，いくぶんかの有用性に期待して使用してもよいものと考えられている．

prednisoloneと併用して1～2 mg/kg/dayで50 mg/dayから開始し，必要に応じて1～2週ごとに25 mgずつ増量する．治療効果の発現は通常3ヵ月以上かかるため，副作用が問題とならない限り，少なくとも6ヵ月以上は続ける必要がある．副作用としては，骨髄抑制，出血性膀胱炎，二次発癌，脱毛，嘔気，嘔吐，口内炎，下痢，胆汁うっ滞を伴う肝障害，間質性肺炎などがある．帯状疱疹の発症もみられる．

3．azathioprine

azathioprine は DNA 合成期に作用し，プリン合成を阻害する代謝拮抗薬であり，T リンパ球の増殖抑制作用を介して免疫抑制作用を発揮する．保険適用は臓器移植による拒絶反応抑制のみである．IPF に対する効果をみた報告は 1 件のみで，しかも小規模な検討である．1991 年の Raghu ら[9]の報告では，開胸肺生検による組織診確定例を対象に prednisolone（1．5 mg/kg/day で 2 週間ののち 20 mg/day）＋プラセボ群 14 例と prednisolone＋azathioprine（3 mg/kg/day）併用群 13 例を比較したところ，肺機能改善や生存率に有意差がなかったが，年齢補正をしたところ，併用群において生存率が有意に高かった．

本邦のガイドラインでは，ステロイド漸減あるいは隔日投与との併用で，2～3 mg/kg/day（理想体重，最大用量 150 mg/day）で，50 mg/day から開始して必要に応じて 7～14 日ごとに 25 mg ずつ増量する．副作用には骨髄抑制，嘔気，嘔吐，下痢などの消化器症状や肝障害があり，WBC 4，000/mm^3以下あるいは血小板 10 万/mm^3未満の場合は，半量まで減量または一時中止とする．肝機能を毎月チェックし，正常上限の 3 倍以上になったら減量または中止とする．

4．cyclosporin A

cyclosporin A（CYA）は，T リンパ球からの IL-2 産生を抑制するほか，アポトーシスの制御，白血球遊走抑制，薬剤排泄機構抑制によるステロイドの効果の亢進作用などにより免疫抑制作用を示す．臓器移植や Behçet 病，乾癬，再生不良性貧血，ネフローゼ症候群などに適応があり用いられているが，IPF への保険適用はない．膠原病に伴う間質性肺炎への使用が報告されてから，IPF や NSIP への試験的投与が行われるようになってきた．急速進行性の amyopathic dermatomyositis に伴う間質性肺炎においての有効性が示されている[10]．現時点で IPF に対する有効性を明確に示した報告はないが，厚生労働省の研究班で臨床試験が進められている．

cyclophosphamide や azathioprine と比較すると，骨髄抑制が少ない点は使いやすいが，有効血中濃度と中毒域との差が小さいため，血中濃度のモニターを行う必要がある．通常，3 mg kg day で開始し，投与 12 時間後のトラフ値を 100～150 ng/m*l* に維持する．副作用には，腎機能障害，高血圧，歯肉肥厚，神経症状，多毛症などがある．食事の影響を受けやすく，経口吸収に個人差があることや，他の薬剤（Ca 拮抗薬，マクロライド系薬，抗真菌薬など）との相互作用があるため，注意が必要である．

5．IPF 急性増悪の治療

IPF の急性増悪は，病理学的にはびまん性肺胞傷害（diffuse alveolar damage：DAD）の像を呈し，薬剤治療の効果に乏しく，きわめて予後不良な病態である．古くから methylprednisolone のパルス療法が行われることが多いが，その効果はきわめて限定されている．パルス療法は methylprednisolone 1，000 mg/day の 3 日間点滴静注を，病状の安定化が得られるまで 1 週間間隔で 1～4 クール投与する．これに加え，免疫抑制薬を併用してもよい．cyclophosphamide 500 mg/day の点滴静注を 1～2 週ごとに併用する方法や，cyclosporin 併用療法が有効との報告もある．

IPF 以外の IIPs の治療○

1．NSIP

cellular NSIP では，ステロイド単独で反応性は良好である．prednisolone 0．5～1 mg/kg day を初期量とし，治療反応性を評価しつつ 2～4 週ごとに 5 mg ずつ減量する．fibrotic NSIP は，IPF 同様に，ステロイドと免疫抑制薬の併用療法を基本的治療法とする．

2．急性間質性肺炎（AIP）

治療反応性に乏しく，予後不良である．治療は，IPF の急性増悪時の内容に準ずる．

3．特発性器質化肺炎（COP）

一般にステロイドへの反応が良好で，多くは数週から 3ヵ月以内の経過で 80% 以上の症例が改

善する．ステロイドは経験的に prednisolone 0.5～1 mg kg/day，経口を 1～2ヵ月投与後，漸減する．再発が高率に生ずるとの報告もあるが，再発しても治療に反応するため，予後は良好とされる．ステロイド治療に反応性が不良の場合は，免疫抑制薬を併用する．

4．剥離性間質性肺炎(DIP)

ほとんどの患者は禁煙とステロイド療法で改善し，10 年後の生存率がほぼ 70% で，IPF/UIP に比べ予後がよい．

5．呼吸細気管支炎を伴う間質性肺炎(RB-ILD)

多くの患者は，禁煙により改善する．ステロイドや免疫抑制薬投与の報告もあるが，反応がよいと報告されている．

6．リンパ球性間質性肺炎(LIP)

ステロイドが中心に用いられるが，cyclophosphamide などの免疫抑制薬も用いられる．ステロイドの効果はさまざまであり，予測不能であるが 50～60% が反応するという．

現在の治療法の限界と今後の展望○

上述したようなステロイドと免疫抑制薬の併用が，現時点での治療法である．その効果が薄い点と，免疫抑制薬長期使用の副作用を考え合わせると，慢性安定期の IPF 症例の多くは無治療で経過観察される場合がほとんどである．呼吸困難など症状が比較的急速に進行している症例では治療が導入される場合が多いが，このような進行例では，すでに十分な効果は得られないのかもしれない．

IPF が慢性進行性に悪化し，5 年生存率が 30% という疾患であることを考えると，発見されたいかなる段階においても治療を開始し，その進行を阻止しうる薬剤の開発が切望される．健診で初期の IPF を見つけ出し，その進行を阻止できるようになることが治療の理想である．このような観点から，筆者らは *N*-acetylcysteine 吸入療法を考案し，臨床応用を進めてきた[11]．また，現在，線維化抑制薬の pirfenidone の臨床試験が進行しており，その成果が期待される．

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High-Resolution Computed Tomography Findings of Lung Cancer Associated With Idiopathic Pulmonary Fibrosis

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Objective: The purpose of this study was to evaluate high-resolution computed tomography (HRCT) findings of lung cancer associated with idiopathic pulmonary fibrosis (IPF).

Methods: Thirty patients with lung cancer who had preceding IPF and were receiving regular follow-up between 1993 and 2002 were examined. Medical records, radiographs (including HRCT scans), and histologic slides were reviewed.

Results: In 28 of the 30 patients, the most common HRCT pattern of lung cancer was a nodular lesion with soft tissue attenuation. Nodule margins were well defined in 23 lesions (82.1%), associated with lobulation in 24 (85.7%), or characterized by spiculation in 14 (50%). Air bronchogram was observed in 16 lesions (57.1%). All nodules were located in the peripheral area of fibrotic lesions. Squamous cell carcinoma and adenocarcinoma were the most frequent histologic types.

Conclusions: The typical HRCT findings of lung cancer were well-defined nodular lesions with lobulation in peripheral areas of the lung.

Key Words: lung cancer, interstitial lung diseases, high-resolution computed tomography

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Idiopathic pulmonary fibrosis (IPF) is known to be associated with an increased risk of developing lung cancer.[1–5] The individuals with lung cancer associated with IPF are predominantly male smokers, and their cancer is usually located in the peripheral lung areas.[2–6] Chest radiographic features of lung cancer developing with IPF have been described as nodular or linear densities that are sometimes accompanied by honeycomb formation.[7] There are only a limited number of studies focusing on computed tomography (CT) findings of lung cancer associated with IPF, however. Lee et al[8] reported that typical CT findings of lung cancer were ill-defined consolidation-like masses at the peripheral portion, which were located mainly in the lower lobe. Conversely, Sakai et al[9] showed that most lung cancer associated with diffuse pulmonary fibrosis consisted mainly of IPF, was round or lobulated in shape with sharp margins, and was located in the peripheral area of honeycombing.

We reviewed the clinical, radiologic, and pathologic findings of patients with lung cancer who had preceding IPF and further clarified the high-resolution computed tomography (HRCT) characteristics of lung cancer associated with IPF.

MATERIAL AND METHODS

We retrospectively studied 30 patients with histologically confirmed lung cancer of 64 patients having IPF during the period from March 1993 through August 2002. Idiopathic pulmonary fibrosis was diagnosed by clinical and HRCT findings according to the American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias.[10] In these 30 patients, the diagnosis of lung cancer was based on transbronchial lung biopsy in 11 patients, on surgery in 6, on sputum cytology in 6, on percutaneous needle biopsy in 6, and on autopsy in 1, respectively.

Medical records were reviewed for age, sex, smoking history, time of diagnosis of IPF, symptoms of IPF, time of diagnosis of primary lung cancer, cancer-related symptoms, visibility of lung cancer on chest radiographs, and treatment.

A CT scan was performed on a CT 9800 scanner or High Speed Advantage scanner (General Electric Medical Systems, Milwaukee, WI). Routine scanning of the entire lung was carried out with a 10-mm section thickness. Additional HRCT images with a 1- to 3-mm section thickness were acquired through the tumor with a bone algorithm using fixed window settings (lung center, −500 Hounsfield units [HU]; width, 1800 HU) for all patients.

A consensus reading of the HRCT images was conducted by 2 observers (AK, KK). The shape of the lung cancer was divided into 2 categories of a nodular lesion with soft tissue attenuation or an undetermined pattern. According to the description of Zwirewich et al,[11] the HRCT findings of the nodular lesion were analyzed on the basis of marginal

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characteristics (well defined, poorly defined, smooth, irregular, spiculation, lobulation, convergence of peripheral vessels and bronchi, and pleural retraction) and internal characteristics (air bronchogram, calcification, and cavitation).

The locations of lung cancer were categorized into the central or peripheral type by an imaginary line located 3 cm away from the pleura, and the lobar distribution was evaluated.[8]

Lung cancer was subtyped according to the World Health Organization histologic classification of lung tumors.[12] The association of carcinomas with areas of fibrotic change was evaluated histologically using 9 surgically resected and 4 autopsied samples.

RESULTS

Clinical Findings

The clinical findings in 30 patients with IPF and lung cancer are summarized in Table 1. Twenty-seven patients were male, and 3 were female. The mean age of the patients was 69 years, ranging from 54 to 84 years.

TABLE 1. Clinical Findings in 30 Patients With IPF and Lung Cancer

Characteristics	Number (%)
Sex	
Male	27 (90)
Female	3 (10)
Mean age (y)	69
Smoking status	
Current	18 (60)
Past	12 (40)
Mean pack-years	56.9
Carcinoma-related symptoms	
Incidental	21 (70)
New complaints	9 (30)
Hoarseness	4
Pain	3
Sputum	2
Clinical stages	
IA/IB	5/4
IIA/IIB	0/1
IIIA/IIIB	3/7
IV	10
Histologic types	
Squamous cell carcinoma	12 (40)
Adenocarcinoma	12 (40)
Small cell carcinoma	5 (17)
Large cell neuroendocrine carcinoma	1 (3)
Treatment	
Chemotherapy	15 (50)
Surgery	10 (33)
Radiotherapy	1 (3)
No treatment	4 (13)

All the patients had a smoking history. Eighteen were current smokers, and 12 were past smokers, with a mean exposure of 56.9 pack-years (range: 16.5–120 pack-years).

In 22 patients (73.3%), the clinical diagnosis of IPF preceded the detection of lung cancer by an average of 4.9 years (range: 0.6–11.0 years). Eight patients (26.7%) had IPF and lung cancer diagnosed at the same time.

Seventeen patients had symptoms of IPF, including dyspnea on exertion, nonproductive cough, and sputum. Lung cancer was incidentally discovered in the follow-up of IPF or in mass screening by chest radiography in 15 patients and by CT in 6. Nine patients presented with new complaints associated with lung cancer, with the most frequent being hoarseness.

Twenty-five lung cancers were visible on chest radiographs. The remaining 5 cancers were invisible on chest radiographs and only detectable on CT (Fig. 1). The size of 3 of these 5 cancers was less than 2 cm in diameter. Two cancers were concealed by the mediastinum on chest radiographs.

The clinical stage was IA in 5 patients, IB in 4, IIB in 1, IIIA in 3, IIIB in 7, and IV in 10, respectively. Ten patients with non-small cell lung carcinoma and 5 patients with small cell lung carcinoma received chemotherapy. Ten patients underwent surgery, including lobectomy in 7 and wedge resection under video-assisted thoracoscopic surgery in 3. Four patients received best supportive care, and 1 patient underwent radiotherapy.

High-Resolution Computed Tomography Findings

The shape of the lung cancer was a nodular lesion in 93.3% (28 of 30) of patients and an undetermined pattern in 6.7% (2 of 30) of patients (see Fig. 1). The mean maximum diameter of nodular lesions was 36 mm, ranging from 10 to 70 mm. Of the 2 patients with an undetermined pattern, 1 with mucinous bronchioloalveolar carcinoma demonstrated diffuse ground-glass opacities resembling acute exacerbation of IPF (Fig. 2) and the other with adenocarcinoma had extensive pleural thickening mimicking malignant pleural mesothelioma (Fig. 3).

The HRCT findings of 28 nodular lesions are listed in Table 2. A sharp and well-defined interface between the nodule and the surrounding lung was observed in 23 lesions (82.1%). An irregular margin was seen in 22 lesions (78.6%). Lobulation and spiculations were found in 24 (85.7%) and 14 (50.0%) lesions, respectively. Air bronchogram was observed in 16 lesions (57.1%). Cavitation was present in 3 lesions of squamous cell carcinoma. Stippled calcification was recognized in 3 lesions.

In the nodular pattern, all lesions were located in the peripheral area of the lung and all but 1 lesion were in contact with the pleura. Nodular lesions were located in the right upper lobe in 6 patients, the right lower lobe in 9, the left upper lobe in 7, and the left lower lobe in 6.

Seventeen lung cancers were peripheral tumors in association with honeycombing on HRCT (see Fig. 1). Of the remaining 13 cancers, 12 were in the upper lobe and 1 was in the lower lobe. Although these cancers were located away from honeycombing on CT, a reticular pattern indicating fibrosis

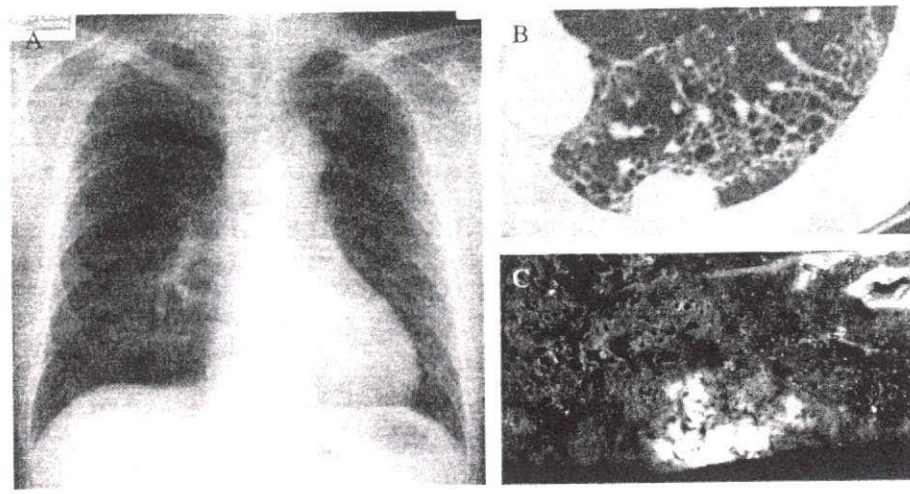

FIGURE 1. An individual with squamous cell carcinoma associated with IPF. A, Chest radiograph shows a reticular pattern. No nodular opacity suggestive of lung cancer is seen. B, High-resolution computed tomography scan at the level of the left lower lung reveals a lobulated nodule located in the peripheral lung field adjacent to honeycombing. C, Gross photograph of the cut surface of the resected left lower lobe shows honeycombing and a lobulated cancerous mass.

was recognized adjacent to the tumor in a subpleural portion (Fig. 4).

Pathologic Findings

The histologic types consisted of 12 squamous cell carcinomas (40%); 12 adenocarcinomas (40%), including 1 mucinous bronchioloalveolar carcinoma; 5 small cell carcinomas (16.7%); and 1 large cell neuroendocrine carcinoma (3.3%) (see Table 1). In 9 surgical and 3 autopsy samples, lung cancer was centered in association with the fibrotic area of the lung, where atypical epithelial proliferation was observed.

DISCUSSION

Our data demonstrated that the characteristic HRCT findings of lung cancer associated with IPF were well-defined, lobulated, nodular lesions with soft tissue attenuation. These CT findings were consistent with those of lung cancer associated with diffuse pulmonary fibrosis as reported by Sakai et al[9] in the context that the shapes of most tumors were round or lobulated with sharp margins. Conversely, our observations were distinctive from those by Lee et al,[8] in which typical CT findings of lung cancer associated with IPF were reported to be ill-defined consolidation-like masses, although HRCT was performed in only 25% of the patients in their study. In addition, the CT findings in our study were different from those of localized bronchioloalveolar carcinoma, which typically represent focal areas of ground-glass opacity.[13,14]

In addition to nodular lesions, we found an undermined pattern in 2 patients, one of which showed diffuse ground-glass opacity attributable to mucinous bronchioloalveolar carcinoma. In this patient, tumor cells spread along the honeycombing wall and did not form a mass lesion. Similarly, Lee et al[8] reported a patient with bronchioloalveolar carcinoma

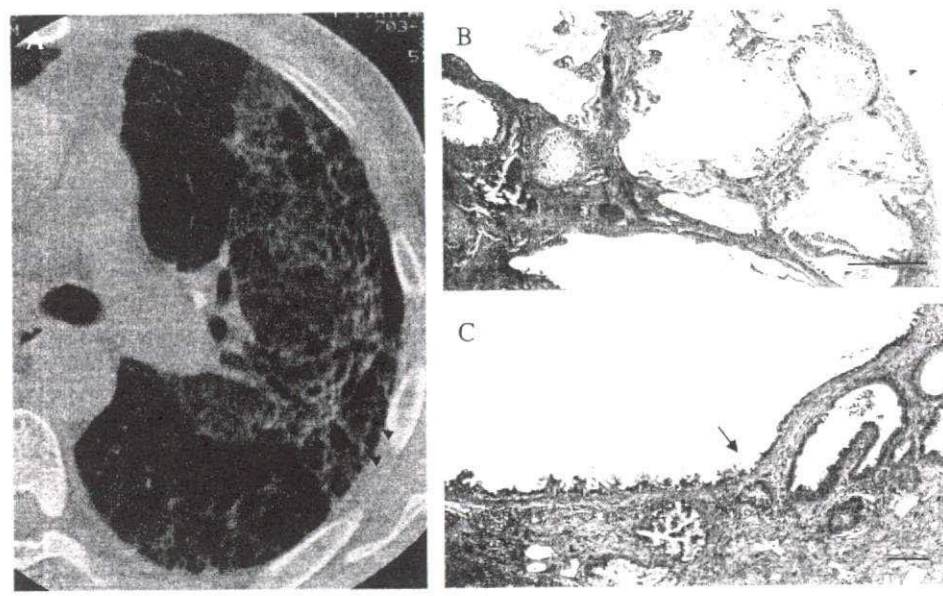

FIGURE 2. Bronchioloalveolar carcinoma associated with IPF. A, High-resolution computed tomography scan reveals peripheral honeycombing (arrowheads) and diffuse ground-glass opacities resembling acute exacerbation of IPF. B, Low-magnification photomicrograph of an autopsied lung specimen shows bronchioalveolar carcinoma invasion of the honeycomb wall. The bar indicates 1 mm (hematoxylin–eosin stain). C, Same as B but higher magnification photograph demonstrates coexistence of bronchiolar metaplasia and bronchioloalveolar carcinoma. The arrow indicates the front of bronchioloalveolar carcinoma. The bar indicates 0.1 mm (hematoxylin–eosin stain).

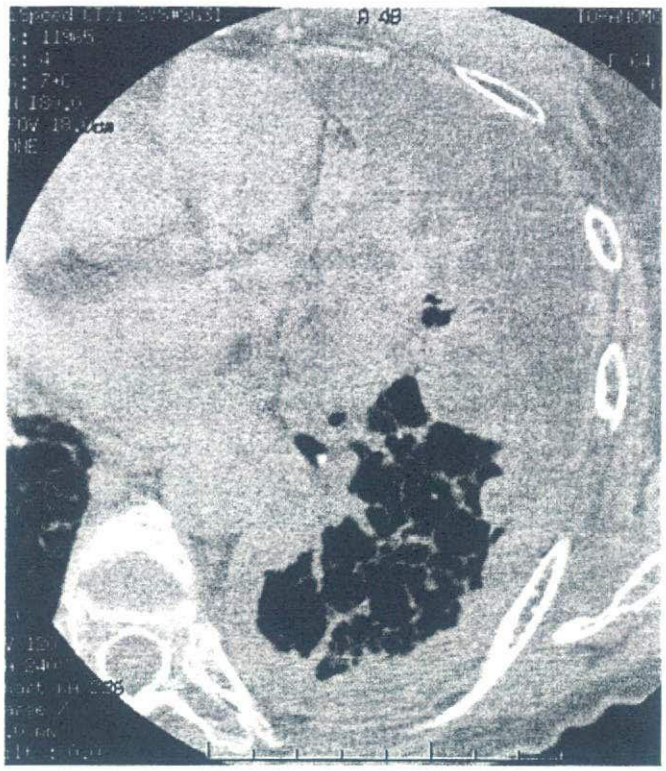

FIGURE 3. High-resolution computed tomography scan of lung adenocarcinoma associated with IPF shows honeycombing and extensive pleural thickening in the left hemithorax resembling malignant pleural mesothelioma.

who showed diffuse air space consolidation. Diffuse parenchymal opacities should be considered as one of the possible CT appearances of lung cancer associated with IPF.

As for localization, all lung cancers in the present study were located in the peripheral areas of the lung, where fibrosis was more predominant than in the central lung areas. Further,

TABLE 2. High-Resolution Computed Tomography Findings of 28 Nodular Lesions of Lung Cancer Associated With IPF

Parameter	No. Cases (%)
Nodular margin	
Well defined	23 (82.1)
Poorly defined	5 (17.9)
Smooth	6 (21.4)
Irregular	22 (78.6)
Lobulation	24 (85.7)
Spiculation	14 (50.0)
Convergence of peripheral vessels	11 (39.3)
Pleural retraction	9 (32.1)
Internal features	
Air bronchogram	16 (57.1)
Cavitation	3 (10.7)
Calcification	3 (10.7)

all but 1 lesion was in contact with the pleura. These findings were consistent with those of previous reports.[2–5] Regarding lobar localization, most of the previous studies emphasized a predominance of the lower lobe.[2,3,8,9] A recent study by Park et al[6] demonstrated the presence of 52% of cancers in the upper lobe, however. Our results, in which 46% of cancers were located in the upper lobe, were close to those of Park et al.[6]

In terms of the association between lung cancer and honeycombing, Sakai et al[9] reported that 82% of the tumors were located in the periphery within the areas of honeycombing. Our study showed that 43% of the cancers were located away from honeycombing on CT, however. This rather high frequency could be explained by the fact that cancer originated from the upper lobe in 46% of our patients. Interestingly, these patients had reticular opacities suggestive of fibrosis adjacent to the tumor as well. Therefore, the newly developed nodules in the peripheral lung, even if located in the

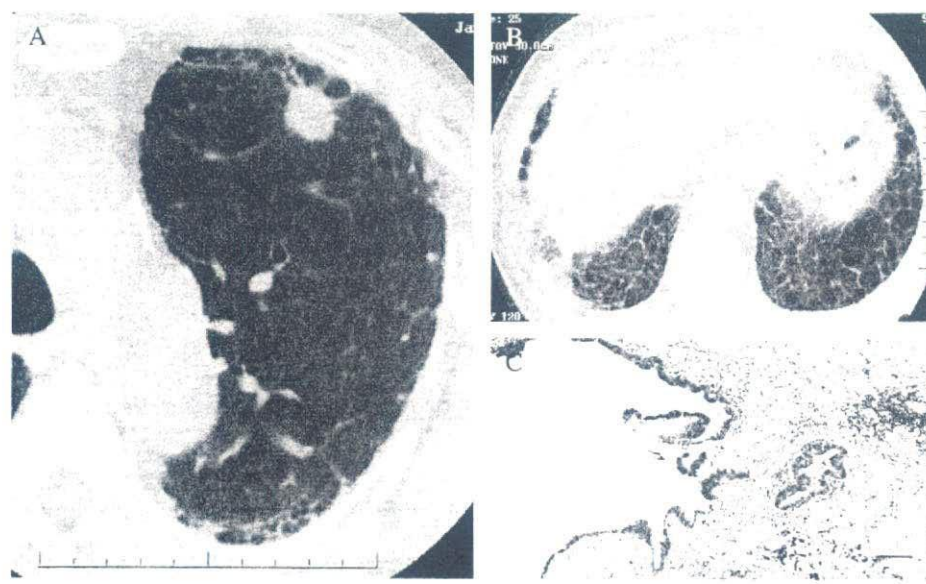

FIGURE 4. Lung adenocarcinoma developing in an individual with IPF. A, High-resolution computed tomography scan reveals a spiculated nodule in an area of subpleural reticulation. B, Computed tomography scan at the level of the lung base demonstrates bilateral honeycombing formation. C, Low magnification of the resected lung shows fibrotic foci and honeycombing lined by adenocarcinoma cells. The bar indicates 0.1 mm (hematoxylin–eosin stain).

upper lobe, where apparent honeycombing is lacking, should be considered as possible lung cancer.

The diversity of histologic types of lung cancer associated with IPF varied among several studies.[1–6,8] Some studies reported that squamous cell carcinoma was the most common histologic type in IPF patients,[1,3,5,6,8,9] whereas other studies showed a predominance of adenocarcinoma.[2,4] In the present study, squamous cell carcinoma and adenocarcinoma were the most frequent histologic types, both accounting for 40%.

It is still unknown why lung cancer is prevalently associated with IPF. Several studies have implicated a close relation between the primary site of lung cancer and fibrosis.[2,4,5,7,9,15,16] For instance, Meyer and Liebow[15] first paid attention to atypical epithelial proliferation in the honeycombing areas in usual interstitial pneumonia and suspected that this might possibly represent a precancerous lesion. This speculation seems to be applicable, because we have also found that lung cancer was situated in association with a fibrotic area in which atypical epithelial proliferation was present. In addition, a smoking habit is likely responsible for the development of lung cancer in the case of preexisting IPF, because, in our study, individuals who had lung cancer with IPF were predominantly men who were current or past smokers, as described in the previous reports.[1–6]

In summary, typical HRCT findings of such lung cancer with IPF are well-defined nodules with lobulation in the peripheral subpleural areas inside or adjacent to the fibrosis. Because it is difficult to find a small-sized lung cancer associated with IPF by chest radiography, routine use of CT is recommended for early detection of lung cancer as well as for evaluating serial changes in IPF.

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若年発症の特発性間質性肺炎に対するタクロリムスの使用知見

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特発性間質性肺炎（IIP）の治療法として prednisolone（PSL）に加えてこれまで様々な免疫抑制剤が投与されてきたが，依然 IIP は予後不良の難治性疾患である．皮膚筋炎に合併する間質性肺炎など，一部の間質性肺炎において，calcineurin inhibitor である tacrolimus が有用であるとする報告が散見される．PSL と cyclosporin A（CsA）の併用療法で治療抵抗性であった IIP に対し tacrolimus を投与し，一定の臨床効果を得ることができた 1 例を経験したので報告する．症例は 43 歳男性．2003 年 3 月に検診で間質性肺炎を指摘され，同 6 月当院で胸腔鏡下肺生検を実施し，unclassified IP と診断された．PSL および CsA の併用療法を開始したが進行性で，2004 年 12 月に在宅酸素療法を開始した．2006 年 4 月進行する労作時呼吸困難（Hugh-Jones V 度）のために入院した．Tacrolimus 0.075 mg/kg にて導入し，トラフ 6.4 ～ 19.4 ng/mL に維持した．自覚症状は Hugh-Jones IV 度へ改善し，胸部 CT 上 GGO も消退し，KL-6，SP-D も低下した．しかしながら，その後肺アスペルギルス症を合併し，最終的には敗血症性ショックのために死亡した．間質性肺炎の新たな治療薬としての tacrolimus の可能性について文献的考察を加えて報告する．

Tacrolimus may be an efficacious agent for idiopathic interstitial pneumonia

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Background: Idiopathic interstitial pneumonias (IIPs) represents a diverse group of pulmonary disorders caused by unknown etiology with variable prognoses and responses to therapy. In the more severe forms of IIPs, such as idiopathic pulmonary fibrosis, no effective therapies have been identified. Among the possible new therapeutic agents for IIPs, tacrolimus, one of the calcineurin inhibitors, has been reported effective for the patients with interstitial lung disease associated with polymyositis or dermatomyositis.

Subject and Clinical Course: In our present study, tacrolimus was administered to a patient with intractable idiopathic interstitial pneumonia. The 40 year-old male patient came to our hospital in June 2003 because of shortness of breath at the Fletcher-Hugh-Jones grade III. Video-assisted lung surgery was performed, and diagnosed pathologically as an 'unclassified-type' of IIP. Prednisolone and cyclosporin A were initiated, and home oxygen therapy was also started later. However, his respiratory conditions deteriorated and dyspnea worsened from the Fletcher-Hugh-Jones grade IV to V. He re-admitted in April 2006, and after obtaining an informed consent, tacrolimus was initiated instead of cyclosporin A. His symptoms gradually improved, and after three weeks of tacrolimus therapy, the extent of the ground glass opacities in the both lower lobes was improved on his chest CT scan. The serum levels of both KL-6 and SP-D were also decreased. However, he eventually developed pulmonary aspergillosis, and died of septic shock after eight weeks of tacrolimus treatment. Postmortum examination revealed both acute alveolar damage and usual interstitial pneumonia along with focal bacterial and cytomegalovirus pneumonias.

Clinical implication: Tacrolimus may be a suitable candidate as one of the new therapeutic agents for intractable IIPs including idiopathic pulmonary fibrosis, although a prospective study with a large number of the patients should be conducted.