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CHEST

Original Research

ACUTE EOSINOPHILIC PNEUMONIA

Alterations in Smoking Habits Are Associated With Acute Eosinophilic Pneumonia*

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Background: **Acute eosinophilic pneumonia (AEP) is characterized by a febrile illness, diffuse pulmonary infiltrates, and pulmonary eosinophilia. The etiology of AEP remains unknown, but several studies have proposed a relationship between cigarette smoking and AEP. However, most studies showing this possibility are single-case reports, and cigarette smoke has not been fully validated as a causative agent of AEP in a large series of patients. The present study was conducted to clarify the etiologic role of cigarette smoking in AEP, with special reference to alterations in smoking habits.**

Methods: **We took a detailed history of smoking habits before AEP onset in 33 patients with AEP, and performed a cigarette smoke provocation test.**

Results: **Of our AEP patients, all but one (97%) were current smokers. Interestingly, 21 of these were new-onset smokers, and 2 had restarted smoking after a 1- to 2-year cessation of smoking. The duration between starting smoking and AEP onset was within 1 month (0.67 ± 0.53 months). Additionally, six of the remaining smokers had increased the quantity of cigarettes smoked daily, fourfold to fivefold, mostly within the month before AEP onset (0.81 ± 0.58 months). Only three smokers had not changed their smoking habits before AEP onset. Cigarette smoke provocation tests revealed positive results in all nine patients tested.**

Conclusion: **These data suggest that recent alterations in smoking habits, not only beginning to smoke, but also restarting to smoke and increasing daily smoking doses, are associated with the development of AEP.** ***(CHEST 2008; 133:1174–1180)***

Key words: acute eosinophilic pneumonia; provocation test

Abbreviations: AEP = acute eosinophilic pneumonia; HRCT = high-resolution CT; VC = vital capacity

Acute eosinophilic pneumonia (AEP) was first described by Allen et al[1] as an idiopathic disease characterized by a febrile illness, diffuse pulmonary infiltrates, and pulmonary eosinophilia. AEP is a rare condition that is clinically distinct from chronic eosinophilic pneumonia.[1,2] Respiratory failure often develops in patients with AEP, but treatment with corticosteroids achieves an excellent response.[1,2] The etiology of AEP is unknown, but several studies[3–9] have proposed that cigarette smoke is potentially related to the onset of AEP. Philit et al[10] reviewed 22 patients with AEP, including 8 current smokers, and found that 6 of the 8 current smokers had started smoking within 3 months before the onset of AEP. More recently, an epidemiologic study[11] of this disease identified 18 patients with AEP among 183,000 US military personnel deployed in or near Iraq, indicating that all of the patients were smokers, with 78% of them recently beginning to smoke. These data suggest a possible association between new-onset smoking and AEP. However, it remained to be determined whether any alterations in smoking

habits, other than new-onset smoking, are related to AEP in a large series of patients. Additionally, there have been few reports to directly prove that cigarette smoking causes AEP. Thus, the present study was conducted to clarify the etiologic role of cigarette smoking in AEP, with special reference to smoking habits. We took a detailed history of the smoking habits before AEP onset in 33 patients to clarify whether particular smoking habits were related to the onset of AEP. Furthermore, to provide direct evidence that cigarette smoking is one of etiologic factors of AEP, we also performed a cigarette smoke provocation test.

Materials and Methods

Patients

The study population included 33 consecutive patients with AEP in our facilities from 1996 to 2006. The diagnosis of AEP was based on the modified Philit criteria[10]: (1) acute onset of febrile respiratory symptoms (< 1 month); (2) hypoxemia; (3) bilateral diffuse pulmonary infiltrates on chest radiography; (4) BAL fluid eosinophilia and/or infiltration of eosinophils in the lung parenchyma at lung biopsy; and (5) absence of known causes of eosinophilic lung diseases, such as drugs and infections. The initial 20 patients were retrospectively reviewed from 1966 to 2002. After approval of the study protocol of a cigarette smoke provocation test by the Ethical Committee of the National Hospital Organization Tenryu Hospital in 2002, the remaining 13 patients from 2003 to 2006 were prospectively studied.

Clinical Data

Clinical data were obtained from medical records. A detailed smoking history, including any alterations in smoking habits before the onset of AEP, was taken for each patient. Signs and symptoms were also recorded.

High-Resolution CT

High-resolution CT (HRCT) examinations of lungs were performed on 1.0-mm-thick sections to evaluate radiographic abnormalities. The HRCT images were reviewed for the presence of each of the following signs: consolidation, ground-glass opacity, nodular opacity, interlobular septal thickening, bronchovascular bundle thickening, and pleural effusion.

BAL and Lung Biopsy

All patients but one underwent BAL. BAL was performed as described previously.[12] In addition, transbronchial lung biopsy was performed in 24 patients.

Cigarette Smoke Provocation Test

To determine whether cigarette smoking induces AEP, we performed a cigarette smoke provocation test. In all provocation tests, we used the same tobacco brand (Mild Seven; Japan Tobacco Inc.; Tokyo, Japan). Briefly, patients were required to smoke a total of five cigarettes at hourly intervals over 4 h. After the exposure, we observed symptoms (fever, cough, and dyspnea) and performed peripheral eosinophil counts, arterial blood gas analysis, and pulmonary function tests at various time points. In addition, a chest radiograph or CT was performed on the following day. The results were considered to be positive when patients had at least one of the symptoms, with two or more of the followings: (1) a decrease in PaO_2 by > 10 torr; (2) a decrease in vital capacity (VC) by > 15%; and (3) deterioration of chest radiograph or CT findings. We used commercially available cigarettes purchased from stores. The study protocol was approved by the Ethical Committee of the National Hospital Organization Tenryu Hospital in 2002. From 2003 to 2006, 13 consecutive AEP patients were recruited to this study. We obtained informed consent from 9 of the 13 patients, and performed the provocation test in these patients. The remaining four patients did not give informed consent to the protocol.

Results

Clinical Characteristics

The clinical characteristics of patients with AEP are shown in Table 1. Twenty-three of the 33 AEP

Table 1—*Clinical Characteristics and Laboratory Findings in Patients With AEP

Characteristics	Data
Male/female gender, No.	23/10
Age, yr	19.3 ± 2.7
Smoking status, %	
Current smoker	32
Ex-smoker	0
Never-smoker	1
Underlying atopic diseases, %	15.2
Duration of symptoms, d	3.5 ± 2.1
Symptoms, %	
Fever	93.9
Dyspnea	81.8
Cough	66.7
Sputum	3.0
Myalgia	27.3
Signs, %	
Crackles	30.3
WBC count, cells/μL	15,614 ± 6,440
Eosinophil count on hospital admission, cells/μL	623 ± 813
Maximal eosinophil count, cells/μL	2,050 ± 1,182
C-reactive protein, mg/dL	8.4 ± 5.9
KL-6, U/mL	131.7 ± 14.8
PaO_2 on room air, torr	60.3 ± 11.6

*Data are presented as mean ± SD unless otherwise indicated.

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patients (69.7%) were male, and the ages at onset were relatively young (mean, 19.3 years; range, 16 to 29 years). Interestingly, all of our AEP patients except one were current smokers. Five patients had atopic diseases (three with bronchial asthma and two with atopic dermatitis). The durations of symptoms prior to hospital admission was within 2 weeks (mean, 3.5 days; range, 1 to 11 days), indicating acute onset of this disease. Common symptoms were fever (93.9%) and dyspnea (81.8%), and crackles were present on chest auscultation in 10 patients (30.3%).

Laboratory Findings

Most patients showed an increase in leukocytes and an elevation of C-reaction protein levels (96.9% and 96.2%, respectively) [Table 1]. On hospital admission, peripheral eosinophilia (> 500 cells/μL) was seen in 13 patients (39.4%), but over the course of hospitalization all patients showed a moderate increase in peripheral eosinophil counts. No patients had an increase in the levels of serum KL-6, a maker of interstitial pneumonia. Hypoxemia was present in all patients.

Smoking Habits

Several previous studies[3–10] have highlighted a link between new-onset smoking and AEP, but little attention has been paid to the alterations in smoking habits other than beginning to smoke. Thus, we carefully obtained the smoking history of each patient to determine any changes in smoking habits. Table 2 lists smoking habits before the onset of AEP in each patient. Interestingly, 23 patients (69.7%) had begun smoking just before the onset of AEP. Among them, 21 patients were new-onset smokers, and the other 2 patients had restarted smoking after a 1- or 2-year cessation of smoking. The duration between starting smoking and the onset of AEP was mostly within 1 month (mean, 0.67 ± 0.58 months). Fifteen patients had started to smoke ≥ 10 cigarettes

Table 2—*Smoking Habits of Patients With AEP Before Its Onset and Results of Cigarette Smoke Provocation Test**

Case No.	Changes in Smoking Habits	Cigarettes Smoked Daily Before AEP Onset	Cigarette Smoke Provocation Test Result
1	Started	0 → 3 cigarettes/d for 14 d	Positive
2	Started	0 → 10 cigarettes/d for 1 mo	Positive
3	Started	0 → 10 cigarettes/d for 3 d	Positive
4	Started	0 → 10 cigarettes/d for 2 mo	Positive
5	Started	0 → 10 cigarettes/d for 12 d	Positive
6	Started	0 → 15 cigarettes/d for 1 mo	N.D.
7	Started	0 → 30 cigarettes/d for 1 mo	N.D.
8	Started	0 → 10 cigarettes/d for 14 d	N.D.
9	Started	0 → 20 cigarettes/d for 6 d	N.D.
10	Started	0 → 5 cigarettes/d for 10 d	N.D.
11	Started	0 → 20 cigarettes/d for 5 d	N.D.
12	Started	0 → 15 cigarettes/d for 1 mo	N.D.
13	Started	0 → 40 cigarettes/d for 7 d	N.D.
14	Started	0 → 10 cigarettes/d for 10 d	N.D.
15	Started	0 → 4 cigarettes/d for 14 d	N.D.
16	Started	0 → 10 cigarettes/d for 21 d	N.D.
17	Started	0 → 6 cigarettes/d for 14 d	N.D.
18	Started	0 → 3 cigarettes/d for 1 d	N.D.
19	Started	0 → 15 cigarettes/d for 23 d	N.D.
20	Started	0 → 3 cigarettes/d for 2 mo	N.D.
21	Started	0 → 20 cigarettes/d for 2 mo	N.D.
22	Restarted	10 cigarettes/d for 2 yr → 0 × 2 yr → 15 cigarettes/d for 10 d	N.D.
23	Restarted	3 cigarettes/d for 2 yr → 0 × 1 yr → 5 cigarettes/d for 18 d	N.D.
24	Increased	10 cigarettes/d for 7 yr → 40 cigarettes/d for 2 mo	Positive
25	Increased	5 cigarettes/d for 2 yr → 20 cigarettes/d for 1 mo	Positive
26	Increased	1 cigarettes/d for 8 mo → 5 cigarettes/d for 25 d	Positive
27	Increased	1 cigarettes/d for 3 yr → 5 cigarettes/d for 20 d	Positive
28	Increased	10 cigarettes/d for 1 mo → 20 cigarettes/d for 15 d	N.D.
29	Increased	4 cigarettes/d for 1 mo → 20 cigarettes/d for 7 d	N.D.
30	Not changed	10 cigarettes/d for 6 mo	N.D.
31	Not changed	10 cigarettes/d for 8 mo	N.D.
32	Not changed	15 cigarettes /d for 2 yr	N.D.
33	None smoker	None	N.D.

*N.D. = not done.

per day (16.3 ± 8.8 cigarettes per day). Additionally, we found that six patients had increased the number of cigarettes they smoked daily just before the onset of AEP. Most of those patients showed a fourfold to fivefold increase (4.2 ± 1.2 folds) in the numbers of cigarettes within the month (0.81 ± 0.58 months) before the onset of AEP. In our AEP patients currently smoking, there were only three patients (9%) who had not changed the number of daily cigarettes before the onset of AEP.

HRCT Findings

Typical HRCT findings are shown in Figure 1. Ground-glass opacity was the most common HRCT finding (90.9%), followed by interlobular septal thickening (81.8%) [Table 3]. Airspace consolidation was present in 63.6% of the patients. In addition, thickening of bronchovascular bundles and bilateral pleural effusion were seen in 72.0% and 60.6% of the patients, respectively.

BAL Analysis and Lung Histology

The percentages of eosinophils in BAL fluid were markedly elevated (52.8 ± 18.6%) [Fig 2]. The averages of total cell number and lymphocyte percentage in BAL fluid were also increased (8.26 ± 7.54 × 10^5/mL BAL fluid and 13.4 ± 9.2%, respectively). The ratios of CD4+/CD8+ lymphocytes were variable among the patients. Microbiological analysis of BAL fluid revealed no infectious agents. Twenty-four patients (72.7%) had a transbronchial lung biopsy. All biopsy specimens revealed marked eosinophilic infiltration in the alveoli and the interstitium.

Table 3—*HRCT Findings in Patients With AEP*

Findings	Patients, No. (%)
Ground-glass opacity	30 (90.9)
Air-space consolidation	21 (63.6)
Nodular opacity	6 (24.0)
Interlobular septal thickening	27 (81.8)
Thickening of bronchovascular bundles	18 (72.0)
Pleural effusion	20 (60.6)

Cigarette Smoke Provocation Test

A cigarette smoke provocation test was performed in nine patients, and all had a positive result (Table 2). A representative clinical course on the provocation test is shown in Figure 3. Typically, 8 to 12 h after smoke exposure, Pao_2 and VC began to decrease with the appearance of symptoms, including cough and dyspnea, and their chest radiograph or CT findings on the following day were worse with increased ground-glass opacities than baseline. Administration of corticosteroid rapidly reversed this decline in Pao_2 and VC, with symptomatic improvement. Between nine patients who underwent the provocation test and those who did not it, there was no

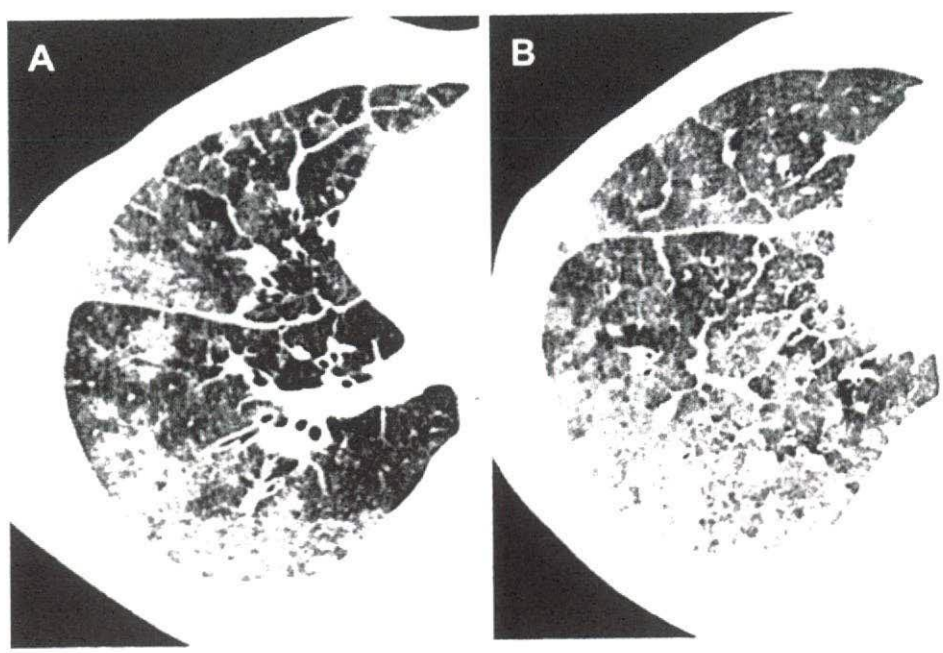

FIGURE 1. HRCT of AEP (case 32). Transverse thin-section CT images of the right lower lobe (*left*, *A*, and *right*, *B*) show patchy consolidations, ground-glass opacities, and interlobular septal thickening with a small amount of pleural effusion.

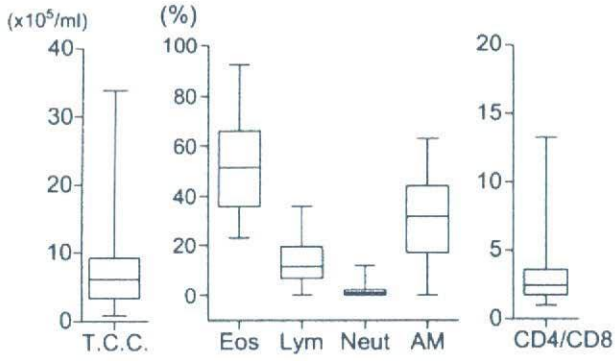

FIGURE 2. BAL findings in patients with acute eosinophilic pneumonia. Values are obtained from 32 patients with acute eosinophilic pneumonia. T.C.C. = total cell counts; Eos = eosinophils; Lym = lymphocytes; Neut = neutrophils; AM = alveolar macrophages.

statistical difference in clinical characteristic, including laboratory data, the results of pulmonary function tests, or BAL findings.

Treatment and Prognosis

Eleven patients (33.3%) with severe respiratory failure were treated with corticosteroids, resulting in a rapid improvement (Table 4). Among them, two patients were administered IV high-dose methylprednisolone for 3 days followed by oral prednisolone (0.5 to 1.0 mg/kg/d). The remaining nine patients received only IV high-dose methyl-prednisolone for 3 days without maintenance therapy of prednisolone. Twenty-two patients had a spontaneous recovery without any treatment, following cessation of smoking. A relapse occurred in only one patient who showed a recurrence of AEP 2 months after discharge when smoking again. Besides this patient showing relapse, all patients quit smoking after discharge. No patient showed lasting impairment of pulmonary function after improvement. No one died during the observation periods.

Table 4—*Treatment and Outcome of Patients With AEP

Variables	Data
Treatment	
Corticosteroids	11 (33.3)
High-dose methylprednisolone	10
Prednisolone	3
No treatment	22 (66.7)
Duration of corticosteroid treatment, d	3.7
Duration between hospital admission and start of treatment, d	8.0 ± 6.2
Response rate to treatment, %	100
Survival/death outcome	33/0
Observation period, mo	12.1 ± 14.5
Relapse	1 (3.0)

*Data are presented as No. (%), No. or mean ± SD.

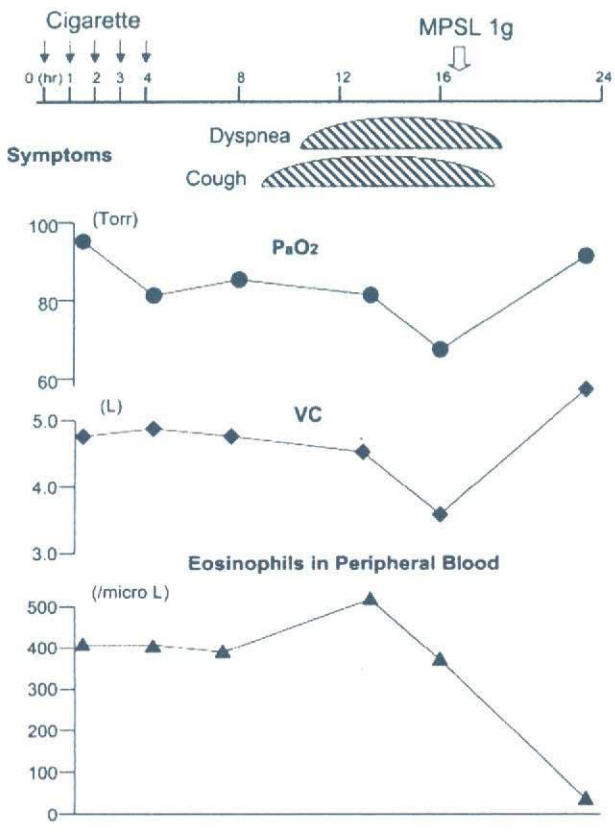

FIGURE 3. Result of a cigarette smoke provocation test in a patient with AEP (case 1). MPSL = methylprednisolone.

DISCUSSION

The present study examined the etiologic role of cigarette smoking by taking a detailed smoking history and performing a cigarette smoke provocation test in AEP. In the 33 AEP subjects, all but 1 were current smokers. Interestingly, alterations in smoking habits just before the onset of AEP, such as initiating the smoking habit or increasing the numbers of cigarettes smoked, were seen in most patients (87.9%). Additionally, a cigarette smoke provocation test revealed a positive response in the nine patients tested. Collectively, these data suggest that cigarette smoking, especially changes in smoking habits, is one of possible etiologic factors of AEP.

Of our AEP patients, most of them (97%) were current smokers. Twenty-three of them had begun smoking, while 6 patients had increased the numbers of cigarettes smoked, just before the onset of AEP. Although several studies[3–11] suggest that new-onset smoking is associated with AEP apart from new-onset smoking, little attention has been focused on

alterations in smoking habits in AEP. Taking into consideration the smoking history in each patient, we found a possible relationship between two smoking conditions, other than new-onset smoking, and the onset of AEP. First is the resumption of smoking after its cessation. Indeed, AEP developed in two of our patients when restarting to smoke after a 1- to 2-year cessation of smoking. Second is the increase in the quantity of cigarettes smoked daily. Six of our patients with AEP had increased the numbers of cigarettes smoked daily just before the onset of AEP. The cigarette smoke provocation test revealed a positive response in these patients tested. So far, little data are available about the initial numbers of cigarettes smoked by new-onset smoking AEP patients. The present study showed that 71% of the patients who had begun smoking smoked ≥ 10 cigarettes per day, indicating that they generally started smoking at a relatively high quantity of daily cigarettes. Taken together, these data suggest an association between the onset of AEP and the alteration of smoking habits, including not only recently beginning to smoke, but also restarting to smoke and increasing daily smoking doses.

The present study clearly provided evidence that cigarette smoking directly induces AEP, as shown by a cigarette smoke provocation test. Notably, all of the AEP patients we tested revealed positive results. A decline in PaO_2 and VC with the appearance of symptoms typically began 8 to 12 h after smoke exposure. To date, there have been three case reports[3,5,8] of cigarette smoke provocation tests in the English literature, but the procedures of smoke exposure varied among the reports. Although a standard method for the cigarette smoke provocation test has not yet been established, we utilized modified Nakamura method, in which patients were challenged with a total of five cigarettes at hourly intervals. In the previous reports, the responses to smoking challenge, such as symptoms, hypoxia, and a decline of VC, appeared within 8 to 16 h after smoking,[3,5,8] consistent with our results.

The mechanism by which cigarette smoke induces AEP is unknown. Cigarette smoke has been shown to be a strong inflammatory stimulus that induces proinflammatory cytokines and chemokines, such as interleukin-6, tumor necrosis factor, and interleukin-8, and recruits activated macrophages and neutrophils to lung tissue.[13–16] However, there is no concrete evidence that cigarette smoke itself directly induces eosinophilic inflammation in the lung. Recently, short-term cigarette smoke exposure was shown to enhance pulmonary eosinophilic infiltration, with a marked increase in the levels of eotaxin in a mouse model of ovalbumin-induced allergic airway inflammation.[17] Apart from cigarette smoke, several putative conditions, such as dust exposures and drugs, have been considered to be associated with the development of AEP.[2,18,19] Possibly, recent cigarette smoking may prime the lung to be more susceptible to these conditions or may enhance the eosinophilic inflammation elicited by them[11]; however, because AEP is an uncommon condition in a smoking population, underlying genetic susceptibility may play a role. Further studies will be required to elucidate the precise pathogenesis of cigarette smoking-induced AEP.

Most of the clinical features of our AEP patients were consistent with those previously described. Our AEP patients were relatively young. They showed an acute febrile illness with diffuse infiltrates on chest radiograph and pulmonary eosinophilia, as assessed by BAL or transbronchial lung biopsy. On HRCT, the most common findings are ground-glass opacity and interseptal thickening, followed by airspace consolidation. These results of HRCT findings were in agreement with a recent report by Daimon et al.[20] The original criteria of AEP defined by Allen et al[1] included hypoxia with < 60 torr, but 54.5% of our patients had $PaO_2 > 60$ torr. Shorr et al[11] reported that some of their AEP patients did not progress to severe respiratory failure, suggesting that less-severe forms of AEP likely exist. Thus, our AEP patients with relatively mild respiratory failure were comparable to these forms. During the observation period, relapse occurred in only one. Originally, no relapse was reported to occur in AEP.[1] However, there are additional two cases of AEP relapse reported in the literature.[5,6] These two cases of AEP were associated with new-onset smoking. Their relapse occurred when resuming smoking after a 1-month cessation of cigarette smoking. Our patient with relapse started again smoking after a 2-month cessation of cigarette smoking. Taken together, these observations suggest that relapse of AEP can occur in patients that resume smoking after its temporary cessation.

There are several major limitations in the present study. First, this is a mostly retrospective study, and so there were major selection and recall biases. Even in the prospective part of this study, such selection biases still existed, because not all the patients gave the consent of the provocation test. Second, although this study included the largest number of AEP patients so far, the sample size might not be large enough to verify the definite etiology of this disease. Third, this study had no control arm. To definitely draw our conclusion that the alterations in smoking habits induce AEP, those major limitations are needed to be improved. Thus, for confirming our observations, large multicentric prospective studies should be required because of a rarity of AEP.

In summary, the present study demonstrated that cigarette smoking is one possible etiologic factor underlying the development of AEP by taking a detailed smoking history and performing a cigarette smoke provocation test. In particular, the recent alteration of smoking habits, such as beginning and restarting to smoke, and increasing the number of cigarettes smoked daily, were closely associated with the development of AEP. Further investigation will be needed to clarify the precise mechanism by which cigarette smoking, especially its alteration, induces AEP.

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SHORT COMMUNICATION

Possible therapeutic effect of direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) on pulmonary oxygenation in acute exacerbations of interstitial pneumonia

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Possible therapeutic effect of direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) on pulmonary oxygenation in acute exacerbations of interstitial pneumonia
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Background and objective: Acute exacerbations of interstitial pneumonias (IP) can occasionally occur, and have an extremely poor prognosis. Recently, direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) was shown to have a beneficial effect in acute exacerbations of IPF. However, little is known about the efficacy of PMX-DHP in acute exacerbations of other IP. This study investigated the effectiveness and safety of PMX-DHP in acute exacerbations of IP.

Methods: The study subjects consisted of five patients with an acute exacerbation of IP, including three with IPF, one with idiopathic interstitial pneumonia (IIP) with atypical radiological findings of IPF, and one with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-related IP. The patients were treated with two courses of 3–12 h each of PMX-DHP, concurrently with corticosteroids alone or plus cyclophosphamide.

Results: After two courses of PMX-DHP, the PaO_2/fraction of inspired oxygen (FiO_2) (P/F) ratio increased rapidly from an average of 93 to 260 mm Hg, and there was radiological improvement in all patients. However, one patient treated for 3 h each time eventually died of respiratory failure, and two patients treated for 6 h each time died from respiratory infections. The other two patients were treated for 12 h each time, and the therapeutic effects lasted longer, with both surviving longer than 48 days. No adverse effects were detected apart from thrombocytopaenia.

Conclusion: PMX-DHP therapy was safe and effective in improving oxygenation in acute exacerbations of IPs, either with corticosteroids alone or plus cyclophosphamide, and may be beneficial for the treatment of this condition.

Key words: acute-phase reaction, haemoperfusion, interstitial pneumonia, oxygenation, polymyxins.

INTRODUCTION

Patients with interstitial pneumonia occasionally show rapid deterioration during the course of their illness. This phenomenon, which is called acute exacerbation of interstitial pneumonia, was first described by Kondoh *et al.* in IPF.[1] Pathological findings in acute exacerbations are reported as diffuse alveolar damage (DAD) superimposed on chronic interstitial fibrosis.[2] Recently, acute exacerbation of IPF (AE-IPF) has been

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widely recognized as a distinct clinical condition, without identifiable causes for the deterioration of IPF,[3–7] and has been shown to occur in approximately 9.6–12.0% of IPF patients at some time during their clinical course.[4,6,7] More recently, acute exacerbation has been also reported in other interstitial pneumonias, such as idiopathic non-specific interstitial pneumonia (NSIP),[8] interstitial pneumonia associated with collagen vascular disease (CVD-IP),[9–11] and with microscopic polyarteritis.[12] This condition has been shown to be generally resistant to intensive anti-inflammatory and immunosuppressive therapy, such as high doses of corticosteroids plus immunosuppressive agents.[5–7] The prognosis of patients with acute exacerbations has been reported to be extremely poor, with a high mortality rate (80–85%) in AE-IPF.[5–7] A new therapy with high efficacy is therefore needed for the treatment of acute exacerbations.

Direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) has been used for the treatment of sepsis, to remove plasma endotoxin which is produced by Gram-negative bacteria, and has proven to be highly effective in this fatal condition.[13–15] However, several studies have also reported that PMX-DHP therapy was beneficial in patients with Gram-positive bacterial infection,[14,15] or with endotoxin-negative infection.[16] Interestingly, treatment with PMX-DHP was shown to improve pulmonary oxygenation in patients with ARDS, which is pathologically characterized by DAD.[16–18] This prompted physicians to consider PMX-DHP as a potential therapy for acute exacerbation of interstitial pneumonia, which also shows a histological pattern of superimposed DAD. The most recent study by Seo *et al.* clearly demonstrated that PMX-DHP had a beneficial effect in AE-IPF.[19] However, little is known about the efficacy of PMX-DHP in acute exacerbations of other interstitial pneumonias, such as NSIP or CVD-IP. This study investigated the effectiveness and safety of PMX-DHP therapy in patients with acute exacerbations of a variety of interstitial pneumonias, including IPF, idiopathic interstitial pneumonia (IIP) with atypical radiological findings of IPF, and CVD-IP. Changes in the serum levels of parameters associated with lung injury, such as cytokines and high-mobility group box protein 1 (HMGB1), were also measured during PMX-DHP therapy.

METHODS

Study design and subjects

This was a prospective study of five consecutive patients with acute exacerbations of interstitial pneumonia; of the five patients, three had IPF, one had IIP with atypical radiological findings of IPF, and one had myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-related interstitial pneumonia. Of the three IPF patients, one was diagnosed by surgical lung biopsy, and two were diagnosed clinically, based on the American Thoracic Society/European Respiratory Society international consensus statement on IIP.[20] In the three IPF patients, acute exacerbations occurred at 36, 40 and 45 months after the initial diagnosis of IPF. The IIP patient with atypical radiologic findings of IPF showed thickening of bronchovascular bundles, no honeycombing, and no subpleural predominance. There was no underlying disease causing the interstitial pneumonia. This patient developed an acute exacerbation 7 months after the initial diagnosis of IIP. The patient with MPO-ANCA-related interstitial pneumonia had a surgical lung biopsy 10 years prior to the acute exacerbation, and had a histological diagnosis of fibrotic NSIP. The biopsy specimens did not show vasculitis or capillaritis. This patient was lost to follow up after the biopsy, and his chronic interstitial pneumonia deteriorated without medication. He developed an acute exacerbation 10 years after the surgical lung biopsy. The serum level of MPO-ANCA was elevated (55 U/mL) at the time of biopsy, and rose further to 254 U/mL at the time of the acute exacerbation. Diffuse alveolar haemorrhage was excluded by BAL in this patient.

The patients were all male, with ages ranging from 68 to 82 years (mean 73 years). The diagnosis of acute exacerbation was based on the criteria of Kondoh *et al.*[1] and Akira *et al.*[3] with slight modifications: (i) aggravation of dyspnoea within 1 month; (ii) newly developing pulmonary ground glass opacity (GGO) and consolidation on high-resolution CT (HRCT) of the chest; (iii) deterioration of hypoxaemia ($PaO_2 \geq 10$ mm Hg compared with a previously stable state); and (iv) absence of apparent infection, pneumothorax, pulmonary thromboembolism or heart failure. To exclude infection, serum antibody titres of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, as well as plasma endotoxin levels, were measured at two different times. Blood and sputum cultures were performed, as was PCR to detect *Pneumocystis jiroveci* in the sputum, and a *Cytomegalovirus* antigenaemia assay. BAL was performed on the two intubated patients, one with IPF and one with MPO-ANCA-related interstitial pneumonia.

The primary end-point in this study was the survival rate 30 days after the initiation of PMX-DHP treatment, and the secondary end-point was improvement of the acute exacerbation of interstitial pneumonia. Improvement of the acute exacerbation of interstitial pneumonia was defined as two or more of the following: (i) improvement of clinical symptoms; (ii) improvement of abnormal opacities on CXR and/or HRCT; and (iii) increase in the PaO_2/fraction of inspired oxygen (FiO_2) (P/F) ratio by more than 30% from baseline. The study protocol was approved by the Ethics Committee of the Hamamatsu University School of Medicine, and written informed consent was obtained directly from each patient.

Treatment for acute exacerbation

Immediately after diagnosis of an acute exacerbation, patients were treated with high dose corticosteroid pulse therapy (methylprednisolone, 1000 mg/day) for 3 days followed by a tapering dose of prednisolone.

When the effect of initial treatment was inadequate, cyclophosphamide pulse therapy (500 mg/2 weeks) was added. In patients requiring mechanical ventilation, intravenous sivelestat sodium hydrate was administered.

PMX-DHP therapy

Concomitant with the administration of corticosteroid alone or with cyclophosphamide, PMX-DHP therapy (PMX; Toray Medical, Tokyo, Japan) was administered. A double-lumen catheter was inserted into a femoral vein. PMX-DHP was administered for 3–12 h at a flow rate of 80–100 mL/min, and subsequently repeated once within 24 h. Nafamostat mesilate and/or heparin sodium were used as anticoagulants.

Measurement of cytokines and high mobility group box protein 1

Blood samples were taken before and after PMX-DHP therapy. The serum levels of IL-6, IL-8, IL-10 and HMGB1 were measured using ELISA. The plasma concentration of neutrophil elastase was determined in four patients (patients 1–4) using enzyme immunoassay.

RESULTS

Clinical effects of PMX-DHP

Of the five patients treated with PMX-DHP, one patient with IPF (Case 3) had received corticosteroid and cyclosporine for 3 years, while the other four were not on any regular medication. A summary of the clinical characteristics, laboratory results and physiological findings on admission is shown in Table 1. Although WCC and CRP levels were increased prior to treatment, blood cultures and plasma endotoxin were negative in all cases. Serum levels of LDH, KL-6 and surfactant protein D (SP-D), all markers of interstitial pneumonia, were elevated, and the P/F ratio was less than 200 mm Hg on admission in all cases. A summary of the treatments for acute exacerbations, including PMX-DHP, is shown in Table 2. In patients 1–3, PMX-DHP was started after 3 days of methylprednisolone pulse therapy. In patients 4 and 5, PMX-DHP was administered concomitantly with the initial methylprednisolone pulse therapy. The duration of PMX-DHP varied from patient to patient. Patient 1, patients 2 and 3, and patients 4 and 5 received 3 h, 6 h and 12 h of PMX-DHP therapy, respectively, twice within a 24-h period.

The clinical courses of the patients treated with PMX-DHP are shown in Fig. 1. In patients 1–3, the P/F ratios declined rapidly to less than 100 mm Hg with deterioration of CXR findings (Fig. 1a) despite the initial methylprednisolone pulse therapy, and the serum LDH levels increased or remained high

Table 1 Clinical characteristics, laboratory results and physiological findings on admission

Patient No.	Age (years)	Gender	Underlying disease	Previous therapy for interstitial pneumonia	Laboratory results							P/F ratio (PaO_2/FiO_2; mm Hg)
					WCC ($\times 10^9$/L)	CRP (mg/L)	LDH (IU/L)	KL-6 (U/mL)	SP-D (ng/mL)	Endotoxin (pg/mL)	Blood culture	
1	72	M	IIP	—	9.4	148	340	904	169	<0.8	Negative	188
2	71	M	MPO-ANCA-related IP	—	15.3	106	253	2300	104	<0.8	Negative	134
3	82	M	Histologically proven IPF	PSL 10 mg/day + cyclosporin A 100 mg/day p.o.	7.1	38	328	1300	157	<0.8	Negative	175
4	68	M	Clinical IPF	—	11.4	100	231	481	260	<0.8	Negative	186
5	71	M	Clinical IPF	—	8.4	35	344	2550	552	<0.8	Negative	195

IIP, idiopathic interstitial pneumonia; IP, interstitial pneumonia; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; p.o., *per os*; PSL, prednisolone.

Table 2 Treatment for acute exacerbation (AE) of interstitial pneumonia including direct haemoperfusion with a polymyxin B immobilized fibre column, and outcome in each of the five patients

Patient No.	Treatment for AE				PMX-DHP						Duration from AE (days)
	Steroid pulse therapy	Treatment after steroid pulse therapy	Cyclophosphamide pulse therapy	Mechanical ventilation	Commencing time from admission (days)	Commencing from the start of steroid pulse therapy (days)	Duration (h)	Number of cycles	Outcome	Cause of death	
1	+	sPSL 120 mg/day i.v.	+	+	3	3	3	2	died	AE of interstitial pneumonia	12
2	+	sPSL 120 mg/day i.v.	+	+	3	3	6	2	died	Pulmonary infection	23
3	+	sPSL 120 mg/day i.v.	+	+	3	3	6	2	died	Pulmonary infection	17
4	+	PSL 50 mg/day p.o.	–	–	2	0	12	2	improved	—	60
5	+	PSL 50 mg/day p.o.	–	–	0	0	12	2	improved	—	48

IIP, idiopathic interstitial pneumonia; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; PMX-DHP, direct haemoperfusion with a polymyxin B immobilized fibre column; p.o., *per os*; PSL, prednisolone; sPSL, soluble prednisolone.

(Fig. 1b). Patient 1 had IIP and was treated with two courses of 3 h each of PMX-DHP. Although the LDH level and WCC increased during PMX-DHP treatment (Fig. 1b,c), the P/F ratio rose markedly from 68 to 323 mm Hg (Fig. 1a) and the lung opacities seen on CXR improved immediately after PMX-DHP therapy (Fig. 2). However, 3 days later the P/F ratio decreased again to 33 mm Hg, and the patient died of respiratory failure 12 days after the onset of the acute exacerbation. The serum KL-6 level in this patient increased from 904 to 2220 U/mL despite PMX-DHP therapy. Patient 2 had MPO-ANCA-related interstitial pneumonia and Patient 3 had histologically proven IPF. These patients were given two courses of 6 h each of PMX-DHP. This therapy promptly raised their P/F ratio from 69 to 266 mm Hg, and from 59 to 300 mm Hg, respectively (Fig. 1a). Their CXR opacities improved (Case 2; Fig. 3) and serum LDH levels and WCC decreased (Fig. 1b,c). Although their P/F ratios remained at 150–200 mm Hg for 7–10 days, they eventually died from respiratory infections 17–23 days after the onset of the acute exacerbation. The serum KL-6 level decreased from 2300 to 1990 U/mL in Patient 2 and from 1300 to 699 U/mL in Patient 3 after PMX-DHP therapy. Patient 4 had clinical IPF and was given two courses of 12 h each of PMX-DHP. The P/F ratio increased gradually from 89 to 261 mm Hg over several days after PMX-DHP therapy (Fig. 1a). Patient 5 received two courses of 12 h each of PMX-DHP therapy, and the P/F ratio increased immediately from 195 to 322 mm Hg (Fig. 1a) with a reduction in serum LDH (Fig. 1b) and WCC (Fig. 1c). The lung opacities on CXR and HRCT also improved immediately after PMX-DHP treatment (Fig. 4). Patients 4 and 5 are still alive, more than 48 days after the onset of the acute exacerbation. The serum KL-6 level increased from 481 to 588 U/mL in Patient 4, and changed marginally from 2550 to 2590 U/mL in Patient 5. Cyclophosphamide pulse therapy was added, and mechanical ventilation was performed in patients 1–3. Sivelestat sodium hydrate was administered intravenously in patients 2 and 3.

Side-effects of PMX-DHP

Peripheral blood platelet levels decreased in four of five patients (patients 2–5) during PMX-DHP treatment. In patients 2 and 4, who developed disseminated intravascular coagulation (DIC), platelet levels decreased from an average of 228×10^9/L to 59×10^9/L. Patient 2 had massive bleeding from a gastric ulcer, possibly associated with the DIC, which developed 4 days after the onset of the acute exacerbation. Patient 4 did not have any severe complications other than respiratory failure, and the cause of DIC was unclear. In these two patients the platelet levels recovered following anticoagulant treatment. In patients 3 and 5, platelet levels decreased from an average of 163×10^9 to 115×10^9/L, and recovered spontaneously. No other side-effects were detected in any of the patients.

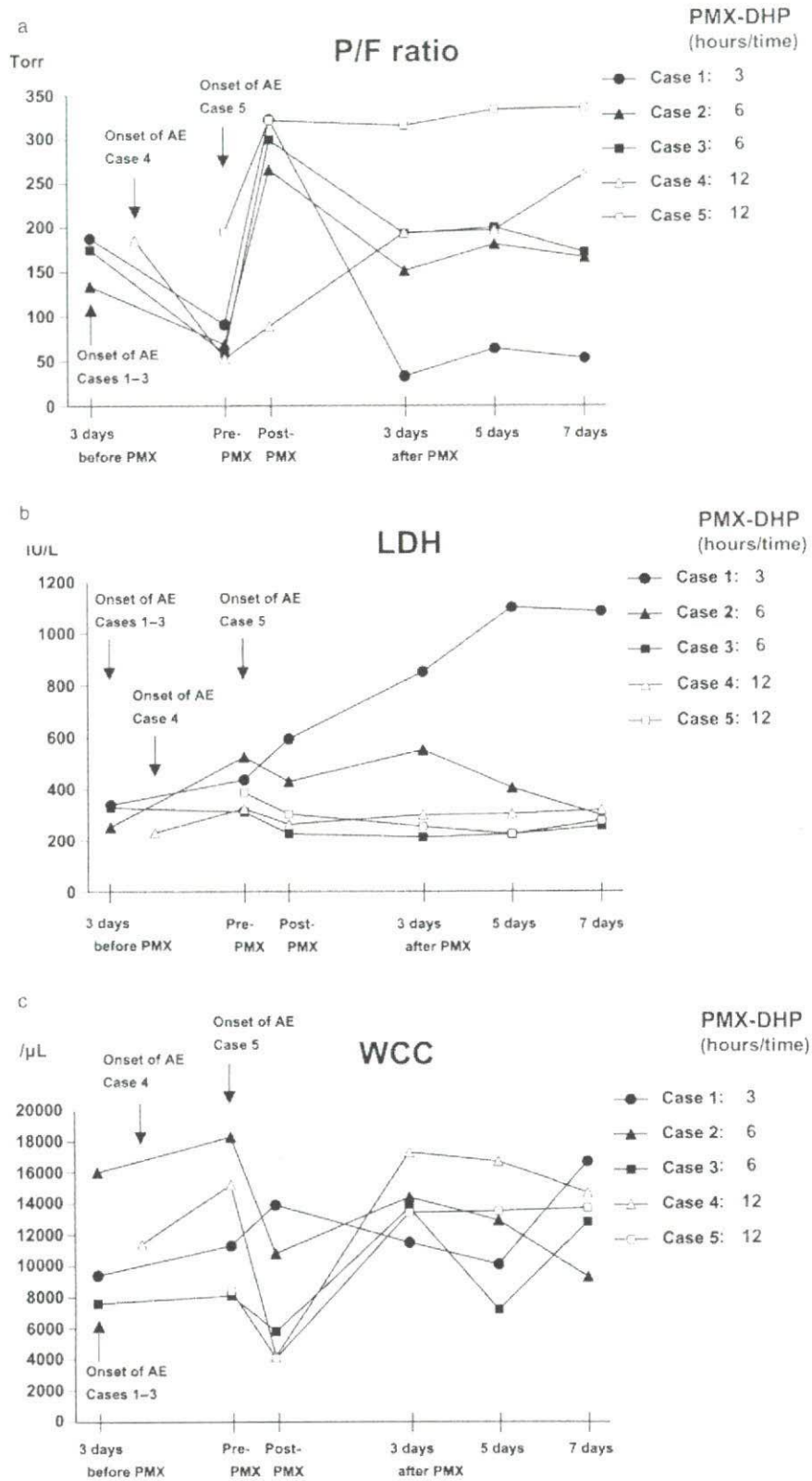

Figure 1 Kinetics of PaO_2/FiO_2 (P/F) ratio (a), serum LDH (b), and peripheral blood WCC (c) in five patients treated with direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP). PMX-DHP was administered for 3 h in Patient 1, 6 h in patients 2 and 3, and 12 h in patients 4 and 5.

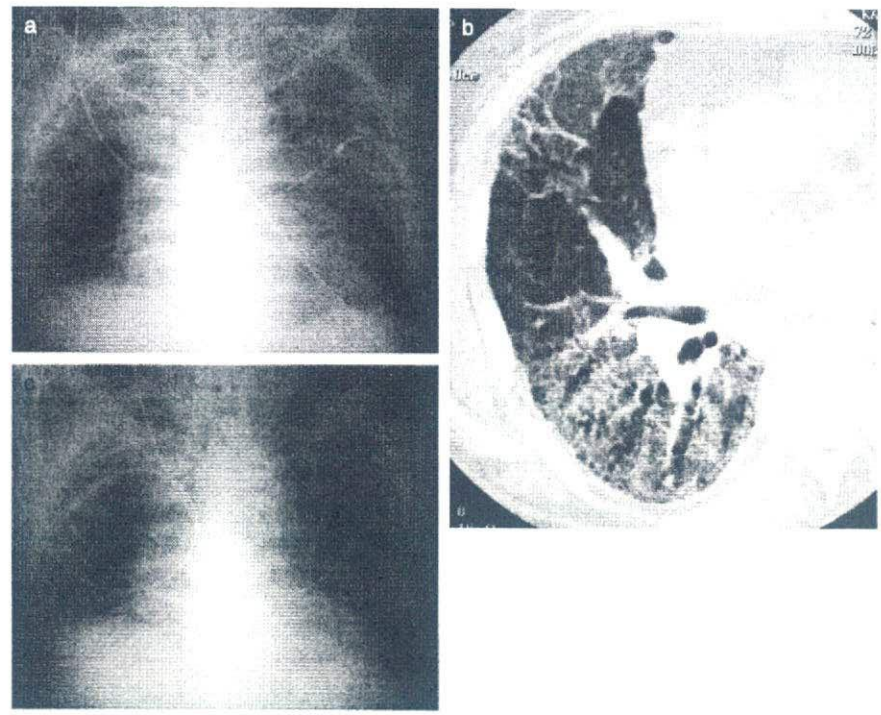

Figure 2 CXR and high-resolution CT (HRCT) of Patient 1, who was diagnosed with idiopathic interstitial pneumonia (IIP). Before direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP), his CXR (a) and HRCT (b) revealed bilateral diffuse ground glass opacities and reticular opacities, without honeycombing. He was treated with two courses of 3 h each of PMX-DHP together with corticosteroids and cyclophosphamide, and the lung opacities on his CXR improved immediately (c).

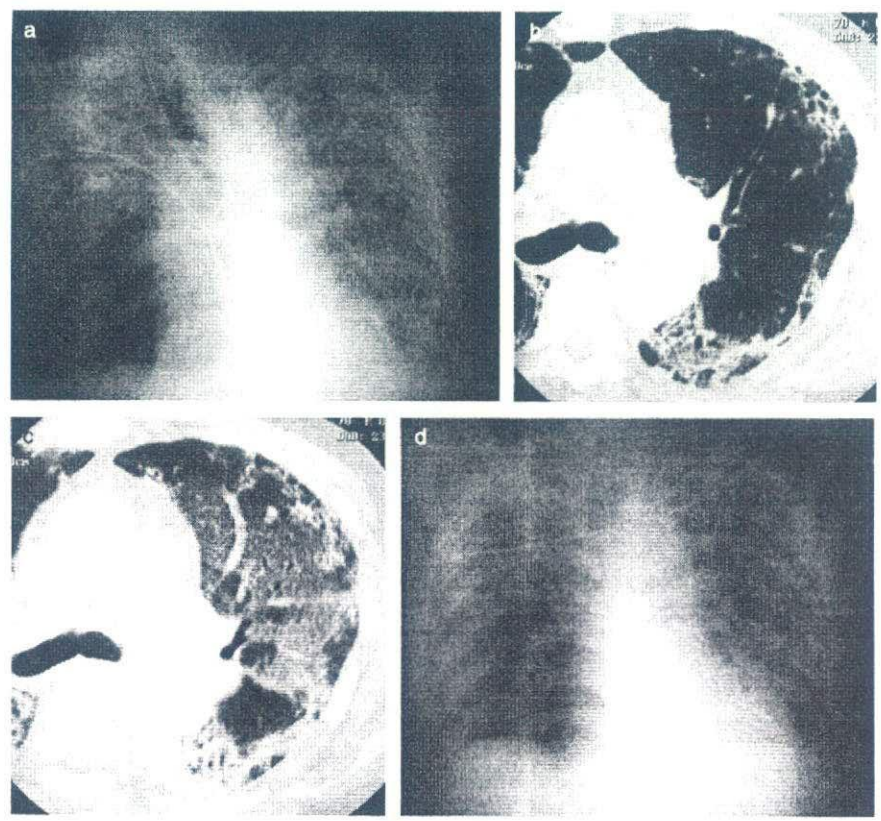

Figure 3 CXR and high-resolution CT (HRCT) of Patient 2, who was diagnosed with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-related interstitial pneumonia. Before direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP), his CXR (a) and HRCT (c) revealed bilateral diffuse ground glass opacities and new reticular opacities. His HRCT just before the acute exacerbation (b) indicated the appearance of chronic interstitial pneumonia, such as traction bronchiectasis. He was treated with two courses of 6 h each of PMX-DHP together with corticosteroids and cyclophosphamide, and the lung opacities on his CXR improved immediately (d).

Kinetics of blood cytokines and high mobility group box protein 1

The serum levels of IL-6, IL-10, IL-8, neutrophil elastase and HMGB1, before and after PMX-DHP therapy were measured (Fig. 5). No significant changes were detected in the serum levels of cytokines, neutrophil elastase or HMGB1 in any of the patients. Three of the four patients who received 6- or 12-h courses of PMX-DHP (patients 2–5) showed a

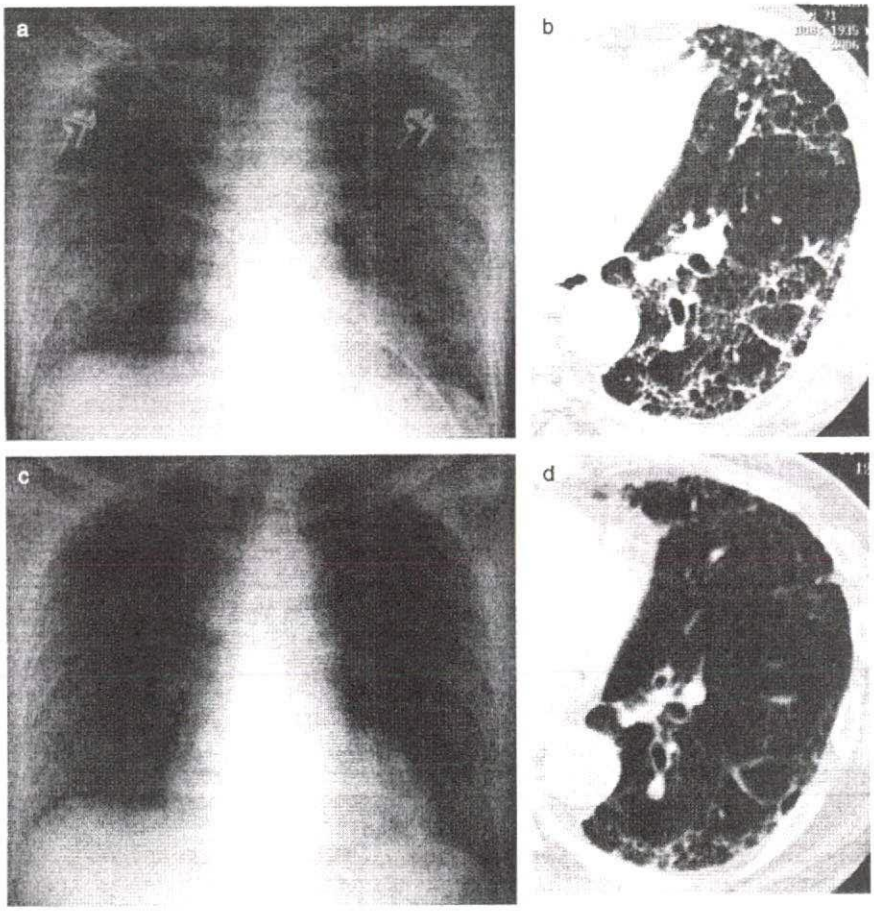

Figure 4 CXR and high-resolution CT (HRCT) of Patient 5, who was diagnosed with clinical IPF. Before direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP), his CXR (a) and HRCT (b) revealed ground glass opacities and reticular opacities, predominantly in the bilateral lower lobes. He was treated with two courses of 12 h each of PMX-DHP together with corticosteroids, and the lung opacities on his CXR (c) and HRCT (d) improved immediately.

decrease in serum IL-6 levels after therapy. IL-10 was not detected in the serum of any of the patients before or after PMX-DHP therapy.

DISCUSSION

The present study demonstrated that PMX-DHP dramatically improved pulmonary oxygenation in acute exacerbations of interstitial pneumonia, either with corticosteroids alone or plus cyclophosphamide, regardless of the aetiology and histology. However, three of five patients eventually died owing to respiratory failure or infection. PMX-DHP therapy appeared to be at least temporarily effective, and a longer duration (12 h) may give a better long-term outcome. Further study may elucidate the optimum method for administration of PMX-DHP for the treatment of acute exacerbations of interstitial pneumonia, such as the optimum duration and number of cycles.

Recently, Seo *et al.* demonstrated that PMX-DHP was an effective therapy for AE-IPF.[19] In that study, four of six patients treated with PMX-DHP showed a dramatic improvement in pulmonary oxygenation and were successfully weaned from mechanical ventilation, resulting in survival for longer than 30 days. However, no data were available on the effectiveness of PMX-DHP for the treatment of acute exacerbations of interstitial pneumonias other than IPF. In the present study, PMX-DHP with corticosteroids alone or plus cyclophosphamide also had a beneficial effect on pulmonary oxygenation in patients with non-IPF interstitial pneumonia. This suggests that PMX-DHP therapy can be used for the treatment of acute exacerbations of interstitial pneumonias with different aetiologies or histology. No serious adverse effects were observed during PMX-DHP therapy. Thrombocytopaenia occurred in four of five patients. Thus, PMX-DHP can safely be administered in patients with respiratory failure owing to an acute exacerbation of interstitial pneumonia.

The improvement in oxygenation with PMX-DHP typically occurred very rapidly. Patients showed a dramatic increase in P/F ratio during or just after PMX-DHP therapy. The improvement was striking in four patients (patients 1, 2, 3 and 5). In patients 1–3, the P/F ratios decreased further (to less than 100 mm Hg) before PMX-DHP, despite intensive therapy during this time. These patients usually do not respond well to any treatment, but PMX-DHP therapy led to a substantial improvement in their condition. On the other hand, oxygenation improved slowly following PMX-DHP treatment in Patient 4. Although the reason for this difference in the pattern of improvement is unclear, responsiveness may vary from patient to patient. With respect to long-term survival, three of the five patients eventually died of respiratory failure

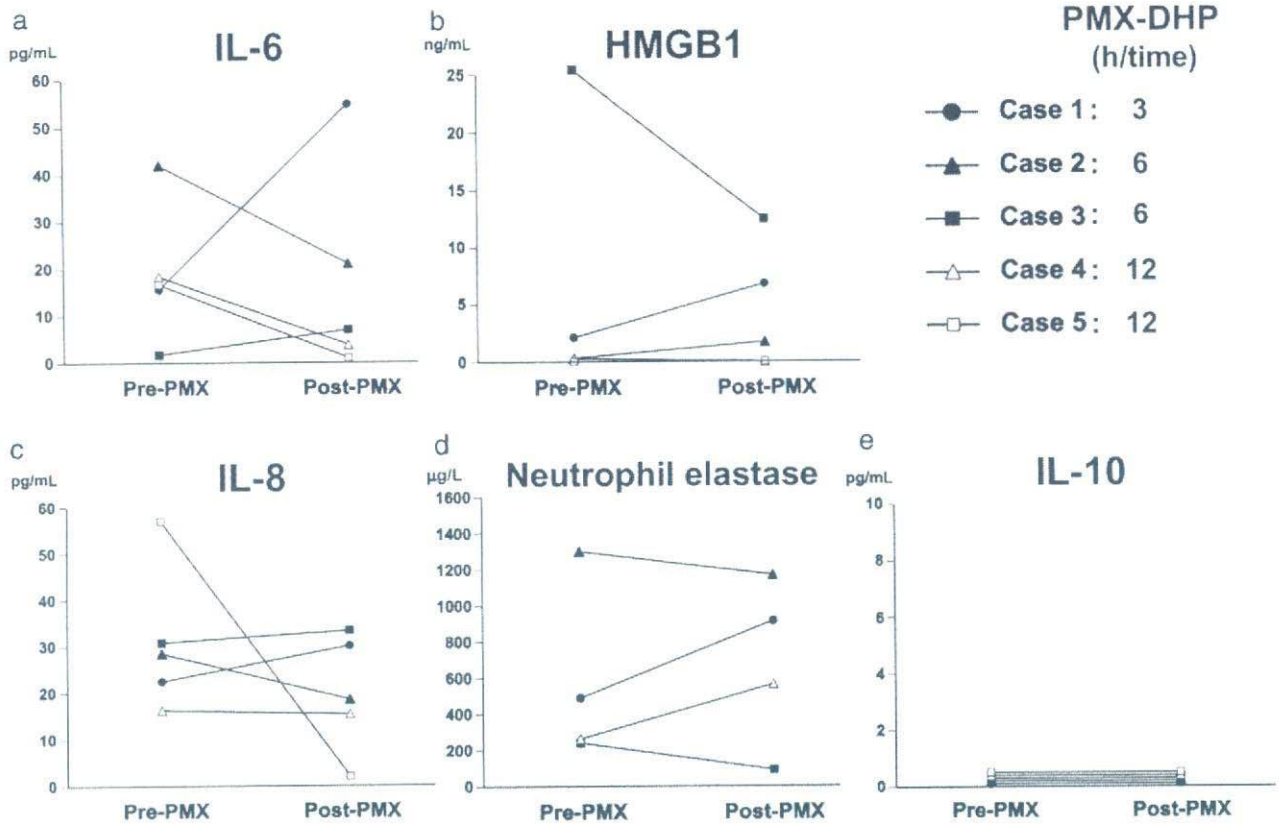

Figure 5 Kinetics of blood cytokines during direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP). (a) IL-6, (b) high mobility group box protein 1 (HMGB1), (c) IL-8, (d) plasma neutrophil elastase and (e) IL-10.

or infection, despite temporary improvements in pulmonary oxygenation after PMX-DHP with corticosteroids alone or plus cyclophosphamide. In contrast, Seo *et al.* reported that PMX-DHP increased pulmonary oxygenation and successfully saved four of six patients with AE-IPF.[19] In that study, two of the three AE-IPF patients with P/F ratios <110 mm Hg died of respiratory failure, whereas all three patients with P/F ratio > 180 mm Hg survived. This suggests that AE-IPF patients with severe respiratory failure do not respond well to PMX-DHP therapy. The P/F ratio was less than 100 mm Hg at the beginning of PMX-DHP therapy in four of the five acute exacerbation patients (Fig. 1a), which might account for their poor outcomes compared with those of the patients in the study of Seo *et al.*[19]

Although two courses of 2–3 h each of PMX-DHP therapy have been used for patients with sepsis,[13–15,17] the optimal duration and number of cycles remains to be determined for acute exacerbations of interstitial pneumonia. Seo *et al.* administered one to five courses of 2 h each in five patients, and 6 h each in another patient,[19] depending on the patient's condition. In the present study, Patient 1 was treated with two courses of 3 h each, but the therapeutic effect was temporary. Patients 2 and 3 were treated with two courses of 6 h each, and the effects lasted for 1–2 weeks. Patients 4 and 5 were treated with two courses of 12 h each, with persistent improvement in pulmonary oxygenation, and both survived. Thus, the longer courses of PMX-DHP appeared to be more effective, but further studies will be required to determine the optimum duration and number of cycles of PMX-DHP therapy in acute exacerbations of interstitial pneumonia.

To date, the mechanism by which PMX-DHP improves oxygenation in acute exacerbations of interstitial pneumonia is unclear. In the present study, PMX-DHP therapy did not significantly decrease the levels of IL-6, IL-8, IL-10, HMGB1 or neutrophil elastase in any patient. The peripheral blood WCC did, however, decrease during the 6 and 12 h courses of PMX-DHP (patients 2–5, Fig. 1c). It is possible that trapping of leukocytes, especially monocytes and neutrophils, within PMX-DHP columns may play an important role in its therapeutic effects. Recent studies have also reported that PMX-DHP reduced blood neutrophil elastase,[15] TNF-α,[21] matrix metalloproteinase-9, which enhances vascular permeability,[18] and intrapulmonary shunt ratio.[22] However, no significant decrease in blood neutrophil elastase was observed in the present study. Further studies are required to elucidate the precise mechanism by which PMX-DHP improves acute exacerbations of interstitial pneumonia.

There were several limitations to this study. First, the number of subjects was small. Second, because all patients treated with PMX-DHP were concurrently

treated with corticosteroids alone or plus cyclophosphamide, it is possible that the observed improvement in pulmonary oxygenation may not be attributable exclusively to PMX-DHP. Thus, further prospective controlled studies, with larger numbers of patients and a placebo group, will be required.

In conclusion, the present study demonstrated that PMX-DHP, either with corticosteroids alone or plus cyclophosphamide, significantly improved pulmonary oxygenation in acute exacerbations of interstitial pneumonia, regardless of the aetiology or histology, suggesting that this therapy has possible benefits in acute exacerbations that do not usually respond to intensive therapy and have an extremely poor outcome. The main limitation of this study was the small number of patients. Therefore, the most effective way to administer PMX-DHP, and the long-term outcome, will need to be further defined in a larger series of patients.

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特集 | 特発性間質性肺炎

特発性間質性肺炎に合併する肺がん治療の現状*

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Key Words：idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis, lung cancer, treatment, acute exacerbation

はじめに

特発性間質性肺炎(idiopathic interstitial pneumonias；IIPs)は特発性肺線維症(idiopathic pulmonary fibrosis；IPF)を代表として7つの疾患に分類されている．なかでもIPFや線維化型非特異性間質性肺炎(fibrotic nonspesific interstitial pneumonia；f NSIP)など線維化を主体とする慢性経過のIPにおいては，その臨床経過の中で肺癌合併(以下，IP合併肺癌)は重要な臨床病態である．つまり，IP合併肺癌においてはさまざまな治療によってIPの急性増悪(acute exacerbation)が生じ，その予後がきわめて不良であることが問題となっており，IP合併肺癌症例ではまさに急性増悪をどう予防するかにかかっているといっても過言ではない．しかし，この分野ではしっかりとしたエビデンスのあるものがほとんどない状況を理解した上で，IP合併肺癌治療について述べてみたい．

特発性間質性肺炎に関する問題

IIPsの診断はわが国の診断基準を満たす典型的IPF以外での病理診断は外科的肺生検が基本であるが，実際の臨床では蜂巣肺を認めないIIPsと診断するしかない場合が多い．IP合併肺癌においては①IP経過中に発見される肺癌，②肺癌発見時に併存しているIP，の大きく2つの病態に分けられる．前者の多くの場合はIPによる症状を認める場合であり，通常はIPの進行例と考えられ，IPFの臨床診断基準を満たす場合が多いものと考えられる．臨床的に有症状例のIPFの場合には50%生存率は2～3年程度であることから，IPFの予後の不良さを十分認識した上で肺癌治療を考慮することが重要となってくる．一方，肺癌発見時に併存するIPは比較的軽微な症例であり，肺癌治療が優先される可能性が高い．また，一方でIP合併症例では第二癌の発生の頻度も高いことも指摘[1]されている．

IPの進行例では，検査(BALやTBLB)や治療によって急性増悪を生じやすいことはよく知られている．一方でIP重症度を評価する指標に明確なものはないのが現状である．わが国では特定疾患申請における重症度があるにすぎない．また，欧米では表1[2]に示すような重症度分類も提示され，エビデンスに基づく指標による重症度分類として臨床上有用と思われる．

IP合併肺癌に対する治療選択肢の考え方

IP合併肺癌症例においてもまず重要なことは，肺癌として適切な病期分類を行うことが優先される．つまり肺癌の病期を確定した上で，併存するIPの評価を行い，総合的に治療方針を決定

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表1　重症度分類

1. FVC＜65%
2. Desaturation with exertion (PaO_2＜88% on room air)
3. Dlco≦50%

Mild impairment＝none of the three features
Moderate impairment＝any one of the features
Severe impairment＝2 or 3 of the features

（文献[2]より引用）

することが重要である．

肺癌症例において根治術が可能かどうかは治療方針決定上重要な問題であり，IP合併例であったとしても可能な限り治癒する可能性を考慮していくことは当然である．一方，根治が不可能な病態であれば，あくまで延命効果を期待する治療ということになるため，リスクをどこまで冒すかは臨床上の判断として非常に難しく，実地臨床での苦悩は大きい．

とくにIIPs，なかでもIPFにおいては自覚症状が出現してからの予後は不良であることを考えれば，肺癌治療の選択肢をどのように考えるかは，臨床上非常に困難な問題でもある．

各種治療手段について

1．外科的治療について

外科的治療は非小細胞肺癌においては治癒が期待できる治療法であり，可能な限り検討すべき治療法である．当然，IP合併肺癌においても標準的な術前評価を行った上で外科的治療の適応を考慮することになる．

IPが存在しない場合において術後にacute lung injury（ALI）/acute respiratory distress syndrome（ARDS）を生じる可能性は3.9～4.2%であったと報告[3][4]されており，IPの存在がなくても臨床的にALI/ARDSすなわち病理学的にはびまん性肺胞障害（diffuse alveolar damage：DAD）を生じる可能がある．その中でLickerらはALIを術早期（3日以内）に発症するprimary ALIとそれ以後に発症するsecondary ALIに分け，後者の予後が不良（死亡率26% vs. 60%）であると指摘し，発症時期による病態が異なる可能性が指摘されており，IP合併肺癌での急性増悪を考える上でも興味深い．

一方，IP合併肺癌症例における外科的切除術後に生じる急性増悪は臨床上の重要な問題である．明らかなIP合併例においては非合併例との比較で術前の呼吸機能評価ではまったく差がないとの報告[5][6][8][9]も数多くみられる．表2にはIP合併ならびに非合併肺癌症例における術後急性増悪ないしALI/ARDS例の検討[5]～[9]が示されており，IP合併肺癌の頻度は151/3,932（平均3.8%：1.5～6.8%）で，そのうち急性増悪は32/151（平均21.2%；0～27.3%），急性増悪発症後の死亡率は17/32（平均53.1%；0～80%）であった．また，IP非合併例では術後ALI/ARDSを生じた頻度は82/3,781（平均2.2%；0.7～3.7%），その死亡率は56/82（平均68.3%；44.4～100%）であり，いわゆる両群でDADを生じる可能性は10倍近く差があった（$p<0.001$）．しかし死亡率には差がなく，いったん急性増悪あるいはALI/ARDSを発症すれば約3分の2程度は死亡することが示された．多くの外科症例においては術前の呼吸機能検査から推測すると%VCは80%以上の症例[5][6][8][9]であり，IPとしては軽症例ということになる．つまり見方を変えれば多くのIP合併肺癌症例では，呼吸機能の状態からはほぼ自覚症状のない病態であっても20%程度の急性増悪を生じ，そのうち約半数以上が死亡するというのが実態であり，IP合併肺癌で外科療法を行う場合には十分なインフォームドコンセント（IC）を得た上で行うことが重要

表2　肺癌手術例におけるIPの頻度と急性増悪

	総数	IP	急性増悪（dead/alive）	non-IP	ALI/ARDS（dead/alive）
Kumar[5]	988	24（2.4%）	5（4/1）	964（97.6%）	36（30/6）
Chiyo[6]	931	36（3.9%）	9（1/8）	895（96.1%）	18（8/10）
千田[7]	477	51（10.7%）	9（6/3）	426（89.3%）	3（3/0）
Takeda[8]	473	7（1.5%）	0（0/0）	466（8.5%）	4（2/2）
Kushibe[9]	1,063	33（3.1%）	9（6/3）	1,030（96.9%）	21（13/8）
合計	3,932	151（3.8%）	32（17/15）	3,781（96.2%）	82（56/26）

かと考えられる．

外科的処置を行うことによって，体内の各種サイトカインに変化が生じ，これが急性増悪への引き金になるとの考え方があるため，その予防対策としてさまざまなものがおこなわれているが，エビデンスといわれるほどの検証がなされているわけではない．これまでに報告されているものとしては，術後急性増悪予防としてマクロライド少量療法，術前，術中，術直後におけるステロイドの短期間投与，好中球エラスターゼ阻害薬であるシベレスタット投与，術中の吸入酸素濃度を50%以下にする，手術時間を可能な限り短縮する，などがある(表3)．いずれの療法も手術によって生じるサイトカイン産生を抑え，生体に対する攻撃因子を抑制することを主眼としている．

実際の処方としては，通常のマクロライド療法と同様にエリスロマイシン400～600mg/日を手術前1～2週間より開始し術後1か月程度内服する．ステロイド投与についてはかえって病状を悪化させるというリスクも考えられるため十分なICが必要である．

外科療法を行った場合に画像上でも評価できないほどの胸膜直下の線維化病変を伴う病態でも急性増悪(臨床的にはARDS)を生じるとの報告[7]もあるが，実際の臨床現場では術前に確認することは困難であり，予防策を講じることも困難である．IPのリスク因子である喫煙は肺癌のリスク因子でもあるため，喫煙症例では臨床的に問題とならない線維化病変の可能性を常に考慮した上で，肺葉切除に臨むことが実際的である．

2．化学療法について

抗癌剤は致死的な肺障害を生じることで有名であり，とくに日本人においては欧米人に比べ明らかに肺障害を生じやすいことが近年イレッサ®や抗リウマチ薬であるアラバ®における薬剤性肺障害の報告から明らかとなった．もともとIPFにおける急性増悪という概念もわが国から発信された病態であることを考慮するとIPの急性増悪の発症の認識も高いと考えられる．もちろん化学療法を施行する際には，該当抗癌剤の薬剤性肺障害の頻度と間質性肺炎に対して禁忌薬があることを熟知しておくことが重要である．表4に薬剤性肺障害の頻度[10]を示すとともに，添付文書からの併存する間質性肺炎症例に対しての禁忌，慎重投与を表5に示す．禁忌薬の中でジェムザール®とカルセド®では胸部単純写真で明らかでかつ臨床症状のある間質性肺炎症例と明確な基準が示され，ジェムザール®ではその他の間質性肺炎では慎重投与と記載されている．当然のことであるが禁忌薬を使用することは倫理的に問題があるばかりではなく，医療事故としては当然問題となってくる．一方で，この場合どの程度までの所見を間質性肺炎とするかという問題があるが，画像上で判別できず切除標本でわずかな間質性肺炎を認める場合においても術後の急性増悪(臨床上はARDS)を生じることが報告されていることからは腹臥位CTで認められる胸膜直下の間質性病変があった場合には間質性肺炎が存在するとして対応すべきと考える．近年，イレッサ®投与におけるコホート研究により肺障害を生じるリスクは間質性肺炎の程度に対してオッズ比が報告されている．また，各種病態によって正常肺が損われることもあり，この面積比も肺障害を生じるリスクファクターとなることも報告されている．表6にはイレッサ®コホートで検討された間質性肺炎の程度と既存正常肺の占有率による薬剤性肺障害のオッズ比を示す[11]．いずれにしろ間質性肺炎の病変分布は薬剤性肺障害の発症に深くかかわっていることは明らかである．

表3　IP合併肺癌症例に対する対処法

1．マクロライド少量投与
2．ステロイド投与
3．術中酸素投与濃度維持(FiO_2 ＜0.5)
4．好中球阻害薬投与(siberestat)
5．手術時間の短縮
6．片肺換気を避ける

現実的に手術不能の非小細胞肺癌においては禁忌薬ではない薬剤を選択して化学療法を行うことになるが，初回化学療法薬で安全に施行できた場合においても病状が進行しPSが不良になれば当然肺障害のリスクは上昇してくる．いずれにしろ，化学療法は延命治療であることを十分認識した上で患者と十分な了解のもとで化学療法を選択するのかBSCを選択するのかを決定し