

## Acute Exacerbation of Pulmonary Fibrosis in Syndrome of Combined Pulmonary Fibrosis and Emphysema Following Lung Surgery : A Report of Two Cases

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We herein report two cases of an acute exacerbation of pulmonary fibrosis in the syndrome of combined pulmonary fibrosis and emphysema (CPFE) following lung surgery, and also review the relevant literature. One is a 76-year-old man, who had been diagnosed with CPFE and lung cancer and undergone lobectomy. He was admitted to our hospital because of aggravation of dyspnea 50 days after lung surgery. The other is a 69-year-old man who had been diagnosed with pulmonary bulla, pulmonary emphysema and idiopathic interstitial pneumonia at 53 years old and was complicated by lung cancer. He underwent right lower lobectomy and presented with slight fever and desaturation 18 days after lung surgery. In both cases, chest computed tomography showed diffuse bilateral ground-glass opacities superimposed on preceding reticular opacities in the lower lung field. They were diagnosed as acute exacerbation of pulmonary fibrosis in CPFE. A strict follow-up is required, because the prevalence of lung cancer may be higher, and acute exacerbation may occur following lung surgery in CPFE patients. HRCT plays an important role in evaluating the occurrence of lung cancer at an early stage and for determining whether there is an acute exacerbation of pulmonary fibrosis in CPFE patients. *Shinshu Med J 60 : 149–156, 2012*

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### I Introduction

Emphysema and idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis (IPF), are conditions defined by distinct clinical, functional, radiological and pathological characteristics. However, the occurrence of both emphysema and pulmonary fibrosis in the same patient has received increased attention as a syndrome of com-

bined pulmonary fibrosis and emphysema (CPFE)<sup>1)</sup>. CPFE is a unique disorder described in several case series of upper lobe emphysema associated with lower lobe fibrosis<sup>1)–5)</sup>, and the distinct features of CPFE in comparison with chronic obstructive pulmonary disease (COPD)<sup>3)</sup> and IPF<sup>5)–7)</sup> have been reported. CPFE may also be a risk factor for lung cancer<sup>3)8)</sup>, and the prevalence of lung cancer may be higher in CPFE patients than in COPD and IPF patients<sup>3)</sup>. CPFE is highlighted as a smoking-related interstitial lung disease<sup>9)</sup>, while it may be under-recognized because of its subnormal spirometry. We herein report the cases of two patients with acute

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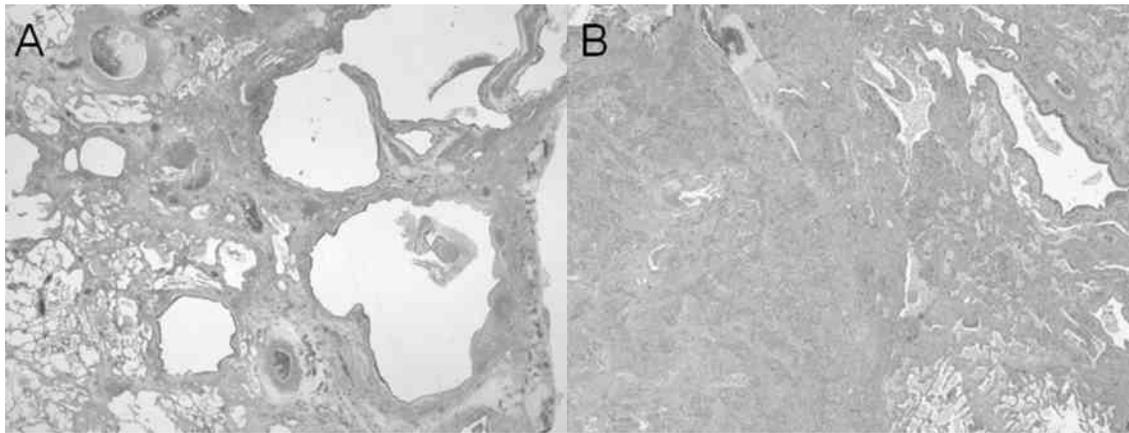


Fig. 1A The histopathological images of Case 1 ( $\times 1.25$ , HE). The histological diagnosis obtained by lobectomy was emphysema, usual interstitial pneumonia (A) and squamous cell carcinoma (B).

exacerbation of pulmonary fibrosis in CPFE following lung surgery for lung cancer, and also review the relevant literature.

## II Case Reports

### A Case 1

The patient was a 78-year-old male who first presented with cough and hemoptum. He was diagnosed with CPFE clinically based on the imaging criteria for CPFE as described by Cottin et al.<sup>1)</sup> High-resolution computed tomography (HRCT) revealed the coexistence of emphysema with an upper lung field predominance and diffuse parenchymal lung disease with significant pulmonary fibrosis with lower lung field predominance. In addition, there was a 4-cm irregular mass about in the left lung S4. The patient was an ex-smoker (50 pack-years). Bronchoscopy was performed and a histological examination revealed squamous cell carcinoma. He underwent left upper lobectomy for lung cancer. The final pathological diagnosis was emphysema, usual interstitial pneumonia and pulmonary squamous cell carcinoma T2bN0M0= Stage IIA (Fig. 1A). The patient was placed under observation without chemotherapy following surgery. He did not receive either steroids or immunosuppressants before admission. He was admitted to the hospital 50 days after lung surgery because of aggravation of dyspnea and desaturation. He had complained of increased dry cough

without fever increasing since 14 days before admission, although he had not visited the hospital until admission. Laboratory findings on admission showed white blood cell count (WBC)  $8500 \text{ mm}^3$ ; lactate dehydrogenase (LDH) 455 IU/L; C-reactive protein (CRP) 18.27 mg/dl; KL-6 1124 U/mL. Arterial blood gas analysis while on 100% oxygen at 3 L/min showed severe hypoxia and hypocarbia (pH 7.34,  $\text{PaCO}_2$  27.3 Torr,  $\text{PaO}_2$  40.3 Torr). HRCT showed new diffuse bilateral ground-glass opacities superimposed on a background of reticular opacities and honeycombing with basal and peripheral predominance (Fig. 1B). Cultures of endotracheal aspirate and blood showed no evidence of either pulmonary infection or sepsis. Echocardiography showed no evidence of left heart failure. These data also confirmed a diagnosis of acute exacerbation of IPF according to the diagnostic criteria of the IPF Clinical Research Network<sup>10)</sup>. He was diagnosed as having an acute exacerbation of pulmonary fibrosis in CPFE. His clinical course is shown in Fig. 1C. He was treated with steroid pulse therapy (1 g of methylprednisolone per day for 3 days), and antibiotics. Although the respiratory failure was severe, he and his family at first refused mechanical ventilation and non-invasive positive pressure ventilation (NPPV). They gave permission to apply NPPV in order to reduce distress and start sivelestat sodium hydrate, and NPPV was applied on day 5 after admission. The respiratory failure progressed

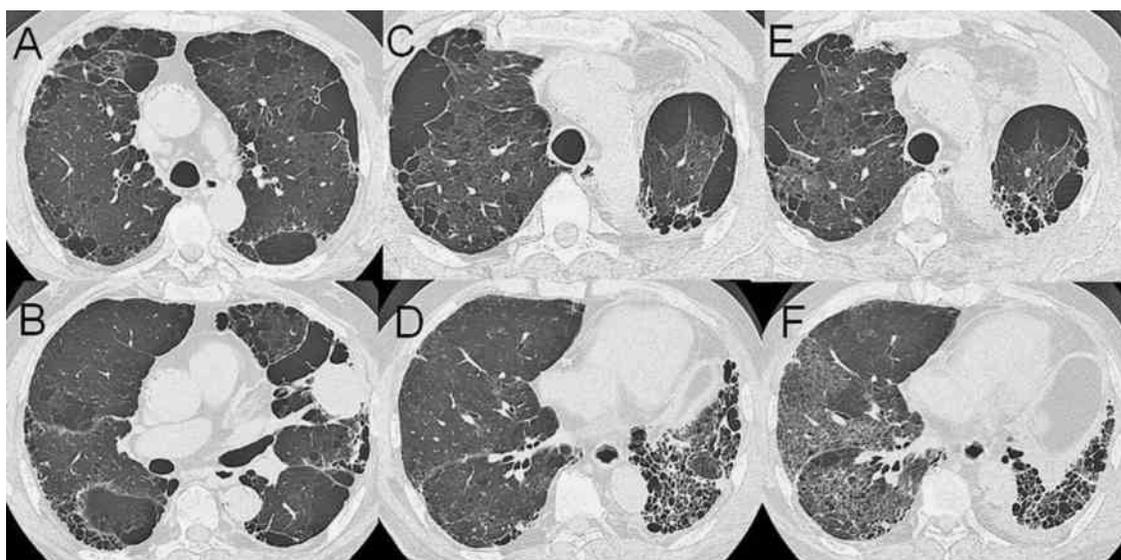


Fig. 1B Chest HRCT images before left upper lobectomy (A and B), after upper lobectomy (C and D) and on admission (E and F) of Case 1.

HRCT scans revealed the coexistence of emphysema with an upper lung field predominance and diffuse parenchymal lung disease with significant pulmonary fibrosis with lower lung field predominance. There was a 4-cm irregular mass in the left lung S4 (B). New diffuse bilateral ground-glass opacities superimposed on a background of reticular opacities and honeycombing with basal and peripheral predominance (E and F).

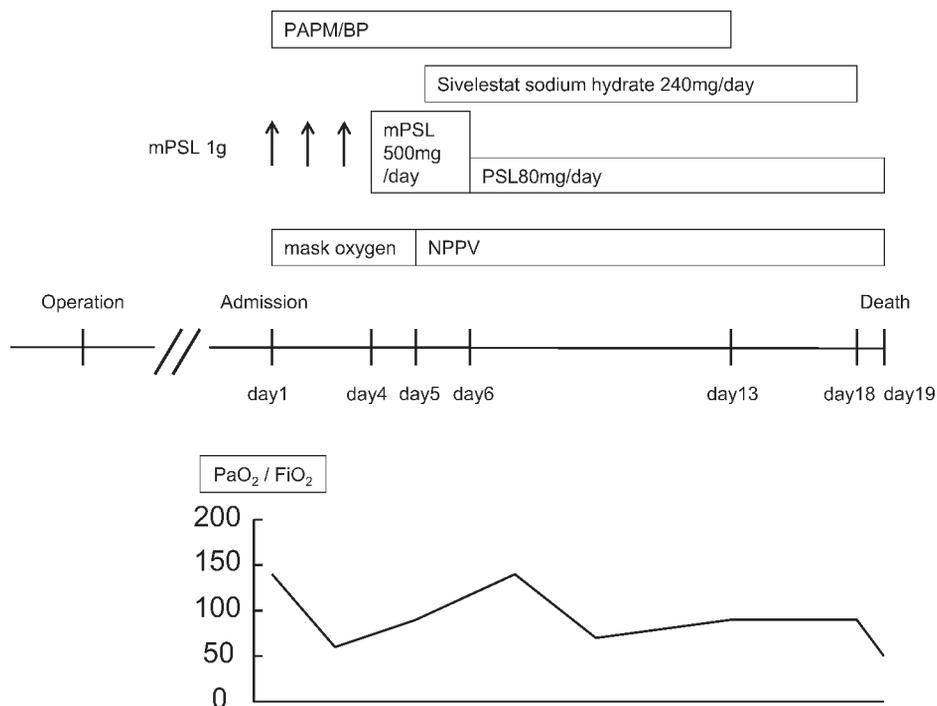


Fig. 1C Clinical course of Case 1. Abbreviations : PAM/BBP : panipenem / betamipron, mPSL : methylprednisolone sodium succinate, PSL : prednisolone, NPPV : non-invasive positive pressure ventilation

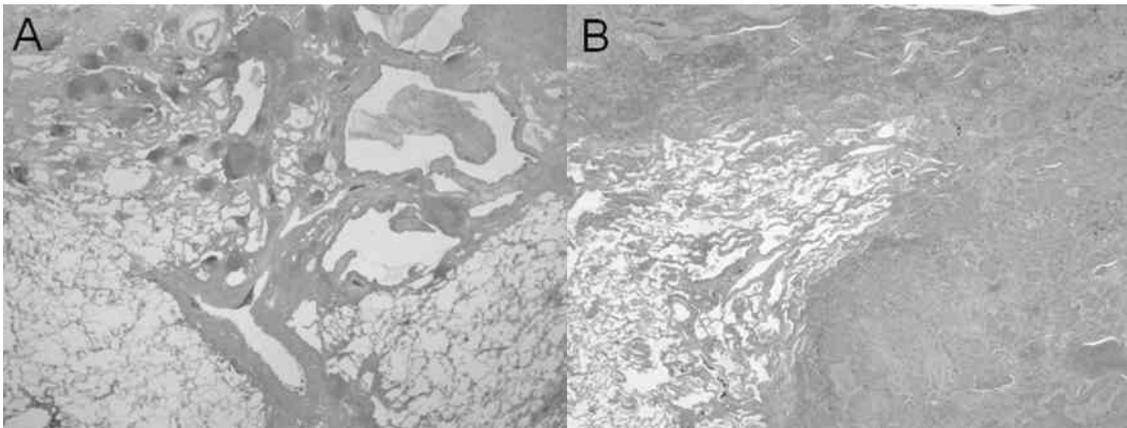


Fig. 2A The histopathological images of Case 2 ( $\times 1.25$ , HE). The histological diagnosis obtained by lobectomy was emphysema, usual interstitial pneumonia (A) and squamous cell carcinoma (B).

despite the therapy and he died due to respiratory failure on day 19 after admission.

#### B Case 2

The patient was a 69-year-old male who was first referred to Shinshu University Hospital because of an abnormal chest shadow detected in an annual checkup and was diagnosed with pulmonary bulla, pulmonary emphysema and idiopathic interstitial pneumonia at 53 years old. He was in the outpatient clinic of Shinshu University Hospital and then diagnosed with CPFE based on the imaging criteria for CPFE described by Cottin et al.<sup>1)</sup> HRCT revealed the coexistence of emphysema with an upper lung field predominance and diffuse parenchymal lung disease with significant pulmonary fibrosis with lower lung field predominance. He had not received steroids and immunosuppressants. He was an ex-smoker (33 pack-years). Follow-up HRCT revealed a 3-cm irregular mass in the right lung S10, and right hilar and mediastinal lymphadenopathy. Bronchoscopy was performed and a histological examination revealed adenocarcinoma. He was admitted to Shinshu University Hospital because of sudden aggravation of dyspnea and chest pain after coughing. He was diagnosed with right spontaneous pneumothorax and received intracostal tube drainage. Persistent leakage and failure of lung expansion continued. He underwent right lower lobectomy on day 20 after admission for both right lung cancer and right spontaneous

pneumothorax. The final pathological diagnosis was emphysema, usual interstitial pneumonia and pulmonary squamous cell carcinoma T2aN1M0= Stage IIA (Fig. 2A). The intercostal tube was removed on day 25 after admission. He presented with aggravation of dyspnea, slight fever and desaturation on day 37 after admission (18 days after lung surgery). Laboratory findings showed WBC 13870  $\text{mm}^3$ ; LDH 464 IU/L; CRP 6.09 mg/dl; KL-6 1123 U/mL. Arterial blood gas analysis while on 100% oxygen at 1 L/min showed hypoxia (pH 7.475, PaCO<sub>2</sub> 38.4 Torr, PaO<sub>2</sub> 55.6 Torr). HRCT showed new diffuse bilateral ground-glass opacities superimposed on a background of reticular opacities and honeycombing with basal and peripheral predominance (Fig. 2B). Cultures of endotracheal aspirate and blood showed no evidence of pulmonary infection or sepsis. Echocardiography showed no evidence of left heart failure. These data also confirmed a diagnosis of acute exacerbation of IPF according to the diagnostic criteria of the IPF Clinical Research Network<sup>10)</sup>. He was diagnosed as having an acute exacerbation of pulmonary fibrosis in CPFE. His clinical course is shown in Fig. 2C. He was treated with steroid pulse therapy (1 g of methylprednisolone per day for 3 days). Respiratory failure progressed and mechanical ventilation was applied on day 39 after admission. The PaO<sub>2</sub>/FiO<sub>2</sub> ratio improved to 251 after intensive treatment, and he was successfully weaned from mechanical venti-

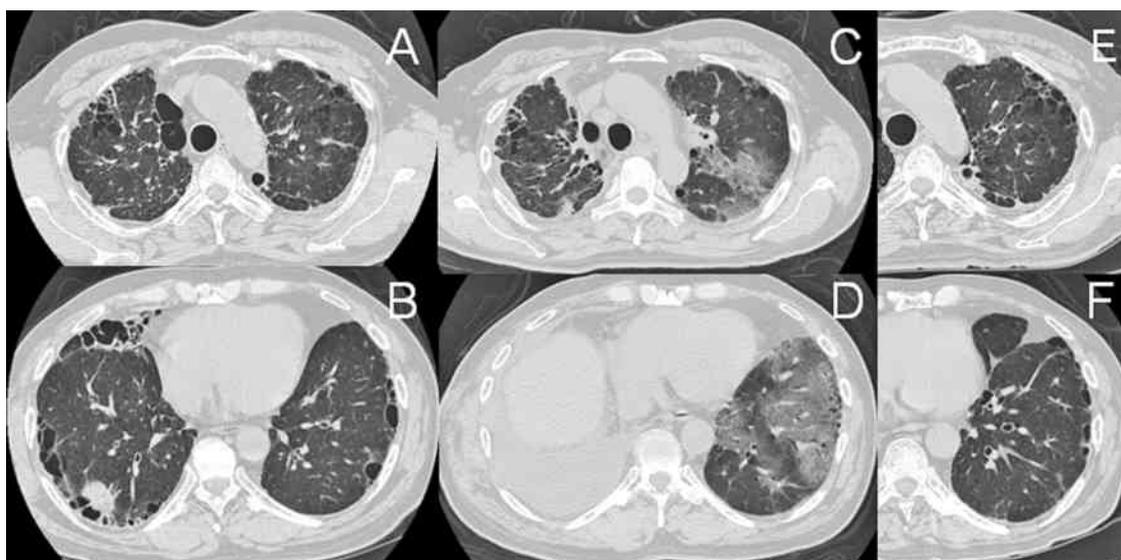


Fig. 2B Chest HRCT images before admission (A and B) and 17 days after lung surgery (C and D) of Case 2.

HRCT scans revealed the coexistence of emphysema with an upper lung field predominance and diffuse parenchymal lung disease with significant pulmonary fibrosis with lower lung field predominance. There was 3-cm irregular mass in the right lung S10 (B). New diffuse bilateral ground-glass opacities superimposed on a background of reticular opacities and honeycombing with basal and peripheral predominance (C and D). The ground-glass opacity on chest CT was ameliorated after treatment (E and F).

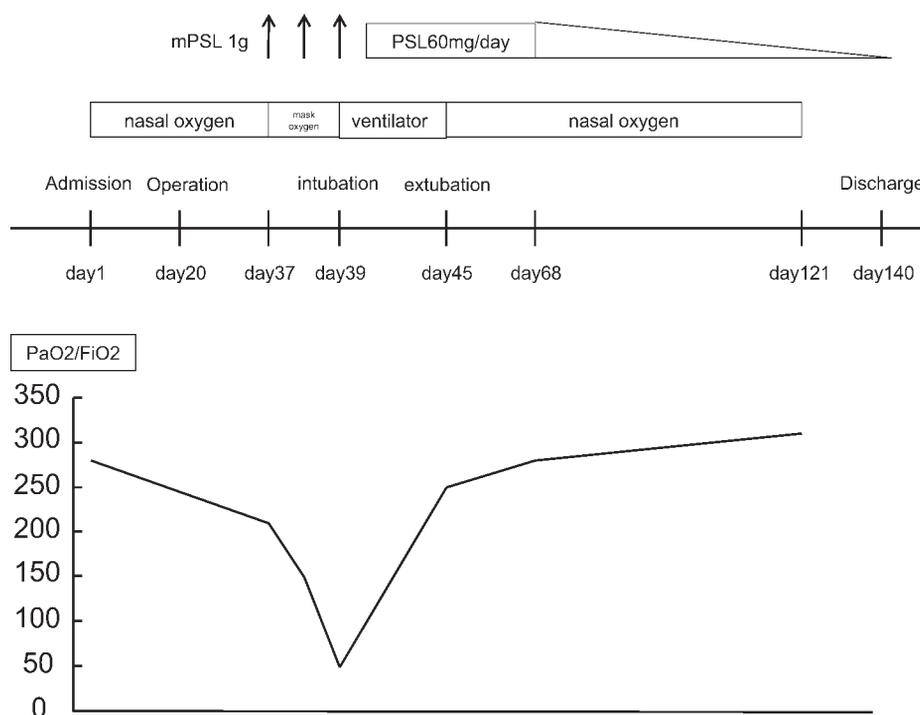


Fig. 2C Clinical course of Case 2. Abbreviations: BS: bronchoscopy, mPSL: methylprednisolone sodium succinate, PSL: prednisolone

lation on day 45 after admission. Prednisolone (1 mg/kg) was administered orally as maintenance therapy and was then tapered over the next one week. Chest X-ray and HRCT showed an improvement of the ground-glass opacities. He was discharged on day 140 after admission.

### III Discussion

We herein describe two cases of acute exacerbation of pulmonary fibrosis in CPFE. CPFE is a unique disorder described in several case series<sup>1)–5)</sup>. Almost all of the patients were male and heavy smokers. CPFE is characterized by subnormal spirometry (mild airflow limitations and mild lung hyperinflation), severe impairment of gas exchange and desaturation during exercise. The chest HRCT shows the coexistence of emphysema with an upper lung field predominance and diffuse parenchymal lung disease with significant pulmonary fibrosis with lower lung field predominance. We previously reported that twenty-two of a series of 47 CPFE patients (46.8 %) had lung cancer, and the prevalence of lung cancer may be higher in CPFE patients than in COPD and IPF patients<sup>3)8)</sup>. CPFE has therefore been suggested to possibly be an important risk factor for lung cancer.

Tobacco smoking is best known for causing not only pulmonary emphysema, but also idiopathic pulmonary fibrosis<sup>11)–13)</sup>. While the exact pathogenesis of CPFE is unknown, tobacco smoking is thought to be the major risk factor for the development of CPFE, as well as COPD<sup>2)</sup>. In addition, CPFE has been highlighted as a smoking-related interstitial lung disease (SRILD)<sup>9)</sup>. The SRILDs include DIP, respiratory bronchiolitis-related interstitial lung disease (RB-ILD), pulmonary Langerhans' cell histiocytosis (LCH)<sup>14)</sup> and IPF<sup>13)</sup>. Pathological findings of diffuse interstitial lung disease in CPFE have been reported to be heterogeneous, such as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP) or organizing pneumonia<sup>1)–4)</sup>, while UIP is the most common pathological finding<sup>2)</sup>. While the reason for the heterogeneous

pathology present in CPFE and the exact pathogenesis of CPFE are unknown, CPFE is considered to be included as a SRILD.

The present cases suggest that an acute exacerbation may occur in CPFE, and that lung surgery for lung cancer is able to trigger an exacerbation of parenchymal lung disease, as well as in the other idiopathic interstitial pneumonias, including IPF. An acute exacerbation of idiopathic interstitial pneumonia is occasionally observed following lung surgery, and it has a high mortality over a short course in IPF<sup>15)</sup>. The triggers of acute exacerbation following lung surgery are considered to be prolonged ventilation at a large tidal volume with oxygen supplementation at a high concentration<sup>16)</sup>. A high concentration of supplemental oxygen leads to the production of endogenous oxygen radicals from cells such as inflammatory cells, and the oxygen radicals could inactivate various enzymes within the alveolar epithelial and capillary endothelial cells to damage not only the cellular membranes, but also the genes within the nuclei<sup>17)</sup>. Therefore, lung-protected mechanical ventilation under appropriate anesthesia is definitely required<sup>16)</sup>. Case 1 and Case 2 were diagnosed as having an acute exacerbation of pulmonary fibrosis in CPFE 50 days and 18 days after lung surgery, respectively. There was thus a difference in the duration of developing acute exacerbation. However, Case 1 had complained of increased dry cough without fever increasing since 14 days before admission, although he had not visited the hospital until admission. There was a possibility that acute exacerbation had already developed 14 days before admission, that is, 36 days after lung surgery in Case 1. There was no cause which could have produced the acute exacerbation other than lung surgery, such as infection or receiving drugs which could induce lung injury.

Usui et al.<sup>8)</sup> retrospectively reviewed the data for 1143 patients with lung cancer. CPFE, emphysema and fibrosis were identified in 8.9 %, 35.3 % and 1.3 % of patients with lung cancer, respectively. The median overall survival of CPFE patients was

significantly lower than that of normal patients or that of patients with emphysema alone. It is of interest that 76 % of lung cancers in patients with CPFE were diagnosed at an advanced stage. In addition, fatal severe acute lung injury occurred more frequently (19.8 %) in CPFE patients, irrespective of the treatment modality. In particular, postoperative lung injury occurred in nine of 33 patients with CPFE (27.3 %). Therefore, the presence of CPFE may result in a higher risk for postoperative lung injury, as well as the presence of interstitial lung disease. Therefore, strict observation may be needed following lung surgery.

When patients with CPFE are complicated by lung cancer, this may have a profound influence on their prognosis because of the poor operability and difficulties in administering chemotherapy. Occasionally, it may be difficult to find a tumor super-

imposed on a background of reticular opacities and honeycombing on chest radiograph or HRCT. Therefore, strict follow-up is required for these patients, and HRCT plays an important role in evaluating the occurrence of lung cancer in the early stage.

In summary, CPFE is considered to be one variant of smoking-related interstitial lung disease. An acute exacerbation may occur in CPFE, as well as in the other interstitial pneumonias. A strict follow-up is therefore required, because the prevalence of lung cancer may be higher, and acute exacerbation may occur following lung surgery. HRCT plays an important role in evaluating the occurrence of lung cancer at an early stage and for determining whether there is an acute exacerbation of pulmonary fibrosis in CPFE patients.

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