Idiopathic Pulmonary Fibrosis
—Acute exacerbation and lung cancer associated with pulmonary fibrosis—

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Abstract: The 5-year survival rate for idiopathic pulmonary fibrosis (IPF) is 30–50%, and the major causes of death are respiratory failure, cardiac failure, lung cancer, infection, and pulmonary thromboembolism. Clinical conditions of acute exacerbation of IPF, which was first reported from Japan and is also now being recognized in Europe and the US, include deterioration of dyspnea, exacerbation in image findings, a decrease in the partial pressure of oxygen in arterial blood, and elevation in the levels of KL-6 and SP-D, in a short period of time. Its clinical characteristics are those of the ARDS and its pathological findings are those of diffuse alveolar damage (DAD). Infection, an inappropriate tapering of the dose of steroids, certain medications, invasive tests, and surgical operations are among the inducing factors. Combination therapy by steroid pulse and cyclosporin-A has been attracting attention. The complication of lung cancer in IPF, which is frequently observed in patients aged 70 or older, is one of the prognostic factors, and the knowledge of IPF is indispensable to treat this. Expression and mutations of various genes during the repairing process of damaged DNA is presumed to be involved in the development of this lung cancer. Special attention is required for the treatment because surgery, administration of anti-cancer drugs, and radiation can possibly induce the acute exacerbation.

Key words: Idiopathic pulmonary fibrosis; Acute exacerbation; Cyclosporin-A; Complication of lung cancer; Microsatellite

Introduction

Idiopathic pulmonary fibrosis (IPF) is a slowly progressive disease with poor prognosis, and the mean survival time and 5-year survival rate have been reported to be 2–4 years and 30–50%, respectively. If the total survival rate is considered, the 5-year survival rate appears

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higher since there are patients who survive longer, while the 5-year survival rate of new patients was 30%. As the cause of death in IPF patients, respiratory failure is most frequent at roughly 40%, followed by cardiac failure, lung cancer, infection, and pulmonary thromboembolism.

**Acute Exacerbation of IPF**

**1. Pathology and diagnosis**

Within a short period of 1 month, bilateral ground glass attenuation/infiltrative opacification develops or is accelerated on a chest radiograph and respiratory failure ensues and worsens. Exacerbation of respiratory failure due to cardiac failure or infection should be excluded for this definition. In Europe and in the USA, the acute worsening of respiratory failure was considered to be the natural history of IPF, and was not recognized as acute exacerbation. A recent review of the new IPF guidelines from the American Thoracic Society (ATS) showed that the term acute exacerbation was included, suggesting the possibility of increasing recognition of the proposal from Japan. In Japan, acute exacerbation has long been recognized as an important disease process related to prognosis for survival in the clinical course of IPF, and the Research Committee on Interstitial Lung Diseases of the Ministry of Health and Welfare has focused on the pathogenesis of IPF and the development of new therapeutic methods to treat this condition.

The pathogenesis of acute exacerbation of IPF where respiratory failure worsens within a short period of time and is refractory to therapy with a high mortality rate, has been investigated from various aspects to reveal its clinical profile. According to the definition (Table 1) of the Research Committee on Diffuse Lung Diseases of the Ministry of Health and Welfare, the diagnosis of “acute exacerbation” can be made when all of the following signs are observed within 1 month of the clinical course: (1) deterioration of dyspnea, (2) bilateral ground glass attenuation/infiltrative opacification appears or becomes more pronounced on a chest radiograph, (3) a significant decrease in partial pressure of oxygen in arterial blood. Definitive pulmonary infection and cardiac failure should be excluded from the definition. To date, the increase in CRP (C-reactive protein) and LDH have been considered related findings, but recently KL-6, SP-D, and SP-A have been used as markers more specific to interstitial pulmonary diseases. These markers might be used in the future instead of LDH as related findings.

KL-6, a kind of free mucin, is a large molecular glycoprotein classified in MUC1, and is a marker which reflects the alveolar damage that occurs as a result of inflammation, rather than inflammation itself. SP-D and SP-A are surfactant proteins and are produced by the type II alveolar epithelium. They have been considered markers which reflect alveolar damage.

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**Table 1  Acute Exacerbation of Idiopathic Pulmonary Fibrosis (definition)**

"Acute Exacerbation" can be diagnosed when deterioration of dyspnea, bilateral ground glass attenuation/opacification appear or become more pronounced on a chest radiograph, and a significant decrease in partial pressure of oxygen in arterial blood are observed within 1 month of clinical course of idiopathic pulmonary fibrosis. Obvious lung infection and cardiac failure are excluded.

Related findings:

1. CRP or LDH often increases.
2. Both the extent and distribution of the ground glass attenuation/opacification can be elucidated by chest CT.

(Cited from the Annual Report for Fiscal 1994 by the Research Committee on Diffuse Lung Diseases, the Ministry of Health and Welfare, 1995; 9–11)
Acute exacerbation is the acute lung injury superimposed on pulmonary fibrosis which includes advanced honeycomb lung. The histologic findings are characteristics of diffuse alveolar damage (DAD). DAD is an acute inflammation which is characterized by hyaline membrane formation and its exudative and proliferative phases (Fig. 2). The cause of IPF itself is unknown, and the pathogenesis of acute exacerbation has not been elucidated.

Prior to the onset of acute exacerbation, the lung might be preset to release various inflammatory mediators. Therefore, acute lung injury is induced when the following causes or factors are encountered.10,11

Acute exacerbation can be induced by a number of factors which include an inappropriate tapering of the dose of steroids, surgical lung biopsy (VATS, etc.), transbronchial lung biopsy (TBLB), bronchoalveolar lavage similar to KL-6. The definition includes appearance or deterioration of bilateral ground glass attenuation/infiltrative opacification on a chest radiograph, while chest CT shows more detailed findings. Chest CT, especially high-resolution CT (HRCT) is now an essential diagnostic tool.

The extent and distribution of ground glass attenuation are seen clearly and accurately on chest CT. In particular, the results obtained by high-resolution CT (HRCT) are invaluable, and may predict the response to steroid therapy. HRCT of acute exacerbation which illustrates diffuse ground glass attenuation or infiltrative opacification is shown (Fig. 1).

In Europe and America, the concept of acute exacerbation is not well recognized, and it has been considered the progression of respiratory failure based upon the natural clinical course of IPF. Acute exacerbation has been considered the final stage of respiratory failure after a long clinical course, since it has been reported that there are no differences in the mean survival time between the patients who succumbed to acute exacerbation of IPF and those patients who succumbed after gradual progress of respiratory failure.7 However, there has been an increasing recognition of acute exacerbation in IPF as a characteristic disease process in Europe and USA4,8,9 through the vigorous exchange of information with Japan.

Table 2 Causes Which May Induce Acute Exacerbation of Idiopathic Pulmonary Fibrosis

| 1. Infection |
| 2. Inappropriate tapering of the dose of steroids |
| 3. Use of drugs which induce interstitial pneumonia |
| 4. Invasive examination/treatment (TBLB, BAL, surgery, etc.) |
| 5. Radiation exposure |
| 6. Pneumothorax |

Fig. 1 HRCT findings of acute exacerbation

Fig. 2 Diffuse alveolar damage
(BAL), the use of drugs which induce interstitial pneumonia (especially anticancer drugs), radiation exposure, general anesthesia, and surgical operation (Table 2). The respiratory failure aggravated obviously by infection is excluded, but the negation of the involvement of viral infection is difficult.

2. Treatment

Therapeutic options for the treatment of IPF have not been clearly established, and the data from prospective randomized clinical trials does not support the efficacy of the empirical use of steroids.\(^{12}\) In addition, the prognosis of acute exacerbation of IPF remains poor. Therefore, the conventional regimen for the treatment of acute exacerbation is methylprednisolone (Solu-Medrol\(^{10}\)) at a daily dose of 500–1,000 mg for 3 consecutive days with concomitant administration of an immunosuppressant such as cyclophosphamide (CPA) when the steroid pulse therapy is ineffective. Data from a multi-center trial of a total of 32 patients with acute exacerbation of IPF (selected according to the diagnostic criteria proposed by the Research Committee on Diffuse Lung Diseases, the MHW), showed no significant differences in the therapeutic modalities, including the dose of steroids, between the patients who succumbed to the disease and those who survived.\(^{10}\)

Since 1995, IPF patients in our department with acute exacerbation have been treated with cyclosporin-A (CYA), an immunosuppressant, from the early stage,\(^{13}\) in addition to the steroid pulse therapy, even though it is not covered by health insurance. Four out of 7 patients are still alive, and they did not experience any episodes of re-exacerbation during the tapering of the dose of steroids,\(^{14}\) while all patients who did not receive CYA eventually succumbed to the disease. Subsequently, in response to questionnaires, it was learnt that 15 (75%) of 20 patients who were administered CYA at a total of 10 hospitals through the whole country succumbed to acute exacerbation, and the efficacy of CYA was not clear. Timing of initial administration and the dose of CYA is different for each patient. Consequently, a multicenter prospective study was considered necessary to assess the efficacy of CYA, and the study is now being planned.

In all cases, treatment of acute exacerbation of IPF is difficult. In addition to the elucidation of the pathogenesis of this condition and its refractoriness to treatment are issues that remain to be resolved.

Complication of Lung Cancer

The frequency of complication by lung cancer in advanced IPF is high and the elucidation of the mechanism by which lung cancer develops in IPF is expected to lead to a better understanding of oncogenesis in general lung cancer. In IPF complicated by lung cancer, the diagnostic procedures and treatment choice for lung cancer are limited and have become the subject of clinical discussion.

1. Mechanism of complication of lung cancer

The frequency of complication of lung cancer in IPF is known to be in the range of 10–15% in general,\(^{15}\) although 30% or more have been reported in patients aged 70 years or older. Whether IPF itself is a risk factor for the development of lung cancer remains controversial, since complication of lung cancer in IPF was more frequently observed in smokers. At present, it is recognized that IPF is an independent risk factor for the development of lung cancer.\(^{15}\)

The molecular mechanism of the development of lung cancer in IPF is unclear. Chronic DNA damage occurs in IPF and the enhanced expression or mutation of various genes may take place during repair. For example, in the bronchial epithelium or pulmonary alveolar epithelium, particularly at the severe metaplastic loci of an IPF patient, expression of p53, a cancer-suppresser gene, or p21, a cell cycle regulator, has been reported.\(^{16}\) These expressions might be inhibiting oncogenesis during
the repair of DNA leading to normal repair. Highly frequent alterations of p53 protein as a result of enhanced expression of the p53 gene are well known in IPF.\textsuperscript{17} Furthermore, the serum anti-p53 autoantibody directed toward accumulated p53 altered protein has been detected in IPF.\textsuperscript{18}

In general, the inhibition of cancer-suppressor genes is considered an important step in oncogenesis. A microsatellite marker, a polymorphism marker scattered in the genome, has been effectively used in investigation/identification of unknown cancer-suppressor genes. The locus amplified by polymerase chain reaction (PCR), which is a method to amplify a specific gene locus and to make it detectable by using the microsatellite marker, is highly polymorphic and heterozygous. The loss of one arm of a chromosome containing this locus is expressed as a loss of heterozygosity (LOH). When the microsatellite locus for analysis in non-cancerous tissue contains cancer-suppressor genes, existence of LOH indicates that this non-cancerous tissue is in the pre-cancerous stage.

The author and colleagues microscopically dissected the metaplastic epithelium of IPF patients complicated with lung cancer and evaluated LOH using the microsatellite marker in the short arm of the 3rd chromosome (3p), which is implicated to contain cancer-suppressor genes, to detect LOH frequently.\textsuperscript{19} In addition, it has been reported that the results of the sputum of IPF patients analyzed using the microsatellite markers at 10 loci scattered in the 8th, 9th and 17th chromosomes showed LOH at least at one locus of the chromosomes in approximately 40% of the patients.\textsuperscript{20} Instability of chromosome replication in cancer cells was observed in the microsatellite locus as the difference in the length of repeated sequences, and is known as microsatellite instability. In the analysis of the sputum of IPF patients, it is reported that approximately 20% of the patients showed microsatellite instability in at least one area.

Therefore, the tendency for an IPF patient to develop lung cancer might be explained by gene abnormalities which occur during the process of the repair of chronic DNA damage.

2. Treatment of lung cancer associated with IPF

If an IPF patient has lung cancer as a complication, conventional options of treatment such as surgery, radiation treatment, or chemotherapy are considered. However, as mentioned above, it should be noted that any of these treatments may induce acute exacerbation. Although the frequency of acute exacerbation attributed to surgery is reported to be at a 10% level,\textsuperscript{21} oxygen at high concentration, high tidal volume, and anesthesia, in addition to surgical invasion, may also induce the exacerbation.

On the other hand, since ventilation is maintained by one lung with a respirator during surgery, tissue damage due to ischemia-reperfusion may happen when sudden bilateral ventilation of the lungs is introduced immediately after completion of surgery. Furthermore, an IPF patient with lung cancer might not be a candidate for surgical operation due to decreased pulmonary functions. Radiation treatment is the therapy which might induce acute exacerbation with the highest frequency, and its application is very limited.\textsuperscript{23,24} In general, as compared to radiation treatment, chemotherapy has been considered less likely to induce acute exacerbation of IPF. However, drugs which may cause drug-induced interstitial pneumonia should not be administered. It is necessary to note that new anti-cancer drugs, which recently have been frequently used, should be carefully administered to patients having interstitial pneumonia or pulmonary fibrosis as an underlying disease [ex. gemcitabine (Gemzar\textsuperscript{®}) and irinotecan (Topotecin\textsuperscript{®}) are contraindicated, and vinorelbine (Navelbine\textsuperscript{®}), docetaxel (Taxotere\textsuperscript{®}), and paclitaxel (Taxol\textsuperscript{®}) require careful monitoring during administration]. Also, it should be noted that administration of
steroid pulse therapy concomitantly with anti-cancer drugs corresponds to the inappropriate tapering of the dose of a steroid, and is a risk factor of acute exacerbation.

The above is an overview of acute exacerbation and lung cancer associated with IPF referring to prognosis for survival of a patient with IPF (idiopathic pulmonary fibrosis). The pathogenesis and treatment of this condition have not yet been established. Future development of research in this area is expected.

REFERENCES


