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Acute exacerbation (AEx) of idiopathic pulmonary fibrosis (IPF) is now a well-known phenomenon during the course of IPF and has a critical impact on the natural course and prognosis. However, the real nature of AEx and the exact pathobiology are not yet clear; therefore the incidence, diagnostic criteria, or treatment methods have not been clearly defined. Recently, the working group on this area proposed a new consensus definition and diagnostic criteria of AEx-IPF based on the available evidences published after the first “Consensus Definition for AE-IPF” proposed by Collard et al. in 2007. This new report is the most up-to-date and extensive review, which was performed by 21 pulmonologists, 3 radiologists, and 2 pathologists; more detailed information is available there.

Although a diffuse alveolar damage (DAD) pattern superimposed on usual interstitial pneumonia (UIP) was recognized among the pathologists many years ago and Kondoh et al. first reported three cases of AE-IPF in 1993, not much interest was paid to AEx-IPF until Martinez and colleagues found an apparently acute and rapid progression of lung disease in almost half of the patients who died of an IPF-related cause among the placebo group of the randomized clinical trial of interferon-γ in 2005. In 2006, Kim et al. reported the clinical, radiologic, and pathologic features of 11 cases of AEx-IPF among 147 patients with IPF, and several other studies reported the significance of AEx-IPF. These studies provoked interest and resulted in the first consensus definition and diagnostic criteria, proposed by an expert committee sponsored by the IPF Clinical Research Network and the National Heart Lung and Blood Institute (NHLBI), in an attempt to standardize future research. Because AEx-IPF has been thought of as an idiopathic acute worsening of respiratory condition in patients with IPF, having a different pathobiology and different outcomes from the worsening caused by known causes, exclusion of other known causes such as infection, which requires an invasive procedure such as bronchoalveolar lavage (BAL), was thought to be the most important step for the diagnosis of AEx-IPF. Therefore the committee defined AEx-IPF as an acute, clinically significant deterioration of unidentifiable cause and proposed five diagnostic criteria including (1) the presence of IPF, (2) a clinical worsening of less than 30 days’ duration, (3) the presence of new radiologic abnormality on high-resolution computed tomography (HRCT) (i.e., bilateral ground-glass opacification/consolidation), (4) no evidence of pulmonary infection by endotracheal aspirate or BAL, and (5) the exclusion of alternative etiologies (e.g., heart failure, pulmonary embolism, or identifiable cause of acute lung injury). Only when all five requirements are satisfied is the diagnosis definite AEx-IPF, and if not, the diagnosis is suspected AEx-IPF. However, in clinical practice, such an invasive procedure is not feasible in many critically ill patients. Therefore, it is very important to clarify the exact nature of AEx-IPF for the diagnosis and the treatment.
The key question is: “What is the real nature-pathobiology of AEx-IPF? Is it an acceleration of the original disease process or other clinically occult, unrecognized secondary conditions such as infection or aspiration?”

**ACUTE EXACERBATION OF IDIOPATHIC PULMONARY FIBROSIS: UNRECOGNIZED OTHER CONDITIONS?**

**An Occult Infection?**

Because of the similarity in clinical features between infection and AEx-IPF and also the potentially increased susceptibility to infection in these patients secondary to therapy or underlying disease, it is difficult to exclude the possibility of infection at the time of diagnosis of AEx-IPF; it may be unrecognized viral infection. Furthermore, epidemiologic studies showed that AEx-IPF is more frequent in patients taking immunosuppressive drugs and in winter and spring seasons, when respiratory viral infection is common. To confirm this hypothesis, Wooten et al. studied the presence of virus in prospectively collected BAL fluid of 43 AEx-IPF patients using multiplex polymerase chain reaction, panviral microarray, and high-throughput cDNA sequencing and found respiratory viruses in only six patients (two rhinoviruses and one each of parainfluenza, coronavirus, herpes simplex, and Epstein-Barr virus) and torque teno virus in 12 patients, but the significance of torque teno virus was not certain because it was detected in a similar percentage of the samples of an acute lung injury control group. Later, Bando et al. reported that it seemed to be unlikely that torque teno virus would be directly involved in the onset of AEx-IPF but it could reflect the immunosuppressive state of the host because of treatment. Several other studies also confirmed the low prevalence of infective organism in AEx-IPF. These results suggest that the majority of AEx-IPF is not infection, although there is still a possibility of viral triggering of acute lung injury and disappearance at the time of clinical presentation.

**Silent Aspiration of Gastric Contents?**

Because aspiration of gastric contents can cause acute lung injury, manifested by DAD on lung biopsy, occult aspiration of gastric contents has been proposed as one possible cause of AEx-IPF. Joyce Lee et al. measured the BAL pepsin level of 24 patients with AEx-IPF and 30 stable IPF controls and showed measurable BAL pepsin in most patients with stable IPF, suggesting that occult aspiration is common in IPF. Eight (33%) of the AEx-IPF patients had high BAL pepsin levels, suggesting that occult aspiration may play a role in some cases. Another study showed a significantly higher rate of gastroesophageal reflux and acute exacerbations in patients with asymmetric IPF, and most of the exacerbation occurred in the more affected side (right lung), the dependent side during sleep. A post hoc analysis of the placebo arms from three clinical trials showed that AEx-IPF occurred only in those subjects not on antacid therapy (proton pump inhibitor or H2 blocker), presumably because antacid therapy reduces the potential for microaspiration-related lung injury. Furthermore, among the 242 patients assigned to the placebo groups of the three trials, 124 patients taking antacid treatment at baseline had a smaller decrease in forced vital capacity (FVC) at 30 weeks, suggesting that antacid treatment could be beneficial in patients with IPF and abnormal acid gastroesophageal reflux seems to contribute to disease progression. However, recent post hoc analyses of the INPULSIS clinical trials showed that the incidence of AEx-IPF among the placebo group who were taking antacids at baseline was very high compared with other groups and FVC had declined in greater degree compared with the patients who received no antacid medication at baseline, suggesting that patients treated with antacid at baseline may actually do worse. The reason for this contradictory result is not certain; it may be due to the persistent acid gastroesophageal reflux after antacid therapy and/or the nonacid components present in the refluxate. These results suggest that although in some patients aspiration may trigger AEx-IPF, the majority of AEx-IPF cases are not caused by aspiration. The role of gastroesophageal reflux in AEx-IPF and IPF itself is not certain, and further prospective study to verify the efficacy of antacid is warranted.

Therefore, it is reasonable to think that most acute exacerbations of IPF are not clinically unrecognized secondary conditions, although those conditions may act as triggering factors.

**ACUTE EXACERBATION OF IDIOPATHIC PULMONARY FIBROSIS: AN ACCELERATION OF IDIOPATHIC PULMONARY FIBROSIS PROCESS?**

The next possibility is that AEx-IPF may be an acceleration of an underlying disease process, enhanced fibroproliferation. Although research is ongoing, the molecular mechanisms underlying AEx-IPF remain poorly understood. Activation of the immune system, disordered coagulation/fibrinolysis, and oxidative stress may all contribute to the pathophysiology of AEx-IPF. Because AEx-IPF is similar to acute respiratory
distress syndrome (ARDS) clinically, radiologically, and pathologically, the pathobiology may also be similar. To investigate this possibility, Collard et al. compared the biomarker profile of stable IPF, AEx-IPF, and ARDS. In ARDS, the levels of the receptor for advanced glycation end-products (RAGE), a marker of type I alveolar epithelial cell (AEC) injury/proliferation, proinflammatory cytokines, markers of endothelial dysfunction, activated coagulation, and inhibited fibrinolysis were all elevated, whereas the AEx-IPF group had lower levels of RAGE and higher levels of Krebs von Lungen-6 (KL-6) and surfactant protein-D (markers of type II AEC proliferation and/or injury), which was similar to stable IPF but in greater degree. The absence of a type I cell injury signature combined with an exuberant elevation of type II cell markers provides support for the hypothesis that AEx-IPF is predominantly a manifestation of the acceleration of an underlying disease process, rather than the result of a second, different kind of injury.

This hypothesis was also supported by a gene expression study by Konishi et al. They found that the global gene expression patterns of AEx-IPF were almost identical to those of stable IPF. AEx-IPF exhibited a fibrosis signature that was identical to stable IPF, no dramatic shift indicating a new process, and no dramatic shift in cellular phenotype. Only 579 genes related to stress response were significantly differentially expressed. There was no indication of any infectious etiology or overwhelming inflammatory response.

These results suggest that the basic pathologic process of AEx-IPF is the same as or similar to that of stable IPF, but more enhanced in degree.

Then what triggers the acute acceleration of IPF disease process?

**TRIGGERING FACTORS**

As discussed previously, infection or aspiration can be triggering factors, although they cannot be the main pathobiologic process of AEx-IPF itself.

1. Infection
2. Aspiration of gastric content
3. Surgery and other procedures

There are many reports about the development of AEx-IPF after the surgery, not only lung resection, but also extrathoracic, and even surgical lung biopsy, or BAL. The mechanism is not certain, but a surgical procedure or mechanical stress by high tidal volume, high oxygen flow, or intraoperative fluid imbalance may trigger AEx-IPF.

4. Air pollution

The relationship between ambient air pollution and exacerbation of respiratory diseases such as asthma and chronic obstructive pulmonary disease is well established, and AEx-IPF may be caused by air pollution. Johansen et al. studied the relationship between the development of AEx-IPF and exposure to air pollution using the data collected by a fixed telemonitoring system situated throughout Korea since 2000 in 505 patients with IPF. They found a significant relationship between AEx-IPF and exposure to ozone and NO₂ during 42 days prior to AE-IPF but not to other pollutants, suggesting that increased exposure to ozone and NO₂ contributes to the development of AEx in some patients.

5. Drugs

Many biologic (etanercept and infliximab) and nonbiologic (ambrisentan) agents, immunomodulatory agents (interferon α/β, everolimus, and leflunomide), and antineoplastic therapies can provoke interstitial pneumonia and may mimic AEx in the patients with preexisting IPF. Minegishi and colleagues reported that the incidence of acute respiratory deterioration related to anticancer treatment was 22.7% among 120 patients with lung cancer accompanied by idiopathic interstitial pneumonia.

Therefore, it seems that AEx-IPF may be the acute acceleration of an underlying fibroproliferative process triggered by these extrinsic or unknown insults in patients with IPF, who already have a predisposition of exaggerated fibrosis secondary to abnormal wound healing. Several studies reported increased incidence of AEx-IPF and/or higher mortality in patients with IPF after lung cancer surgery or major thoracic surgery compared with the patients without IPF, which suggests the increased susceptibility of IPF patients to extrinsic insults. Voltolini et al. reported that patients with interstitial lung disease (ILD), mostly IPF, had a higher incidence of postoperative ARDS (presumable AEx-IPF) compared with patients without ILD (13% vs. 1.8%, P < .01).

**RISK FACTORS**

Most of the studies showed that AEx-IPF is more common in patients with advanced disease, low FVC, low diffusing capacity for carbon monoxide, low 6-min walk distance, pulmonary hypertension, poor baseline oxygenation, increased dyspnea score, and recent decline in FVC. Younger age, comorbid coronary artery disease, higher body mass index, a history of AEx, and elevated serum level of KL-6 at baseline have been reported to be associated with increased risk for AEx-IPF.
Biomarkers
In addition to serum KL-6, neutrophil elastase, and lactate dehydrogenase levels, which have been suggested as markers of AEx-IPF, there are several new possible biomarkers. The levels of α-defensins, circulating fibrocytes, high-mobility group box-1, monocyte chemotactic protein-1, soluble ST2 protein, annexin-1, markers of oxidative stress, heat shock protein 47, heat shock protein 70, galectin-3, a mediator of fibrosis induced by TGF-β, and intercellular adhesion molecule-1 were reported to be elevated in the peripheral blood of patients with AEx-IPF. Tachibana et al. demonstrated in 19 patients with AEx-IPF that increased serum IL-7, an inhibitor of transforming growth factor-β production and fibroblast signaling, was associated with better prognosis in AEx-IPF.

New Definition for Acute Respiratory Deterioration in Idiopathic Pulmonary Fibrosis
The consensus opinion of the international working group was that the definition should include any acute respiratory event characterized by new bilateral ground-glass opacification/consolidation not fully explained by cardiac failure or fluid overload, because there is little clinical or biologic support for distinguishing idiopathic from nonidiopathic respiratory events. However, cardiogenic pulmonary edema is believed to have a distinct pathobiology and favorable prognosis compared with other causes of acute respiratory deterioration with bilateral radiologic involvement, which parallels the Berlin criteria for ARDS and excludes isolated congestive heart failure. Therefore the revised definition of AEx of IPF is: an acute, clinically significant, respiratory deterioration characterized by evidence of new, widespread alveolar abnormality in patients with IPF. It is more inclusive and results in diagnostic criteria that are more feasible for clinicians and clinical trialists, who have had difficulty in the requirement for invasive microbiologic evaluation of the 2007 criteria.

New Diagnostic Criteria
There are two changes from the previous 2007 consensus diagnostic criteria.
1. Removing “idiopathic” from the diagnostic criteria of acute exacerbation
   Because of the changing definition of AEx-IPF, the exclusion of infection or other potential triggers is no longer required. However, the committee stated that this change should not discount the clinical relevance of identifying infection when present, because its treatment may be important to the overall management of the patient. In addition, they suggested that future studies are needed to test whether aggressive investigation (e.g., BAL, bronchoscopic cryobiopsy, surgical lung biopsy) of patients with AEx-IPF improves outcomes.
2. Changing the time interval from 30 days to “typically less than 1 month”
   There was a majority opinion that the 30-day time period was arbitrary and should be made more flexible to allow for cases that fall outside the time window by a few days to weeks. The phrase “typically less than 1 month” seems to retain precision but allow for the inclusion of exceptions that physicians feel clinically represent acute exacerbations. A more flexible time interval than this may lead to heterogeneity among clinical trial endpoint definitions for AEx and that this could complicate comparisons between trials.
   The new consensus report emphasized the importance of HRCT in the diagnosis of AEx-IPF and stated that HRCT of the chest should be obtained in all patients in whom it can be safely performed. Transbronchial biopsy is of limited utility, and surgical lung biopsy should generally be avoided because of its high morbidity in the nonelective setting.
   Although the new consensus criteria excluded the workup for infection for the diagnosis, it is still important to exclude the possibility of the presence of active infection, not as a triggering factor, because the treatment is different. Considering that corticosteroid is still widely used for AEx-IPF and also one therapeutic candidate for future clinical trial, misdiagnosis of infection as AEx-IPF can be a big mistake. Furthermore, clinical and radiologic features of infection, especially viral infection, are similar to AEx-IPF, and actually Song et al. reported that almost half of the patients with acute respiratory deterioration among those with IPF had infection. Recently Moua et al. also reported the high frequency of infection (20%) among the patients admitted because of acute respiratory worsening.

Management
Supportive care remains the mainstay of treatment for AEx-IPF, focused on palliation of symptoms and correction of hypoxemia with supplemental oxygen. Because of high in-hospital mortality (90%) of the patients with respiratory failure, the international guidelines on the management of IPF made a weak recommendation against the use of mechanical ventilation in these patients, although it is “a value-laden decision that is best made by the patient, clinician, and family ahead of time” based on a firm understanding of the patient’s goals of care.
The guidelines also give a weak recommendation of corticosteroids for the majority of patients with AEx-IPF, based on a high value on anecdotal reports of benefit and the high mortality associated with AEx-IPF. There are some data suggesting that response to high-dose corticosteroid treatment may depend on the type of HRCT lesion, with better responses achieved in those with a peripheral pattern and the organizing pneumonia pattern of pathology compared with the DAD pattern. Because of the difficulty in exclusion of infection, especially in the early phase, broad-spectrum antibiotics are commonly used.

Kubo et al. reported better survival in the anticoagulation group, mostly due to reduced mortality associated with AEx-IPF, suggesting the efficacy of anticoagulation in the treatment of AEx-IPF; however, because of the small sample size and methodologic limitations of this study, the benefit of anticoagulation therapy is controversial and a recent clinical trial of anticoagulation in patients with IPF showed, actually, increased mortality in the warfarin-treated group.

There are several innovative treatments for AEx-IPF mostly tried in Japan, including polymixin B–immobilized fiber column (PMX) hemoperfusion and tacrolimus, intravenous thrombomodulin, intravenous immunoglobulin, rituximab combined with plasma exchange, and interferon-γ, sildenafil, and ambrisentan, “triple therapy” (combination of prednisone, azathioprine, and acetylcysteine), and warfarin actually increased the risk of IPF.

**PROGNOSIS**

AEx-IPF is certainly a leading cause of hospitalization and death among patients with IPF, and up to 46% of deaths in IPF are preceded by an AEx. In a retrospective review of 461 patients with IPF, 96 (21%) patients were hospitalized for AEx-IPF over a median follow-up period of 22.9 months. Patients with an AEx-IPF had a lower median survival time than those who had not suffered an AEx-IPF (15.5 vs. 60.6 months from the diagnosis of IPF) and lower 5-year survival rates (18.4% vs. 50.0%). Collard et al. reported that patients with both definite AEx-IPF and suspected AEx-IPF have a similar prognosis.

**PREVENTION**

Clinical trials of several investigational treatments for IPF suggested that chronic treatment of IPF might reduce the incidence of AEx-IPF. A trial of sildenafil, a phosphodiesterase-5 inhibitor, showed a numerical reduction in AEx-IPF in patients given sildenafil versus placebo (3.4% vs. 7.6%), but the number of events was small and the difference was not statistically significant. A Phase II study of pirfenidone in Japanese patients with IPF was terminated early based on a higher frequency of AEx-IPF in the placebo group than in the pirfenidone group. However, in a Phase III trial in Japan, no significant differences were observed. The definitive Phase III clinical trials of pirfenidone did not report acute exacerbations as an endpoint.

Pirfenidone has been suggested to reduce the risk of AEx postoperatively, but these data are only observational and therefore are at high risk for confounding. All three placebo-controlled clinical trials of nintedanib included AEx as a key secondary endpoint. In a Phase II trial of nintedanib, time to first investigator-reported AEx was delayed in the nintedanib group. However, in Phase III trials, one trial demonstrated a significant reduction in the risk of acute exacerbations with nintedanib, but the other trial showed no significant difference. Pooled data demonstrated a 68% reduction in the risk of an adjudicated confirmed or suspected AEx with nintedanib therapy (5.7% on placebo vs. 1.9% on nintedanib, \( P = .01 \)). Pooled data and metaanalyses of data from the Phase II TOMORROW trial and two Phase III INPULSIS trials including 1231 patients (nintedanib \( n = 723 \), placebo \( n = 508 \)) showed the hazard ratio for time to first AEx was 0.53 (95% CI: 0.34, 0.83; \( P = .0047 \)) in favor of nintedanib. No other trial drugs (acyclovir, ceftriaxone monotherapy, bosentan, interferon-γ, sildenafil) showed impact on prevention of AEx-IPF, and ambrisentan, imatinib, “triple therapy” (combination of prednisone, azathioprine, and acetylcysteine), and warfarin actually increased the risk of IPF.

**CONCLUSION**

AEx-IPF is an important event exerting a critical impact on the prognosis of patients with IPF, but the real nature, etiology, pathobiology, and therapy are not yet clear. Many studies performed after the 2007 consensus report suggested that AEx-IPF may be an acute acceleration of an underlying fibroproliferative process triggered by various extrinsic or unknown insults in patients with IPF, who already have a predisposition to exaggerated fibrosis due to abnormal wound healing. Previously, it was defined as an idiopathic acute worsening of respiratory condition in patients with IPF, but recently an international working group proposed a new definition, which removes “idiopathic” and thus excludes the necessity of invasive procedures for the diagnosis, because there is little clinical or biologic support for distinguishing idiopathic from nonidiopathic respiratory events. It is hoped that this new definition and diagnostic criteria will improve the feasibility of future research to find effective treatment.
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