Acute Exacerbation of Idiopathic Pulmonary Fibrosis

İdiyopatik Pulmoner Fibrozisin Akut Alevlenmesi

Tomoo Kishaba

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common cause of chronic diffuse parenchymal disease of unknown cause. However, IPF patients sometimes develop acute exacerbation (AE), which is a life-threatening condition. The cause of AE of IPF remains unknown. The new criteria for AE of IPF have been proposed last year, wherein both idiopathic and triggered AE were proposed. Triggered AE includes infection, post-procedure and post-operation, drug toxicity, and aspiration. Therefore, detailed history taking is crucial. In this review, the definition, clinical symptoms, chest imaging, management, and prognosis for AE of IPF are described.

Keywords: Acute exacerbation, idiopathic pulmonary fibrosis, new criteria, idiopathic, triggered

ÖZ

İdiyopatik pulmoner fibrozis (IPF) nedeni bilinmeyen kronik diffüz parankimal akciğer hastalıklarının bir formudur. Ancak, IPF hastalarında bazen yaşamı tehdit eden bir durum olan akut alevlenme (AA) gelişir. Bu AA ve IPF'nin nedenleri henüz bilinmemektedir. IPF'nin akut alevlenmesi için yeni kriterler geçen yıl sunulmuştur. Bu yeni kriterlerde, hem idiyopatik hem de tetiklenen AA üzerinde durulmuştur. Tetiklenen AA enfeksiyon, post-prosedür, post-operasyon, ilaç toksisitesi ve aspirasyonu kapsamaktadır. Bu nedenle, detaylı öykü almak çok önemlidir. Bu derlemede, IPF'nin akut alevlenmesinin tanımı, klinik semptomları, göğüs görüntülemesi, yönetimi ve prognozu sunulmaktadır.

Anahtar Kelimeler: Akut alevlenme, idiyopatik pulmoner fibrozis, yeni kriterler, idiyopatik, tetiklenen

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic relentless interstitial lung disease of unknown cause [1, 2]. IPF patients have variable clinical courses, including chronic stable, progressive to acute exacerbation (AE) [3-5]. Among them, AE is a progressive and life-threatening circumstance. Therefore, a correct diagnosis of AE of IPF is important. The National Institutes of Health-sponsored IPF Clinical Trials Network (IPFnet) has published the criteria for AE of IPF based on clinical, imaging, and histological findings in 2007 [6]. The criteria consisted of progressive dyspnea within 30 days, the presence of new ground glass opacity (GGO) or consolidation on high-resolution computed tomography (HRCT) of the chest, and exclusion of alternative causes, such as infection, heart failure, and pulmonary embolism. The criteria contributed to the standardization of AE of IPF and less heterogeneity of clinical research for AE of IPF. However, broncho-alveolar lavage (BAL) was required for excluding causes, particularly infection in the 2007 guideline. Patients with AE of IPF usually exhibit severe distress. Therefore, invasive procedures, such as BAL, cannot be performed for all patients in daily practice. This issue is controversial, and there were no definite criteria for the diagnosis of IPF based on chest HRCT findings in 2007. Several articles have reported regarding HRCT findings and AE of IPF over 9 years [7-10]. Furthermore, the new IPF guideline was published in 2011 and 2015 [11, 12]. Based on the history, an International Working Group Report published the revised criteria for AE of IPF [13].

Definition

The purpose of this report was to provide a comprehensive update on AE of IPF, particularly the literature published since the 2007 IPF net perspective. In addition, this report provides the current knowledge in this field for physicians. The group proposed a new framework for AE of IPF for the feasibility of future research (Figure 1). Moreover, they revised the definition

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Table 1. Comparison between 2007 and 2016 criteria of AE of IPF

	IPF diagnosis	Course	HRCT findings	Exclusion
2007 guideline	Previous or concurrent diagnosis	Less than1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Exclusion of alternative etiologies, such as infection, heart failure, and pulmonary embolism; BAL is required
2016 guideline	Previous or concurrent diagnosis	Typically less than 1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Deterioration not fully explained by heart failure or fluid overload

AE: acute exacerbation; IPF: idiopathic pulmonary fibrosis; HRCT: high resolution computed tomography; GGO: ground-glass opacity; UIP: usual interstitial pneumonia; BAL: broncho-alveolar lavage

and diagnostic criteria for AE of IPF. Regarding framework, the clinical course was defined as typically <1 month duration, indicating that more broad criteria are practical. In this stage, extra-parenchymal causes, such as pneumothorax, pleural effusion, and pulmonary embolism, should be excluded. Chest radiograph or CT with contrast material is usually used to exclude the causes. As the next step, we seek new bilateral GGO or consolidation with chest HRCT. The important issue is that these abnormal shadows do not have a relationship with cardiac failure or fluid overload. The two conditions have favorable prognosis compared with AE.

This concept parallels the Berlin criteria for acute respiratory distress syndrome (ARDS) [14]. Both cardiac failure and fluid overload were excluded by history, physical findings, and medical chart. When these two steps were passed with the background of IPF patients, AE was diagnosed. Finally, AE was divided into two categories both triggered and idiopathic. The intention of this working group was to prove that these two categories have different pathobiology. Therefore, future validation in a multicenter study will be needed.

According to the new framework, the working project group revised the definition of AE to an acute, clinically significant, respiratory deterioration characterized by the evidence of a new widespread alveolar abnormality. In addition, they proposed revised diagnostic criteria comprising four items:

1) Previous or concurrent diagnosis of IPF
2) Acute worsening or development of dyspnea of typically <1 month duration
3) CT with new bilateral GGO and/or consolidation superimposed on a background pattern consistent with the usual interstitial pneumonia pattern
4) Deterioration not fully explained by cardiac failure or fluid overload

The previous and new criteria of AE are compared and provided in Table 1).

Clinical symptoms

The clinical course is of usually <1 month [14]. The most important symptom is exertional progressive dyspnea, and the change of dyspnea grade is remarkable. IPF patients sometimes develop AE within 1 week. Such cases have severe dyspnea even at rest. Reduced forced vital capacity (FVC), non-smoker, and elevation of Krebs von den Lungen-6 (KL-6) have been reported as candidate risk factors for AE [15-18]. Recently, Arai et al. [19] reported a diffuse HRCT pattern, lower serum IgG, and higher serum surfactant protein-D in AE diagnosis. Long-term oxygen therapy (LTOT) before AE and positive pressure ventilation (PPV) use for AE were significant poor prognostic factors [19].

Chest imaging

The latest IPF guideline stated that chest HRCT is a relatively important diagnostic tool for IPF [11]. Honeycombing, traction bronchiectasis, and reticulation are crucial findings of fibrosis. Also, these typical findings in lower lung field peripheral dominant raise a possibility of underlying IPF [20, 21]. For diagnosis of AE, we should find superimposed new bilateral GGO or consolidation. If patients have extra-pulmonary symptoms, such as high fever, abdominal pain, vomiting, and shaking chill, sepsis associated ARDS is an important differential diagnosis. Focal consolidation or GGO is associated with bacterial pneumonia. When a bilateral new shadow with reticulation is observed in the upper lung field dominant, heart failure or alveolar hemorrhage are the leading differential diseases. In terms of prediction of mortality based on imaging, Akira et al. [22] published three patterns of AE of IPF, which consists of diffuse, multifocal, and peripheral. The diffuse pattern showed worse prognosis compared to multifocal and peripheral patterns. In addition, Kishaba et al [23] reported two stagings based on clinical parameters and the extent of the new shadow. They showed that the extensive group had poorer prognosis compared with the limited group [23].

Management

Managing AE of IPF is challenging. The steroid pulse therapy is often used, and maintenance prednisolone therapy is used anecdotally. In the acute phase, high-dose prednisolone is maintained. Arai et al. [19] reported that high-dose prednisolone of ≥0.6 mg/kg was a significant prognostic factor for no-PPV patients. After starting prednisolone, cellular immunity decreased. Therefore, we should carefully monitor the emergence of opportunistic infection, such as bacterial pneumonia and cytomegalovirus infection. Neutrophil elastase inhibitor, such as sivelestat, is a possible drug and early introduction may be effective [24]. However, there is scarce evidence regarding sivelestat for AE of IPF. Therefore, future multicenter studies will be required. AE of IPF has a hypercoagulable state [25]. Therefore, recombinant human thrombomodulin (rhTM) is an attractive drug and several articles regarding the effectiveness for AE of IPF have been reported [26-28]. Contraindication of rhTM is hemoptysis and bleeding tendency. If patients with AE of IPF have no contraindication, early introduction of rhTM with steroid pulse therapy may be effective for some patients. Recently, nintedanib has been reported effective for mild AE of IPF [29]. The role of nintedanib for both acute and chronic phase of IPF is of interest.

Prognosis and prevention

Prognosis of AE of IPF is usually poor and median survival is from 3 months to <1 year [30-32]. Regarding the prevention of AE of IPF based on risk factors, nintedanib is a promising agent [33-35]. Furthermore, perioperative pirfenidone (PFD) have been reported to prevent AE of IPF in lung cancer patients [36, 37]. PFD has an anti-inflammatory effect. Therefore, it may prevent perioperative lung injury.

In conclusion, both early detection of IPF and risk stratification for AE prediction are crucial for the prevention of AE.

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