Acute exacerbation (AE) is the most severe complication of idiopathic pulmonary fibrosis (IPF). In 2016, the definition and diagnostic criteria for AE-IPF were updated by an international working group. The new definition includes any acute, clinically significant respiratory deterioration (both idiopathic and triggered events) characterized by evidence of new widespread alveolar abnormality in patients with IPF. There are no currently proven beneficial management strategies for idiopathic and triggered AE-IPF. This is the first report describing AE-IPF triggered by Aspergillus empyema, which was improved by a combination of corticosteroid, systemic antifungal therapy, local antifungal therapy, and additional pharmacological therapies. Future research may reveal optimal strategies for both idiopathic and triggered AE-IPF.

1. Introduction

Acute exacerbation (AE) is the most severe complication of idiopathic pulmonary fibrosis (IPF) [1–8]. In 2016, an international working group revised the definition and diagnostic criteria for AE-IPF [5]. In the new criteria, AE-IPF can be diagnosed from both idiopathic and triggered events resulting in worsening respiratory symptoms and widespread alveolar damage [4,5]. There are no currently proven beneficial management strategies for patients with idiopathic and triggered AE-IPF [5]. This is the first case report to show AE-IPF triggered by Aspergillus empyema, which was successfully treated with a combination of corticosteroid, systemic antifungal therapy, local antifungal therapy, and additional pharmacological therapies.

2. Case report

In July 2008, a 56-year-old man was referred to our hospital because of exertion dyspnea and abnormal chest X-ray findings indicating interstitial lung disease (ILD) in primary care. He was an ex-smoker (56 pack-years) and had no medical illness, no environmental exposure, and no family history. There were no extra-thoracic manifestations to pack-years) and had no medical illness, no environmental exposure, and no family history. There were no extra-thoracic manifestations indicating interstitial lung disease (ILD) in primary care. He was an ex-smoker (56 pack-years) and had no medical illness, no environmental exposure, and no family history. There were no extra-thoracic manifestations to pack-years) and had no medical illness, no environmental exposure, and no family history. There were no extra-thoracic manifestations to pack-years) and had no medical illness, no environmental exposure, and no family history.
positive for *Aspergillus fumigatus*. Serum *Aspergillus* galactomannan antigen test was negative, but serum *Aspergillus* precipitating antibody test was positive. With a diagnosis of *Aspergillus* empyema, treatment was switched to intravenous voriconazole (VRCZ). On day 47, while continuing systemic antifungal therapy, he experienced worsening of dyspnea. Laboratory examinations revealed a WBC count of 8900/mm³ (neutrophils: 72.8%) and CRP of 18.25 mg/dl. The levels of serum brain natriuretic peptide and procalcitonin were 9.8 (< 18.4) pg/ml and 0.148 (< 0.5) ng/ml, respectively. Arterial blood gas analysis showed PaO₂ of 61.0 Torr and PaCO₂ of 31.3 Torr on 2L/min of O₂ via a nasal cannula. A chest CT scan showed new bilateral widespread consolidation and ground-glass opacity superimposed on a background honeycomb pattern (Fig. 3). Considering these findings and the clinical course, he was diagnosed with AE-IPF triggered by *Aspergillus* empyema.

He was treated with a combination of corticosteroid (methylprednisolone 1mg/Kg/day followed by titration of prednisolone) and intravenous recombinant human soluble thrombomodulin (rhTM). Intravenous VRCZ and pirfenidone were continued. On day 61, a chest CT scan showed improvement in bilateral consolidation and ground-glass opacity, but new right bulla effusion and left pleural effusion. Chest tubes were inserted to the right bulla and left thoracic cavity. Both effusion cultures were positive for *Aspergillus fumigatus*. Systemic antifungal therapy was switched from intravenous VRCZ to intravenous liposomal amphotericin-B. Because of poor resolution, intrathoracic infusion of amphotericin-B (AMPB) was added (2mg/day with a gradual dose increase to 10mg/day from each chest tube). On day 95, cultures of the right bulla and left pleural effusions converted to negative. He was discharged 120 days after admission (Fig. 4).
3. Discussion

We have described a case of AE-IPF triggered by Aspergillus empyema. The new 2016 definition and diagnostic criteria for AE-IPF include any acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality. This revision resulted from difficulty in distinguishing idiopathic events from respiratory events triggered by known causes (infection, post-procedural/postoperative, drug toxicity, and aspiration) [5]. Nevertheless, identifying a trigger is still important as it may affect the overall management of the patient. Oda et al. [9] showed that Aspergillus infection was present in 12% of AE-IPF autopsy cases. Other reports also showed that Aspergillus infection was seen in patients with acute respiratory distress syndrome, which has the pathological characteristic of diffuse alveolar damage similar to AE-IPF [10,11]. In a previous report, it was hypothesized that inhalation of unknown mycotoxins, somatic antigens, or bioactive substances produced by Aspergillus may provoke an immunological response in the lung [12]. Although the direct relevance remains unknown, Aspergillus infection may be an important trigger in AE-IPF.

Aspergillus empyema is a rare clinical entity [13,14]. In the present case, risk factors such as diabetes, chemotherapy, and corticosteroid therapy other than interstitial pneumonia were not observed [15]. Kurosaki et al. [16] showed that pulmonary aspergillosis is a major complication of interstitial pneumonia and associated with poor outcomes. Destruction of airways and airspaces due to IPF might also have contributed to its persistence and eventual progression also in the present case.

Despite the high mortality rate, there is no established standard therapy for Aspergillus empyema [17]. Systemic antifungal therapy can facilitate a limited response, and previous reports have showed cases of Aspergillus empyema successfully treated with a combination of

Fig. 3. Chest CT scan at the diagnosis of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) on day 47. New bilateral widespread consolidation and ground-glass opacity superimposed on a background honeycomb pattern.

Fig. 4. Chest CT scan at discharge from the hospital. Improvement in bilateral consolidation, ground-glass opacity, and effusions.
systemic antifungal therapy, local antifungal therapy (intratracheal infusion of APHMB-B), and surgical approaches including drainage [15,18–20]. Our case was also poorly responsive to systemic antifungal therapy, and required drainage and local antifungal therapy. These aggressive treatment approaches may improve survival in cases of Aspergillus empyema.

There is as yet no proven pharmacological therapy for AE-IPF. The evidence-based IPF guidelines in 2011 recommended corticosteroid therapy for the majority of patients with AE-IPF (weak recommendation, very low-quality evidence) [21]. On the other hand, corticosteroid therapy is generally regarded as a risk factor in fungal infections [15], and Papiris et al. [22] showed that avoiding steroids in IPF patients may be effective in patients with AE-IPF (weak recommendation, very low-quality evidence) [21]. On the other hand, corticosteroid therapy is generally regarded as a risk factor in fungal infections [15], and Papiris et al. [22] showed that avoiding steroids in IPF patients may be effective in patients with AE-IPF (weak recommendation, very low-quality evidence) [21].

In conclusion, this is the first report describing AE-IPF triggered by Aspergillus empyema, which was improved with combination therapy. Whether triggered AE-IPF has a different clinical course or therapeutic response from idiopathic AE-IPF remains unknown. Further studies are needed to determine the optimal strategies for both idiopathic and triggered AE-IPF.

Financial disclosure and conflicts of interest

All of the authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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A. Suzuki et al. Respiratory Medicine Case Reports 23 (2018) 103–106