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Case report

Acute exacerbation of idiopathic pulmonary fibrosis triggered by *Aspergillus* empyema

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ABSTRACT

Acute exacerbation (AE) is a severe and life-threatening 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 suggest the presence of an underlying connective tissue disease. Based on the integration of clinical information, radiological findings, and histopathological findings from surgical lung biopsy, he was diagnosed with IPF. He demonstrated a gradual worsening of pulmonary function over 4 years (forced vital capacity [% pred.] 4.02L [108%] → 3.78L [102%]). In April 2012, he started treatment with pirfenidone, which resulted in the stability of pulmonary function.

In May 2014, he presented with a 1-month history of cough and dyspnea. Initial vital signs revealed a temperature of 37.0 °C, respiratory rate of 16 breaths per minute, and O_2 saturation of 93% on room air. Fine crackles were heard in the bilateral lung fields. Laboratory examinations revealed a white blood cell (WBC) count of 8800/mm^3 (neutrophils: 69.5%) and C-reactive protein (CRP) of 7.89 mg/dl. A computed tomographic (CT) scan of the chest showed consolidation of the left lower lobe superimposed on a background honeycomb pattern (Fig. 1). He was initially diagnosed with bacterial pneumonia and was admitted for antimicrobial therapy (ceftriaxone and azithromycin). No significant bacteria were detected in sputum smear and culture test. On day 22, he developed left-sided chest pain and worsening dyspnea. A chest CT scan showed remaining consolidation in the left lower lobe, pleural effusion and pneumothorax on the left side (Fig. 2). A chest tube was inserted into the left thoracic cavity, and his symptoms improved. Pleural effusion culture was

Abbreviations: AE, acute exacerbation; AMPH-B, amphotericin-B; CRP, C-reactive protein; CT, computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; rhTM, recombinant human soluble thrombomodulin; VRCZ, voriconazole; WBC, white blood cell

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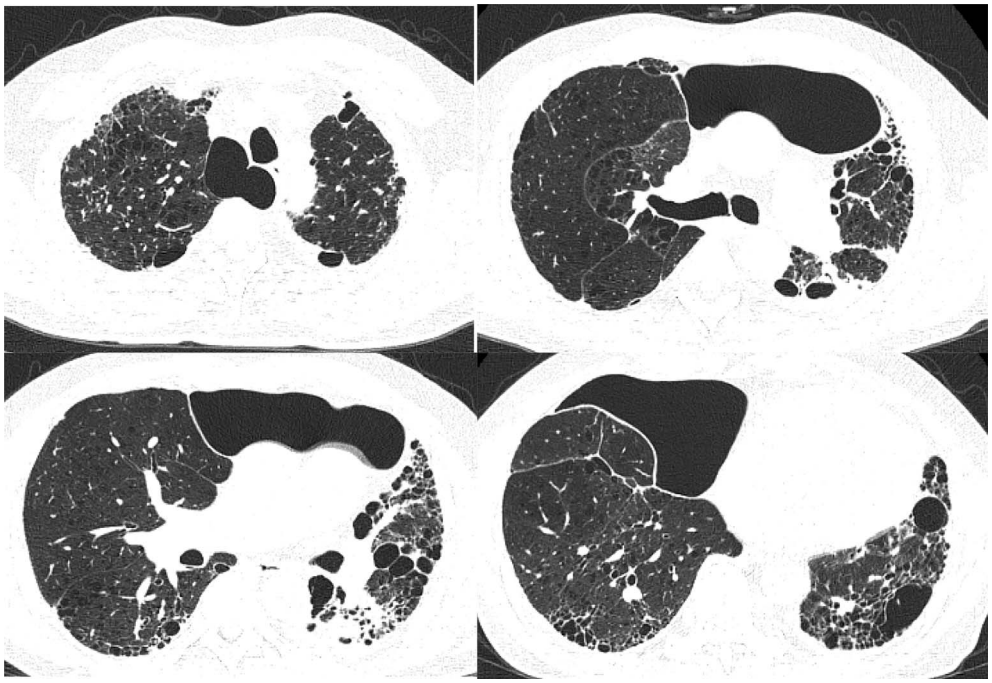

Fig. 1. Chest computed tomographic (CT) scan on admission Consolidation superimposed on a background honeycomb pattern in the left lower lobe.

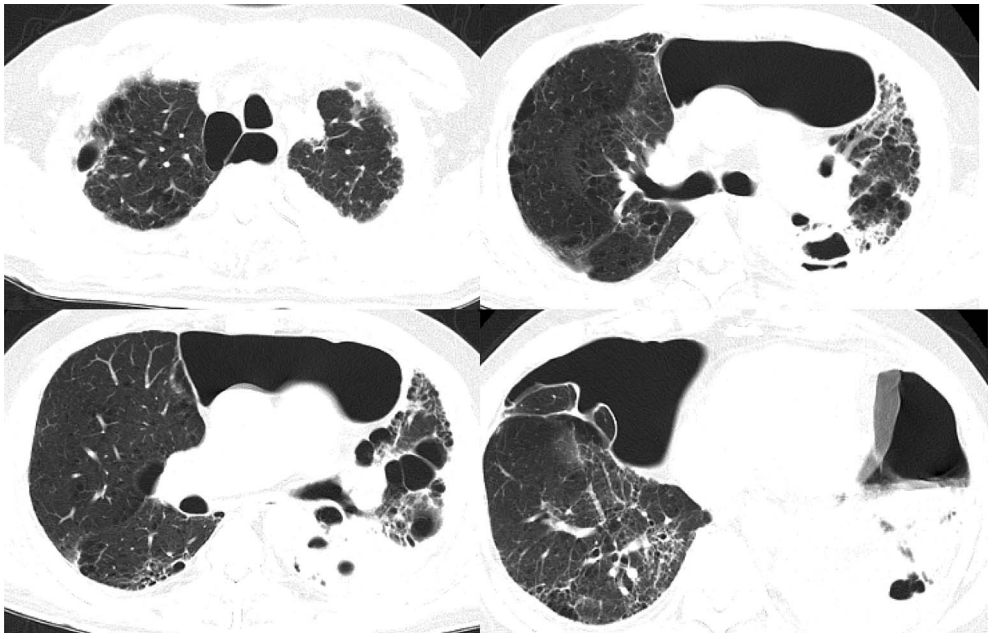

Fig. 2. Chest CT scan at the diagnosis of *Aspergillus* empyema and pneumothorax on day 22 Remaining consolidation in the left lower lobe and left-sided pleural effusion and pneumothorax.

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/mm^3 (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 PaO_2 of 61.0 Torr and $PaCO_2$ of 31.3 Torr on 2L/min of O_2 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 (AMPH-B) was added (2mg/day with a gradual dose increase to 10mg/day from each chest tubes). On day 95, cultures of the right bulla and left pleural effusions converted to negative. He was discharged 120 days after admission (Fig. 4).

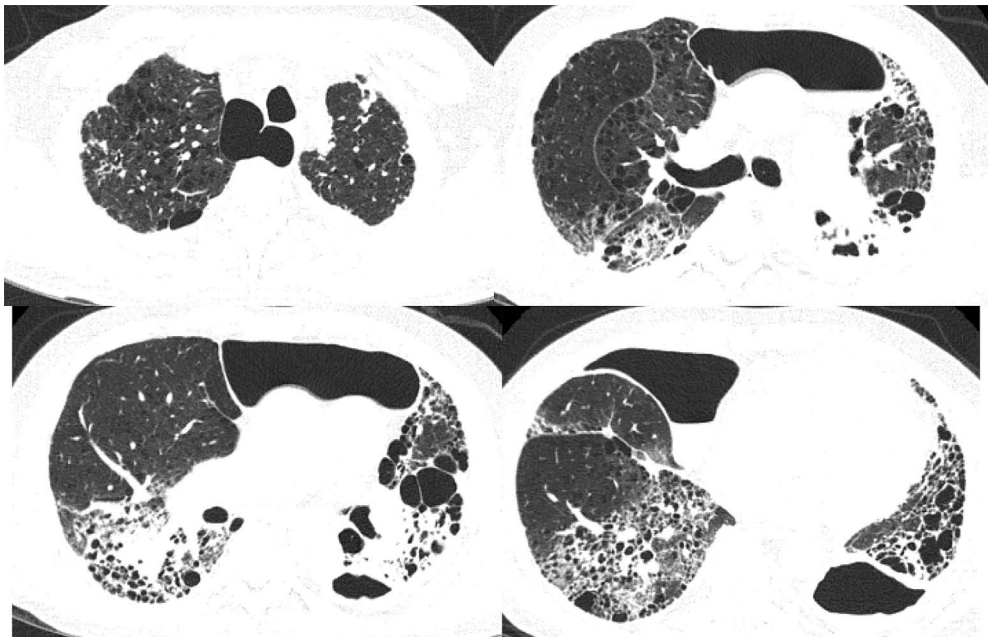

Fig. 3. Chest CT scan at the diagnosis of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) on day 47 New bilateral widespread consolidation and ground-glass opacity superimposed on a background honeycomb pattern.

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, postprocedural/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

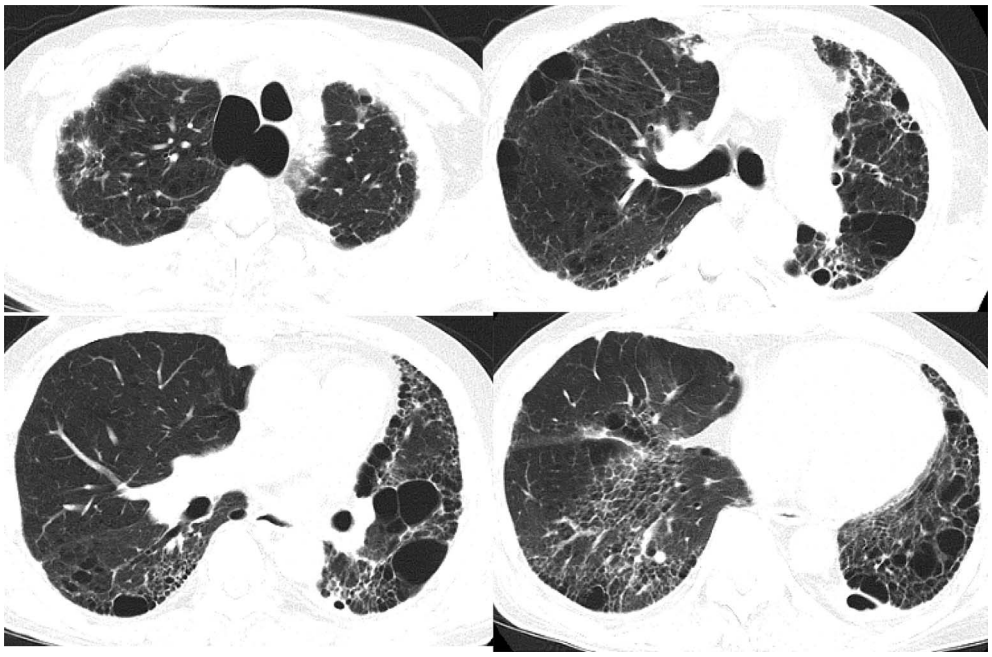

Fig. 4. Chest CT scan at discharge from the hospital Improvement in bilateral consolidation, ground-glass opacity, and effusions.

systemic antifungal therapy, local antifungal therapy (intrathoracic infusion of APMH-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 favor the natural history of the disease even at the moment of AE. We struggled with this dilemma and after careful consideration finally decided to use corticosteroid. In addition, several investigators have reported the efficacy of rhTM for AE-IPF, which regulates the coagulation pathway mainly by reducing thrombin-mediated clotting and enhancing protein C activation [23,24]. Another recent retrospective study for AE-IPF showed that 3-month survival was significantly better in patients treated with pirfenidone than in a control group [25]. The combination therapy in our case might be associated with the favorable outcome. Further research and discussion are needed to determine whether immunosuppressive therapy including corticosteroid should be performed in infection-triggered AE-IPF.

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.

References

[1] Y. Kondoh, H. Taniguchi, Y. Kawabata, T. Yokoi, K. Suzuki, K. Takagi, Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases, Chest 103 (1993) 1808–1812.

[2] B. Ley, H.R. Collard, T.E. King Jr., Clinical course and prediction of survival in idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 183 (2011) 431–440.

[3] M. Natsuizaka, H. Chiba, K. Kuronuma, M. Otsuka, K. Kudo, M. Mori, M. Bando, Y. Sugiyama, H. Takahashi, Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences, Am. J. Respir. Crit. Care Med. 190 (2014) 773–779.

[4] Y. Kondoh, V. Cottin, K.K. Brown, Recent lessons learned in the management of acute exacerbation of idiopathic pulmonary fibrosis, Eur. Respir. Rev. 26 (145) (2017), http://dx.doi.org/10.1183/16000167.0050-2017 pil: 170050.

[5] H.R. Collard, C.J. Ryerson, T.J. Corte, G. Jenkins, Y. Kondoh, D.J. Lederer, J.S. Lee, T.M. Maher, A.U. Wells, K.M. Antoniou, J. Behr, K.K. Brown, V. Cottin, K.R. Flaherty, J. Fukuoka, D.M. Hansell, T. Johkoh, N. Kaminski, D.S. Kim, M. Kolb, D.A. Lynch, J.L. Myers, G. Raghu, L. Richeldi, H. Taniguchi, F.J. Martinez, Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report, Am. J. Respir. Crit. Care Med. 194 (2016) 265–275.

[6] J.W. Song, S.B. Hong, C.M. Lim, Y. Koh, D.S. Kim, Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors, and outcome, Eur. Respir. J. 37 (2011) 356–363.

[7] A. Suzuki, Y. Kondoh, The clinical impact of major comorbidities on idiopathic pulmonary fibrosis, Respir. Investig. 55 (2017) 94–103.

[8] A. Suzuki, H. Taniguchi, M. Ando, Y. Kondoh, T. Kimura, K. Kataoka, T. Matsuda, T. Yokoyama, K. Sakamoto, K. Hasegawa, Prognostic evaluation by oxygenation with positive end-expiratory pressure in acute exacerbation of idiopathic pulmonary fibrosis: a retrospective cohort study, Clin. Respir. J. (2016), http://dx.doi.org/10.1111/crj.12602 ([Epub ahead of print]).

[9] K. Oda, H. Ishimoto, S. Yamada, H. Kushima, H. Ishii, T. Imanaga, T. Harada, Y. Ishimatsu, N. Matsumoto, K. Naito, K. Yatera, M. Nakazato, J. Kadota, K. Watanabe, S. Kohno, H. Mukae, Autopsy analyses in acute exacerbation of idiopathic pulmonary fibrosis, Respir. Res. 15 (2014) 109 1186/212931-014-0109-y.

[10] D.M. Hwang, D.W. Chamberlain, S.M. Poutanen, D.E. Low, S.L. Asa, J. Butany, Pulmonary pathology of severe acute respiratory syndrome in Toronto, Mod. Pathol. 18 (2005) 1–10.

[11] N. Jung, S. Mronga, S. Schroth, T. Vassiliou, F. Sommer, E. Walthers, C. Aepinus, A. Jerrentrup, C. Vogelmeier, A. Holland, R. Koczulla, Gardening can induce pulmonary failure: Aspergillus ARDS in an immunocompetent patient, a case report, BMC Infect. Dis. 14 (2014) 600, http://dx.doi.org/10.1186/s12879-014-0600-6.

[12] A. Sakurai, H. Yanai, T. Ishida, H. Kuwata, K. Kamei, S. Izumi, Possible relationship between organizing pneumonia and chronic pulmonary aspergillosis: a case report and literature review, Respir. Investig. 55 (2017) 74–78.

[13] T.F. Patterson, G.R. Thompson 3rd, D.W. Denning, J.A. Fishman, S. Hadley, R. Herbrecht, D.P. Kontoyiannis, K.A. Marr, V.A. Morrison, M.H. Nguyen, B.H. Segal, W.J. Steinbach, D.A. Stevens, T.J. Walsh, J.R. Wingard, J.A. Young, J.E. Bennett, Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America, Clin. Infect. Dis. 63 (2016) e1–e60.

[14] M.K. Goel, D. Juneja, S.K. Jain, S. Chaudhuri, A. Kumar, A rare presentation of aspergillus infection as empyema thoracis, Lung India 27 (2010) 27–29.

[15] N. Ashizawa, S. Nakamura, S. Ide, M. Tashiro, T. Takazono, Y. Imamura, T. Miyazaki, K. Izumikawa, Y. Yamamoto, K. Yanagihara, Y. Miyazaki, S. Kohno, Successful treatment of aspergillus empyema using open window thoracostomy salvage treatment and the local administration of an antifungal agent, Intern. Med. 55 (2016) 2093–2099.

[16] F. Kurosaki, M. Bando, M. Nakayama, N. Mato, T. Nakaya, H. Yamasawa, T. Yoshimoto, N. Fukushima, Y. Sugiyama, Clinical features of pulmonary aspergillosis associated with interstitial pneumonia, Intern. Med. 53 (2014) 1299–1306.

[17] S.C. Ko, K.Y. Chen, P.R. Hsueh, K.T. Luh, P.C. Yang, Fungal empyema thoracis: an emerging clinical entity, Chest 117 (2000) 1672–1678.

[18] M. Purohit, A. Guleri, J. Zacharias, Salvage therapy with topical antifungal for Aspergillus fumigatus empyema complicating extrapleural pneumonectomy, Interact. Cardiovasc. Thorac. Surg. 15 (2012) 518–519.

[19] Y. Nakanishi, K. Wakamatsu, Y. Nomoto, M. Kawasaki, K. Takayama, J. Yatsunami, N. Tsuruta, S. Hashimoto, N. Hara, Empyema following the percutaneous instillation of antifungal agents in patients with aspergillosis, Intern. Med. 35 (1996) 657–659.

[20] T. Matsuda, Y. Koreeda, H. Mataki, T. Taira, S. Noma, I. Higashimoto, A case of Aspergillus empyema successfully treated with combination therapy of voriconazole and micafungin: excellent penetration of voriconazole and micafungin into pleural fluid, Intern. Med. 49 (2010) 1163–1169.

[21] G. Raghu, H.R. Collard, J.J. Egan, F.J. Martinez, J. Behr, K.K. Brown, T.V. Colby, J.F. Cordier, K.R. Flaherty, J.A. Lasky, D.A. Lynch, J.H. Ryu, J.J. Swigris, A.U. Wells, J. Ancochea, D. Bouros, C. Carvalho, U. Costabel, M. Ebina, D.M. Hansell, T. Johkoh, D.S. Kim, T.E. King Jr., Y. Kondoh, J. Myers, N.L. Müller, A.G. Nicholson, L. Richeldi, M. Selman, R.F. Dudden, B.S. Griss, S.L. Protzko, H.J. Schünemann, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, Am. J. Respir. Crit. Care Med. 183 (2011) 788–824.

[22] S.A. Papiris, K. Kagouridis, L. Kolilekas, A.I. Papaioannou, A. Roussou, C. Triantafillidou, K. Baou, K. Malagari, S. Argentos, A. Kotanidou, A. Karakatsani, E.D. Manali, Survival in idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach, BMC Pulm. Med. 15 (2015) 162, http://dx.doi.org/10.1186/s12890-015-0146-4.

[23] K. Kataoka, H. Taniguchi, Y. Kondoh, O. Nishiyama, T. Kimura, T. Matsuda, T. Yokoyama, K. Sakamoto, M. Ando, Recombinant human thrombomodulin in acute exacerbation of idiopathic pulmonary fibrosis, Chest 148 (2015) 436–443.

[24] T. Isshiki, S. Sakamoto, A. Kinoshita, K. Sugino, A. Kurosaki, S. Homma, Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study, Respiration 89 (2015) 201–207.

[25] K. Furuya, S. Sakamoto, H. Shimizu, M. Sekiya, A. Kinoshita, T. Isshiki, K. Sugino, K. Matsumoto, S. Homma, Pirfenidone for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study, Respir. Med. 126 (2017) 93–99.