1. Introduction

Although the development of new antifibrotic agents (pirfenidone, nintedanib) has modified the disease progression of idiopathic pulmonary fibrosis (IPF), there is still no effective treatment for acute exacerbation of interstitial lung diseases (ILD) including IPF. We herein report a case of acute exacerbation of ILD (AE-ILD) treated only with nintedanib without any environmental changes and any other medications such as corticosteroid therapy, diuretic and anti-biotics, which resulted in the gradual improvement of the patient's clinical symptoms, high-resolution computed tomography findings, and forced vital capacity. This case might suggest the possibility that nintedanib not only modifies the disease progression of Idiopathic Pulmonary Fibrosis (IPF), but also facilitate the recovery from the acute exacerbation of ILD.

2. Case

A 75-year-old man visited our hospital in January 2018 because of worsening dry cough and dyspnea on effort within 1 month. He was an ex-smoker (1 pack/day from 20 to 65 years of age) and had no family history of lung disease. There was no suspicion of pulmonary infection, new medications, connective tissue disease, or occupational exposure relevant to interstitial lung disease.

The patient had originally been referred to our hospital from a local clinic because of suspected ILD during a regular checkup with fine crackles at both lung bases in March 2016. At that time, he was asymptomatic, had normal pulmonary function test results [forced vital capacity (FVC), 3.14 L (100%); forced expiratory volume in 1 s (FEV1), 2.72 L (125%); FEV1/FVC ratio, 87%], and SpO2 level of 96% at rest; however, a chest radiograph and computed tomography (CT) scan showed a basal and peripheral-dominant reticular abnormality without obvious honeycombing (Figs. 1A, 2A and 3A and B). The serum levels of Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) were 1000 U/mL (normal, < 500 U/mL) and 317 ng/mL (normal, < 110 ng/mL), respectively. Based on his HRCT findings with probable UIP he was diagnosed as clinically suspected of having IPF because he did not declare any environmental exposures at this moment [7]. After the second visit in April 2016, however, he was lost to follow-up.

In January 2018, he returned to our hospital because he had become unable to walk for 200 m on flat roads without rest during the previous 1 month. His temperature was 37.1 °C, his SpO2 was 98% at rest (no arterial blood gas data were obtained at this visit), and fine crackles
were noted at both lung bases. His pulmonary function had markedly dropped to an FVC of 2.18 L (71%), and a chest radiograph showed a remarkably reduced lung volume with a peripheral-dominant reticular abnormality and ground-glass opacity (Fig. 1B). A high-resolution CT (HRCT) scan showed basal- and peripheral-dominant honeycombing (Fig. 3C) and diffuse ground-glass opacities in all lung fields (Fig. 2B). Blood tests showed a white blood cell count of 11,200/μL (neutrophils, 71.0%; lymphocytes, 14.7%), hemoglobin (Hb) level of 15.1 g/dL, lactate dehydrogenase (LDH) level of 298 IU/L (normal, < 210 IU/L), and C-reactive protein (CRP) level of 2.23 mg/mL (normal, < 0.3 mg/mL). There was no evidence of pulmonary infection or congestive heart failure. At this moment, the patient did not declare the environmental exposures. Therefore, according to the criteria of acute
exacerbation of IPF [3]; 1) Previous diagnosis of IPF 2) Acute worsening or development of dyspnea less than one month 3) New bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern 4) Deterioration not fully explained by cardiac failure or fluid overload; the patient was diagnosed with AE-IPF. We recommended hospitalization and treatment with a corticosteroid, but he refused because one of his family knew the adverse effects of corticosteroid very well and worried about them too much. Thus, our only option was careful administration of an antifibrotic agent, tyrosine kinase inhibitor (nintedanib at 300 mg/day), on an outpatient basis. We prescribed no corticosteroids, diuretics, or antibiotics. Of course, we informed the patient and his family that this was not the first choice of the treatment of AE-IPF and that his condition might be getting worse without taking corticosteroid.

After 1.5 months of nintedanib administration, the patient’s symptoms gradually improved, and he was able to walk upstairs slowly. At 3 months after beginning nintedanib administration, a follow-up chest radiograph (Fig. 1C) and CT scan (Fig. 2C) showed partial improvement of the ground-glass opacities and a slight increase in the FVC (2.30 L, 75%) (Table 1). The blood levels of LDH (236 IU/L), CRP (0.30 mg/mL), and KL-6 (2830 U/mL) were decreased, but the level of SP-D was not (400 ng/mL).

The patient continued taking nintedanib without any adverse effects. The 9-month follow-up chest radiograph, CT scan (Figs. 1D and 2D), and levels of KL-6 and SP-D showed further improvement, and the FVC was maintained (Table 1). Surprisingly, at this time the patient declared for the first time that he had some environmental exposures, including usage of a feather duvet and inhalation of fertilizer containing chicken waste during field work. Therefore, the patient had continued to use the feather duvet and the fertilizer containing chicken waste for field work during 9-month nintedanib treatment period.

However, we had to consider the possibility that his diagnosis in January 2018 might have been acute exacerbation of chronic hypersensitivity pneumonitis instead of IPF.

3. Discussion

Nintedanib is a tyrosine kinase inhibitor that targets fibroblast growth factor receptor (FGFR) 1, 2, and 3; platelet-derived growth factor receptor (PDGFR) α and β; vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3; and Src family tyrosine kinases Lck, Lyn, and Flt-3 [8]. Findings from the INPULSIS-ON trial suggest that the effect of nintedanib on slowing the progression of IPF as measured by the FVC persists beyond 4 years [6]. Additionally, treatment with nintedanib might reduce the risk of acute exacerbation of patients with IPF [5,6]. However, there is no standardized therapy for AE-ILD including IPF, and the therapeutic effect of nintedanib on acute exacerbation remains unclear. To the best of our knowledge, there has been only one case report by Tomioka et al. [9], which described a patient with AE-IPF in whom treatment with nintedanib improved the clinical condition. Similarly, our patient with ILD was treated only with nintedanib on an outpatient basis and showed gradual improvement in his symptoms, FVC, CT findings, and blood test results.

Nintedanib is therapeutically effective for AE-ILD for several possible reasons. First, it has been demonstrated that the percentage of neutrophils in the bronchoalveolar lavage fluid (BALF) is significantly higher during the course of AE-IPF than in stable IPF. This increase in neutrophils is caused by overexpression of proinflammatory cytokines produced by activated alternative M2 macrophages with chemotaxis of neutrophils [10,11]. Additionally, nintedanib reportedly exerted anti-

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**Table 1**
The changes in forced vital capacity (FVC) and blood test results.

|                      | March 2016 | January 2018 | April 2018 | October 2018 |
|----------------------|------------|--------------|------------|--------------|
| Nintedanib           | –          | start        | +          | +            |
| FVC (L)              | 3.14       | 2.18         | 2.30       | 2.26         |
| %FVC (%)             | 99.7       | 71.2         | 74.7       | 72.9         |
| LDH (U/L)            | 264        | 298          | 236        | 251          |
| CRP (mg/dL)          | 0.60       | 2.23         | 0.30       | 1.09         |
| KL-6 (U/mL)          | 1000       | 4640         | 2830       | 1820         |
| SP-D (ng/mL)         | 317        | 366          | 400        | 351          |
inflammatory activity in a silica-induced lung inflammation and fibrosis mouse model as demonstrated by reduced lymphocyte and neutrophil counts in the BALF, diminished interleukin-1β (IL-1β) and keratinocytederived chemokine (KC) concentrations in lung homogenates, and reduced inflammation and granuloma formation in the histological analysis [12]. Second, a multicenter retrospective analysis in Japan showed that polymyxin-B direct hemoperfusion (PMX-B DHP) significantly improved the survival rate and the PaO₂/FiO₂ ratio in patients with acute exacerbation of IPF [13,14]. When patients with AE-IPF were treated with PMX-B DHP, serum pro-inflammatory cytokines including PDGF, FGF basic, and transforming growth factor-β (TGFβ) were absorbed by PMX-B DHP. In addition, improved pulmonary oxygenation after PMX-B DHP was well correlated with the quantities of eluted VEGF, which potentially increased alveolar permeability [15]. As mentioned above, nintedanib is a receptor tyrosine kinase inhibitor that targets FGFR 1, 2, and 3; PDGFR α and β; and VEGFR 1, 2, and 3. Taken together, these evidences provide a convincing explanation for the possible therapeutic effect of nintedanib on acute exacerbation of ILD by attenuating the neutrophilic inflammation, normalizing alveolar permeability, and inhibiting profibrotic signals.

Considering that our patient had some environmental exposures such as usage of a feather duvet and the fertilizer containing chicken manure from the basal lungs, and our patient conditions improved without immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis, Intern. Med. (Tokyo, Jpn.) 51 (12) (2012) 1487–1491.

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