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【 CASE REPORT 】

Acute Exacerbation of Pleuroparenchymal Fibroelastosis Secondary to Allogenic Hematopoietic Stem Cell Transplantation

Yasushi Murakami[1], Koji Sakamoto[1], Yuki Okumura[2], Atsushi Suzuki[1], Shinji Mii[3], Mitsuo Sato[1,4], Toyoharu Yokoi[5], Naozumi Hashimoto[1] and Yoshinori Hasegawa[1,6]

Abstract:
In this article, we report a case with pleuroparenchymal fibroelastosis (PPFE) following hematopoietic stem cell transplantation (HSCT) that developed acute respiratory failure with new bilateral ground glass opacity, which could not be explained by either a pulmonary infection, drug toxicity or extraparenchymal causes. Although combination therapy with multiple immunosuppressants was transiently effective, the patient died from a recurrent exacerbation. Autopsied lungs demonstrated diffuse alveolar damage superimposed on PPFE. There was no evidence of any coexisting interstitial pneumonia with the usual interstitial pneumonia (UIP) pattern. Our case suggests that acute exacerbation can occur in patients with post-HSCT PPFE, even when a coexisting UIP pattern is absent.

Key words: pleuroparenchymal fibroelastosis, hematopoietic stem cell transplantation, acute exacerbation, corticosteroid, diffuse alveolar damage, autopsy

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Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare type of fibrotic interstitial lung disease (ILD) characterized by upper lobe-dominant progressive pulmonary fibrosis, which can occur secondary to various underlying diseases or medical procedures, including hematopoietic stem cell transplantation (HSCT) (1, 2). During the clinical courses of fibrotic ILDs, physicians should pay attention to the development of an acute exacerbation (AE), a life-threatening event first described in idiopathic pulmonary fibrosis (IPF). AE can occur in all forms of fibrotic ILDs and it can have a significant negative prognostic effect (3, 4). Over the past two decades, the accumulation of cases has improved our understanding of the clinical characteristics of PPFE. However, whether AE can develop in patients with PPFE still remains controversial. We herein report a patient with PPFE secondary to allogenic HSCT who developed acute respiratory failure with new bilateral ground glass opacity (GGO), which was considered to be AE of PPFE.

Case Report

A 49-year-old man underwent allogenic HSCT with umbilical cord blood for the treatment of refractory aplastic anemia. A conditioning regimen composed of total body irradiation, cyclophosphamide, and fludarabine was given prior to HSCT. He was an ex-smoker (28 pack-years), and had no remarkable history of environmental exposure or familial history. Chest X-Ray and computed tomography (CT) performed before HSCT showed no abnormal findings. After HSCT, he achieved sustained hematologic remission without clinically apparent graft-versus-host disease (GVHD), except

[1]Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Japan, [2]Department of Pathology and Laboratory Medicine, Nagoya University Hospital, Japan, [3]Department of Pathology, Nagoya University Graduate School of Medicine, Japan, [4]Department of Pathophysiological Laboratory Sciences, Nagoya University Graduate School of Medicine, Japan, [5]Department of Pathology, Tsushima City Hospital, Japan and [6]Department of Respiratory Medicine, National Hospital Organization, Nagoya Medical Center, Japan
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Correspondence to Dr. Koji Sakamoto, sakakoji@med.nagoya-u.ac.jp

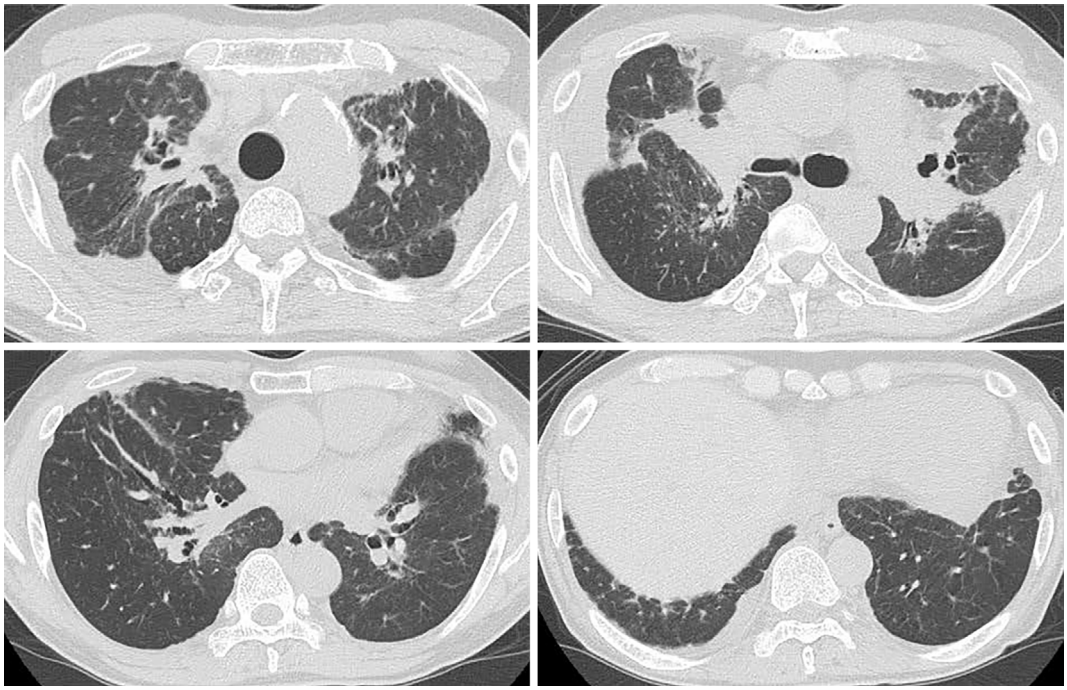

Figure 1. Chest computed tomography before admission. Dense subpleural areas of airspace consolidation with traction bronchiectasis are prominent in the bilateral upper lobes. The basal subpleural regions reveal slight reticular opacities.

for some mild sicca symptoms, and he demonstrated an uneventful course during the outpatient follow-up thereafter.

Four years after HSCT, he began complaining of nonproductive cough and dyspnea on exertion, without a recurrence of any hematologic abnormalities. Based on the chest CT findings including bilateral lung volume loss, subpleural consolidation with alveolar collapse, and traction bronchiectasis prominent in the upper lobes, PPFE was suspected as a late complication of HSCT. He received only supportive care without histopathological confirmation, and his general condition and respiratory symptoms worsened over time. Eight years after HSCT, his pulmonary function showed a severe restrictive impairment with a high residual volume (RV) / total lung capacity (TLC) ratio [forced vital capacity (% pred.): 1.41 L (39.7%); RV/TLC (% pred.): 32.7% (123.4%)]. Chest CT revealed a progression of bilateral lung volume loss, and subtle reticular shadows in the basal lung regions (Fig. 1). His body weight decreased to 40.5 kg (body-mass index: 16.0 kg/m^2). He initiated long-term oxygen therapy (oxygen flow of 1 L/min at rest and 3 L/min on exercise via a nasal cannula).

Nine years after HSCT, he was admitted to our hospital after several days of fever and a worsening shortness of breath. His vital signs at admission revealed a body temperature of 37.6℃, respiratory rate of 36 breaths per minute, and oxygen saturation of 98% on 4 L/min of oxygen via a nasal cannula. On chest auscultation, fine crackles were present in the bilateral lung field. He had no findings associated with GVHDs or collagen vascular diseases. He had been on the same medication for several years, which had no immunosuppressive effects or known pulmonary toxicities. Blood tests showed a white blood cell count of 14,600 /mm^3 (neutrophils: 70.3%), Krebs von den Lungen-6 of 778 U/mL, C-reactive protein of 14.8 mg/dL, and procalcitonin of 0.1 ng/mL. An arterial blood gas analysis demonstrated partial pressure of arterial oxygen (PaO_2) of 88.5 Torr and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of 49.3 Torr on 4 L/min of oxygen via a nasal cannula. Chest CT revealed new GGO in the left lower lobe (Fig. 2). Under a suspicion of community-acquired pneumonia, we started intravenous piperacillin-tazobactam and oral azithromycin. No significant pathogens were detected in the sputum and blood culture tests.

On day 7 after admission, his respiratory status deteriorated, and high-flow nasal cannula oxygen therapy was initiated (flow rate of 40 L/min and fraction of inspired oxygen of 0.6). Chest CT showed bilateral widespread areas of GGO and consolidation (Fig. 3). His plasma brain natriuretic peptide level was slightly elevated (109.9 pg/mL), but echocardiography revealed a preserved ejection fraction, and no significant diastolic dysfunction and valve abnormalities. We considered the clinical presentation of the case to closely meet the diagnostic criteria of AE-IPF (3), including an acute worsening of respiratory insufficiency with new bilateral opacities on chest CT, and the exclusion of alternative causes of acute respiratory failure such as infection or cardiac failure. Given that the same criteria are widely adopted for diagnosing AE in other type of ILDs (4-7), we clinically suspected that AE was complicated in the current case with post-HSCT PPFE. He received two cycles of methylprednisolone pulse therapy (1,000 mg daily for 3 consecutive days with a 7-day interval) followed by mainte-

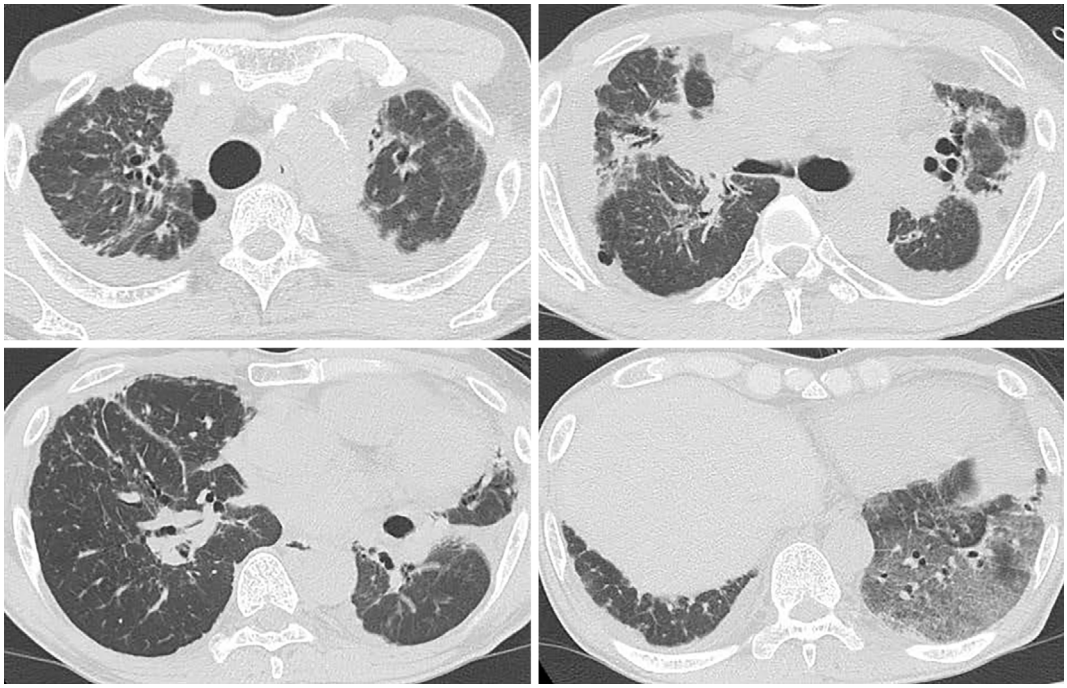

Figure 2. **Chest computed tomography at admission. Diffuse ground-glass opacities are observed in the left lower lobe.**

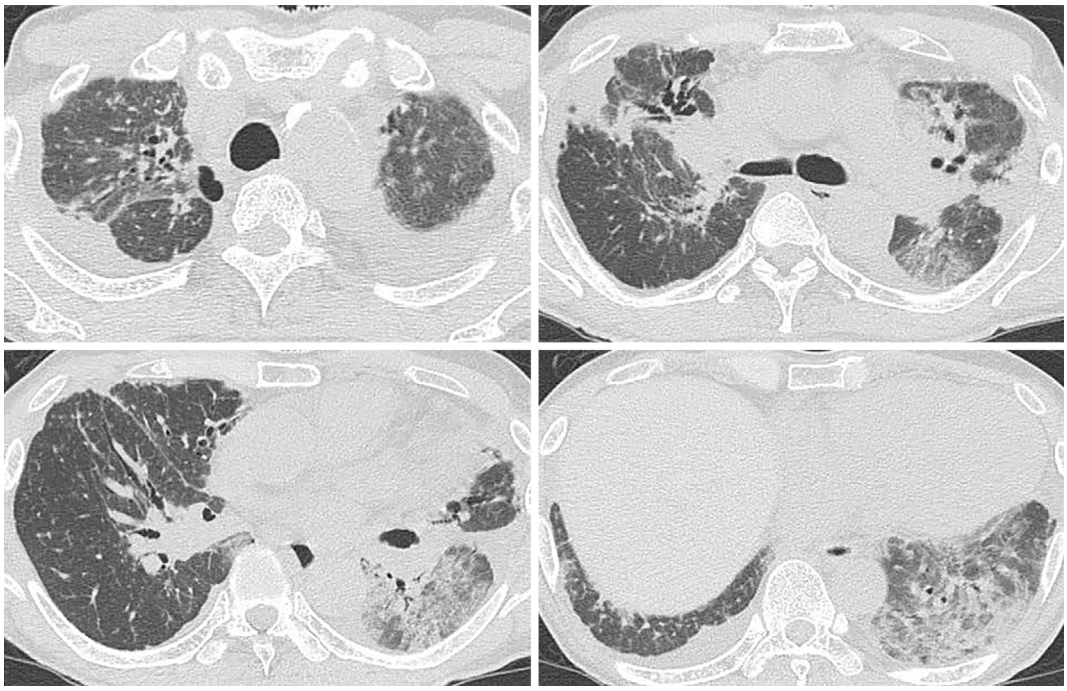

Figure 3. **Chest computed tomography at the diagnosis of an acute exacerbation on day 7. Bilateral widespread areas of ground-glass opacities and consolidation are present.**

nance prednisolone, and his respiratory condition and radiographic findings improved to the baseline level. On day 33, a gradual tapering of the prednisolone induced a recurrent exacerbation of the disease, and two additional cycles of methylprednisolone pulse therapy were given, but showed no clinical benefit. On day 82, intravenous cyclophosphamide and oral tacrolimus were added to prednisolone, and his respiratory condition was transiently stabilized. However, he developed pneumothorax and a flare up of disease following steroid tapering (Fig. 4), thus resulting in death on day 138. No evidence of an opportunistic pulmonary infection was detected during his clinical course.

Autopsy revealed relatively small lungs with diffuse pleural thickening that was marked in both upper lobes. Microscopically, pleura and subpleural parenchyma showed band-like dense fibroelastosis (Fig. 5). Deep lung parenchyma

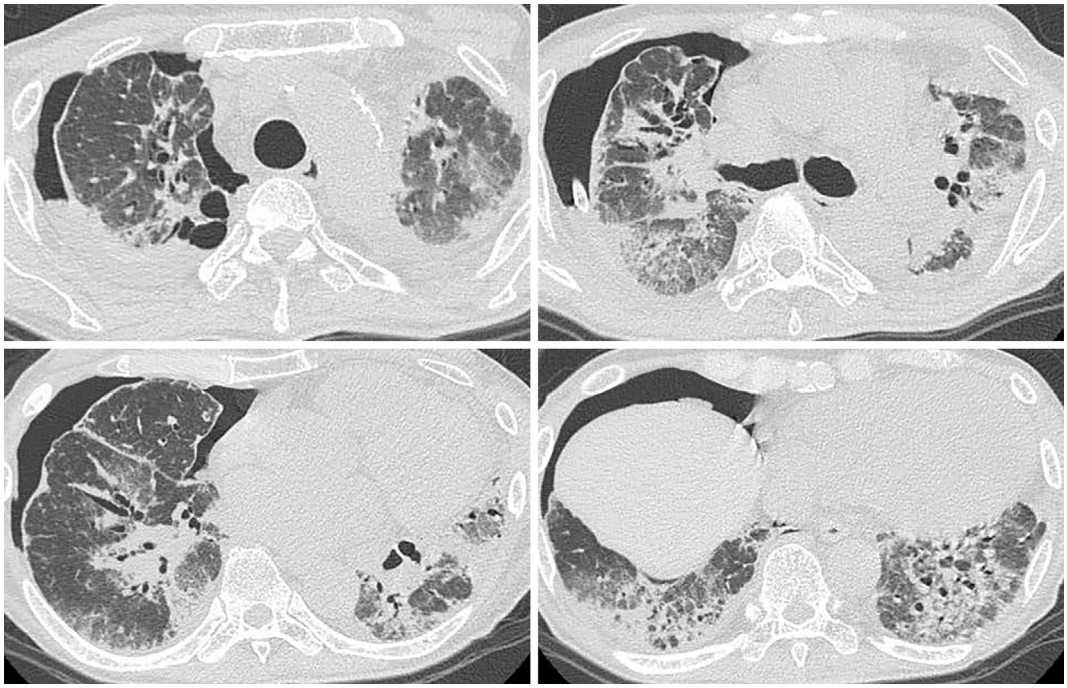

Figure 4. Chest computed tomography on day 135 after admission. Right-side pneumothorax and diffuse ground-glass opacities in both lungs are observed.

apart from the pleura showed extensive alveolar septal organizing fibrosis accompanied by type 2 pneumocyte hyperplasia and occasional foci of hyaline membrane formation, suggesting diffuse alveolar damage (DAD) mainly in the organizing phase. There were no definite fibroblastic foci or active inflammation within or around PPFE lesion, although they could have possibly been present but were blurred by superimposing DAD. In addition, there was a marked intra-alveolar accumulation of foamy macrophages, which was thought to be an unusual feature of DAD. There was no remarkable infiltration of inflammatory cells such as neutrophils or lymphocytes, which are suggestive of infection or GVHD as possible known triggers of acute lung injury. Co-existing interstitial pneumonia with an usual interstitial pneumonia (UIP) pattern, bronchiolitis obliterans (BO), pulmonary alveolar proteinosis-like changes, or pulmonary embolism were not found. An immunohistochemical study to further characterize the subpleural fibroelastotic lesions demonstrated that spindle cells in the fibrotic areas were shown to be weakly positive for podoplanin. There was no histological evidence of infection or chronic GVHD in other organs. His bone marrow showed no evidence of recurrent aplastic anemia or other hematologic abnormalities.

Discussion

Since first described as idiopathic pulmonary upper lobe fibrosis by Amitani et al. (8), PPFE has been increasingly recognized by physicians, and the idiopathic form (iPPFE) is now listed as a rare type of idiopathic interstitial pneumonia in the international classification (9). Most cases of PPFE are idiopathic, but some cases occur secondary to various underlying diseases or medical procedures (1, 2). The clinical features of PPFE include upper lobe-dominant progressive fibrosis, a flat chest, low body weight, distinct pulmonary function with restrictive pattern and high rates of pneumothorax (10, 11). Patients at an advanced stage often develop hypercapnic respiratory failure, which may be associated with alveolar hypoventilation and chest wall deformity, as was observed in our case (1, 10, 12). There is currently no effective treatment for PPFE, and its prognosis remains dismal (1, 2). Regarding the diagnosis, several researchers have suggested that a surgical lung biopsy is not required to establish the diagnosis of PPFE because of the high risk of postoperative complication (10, 13). We could obtain an antemortem diagnosis of PPFE without a pathological evaluation based on the proposed diagnostic criteria including the chest CT findings, high RV/TLC ratio on spirometry, and low-body weight (10, 13).

After HSCT, PPFE can develop as a rare late-onset noninfectious pulmonary complication (14). The reported incidence of PPFE is 0.28% among HSCT recipients (14), and the time to diagnosis from transplantation has been reported to range from 1 to 16 years (15-24). Alkylating agents and irradiation for conditioning or chronic GVHD have been considered possible causes of post-HSCT PPFE (14). Although there are only several case reports and case series in the existing literature, the clinical features and disease courses of post-HSCT PPFE seem to be similar to those of iPPFE (15-24). They are refractory to immunosuppressive treatments, and usually follow progressive clinical courses. Therefore, physicians should recognize this rare pulmonary complication and monitor patients carefully after HSCT. When the diagnosis of PPFE is established, lung transplanta-

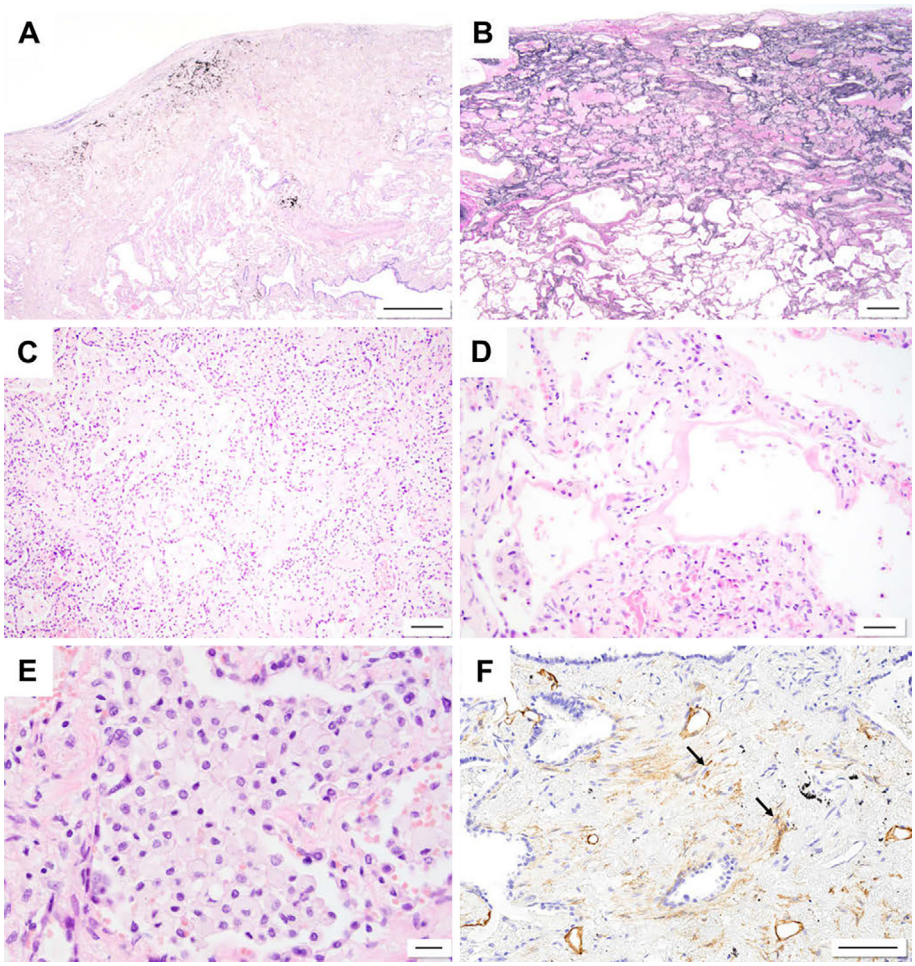

Figure 5. **Autopsy findings in the lungs. A) Pleura and subpleural parenchyma showed band-like dense fibroelastosis. B) Elastic fibers are abundant in the subpleural fibrotic area. C), D) The lung parenchyma apart from the pleura showed an extensive alveolar septal organizing fibrosis accompanied by type 2 pneumocyte hyperplasia and occasional foci of hyaline membrane formation, suggesting diffuse alveolar damage (DAD) mainly in the organizing phase. E) Marked intra-alveolar accumulations of foamy macrophages are observed in the area with preserved alveolar architectures. F) Spindle cells in fibrotic area are weakly positive for podoplanin (Black arrows). Staining: A), C), D), E) Hematoxylin and Eosin staining; B) Elastica van Gieson; F) Podoplanin immunostaining. Scale bar: A) 900 μm; B) 500 μm; C) 100 μm; D) 50 μm; E) 20 μm; F) 90 μm.**

tion may be considered as a favorable treatment option (25, 26).

The current case with post-HSCT PPFE developed acute respiratory failure with new bilateral lung abnormalities, and we carefully assessed the identifiable causes of acute lung injury (ALI) regarding the clinical and pathological aspects. Cardiac failure was ruled out with normal echocardiography findings. In addition, there was no evidence of any pulmonary embolism, pulmonary infections, or potential causes of extrapulmonary acute respiratory distress syndrome in the autopsy study. Drug induced ILD was unlikely because the patient has been on the same medications with no known pulmonary toxicities for several years. Furthermore, late-onset noninfectious pulmonary complication following HSCT is another possible explanation for ALI in this case. It is well recognized that HSCT recipients can develop immune-mediated ALI, known as idiopathic pneumonia syndrome (IPS), even if chronic ILDs are absent (27). However, this type of pulmonary complication typically occurs within 3 months to 2 years after HSCT, and it is often related to GVHDs in other organs (27, 28). In our case, the occurrence of ALI was quite late after HSCT (9 years), and any signs suggestive of GVHD could not be found in any other organ either clinically or in pathological examinations. Therefore, the possibility of IPS was considered to be low. We eventually suspected that the patient had AE based on the diagnostic criteria for AE-IPF (3), which are widely adopted for diagnosing AE in other ILDs including nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis, connective tissue disease associated ILDs, and unclassified interstitial pneumonia (4-7). To date, several individual cases with PPFE suspected to have AE have been reported (10, 12, 29, 30). Although most of these episodes were AE that occurred in patients with iPPFE and a con-

comitant UIP pattern, Nei and colleagues reported AE in a patient with iPPFE without any evidence of other coexisting fibrotic ILDs (30). These reports and our case support the hypothesis that PPFE can be associated with the development of AE regardless of the coexistence of a UIP pattern. However, we could not completely reject the possibility of unknown causes of ALI, and it still remains unclear whether PPFE can directly become associated with AE during the clinical course. Further large-scale clinical studies are needed to determine whether AE can be a complication of PPFE without any other type of coexisting fibrotic ILDs.

An autopsy study provided several other important findings. First, our case had no histological evidence of chronic GVHD in the lungs or other organs. A recent review by Higo et al. suggested that post-HSCT PPFE may be induced mainly by chronic GVHD because of the high incidence of BO in patients with post-HSCT PPFE (31). In the present case, there were no histological findings suggesting BO or other types of lung complication with chronic GVHDs. Various factors besides a graft-versus-host immune reaction, including whole body irradiation, chemotherapeutic agents, and immunosuppressants after HSCT, may contribute to the development of PPFE in post-HSCT patients. Additional studies are anticipated to elucidate the predisposing factors of post-HSCT PPFE. Second, our case showed the histological pattern of DAD, which is the most common finding of AE in fibrotic ILDs (32, 33). A histological evaluation of ALI suspected AE of PPFE has been reported in only one case, and it demonstrated DAD (30). We observed an organizing hyaline membrane, interstitial and intra-alveolar proliferation of fibroblasts along with some infiltration of inflammatory cells in the lesion of organizing DAD, but no fibroblastic foci in the autopsied lungs, suggesting that the main process of ALI in this case was organizing DAD, not a rapidly progressive fibrosing process. Third, massive infiltration of macrophages with foamy cytoplasm was found in the preserved alveolar regions. Intra-alveolar aggregates of foamy macrophages are generally associated with bronchobronchiolar obstruction, drug toxicities, or metabolic disorders (34). The clinical significance of this finding in our case is unclear. However, macrophages are potential key players in the development of post-HSCT pulmonary complications (35, 36). In addition, the infiltration of foamy macrophages is one of the characteristic pathological findings in the early inflammatory changes of BO (37). Therefore, we speculate that the marked accumulation of foamy macrophages found in our case might reflect an immunological reaction to HSCT and play a pathogenic role. Last, we found an accumulation of podoplanin-positive spindle cells in the fibrotic region of autopsied lungs. Enomoto et al. reported that podoplanin-positive myofibroblasts might reflect mesothelial-to-mesenchymal transition, and this could be a pathological hallmark of iPPFE (38). Our findings suggest that a fibrotic process similar to iPPFE was also involved in the current case with post-HSCT PPFE.

Conclusion

In conclusion, we herein described a case of acute respiratory failure that occurred in a patient with PPFE secondary to HSCT. The therapeutic effects of corticosteroids and immunosuppressive agents were not satisfactory, and the patient finally died from a recurrent exacerbation. The autopsy showed findings consistent with DAD and no histological evidence of a coexisting UIP pattern. While it is impossible to completely rule out the possibility that DAD was triggered by some unknown etiology, our case suggests that AE can occur in patients with post-HSCT PPFE, even when a coexisting UIP pattern is absent. Further investigations are warranted to develop optimal management strategies for post-HSCT PPFE patients.

The authors state that they have no Conflict of Interest (COI).

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