



Case report

Combination of pleuroparenchymal fibroelastosis with non-specific interstitial pneumonia and bronchiolitis obliterans as a complication of hematopoietic stem cell transplantation — Clues to a potential mechanism

Zun Pwint Oo^{a,b}, Andrey Bychkov^{c,d}, Yoshiaki Zaizen^a, Mari Yamasue^e, Jun-ichi Kadota^f, Junya Fukuoka^{a,c,d,*}

^a Department of Pathology, Nagasaki University Hospital, Nagasaki, Japan

^b Department of Pathology, University of Medicine, Mandalay, Myanmar

^c Department of Pathology, Kameda Medical Center, Kamogawa, Chiba, Japan

^d Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

^e Oita University Hospital, Oita, Japan

^f Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, Yufu, Oita, Japan



ARTICLE INFO

Keywords:

Graft-versus-host disease

HRCT

Interstitial lung disease

Pathology

Pulmonary fibroelastosis

ABSTRACT

Pleuroparenchymal fibroelastosis (PPFE) is a newly described entity of interstitial lung disease, which has been recently recognized as a rare complication of bone marrow transplantation. We report a case of 30-year-old man who developed a unique combination of pleuroparenchymal fibroelastosis with cellular and fibrotic non-specific interstitial pneumonia (NSIP) and bronchiolitis obliterans (BO) sixteen years after hematopoietic stem cell transplantation. Histological examination revealed almost exclusive infiltration of CD3-positive T lymphocytes associated with lymphoepithelial lesions and multi-focal denudation of covering epithelial cells in all components. This case suggests PPFE, NSIP, and BO might be conditions of the same spectrum, pathogenetically related to chronic graft-versus-host disease. Immunostaining for CD3 and CD20 in transbronchial lung biopsies may be helpful for identifying graft-versus-host-driven interstitial lung disease.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is increasingly used in the management of various hematologic malignancies. In Japan, more than 5000 procedures are performed annually [1]. Pulmonary complications of HSCT are the major cause of mortality and morbidity in the post-transplant period [2]. With the better management of infectious complications, the prevalence of non-infectious pulmonary sequelae shows a growing trend [3]. Among them, late-onset non-infectious respiratory complications such as bronchiolitis obliterans (BO), organizing pneumonia (OP), and interstitial pneumonia were reported among life-threatening post-HSCT conditions with the incidence of 1.7–25.6% [2]. Very recently, pleuroparenchymal fibroelastosis (PPFE) has been added to this spectrum [4]; however, the underlying mechanism of PPFE in HSCT is not fully understood.

Herein, we present a case with the unique constellation of PPFE, non-specific interstitial pneumonia (NSIP) and BO developed after

HSCT. Furthermore, we elaborate on the possible pathophysiology based on immunohistochemical findings.

2. Case report

A 30-year-old male patient who suffered from acute lymphoblastic leukemia was treated with allogeneic HSCT in 2000. Sixteen years later, he suffered with dry cough and progressive dyspnea on exertion. Later on, he developed pneumothorax thrice. Blood tests revealed a slight elevation of C-reactive protein (0.91 mg/dl) but no elevation of KL-6 and surfactant protein D. Pulmonary function tests were not performed because of pneumothorax. Chest high-resolution computed tomography (HRCT) showed pleural and subpleural thickening with severe fibrotic changes in the marginal parenchyma, flat chest, mosaic perfusion, and reticular shadows in both lungs, added by pneumomediastinum (Fig. 1).

Video-assisted thoracoscopic surgery was performed and wedge biopsies from segments 5 and 10 of the right lung were taken.

* Corresponding author. Department of Pathology, Nagasaki University Hospital, 1-7-1, Sakamoto, Nagasaki, 852-8523, Japan.

E-mail addresses: dr.zunpwintoo@gmail.com (Z.P. Oo), bychkov.andrey@kameda.jp (A. Bychkov), zaizen_yoshiaki@nagasaki-u.ac.jp (Y. Zaizen), sai-mari@oita-u.ac.jp (M. Yamasue), kadota@oita-u.ac.jp (J.-i. Kadota), fukuokaj@nagasaki-u.ac.jp (J. Fukuoka).

<https://doi.org/10.1016/j.rmcr.2019.02.001>

Received 31 December 2018; Accepted 3 February 2019

2213-0071/© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

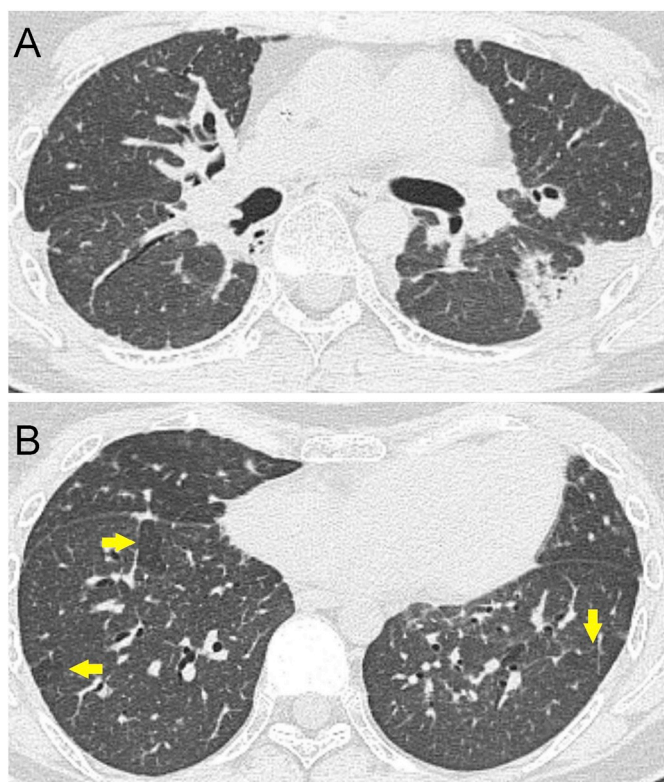


Fig. 1. HRCT of the patient. Subpleural consolidation associated with pleural thickening (A) and mosaic attenuation (arrows) (B).

Microscopically, subpleural and peribronchial fibroelastosis (Fig. 2A and B), constrictive bronchiolitis (Fig. 2C and D) and cellular and fibrotic non-specific interstitial pneumonia (NSIP pattern) (Fig. 2E) were found. Immunohistochemistry revealed that cellular infiltrates were almost exclusively made of CD3-positive cells with just a few occasional CD20-positive cells (Fig. 2H–K). These inflammatory cells permeated into both alveolar and bronchial epithelial lining cells creating lymphoepithelial lesions (LELs) and erosions (Fig. 2F). AE1/AE3 immunostaining confirmed multiple foci of alveolar cell denudation (Fig. 2G). Such LELs and erosions were consistently observed in all the areas with morphology of PPFE, NSIP, and BO. The patient is currently on immunosuppressive therapy and the condition is stable.

3. Discussion

We herein report a case of cellular and fibrotic NSIP in association with PPFE and BO after HSCT. PPFE is a rare complication of bone marrow transplantation accounting for 0.3% of all HSCT cases [4]. However, it is becoming increasingly recognized in the last decade, especially in the Asian population. We found eight case reports and case series, which described 36 patients who developed PPFE after HSCT (Table 1) [4–11]. Mean age was 31.6 (range – 8–61 years) and male to female ratio was 21:15. Twenty-eight cases were from Japan, two from Korea and six were from European countries. Mean interval between bone marrow transplantation and respiratory symptoms onset was 3.5 years, ranged from just 3 months to as long as 16 years. Thirty patients

were already expired at a time of the report, two patients had progressive deterioration, two had stable to slowly progressive pattern and another two were not reported with regard to disease outcome. A combination of PPFE and BO was found in 21 patients and variable degrees of inflammatory cell infiltrations were found in nine patients whereas the exact pattern was not mentioned apart from cases reported by Takeuchi et al. [6] The commonly considered potential causes included chronic graft-versus-host disease (cGVHD), total body irradiation, and chemotherapy, e.g. cyclophosphamide conditioning treatment. However, the exact mechanism of development of PPFE after bone marrow transplantation has not been addressed.

BO is considered diagnostic for pulmonary cGVHD [12] and the present case showed that in addition to BO, areas of PPFE in NSIP and BO showed LELs dominated by lymphocytes along with multiple foci of alveolar erosion. Immunostaining with CD3 and CD20 showed almost exclusive infiltration of T lymphocytes. It is widely accepted that activated donor T cells are the key pathogenic players in cGVHD [13]. The finding of exclusive infiltration by CD3⁺ cells in the present case allowed us to speculate that NSIP and PPFE may also be in the same spectrum of cGVHD similar to BO.

Another intriguing finding was the presence of frequent LELs and erosions confirmed by AE1/AE3. The denudation of alveolar and bronchiolar lining epithelia was scattered at the transition zone between the affected area and adjacent normal parenchyma. This raised a hypothesis that the graft T cells might attack epithelial cells and create erosions followed by healing scar as fibrosis to develop lesions of PPFE, NSIP, and BO. PPFE may follow after the collapse due to the insufficiency of surfactant triggered by the denudation of epithelial cells. Takeuchi et al. reported 20 cases of interstitial lung disease after HSCT and found that PPFE, NSIP, and BO were seen frequently together with six of out twenty cases having cellular NSIP similarly to the present case [6]. They also speculated that all lesions could be a part of the cGVHD although the possible mechanism was not addressed.

Furthermore, our patient developed pneumothorax thrice and pneumomediastinum once. Usually, air-leak syndrome (ALS) such as pneumothorax, pneumomediastinum, and subcutaneous emphysema is considered as a complication of BO due to collapsed fibrosis [8]. Interestingly, there is also a possible link between ALS and PPFE. Ishii et al. reported five cases of PPFE without BO, which suggests that PPFE itself may also lead to ALS [8].

Additionally, a case reported by Okimoto et al. developed PPFE without BO after HSCT [10]. As BO is a diagnostic feature for pulmonary cGVHD, Okimoto et al. speculated that the development of PPFE was not associated with GVHD. However, the patient reported by Okimoto et al. did have cGVHD in other organs such as liver and skin so it may not be justifiable to deny cGVHD as the possible contributor just because of the lack of BO and unresponsiveness to immunosuppressive therapy. It is obvious that the development of PPFE after HSCT may have heterogeneous mechanisms other than cGVHD; nonetheless, this does not rule out the possibility of cGVHD as one of the mechanisms for PPFE. Further studies focusing on the nature and interactions of inflammatory cells and LELs in the cases of PPFE with cGVHD are highly anticipated.

In conclusion, we report a case of PPFE after allogeneic HSCT in which cellular and fibrotic NSIP was found in addition to BO. Although it is a rare combination, our case, in addition to the previous cases reported by Takeuchi et al. highlights the necessity to evaluate the composition of cellular infiltrates in post-HSCT lung disease. This can be a key in understanding the pathophysiology of PPFE in cases with chronic GVHD after HSCT. Moreover, in cases with contraindications

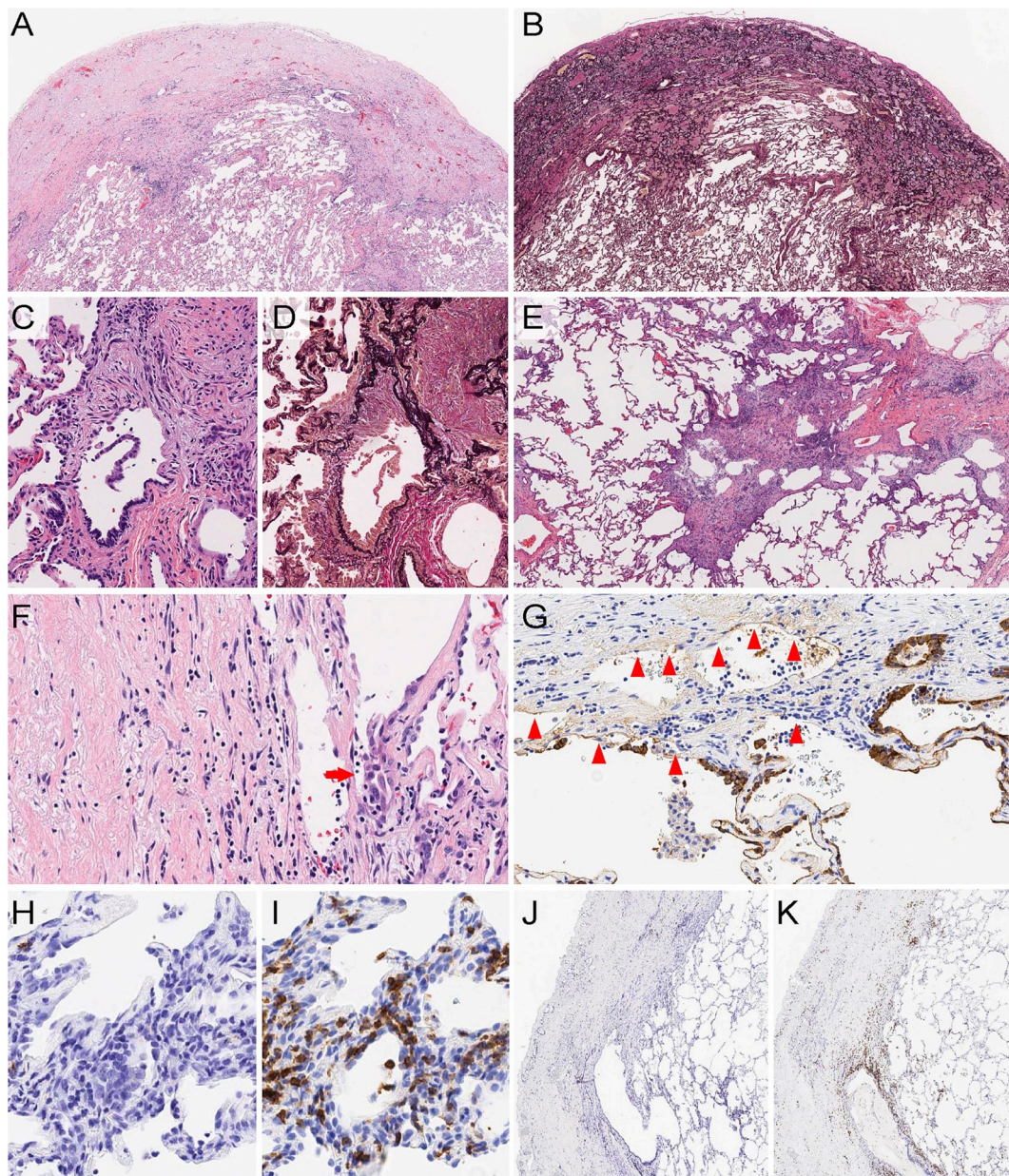


Fig. 2. Histological and immunohistochemical findings (A) Area of PPFE showing markedly thickened pleura and subpleural fibroelastosis. (B) Elastica van Gieson staining of the same field shows the increase of elastic fibers. (C–D) Area of BO shows constrictive change by collagenous fibrosis. Note denudation of covering epithelia. (E) Diffuse cellular infiltrates showing NSIP pattern. (F) The transitional area between PPFE and adjacent lung shows denudation and inflammatory cells infiltration into epithelial lining cells creating lymphoepithelial lesions (arrow). (G) AE1/AE3 immunostaining highlights denuded lining epithelia (arrowheads). (H–K) Immunostaining for CD20 (H, J) and CD3 (I, K) reveals almost exclusive CD3 positive cells in NSIP (H, I) and PPFE (J, K). Hematoxylin and eosin (A, C, E, F), elastica van Gieson (B, D), immunohistochemistry (G–K); $\times 50$ (A, B), $\times 400$ (C, D, F, G–I), $\times 100$ (E, J, K).

for video-assisted thoracoscopic surgery biopsy, performing immunostaining for CD3 and CD20 in transbronchial lung biopsies may be helpful to identify GVHD-driven interstitial lung disease.

Conflicts of interest

None.

Informed consent

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Financial support

No grants or funding have been received for this study.

Table 1
Summary of reported PPFE cases after bone marrow transplantation.

Source	Patients	Age	Sex	Underlying disease	Manifestation after BMT (years)	Histological findings
Present case	1	30	M	ALL	16	PPFE, BO, cellular and fibrotic NSIP
Thusen, 2011 [5]	4	13	F	AA	2.8	subpleural fibrosis, BO, mild patchy inflammation
		23	M	AML	12	subpleural and paraseptal fibroelastosis, BO
		32	M	ALL	16	subpleural fibroelastosis, BO, pneumothorax
		55	F	AML	2	PPFE, BO, widespread pulmonary fibrosis
Fujikura, 2014 [7]	1	31	F	ALL	9	PPFE, BO
Takeuchi, 2015 [6]	20	27.5 (8–57)	11 M	AML (12)	1.2 (0.4–3.8)	BO (20)
			9 F	MDS (2)		PPFE (15)
				ALL (1)		NSIP fibrotic (9)
				Primary macroglobulinemia (1)		NSIP cellular (6)
				SCID (1)		
				Aplastic anemia (1)		
				Chediak-Higashi syndrome (1)		
				Neuroblastoma (1)		
Mariani, 2016 [4]	2	33	M	AML	13	PPFE was diagnosed by HRCT
		61	F	AML	5	
Matsui, 2016 [11]	1	40	M	HL	2.7	PPFE, diffuse interstitial fibrosis
Ishii, 2016 [8]	5	44	F	MDS (RA)	3.3	PPFE, fibrotic lesions, no significant inflammatory cell infiltration
			M	MDS (RA)	1.1	
			M	CML	9.1	
			M	ALL	6.4	
			M	AA	8.8	
Cha, 2017 [9]	2	54	M	AML	2	PPFE, diffuse lymphocytic infiltration
			M	AML	n/a	PPFE, BO, patchy lymphocytic infiltration
Okimoto, 2018 [10]	1	45	F	MDS	5	PPFE

AA, aplastic anemia.

ALL, acute lymphoblastic leukemia.

AML, acute myeloid leukemia.

BO, bronchiolitis obliterans

BMT, bone marrow transplantation.

CML, chronic myeloid leukemia.

HL, Hodgkin lymphoma.

HRCT, high resolution computed tomography.

MDS, myelodysplastic syndrome.

NSIP, non-specific interstitial pneumonia.

RA, refractory anemia.

SCID, severe combined immunodeficiency.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2019.02.001>.

References

- [1] Japanese Data Centre for Hematopoietic Cell Transplantation, Activities and Outcomes of Hemopoietic Stem Cell Transplantation in Japan, (2016) <http://www.jdchct.or.jp/en/data/slide/2016/>.
- [2] S. Yoshihara, G. Yanik, K.R. Cooke, S. Mineishi, Bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans organizing pneumonia (BOOP), and other late-onset noninfectious pulmonary complications following allogeneic hematopoietic stem cell transplantation, *Biol. Blood Marrow Transplant.* 13 (2007) 749–759, <https://doi.org/10.1016/j.bbmt.2007.05.001>.
- [3] D. Maria, Z. Jihane, O.S. Ayman, Major pulmonary complications after hematopoietic stem cell transplant, *Exp. Clin.* 14 (2016) 259–270, <https://doi.org/10.6002/ect.2015.0275>.
- [4] F. Mariani, B. Gatti, A. Rocca, F. Bonifazi, A. Cavazza, S. Fanti, S. Tomassetti, S. Piciucchi, V. Poletti, M. Zompatori, Pleuroparenchymal fibroelastosis: the prevalence of secondary forms in hematopoietic stem cell and lung transplantation recipients, *Diagn. Interv. Radiol.* 22 (2016) 400–406, <https://doi.org/10.5152/dir.2016.15516>.
- [5] J.H. Von Der Thusen, D.M. Hansell, M. Tominaga, P.A. Veys, M.T. Ashworth, C.M. Owens, A.G. Nicholson, Pleuroparenchymal fibroelastosis in patients with pulmonary disease secondary to bone marrow transplantation, *Mod. Pathol.* 24 (2011) 1633–1639, <https://doi.org/10.1038/modpathol.2011.114>.
- [6] Y. Takeuchi, A. Miyagawa-Hayashino, F. Chen, T. Kubo, T. Handa, H. Date, H. Haga, Pleuroparenchymal fibroelastosis and non-specific interstitial pneumonia: frequent pulmonary sequelae of haematopoietic stem cell transplantation, *Histopathology* 66 (2015) 536–544, <https://doi.org/10.1111/his.12553>.
- [7] Y. Fujikura, S. Kanoh, Y. Kouzaki, Y. Hara, O. Matsubara, A. Kawana, Pleuroparenchymal fibroelastosis as a series of airway complications associated with chronic graft-versus-host disease following allogeneic bone marrow transplantation, *Intern. Med.* 53 (2014) 43–46, <https://doi.org/10.2169/internalmedicine.53.1124>.
- [8] T. Ishii, S. Bandoh, N. Kanaji, A. Tadokoro, N. Watanabe, O. Imataki, H. Dobashi, Y. Kushida, R. Haba, H. Yokomise, Air-leak syndrome by pleuroparenchymal fibroelastosis after bone marrow transplantation, *Intern. Med.* 55 (2016) 105–111, <https://doi.org/10.2169/internalmedicine.55.4539>.
- [9] Y.J. Cha, J. Han, M.P. Chung, T.J. Kim, S. Shin, Pleuroparenchymal fibroelastosis in heterogeneous clinical conditions: clinicopathologic analysis of 7 cases, *Clin. Res. J.* 12 (2018) 1495–1502, <https://doi.org/10.1111/crj.12696>.
- [10] T. Okimoto, Y. Tsubata, M. Hamaguchi, A. Sutani, S. Hamaguchi, T. Isobe, Pleuroparenchymal fibroelastosis after haematopoietic stem cell transplantation without graft-versus-host disease findings, *Respirol. Case Rep.* 6 (2018) e00298, <https://doi.org/10.1002/rcr2.298>.
- [11] T. Matsui, T. Maeda, T. Kida, J. Fujita, H. Tsuji, E. Morii, Y. Kanakura, Pleuroparenchymal fibroelastosis after allogeneic hematopoietic stem cell transplantation: important histological component of late-onset noninfectious pulmonary complication accompanied with recurrent pneumothorax, *Int. J. Hematol.* 104 (2016) 525–530, <https://doi.org/10.1007/s12185-016-2038-7>.
- [12] A.H. Filipovich, D. Weisdorf, S. Pavletic, G. Socie, J.R. Wingard, S.J. Lee, P. Martin, J. Chien, D. Przepioraka, D. Couriel, E.W. Cowen, P. Dinndorf, A. Farrell, R. Hartzman, J. Henslee-Downey, D. Jacobsohn, G. McDonald, B. Mittleman, J.D. Rizzo, M. Robinson, M. Schubert, K. Schultz, H. Shulman, M. Turner, G. Vogelsang, M.E.D. Flowers, National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. diagnosis and staging working group report, *Biol. Blood Marrow Transplant.* 11 (2005) 945–956, <https://doi.org/10.1016/j.bbmt.2005.09.004>.
- [13] R.B. Presland, Biology of chronic graft- vs -host disease: immune mechanisms and progress in biomarker discovery, *World J. Transplant.* 6 (2016) 608, <https://doi.org/10.5500/wjt.v6.i4.608>.