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## Case Report

# A case of thoracic air leak syndrome with pleural parenchymal fibroelastosis after treatment for hematologic malignancy while awaiting lung transplantation: Imaging and pathological findings of rapid loss in lung volume

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## ABSTRACT

We report the case of a 29-year-old man who underwent umbilical cord blood transplantation for chronic myelogenous leukemia 14 years previously. He was diagnosed with secondary pleuroparenchymal fibroelastosis (sPPFE) following treatment for hematologic malignancies (sPPFE after HM-Tx) 2.5 years ago. On computed tomography, pleural thickening in the upper lobe, lung volume loss, and recurrent bilateral pneumothorax were detected. Although he waited for cadaveric lung transplantation (LTx) for 1.5 years, his respiratory failure worsened, and he died. Pathological autopsy and clinical course indicated sPPFE. After diagnosing sPPFE after HM-Tx, the timing for deciding LTx is critical, especially when pneumothorax recurs.

## 1. Introduction

In recent years, cases of secondary pleuroparenchymal fibroelastosis (sPPFE) have been reported following the treatment of hematologic malignancies (sPPFE after HM-Tx) [1]. sPPFE after HM-Tx is a progressive disorder and has no treatment other than lung transplantation (LTx). Moreover, some patients with sPPFE after HM-Tx present with recurrent pneumothorax (i.e., thoracic air-leak syndrome [TALS]), which is resistant to treatment, leading to poor prognosis [1,2]. LTx is widely performed, especially in Europe and the United States, while LTx has been not yet common in other countries. Especially in Japan, the waiting duration for cadaveric LTx is problem, because it is > 800 days [3]. Moreover, since sPPFE after HM-Tx is rare, the clinical course remains unclear, thus, making an

*Abbreviations:* BMT, bone marrow transplantation; BO, bronchiolitis obliterans; CT, computed tomography; GVHD, graft-versus-host disease; LONIPC, late-onset noninfectious pulmonary complication; LTx, lung transplantation; mMRC, modified Medical Research Council; sPPFE, secondary pleuroparenchymal fibroelastosis; sPPFE after HM-Tx, secondary pleuroparenchymal fibroelastosis following treatment for hematologic malignancies; TALS, thoracic air-leak syndrome; UCBT, umbilical cord blood transplantation; VC, vital capacity.

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appropriate prognosis for LTx difficult.

Herein, we report a case of sPPFE after HM-Tx in a 29-year-old man that progressed rapidly with repeated pneumothorax during the waiting period for LTx, in which imaging and pathological findings showed rapid loss in lung volume.

## 2. Case presentation

A 27-year-old man visited our hospital with a cough lasting for more than a month. Twelve years earlier (at age 15), he underwent umbilical cord blood transplantation (UCBT) for the acute transformation of chronic myelogenous leukemia after receiving imatinib for two months. Neither acute nor chronic graft-versus-host disease (GVHD) occurred after UCBT. The patient was administered imatinib one year after UCBT (age 16 years) and achieved complete molecular remission two years after UCBT (age 18 years). At the first visit to our department, his SpO<sub>2</sub> was 97% in ambient air. The thorax was flattened. Chest computed tomography (CT) showed pleural thickening at the apex of the lung (Fig. 1A), and pulmonary function test showed severe restrictive ventilation impairment (vital capacity [VC], 1.84 L; %VC, 36%) (Table 1). Moreover, the patient experienced pneumothorax twice when he was 25 and 26 years old, and PPFE was clinically diagnosed.

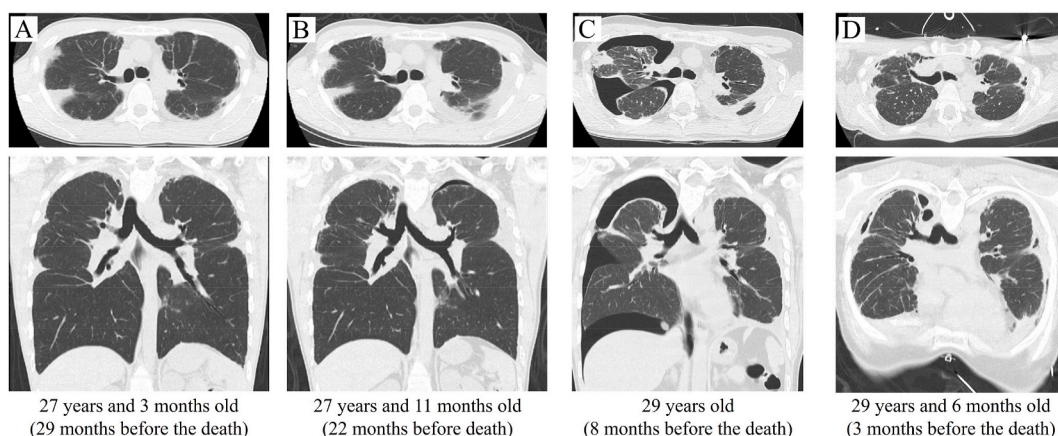
Although he was considered for LTx 4 months after the first visit (at age 27 years and 7 months), he did not register because his respiratory condition was stable (normoxia at room air, modified Medical Research Council (mMRC) 1–2 when he had no pneumothorax). However, he developed recurrent bilateral pneumothorax (in most cases, pneumothorax was minimal without the requirement of drainage), and the imaging findings revealed slowly progressive pleural thickening with predominance at the pulmonary apex and reduction of lung and thorax volumes (Fig. 1B, C, D and Fig. 2), and his respiratory function worsened over time (Table 1). Moreover, despite thoracic drainage, his lungs were not fully dilated and were fixed in a collapsed state. He registered for LTx at age 28 years and 7 months.

The patient had pneumothorax recurrence and was admitted to our hospital because of exacerbation of respiratory failure 8 months later (mMRC 3). Although he did not require oxygen therapy during admission, his dyspnea gradually worsened, and hypercapnia and hypoxemia appeared (mMRC 4) at age 29 years and 4 months. This eventually led to tracheostomy and high-flow oxygen therapy. His general condition worsened, and he was no longer able to tolerate LTx. His symptoms worsened from approximately 70 days after admission, and he had to be treated with palliative care. He died 6 months later. An autopsy was performed. Macroscopically, pleural fibrosis with predominant pleural thickening of the upper lobe was observed in both the right and left lungs (Fig. 3A and B). Histopathological analysis showed pleural thickening owing to increased fiber content and increased number of elastic fibers in the lung parenchyma just below the pleura. Elastic fiber growth continued into the interlobular septa, and the thickened interlobular septa were connected to the alveolar septa (septum), which were thickened by fiber growth (Fig. 3C). However, there were mild and focal histological changes going to bronchial abnormality, including bronchiolitis obliterans (BO) or other interstitial pneumonia, but limited and not so definitive alteration as in the earlier reports [4].

## 3. Discussion

Our findings suggest that PPFE should be considered as a pulmonary complication even 10 years or more after treatment for hematologic malignancies, including UCBT. Moreover, complication of TALS can progress the loss of lung volume rapidly, as visually depicted by the CT findings and the change in lung volume calculated using CT volumetry in our case. The prognosis of sPPFE after HM-Tx can be poor, especially when repeated pneumothorax occurs.

PPFE can be an important pulmonary complication that warrants attention in patients, years after treatment for hematologic malignancies. Symptoms may appear decades after hematologic malignancy remission (5). BO is widely known as a pulmonary

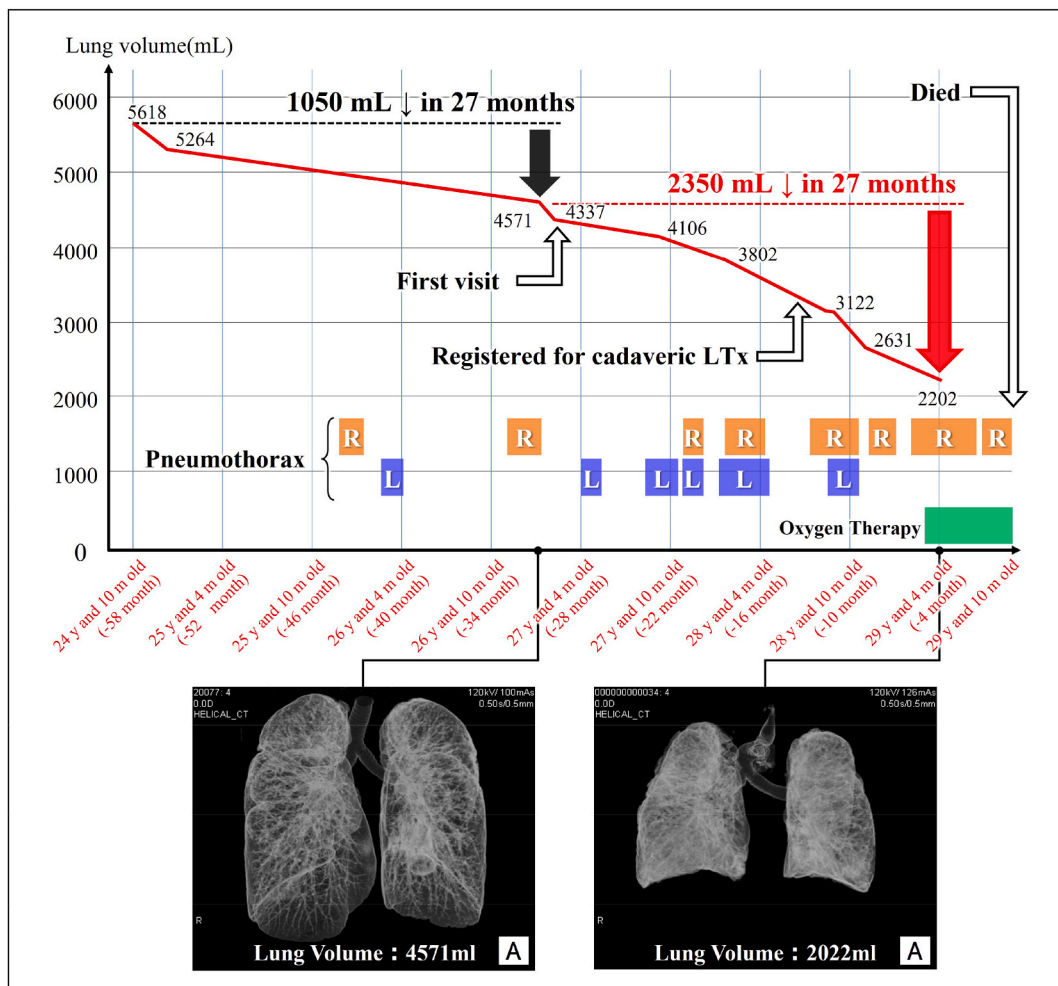


**Fig. 1.** (A–D) Chest computed tomography (CT) at the patient's first visit showed pleural thickening at the apex of the lung (A). Then, he developed recurrent bilateral pneumothorax, and the imaging findings showed progressive pleural thickening with predominance at the pulmonary apex and reduction in the lung and thorax volumes (B–D).

**Table 1**  
The time course of the results of pulmonary function tests.

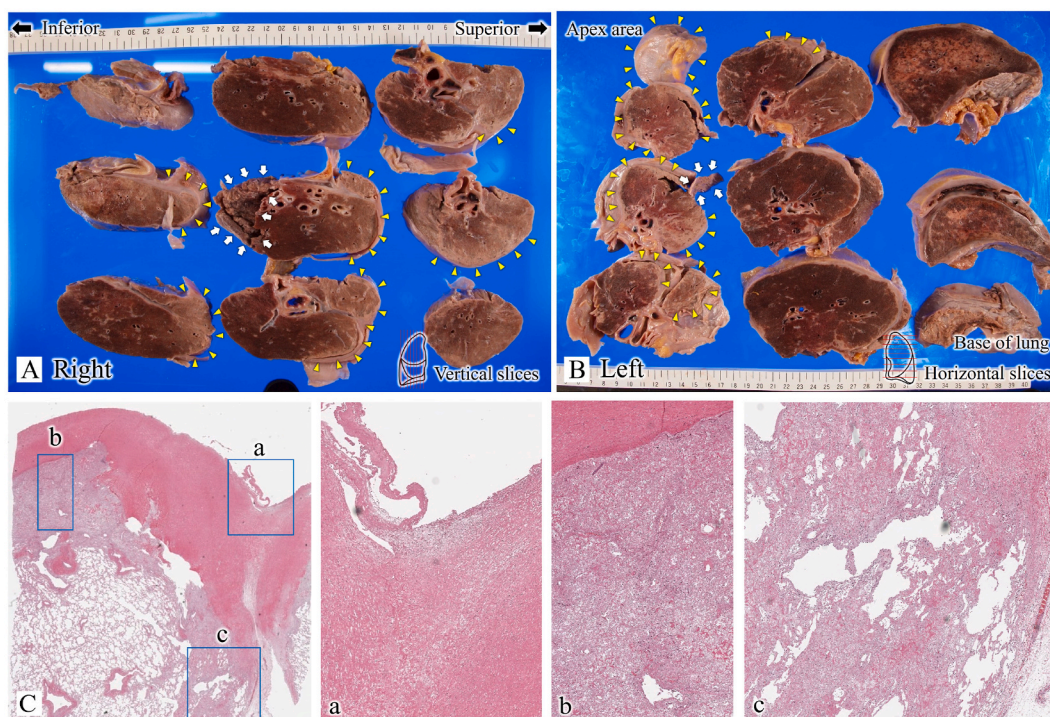
	27 years and 5 months old (2 years and 8 months before death)	27 years and 9 months old (1 year and 5 months before death)	28 years and 0 months old (1 year and 10 months before death)
VC (% predicted)	1.84 L (36%)	1.69 L (33%)	1.51 L (30%)
FEV1 (% predicted)	1.73 L (39%)	1.76 L (39%)	1.57 L (35%)
FEV1%	96.1%	100.0%	98.1%
RV (% predicted)	2.31 L (159%)	2.46 L (168%)	2.28 L (157%)
TLC (% predicted)	4.06 L (67%)	4.15 L (68%)	2.79 L (63%)
%DLco	N/A	61%	64%
%DLco/VA	N/A	83%	100%

DLco, diffusing capacity of the lung carbon monoxide; FEV1, forced expiratory volume in 1.0 second; N/A, not available; RV, residual volume; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity. The patient died at 29 years and 10 months of age.



**Fig. 2.** The clinical course and the lung volume calculated from computed tomography (CT) data of the patient. Total lung volumes were calculated based on CT image data using 3D-CT volumetry of an AZE Virtual Place Lexus workstation (AZE Co, Ltd., Tokyo, Japan).

disorder caused by chronic GVHD [1]. Recently, restrictive lung diseases similar to PPFE have also been reported as pulmonary complications after HM-Tx [1]. GVHD and antineoplastic drugs are presumed to be the causative factors in the pathogenesis of sPPFE after HM-Tx, although the detailed mechanism remains unclear. The incidence of PPFE as a late-onset noninfectious pulmonary complication (LONIPC) after hematopoietic stem cell transplantation ranges from 0.5 to 1.5% [5,6]. Because of its rare frequency, the



**Fig. 3.** The right lung was imaged with vertical slices (A) and the left lung with horizontal slices (B). Macroscopically, pleural fibrosis extending towards the lung parenchyma with upper lobe predominant pleural thickening was observed in both the right and left lungs (yellow triangles). Lung collapse due to pneumothorax was present in part of the lower lobe of the right lung and the upper lobe of the left lung (white arrows). Histopathological analysis showed that pleural thickening was due to increased fiber content, and the number of elastic fibers increased in the lung parenchyma just below the pleura (C-a) (Hematoxylin and eosin (HE) staining, x40). Elastic fiber growth continued into the interlobular septa, and the thickened interlobular septa were connected to the alveolar septa (septum), which were thickened by fiber growth (C-b, c) (Hematoxylin and eosin (HE) staining, x40). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

concept of disease is not well known; there are many unknowns, and the recognition of the disease is insufficient, which may delay its detection.

Tanizawa et al. evaluated the prognosis of patients with fibrotic interstitial lung disease registered for LTx in Japan. In this study, LONIPCs with radiological PPFE were associated with better survival than fibrotic interstitial lung disease without radiological PPFE [7]. However, PPFE presents two distinct patterns: a rapid decline in forced vital capacity over a short period and a slow decline over a longer period, suggesting that the disease follows a heterogeneous clinical course [8]. We searched the literature for fatal cases of sPPFE after HM-Tx, which were diagnosed prenatally and with an identifiable duration of clinical course, and four studies reporting 10 cases were found [2,6,9,10]. The evaluation of these cases and our case (11 cases in total) is presented in Table 2. The median age at death was 38 years, and eight of the 11 patients developed pneumothorax. The median time from the onset of PPFE to death was 37 months (range: 4–132 months). Contrastingly, the average waiting period for cadaveric LTx is approximately 29 months in Japan. Therefore, careful judgment is needed regarding the timing of transplant registration in anticipation of the waiting period because deaths may occur during the waiting period. LTx registration should always be considered after the diagnosis of PPFE, and it is important to distinguish between rapidly progressive and slowly progressive types. Further case studies are needed to identify the characteristics of the rapidly progressive type.

TALS is a rare complication of allogeneic bone marrow transplantation (BMT), such as pneumothorax, mediastinal emphysema, and subcutaneous emphysema [11]. While TALS is known to occur secondary to BO, PPFE after allogeneic BMT can cause TALS [2]. Ishi et al. reported five cases of TALS with PPFE as LONIPCs [2]. The duration from the onset of pneumothorax to death was 4–37 months (average 21.4 months). LTx should be considered when patients with sPPFE present with pneumothorax. In our case, pleural thickening with subpleural fibrosis was seen mainly in the upper lobe, and there was a loss of lung volume that progressed with the onset of recurrent bilateral pneumothorax. Lung volume was measured using CT images that evaluated the progress of sPPFE after HM-Tx (Fig. 2). The lung volume calculated from CT data decreased from 4,571 mL to 2,202 mL (–52%) in 2.3 years before the patient's death. The progression of the loss in lung volume changed rapidly when pneumothorax on both sides began to recur. This clinical course may have been due to inadequate expansion of the collapsed lung caused by pneumothorax, followed by reduction of the thorax and consequent decrease in lung capacity. The rapidly progressive type mentioned above could include cases in which rapid lung volume loss occurs subsequent to TALS. If a patient with sPPFE after HM-Tx begins to have a recurrent pneumothorax, it is essential to consider LTx because of the potential for the rapid deterioration of the respiratory condition.

**Table 2**

Fatal cases of secondary pleuroparenchymal fibroelastosis following treatment for hematologic malignancies that were diagnosed prenatally and with an identifiable duration of the clinical course.

No	Ref.	Age at death	Sex	Primary disease	Transplantation	Chemotherapy	GVHD	Pneumothorax	Number of Pneumothorax	Treatment of Pneumothorax	Duration between Transplantation and Onset of PPFE	Duration between Onset of PPFE and death	Duration between Transplantation and death
1	Mariani, 2016	41	Male	AML	allogeneic HSCT	ICE, cyclophosphamide	A and C GVHD	(-)	(-)	N/A	156 months	96 months	252 months
2	Ishii, 2016	44	Female	MDS	allogeneic BMT	fludarabine melphalan	(-)	(+) bilateral	N/A	Drainage Bleb/bullectomy	39 months (Onset of PPFE)	13 months	52 months
3	Ibid.	38	M	CML	allogeneic BMT	cyclophosphamide	(-)	(+) right	N/A	Drainage Pulmorrhaphy	109 months (Onset of PPFE)	16 months	125 months
4	Ibid.	28	M	AML	allogeneic BMT	cyclophosphamide busulfan	(-)	(+) bilateral	N/A	Drainage Pleurodesis	77 months (Onset of PPFE)	37 months	114 months
5	Ibid.	50	M	AA	allogeneic BMT	cyclophosphamide	C-GVHD (limited)	(+) bilateral	N/A	Drainage Pleurodesis	106 months (Onset of PPFE)	4 months	110 months
6	Watanabe, 2014	19	M	Hematologic malignancy	allogeneic BMT	N/A	N/A	(+)	2	N/A	36 months (Onset of PPFE)	25 months	61 months
7	Ibid.	37	F	N/A	allogeneic BMT	N/A	N/A	(+)	4	N/A	168 months (Onset of PPFE)	56 months	224 months
8	Narmkoong, 2017	59	M	ALL	allogeneic HSCT	cyclophosphamide	A and C GVHD	(-)	(-)	(-)	90 months	42 months	132 months
9	Ibid.	26	M	AML	allogeneic HSCT	cyclosporine A, cyclophosphamide	A and C GVHD	(+)	N/A	N/A	41 months	132 months	173 months
10	Ibid.	49	F	CML	allogeneic HSCT	cyclosporine A, cyclophosphamide	A and C GVHD	(-)	(-)	(-)	109 months	60 months	169 months
11	Our Case	29	M	CML blastic crisis	allogeneic CBT	imatinib		(+)	2	N/A	131 months	29 months	161 months

AA, aplastic anemia; A GVHD acute graft versus host disease; ALL, acute lymphoid leukemia; AML, acute myeloblastic leukemia; BMT, bone marrow transplant plantation; CBT, cord blood transplantation, C GVHD, chronic graft versus host disease; CML, chronic myelogenous leukemia; HSCT, hematopoietic stem cell transplantation; ICE, ifosfamide-carboplatin-etoposide chemotherapy; MDS, myelodysplastic syndrome; PPFE, pleuroparenchymal fibroelastosis.

#### 4. Conclusion

In summary, TALS with sPPFE after HM-Tx can show very rapid progression due to lung volume loss and a fatal clinical course while awaiting LTx. The timing of LTx registration in such cases can be critical, especially when pneumothorax recurs. The clinical management with attention to this time course might result in timely surgeries and a reduction in the mortality rate of this condition.

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#### Declarations of competing interest

None.

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