Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7402-21
Intern Med 61: 533-540, 2022
http://internmed.jp

【 CASE REPORT 】

Pleuroparenchymal Fibroelastosis with a Predominantly Airway-centered Distribution: A Late Complication of Chemotherapy

Kanako Katayama[1], Toru Arai[2], Takehiko Kobayashi[1], Sayoko Shintani[1], Naoko Takeuchi[1], Yoshinobu Matsuda[3], Chikatoshi Sugimoto[2], Yasushi Inoue[1], Maiko Takeda[4], Takahiko Kasai[4], Masanori Akira[5] and Yoshikazu Inoue[2]

Abstract:
Airway-centered fibroelastosis is a distinct entity characterized by prominent airway-centered elastosis of the upper lobe with little or no pleural involvement. Little is known regarding its etiology; however, it was reported to have an idiopathic or asthma-associated etiology. We document, for the first time, 2 women (19 and 60 years old) who developed pleuroparenchymal fibroelastosis with a predominantly airway-centered distribution as a late complication (6 and 9 years later, respectively) of chemotherapy. The disease rapidly progressed following the manifestation of symptoms, and they subsequently died (3 and 2 years later, respectively). Therefore, post-chemotherapy long-term monitoring for this disease is warranted.

Key words: airway-centered fibroelastosis, pleuroparenchymal fibroelastosis, etiology, chemotherapy, cyclophosphamide, late-onset

(Intern Med 61: 533-540, 2022)
(DOI: 10.2169/internalmedicine.7402-21)

Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a form of upper-lobe-dominant progressive pulmonary fibrosis characterized by subpleural elastosis (1-3). Idiopathic PPFE is an interstitial lung disease of unknown etiology with no clear association with smoking according to the American Thoracic Society/European Respiratory Society guidelines (2, 3). Most patients with PPFE are considered idiopathic. PPFE in some patients has been reportedly induced by lung, bone marrow or hematopoietic cell transplant, immunosuppressive agents, or occupational exposure (4-7). A limited number of cases with PPFE have been reported as a lung toxicity following chemotherapy without transplantation and thoracic radiotherapy (1, 5, 8). Based on these cases with PPFE, alkylating agents, especially cyclophosphamide and bischloroethylnitrosourea, are causally related to PPFE. Two of our patients developed PPFE as a late complication of chemotherapy; the fibroelastosis was prominently centered on airways with minimal pleural involvement, mimicking so-called "airway-centered fibroelastosis" (9).

Airway-centered fibroelastosis has recently been described as a unique and distinct entity in five non-smoking middle-aged women with evidence of prominent airway-centered elastosis in their lung samples (9). Following the publication of this report, a few cases with similar characteristics have been reported (10-12). The clinical course of previously reported cases indicates that patients with airway-centered fibroelastosis have progressive disease and a poor prognosis. Airway-centered fibroelastosis was previously reported to be idiopathic or asthma-associated; however, a clear profile has

[1]Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Japan, [2]Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Japan, [3]Department of Psychosomatic Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Japan, [4]Department of Pathology, National Hospital Organization Kinki-Chuo Chest Medical Center, Japan and [5]Department of Radiology, National Hospital Organization Kinki-Chuo Chest Medical Center, Japan
Received for publication February 22, 2021; Accepted for publication July 5, 2021
Correspondence to Dr. Yoshikazu Inoue, giichiyi@me.com

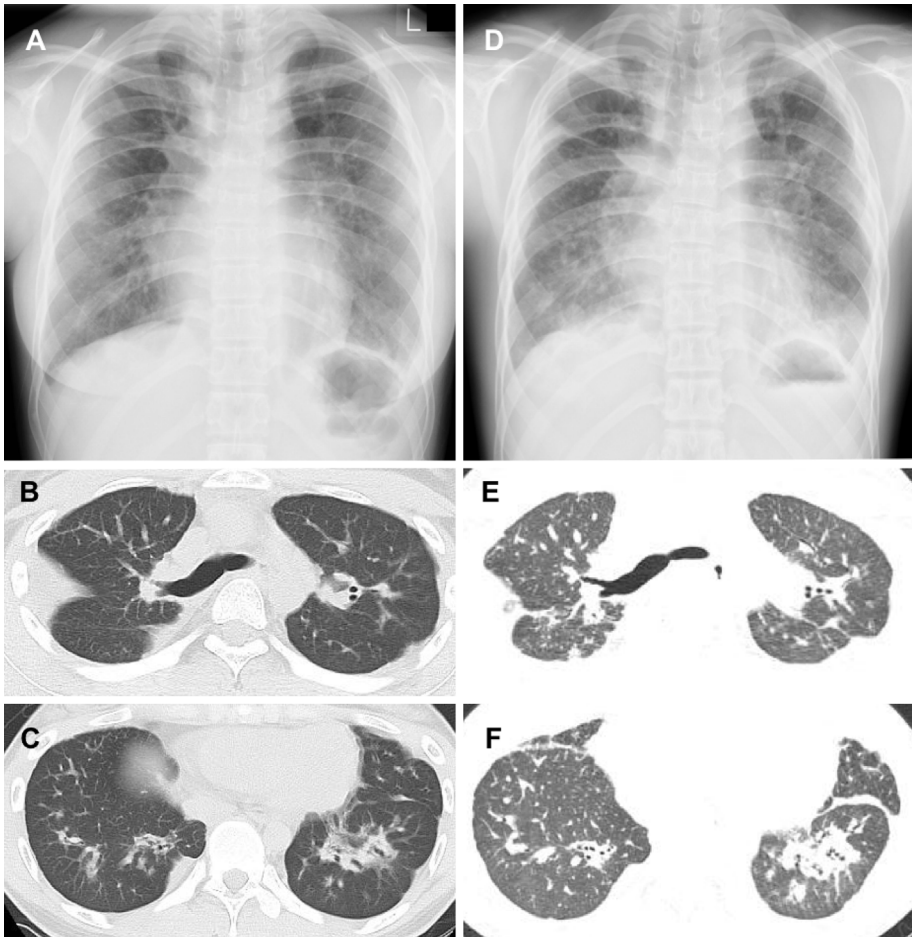

Figure 1. Radiological findings of Case 1. (A) Chest radiography performed at the onset of symptoms (six years after chemotherapy) showed abnormal shadows and volume loss predominantly in the upper lung fields. (B, C) High-resolution computed tomography (HRCT) at the same time showed central consolidation along the bronchovascular bundle, marked peribronchial thickness with traction bronchiectasis, subpleural patchy consolidations, and volume loss predominantly in the upper lobe. (D) Chest radiography performed about seven and a half years after chemotherapy showed increased pulmonary infiltrates and volume loss of the lungs. (E, F) HRCT at the same time showed worsening of the infiltrates in the upper lobe and increasingly prominent high-density shadows along the bronchovascular bundle.

not yet been defined due to its rare occurrence (9). There have been no reports of patients developing airway-centered fibroelastosis following chemotherapy. The accumulation of cases may improve our comprehension of this disease and lead to a timelier diagnosis and treatment.

We herein report two cases of PPFE with a predominantly airway-centered distribution that developed as a late complication of chemotherapy.

Case Reports

Case 1

An 18-year-old woman presented to a local doctor with a dry cough. A chest radiograph indicated abnormal shadows and volume loss predominantly in the upper lung fields (Fig. 1A). High-resolution computed tomography (HRCT) revealed central consolidation along the bronchovascular bundle, marked peribronchial thickness with traction bronchiectasis, subpleural patchy consolidations, and volume loss predominantly in the upper lobes (Fig. 1B-C). Bronchoscopy was performed, and a bronchoalveolar lavage (BAL) examination from the left B5 revealed a total cell count of 3.2×10^5/mL, of which 78.3%, 15.7%, 4.7%, and 1.3% were macrophages, lymphocytes, neutrophils, and eosinophils, respectively. The CD4/CD8 lymphocyte ratio in the BAL was 0.56. The microbiological and cytological examination results were negative. Transbronchial lung biopsy (TBLB) specimens revealed signs of peribronchiolar fibroelastosis in the airway wall and fibrous alveolitis in the adjacent alveolar region. A 20-mg dose of prednisolone was administered daily for 2 weeks; however, no improvement in her clinical findings were observed, and the treatment was discontinued. She experienced dyspnea on exertion, which progressively worsened, and she was referred to our institution one year later following the onset of symptoms.

She had been diagnosed with acute lymphoblastic leukemia (ALL) at nine years old and underwent multidrug chemotherapy (including cyclophosphamide, cytarabine, daunorubicin, dexamethasone, L-asparaginase, leucovorin, methotrexate, prednisone, THP-adriamycin, vincristine, and 6-mercaptopurine) according to the Japan Association of Childhood Leukemia Study ALL-02 standard risk protocol until 12 years old (13). She remained in complete remission at first. Therefore, she did not undergo any radiotherapy or hematopoietic stem cell transplantation. She had no remarkable medical history, with the exception of ALL. She did not have asthma or other atopic diseases. She had not taken any medicine, including herbal medicine or supplements. There was no family history of pulmonary fibrosis. She was a non-smoking college student and reported no known exposure to environmental allergens or asbestos.

On a physical examination, she was cachectic and had a flattened thoracic cage, and her body mass index was 17.3 kg/m^2. Her pulse rate, blood pressure, and respiratory rate were 76 pulses/min, 106/65 mmHg, and 18 breaths/min. Her heart sounds were normal; no crackle or rhonchus was audible. Her fingers were not clubbed, and the joints of her extremities were neither tender nor swollen. Laboratory tests revealed the following results: Krebs von den Lungen-6 (KL-6)=281 IU/mL (normal <500 IU/mL), surfactant protein-D (SP-D)=123.7 ng/mL (normal <110 ng/mL), and surfactant protein-A=49.7 ng/mL (normal <43.8 ng/mL). Her blood cell count and C-reactive protein level were normal. There was no clinical or serological evidence of connective tissue disease, vasculitis, or hypersensitivity pneumonitis. The results of an arterial blood gas analysis on room air were as follows: pH 7.349, partial pressure of carbon dioxide ($PaCO_2$) 43.9 Torr, and PaO_2 93.6 Torr (first alveolar-arterial oxygen gradient 5.1 Torr). Pulmonary function tests revealed the following findings: a forced vital capacity (FVC) of 0.60 L (19.6% predicted), forced expiratory volume in 1 s (FEV1) of 0.54 L (20.8% predicted), FEV1/FVC ratio (FEV1%) of 90.0%, residual volume (RV) of 0.73 L (83.9% predicted), total lung capacity (TLC) of 1.33 L (30.7% predicted), and RV/TLC (%) of 54.9%. A six-minute walking test demonstrated a walking distance of 216 m with minimum SpO_2 of 85%. Transthoracic echocardiography revealed mild pulmonary hypertension with an estimated systolic pulmonary artery pressure of 32.5 mmHg.

Due to a marked decline in her lung function, she was unable to undergo video-assisted thoracoscopic surgery for a multi-disciplinary diagnosis. The lung fibrosis progressed rapidly with marked traction bronchiectasis; a diagnosis of progressive fibrosing interstitial lung disease was thus formulated, and treatment with nintedanib was initiated. Due to her appetite worsening, the treatment was ceased after seven months. She also started receiving long-term oxygen treatment and was registered for a lung transplantation. The chest radiograph and HRCT at this time, compared with that taken at a previous hospital, showed worsening infiltration of the upper lobes and high density with increasingly prominent shadows along the bronchovascular bundle (Fig. 1D-F). Thereafter, the patient repeatedly developed bilateral pneumothorax and had progressively worsening hypercapnic chronic respiratory failure. Three years after the onset of her respiratory symptoms, she was hospitalized with a left pneumothorax with a complication of acute exacerbation. Chest radiography showed ground-glass opacity in the lung opposite the pneumothorax. She died of progressive respiratory insufficiency, three years following the onset of symptoms.

On an autopsy, both lungs showed a white fibrotic lesion in the peribronchial and subpleural regions. The major pathologic findings of the lungs were as follows: 1) airway-centered fibroelastosis, associated with fibrosing nonspecific interstitial pneumonia and 2) diffuse alveolar damage and focal bronchitis. Bone marrow finding showed no recurrent or metastatic findings of acute lymphocytic leukemia. A histopathologic evaluation of the lungs revealed fibroelastosis with a predominantly airway-centered distribution, as confirmed by Elastica van Gieson staining (Fig. 2). The patient was diagnosed with chemotherapy-induced PPFE with a predominantly airway-centered distribution.

Case 2

A 60-year-old woman presented to a local doctor with a complaint of dry cough and dyspnea on exertion. Two months later, she had developed back pain. Chest radiography revealed abnormal shadows in the upper lung fields, and she was referred to our institution.

Her medical history included glaucoma and thyroid cancer. She had undergone a partial thyroidectomy at 46 years old, followed by radiotherapy and daily administration of cyclophosphamide for 5 years. She had never smoked and had no occupational or environmental exposure. She did not have asthma or any other atopic diseases and had not taken any medicine. There was no family history of pulmonary fibrosis.

On a physical examination, her body mass index at the first admission to our hospital was 21.6 kg/m^2. Her heart sounds were normal, and no crackle or rhonchus was audible. Her fingers were not clubbed, and the joints of her extremities were neither tender nor swollen. Laboratory tests revealed the following results: KL-6=433 IU/mL, and SP-D =130 ng/mL. Her blood cell count and C-reactive protein level were normal. There was no clinical or serological evidence of connective tissue disease, vasculitis, or hypersensitivity pneumonitis. The results of an arterial blood gas analysis with the patient on room air were as follows: pH 7.413, $PaCO_2$ 45.8 Torr, and PaO_2 84.3 Torr. Pulmonary function tests revealed the following findings: FVC of 1.39 L (56.7% predicted), FEV1 of 1.20 L (48.9% predicted), FEV1% of 86.3%, RV of 0.73 L (61.9% predicted), TLC of 2.20 L (57.9% predicted), RV/TLC (%) of 33.3%, and the percent predicted of diffusion lung capacity for carbon monoxide of 35.2%. A chest radiograph revealed pleural thickening and infiltrates in the middle and upper lung fields (Fig. 3A). HRCT revealed consolidation along the broncho-

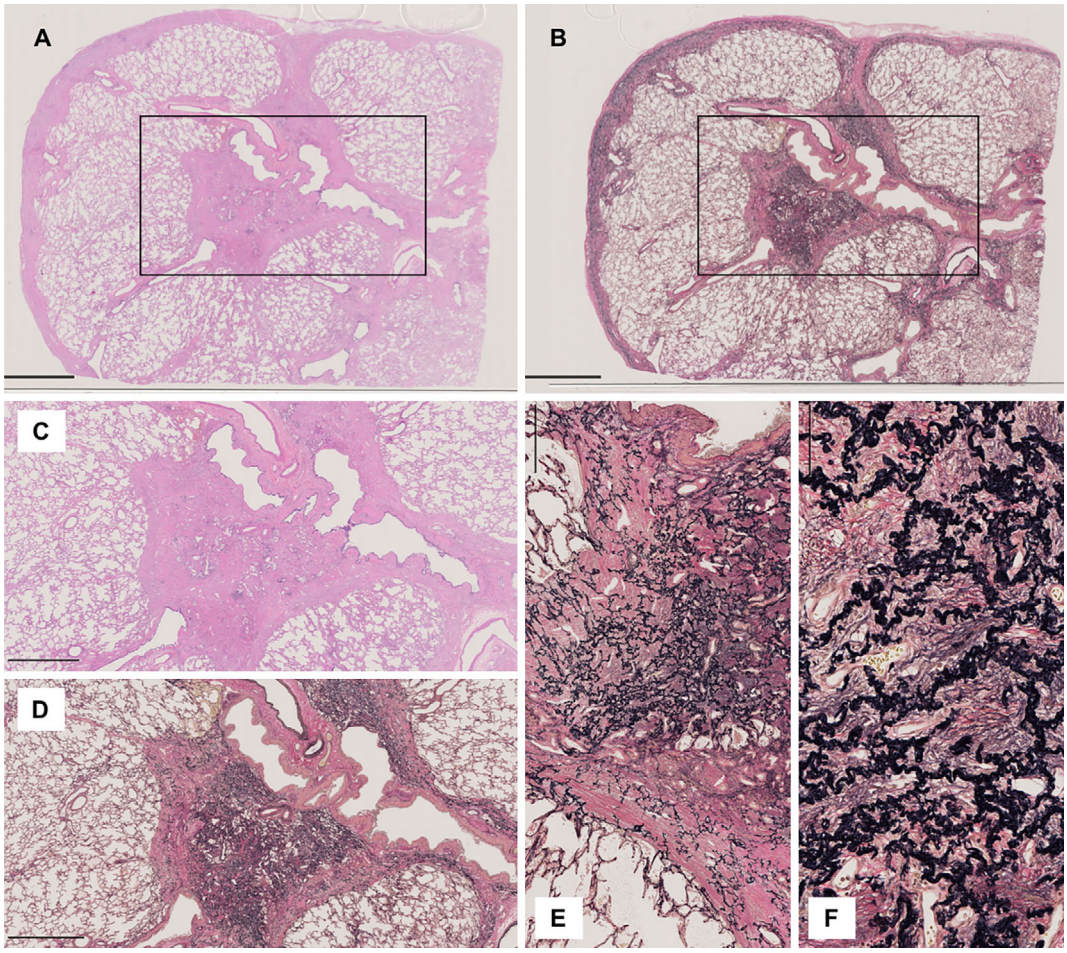

Figure 2. Pathological findings of Case 1. (A, B) Autopsy specimens (left upper lobe) showed prominent airway-centered and subpleural fibroelastosis [A; Hematoxylin and Eosin (H&E) staining, B; Elastica van Gieson staining, low power]. (C, D) Higher magnification view of A and B, respectively, shows peribronchiolar dense fibrotic areas containing elastic fibers (C; H&E staining, D; Elastica van Gieson staining, mid power). (E, F) The specimens also show peribronchiolar fibroelastosis. The lumen of the alveolar space is replaced by fibrosis, and a marked increase and aggregation of elastic fiber is observed (Elastica van Gieson staining, E; mid power, F; high power).

vascular bundle with traction bronchiectasis and pleural thickening predominantly in the upper lobes (Fig. 3B-C). BAL was performed from the right B^5, and the BAL fluid (BALF) recovery rate was 45%. The total cell count in the fluid was 1.32×10^5/mL, of which 83.8%, 8.4%, 7.2%, and 0.4% were macrophages, lymphocytes, neutrophils, and eosinophils, respectively. The CD4/CD8 lymphocyte ratio was 4.17. No microorganisms were detected in the BALF. The TBLB specimens did not reveal any specific findings.

At this point, the differential diagnosis included sarcoidosis, chronic hypersensitivity pneumonitis, and PPFE. As symptoms such as dyspnea on exertion and dry cough worsened during the follow-up of approximately one and a half years, surgical lung biopsy specimens were obtained to establish a definitive diagnosis. The specimen showed mainly peribronchiolar fibroelastosis with focal pleural involvement (Fig. 4). Since her disease was suspected to be a reaction to a cytotoxic agent administered for the treatment of thyroid cancer, we inquired regarding her post-operative medication from her former physician. It became evident that she had received cyclophosphamide treatment for five years; hence, she was diagnosed with cyclophosphamide-induced late-onset PPFE with a predominantly airway-centered distribution. Increased diffuse infiltrate and volume loss in the upper fields were apparent on chest radiography (Fig. 3D). On HRCT, fibrotic changes along the bronchovascular bundle with traction bronchiectasis and volume reduction of the lungs worsened (Fig. 3E, F). She subsequently experienced repeated bilateral pneumothoraces, and her lung function test results progressively worsened, causing severe ventilation failure and respiratory acidosis (pH 7.319, $PaCO_2$ 88.9 Torr, PaO_2 85.5 Torr on 1.5 L/min of oxygen via a nasal cannula). Four years following the onset of symptoms, she died of respiratory failure.

Discussion

To our knowledge, this is the first report on cases of post-

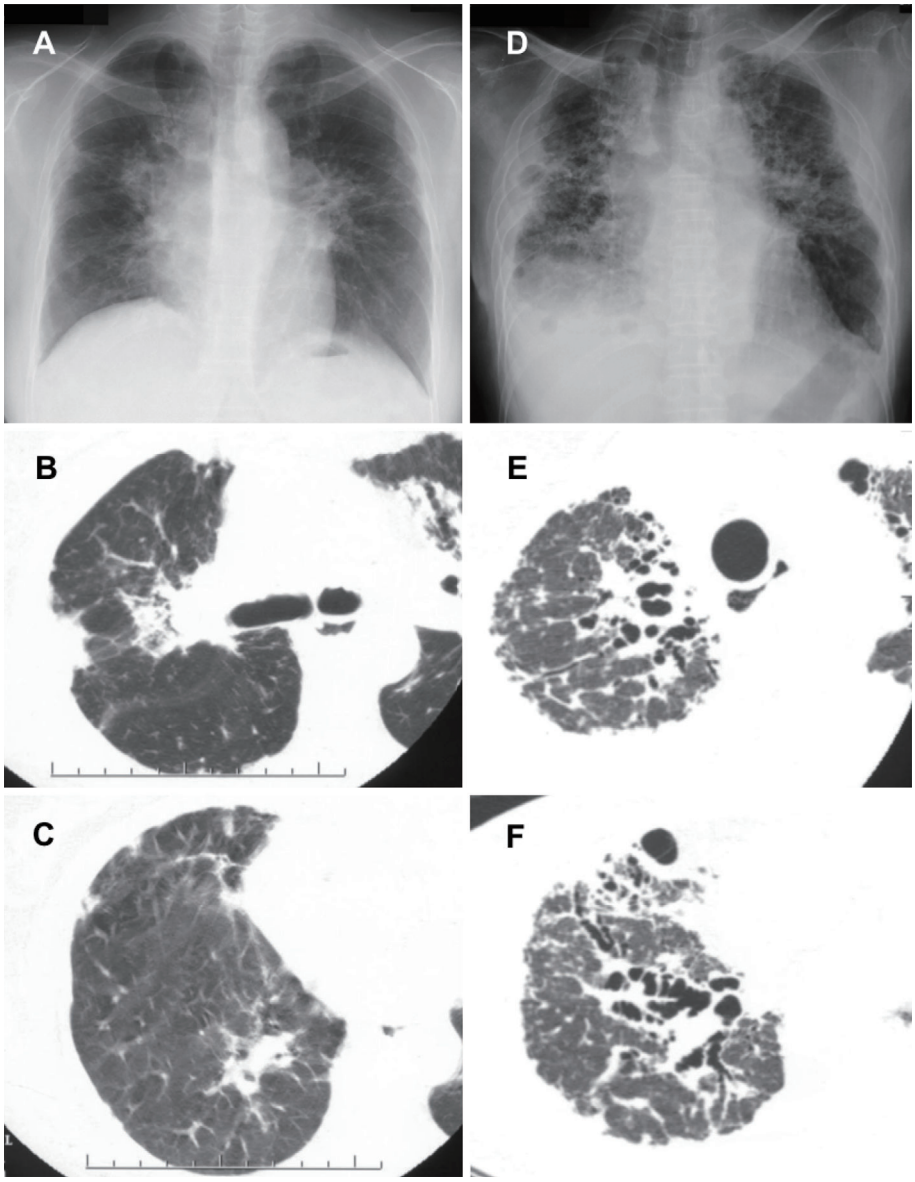

Figure 3. **Radiological findings of Case 2. A chest radiograph taken at the first visit to our hospital (nine years after the administration of cyclophosphamide) showed pleural thickening and infiltrates in the middle and upper lung fields (A). High-resolution computed tomography (HRCT) at the same time showed consolidation and ground-glass opacity along the bronchovascular bundle with traction bronchiectasis and pleural thickening predominantly in the upper lobe (B-C). A chest radiograph taken 11 years after the administration of cyclophosphamide showed increased diffuse infiltrates and volume loss in the upper fields (D). At the same time, HRCT showed fibrotic changes along the bronchovascular bundle with traction bronchiectasis, and worsened volume reduction of the lungs (E-F).**

chemotherapy PPFE with a predominantly airway-centered distribution. The etiology of PPFE remains unknown; most patients with PPFE are considered idiopathic. Some cases with PPFE reportedly develop following a history of stem cell transplantation or as a consequence of chronic lung rejection in lung transplant recipients (14, 15). To date, only a limited number of cases with PPFE as a manifestation following chemotherapy, not in combination with hematopoietic stem cell transplantation or thoracic radiotherapy, have been reported (1, 5, 8). Six reported cases and our two cases, as complications of chemotherapy, are reviewed in Table. All eight cases were also late-onset following chemotherapy, and the time period from the end of chemotherapy and the first noticeable symptom or radiological abnormality ranged from 0.5 to 16 years. Remarkably, seven of the eight cases received cyclophosphamide before the development of the disease. Of the cases shown in Table, six of the seven reported cases developed pneumothorax. In their clinical courses, one patient was alive two years following the onset of symptoms (whether or not the patient's condition deteriorated remains unknown), and three patients' conditions deteriorated. The remaining four patients developed pneumothorax and subsequently died. While in the previously reported cases of PPFE, the fibroelastosis was mainly distributed in

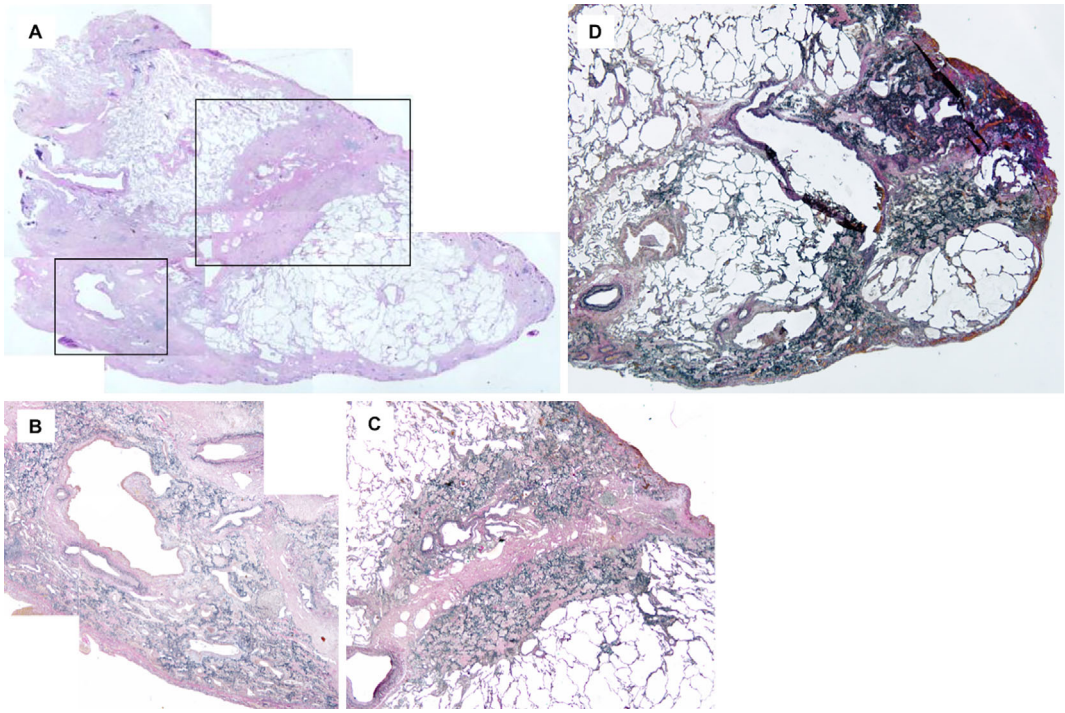

Figure 4. **Pathological findings of Case 2. (A) A surgical lung biopsy specimen (segment 8 of the right lower lobe) showed predominantly peribronchiolar centroacinar distribution with pleural thickening (Hematoxylin and Eosin staining, low power). (B, C) Higher-magnification views of (A) showed peribronchial elastosis (Elastica van Gieson staining, mid-power). (D) Another specimen of the same segment of the lung showed prominent peribronchiolar and subpleural fibrosis and elastosis (Elastica van Gieson staining, mid-power).**

the subpleural area, in the present cases, it was predominantly centered on the airway.

Airway-centered fibroelastosis has been originally described in five female patients in recent years (9). In a previous report, it was characterized by extensive airway-centered fibroelastosis of the upper lobes on histology and marked bronchial abnormalities with bronchial wall thickening, bronchial wall deformation, and bronchiectasis, along with progressive parenchymal retraction and predominantly subpleural upper-lobe consolidation on HRCT. The diagnosis requires histopathological evidence of elastosis with a typical HRCT pattern (9). In patients with airway-centered fibroelastosis, it is prominently centered on airways with minimal or no pleural involvement. The pathological and radiological characteristics were consistent in both cases in our report. The centrilobular region is in contact with other lobes constituting the perilobular region. Since the region of fibroelastosis in PPFE patients can be broadly described as perilobular, the affected area in PPFE with airway-centered fibroelastosis patients can be described similarly. With a difference in the distribution of fibroelastosis, airway-centered fibroelastosis is considered a subtype of PPFE. The laboratory findings in two of our patients with normal or close to the upper range of normal serum KL-6 levels and elevated SP-D values were consistent with the features reported in patients with PPFE (16, 17).

Regarding the clinical features in the previous report, out of five middle-aged female patients with airway-centered fibroelastosis who had never smoked, four had chronic asthma, all had a progressive disease course, and two required lung transplantation (9). The authors hypothesized that airway-centered fibroelastosis may be idiopathic or asthma-associated. Since this report, three patients diagnosed with airway-centered fibroelastosis were reported. Kronborg-White et al. reported a 55-year-old man who was a former smoker and had been diagnosed with an airway-centered fibroelastosis of unknown etiology who did not complain of asthma but had alveolar consolidations around centriacinar regions mimicking sarcoidosis on radiological findings (10). Bargagli et al. reported a 48-year-old non-smoking woman who was diagnosed with airway-centered fibroelastosis associated with non-necrotizing granulomas of unknown etiology (11). She did not have any asthma complications, and her condition progressively deteriorated. She required a bilateral lung transplant a few years following her diagnosis. Minomo et al. reported a 26-year-old man with a history of asthma who was diagnosed with airway-centered fibroelastosis of unknown etiology. He developed pulmonary hypertension and died six years following his diagnosis (12). The condition of our two patients also deteriorated rapidly, and they both died a few years following the onset of symptoms. Thus, recent reports have shown no consistency regarding a history of asthma or smoking in these patients (10-12). In a previous report, patients with airway-centered fibroelastosis

Table. Data of Reported Cases of Chemotherapy-induced Pleuroparenchymal Fibroelastosis (PPFE) and Our Cases.

	Patient number							
	1	2	3	4	5	6	Case 1	Case 2
Predominant distribution	Subpleural	Subpleural	Subpleural	Subpleural	Subpleural	Subpleural	Airway-centered	Airway-centered
Sex	Female	Male	Male	Male	Male	Female	Female	Female
Age at diagnosis*, y	65	28	32	28	27	15	21	62
Smoking status	Never-smoker	Never-smoker	Current smoker	Never-smoker	Never-smoker	Never-smoker	Never-smoker	Never-smoker
BMI, kg/m^2	-	-	18	16	19	16	17	22
Spontaneous pneumothorax	-	Yes	Bilateral	Yes	Bilateral	No	Bilateral	Bilateral
Outcome**	Alive [2]	Deterioration (Lung transplantation)	Deterioration [19]	Death [2]	Death [15]	Deterioration [4]	Death [3]	Death [4]
Neoplastic condition	Breast cancer	Mature B-cell acute lymphoblastic leukemia	Acute T-lymphoblastic leukemia	Acute T-lymphoblastic leukemia	Oligodendroglioma	Pylocytic astrocytoma	Acute lymphoblastic leukemia	Thyroid cancer
Age at diagnosis of malignancy, y	61	14	14	4	24	5	9	46
Age at treatment termination, y	-	-	17	10	25	12	12	51
Time from chemotherapy end to onset***	4 y	7 y	5 y	16 y	1 y	6 m	6 y	9 y
Chemotherapy regimen	61 y of age: CPA, MTX, 5-FU TAM	14 y of age: CPA, VP-16, MTX, Ara-C, THP	14 y of age: CPA, VCR, PS, DRB, L-ASP, intrathecal MTX, Ara-C; consolidation: CPA, VCR, MTX. 17 y of age: maintenance: CPA, VCR, Ara-C, L-ASP, PS, MTX, 6-MP	4 y of age: VCR, RUB, PS, intrathecal MTX, cytosine-TGN 7 y of age: CPA, TGN, RUB, HU, MTX, BCNU, Ara-C, VCR 10 y of age: VCR, RUB, L-ASP, PS, CPA, VCR, ADR, Ara-C	24 y of age: ACNU, BCNU, second line: CBDCA, VP-16 third line: oral PCZ	5 y of age: CBDCA, VP-16, CPA, PCZ, CDDP, VCR. 11 y of age: vinblastine. 12 y of age: TGN, PCZ, CCNU, VCR.	9 y of age: PS, VCR, DRB, L-ASP, intrathecal MTX, CPA, Ara-C, DEX, Leucovorin 10 y of age: PS, VCR, THP-ADR, 6-MP	46-51 y of age: CPA
Irradiation type	None	None	None	Craniospinal and Testicular	Brainstem	None	None	Cervical
Ref	1	8	5	5	5	5	Our Case 1	Our Case 2

PPFE: pleuroparenchymal fibroelastosis, BMI: body mass index, y: years, m: months, CPA: cyclophosphamide, MTX: methotrexate, 5-FU: fluorouracil, TAM: tamoxifen, VP-16: etoposide, Ara-C: cytosine arabinoside, THP: pirarubicin, VCR: vincristine, PS: prednisone, DRB: daunorubicin hydrochloride, L-ASP: L-asparaginase: 6-MP: 6-mercaptopurine, RUB: rubidomycin, TGN: thioguanine, HU: hydroxyurea, BCNU: 1,3-bis-(2-chloroethyl)-1-nitrosourea, ADR: adriamycin, ACNU: N'-[(4-amino-2-methylpyrimidin-5-yl)methyl]-N-(2-chloroethyl)-N-nitrosourea, CBDCA: carboplatin, PCZ: procarbazine, CDDP: cisplatin, CCNU: N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosourea

* Age at PPFE or airway-centered fibroelastosis diagnosis

** Outcome [years after symptom onset]

*** Time from chemotherapy end to onset of chest symptom or abnormality on chest radiography

were more likely to have asthma as a clinical symptom, and the authors did not describe pathological findings of asthma-type bronchitis/bronchiolitis (9). Therefore, the relationship between asthma and the onset of the disease is unclear. The causal relationship between the onset of fibroelastosis and smoking history is also currently unknown. Our cases did not have asthma complications and were considered to have been induced by chemotherapy agents.

In case 1, the patient had received many types of drugs for ALL, and it is unclear which drug was the primary causative factor. However, in most reported cases of late-onset PPFE due to chemotherapy, cyclophosphamide was associated. Furthermore, both patients described in the present report received cyclophosphamide during chemotherapy.

Malik et al. identified two patterns of cyclophosphamide-induced lung injury (18). One is early-onset pneumonitis that improved following the discontinuation of cyclophosphamide, and the other was late-onset pleuropulmonary fibrosis developing and progressing following the discontinuation of cyclophosphamide. Late-onset cases are clinically similar to PPFE cases, and pleural thickening is generally thought to be a characteristic feature. However, their diagnosis remains unclear, as these cases were reported before PPFE was identified as a distinct clinicopathological entity, and the pathological findings were not described in most cases. Hamada et al. reported a case of cyclophosphamide-induced late-onset lung disease in which the autopsied lung was pathologically assessed (19). The major pathologic findings of the lungs were multifocal fibrotic lesions involving the peribronchial region as well as subpleural lesions of both the upper lobes accompanied by markedly increased elastic fibers within the alveolar walls. Chest computed tomography indicated that the pulmonary lesions were mainly distributed in the pleural regions and along the bronchovascular bundles. These pathological and radiological findings are similar to those observed in airway-centered fibroelastosis. This case also rapidly progressed with occasional episodes of pneumothoraces until her death three years following the onset of symptoms. The increased study of such cases is necessary to determine the mechanism, characteristics, and risk factors associated with the development of late-onset PPFE due to cyclophosphamide.

In conclusion, we report for the first time two cases of PPFE with predominantly airway-centered distribution that developed as a late complication of chemotherapy. Cases treated with chemotherapy, especially cyclophosphamide, need to receive long-term follow-up. Currently, airway-centered fibroelastosis is considered refractory to any medication and has a poor prognosis; therefore, it should be diagnosed as early as possible and receive treatments, such as lung transplantation. Additional reports and studies are required to improve our understanding of the disease and its etiology and to develop novel treatment approaches to improve its poor prognosis.

This study was approved by the Institutional Review Board of the NHO Kinki-Chuo Chest Medical Center.

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

Acknowledgements

We would like to thank Dr. Shinji Konami of the Department of Pediatrics, Wakayama Medical University, for the clinical contributions to this report, and Dr. Masanori Kitaichi of the Department of Pathology, National Hospital Organization Minami Wakayama Medical Center, for the pathological evaluation.

References

1. Frankel SK, Cool CD, Lynch DA, Brown KK. Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity. Chest **126**: 2007-2013, 2004.
2. Reddy TL, Tominaga M, Hansell DM, et al. Pleuroparenchymal fibroelastosis: a spectrum of histopathological and imaging phenotypes. Eur Respir J **40**: 377-385, 2012.
3. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med **188**: 733-748, 2013.
4. Mariani F, Gatti B, Rocca A, et al. Pleuroparenchymal fibroelastosis: the prevalence of secondary forms in hematopoietic stem cell and lung transplantation recipients. Diagn Intern Radiol **22**: 400-406, 2016.
5. Beynat-Mouterde C, Beltramo G, Lezmi G, et al. Pleuroparenchymal fibroelastosis as a late complication of chemotherapy agents. Eur Respir J **44**: 523-527, 2014.
6. Xu L, Rassaei N, Caruso C. Pleuroparenchymal fibroelastosis with long history of asbestos and silicon exposure. Int J Surg Pathol **26**: 190-193, 2018.
7. Huang Z, Li S, Zhu Y, Zhu H, Yi X. Pleuroparenchymal fibroelastosis associated with aluminosilicate dust: a case report. Int J Clin Exp Pathol **8**: 8676-8679, 2015.
8. Chen F, Matsubara K, Miyagawa-Hayashino A, et al. Lung transplantation for pleuroparenchymal fibroelastosis after chemotherapy. Ann Thorac Surg **98**: e115-e117, 2014.
9. Pradere P, Gauvain C, Danel C, et al. Airway-centered fibroelastosis: a distinct entity. Chest **149**: 767-774, 2016.
10. Kronborg-White S, Ravaglia C, Dubini A, et al. Cryobiopsies are diagnostic in pleuroparenchymal and airway-centered fibroelastosis. Respir Res **19**: 135, 2018.
11. Bargagli E, Rottoli P, Torricelli E, et al. Airway-centered pleuroparenchymal fibroelastosis associated with non-necrotizing granulomas: a rare new entity. Pathobiology **85**: 276-279, 2018.
12. Minomo S, Arai T, Tachibana K, et al. Airway-centered fibroelastosis accompanied by subpleural lesions of unknown cause in a young man who later developed pulmonary hypertension. Intern Med **59**: 695-700, 2020.
13. Suzuki N, Yumura-Yagi K, Yoshida M, et al. Outcome of childhood acute lymphoblastic leukemia with induction failure treated by the Japan Association of Childhood Leukemia Study (JACLS) ALL F-protocol. Pediatr Blood Cancer **54**: 71-78, 2010.
14. Thüsen JH, von der Hansell DM, Tominaga M, et al. Pleuroparenchymal fibroelastosis in patients with pulmonary disease secondary to bone marrow transplantation. Mod Pathol **24**: 1633-1639, 2011.
15. Hirota T, Fujita M, Matsumoto T, et al. Pleuroparenchymal fibroelastosis as a manifestation of chronic lung rejection? Eur Respir J **41**: 243-245, 2013.
16. Watanabe K, Nagata N, Kitasato Y, et al. Rapid decrease in forced vital capacity in patients with idiopathic pulmonary upper lobe fibrosis. Respir Investig **50**: 88-97, 2012.
17. Kusagaya H, Nakamura Y, Kono M, et al. Idiopathic pleuroparenchymal fibroelastosis: consideration of a clinicopathological entity in a series of Japanese patients. BMC Pulm Med **12**: 72, 2012.
18. Malik SW, Myers JL, DeRemee RA, Specks U. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. Am J Respir Crit Care Med **154**: 1851-1856, 1996.
19. Hamada K, Nagai S, Kitaichi M, et al. Cyclophosphamide-induced late-onset lung disease. Intern Med **42**: 82-87, 2003.