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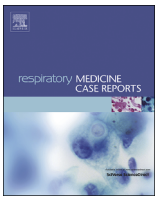

Case Report

Two cases of airway-centered fibroelastosis treated with an antifibrotic agent and corticosteroids

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ABSTRACT

Airway-centered fibroelastosis is characterized by peribronchovascular fibroelastosis, predominantly in the upper lobes, with little-to-no pleural involvement. In this study, we describe two cases of airway-centered fibroelastosis diagnosed based on radiological and pathological findings. The first case comprised a 44-year-old man whose forced vital capacity improved over three months following treatment with nintedanib. The second case involved a 50-year-old woman who was treated with oral corticosteroids but yielded an unfavorable outcome. An effective treatment for airway-centered fibroelastosis has not yet been identified; therefore, this study may help contribute to a more thorough discussion regarding treatment strategies for this disease.

1. Introduction

Airway-centered fibroelastosis is a rare interstitial lung disease (ILD) characterized by peribronchovascular elastosis, predominantly in the upper lobes, with little-to-no pleural involvement [1]. Some patients experienced acute attacks of wheezing and dyspnea [1]; however, the presentation of airway-centered fibroelastosis remains to be elucidated. This condition was first described in 2016 [1], and few cases have been reported worldwide [1–4]. Herein, we present two cases of airway-centered fibroelastosis to increase the awareness pertaining to this disease.

2. Case reports

2.1. Case 1

A 44-year-old man with no relevant medical history was referred to our hospital with consolidation in the upper lobes of both lungs that was detected incidentally on chest computed tomography (CT) during a routine medical checkup. The patient was asymp-

Abbreviations: BALF, bronchoalveolar lavage fluid; CT, computed tomography; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; and PPFE, pleuroparenchymal fibroelastosis.

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tomatic in the previous year and denied any allergies. He was an ex-smoker and had one pet bird during his childhood; however, no other significant work or environmental exposure or contact with domestic animals was reported.

Physical examination revealed normal breathing sounds and no superficial lymphadenopathy. No clubbing, cyanosis, or edema was observed. Laboratory examinations revealed a Krebs von den Lungen-6 (KL-6) level of 382 U/mL and a bird-specific IgG antibody level of 9.96 mgA/L. Chest radiography revealed consolidation in the upper lung fields and bilateral hilar elevation (Fig. 1A). High-resolution CT (HRCT) showed pulmonary consolidation, primarily at the apex along the bronchovascular bundle (Fig. 1B and C). A few bullae were observed in the upper lobes.

To differentiate between pulmonary Langerhans cell histiocytosis, fibrotic hypersensitivity pneumonitis, and sarcoidosis, bronchoscopy and surgical lung biopsy were performed. Bronchoalveolar lavage fluid (BALF) analysis revealed a normal cellular distribution. Transbronchial lung cryobiopsy was performed on the right B^3a, and the specimen showed peribronchiolar fibroelastosis (Fig. 2A and B). Surgical lung biopsy specimens from the right S^3 also revealed peribronchiolar fibroelastosis with alveolar collapse (Fig. 2C and D). No lymphocyte infiltration, non-caseating granulomas, or Langerhans cells were observed. The patient was pathologically diagnosed with airway-centered fibroelastosis.

As forced vital capacity (FVC) declined from 4.61 L to 4.46 L, nintedanib was initiated. Three months after nintedanib administration, follow-up chest radiography and CT revealed no exacerbation. FVC slightly increased to 5.07 L, and no adverse effects were reported.

2.2. Case 2

A 50-year-old woman was diagnosed with diffuse large B-cell lymphoma at 30 years of age. The patient was treated with subtotal gastrectomy and the following chemotherapy regiment: one course of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), one course of MEPP (mitoxantrone, etoposide, cisplatin, and prednisone), and two courses of proMACE (prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide). The patient achieved complete remission without additional treatments, including bone-marrow transplantation.

The patient's chief complaint at presentation was dyspnea that had persisted for three months. The patient never smoked, and no signs of toxic environmental exposure were observed, except in the duvet.

Physical examination revealed normal breathing sounds and no superficial lymphadenopathy. No clubbing, cyanosis, or edema was observed. Laboratory examination revealed a KL-6 level of 430 U/mL and a WBC count of 8400/μL. Chest radiography revealed diffuse reticular and linear opacifications with left lung predominance and decreased volume (Fig. 3A). CT revealed peribronchiolar

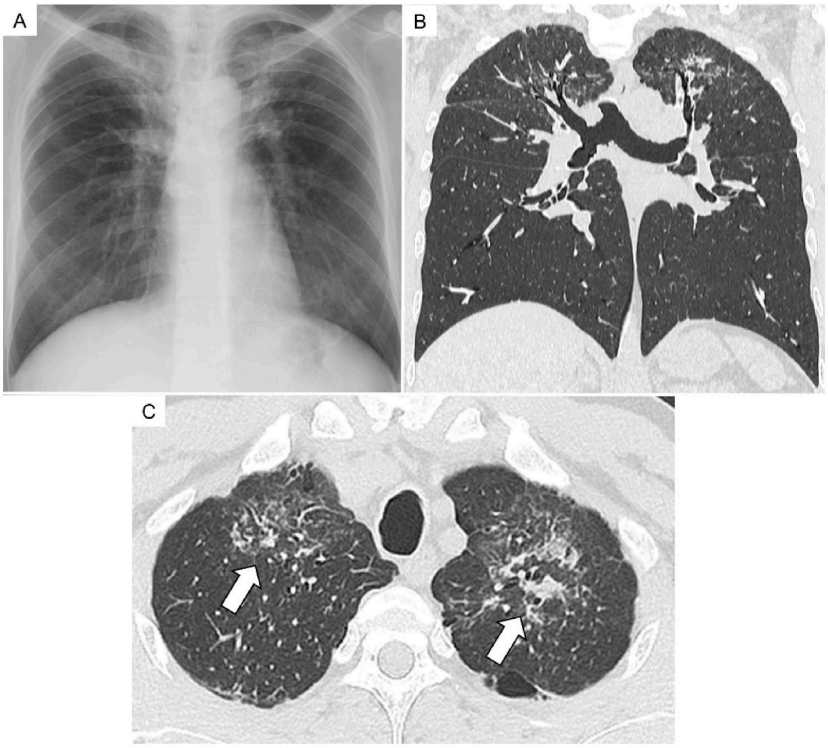

Fig. 1. Radiological findings in case 1
(A) Chest radiograph taken at the first visit to our department shows consolidation in the upper lung fields and volume reduction in both lungs. Coronal (B) and axial (C) high-resolution computed tomography images at the first visit show consolidation along the bronchovascular bundle (white arrowhead) and upper-lobe volume reduction.

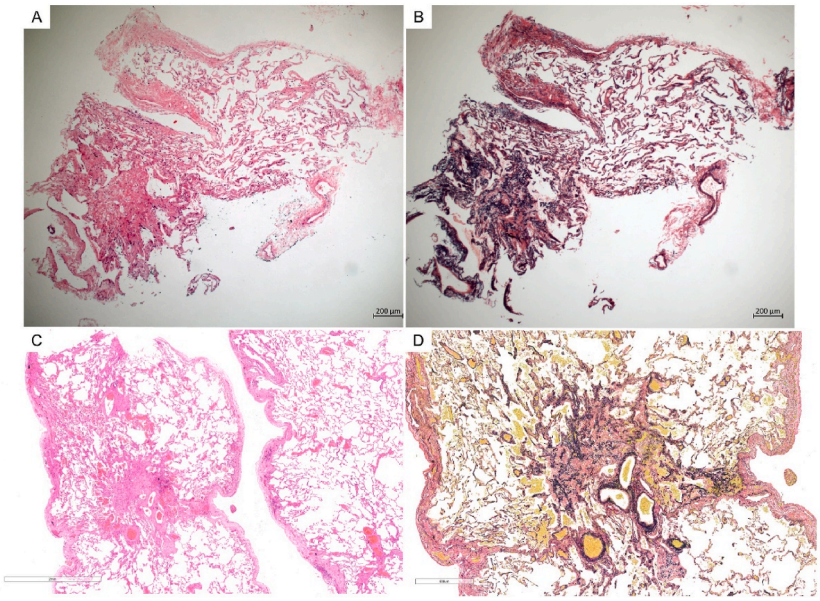

Fig. 2. Histopathological findings in case 1
Lung tissue obtained via transbronchial lung cryobiopsy from the right B^3b shows fibroelastosis along the respiratory bronchiole with hematoxylin and eosin (HE) (A) and elastica van Gieson (EVG) (B) staining. Lung tissue obtained via surgical lung biopsy of the right S^3 shows fibroelastosis around the bronchioles on HE (C) and EVG (D) staining.

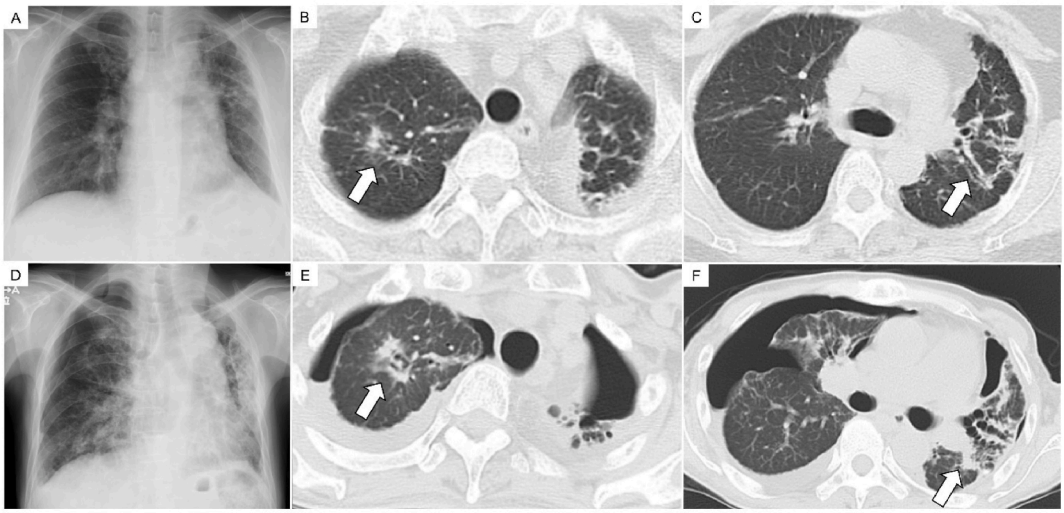

Fig. 3. Radiological findings in case 2
Chest radiograph taken at the first visit to our department shows diffuse reticular opacity predominantly in the left lung and diaphragm elevation (A). Chest computed tomography (CT) shows consolidation along the bronchovascular bundles in right upper lobe (B) and consolidation, bronchiectasis, and pleural thickening in left upper lobe (C) (white arrowhead). Chest radiography (D) and chest CT (E–F) performed 2 years and 7 months later show bilateral pneumothorax (D–F), deterioration of consolidation along the bronchovascular bundles (E–F), bronchiectasis, and pleural thickening (E) (white arrowhead).

consolidation in the upper lobes of both lungs (Fig. 3B and C). Localized pleural fibrosis was observed in the upper lobes. Pulmonary function tests revealed both restrictive and obstructive ventilatory impairment (FVC, 0.95 L [42.1 %]; forced expiratory volume in 1s, 0.94 L [52.2 %]), with poor diffusing capacity of carbon monoxide (64.1 %).

BALF analysis showed normal cellular distribution. Transbronchial lung biopsy was performed, but no alveolar structures were sampled. Surgical lung biopsy specimens from the left S^{1+2} and S^{10} showed pleural thickening and peribronchiolar elastosis.

Oral corticosteroids (prednisolone, 40 mg/body) were administered. However, no significant improvements in imaging findings and respiratory function were observed one month following treatment. Accordingly, prednisolone was discontinued.

At the age of 52 years, the patient experienced bilateral pneumothorax. Chest tube drainage was performed, but re-expansion of the lungs was incomplete. Long-term oxygen therapy was initiated as dyspnea, and desaturation on exertion persisted. Five months after initial pneumothorax, the patient's symptoms recurred. Chest radiography revealed exacerbation of the bilateral pneumothorax

and decreased volume (Fig. 3D), and HRCT confirmed worsening of peribronchial fibrosis (Fig. 3E and F). During the second episode of pneumothorax, respiratory acidosis worsened, and the patient died.

Autopsy revealed prominent fibroelastosis along the bronchovascular bundles in the right S^2 and S^{10} and pleuroparenchymal fibroelastosis in the left S^{1+2} (Fig. 4A–C). The patient was diagnosed with airway-centered fibroelastosis.

3. Discussion

The findings in our patients are distinct from those previously reported. Clinically, airway-centered fibroelastosis presents with acute exacerbations, including cough, dyspnea, and wheezing [1]. Previous reports have shown that airway-centered fibroelastosis is associated with chronic asthma and previous chemotherapy treatment [1,4]. Interestingly, no history of asthma was noted in both patients in this study, and the first patient never underwent chemotherapy. Our patients were diagnosed with airway-centered fibroelastosis based on multidisciplinary discussions after fibrotic hypersensitivity pneumonitis, sarcoidosis, and smoking-related ILD were excluded.

Airway-centered fibroelastosis is a newly recognized, rare form of ILD, with only nine cases reported in the English literature [1–4]. The cases are summarized in Table 1. The diagnosis of airway-centered fibroelastosis requires both histopathological evidence of elastosis and a typical HRCT pattern [1]. HRCT should reveal significant bronchial abnormalities characteristic of airway centered fibroelastosis, including bronchial-wall thickening, bronchial-wall deformation, bronchiectasis, and progressive parenchymal retraction. In addition, characteristic histopathological findings are extensive peribronchovascular fibroelastosis of the upper lobes.

Airway-centered fibroelastosis is also characterized by moderate-to-severe functional abnormalities [1]. In our patients, the disease was characterized by ventilatory impairment, central consolidation along the bronchovascular bundle with traction bronchiectasis on HRCT, and pathologically confirmed airway-centered fibroelastosis, particularly in one patient in whom autopsy was performed.

Pleuroparenchymal fibroelastosis (PPFE) is an important differential diagnosis. The CT findings of PPFE include upper-lobe pleural thickening with subpleural fibrosis [2,5], which is minimal in airway-centered fibroelastosis [1]. The patient in case 2 exhibited imaging and pathological features of PPFE in addition to those of airway-centered fibroelastosis; therefore, she was diagnosed with airway-centered fibroelastosis concomitant with PPFE. However, the difference between these two diseases remains unclear, and the corresponding conditions may overlap.

Primary studies have described drug-induced PPFE. It has been noted that cyclophosphamide was used in the majority of cases of late-onset PPFE [3]. Katayama et al. reported two cases of airway-centered fibroelastosis induced by chemotherapy with cyclophosphamide [3]. In this study, case 2 had undergone chemotherapy with cyclophosphamide, and the pathological and radiological findings were similar to those previously reported. Further studies are required to clarify the pathophysiology, characteristics, and risk factors of airway-centered fibroelastosis.

No obviously effective drug therapy has been established for PPFE or airway-centered fibroelastosis [5]. In patients with PPFE, nintedanib may be associated with a slower decline in lung function [6], with varying results [6,7]. Similarly, pirfenidone prevents

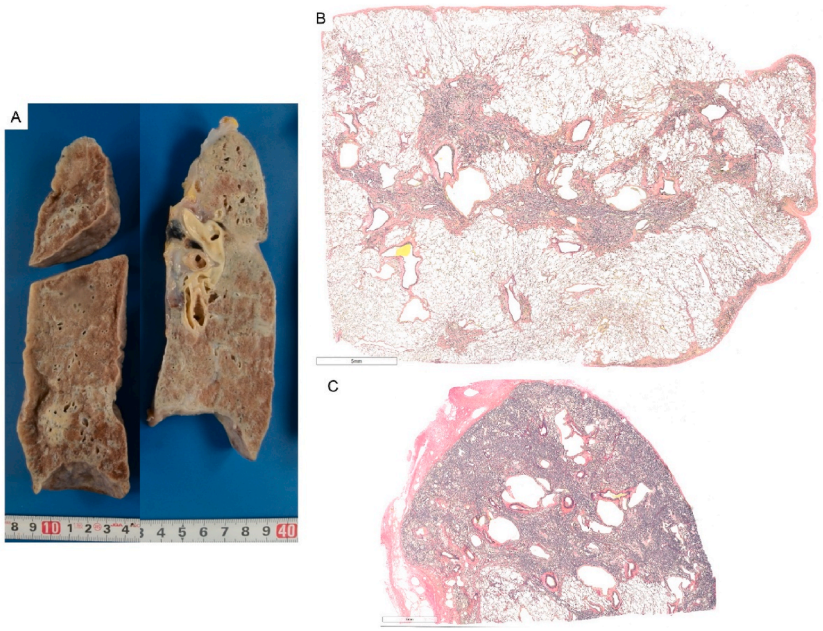

Fig. 4. Histopathological findings of the autopsy lung in case 2
Gross photograph showing fibroelastosis along the bronchovascular bundles in the right S^2 and S^{10} (A). A panoramic view of elastica van Gieson staining showing localized fibroelastosis along the membranous and respiratory bronchioles in the right S^2 (B) and pleuroparenchymal fibroelastosis in the left S^{1+2} (C).

Table 1
Clinical characteristics of patients.

Patient	Age, years	Sex	Exposure to noxious agents	Asthma	Chemotherapy for	Oral corticosteroids	Antifibrotic agents	Lung transplantation
1	47	Female	chlorine inhalation	Yes	None	Yes	No	No
2	40	Female	Farm worker	Yes	None	Yes	No	No
3	38	Female	No	Yes	None	Yes	No	Double-lung transplantation
4	46	Female	No	Yes	None	Yes	No	Double-lung transplantation
5	56	Female	No	Yes	None	Yes	No	No
6	55	Male	Unknown	No	None	Unknown	No	No
7	19	Female	No	No	ALL	Yes	No	No
8	60	Female	No	No	Thyroid cancer	Unknown	No	No
9	26	Male	Down quilt	Yes	None	No	Pirfenidone with add-on nintedanib	No
10	44	Male	Bird (only in childhood)	No	None	No	Nintedanib	No
11	50	Female	No	No	DLBCL	Yes	No	No

Abbreviations: ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma.
References: patients 1–5 [1]; patient 6 [2]; patients 7, 8 [3]; patient 9 [4].

%FVC reduction in a limited number of patients with PPFE [8]. In addition, in patients with progressive fibrosing ILD (PF-ILD), disease progression was slower in the nintedanib group than in the placebo group [9]. One study has shown that pirfenidone may attenuate the progression of PF-ILD [10], though the results should be interpreted with caution [10,11]. In a previous study, the only one patient with airway-centered fibroelastosis treated with antifibrotic agents showed poor prognosis [4]. Since case 1 showed a decrease in FVC, nintedanib was initiated, and FVC improved for three months. As the efficacy of nintedanib in airway-centered fibroelastosis remains uncertain, we will carefully follow-up this patient.

The efficacy of the empirical use of prednisolone also remains to be elucidated, and no effect was observed in case 2. Lung transplantation is an option, and successful transplantation has been reported in several patients with PPFE [12,13]. Lung transplantation has been also performed in two cases of airway-centered fibroelastosis [1]. While one patient remained well after the transplantation, the other patient died five months after transplantation because of massive hemoptysis of unknown origin [1]. As no standard treatment for airway-centered fibroelastosis has been established, lung transplantation should be considered for the management of deteriorating airway-centered fibroelastosis.

In conclusion, we presented two rare cases of airway-centered fibroelastosis. Differential diagnoses, such as PPFE, hypersensitivity pneumonitis, sarcoidosis, and smoking-related ILD, should be considered. Although treatment modalities have not been established, antifibrotic agents are potential options.

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CRediT authorship contribution statement

Miwa Kamatani: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Minoru Inomata:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Akari Misumi:** Investigation. **Ken Ito:** Investigation. **Takashi Maeda:** Investigation. **Haruka Chin:** Investigation. **Yu Ito:** Investigation. **Keita Sakamoto:** Investigation. **Nobuyasu Awano:** Investigation. **Naoyuki Kuse:** Investigation. **Yoshiaki Furuhata:** Investigation. **Yuan Bae:** Investigation. **Hiroaki Sugiura:** Investigation. **Tamiko Takemura:** Investigation. **Takehiro Izumo:** Supervision, Project administration, Investigation.

Declaration of competing interest

No conflicts of interest.

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