Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3256-19
Intern Med 59: 695-700, 2020
http://internmed.jp

【 CASE REPORT 】

Airway-centered Fibroelastosis Accompanied by Subpleural Lesions of Unknown Cause in a Young Man Who Later Developed Pulmonary Hypertension

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Abstract:
A 26-year-old man with a history of bronchial asthma was found to have high-density shadows along the bronchovascular bundle and in the subpleural area on computed tomography of the chest. Surgical lung biopsy specimens from the right S^5 showed fibroelastosis in the subpleural and central airway area with alveolar destruction. He was diagnosed with airway-centered fibroelastosis of unknown cause after multidisciplinary discussions. The patient developed pulmonary hypertension and died 6 years later. The patient was younger in comparison to patients in earlier reports and had more obvious subpleural fibroelastic lesions in the upper lobes than in previously described cases.

Key words: airway-centered fibroelastosis, bronchial asthma, bronchial abnormality, pulmonary hypertension, subpleural lesions, upper lobes

(Intern Med 59: 695-700, 2020)
(DOI: 10.2169/internalmedicine.3256-19)

Introduction

Airway-centered fibroelastosis was first proposed as a pathological entity with a specific clinical and imaging presentation in 2016 (1). The characteristics of the 5 reported cases are extensive airway-centered fibroelastosis of the upper lobes on histopathology, bronchial abnormality, and predominantly subpleural upper lobe consolidation on high-resolution computed tomography (CT) of the chest (1). The reported patients have all been middle-aged women who were previously diagnosed with bronchial asthma and obstructive or restrictive respiratory dysfunction (1). We herein report a rare case of airway-centered fibroelastosis in a young man with obvious parenchymal fibroelastosis in subpleural lesions of both upper lobes who developed pulmonary hypertension.

Case Report

A 26-year-old man presented to a local doctor with a complaint of cough in 2011. A chest radiograph showed an infiltrative shadow and loss of volume predominantly in both upper lung fields. CT of the chest showed high-density shadows mainly in the upper lung fields (Fig. 1a-c). These findings prompted a referral to our institution. The patient's past medical history included bronchial asthma since his teenage years, which was treated with an inhaled corticosteroid and a long-acting beta-agonist (salmeterol/fluticasone). He was a non-smoking clerical worker in a welding factory and had not inhaled mine dust. He used a down quilt and had no pets. His family history included a father with liver disease, a mother with hypertension and hyperlipidemia, and a younger brother with allergic rhinitis. His body mass index on the first admission to our hospital was 24.7. Wheeze was detected on chest auscultation and clubbed fingers were

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Received: April 25, 2019; Accepted: July 31, 2019; Advance Publication by J-STAGE: October 7, 2019
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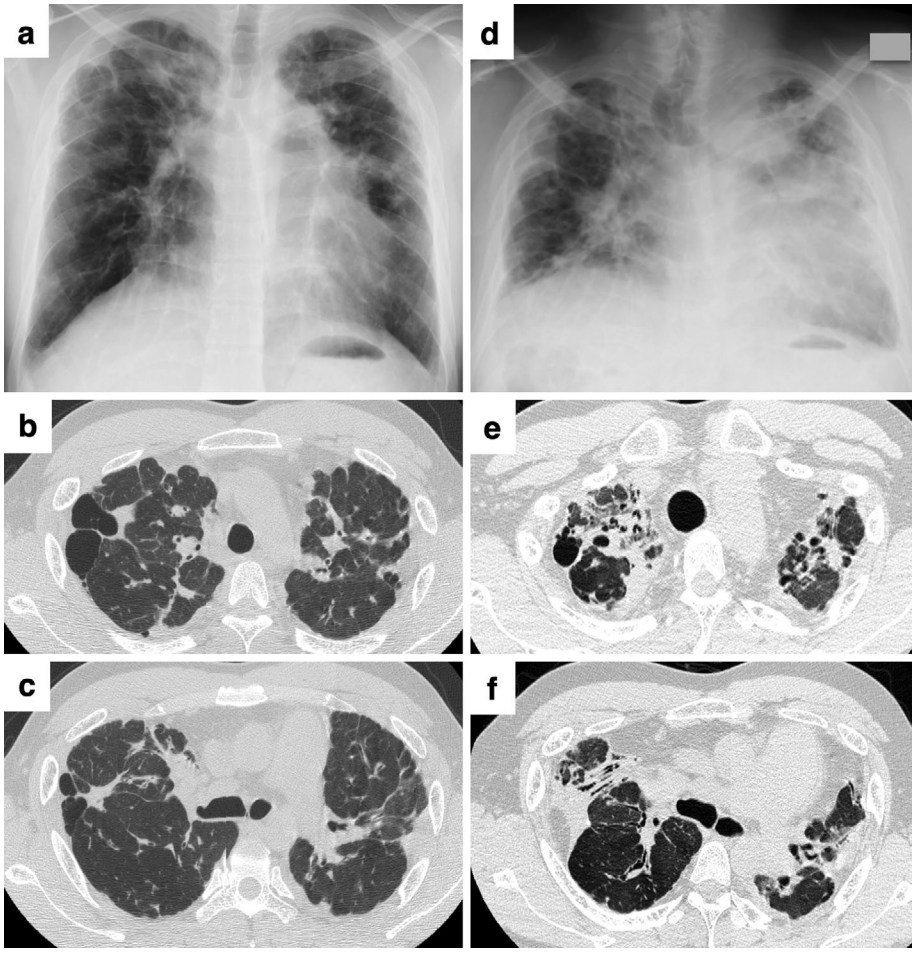

Figure 1. **(a) A chest radiograph acquired in 2011 showing abnormal shadows and volume loss predominantly in the upper lung fields. (b, c) A computed tomography (CT) scan of the chest obtained in the same year showing high-density shadows along the bronchovascular bundle and in the subpleural area. (d) A chest radiograph from 2016 shows progression of the abnormal shadows and volume loss, predominantly in the upper lung fields, with tracheobronchial tortuosity. (e, f) A CT scan of the chest, also from 2016, showing further progression of the high-density shadow along the bronchovascular bundle in the subpleural area, again predominantly in the upper lung fields.**

observed. The laboratory findings are shown in Table 1. His white blood cell count was 10,500/μL, with 71.4% neutrophils and 1.3% eosinophils. His serum immunoglobulin (Ig) E level was 387 mg/dL and his serum was positive for anti-SS (Sjögren's syndrome-related antigen)-B. Pulmonary function tests showed combined respiratory dysfunction. A bronchodilator reversibility test using a short-acting beta-2 agonist (SABA) was negative. The findings of an arterial blood gas analysis were within the normal range (Table 2). His 6-minute walk test result was 100 m, with a minimum percutaneous oxygen saturation of 84%. Bronchoalveolar lavage (BAL) was performed in the right B^5. The bronchoalveolar lavage fluid (BALF) recovery rate was 52%; the total cell count in the fluid was 3.73×10^5/mL, with a cell analysis revealing 79.5% macrophages, 17.7% lymphocytes, 0.6% neutrophils, and 1.4% eosinophils. The CD4/CD8 lymphocyte ratio was 0.49. No microorganisms were detected in the BALF. Transbronchial lung biopsy specimens of the right B^8 showed infiltration of lymphoid cells into the bronchial wall without any granulomas. Chronic hypersensitivity pneumonia or interstitial pneumonia associated with Sjögren's syndrome was suspected based on the above findings. Chronic hypersensitivity pneumonia was excluded because specific antibodies against extracts of pigeon, parrot, and budgerigar droppings were negative, as was an antigen avoidance test. No evidence of Sjögren's syndrome was found on Schirmer or Saxon tests, or in a lip biopsy specimen. A surgical lung biopsy specimen of the right S^5 was performed to obtain a definitive diagnosis. The specimen showed fibroelastosis in the subpleural and airway center areas with collapse of the alveolar structure (Fig. 2). There were no histological findings in the specimen suggestive of asthma, such as hypertrophy of the smooth muscle or mucous gland enlargement. In view of these findings, the patient was diagnosed with idiopathic interstitial pneumonias (IIPs) other than idiopathic pulmonary fibrosis [according to the 2002 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic

Table 1. Laboratory Data on Admission.

WBC	10,500 /μL	BUN	11.2 mg/dL	Anti SS-A antibody	<5.0 U/mL
Neu	71.4 %	Cr	0.75 mg/dL	Anti SS-B antibody	30.6 U/mL
Lym	22.5 %	Na	140 mmol/L	HCV antibody	(-)
Mon	4.4 %	K	4.5 mmol/L	HBs antigen	(-)
Eos	1.3 %	Cl	106 mmol/L	HIV1,2	(-)
Bas	0.4 %	CRP	0.14 mg/dL	HTLV-1	(-)
RBC	473 $\times 10^4/mm^3$	IgG	940 mg/dL	Aspergillus antigen	(-)
Hb	13.9 g/dL	IgA	264 mg/dL	B-D glucan	2 pg/mL
Ht	42.1 %	IgM	100 mg/dL	Anti-TBGL antibody	2.7 U/mL
PLT	42.4 $\times 10^4/mm^3$	IgE	387 mg/dL	sIL-2R	269 U/mL
TP	7.3 mg/dL	KL-6	455 mg/dL	CEA	1.3 ng/mL
Alb	4.6 mg/dL	SP-D	32 IU/mL	CYFRA	1.5 ng/mL
AST	15 IU/L	SP-A	33.2 U/mL	ProGRP	37.4 pg/mL
ALT	19 IU/L	ACE	11.2 IU/L	NT-proBNP	7 ng/mL
LDH	163 IU/L	ANA	40 times		

ACE: angiotensin-converting enzyme, ALT: alanine aminotransferase, ANA: antinuclear antibody, AST: aspartate aminotransferase, Bas: basophils, B-D: beta-D, BUN: blood urea nitrogen, CEA: carcinoembryonic antigen, Cl: chlorine, Cr: creatinine, CRP: C-reactive protein, CYFRA: cytokeratin 19 fragment, Eos: eosinophils, Hb: hemoglobin, HCV: hepatitis C virus, HIV: human immunodeficiency virus, Ht: hematocrit, HTLV-1: human T-cell leukemia virus type 1, Ig: immunoglobulin, K: potassium, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, Lym: lymphocytes, Mon: monocytes, Na: sodium, Neu: neutrophils, Nt proBNP: N-terminal pro-B-type natriuretic peptide, PLT: platelets, ProGRP: pro-gastrin-releasing peptide, RBC: red blood cells, sIL-2R: soluble IL-2 receptor, SP: surfactant protein, SS: Sjögren's syndrome-related antigen, TBGL: tuberculous glycolipid, TP: total protein, WBC: white blood cells

Table 2. Pulmonary Function Tests and Results of Arterial Blood Gas Analysis on Admission.

Parameter			
FVC	2.63 L	ABG (spinal, in room air)	
FVC, % predicted	61.4 %	pH	7.39
FEV_1	1.39 L	PaO_2	102 Torr
FEV_1, % predicted	35.1 %	$PaCO_2$	40.6 Torr
FEV_1/FVC	52.0 %	HCO_3^-	23.9 Torr
RV	1.42 L	BE	-0.5 mmol/L
RV, % predicted	103.0 %	$AaDO_2$	2.0 Torr
TLC	4.06 L		
TLC, % predicted	63.3 %		
RV/TLC	34.9 %		
DL_{CO}	19.1 mL/min/mmHg		
DL_{CO}, % predicted	64.3 %		
Bronchodilator reversibility test			
FEV_1 (Pre)	1.27 L		
FEV_1 (Post)	1.29 L (improvement of 20 mL, 1.5%)		

ABG: arterial blood gas, $AaDO_2$: alveolar-arterial difference in O_2, BE: base excess, DL_{CO}: diffusing capacity of the lungs for carbon monoxide, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, RV: residual, TLC: total lung capacity

Interstitial Pneumonias (2)] at a multi-disciplinary discussion and was followed up without specific treatment.

In 2012, he developed left pneumothorax, which that was treated with bullectomy using video-assisted thoracoscopy. The resected specimen also showed fibroelastosis around the bulla (not shown). In 2014, he developed a *Mycobacterium massiliense* infection that was treated with clarithromycin, sitafloxacin, and faropenem. Chest radiography and high-resolution CT indicated the progression of the high-density shadows along the bronchovascular bundle and in the subpleural area, and loss of volume predominantly in the upper lung fields (Fig. 1d-f). His forced vital capacity had decreased to 1.49 L (61.4% predicted). Right heart catheterization revealed a mean pulmonary artery pressure of 25 mmHg, a pulmonary capillary wedge pressure of 13 mmHg, and pulmonary vascular resistance of 2.4 WU. Thus, the patient was diagnosed with pulmonary hypertension. The patient was then started on supplemental oxygen during exercise. Given that the progression of fibrosis seen on high-resolution CT and the decline in forced vital capacity were

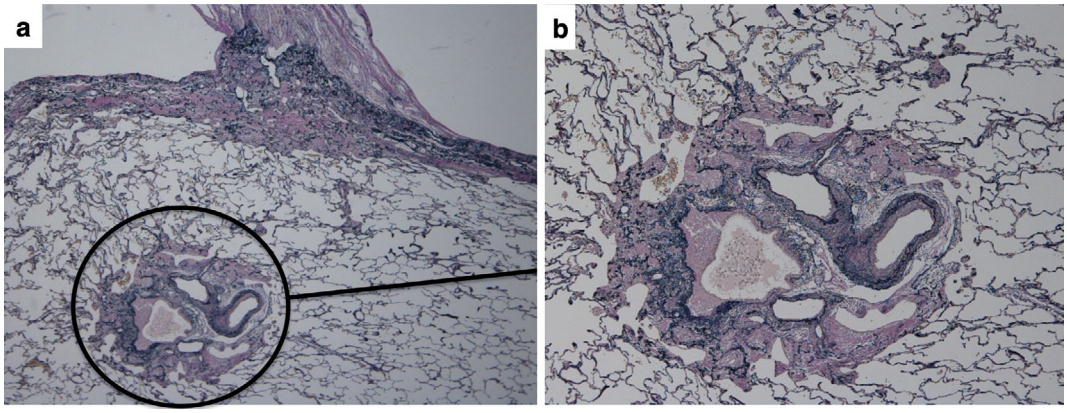

Figure 2. **(a) A surgical lung biopsy specimen of the right S^5 showing fibroelastosis in the subpleural and airway area with collapse of the alveolar structure (Elastica van Gieson staining, ×4). (b) A higher magnification view of (a) shows fibroelastosis in the airway area (Elastica van Gieson staining, ×10).**

similar to that seen in idiopathic pulmonary fibrosis, pirfenidone with add-on nintedanib was prescribed as salvage medication. However, there was no improvement in his clinical findings. Given his worsening respiratory condition but controlled mycobacterial infection, he was registered for lung transplantation in 2015. In the same year, he had an episode of asthma worsening that was relieved by SABA. In 2017, his pulmonary hypertension worsened; by that time, he had a mean pulmonary artery pressure of 32 mmHg, a pulmonary capillary wedge pressure of 9 mmHg, and a pulmonary vascular resistance of 4 WU. Six months after the last right heart catheterization, he was found in a state of cardiopulmonary arrest in his home and died in a local hospital (Fig. 3).

Discussion

We encountered a case of airway-centered fibroelastosis. This disease entity was first reported in 2016 (1). In our patient, the disease was characterized by extensive airway-centered fibroelastosis of the upper lobes on histopathology and marked bronchial abnormalities with bronchial wall thickening, bronchial wall deformation, and bronchiectasis, as well as progressive parenchymal retraction and predominantly subpleural upper lobe consolidation on high-resolution CT. The patients described in a previous report (1) were diagnosed with bronchial asthma and experienced chronic dyspnea with an acute worsening of wheeze. Despite inhaled and oral corticosteroids, the disease progressively deteriorated and resulted in chronic respiratory failure (1).

The main differential diagnosis of airway-centered fibroelastosis is pleuroparenchymal fibroelastosis (PPFE), which is a rare entity characterized by pleural and subpleural parenchymal fibrosis that predominantly occurs in the upper lobes (3). Pradere et al. identified four major differences in the clinical, physiological, radiological, and pathological characteristics between airway-centered fibroelastosis and PPFE (1). First, all patients with airway-centered fibroelastosis but not those with PPFE had an acute worsening of cough, dyspnea, and wheeze. Second, the patient's pulmonary function test results revealed an obstructive pattern in patients with airway-centered fibroelastosis and mainly a restrictive pattern in those with PPFE. Third, pleuroparenchymal thickening was a key feature in patients with PPFE but was minimal or absent in those with airway-centered fibroelastosis, who were more likely to show marked bronchiolar and bronchial changes on high-resolution CT. Finally, the histological findings of PPFE were severe fibrosis of the visceral pleura and prominent homogeneous subpleural fibroelastosis, whereas those of airway-centered fibroelastosis were prominent bronchiolar and bronchial changes with minimal pleural involvement. Our patient developed an acute worsening of cough, dyspnea, and wheeze and a combined pattern of respiratory dysfunction during his clinical course. Furthermore, the radiological and pathological findings of bronchiolar and bronchial changes were more prominent than the lesions described in the previous reports on PPFE (4-7), although the subpleural fibroelastic lesions in the upper lobes were more obvious than the lesions described in the previous report on airway-centered fibroelastosis (1). Interestingly, our patient had a relatively high body mass index and clubbed fingers, which have been rare findings in PPFE (8, 9). Given all of these findings and the patient's clinical course, our diagnosis was airway-centered fibroelastosis after several multidisciplinary discussions. However, PPFE includes a variety of abnormalities, such as interstitial lung disease in the lower lobes, and may be idiopathic, genetic, the result of previous bone marrow transplantation, drug-induced, or autoimmune-related (10-15). Thus, our case could be categorized as "unclassifiable IIP" or as part of a broad spectrum of idiopathic PPFE characterized by distinctive airway impairment with bronchial asthma.

Apart from the obvious subpleural fibroelastic lesions in the upper lobes, our patient had several characteristics that

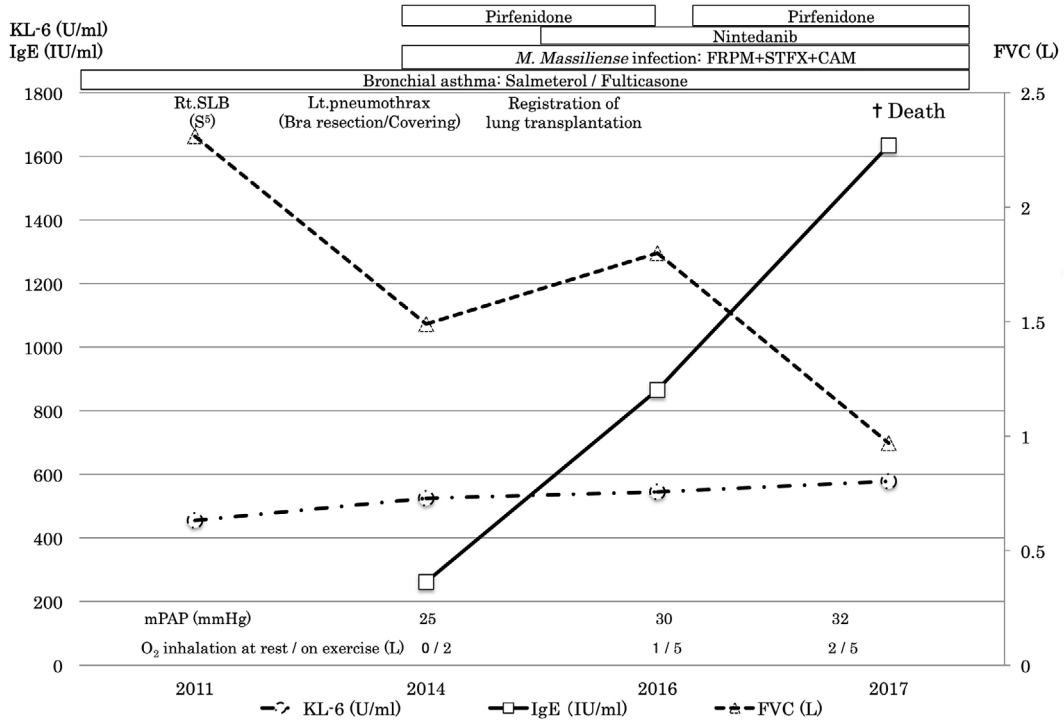

Figure 3. The clinical course. There was an increase in the amount of supplemental oxygen required as the patient's forced vital capacity deteriorated with the progression of the underlying disease, which was complicated by *Mycobacterium massiliense* infection and pulmonary hypertension. Although the KL-6 level remained almost within the normal range throughout the clinical course, there was a steady increase in the immunoglobulin E level with progression of the disease. CAM: clarithromycin, FROM: faropenem, FVC: forced vital capacity, IgE: immunoglobulin E, KL-6: Krebs von den Lungen-6, mPAP: mean pulmonary artery pressure, STFX: sitafloxacin

were different from those reportedly associated with airway-centered fibroelastosis. First the patient was a young man, whereas the previous 5 cases were all middle-aged women of 38-56 years of age (1). Second, the symptoms of asthma were stable, except for one acute worsening of asthma (that responded to SABA), and there was an increase in the serum IgE level. Interestingly, the serum IgE level increased as the disease progressed in our patient (Fig. 3), although other causes of IgE elevation, such as *Aspergillus*, were not detected in sputum or serological tests during the clinical course. It has been reported that IgE-driven stimulation leads to the production and secretion of extracellular matrix protein with deposition of collagen, which are key factors in airway wall remodeling (16, 17). Thus, it may be that an atopic factor and not bronchial asthma itself was involved in the progression of airway-centered fibroelastosis. Third, our patient developed pulmonary hypertension as part of the clinical course of his disease. An effect of nintedanib on pulmonary hypertension cannot be excluded, as previously reported (18). Our patient's worsening pulmonary hypertension coincided with a declining forced vital capacity, so was attributed to chronic lung disease (19). We therefore treated his lung disease with drugs and oxygen therapy, but did not treat his pulmonary arterial hypertension pharmacologically. It was likely that pulmonary hypertension contributed to the ultimately fatal outcome in this patient. Airway-centered fibroelastosis is an emerging disease concept but is not established as a disease entity. Hence, further studies are needed to confirm this concept and how it differs from PPFE.

In conclusion, we encountered a young adult man with airway-centered fibroelastosis who had obvious subpleural lesions of unknown cause and developed pulmonary hypertension. Further studies are required to clarify the etiology and clinical course of this newly recognized condition.

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

Acknowledgement

We would like to thank Dr. Yasunobu Funakoshi and other surgical staff members for performing the surgical lung biopsies, Dr. Masanori Kitaichi for the pathological evaluation of those biopsies, and Mr. Tomoaki Teramoto for the cytological evaluation of the BALF.

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