

[CASE REPORT]

Asymmetrical Interstitial Lung Disease Suggested to Be Due to Hypoplasia of the Unilateral Pulmonary Artery: A Case Report with a 20-year Follow-up

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Abstract:

We herein report a case of asymmetrical interstitial lung disease (ILD) that remained almost completely asymmetrical over time on chest computed tomography (CT). An open lung biopsy from the right lung showed severe pleural adhesion, obstruction of the pulmonary artery, and dilated systemic arteries in addition to the usual interstitial pneumonia pattern. Three-dimensional CT angiography showed partial defects of pulmonary arteries on the affected side. After excluding other known causes of ILD and gastroesophageal reflux, we suspected that decreased pulmonary artery perfusion in the present case may have been responsible for the observed asymmetrical unilateral fibrosis.

Key words: usual interstitial pneumonia, idiopathic pulmonary fibrosis, interstitial lung disease, asymmetrical disease, pulmonary artery

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause (1). Although the histopathological pattern of IPF is usual interstitial pneumonia (UIP), various diseases and other factors can cause UIP, including collagen vascular diseases, chronic hypersensitivity pneumonitis, occupational exposure, and certain drugs. An association between UIP and hypoplasia of the pulmonary artery has rarely been described.

We herein report a unique case of asymmetrical interstitial lung disease (ILD) with a UIP pattern suggesting that hypoplasia of the unilateral pulmonary artery may be related to the development of UIP in the affected lung.

Case Report

A 74-year-old woman was admitted to our hospital in August 2014 for a further examination of ILD. She had been irregularly followed up at our outpatient clinic since 2001 when she had noticed dry cough and right back pain, and asymmetrical ILD had been detected in the right lung. She had been aware of the onset of exertional dyspnea in 2013.

She was an ex-smoker with a history of 15 pack-years, and her medical history included uterine myoma at the 37 years old, herpes zoster at 57 years old, and gallstones and hypertension at 67 years old. Her domestic and occupational environmental exposures and drug toxicity were unremarkable. Regarding her family history, her parents and brother had hypertension.

Fine crackles were noted in the right lung, but no arthralgia, clubbing, skin eruption, photosensitivity, muscle weakness, or Raynaud's phenomenon was found. Her blood tests

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showed a white blood cell count of 7,250/ μ L, Hb of 14.1 g/dL, platelet count of $25.7 \times 10^4/\mu$ L and C-reactive protein of 0.2 mg/dL. Her hepatic and renal parameters were normal, and immunological test findings were negative for autoimmune antibodies, including RNA, on immunoprecipitation assays. Serum Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) levels were 661 U/mL (normal: <500 U/mL) and 228.2 ng/mL (normal: <110 ng/mL), respectively.

Chest X-ray showed reticular opacities accompanied by volume reduction of the right lung (Fig. 1). On reviewing



Figure 1. Chest X-ray findings at the time of the surgical lung biopsy in 2014 showing reticular opacities accompanied by reduction of the volume of the right lung.

her medical chart, her oldest chest X-ray findings showed slight reticular opacities in the right lower lung in March 1994. High-resolution computed tomography (HRCT) performed six years ago (in 2008) showed asymmetrical linear opacities and ground-glass opacities with traction bronchiectasis in the right lung (Fig. 2a) that had slightly progressed by 2014 (Fig. 2b). Pulmonary function tests showed a forced expiratory volume in 1 second of 101.1% the predicted value, forced vital capacity (FVC) of 87.4% the predicted value, and diffusing capacity of the lung for carbon monoxide (DLco) of 75.5% the predicted value. In 2008, 6 years earlier, FVC and DLco had been 92.7% the predicted value and 68.8% the predicted value, respectively.

During the 6-minute walking test, no desaturation was found [percutaneous oxygen saturation (SpO₂) 98% at rest and nadir 91%] when the patient walked 375 m. Gastroesophageal reflux disease (GERD) symptoms were not present on an evaluation by the Frequency Scale for the Symptoms of GERD questionnaire (2) with a score of 0. Upper endoscopy did not show esophagitis, esophageal stenosis, or Barrett's esophagus.

For the histological diagnosis, due to total pleural adhesion, a surgical open lung biopsy rather than a thoracoscopic biopsy was taken from the right S² and S¹⁰. The right S² showed patchy fibrosis throughout and engorged systemic arteries on the pleura. Fibrosis appeared to have a peripheral lobular distribution with fibroblastic foci (Fig. 3a, b). The pulmonary artery was completely obstructed due to muscle extension of the intima, and the corresponding bronchial artery was markedly dilated (Fig. 3c, d). The right S¹⁰ was

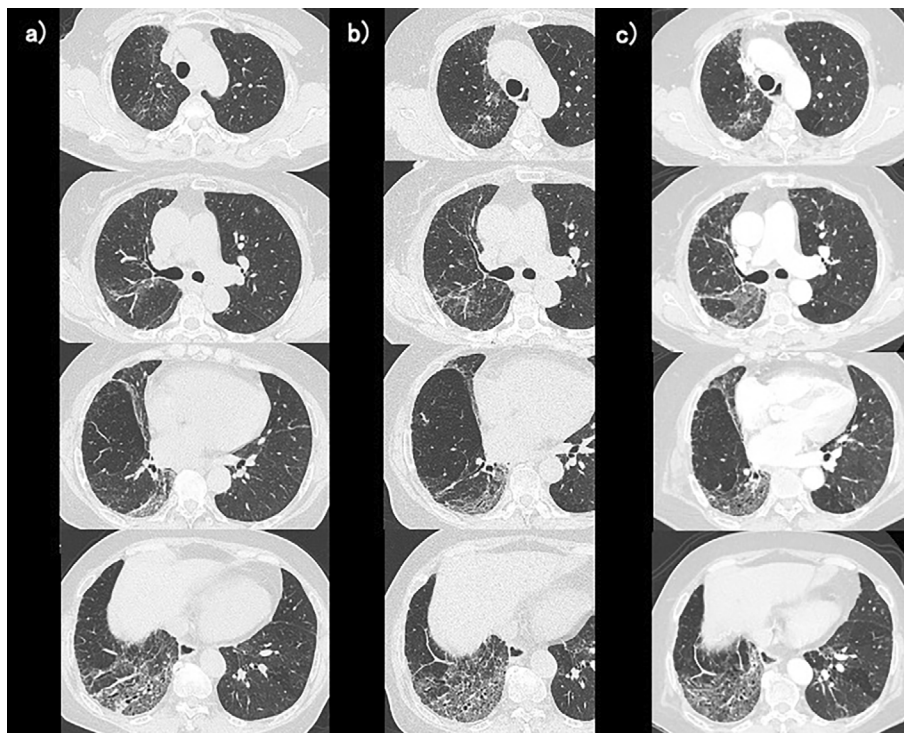


Figure 2. Chest high-resolution computed tomography images from 2008 showing asymmetrical linear opacities and ground-glass opacities with traction bronchiectasis in the right lung (a) that had slightly progressed in 2014 (b) and still showed similar asymmetrical interstitial opacities in 2019 (c).

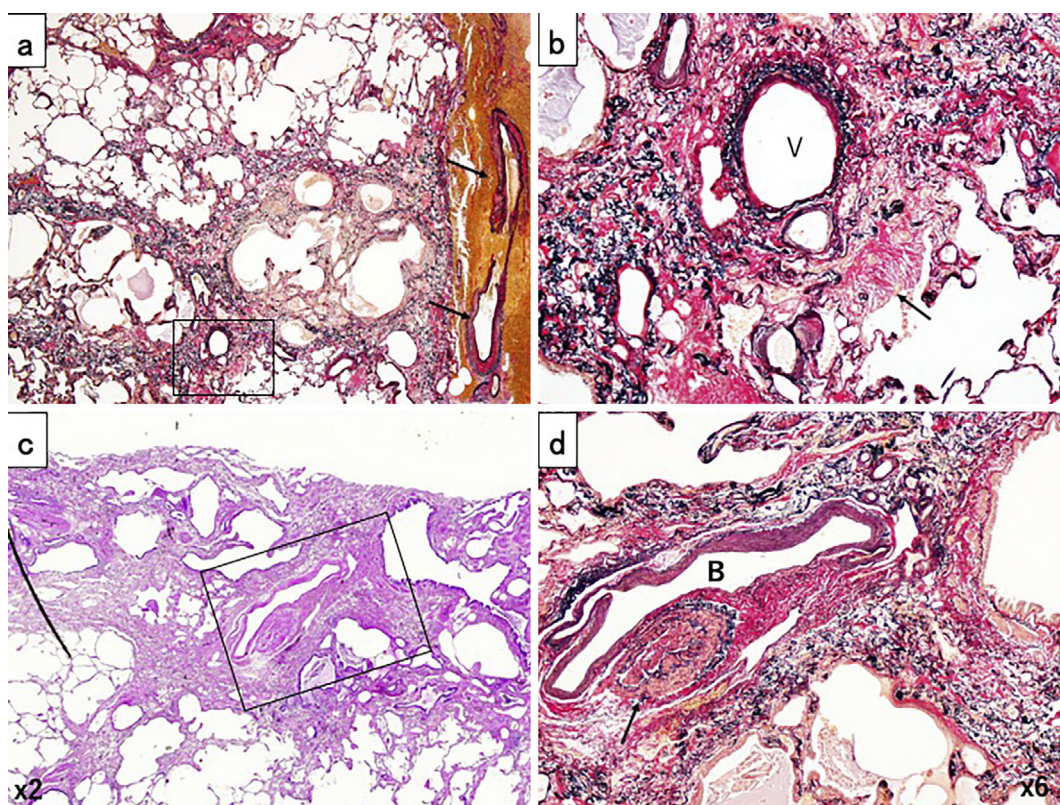


Figure 3. Histological features of the right S². (a) Irregular-shaped peripheral zonal fibrosis is seen. A dilated systemic artery is present in the pleura (arrow). Elastica van Gieson staining (EvG), $\times 20$. (b) Dense fibroelastosis located around the vein (V) with attachment of a newly formed fibroblastic focus (arrow). Box from (a) EvG, $\times 100$. (c) Irregular-shaped fibrosis with structural remodeling. Hematoxylin and Eosin staining, $\times 20$. (d) Complete obstruction of the pulmonary artery (arrow) due to muscularization of the intima, showing a markedly dilated bronchial artery (B). Box from (c) EvG, $\times 60$.

completely replaced by dense fibrosis exhibiting honeycombing, and a newly generated systemic artery was seen in the fatty tissue around the lung (Fig. 4a). Fibroblastic foci were visibly attached to peripheral areas of dense fibrosis (Fig. 4b), and obliteration of the pulmonary artery and dilation of the bronchial artery was seen (Fig. 4c). Although these findings are consistent with a UIP pattern (1), severe pleural adhesions and the abnormal vascular distribution suggested an alternative diagnosis of IPF (3).

The patient has since been receiving supportive care using antitussive drugs. Chest HRCT findings obtained five years later in 2019 still showed similar asymmetrical interstitial opacities (Fig. 2c). In addition, CT with enhancement (Fig. 5a) and three-dimensional CT angiography (Fig. 5b) revealed partial defects of the pulmonary arteries on the affected side. Regarding other anomalies of the great vessels, an aberrant right subclavian artery was observed (not shown). The FVC was restored to 87.3% the predicted value, and DLco slightly decreased to 50.3% the predicted value in 2019. Serum KL-6 and SP-D levels were 707 U/mL and 226.8 ng/mL, respectively. To date, about 20 years after the first hospital visit, the patient has been stable without any worsening of her respiratory symptoms.

Discussion

We herein report a case of asymmetrical ILD with a UIP pattern that remained frankly asymmetrical over time. Based on the exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, drug toxicity), a diagnosis of asymmetrical IPF was deemed most likely (4, 5). However, IPF is a progressive disease with a median survival of three to five years (6, 7). The present case may be unique from the perspective of IPF disease behavior (8) in that the disease has remained stable without any specific antifibrotic therapy for the last 20 years, although the HRCT findings have shown slight progression of fibrosis.

The updated clinical practice guidelines for the diagnosis of IPF (1) mention that the distribution of lesions is often heterogeneous, occasionally diffuse, and may be asymmetrical on HRCT. Such asymmetrical IPF disease has attracted attention recently. Tcherakian et al. (4) studied 32 patients with asymmetrical IPF compared with 64 matched controls with symmetrical IPF. The asymmetrical involvement is defined by an asymmetry ratio of >0.2 on HRCT (4). The evaluation of the asymmetry ratio is as follows: 1) the extent

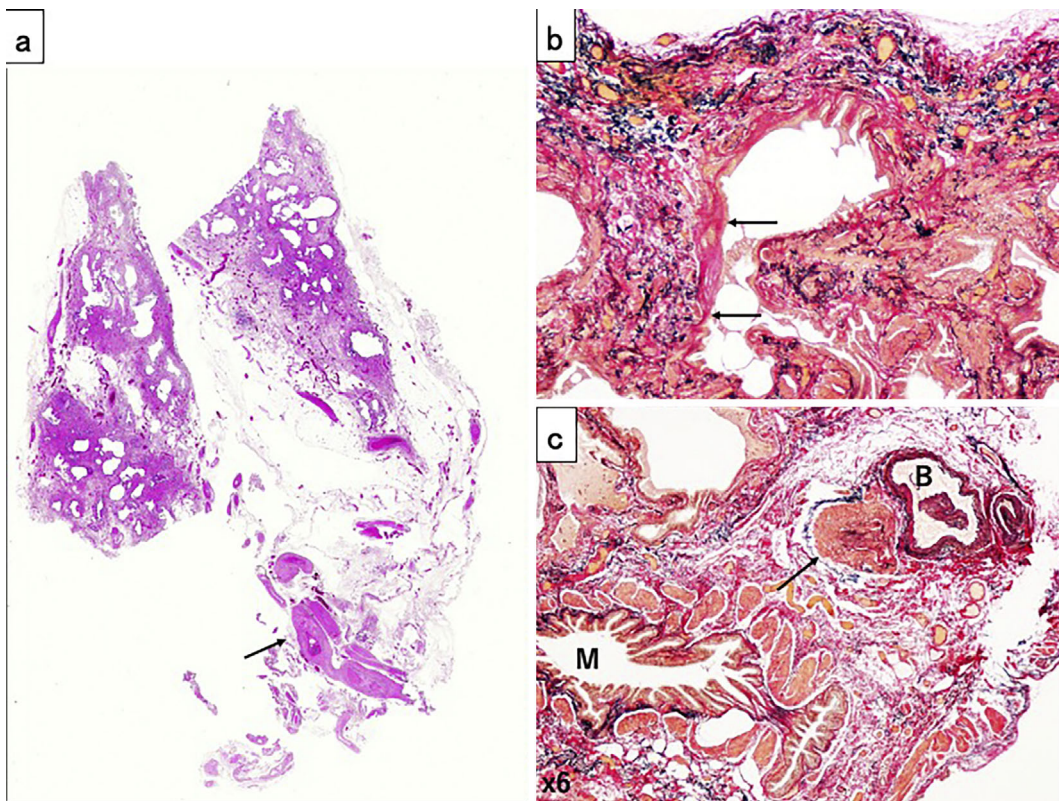


Figure 4. Histological features of the right S¹⁰. (a) The right S¹⁰ is totally replaced by dense fibrosis showing honeycombing and a newly formed systemic artery (arrow) in the fatty tissue attached to the lung. Hematoxylin and Eosin staining, Panoramic view. (b) Established peripheral dense fibroelastosis still accompanies fibroblastic foci (arrow). EvG, ×60. (c) Complete obstruction of the pulmonary artery (arrow) due to muscularization of the intima accompanying the markedly dilated bronchial artery (B) next to a membranous bronchiole (M). EvG, ×60.

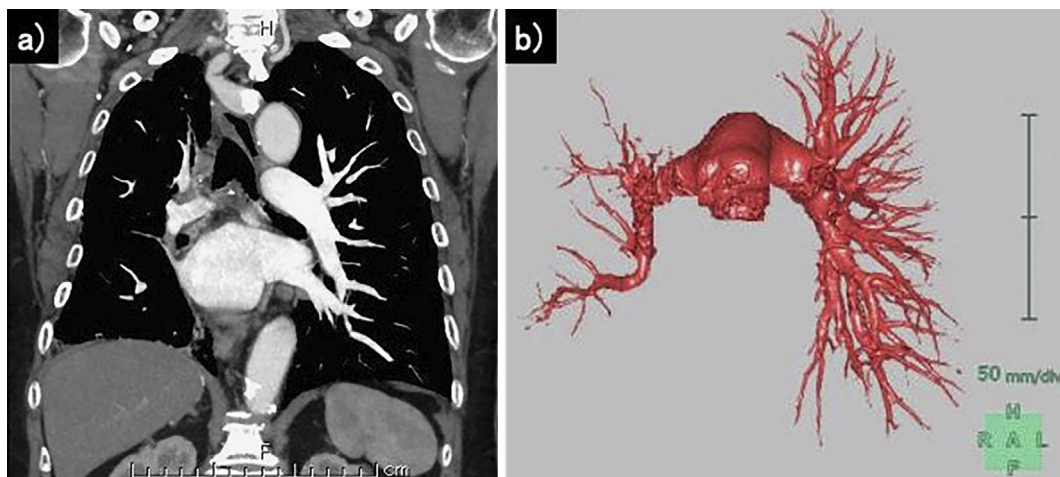


Figure 5. Contrast-enhanced chest computed-tomography (CT) with coronal reconstruction (a) and a three-dimensional CT angiogram (b) showing partial defects of the pulmonary arteries on the right side.

of fibrosis is measured as the proportion of the involved lung surface at each of 5 levels (between 0% and 100%, censored at 5%), 2) right and left fibrosis scores are the average of the 5 measures obtained for each lung, and 3) the asymmetry ratio is calculated as (most affected - least affected fibrosis score) / (most affected + least affected fibro-

sis score). The asymmetry ratio of the present case based on this method was 0.96 and 0.92 using HRCT images from 2008 and 2019, respectively. A ratio of 0 corresponds to perfect symmetry between the two lungs, and a value of 1 corresponds to strictly unilateral fibrosis (4). The present case was therefore concluded to have presented with essen-

tially unilateral fibrosis.

Tcherakian et al. (4) also reported that the right side was more likely to be involved than the left in patients with asymmetrical IPF, as seen in the case described here. They suggested that GERD may be responsible for asymmetrical disease progression because patients with asymmetrical IPF differed significantly from those with symmetrical IPF in that they had a much higher frequency of GERD and acute exacerbations (4). However, in the present case, although we did not perform 24-hour ambulatory pH monitoring, GERD was unlikely, and acute exacerbation was not observed during the long follow-up period of 20 years. Callahan et al. (5) also studied 14 asymmetrical IPF cases and found no statistically significant differences in number of GERD and IPF exacerbations compared with 28 symmetrical IPF controls.

The asymmetrical progression of pulmonary fibrosis in the present case may have been due to hypoplasia of a unilateral pulmonary artery. The present case showed pleural and vascular abnormalities in addition to the UIP pattern, i.e. severe pleural adhesion, obstruction of the pulmonary artery, and dilated systemic artery (including bronchial artery) as revealed on a surgical lung biopsy. Partial defects of the pulmonary arteries on the affected side were also visible on 3D CT angiograms. These findings imply decreased pulmonary artery perfusion and development of systemic vessel collateralization to supply the affected lung via intrapulmonary bronchopulmonary arterial anastomoses or transpleural systemic-pulmonary artery anastomoses (9). As Ryu et al. (10) suggested, a pressure gradient between the systemic and the pulmonary arteries or high oxygen saturation level may induce lung injury, resulting in fibrosis. A previously reported case showed unilateral IPF-like changes in the right middle and lower lobes owing to congenital absence of the right interlobar pulmonary artery, with sparing of the upper lobe (10). Ryu et al. (11) also studied the HRCT findings of proximal interruption of the right pulmonary artery showing reticular opacities, septal thickening, subpleural consolidation, cystic lung changes, and pleural thickening. Sakai et al. (12) evaluated the CT findings of unilateral proximal interruptions of the pulmonary artery in adults, showing the formation of pleural thickening or interstitial fibrotic changes, including honeycombing, in addition to enlarged bronchial arteries. These studies suggest that fibrotic changes to the affected lung might have been caused by the absence of pulmonary artery perfusion and development of systemic vessel collateralization (11).

Regarding absent pulmonary artery perfusion, these studies described only the radiological findings of parenchymal changes of the lung. There are few reports on the histopathological findings of similar cases. Chong et al. (13) reported a case of histologically confirmed unilateral UIP with ipsilateral slow-growing pulmonary artery sarcoma that resulted in chronic pulmonary ischemia and a systemic arterial supply. Although the two aforementioned studies of asymmetrical IPF included cases diagnosed by a surgical lung bi-

opsy [n=9 (4) and n=10 (5)], the histopathological findings of pleural or vascular abnormalities were not mentioned. Therefore, the present case is important in that it demonstrated that a low pulmonary artery perfusion capacity and systemic-pulmonary anastomoses can cause UIP changes. The reason for the pulmonary arterial hypoplasia is unknown.

In conclusion, we encountered a case of asymmetrical ILD with a UIP pattern that remained almost completely asymmetrical over an extended period of time. Asymmetrical IPF may be favored by several underlying conditions, with decreased pulmonary artery perfusion and development of systemic vessel collateralization being potentially responsible for asymmetrical disease progression.

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

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