【 CASE REPORT 】

Airway-centered Interstitial Fibrosis Involving Smooth Muscle Hyperplasia with Severe Pulmonary Hypertension

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Abstract:

In the 2013 updated classification of the American Thoracic Society/European Respiratory Society, airway-centered interstitial fibrosis (ACIF) is included as a bronchiolocentric pattern of interstitial pneumonia (IP) among idiopathic IPs. We encountered a case of severe pulmonary hypertension (PH) with chronic IP. The patient initially presented with shortness of breath and often lost consciousness due to PH, and seven years after his first visit, he ultimately died. An autopsy revealed ACIF and usual IP. In particular, the ACIF comprised non-atypical smooth muscle hyperplasia, and pulmonary hypertensive vascular degeneration was detected. This case may represent a new pathological feature of ACIF.

Key words: airway-centered interstitial fibrosis, smooth muscle hyperplasia, pulmonary hypertension

(Intern Med 59: 2029-2034, 2020)
(DOI: 10.2169/internalmedicine.4199-19)

Introduction

Airway-centered interstitial fibrosis (ACIF) has various names and has been barely reported since its first mention in 2002 (1). In the 2013 American Thoracic Society/European Respiratory Society updated classification of idiopathic interstitial pneumonias (IPs) and bronchiolocentric patterns of IP, the term ACIF was separated from the new entities of idiopathic IPs and included as a rare histological pattern (2).

ACIF has been assumed to have an etiology that is related to inhalants, such as smoking and environmental and occupational exposure. Differentiating it from hypersensitivity pneumonitis is imperative (1, 3). The variable amount of bronchiolar and peribronchiolar fibrosis and inflammation is the common histopathologic denominator (4). However, the disease concept and clinical picture of ACIF remain unclear. Although several cases have been treated with steroids, the natural course and response to treatment have not been characterized, and the complications are unknown (1, 3-5).

We herein report a rare case of ACIF that had specific histopathological findings and was accompanied by severe pulmonary hypertension (PH).

Case Report

A 73-year-old Japanese man who worked as a turner was rushed to our hospital due to loss of consciousness (LOC). He was a previous smoker of 38 pack-years and had had diabetes mellitus and chronic kidney disease for more than 10 years.

Seven years ago, he had been diagnosed with IP based on an abnormal shadow revealed by chest radiography, but no further investigations had been conducted during the follow-up, and no specific treatment had been applied due to the absence of respiratory symptoms. One year ago, he started to experience shortness of breath during exercise and often lost consciousness.

A pulmonary function test revealed normal ventilator performance (vital capacity: 3.19 L, 99.4% predicted; forced expiratory volume in 1 second as percent of forced vital capacity: 83.5%) but with severe diffusing capacity disturbance for carbon monoxide (DLco: 6.32 mL/min/mmHg, %DLco: 36.8%). Thus, chronic hypoxia was confirmed, and long-term oxygen therapy was started. Despite oxygen inhalation (5 L/min of oxygen supplementation on exertion), he
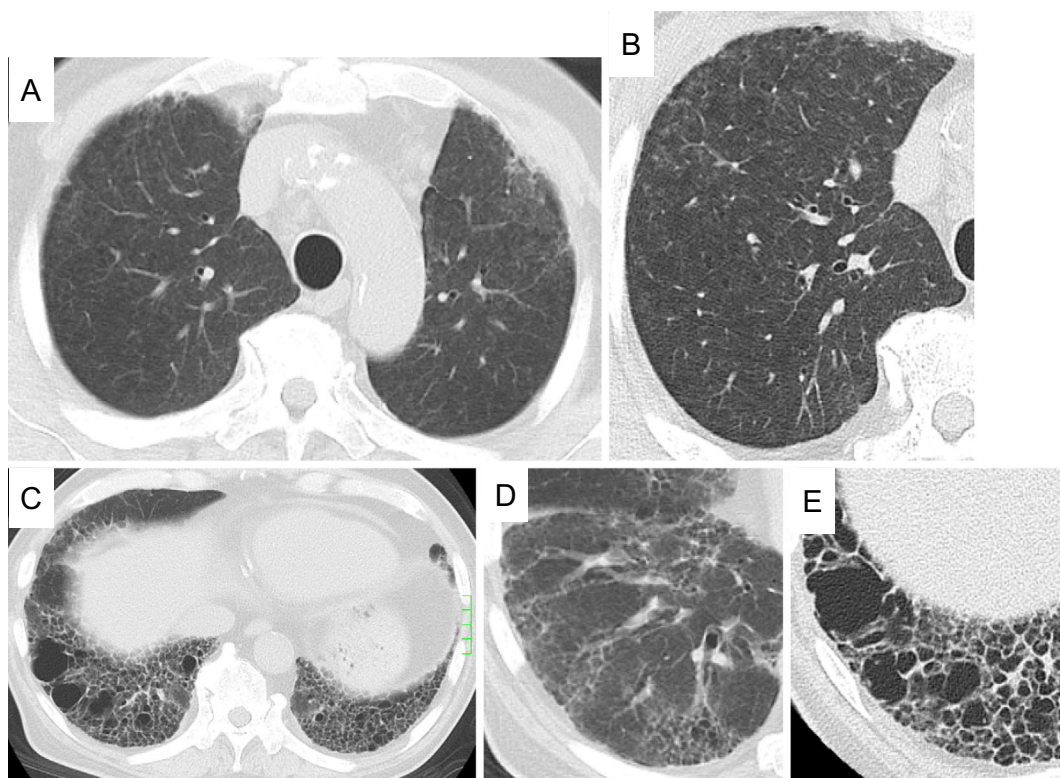
Figure 1.   Chest computed tomography on admission. There are (A, B) reticulonodular densities with subpleural distribution in the upper lungs and (C-E) perilobular fibrosis, traction bronchioeclasis, and honeycombing in the bases of both lungs.

experienced worsening shortness of breath and more frequent episodes of LOC, even with light exertion. There was no obvious cerebrovascular disease that could account for the episodes of LOC, but echocardiography detected a tricuspid regurgitation pressure gradient (TRPG) of 70 mmHg, and chest computed tomography (CT) revealed IP progression. He consistently refused to submit to pulmonary perfusion scintigraphy to identify pulmonary thrombosis and bronchoscopy to determine the cause of his IP. Therefore, PH complicated with IP was considered to be the cause of his LOC.

At admission, he had regained consciousness and had a temperature of 37.0 °C, pulse rate of 95 beats per minute, blood pressure of 96/64 mmHg, and oxygen saturation of 96% at 3 L/min of oxygen supplementation. He had a distended neck vein, clubbing of the fingers and pitting leg edema. Chest auscultation revealed an accentuated second heart sound and fine crackles in the posterior lower lung fields. Laboratory evaluations revealed elevated serum levels of lactate dehydrogenase (298 IU/L), N-terminal pro-brain natriuretic peptide (15,170 pg/mL), and creatinine (2.67 mg/dL). The high serum creatinine level was attributed to chronic kidney disease. The values of C-reactive protein, white blood cell, Krebs von den Lungen-6, and surfactant protein-D were not elevated, but the level of fibrin degradation products was slightly elevated (2.6 μg/mL).

An arterial blood gas analysis under 3 L/min oxygen supplementation revealed PaO_2 of 98.6 mmHg, $PaCO_2$ of 31.8 mmHg, and alveolar-arterial oxygen difference of 118 mmHg. Chest radiography revealed diffuse pulmonary infiltrates in the bilateral lower lung fields. Chest CT revealed reticulonodular infiltrates with subpleural distribution in the bilateral upper and middle lobes and perilobular fibrosis, traction bronchioeclasis, and honeycombing in the bases of both lungs (Fig. 1). In the mediastinal window on chest CT, the pulmonary artery, especially the pulmonary trunk, was enlarged. The chest imaging findings six months before and at this point were generally the same, with no new findings, such as ground-glass opacity, suggesting acute exacerbation of IP. During the seven-year clinical course, reticulonodular densities in the upper and middle lobes and perilobular fibrosis, traction bronchioeclasis, and honeycombing in both lung bases progressed gradually.

Echocardiography at this point revealed right ventricular and atrial dilatation and a TRPG of 100 mmHg, which was higher than the TRPG 4 months before. The left ventricular ejection fraction was in the normal range at 64.5%, but the cardiac index decreased to as little as 1.4 L/min/m^2, and the left ventricle was D-shaped. Based on these findings, his LOC was suspected to have been caused by insufficient left ventricular forward stroke volume due to PH, which was likely secondary to the damage of the pulmonary vascular bed and hypoxic pulmonary vasoconstriction from the IP. Pulmonary thromboembolism could not be ruled out because his renal disease prevented him from undergoing contrast-enhanced CT. Upon admission, he was placed on bed rest
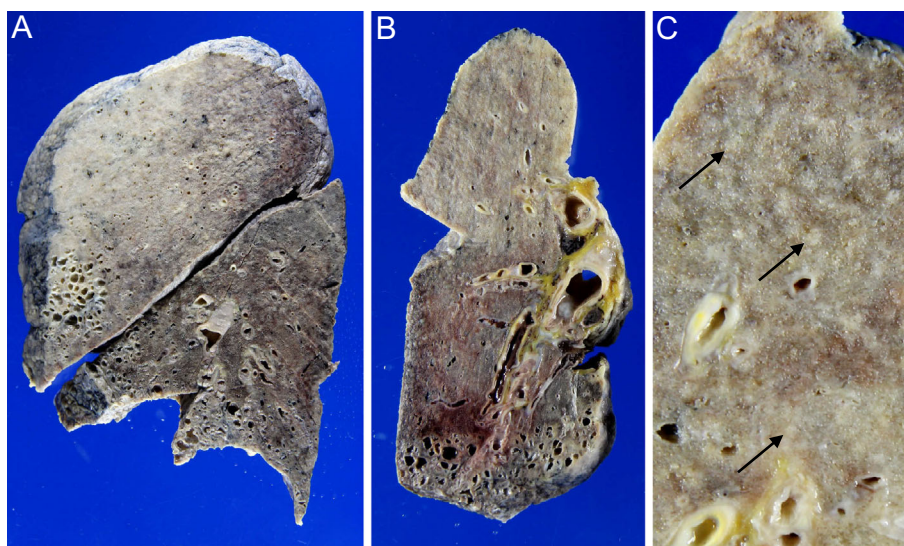
Figure 2. Gross findings of the lungs on autopsy. Both lungs (A, left; B, right) show marked fibrosis and honeycombing, predominantly in the lower zones. (C) The upper lobes and right middle lobe are relatively spared from architectural distortion but are noted to have scattered small, white lesions of 1-2 mm in diameter (arrows).

and given optimum oxygen therapy and diuretics. However, his arterial blood oxygen saturation decreased significantly with light exertion, and three days later, his condition suddenly deteriorated, resulting in his death. An autopsy was performed to verify the direct cause of death and determine the details of the IP and PH.

On an autopsy, a gross examination of the lungs (left 430 g, right 530 g) revealed marked fibrosis and honeycombing, predominantly in the lower zones (Fig. 2A, B). The upper lobes and right middle lobe were relatively spared from the architectural distortion by the fibrotic process but were noted to have scattered small white lesions of 1-2 mm in diameter (Fig. 2C). There were mild anthracosis and minimal emphysematous changes. The proximal pulmonary arteries were atherosclerotic.

Microscopically, the lung tissue specimens from the upper, middle, and superior segment of lower lobes revealed numerous bronchiolocentric lesions of 1-2 mm in diameter (Fig. 3A). The lesions comprised thickened bronchiolar and alveolar walls with striking smooth muscle hyperplasia and mild fibrosis with minimal inflammatory infiltrates (Fig. 3B). Immunohistochemically, the markedly hyperplastic smooth muscle cells were positive for h-caldesmon (Fig. 3C), α-smooth muscle actin, and desmin and negative for HMB-45. Routine hematoxylin-eosin staining, polarizing microscopy, and Prussian blue staining did not demonstrate deposition of visible/pigmented dust, birefringent dust, and ferruginous bodies, respectively. Furthermore, there was no granuloma.

A histological examination of the pulmonary vasculature revealed medial hypertrophy and concentric intimal fibrosis in the muscular pulmonary arteries (Fig. 3D, E). There were no plexiform lesions or dilatations. The muscular pulmonary arteries involved in the bronchiolocentric lesions of the up-

per zones tended to show wrinkling of the walls (Fig. 3F). Pulmonary thromboembolism was not revealed. No significant changes were observed in the pulmonary veins.

The lung tissue from the lower lobes, especially the lung bases, revealed advanced fibrosis and honeycombing with normal parenchyma and occasional fibroblastic foci (Fig. 4). The findings in the lower lobes were compatible with those of the usual UP (UIP) pattern. However, the bronchiolocentric lesions in the upper zones were thought to be peculiar interstitial lung lesions and differed from the UIP pattern of fibrosis.

The heart weighed 530 g and showed cor pulmonale.

Discussion

ACIF has been variably called bronchiolocentric IP, centrilobular fibrosis, and bronchiolitis interstitial pneumonitis (1, 6, 7). However, the histopathological findings associated with these definitions differ slightly. The literature on ACIF has been relatively scarce, but several small-scale retrospective studies have gradually clarified the pathology, imaging findings, and clinical features of ACIF. Almost all of the studies on ACIF were mainly based on histopathology, and the pathological outline was fibrosis of the peripheral bronchiole and its surrounding alveolar tissue, with preservation of the existing lung structures. The other reported findings of ACIF were varying degrees of inflammatory cell infiltration, necrosis/regeneration of the bronchiolar epithelium, and peribronchiolar metaplasia of the epithelium, with accompanying fibrosis in many cases (1, 3-6). The distribution of fibrosis varied among the cases, from being localized in the bronchioles to further extension to the peripheral alveoli.

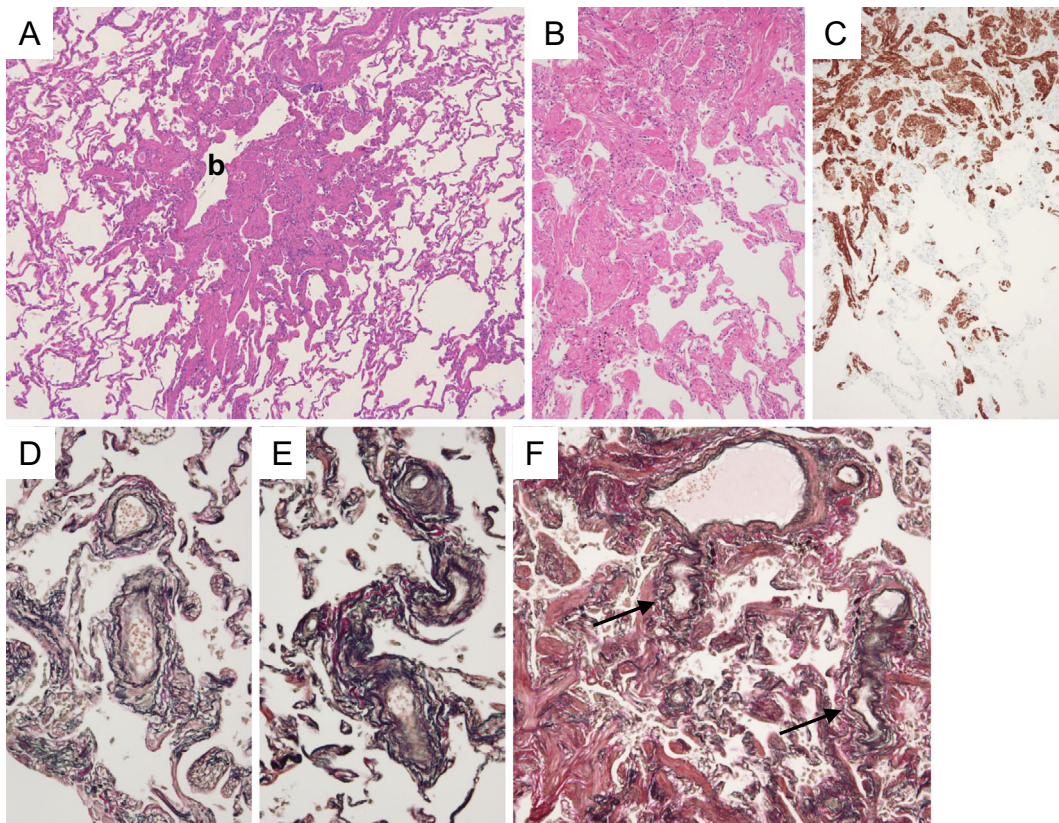The peripheral airways tend to present with various patho-

Figure 3. Microscopic findings of the upper lobes of the lungs. (A) There are numerous bronchiolocentric lesions of 1-2 mm in diameter (b, bronchiole) [Hematoxylin and Eosin (H&E) staining; original magnification, ×40]. (B) The lesions comprise thickened bronchiolar and alveolar walls with striking smooth muscle hyperplasia and mild fibrosis with minimal inflammatory infiltrates (H&E staining; original magnification, ×100). (C) Immunostaining for h-caldesmon confirms the marked hyperplasia of smooth muscle cells (original magnification, ×100). The muscular pulmonary arteries are observed to have (D) medial hypertrophy and (E) concentric intimal fibrous thickening (elastica van Gieson stain; original magnification, ×200). (F) The muscular pulmonary arteries involved in the bronchiolocentric lesions tend to show wrinkling of the walls (arrows) (elastica van Gieson stain; original magnification, ×100).
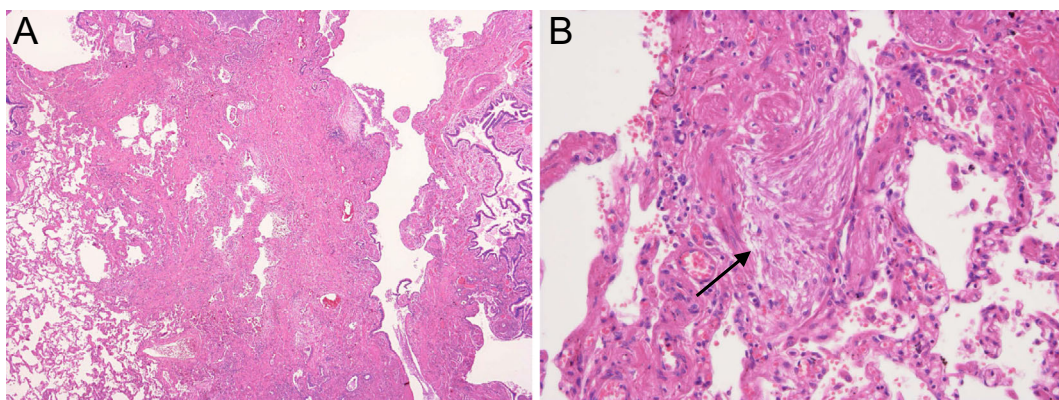

Figure 4. Microscopic findings of the lower lobes of the lungs. (A) The lower lobes, especially the lung bases, are observed to have advanced fibrosis and honeycombing, along with normal parenchyma (left) [Hematoxylin and Eosin (H&E) staining; original magnification, ×20]. (B) There are occasional fibroblast foci (arrow) (H&E staining; original magnification, ×200).

logical condition, it is very difficult to determine the etiology of ACIF as idiopathic. Therefore, ACIF needs to be distinguished from other lung conditions caused by inhalation exposure, connective tissue diseases (CTDs), and microaspi-

ration (3, 6). Inhalation exposure includes that via smoking, the environment, and one's occupation and may cause hypersensitivity pneumonitis (HP), which shares some characteristics with ACIF in terms of an upper lobe predominance, CT imaging findings of reticulonodular shadows and bronchial thickness, and effective treatment with corticosteroids (3, 4). However, one histopathological characteristic of HP is the presence of granuloma and multinucleated giant cells, which are not observed in hardly any reported ACIF cases (8). Typical CTDs with airway disorders, such as rheumatoid arthritis and Sjögren syndrome, are the other conditions that need to be differentiated from ACIF based on the histopathological findings of follicular bronchiolitis and cellular bronchiolitis, which are characterized by lymphoid follicles with germinal centers or transmural cellular infiltration of small, round cells around the bronchiole; various serum markers; and clinical symptoms, such as those in articular and salivary and tear glands (9).

Our case showed chronic IP complicated by severe PH of unknown etiology, and the autopsied lungs revealed characteristic histopathological findings of fibrosis and pulmonary hypertensive vascular degeneration. Because the upper lobe-predominant lesions in our case were bronchiolocentric and contained mild fibrosis and smooth muscle hyperplasia, we speculated that the lesions might be a form of ACIF. The history of smoking and occupational dust inhalation may have been involved in the development of ACIF. In addition, the upper lobe-predominant distribution may suggest a relationship with some kind of inhaled antigen. However, there were no findings of granuloma, notable deposition of carbon dust or aggregation of smoker's macrophages. An elemental analysis of the lung tissue is required as an additional test to distinguish ACIF from hard metal lung disease (10). There were no histopathological or clinical findings suggesting a CTD.

Notably, in our case, the alveolar septum around the respiratory bronchioles was thickened, mainly by striking smooth muscle hyperplasia that lacked marked collagen deposition, elastosis, or epithelial metaplasia. Although Churg et al. reported the presence of muscularized bronchioles in some of their ACIF cases, the prominence of smooth muscle hyperplasia in our case was a unique finding and has not been described as a feature of ACIF before (4). A very similar histopathological finding to our case was reported under the name of diffuse smooth muscle proliferation of the lungs (DSMPL) in patients with idiopathic PH as a rare possible cause of PH (11, 12). To our knowledge, only four cases of DSMPL have been reported previously (11-14). Kay et al. explained that DSMPL might cause distortion, obstruction, and focal thrombosis of small muscular pulmonary arteries and lead to PH (11). Although wrinkling of the arterial walls in the bronchiolocentric lesions was observed, thrombi were not identified in our case. It is important to note that most of these DSMPL cases were reported more than 20 years ago, when the concept of ACIF had not been established. Therefore, the difference between ACIF and DSMPL needs to be clarified through further studies. From the perspective of the histological differential diagnosis of smooth muscle hyperplasia, all previous reports considered the differentiation between DSMPL and pulmonary lymphangioleiomyomatosis to be important. Negativity for HMB-45 in the proliferating smooth muscle cells in our case and in the previously reported cases suggested that the lesions differed from those of lymphangioleiomyomatosis (11, 12, 14).

In addition to the upper lobe-predominant ACIF lesions, our case showed UIP lesions that contained air space enlargement and fibrotic architectural destruction in the lower lobes. Churg et al. and Mark et al. reported ACIF cases with a UIP pattern, but these cases were rare, and the relationship between the two patterns of fibrosis has not been described thus far (4, 7). Further studies will be required to clarify whether or not ACIF and UIP lesions have a common underlying cause.

The autopsy findings of the present case imply severe PH was the cause of death. One reason an autopsy was performed was to investigate the etiology or pathophysiology of PH histologically. To our knowledge, ACIF accompanied by PH has never been reported. Although the pathophysiological mechanisms of PH associated with IP are poorly understood, PH of IP is attributed to increased pulmonary vascular resistance due to the obliteration of or decrease in the vascular bed by parenchymal fibrosis, hypoxic pulmonary vasoconstriction, and pulmonary artery remodeling, including medial hypertrophy and intimal fibrosis (15). In our case there was widespread pulmonary artery remodeling in the peripheral pulmonary artery branches. During the seven-year clinical course, chest CT showed slow progression of ACIF in the upper and middle lobes and gradual progression of UIP in the base of the lungs. It can be presumed that extensive progression of ACIF and UIP lesions resulted in severe hypoxia on exertion and PH due to hypoxic pulmonary vasoconstriction and the reduction in the size of the pulmonary vascular bed. Furthermore, wrinkling deformation of the wall of muscular pulmonary arteries in ACIF lesions might have been involved in the development of pulmonary vascular resistance.

In summary, we reported a case of severe PH associated with unique interstitial lung lesions that comprised upper lobe-predominant airway-centered disease with marked smooth muscle hyperplasia and lower lobe-predominant UIP pattern fibrosis. The etiology of PH in our case could not be completely elucidated, even by autopsy, and this case highlighted the difficulty in performing intervention for PH caused by IP. Although severe PH patients with IP often die suddenly during exertion, there is still no consensus concerning PH treatment, including pulmonary vasodilators. Therefore, the accumulation of similar cases is needed.

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