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Case report

An autopsy case of idiopathic pulmonary fibrosis with remarkable honeycomb cyst expansion

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ABSTRACT

Herein, we report an autopsy case of idiopathic pulmonary fibrosis (IPF) in which remarkable honeycomb cyst expansion appeared in the clinical course. Radiological findings initially showed subpleural predominant reticulation that had progressed to usual interstitial pneumonia with honeycomb cysts, along with a restrictive pattern in the pulmonary function tests. The diameter of honeycomb cysts had gradually increased, and some cysts had abruptly expanded at the end stage. Based on pathological findings of autopsy specimens, bronchiectasis, alveolar collapse due to inflammation, and check-valve mechanism caused by a slit-like orifice of the cysts could have contributed to honeycomb cyst expansion.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as chronic, progressive, and fibrosing interstitial pneumonia of unknown cause. The hallmark for diagnosis is a usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT), predominantly a basal and subpleural honeycomb pattern [1]. The diameter of honeycomb cysts often ranges from 0.3 to 1.0 cm. Although such cysts are known to occasionally expand up to 2.5 cm with disease progression [2,3], the mechanism of cyst expansion is not fully understood [4,5]. In addition, few studies have reported sequential changes in honeycomb cysts from disease onset to the end stage [6].

In this study, we report a case of IPF with overall changes on chest X-ray, HRCT, and pulmonary function tests (PFTs). Some honeycomb cysts showed remarkable expansion, with lung structures destroyed at the end stage. We obtained characteristic pathological features of lung tissues from autopsy specimens and discussed the mechanisms of cyst expansion.

2. Case presentation

The patient was a 62-year-old male who presented with exertional dyspnea. He had a family history of IPF (two siblings) and a medical history of gastro-esophageal reflux disease. He had smoked 40 cigarettes per day for 44 years and had no history of connective tissue disease or exposure to dust. On examination, his oxygen saturation was 98% while breathing room air and he had clubbed

Abbreviations: HRCT, High-resolution computed tomography; IPF, Idiopathic pulmonary fibrosis; PFT, Pulmonary function tests; VC, Vital capacity; KL-6, Krebs von den Lungen-6.

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fingers and bibasilar fine crackles. Chest X-ray and HRCT revealed reticulation in the subpleural area of the lower lobes (Fig. 1A and E). Over the next 4 years, the area of reticulation had gradually enlarged, and honeycomb cysts were detected in the right lower lobe (Fig. 1F). His vital capacity (VC) in PFTs declined from 3.17 L to 2.55 L, and serum Krebs von den Lungen-6 (KL-6) level had increased during this period (Table 1). He was thus diagnosed with IPF [7] and was eventually started on nintedanib (300 mg/day). Pirfenidone (1800 mg/day) was added to nintedanib the next year; however, these agents did not inhibit disease progression, including volume reduction of both lungs (Fig. 1B and G). At age 68, long-term oxygen therapy was administered for his worsening dyspnea after distal gastrectomy for stomach cancer. Moreover, an acute exacerbation occurred in the same year. Afterward, honeycomb cysts spread to the left lower lobe with some cysts showing slight expansion (Fig. 1H).

His first admission to our hospital was 7 years after the disease onset, when extensive fibrosis was found in the X-ray, and remarkable cyst expansion appeared on HRCT imaging (Fig. 1C and I). He was discharged home once but was re-hospitalized because of desaturation 2 months later. Progressive fibrosis and further expansion of these cysts (up to 4.3 cm in diameter) was observed (Fig. 1D and J). The volume ratio of cysts to lung fields was shown to increase abruptly to more than 20% from the analysis using SYNAPSE VINCENT version 5.3 (FUJIFILM Medical Systems, Tokyo, Japan) (Table 1). From a coronal section of chest HRCT, the shape of the smaller cysts was noted to be irregular, and these cysts were continuous with dilated bronchi. In contrast, the larger cysts had smooth edges and a rounded shape, and proximal bronchial stenoses were observed in some of these larger cysts (Fig. 1K).

The patient died of pneumonia and respiratory failure during his second hospitalization, and an autopsy was then performed. Cut surface of the lung showed multiple expanded cysts (Fig. 2A), and some cysts containing purulent discharge inside (Fig. 2B). Other cysts were adjacent to dilated bronchi macroscopically, and their continuity with bronchioles was detected histologically (Fig. 2C and E). Furthermore, a slit-like orifice area was found between a large, rounded cyst and a bronchiole, and a flap-like wall of the bronchiole was identified at the orifice area on the surface of the cyst (Fig. 2D).

3. Discussion

We have reported an autopsy case of IPF in which some honeycomb cysts had expanded remarkably at the end stage of disease. Previous studies have shown that honeycomb cysts in IPF gradually increase in size during the clinical course [2,3]. However, to the best of our knowledge, no reports have mentioned such a rapid cyst expansion in the natural history in IPF.

There have been several explanations for the pathogenesis of cyst formation: bronchiectasis, dissolution of alveolar septa, and air trapping caused by check-valve mechanism [3–5]. Firstly, in this study, HRCT images indicated that some cysts were continuous with dilated bronchi, and this continuity was also evident in postmortem specimen. These findings suggest that bronchiectasis was a contributing factor for cyst formation. Secondly, autopsy specimen showed purulent discharge within some cysts, indicating tissue

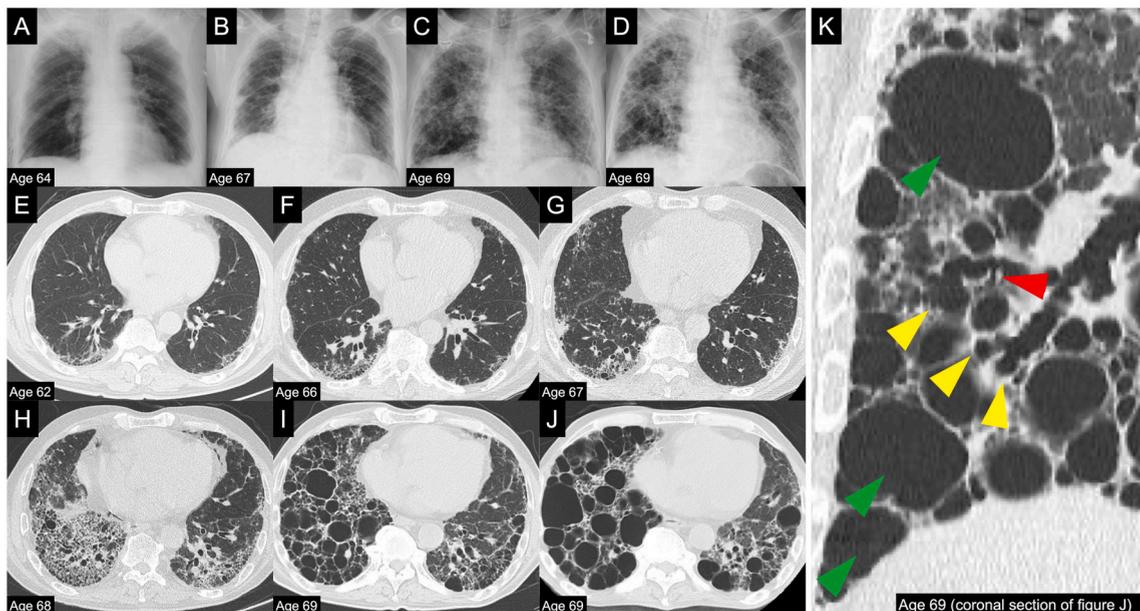


Fig. 1. Radiological findings.

Early chest X-ray showed bibasilar reticulation, and it progressed with volume reduction of both lungs (A, B). Extensive fibrosis in both lungs was noted at age 69 (C), and it worsened during the following 2 months (D). Early HRCT imaging showed reticulation in the lower lobes (E). The area of reticulation had gradually enlarged and honeycomb cysts were detected in the right lower lobe (F, G). Subsequently, honeycomb cysts spread to the left lower lobe with some cysts showing slight expansion (H). Seven years after the disease onset, remarkable cyst expansion appeared (I), and it showed further expansion in both lungs (J). A coronal section showed that the shape of the smaller cysts was irregular, and they were continuous with dilated bronchi (K). In contrast, the larger cysts had smooth edges and a rounded shape (green arrows), and proximal bronchial stenoses were observed in some of these larger cysts (red arrow).

HRCT: high-resolution computed tomography.

Table 1
Changes in biomarkers, pulmonary function tests, and cyst ratio on CT.

Age	62	64	66	67	68	69		
Month					March	May	May	July
Event			Diagnosis, Started nintedanib	Started pirfenidone	HOT administered	Acute exacerbation	First admission	Second admission
VC [L]	3.17	2.78	2.55	2.00	2.06	1.65	–	–
%VC [%]	88.5	78.5	72.4	57.3	59.7	47.8	–	–
KL-6 [U/ mL]	531	1100	1081	880	959	1662	1205	700
Cysts ^a [%]	5.0	7.9	8.3	8.6	8.0	9.6	20.0	29.3

^a Cysts: The volume ratio of cysts to lungs was calculated on CT. CT scanning was performed with 1–5-mm-thick samples at 1–5-mm slice intervals. All images were analyzed using SYNAPSE VINCENT version 5.3 (FUJIFILM Medical Systems, Tokyo, Japan). Bronchi and bronchioles were excluded, and cysts were detected in isolated lung parenchyma. The cyst threshold was –950 HU on CT. CT: computed tomography, HOT: home oxygen therapy, VC: vital capacity, KL-6: Krebs von den Lungen-6.

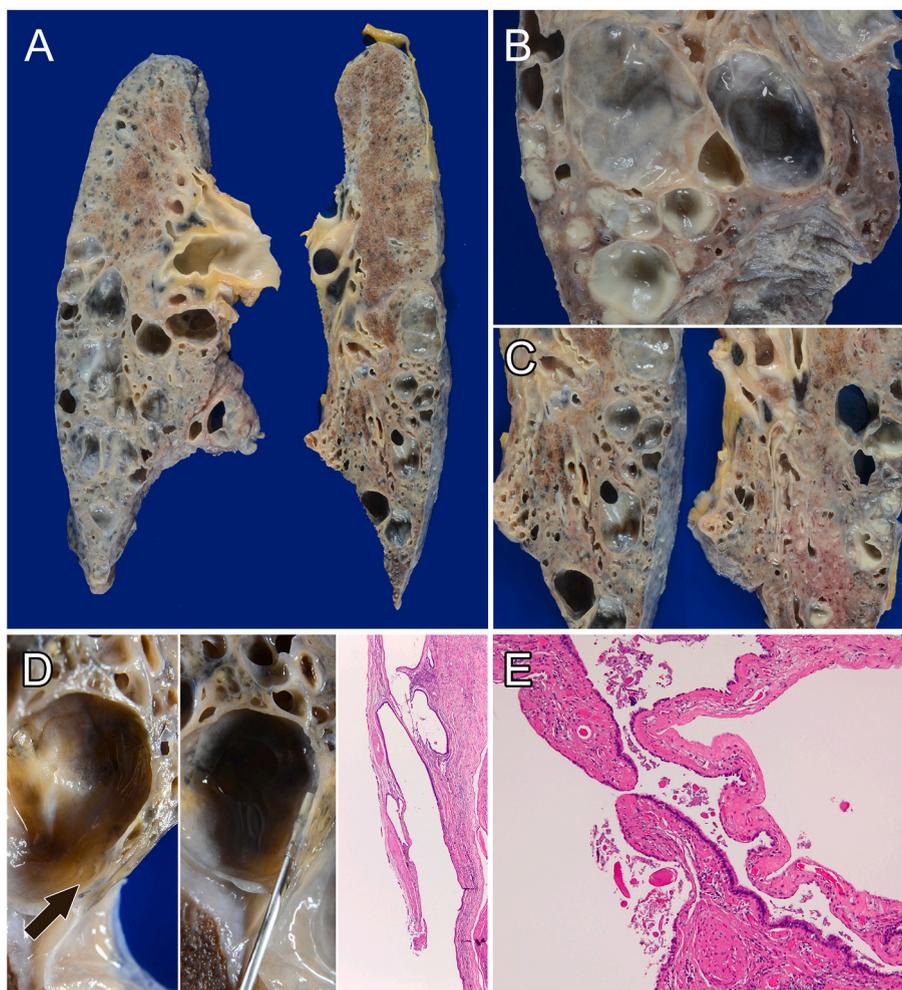


Fig. 2. Pathological findings.

Macroscopic findings of the cut surface of bilateral lungs revealed a predominantly basal and subpleural honeycomb pattern, which was consistent with idiopathic pulmonary fibrosis, and multiple expanded cysts (A). Another cut surface showed some cysts containing purulent discharge (B) and bronchiectasis adjacent to cysts (C). As for the continuity between cysts and airway, a slit-like orifice area was found between a large, rounded cyst, and a bronchiole (D, black arrow). Through this orifice, a bougie could be inserted from the cyst into the bronchiole. Pathologically, a flap-like wall of the bronchiole covered by ciliated columnar epithelium constituted this orifice. The end of the flap was protruding toward the inside of the cyst (D). Another example of continuity between a cyst and a bronchus (E).

inflammation due to pneumonia. It was reported that inflammatory cytokines or chemicals induce dissolution of alveolar septa and cyst formation [8,9]. This patient had a history of gastro-esophageal reflux disease. Chemical pneumonia and inflammation caused by repetitive aspiration of gastric acid was a possible examination for dissolution of alveolar septa. On the other hand, this patient had experienced an acute exacerbation of IPF in the clinical course. Considering that cysts rapidly expanded after acute exacerbation on HRCT, it was suggested that acute exacerbation could induce inflammatory cytokines, and contribute to the destruction of alveolar structures [10,11].

More importantly, radiological findings showed that large cysts had smooth edges and a rounded shape, suggesting that air trapping contributed to the enlargement of cysts. From macroscopic examination of postmortem specimen, we identified a slit-like orifice area between a large, rounded cyst and a bronchiole. Additionally, this orifice was microscopically constituted by a flap-like wall of the bronchiole, and the end of this flap was protruding toward the inside of the cyst. These morphological findings strongly suggest that air trapping caused by check-valve mechanism was the mainstay of large, rounded cyst formation. Previous literatures have mentioned that distorted and stenotic bronchi could work as check valves [4], but flap-like structure derived from bronchioles is also a good candidate for cyst formation from this study.

There is little evidence about the clinical course of IPF; for instance, serial changes in radiological findings, PFTs, and biomarkers [6]. In this study, lung lesions on HRCT started with predominantly subpleural reticulation. Development of honeycomb pattern from this reticulation was preceded by progressive restrictive pattern in PFTs. On the other hand, serum KL-6 level did not correlate with radiological progression or with the decline in PFT values [12–14]. These findings suggest that results in PFTs are more sensitive to disease progression than radiological changes and serum biomarkers. PFTs not only reflect patients' symptoms, such as exertional dyspnea, but also play an important role in predicting radiological disease progression. Additionally, the prognosis was unfavorable after remarkable cyst expansion. Further studies are required to investigate the correlation between the honeycomb cyst expansion and prognosis.

4. Conclusion

We reported an autopsy case of IPF in which honeycomb cysts showed remarkable expansion at the end stage of disease. Radiological and pathological findings suggested that flap-like walls derived from bronchioles foamed slit-like orifice, and check-valve mechanism caused by these structures mainly contributed to cyst expansion among the proposed mechanisms.

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Declarations of competing interest

None.

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