Original

Follow-up Observation of Pneumoconiosis Patients with Comorbid Interstitial Pneumonia: An Observational Study

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Abstract

The frequent co-occurrence of interstitial pneumonia (IP) with pneumoconiosis has been reported in several studies. However, data on the prognosis of IP in this context, including the incidence of acute exacerbation (AE), are scarce. This study aimed to investigate the clinical course of IP complicating pneumoconiosis. We analyzed the follow-up data of 517 out of 559 pneumoconiosis patients who initially underwent high-resolution computed tomography (HRCT) screening for IP and subsequently had follow-up CT examinations. We investigated the occurrence of AE and the development of new interstitial lung abnormalities. The observation period for each patient was defined as the duration from the initial IP screening HRCT to the final CT examination (in months). A total of 517 patients (92% of the initial cohort) were included in the analysis. The mean observation period was 40.4 ± 0.7 months. Among 98 patients with co-existing IP, AE was observed in three individuals during the observation period: two cases were attributed to lung cancer as a trigger, and one case had an unknown etiology. The incidence of AE was 0.09% (per 100 person-years), which is considerably lower than the 5%–15% reported for idiopathic pulmonary fibrosis (IPF). Furthermore, 10 new cases of interstitial lung abnormalities were identified (2.4%) during the follow-up period, comprising 9 cases of interstitial lung abnormality (ILA) and 1 case of probable usual interstitial pneumonia (UIP). The 50% observation period for pneumoconiosis with concomitant IP (54 months) was significantly shorter than that for pneumoconiosis without IP (58 months) ($p < 0.05$). This study identified three cases of AE among pneumoconiosis patients with IP. Notably, only one case was idiopathic, while the others were associated with lung cancer. The higher prevalence of IP in pneumoconiosis patients compared to the general population is expected, likely due to alveolar epithelial damage induced by dust inhalation. Consistent with this, we observed 9 new cases with ILA and 1 with probable UIP. However, the lower frequency of AE in pneumoconiosis-associated IP compared to IPF suggests a distinct pathobiological mechanism, potentially similar to asbestosis, where IP is primarily driven by dust deposition. Further detailed pathological investigations, including genetic studies, are warranted to elucidate these differences.

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—Key words—

pulmonary fibrosis, acute exacerbation, computed tomography

Introduction

Pneumoconiosis is a chronic lung disease caused by inhalation of dust, typically characterized by nodular opacities that can progress to progressive massive fibrosis (PMF) in the upper lung fields in these patients. Separately, interstitial pneumonia (IP) is frequently observed in the lower lung fields in these patients, as reported in several studies[1)-4)]. Our previous HRCT (high-resolution CT) studies also reported that approximately 14% of pneumoconiosis patients had comorbid IP[5)].

Idiopathic pulmonary fibrosis (IPF), which is considered the most common form of IP, had an average survival period of 35 months in reports prior to the widespread use of anti-fibrotic drugs. Acute exacerbations (AEs) often occurred while the course of IPF, accounting for 40% of deaths[6)]. Furthermore, nintedanib, an anti-fibrotic drug, has been approved for IP associated with pneumoconiosis in Japan[7)]. Therefore, it is important to investigate whether the prognosis of IP in pneumoconiosis and the occurrence of AEs is similar to those of IPF.

Previous studies on the prognosis of IP associated with pneumoconiosis have all been retrospective. McConnochie et al. studied 45 coal miners with interstitial pneumonia (23 deaths and 22 survivors) reported an average survival period of 11.4 ± 5 years, which was longer than the 4.5 years reported for IPF[8)]. There was no mention of AEs in their study. Similarly, Arakawa et al. reported on the clinical course of 14 silicosis patients selected from medical records between 1986 and 2006 who initially did not exhibit clear chronic IP. They reported no AEs in their follow-up[3)].

To address the occurrence of AEs, we conducted a retrospective cohort study using 517 (92%) of 559 pneumoconiosis patients who underwent HRCT screening between 2018 and December 2019 and subsequently underwent repeat chest CT (including low-dose CT) scans. The detailed data for the IP group is available in the previous report[5)]. We investigated the subsequent prognosis of cases diagnosed with IP and the presence of newly developed ILA (Interstitial Lung Abnormality). Furthermore, we compared the prognosis between pneumoconiosis patients with and without comorbid IP at the time of the initial screening.

Subjects and Methods

1. Subjects

The study included 517 pneumoconiosis patients from an initial cohort of 559 who visited or were hospitalized at the three participating institutions. These patients underwent HRCT after obtaining written consent between 2018 and December 2019. These 517 patients subsequently received regular follow-up CT examinations (including low-dose CT) at the three institutions or according to their pneumoconiosis health management handbook.

The initial HRCT imaging was approved by the Institutional Review Board of the Japan Organization of Occupational Health and Safety in 2018 (Notification No. 8). Ethical approval for the present study was newly obtained from the Institutional Review Board of the Japan Organization of Occupational Health and Safety (Notification No. 2023-8).

2. Methods

The observation period was defined as the duration (in months) from the HRCT scan to the last confirmed CT scan up to 2024. Criteria for AE of IP were determined based on the 2016 American Thoracic Society (ATS) guidelines[9)]. Cases with an unknown cause, equivalent to idiopathic acute exacerbation in Japan, were classified as “idiopathic”, while those with identifiable triggers such as lung cancer or infection were classified as “triggered”. The observation periods for pneumoconiosis patients with and without comorbid IP were compared using the Kaplan-Meier method. Statistical analysis was performed using IBM SPSS Statistics Base version 24. A Log Rank $\chi 2$ test was used for comparison, and $p < 0.05$ was considered statistically significant.

Results

Table 1 shows the number of subjects, age, and mean observation period for each institution. During the mean observation period of 40.4 ± 0.7 months, three cases of AE were observed (Table 2). Of these three cases, one was an idiopathic case with no identifiable trigger (Fig. 1, 2), while the remaining two cases (Fig. 3, 4) were

Table 1 Number of Subjects and Interstitial Pneumonia Cases at Each Hospital

Hospital	Number of subjects	IP cases	ILA cases	Observation Period (months, mean ± SE)
Hokkaido Chuo	296	64	18	429 ± 1.3
Asahi	123	17	12	40.2 ± 1.1
Okayama	63	8	4	41.5 ± 2.4
Toyama	35	9	5	33.1 ± 2.0
Total	517	98*	39	40.4 ± 0.7

IP: Interstitial Pneumonia; ILA: Interstitial Lung Abnormality
*Breakdown: definite UIP 41 cases, probable UIP 17 cases, NSIP 7 cases, unclassified 33 cases.

Table 2 List of Acute Exacerbation Cases

Case	Occupational History	ILO classification	Interstitial Pneumonia	Trigger
1	Tunnel (36 years)	4B	AEF	None
2	Coal Mine (42 years)	1/0	Definite UIP	Lung Cancer
3	Coal Mine (36.8 years)	4A	Definite UIP	Lung Cancer

ILO: International Labor Organization; AEF: Airway Enlargement with Fibrosis; UIP: Usual Interstitial Pneumonia

associated with lung cancer and classified as lung cancer-triggered cases. Images of these cases are shown. Fig. 1–a shows a pneumoconiosis patient with a large opacity equivalent to 4B of ILO classification in the upper lung fields. The screening CT (Fig. 1–b) showed thick-walled cystic changes and surrounding IP findings in the lower lung fields, diagnosed as Airway Enlargement with Fibrosis (AEF) (Fig. 1–b). The first AE was observed in July 2021, with ground-glass opacities, particularly in the right lower lung field, on the chest radiography (CR) image of July 21 (Fig. 1–c). CT also showed ground-glass opacities spreading in the lower lung fields (Fig. 1-d). The condition improved with steroid pulse therapy. The second AE was observed in the right upper lung field (Fig. 2–a, 2–b). After steroid pulse therapy, the condition also improved again (Fig. 2–c, 2–d).

In Case 2, ground-glass opacities not observed at entry were found in the left lung (Fig. 3–a), and a UIP pattern was observed in both lower lung fields (Fig. 3–b). At the time of AE, tumor enlargement and ground-glass opacification were noted (Fig. 3–c). In case of Case 3, a UIP pattern was admitted on both lower lung fields (Fig. 4–a). Ground-glass opacification was noted on the left lower lung field, and a tumor shadow was observed on the right lower lung (Fig. 4–b). This AE was considered as triggered by lung cancer.

Three AEs were observed out of 98 cases, resulting in an incidence of 0.09 per 100 person-years.

Furthermore, during this period, 9 new cases of ILA and 1 case of probable UIP were observed in the group of pneumoconiosis patients who had not previously shown IP.

Finally, we compared the observation periods between pneumoconiosis patients with and without comorbid IP. The median observation period for 50% survival in pneumoconiosis patients without IP was 58 months, while for those with comorbid IP, it was 54 months, showing a statistically significant difference ($p=0.013<0.05$) (Fig. 5).

Discussion

In this study, we observed 3 cases of AE of IP among 97 pneumoconiosis patients with IP, who were followed for approximately 40 months out of 517 total patients. One case was an idiopathic AE as defined in Japan, while the other two cases experienced AE during the course of lung cancer. The incidence was 0.09 per 100 person-years. Even when limited to 58 cases of definite UIP and probable UIP, the incidence was 1.05 per 100 person-years, which was lower than the reported incidence of 5–15% for AE in IPF[10].

Furthermore, during this observation period, we newly identified 9 cases of ILA and 1 case of probable UIP. This further demonstrates the propensity for pneumoconiosis to induce ILAs. Including pre-existing ILA lesions, the total number of ILA cases among 517 patients becomes 52 (10.1%), exceeding the reported rate of

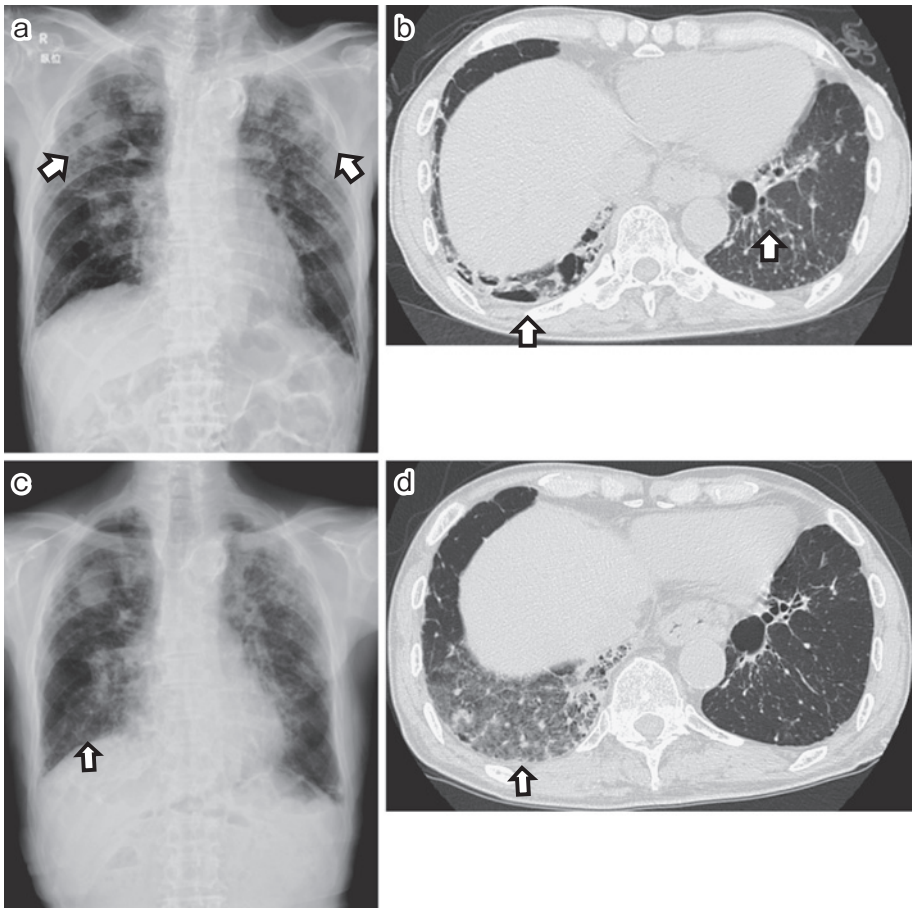

Fig. 1 Images of Case 1: Screening and First Acute Exacerbation.
(a) Chest radiography image of Case 1 at screening (August 2019). Shows large opacities consistent with 4B (arrows) in both upper lung fields, characteristic of a pneumoconiosis patient classified as Stage 3 B. Interstitial pneumonia is not evident. (b) High-Resolution CT image of Case 1 on the same day in 2019, shows thick-walled cystic opacities (arrows) and surrounding interstitial pneumonia findings in the cross-section immediately above the diaphragm, diagnosed as comorbid AEF (Airway Enlargement with Fibrosis). (c) Chest radiography image of Case 1 during the first acute exacerbation (July 2021). Compared to the chest radiography image at the time of study participation, there is decreased translucency (arrows) above the right diaphragm. (d) CT image of Case 1 during the first acute exacerbation. Shows widespread ground-glass opacities (arrows) in the right lower lung field.

4–9% in smokers aged 60 years or older by Hatabu et al.[11]. Since our screening only included subpleural non-fibrotic and subpleural fibrotic lesions within the ILA classification, the ratio would be even higher if ground-glass abnormality with central predominance were included.

Previous reports by McConnochie et al. indicated that the prognosis of IP in coal miners is 11.4 ± 5 years, following a milder course compared to the maximum average prognosis of 4.5 years for non-occupational IP. Additionally, Arakawa et al.'s report on 14 silicosis patients with IP, observed for 15.4 years by CT, reported no AEs[3]. Although our definition of AE in IP is broader than the conventional Japanese definition, we reported an idiopathic AE in a pneumoconiosis patient with a large opacity and AEF lesion. The incidence of AE is low, as previously stated. We also reported a high incidence of ILA in pneumoconiosis patients. Although the imaging findings may appear similar to idiopathic IP, these lesions are thought to have different pathological mechanisms, and further detailed pathological studies are anticipated.

Limitations of this study include a shorter mean observation period of 40 months compared to two previous reports[3,9] that observed cases for over 10 years, despite having a larger number of pneumoconiosis patients with comorbid IP than conventional reports. Also, while HRCT was used for initial screening, low-dose CT was used for subsequent follow-up, which may potentially affect the diagnosis of ILA. And all three cases of AE co-

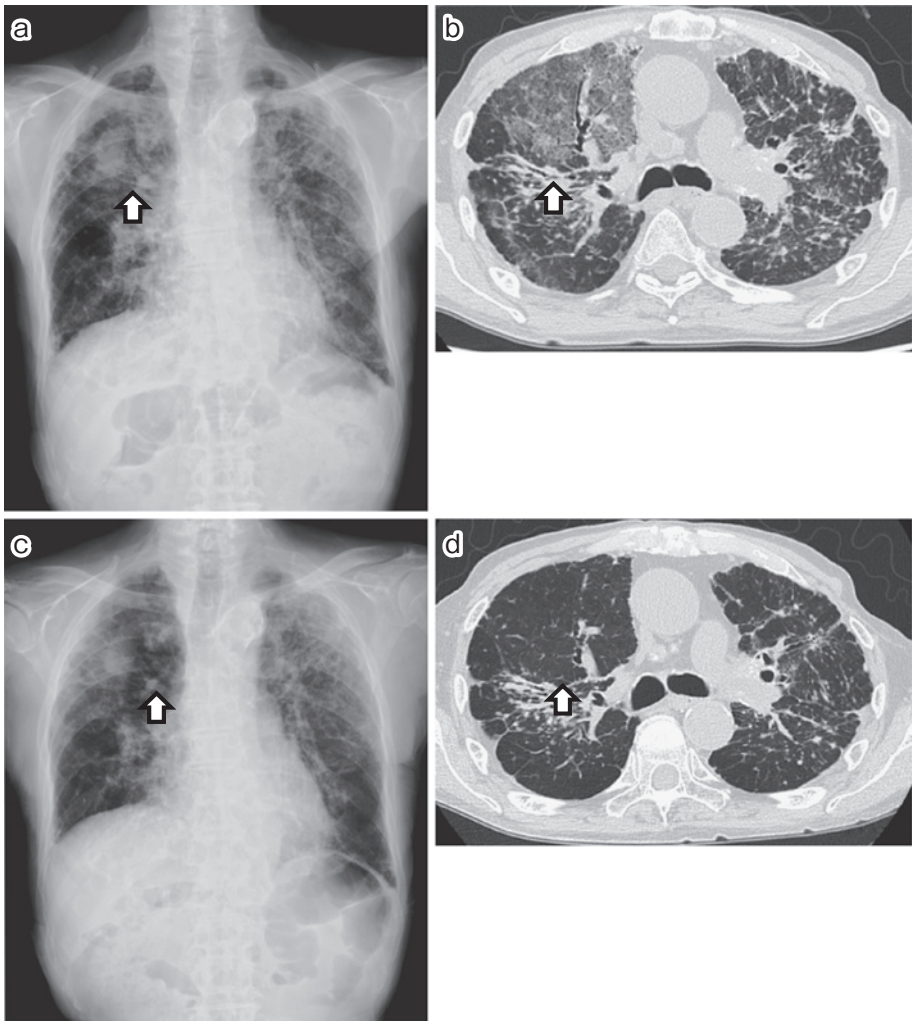

Fig. 2 Image Findings of Case 1: Second Exacerbation.
(a) Chest radiography image during acute exacerbation (June 2022 (arrows)) shows decreased translucency in the right upper lung field. (b) CT image showing ground-glass opacities corresponding to the chest radiography image (arrows). Diagnosed as the second acute exacerbation. (c) Chest radiography image after steroid pulse therapy (August 2022), shows improved translucency in the right upper lung field (arrows). (d) CT image after acute exacerbation improvement (August 2022), shows disappearance of ground-glass opacities in the right lower lung field (arrows).

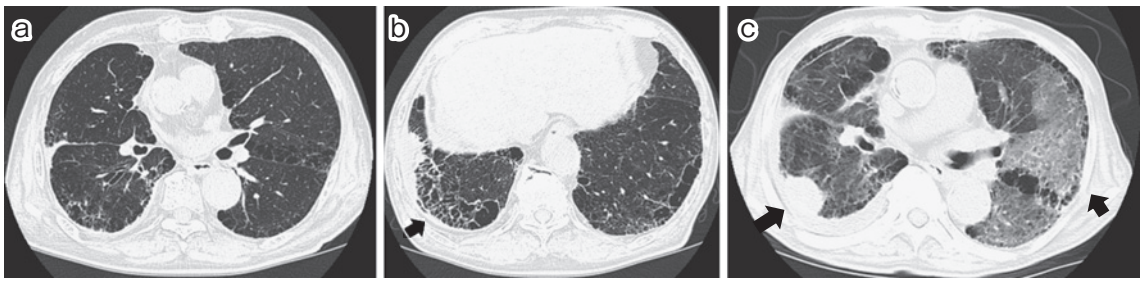

Fig. 3 Case 2: An Acute Exacerbation Case Triggered by Lung Cancer.
(a) CT image at the time of interstitial pneumonia screening. Interlobular septal thickening accompanied by subsequent thickening of the pleura are observed. Slight fibrotic changes are seen on the right lung field. (b) CT image at the time of interstitial pneumonia screening. Interstitial pneumonia findings are present at the subpleural zone. A definite UIP (Usual Interstitial Pneumonia) pattern is observed (arrows). (c) CT image at the time of acute exacerbation. The left upper lung field shows ground-glass opacification area. The other side of the lung shows a tumor growing from the pleura with effusion (arrows).

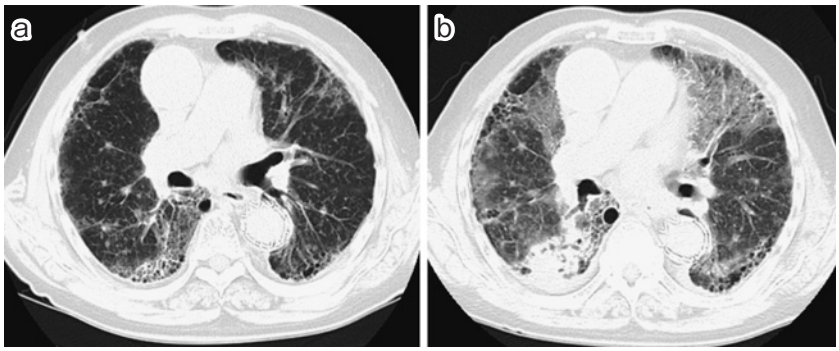

Fig. 4 Case 3: Another Case of Acute Exacerbation Triggered by Lung Cancer.
(a) CT image at the time of IP screening. IP findings are seen at the subpleural zone. A definite UIP pattern is observed. (b) CT image at the time of acute exacerbation. The right lung field shows a tumor growing from the pleura with effusion. The left upper lung field shows a ground-glass opacification area.

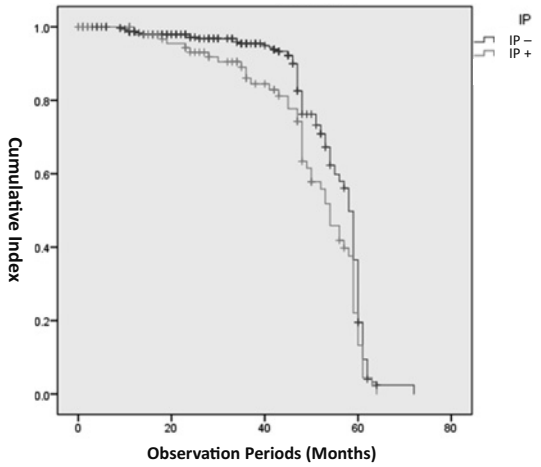

Fig. 5 Comparison of Observation Periods Based on the Presence or Absence of Interstitial Pneumonia.
The median observation period for 50% survival in pneumoconiosis patients without interstitial pneumonia (58 months) was significantly longer than that in pneumoconiosis patients with interstitial pneumonia (54 months) (Log Rank $\chi 2 = 6.186$, $p = 0.013 < 0.05$).

incided with the definition of ATS, the exact causes of them remained unclear. However, AEs are clinically identifiable conditions accompanied by respiratory failure during a short period of time, so we believe there were no missed detections based on patient history and imaging. This study is a retrospective-cohort study involving 98 subjects, and it differs from the two previous studies[3][8] in that it focused on AEs and was able to follow the clinical course.

In conclusion, this is the first retrospective-prospective study to observe the clinical course of IP associated with pneumoconiosis. We observed one case of idiopathic AE in a pneumoconiosis patient with large opacities and AEF. Among the entire cohort of 98 patients, the frequency of AE was lower than that of IPF, as previously reported. Detailed pathological investigations of pneumoconiosis-associated IP, which appear similar to IPF on imaging, are warranted.

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間質性肺炎を合併したじん肺患者の経過観察―後方視的コホート研究―

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―キーワード―
肺線維症，急性増悪，CT

じん肺に間質性肺炎（以下 IP）の合併頻度が多いことはいくつか報告されている．しかし，合併した IP の予後を報告したものがないため，今回それらを検討した．

対象と方法：IP の合併を HRCT で調べたじん肺患者 559 例中，その後の経過で CT 検査を受けた 517 名の経過を調べた．急性増悪の有無，新たな間質性肺病変発生の有無を調査した．IP スクリーニングの HRCT 検査から最後に CT 検査を受けるまでの期間をその患者の経過観察期間（月数）とした．

結果：対象は 517 名（前回の 92%）．平均観察期間は 40.4±0.7 カ月間．期間中，IP を持つ 98 名の内，肺癌を誘因とした 2 名と誘因不明の 1 名に急性増悪（AE）が見られた．頻度は 0.09%（100 人・年）であり，特発性肺線維症の頻度 5%～15% よりも低かった．また，この期間中，新たに間質性肺病変を合併した症例は，10 例（2.4%）で，ILA（interstitial lung abnormality）9 例，probable UIP 1 例であった．IP を伴うじん肺の 50% 観察期間 54 カ月は，間質性肺炎を伴わないじん肺の 50% 観察期間 58 カ月よりも有意に短かった（$p<0.05$）．

考察：今回，IP をもつじん肺中 3 名に急性増悪を認めた．特発性とされたのは 1 例のみで，他は肺癌が誘因であった．じん肺に伴う IP は粉じん吸入により肺胞上皮が障害されることで一般人口よりも IP の頻度が高いことは予想される．今回も新たに ILA 所見を持つじん肺が 10 例いた．ただし，急性増悪の頻度が低いことは，石綿肺と同様に粉じん沈着による IP であり，免疫学的な機序が働きにくいため，増悪頻度が低いかもしれない．じん肺以外の間質性肺炎と画像的には同様に見える間質性肺炎ではあるが，病理学的には異なることが予想され，今後遺伝子レベルでの検討を含めた詳細な病理学的検証が必要と考える．

［COI 開示］本論文に関して開示すべき COI 状態はない

（日職災医誌，74：48―55，2026）