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Pleuroparenchymal fibroelastosis (PPFE)-like finding on CT in daily practice –prevalence and serial changes

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ABSTRACT

Objective: To characterize the prevalence of PPFE (pleuroparenchymal fibroelastosis)-like finding on CT in daily practice and to identify the risk factors for its progression.

Matelials & methods: 2416 consecutive daily CT examinations were screened for PPFE-like finding. CT images with PPFE-like finding were retrospectively reviewed for the extent, maximum height, presence or absence of intraalveolar fibroelastosis (IAFE), emphysema, interstitial lung disease (ILD), suprasternal depression at the level of clavicle end, and bronchiectasis in upper lobe, and anterior-posterior/transverse diameter ratio (AT ratio) of thoracic cage. Serial CT scans more than 3 years before the baseline scan were also reviewed and compared when available.

Results: 380 patients (median age of 65, M:F = 153:227) were recognized as having PPFE-like finding. The lowest level of PPFE-like finding was T5 in median, horizontal extent was 0–25 % in 229/380, 25–50 % in 66 and >50 % in 24. Median height was 8.0 mm. IAFE was seen in 75, emphysema in 71, ILD in 59, chronic bronchial disorder in 71, suprasternal depression in 148, upper-lobe bronchial dilatation in 124. Mean AT ratio was 0.63. Serial images were available in 131 patients. 11 showed significant progression, 57 showed mild progression. Existing ILD lesion and >25 % horizontal extent were significantly related to significant progression.

Conclusions: PPFE-like finding was seen relatively in high proportion. Extensive lesion in axial plane and co-existing ILD might be risk factors of progression.

1. Introduction

Pleuroparenchymal fibroelastosis (PPFE) is one of the morphological patterns of interstitial lung disease (ILD) which shows subpleural atelectatic induration with fibroelastosis and fibrous thickening of pleura similar to “apical cap fibrosis [1]” seen on histology [2]. PPFE may be idiopathic or associated with conditions including post-hematopoietic stem cell transplantation, connective-tissue diseases and other types of ILD [2]. Idiopathic upper lobe pulmonary fibrosis, as reported in Japanese patients, is also included in this category [3].

Although some concepts similar to PPFE were seen in the papers published decades ago [4–10], PPFE has been increasingly recognized since Frankel et al. published the first paper with the designation of PPFE [11]. In 2013, idiopathic PPFE was added to ATS/ERS/JRS/ALAT classification of idiopathic interstitial pneumonias (IIPs) as one of the “rare IIPs” [12]. On CT, PPFE shows predominantly subpleural consolidation with/ without air-bronchogram, with an upper lobe predominance and associated volume loss [12]. It is usually more extensive than “apical cap fibrosis”, but its histological/radiological appearances are quite similar to “apical cap fibrosis”. Although a certain number of cases can progress and have a poor prognosis, there are no clear distinctions that allow separation of PPFE from “apical cap fibrosis” or old inflammatory changes that may demonstrate similar chest imaging findings. As idiopathic PPFE cases shows a poor prognosis, we radiologists need to find possible patients to progress and to suggest a consultation to a pulmonologist.

To our knowledge, there are few reports which shows the prevalence and demographic characteristics of patients with incidental or clinically significant PPFE-like finding therefore need further study.

Our purposes of this study are to characterize the prevalence of

Abbreviations: PPFE, pleuroparenchymal fibroelastosis; IAFE, intraalveolar fibroelastosis.

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PPFE-like finding on CT in daily practice and to identify risk factors for its progression, which should be considered as a disease.

2. Material and methods

This is a retrospective study using clinically indicated tests. This study protocol was approved by our institutional review board and written informed consent was waived.

2.1. Population

3069 patients, removing the duplicate cases from consecutive 3760 CT examinations in the archives of our hospital obtained between Dec 2015 and Mar 2016, were retrospectively reviewed. Among those, 653 cases fulfilled our exclusion criteria: massive pleural effusion, history of radiation exposure to lung or of thoracic operation, active infection or malignancy in question area, and apparent pleural disease. Out final study cohort consisted of 2416 consecutive CT examinations (median age of 67, range 0–99, male: female = 1225: 1191).

2.2. CT examinations

All the CT images were obtained using a routine clinical protocol on a 192-slice multi-detector CT (MDCT) scanner (Somatom Force, Siemens, Erlangen, Germany) or a 320-slice MDCT scanner (Aquilion One, Toshiba Medical Systems/Canon, Tokyo, Japan), or a 64-slice MDCT scanner (Light Speed/I, GE Medical Systems, Milwaukee, WI, USA). Images were obtained in a supine position from the lung apices to the bases at full inspiration using exposure parameters with automatically modulated mAs and with 120kVp. Images were reconstructed using a high spatial resolution algorithm with contiguous 1- or 1.25-mm section thickness and reviewed using Digital Imaging Communications in Medicine viewing software (ShadeQuest/ViewR-DG, Yokogawa Medical Solutions, Tokyo, Japan) at appropriate window settings for viewing the lung parenchyma (width = 1500HU; level= -500HU).

2.3. Baseline CT evaluations

2.3.1. PPFE screening

2416 CT scans were screened for PPFE-like finding by either of two pairs of experienced radiologists by consensus (with 21years and 3 years or with 18 years and 10 years of experience in chest CT image interpretation), and by one thoracic radiologist (with 17years of experience). A PPFE-like finding designation required as follows; 1) dense wedge-shaped or band-like consolidation, 2) adjacent to pleura, 3) mainly distributed in the upper lung zone, 4) lesions below the intersection level of 1st rib and clavicle and 5) without calcification (avoid the contamination of old tuberculous lesion).

2.3.2. CT evaluation of cases with PPFE-like finding

Cases with PPFE-like finding were retrospectively reviewed by two thoracic radiologists independently and the cases with discrepancy were determined by consensus.

Evaluated CT findings are the vertical extent (the most inferior lesion shown as a thoracic vertebral level) and the horizontal extent (proportion of lesion to the whole circumference at the most affected section, $0 \leq 25\%, >25$ and $\leq 50\%, >50\%$) of PPFE-like finding, maximum PPFE height (mm, the distance from the pleura to the most inner side of PPFE), presence or absence of intraalveolar fibroelastosis [2] (IAFE, the lesion showing similar dense consolidation along interlobular septa or bronchovascular bundle away from the pleura), emphysema, chronic bronchial disorder (bronchiectasis and centrilobular small nodules indicating chronic active inflammation), suprasternal depression (a depression of median anterior chest wall) [13] at the level of clavicle end, bronchiectasis in upper lobe (away from PPFE), and the anterior-posterior/transverse diameter ratio (AT ratio) of thoracic cage at the level of bronchial bifurcation. The presence or absence of ILD in the lower lung zone, and its pattern was also recorded when available.

Table 1
CT findings of the patients with PPFE-like finding in the baseline CT.

CT findings	N = 380
Vertical extent (the lowest T level of PPFE-like finding)	T3-12 (median T5)
Horizontal extent	0 < , ≤25 %: 229, 25 < , ≤50 %: 66, >50 %: 24
Height of the highest lesion	3.0–31 mm (median 8.0 mm)
IAFE	75 (19.7 %)
Emphysema	71 (18.7 %)
lower zone ILD pattern	59 (15.5 %) UIP: 35, NSIP: 18, PPFE: 4, others: 2
Chronic bronchial disorder	71(18.7 %)
Suprasternal depression	148 (38.9 %)
Upper-lobe bronchial dilatation	124 (32.6 %)
AT ratio of thoracic cage	0.39−0.95 (0.63)

PPFE: pleuroparenchymal fibroelastosis, IAFE: intraalveolar fibroelastosis, ILD: interstitial lung disease, AT ratio: anterior-posterior/transverse diameter ratio, UIP: usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia.

2.4. Serial CT evaluations

Previous CT images over 3 years older than the baseline CTs were also reviewed for the same findings and compared with baseline CTs when available. Serial changes of the lesion between scans were classified into following 3 categories, 0: no change, 1: mild progression (PPFE-increase without associated loss of volume), 2: significant progression (increasing PPFE-like finding with associated loss of volume).

Previous CT findings in cases with significant progression in the course were compared to those without.

2.5. Statistical analyses

Group comparisons were made by using Student's t-test, Wilcoxon rank-sum, x2 statistic and Fisher exact tests. Independent determinates of the progression of PPFE were identified using multivariate logistic regression analyses by stepwise method (with removal at a level of significance of $P = 0.1$). P values less than 0.05 was considered significant. Inter-observer agreement was classified as follows: poor, κ = 0–0.20; fair, κ = 0.21–0.40; moderate, κ= 0.41–0.60; good, κ = 0.61–0.80; and excellent, $\kappa = 0.81$–1.00. Statistics were performed using JMP, 9.0.0. (SAS Institute Inc.).

3. Results

The inter-observer agreements of the presence of PPFE-like lesion was good ($\kappa = 0.78$) and the significant changes in PPFE-like lesions was good ($\kappa = 0.70$).

3.1. Baseline CT evaluation

380 cases out of 2416 patients (15.7 %) fulfilled our PPFE criteria, the median age was 65 (range 23–94), male: female = 153:227. Suprasternal depression was seen in 38.9 % of the patients (shown in Table 1).

3.2. Results of serial CT images

131 cases of CT scans over 3 years older than the baseline scan were available. The median age was 66 (range 31–91), male: female = 54:77. Interval of the scans was 1102—4350days (median 1842 days). 61 patients did not progress at all, 58 showed mild progression and 12 showed significant progression.

In univariate analyses, vertical extent lower than T5, horizontal

Table 2
Univariate analysis for comparison of findings on prior CT with baseline CT.

	Significant progression n = 12	Stable/mild progression n = 119	*P* values
Age	75.5 (44–91)	66 (31–87)	0.049*
Male gender	7 (58.3 %)	47 (39.5 %)	0.231
The lowest level: below T5	7 (58.3 %)	30 (25.2 %)	0.037*
Horizontal extent >25 %	9 (75.0 %)	31 (26.1 %)	0.001*
Average height of PPFE-like finding (mm)	8.5 (0–14)	7 (0–15)	0.067
IAFE	6 (50.0 %)	22 (18.5 %)	0.021*
Emphysema	3 (25.0 %)	23 (19.3 %)	0.705
lower zone ILD	5 (41.7 %) (UIP: 2, NSIP: 2, Others: 1)	13 (10.9 %) (UIP: 3, NSIP: 10)	0.012*
Chronic bronchial disorder	4 (33.3 %)	17 (14.3 %)	0.102
suprasternal depression	3 (25.0 %)	46 (38.7 %)	0.534
Upper-lobe bronchial dilatation	2 (16.7 %)	20 (16.8 %)	1.000
AP ratio of thoracic cage	0.63 (0.58–0.77)	0.63 (0.47–0.80)	0.799

T: thoracic vertebra, PPFE: pleuroparenchymal fibroelastosis, IAFE: intra-alveolar fibroelastosis, ILD: interstitial lung disease, AP ratio: anterior-posterior ratio, UIP: usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia.

Table 3
Multivariate analysis for comparison of findings on prior CT with baseline CT.

Findings in prior CT images	Odds ratio	95 % confidential interval	P value
Age	1.073	0.859–0.999	0.049*
Horizontal extent of PPFE-like finding >25 %	7.356	1.909- 36.612	0.003*
lower zone ILD	4.025	0.907–17.149	0.066

ILD: interstitial lung disease.

extent over 25 % of whole circumference, presence of IAFE, lower zone ILD were associated with the progression of PPFE. Increasing of age and the PPFE height were also correlated to the progression of PPFE (Table 2). In multivariate analyses, aging and extensive lesion on the axial plain (>25%) were independent risk factor of the progression (P = 0.049 and 0.003, respectively) (shown in Table 3). Representative cases were shown in (Figs. 1–3) .

4. Discussion

We defined PPFE-like finding as demonstrating a lesion below the intersection level of the 1 st rib and clavicle, and without calcification. The PPFE-like finding is not equal to “idiopathic PPFE” as a disease but means CT appearance which looks like idiopathic PPFE. The previous reports about PPFE were based on the histological findings of PPFE and consisted of small numbers of cases [2,14], there has been no clear radiological definition previously. Recently, larger study of idiopathic PPFE cases propounded a modified PPFE criteria [15]. In our study, PPFE-like finding based on our criteria was seen in 15.7 % of routine daily practice cases and was not infrequent. According to the original paper of the apical cap fibrosis by Butler II et al., the prevalence of apical cap fibrosis in autopsy cases was 26 % [1], which might include PPFE in their apical cap. In this autopsy study, the lesion was seen more frequently in male patient [1], different from our study. Our separating line from the apical cap and the exclusion criteria may decrease the prevalence and the frequency in male compared to the apical cap.

PPFE-like finding was seen in elder patients in most (median age of 65), not seen in the children. Also, aging was an independent risk factor of PPFE progression in serial CT evaluation (p = 0.049). Patients with apical cap fibrosis were reported to be older than those without (p < 0.01), and older patients tended to have larger caps [1]. However, some reported progressive PPFE cases [3,10] including familial type were seen in younger patients. PPFE-like finding can occur as a result of aging, but aging is not the only associated factor.

Emphysema, chronic bronchial disorder and lower zone ILD were seen in a relatively higher percentage. In the previous study of apical cap [1], striking correlation between the presence of the cap and chronic bronchiolitis was present.

Suprasternal depression in 38.9 % of all patients with PPFE, which was uncertain relationship to PPFE-like finding. Jacob et al. [13] reported that all the cases with suprasternal depression in their cases of hypersensitivity pneumonitis had some degree of PPFE-like finding. Suprasternal depression might be related to PPFE and the thoracic shape.

Idiopathic upper lobe pulmonary fibrosis has been reported to be flat chest [3]. The thoracic cage becomes flattened in the progression of PPFE [16], and another report showed a reversibility of the flattened chest after lung transplantation for PPFE [17]. Our study showed AT ratio of thoracic cage was not associated with the progression of PPFE-like finding. A flattened chest might result from progressive PPFE but may not cause PPFE progression.

On multivariate analysis in our study, extensive PPFE lesion in the axial plane (>25 %) was an independent risk factor of PPFE progression (p = 0.023). Stiffening of subpleural lung may result in collapse of adjacent parenchyma and cause the further atelectatic induration of the lung.

Although not significant, lower zone ILD (p = 0.066) tended towards association with PPFE progression. Enomoto et al. reported in their article of idiopathic PPFE that lower UIP/possible UIP-pattern ILD did not showed a prognostic significance compared to those with other pattern or without ILD [15]. As there is no previous report about the risk of progression of PPFE, IPF patients with PPFE component was reported to tend to show shorter survival than those without PPFE [18]. Also, co-existing radiological PPFE-like finding in hypersensitivity pneumonitis cases was reported as an independently associated with impaired lung function and increased mortality [13]. Paying attention to the radiological PPFE lesion in cases with ILD would be important.

Regarding the classification of PPFE associated with other pattern of ILD, there is no definite criteria at this point. The latest IIPs classification [12] recommends classifying the mixed patterns of ILD as a category of unclassifiable. However, focal PPFE pattern can be seen in the patients with IPF [18], the significance of focal additional pattern is still unclear.

Our study has several limitations. At first, this is a retrospective and single center study. No histological confirmation was performed. Although we could show the prevalence of PPFE-like finding using our definition, baseline characteristics of PPFE patients were not compared to non-PPFE population. Regarding our serial evaluation, small numbers of patients were available. Also, the important thing is that patients without CTs over 3 years prior to baseline CT were not evaluated for serial changes. Therefore, truly progressive cases which cannot be evaluated the serial images due to a poor prognosis might not be included. For the evaluation of the serial changes, the determination of progress was defined subjective as there was no information of pulmonary function data for this retrospective study,

In conclusion, PPFE lesion was seen relatively in high proportion even using our strict criteria excluding apical cap fibrosis. Most PPFE-like finding could be considered as just an incidental finding, but extensive lesion in the axial plane and co-existing ILD might be risk factors of progression.

CRediT authorship contribution statement

Ryoko Egashira: Conceptualization, Methodology, Formal analysis, Validation, Writing - original draft. **Ken Yamaguchi:** Investigation. **Tetsuya Kondo:** Investigation. **Takahiko Nakazono:** Investigation. **Shuichi Fukui:** Investigation. **Hiroyuki Irie:** Supervision, Writing - review & editing.

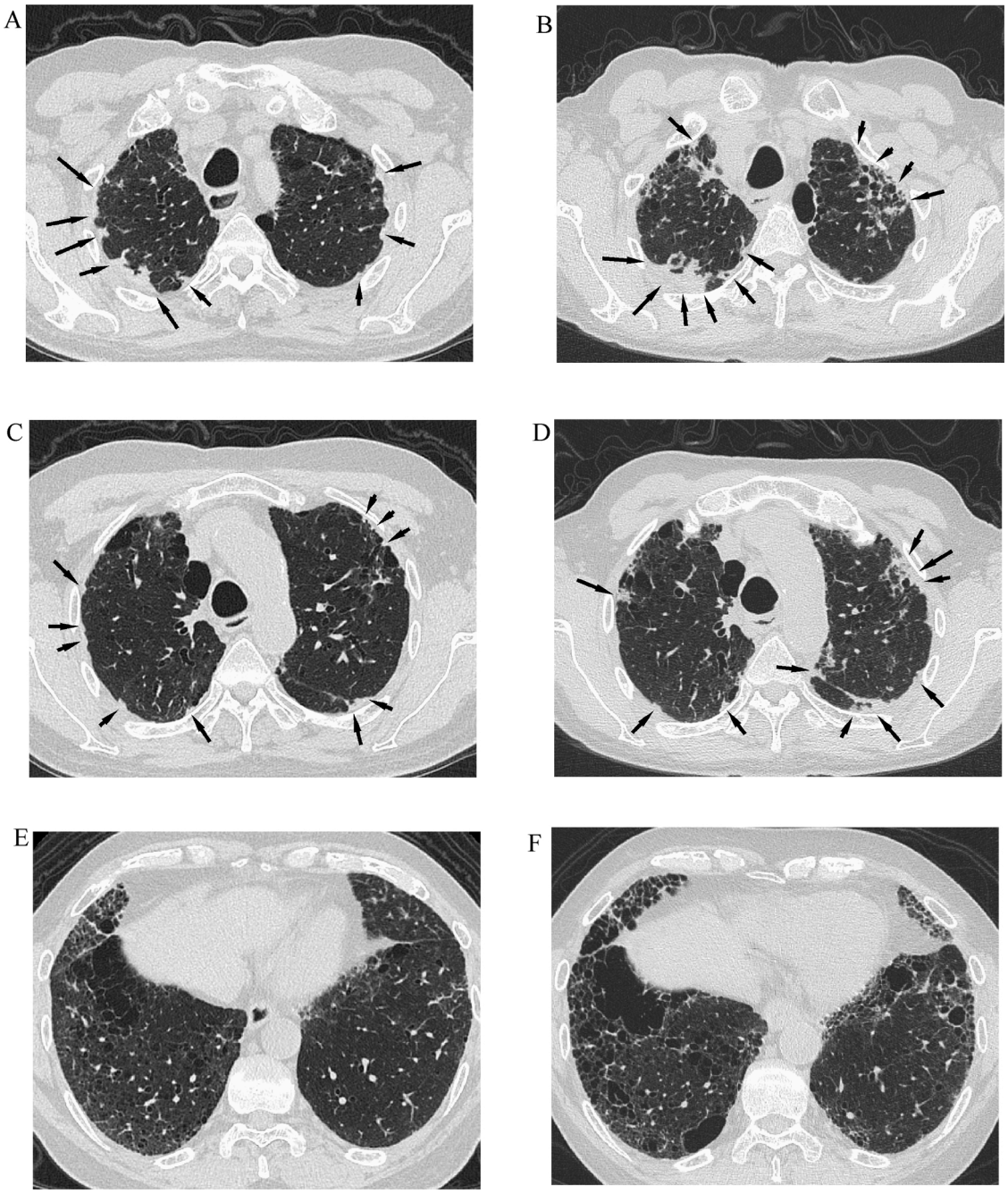

Fig. 1. 70-year-old man with pleuroparenchymal fibroelastosis (PPFE)-like finding on CTs which were underwent for the routine check-up after an operation of colorectal cancer.
Axial CT images at the top and middle level of aortic arch show bilateral and subpleural dense consolidation with trivial air bronchogram consistent with PPFE (1A, C. arrows). Five-years later, the dense consolidation became more extensive(arrows), and the thoracic cage became smaller (1B, D). CT images at the basal level show subpleural reticular opacities with mild tractionbronchiolectasis and clustered cystic changes consistent with probable UIP-pattern interstitial pneumonia, which also progressed over time (1E, F).

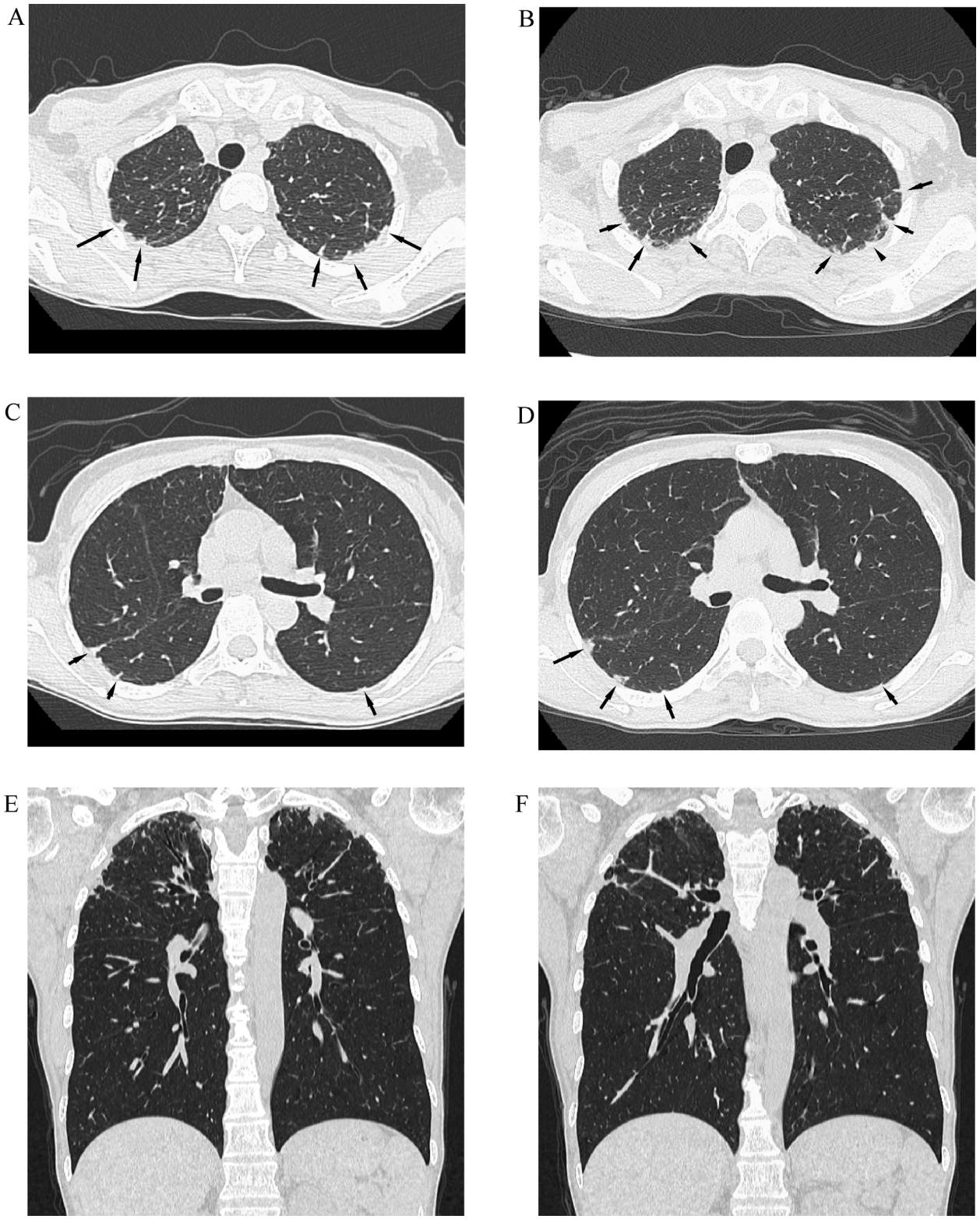

Fig. 2. 40-year-old woman with pleuroparenchymal fibroelastosis (PPFE)-like finding on CTs which were initially taken for an investigation of chronic cough. Initial CT images at the apical and hilar levels show bilateral and subpleural dense consolidation with mild distortion consistent with PPFE (2A, C. arrows). Three-years later, mild increasing of the PPFE-like lesions (2B, D), and the upward shift of the interlobar fissure can be seen (arrowheads).

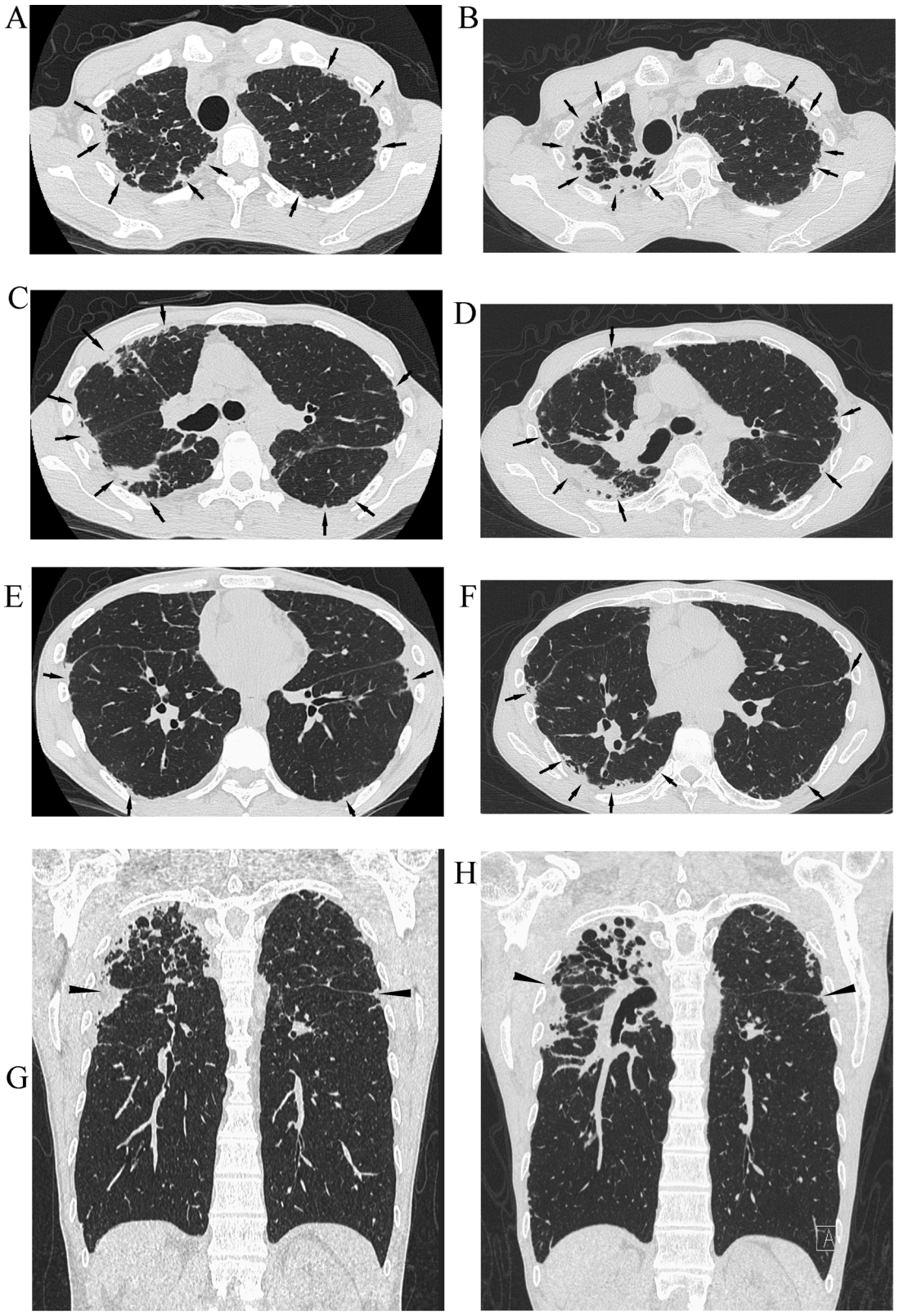

Fig. 3. 37-year-old man with pleuroparenchymal fibroelastosis (PPFE)-like finding on CTs detected for an investigation of pleuritis.
Initial CT images at the apical, bifurcation and lower levels show bilateral and subpleural dense consolidation (arrows) with traction bronchiectasis and distortion consistent with PPFE (3A, C, E, G). CT images taken15-years later (3B, D, F, H) show increased consolidation with associated severe volume loss and distortion. The upward shift of the interlobar fissures (arrowheads) and the shrinkage of thoracic cage are also recognized.

Declaration of Competing Interest

The authors report no declarations of interest.

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