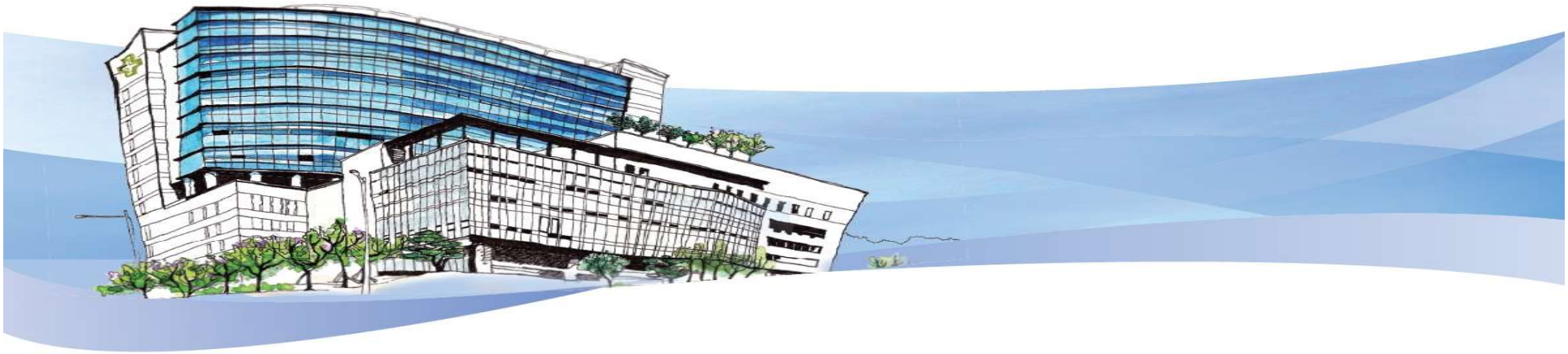


An Evolving ILD

:Pleuroparenchymal Fibroelastosis

Contents

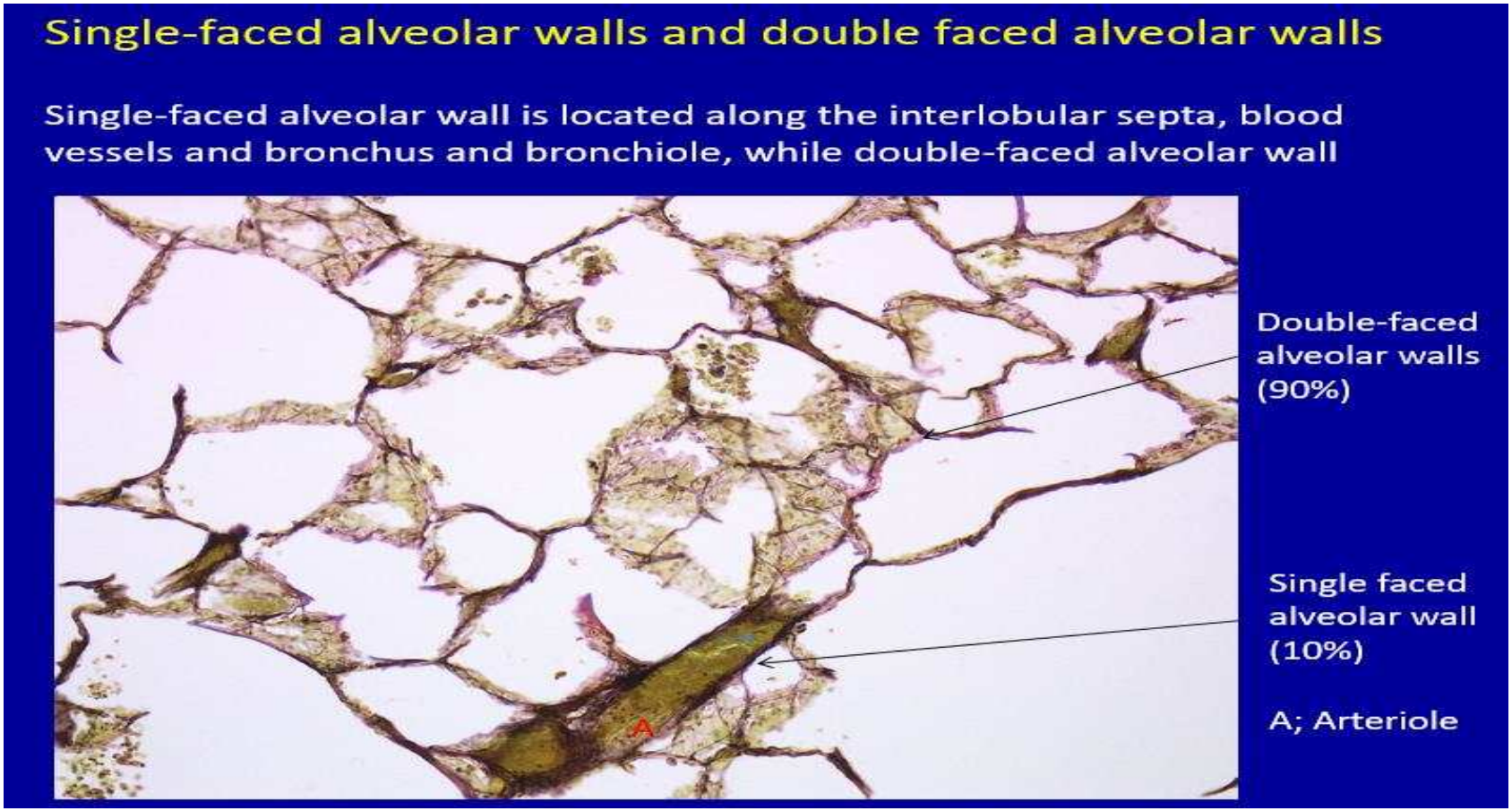
특발성간질성폐렴(IIP) 분류

표 1. ATS/ERS 분류에 따른 특발성간질성폐질환[1]

- 주요 특발성간질성폐렴(Major idiopathic interstitial pneumonias, Major IIP)
  - 특발성폐섬유증(Idiopathic pulmonary fibrosis, IPF)
  - 특발성비특이간질성폐렴(Idiopathic nonspecific interstitial pneumonia, idiopathic NSIP)
  - 호흡세기관지염-간질성폐질환(Respiratory bronchiolitis-interstitial lung disease, RB-ILD)
  - 박리간질성폐렴(Desquamative interstitial pneumonia, DIP)
  - 특발성기질화폐렴(Cryptogenic organizing pneumonia, COP)
  - 급성간질성폐렴(Acute interstitial pneumonia, AIP)
- 희귀 특발성간질성폐렴(Rare idiopathic interstitial pneumonias, rare IIP)
  - 특발성림프구간질성폐렴(Idiopathic lymphoid interstitial pneumonia, idiopathic LIP)
  - 특발성흉막실질섬유탄력섬유증(Idiopathic pleuroparenchymal fibroelastosis, idiopathic PPFE)
- 분류불가능 특발성간질성폐렴(Unclassifiable idiopathic interstitial pnemonias, unclassifiable IIP*)

Why does fibrosis occur in the perilobular area?

- Collection of venous and lymphatic drainage
- Single faced alveolar walls in the subpleural and paraseptal area



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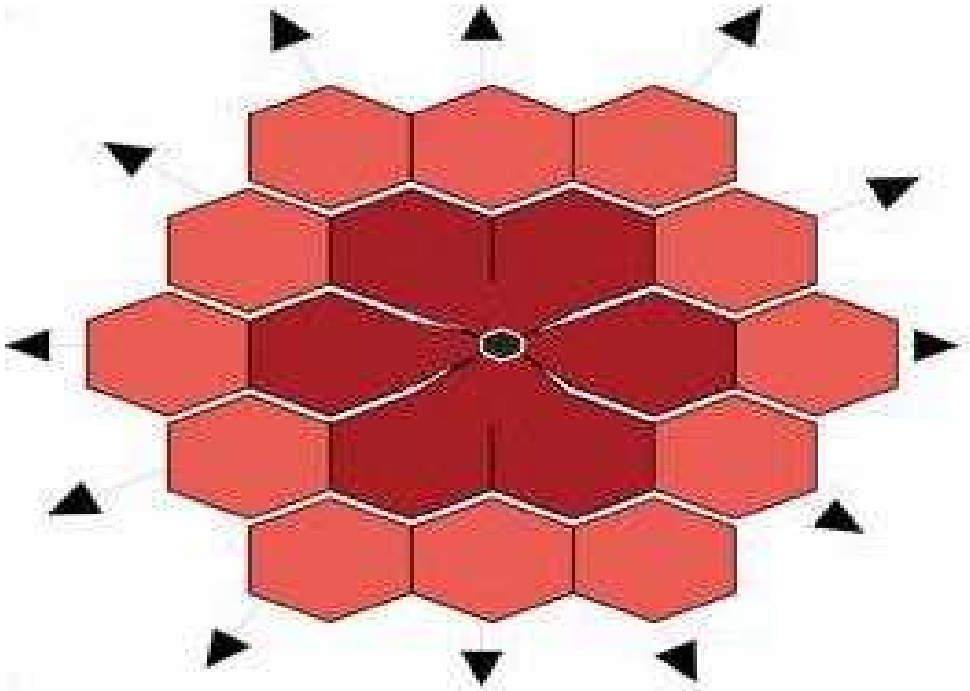
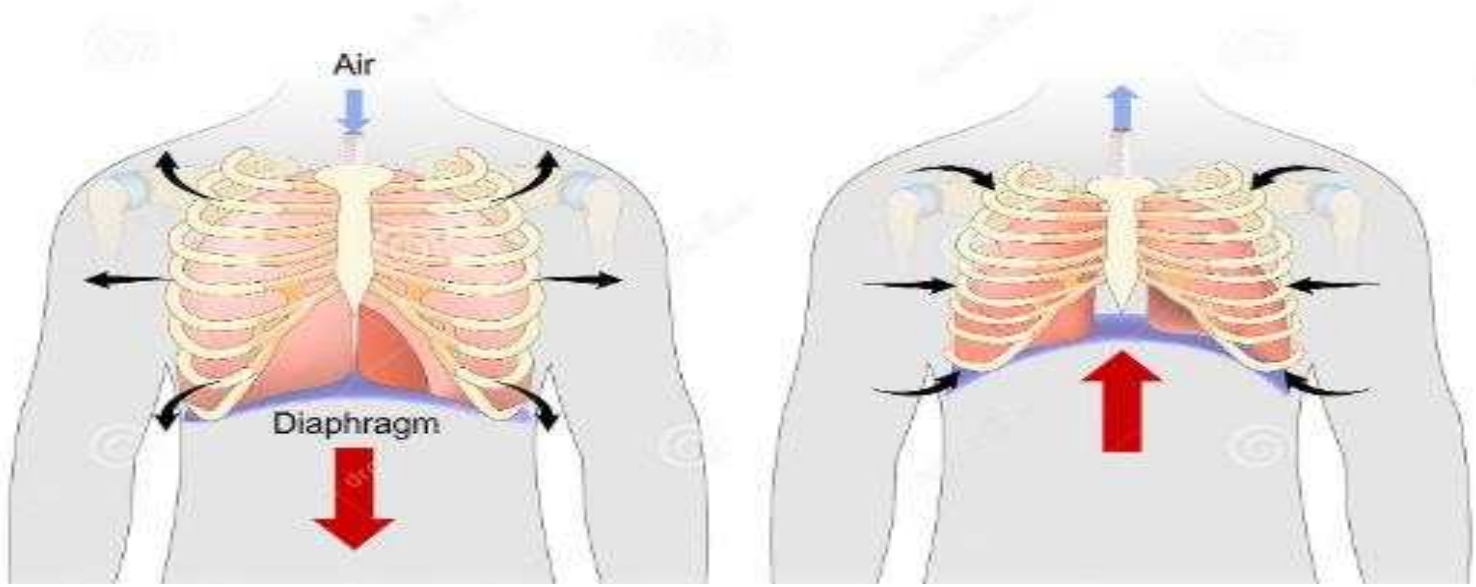


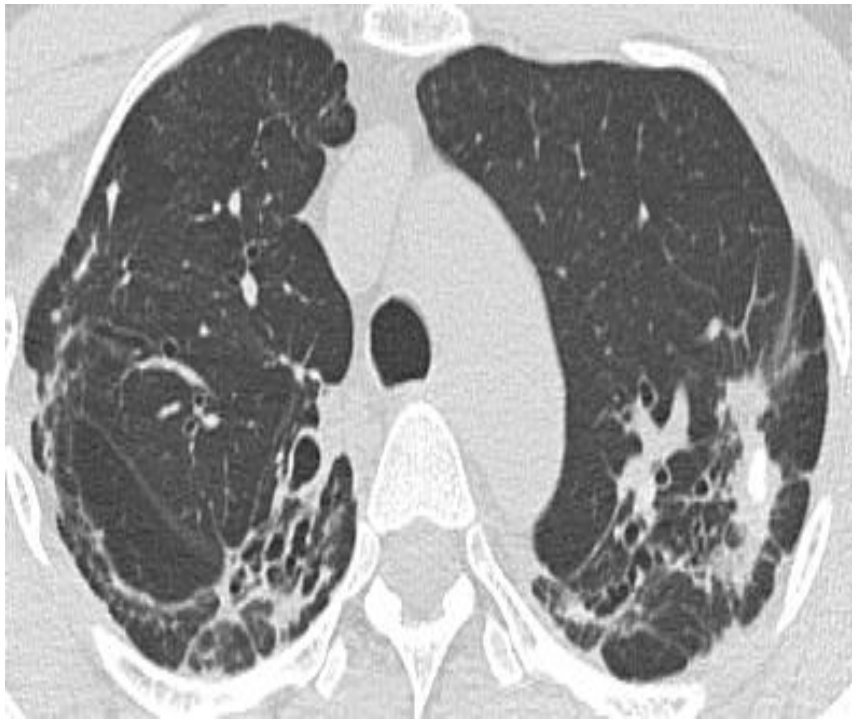
Why does fibrosis occur in the perilobular area?

- Collection of venous and lymphatic drainage
- Single faced alveolar walls in the subpleural and paraseptal area
- Lung movement intensity at the diaphragm
- TGF-β (vulnerable to pressure)



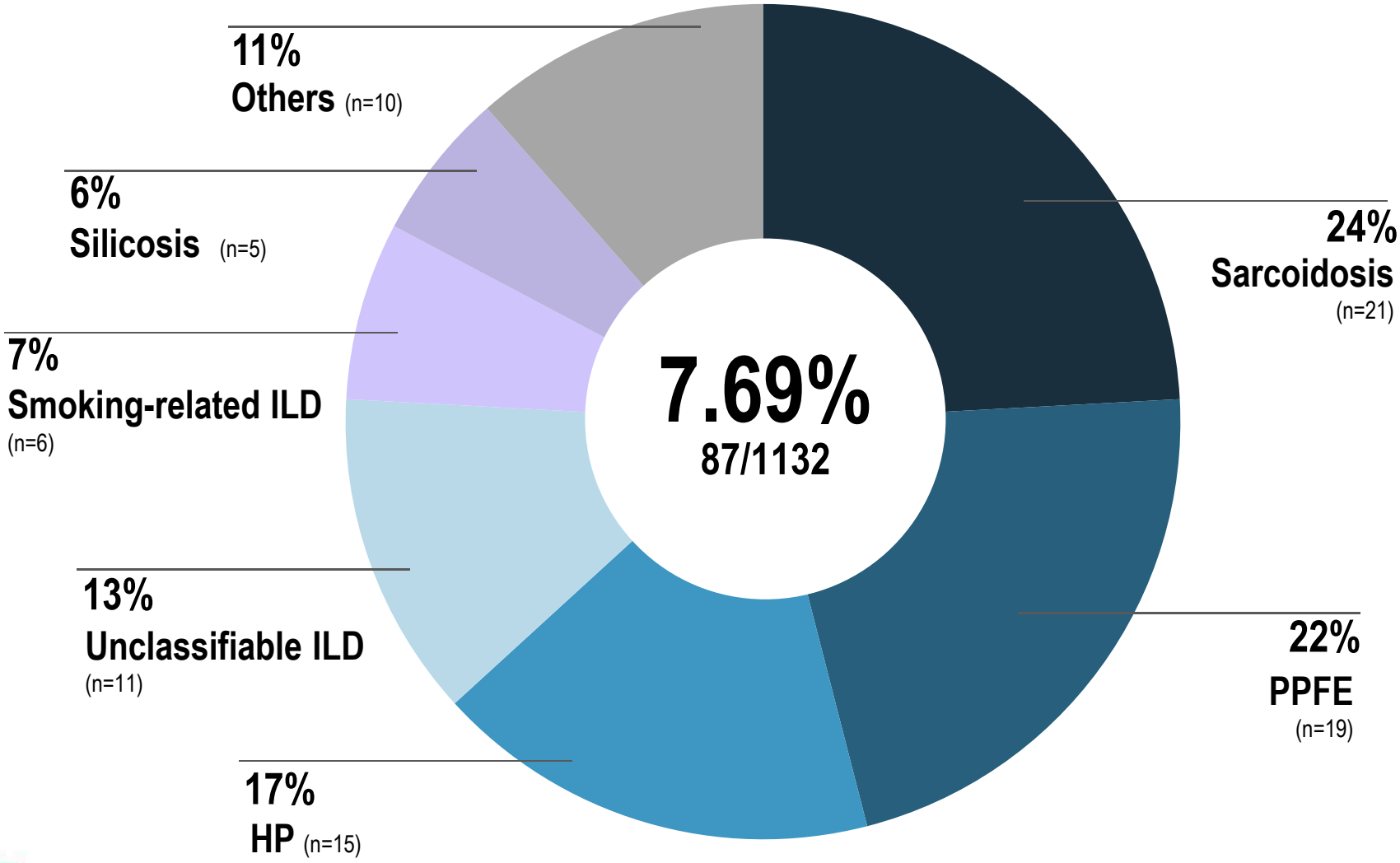
ILD in upper lung field

Eosinophilic pneumonia



Sequelae of tuberculosis

Upper lobe predominant fibrosing interstital lung disease



INJE UNIVERSITY
HAEUNDAE PAIK HOSPITAL

AJRCCM 2018;197:A1688

Upper lobe predominant fibrosing interstital lung disease

Upper lobe predominant fibrosing ILD (n=87/1132)	7.69 %
Sarcoidosis	24%
PPFE	22%
Hypersensitivity pneumonitis	17%
Unclassifiable ILD	13%
Smoking-related ILD	7%
Silicosis	6%
Others	10%

AJRCCM 2018;197:A1688

Pleuroparenchymal fibroelastosis (PPFE)

- Amitani'disease – Case series of Japan in **1992**

  (pulmonary upper-lobe fibrosis)

- First report in **2004** by Frankel et al.

→ idiopathic pleuroparenchyma fibroelastosis, iPPFE

- Radiologic and histopathological criteria by Reddy et al. in **2012**
- Rare IIP in the international consensus classification of IIP in **2013**

- Predominantly upper lobe involvement with pleural fibrosis and subjacent parenchymal fibrosis

Similar Disease Concept as PPFE

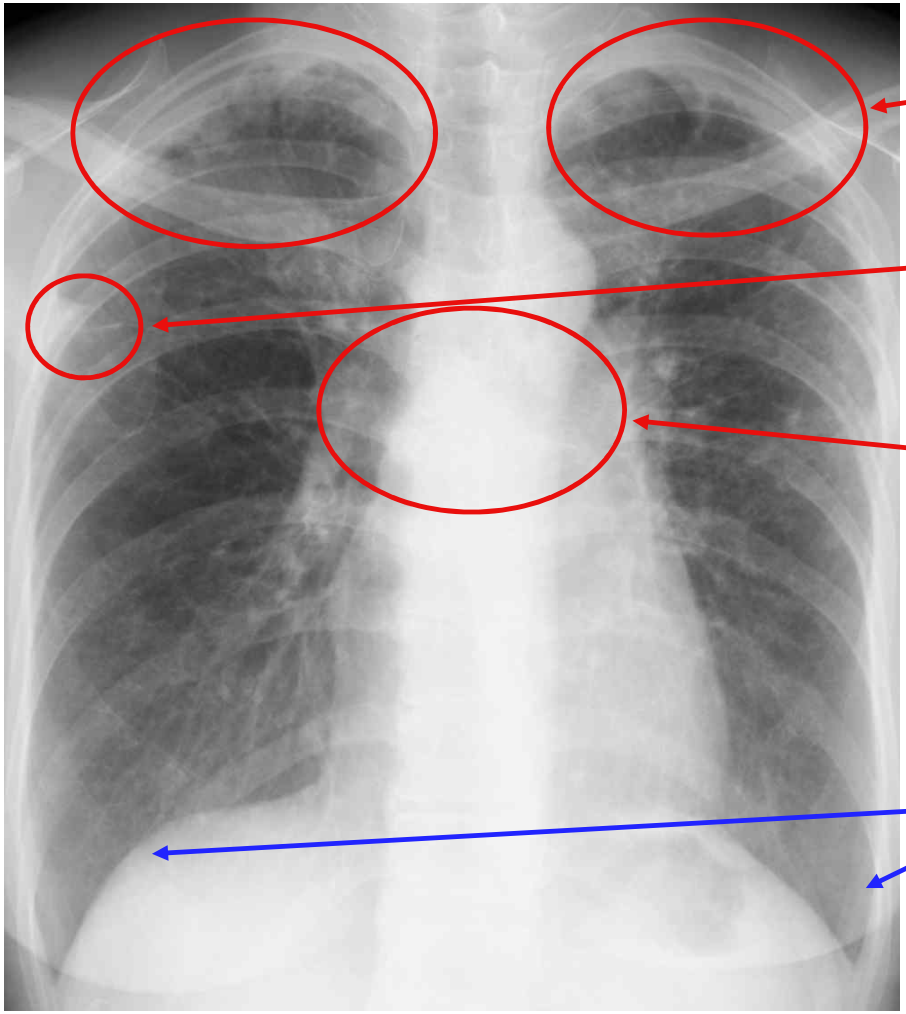
- Chronic idiopathic pneumonia (1962)
- Pulmonary upper lobe fibrocystic changes (1978)
- Upper lobe fibrosis and cavitation (1980)
- pulmonary apical fibrocystic disease (1981)
- idiopathic progressive pleuropulmonary fibrosis (1984)
- Apical pulmonary fibrosis (1988)
- Idiopathic pulmonary upper lobe fibrosis (1992)
- Marked pulmonary fibrosis in the upper lobe (1999)
- Upper lobe fibrosis (2003, 2005)
- PPFE (2004)
- Upper lobe-dominat pulmonary fibrosis (2010)

Diagnostic Criteria

Category	Histopathology	High-Resolution Computed Tomography
Definite PPFE	Upper zone pleural fibrosis with subjacent Intra-alveolar fibrosis accompanied by alveolar septal elastosis	Pleural thickening with associated sub-pleural fibrosis concentrated in the upper lobes with less marked or no lower lobe involvement
Consistent with PPFE	Intra-alveolar fibrosis present but *1*) not accompanied by significant pleural fibrosis, *2*) not predominantly sub-pleural, or *3*) not present in an upper lobe biopsy	Upper lobe pleural thickening with associated sub-pleural fibrosis but *1*) distribution not concentrated in the upper lobes or *2*) with features of coexistent disease elsewhere
Inconsistent with PPFE	Absence of features in "definite PPFE" and "consistent with PPFE" categories	Absence of features in "definite PPFE" and "consistent with PPFE" categories

AJRCCM 2019;11:1351-1359

Chest radiograph image of PPFE



Bilateral apical irregular subpleural thickening

Interlobar pleura elevation

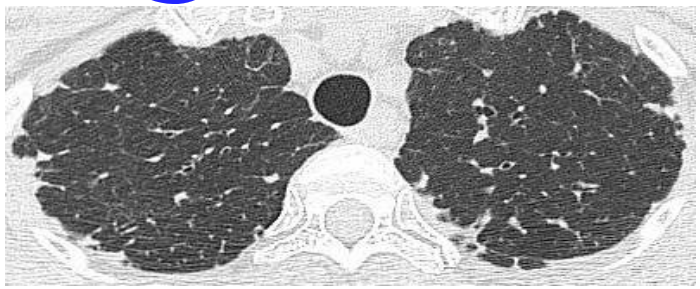
Hilar retraction upwards

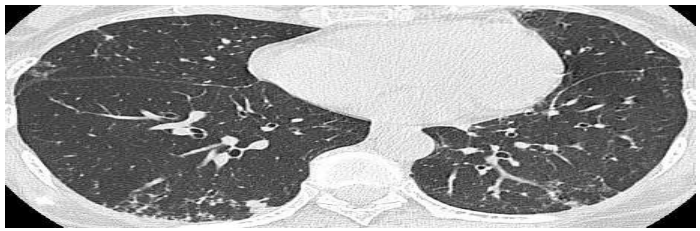
With involvement of lower lobes being less marked or absent

Upper lobe volume loss

Chest CT image of PPFE

dense pleural thickening subpleural consolidation





Histological features of PPFE

major

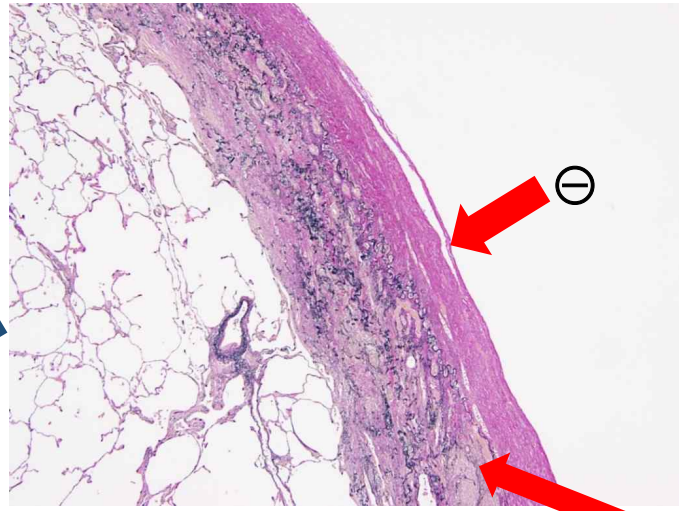
⊖Pleural fibrosis (±)

⊖Subpleural intra-alveolar fibrosis (purple, pink)

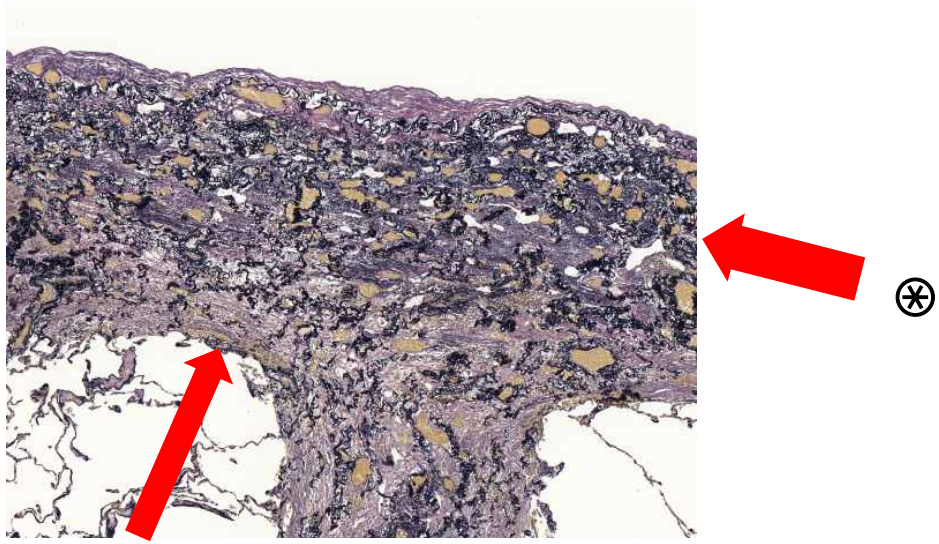
⊛Band-like aggregate of elastic fibers (black)

④Sparing of the parenchyma distant from the pleura

⑤Small number of fibroblastic foci



Hematoxylin eosin stain



Elastica van Gieson stain

Clinical and Physiologic feature of PPFE

- Prevalence: Unknown (5.9% ~ 7.7% from ILD cohort, 7.5% after lung transplantation)
- Common symptoms: dry cough, exertional dyspnea
- Unrelated to smoking and sex
- Familial link: up to 57%, more common than other ILD
- Genetic mutation: TERC (telomerase reverse transcriptase), TERT(telomere reverse RNA composition)

Characteristic	Total	PPFE	No PPFE	*P*-value
Number of subjects	445	28	417	
Pneumomediastinum	25 (5.6)	6 (21.4)	19 (4.6)	<0.001
Pneumothorax	20 (4.5)	5 (17.9)	15 (3.6)	<0.001
Pneumothorax or pneumomediastinum	42 (9.4)	9 (32.1)	33 (7.9)	<0.001
Pneumonia	62 (13.9)	6 (21.4)	56 (13.4)	0.237
Acute exacerbation	78 (17.5)	5 (17.9)	73 (17.5)	0.962
Lung cancer	6 (1.3)	0	6 (1.4)	0.523
PTE	6 (1.3)	0	6 (1.4)	0.523
PHT	118 (26.5)	6 (21.4)	112 (26.9)	0.529

Oda et al. 66.7% vs 23.2%, *P = 0.01*

Tanizawa et al. 80% vs 26.1%, *p < 0.001*

Multiple bullae in the upper lobe !

Low Body Mass Index and Weight Loss

- Progressive weight loss (disease progression, infection, malignancy)
- Low BMI (especially Japan)

	Japanese patients	
	Nintedanib 150 mg bid (*n* = 76)	Placebo (*n* = 50)
Age, mean years (SD)	68.4 (7.6)	68.2 (6.2)
Male (%)	62 (81.6)	40 (80.0)
Weight, mean kg (SD)	63.8 (11.6)	63.8 (11.6)
BMI, mean kg/m^2 (SD)	24.4 (3.4)	24.6 (3.5)
Ex- or current-smoker (%)	66 (86.8)	40 (80.0)
Time since diagnosis, mean years (SD)	1.6 (1.4)	1.2 (1.0)
FVC, mean mL (SD)	2422 (672)	2495 (741)
FVC, mean % predicted (SD)	80.9 (16.6)	83.3 (22.2)
FEV_1/FVC ratio, mean % (SD)	83.3 (5.8)	83.0 (7.9)
DL_{CO}, mean % predicted (SD)†	44.6 (11.4)	45.3 (12.1)
SGRQ, mean total score (SD)‡	35.1 (18.1)	35.0 (18.7)
Systemic corticoid therapy (%)	9 (11.8)	7 (14.0)

52 patients with PPFE by MDD

Patients, number	52
Age, years	62.5 (14.5)
Gender, male/female	31/21
History of pneumothorax, number	19
History of acute exacerbation, number	7
mMRC scale	1 (2)
Brinkman index	0 (220)
Body mass index	17.8 (2.8)
Serum KL-6, U/mL	546 (390)
Serum SP-D, ng/mL	208 (195)
Serum SP-A, ng/mL	46.1 (34.3)

Respirology 2017;22:750-757
Respiratory Medicine 2018;141:190-197

Low Body Mass Index and Weight Loss

	IPF (n = 131) UIP/IPF 50 (38.2%), cIPF 81(61.8%)	iPPFE (n = 43)
Age, yr	69.0 [64.0–75.0]	69.0 [64.0–74.0]
Sex, male/female	117 (89.3%)/14 (10.7%)	27 (62.8%)/16 (37.2%)
Observation period, mo	53.3 [31.6–86.1]	31.3 [18.2–47.2]
Never or former/current smoker	20 (15.3%), 111 (84.7%)	29 (67.4%), 14 (32.6%)
Smoking pack-year	35.0 [20.0–60.0]	0 [0–12.5]
acute exacerbation, yes	39 (29.8%)	8 (18.6%)
Height, cm	162.1 [157.0–166.0]	159.0 [152.0–165.0]
Weight, kg	60.0 [52.1–67.0]	42.3 [35.8–48.0]
BMI, kg/m^2	23.1 [21.3–24.7]	17.2 [14.7–18.5]
ESM_{CSA}, cm^2	32.8 [27.1–37.7]	23.4 [17.8–30.6]
ESM_{MA}, HU	42.0 [35.7–45.7]	43.5 [38.2–48.7]
Pulmonary Function Test		
FVC, %-pred	80.5 [66.4–92.9] (n = 120)	54.4 [45.8–67.5] (n = 37)
FEV_1/FVC, %	83.5 [79.4–88.0] (n = 120)	96.3 [91.4–100] (n = 37)
DLCO, %	68.6 [55.4–97.1] (n = 52)	68.7 [47.9–91.9] (n = 24)

Scientific reports 2018;8:14074

Low Body Mass Index and Weight Loss

Characteristic	Total	PPFE	No PPFE	*P*-value
Number of subjects	445	28	417	
Age (years)	66.4 ± 7.8	67.3 ± 7.0	66.3 ± 7.8	0.482
Male	340 (76.4)	25 (89.3)	315 (75.5)	0.098
Ever-smokers	321 (72.1)	20 (71.4)	301 (72.2)	0.999
BMI (kg/m^2)	24.2 ± 3.1	21.2 ± 3.0	24.4 ± 3.1	<0.001
C-reactive protein (mg/dL)	0.7 ± 2.1	0.5 ± 0.7	0.7 ± 2.2	0.082
ABGA				
PaO_2 (mm Hg)	99.7 ± 19.9	99.6 ± 12.8	99.7 ± 20.3	0.972
$PaCO_2$ (mm Hg)	34.8 ± 5.8	36.5 ± 8.6	34.7 ± 5.6	0.107
Pulmonary function				
FVC (% predicted)	68.7 ± 15.7	58.7 ± 16.9	69.4 ± 15.4	0.003
DL_{CO} (% predicted)	54.9 ± 16.2	52.2 ± 17.4	55.1 ± 16.2	0.408
TLC (% predicted)	69.3 ± 13.3	62.7 ± 11.9	69.7 ± 13.3	0.005
RV (% predicted)	53.5 ± 15.4	56.0 ± 20.9	53.4 ± 14.9	0.517
RV/TLC	0.32 ± 0.08	0.36 ± 0.13	0.31 ± 0.08	0.003
6MWT				
Distance (m)	410.4 ± 111.9	421.7 ± 116.4	409.7 ± 111.7	0.601
SpO_2 nadir (%)	90.1 ± 6.7	91.5 ± 4.6	90.0 ± 6.9	0.135
BAL fluid				
Neutrophils (%)	14.3 ± 19.1	16.2 ± 20.9	14.1 ± 19.0	0.627
Lymphocytes (%)	13.1 ± 12.4	10.6 ± 8.4	13.3 ± 12.7	0.140

Respirology 2020. Online ahead of print

Alveolar collapse in upper lobe
→ compensatory hyperinflation in lower lobe

- Bilateral apical irregular subpleural thickening
- Interlobar pleura elevation
- Hilar retraction upwards

Upper lobe volume loss

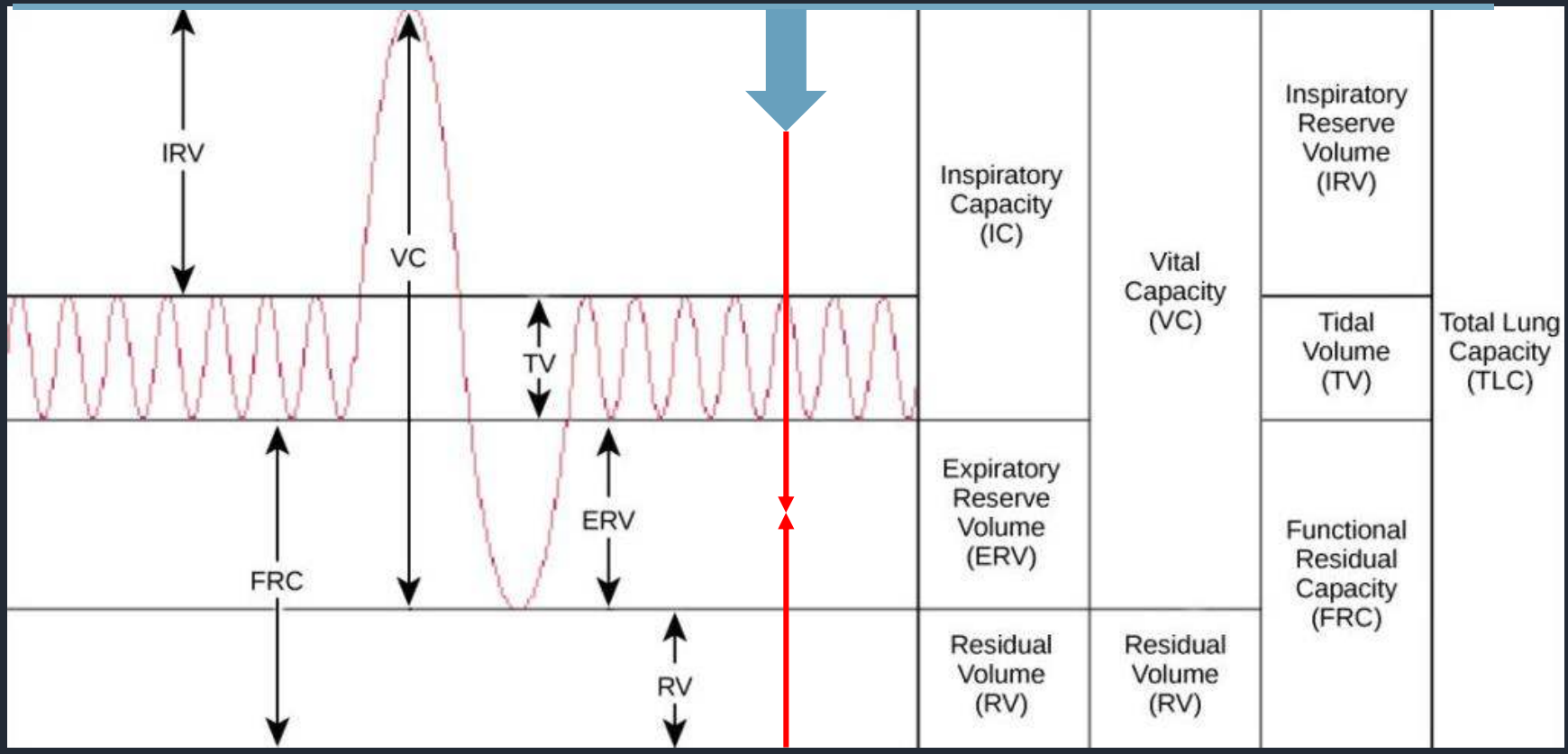
↓

Compensatory hyperinflation in lower lobe

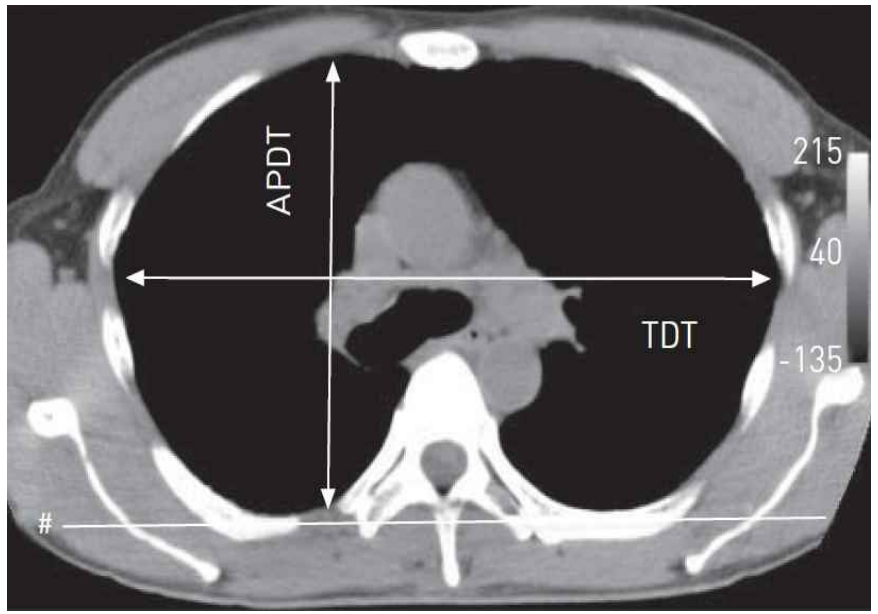
- ✓ TLC(감소) – RV (증가) = VC (감소)
- ✓ RV/TLC (증가)
- ✓ DLco (상대적으로 정상)

TLC 감소

- ✓ Work of Breathing 증가
- ✓ Energy Expenditure 증가
- ✓ Low BMI & Weight loss

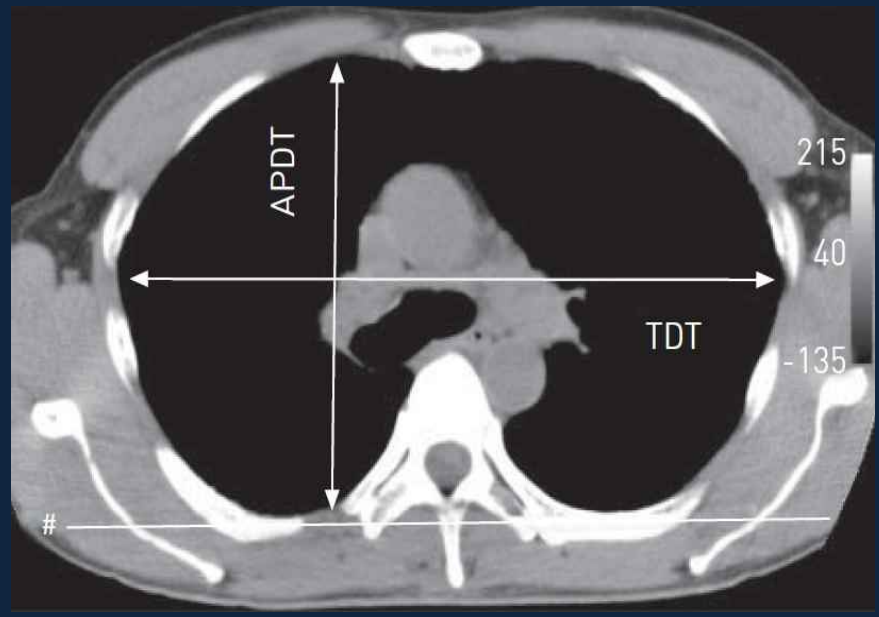


Slender statue and flattened thoracic cage



“ Anterior-posterior diameter 감소 ”

APDT / Transthoracic diameter 감소



Upper lobe only vs Lower lobe involvement

Table 3. Radiological and pathological findings of the patients (n = 26)

Characteristic	Value
Distribution on HRCT	
Upper lobe alone	4 (15.4)
Upper and lower lobe	22 (84.6)
Radiological pattern (lower lobes)	22
UIP pattern	13 (59.1)
PPFE pattern	8 (36.4)
Unclassifiable	1 (4.5)
Pathologic findings (lower lobes)	13
UIP pattern	6 (46.2)
OP pattern	4 (30.8)
PPFE pattern	2 (15.4)
Unclassifiable	1 (7.6)

KJIM 2020. Epub ahead of print

Upper lobe only vs Lower lobe involvement

Baseline patient characteristics.

Patients, number	52
Age, years	62.5 (14.5)
Gender, male/female	31/21
History of pneumothorax, number	19
History of acute exacerbation, number	7
mMRC scale	1 (2)
Brinkman index	0 (220)
Body mass index	17.8 (2.8)
Serum KL-6, U/mL	546 (390)
Serum SP-D, ng/mL	208 (195)
Serum SP-A, ng/mL	46.1 (34.3)
Pulmonary function tests	
FVC, liter	1.98 (0.85)
FVC, %predicted	66.8 (21.3)
DLco, %predicted	73.2 (40.2)
TLC, liter	3.56 (1.32)
TLC, %predicted	72.5 (20.4)
RV/TLC, %	42.7 (9.3)
RV/TLC, %predicted	126.4 (37.8)
Six minute walk test	
Walk distance, meter	470 (193)
Walk distance, %predicted	88.1 (40.5)
Lowest SpO_2, %	93 (5)
GAP score	3 (2)
Flat chest index	0.580 (0.08)
Presence of lower lung lesion on CT	43
Time after diagnosis, months	36 (39)

82.7%

Respiratory Medicine 2018;141:190-197

Dominant patterns of CT image and histology in lower lung fields, and survival.

Dominant pattern of CT image	Total number	Survivors	Non-survivors
PPFE	13	6	7
UIP	*21	3	15
Inconsistent with UIP	9	5	4
No fibrosis	9	7	2
Dominant pattern of histology			
PPFE	14	7	7
UIP	**18	4	12
Not UIP or unclassifiable IP	***10	4	5
No fibrosis or not biopsied	10	6	4

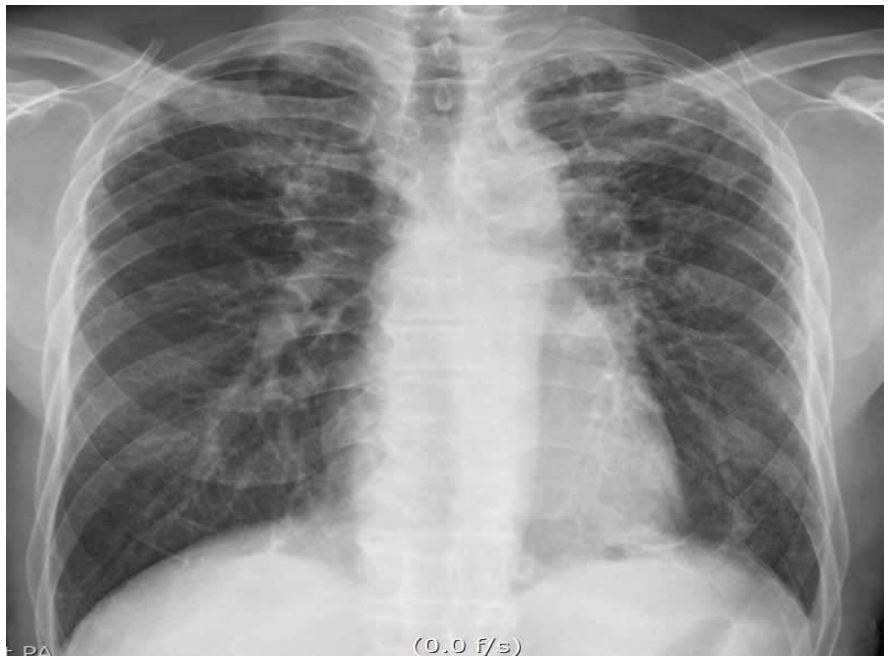
High incidence of lower lobe involvement (UIP > PPFE)

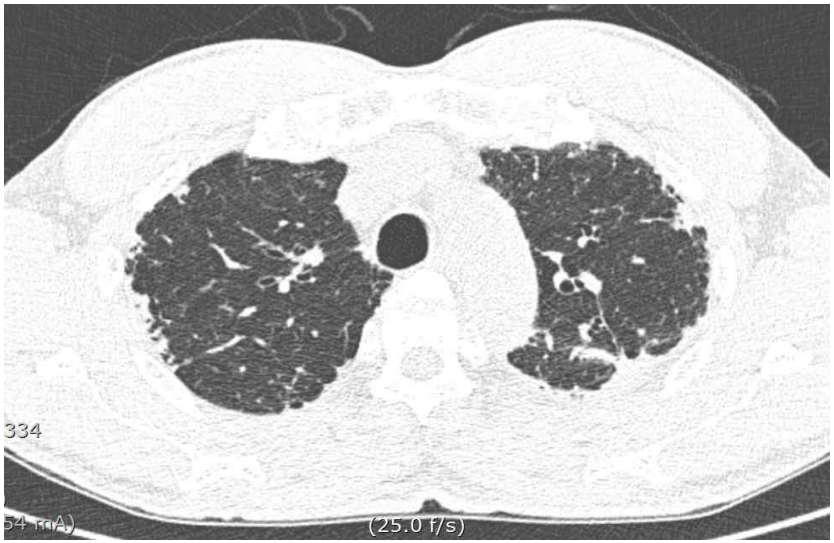
PPFE with other ILD vs PPFE progression vs IPF progression

No gender preponderance
Age at onset
Wide-ranging, younger than in idiopathic pulmonary fibrosis(IPF)
Smoking history
Unrelated to the incidence of PPFE
Clinical symptoms
Exertional dyspnea and dry cough with insidious onset Chest pain due to pneumothorax Loss of body weight
Physical findings
Slender stature and flattened thoracic cage Crackles sometimes audible
Ventilatory Impairment
Decreased FVC Increased FEV_1/FVC (%) Decreased TLC Increased RV/TLC (%)
Gas Exchange Impairment
Decreased DLco Normal or minimally decreased DLco/VA

Case 1

- M/63
- 2017년 S병원에서 VATS 시행 후 PPFE 진단
- 치료 없다는 이야기 듣고 공기 좋은 곳에서 생활 중
- 최근 운동 시 호흡곤란으로 검사 위해 내원함

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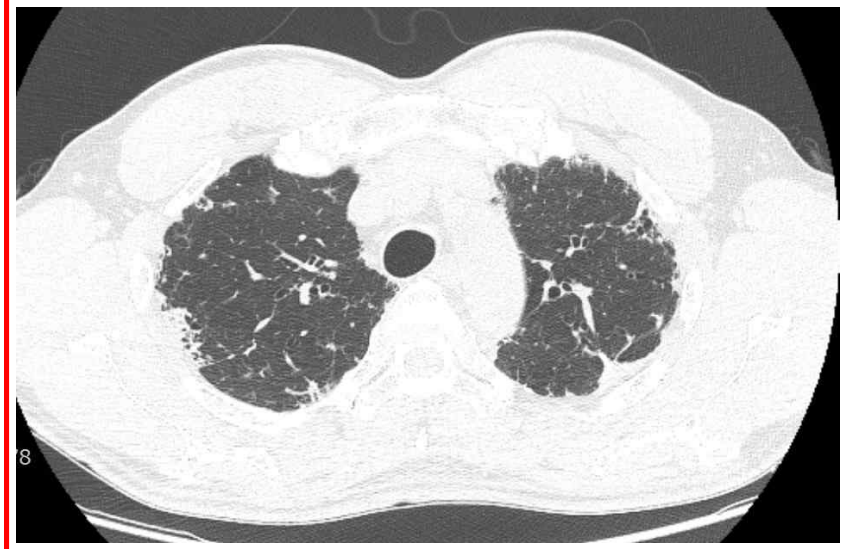

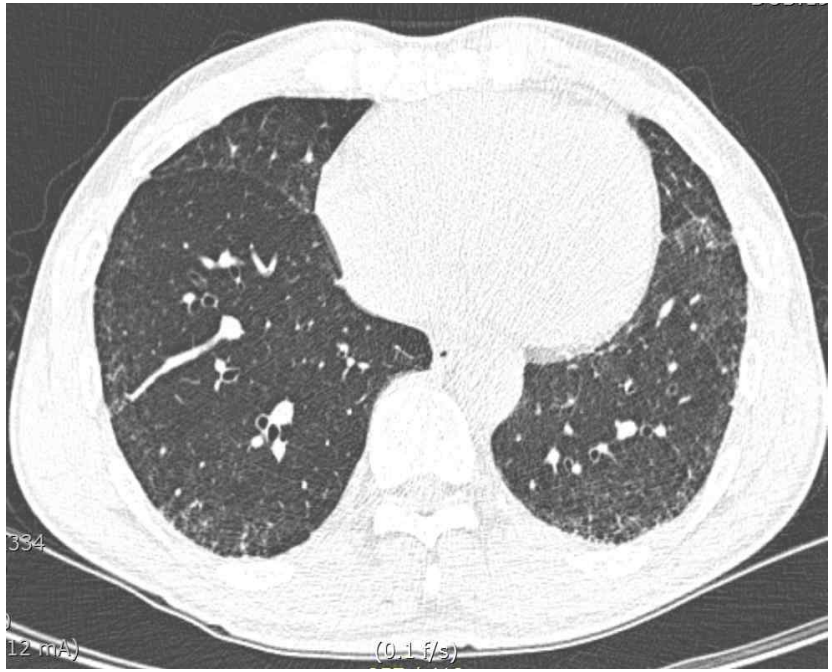
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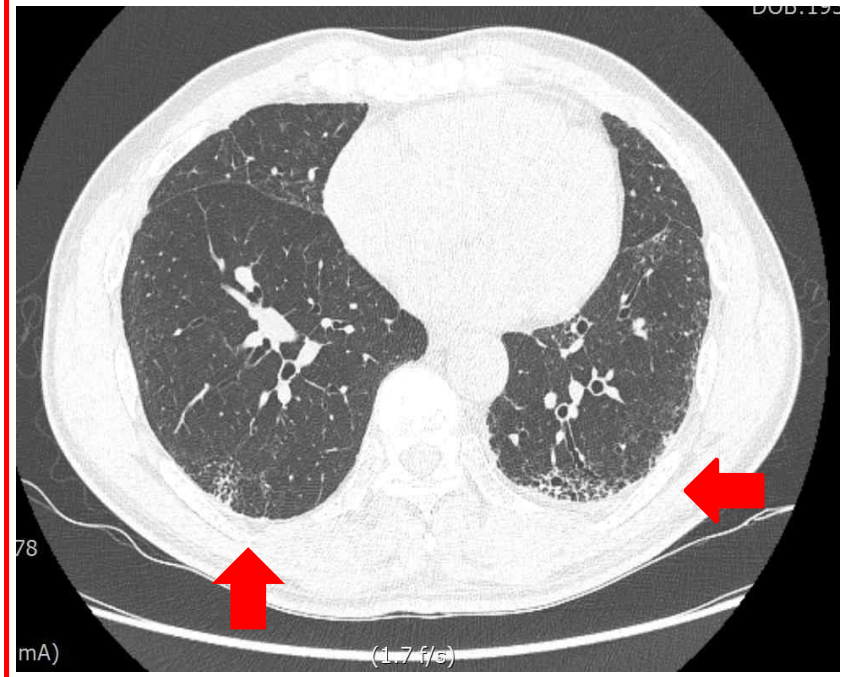
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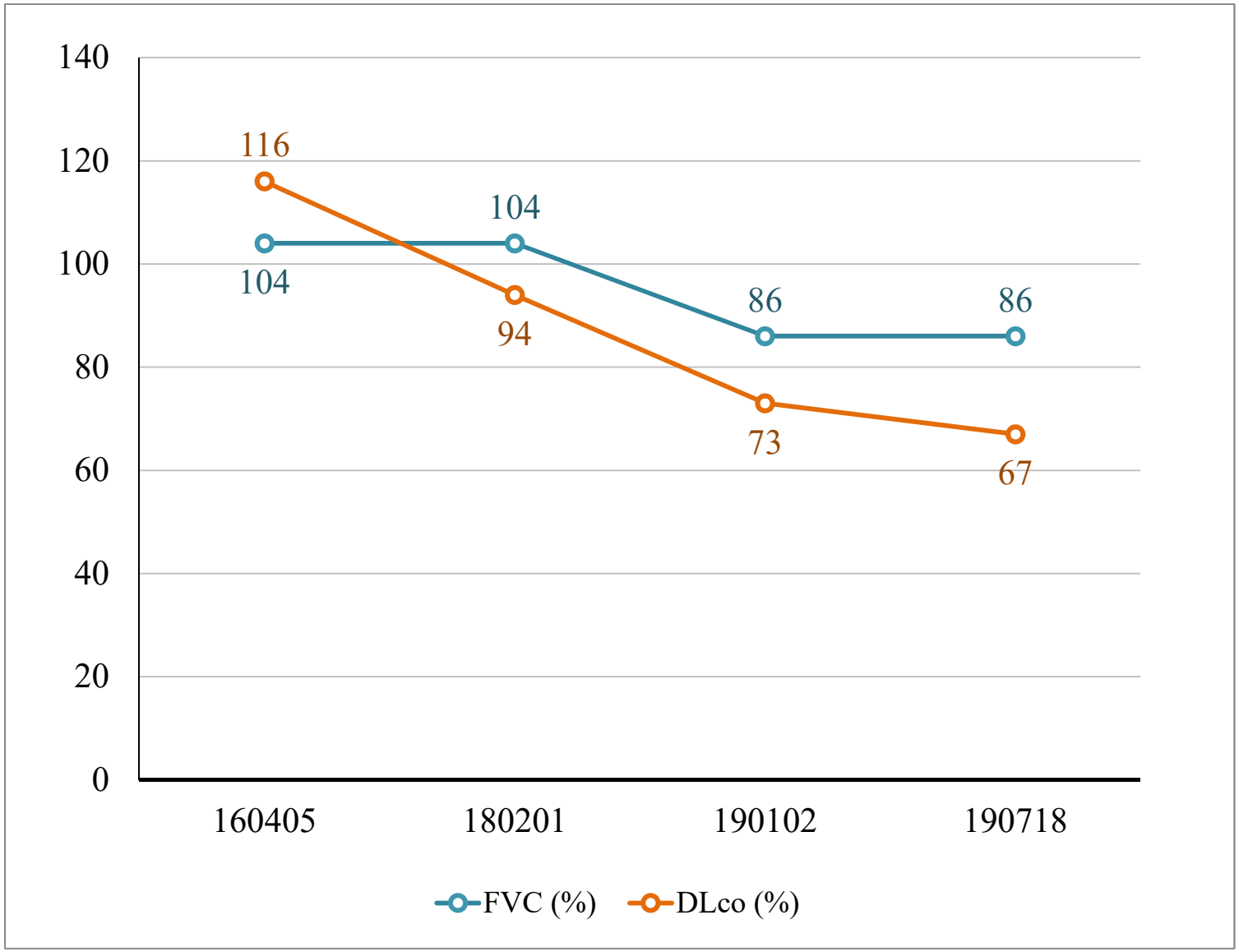

140
120
100
80
60
40
20
0
116
104
104
94
86
86
73
67
160405
180201
190102
190718
FVC (%)
DLco (%)

Case 1 summary

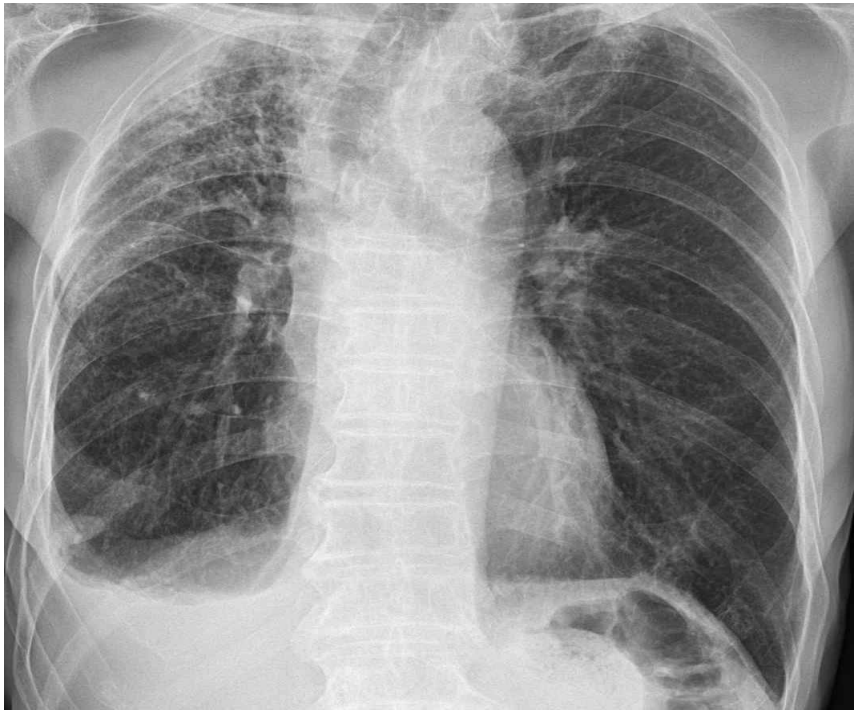
- Biopsy proven PPFE
- Lower lung involvement (high incidence, UIP)
- Rapid progression of PPFE

- Treatment ?
- No RCT

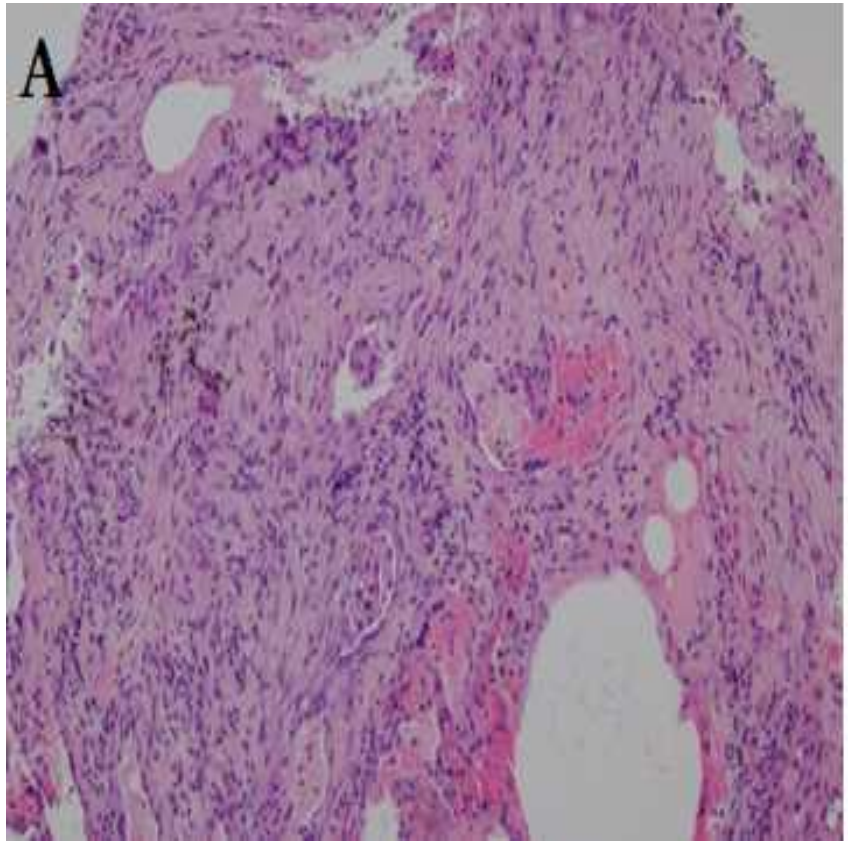
- But…Anti-fibrotic agent ! **(경기관지 폐냉동생검)**

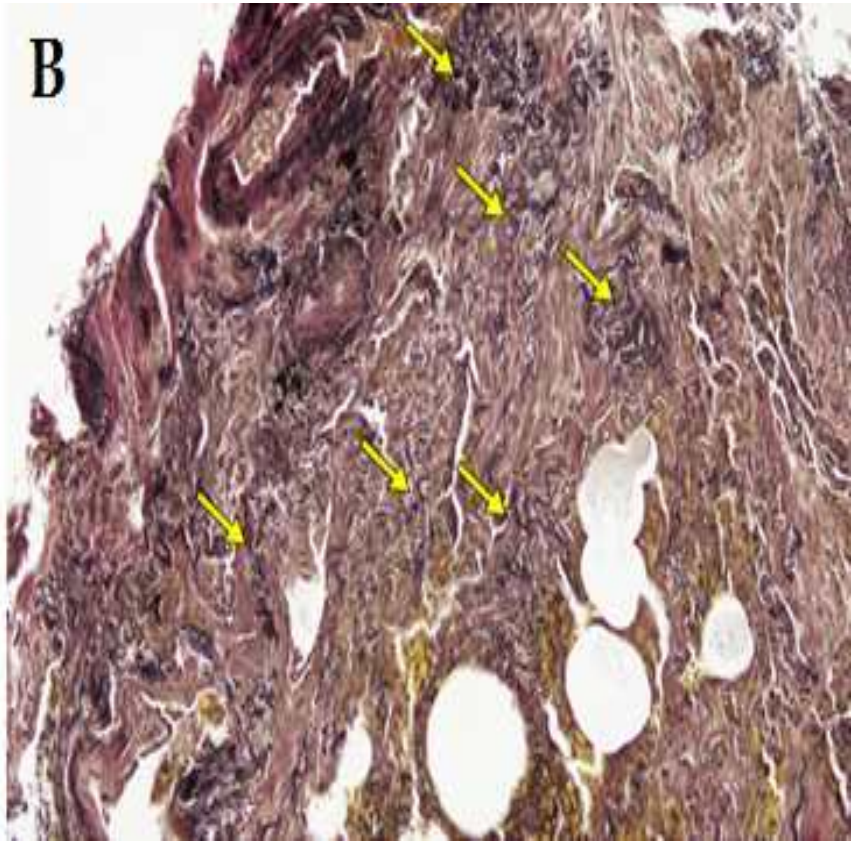
Case 2

- M/74
- 1년 전부터 평지를 걸어갈 때 지속되는 호흡곤란으로 내원
- Ex-smoker 20pyrs, 30년 전 중단, 폐결핵(-)
- 가족력(-), 고무 제조 공장에서 30년간 근무



	%, predicted
FEV1/FVC	93
FVC (%)	49
BMI	19.5kg/m^2

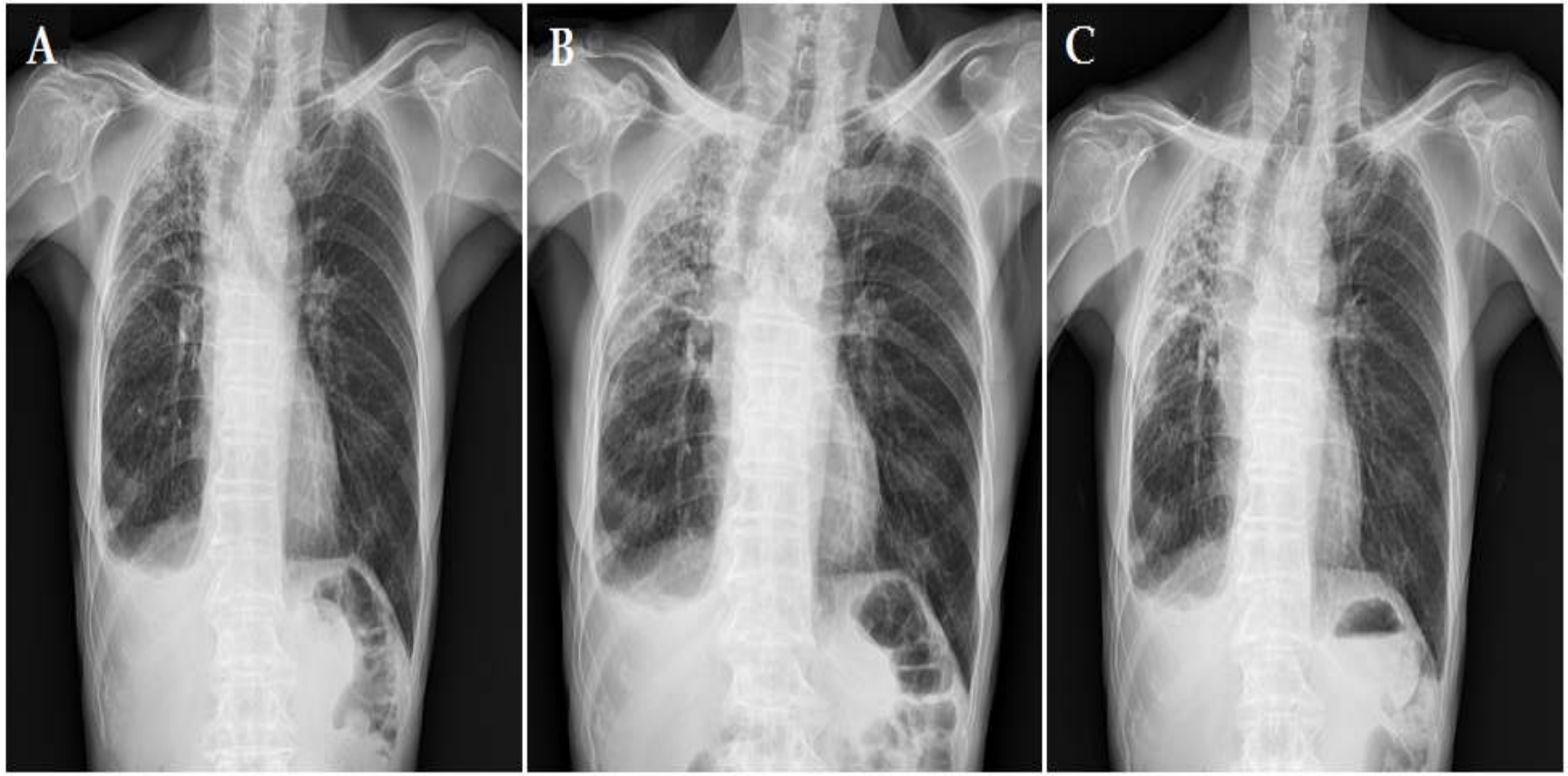




H&E stain
Dense alveolar collapse with elastosis

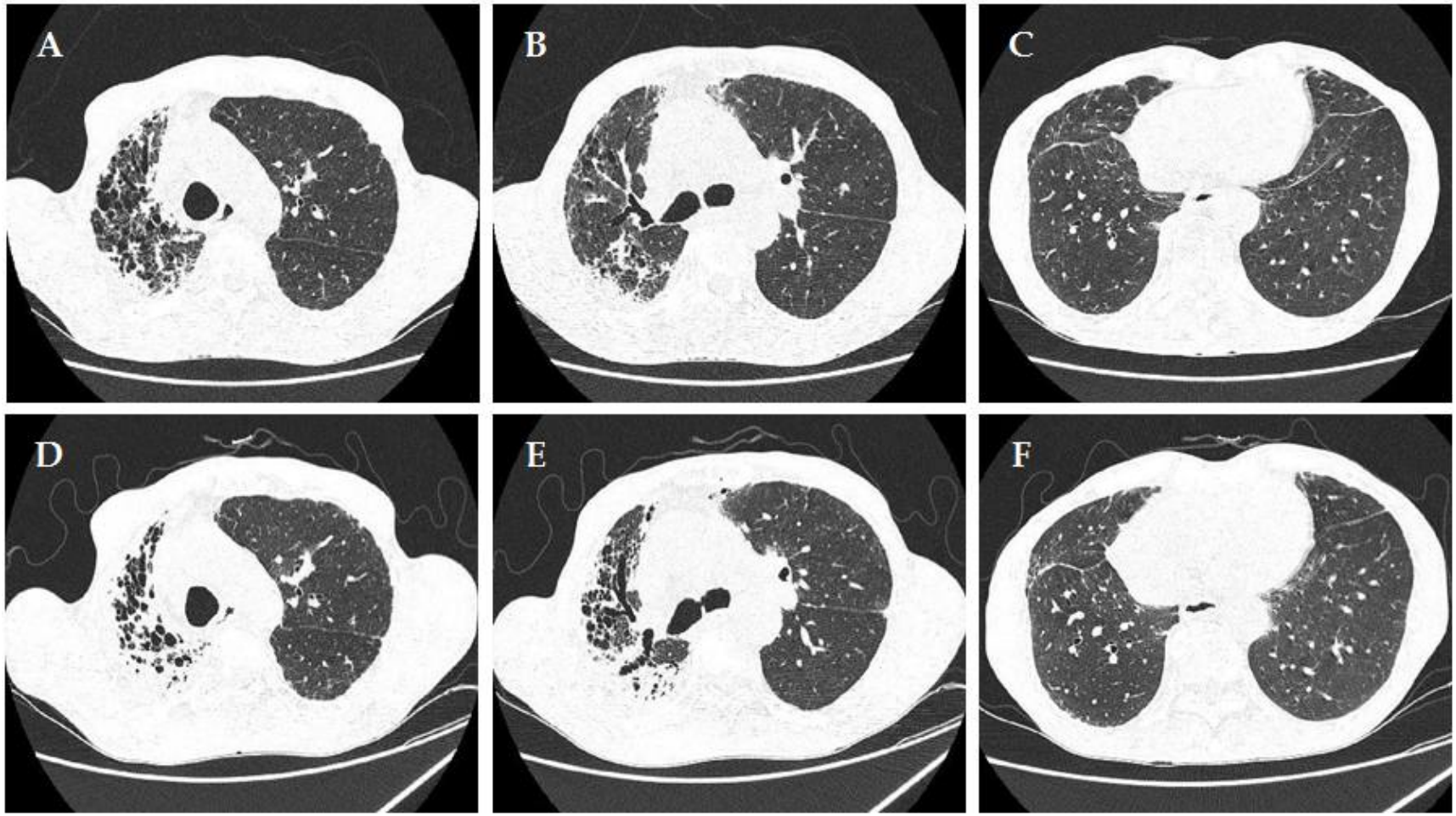
EVG stain
Septal elastosis with intra-alveolar collagenosis

Rapid progression



Initial visit → 6 months later

Rapid progression



Initial visit → 6 months later

Case 2 summary

- Biopsy proven PPFE
- Unilateral lung involvement
- Rapid progression of PPFE

- Treatment ?
- No RCT

- But…Short term use of steroid, Pulmonary Rehab and weight gain !

Summary

- Upper lung predominant ILD – PPFE
- PPFE may not be as rare as previously perceived
- Unique features
- Frequent co-involvement of lower lung
- Classification, relevant underlying conditions, treatment ?
- Korean registry in the future

감사합니다