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# Pleuroparenchymal Fibroelastosis

## A Review of Histopathologic Features and the Relationship Between Histologic Parameters and Survival

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# BACKGROUND

Interstitial lung disease (**ILD**)/

Diffuse parenchymal lung disease (**DPLD**)

DPLD of known cause e.g. drugs or association e.g. collagen vascular disease

Idiopathic interstitial pneumonitis (**IIPs**)

Granulomatous DPLD e.g. sarcoidosis

Other forms of DPLD e.g. LAM,HX ete

# BACKGROUND

**IIPs** (Idiopathic Interstitial Pneumonias) :

- 2002 the ATS/ERS classification of IIPs
- the updated 2013 ATS/ERS classification of IIPs
  - a supplement to the previous 2002 classification of IIPs

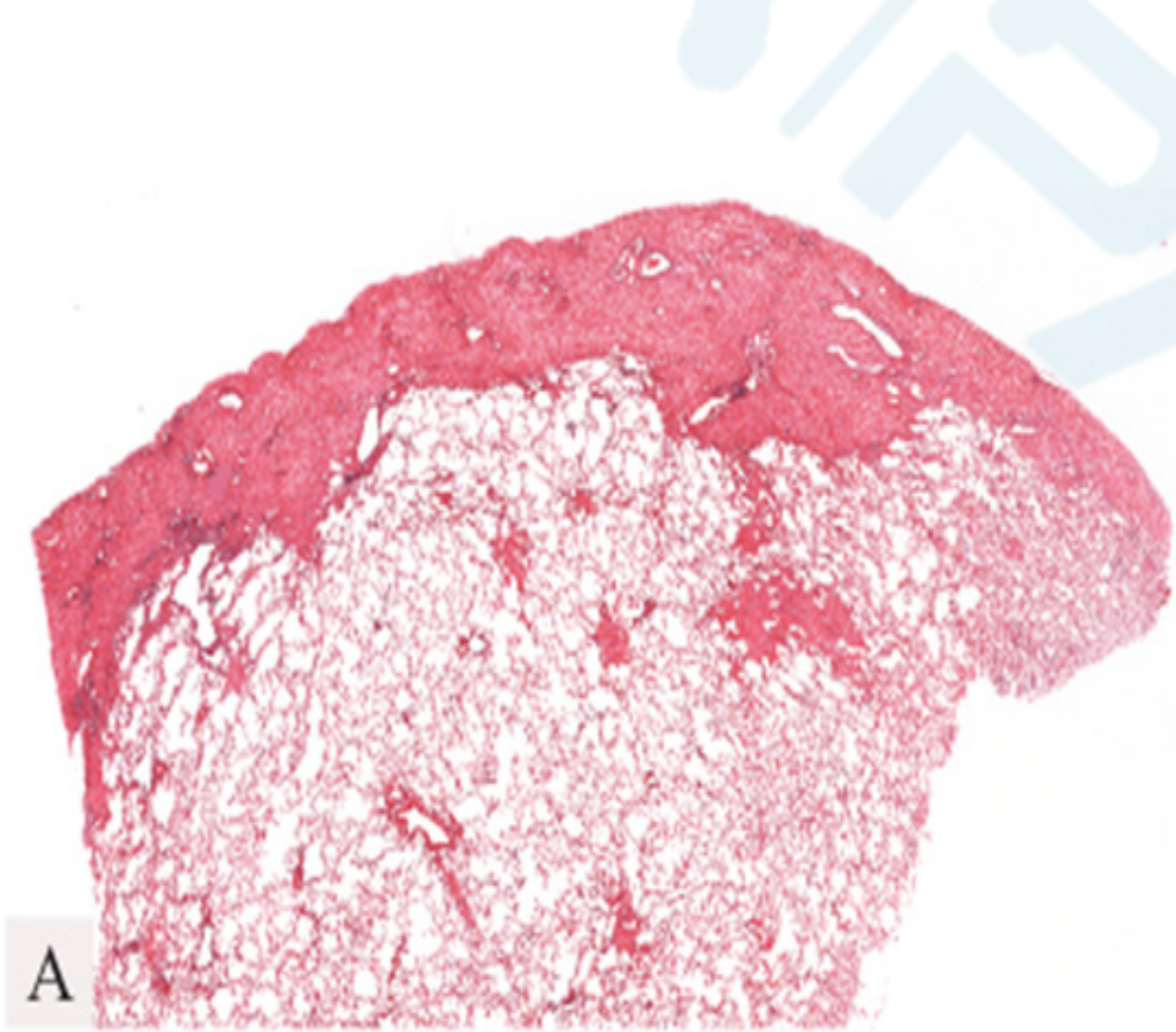
# 2013 ATS/ERS classification of IIPs

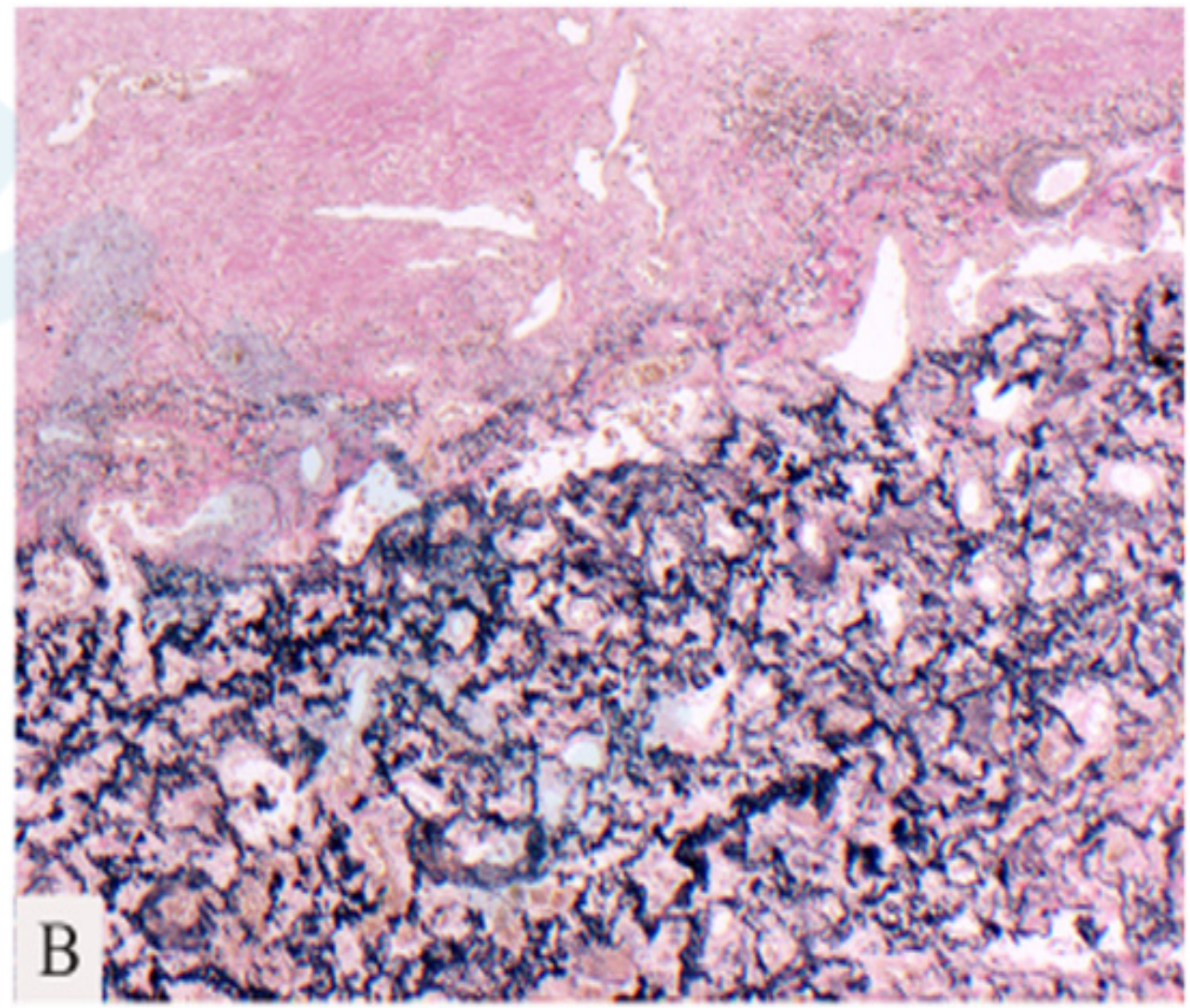
**TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES**

| |
|---|
| Major idiopathic interstitial pneumonias |
| Idiopathic pulmonary fibrosis **(IPF/UIP)** |
| Idiopathic nonspecific interstitial pneumonia |
| Respiratory bronchiolitis–interstitial lung disease |
| Desquamative interstitial pneumonia |
| Cryptogenic organizing pneumonia |
| Acute interstitial pneumonia |
| Rare idiopathic interstitial pneumonias |
| Idiopathic lymphoid interstitial pneumonia |
| Idiopathic pleuroparenchymal fibroelastosis |
| Unclassifiable idiopathic interstitial pneumonias* |

# BACKGROUND

**PPFE** (Pleuroparenchymal Fibroelastosis ) :

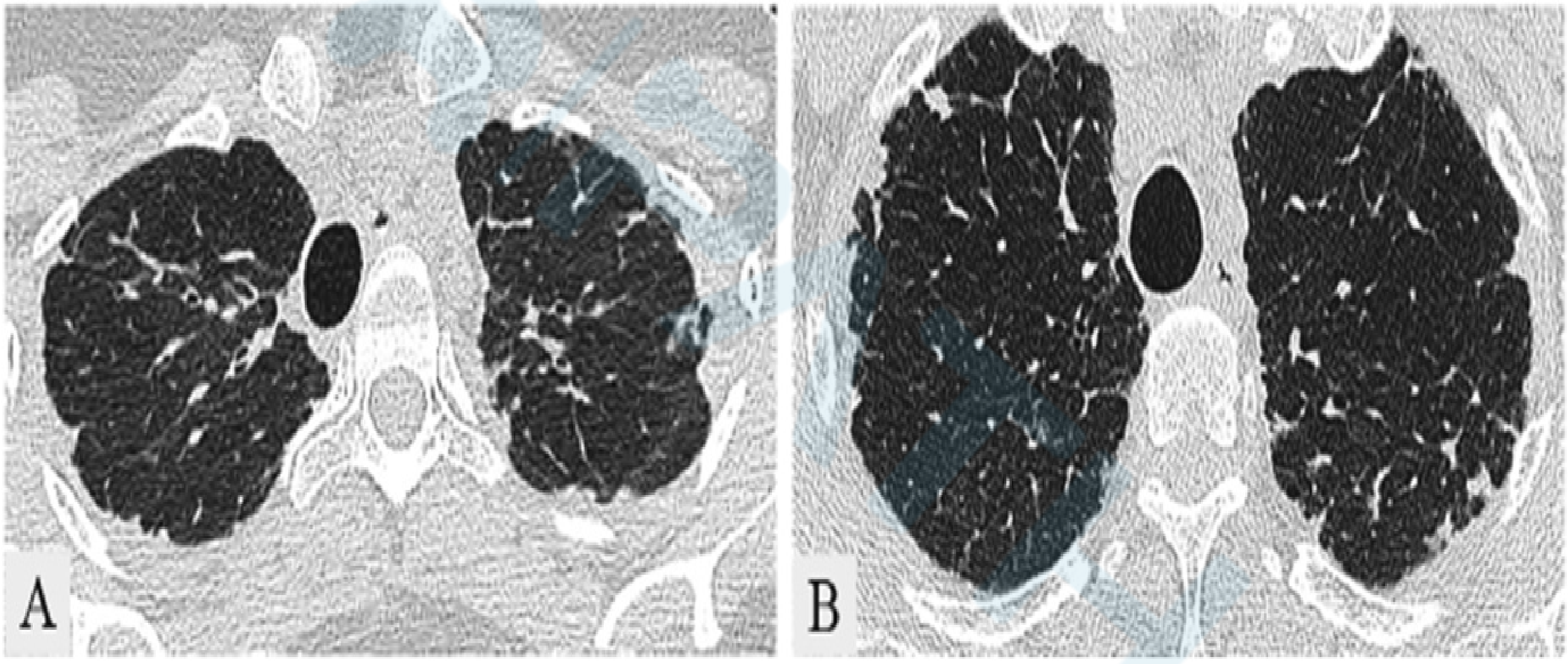


# BACKGROUND

- characteristic image(HRCT)
  - shows dense subpleural consolidation with traction bronchiectasis, architectural distortion, and upper lobe volume loss
- concurrent histologic patterns of interstitial lung disease
  - UIP/IPF and hypersensitivity pneumonitis (HP)
- carry a poor prognosis
  - may require lung transplantation in severe cases

# **PPFE-** HRCT



# INTRUDUCTION

- have a considerable increase in cases presenting at our institution in recent years
- the histopathologic changes can vary in severity between different patients
- no studies correlating histopathologic features with clinical survival

# INTRUDUCTION

- Aims - review a cohort of PPFE diagnosed at our institution
  - assess key diagnostic histologic criteria (IAFE and visceral pleural fibrosis)
  - assess the incidence of coexistent individual histologic patterns and individual histologic parameters
  - assess a relationship between histopathologic parameters and survival

# MATERIALS AND METHODS

## Search for cases

- in the diagnostic pathology archives of the Royal Brompton and Harefield NHS Foundation Trust
- “PPFE” or “pleuroparenchymal fibroelastosis”
- 2004 .01 - 2017 .03

# METHODS

56 cases were identified

- 13 cases were excluded (no slides)
- 43 cases
  - confirmed as PPFE by 3 pathologists
  - with imaging and clinical data assessed in a multidisciplinary setting to exclude other causes of IAFE such as an apical fibrous cap
  - HE–stained slides； EVG–stained slides

# METHODS

- assessed the histopathologic features

  - histologic parameters (a semiquantatitive grading system)

    - the amount of fibroblastic foci

      - the leading edge between the fibrosis and the adjacent lung

      - scored semiquantitavely as 0 to 6

        0 – absence;  6 - the highest number

      - simplified to a 3-tiered scoring system

        mild (1 , 2), moderate (3 , 4), and marked (5 ,  6)

    - IAFE

      - graded as 0=absent, 1=mild, 2=moderate or 3=marked

# METHODS

- Visceral pleural fibrosis
  - 0=absent, 1=mild, 2=moderate or 3=marked
- inflammation in areas of fibrosis
  - 0=absent
  - 1=mild if occasional inflammatory aggregates were seen
  - 3=marked if aggregates and diffuse inflammation was noted
  - 2=moderate if between both
- vascular fibrointimal thickening in arteries and veins
  - 0=absent, 1=mild, 2=moderate or 3=marked on EVG stains
- granulomas (absent or present)

# METHODS

- 13/43 patients had more than one lobe showing PPFE
  - 11 patients : 2 biopsied sites
  - 2 patients: 3 biopsied sites
  - 58 biopsies in total(43 patients)
  - Histologic parameters were graded separately for each site
- Note: different histologic patterns or additional histologic features in additional biopsy sites

# METHODS

- The survival time from biopsy - in months
  - either survival time from biopsy to March 1, 2017 if the patient was alive, or time from biopsy to date of death if the patient was deceased
- Record the following data from the medical records
  - age in years, sex, family history of lung fibrosis, ethnicity, smoking status, and comorbidities

# METHODS

- Statistical analysis - using STATA software
  - Cox proportional hazards regression

    examine the prognostic value of histologic and clinical variables in predicting mortality

# RESULTS

## 43 patients

- M/F： 26/17　 8 ~78 years (55.5)
- Ethnicity(27): 22 white, 4 Asian, and 1 Hispanic
- Smoking status(36):
  - 1 was a current smoker, 12 were ex-smokers and 23 were never-smokers

- Comorbidities(27):
  - 3 patients had been diagnosed and treated for respiratory infections before the diagnosis of PPFE
  - 2 patients had rheumatoid arthritis
  - 1 had pulmonary hypertension
  - 21 patients had no reported comorbidities
- Symptoms(27):
  - all had reported cough and/or shortness of breath
  - 3 of these patients additionally having hemoptysis

# RESULTS

- Tuberculosis status and/ or relevant microbiological tests(34)
  - None of these had a history of tuberculosis or positive microbiology results showing Mycobacterium
- CT imaging(32)
  - all of these patients showing radiologic features consistent with PPFE

# RESULTS

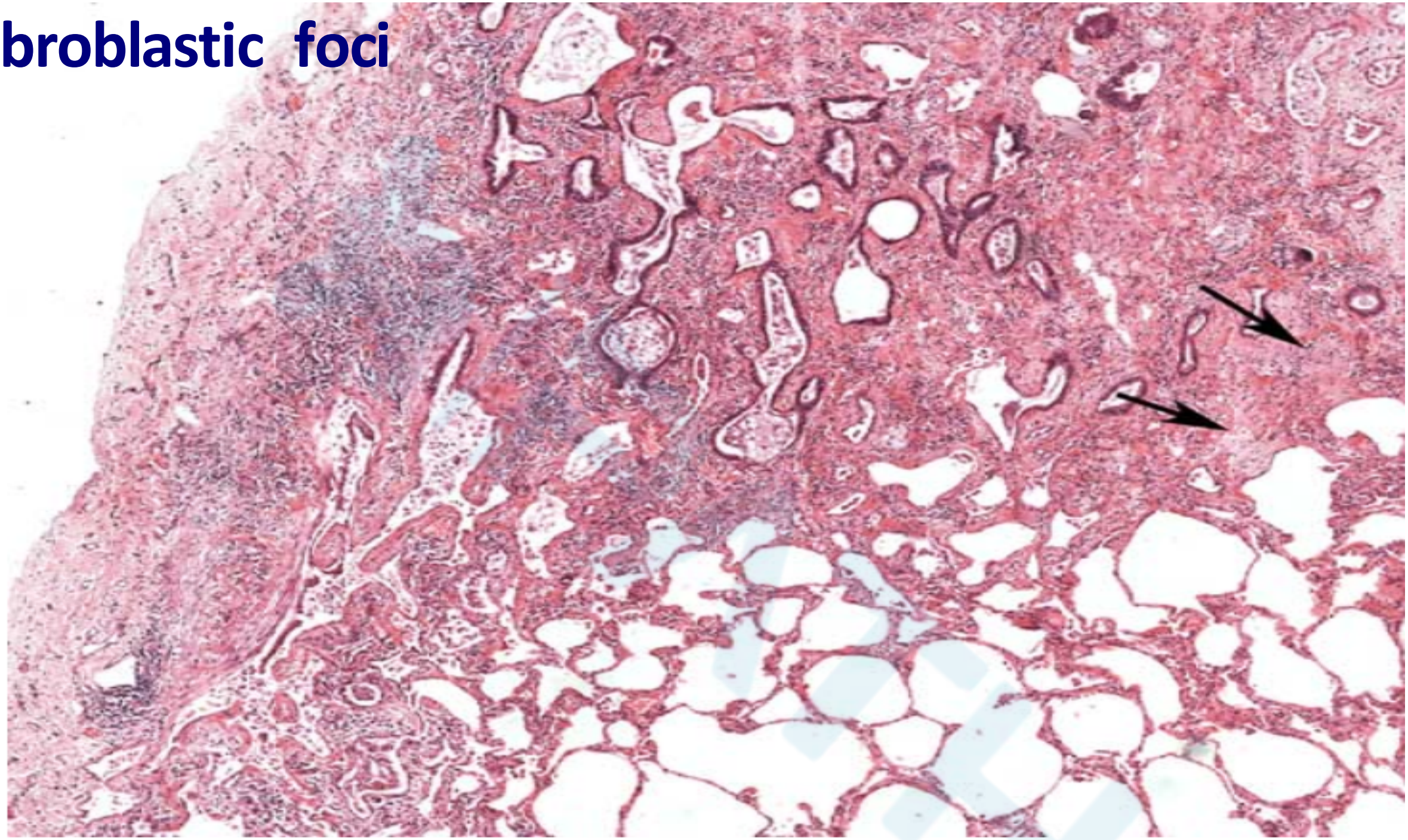
- 58 biopsies (43 patients)
  - 40 upper lobe biopsies, 4 middle lobe biopsies, and 14 lower lobe biopsies
  - 54 biopsies were surgical lung biopsies, 2 were cryobiopsies (from 1 patient) and 2 were autopsy histology specimens (from 1 patient)

# RESULTS

**TABLE 1.** Summary of Histopathologic Parameters of 58 Lung Biopsies Showing PPFE

| | n (% Cases) | | | |
|---|---|---|---|---|
| **Histopathogic Parameters** | **Absent** | **Mild** | **Moderate** | **Marked** |
| Intra-alveolar fibroelastosis (N = 58) | 0 | 11 (19) | 15 (26) | 32 (55) |
| Visceral pleural fibrosis (N = 58) | 15 (27) | 16 (28) | 14 (25) | 11 (20) |
| Fibroblastic foci (N = 58) | 0 | 26 (45) | 21 (36) | 11 (19) |
| Inflammation in areas of fibrosis (N = 58) | 0 | 12 (21) | 25 (43) | 21 (36) |
| Vascular fibrointimal thickening in veins (N = 57) | 5 (9) | 9 (16) | 35 (61) | 8 (14) |
| Vascular fibrointimal thickening in arteries (N = 56) | 5 (9) | 10 (18) | 33 (59) | 8 (14) |

# Fibroblastic foci



- **FIGURE 1.**showing interface of PPFE and adjacent lung

  (High power HE stain)

  minimal fibroblastic foci

mild (1 , 2);  moderate (3 , 4); marked (5 , 6)

# Fibroblastic foci

- **FIGURE 2.** showing interface of PPFE and adjacent lung
  (High power HE stain)
  high numbers of fibroblastic foci

# RESULTS

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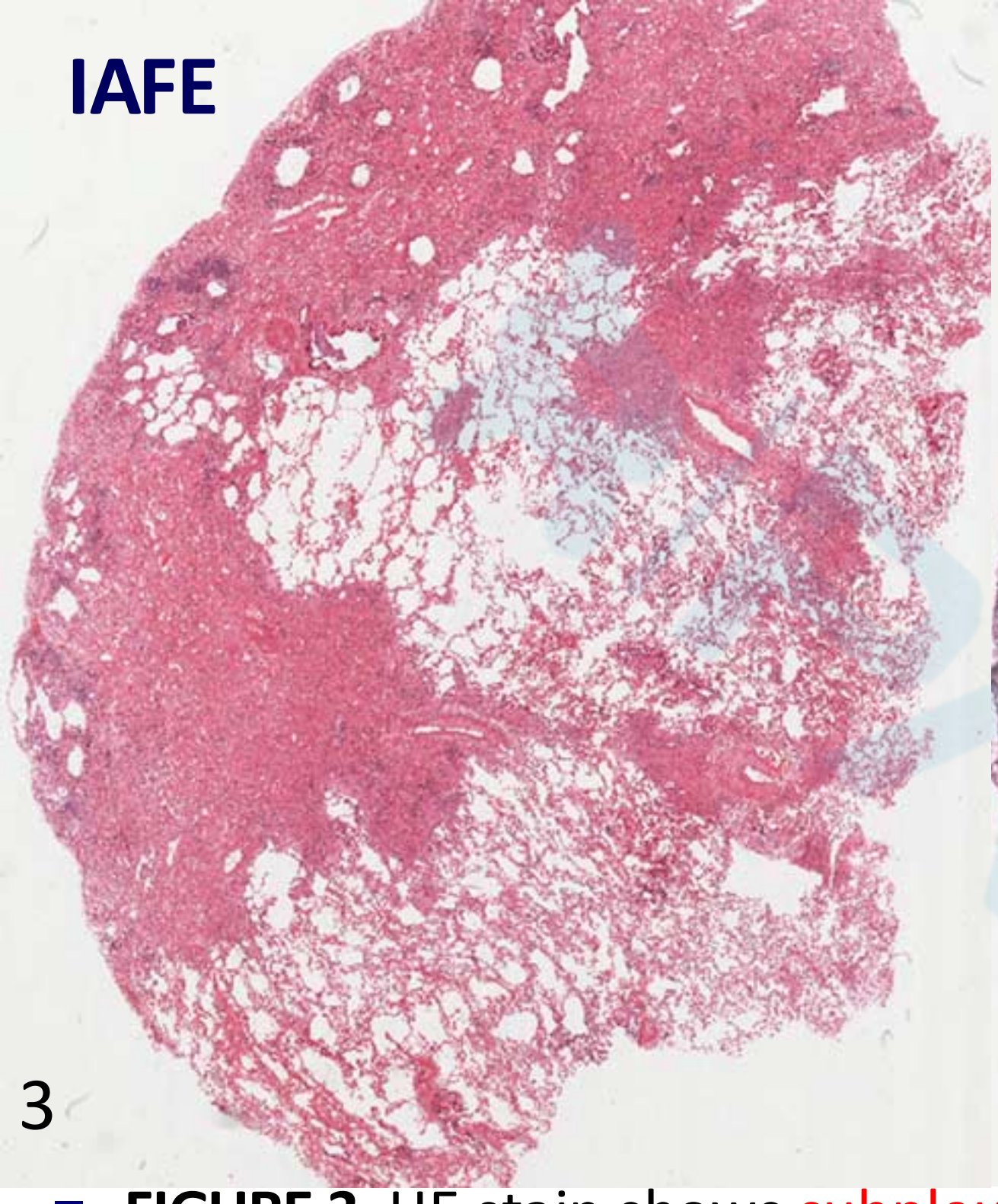
IAFE



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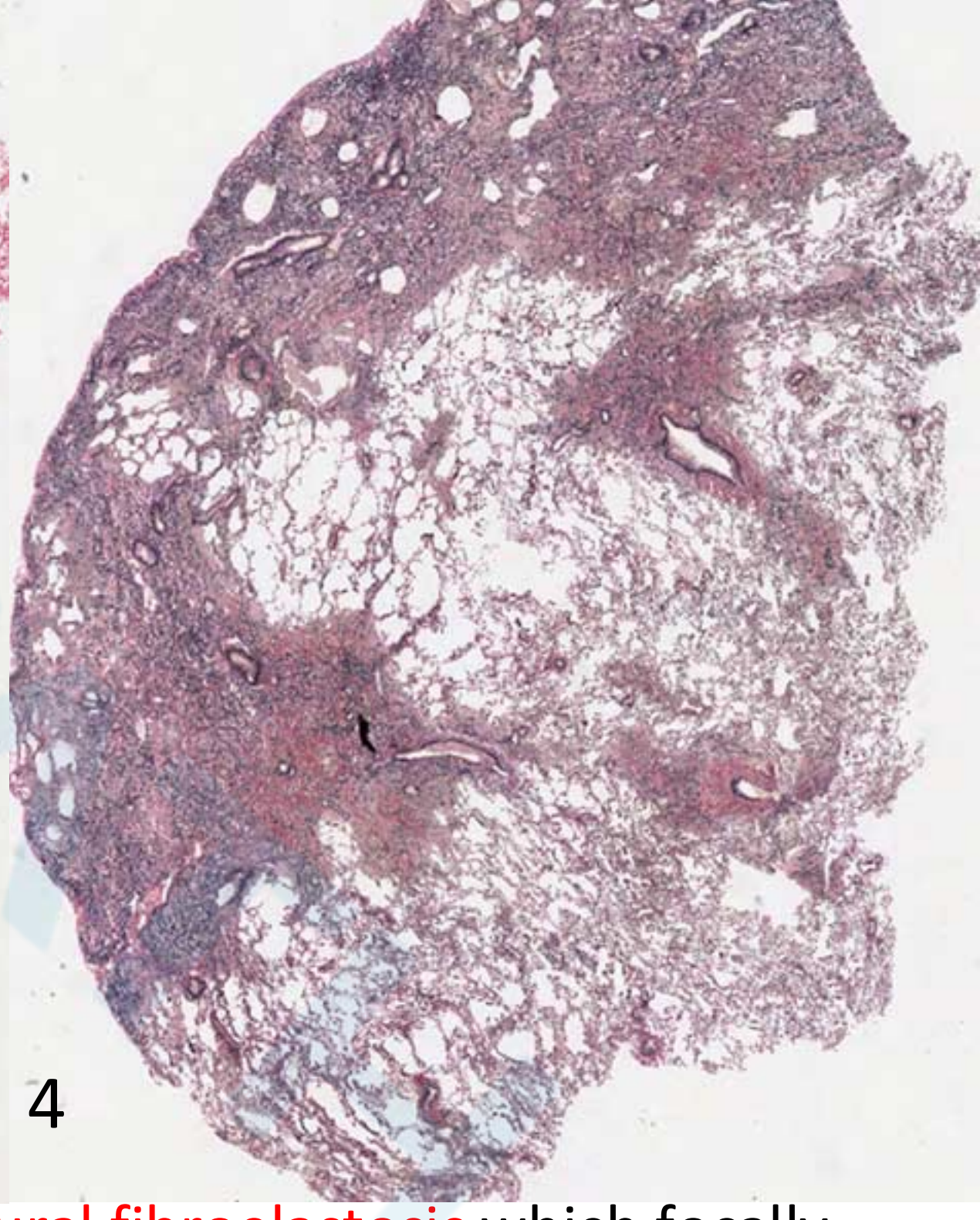

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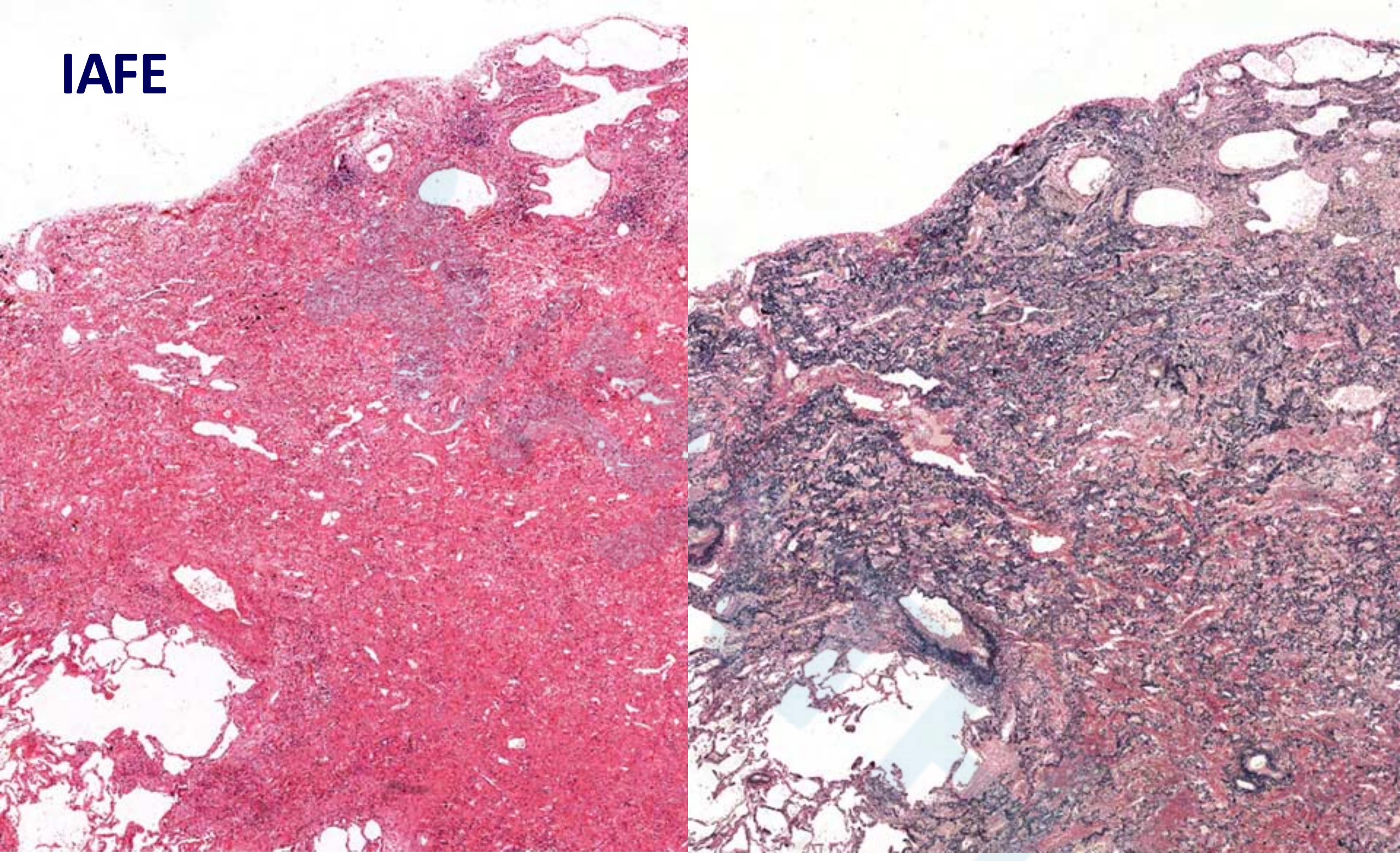
- **FIGURE 3.** HE stain shows subpleural fibroelastosis which focally extends into lung parenchyma.
- **FIGURE 4.** EVG stain shows increase in subpleural elastin fibers.

IAFE



- **FIGURE 5.** HE stain shows marked subpleural fibroelastosis.
- **FIGURE 6.** EVG stain shows characteristic network of elastin fibers.

# RESULTS

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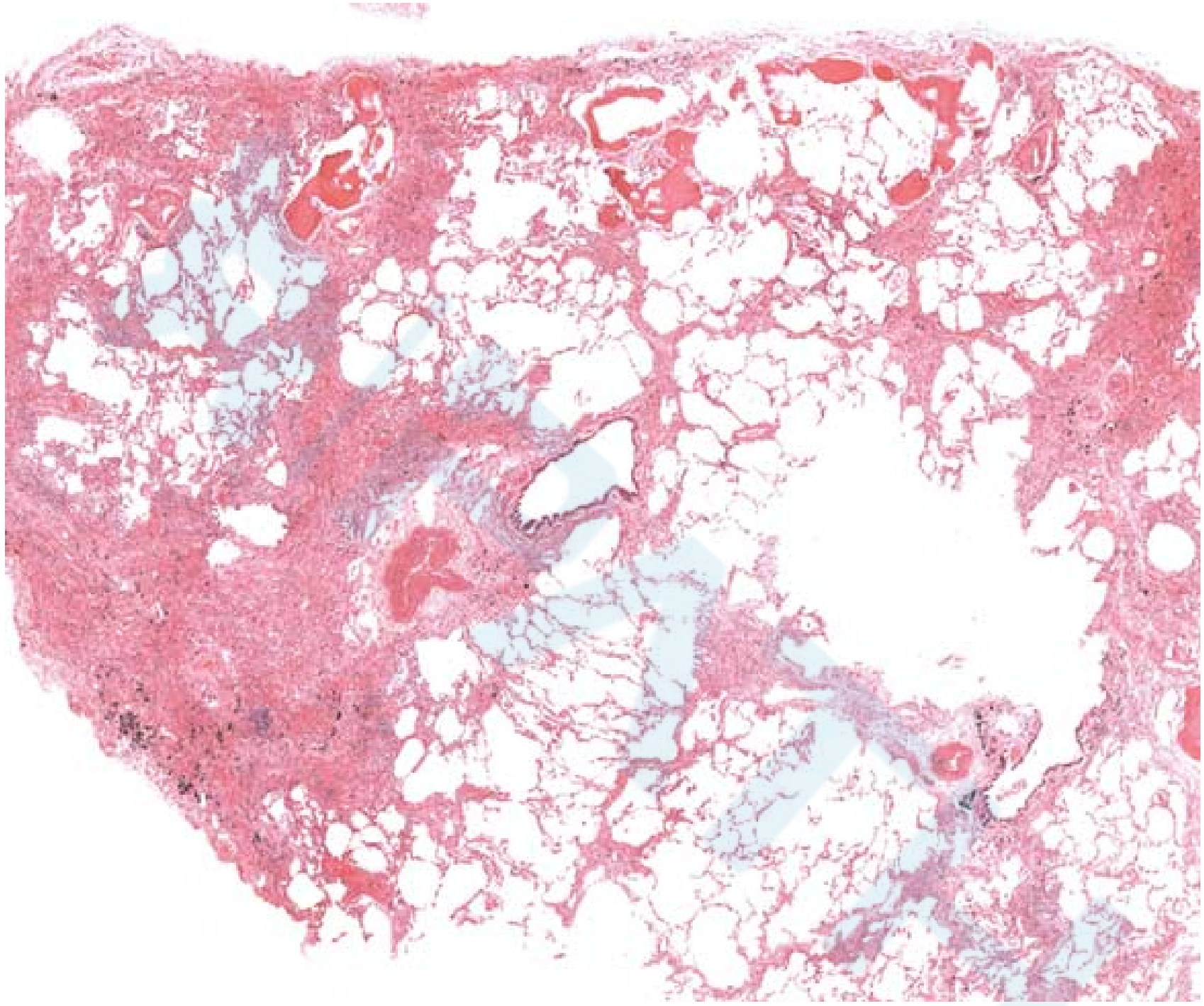
# RESULTS

- 15 /43 patients (35%) showed other histopathologic features within the same lobe as PPFE
  - 15 (35%) having granulomas
  - 1 (2%)having an aspergilloma
  - 2 (4%) with vasculitis

# RESULTS

- 10 /43(24%) patients showed a different pattern of interstitial lung disease in a separate lob to the PPFE biopsies
  - 5 (12%) showed a UIP pattern
  - 5 (12%) showed features of HP
  - None of the patients with features of HP showed areas with a UIP pattern.



- **FIGURE 7.** Low power HE stain showing UIP with subpleural and paraseptal fibrosis and fibroblastic foci.

- **FIGURE 8.** HE stain showing pattern of HP seen in separate lobe to PPFE. HP shows bronchocentric pattern of inflammation and loose granulomas (Fig. 9).
- **FIGURE 9.** High power HE stain. Loose nonnecrotizing granuloma seen in HP.

# RESULTS

- Survival data (42/43)
  - 27 (64.3%) were alive and 15 (35.7%) were deceased
  - mean survival time： 29.6 months
  - a mean follow-up of 32.9 months (range: 1 to 123 mo)

    the patient with only 1 month follow-up died within a month from biopsy

# RESULTS

- Multivariate Cox proportional hazards regression analysis
  - male sex was a predictor of increased risk of mortality (adjusting for age ) (hazard ratio, 5.31; P=0.04)

**TABLE 2.** Proportional Hazards Regression Analysis of Survival Based on Histopathologic Data

| Variable(s) Analyzed, All Hazard Ratios Adjusted for Age and Sex | Hazard Ratio | *P* | 95% Confidence Interval | No. Patients |
|---|---|---|---|---|
| Fibroblastic foci, upper lobe biopsies | 0.87 | 0.4 | 0.61-1.24 | 40 |
| Inflammation, upper lobe biopsies | 0.57 | 0.38 | 0.2-2.0 | 40 |
| Vascular fibrointimal thickening in arteries, upper lobe biopsies | 1.3 | 0.5 | 0.6-2.9 | 40 |
| Vascular fibrointimal thickening in veins, upper lobe biopsies | 2.2 | 0.1 | 0.85-5.9 | 40 |
| Visceral pleural thickening, upper lobe biopsies | 1.2 | 0.4 | 0.75-1.96 | 40 |
| Intra-alveolar fibroelastosis, upper lobe biopsies | 1.2 | 0.4 | 0.5-2.6 | 40 |
| Presence of granulomas in any lobe | 0.27 | 0.049 | 0.07-0.99 | 42 |
| Presence of separate IIP in any lobe | 0.56 | 0.39 | 0.16-2.04 | 41 |
| Presence of usual interstitial pneumonia, in any lobe | 0.77 | 0.73 | 0.16-3.62 | 41 |
| Presence of hypersensitivity pneumonitis, in any lobe | 0.44 | 0.43 | 0.05-3.43 | 41 |

- coexistent granulomas have a significant decrease in mortality
- the 36 patients with available smoking history
  - granulomas was still significantly protective against mortality (adjust for sex, age at time of biopsy, and smoking status)

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- Have no significant effect on mortality

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- The presence of UIP or Hp have no significant effect on mortality.

# DISCUSSION

- PPFE is not as rare as initially thought.
  - While PPFE was viewed as rare before being added to the IIPs in 2013, increased awareness of its existence has prompted a significant increase in publications.

# DISCUSSION

- Literature: some PPFE have coexistent interstitial lung diseases in other lobes (UIP/IFP; HP)
  - In our series, the incidence was 25%(10) overall, which is lower than other series reporting 43% and 75%.
  - the presence of UIP or HP did not significantly affect mortality (our series)

    - the number of cases for statistical analysis (5 UIP and 5 HP) was low.

# DISCUSSION

- This study assess whether the extent of histologic parameters in PPFE provided potentially useful prognostic or etiologic data.
- In severa studies of UIP/IPF, fibroblastic proliferation correlated with mortality.
- Our data showed that fibroblastic proliferation no significant effect on mortality in PPFE.
- which supports the pathogenesis of PPFE being different to UIP.

# DISCUSSION

- granulomas was significantly associated with a decreased risk of mortality (adjusting for gender, age at time of biopsy and smoking status).

- Hypothesis: PPFE might represent a progressive fibrosing immune-mediated response to identified or unidentified infection, inhaled antigen or allergen and that the presence of granulomas may be a marker of such cases.

# DISCUSSION

- Male was a predictor of increased risk of mortality in our cohort.
  - This has not been reported and may provide new prognostic information about PPFE.
- 2 patients in our study had a family history of pulmonary fibrosis.
  - This supports the possibility of an underlying genetic cause in these rare familial cases of PPFE.

# DISCUSSION

- Transbronchial Cryobiopsy is a less invasive procedure which offers advantages with regards to decreased risk and complications versus surgical lung biopsy. But the pleura sample is unavailable.
- Multidisciplinary discussion with review of imaging findings was essential, especially for the evaluation of pleura.
- multidisciplinary discussion is equally important in cases diagnosed on surgical lung biopsy, as IAFE is not specific to PPFE.

# LIMITATION

- Did not have complete clinical history and smoking status data for all patients.
- The number of cases included in the study was low for the purposes of statistical analysis.

# CONCLUSION

- PPFE is more common than previously thought;
- not infrequently showing coexistent pathology，specifically UIP and granulomatous lung disease
- Granulomas may have prognostic significance.

# THANK YOU

**Table 7-1.** International Consensus Classification of Idiopathic Interstitial Pneumonias (2002)

| Histopathologic Pattern | Clinical-Radiologic-Pathologic Diagnosis |
|---|---|
| Usual interstitial pneumonia | Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis |
| Nonspecific interstitial pneumonia | Nonspecific interstitial pneumonia ("provisional") |
| Respiratory bronchiolitis | Respiratory bronchiolitis interstitial lung disease |
| Desquamative interstitial pneumonia | Desquamative interstitial pneumonia |
| Organizing pneumonia | Cryptogenic organizing pneumonia |
| Diffuse alveolar damage | Acute interstitial pneumonia |
| Lymphoid interstitial pneumonia | Lymphoid interstitial pneumonia |