GUIDELINE of IPF

– Official Statements in 2011 and 2013

이 홍 렬, M.D., Ph.D.

Division of Pulmonary and Critical Care Medicine
Department of Internal Medicine
Inha University College of Medicine

American Thoracic Society

Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment
International Consensus Statement

Am J Respir Crit Care Med Vol 161. pp 646–664, 2000

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

American Thoracic Society

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

Am J Respir Crit Care Med Vol 165. pp 277–304, 2002

American Thoracic Society Documents

An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013

Progress in Diagnosis of IPF since 2000 and 2002

Diagnostic Process in IIP

- ***C***linico-***R***adiologic-***P***athologic Diagnosis (CRP Diagnosis)
  = ***M***ulti-***D***isciplinary ***D***iscussion (MDD)

- Clinical Evaluation History and Physical examination
  PFT Restriction ± impaired gas exchange

- HRCT

- Surgical Lung Biopsy

Am J Respir Crit Care Med Vol 165. pp 277–304, 2002

Definite Diagnosis of IPF in the Presence of Surgical Lung Biopsy (2000)

1. Exclusion of known causes of ILD

2. Abnormal pulmonary function studies

3. Abnormalities on conventional chest radiographs or HRCT scans

Am J Respir Crit Care Med Vol 161. pp 646–664, 2000

Diagnosis of IPF in absence of Surgical Lung Biopsy (2000)

Major Criteria

1. Exclusion of known causes of ILD
2. Abnormal pulmonary function studies
3. Abnormality on HRCT scans
4. Transbronchial lung biopsy or BAL

Minor Criteria

1. Age > 50 years
2. Insidious onset of otherwise unexplained dyspnea on exertion
3. Duration of illness > 3 months
4. Bibasilar, inspiratory crackles (dry or 'Velcro' type in quality)

→ In the immunocompetent adult,
all of the major criteria **+** at least three of the four minor criteria

Am J Respir Crit Care Med Vol 161. pp 646–664, 2000
Am J Respir Crit Care Med Vol 165. pp 277–304, 2002

Diagnostic Criteria (2011)

1. Exclusion of known causes of ILD

2. In patients not subjected to surgical lung biopsy

   → UIP pattern on HRCT

3. In patients subjected to surgical lung biopsy

   → Specific combinations of

   HRCT and surgical lung biopsy pattern

The major and minor criteria proposed in the 2000 ATS/ERS Consensus Statement have been eliminated

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

- Bronchoalveolar Lavage
- Transbronchial Lung Biopsy
- Serologic test for CTD

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

DEFINITION OF UIP PATTERN

HRCT Features

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

Definition of abbreviation: UIP = usual interstitial pneumonia.

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

UIP Pattern (All Four Features)

- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing +/– traction bronchiectasis
- Absence of features
  listed as inconsistent with UIP pattern

Possible UIP Pattern (All Three Features)

- Subpleural, basal predominance
- Reticular abnormality
- Absence of features
  listed as inconsistent with UIP pattern

Inconsistent with UIP Pattern (Any of the Seven Features)

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive ground glass abnormality
- Profuse micronodules
- Discrete cysts
- Diffuse mosaic attenuation/air-trapping
- Consolidation

DEFINITION OF UIP PATTERN

Histopathology Features

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

Definition of abbreviations: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

UIP Pattern (All Four Criteria)

- Marked fibrosis/architectural distortion, ± honeycombing in a subpleural/paraseptal distribution
- Patchy involvement of lung parenchyma by fibrosis
- Fibroblastic foci
- Absence of features against a diagnosis of UIP suggesting an alternative diagnosis

Probable UIP Pattern

- Marked fibrosis/architectural distortion, ± honeycombing
- Absence of either patchy involvement or fibroblastic foci, but not both
- Absence of features against a diagnosis of UIP suggesting an alternative diagnosis

OR

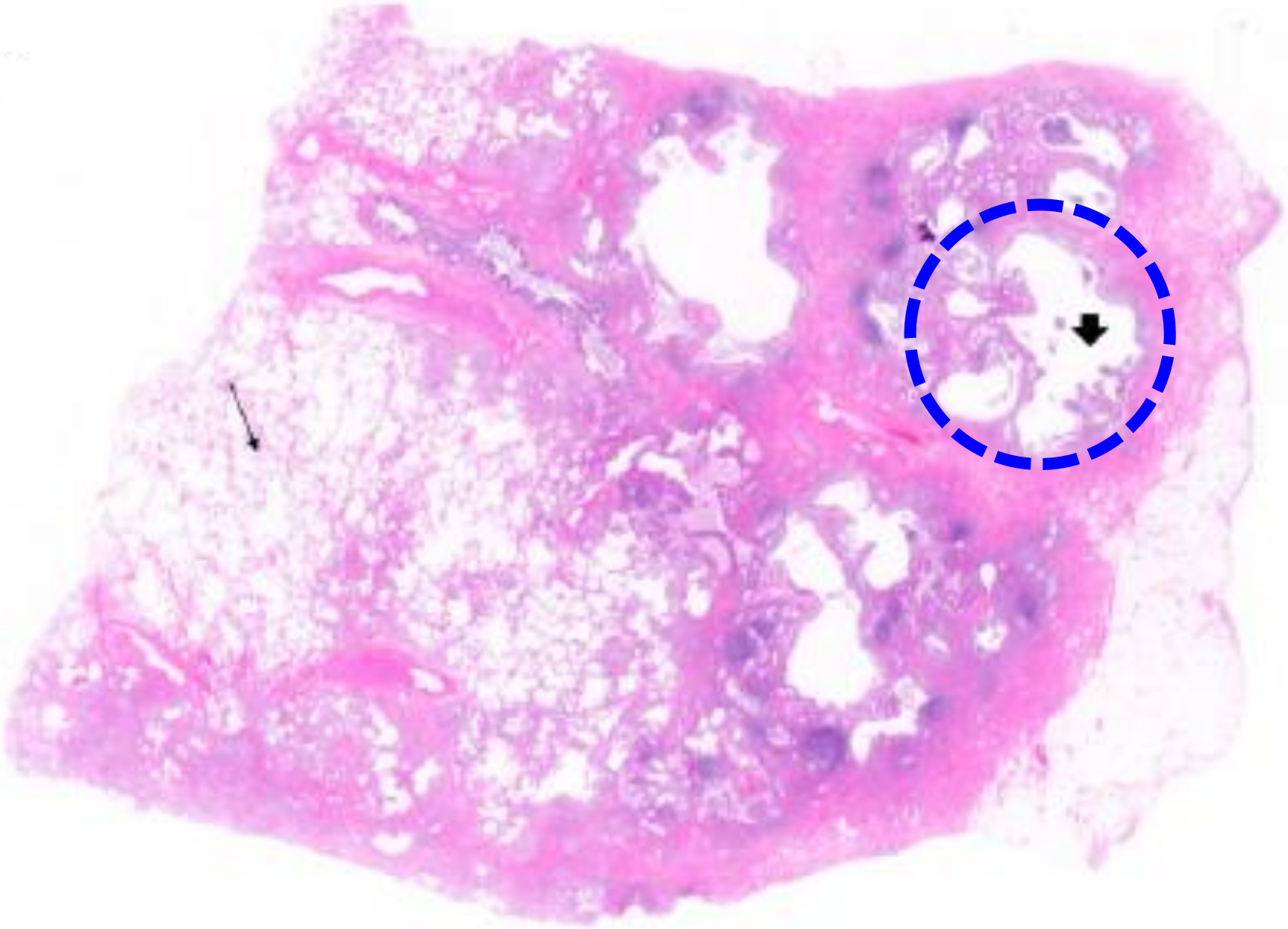
- Honeycomb changes only

Possible UIP Pattern (All Three Criteria)

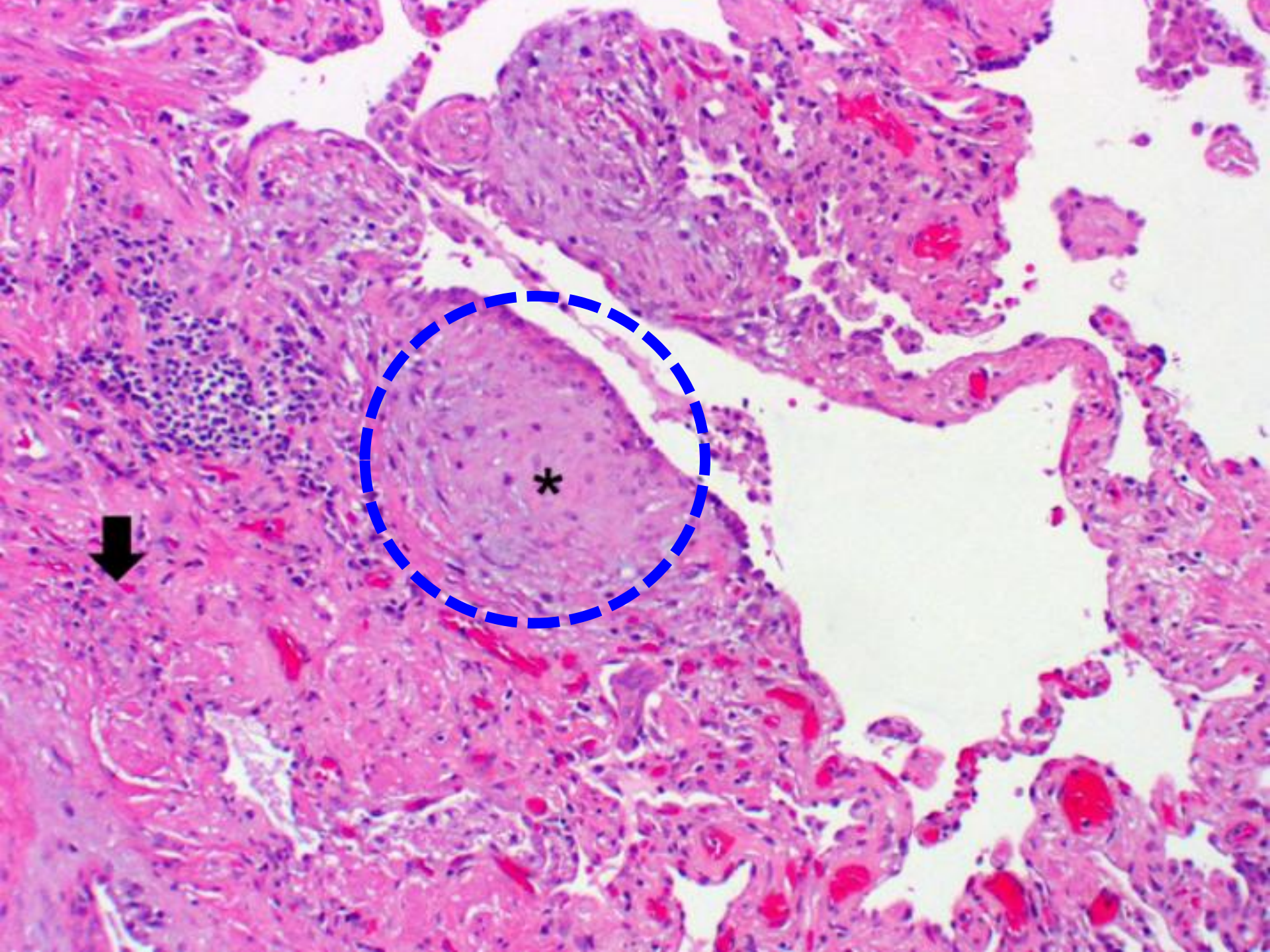
- Patchy or diffuse involvement of lung parenchyma by fibrosis ± interstitial inflammation
- Absence of other criteria for UIP
- Absence of features against a diagnosis of UIP suggesting an alternative diagnosis

Not UIP Pattern (Any of the Six Criteria)

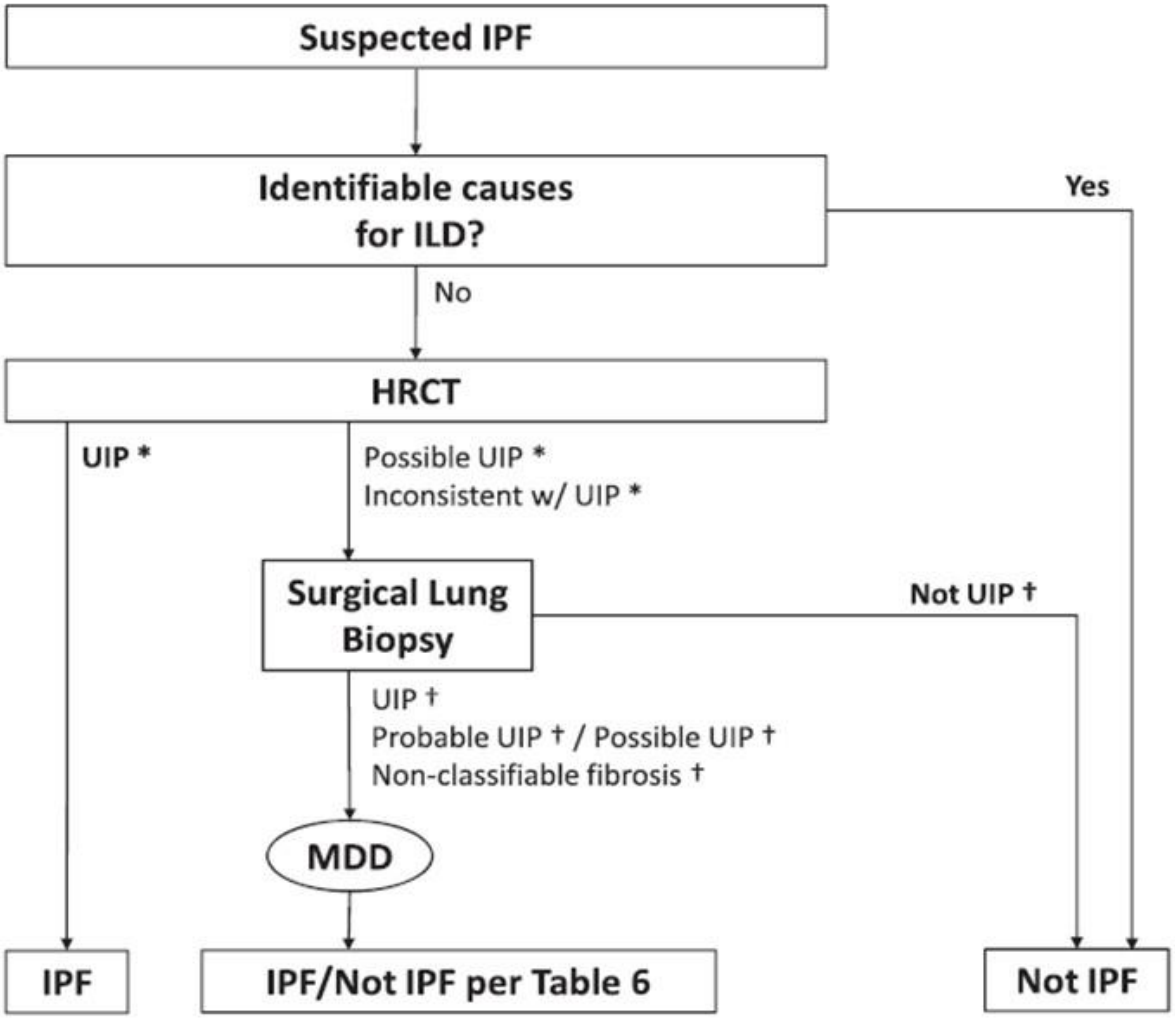
- Hyaline membranes
- Organizing pneumonia
- Granuloma
- Marked interstitial inflammatory cell infiltrate
- Predominant airway centered changes
- Other features suggestive of an alternative diagnosis



Am J Respir Crit Care Med Vol 183. pp 788–824, 2011



Diagnostic Algorism for IPF



Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Combination of HRCT and Surgical Lung Biopsy for the Diagnosis of IPF

HRCT pattern	Surgical Lung Biopsy Pattern (when performed)	Diagnosis of IPF?
UIP	UIP	YES
	Probable UIP	
	Possible UIP	
	Unclassifiable fibrosis*	
	Not UIP	No

* Fibrosis that does not meet the criteria for UIP pattern and the other IIPs

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Combination of HRCT and Surgical Lung Biopsy for the Diagnosis of IPF

HRCT pattern	Surgical Lung Biopsy Pattern (when performed)	Diagnosis of IPF?
Possible UIP	UIP	YES
	Probable UIP	YES
	Possible UIP	Probable[†]
	Unclassifiable fibrosis	Probable[†]
	Not UIP	No

[†] MDD should include discussions of potential for sampling error and a re-evaluation of adequacy of HRCT technique

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Combination of HRCT and Surgical Lung Biopsy for the Diagnosis of IPF

HRCT pattern	Surgical Lung Biopsy Pattern (when performed)	Diagnosis of IPF?
Inconsistent with UIP	UIP	Possible†
	Probable UIP Possible UIP Unclassifiable fibrosis Not UIP	No

† MDD should include discussions of potential for sampling error and a re-evaluation of adequacy of HRCT technique

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Progress in Classification of IIP

Since 2002

Idiopathic Interstitial Pneumonias (IIPs)

- ATS/ERS International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonias (2002)

  Idiopathic pulmonary fibrosis (IPF)

  Nonspecific interstitial pneumonia (NSIP)

  Cryptogenic organizing pneumonia (COP)

  Acute interstitial pneumonia (AIP)

  Respiratory bronchiolitis-interstitial lung disease (RB-ILD)

  Desquamative interstitial pneumonia (DIP)

  Lymphoid interstitial pneumonia (LIP)

Am J Respir Crit Care Med Vol 165. pp 277–304, 2002

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

Major idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis
- 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*

Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013

Unclassifiable IIP

- Inadequate CRP data
- Major discordance between CRP findings
  - Previous therapy
  - New entity, or unusual variant of recognized entity,
  - Multiple HRCT and/or pathologic patterns

TABLE 2. CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

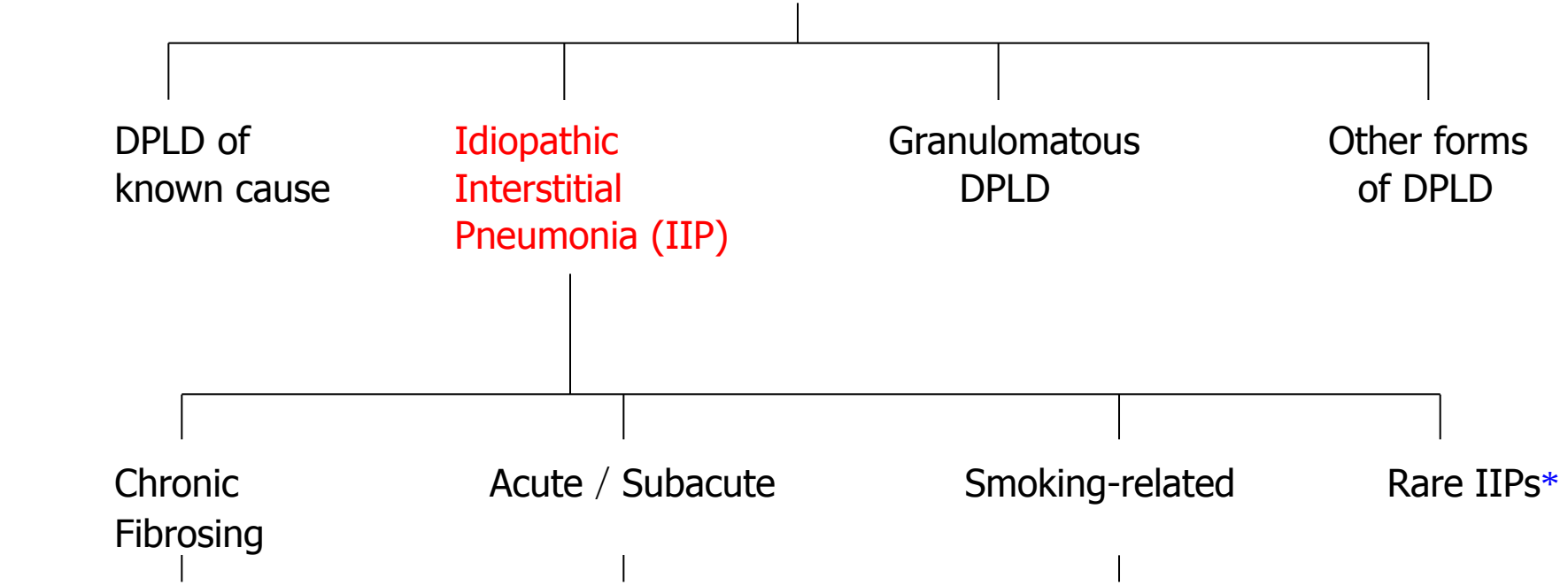
Category	Clinical–Radiologic–Pathologic Diagnoses
Chronic fibrosing IP	Idiopathic pulmonary fibrosis
	Idiopathic nonspecific interstitial pneumonia
Smoking-related IP*	Respiratory bronchiolitis-interstitial lung disease
	Desquamative interstitial pneumonia
Acute/subacute IP	Cryptogenic organizing pneumonia
	Acute interstitial pneumonia

Definition of abbreviation: IP = interstitial pneumonia.

* Desquamative interstitial pneumonia can occasionally occur in nonsmokers.

Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013

Diffuse Parenchymal Lung Disease (DPLD)



Rare IIPs	Idiopathic lymphoid interstitial pneumonia Idiopathic pleuropulmonary fibroelastosis (PPFE)
Rare Histologic Patterns	Acute fibrinous and organizing pneumonia (AFOP) Interstitial pneumonias with bronchiolocentric distribution

Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013

Progress in Specific IIPs

Since 2002

Idiopathic Pulmonary Fibrosis

- Updated evidence-based guideline

  for the diagnosis and management of IPF in 2011

TABLE 7. SELECTED FEATURES ASSOCIATED WITH INCREASED RISK OF MORTALITY IN IDIOPATHIC PULMONARY FIBROSIS

Baseline factors*
Level of dyspnea†
D_{LCO} < 40% predicted
Desaturation ⩽ 88% during 6MWT
Extent of honeycombing on HRCT†
Pulmonary hypertension
Longitudinal factors
Increase in level of dyspnea†
Decrease in Forced Vital Capacity by ⩾ 10% absolute value
Decrease in D_{LCO} by ⩾ 15% absolute value
Worsening of fibrosis on HRCT†

Definition of abbreviations: 6MWT = 6-minute-walk test; D_{LCO} = diffusion capacity for carbon monoxide; HRCT = high-resolution computed tomography.

* Baseline forced vital capacity is of unclear predictive value.

† Currently, there is no uniformity in approach to quantification.

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Combined Pulmonary Fibrosis and Emphysema (CPFE)

- It is not clear if IPF with coexisting emphysema represents a distinct clinical phenotype with a distinct prognosis or whether emphysema in these cases is simply a comorbidity

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

- Coexisting patterns of PF and E

  Heterogeneous population of patients, not a distinctive IIP

- Increased or preserved lung volumes

- Increased risk of developing pulmonary hypertension

  – Poor prognosis

→ When coexisting patterns occur,

MDD may determine the clinical significance of individual patterns

Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013

nonspecific interstitial pneumonia (NSIP) as a provisional diagnosis. Concern was expressed that NSIP was a "wastebasket" category, difficult to distinguish from other idiopathic interstitial pneumonias.

Am J Respir Crit Care Med Vol 165. pp 277–304, 2002

This multidisciplinary workshop showed that there is a consensus among experts that idiopathic NSIP is a distinct clinical entity with characteristic clinical, radiologic, and pathologic features that differ from other IIPs.

1. The clinical presentation is breathlessness and cough of usually 6 to 7 months' duration, predominantly in women, never-smokers, and in the sixth decade of life. Most patients have a restrictive ventilatory defect on lung function testing.
2. Key features on HRCT are bilateral, symmetric, predominantly lower lung reticular opacities with traction bronchiectasis and lower lobe volume loss that is usually diffuse or subpleural in the axial dimension, but sometimes spares the subpleural lung (Table 5).
3. The key histopathologic features of the NSIP pattern are the uniformity of interstitial involvement with a spectrum from a cellular to a fibrosing process (Tables 3 and 6).
4. The majority of patients with idiopathic NSIP have a good prognosis, with a 5-year mortality rate estimated at less than 18%.

Idiopathic Nonspecific Interstitial Pneumonia
Report of an American Thoracic Society Project
Am J Respir Crit Care Med Vol 177. pp 1338–1347, 2008

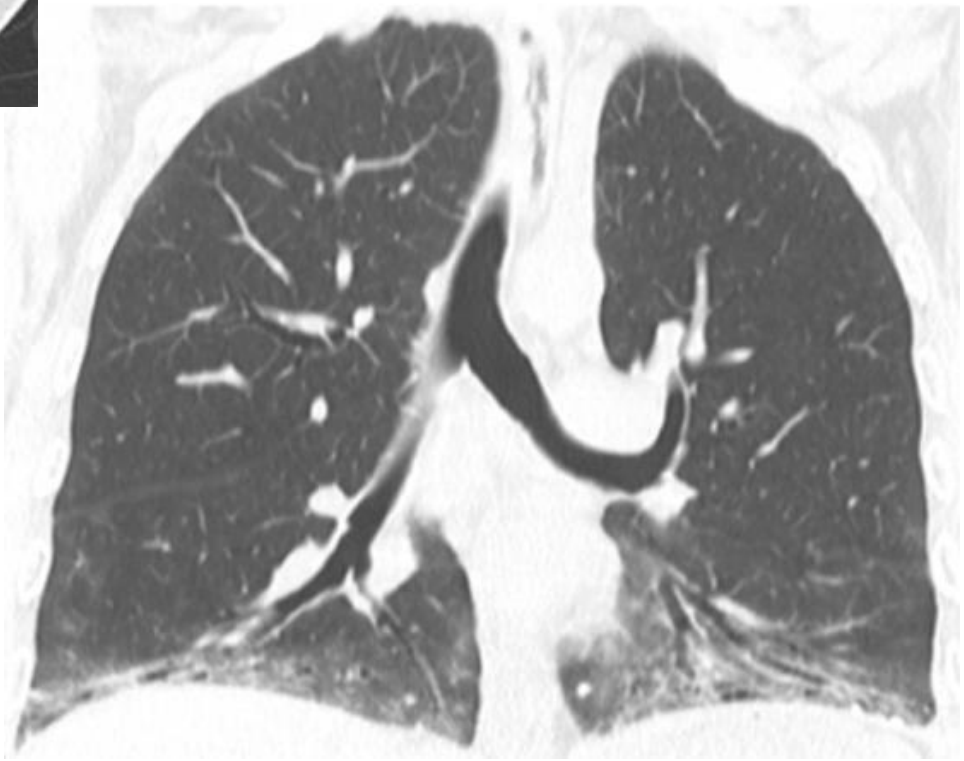
Idiopathic Nonspecific Interstitial Pneumonia

- Idiopathic vs. With associated conditions
  – CVD, HP, Drug toxicity and Familial PF
  – "MDD"

- HRCT
  Bilateral GGO
  Reticular opacities with traction bronchi(ol)ectasis
  Subpleural sparing
  Consolidation
  Honeycombing

- Histologic Features
  Predominantly fibrotic patterns

- Prognosis
  Variable, Stable or improve on treatment
  Some evolve to end-stage fibrosis and eventually die of the disease



Respiratory Bronchiolitis–Interstitial Lung Disease

- DDx. with DIP

  Histologic spectrum – extent and distribution

  Clinical presentation, imaging findings, response to therapy

- HRCT

  GGO and centrilobular nodules

- Possible diagnosis in smokers, without surgical biopsy

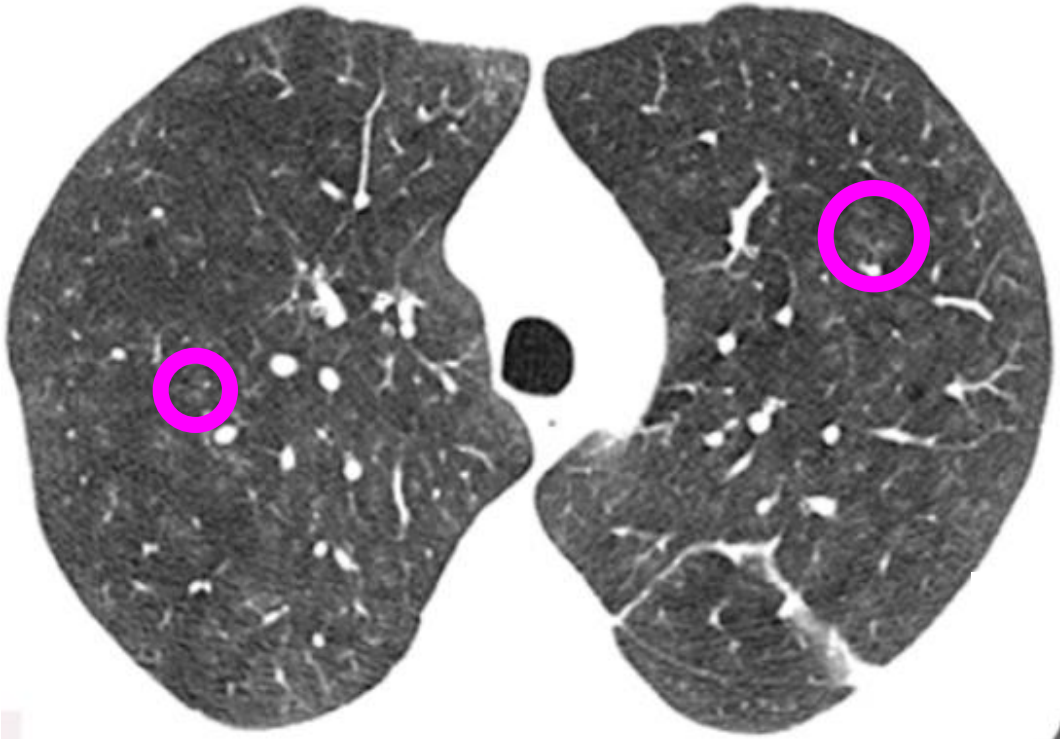
  by HRCT findings + BAL (Smokers' macrophage + Absence of lymphocytosis)

- Improve after cessation of smoking

  No report of progression to fibrosis

  Heterogeneous course

  In a significant minority, progression despite smoking cessation




Spin
Tilt . 0

Desquamative Interstitial Pneumonia

- Recognized in nonsmokers
  - Perhaps extension of childhood DIP (SP gene mutation)
- 10-year survival, approximately 70%,
  with resistance to treatment in a significant minority

Cryptogenic Organizing Pneumonia

- HRCT

  Patchy and often migratory consolidation
  in a subpleural, peribronchial or band-like pattern

  Perilobular opacities and reversed halo sign

  Rare pleural effusion → Small unilateral or bilateral in 10-30%

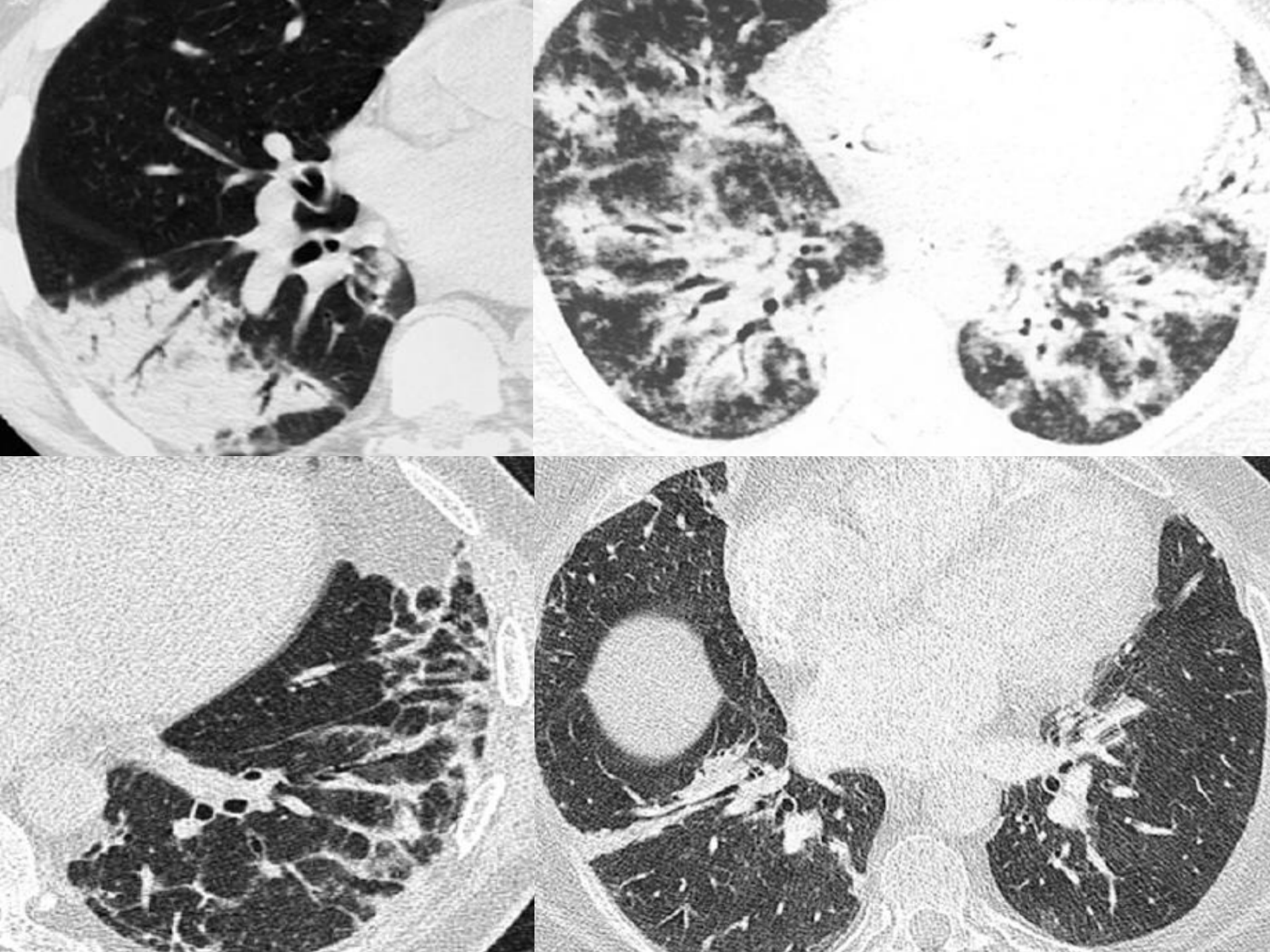
- Good response to oral corticosteroids – Majority recover completely

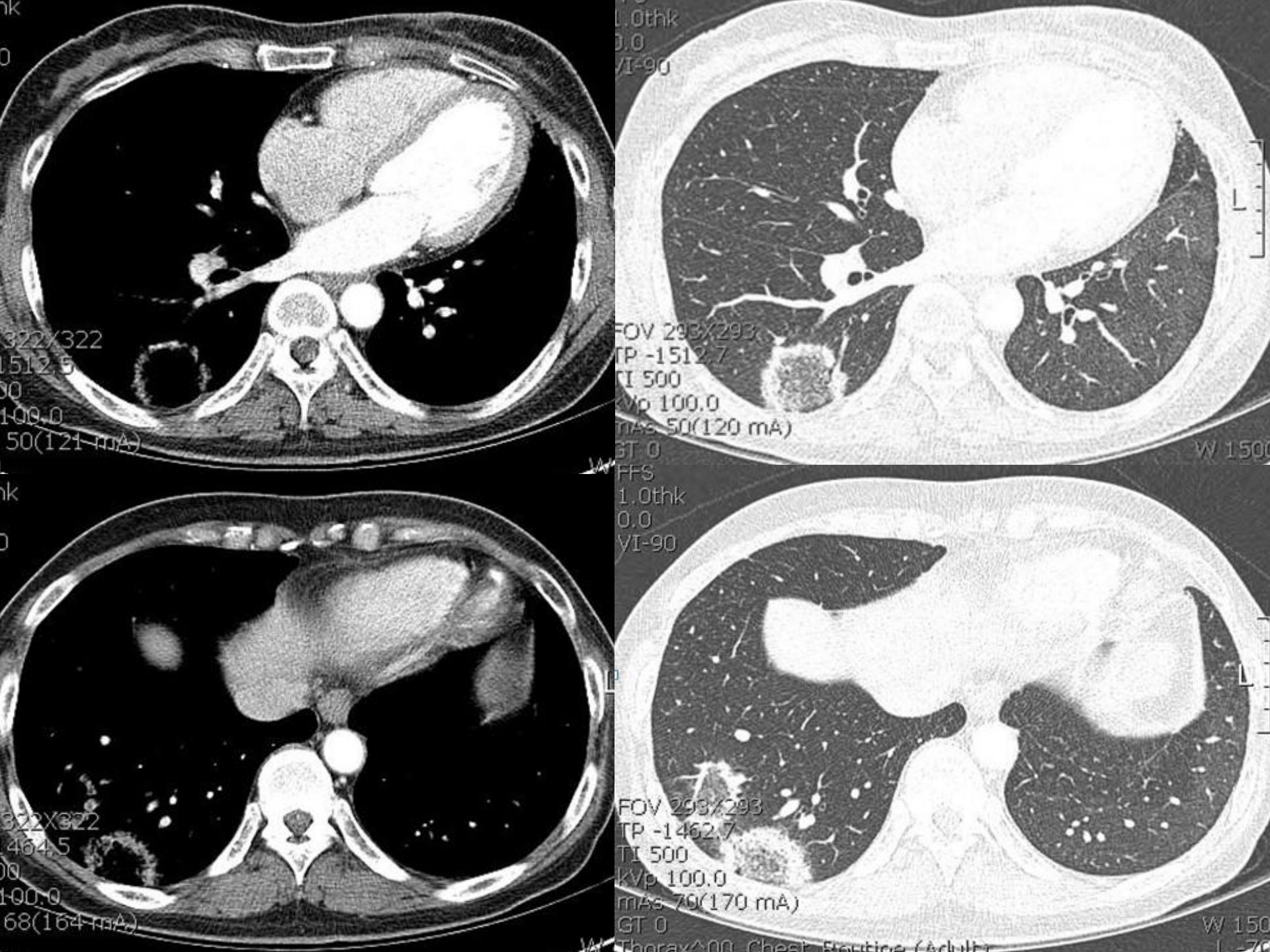
  Need at least 6 months because of frequent relapse

  Reticular opacities

  Subgroup does not completely resolve despite prolonged treatment

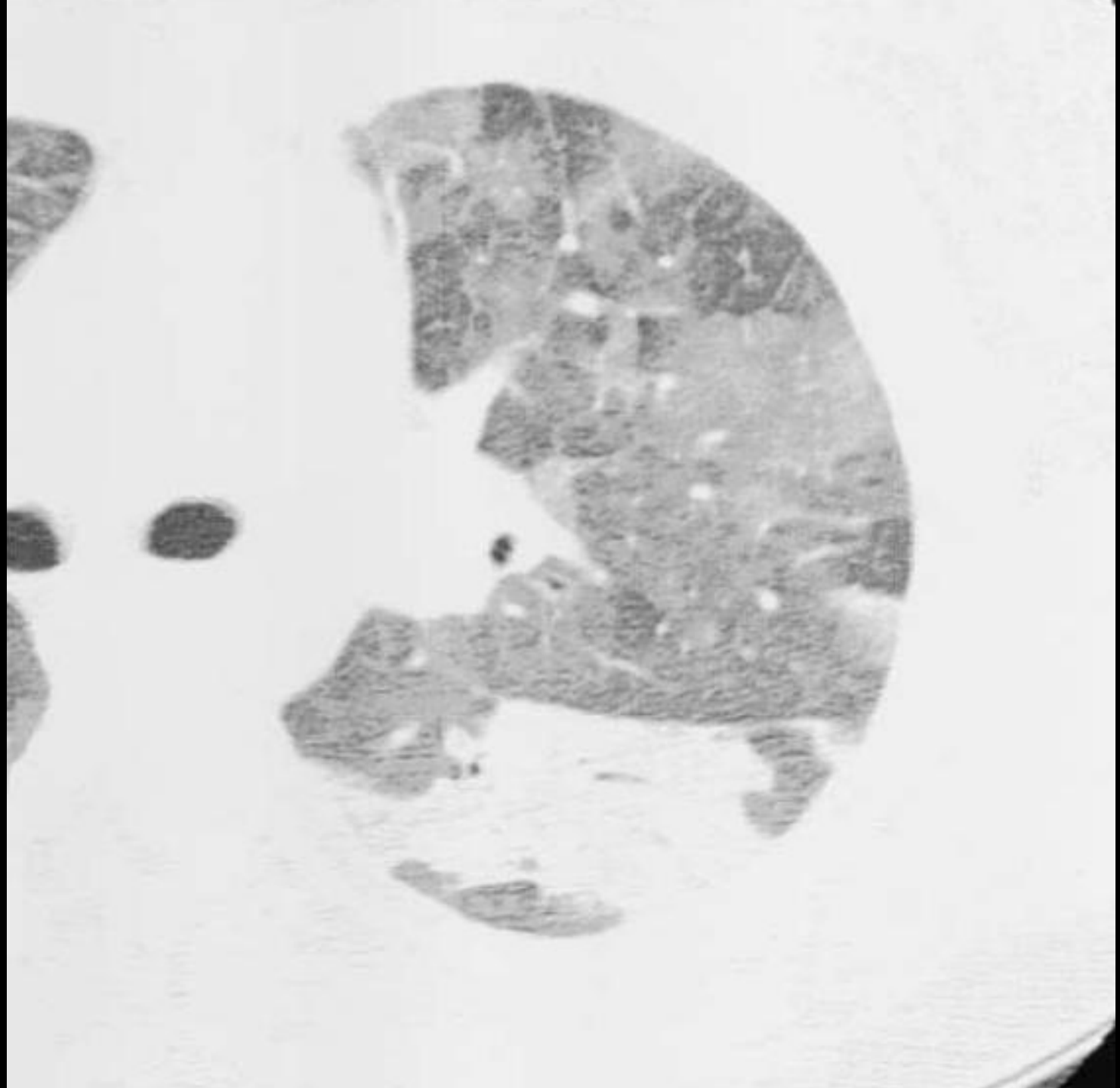
  Some are characterized by residual or progressive interstitial fibrosis
  ± recurrent episode




FOV 293X293
TP -1512.7
TI 500
kVp 100.0
mAs 50(120 mA)
GT 0
FFS
1.0thk
0.0
VI-90
FOV 293X293
TP -1462.7
TI 500
kVp 100.0
mAs 70(170 mA)
GT 0

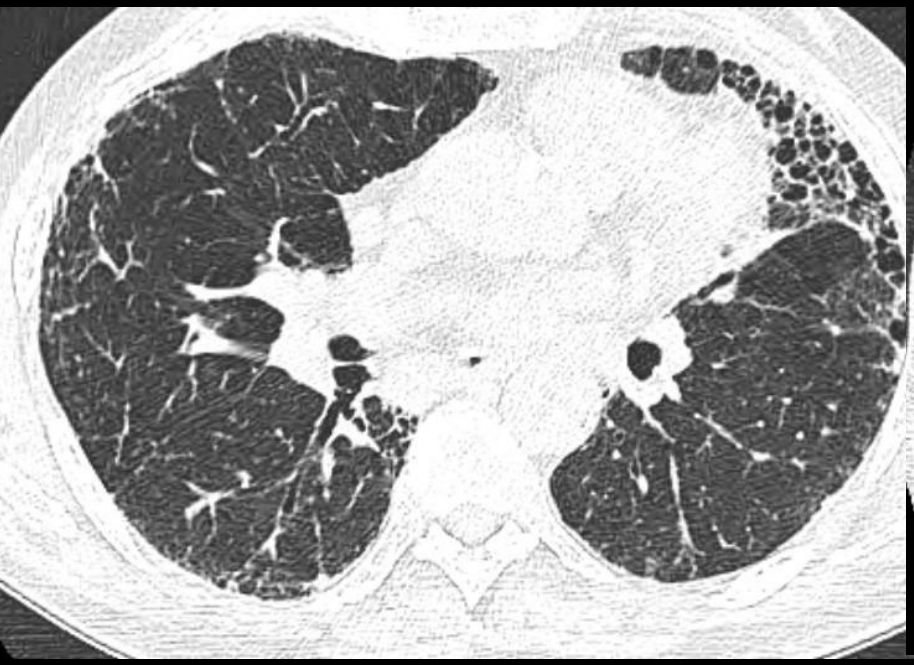
Acute Interstitial Pneumonia

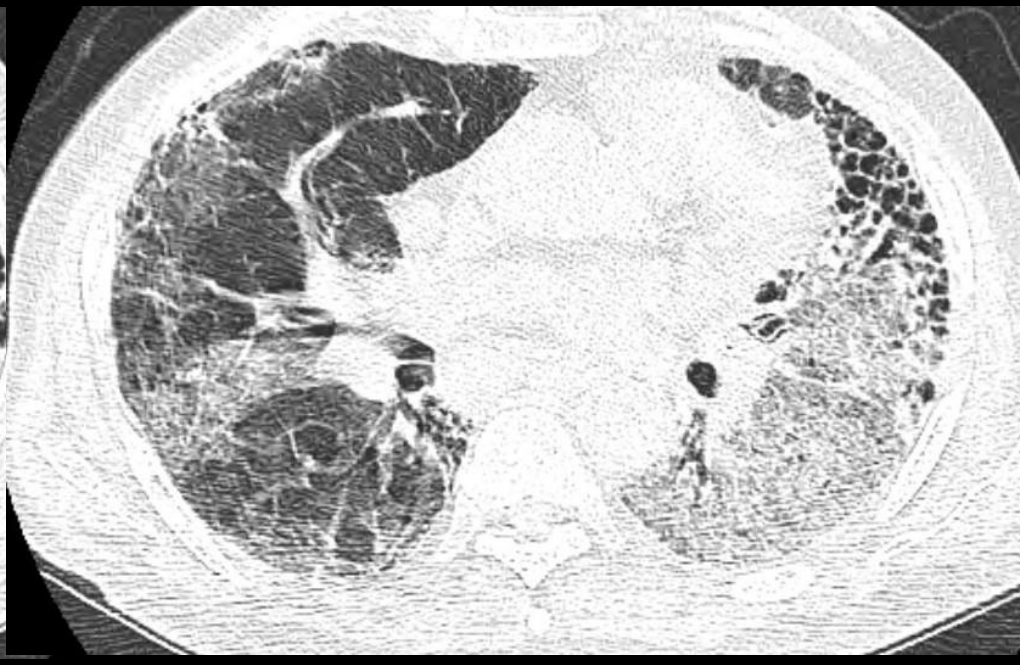
- No proven treatment with more than 50% mortality
- Survivors usually have a good long-term prognosis
  - Similar to ARDS survivors
- Some experience recurrences or chronic, progressive interstitial lung diseases
  - Progress to a pattern similar to fibrotic NSIP or to severe fibrosis resembling honeycombing

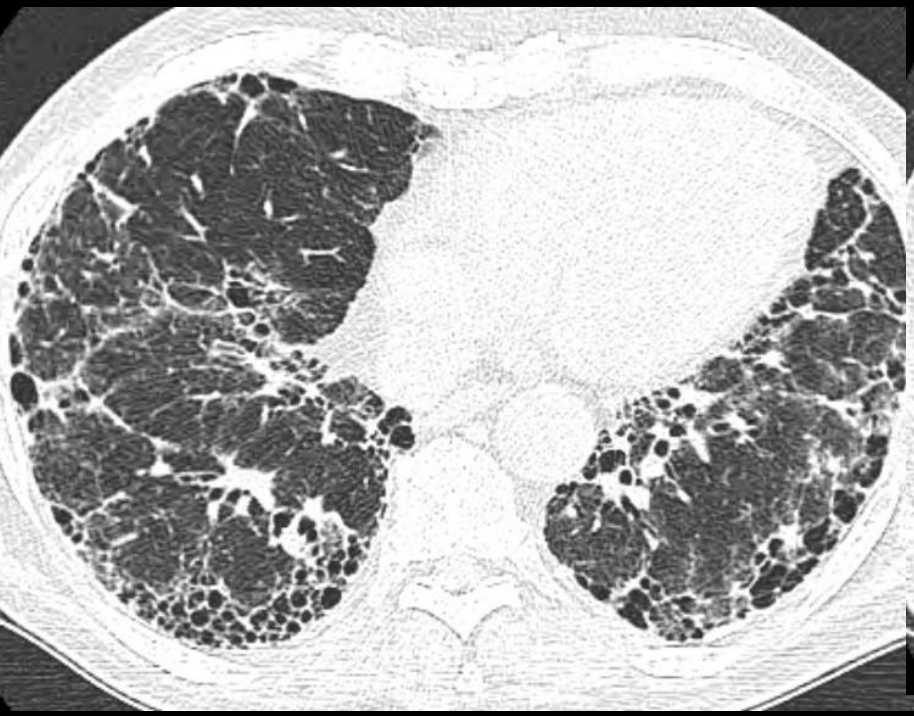


Acute Exacerbation of IIP

- Mostly in IPF, but possible in other fibrosing IPs
- Diagnostic criteria
- Acute exacerbation of IPF
  - New bilateral GGO and/or consolidation
    superimposed on a reticular pattern or honeycombing
  - Pathology
    Mixed pattern of UIP and DAD
    OP and prominent fibroblastic foci as acute component







Rare IIPs

Idiopathic lymphoid interstitial pneumonia

Idiopathic pleuropulmonary fibroelastosis (PPFE)

Idiopathic lymphoid interstitial pneumonia

- Idiopathic cases, still rare
- Unchanged criteria proposed in 2002

Idiopathic pleuropulmonary fibroelastosis (PPFE)

- Predominant upper lobes

  Fibrosis involving the pleura and subjacent lung parenchyme

  Intraalveolar fibrosis with accompanying alveolar septal elastosis

- HRCT

  Bilateral irregular pleuroparenchymal thickening

  Dense subpleural reticular pattern with fibrosis

Eur Respir J 2012;40:377-85
AJRCCM 2013;188:733-748

Idiopathic pleuropulmonary fibroelastosis (PPFE)

- Majority of cases, probably idiopathic

  Infection (aspergillosis), autoimmune, familial

- Adults with a median age of 57 yrs and no sex predilection

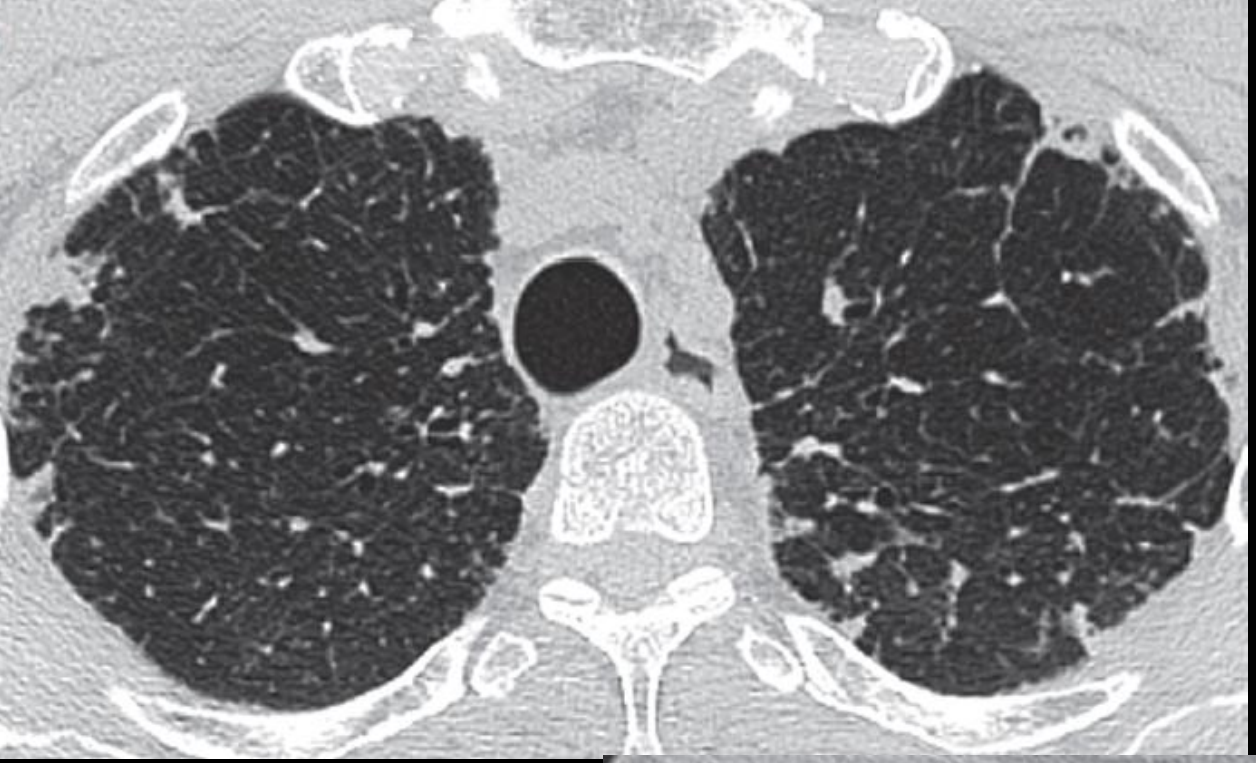
  Pneumothorax

  Recurrent infection

  Familial history of ILD and nonspecific autoantibodies

  Progressed in 60% with death from disease in 40%

Eur Respir J 2012;40:377-85
AJRCCM 2013;188:733-748



Rare Histologic Patterns

Not included as new IIP entities

because current data do not support these as distinct IIPs

Acute fibrinous and organizing pneumonia (AFOP)

Interstitial pneumonias with bronchiolocentric distribution

Acute fibrinous and organizing pneumonia (AFOP)

- Acute or subacute clinical setting of DAD or OP
  but differs from the classic histologic criteria of them

- Histology

  Organizing intraalveolar fibrin deposition (fibrin ball)

  + Associated OP

  – Typically patchy distribution

    No classical hyaline membranes of DAD

  – Intraalveolar fibrin-like pattern in EP

Arch Pathol Lab Med 2002;126:1064-70
AJRCCM 2013;188:733-748

Acute fibrinous and organizing pneumonia (AFOP)

- HRCT

  Bilateral basal opacities and areas of consolidation

- Idiopathic

  Associated with CVD, HP, or drug reaction

- Onset of dyspnea, fever, cough and hemoptysis

  2 distinct patterns of progression and outcome

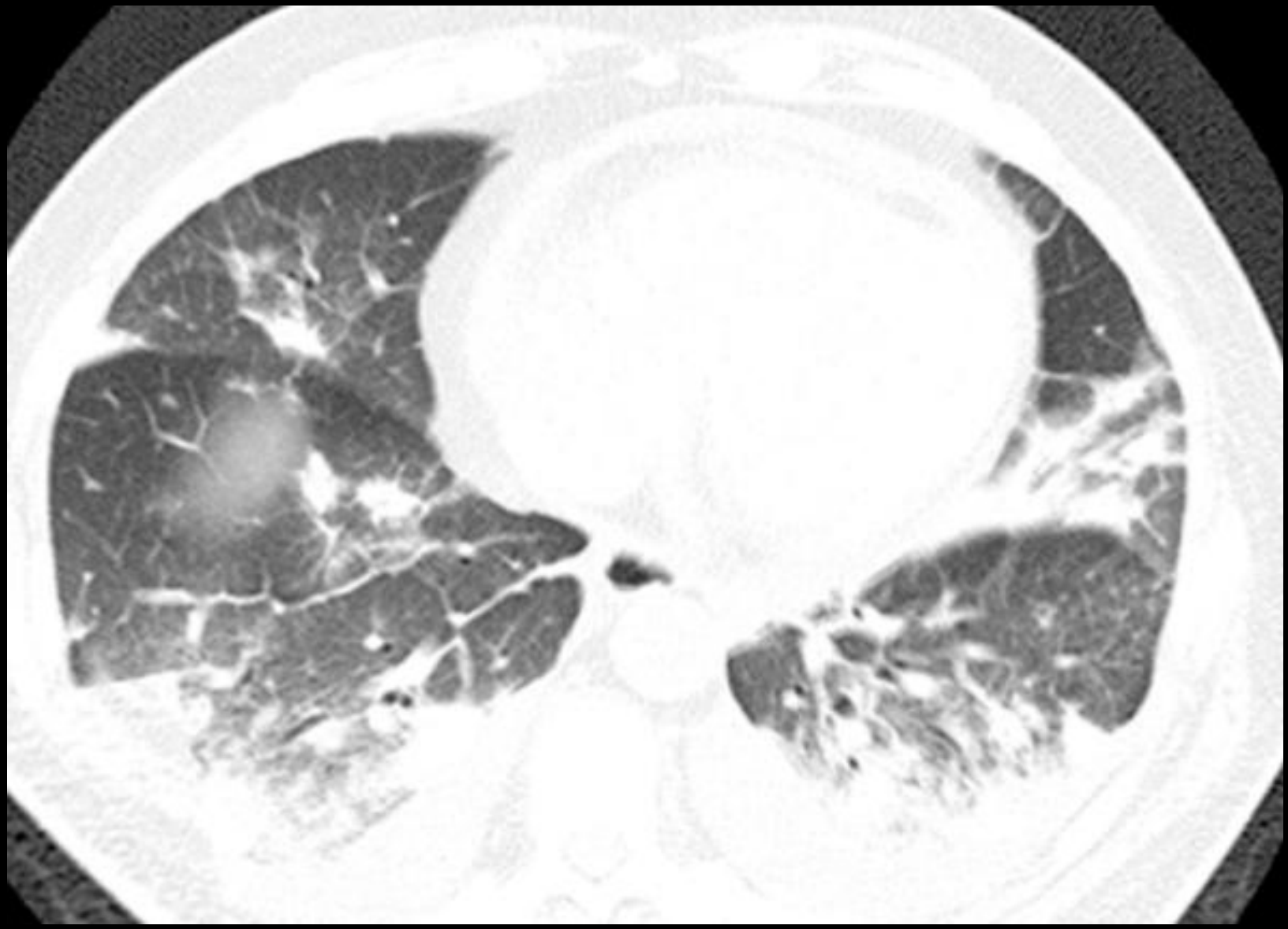
  – Acute or subacute

  – Mechanical ventilation (30%)

  Overall mortality rate, similar to DAD ($>$ 50%)

Arch Pathol Lab Med 2002;126:1064-70

AJRCCM 2013;188:733-748



Interstitial pneumonias with bronchiolocentric distribution

Idiopathic Bronchiolocentric Interstitial Pneumonia

Mod Pathol 2002;15(11):1148–1153

Airway-centered Interstitial Fibrosis

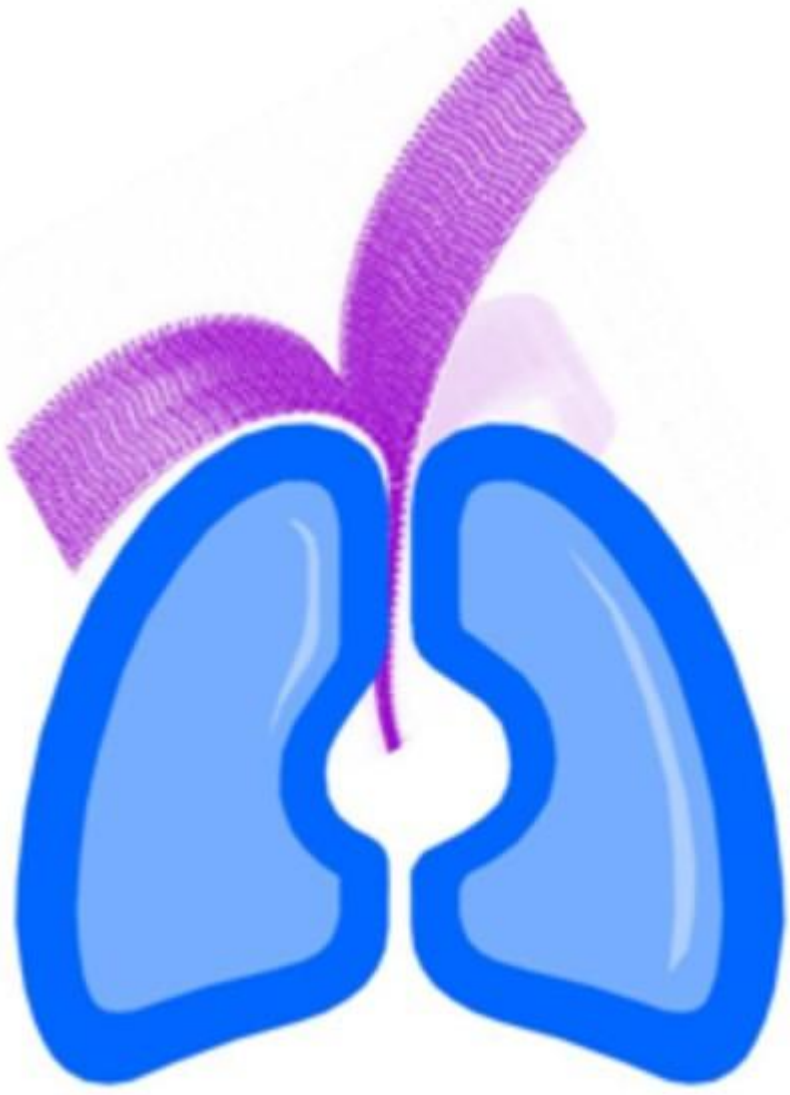
A Distinct Form of Aggressive Diffuse Lung Disease

Am J Surg Pathol 2004;28:62–68

Peribronchiolar Metaplasia: A Common Histologic Lesion in Diffuse Lung Disease and a Rare Cause of Interstitial Lung Disease

Clinicopathologic Features of 15 Cases

Am J Surg Pathol 2005;29:948–954



Living With Pulmonary Fibrosis

The **Pulmonary Fibrosis Trust** exists to help people who are "Living with Pulmonary Fibrosis".

This support may be emotional support, financial support, or practical support.