CT in the Diagnosis of Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

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No Relevant Disclosures

Weill Cornell Medicine
Radiology

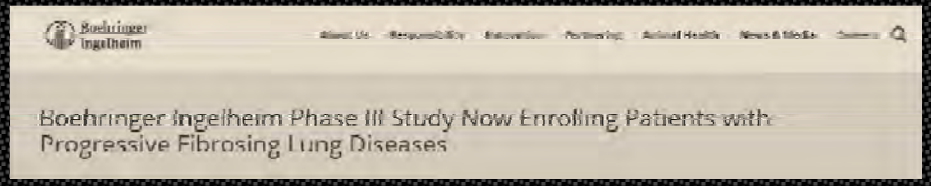
Concept of PF-ILD

- "The response to lung injury includes the initial development of fibrosis that becomes progressive, self-sustaining, and independent of the original clinical association or trigger"

Flaherty KR, Brown KK, Wells AU, *et al*. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. *BMJ* 2017

Nintedanib PF-ILD Trial

- Enrolling patients with *various fibrosing lung diseases (PF-ILDs)*
- First trial to group patients based on the clinical *behavior* of their disease
- Need “scarring” on CT and clinical progression



https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-phase-iii-study-now-enrolling-patients-progressive-fibrosing-lung

CT Findings of Fibrosis

severity

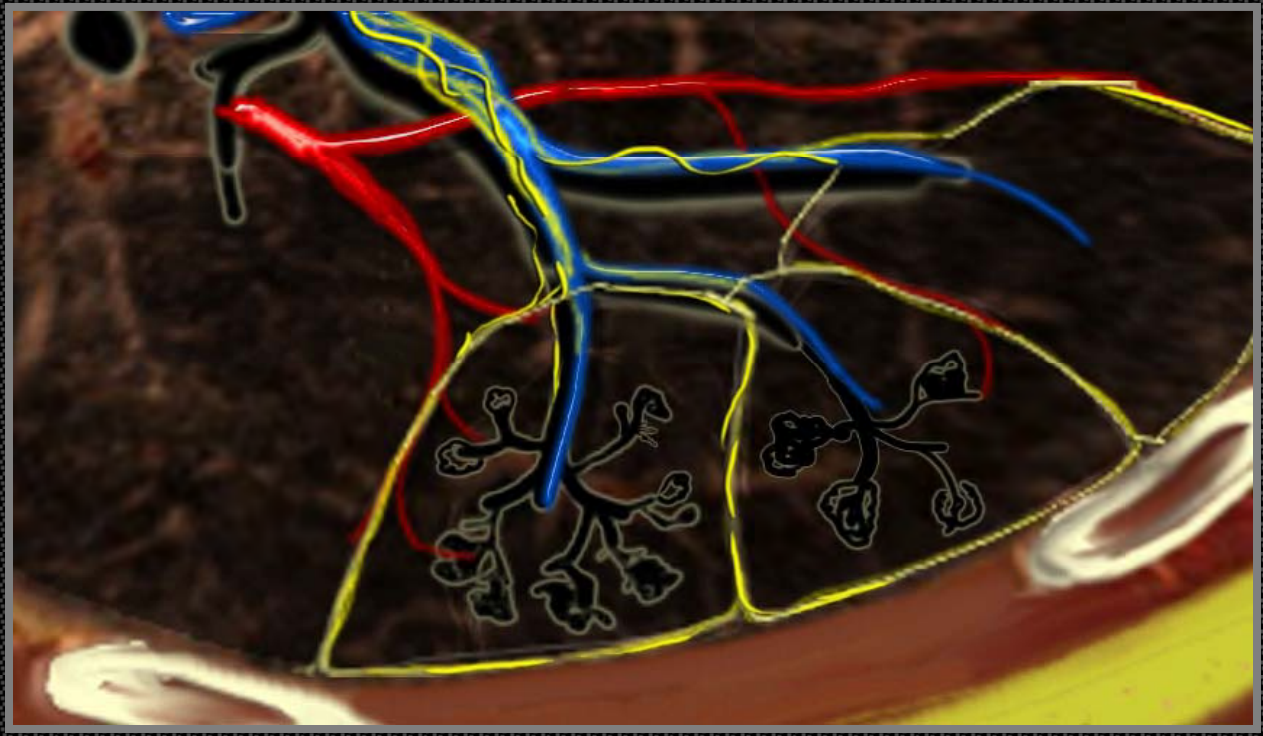
- Reticulation
  - Interlobular septal thickening
  - Intralobular lines
  - Lobular distortion, irregular interfaces
- Traction bronchiectasis or bronchiolectasis
- Honeycombing (HC)

More severe, less reversible

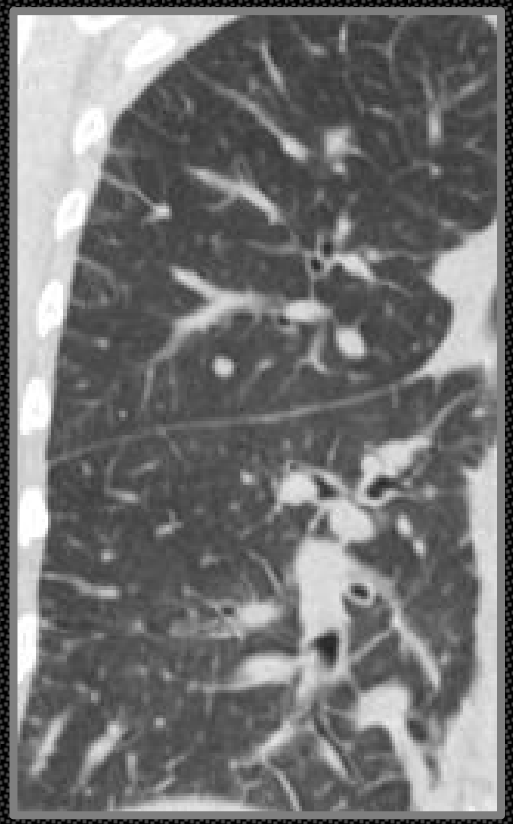
GGO may also indicate fibrosis alone when superimposed on the above findings

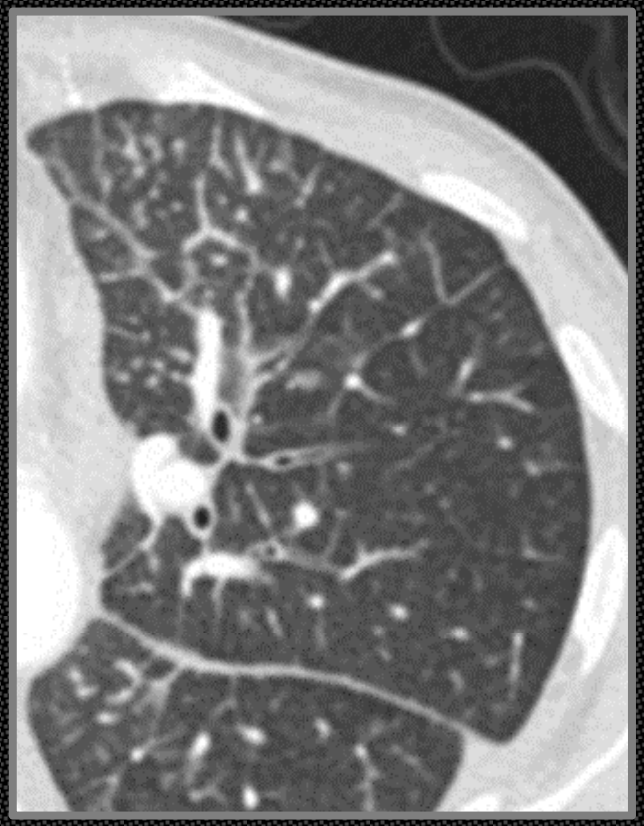
Interstitial Anatomy in Yellow

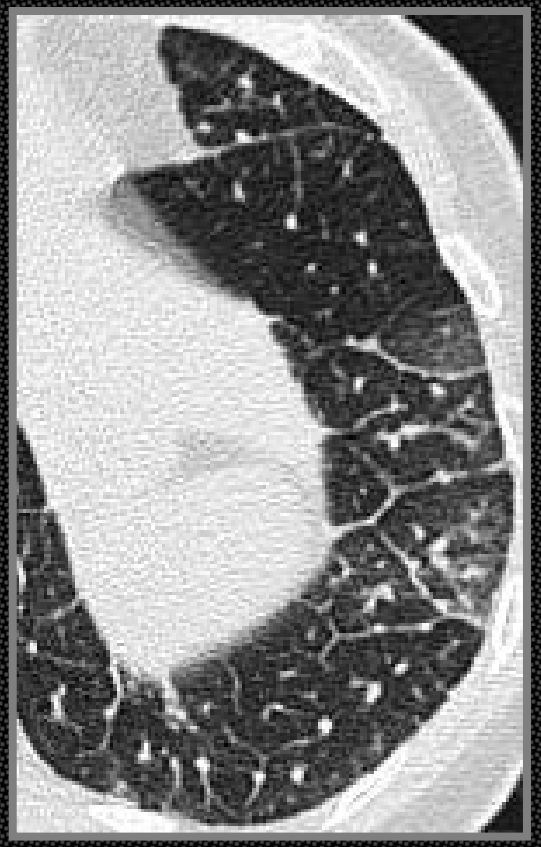
From Smithuis et al. in The Radiology Assistant, Radiologic Society of The Netherlands



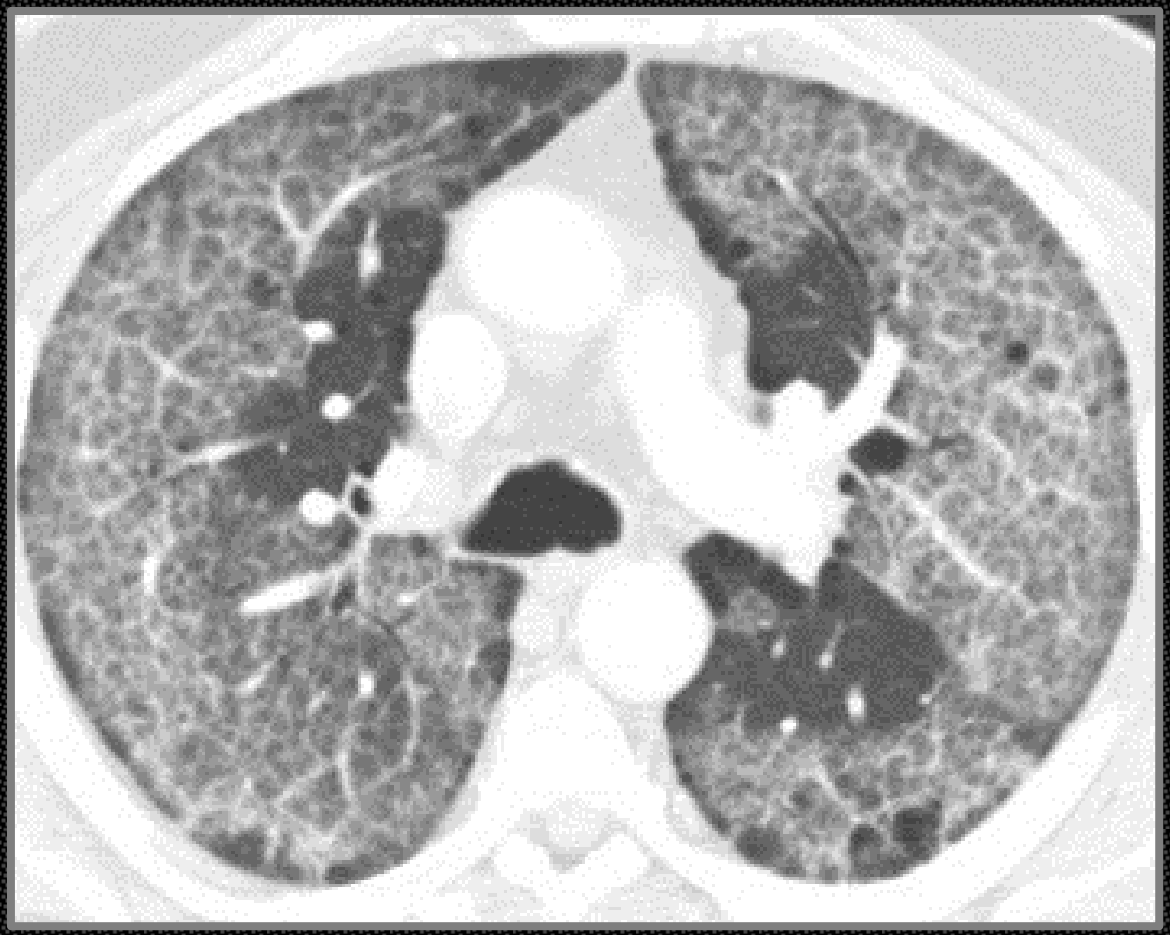
Interlobular Septal Thickening



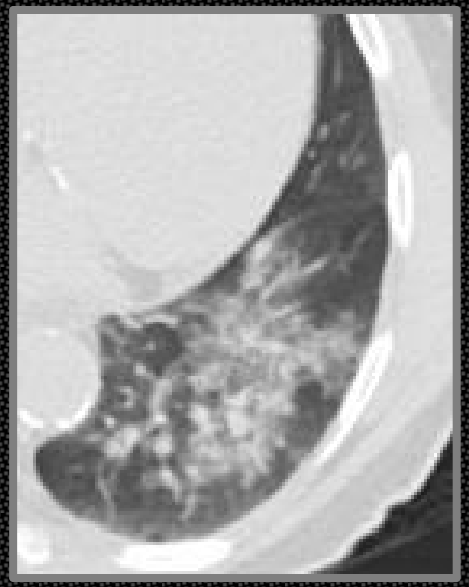


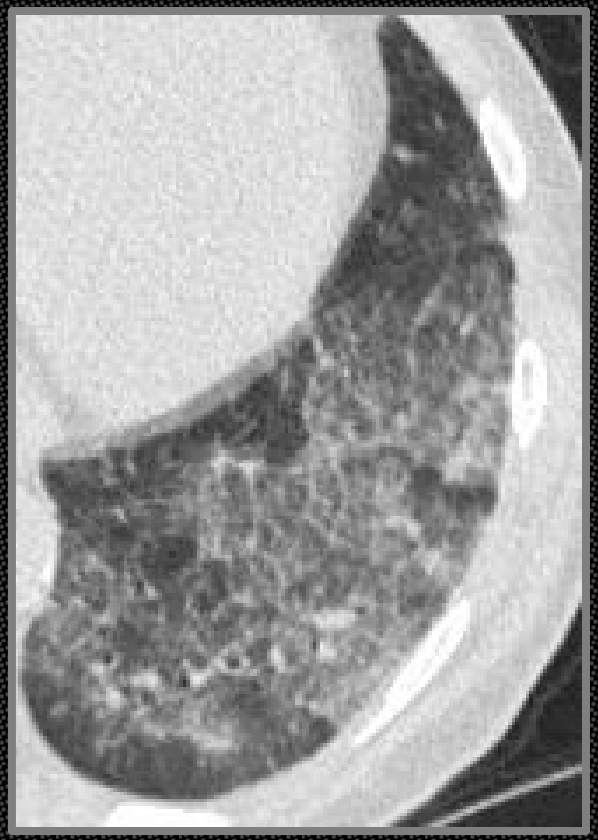


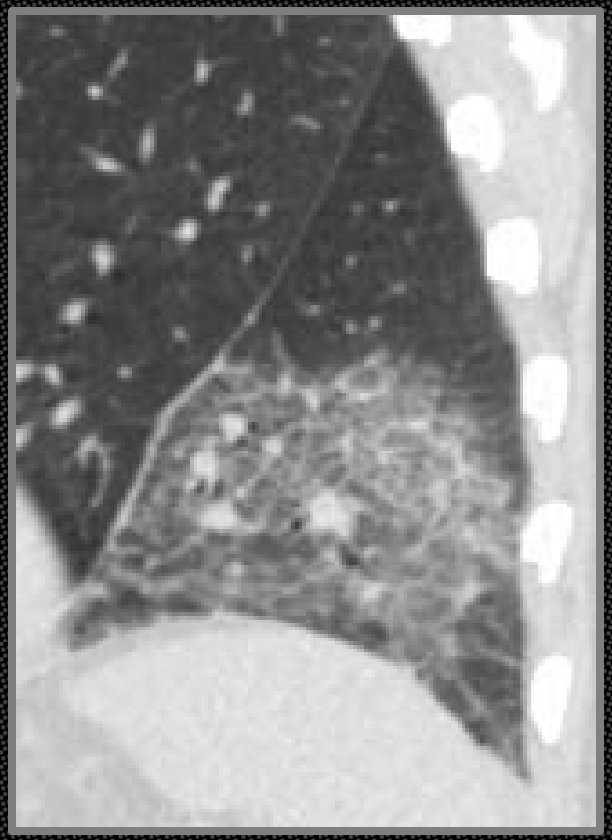
Reticulation: Intralobular Lines



Intralobular Lines: Onset of Fibrosis







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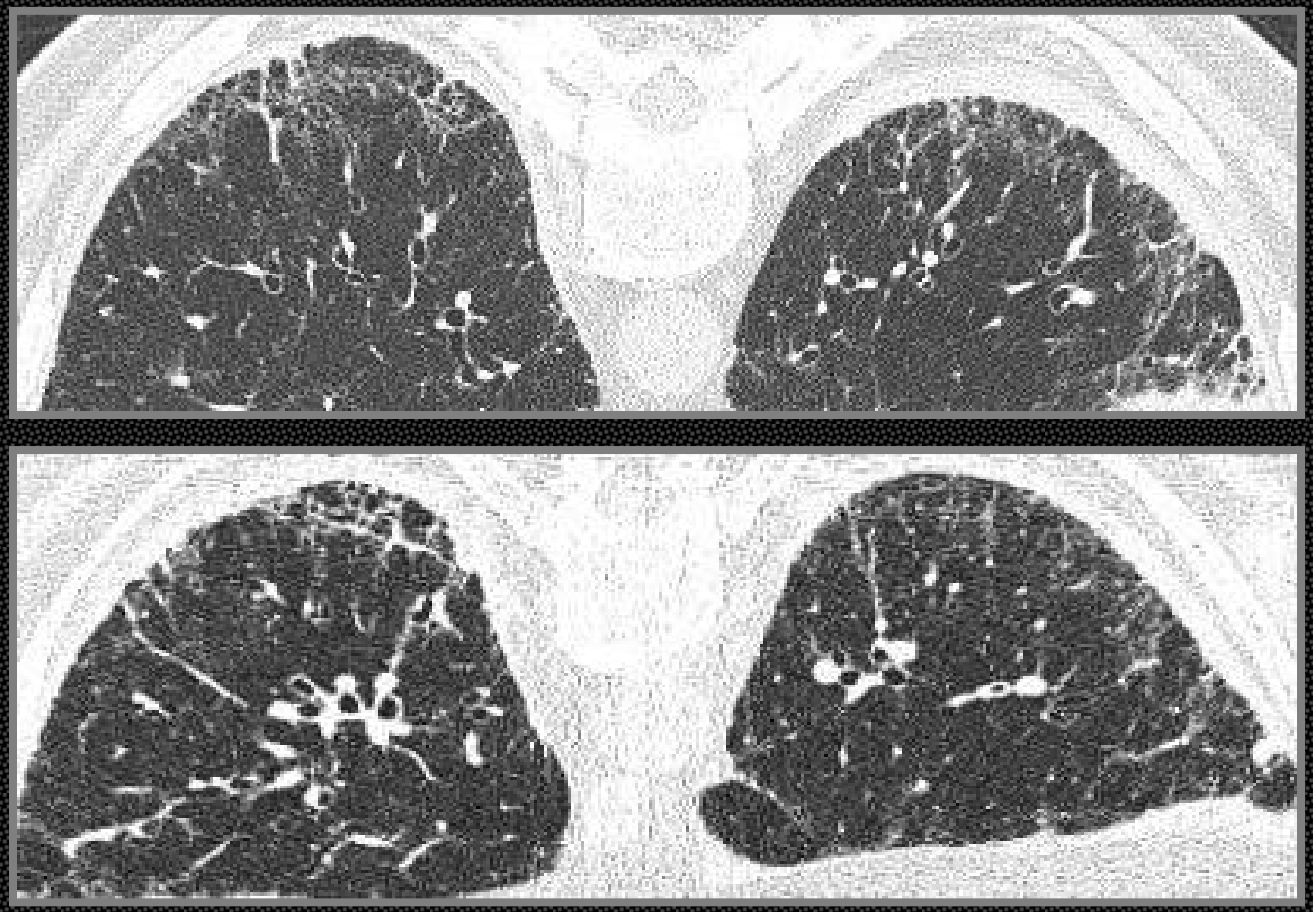
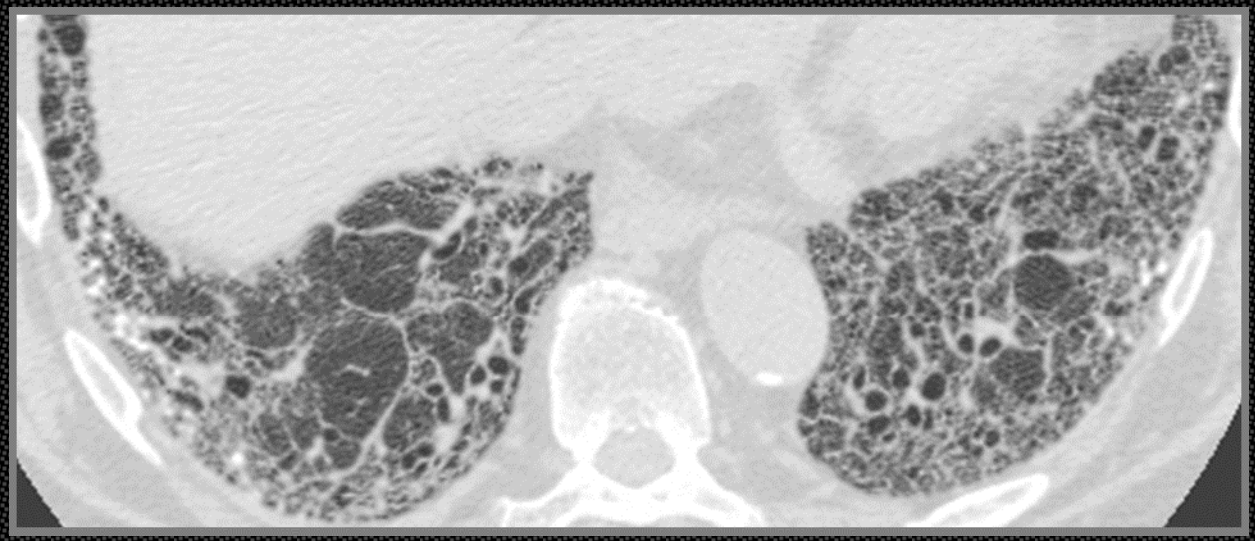
Reticulation: Lobular Distortion



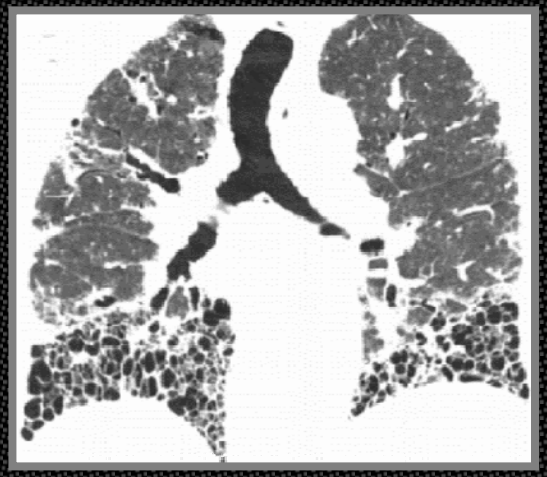
Traction Bronchiolectasis

"irregular dilatation caused by surrounding retractile pulmonary fibrosis seen as cysts (bronchi) or microcysts (bronchioles)"



Honeycombing (HC)

" Clustered cystic spaces, typically of comparable diameters on the order of 3-10 mm, but occasionally as large as 2.5 cm, *usually subpleural* and characterized by well-defined walls"



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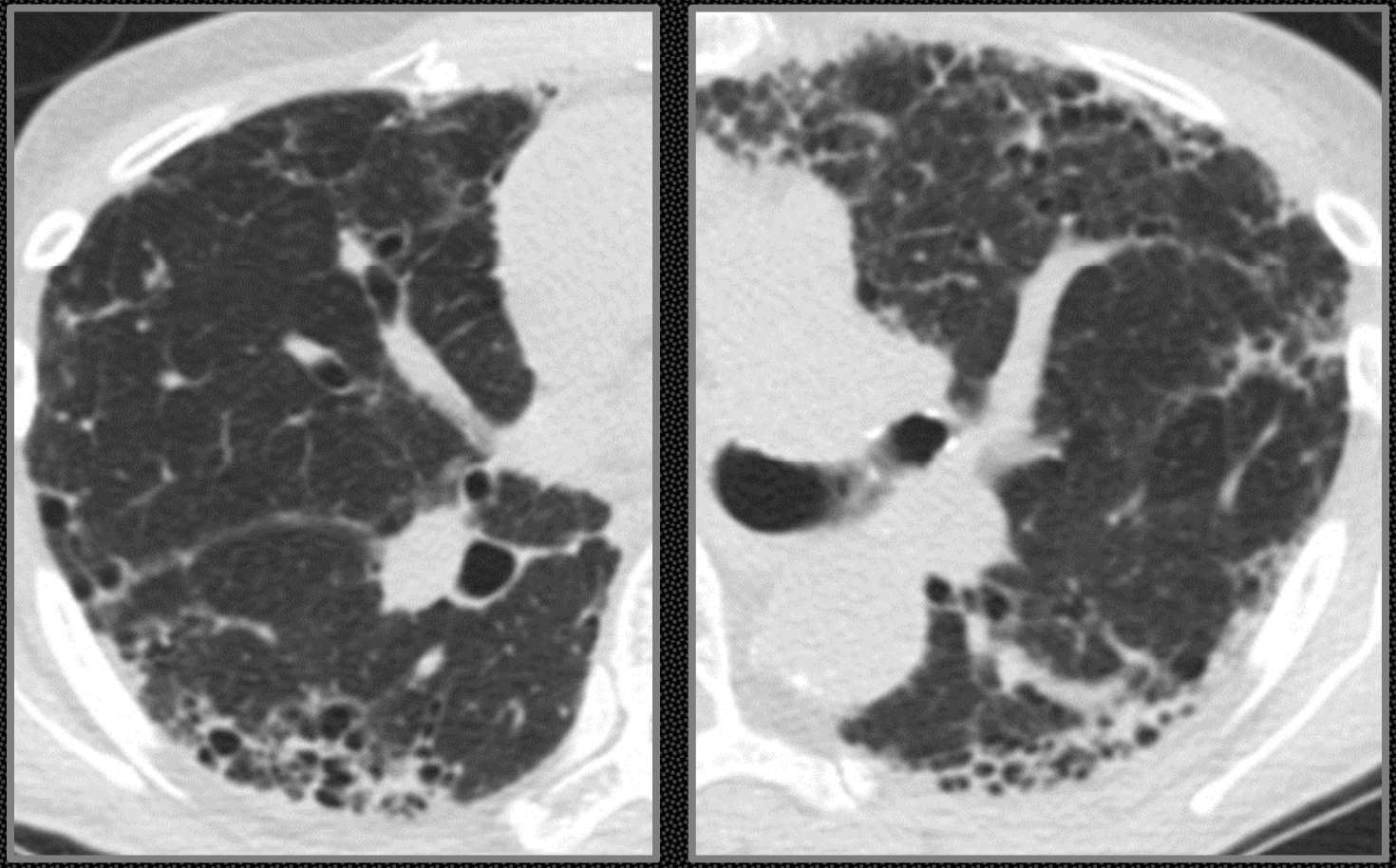
Traction and HC: Advanced Fibrosis



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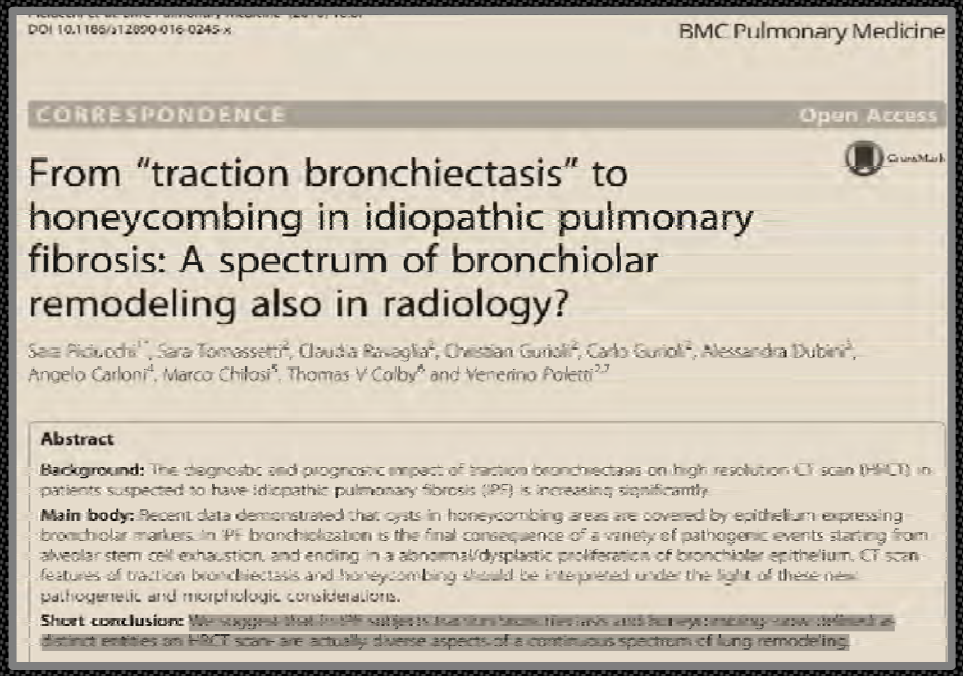
Traction and HC as a Continuum



DOI 10.1186/s12890-016-0245-x

BMC Pulmonary Medicine

CORRESPONDENCE Open Access

From "traction bronchiectasis" to honeycombing in idiopathic pulmonary fibrosis: A spectrum of bronchiolar remodeling also in radiology?

Sara Piciucchi[1*], Sara Tomassetti[2], Claudia Ravaglia[2], Christian Gurioli[2], Carlo Gurioli[2], Alessandra Dubini[2], Angelo Carloni[2], Marco Chilosi[3], Thomas V Colby[4] and Venerino Poletti[2,3]

Abstract

Background: The diagnostic and prognostic impact of traction bronchiectasis on high resolution CT scan (HRCT) in patients suspected to have idiopathic pulmonary fibrosis (IPF) is increasing significantly.

Main body: Recent data demonstrated that cysts in honeycombing areas are covered by epithelium expressing bronchiolar markers. In IPF bronchiolization is the final consequence of a variety of pathogenic events starting from alveolar stem cell exhaustion, and ending in a abnormal/dysplastic proliferation of bronchiolar epithelium. CT scan features of traction bronchiectasis and honeycombing should be interpreted under the light of these new pathogenetic and morphologic considerations.

Short conclusion: [illegible] distinct entities on HRCT scans are actually diverse aspects of a continuous spectrum of lung remodeling.

"Honeycombing and traction bronchiectasis/ bronchiolectasis, previously defined separately, represent diverse aspect of a continuous spectrum"

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More severe, less reversible

GGO may also indicate fibrosis alone when superimposed on the above findings

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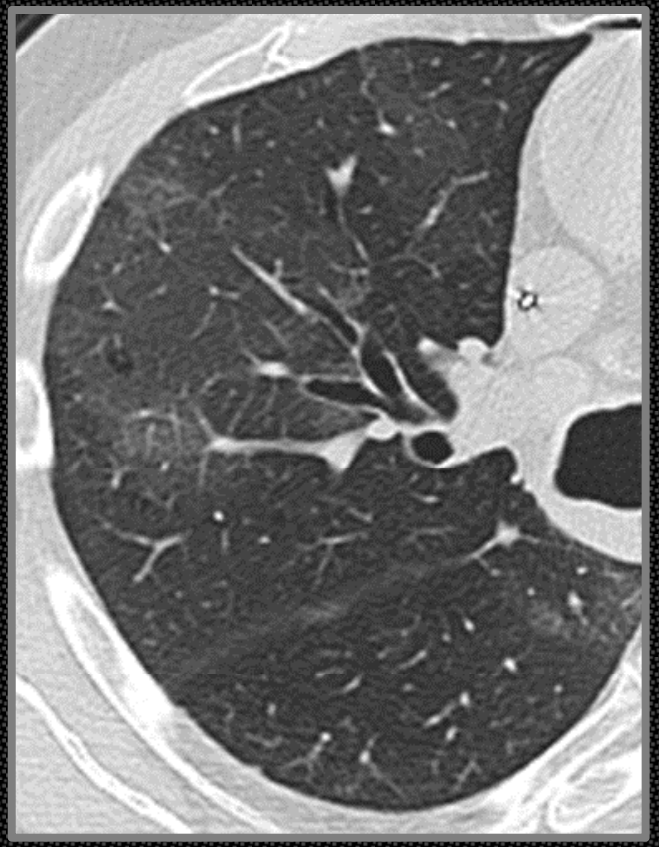
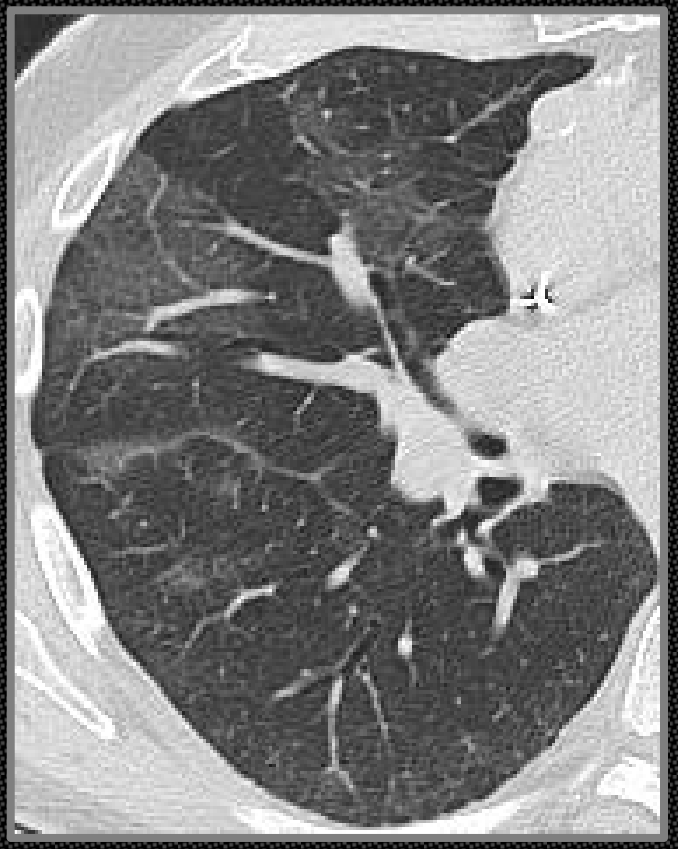
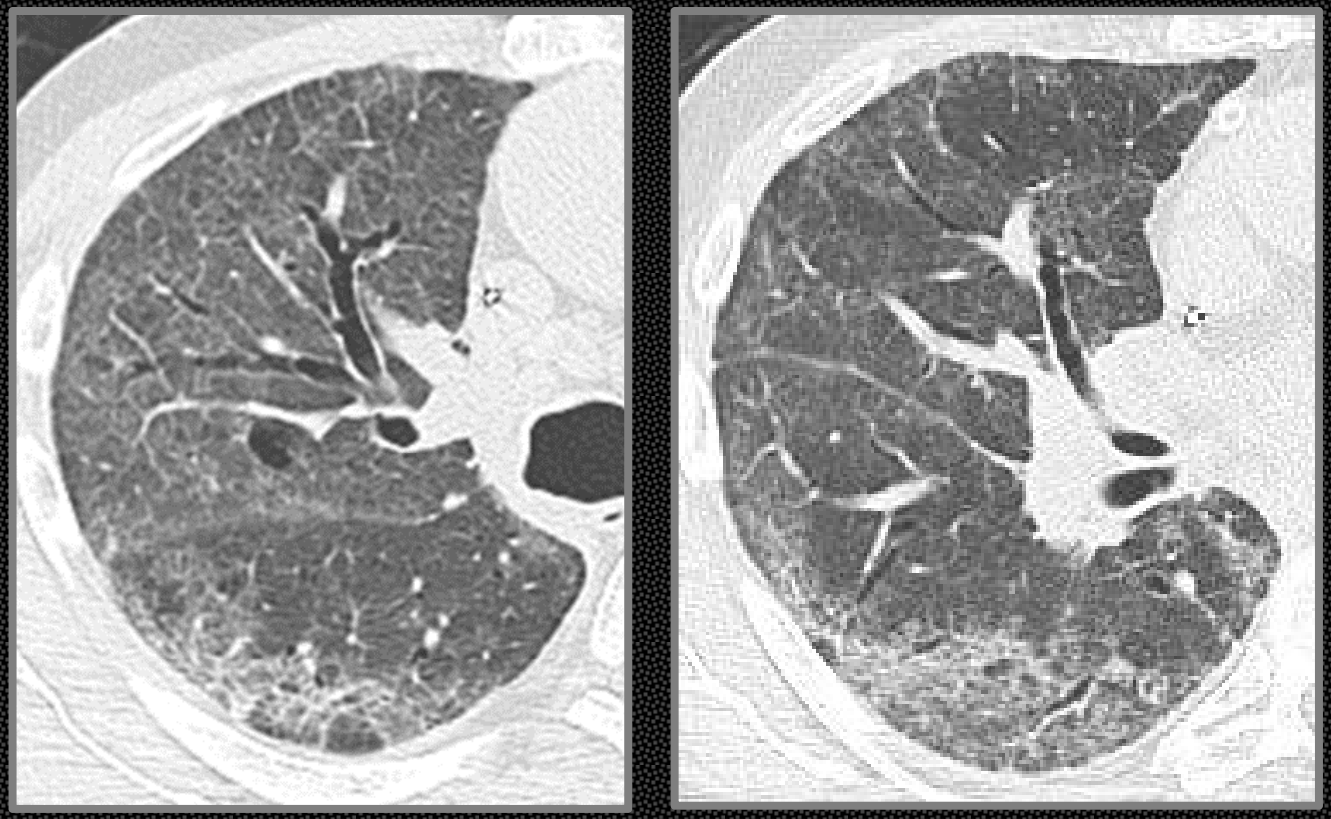
GGO without Fibrosis

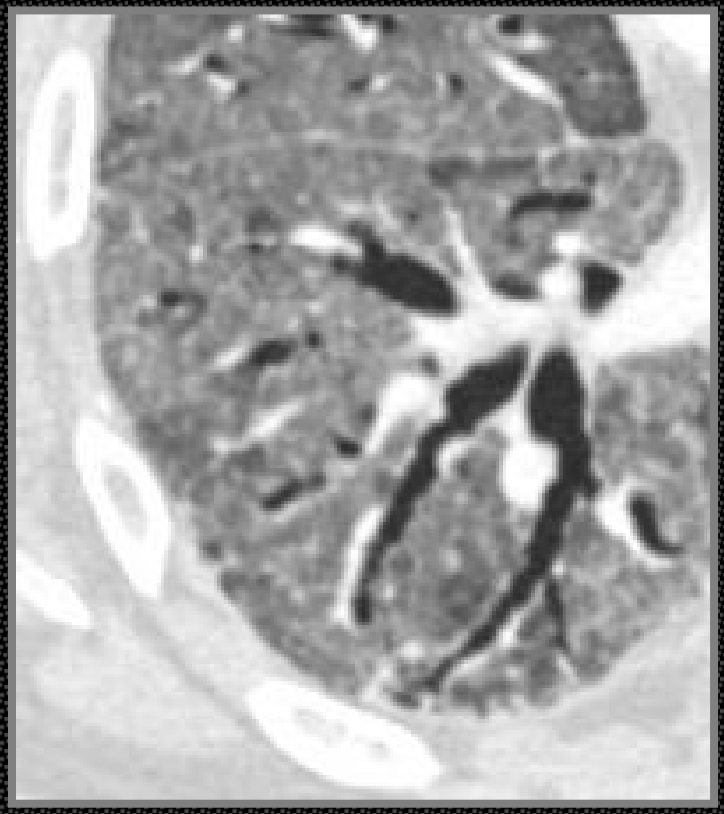


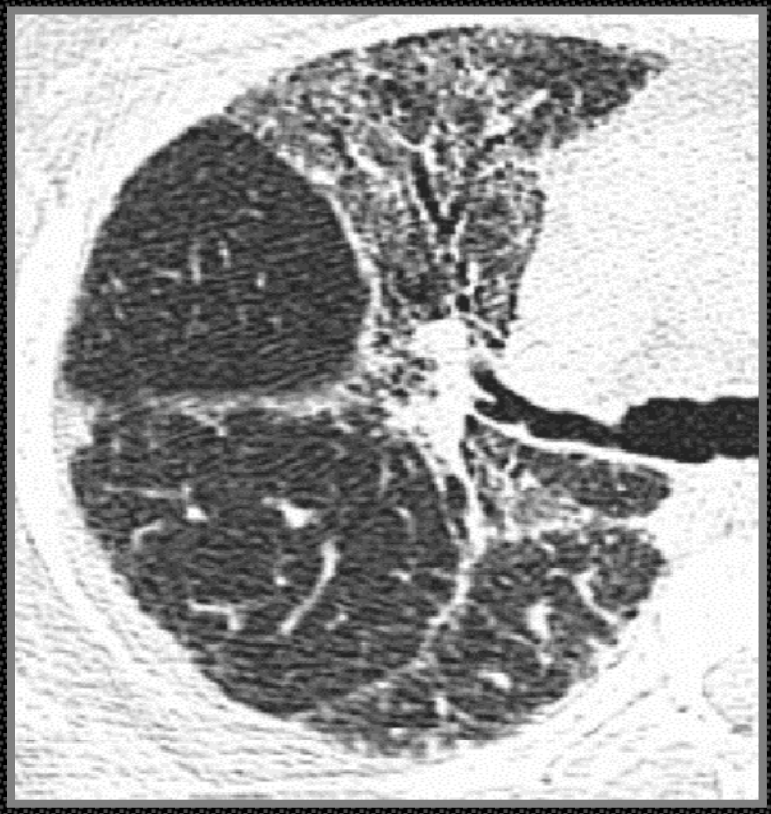


GGO with Fibrosis

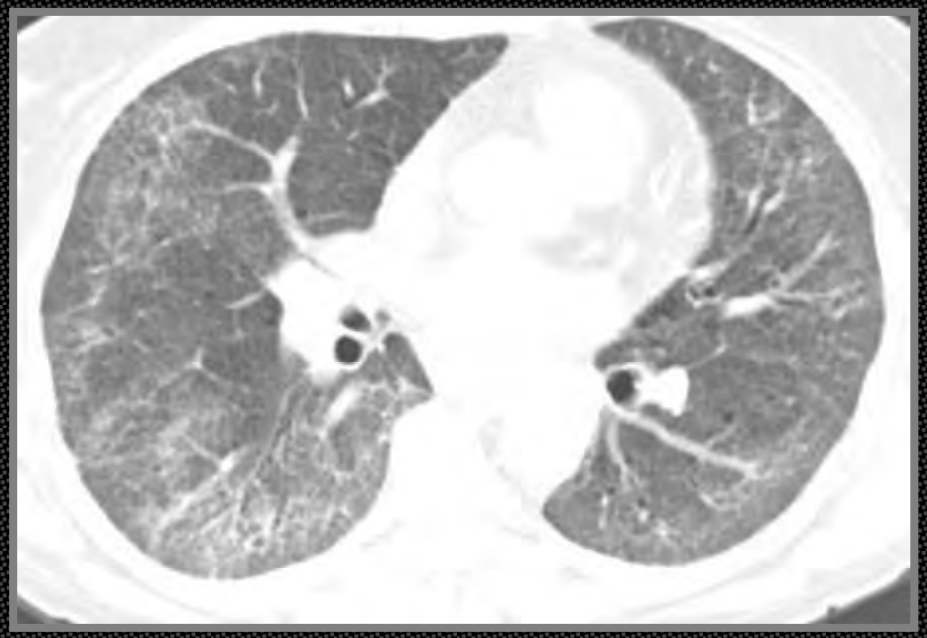


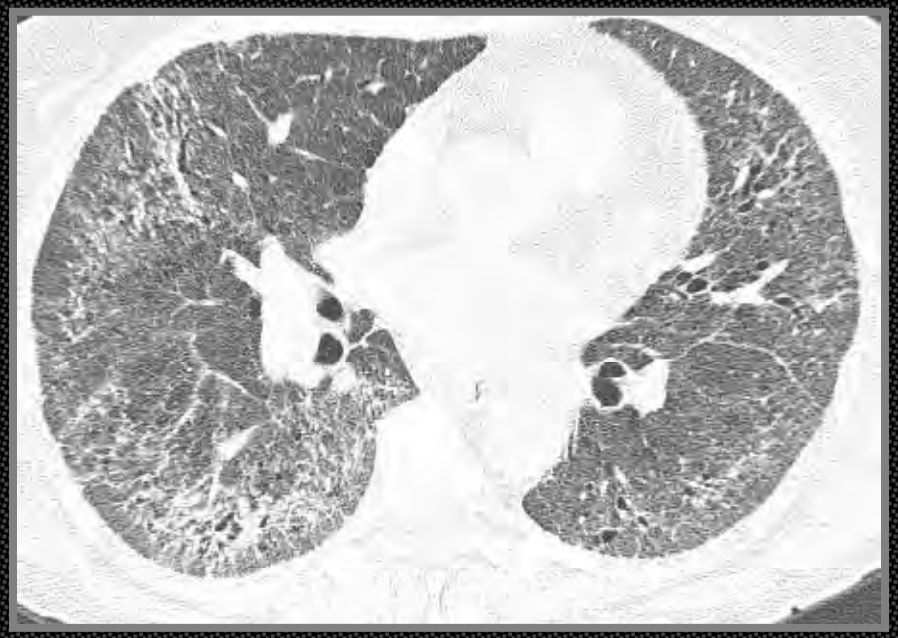
GGO with Fibrosis





GGO and Collimation





Question

- Ground glass opacity (GGO) indicates
  - A. Interstitial disease
  - B. Airspace disease
  - C. Reversible disease
  - D. Irreversible disease
  - E. Something beneath the resolution of CT

CT Findings of Fibrosis

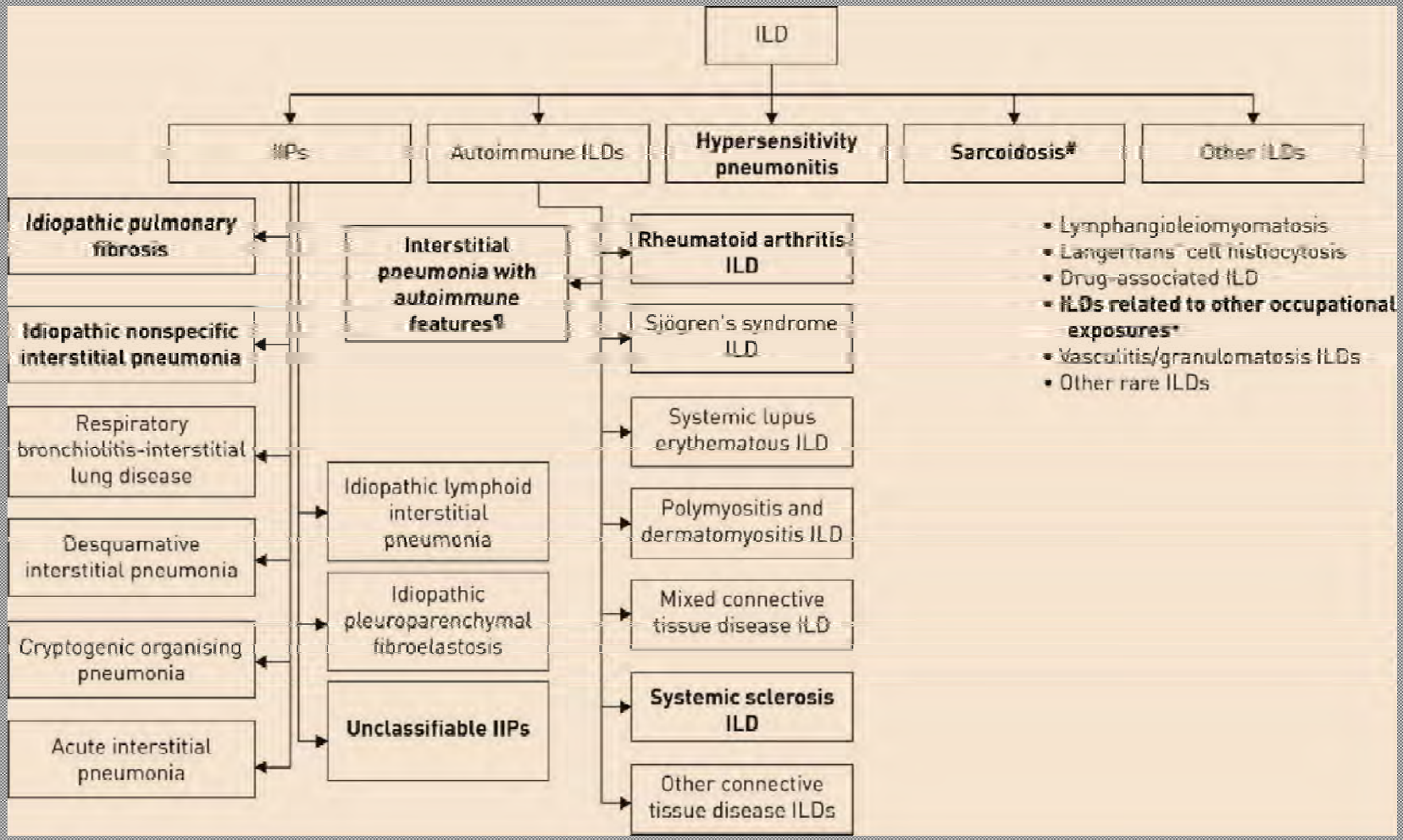
severity

- Reticulation
  - Interlobular septal thickening
  - Intralobular lines
  - Lobular angulation, irregular interfaces
- *Traction bronchiectasis or bronchiolectasis, honeycombing (HC)*

More severe, less reversible

GGO may also indicate fibrosis alone when superimposed on the above findings

Types of interstitial lung disease (ILD) most likely to have a progressive-fibrosing phenotype (indicated in bold)

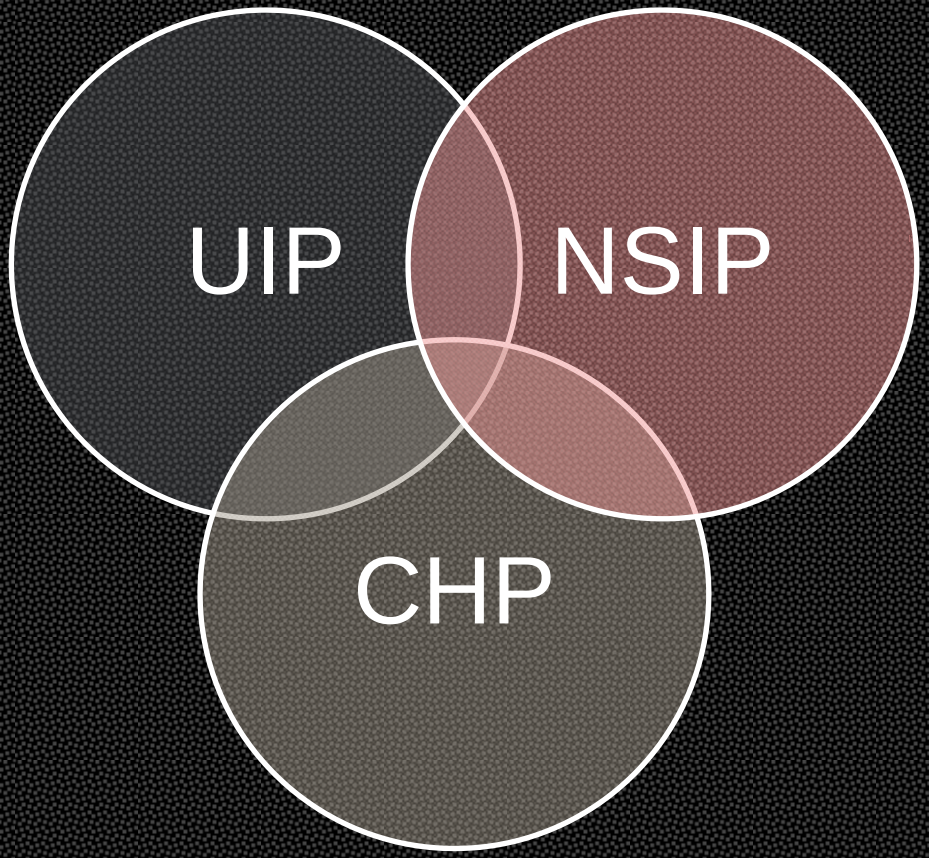


Cottin V *et al*. *Eur Respir Rev* 2018;27:180076

PF-ILD

- Usual interstitial pneumonia (UIP)
- Chronic hypersensitivity pneumonitis (CHP)
- Nonspecific interstitial pneumonia (NSIP)

Patterns of PF-ILD



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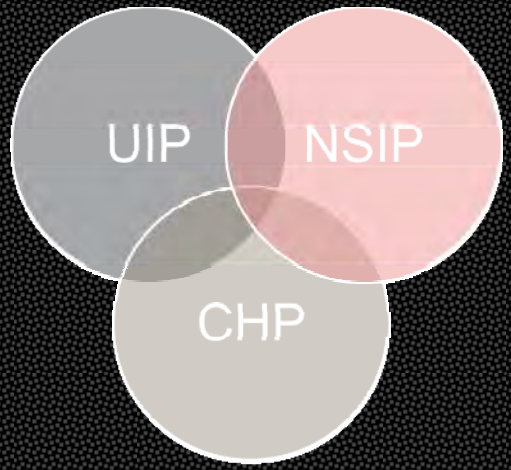
PF-ILD: Causes

- Usual interstitial pneumonia (UIP)
- Chronic hypersensitivity pneumonitis (CHP)
- Nonspecific interstitial pneumonia (NSIP)



UIP Pattern

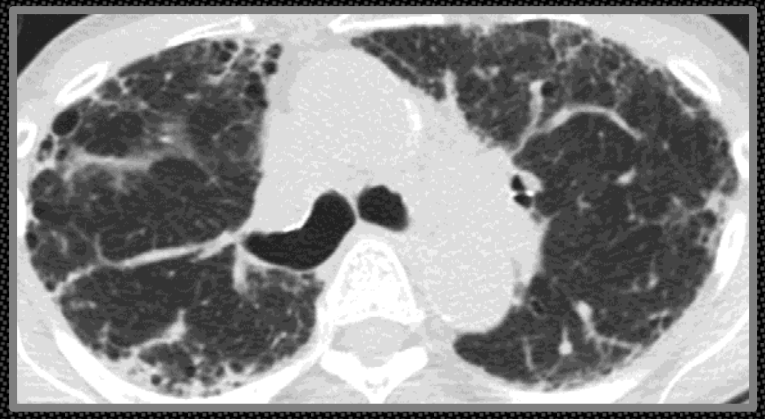
- Idiopathic (IPF)
- CVD
- Asbestosis
- Drug toxicity
- CHP

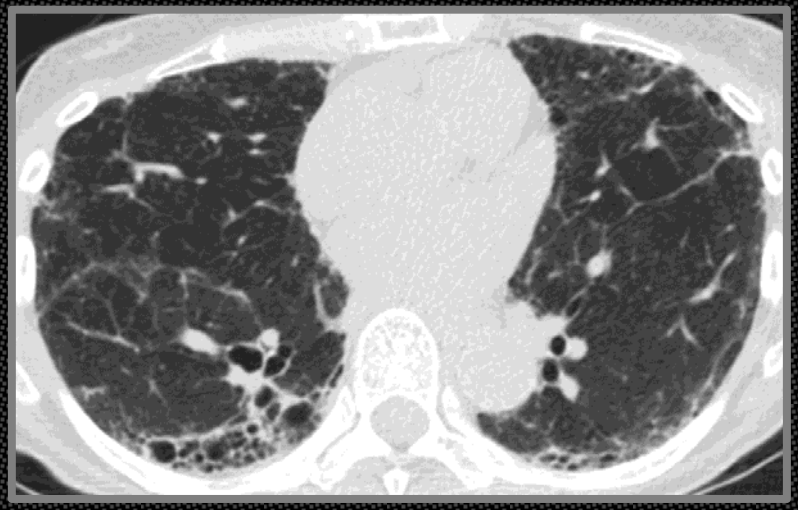
2011 ATS/ERS/JRS/ALAT Statement

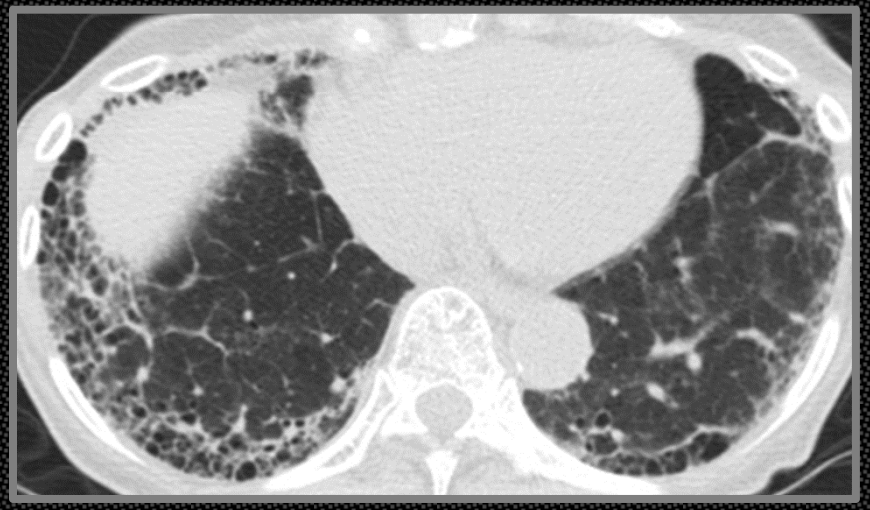
HRCT Criteria for UIP Pattern

- Definite UIP pattern (all 4 features):
  - Subpleural, basal predominance
  - Reticular abnormality
  - *Honeycombing* with or without traction bronchiectasis
  - Absence of features listed as inconsistent with UIP pattern (air trapping, cysts, others)

Definite UIP







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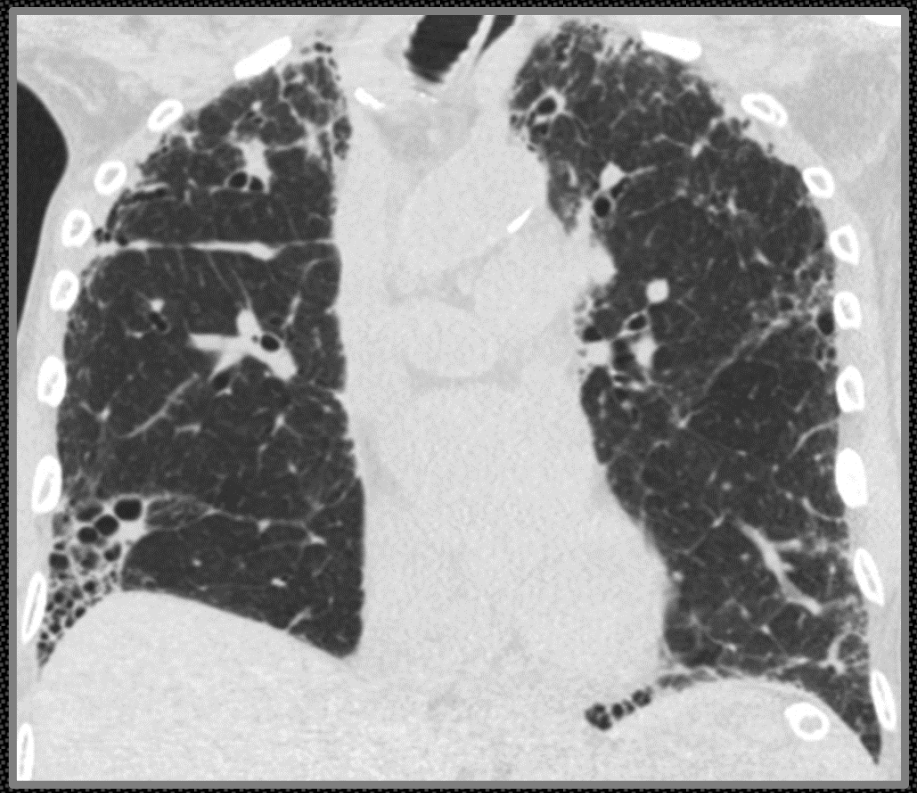
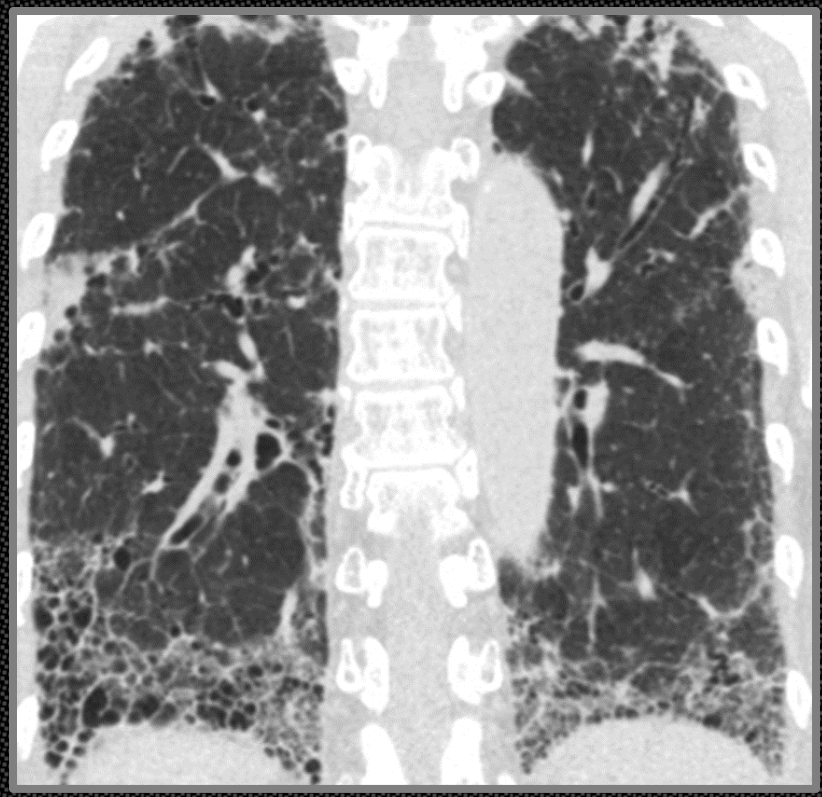
Definite UIP: Coronal Reformats





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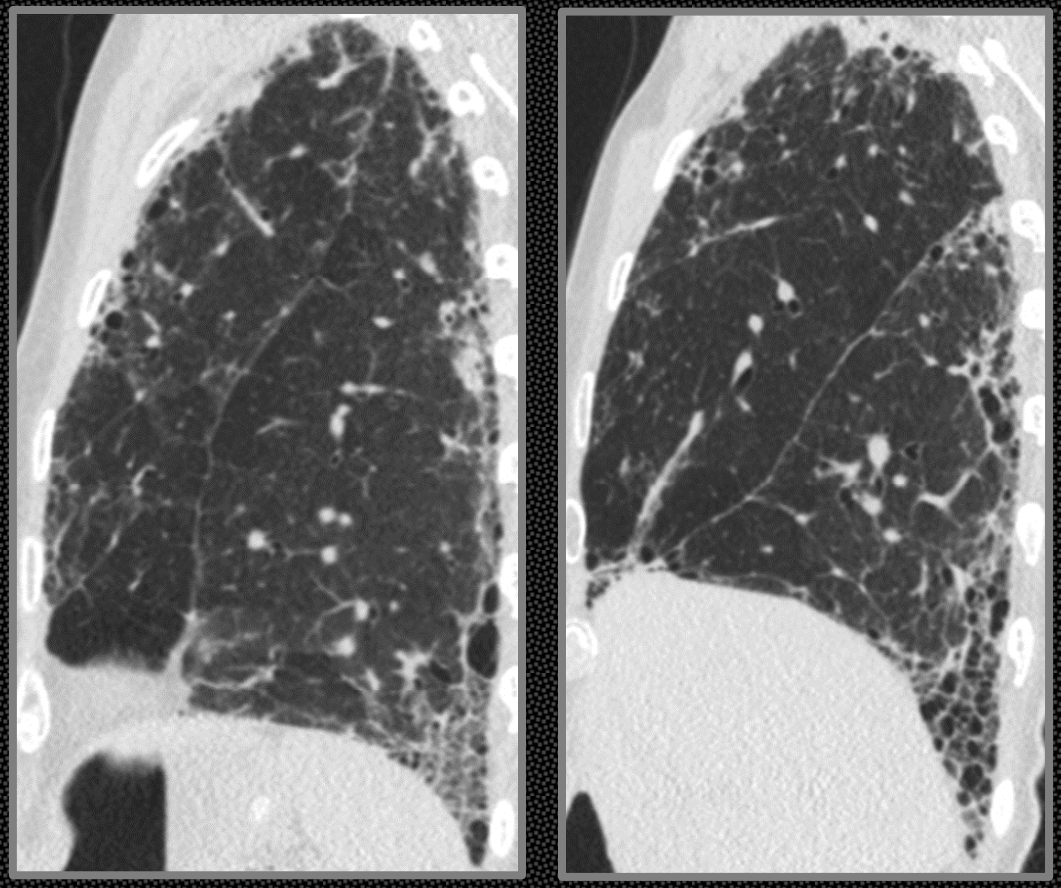
Definite UIP: Sagittal Reformats



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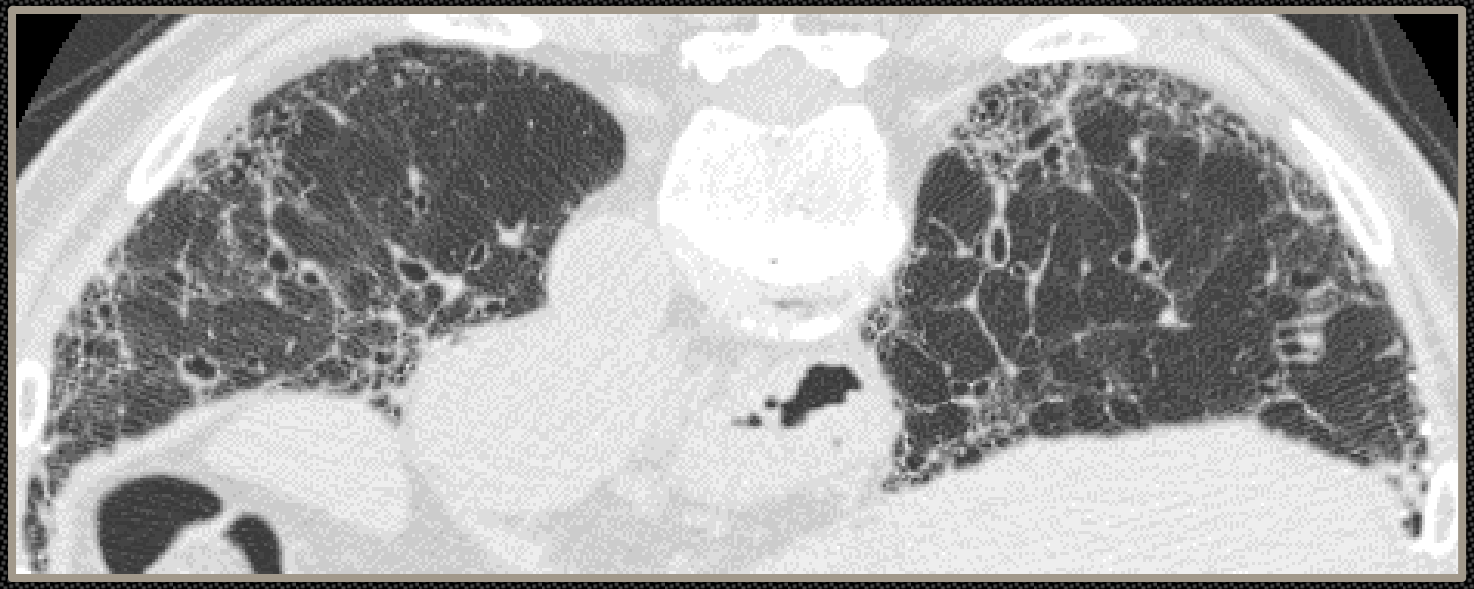
Problems with the Guidelines

- Definite UIP pattern (all 4 features):
  - Subpleural, basal predominance
  - Reticular abnormality

Must have some upper lobe involvement, non-segmental distribution, and reticulation should include features of fibrosis, fibrosis should be heterogeneous

Heterogeneity of the Fibrosis in UIP

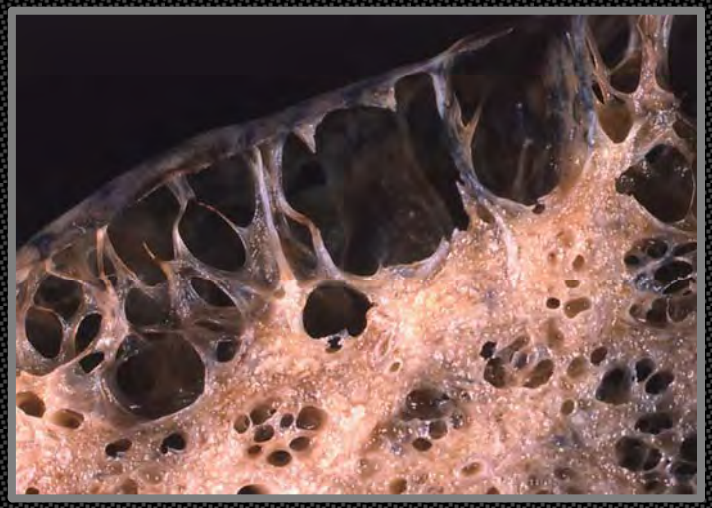


Problems with the Guidelines

- Definite UIP pattern (all 4 features):
  - Honeycombing with or without traction bronchiectasis

Easy to confuse other pathology with HC and falsely diagnose definite UIP, HC occurs in other non-UIP ILD, and the distinction of traction bronchiectasis from HC is arbitrary and unnecessary.

Clustered Subpleural Cystic Spaces



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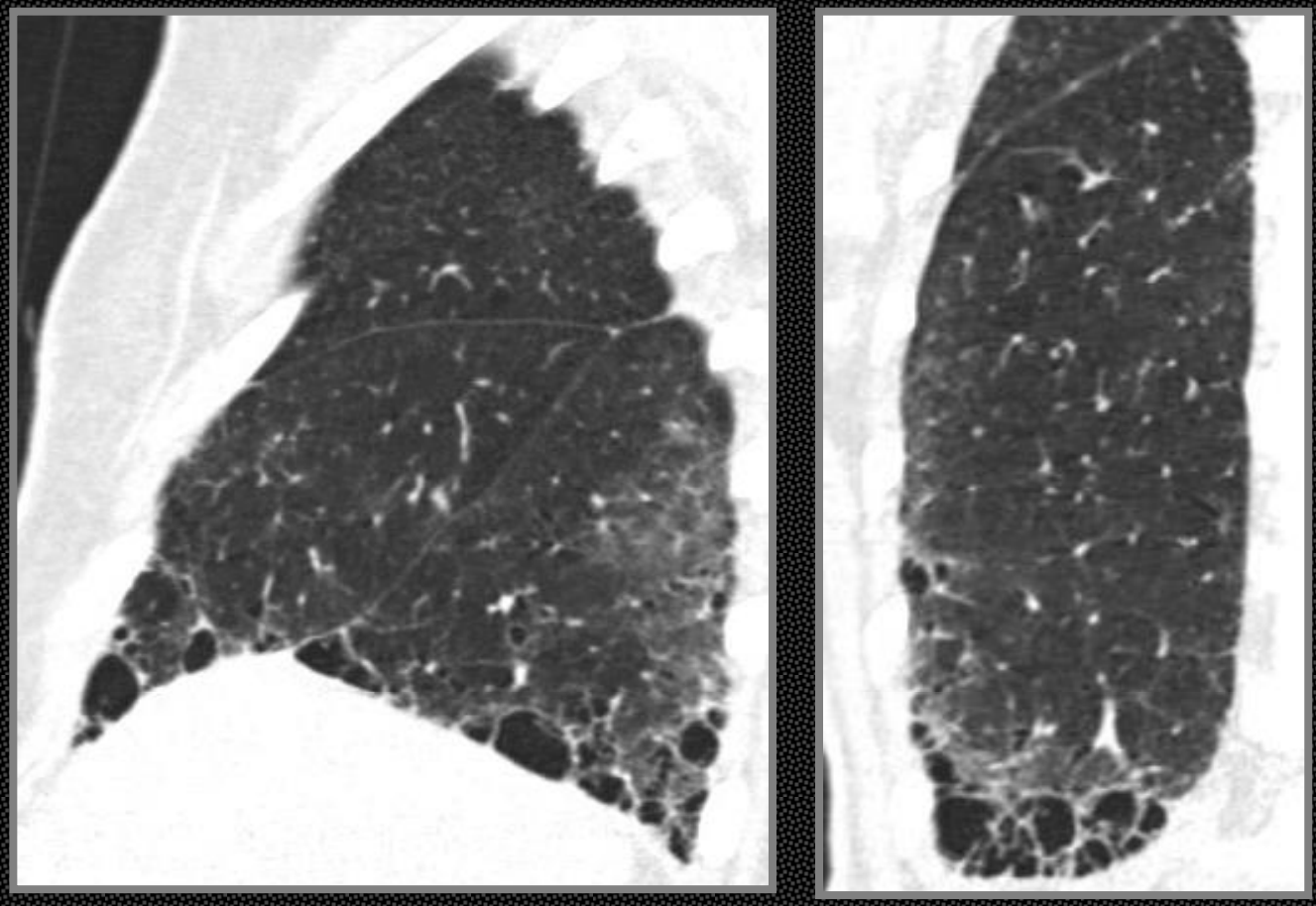
Clustered Subpleural Cystic Spaces



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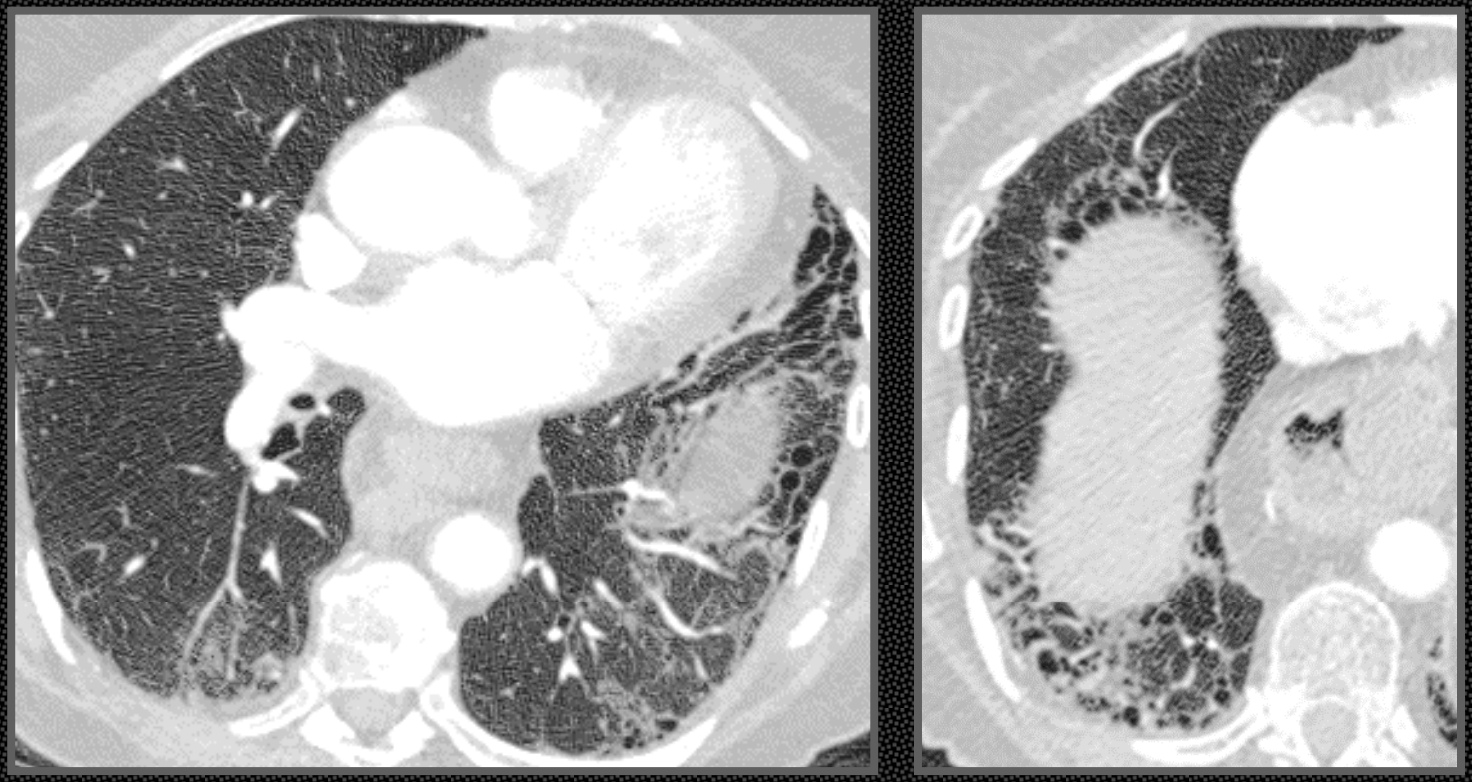
Clustered Subpleural Cystic Airspaces



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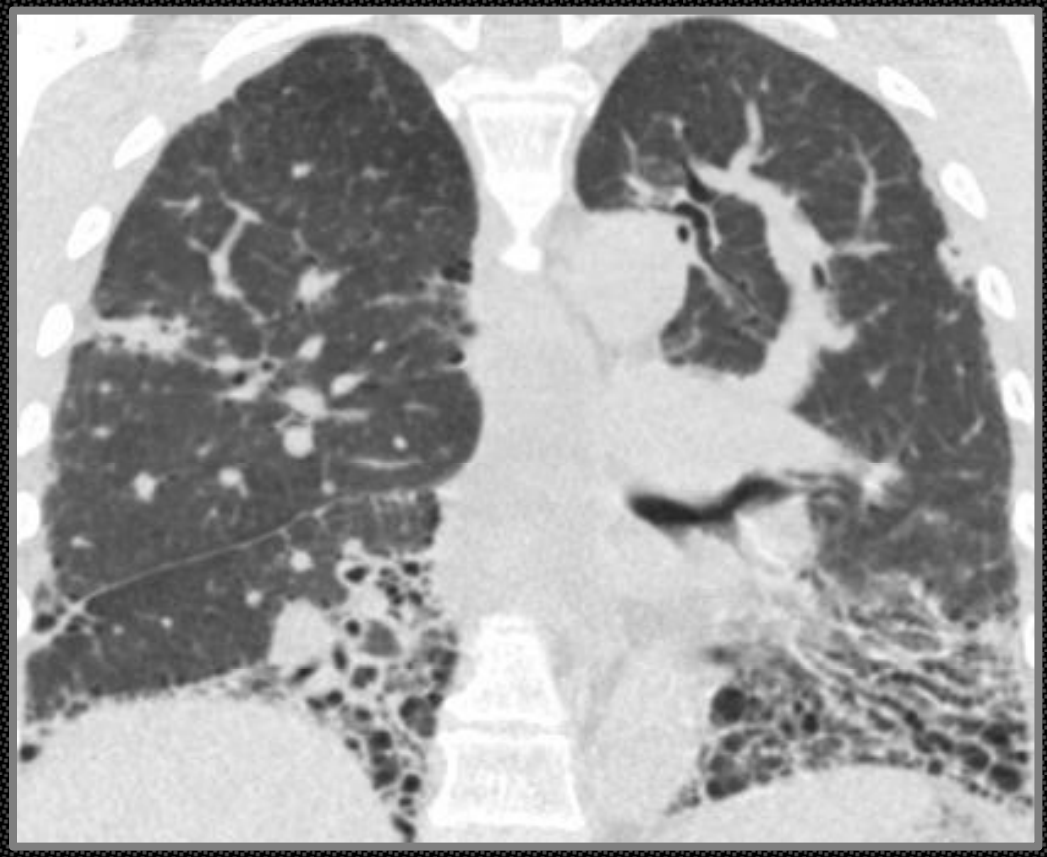
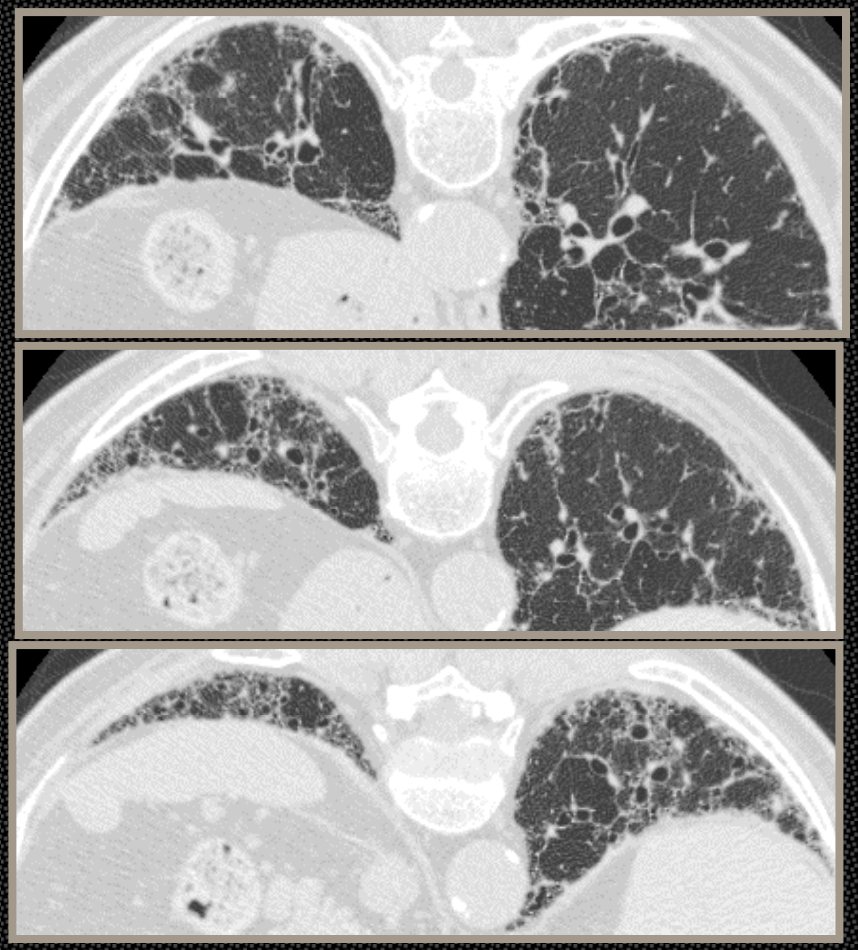
HC Occurs on Other Fibrotic ILDs



Non-Definite UIP (Traction no HC)



Problems with the Guidelines

- Definite UIP pattern (all 4 features):
  - Absence of features listed as inconsistent with UIP pattern (air trapping, cysts, others)

Air trapping can occur in any PF-ILD, does not always occur in CHP, and the degree of expiratory effort is completely variable

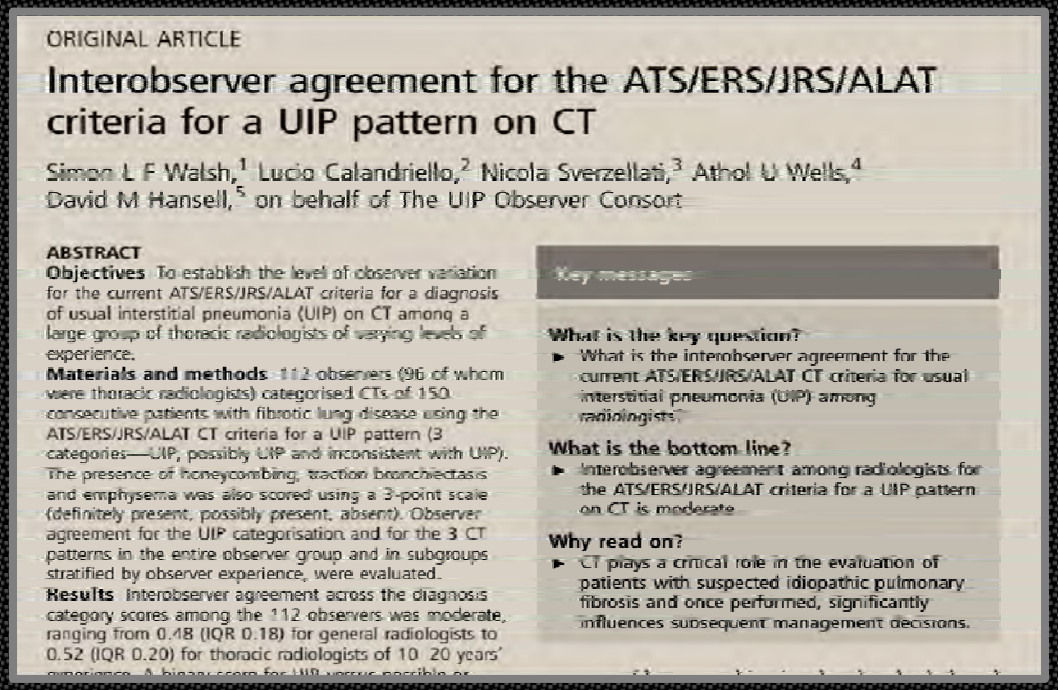
UIP Diagnosis: Modified Criteria

- UIP pattern (all features):
  - Peripheral reticulation with lobular distortion and intralobular lines
  - Subpleural, basal predominance but with some upper lobe involvement
  - Non-segmental
  - Traction bronchiectasis *and/or* HC
  - *Heterogenous* appearance to the fibrosis

Advantages of These Criteria

- Better observer agreement, easy to teach
- Improves distinction of UIP from other entities (including non-PF-ILD diagnoses)
  - Reduce or eliminate false positives
- Enable earlier UIP diagnosis

Limitations of Existing Guidelines



ORIGINAL ARTICLE

Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT

Simon L F Walsh,[1] Lucio Calandriello,[2] Nicola Sverzellati,[3] Athol U Wells,[4] David M Hansell,[5] on behalf of The UIP Observer Consort

ABSTRACT

Objectives To establish the level of observer variation for the current ATS/ERS/JRS/ALAT criteria for a diagnosis of usual interstitial pneumonia (UIP) on CT among a large group of thoracic radiologists of varying levels of experience.

Materials and methods 112 observers (96 of whom were thoracic radiologists) categorised CTs of 150 consecutive patients with fibrotic lung disease using the ATS/ERS/JRS/ALAT CT criteria for a UIP pattern (3 categories—UIP, possibly UIP and inconsistent with UIP). The presence of honeycombing, traction bronchiectasis and emphysema was also scored using a 3-point scale (definitely present, possibly present, absent). Observer agreement for the UIP categorisation and for the 3 CT patterns in the entire observer group and in subgroups stratified by observer experience, were evaluated.

Results Interobserver agreement across the diagnosis category scores among the 112 observers was moderate, ranging from 0.48 (IQR 0.18) for general radiologists to 0.52 (IQR 0.20) for thoracic radiologists of 10–20 years' experience. A binary score for UIP versus possible or

Key messages

What is the key question?

- What is the interobserver agreement for the current ATS/ERS/JRS/ALAT CT criteria for usual interstitial pneumonia (UIP) among radiologists?

What is the bottom line?

- Interobserver agreement among radiologists for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT is moderate

Why read on?

- CT plays a critical role in the evaluation of patients with suspected idiopathic pulmonary fibrosis and once performed, significantly influences subsequent management decisions.

"Based upon the results of this study, modification of these criteria may be necessary to improve observer agreement."

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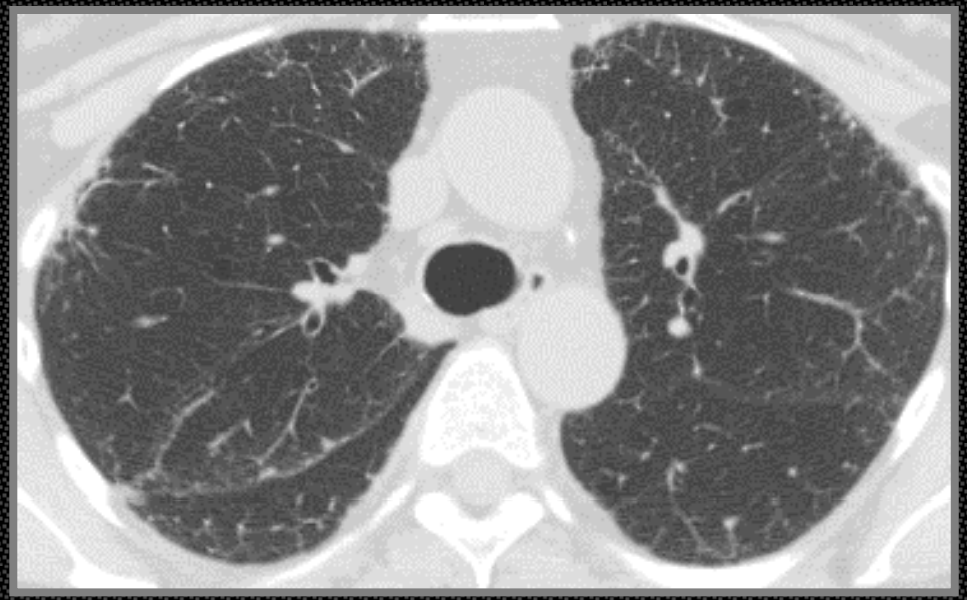
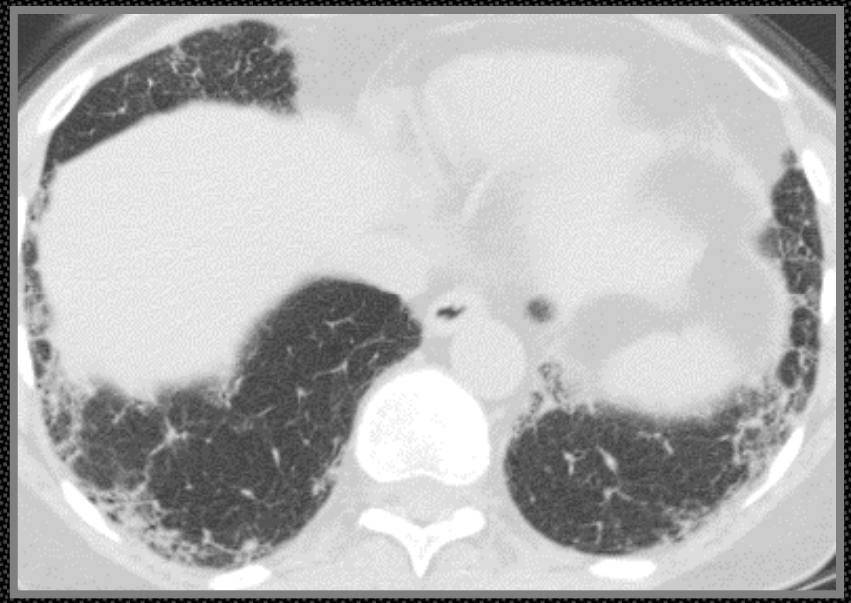
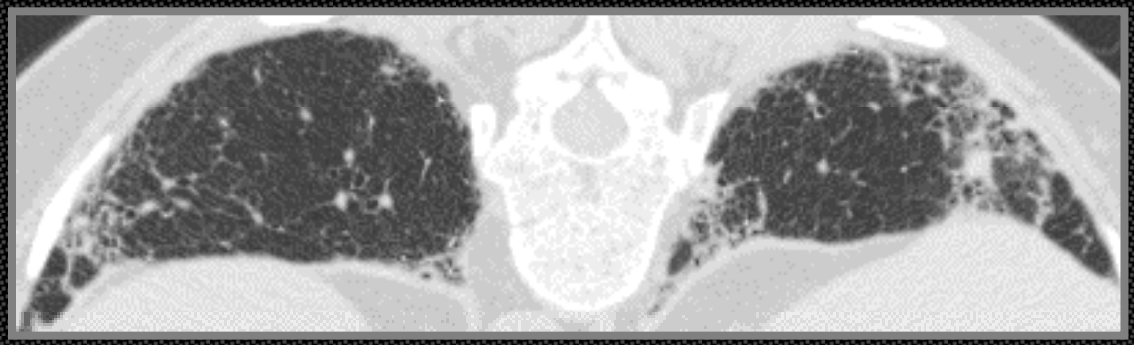
UIP: CT Diagnosis







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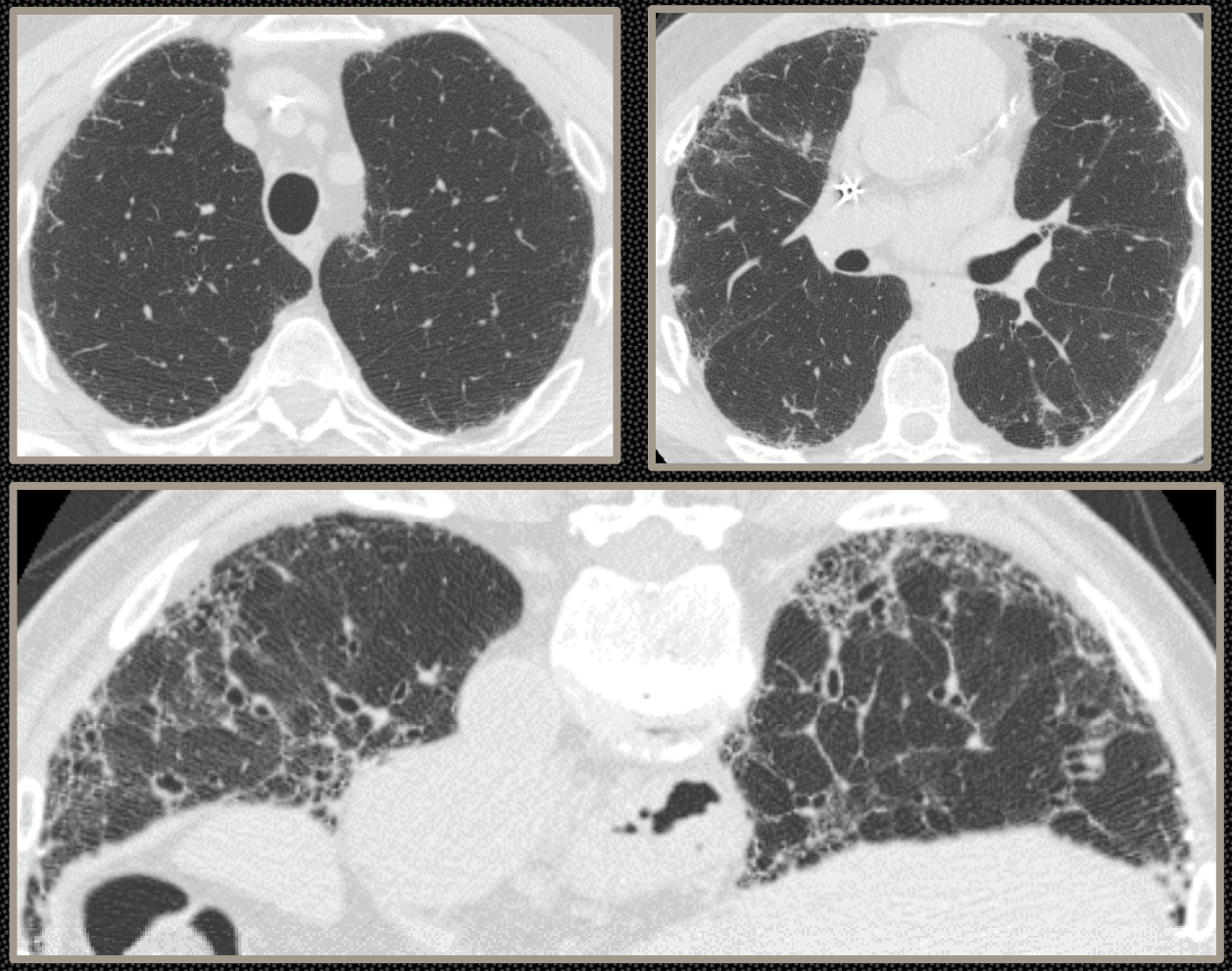
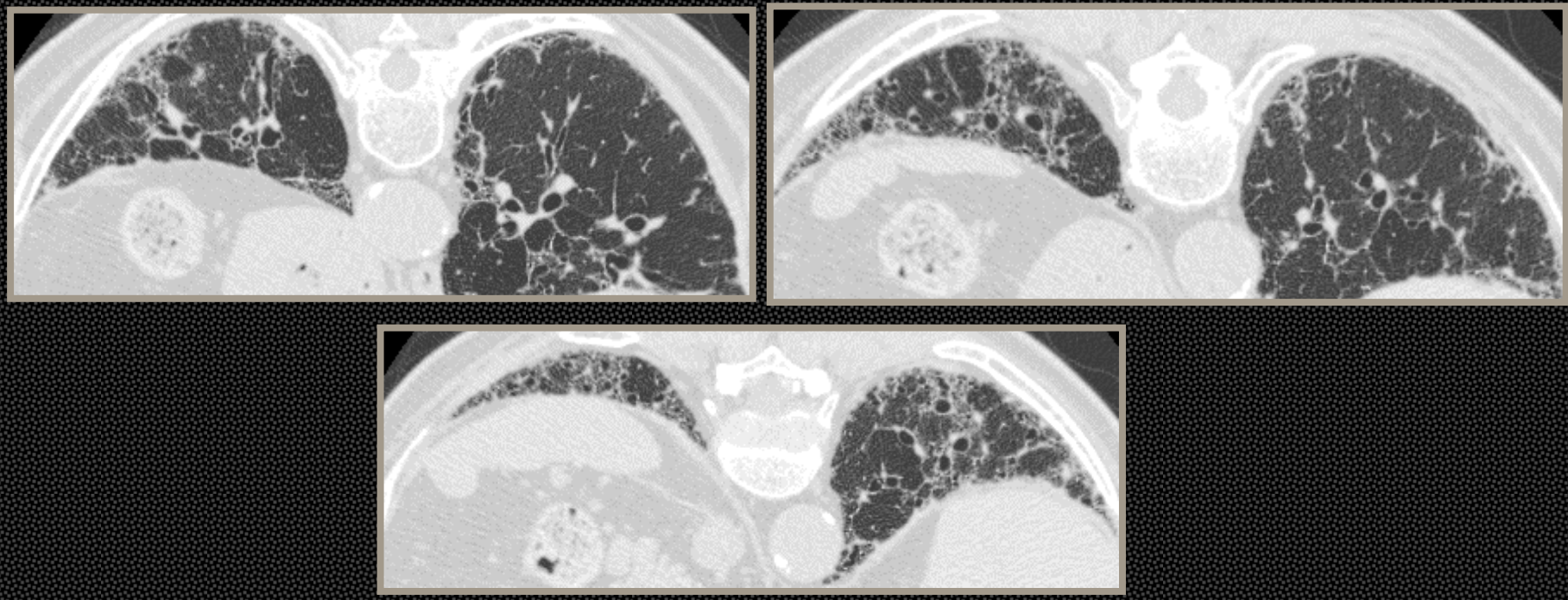
UIP: CT Diagnosis



“Definite UIP” Without HC



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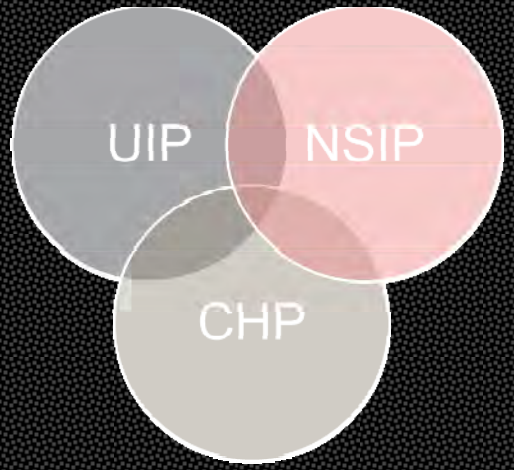
UIP Diagnosis Without Honeycombing

- UIP pattern (5 features):
  - Peripheral reticulation with lobular distortion and intralobular lines
  - Subpleural, basal predominance but with some upper lobe involvement
  - Non-segmental
  - Traction bronchiectasis and/or HC
  - Heterogenous appearance to the fibrosis

PF-ILD: Causes

- Usual interstitial pneumonia (UIP)
- Chronic hypersensitivity pneumonitis (CHP)
- Nonspecific interstitial pneumonia (NSIP)



CHP: Overview

- CHP implies fibrosis, which carries a worse prognosis (by CT or histology)
- Can be difficult to separate CHP and UIP on OLB (especially in advanced disease)
- Many patients (at least 50%) have no recognizable antigen exposure
- Some previous UIP/IPF now reclassified as CHP

Churg A , *Arch Pathol Lab Med* 142, January 2018

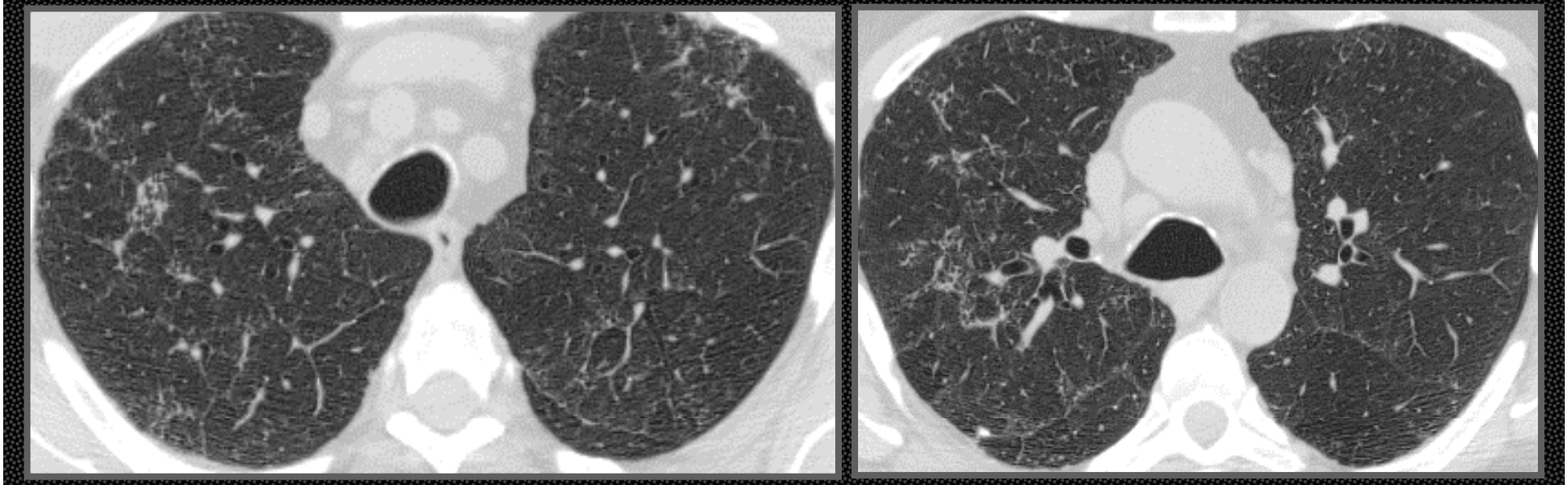
CHP: Pathology

- Peribronchiolar (centrilobular) fibrosis, upper zone
- Extends from centrilobular region to adjacent bronchiole, interlobular septum, or pleura (“bridging fibrosis”) (intralobular lines)
- Fibrotic NSIP in areas, granulomata may be absent

CHP: CT Appearance

- GGO superimposed on reticulation
  - Intralobular lines often prominent
- Peribronchovascular, upper-mid zone
- Variable secondary lobule size, many hyperlucent, air trapping variable
  - “Headcheese sign”
- Centrilobular nodules absent when no antigen

CHP: Mold



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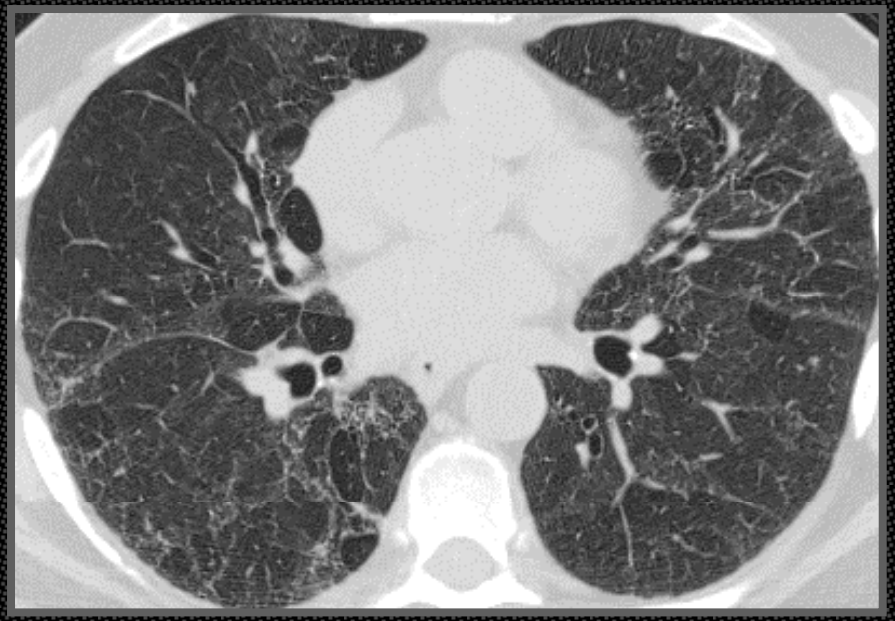
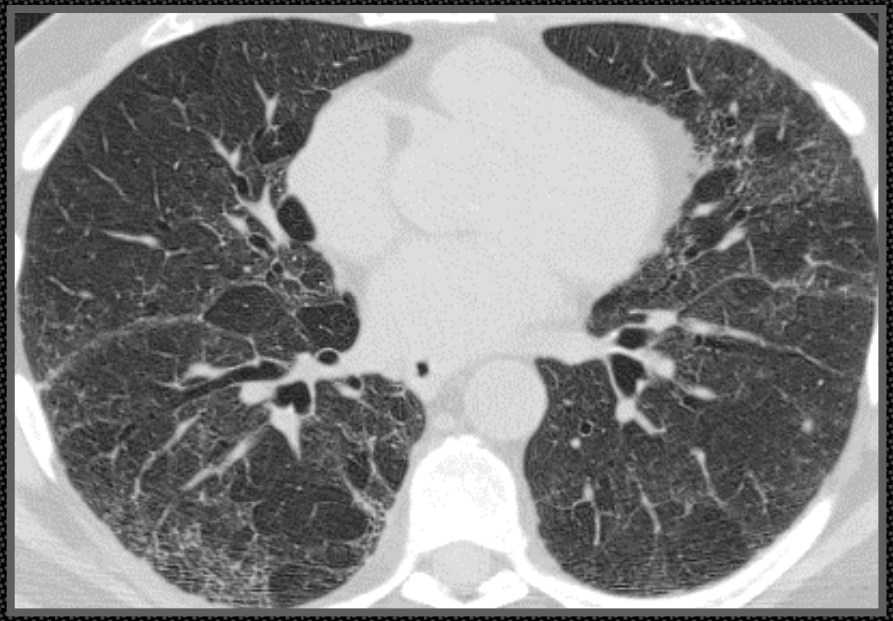
CHP: Mold





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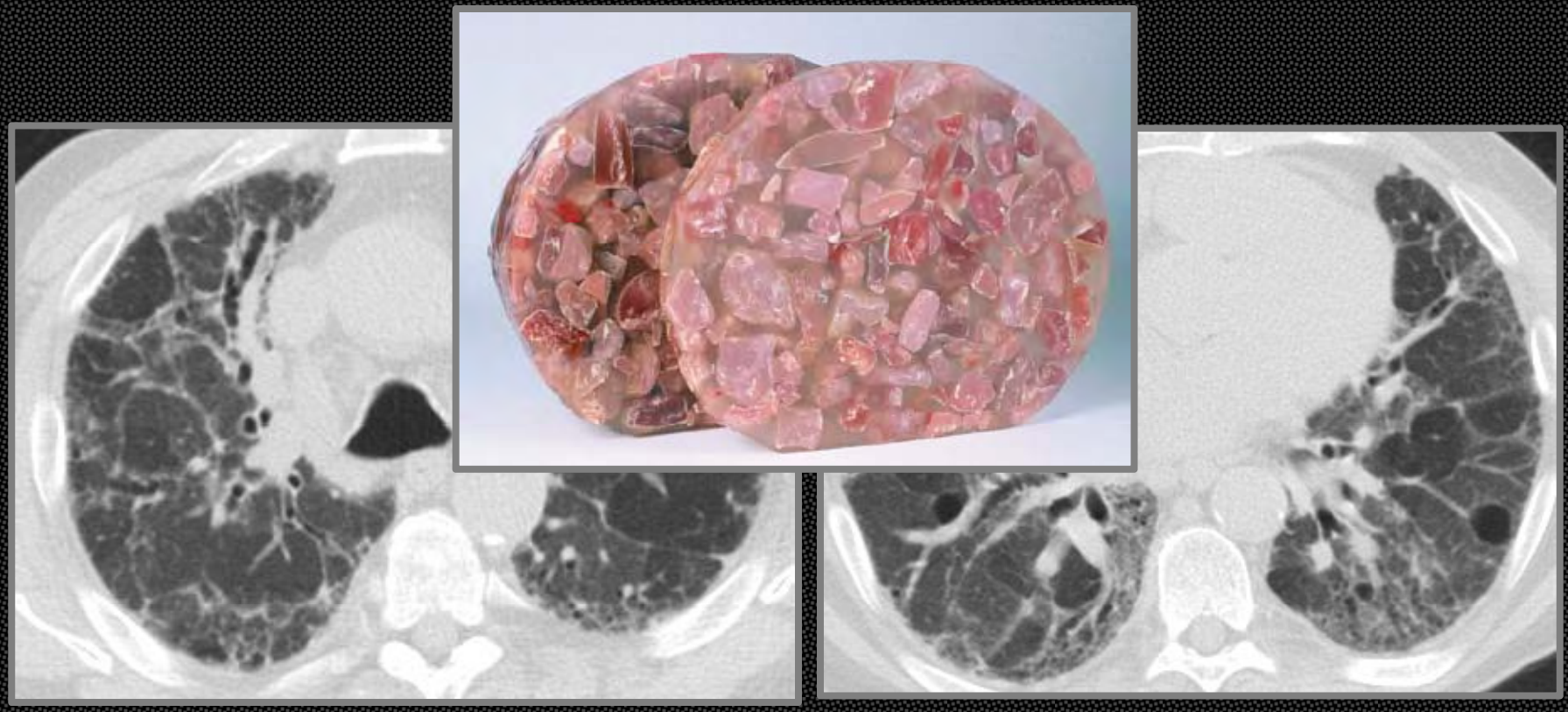
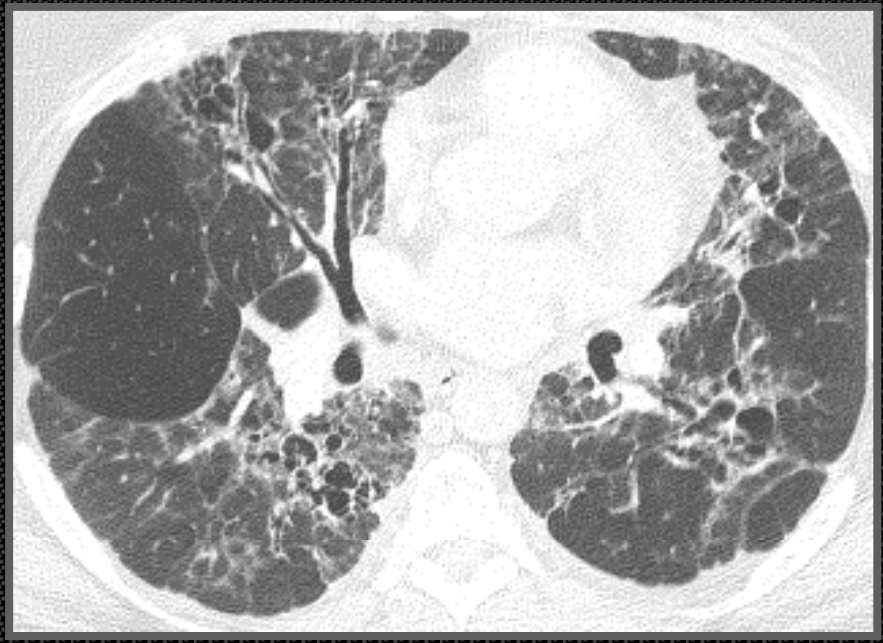
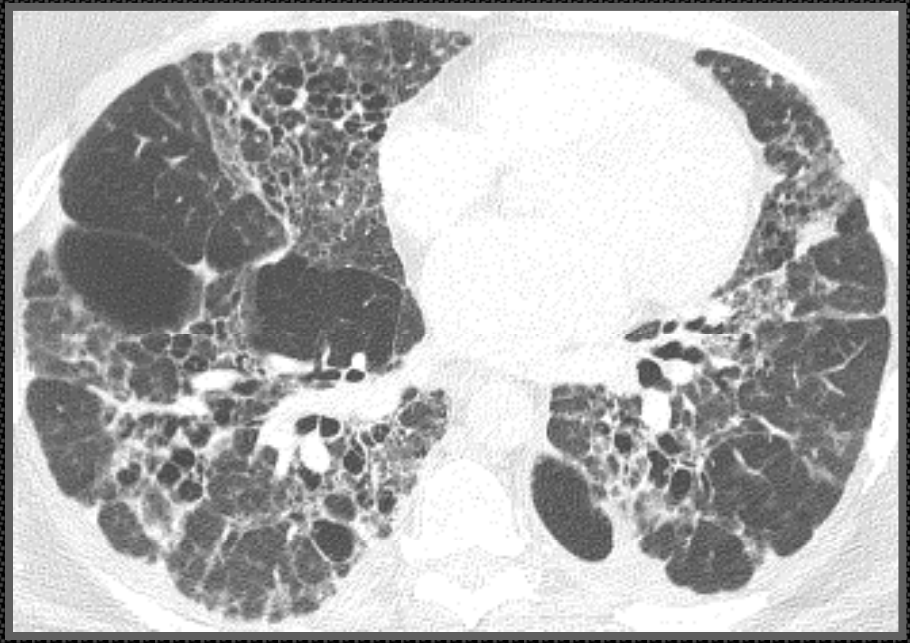
CHP: Headcheese Sign



CHP: Headcheese Sign





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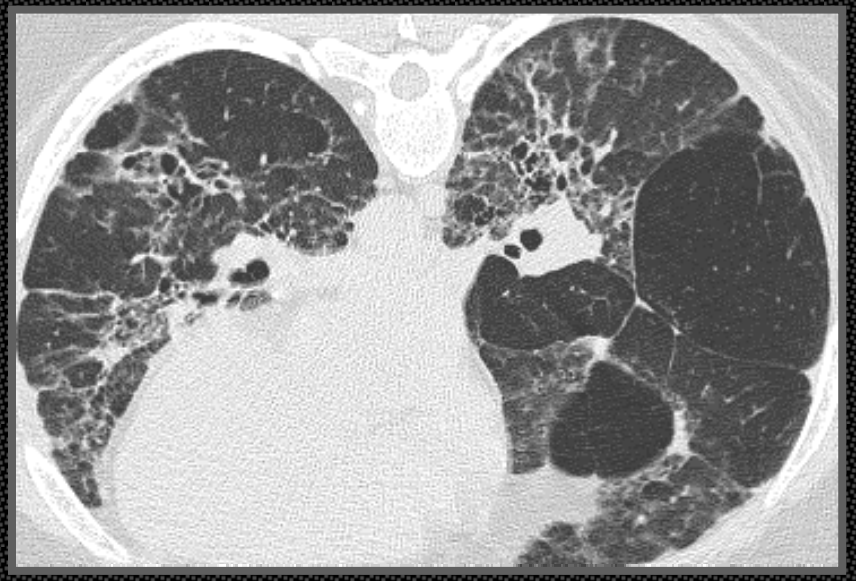
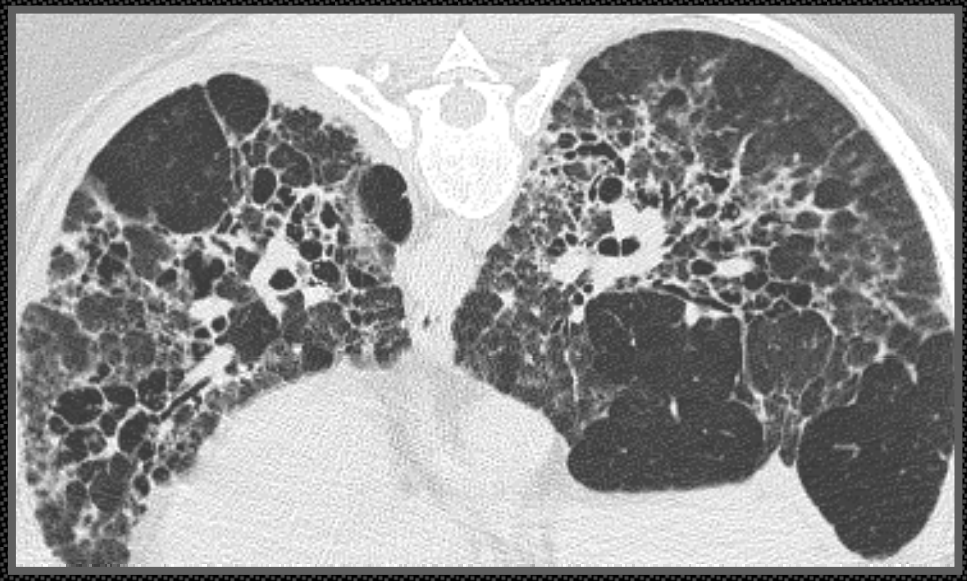
CHP: Headcheese Sign





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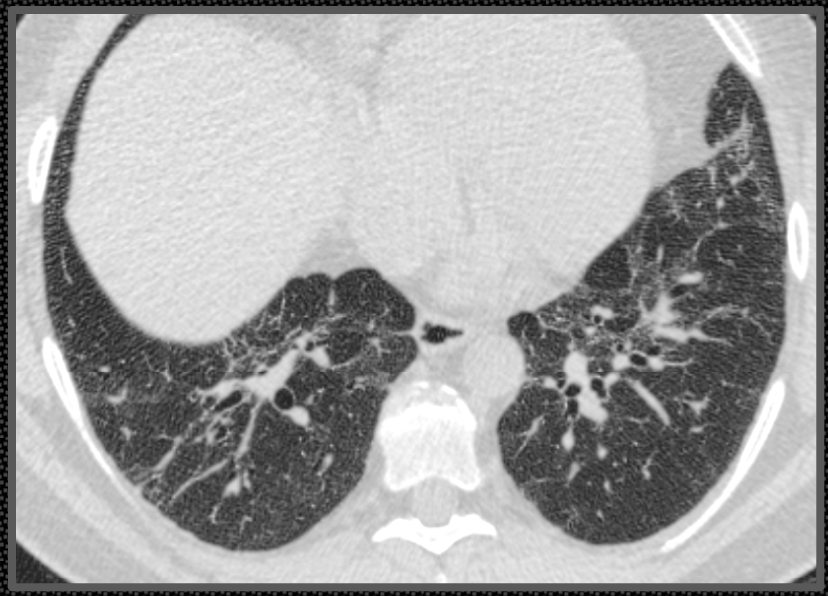
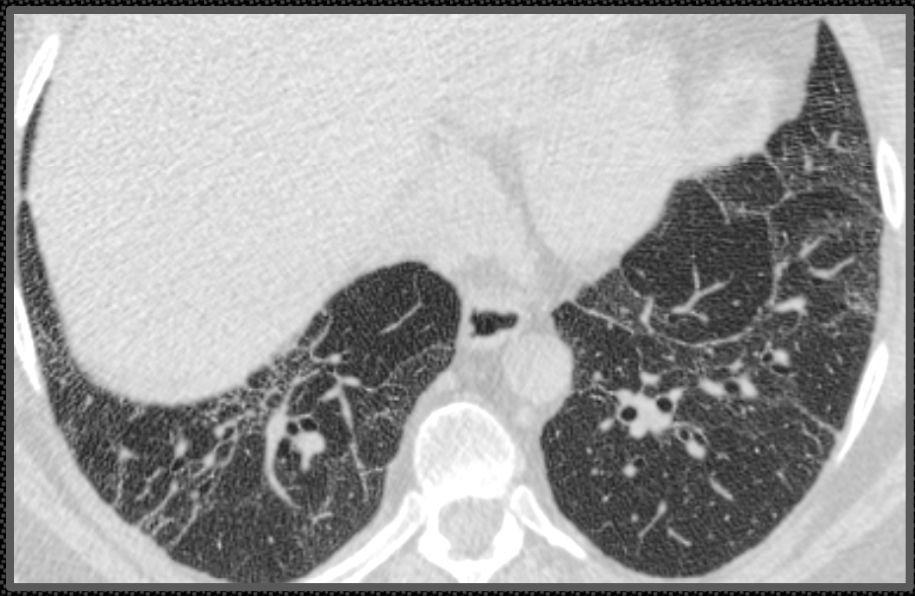
Sarcoidosis and Headcheese





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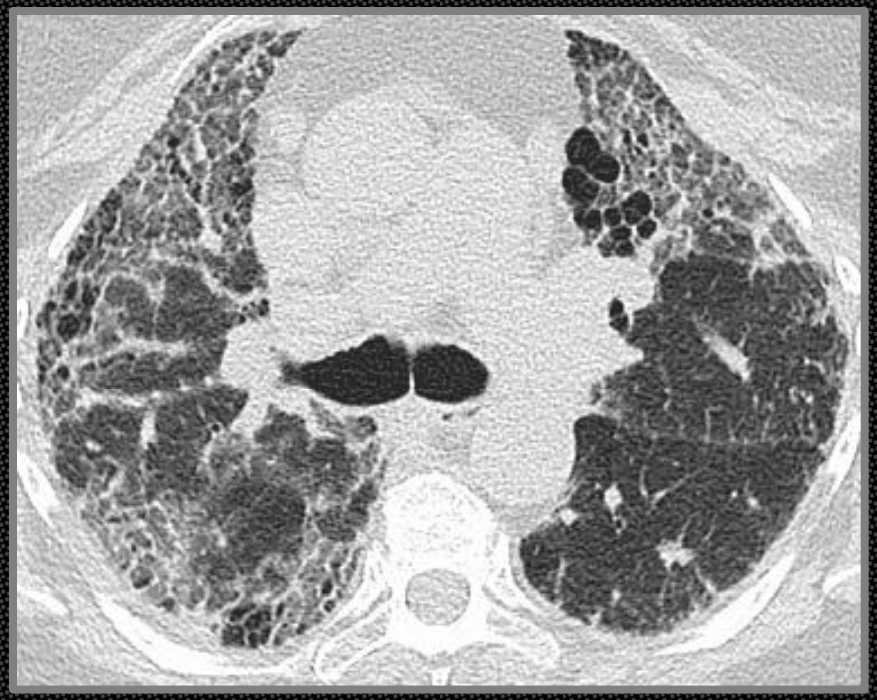
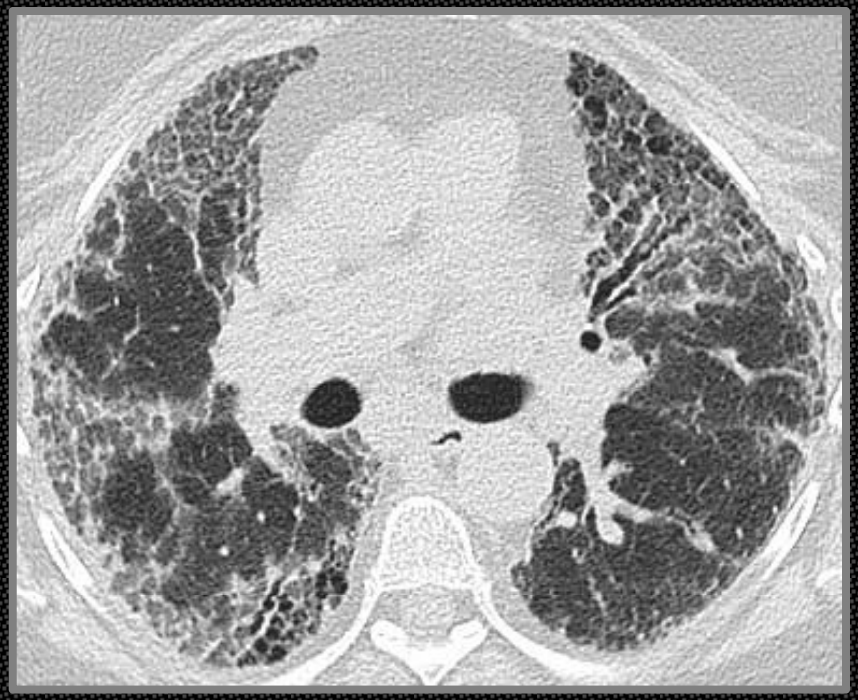
CHP: Intralobular Lines





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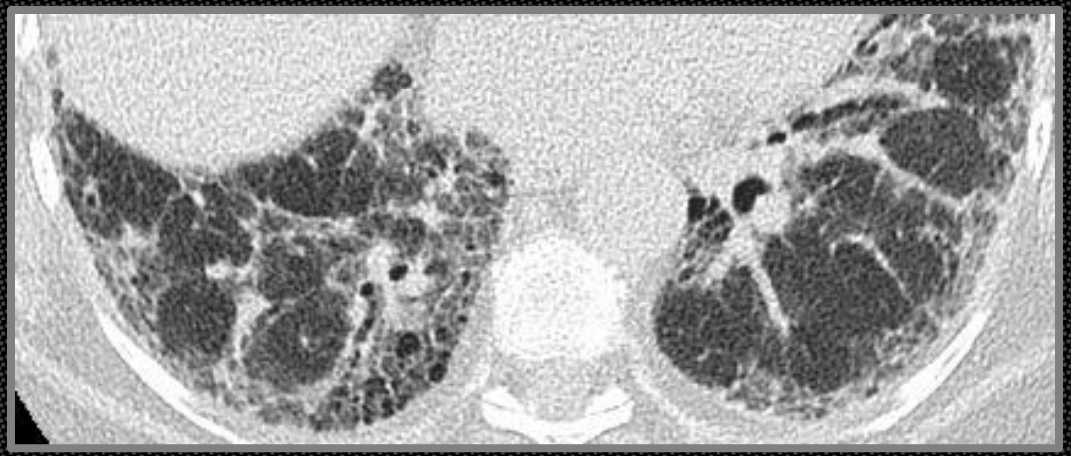
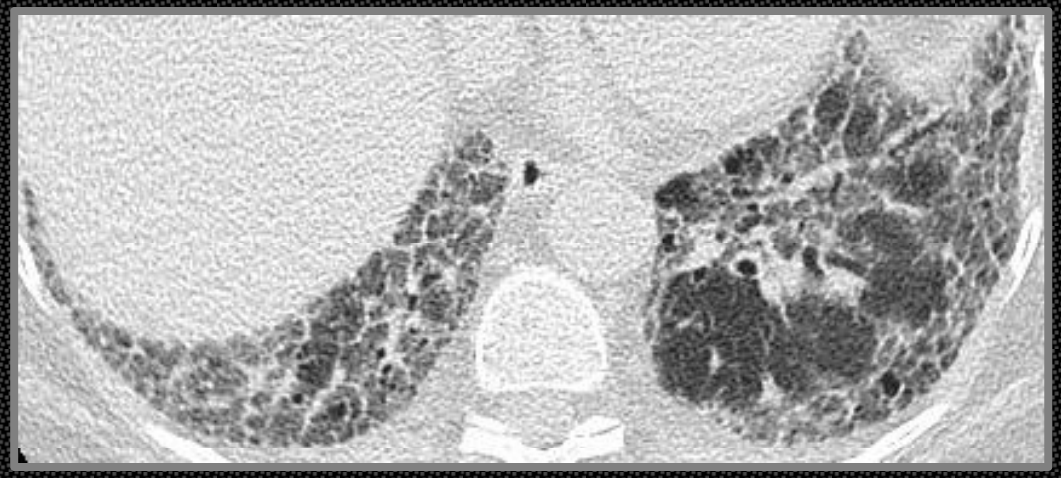
CHP: Intralobular Lines





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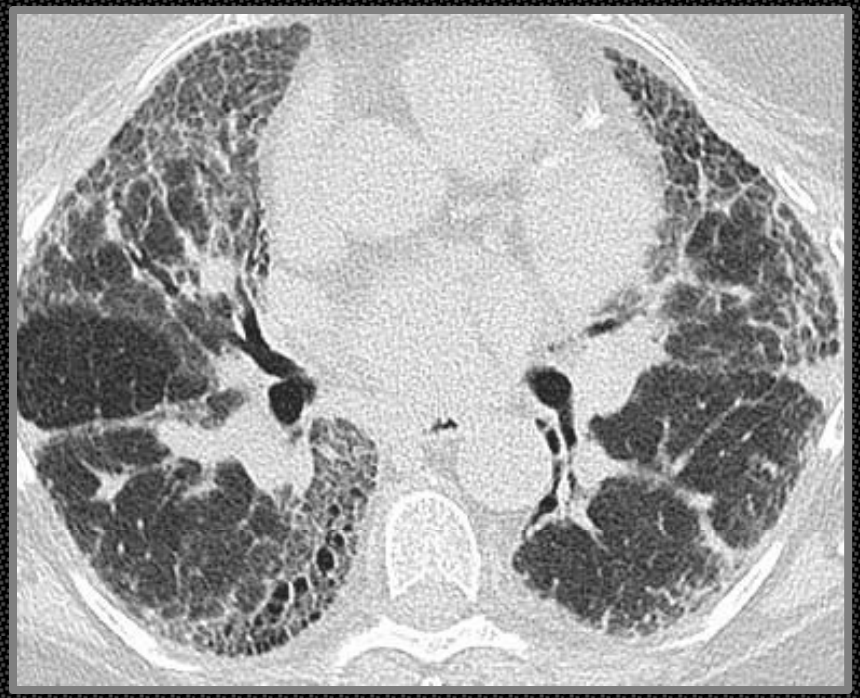
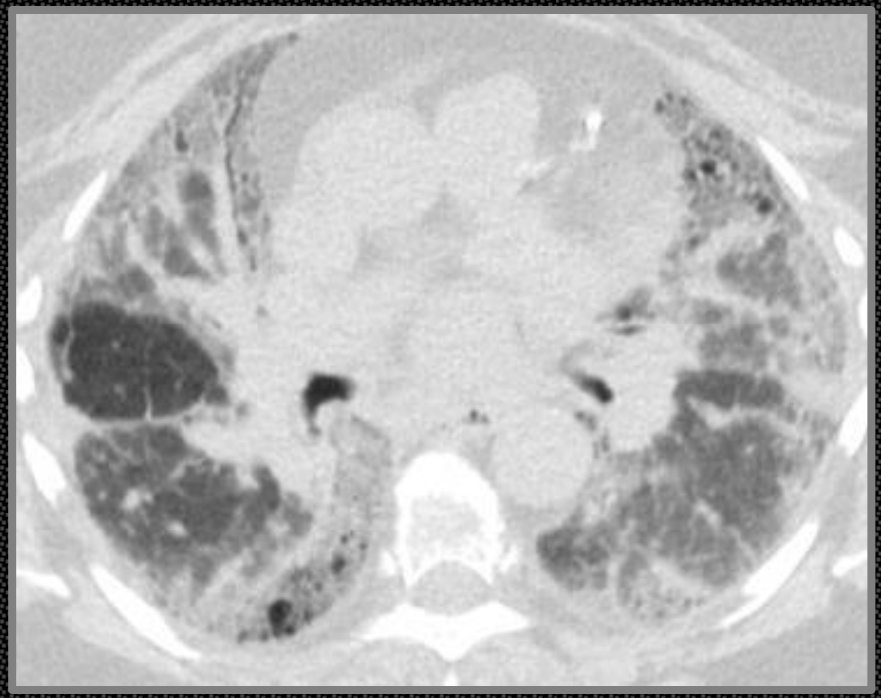
CHP: Expiratory Scanning





Question 2

- The biggest problem with expiratory CT is
  - A. Instructions are complicated
  - B. Technologists are not uniformly trained
  - C. Variable patient expiratory effort
  - D. Non contiguous scans
  - E. Lack of reader agreement

CT-Biopsy Discordance

Radiologic–pathologic discordance in biopsy-proven usual interstitial pneumonia

Kunihiro Yagihashi[1,2,3], Jason Huckleberry[4], Thomas V. Colby[5], Henry D. Tazelaar[5], Jordan Zach[2], Baskaran Sundaram[6], Sudhakar Pipavath[7], Marvin I. Schwarz[8] and David A. Lynch[2] for the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet)[9]

Top reason (70%): multifocal air trapping on CT as "inconsistent" with UIP

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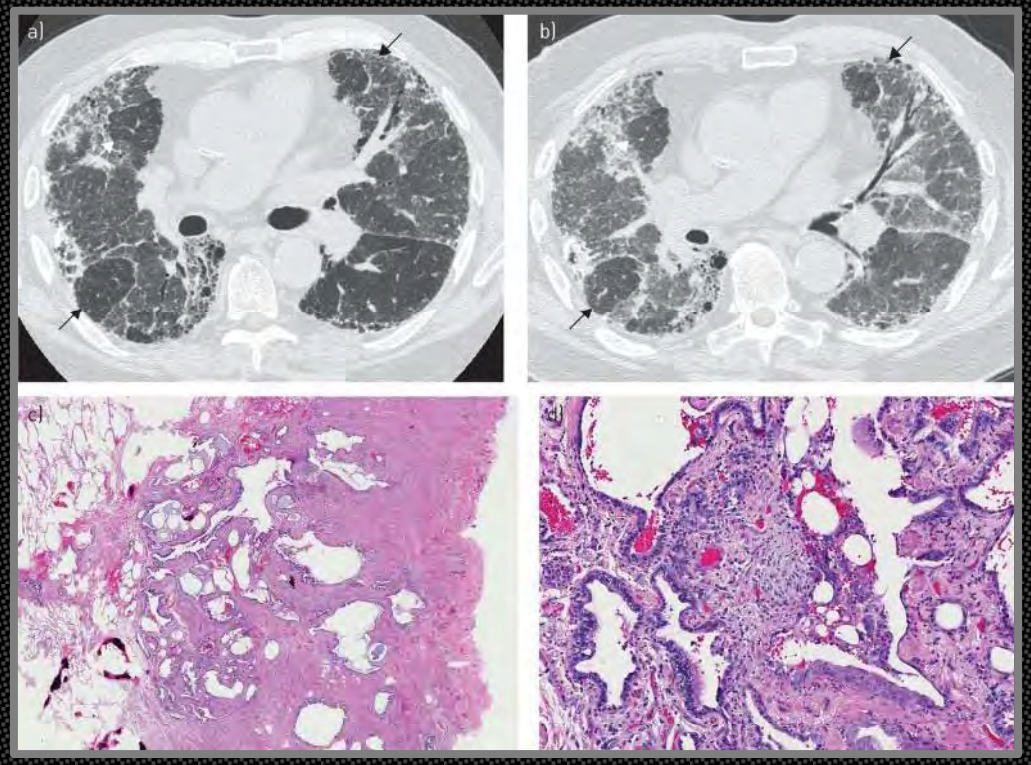
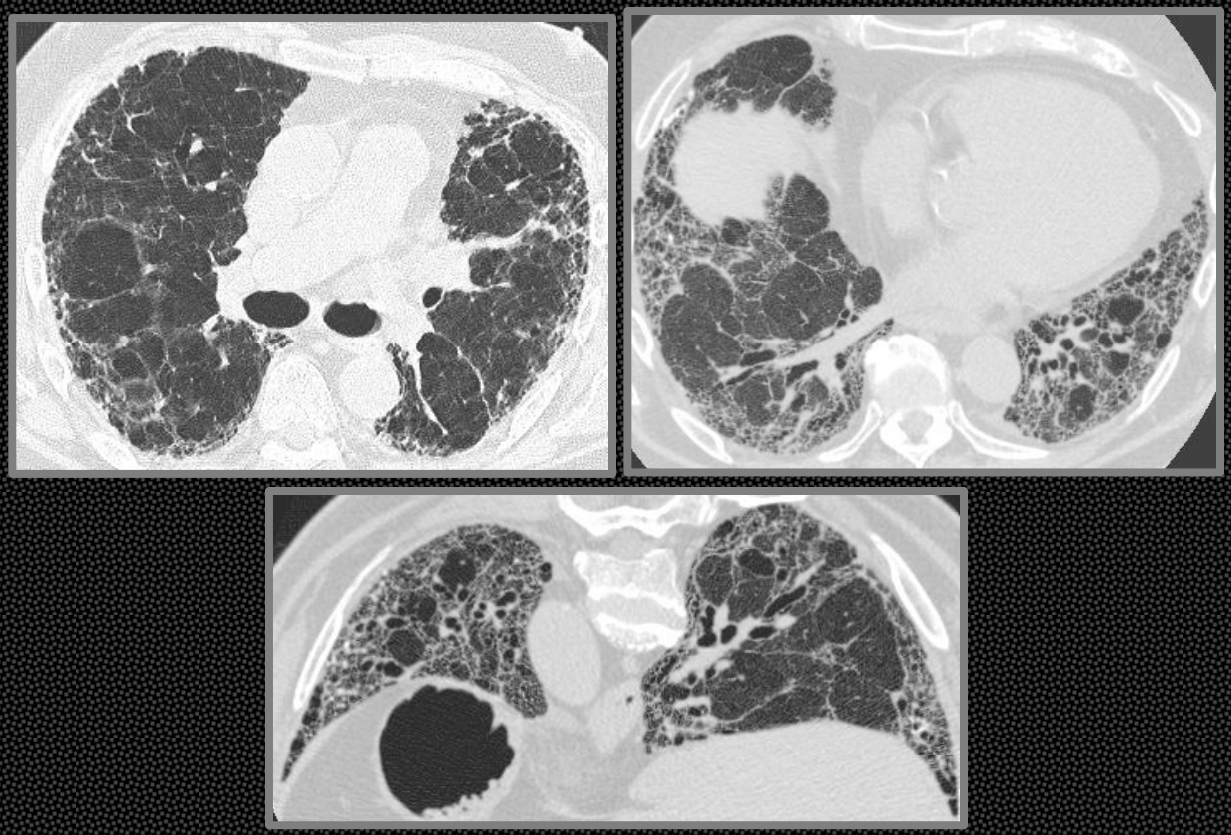
CHP on CT, UIP on Biopsy



Yagihashi K *et al*. *Eur Respir J* 2016;47:1189-1197

OLB: UIP 2010



Is idiopathic CHP a distinct entity? Should it be included in IPF?

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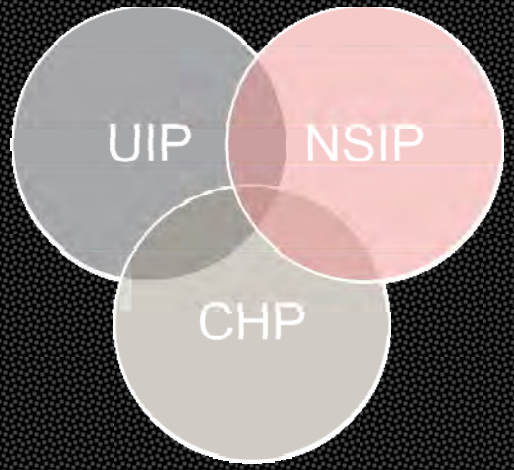
PFILD: Causes

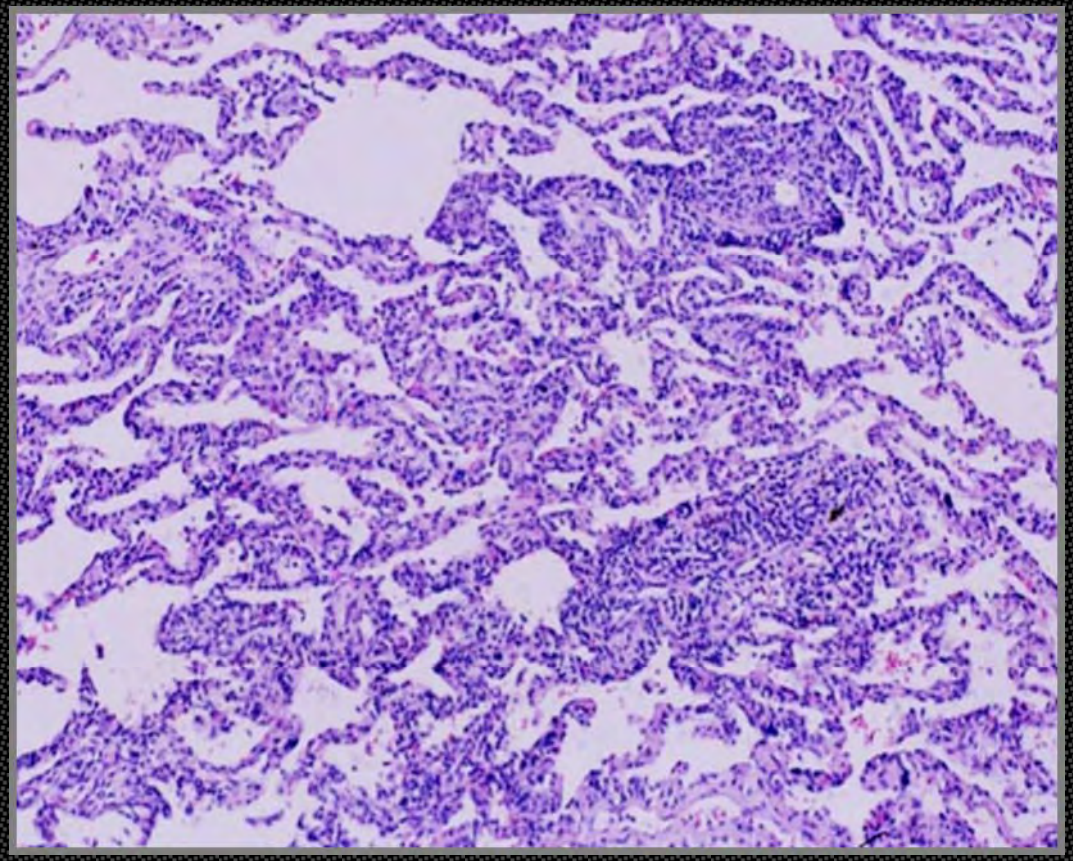
- Usual interstitial pneumonia (UIP)
- Chronic hypersensitivity pneumonitis (CHP)
- Nonspecific interstitial pneumonia (NSIP)



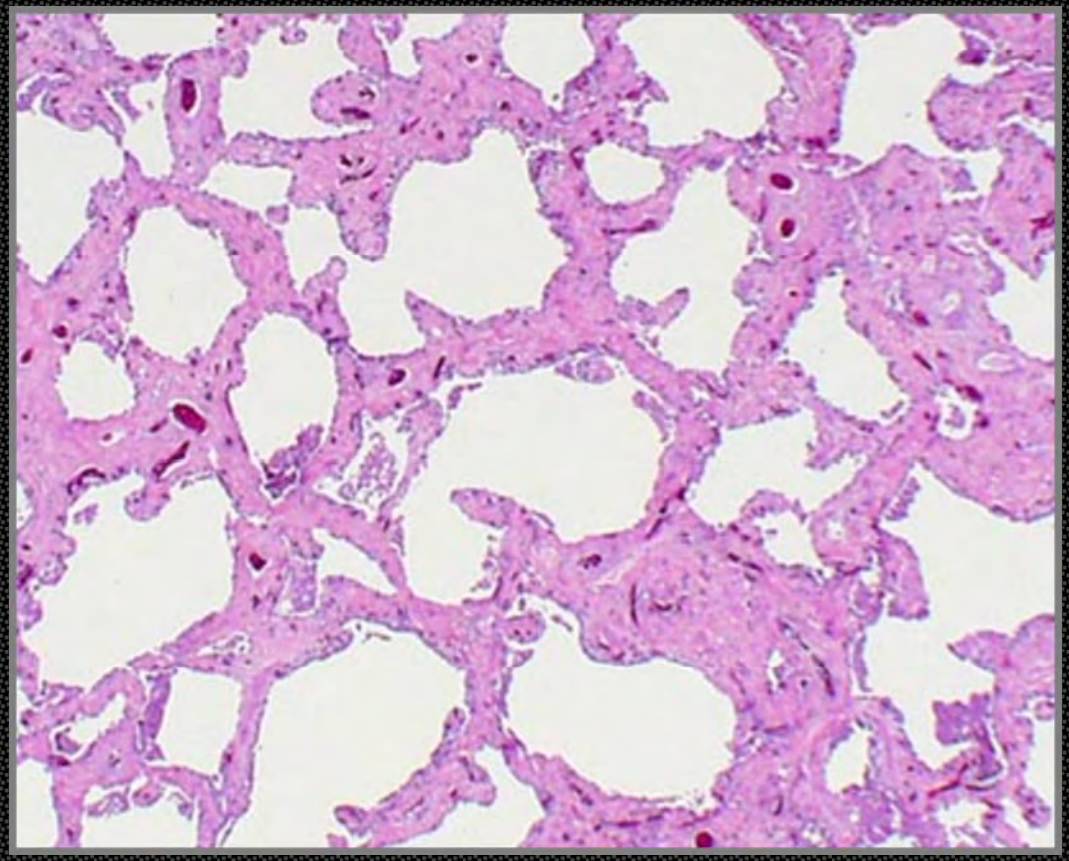
NSIP Pattern

- CVD (often with OP)
  - can precede CVD diagnosis (IPAF)
- Drug reaction
- HP
- Post DAD or post OP/COP
- Idiopathic

Cellular NSIP



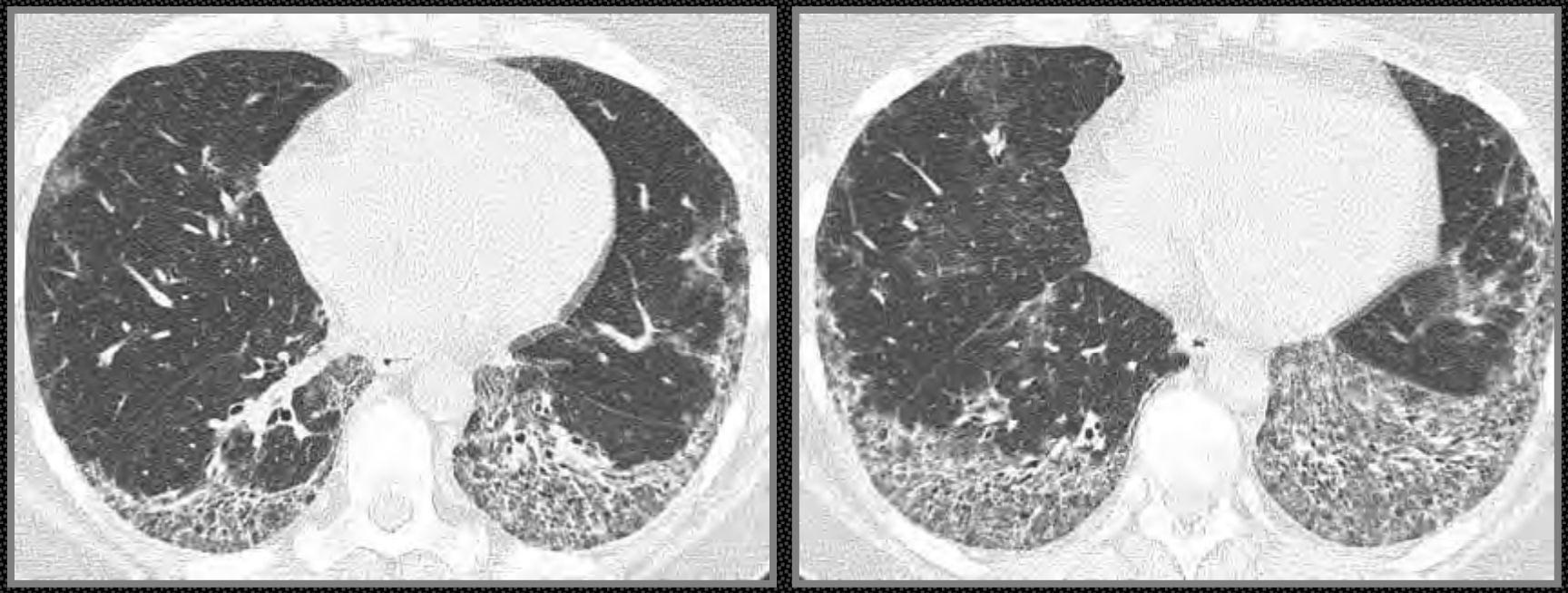
Fibrotic NSIP



NSIP Pattern: CT Features

- GGO superimposed on reticulation
  - Traction bronchiolectasis, HC in the fibrotic form
- Often lower zone predominant, can be only lower but should be non-segmental (aspiration ddx)
- Homogeneous
- Subpleural sparing
- Inferior central RML involvement

NSIP Pattern: Rheumatoid Arthritis



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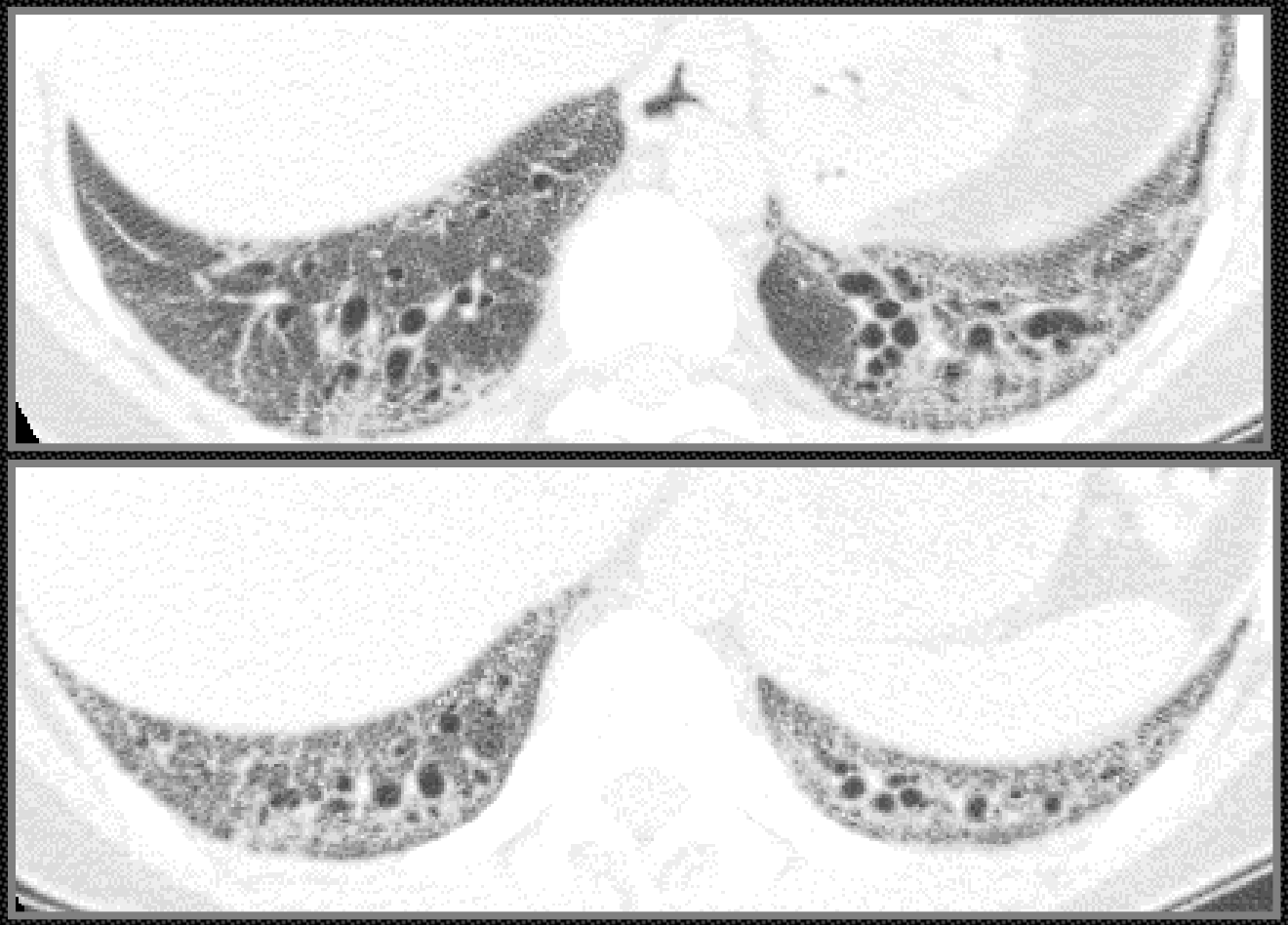
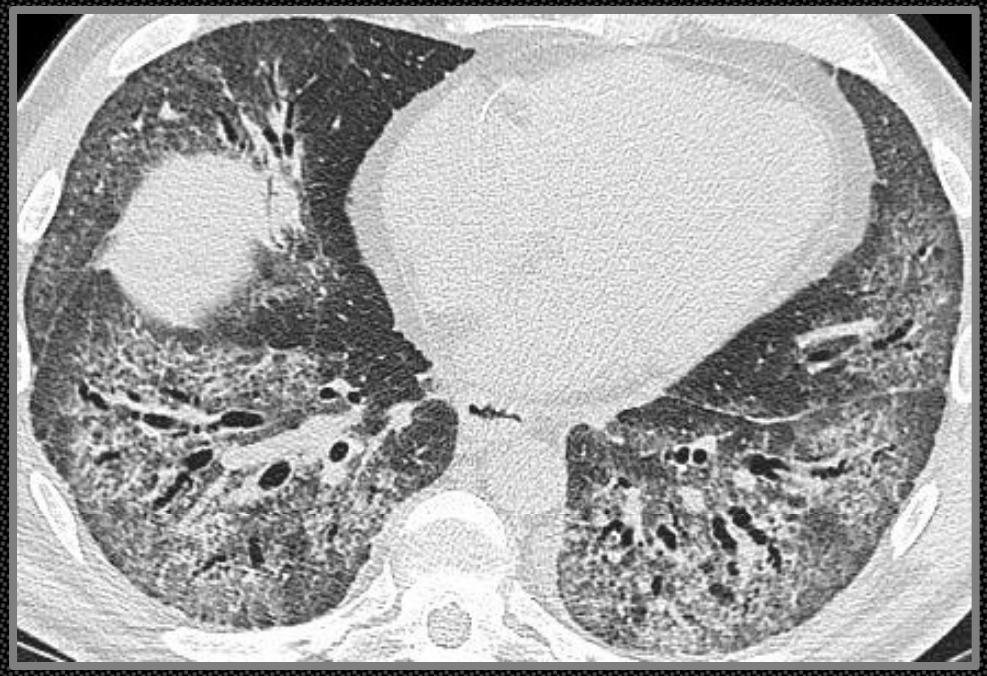
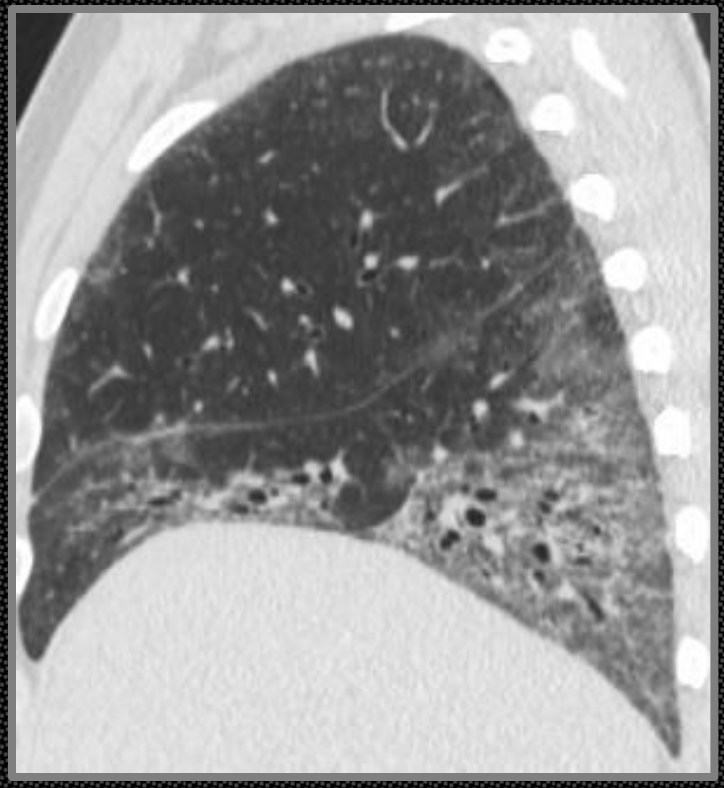
NSIP Pattern: Scleroderma



NSIP: The Bottom of the RML





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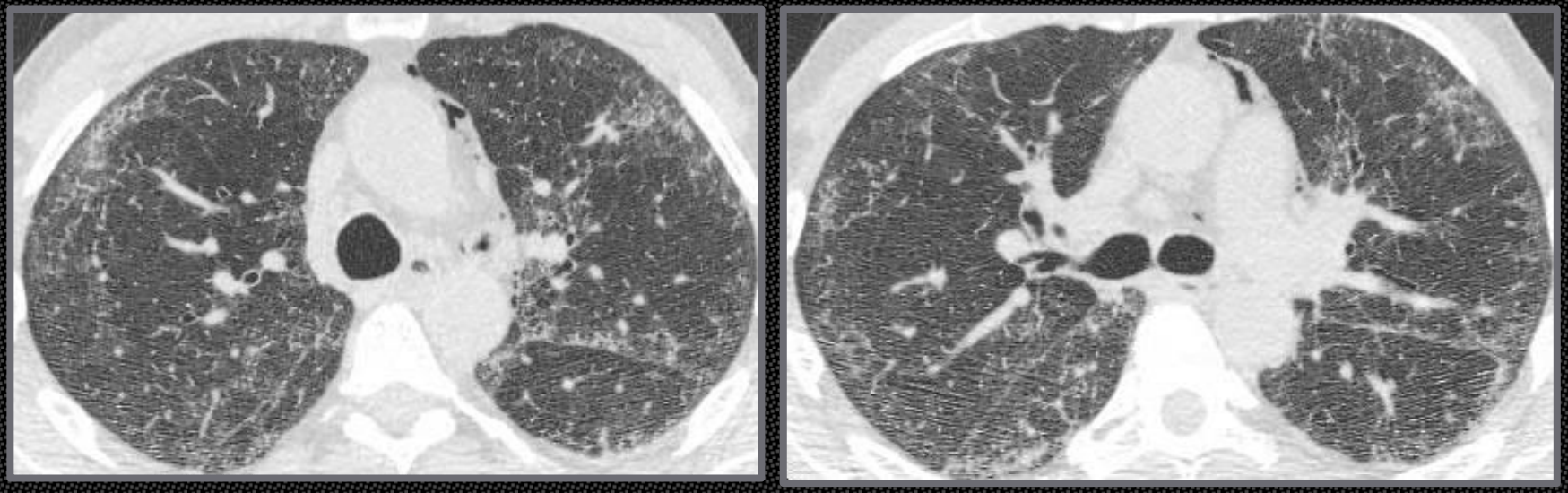
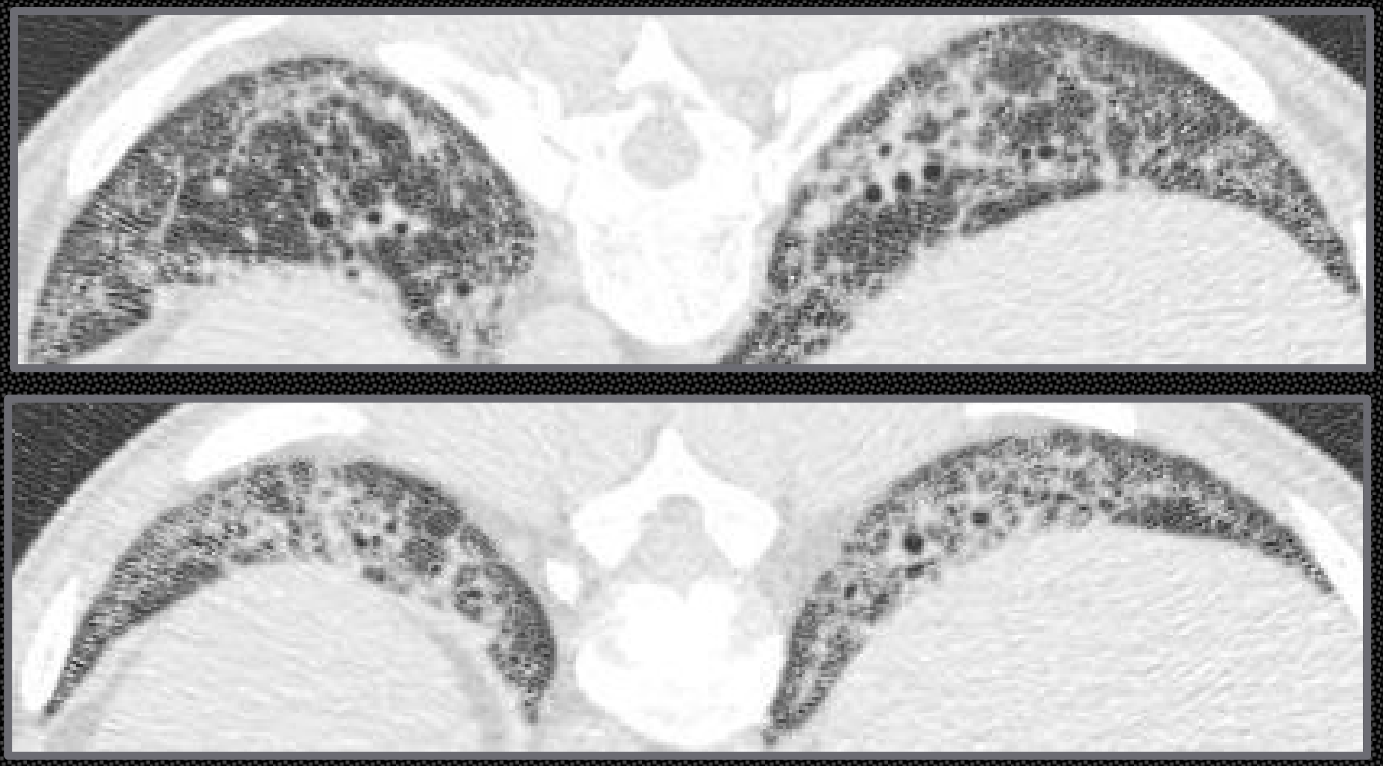
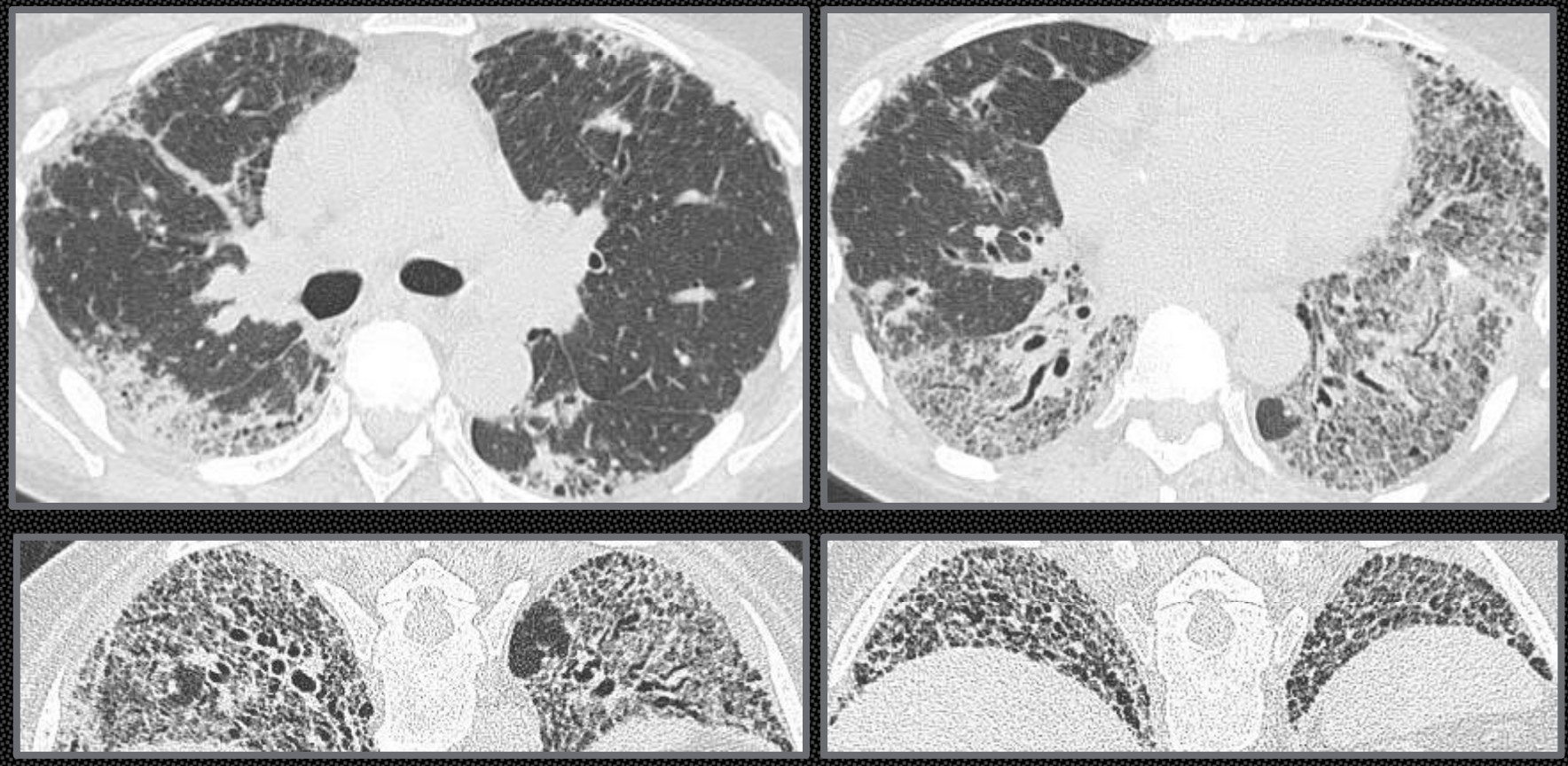
NSIP and Subpleural Sparing: MCTD



NSIP and Subpleural Sparing: MCTD



NSIP: Predated Scleroderma Onset



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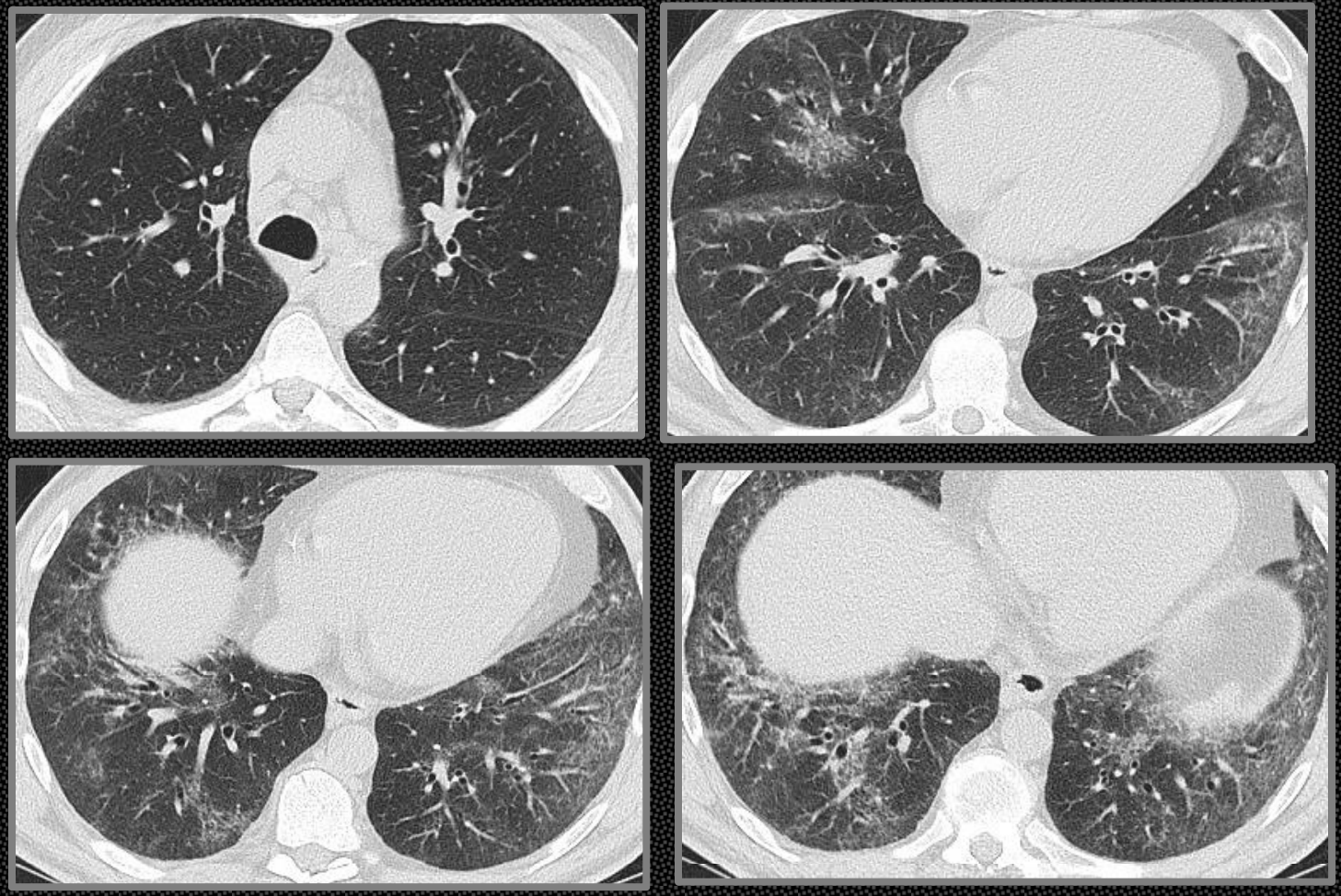
Idiopathic NSIP



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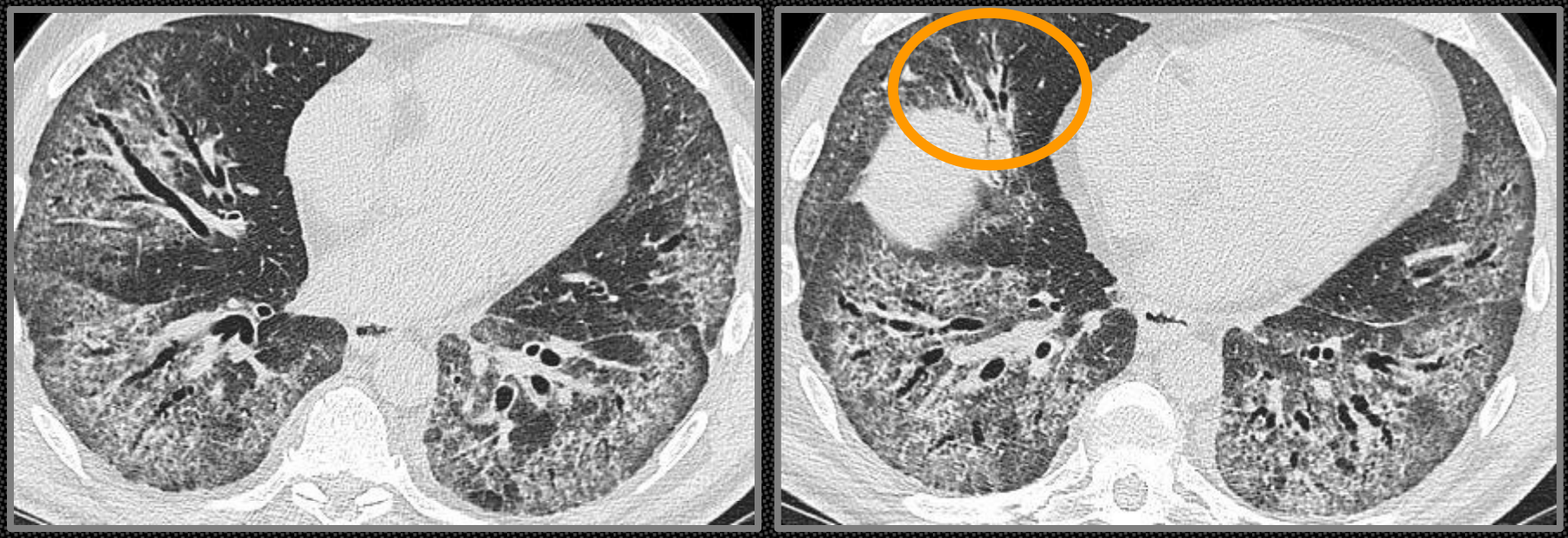
2 Years Later: Fibrotic NSIP Pattern



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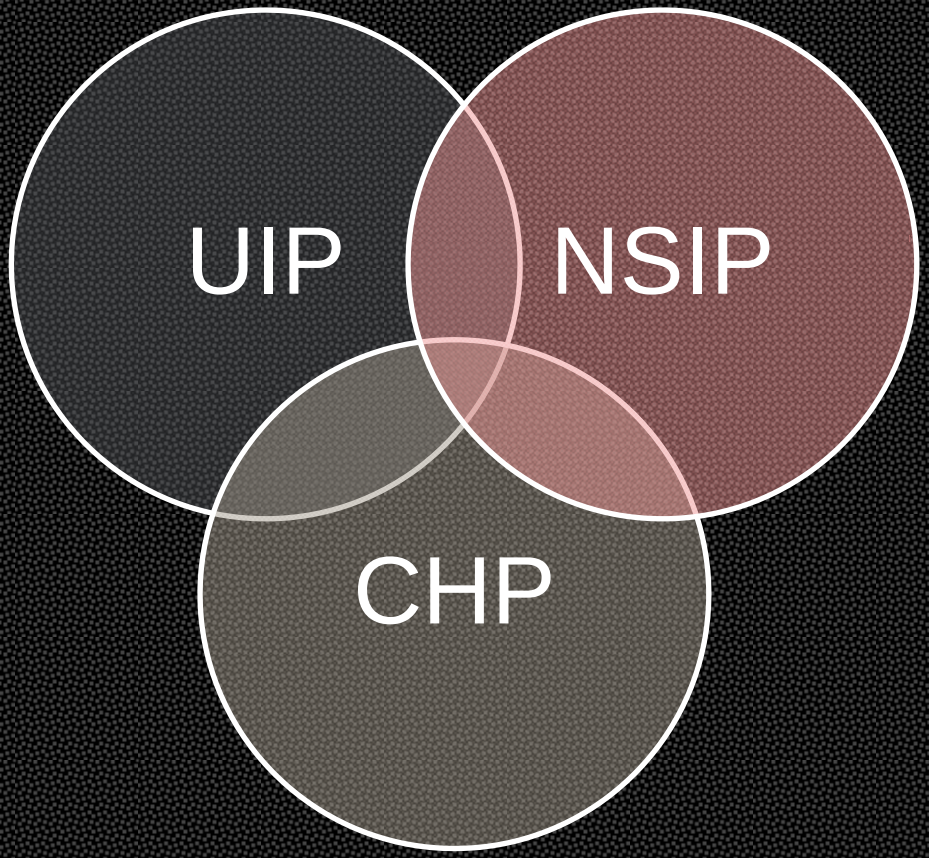
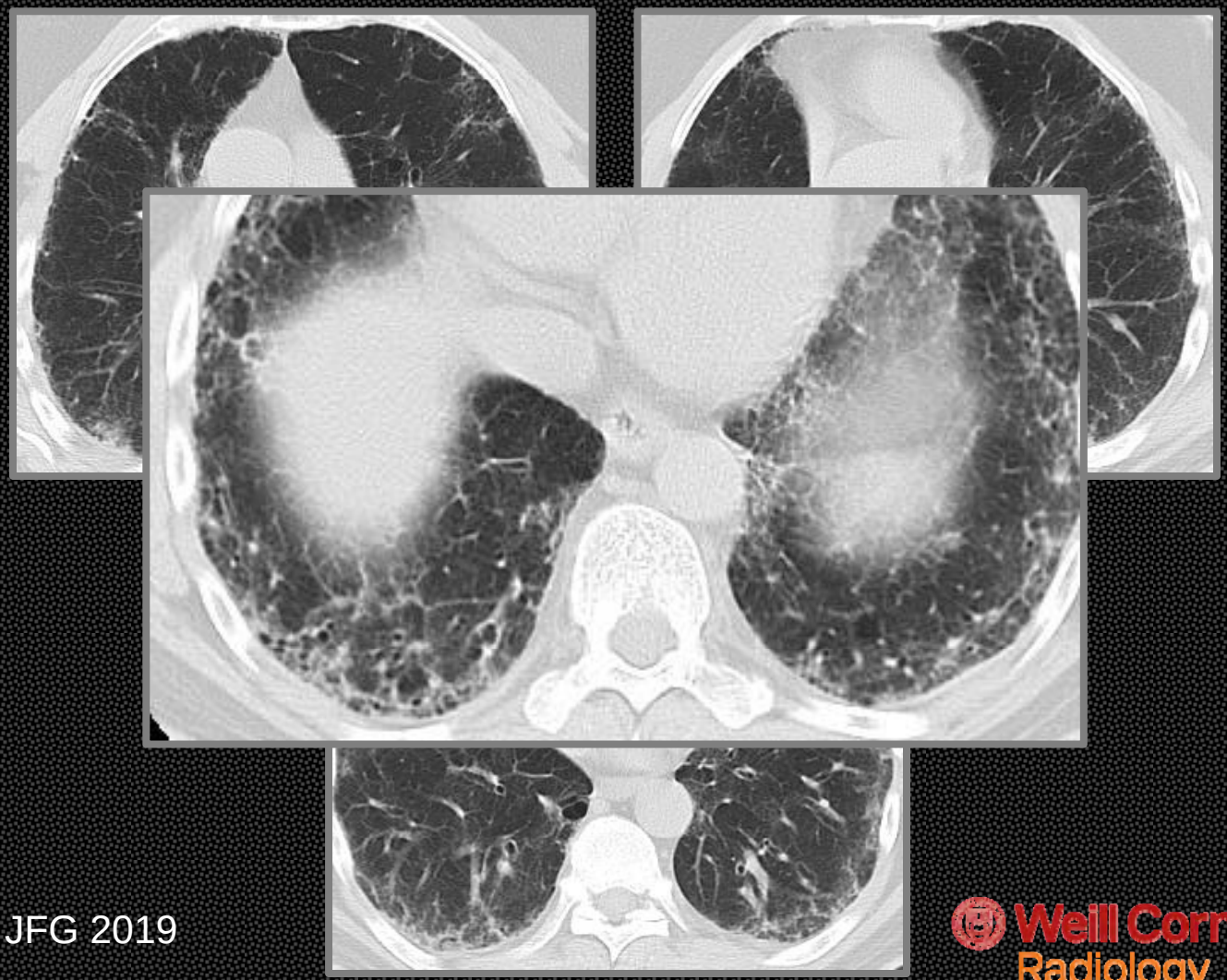
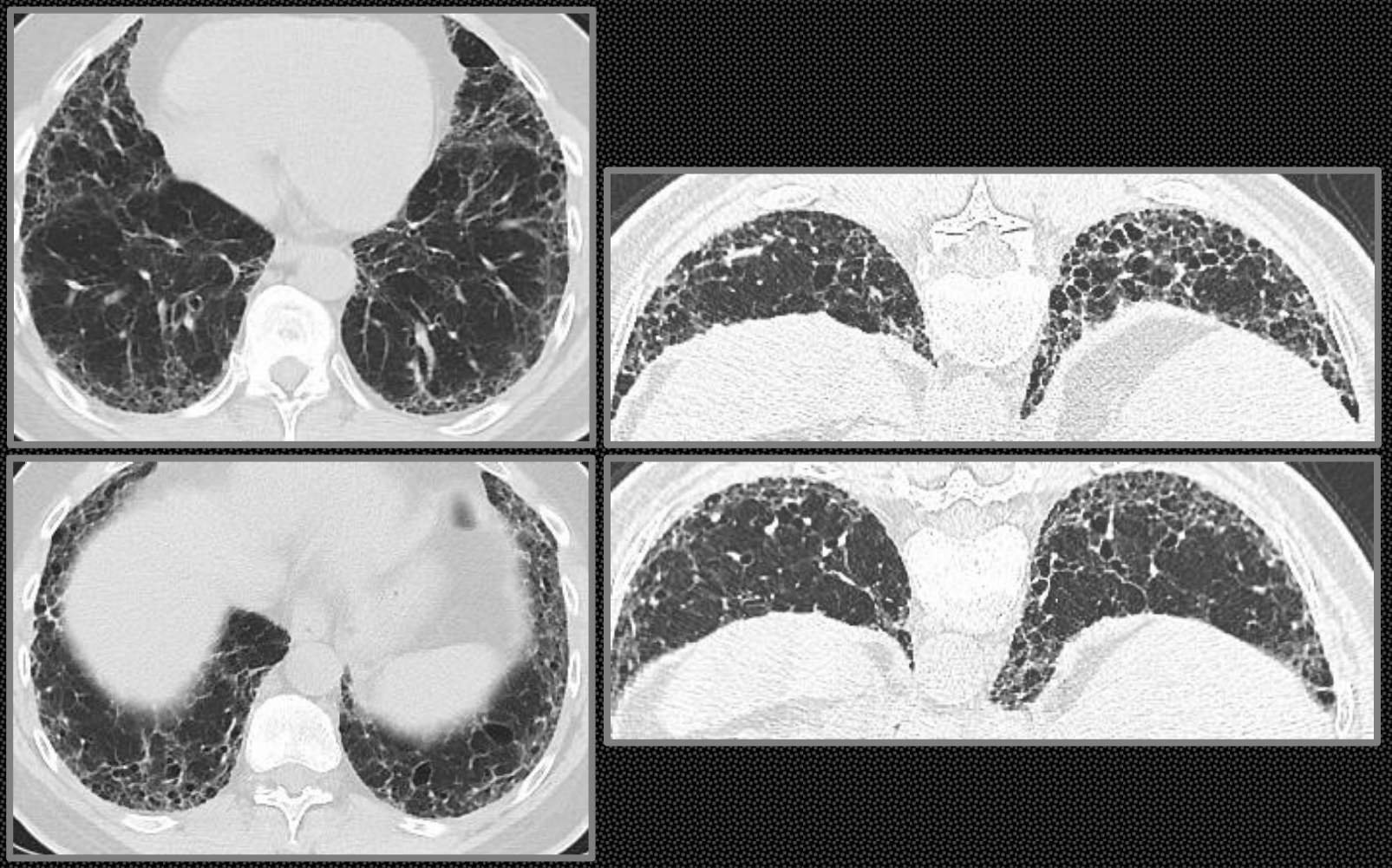
Summary Case



2010: NSIP/UIP



2014: Fibrotic NSIP



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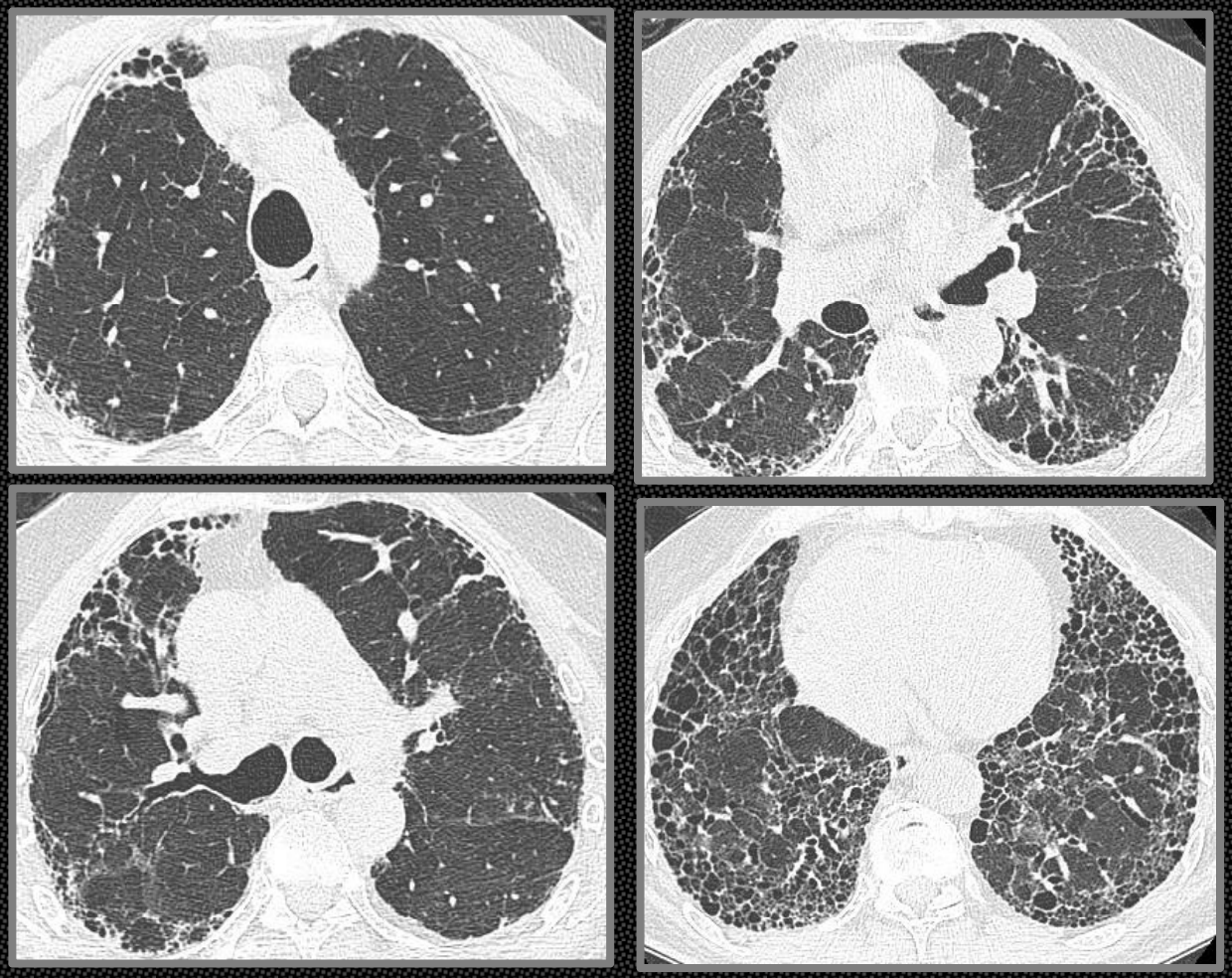
2018: Clear PF-ILD



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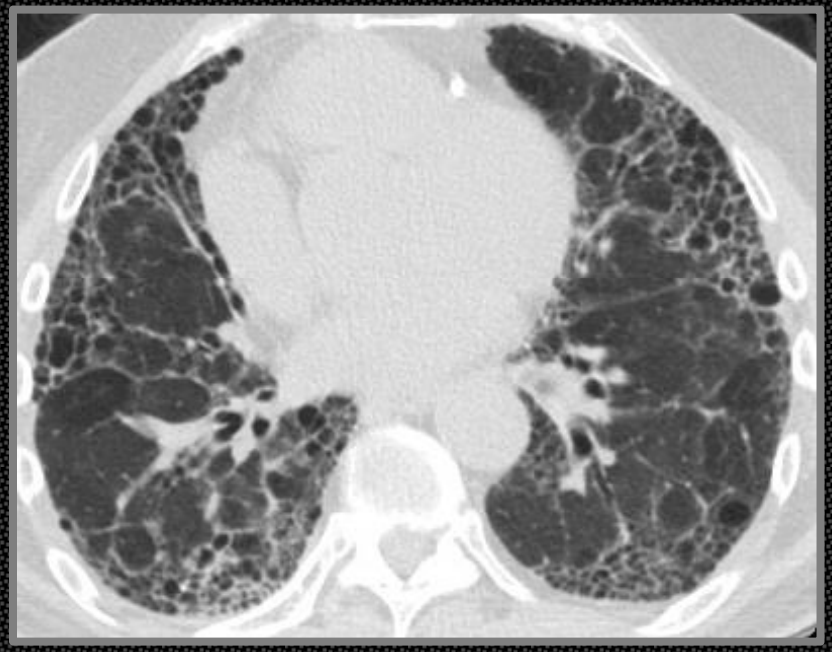
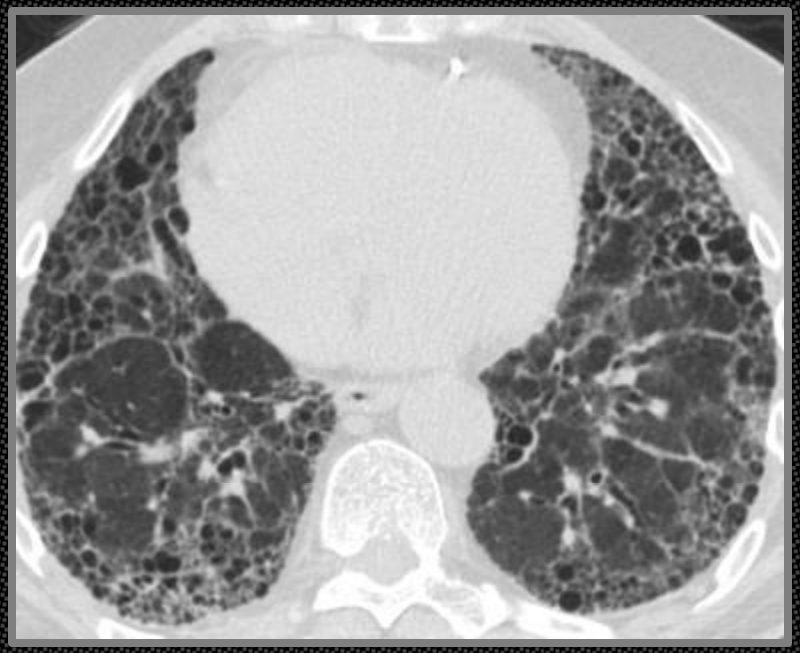
2018 Expiratory: CHP





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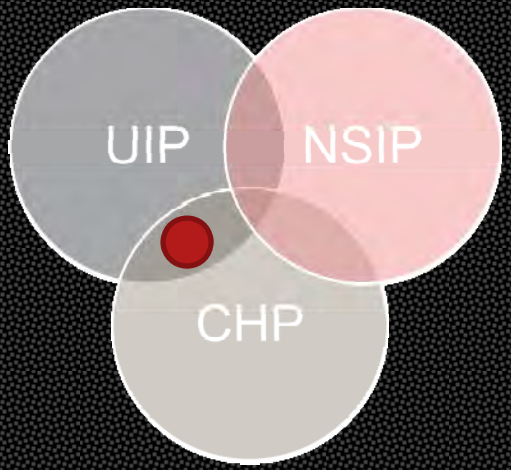
PF-ILD Dictation Template

- "The imaging features are consistent with (progressive) fibrotic interstitial lung disease (PF-ILD) with a (definite UIP, CHP, fibrotic NSIP, overlapping, or other) pattern

PF-ILD Dictation Template

- "The imaging features are consistent with (progressive) fibrotic interstitial lung disease (PF-ILD) with a (definite UIP, CHP, fibrotic NSIP, overlapping, or other) pattern"
- Attempt to quantify and specify fibrosis extent, severity



Concept of PF-ILD: Questions

- Does every PF-ILD carry a poor prognosis? Should all be treated with anti-fibrotic agents?
- Is it reasonable to expand “IPF” to include cases of CHP with no clear inciting antigen?
- How to group patients on treatment (according to CT pattern, severity of fibrosis) and what CT criteria are important to follow (if any)?
- Fibrosis quantification, which findings may respond to therapy, overall role of CT unclear

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