Fibrotic lung diseases: Basic Principles, Common Problems, and Reporting

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Disclosures

Relevant financial relationships:

None

Off-label usage:

None

Learning Objectives

At the end of this course, the participant should be able to do the following:

- Explain the prognostic and therapeutic implications of a diagnosis of IPF versus other fibrotic ILDs
- Describe the international consensus criteria for the diagnosis of IPF, and explain when and how the surgical lung biopsy is used to establish this diagnosis
- Explain the histologic similarities and differences among diseases that produce a UIP pattern
- Explain how to formulate a clinically useful pathology report for fibrotic ILDs

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Lecture Outline

- Basic Principles
- Diagnostic Approach to Common Fibrotic ILDs
- Formulating a Clinically Useful Report

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Medical Training

Biology:	Medicine:
"Disease"	Clinical pattern
↓	↓
Pathology pattern	Pathology pattern
↓	↓
Clinical pattern	"Disease"

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Harsh Reality

Biology:	Medicine:
"Disease"	Clinical pattern Y
↓	↓
Path patterns A, B, or C	Pathology pattern C
↓	↓
Clinical patterns X, Y, or Z	"Disease" R, S, or T

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Diffuse Interstitial Lung Disease:
Patterns change over time

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Part I: Basic Principles

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Diffuse Parenchymal Lung Disease (DPLD)

- DPLD of known cause or association
  - Connective Tissue Diseases
    - RA, SS, lupus, DM/PM, etc.
    - Vasculitic Syndromes
  - Iatrogenic
    - Drug Reactions
    - Radiation
  - Infections / Aspiration / Sepsis
  - Environmental
    - Toxic Exposures
    - Pneumoconioses
  - Miscellaneous
- Idiopathic Interstitial Pneumonias (IIPs)
  - Idiopathic Pulmonary Fibrosis (IPF)
  - Idiopathic Nonspecific Interstitial Pneumonia (NSIP)
  - Respiratory Bronchiolitis-Interstitial Lung Disease (RB-ILD)
  - Desquamative Interstitial Pneumonia (DIP)
  - Cryptogenic Organizing Pneumonia (COP)
  - Acute Interstitial Pneumonia (AIP)
  - Idiopathic Lymphoid Interstitial Pneumonia (LIP)
  - Idiopathic Pleuroparenchymal Fibroelastosis (PPFE)
  - Unclassifiable IIPs
- Granulomatous DPLD: Sarcoidosis, HP
- Others: PLCH, CEP

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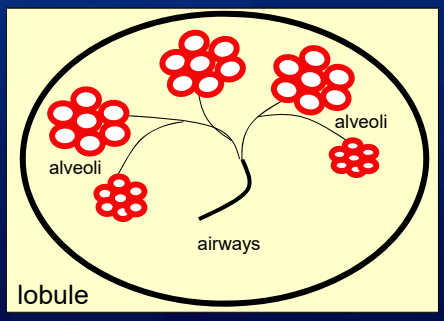
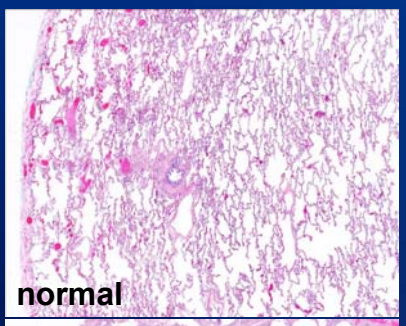
AJRCCM 2002;165:277-304; and *AJRCCM* 2013;*188:733-48.*

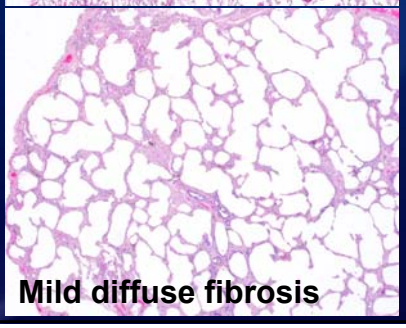
Basic principles of lung injury and repair



mild to moderate injury



normal



Mild diffuse fibrosis

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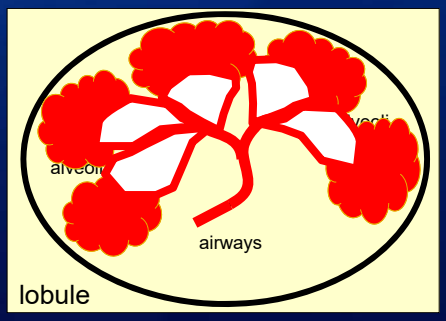
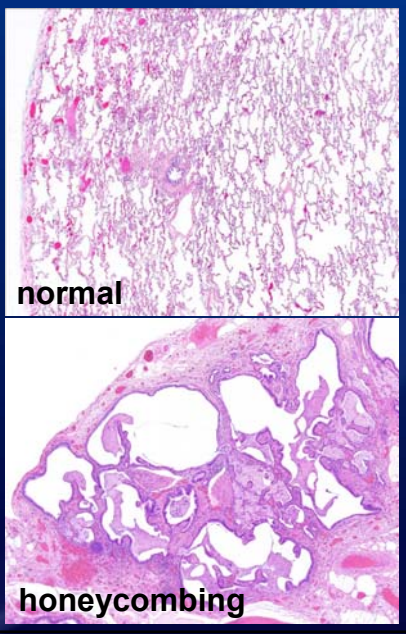
Basic principles of lung injury and repair



severe injury



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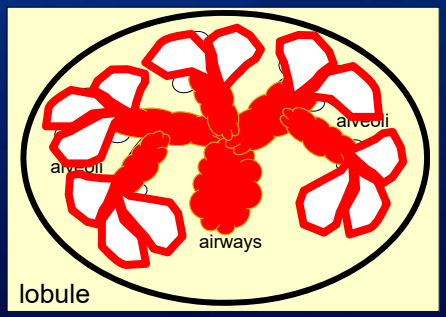
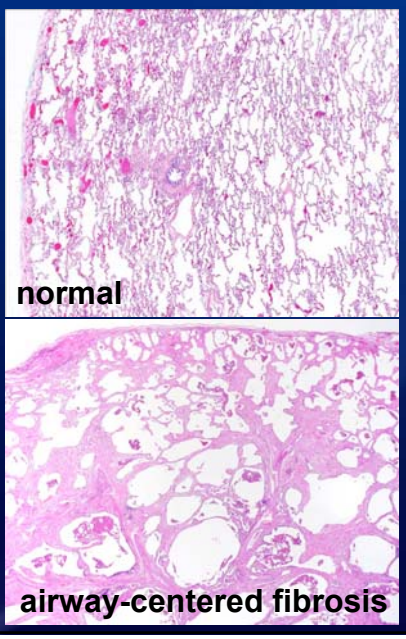
Basic principles of lung injury and repair



inhalational injury:
central



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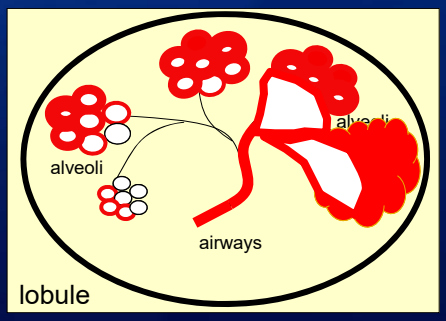
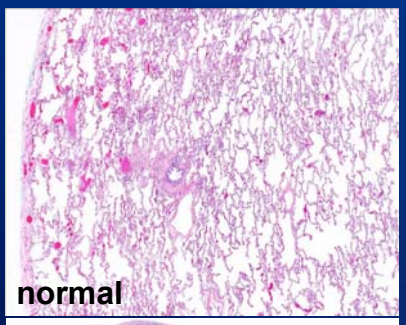
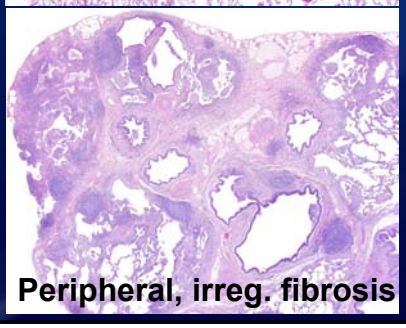
Basic principles of lung injury and repair



autoimmune injury:
peripheral, diffuse, irregular





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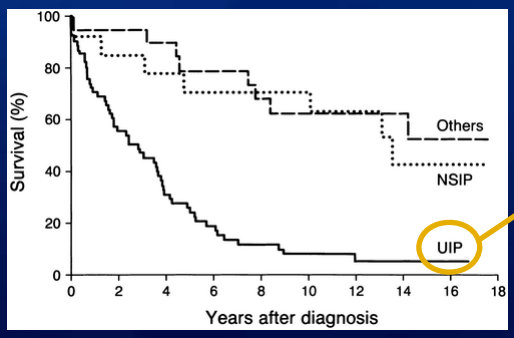
Prognostic significance of <u>histologic patterns</u> of ILD



<u>Idiopathic</u>
- IPF

<u>Non-idiopathic</u>
- Chr HP
- CTD
- Asbestosis
- Chr drug rxn
- Etc.

Bjoraker JA et al., *Am J Respir Crit Care Med* 1998 Jan;157(1):199-203

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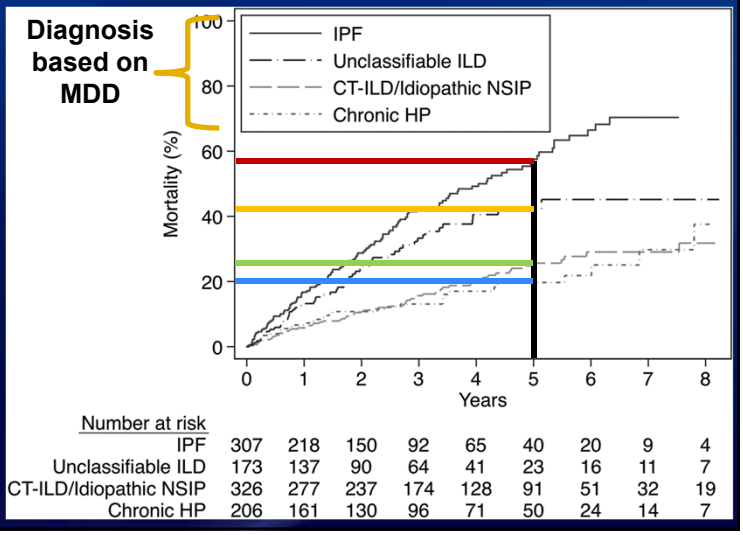
Prognostic significance of <u>etiology</u> of ILD



CHEST

Chest. 2014;145(4):723-728.

Unadjusted Kaplan-Meier figure stratified by ILD subtype. CT-ILD = connective tissue disease-associated interstitial lung disease; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia.

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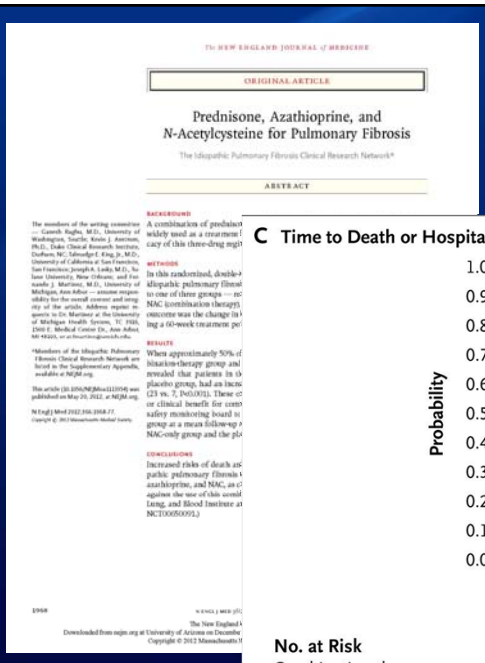

ORIGINAL ARTICLE

Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

ABSTRACT

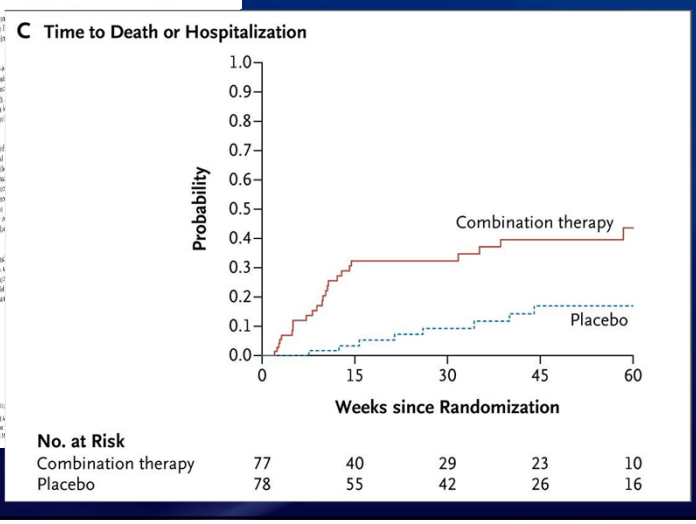
BACKGROUND

METHODS

RESULTS

CONCLUSIONS

N Engl J Med. 2012 May 24;366(21):1968-77.



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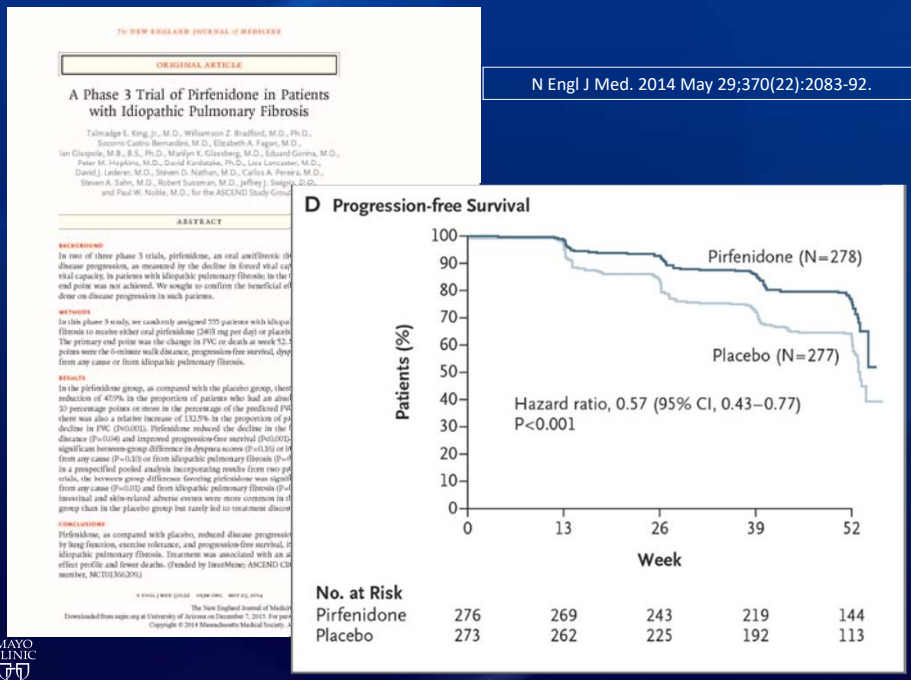

N Engl J Med. 2014 May 29;370(22):2083-92.

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Treatment Differences in 2018

IPF	CTD-ILD	Chr HP
• Anti-fibrotic agents (perfenidone, nintedanib) • PPI • AVOID immunosuppression	• Prednisone • Azathioprine • Mycophenolate • Methotrexate • Cyclophosphamide • Rituximab	• Removal of offending antigen • Steroids • Rituximab?

- **Pattern matters**
- **Etiology matters**

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Part II: Diagnostic Approach to Fibrotic ILDs

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Algorithmic approach to Fibrotic ILD

Don't panic. → Fibrosis?

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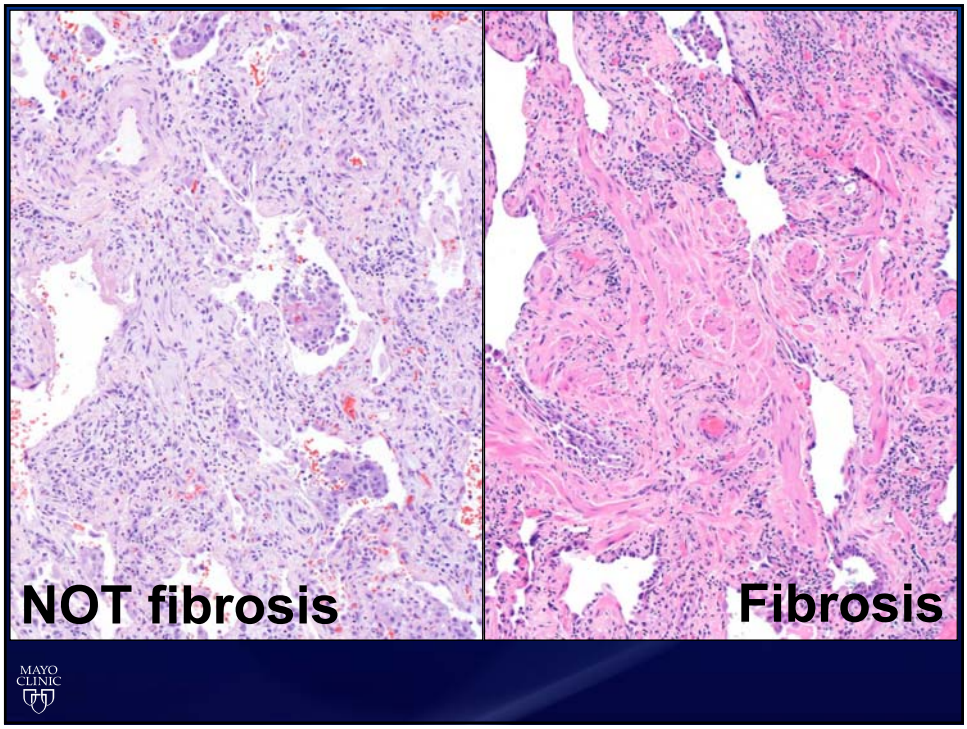

Algorithmic approach to Fibrotic ILD

Don't panic. → Fibrosis? → yes → UIP? → yes → "UIP" → UIP of IPF? (multidisciplinary discussion)

Fibrosis? → no → Acute lung injury
-DAD, OP, infection, drug rxn, CTD, infarct, vasculitic syndrome, EP, idiopathic, etc.
Cellular infiltrates
-Infection, HP, drug rxn, CTD, LIP, EP, vasculitic syndrome, lymphoma, etc.
Alveolar filling
-OP / Org. DAD, RB, infection, PAP, malignancy, etc.
Nodules
-Neoplasia, nodular LH, granulomas, infection, PLCH, pneumoconiosis, etc.
Small airway disease
-Constrictive bronchiolitis, chronic aspiration, immunodeficiency, IBD, etc.
Vascular disease
-Pulm. HTN, PVOD, PCH, intravenous talcosis, thromboembolic disease, vasculitic syndrome, etc.
Misc.

UIP? → no → Connective tissue disease
Idiopathic NSIP
DIP / SRIF
Pneumoconiosis
Sarcoidosis / berylliosis
Small airway disease
PLCH
Malignancy
IgG4-related disease
Erdheim-Chester
Hermansky-Pudlak
PPFE
Misc.

UIP of IPF? → yes → UIP/IPF

UIP of IPF? → maybe, no → -Connective tissue disease?
-Chronic HP?
-Advanced PLCH?
-End-stage sarcoidosis?
-Erdheim-Chester?
-Hermansky-Pudlak?
-Other?

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Idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis

- Idiopathic (dx of exclusion!)
- Most common in elderly (usu. >60 yrs)
- Strongly associated with smoking
- Relentlessly progressive
- Median survival <3 yrs
- UIP pattern on imaging
- UIP pattern on histology

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Usual Interstitial Pneumonia

- UIP is a pathologic PATTERN, not a disease!
- Spatially heterogeneous fibrosis
  - Patchy
  - Architectural distortion (honeycombing)
  - Subpleural / peripheral
  - Lower lung zones
- Temporally heterogeneous fibrosis
  - Old fibrosis
  - Young fibrosis – fibroblast foci

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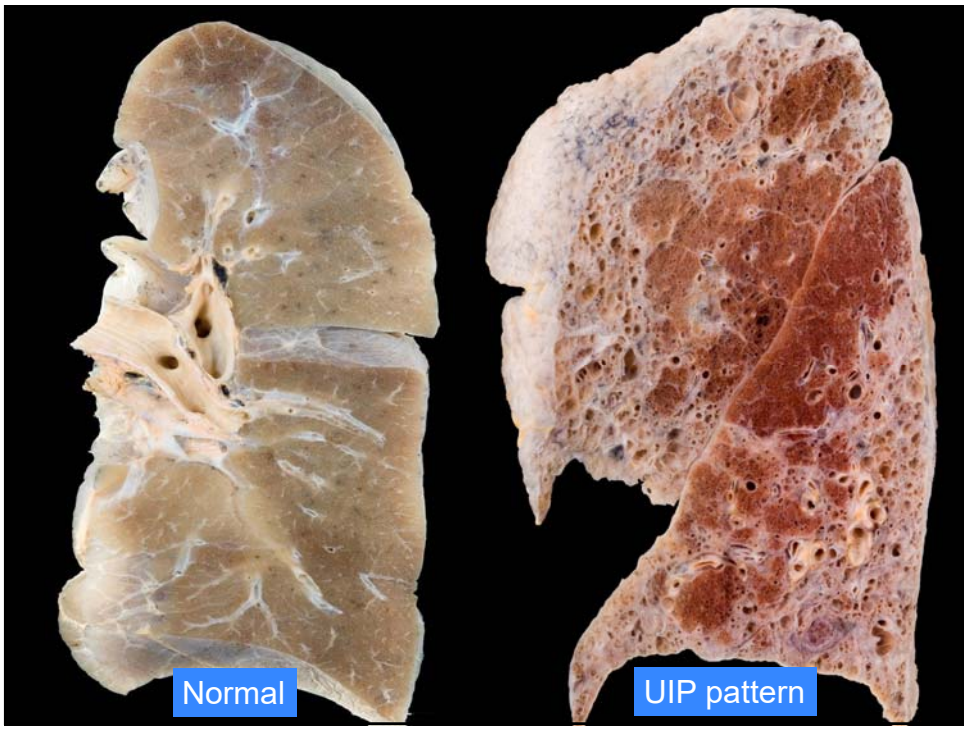
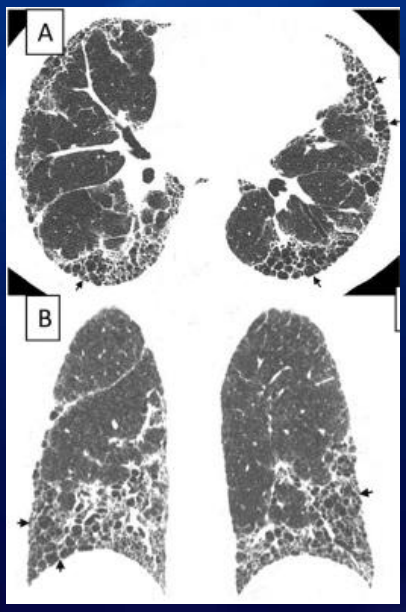


Radiologic UIP pattern in IPF



- Reticular abnormalities (i.e. fibrosis)
- Subpleural, basal predominance
- Honeycombing ± traction bronchiectasis
- No features inconsistent with UIP pattern

Raghu G et al., Am J Respir Crit Care Med. 2011;183:788-824

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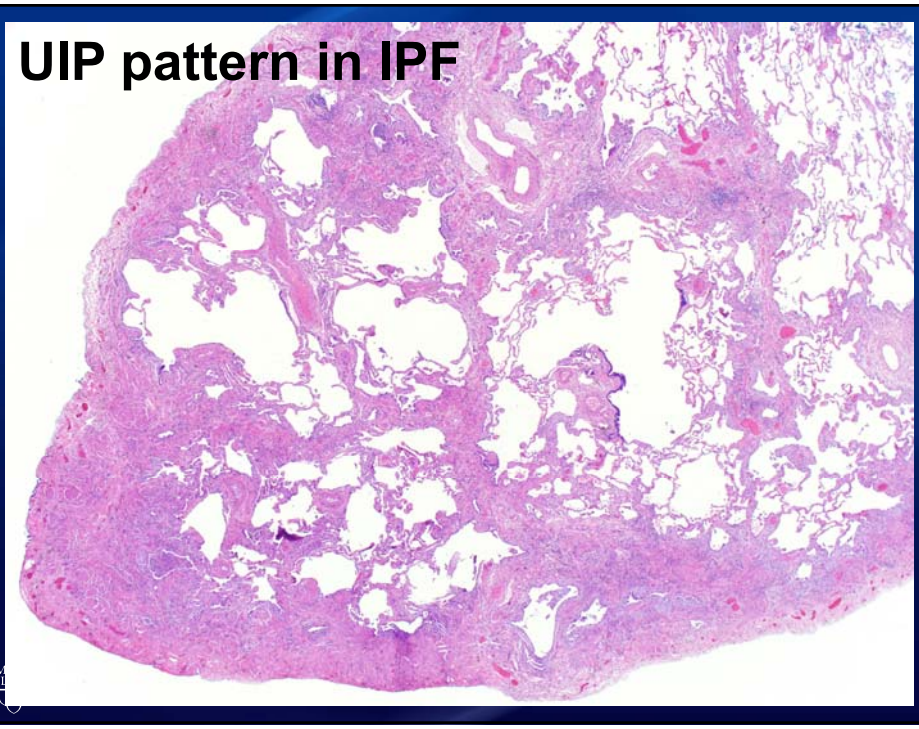
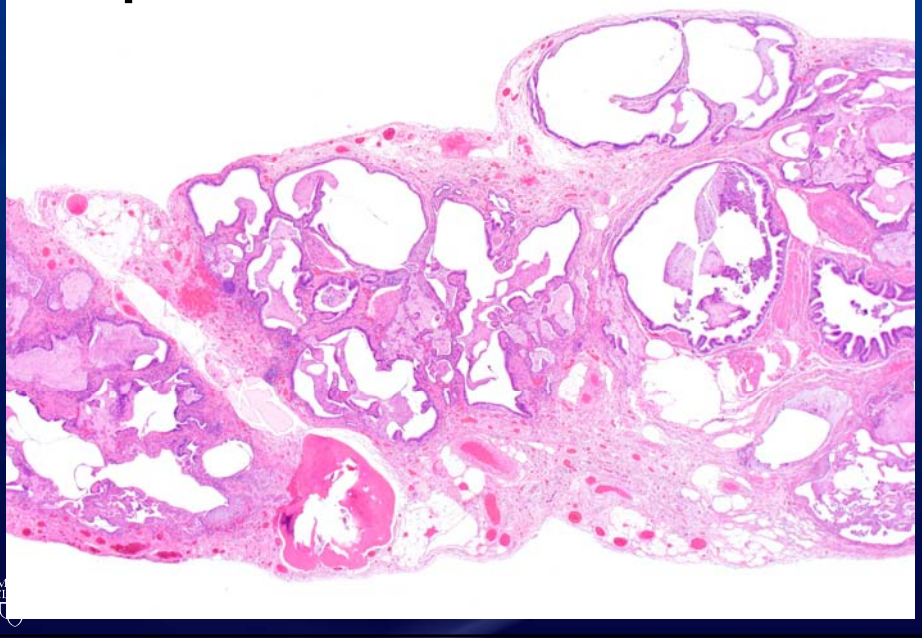
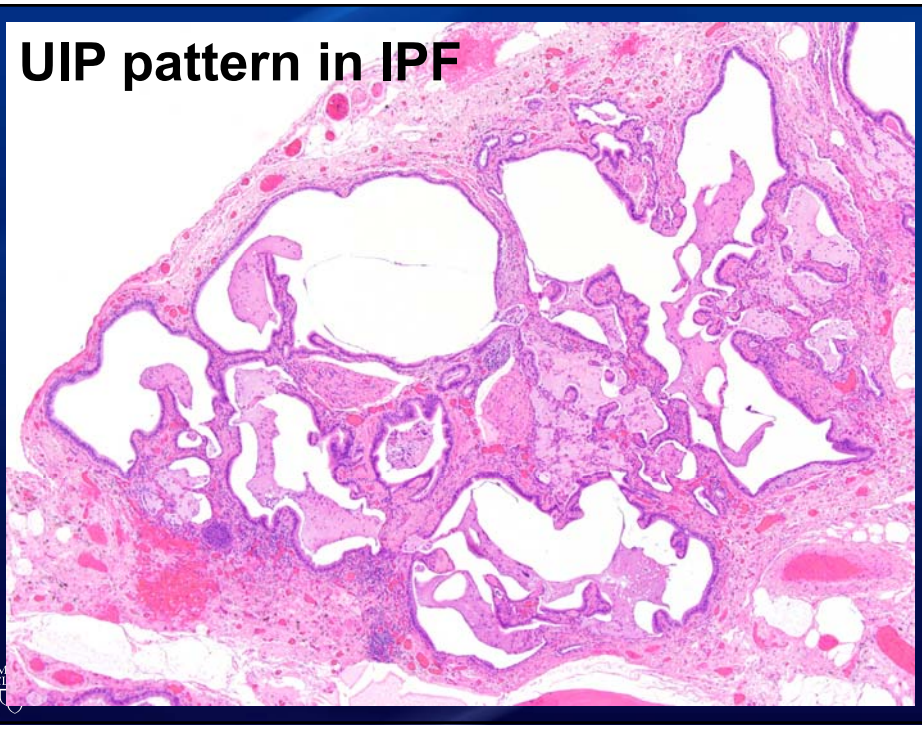
UIP pattern in IPF

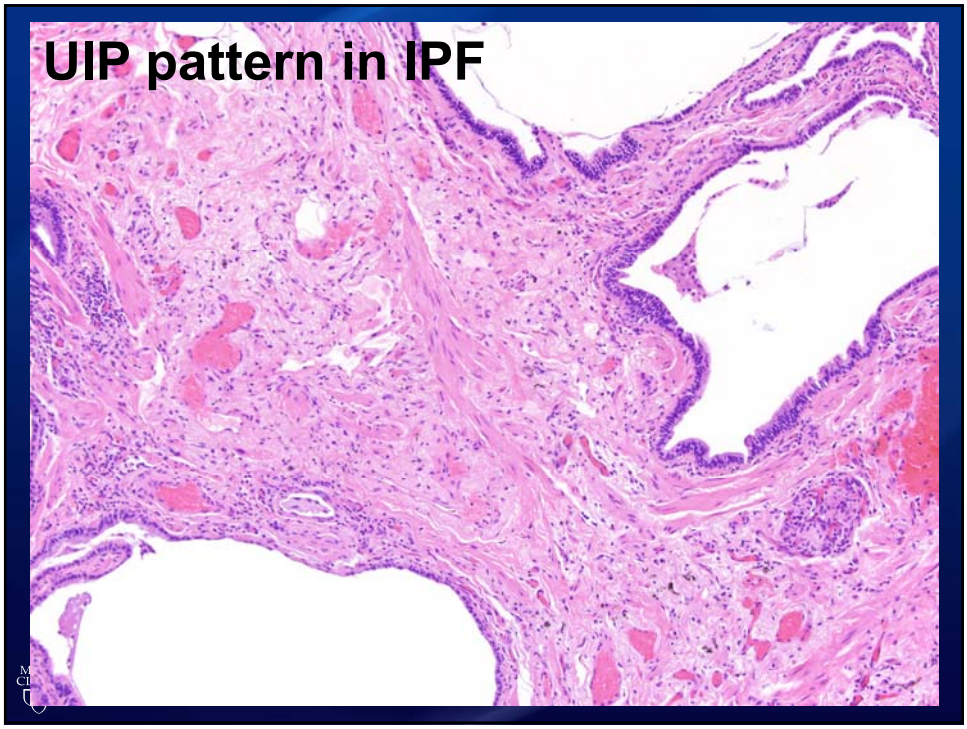


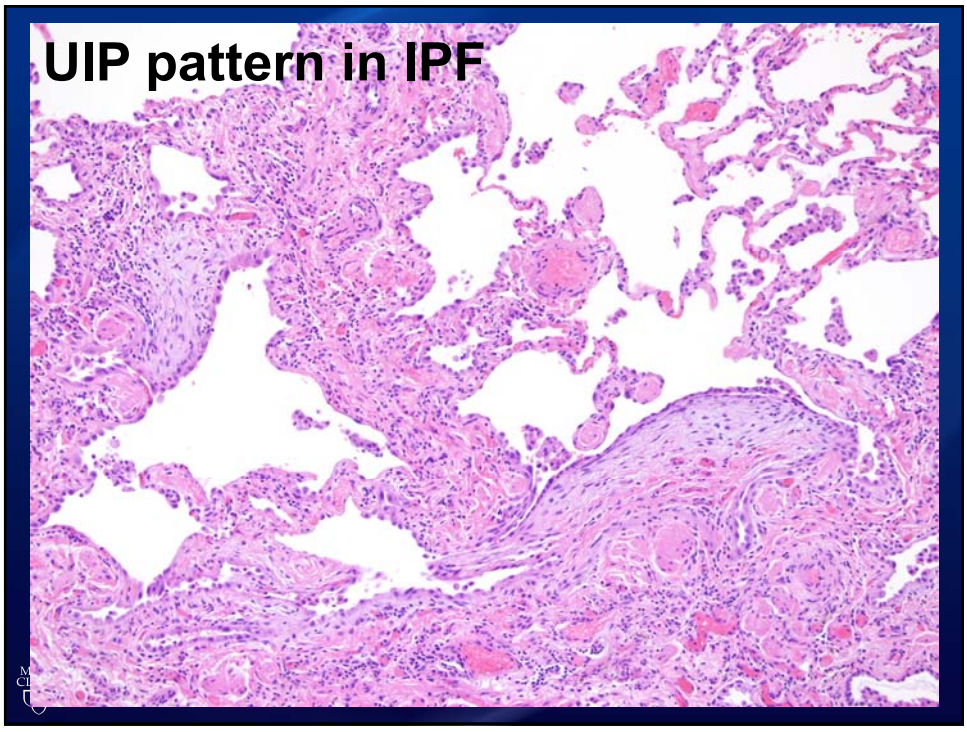
UIP pattern in IPF



UIP pattern in IPF




UIP pattern in IPF


UIP pattern in IPF

Histologic UIP pattern in IPF

UIP Pattern (All Four 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)

Raghu G et al., Am J Respir Crit Care Med. 2011;183:788-824

Diagnosis of IPF: ATS/ERS/JRS/ALAT Guidelines

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.
* Can be associated with acute exacerbation of idiopathic pumonary fibrosis.
† An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.
‡ This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.

Raghu G et al., Am J Respir Crit Care Med. 2011;183:788-824

Dx of IPF: ATS/ERS/JRS/ALAT Guidelines

TABLE 6. COMBINATION OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY AND SURGICAL LUNG BIOPSY FOR THE DIAGNOSIS OF IPF (REQUIRES MULTIDISCIPLINARY DISCUSSION)

HRCT Pattern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis of IPF?†
UIP	**UIP** **Probable UIP** **Possible UIP** **Nonclassifiable fibrosis‡**	**YES**
	Not UIP	No
Possible UIP	**UIP** **Probable UIP**	**YES**
	Possible UIP Nonclassifiable fibrosis	Probable§
	Not UIP	No
Inconsistent with UIP	UIP	Possible§
	Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP	No

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

Bold type indicates combinations of HRCT and surgical lung biopsy patterns that correspond with a diagnosis of IPF (a YES in the far right column). The combination of UIP HRCT and probable UIP or possible UIP or Nonclassifiable fibrosis (surgical lung biopsy patterns) (for example) equals a diagnosis of IPF; the combination of UIP HRCT and Not UIP (surgical lung biopsy pattern) does not make the diagnosis of IPF.

* Patterns as described in Tables 4 and 5.

‡ Nonclassifiable fibrosis: Some biopsies may reveal a pattern of fibrosis that does not meet the above criteria for UIP pattern and the other idiopathic interstitial pneumonias (1) (*see text*). These biopsies may be termed "nonclassifiable fibrosis."

† The accuracy of the diagnosis of IPF increases with multidisciplinary discussion (MDD). This is particularly relevant in cases in which the radiologic and histopathologic patterns are discordant (e.g., HRCT is inconsistent with UIP and histopathology is UIP). There are data to suggest that the accuracy of diagnosis is improved with MDD among interstitial lung disease experts compared to clinician-specialists in the community setting (126); timely referral to interstitial lung disease experts is encouraged.

§ Multidisciplinary discussion should include discussions of the potential for sampling error and a re-evaluation of adequacy of technique of HRCT. NOTE: In cases with an "inconsistent with UIP" HRCT pattern and a "UIP" surgical lung biopsy pattern, the possibility of a diagnosis of IPF still exists and clarification by MDD among interstitial lung disease experts is indicated.

Raghu G et al., Am J Respir Crit Care Med. 2011;183:788-824

Connective tissue disease-associated ILD

CTD-associated ILD

- Lung fibrosis due to CTD
- Most common: RA, PSS, SLE, PM/DM, SS
- Significant ILD ~15%, subclinical nearly 50%
- ~10% present initially with ILD!
- UIP histology: usually RA (others usually NSIP)
- Imaging: UIP or NSIP
- Treatment: Steroids, immunosuppression, LTx

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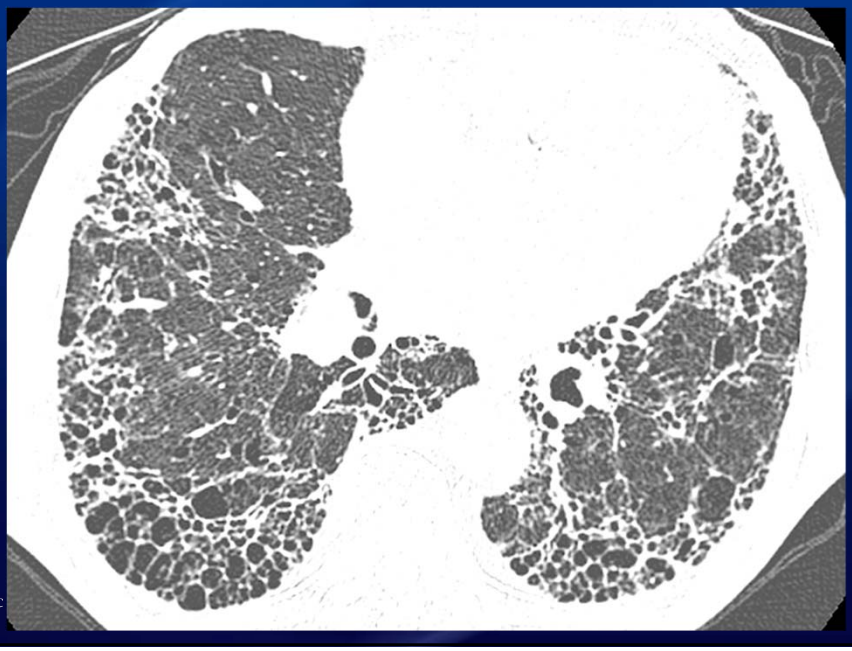
Rheumatoid arthritis – radiologic UIP



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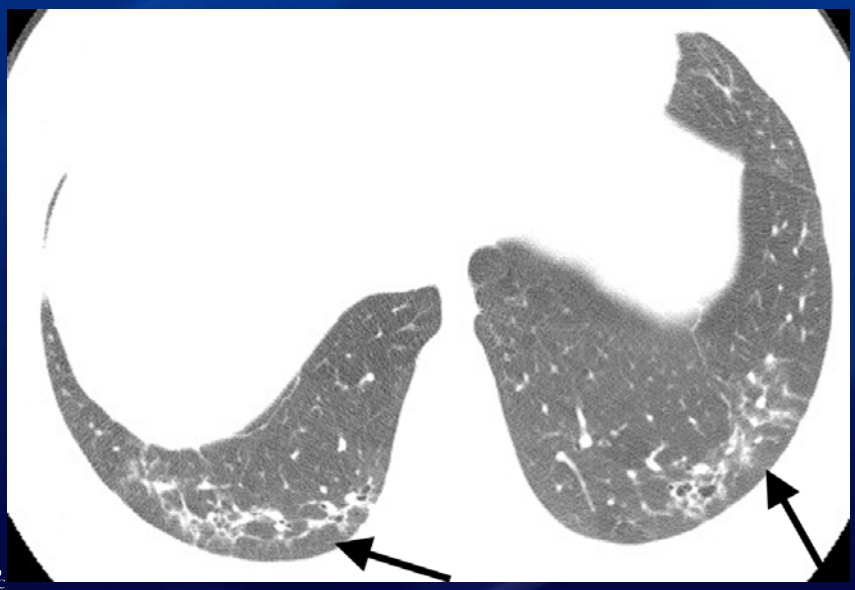
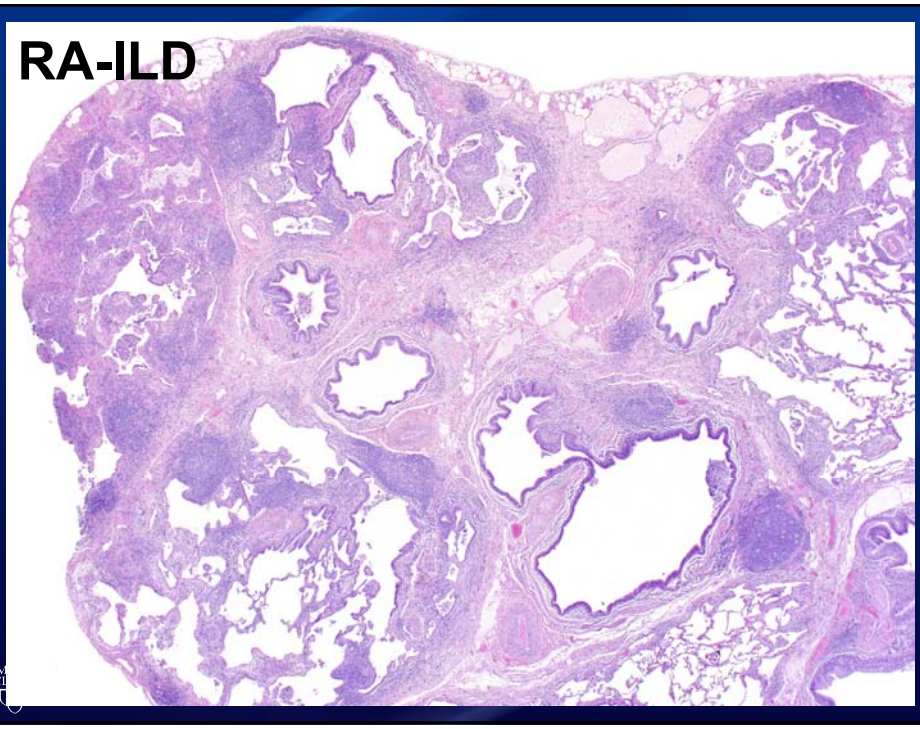
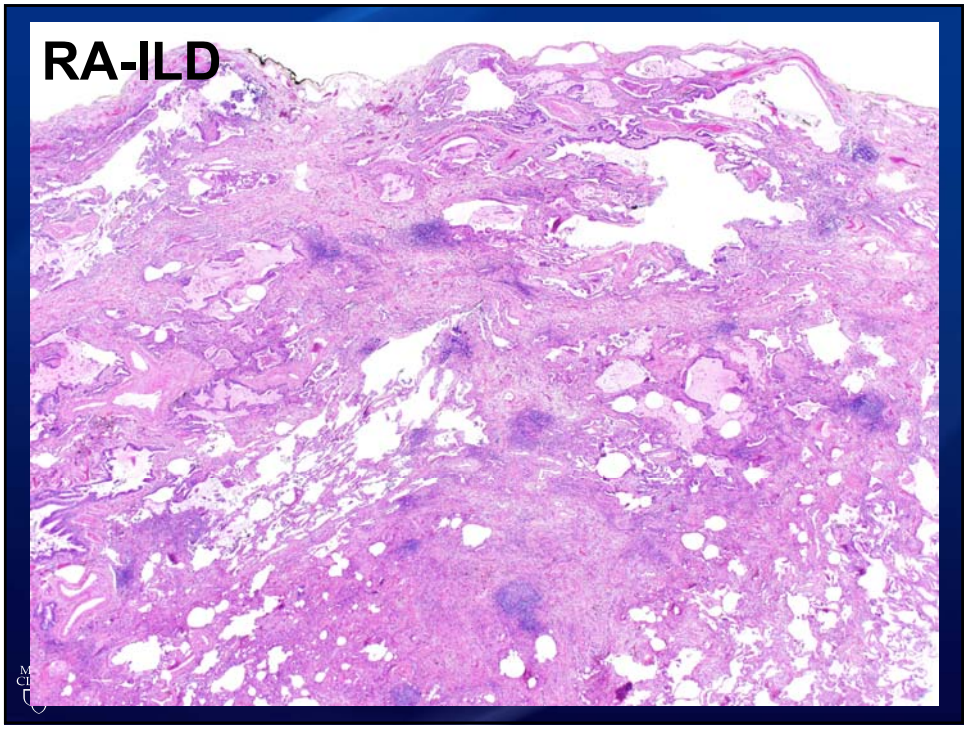
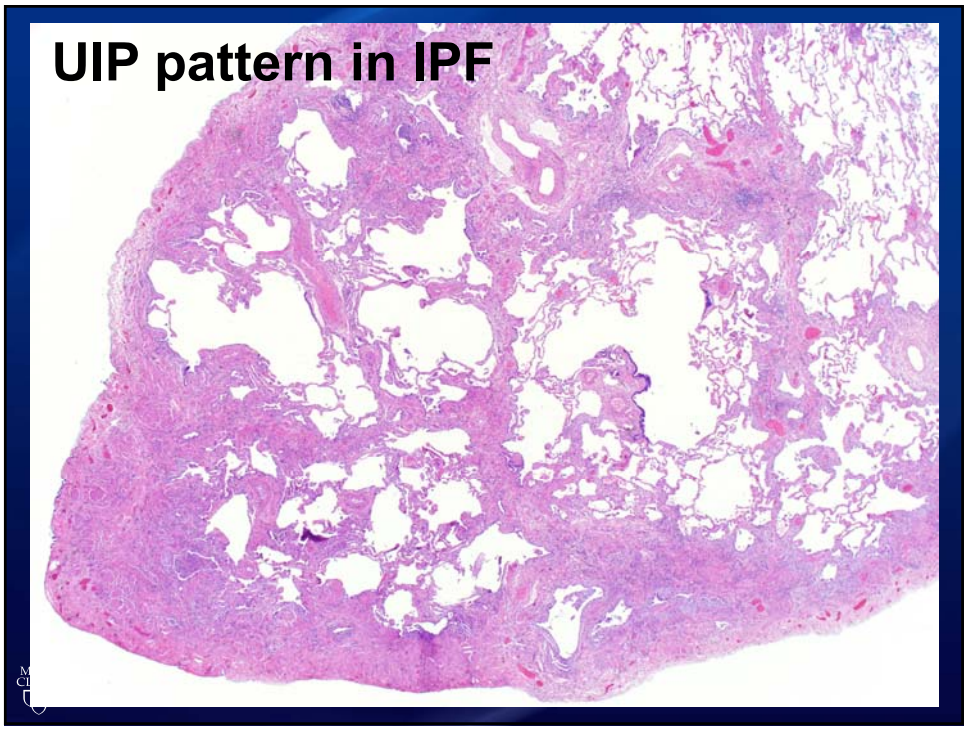
RA with radiologic NSIP pattern

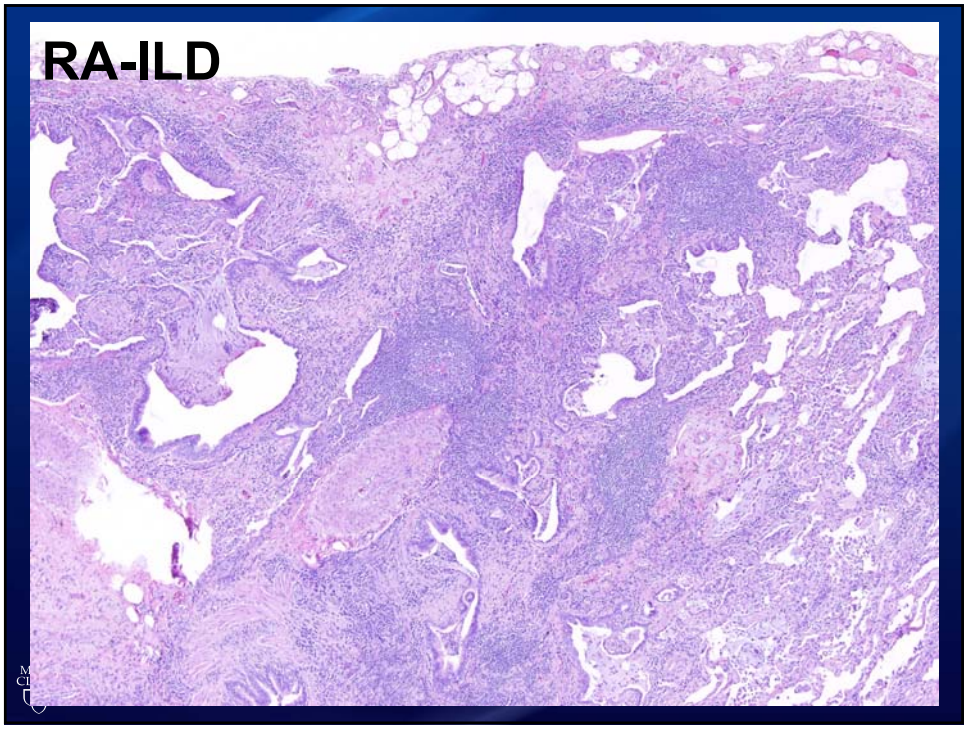


RA-ILD




RA-ILD


UIP pattern in IPF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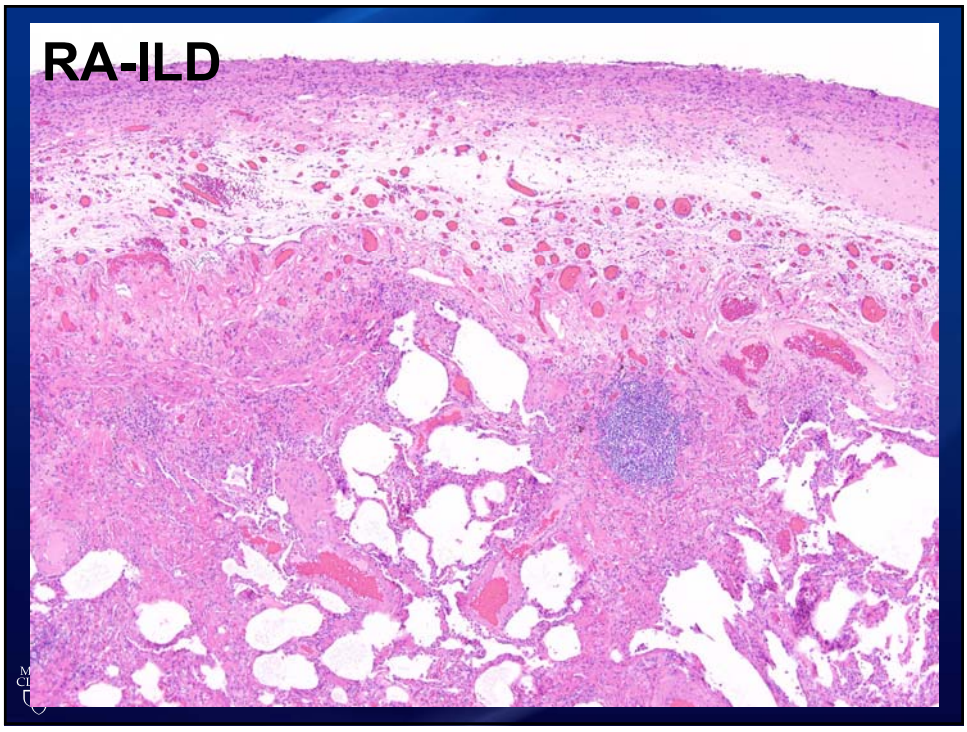
RA-ILD

Chronic hypersensitivity pneumonitis

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Chronic HP

- Lung fibrosis due to exaggerated immune response to inhaled organic antigen
- Antigens: Avian, fungal, bacterial, protozoal proteins, or LMW organic compounds
- Usually NOT smokers
- Treatment: Removal of antigen, steroids, LTx

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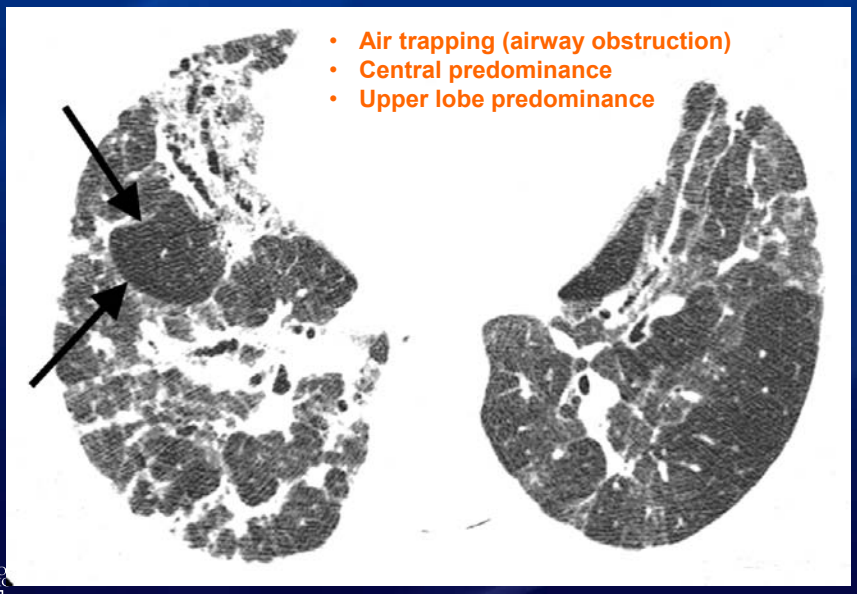
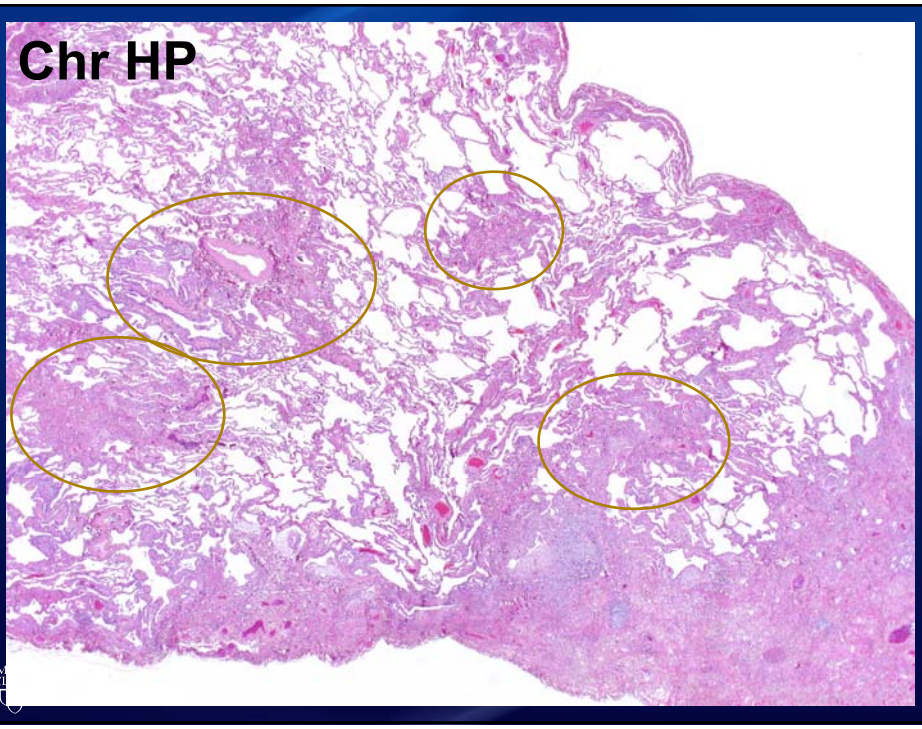
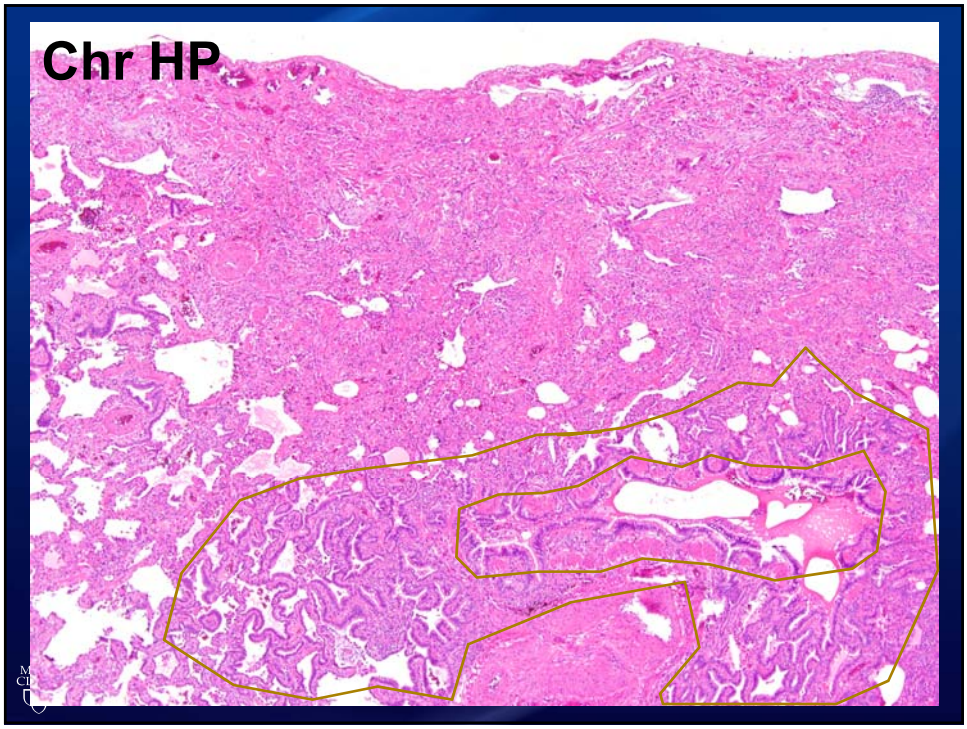
Chronic HP

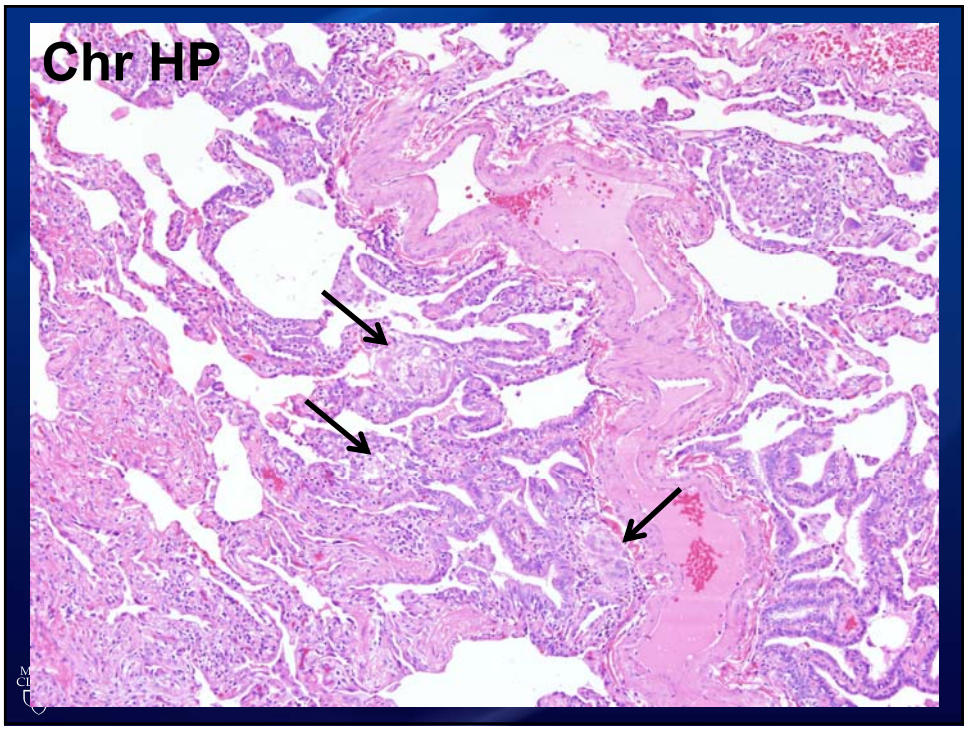


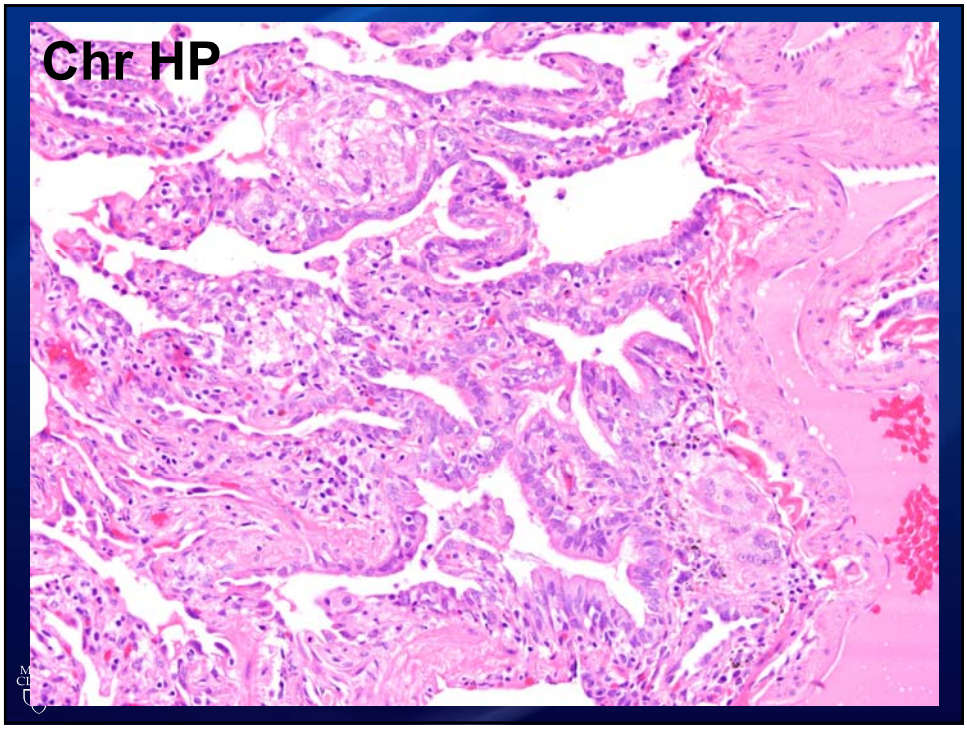
- Air trapping (airway obstruction)
- Central predominance
- Upper lobe predominance

Chr HP




Chr HP


Chr HP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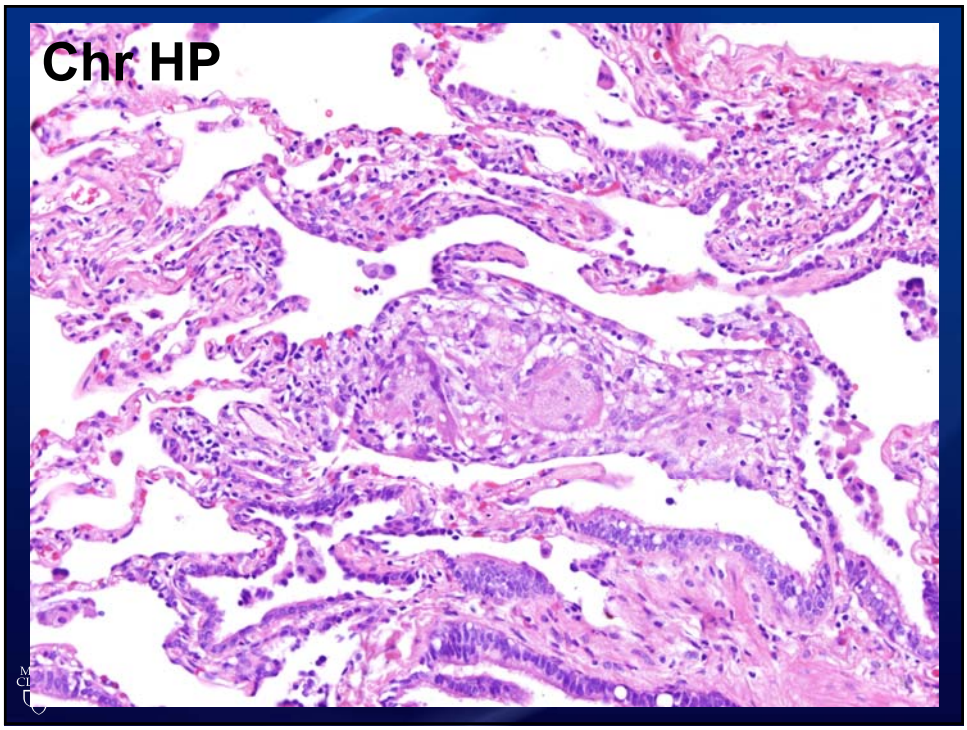
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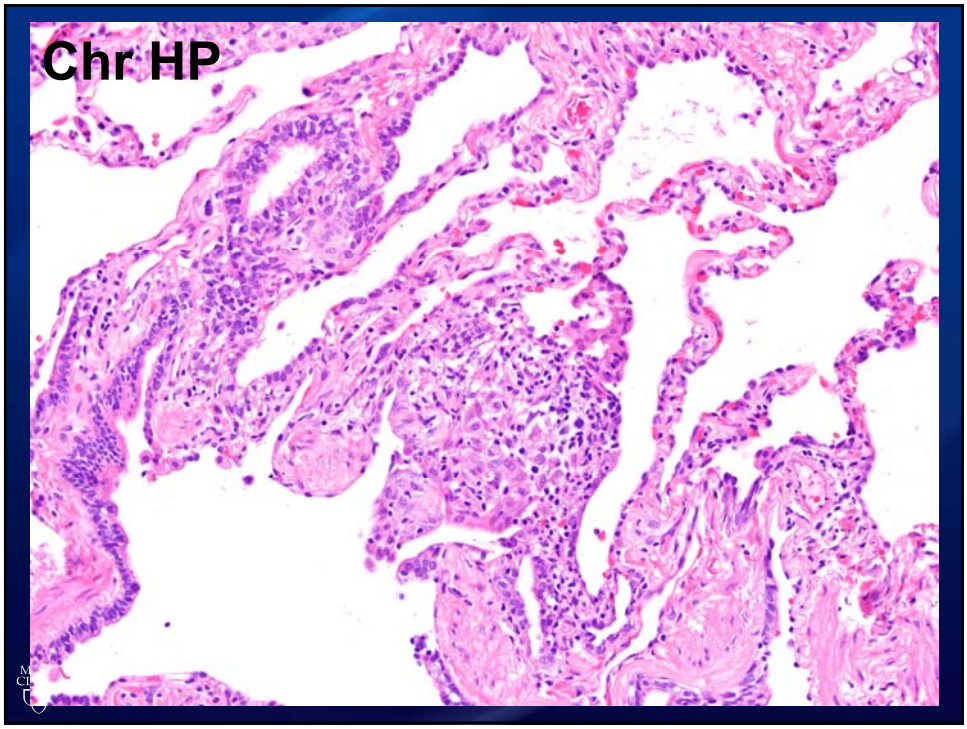
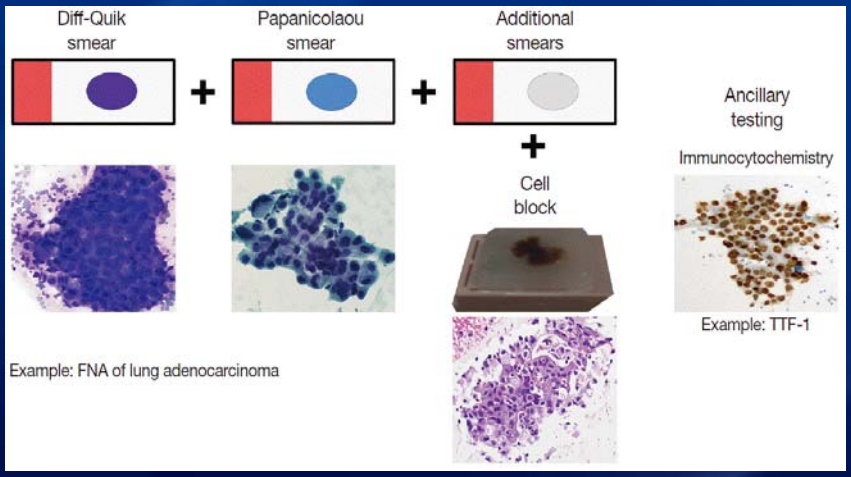


Part III: Formulating a Clinically Useful Pathology Report

Pathology Reporting: Clinician Expectations

- What do you see?
- How bad is it?
- What is causing it?
- How do I treat it?



Adapted from Roh MH, J Pathol Transl Med. 2015:49:300-9.

Pathology Reporting: Clinician Expectations

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Lymph node, left supraclavicular, core biopsy:
Metastatic adenocarcinoma, poorly differentiated, most likely from the lung (see Comment).

Comment: Immunostaining for TTF-1 is positive, indicating that the tumor most likely arose in the lung. Material will be sent to an outside lab for molecular testing for potential targetable mutations, and will be reported separately.

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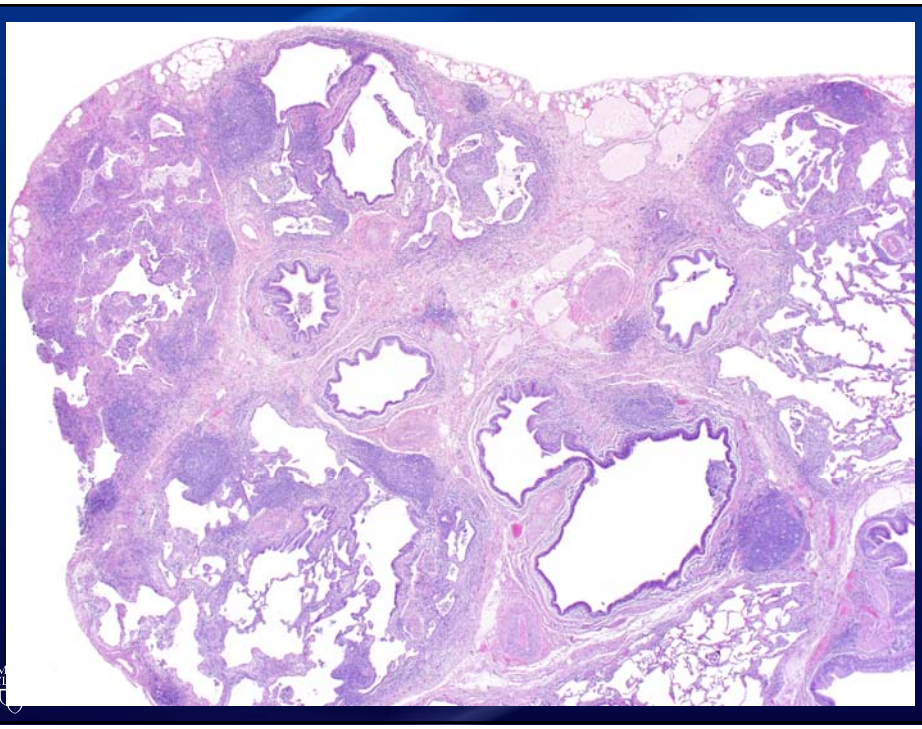

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Clinician Toolbox for ILD

1. Antibiotics
2. Bronchodilators and anti-tussives
3. Immunosuppression
4. Small molecule therapy for IPF (perfenidone and nintedanib)
5. PPIs for GERD and microaspiration
6. Pulm HTN disease-modifying agents
7. Transplantation

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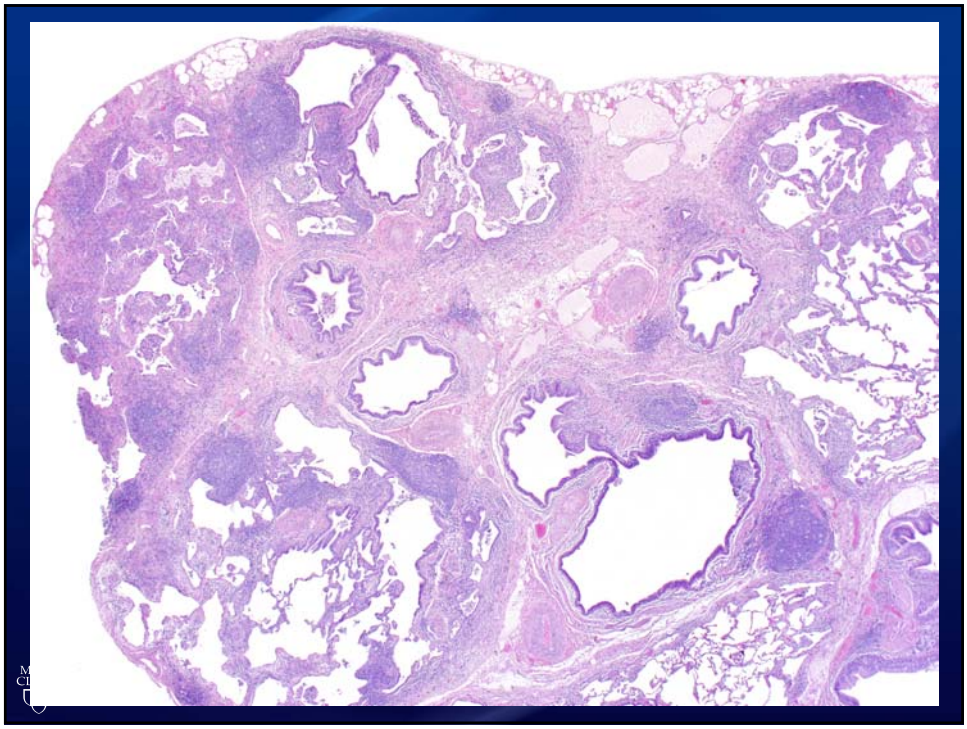

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Take-home messages

- UIP is a pattern, NOT a disease!
- Not all UIP is idiopathic
  - Prognosis
  - Treatment
  - Family members
  - Research (future treatment)
- Pay attention to sub-characteristics
- Clinical history, imaging often provides clues
- Multidisciplinary discussion often required

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QUESTIONS?

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