Non-neoplastic Lung Pathology IV

ILD with Airway Centering and Bronchiolitis

TV COLBY MD

COMMENTARY: KO LESLIE MD

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Format:

- Case presentations
- Airway-centered ILD
- Bronchiolitis
- Disease entities: HP, PLCH, GIP, Bronchiolitis patterns, Follicular bronchiolitis

To be discussed:

Hypersensitivity pneumonitis (HP)

Chronic hypersensitivity pneumonitis (ChrHP)

Pulmonary Langerhans Cell Histiocytosis (PLCH)

Giant cell interstitial (Cobalt) pneumonitis (GIP)

Bronchiolocentric interstitial pneumonia

Bronchiolitis: cellular, constrictive, aspiration

Follicular bronchiolitis

Refs:

Leslie KO and Wick MR. Practical Pulmonary Pathology (Elsevier 2017)

Colby TV. Bronchiolitis: Pathologic considerations. Am J Clin Pathol 1998; 109: 101.

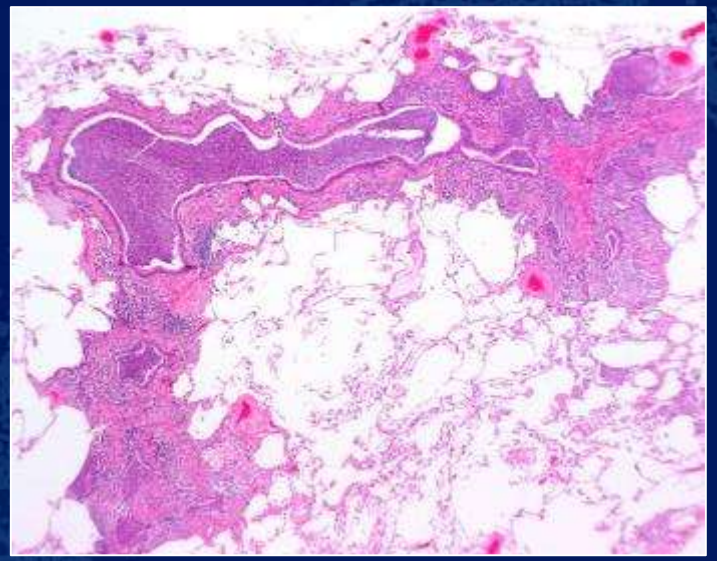
Pathologic diagnosis in non-neoplastic lung disease requires integration of:

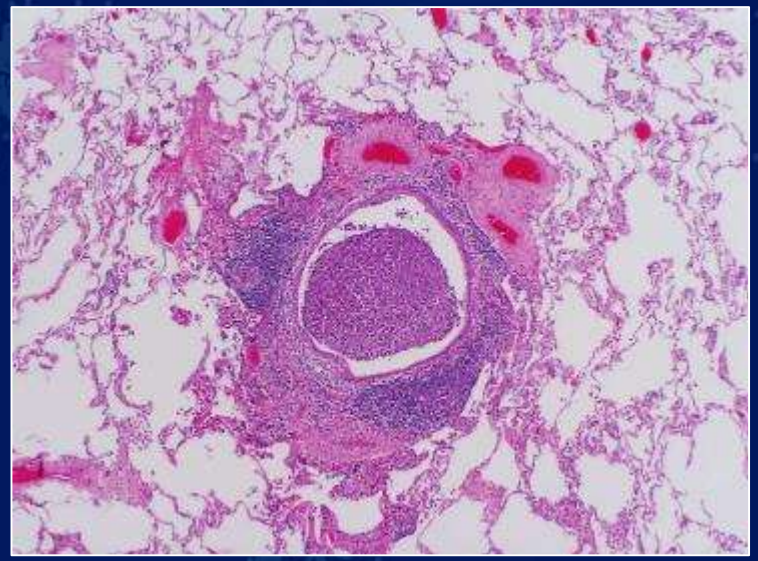
1. Information from four domains:
   a. Clinical /laboratory (?immunosuppressed)
   b. Radiologic findings (and Dx/Dx)
   c. Pathologic injury pattern(s) identified
   d. Individual disease entity that fits
2. Knowledge of the clinical question

"What question(s) am I answering with this Bx?"

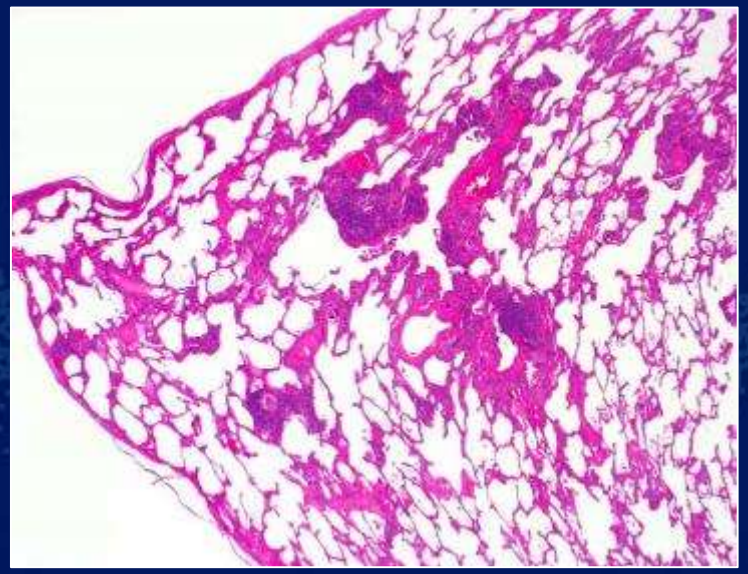
Bronchiolitis *vs* Bronchiolocentric IP

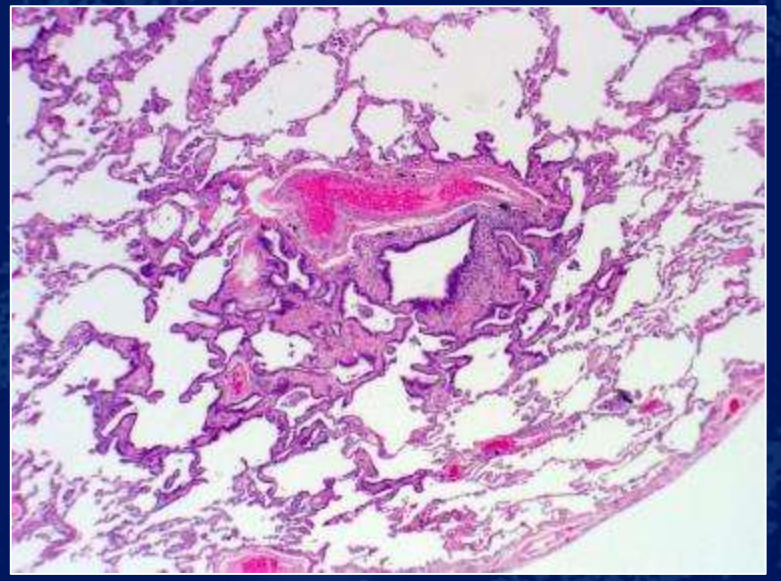
Bronchiolitis (In IBD)





Bronchiolocentric ILD (HP)





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Bronchiolitis *vs* Bronchiolocentric ILD

This distinction is not always straightforward and differs with modalities of assessment

Clinical findings

Functional char

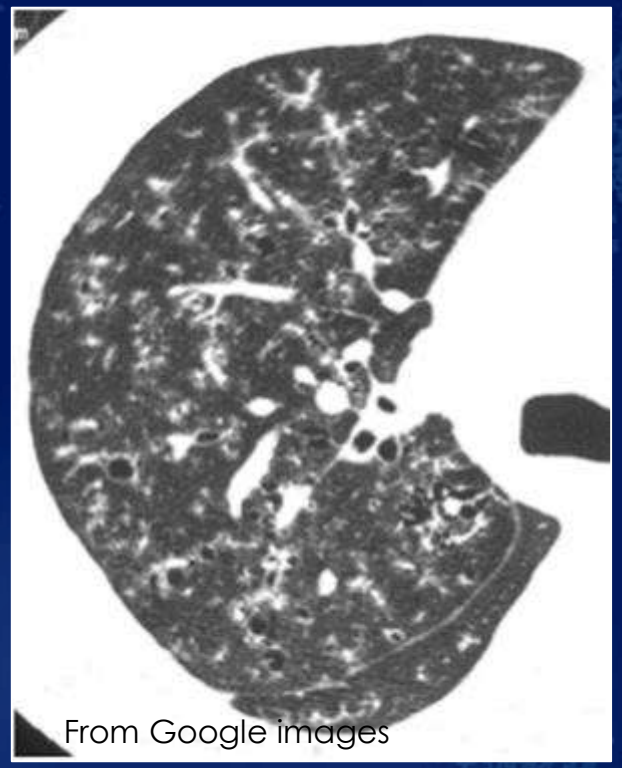
Radiol

H

There is appreciable overlap

These will be discussed separately for sake of simplicity

Bronchiolitis *vs* Bronchiolocentric ILD?



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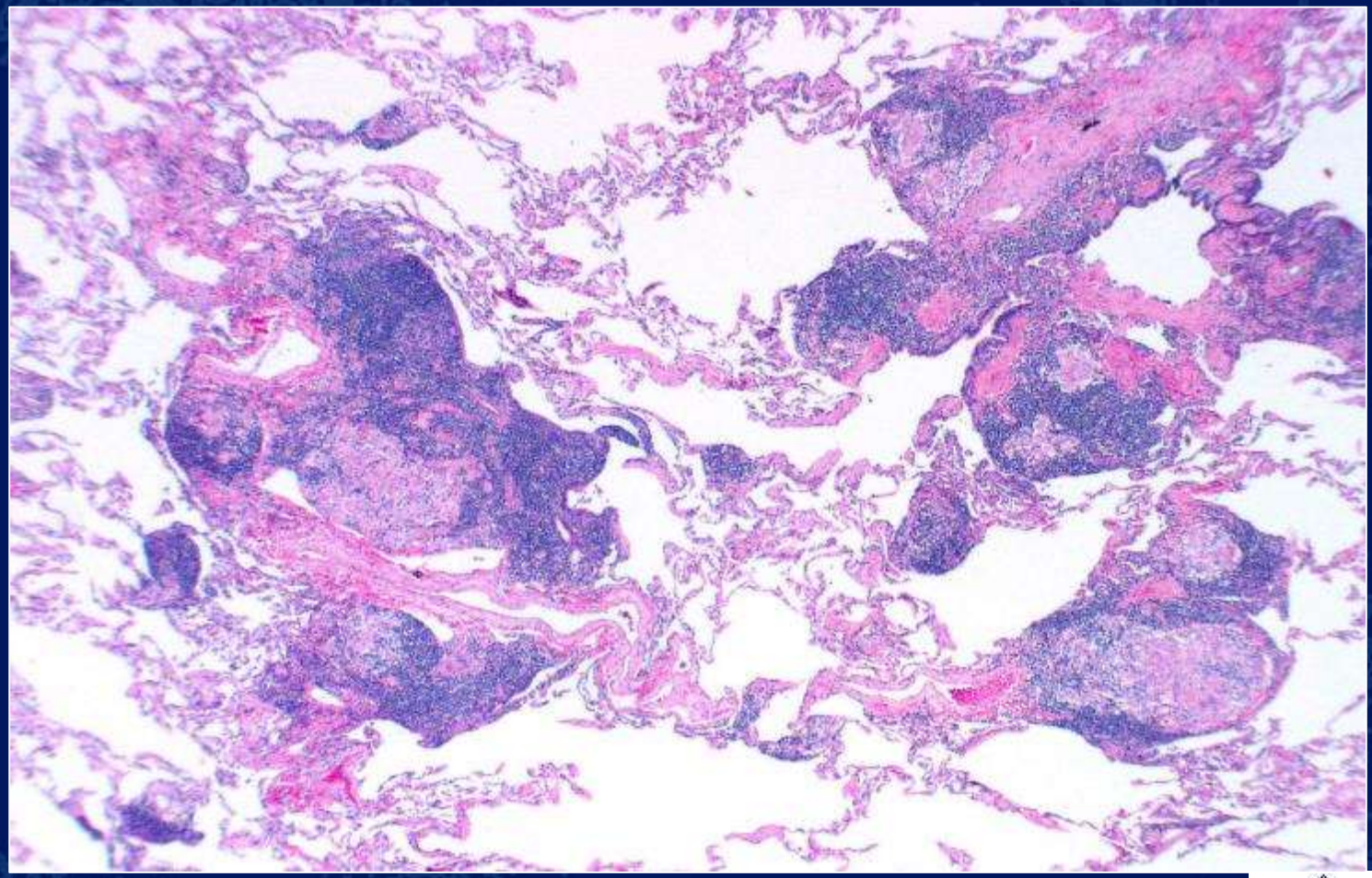

Clinically and radiologically this might be considered an ILD

Follicular bronchiolitis with granulomas in Sjogren's

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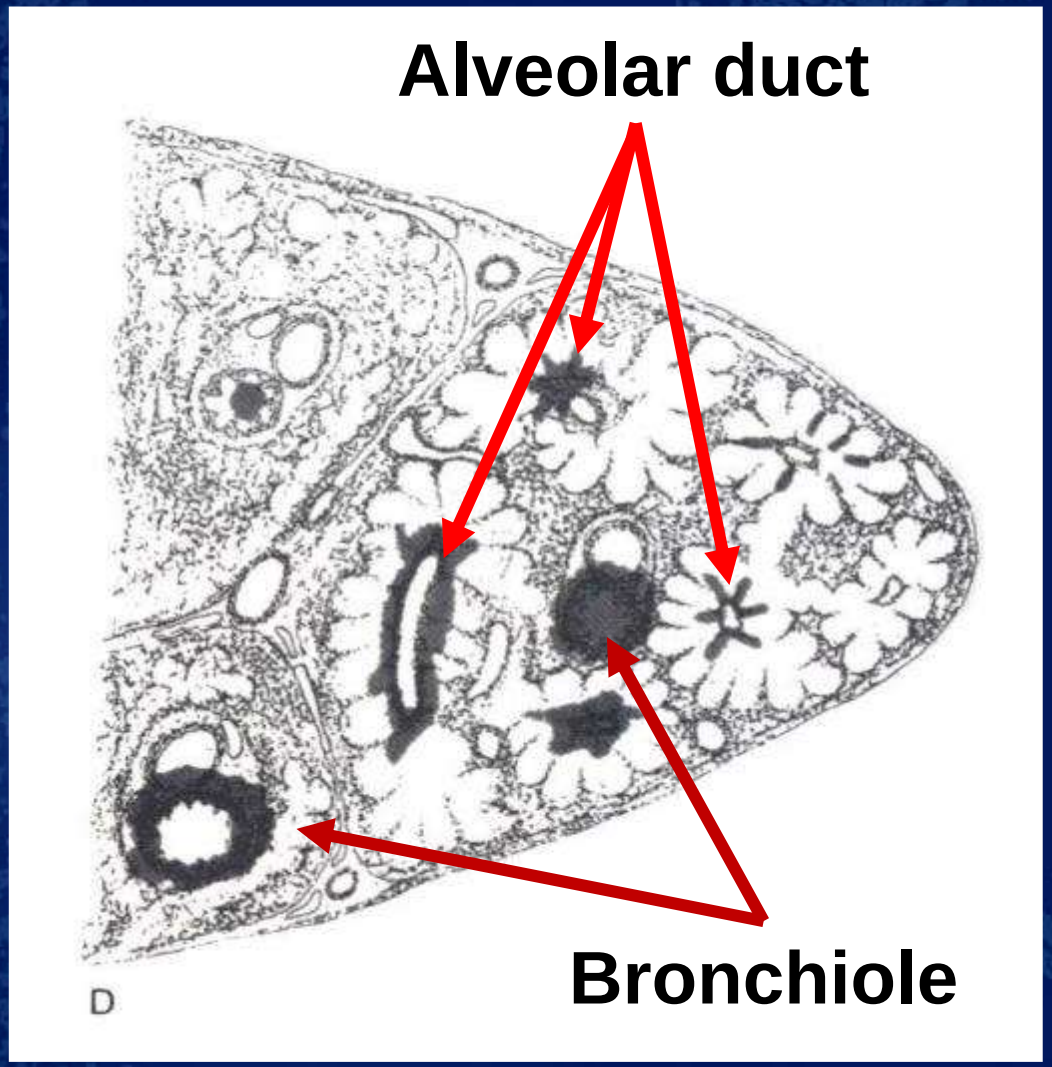
CENTRILOBULAR / BRONCHIOLOCENTRIC INJURY



Center on bronchiole and/or alveolar duct.

Suggest inhalation Injury:

- -Infection
- -Smoke (RB-ILD, PLCH)
- -Organic antigens (HP)
- -Dust/pneumoconioses
- -Many misc.

Hypersensitivity Pneumonitis (HP)
(Nonfibrotic and Fibrotic Subtypes)

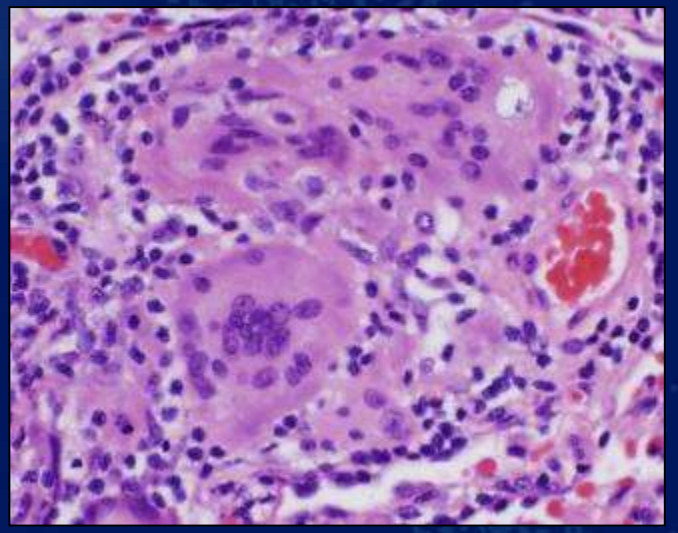
ILD caused by the inhalation of (primarily) organic antigens in a susceptible individual

TABLE I. Causative agents of hypersensitivity pneumonitis

Agent*	Source	Disease
Microbes		
Thermophilic actinomycetes	Moldy plant materials	Farmer's lung
Saccharopolyspora rectivirgula (Micropolyspora faeni)	Moldy hay	
Thermoactinomyces vulgaris	Moldy hay, compost	Farmer's lung, mushroom-worker's lung, composter's lung
Thermoactinomyces sacchari	Sugar cane residue	Bagassosis
Bacillus subtilis	Detergent enzymes	Detergent-worker's lung
Aspergillus clavatus	Moldy grains	Malt-worker's lung
Aspergillus versicolor	Animal bedding	Dog house disease
Aspergillus species	Tobacco mold	Tobacco worker's lung
Penicillium casei	Cheese mold	Cheese washer's lung
Penicillium frequentans	Moldy cork	Suberosis
Penicillium chrysogenum	Moldy wood dust	Woodworker's lung
Cryptostroma corticale	Moldy maple bark	Maple bark-stripper's lung
Aureobasidium pullulans	Moldy sequoia dust	Sequoiosis
Aureobasidium species	Contaminated water	Sauna-taker's disease
Alternaria species	Wood or wood pulp	Woodworker's lung
Merulius lacrymans	—	Dry rot lung
Botrytis cinerea	Grape mold	Winegrower's lung or Spätlese lung
Trichosporon cutaneum	Mold in Japanese homes	Summer-type HP
Cephalosporium	Sewage	Sewage-worker's lung
Mucor stolonifer	Paprika	Paprika-splitter's lung
Candida albicans	Saxophone mouthpiece	Sax lung
Mycobacterium avium-intracellulare	Contaminated water	Hot tub lung
Mixed ameba, fungi, and bacteria	Cold mist and other humidifiers, air conditioners	Nylon plant or office worker's or air conditioner's lung, ventilation pneumonitis
Bacteria and fungi	Contaminated metal-working fluids	Machine-operator's lung
Animals		
Avian proteins	Bird excreta, blood, or feathers	Bird-breeder's lung, bird-fancier's lung, pigeon-breeder's lung
Rat proteins	Rat urine or serum	Rodent-handler's lung
Gerbil proteins	Gerbil	Gerbil-keeper's lung
Animal fur protein	Animal fur	Furrier's lung
Ox and pork protein	Pituitary snuff	Pituitary snuff taker's lung
Mollusk shell protein	Mollusk shell dust	Oyster shell lung
Fish	Fish meal dust	Fishmeal-worker's lung
Wheat weevil	Flour	Miller's lung
Silk worm larvae proteins	Silk worm larvae	Sericulturist's lung
Plants		
Soybean	Soybean hulls	Soybean-worker's lung
Coffee	Coffee bean dust	Coffee-worker's lung
Lycoperdon species	Puffballs	Lycoperdonosis
Chemicals		
Isocyanates	Paints, plastics	Paint refinisher's lung
Anhydrides	Plastics	Chemical worker's lung, plastic-worker's lung, epoxy worker's lung
Pauli's reagent	—	Pauli's reagent lung
Bordeaux mixture	Vineyard fungicide	Vineyard-sprayer's lung
Pyrethrum	Insecticides	Insecticide lung
Metals		
Cobalt	—	Hard metal lung disease
Beryllium	—	Berylliosis

*The more frequent causative agents are listed in bold type.

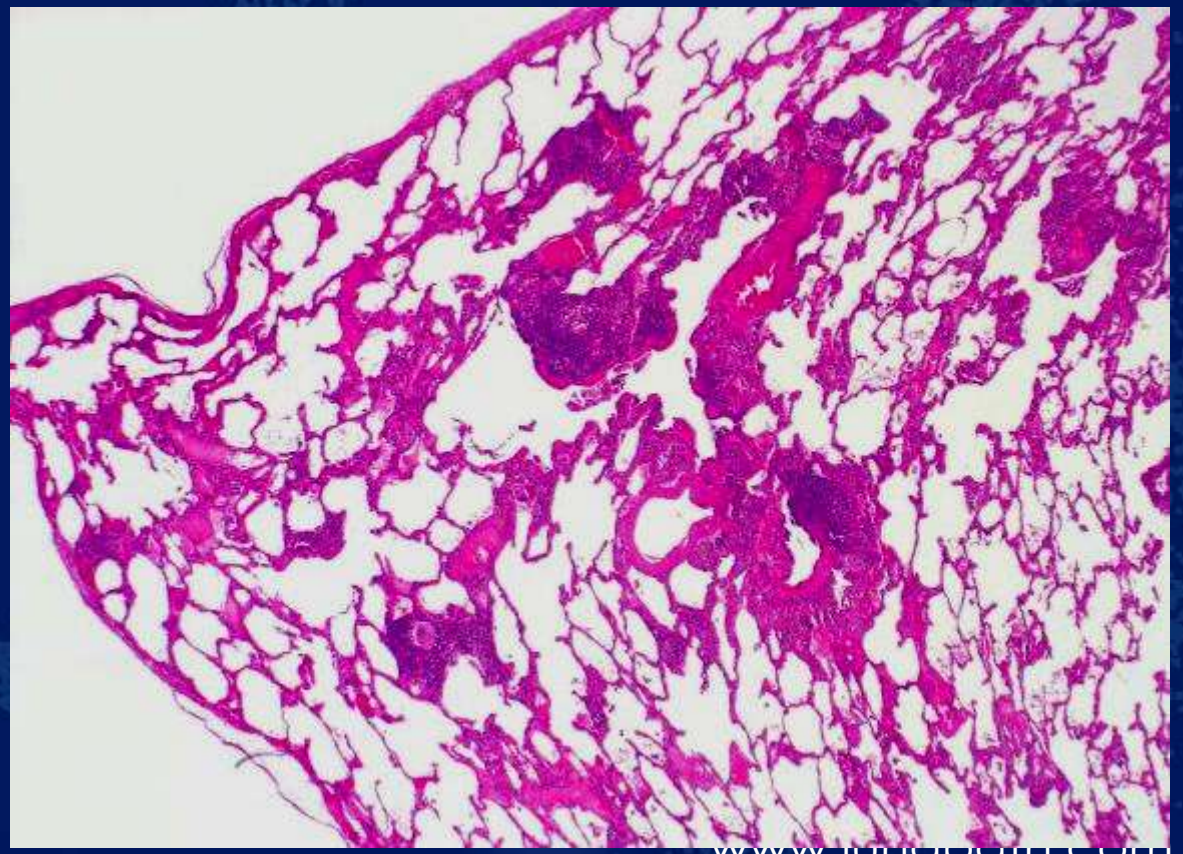
Hypersensitivity Pneumonitis (HP)
(Nonfibrotic and Fibrotic/Chronic HP)

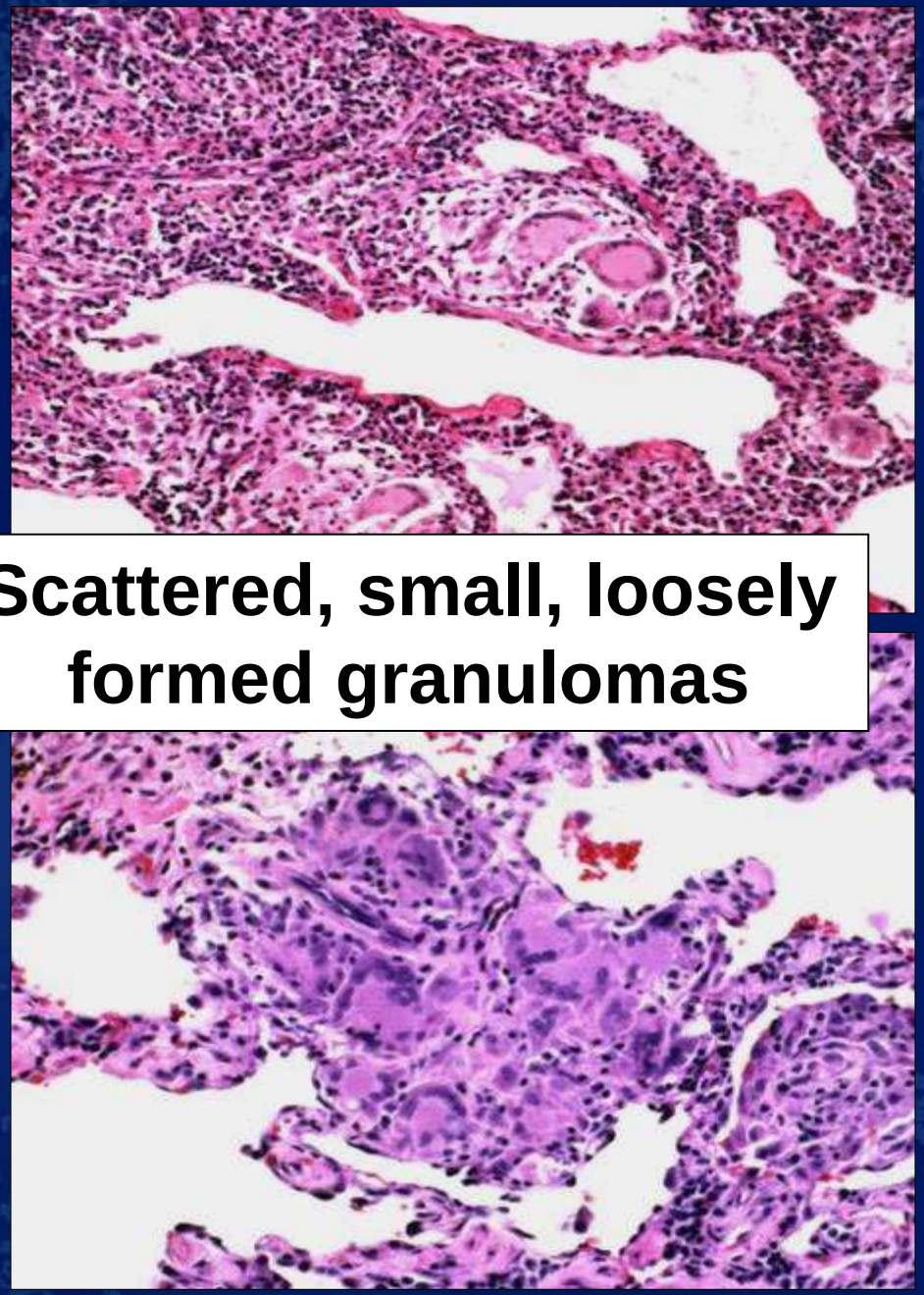


BAL lymphocytosis (usually > 20%)

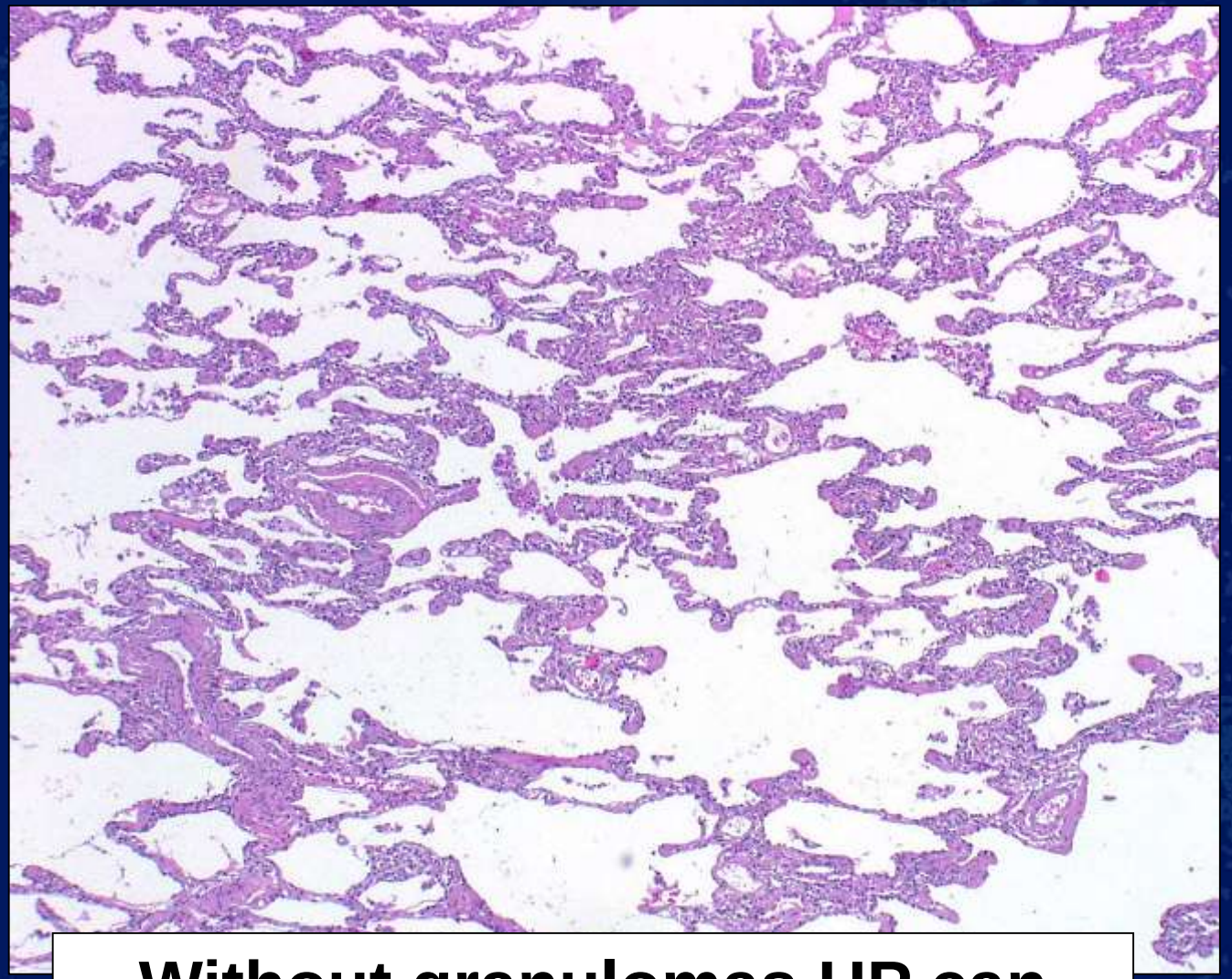
Histopathology:

- Bronchiolocentric
- Cellular infiltrate
- Granulomas
- +/- OP, fibrosis (Fibr HP)





Scattered, small, loosely formed granulomas



Without granulomas HP can produce a cellular or fibrotic NSIP Pattern

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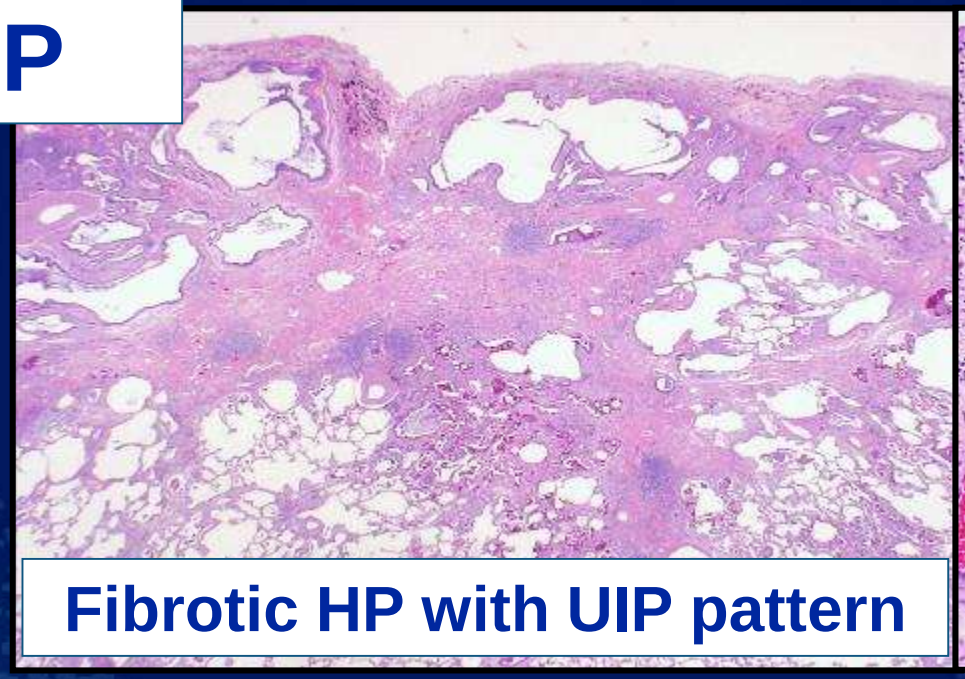
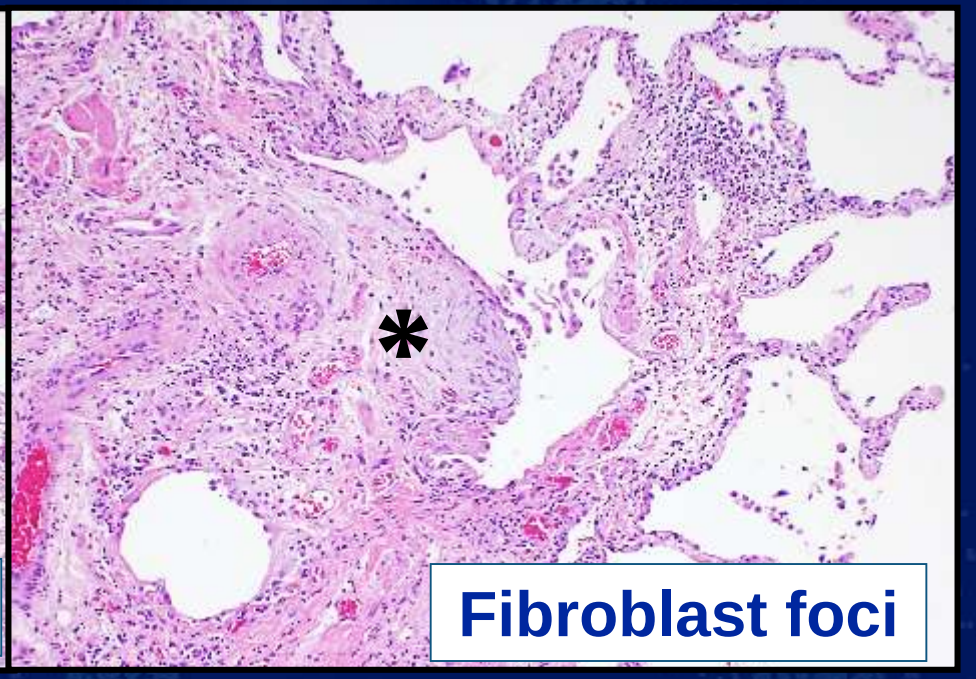
Fibrotic HP

Akashi T,.Am J Clin Pathol. 2009;131:405-15.

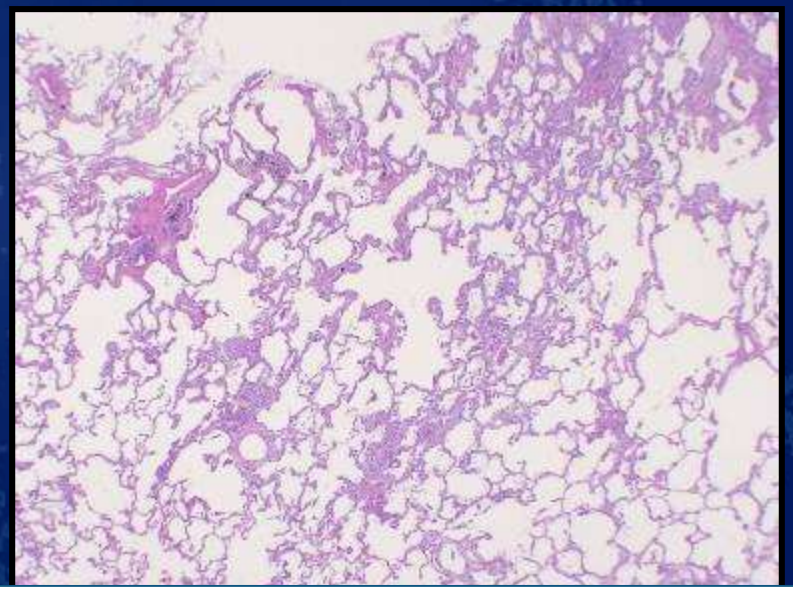
Takemura T. Histopathology. 2012; 61:1026-35.

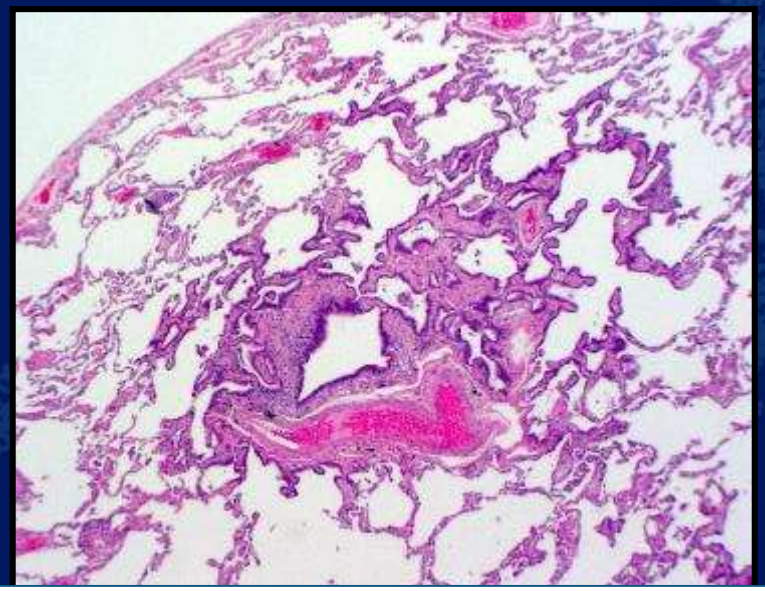


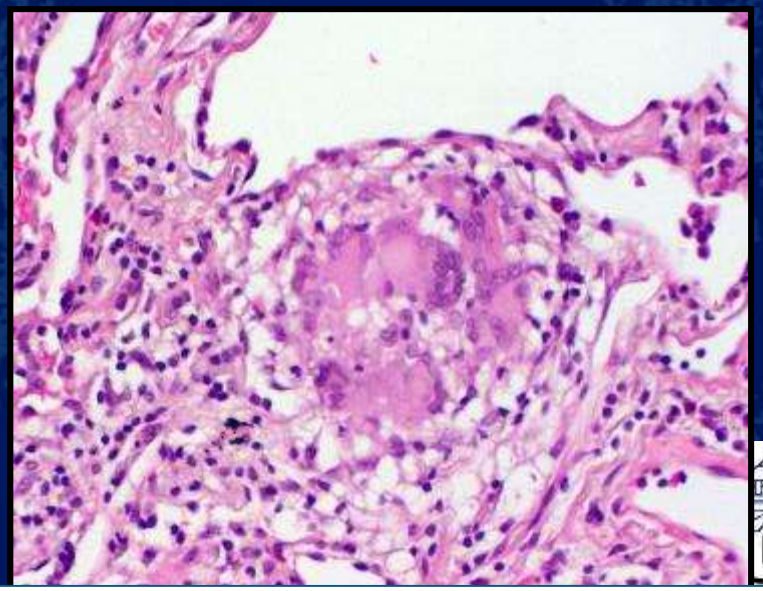
Fibrotic HP with UIP pattern



Fibroblast foci

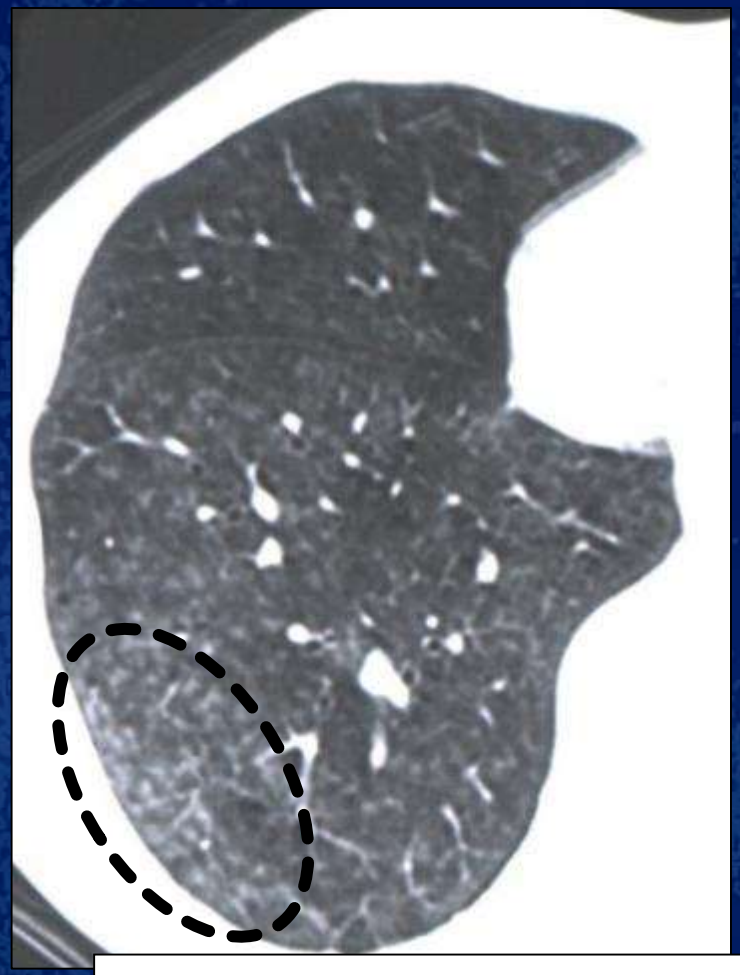


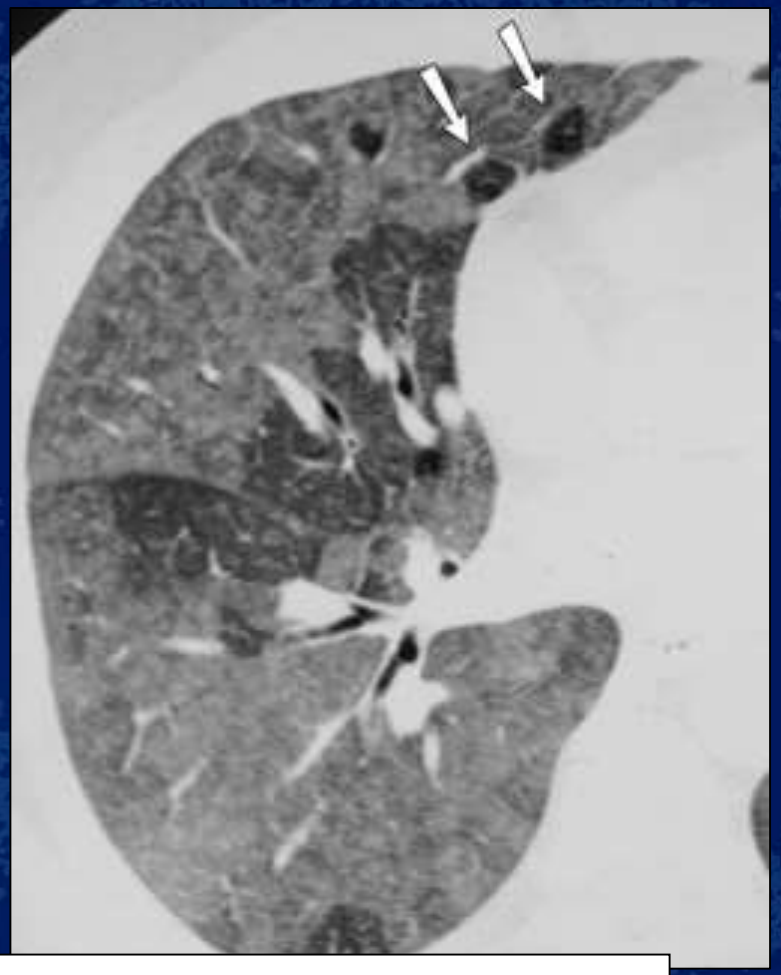




Fibrotic HP Clues: Incr. inflammation, centrilobular pathology, granulomas

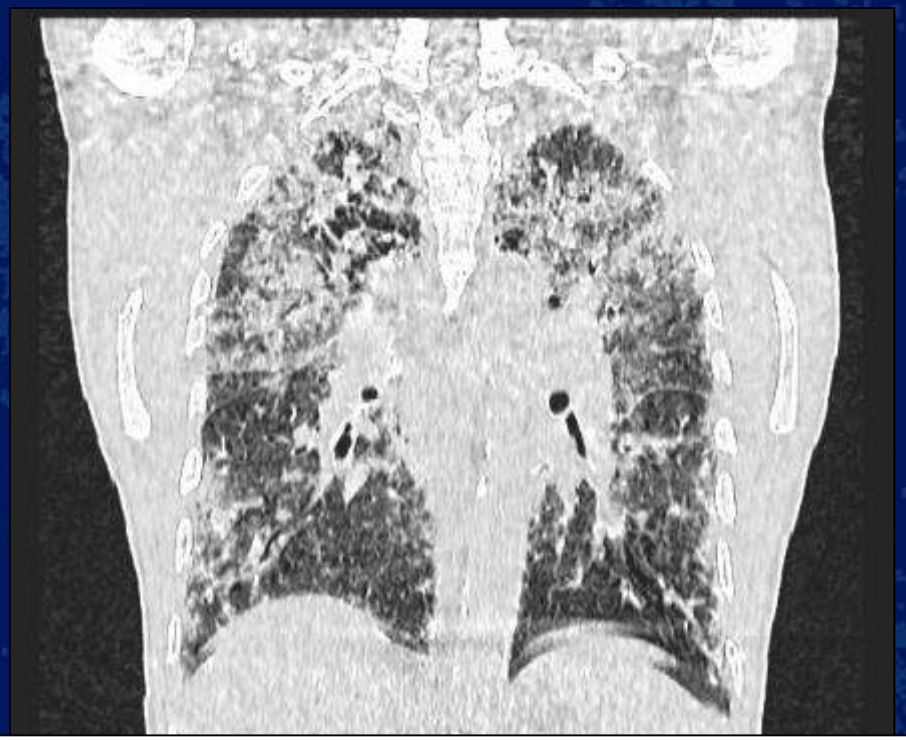
Radiology in HP…is distinctive





Centrilobular nodules and/or air trapping

(From Kazerooni)



Upper lobe distribution

(ChrHP from Google images)

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HP Evaluation

Four domains

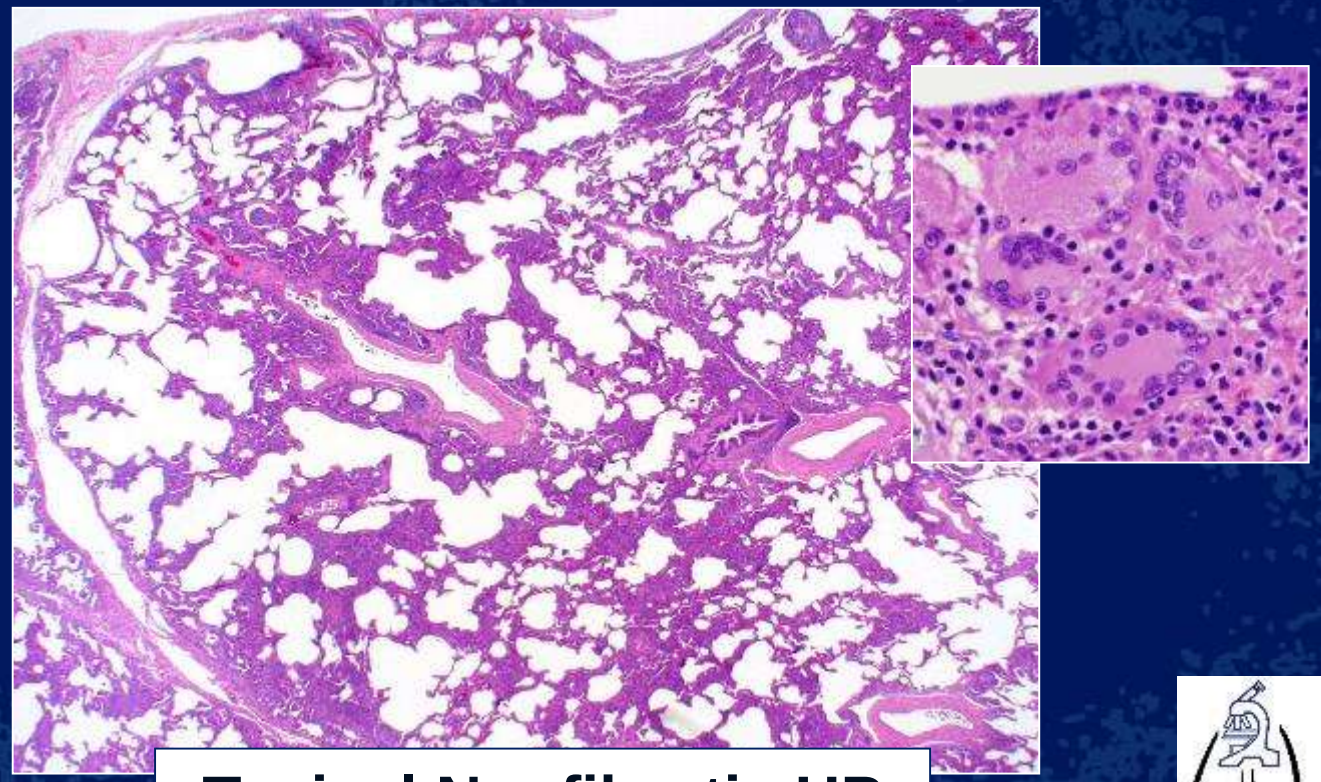
Clinical/Lab presentation

Radiologic findings

Pathologic injury pattern(s)

Disease entity that fits

Classic exposure and classic radiology need not be present



Typical Nonfibrotic HP

Diagnosis is pathology driven: "Changes typical of HP (fibrotic vs nonfibrotic)

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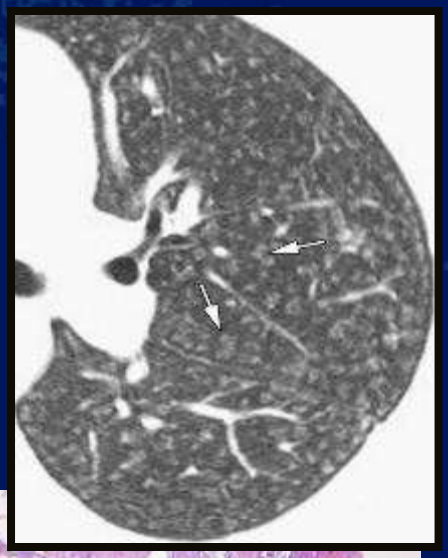
HP Evaluation

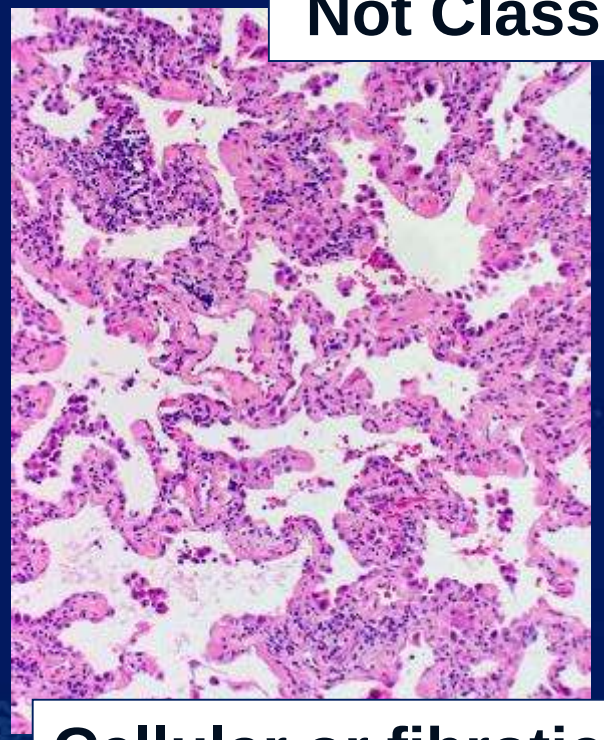
Four domains

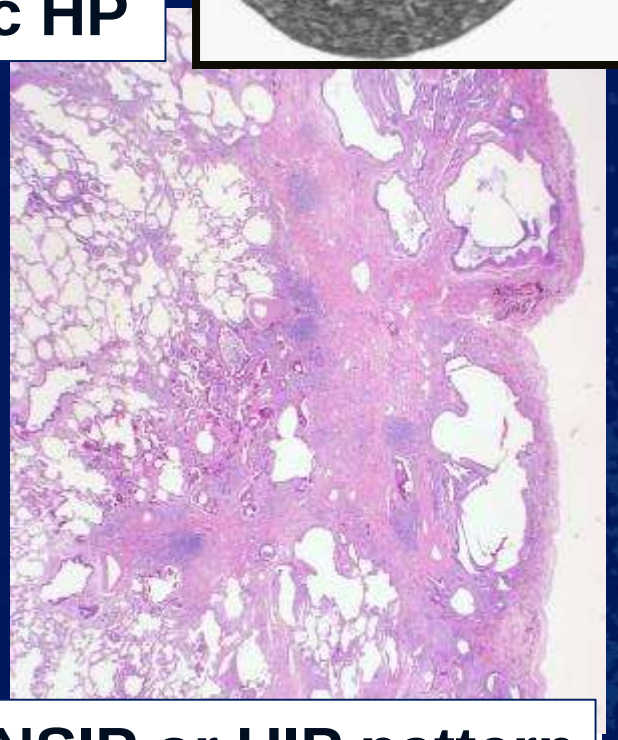
- Clinical/Lab presentation
- Radiologic findings
- Pathologic injury pattern(s)
- Disease entity that fits

Compelling clinical, BAL, radiologic findings for HP



Not Classic HP





Cellular or fibrotic NSIP or UIP pattern (No granulomas, +/- centrilobular)

HP diagnosis is Clin-Rad driven. Pathology nonspecific but c/w HP (Fibr or nonFibr)**

How common is Fibrotic HP ??

Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study

(Lancet Respir Med 2013; 1: 685.)

Ferran Morell, Ana Villar, María-Ángeles Montero, Xavier Muñoz, Thomas V Colby, Sudhakar Pipvath, María-Jesús Cruz, Ganesh Raghu

46 consecutive pts diagnosed with IPF (2011 guidelines)
20/46 reinterpreted as Chr HP (details available)
The study implicated….

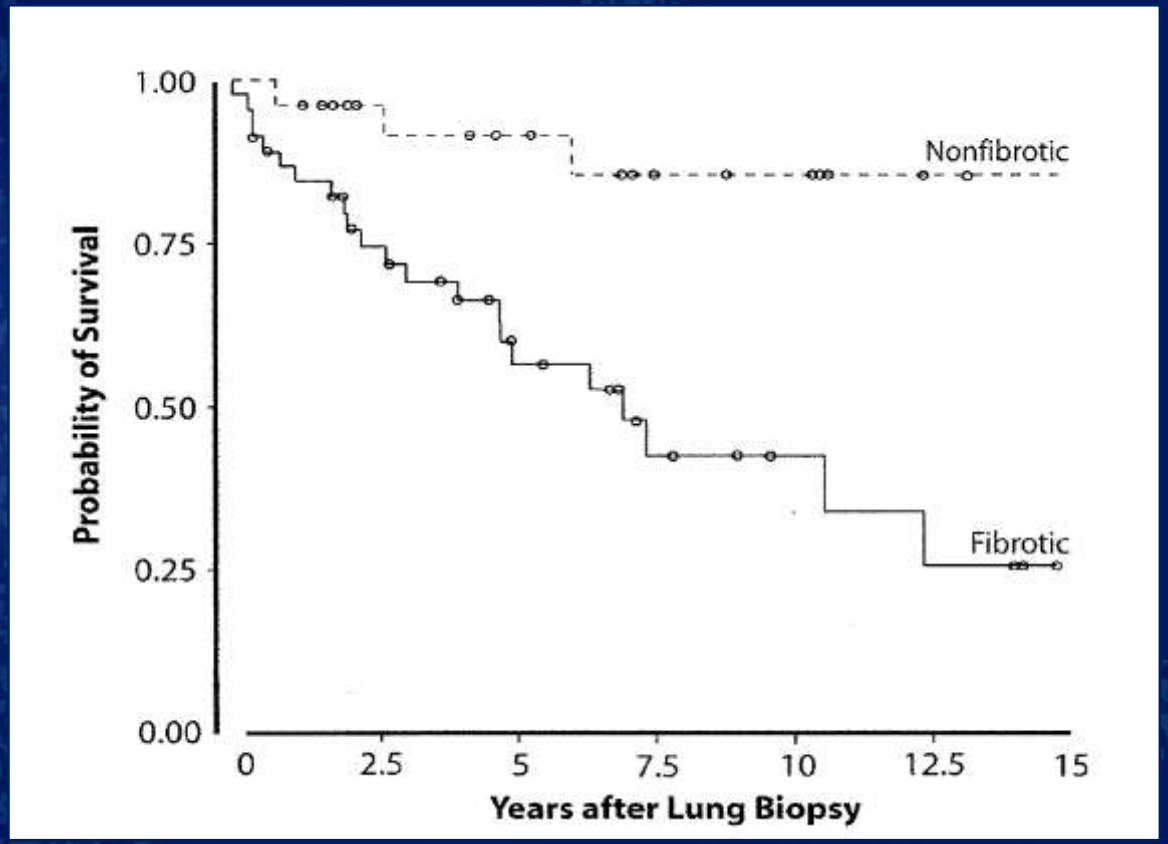
…Feathers pillows and bedding

Images from Google

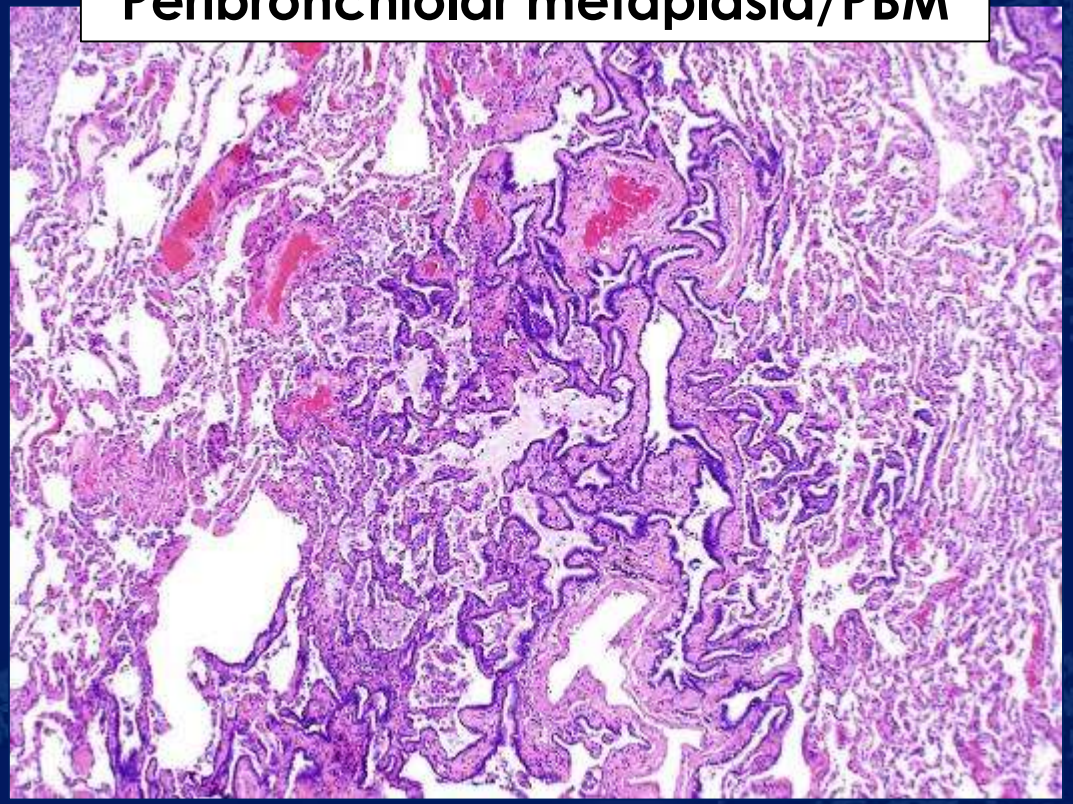
THE EFFECT OF FIBROSIS ON SURVIVAL IN PATIENTS WITH HP

(Voulekis in Am J Med 2004; 116: 662)

46 of 72 pts identified were classified as "fibrotic"
No correlation with implicated antigen



Peribronchiolar metaplasia/PBM



Current Guidelines for HP

(Raghu et al Am J Resp Crit Care Med 2020; 202: e36.

Nonfibrotic HP **Fibrotic HP**

Radiologic and Pathologic Criteria for:

Typical…

Compatible with…

Indeterminate for…

This scheme provides a framework for clinicians to diagnose and manage patents.

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COMMENTARY……

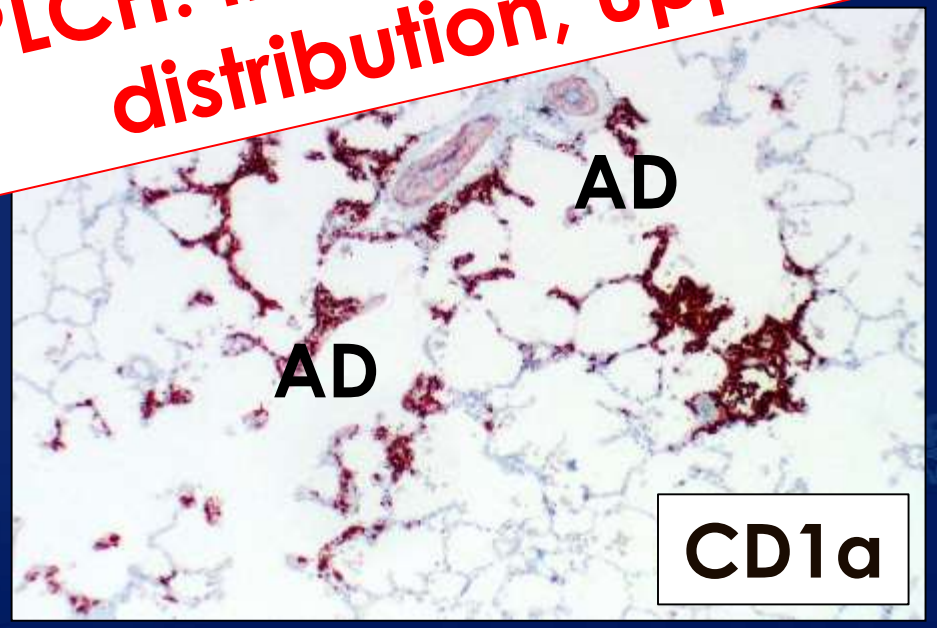
Pulmonary Langerhans Cell histiocytosis (PLCH)

Current evidence strongly supports cigarette smoking and Langerhans Cell proliferation in the lung

BRAF V600E mutation co

Early lesions are

PLCH: Inhalational etiology, airway-centered distribution, upper lobe predominance



Langerhans cells stain with:
CD1a, S-100, Langerin

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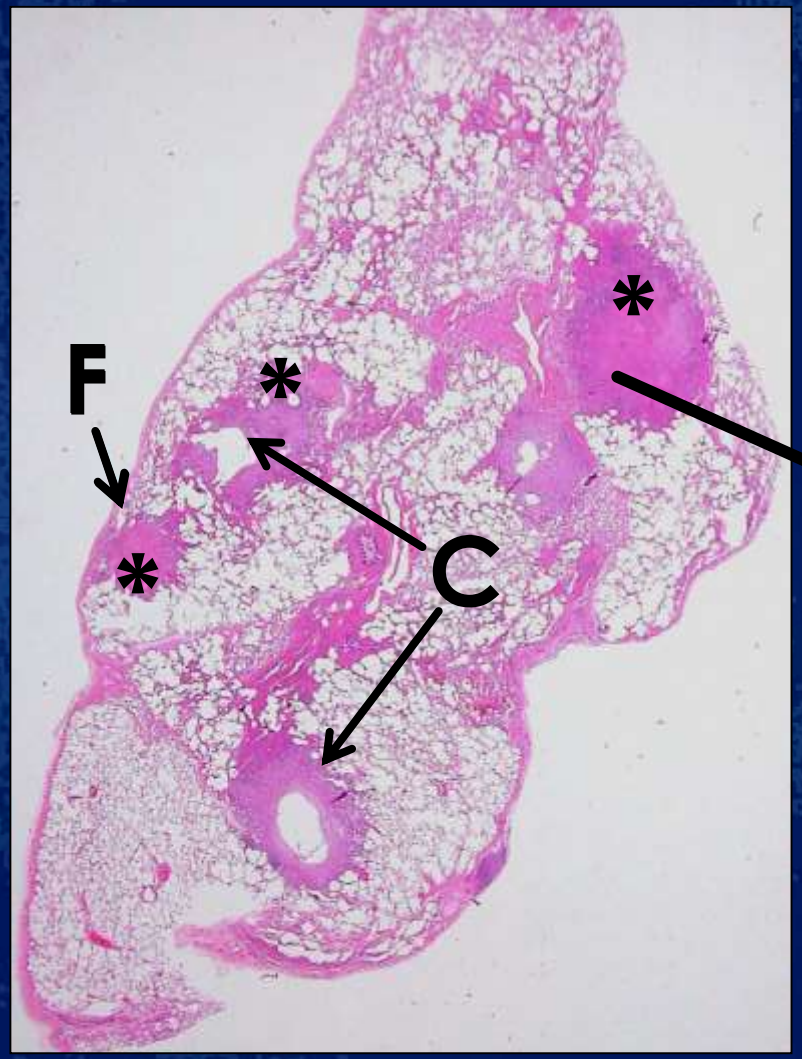
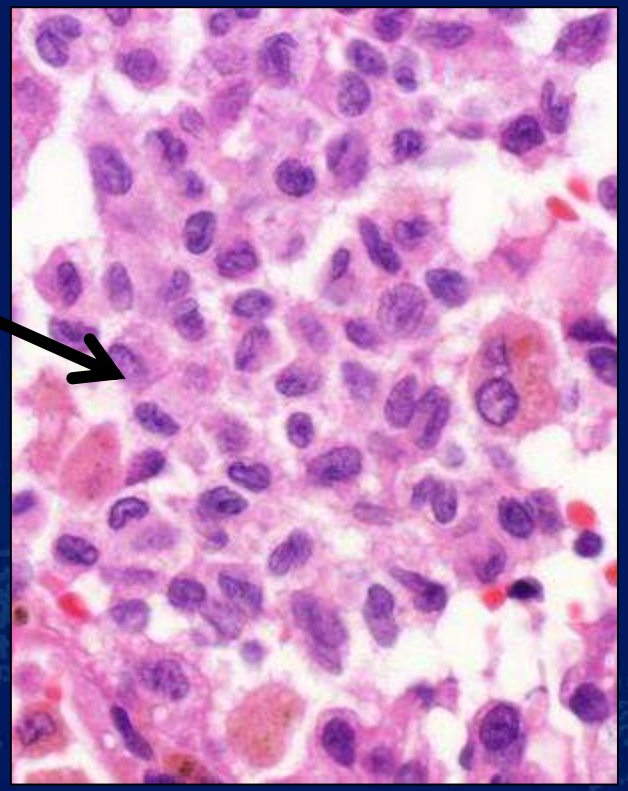
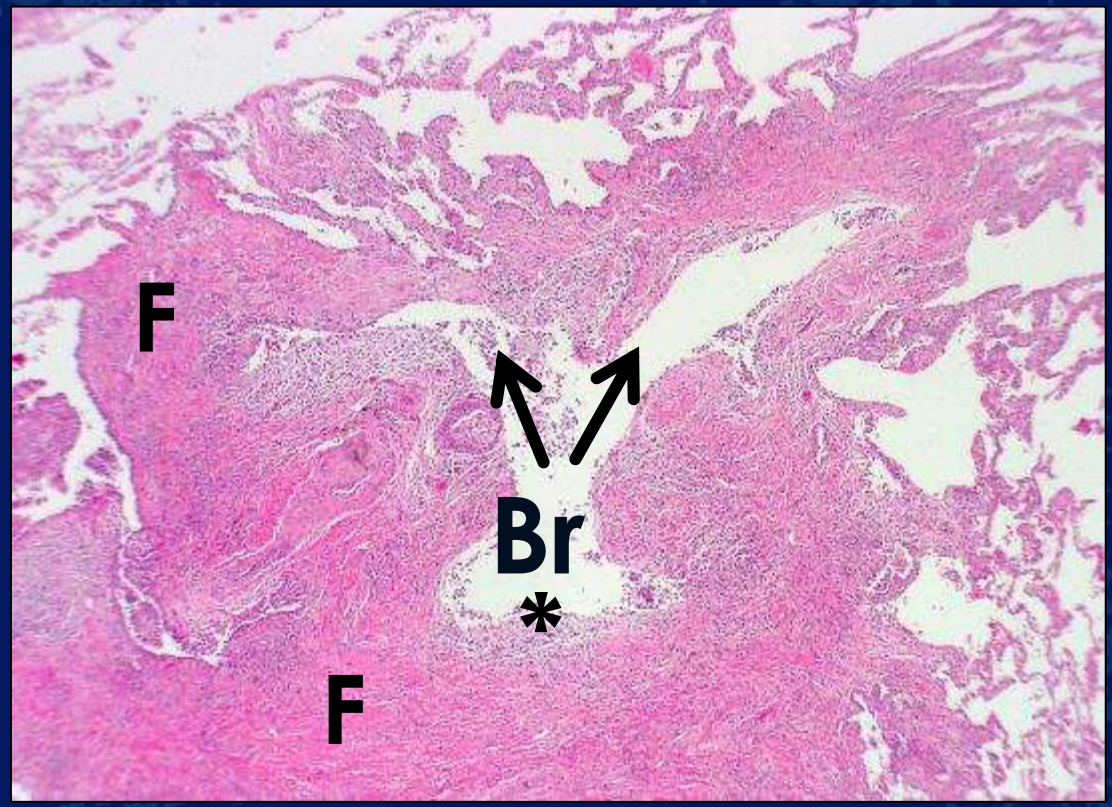
Langerhans cell proliferation leads to cellular centrilobular nodules* that become fibrotic (F) and cavitate (C) over time







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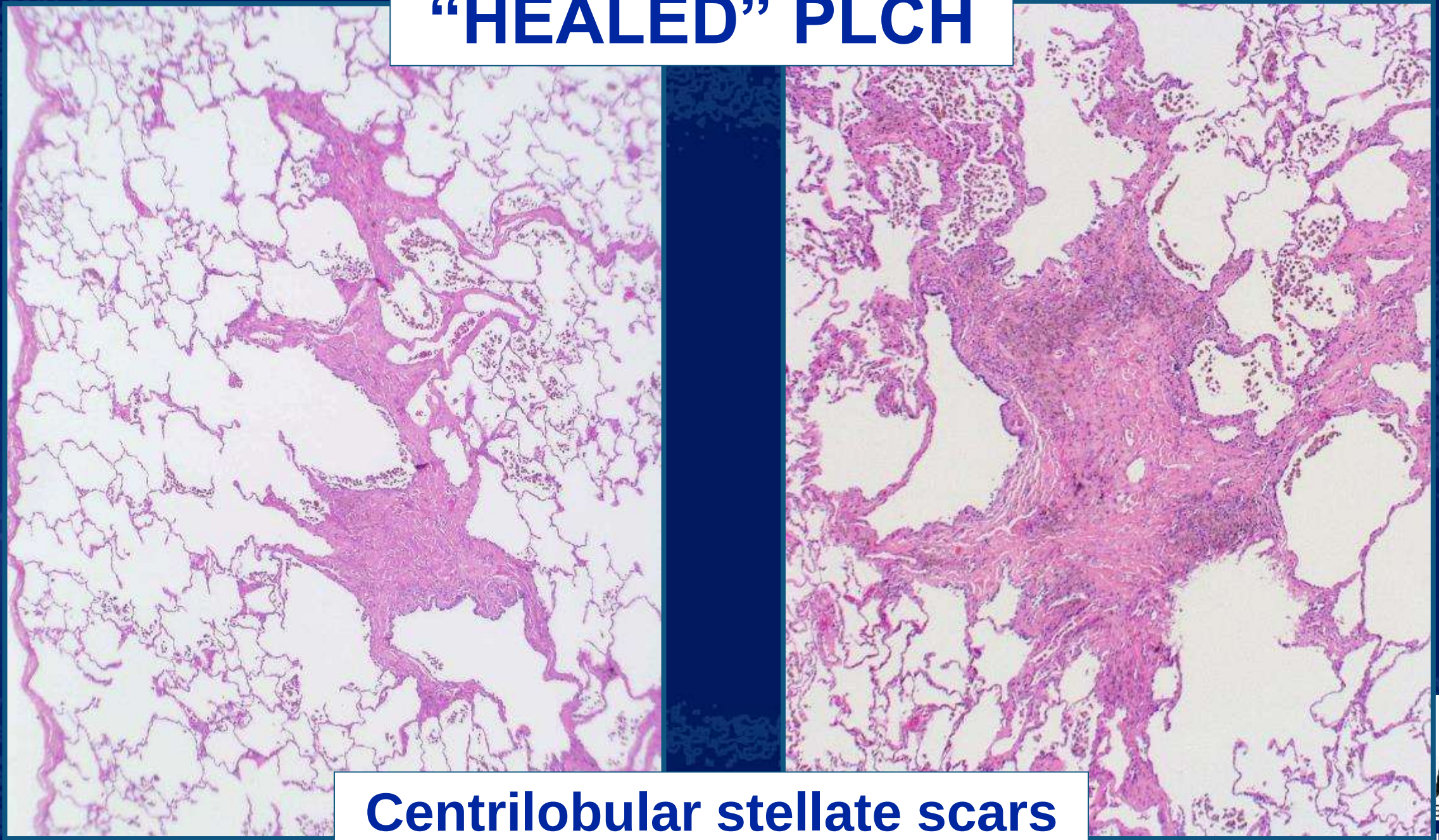
“HEALED” PLCH



Centrilobular stellate scars

PLCH Evaluation

Four domains

Clinical/Lab presentation

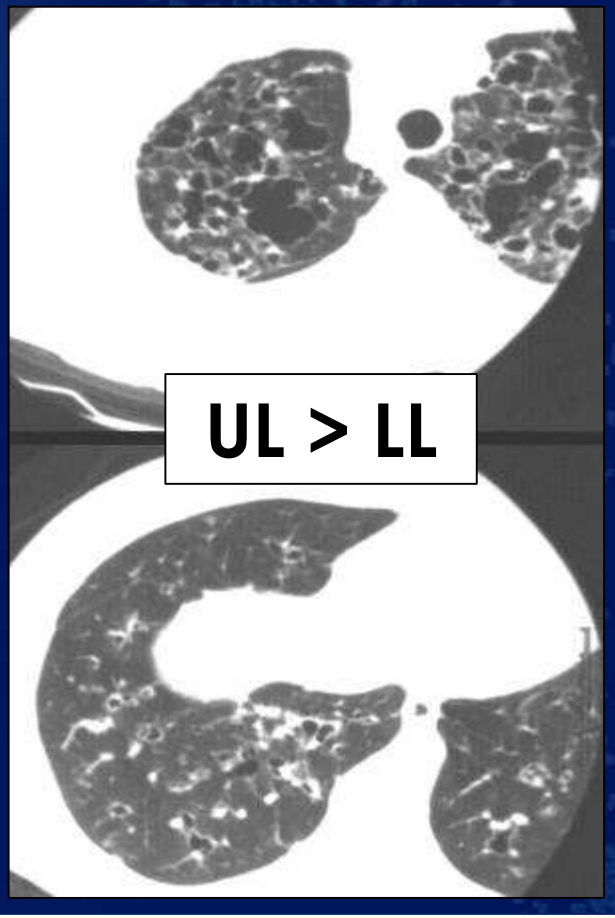
Radiologic findings

Pathologic injury pattern(s)

Disease entity that fits

Smoker

Typical CT findings



Unique histology in the active phase

Scarred phase distinctive but no LCs

Definitive Dx in active phase

"c/w PLCH" in fibrotic phase

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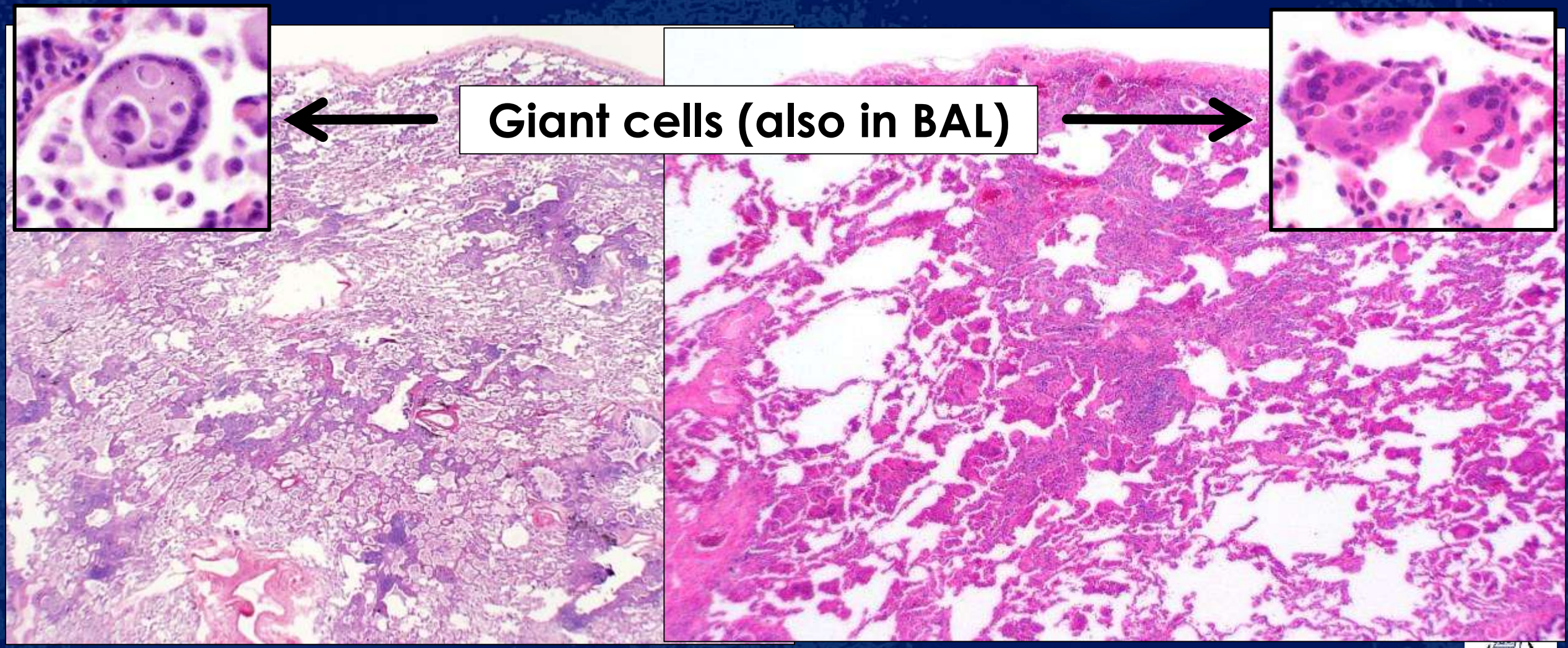
Another unique centrilobular ILD



Cobalt induced ILD (Giant cell interstitial pneumonia/GIP)

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HARD METAL/COBALT PNEUMOCONIOSIS

Hard metal: A metal of unusual hardness containing cobalt and tungsten carbide.

Cobalt implicated as cause of ILD

0.7 to 13% of exposed workers have evidence of ILD

Typical occupations: drill bits, grinding wheels, cut tools, jet engines, diamond polishing, paint and pigment, oil/chemical industry

REVIEW! Idiopathic Interstitial Pneumonias (IIPs)

Major IIPs

- Idiopathic Pulmonary Fibrosis (UIP)
- Idiopathic NSIP (NSIP)
- RB-ILD (RBILD)
- DIP (DIP)
- Cryptogenic Organizing Pneumonia/COP (OP)
- Acute Interstitial Pneumonia/AIP (DAD)

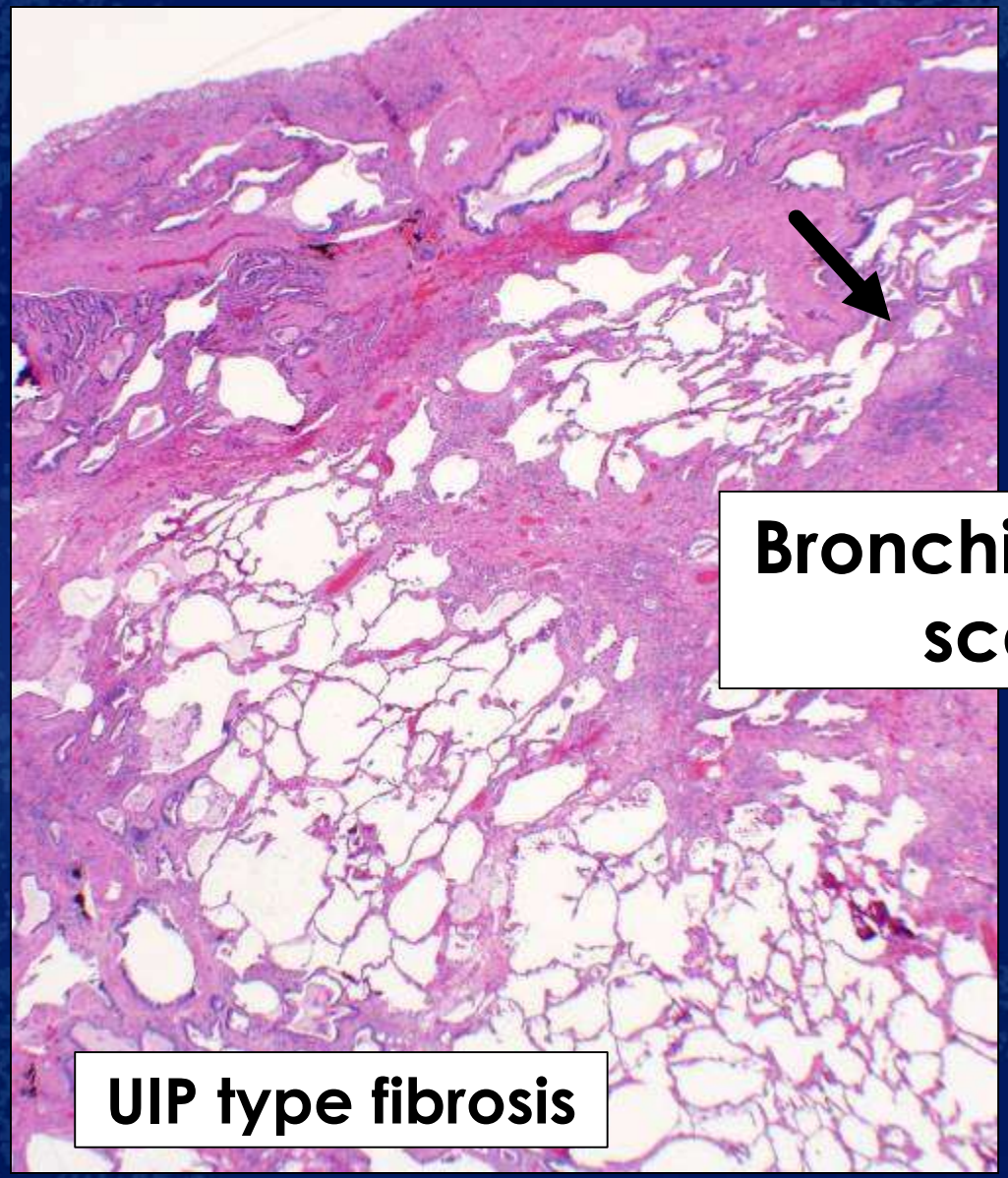
Minor IIPs

- Idiopathic lymphocytic interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)

Unclassifiable IIPs

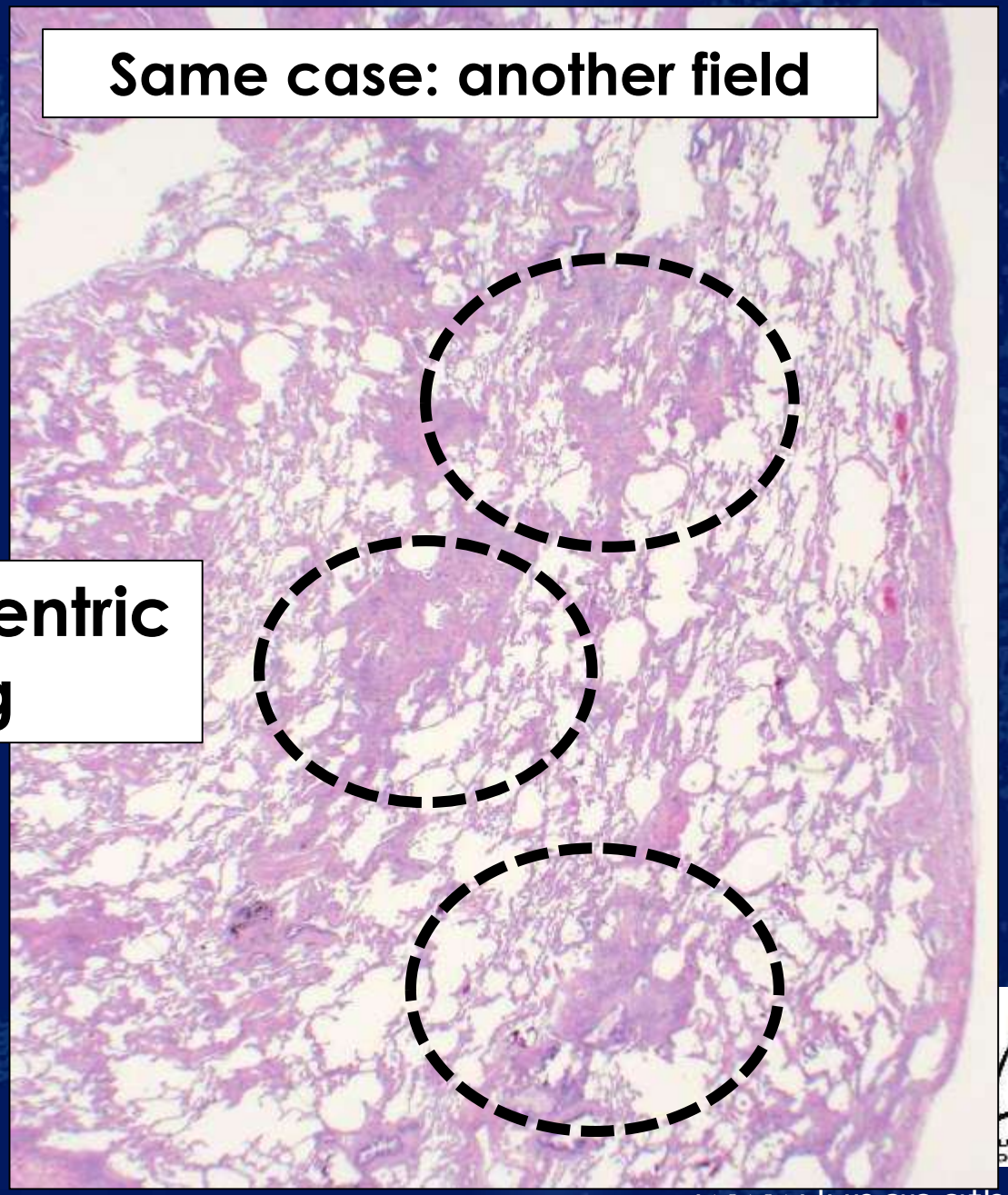
Am J Resp and Crit Care Med 2013; 188: 733

What do you see?



UIP type fibrosis

Bronchiolocentric scarring



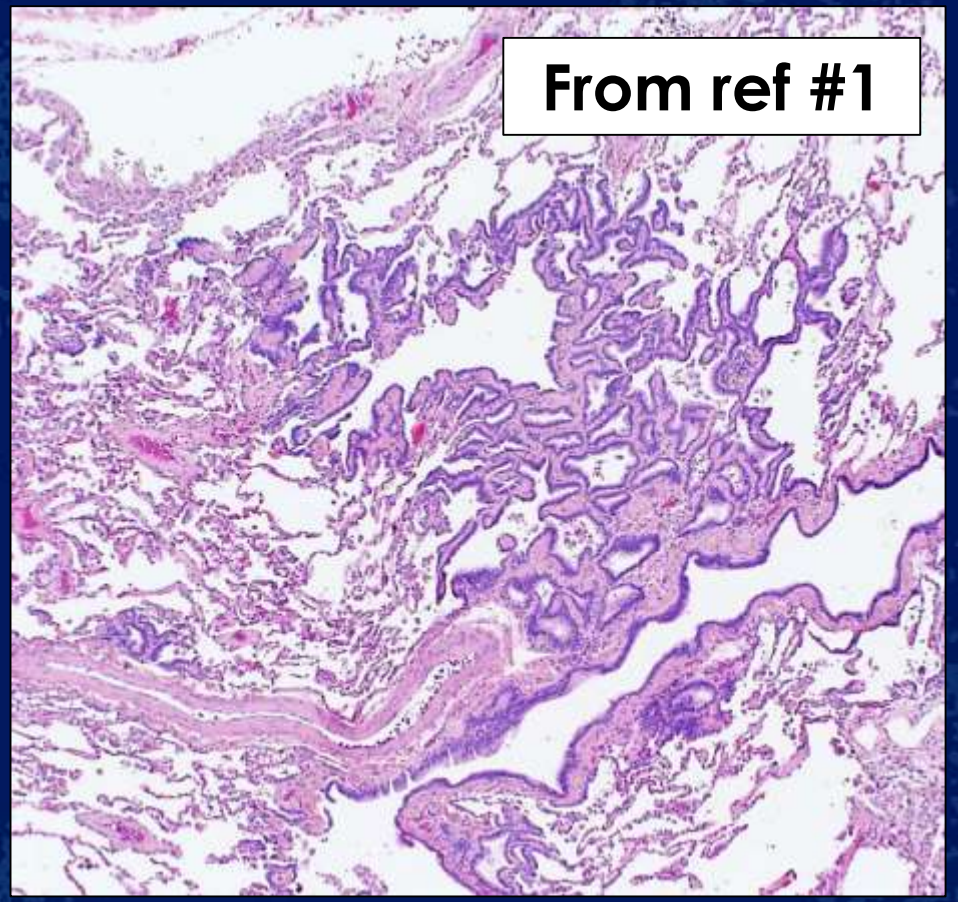
Same case: another field

Is there an Idiopathic Bronchiolocentric Interstitial Pneumonia???

1. IDIOPATHIC BRONCHIOLOCENTRIC INTERSTITIAL PNEUMONIA (BrIP)
(Yousem and Dacic in Mod Pathol 2002; 15:1148-1153)

2. AIRWAY CENTERED INTERSTITIAL FIBROSIS: A DISTINCT FORM OF AGGRESSIVE DIFFUSE LUNG DISEASE
(Churg et al. in AJSP 2004;28:62-68)

3. PERIBRONCHIOLAR METAPLASIA: A COMMON HISTOLOGIC LESION IN DIFFUSE LUNG DISEASE AND RARE CAUSE OF ILD: 15 CASES
(Fukuoka et al. in AJSP 2005;29:948-954)



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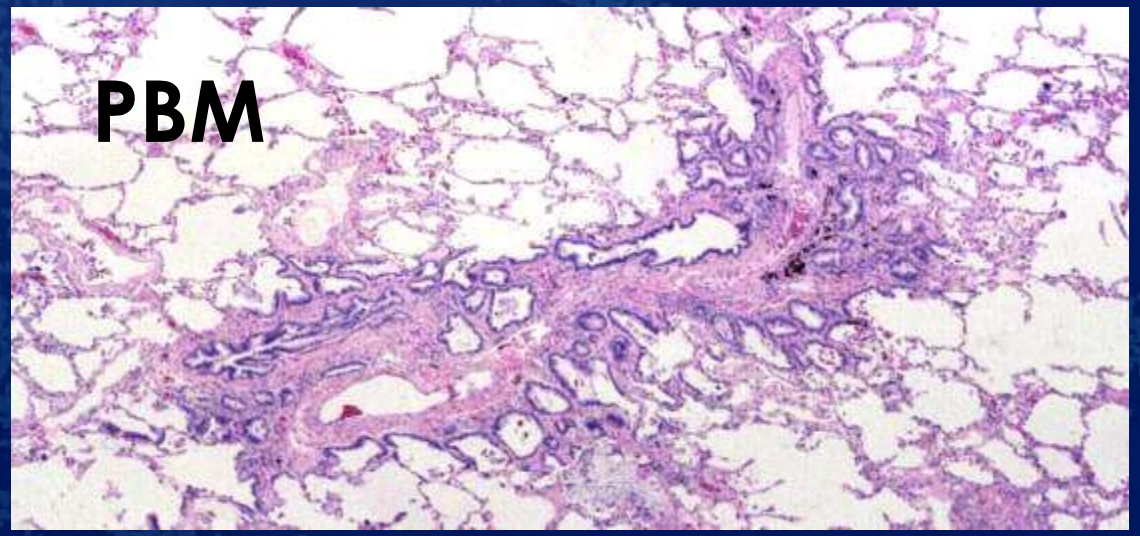
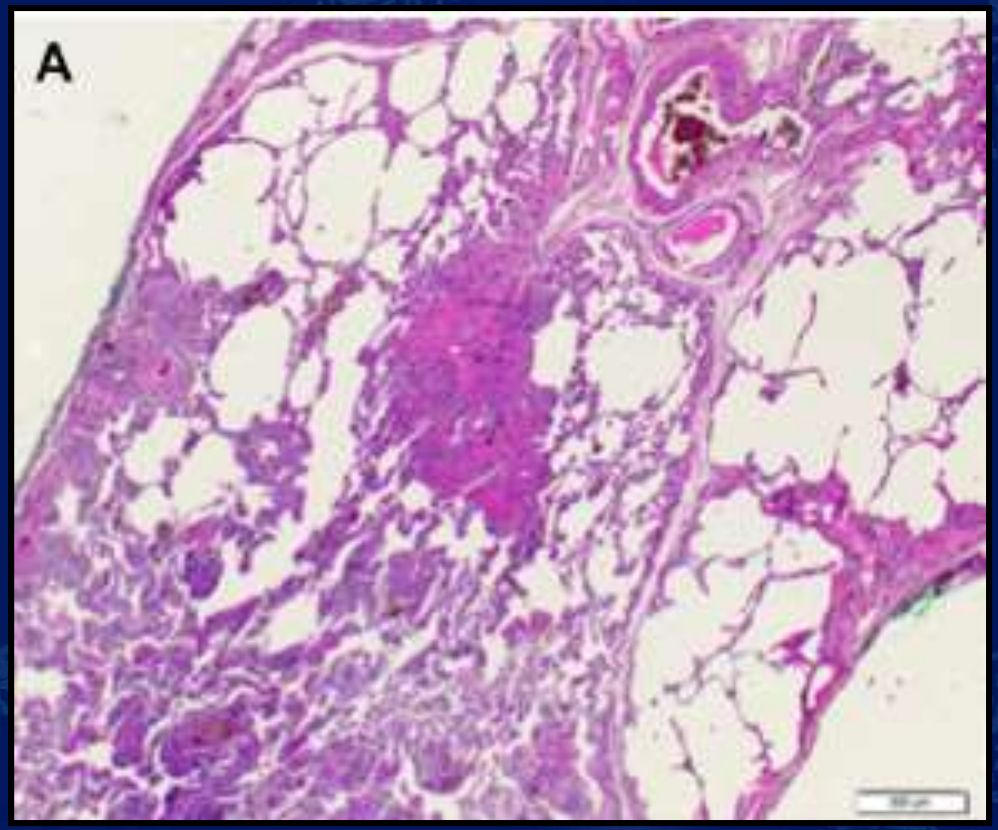
Recent interest in airway centered ILD

Airway-centered interstitial fibrosis: etiology, clinical findings and prognosis **Resp Res 2015; 16: 55**

68 patients with ACIF (Among 600 pts with SLBx's for ILD)

Airway centered fibrosis	100%
Airway inflammation	98%
Peribronchiolar metaplasia	88%





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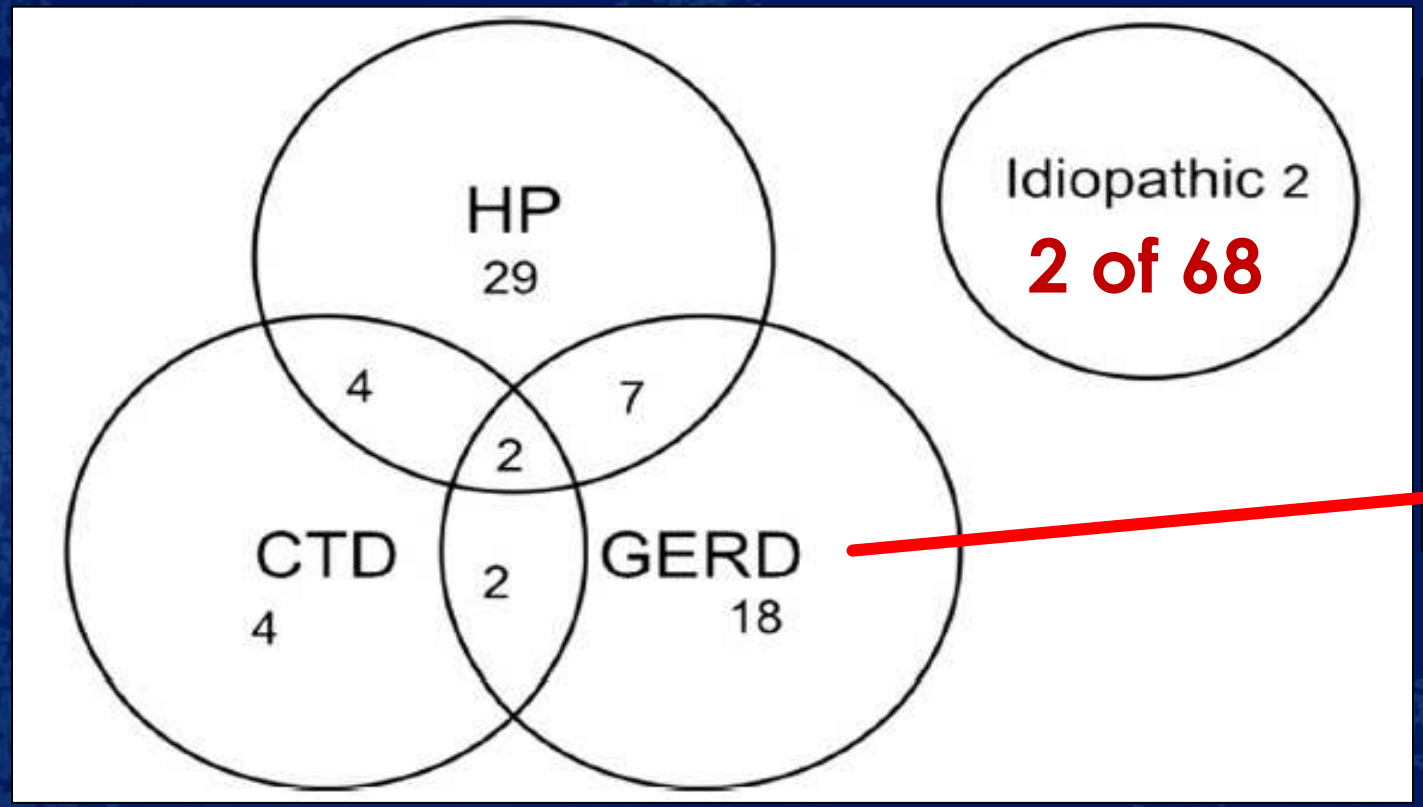
Airway-centered interstitial fibrosis: etiology, clinical findings and prognosis

Resp Res 2015; 16: 55

Multidisciplinary discussion (MDD) diagnoses in 68 patients

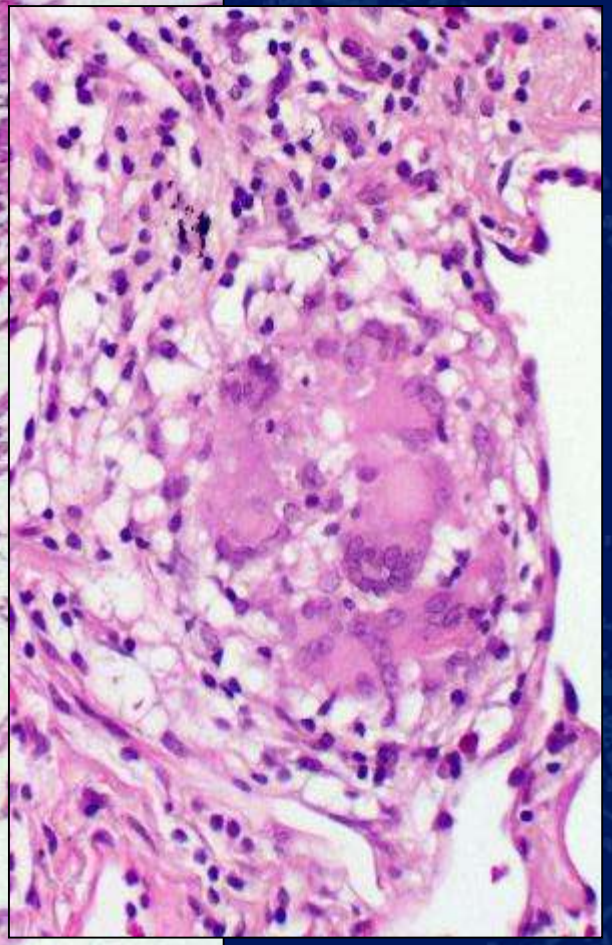


Implications for pathologist-Think:

Fibrotic HP

Aspiration **More to come**

CASE: Peribronchiolar Metaplasia (PBM)



Four domains

Clinical/Lab presentation

Radiologic findings

Pathologic injury pattern(s)

Disease entity that fits

Dx: Probable fibrotic HP

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COMMENTARY……

Aspiration can produce localized mass, ILD, or Bronchiolitis

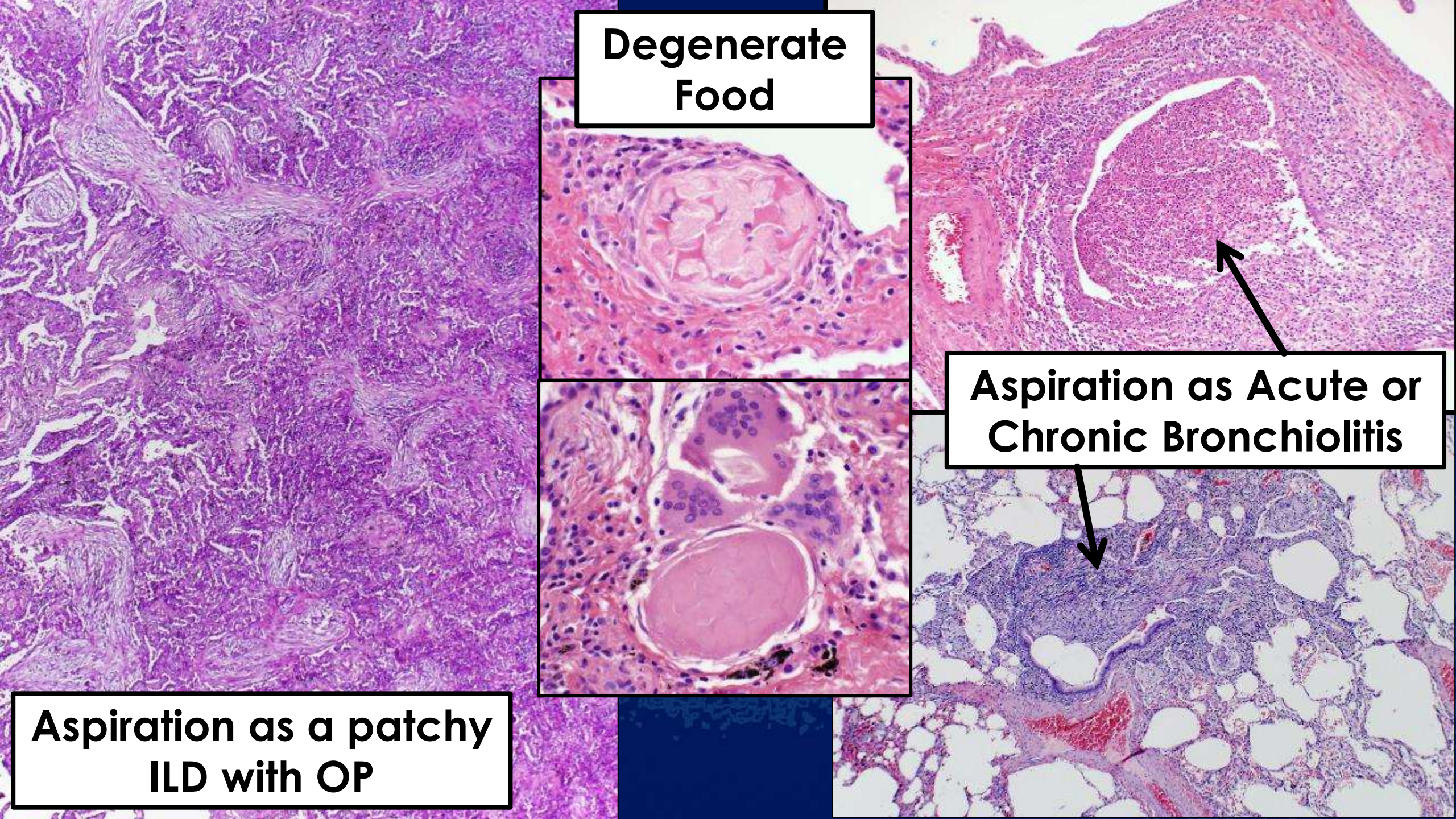
(Mukhopadhyay S, Katzenstein AL. in AJSP 2007; 31: 752)

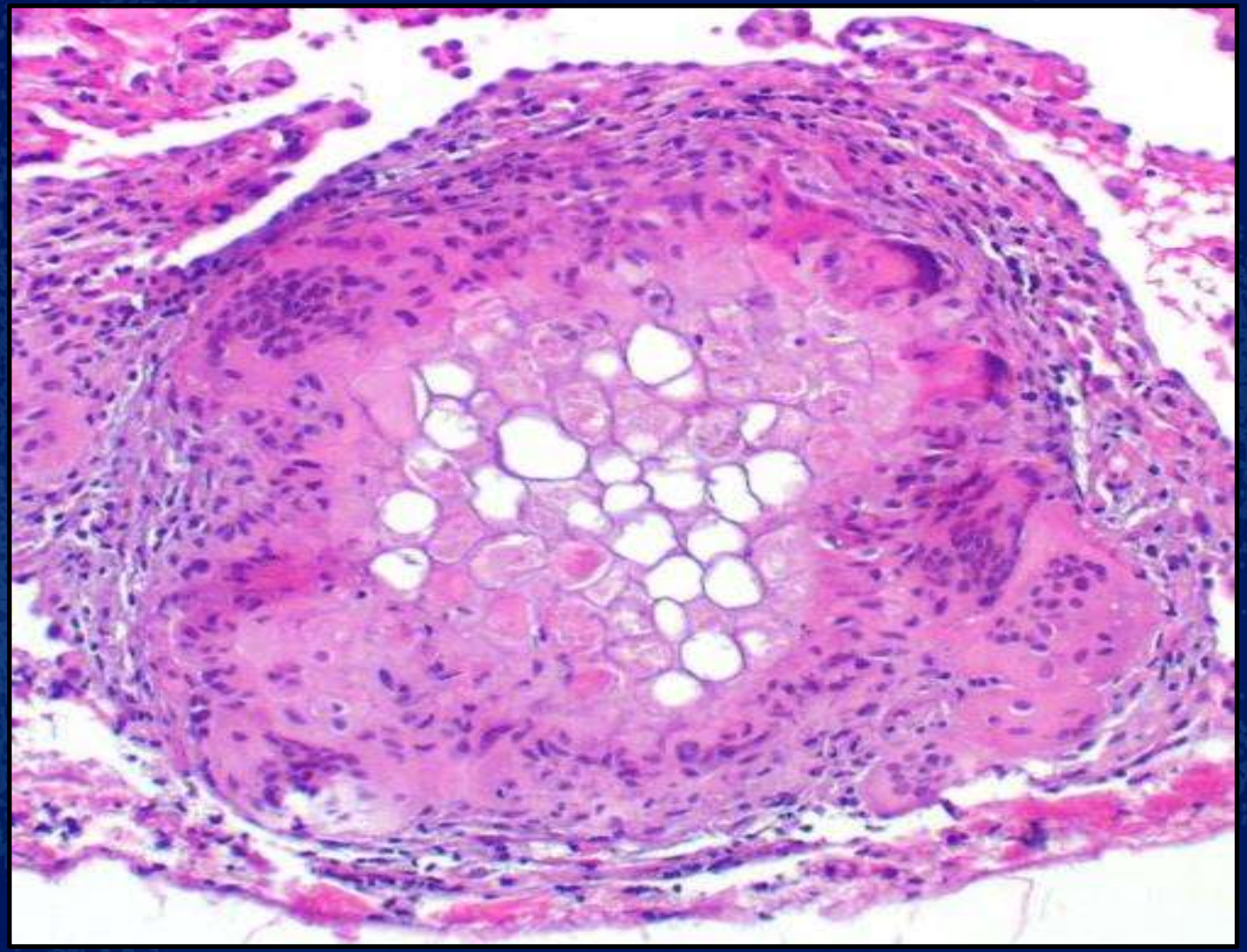
59 cases of lung disease due to aspiration of food or other particulates

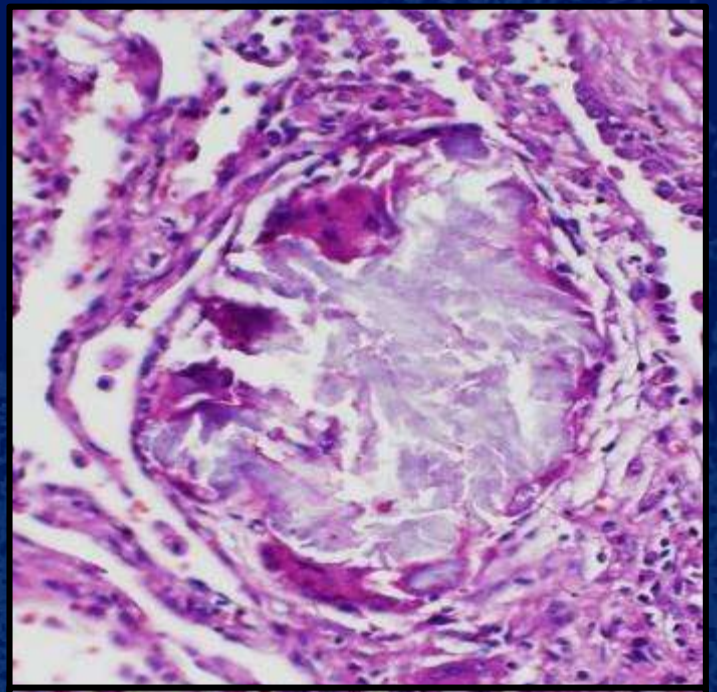
Sx: dyspnea, cough, fever, recurrent pneumonias

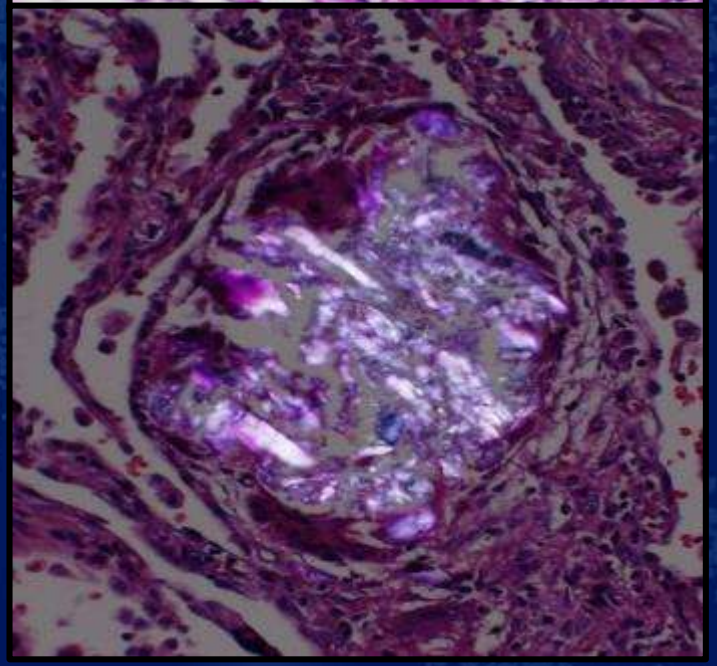
Radiology: Bilateral infiltrates in 50%; unilateral in 50%; infiltrates could be "diffuse."

→ "Interstitial lung disease/ILD"


Degenerate Food
Aspiration as Acute or Chronic Bronchiolitis
Aspiration as a patchy ILD with OP







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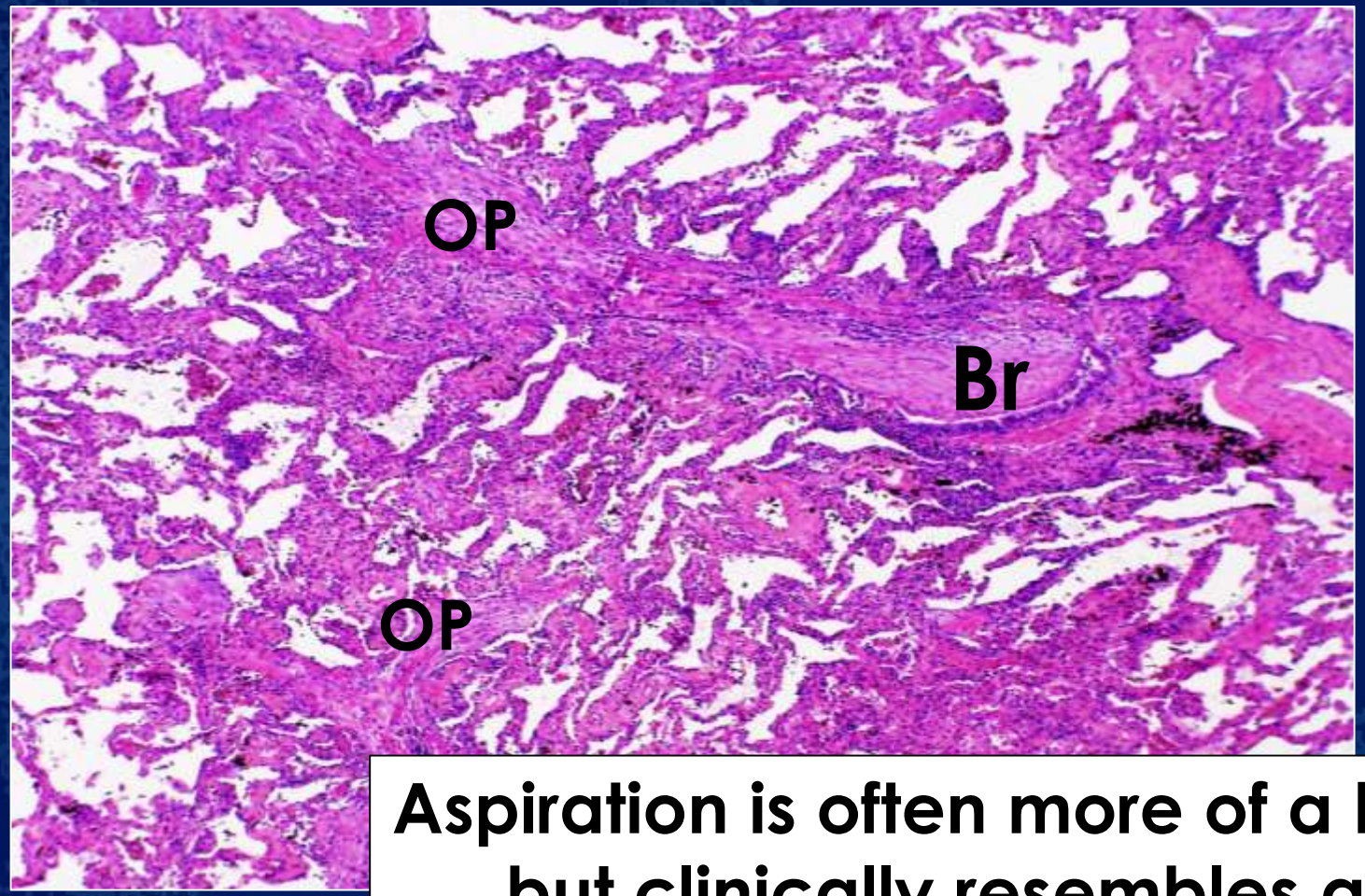
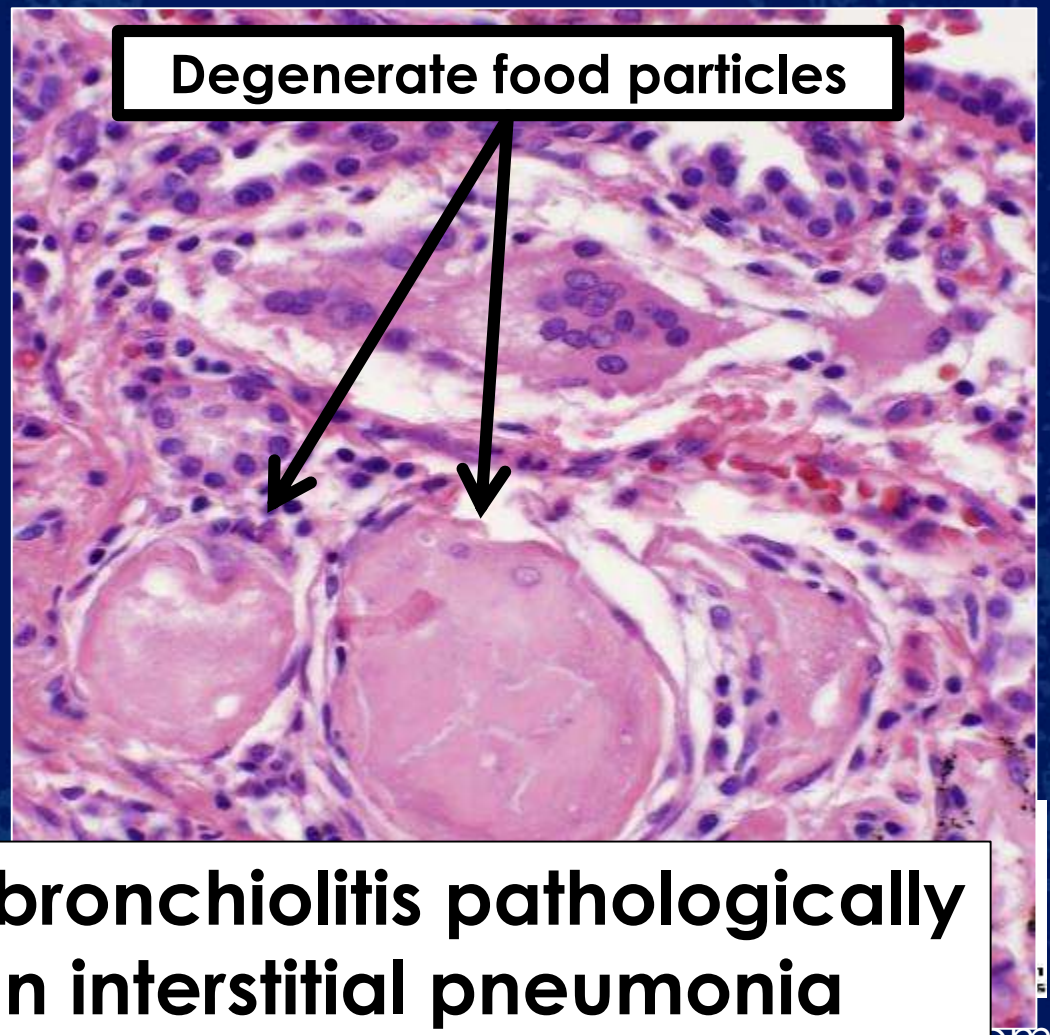
Aspiration as a cause of a bronchiolocentric IP

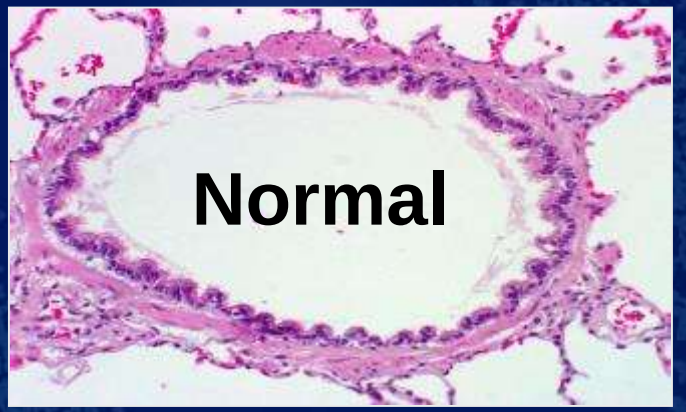
Chronic aspiration:

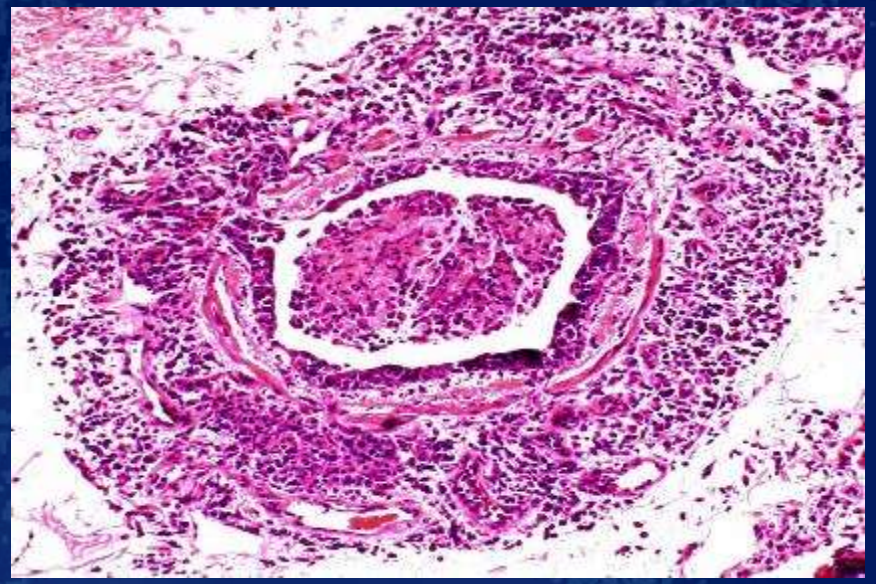




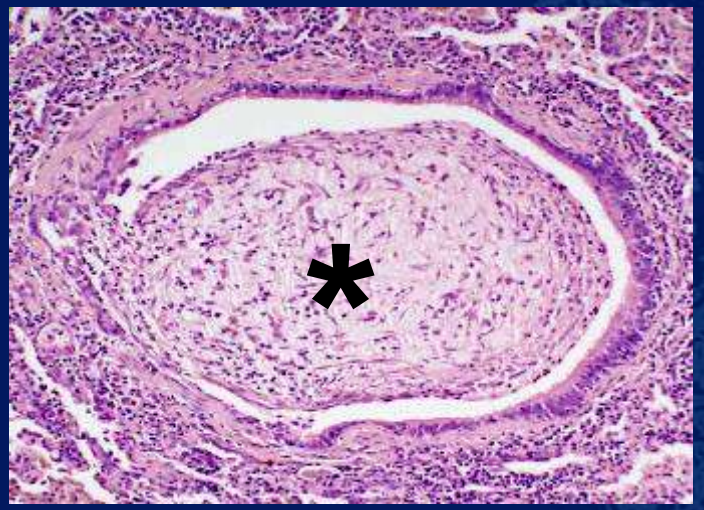
Aspiration is often more of a bronchiolitis pathologically but clinically resembles an interstitial pneumonia

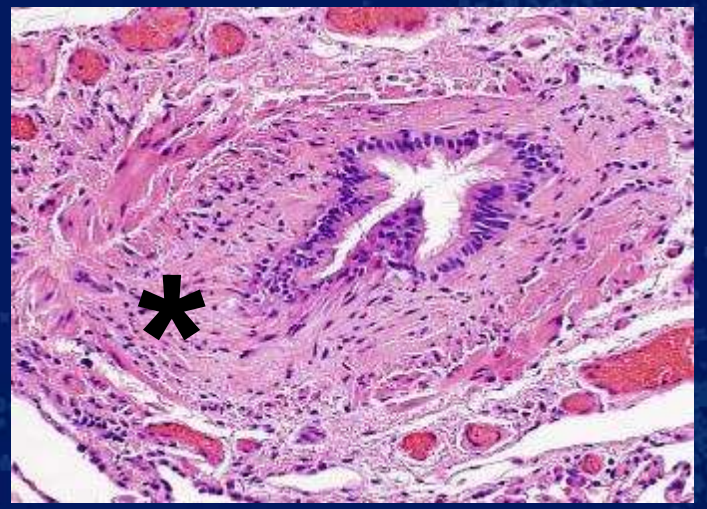
BRONCHIOLITIS
(inflammation of bronchioles)





Cellular infiltration
(+/- fluid, mucus)





Mesenchymal reactions 1* and 2*

The clinical, radiologic and functional effects of these lesions vary from case to case

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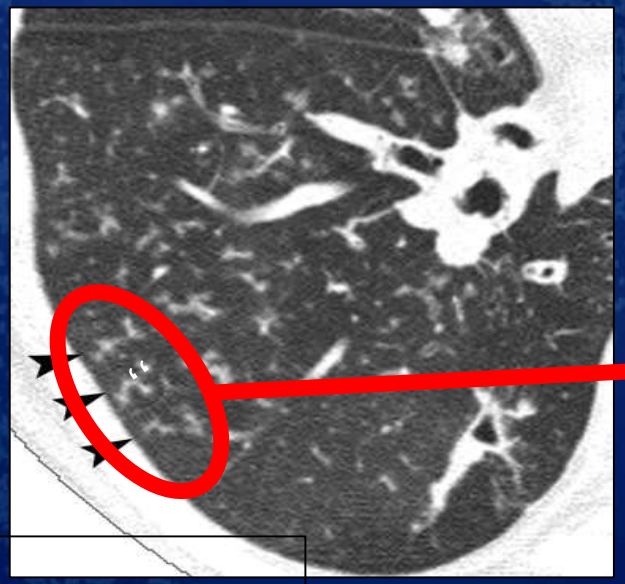
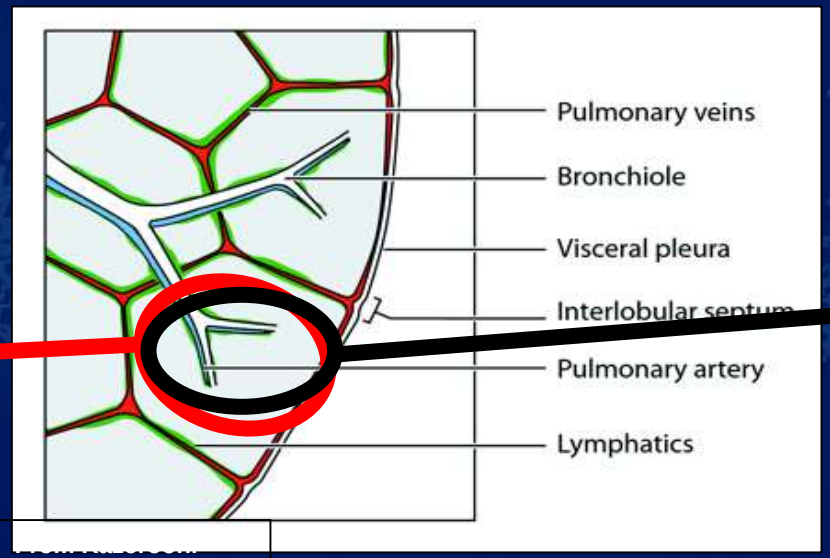
SMALL AIRWAYS/BRONCHIOLES

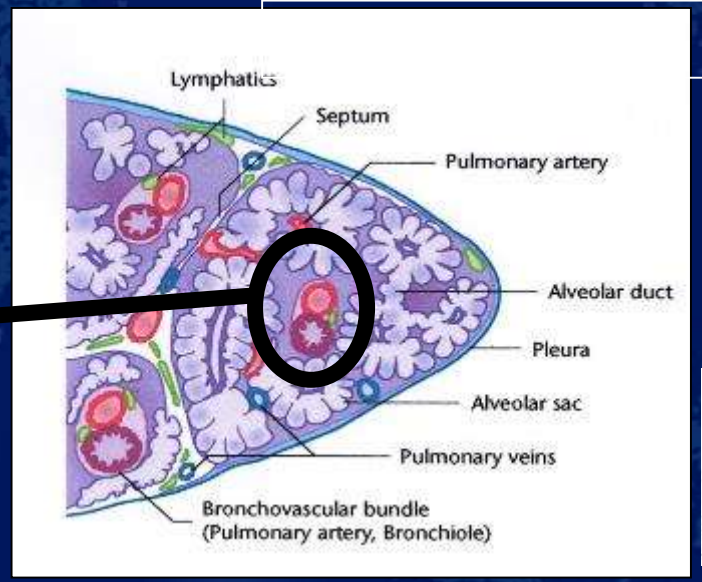
Small airways are ≤ 2 mm

Unless abnormalities are present, small airways are not visible on HRCT.

Abnormal small airways often apparent on HRCT







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BRONCHIOLAR PATHOLOGY
Major Pathologic Groups

Cellular/exudative reaction dominates

Mesenchymal reaction predominates with:

1) Organization with intraluminal polyps
2) Subepithelial fibrosis and scarring with partial or complete luminal compromise
3) Peribronchiolar scarring with luminal patency

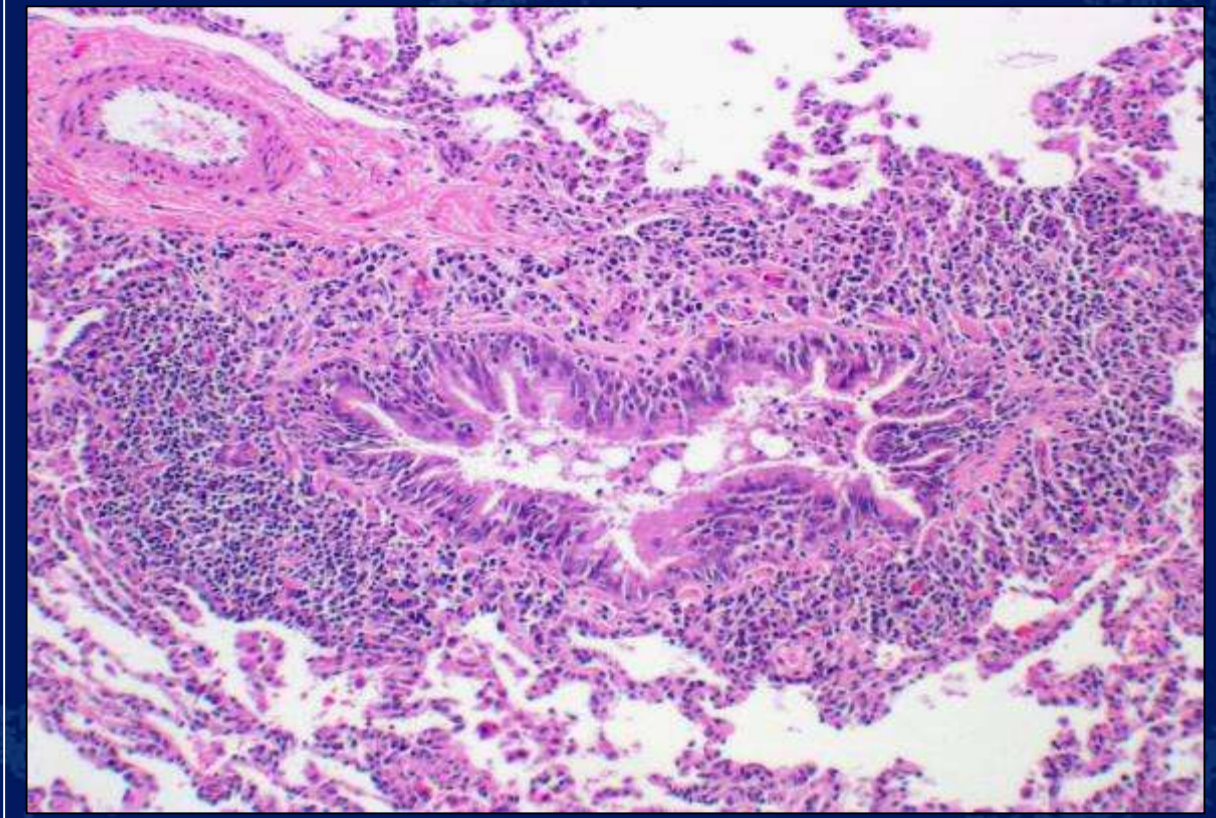
Mixed patterns (are actually most common)

Cellular Bronchiolitis

Cellular/exudative reaction dominates

Acute, chronic, follicular bronchiolitis

- Infections (viral, bacterial, et.al.)
- Aspiration
- Collagen vascular diseases
- Lung/bone marrow transplantation
- Inflammatory bowel disease
- Idiopathic
- As part of interstitial pneumonia
  - RB-ILD
  - Extrinsic allergic alveolitis



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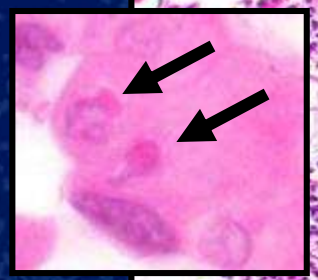
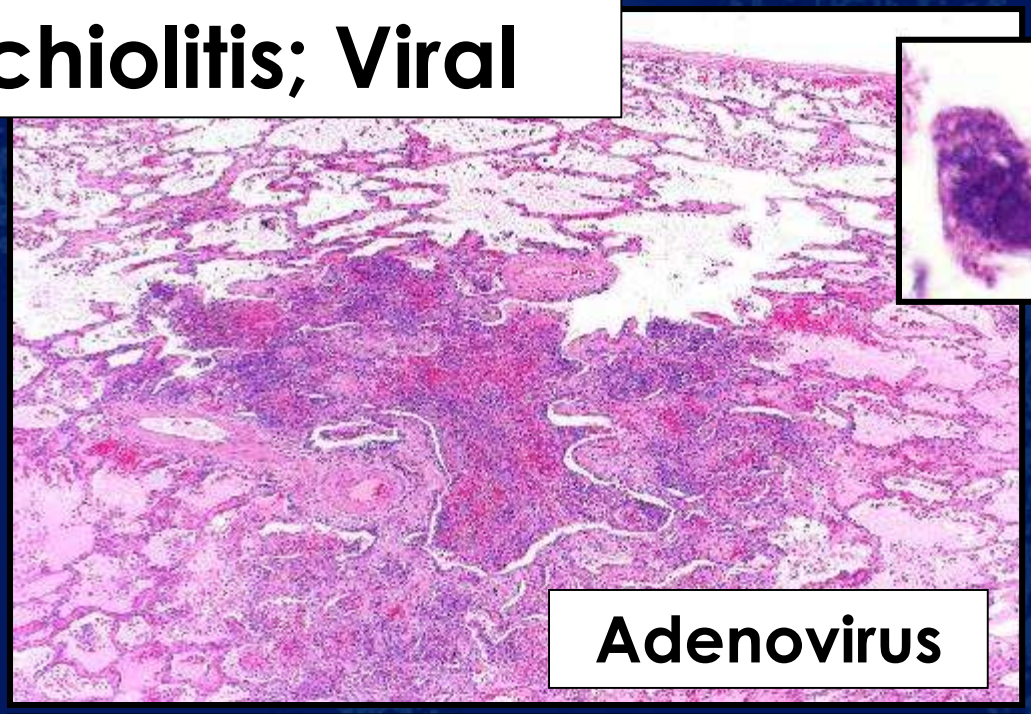
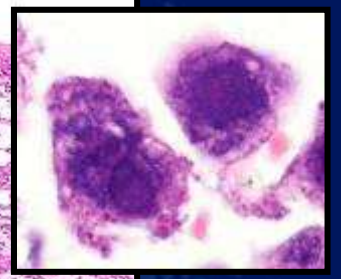
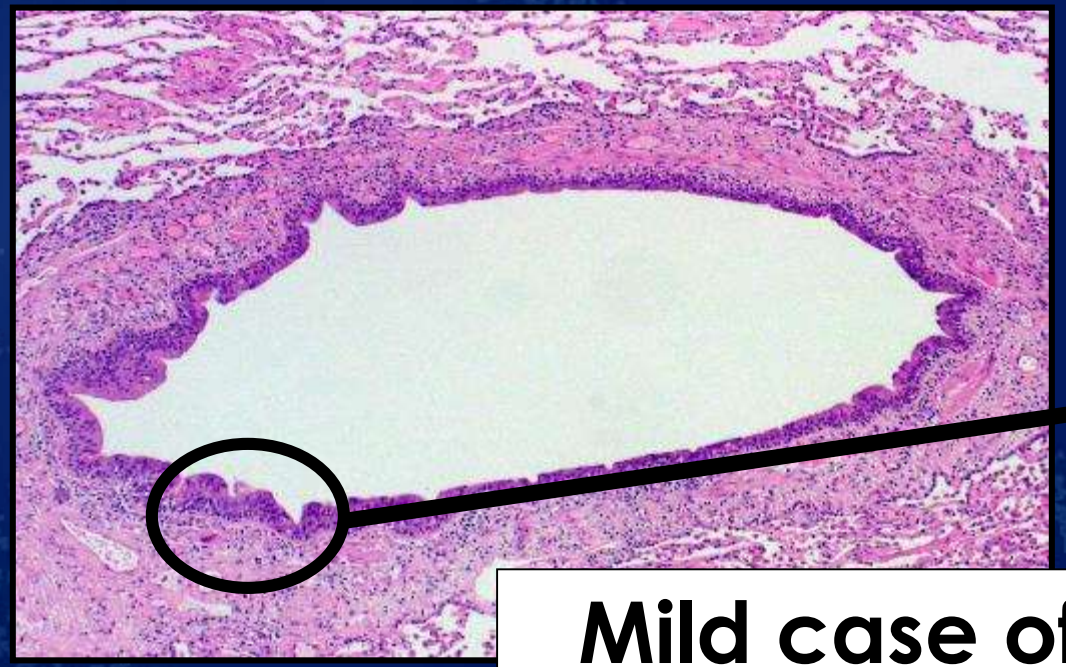
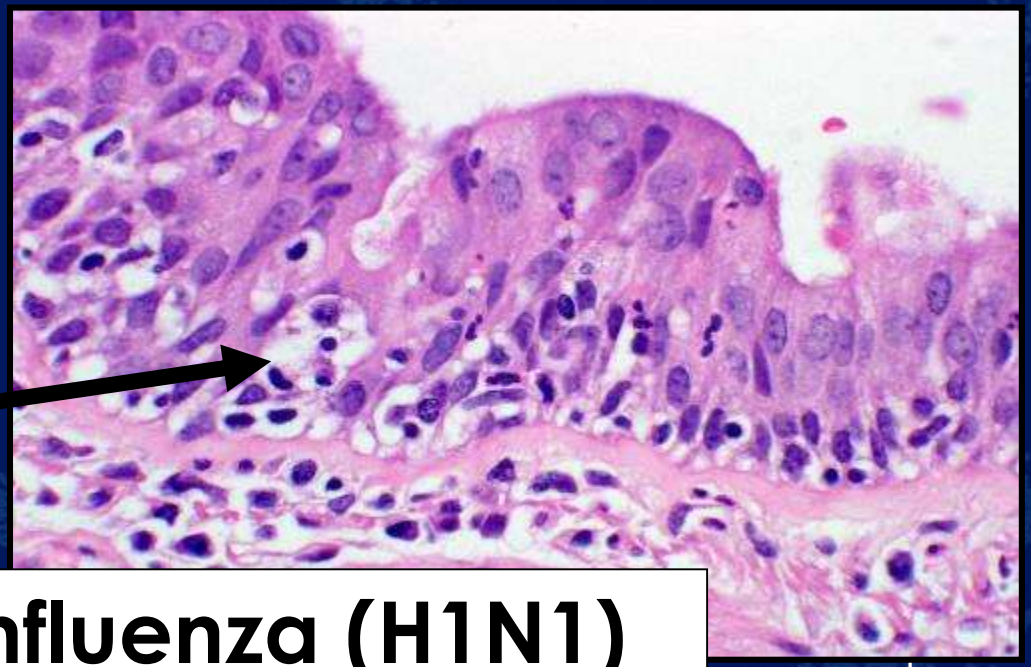
Infectious Bronchiolitis; Viral





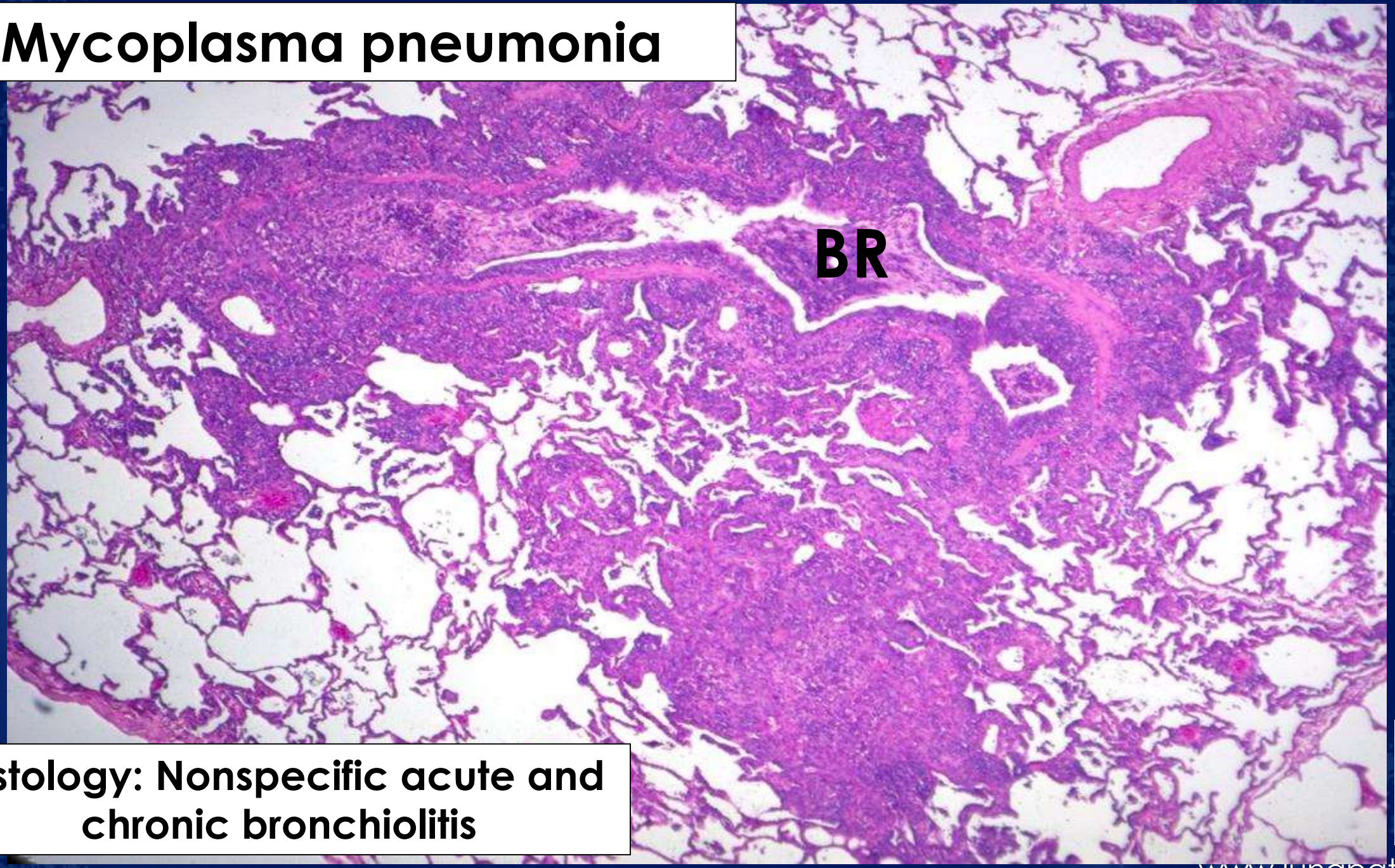






Mild case of Influenza (H1N1)

Mycoplasma pneumonia



Histology: Nonspecific acute and chronic bronchiolitis

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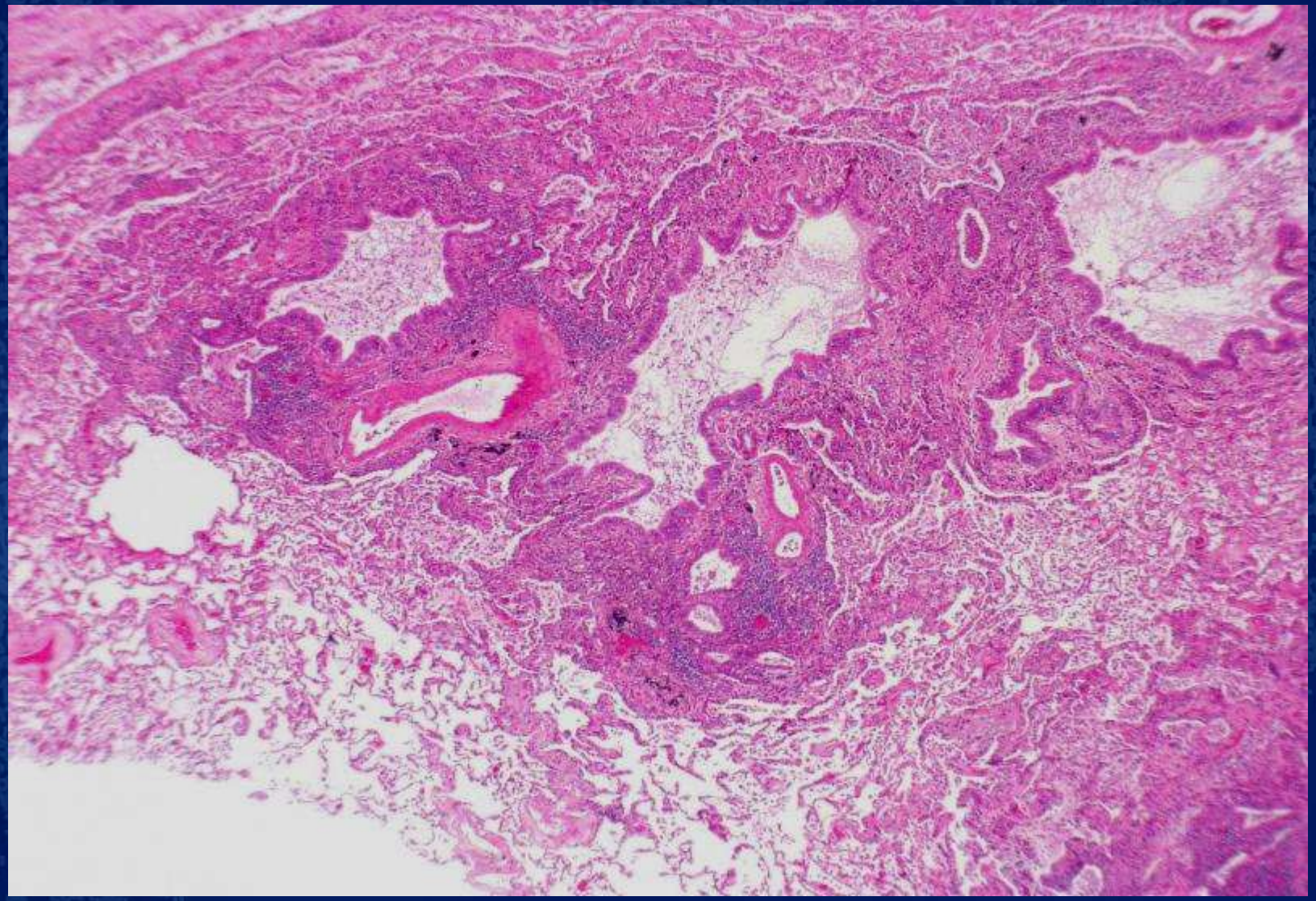
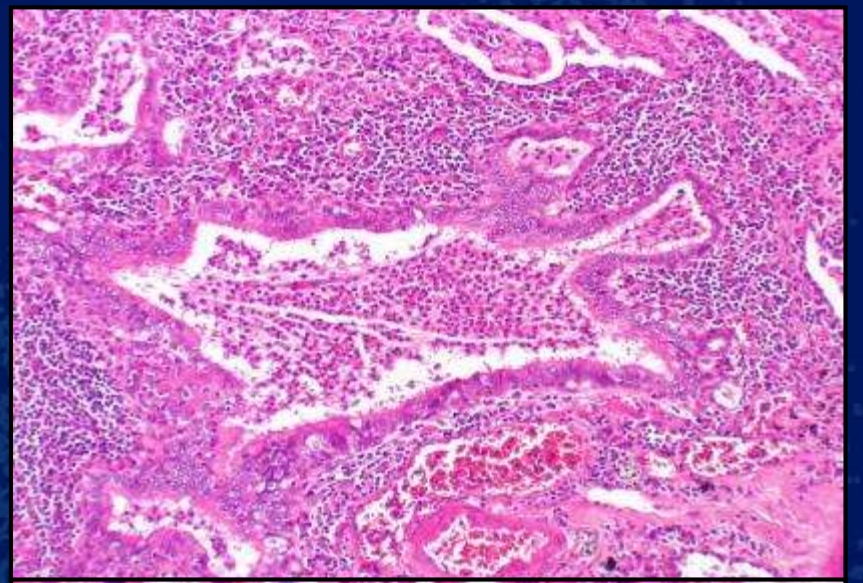
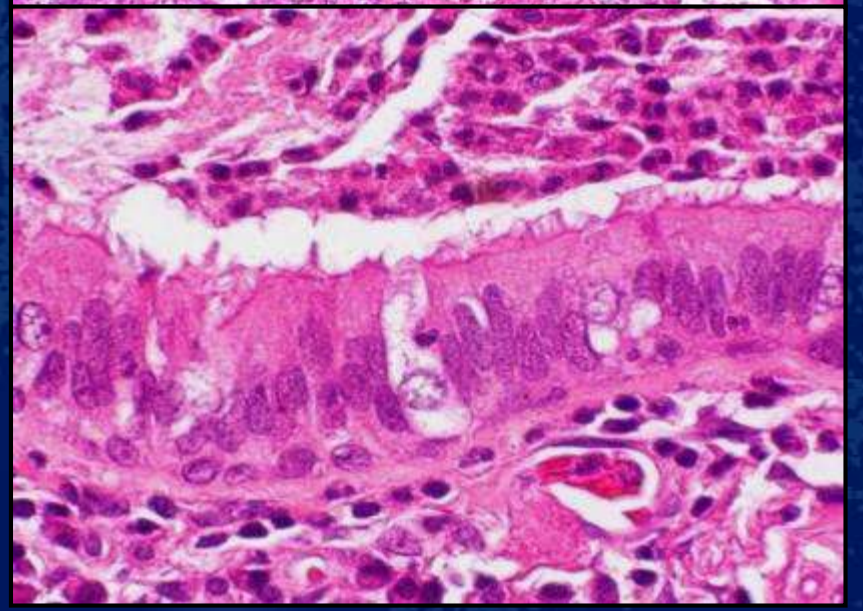
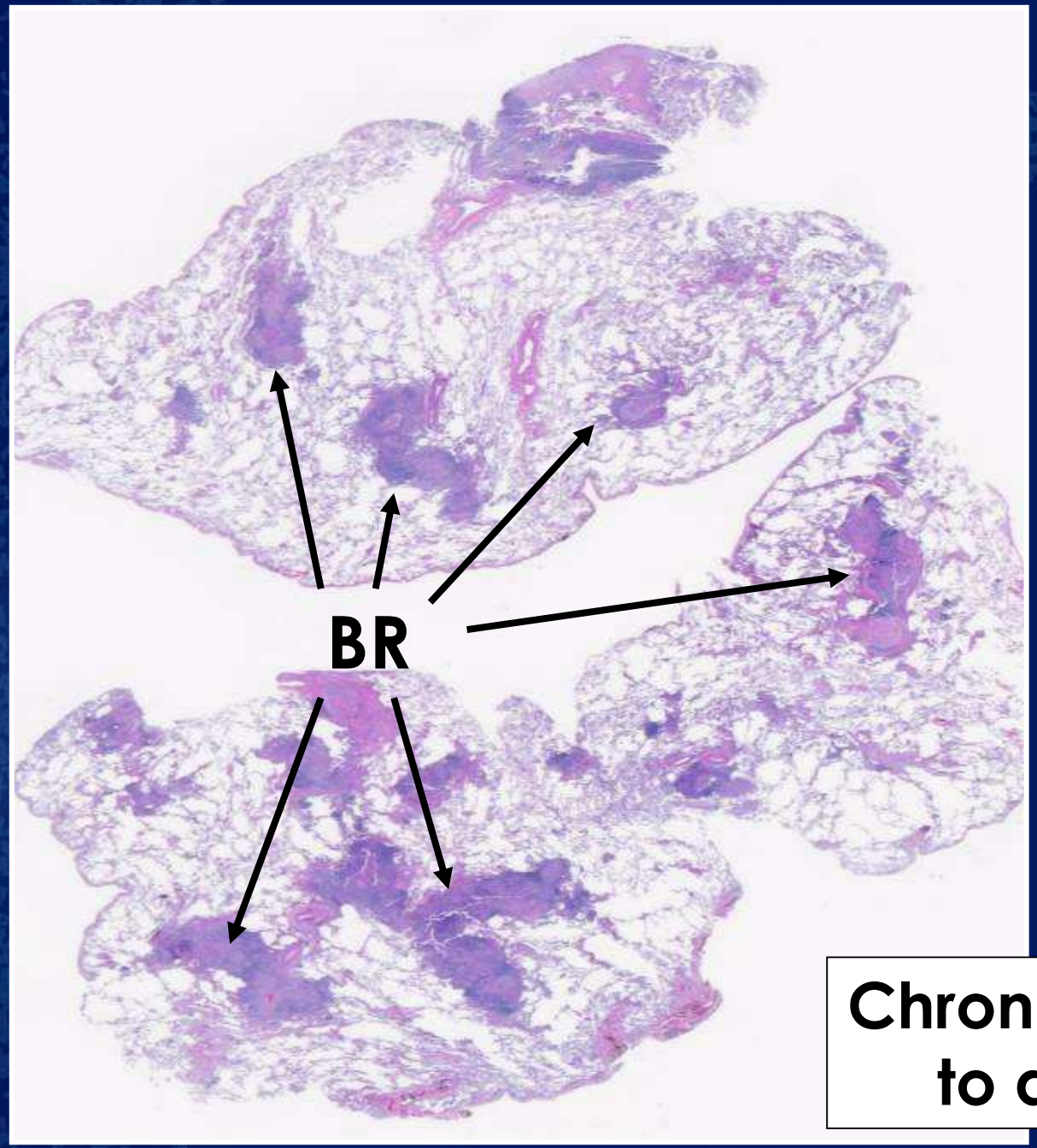
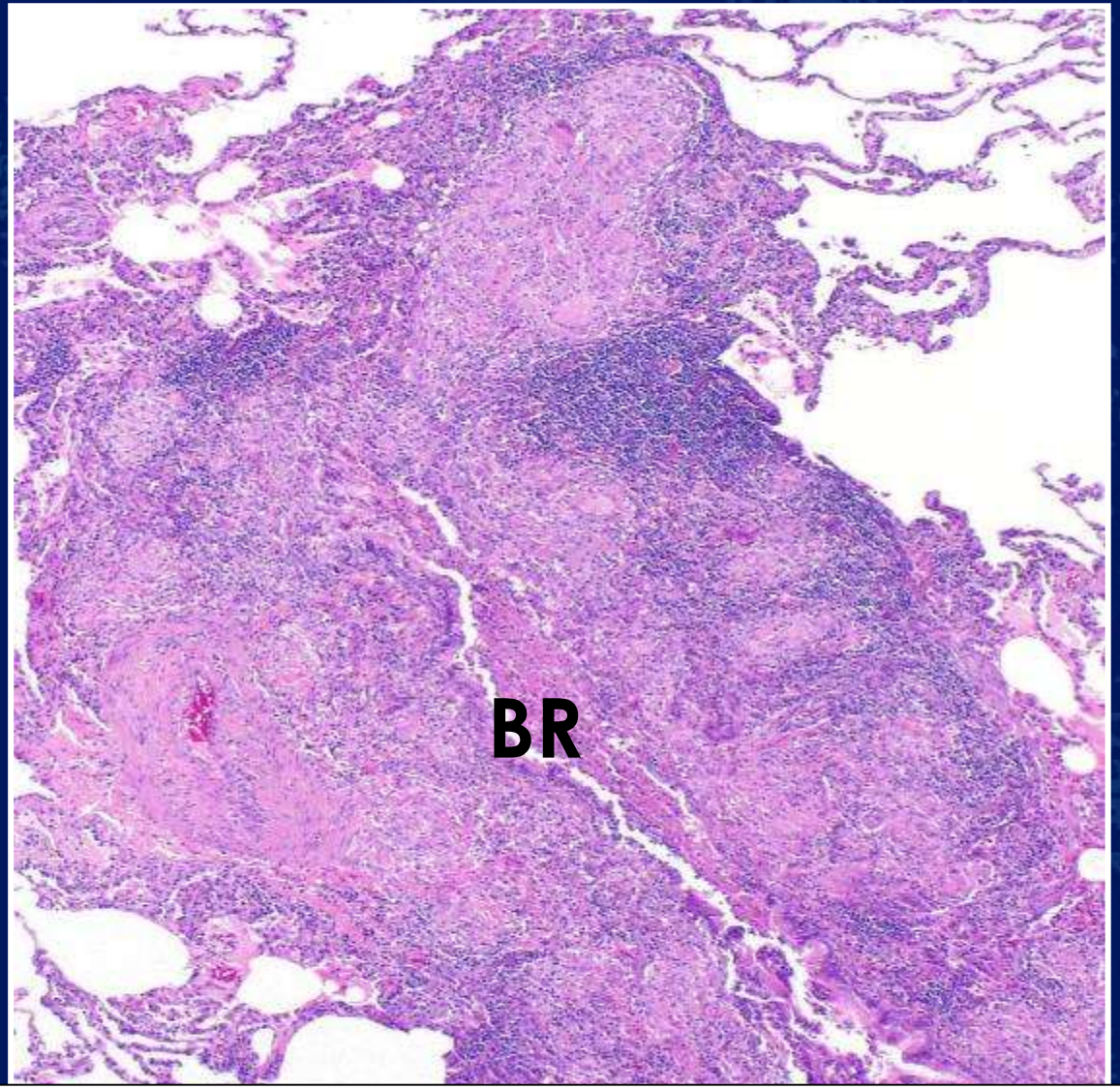
Acute and chronic bacterial bronchiolitis in Primary Ciliary Dyskinesia





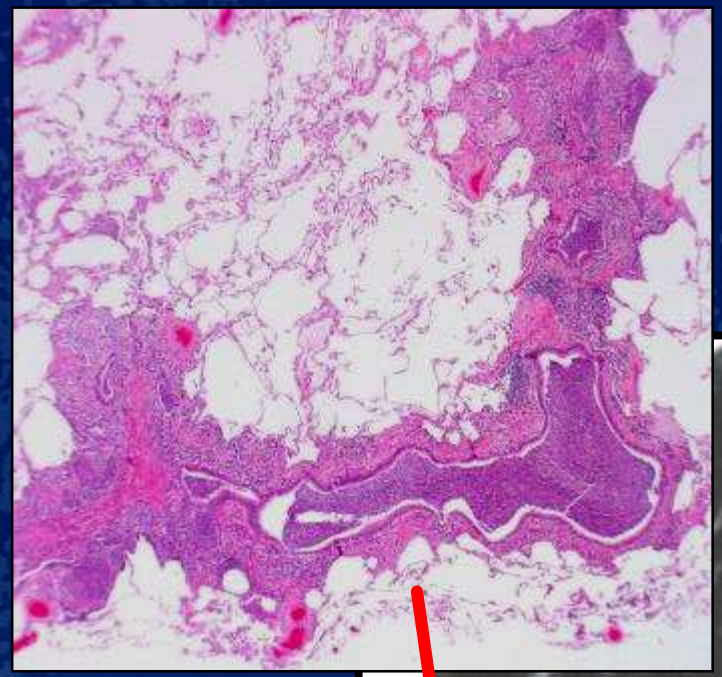


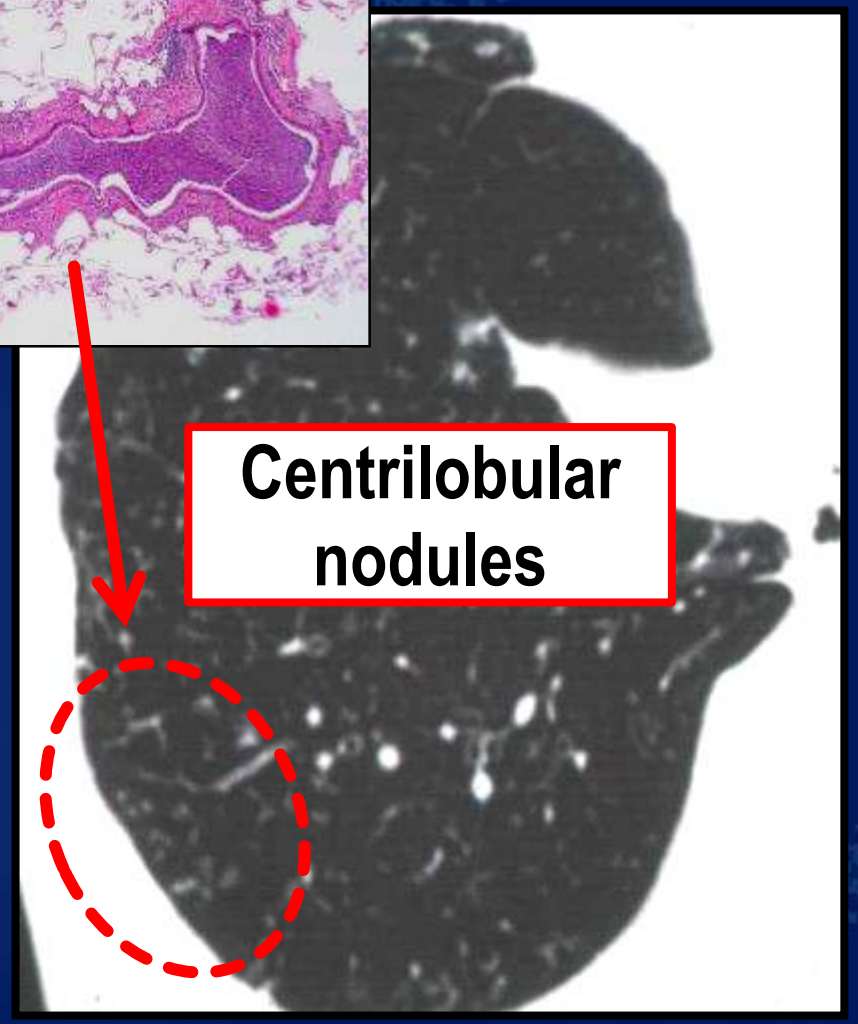




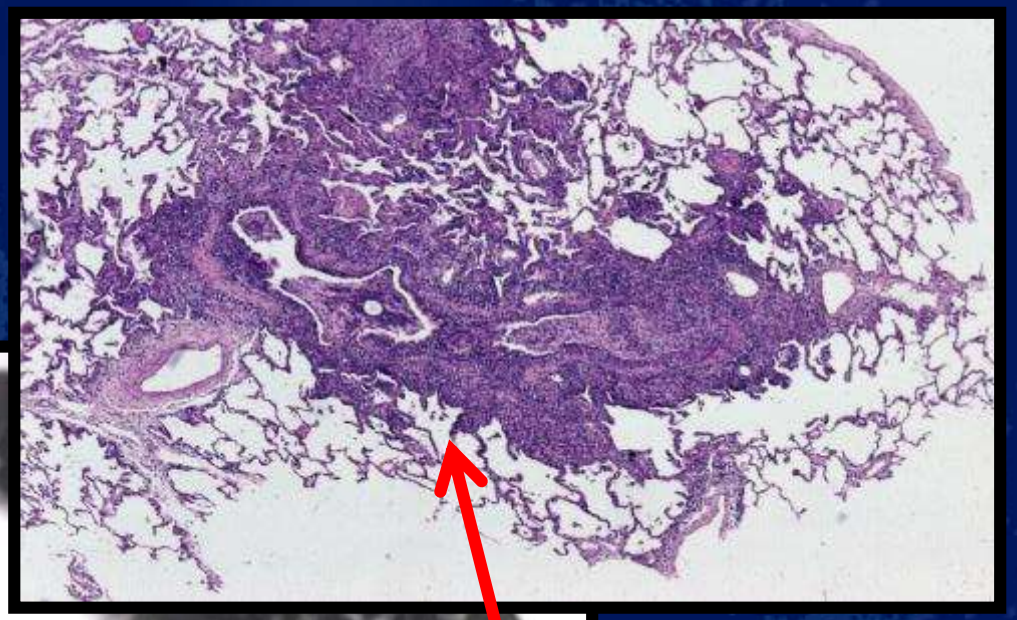
Chronic granulomatous bronchiolitis due to atypical mycobacteria infection

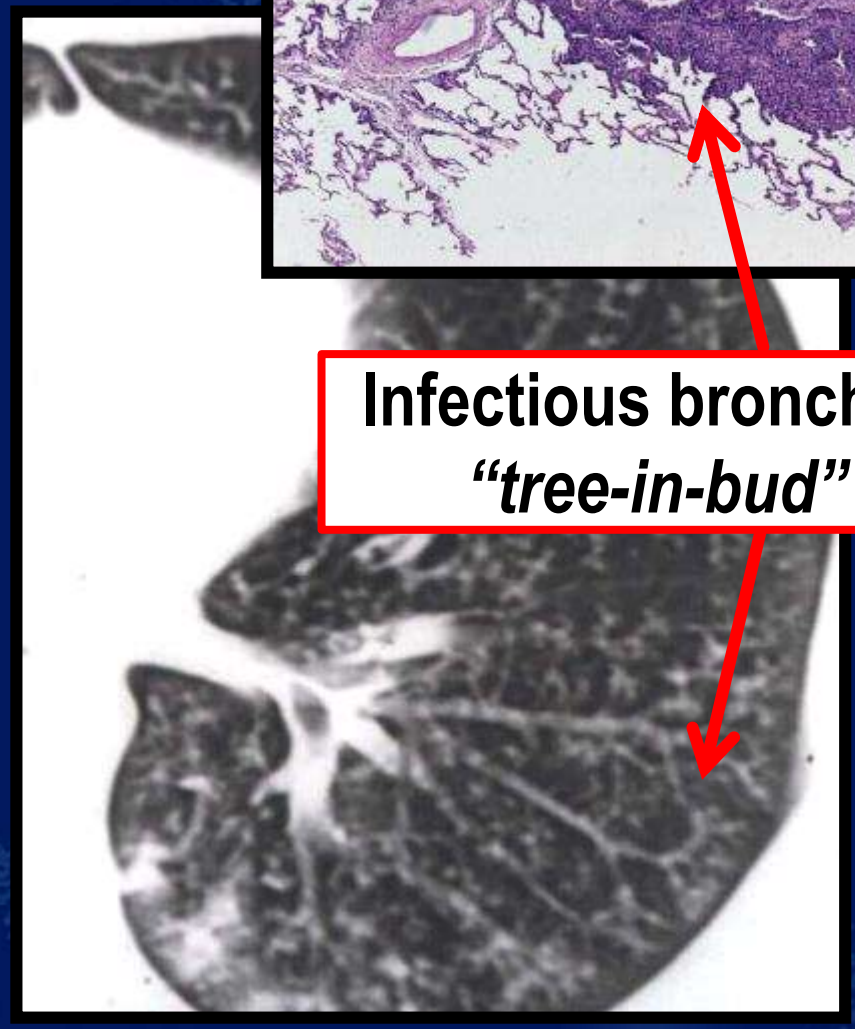
HRCT in Bronchiolitis





Centrilobular nodules





Infectious bronchiolitis with *"tree-in-bud"* pattern

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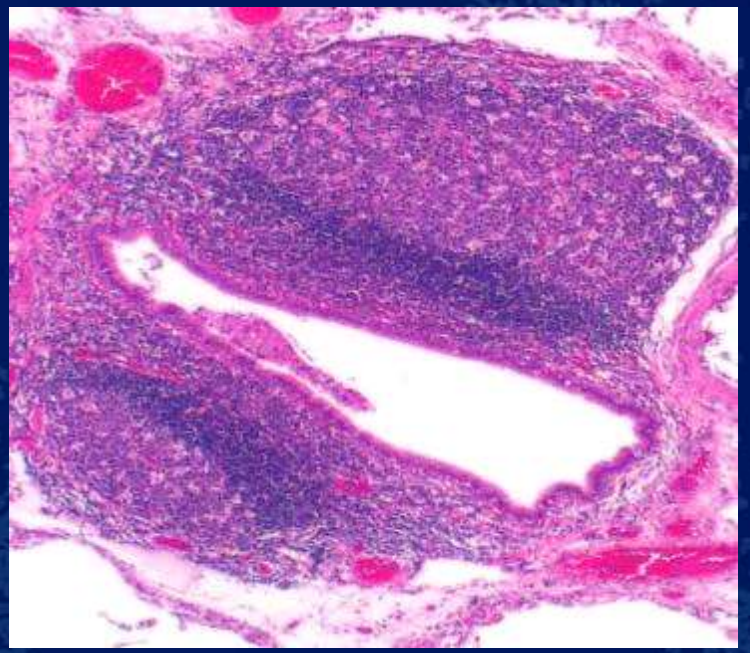
FOLLICULAR BRONCHIOLITIS



Definition: Lymphoid hyperplasia along bronchioles (a reflection BALT hyperplasia)

Causes and Associations:

- Connective tissue disease (especially RA, Sjogrens)
- Immunoglobulin deficiencies (including HIV)
- Hypersensitivity reaction
- Chronic infection/inflammation

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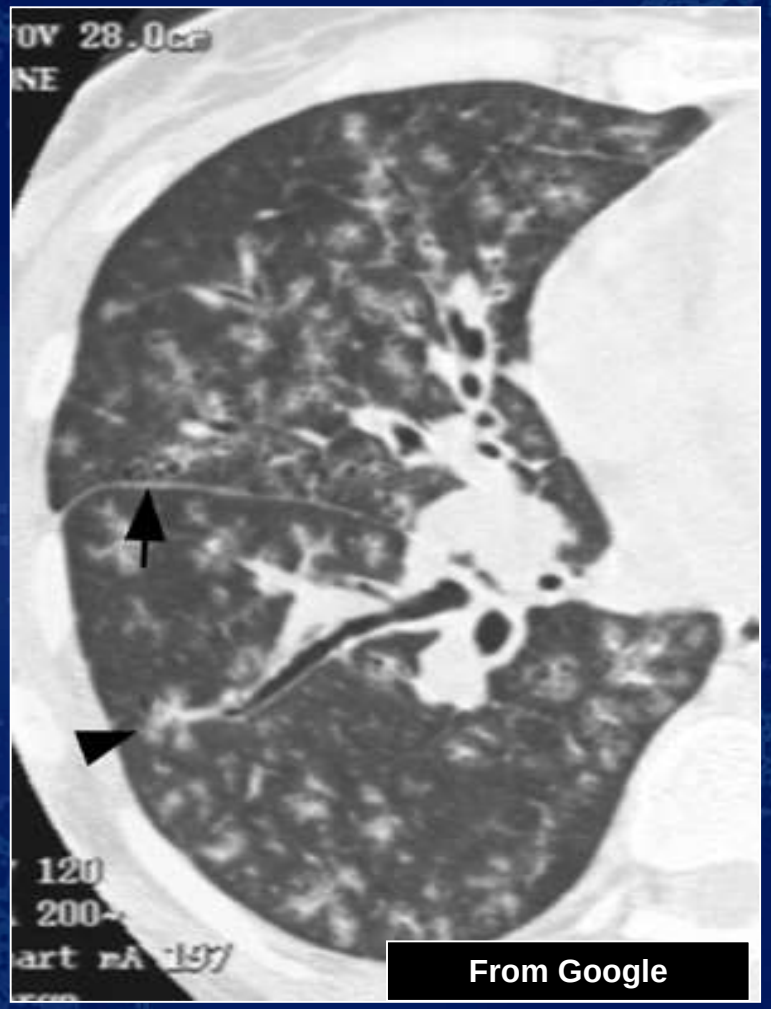
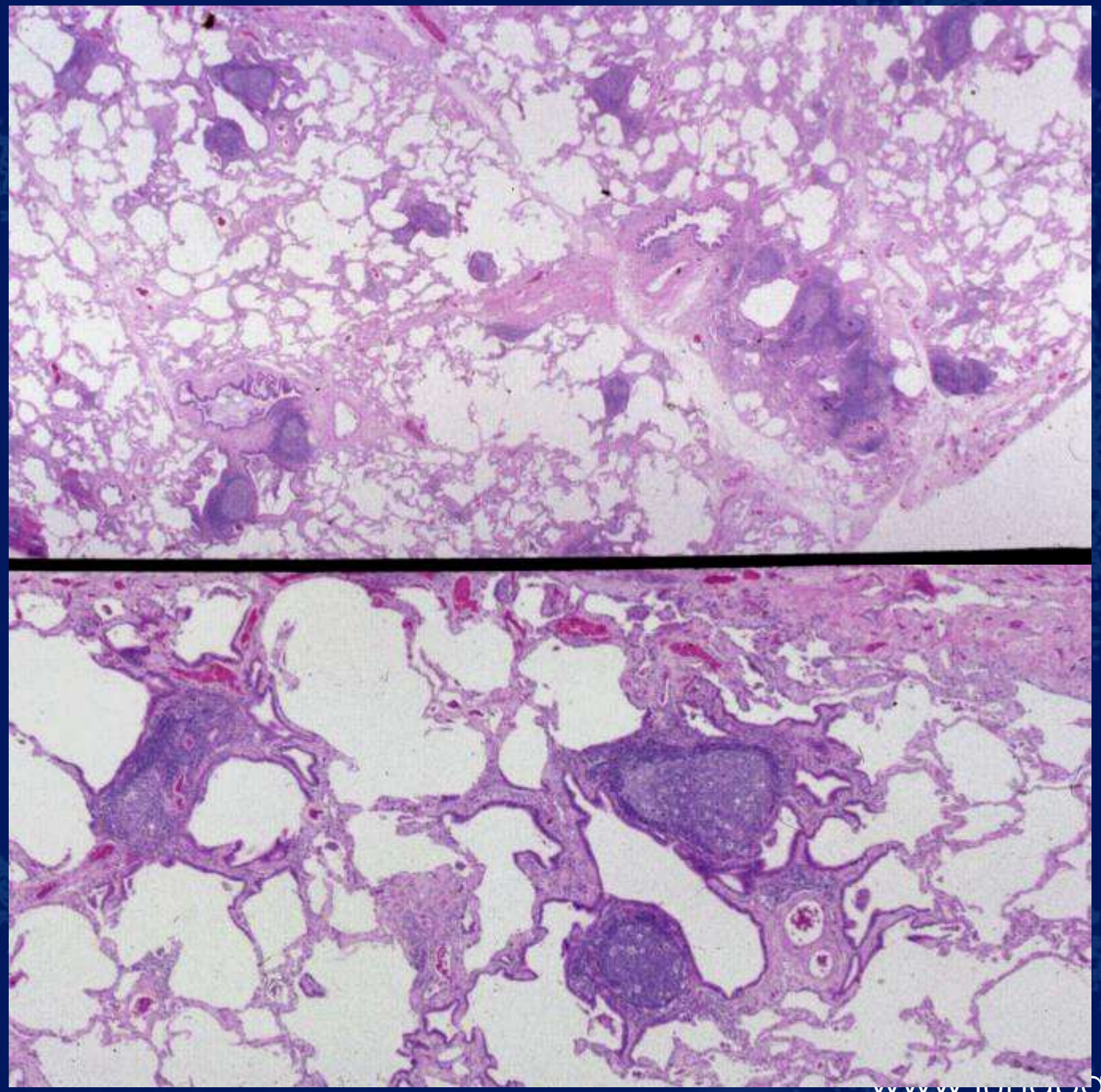
Follicular bronchiolitis in RA

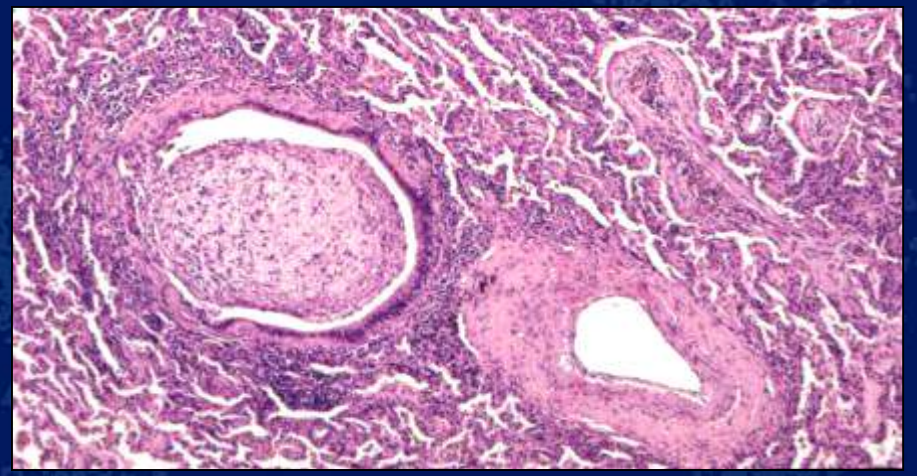




Mesenchymal reactions #1 and #2 in bronchioles

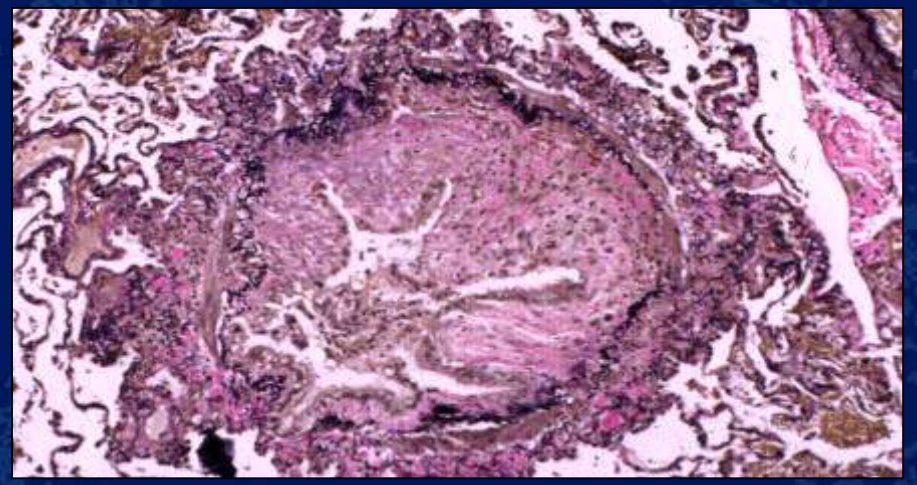
1) Organization with intraluminal polyps

   (Terms: bronchiolitis obliterans, organizing pneumonia (OP)



2) Subepithelial fibrosis and scarring with partial or complete luminal loss

   (Terms: constrictive bronchiolitis, bronchiolitis obliterans, obliterative bronchiolitis)



Both of these have been called *"bronchiolitis obliterans"*

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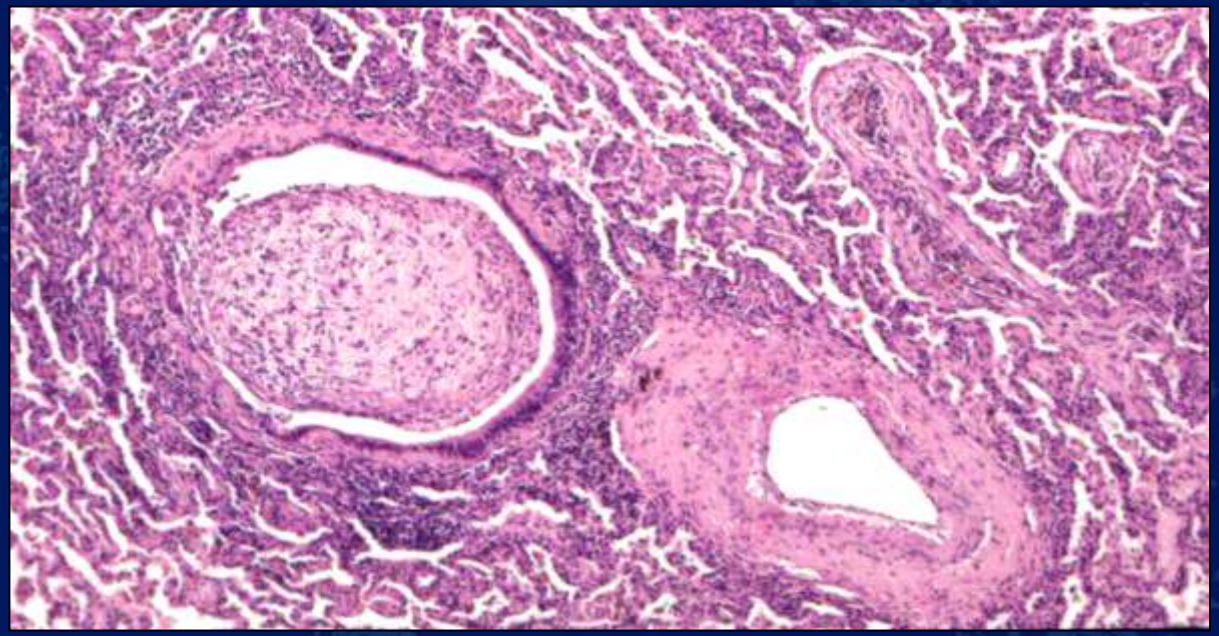
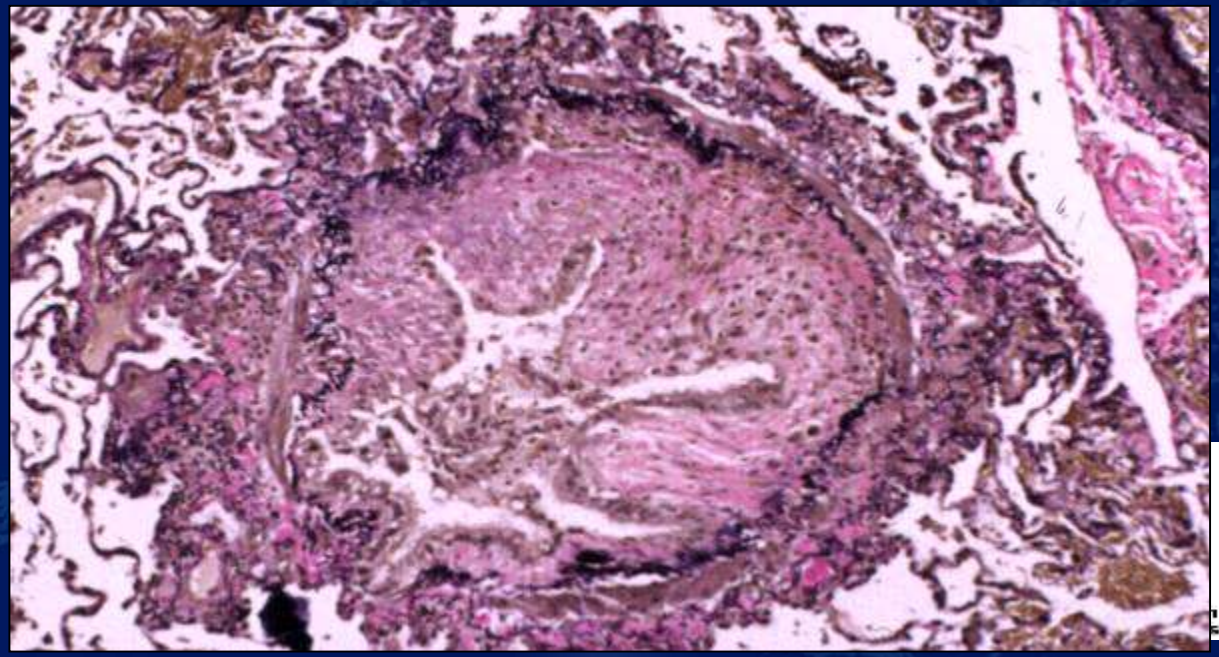
OP with intraluminal polyps

Common reparative reaction
Infiltrative lung disease clinically

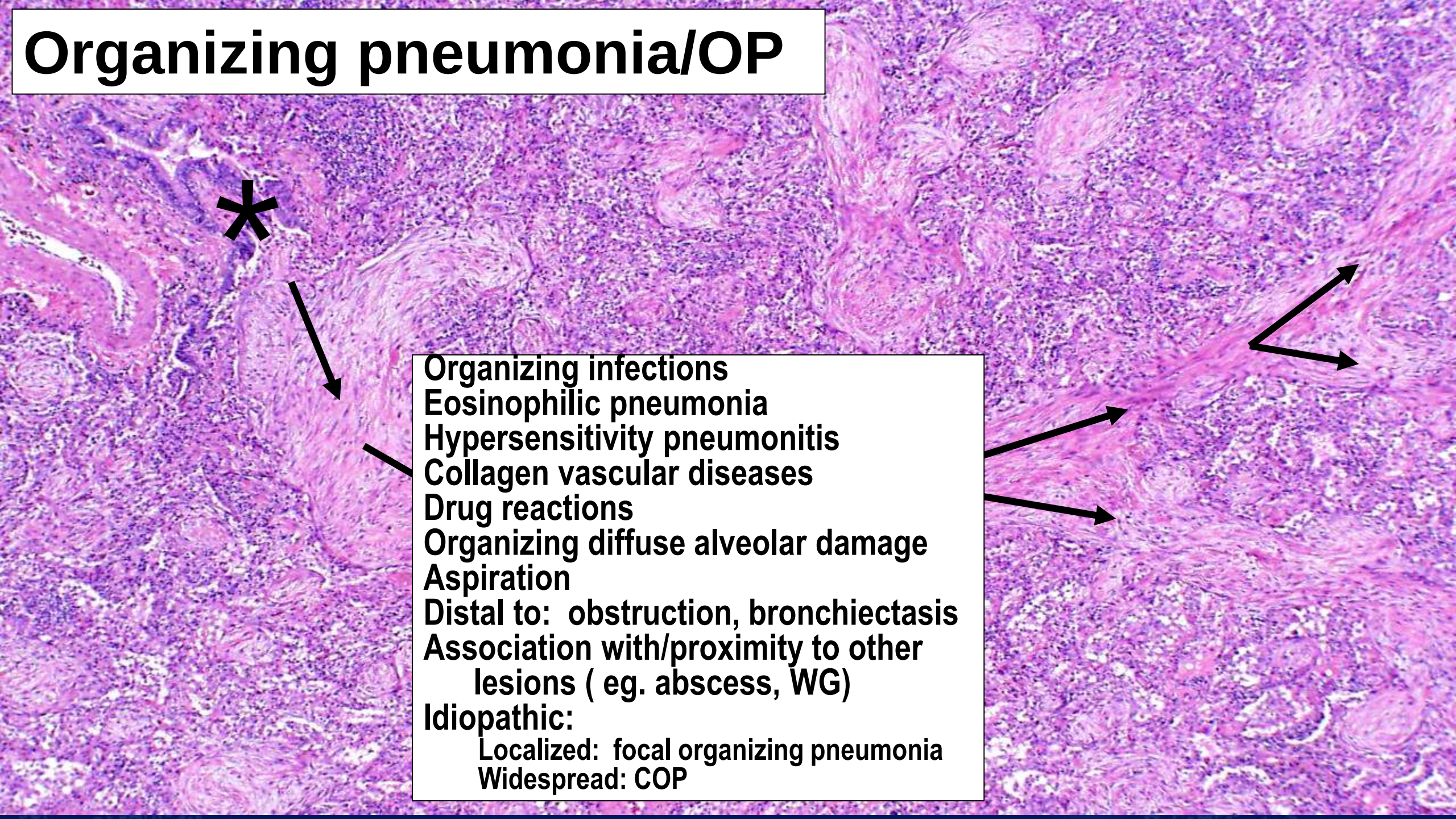


Constrictive bronchiolitis

Uncommon
Usually "pure" (restricted to membranous bronchioles)
Obstructive disease clinically



Organizing pneumonia/OP

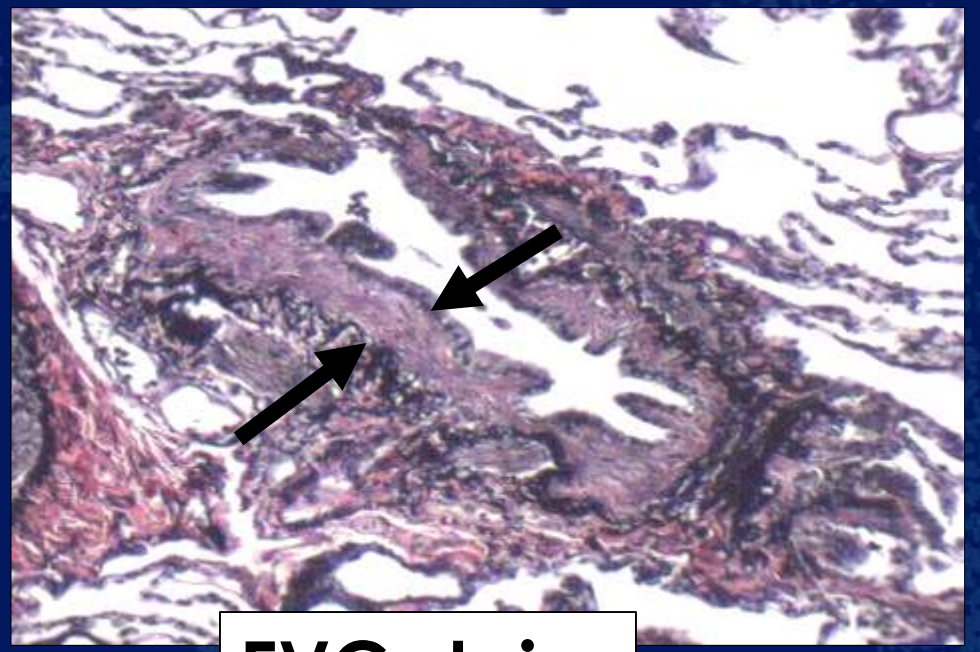


Organizing infections
Eosinophilic pneumonia
Hypersensitivity pneumonitis
Collagen vascular diseases
Drug reactions
Organizing diffuse alveolar damage
Aspiration
Distal to: obstruction, bronchiectasis
Association with/proximity to other lesions (eg. abscess, WG)
Idiopathic:
- Localized: focal organizing pneumonia
- Widespread: COP

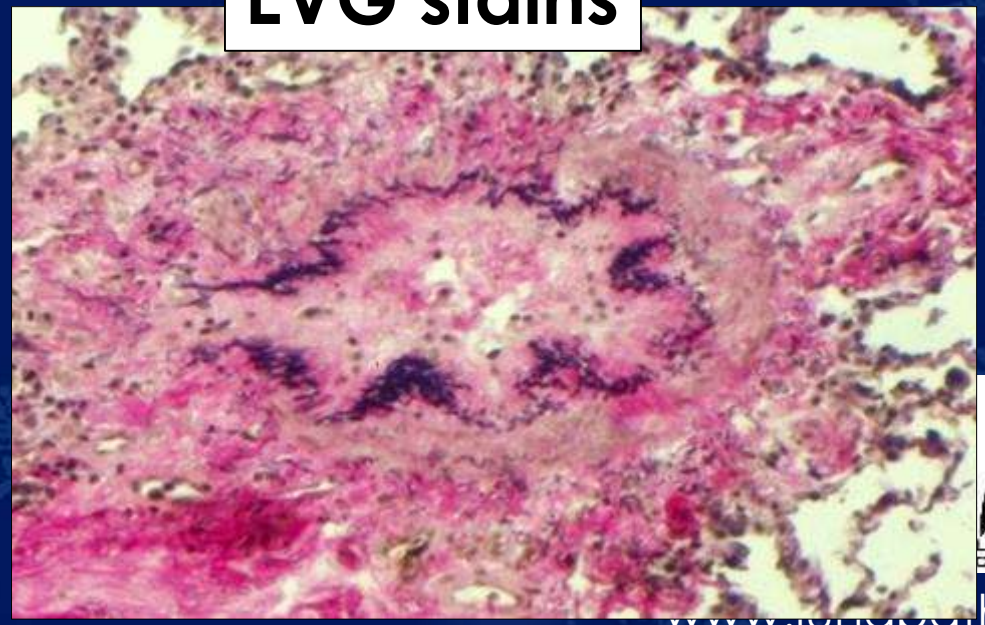
CONSTRICTIVE BRONCHIOLITIS

Causes

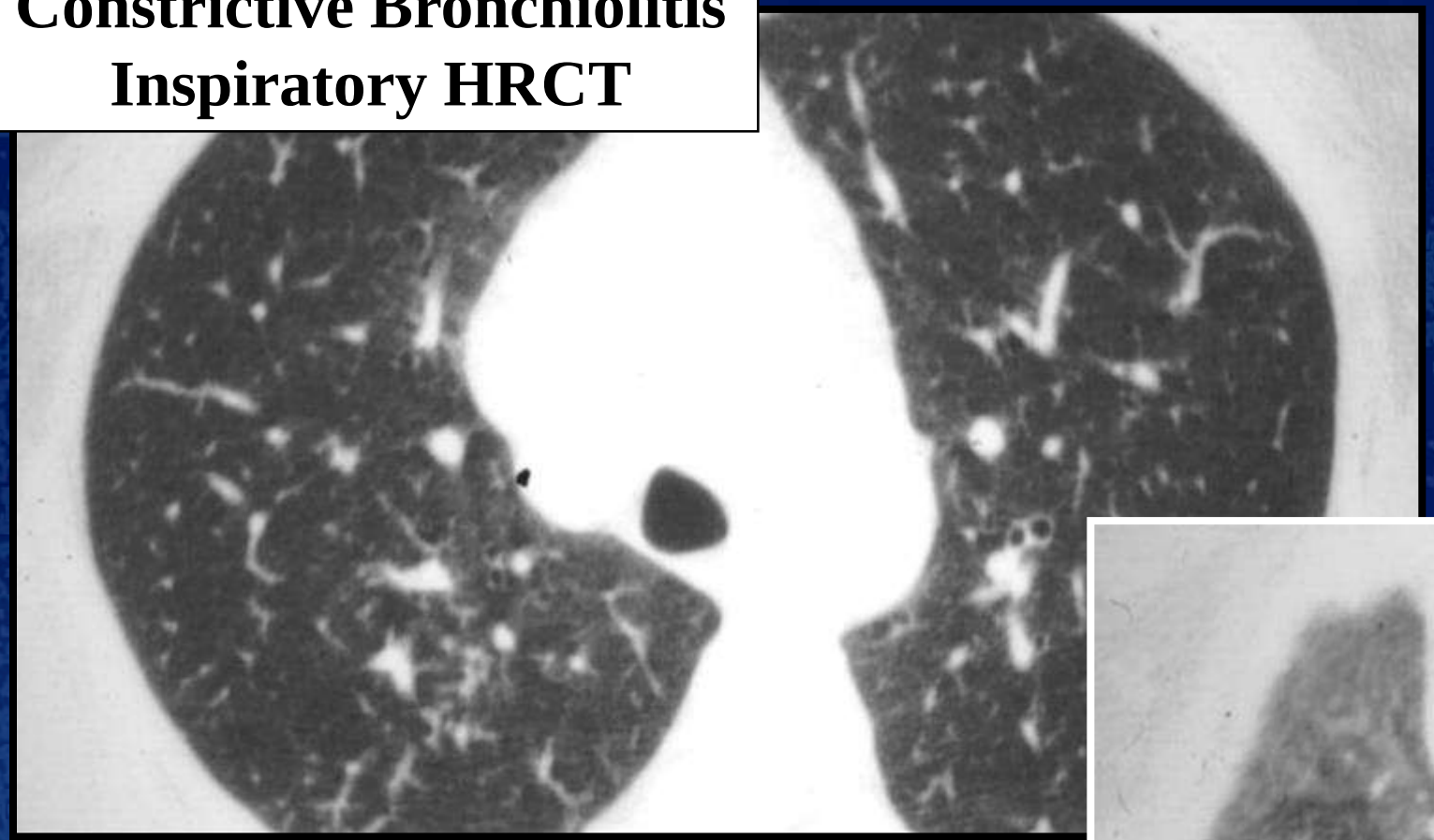
- Post infectious (e.g. adenovirus)
- Fume exposure-related
- Transplantation (lung, GVH in BM Tx)
- Collagen vascular disease-associated
- Drug reaction (e.g. penicillamine)
- Inflammatory bowel disease-associated
- Bronchiolar NE cell hyperplasia
- Idiopathic
- Secondary (e.g. bronchiectasis)



EVG stains



Constrictive Bronchiolitis
Inspiratory HRCT

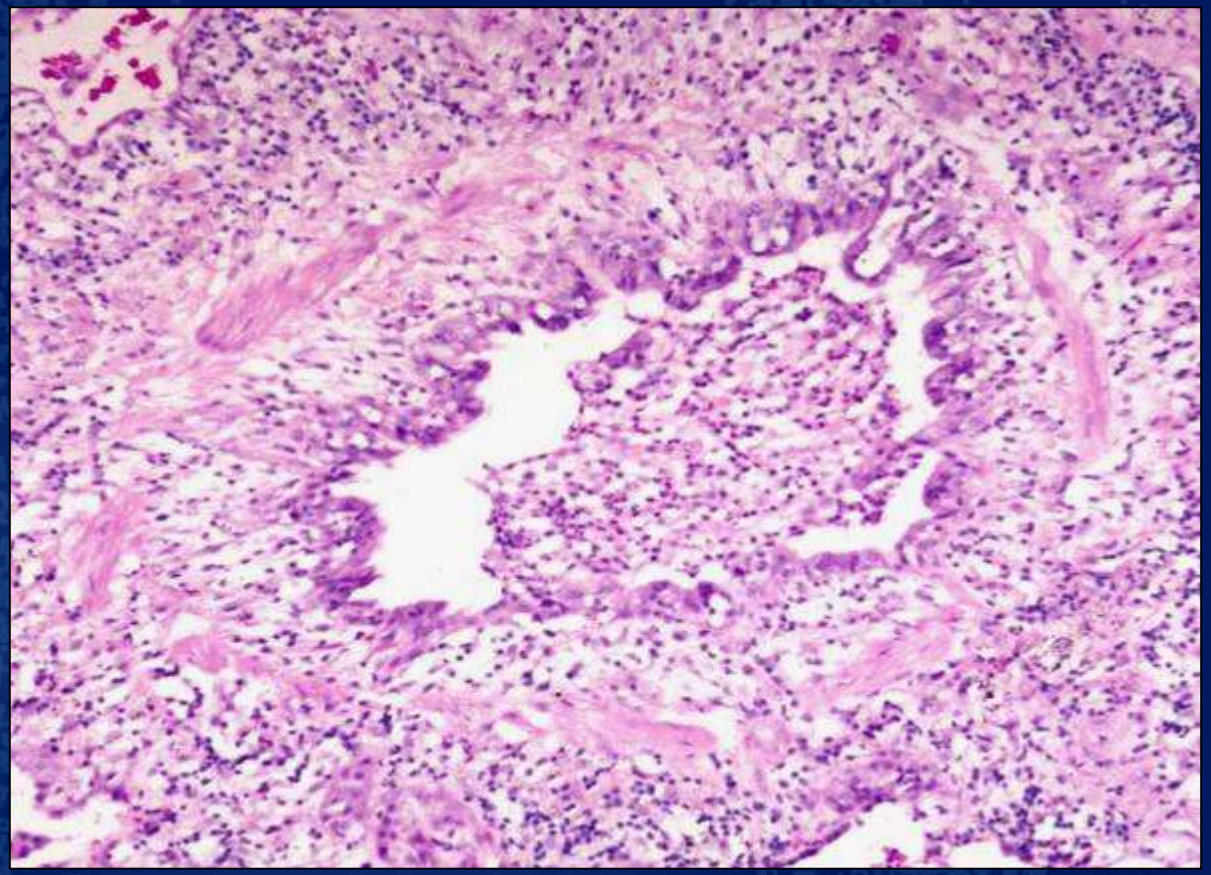


Mosaic pattern with air trapping

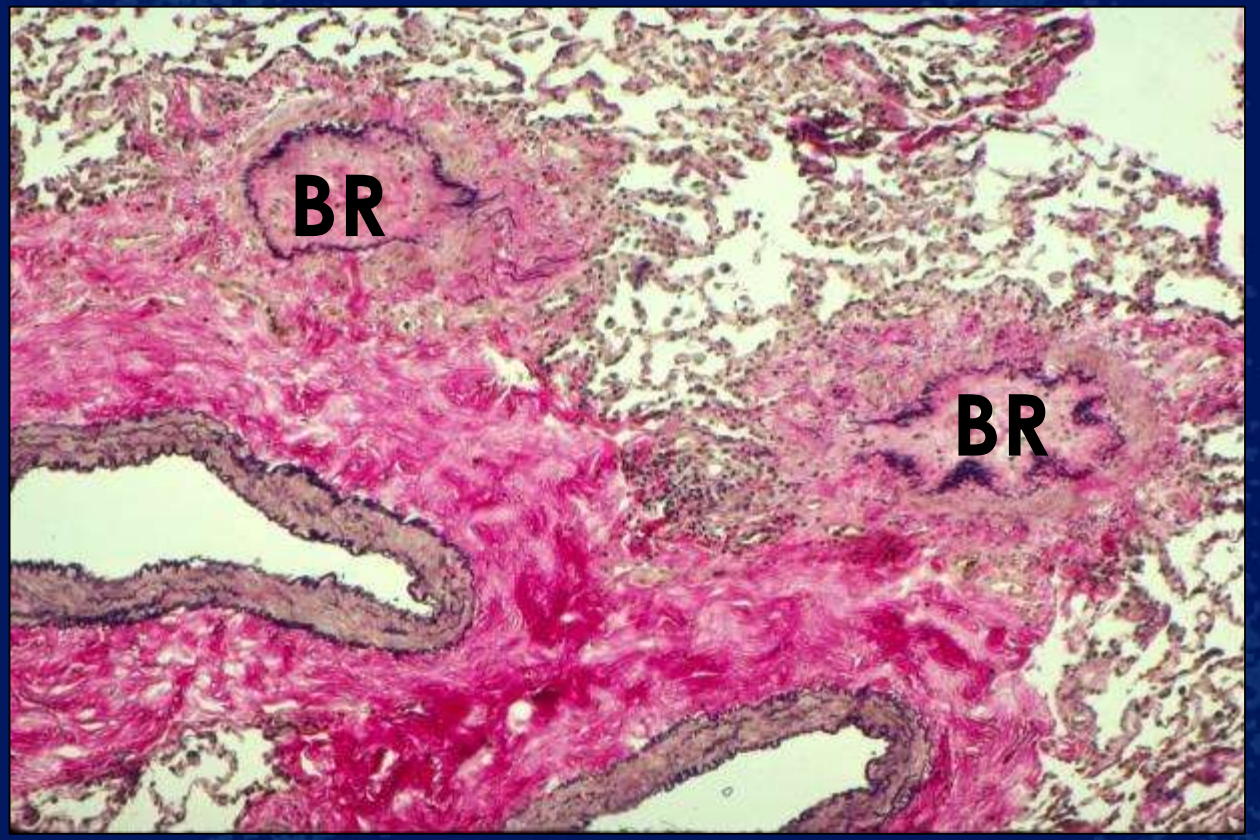
Expiratory HRCT

SEQUELAE OF BRONCHIOLITIS: Depend on the cause

Return to normal vs mild scarring vs severe scarring

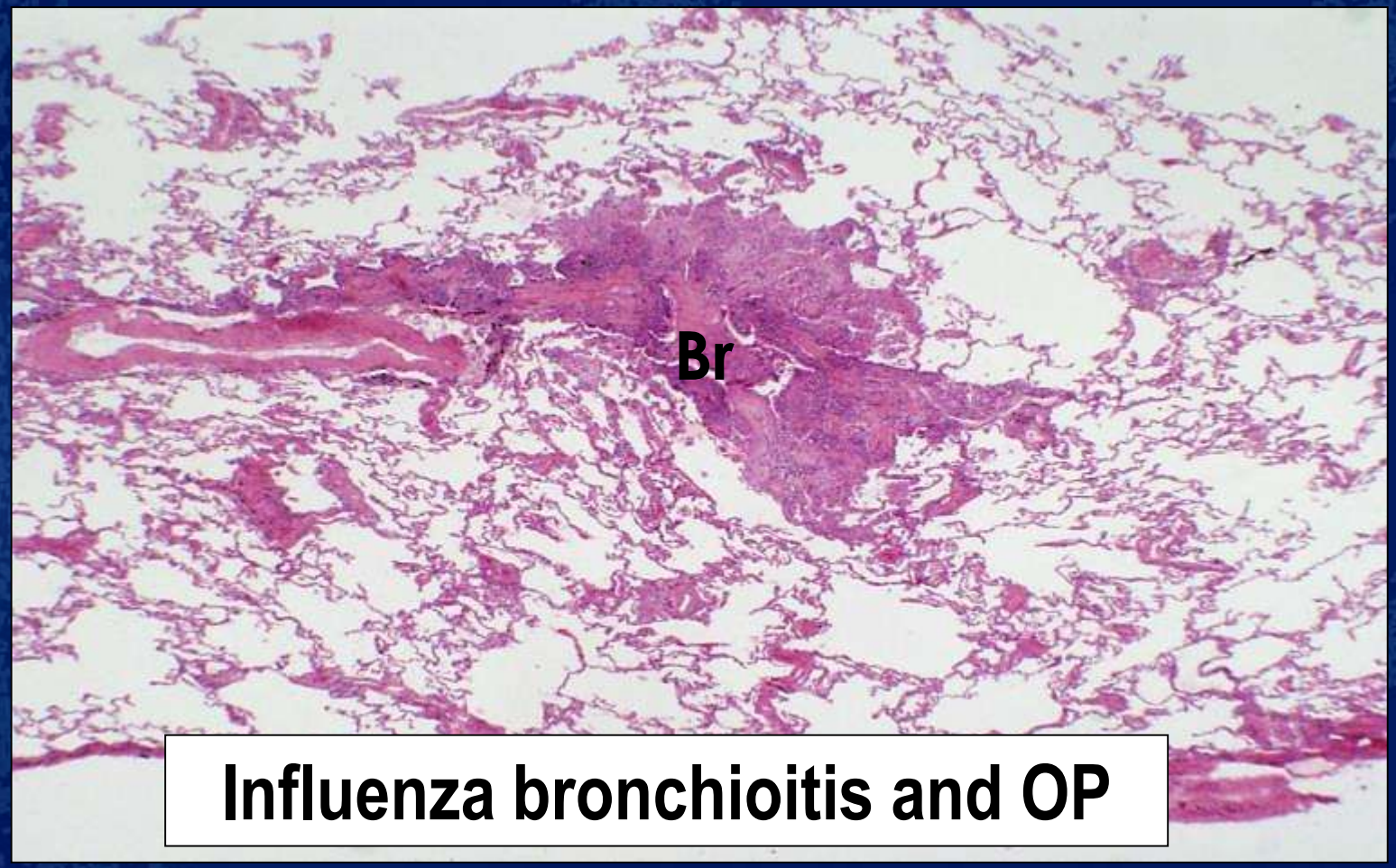


Acute mycoplasma



Post mycoplasma constrictive bronchiolitis

Pathologic Changes in the Bronchioles Produce Clinically Diverse Syndromes and distinction from Interstitial Lung Disease may be difficult and arbitrary



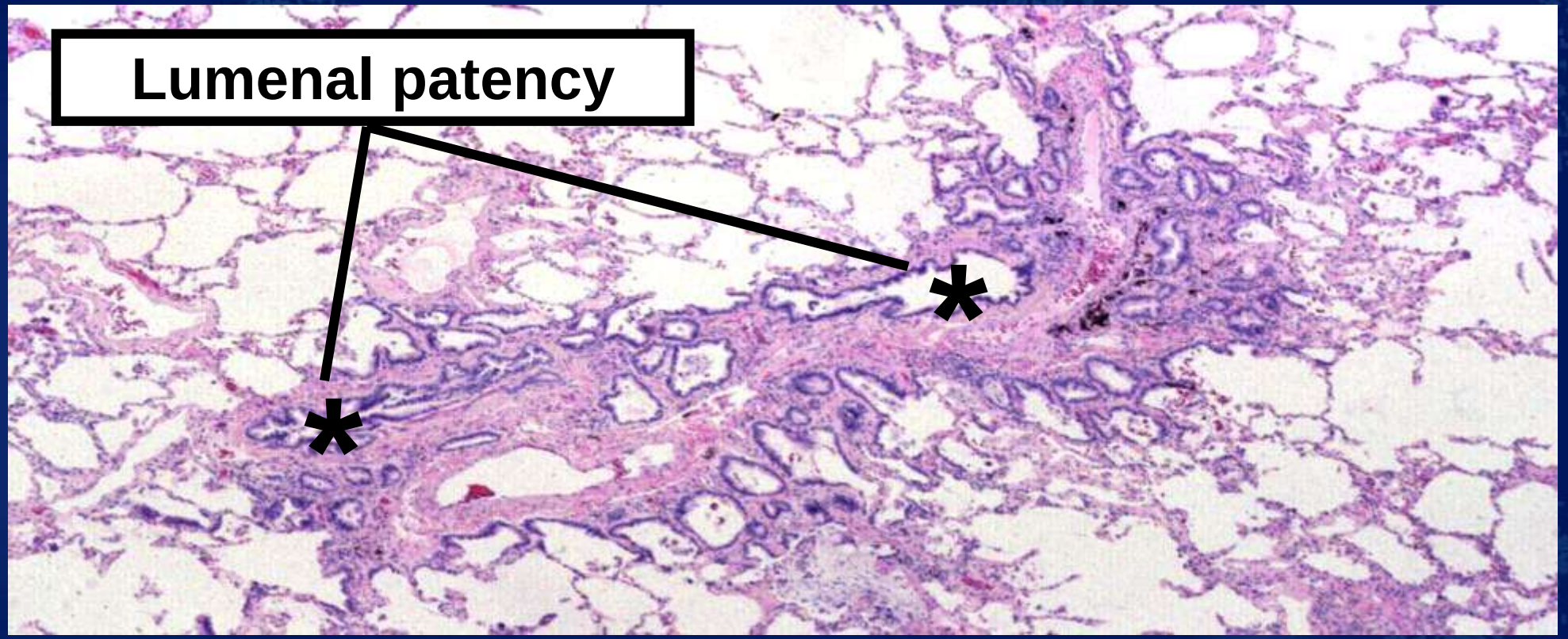
Influenza bronchioitis and OP

Lumenal patency is often maintained in small airway pathology

BRONCHIOLAR PATHOLOGY

Mesenchymal reaction #3 predominates with:

<u>Peribronchiolar scarring with luminal patency</u>
(Peribronchiolar metaplasia/PBM)



PERIBRONCHIOLAR METAPLASIA (PBM)

Causes of PBM

Prior infection

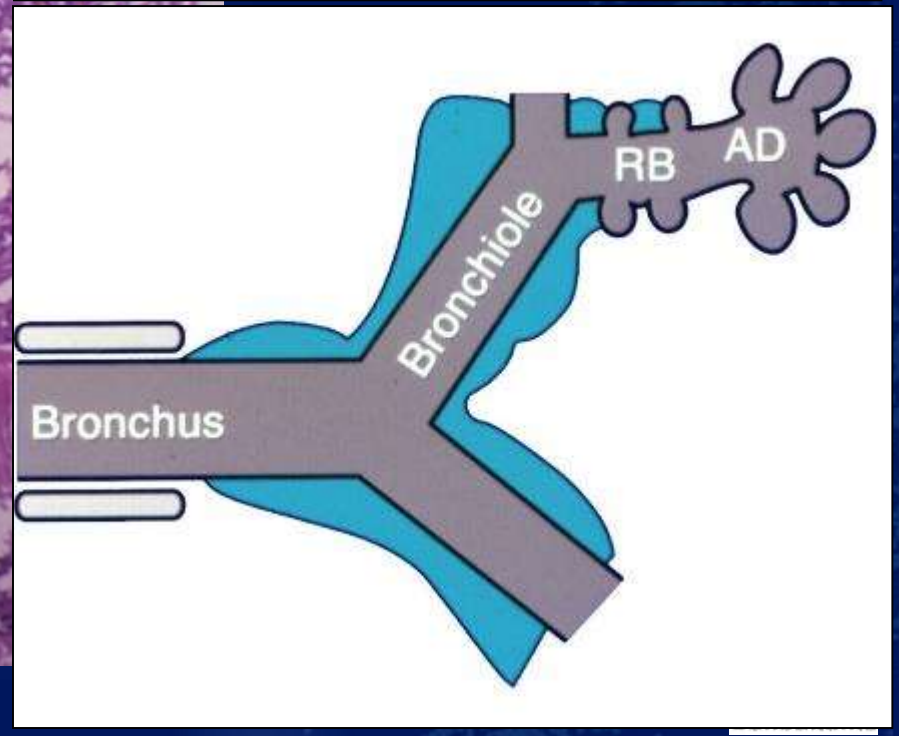
Hypersensitivity pneumonitis

Healed ARDS

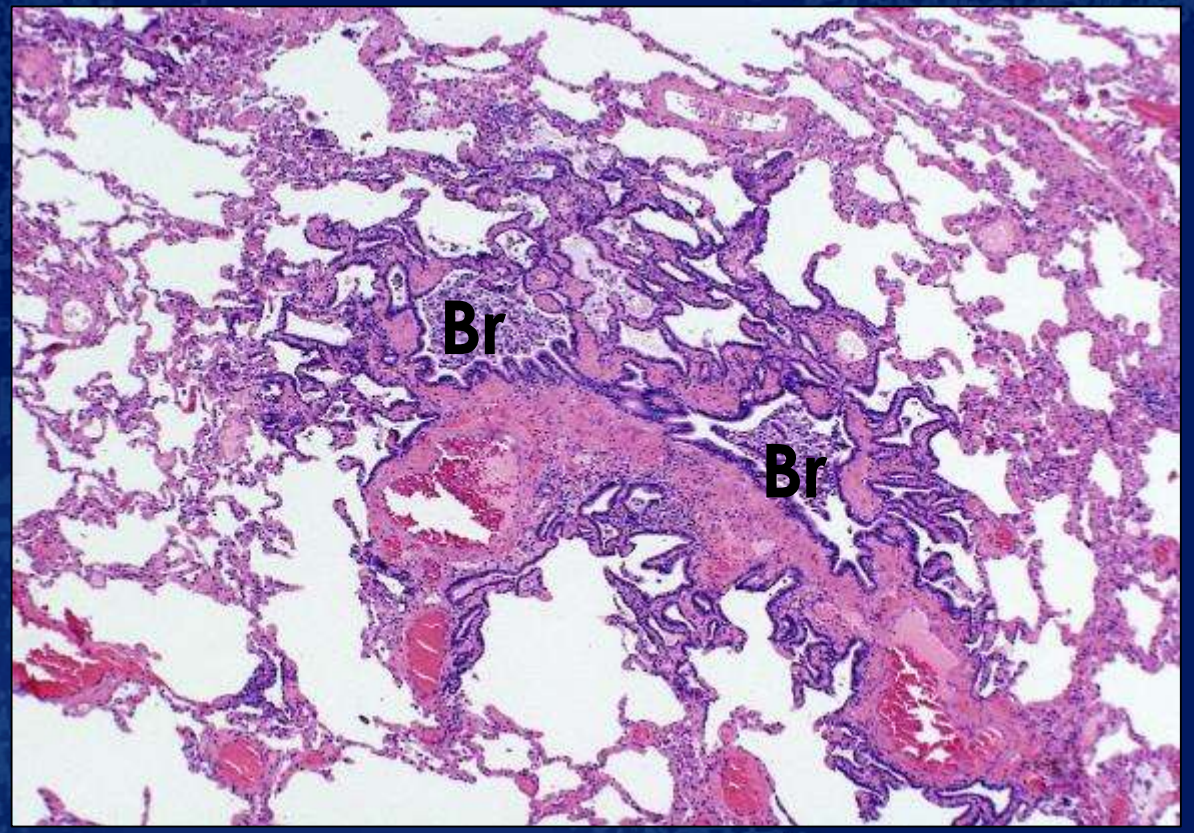
Unknown/incidental finding (the majority of cases)

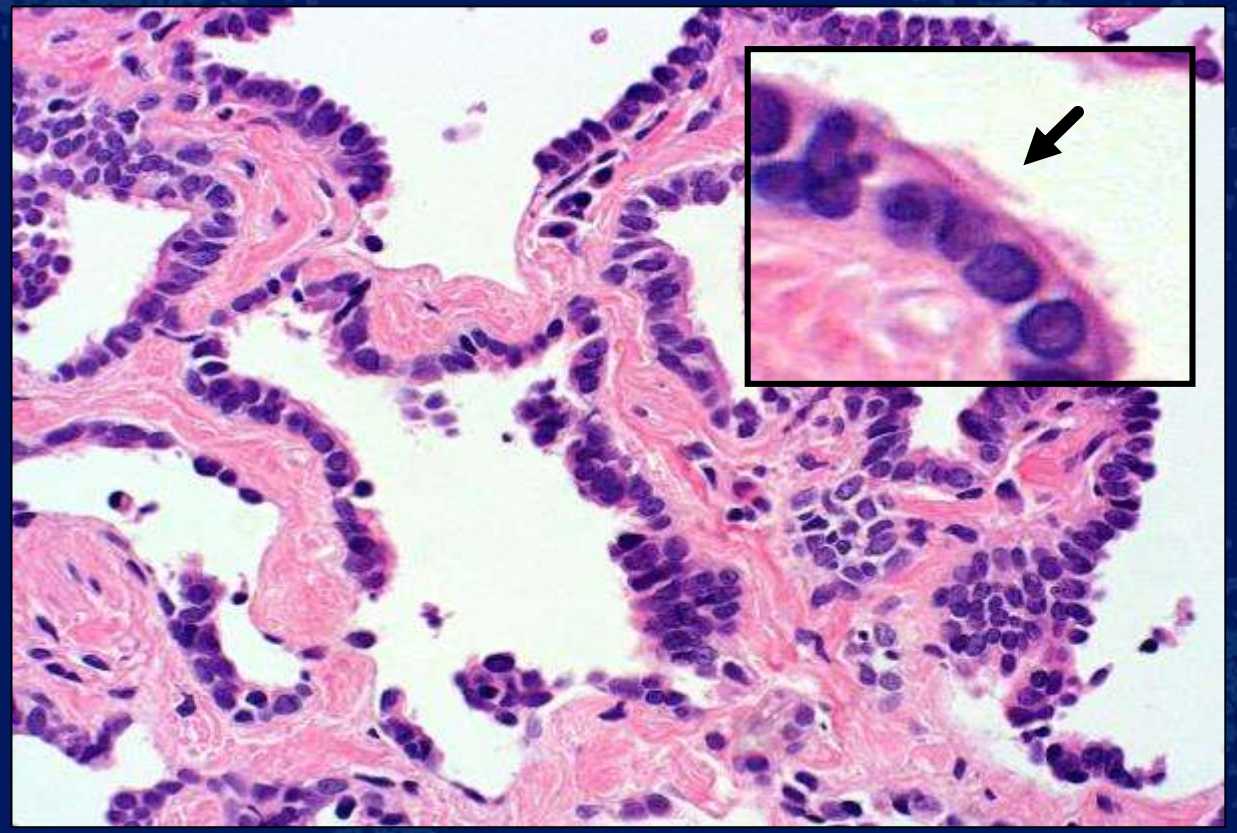
Peribronchiolar fibrosis along the airway

Lumenal patency



Peribronchiolar Metaplasia (PBM)





We consider PBM a residue of small airway injury yet accept it as a common component of interstitial lung disease.

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BRONCHIOLAR PATHOLOGY: SUMMMARY

Cellular/exudative reaction

Mesenchymal reaction

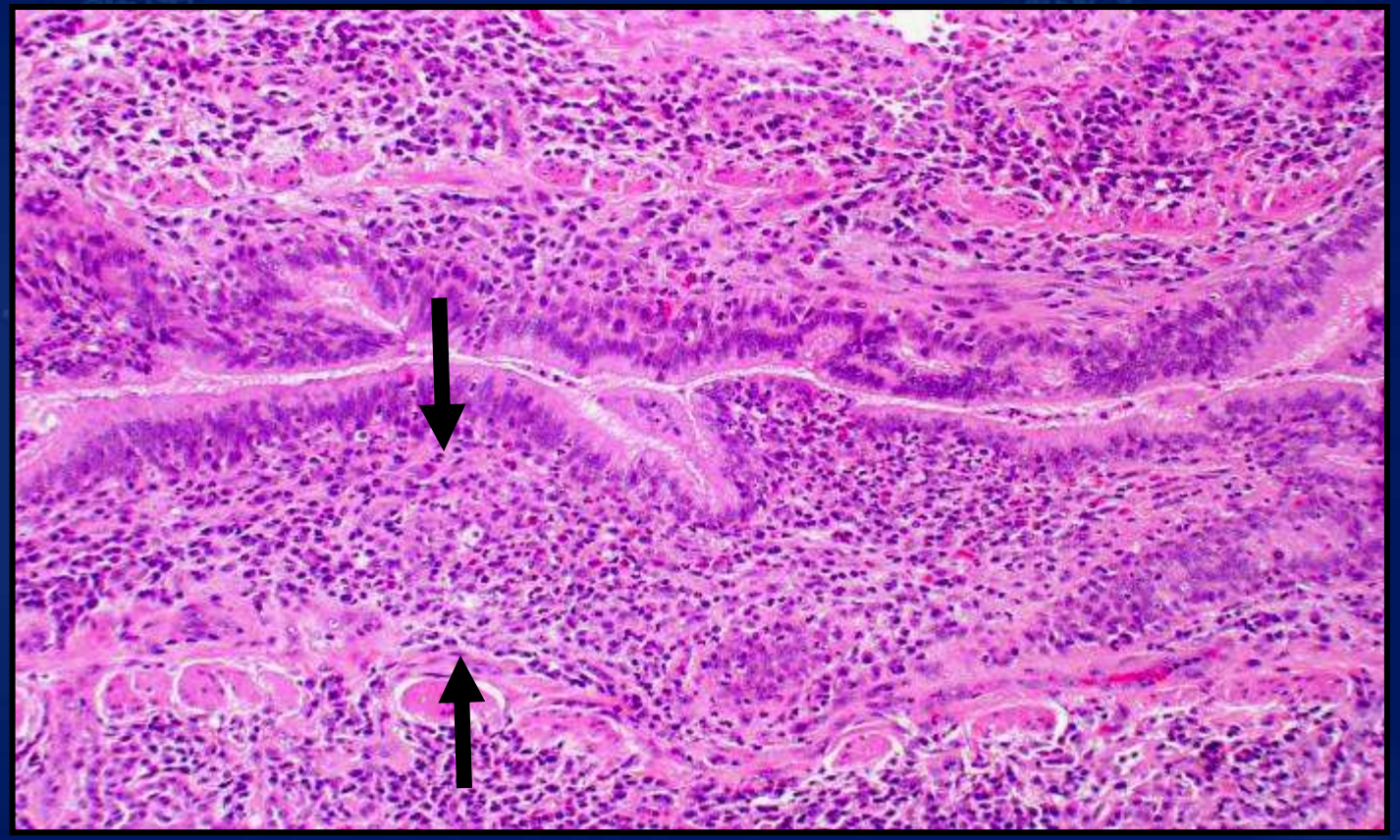
1) Organization with intraluminal polyps
   (part organizing pneumonia)
2) Subepithelial fibrosis/scarring with luminal compromise
   (constrictive bronchiolitis)
3) Peribronchiolar scarring (PBM)

Mixed patterns

CHRONIC BRONCHIOLITIS IN PRACTICE: THE REALITY

Many cases show a spectrum of changes with both cellular and mesenchymal components

Eg.



BRONCHIOLAR PATHOLOGY: Evaluation

Four domains

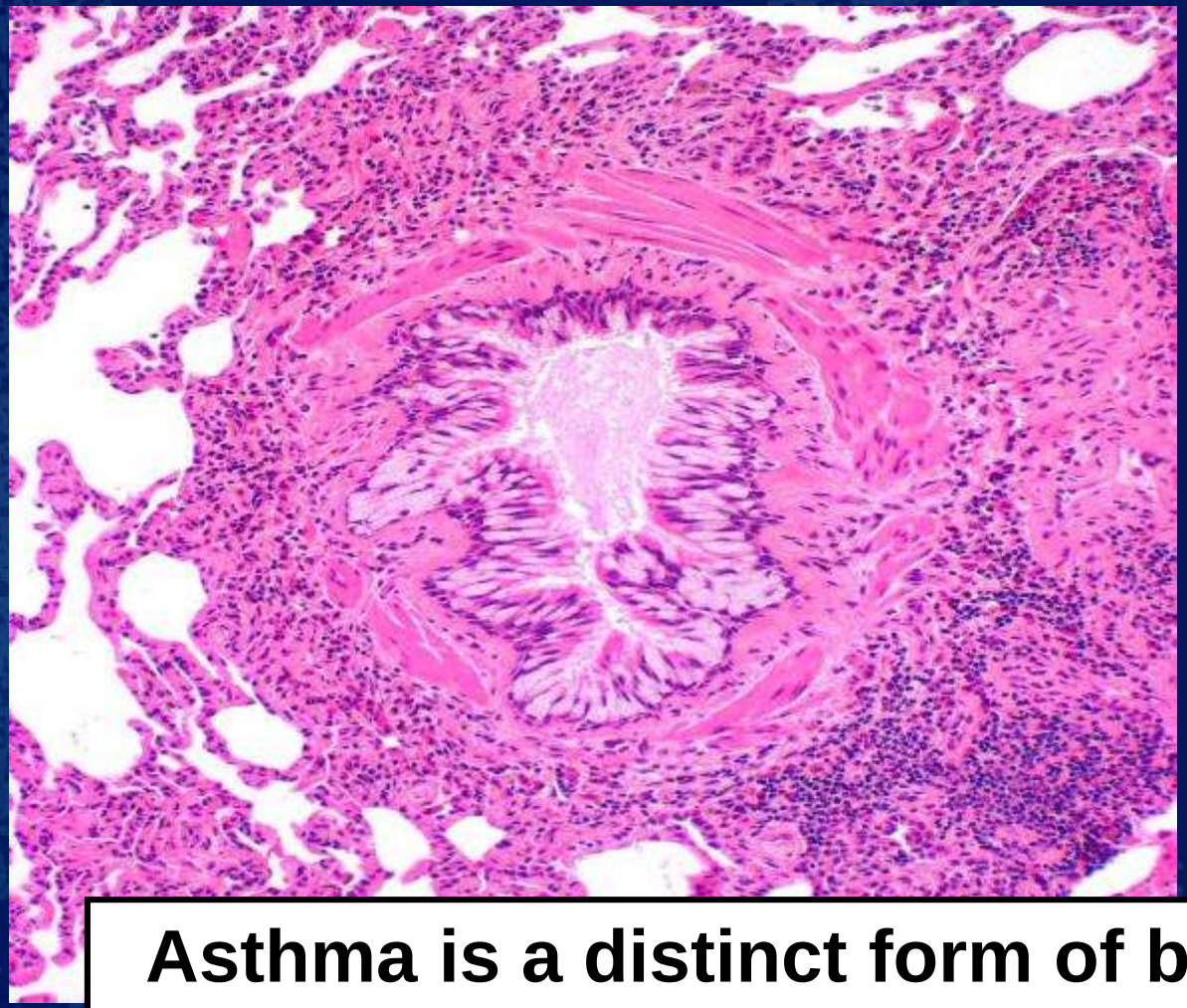
- Clinical/Lab presentation
- Radiologic findings
- Pathologic injury pattern(s)
- Disease entity that fits

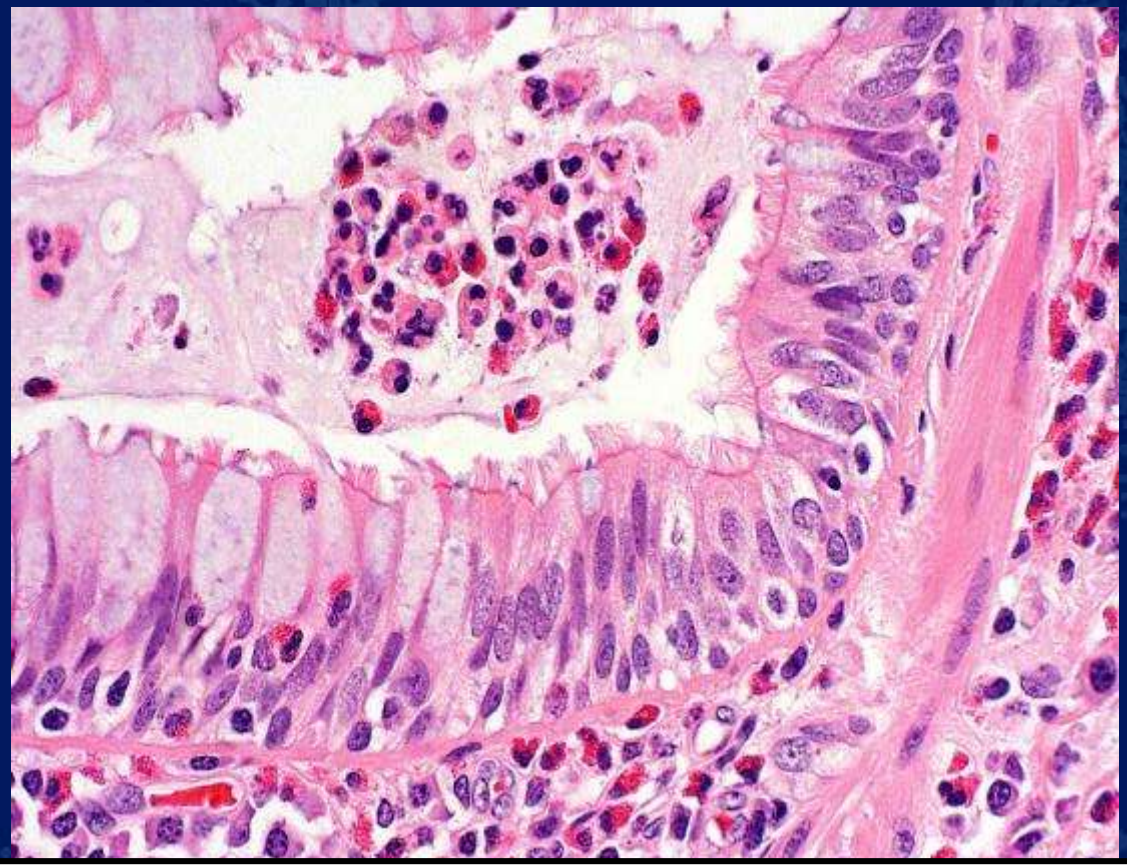
Diverse clinical and radiologic findings may suggest airway disease (ie. obstruction) or ILD

Spectrum of cellular and mesenchymal changes +/- lumenal compromise…

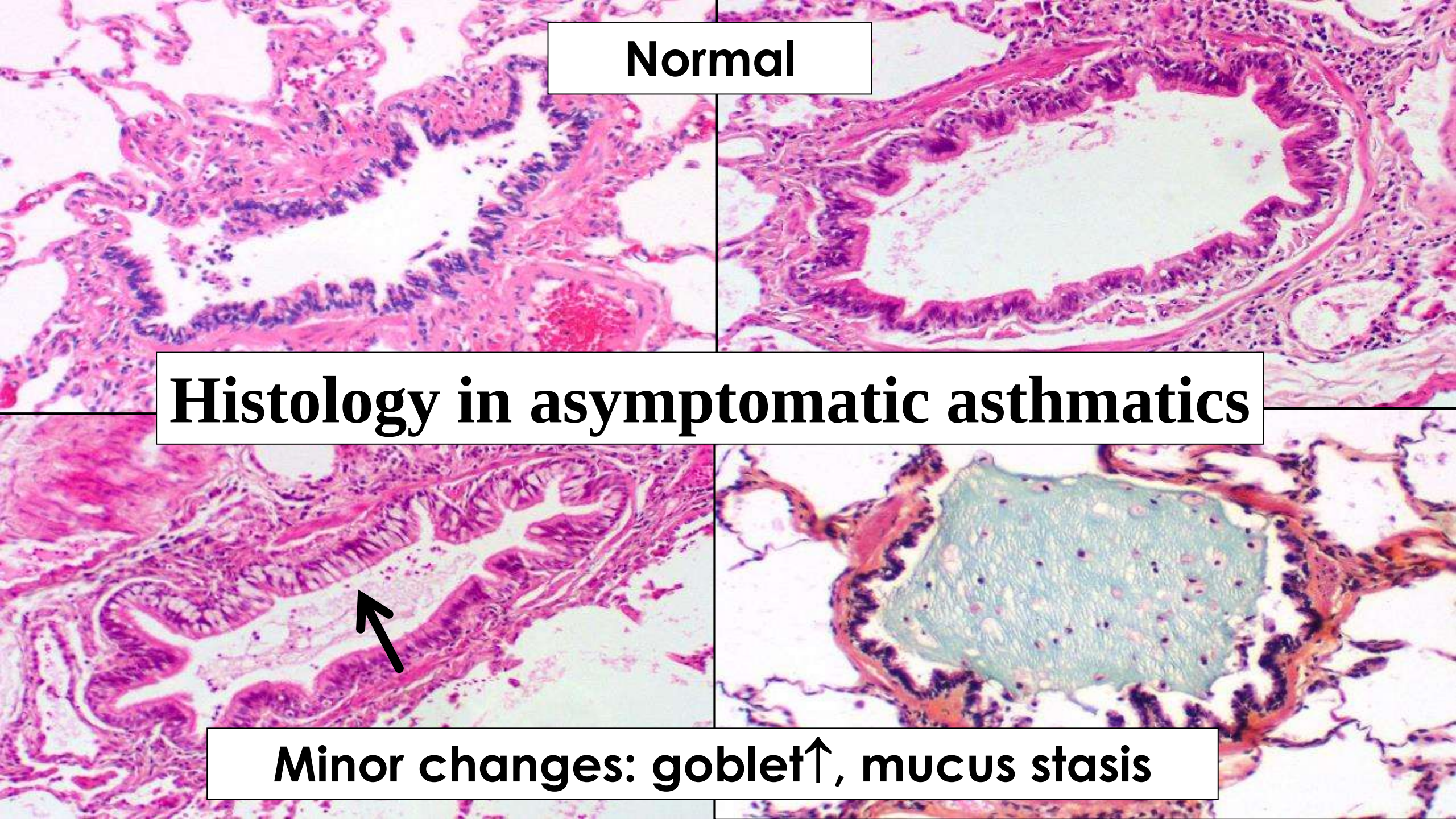
….and hence ascribing a clinical diagnosis is of necessity multi-disciplinary

CLINICOPATHOLOGIC ENTITIES
with small airway pathology





Asthma is a distinct form of bronchiolitis (and bronchitis) with:
Eosinophils, goblet cell metaplasia, smooth muscle↑ and BM ↑


Normal
Histology in asymptomatic asthmatics
Minor changes: goblet↑, mucus stasis

Thank you for your attention!

COMMENTARY…..

?QUESTIONS