

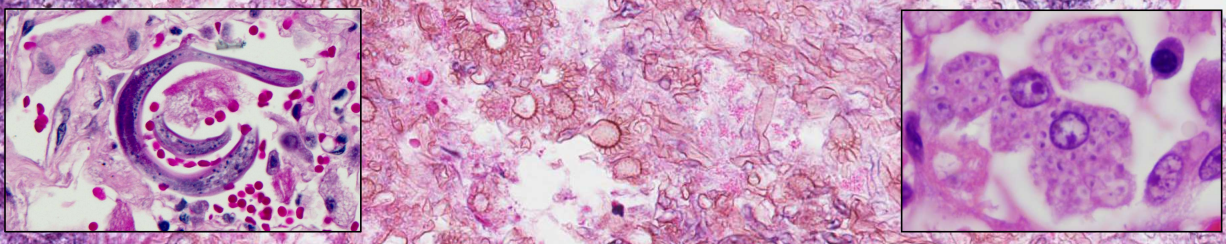
1

Objectives

- Describe histologic features that allow a specific diagnosis in non-neoplastic lung pathology.
- Assess when expert opinion or send out may be necessary for diagnosis.

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2



NON-NEOPLASTIC LUNG PATHOLOGY

DO YOU HAVE TO SEND EVERYTHING OUT TO AN EXPERT?

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SANJAY MUKHOPADHYAY, MD
STAFF PATHOLOGIST
CLEVELAND CLINIC
CLEVELAND, OHIO, USA
[@smlungpathguy](#)

3

You can handle most bugs

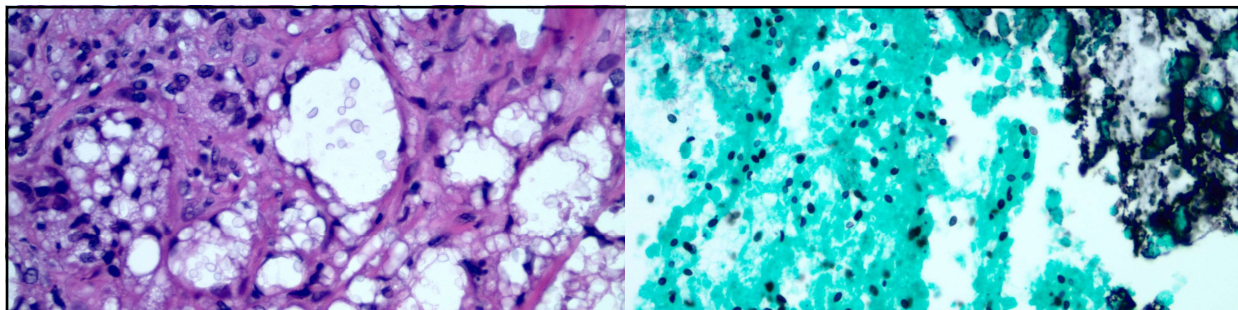
- Mycobacteria (necrotizing and non-necrotizing granulomas)
- Fungi (granulomas)
 - Histoplasma (necrotizing)*
 - Cryptococcus (necrotizing, non-necrotizing)
 - Coccidioides (necrotizing)
 - Blastomyces (necrotizing - suppurative)
- Bugs that are seen mostly in immunosuppressed patients
 - Pneumocystis*
 - CMV
 - Nocardia
- Aspergillus* (wide variety of tissue reactions)

*Common

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Mukhopadhyay S, Gal AA. Arch Pathol Lab Med 2010;134:667-90

4



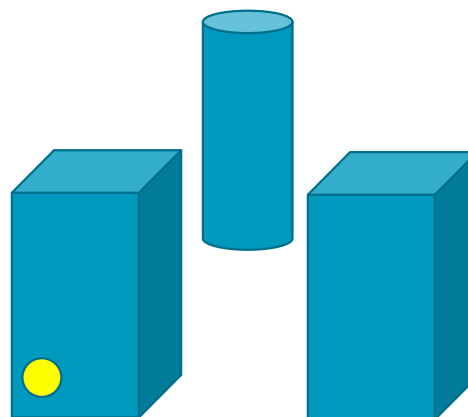
FUNGAL YEASTS

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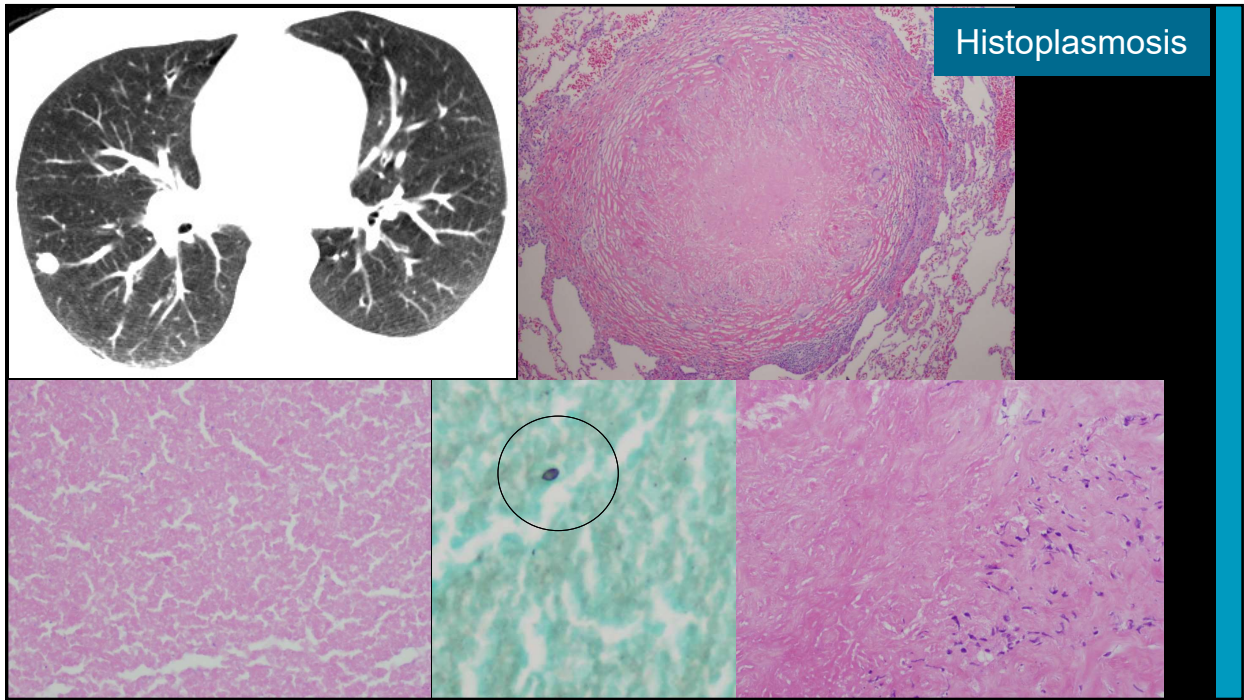
Pulmonary histoplasmosis (healed)

- Residuum of healed acute histoplasmosis: necrotizing granuloma identical to TB
- Incidental finding of lung nodule
- Cultures always negative because organisms are dead
- No treatment required



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Core needle biopsy in benign lung lesions: pathologic findings in 159 cases

Erika E. Duxtader MD*, Sanjay Mukhopadhyay MD, Anna-Luise A. Katzenstein MD

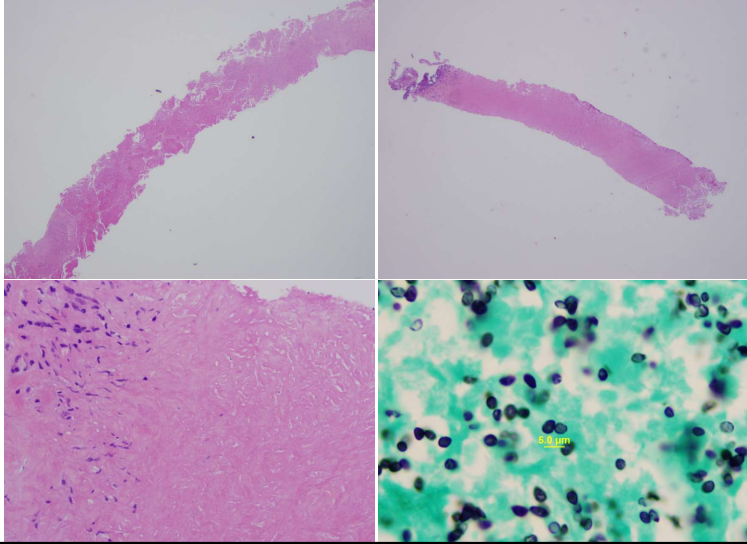


Table 3 Benign diagnoses on core needle biopsies of lung

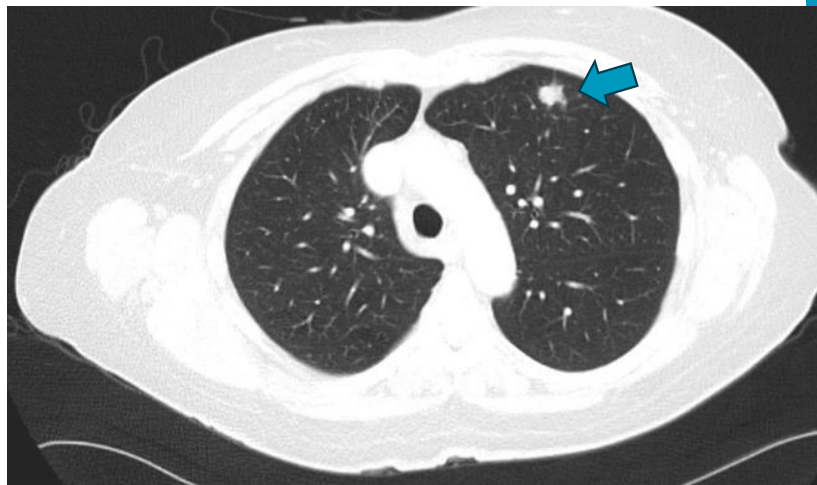
	No. of cases (total = 159)
Specific diagnoses	122 (77%)
Necrotizing granulomatous inflammation	45
No organism identified	30
Organism identified	15
<u>Histoplasma (10)</u>	
Coccidioides (2)	
Mycobacteria (2)	
Cryptococcus (2)	
Scar	28
Organizing pneumonia	13
Benign neoplasm	11
Hamartoma	8
Solitary fibrous tumor	2
Schwannoma	1
Non-necrotizing granulomatous inflammation	8
No organism identified	5
Organism identified	3
Cryptococcus (2)	
Fungal hyphae (1)	
Other specific diagnoses	17
Abscess	5
Nodular amyloidosis	3
Intranuclear lymph node	3

Duxtader EE, et al. *Hum Pathol* 2010;41(11):1530-5

8

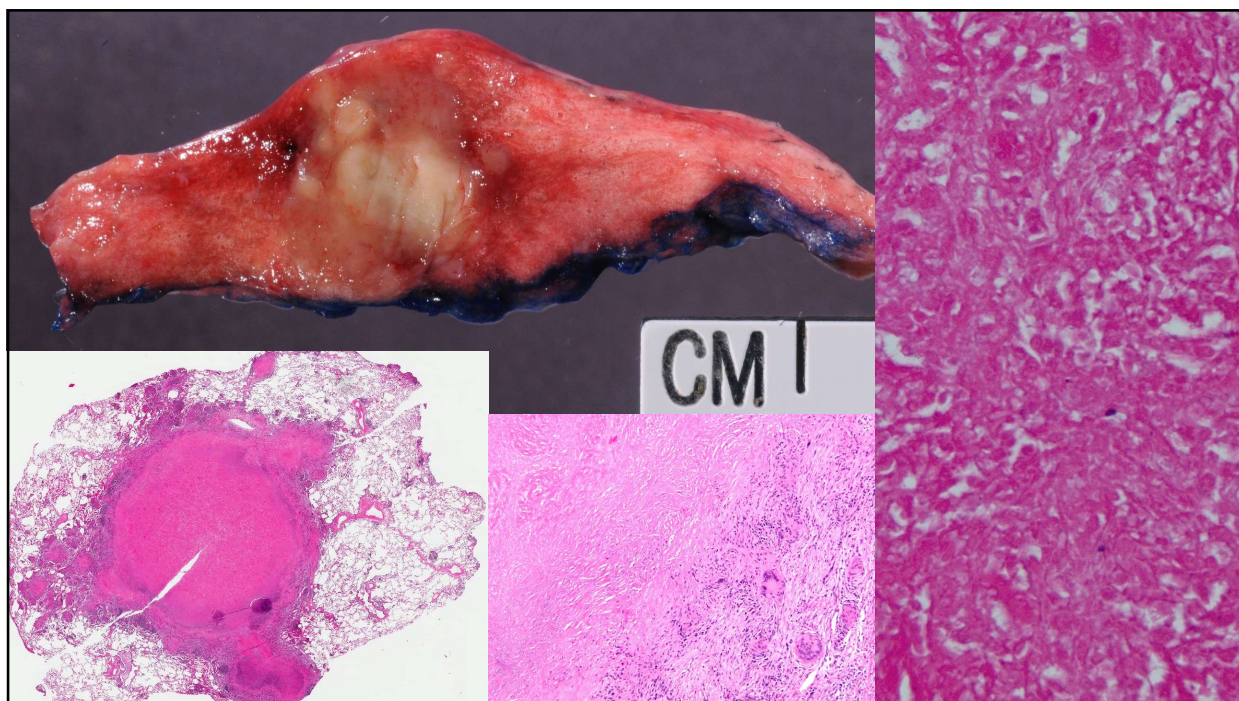
Fungal yeasts - how far can we go with histology alone?

- 64/F
- Breast cancer, new lung nodule

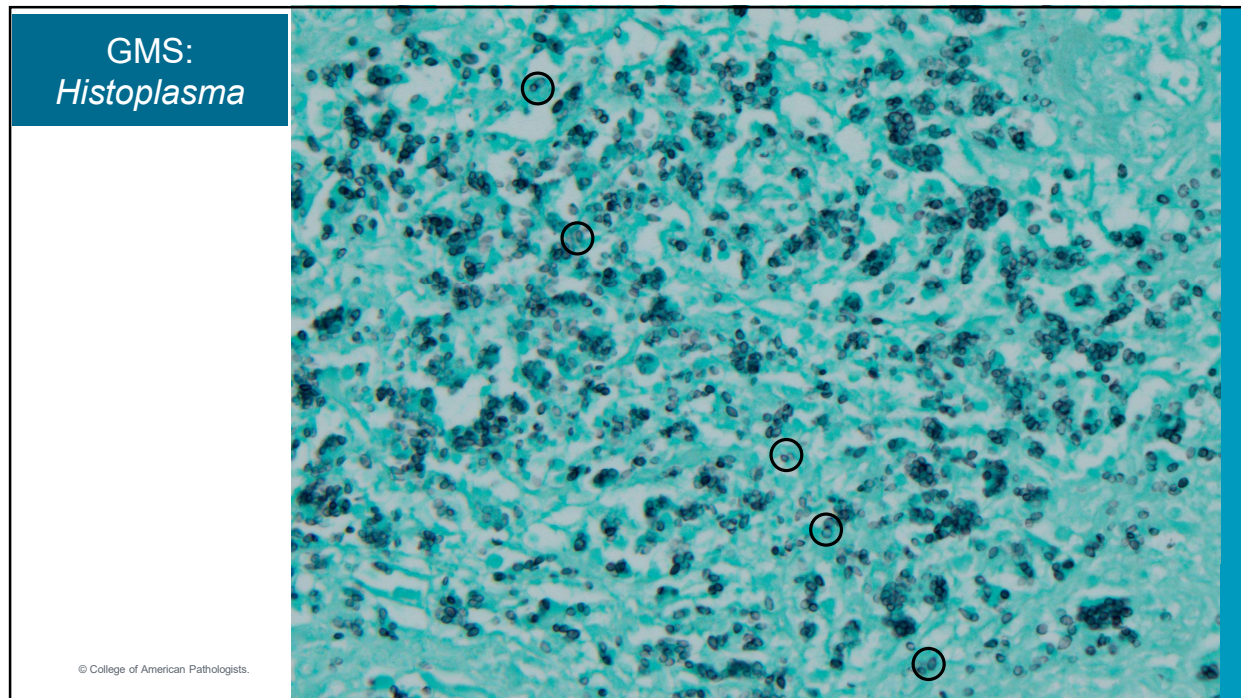


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Fungal yeasts - how far can we go with histology alone?

Converted Final Diagnosis [3]

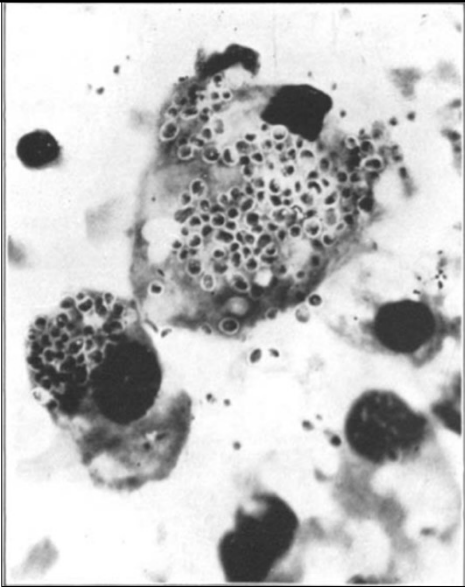
Lung, left upper lobe, wedge resection - Necrotizing granulomatous inflammation (numerous *Histoplasma* yeasts present) (See comment).

Converted Diagnosis Comment

Sections show a well-formed necrotizing granuloma consisting of a large necrotic center surrounded by a fairly robust palisade of epithelioid histiocytes and a few multinucleated giant cells. Smaller satellite necrotizing granulomas and tiny non-necrotizing granulomas are present around the main nodule. Special stains for microorganisms (AFB/Ziehl-Neelsen, AFB/Fite and GMS) were performed on 2 blocks. GMS stains on both blocks show numerous oval-to-tapered *Histoplasma* yeasts with occasional narrow-based budding within the necrotic center of the main granuloma. Ziehl-Neelsen and Fite stains on both blocks are negative. The findings fit with a histoplasmosis. Please also see results of cultures; tissue was submitted for cultures directly from the center of the necrotizing granuloma at the time of frozen section.

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12



cases of disseminated histoplasmosis susceptible macrophages provide an environment favoring persistence of the organism and in more severe cases macrophages actually support and promote intracellular growth.

There are few exceptions to the monotonously consistent finding of organisms demonstrable only within the cytoplasm of macrophages. In heavy infection a few single yeast forms may occasionally be seen free within tissue spaces. We believe that these have probably been released from disintegrated macrophages. In frankly necrotic tissue clumps of extracellular organisms appear to represent the same phenomenon of survival of the parasite past the death of the phagocyte. Histoplasmosis endocarditis is the one clear exception. In this condition extracellular fungal proliferation is observed

Darling S. *J Exp Med* 1905;344:665-71.

Goodwin RA. *Medicine (Baltimore)* 1980;59(1):1-33.

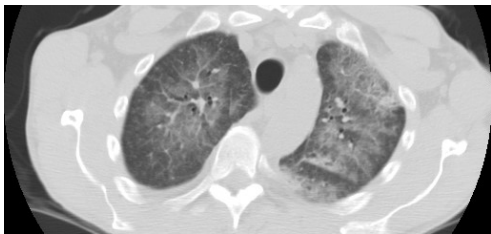
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13

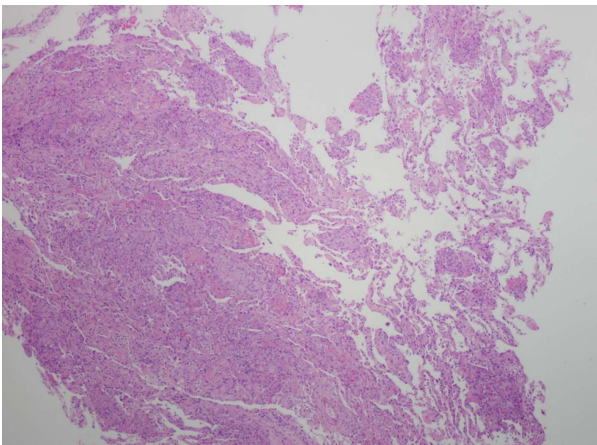
Visibility of *Histoplasma* within histiocytes on hematoxylin and eosin distinguishes disseminated histoplasmosis from other forms of pulmonary histoplasmosis ☆

Sanjay Mukhopadhyay MD^{a,b,*}, Erika E. Doxtader MD^b

^aDepartment of Anatomic Pathology, Cleveland Clinic, Cleveland, OH, USA
^bDepartment of Pathology, State University of New York Upstate Medical University, Syracuse, NY 13210



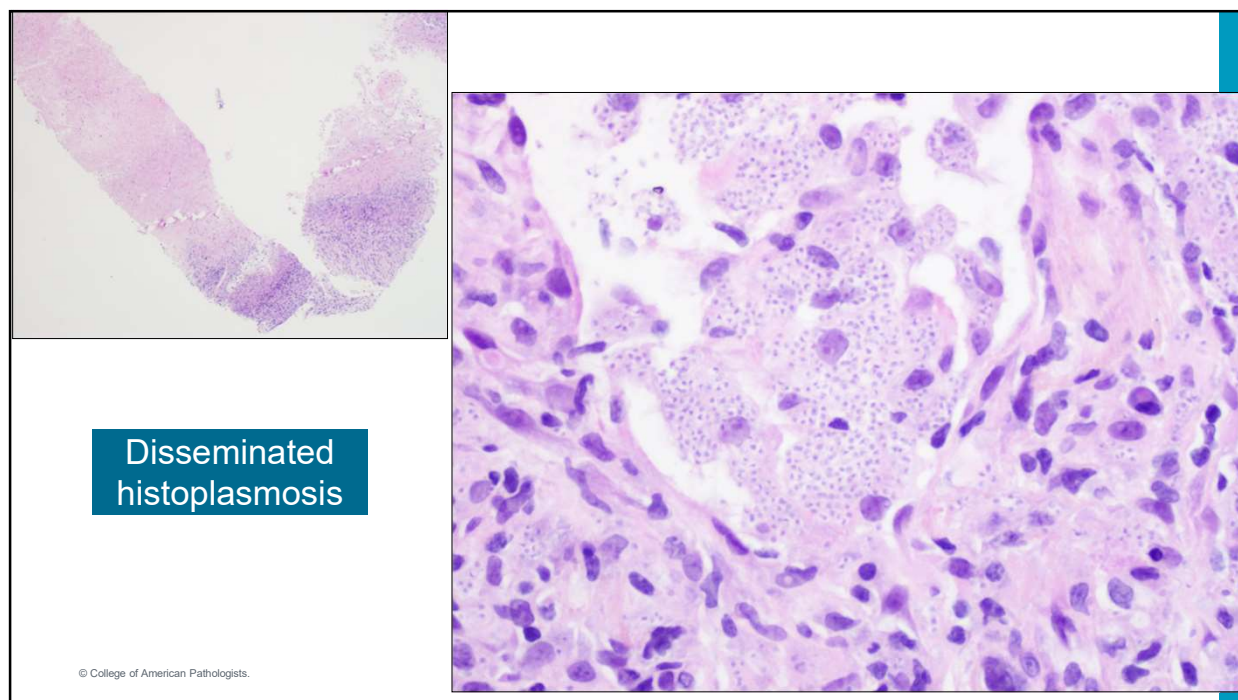
53/M, renal transplant, CMV-pos donor, pred/mycophen
Fever, dyspnea, LUL infiltrate - later bilateral opacities
Clinical: CMV pneumonia vs. lymphoma



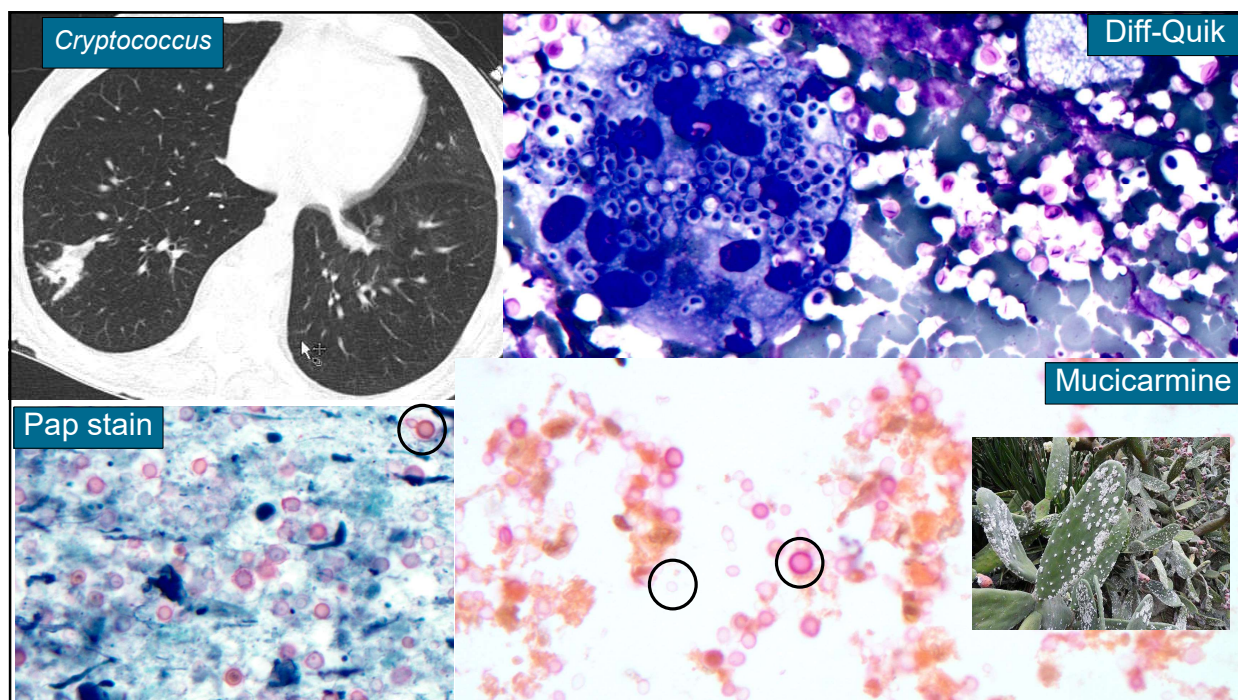
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14

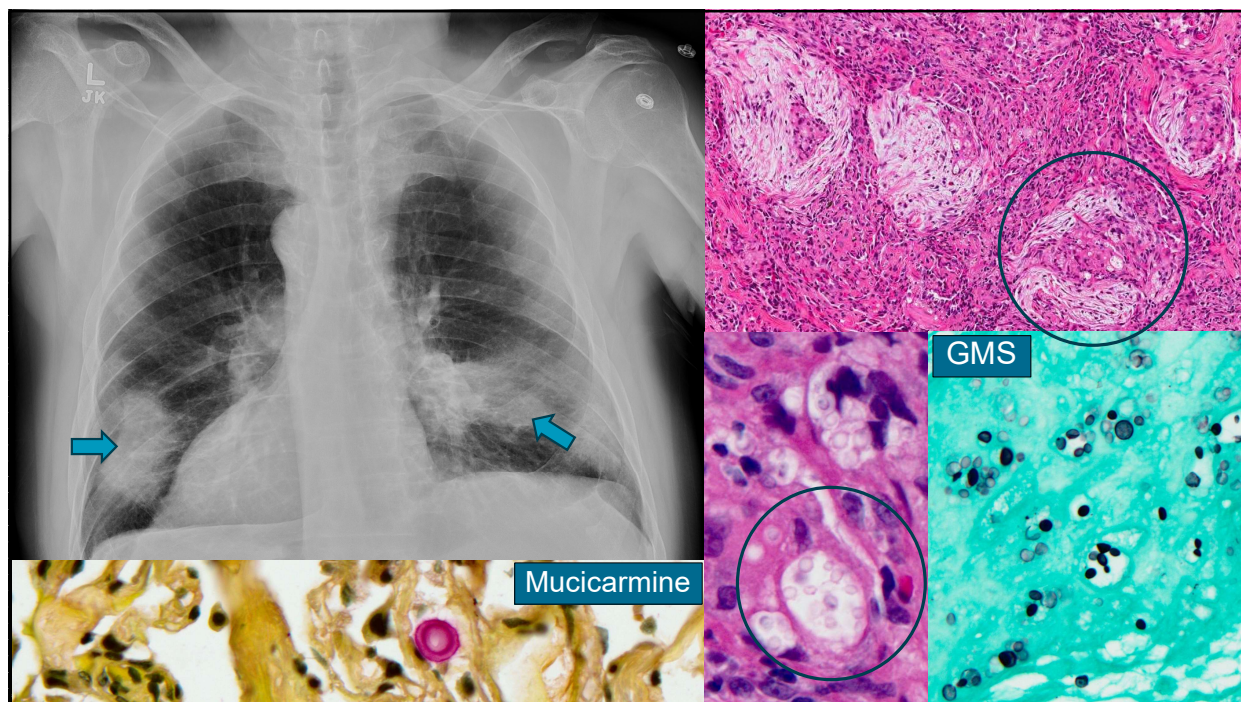
Non-neoplastic Lung Pathology: Do You Have to Send Everything Out to an Expert?,
Dr. Sanjay Mukhopadhyay, June 12, 2025



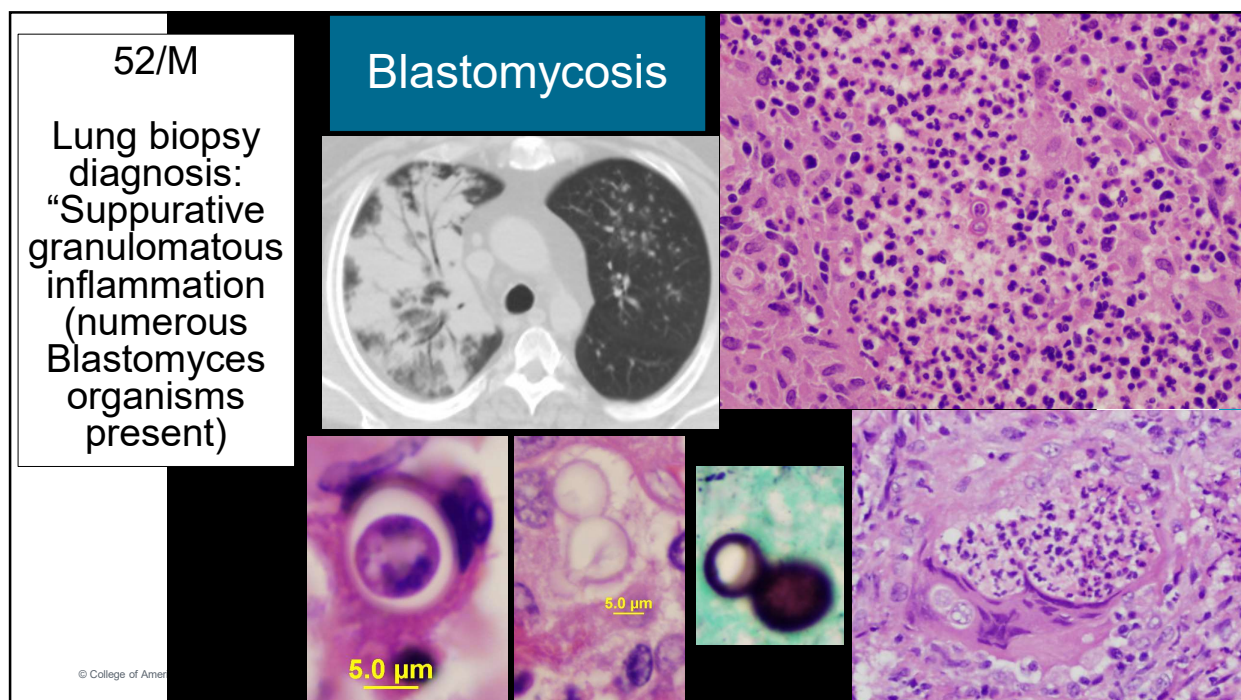
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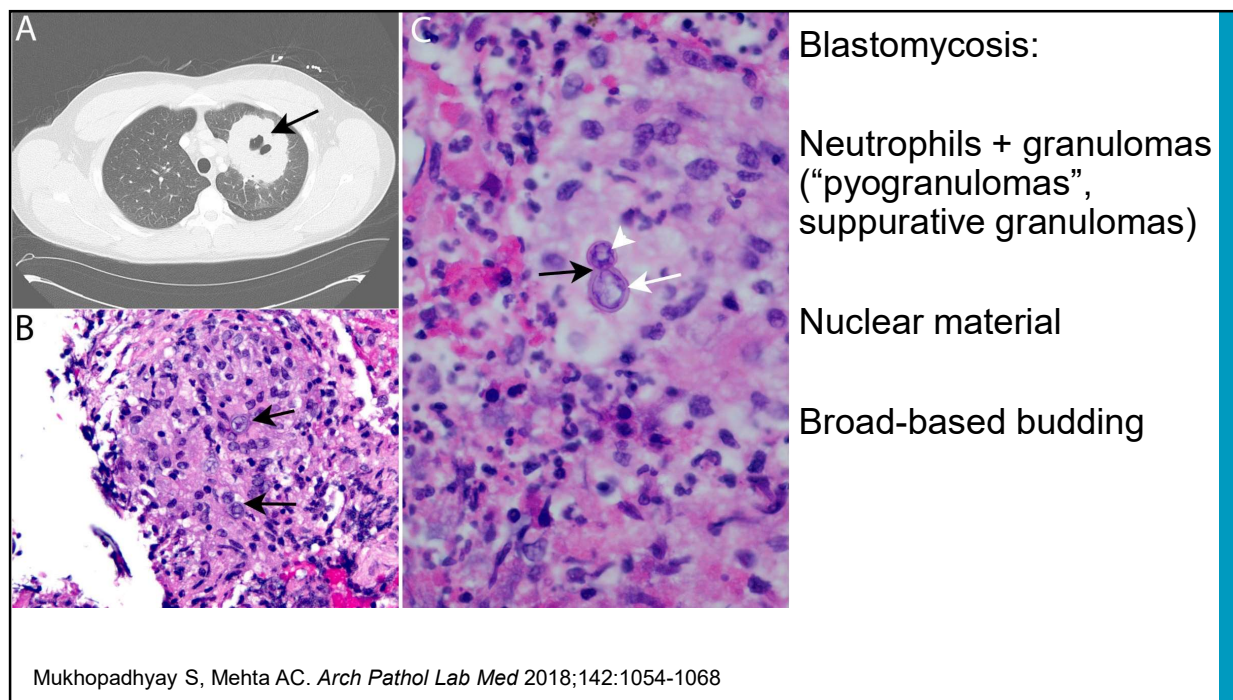
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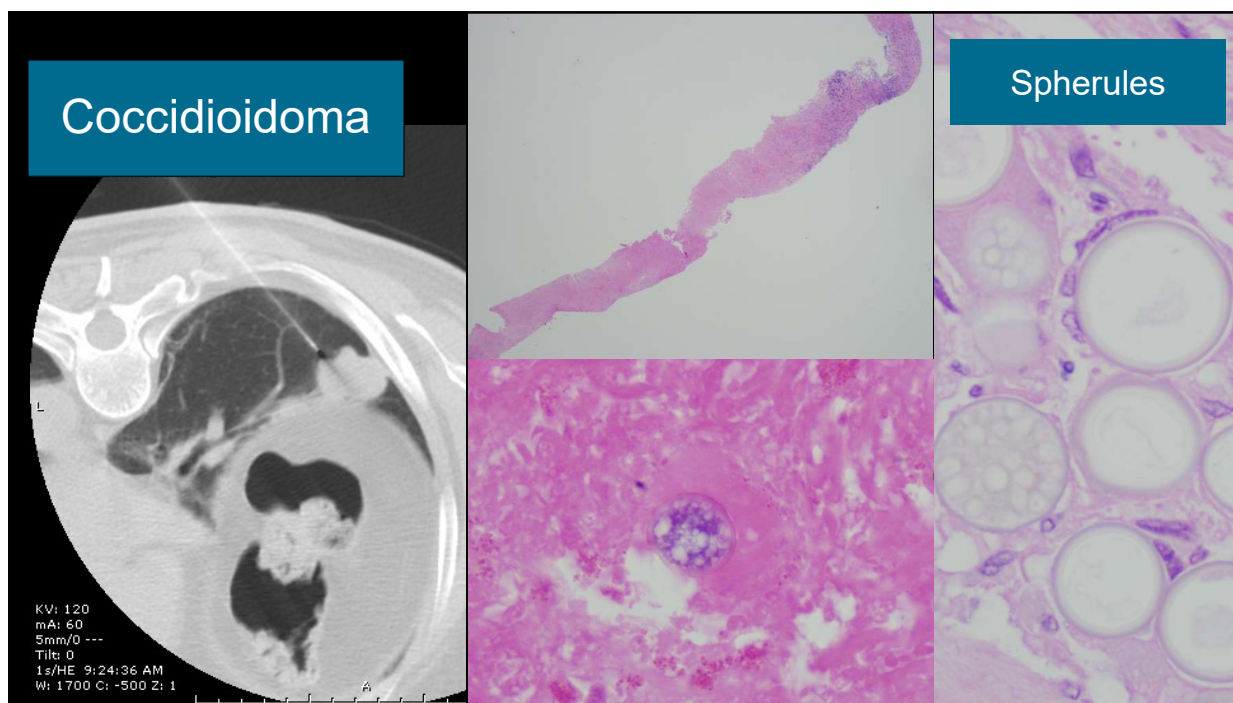
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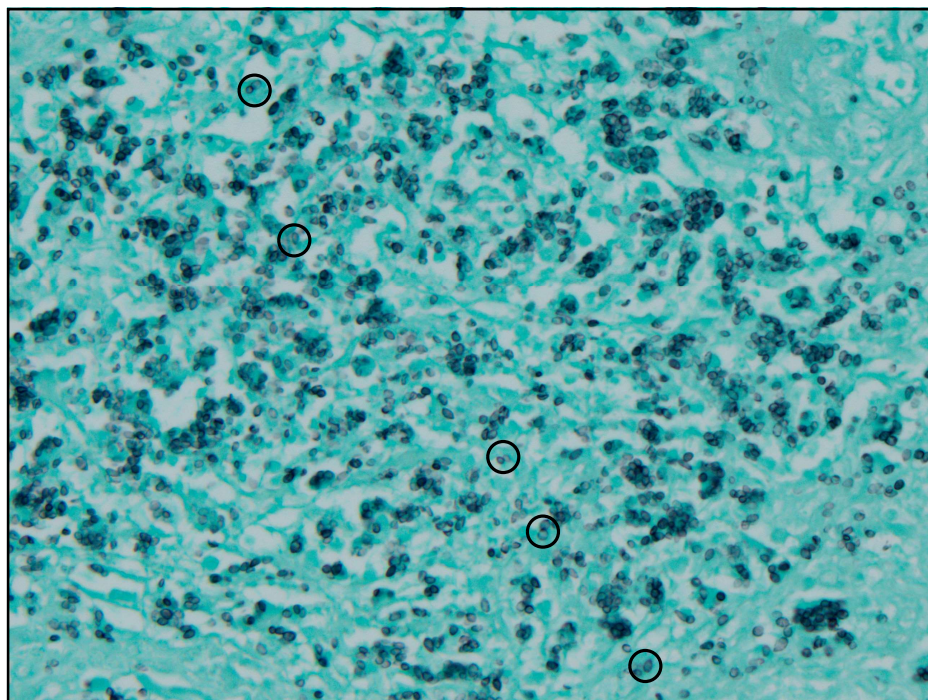
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20



Histoplasma
yeasts

Small, uniform

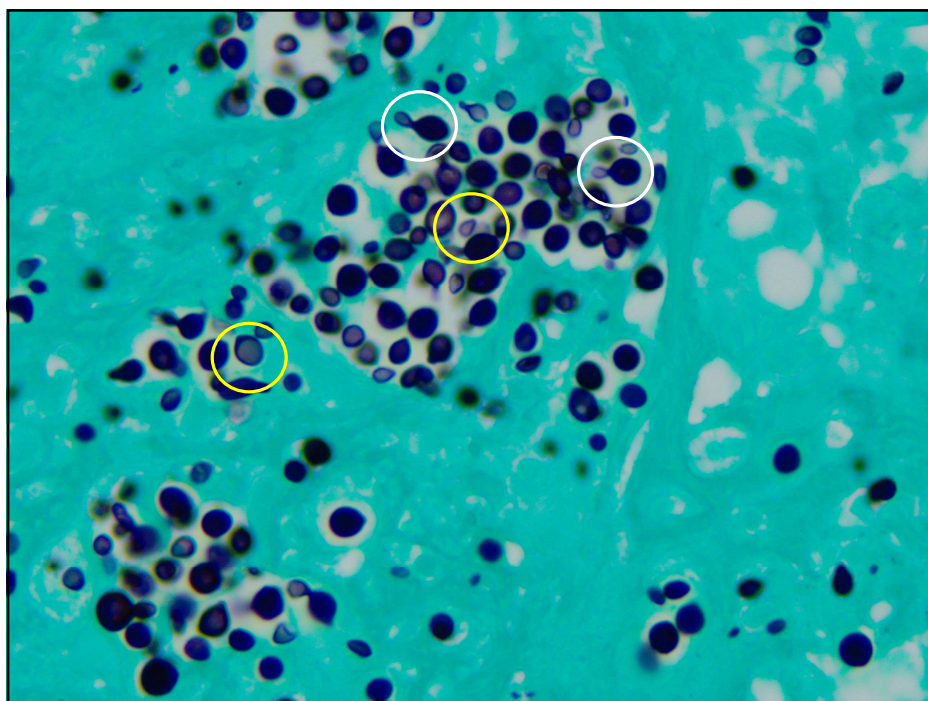
Oval or tapered

Narrow-based
budding

GMS is best
stain

Negative for
mucicarmin

21



Cryptococcus
yeasts

Small, lots of
size variation

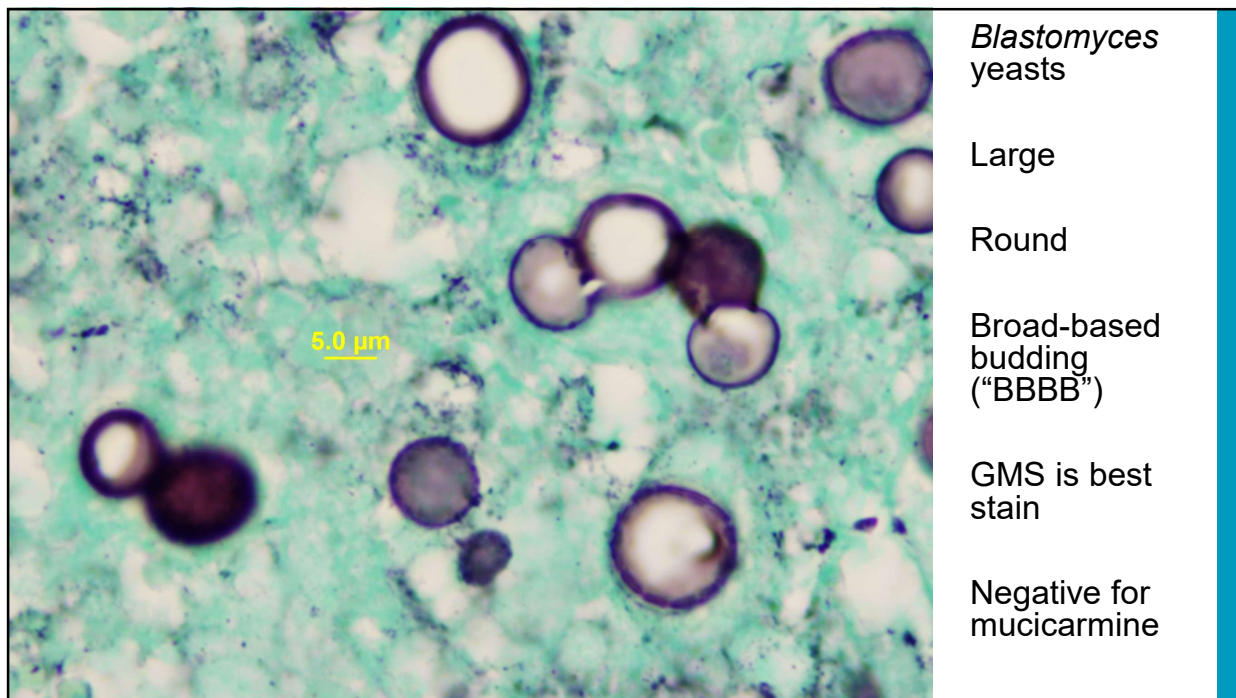
Round

Narrow-based
budding

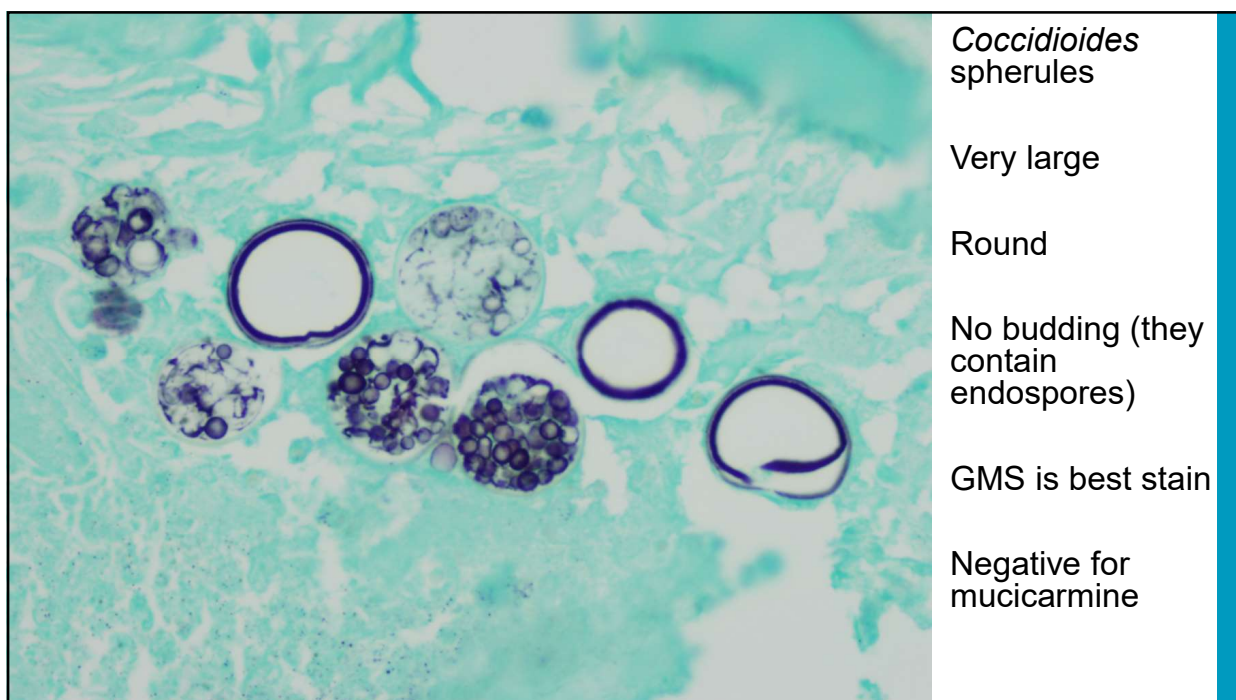
GMS is best
stain

Positive for
mucicarmin

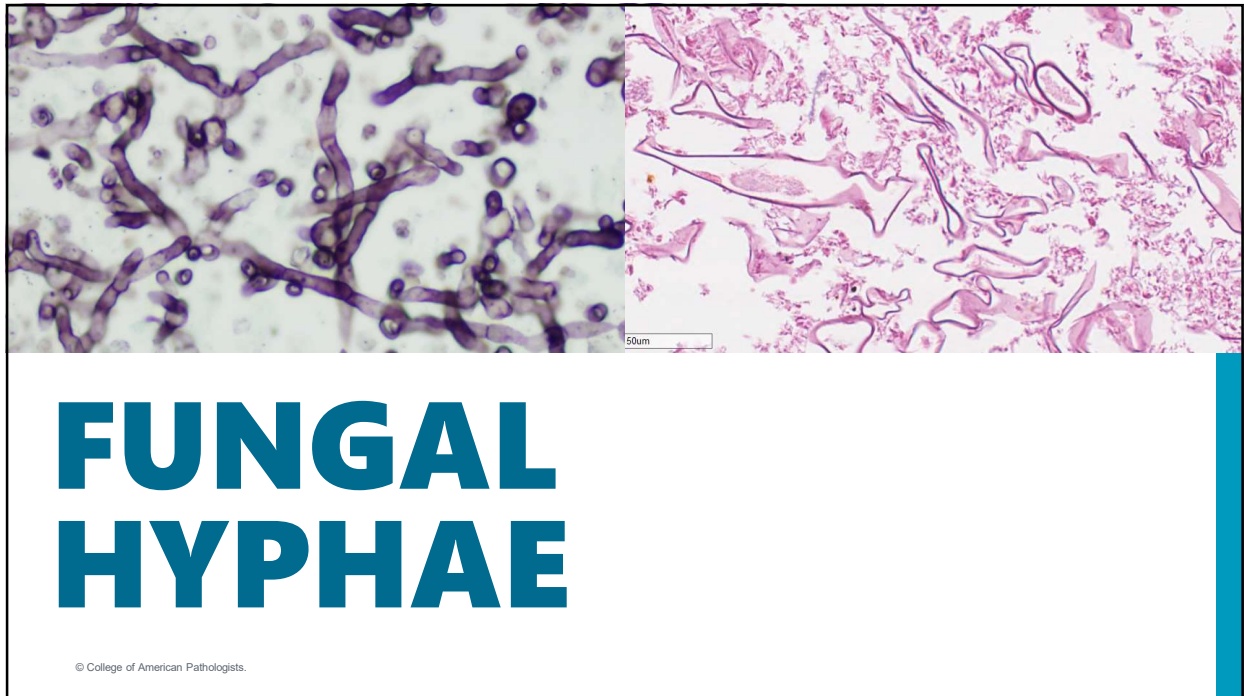
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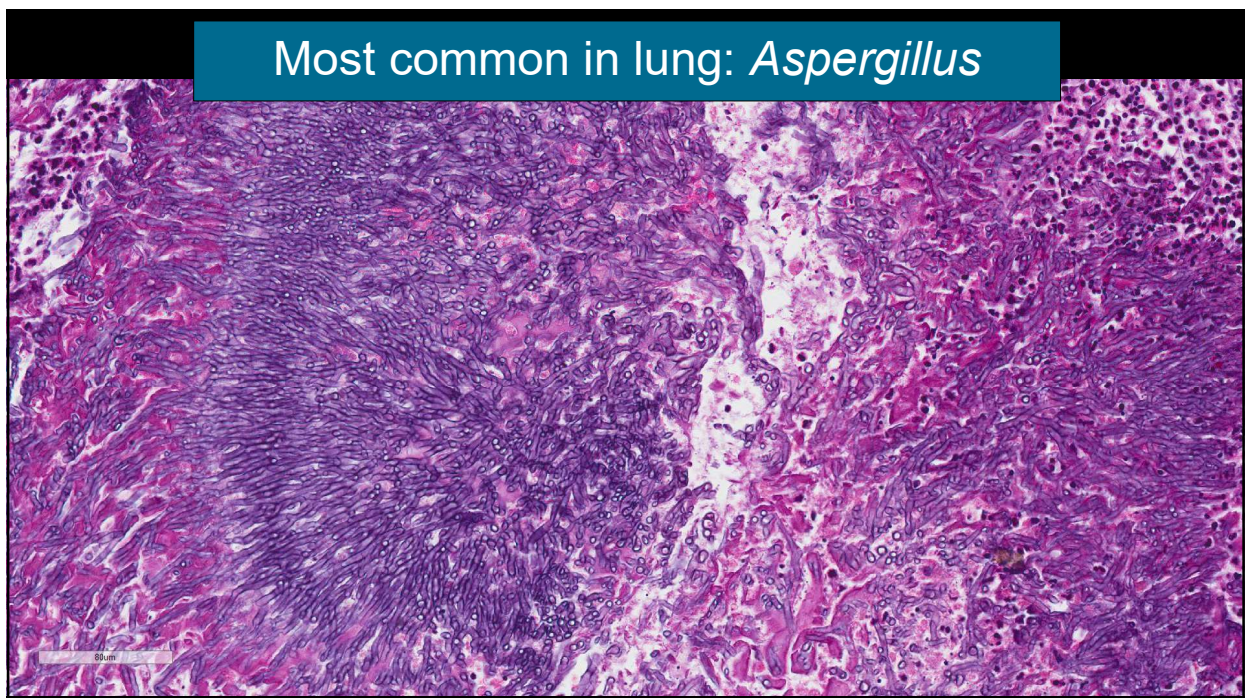
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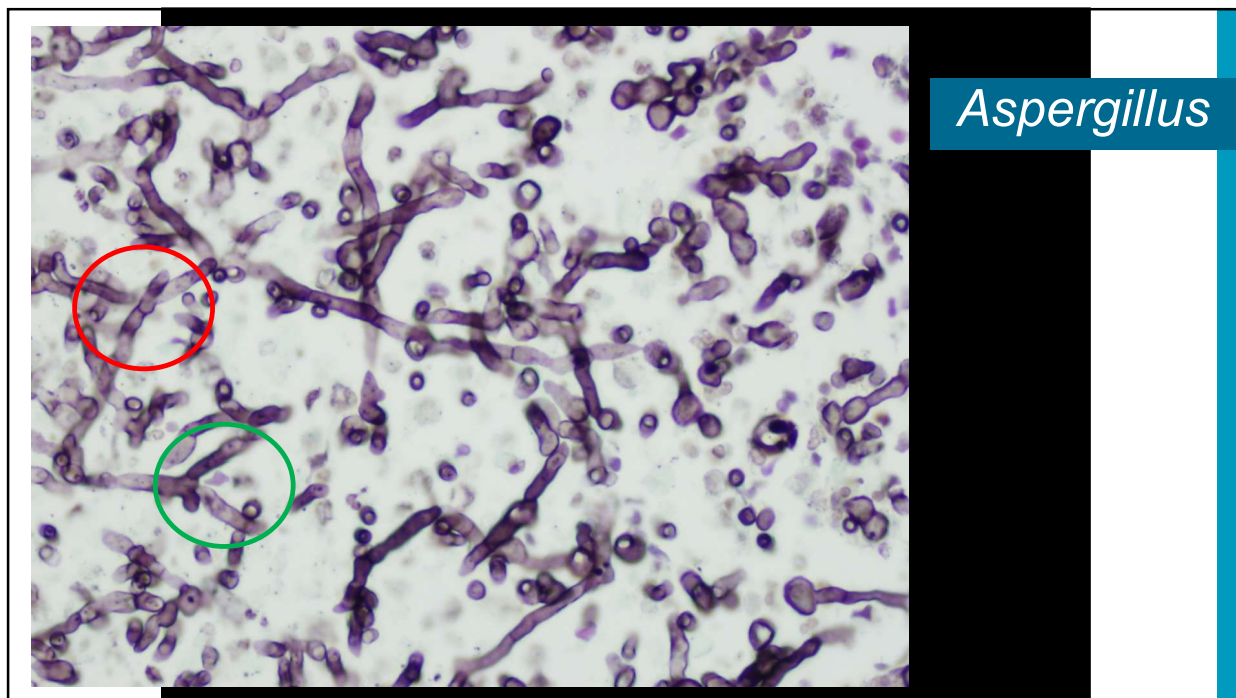
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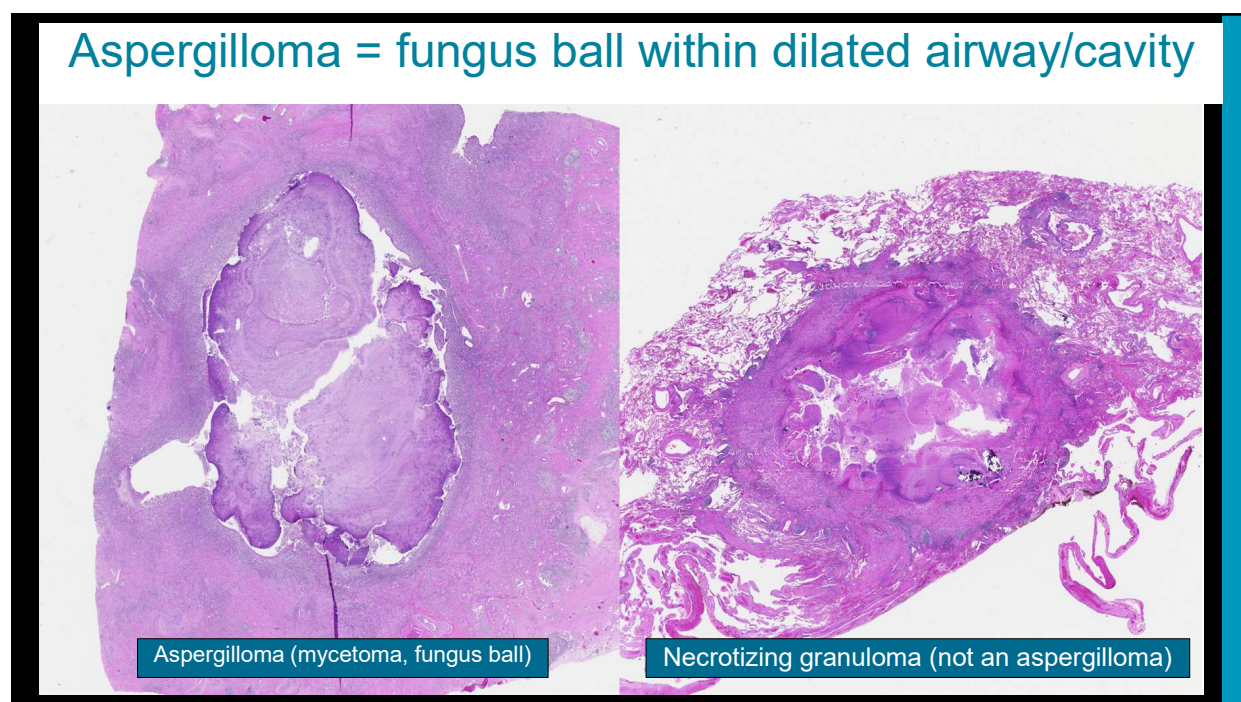
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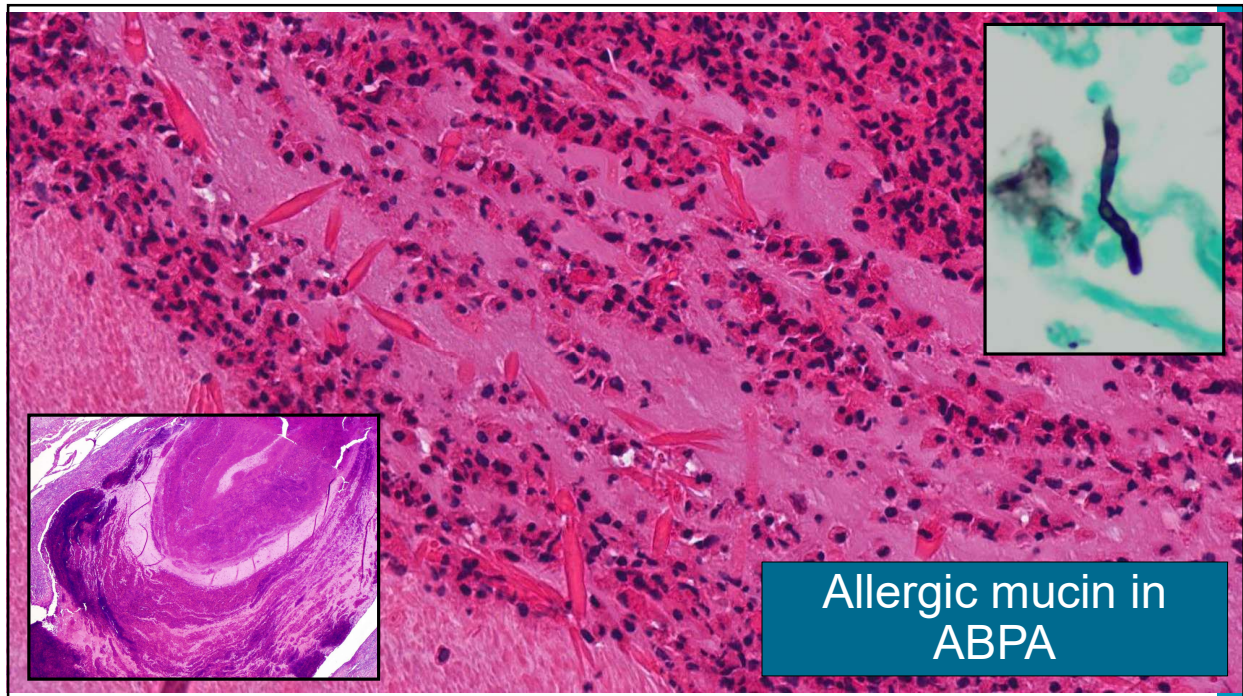
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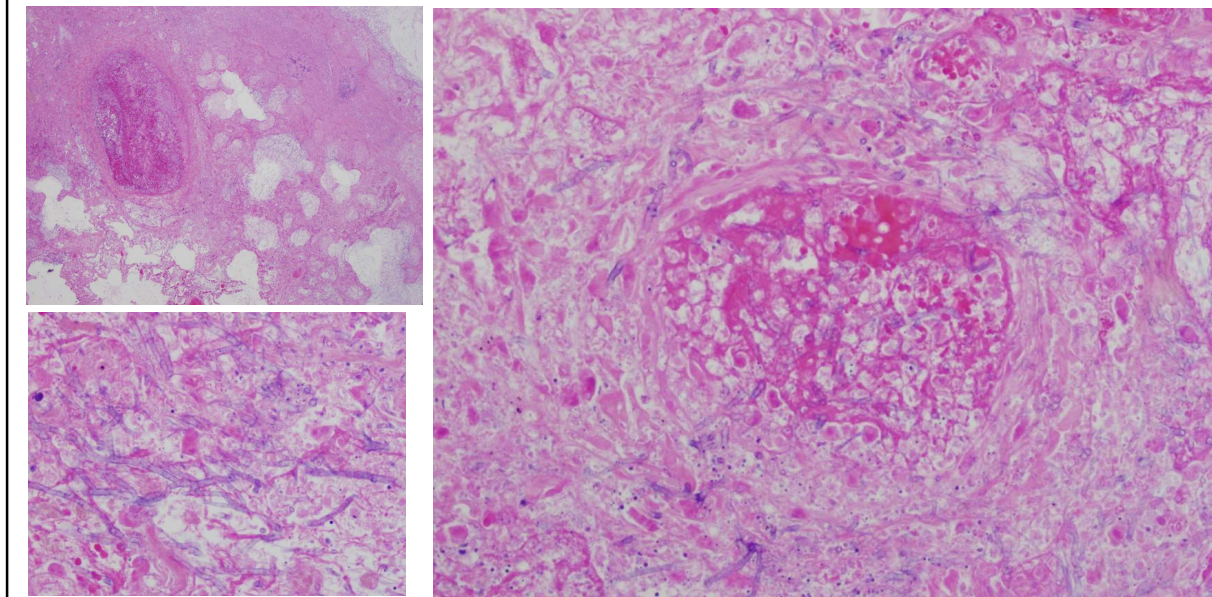


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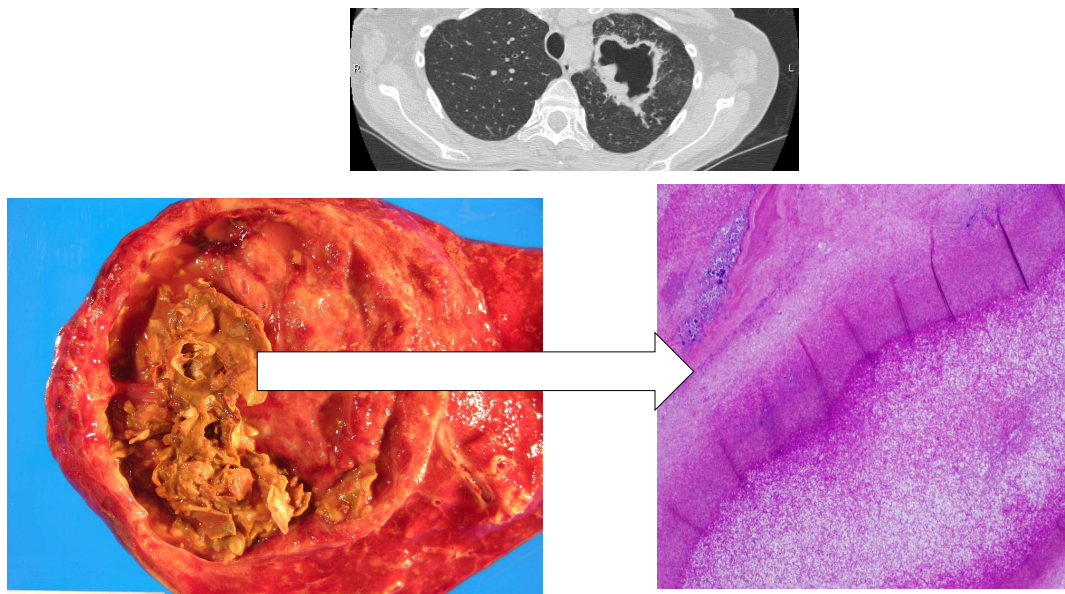
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Invasive aspergillosis



30

Chronic necrotizing (cavitary) aspergillosis

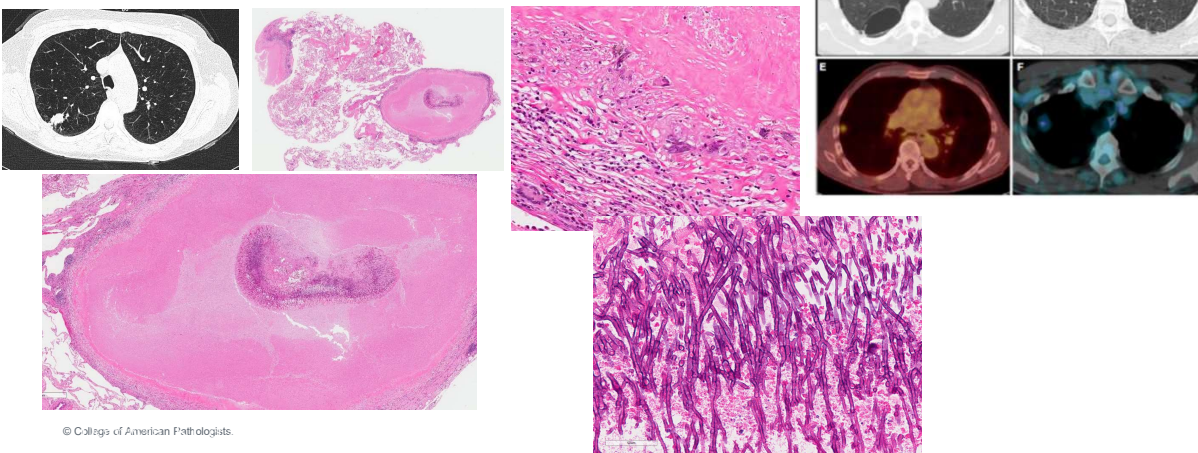


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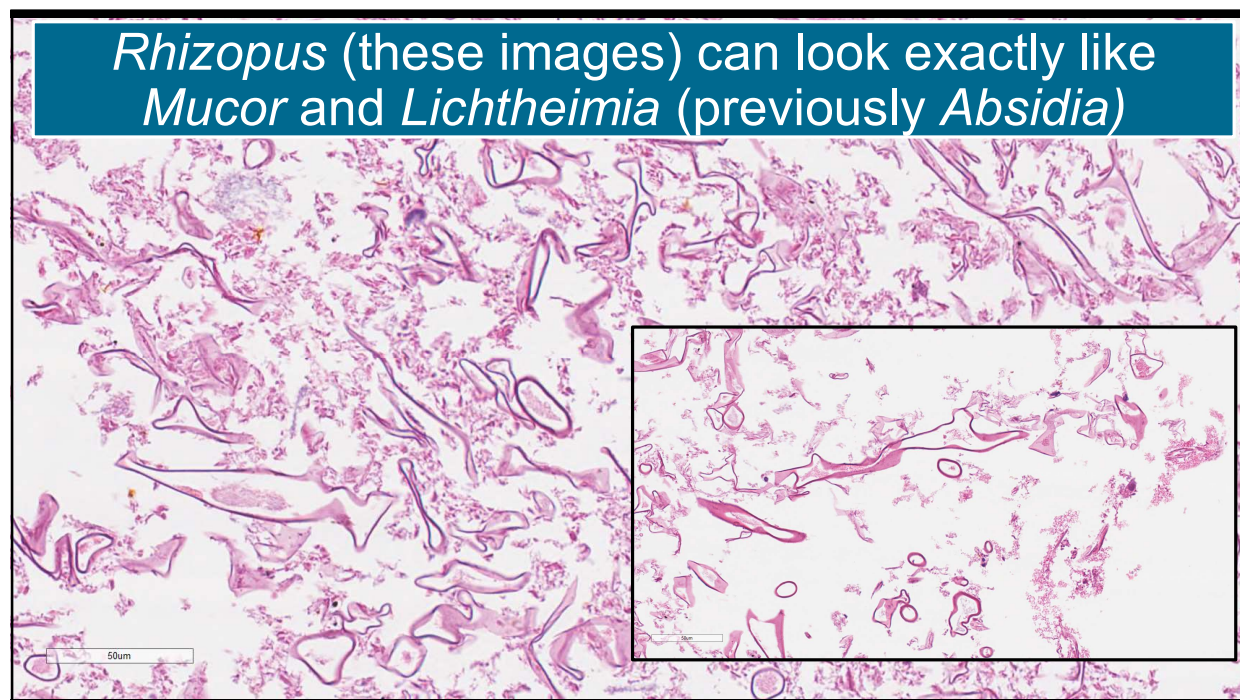
Expanding the spectrum of chronic necrotising (semi-invasive) aspergillosis: a series of eight cases presenting as radiologically solid lung nodules mimicking malignancy

Josephine K Dermawan,¹ Subha Ghosh² & Sanjay Mukhopadhyay²

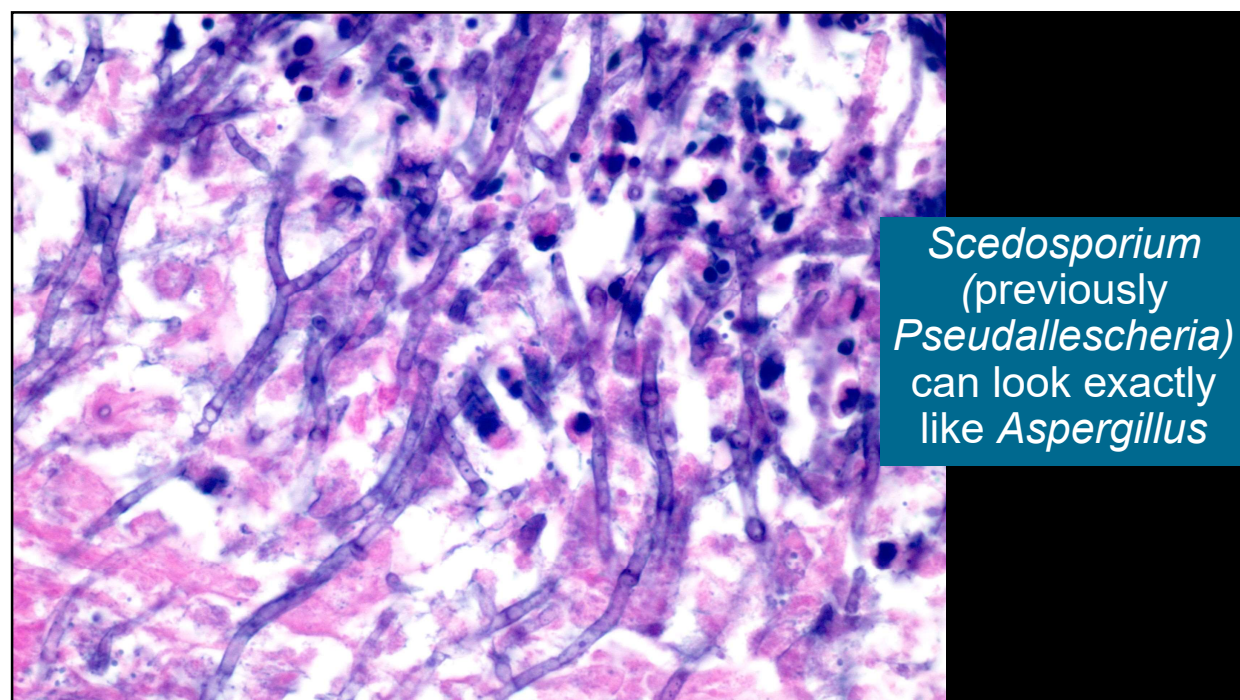
¹Department of Pathology, Cleveland Clinic, and ²Department of Thoracic Radiology, Cleveland Clinic, Cleveland, OH, USA



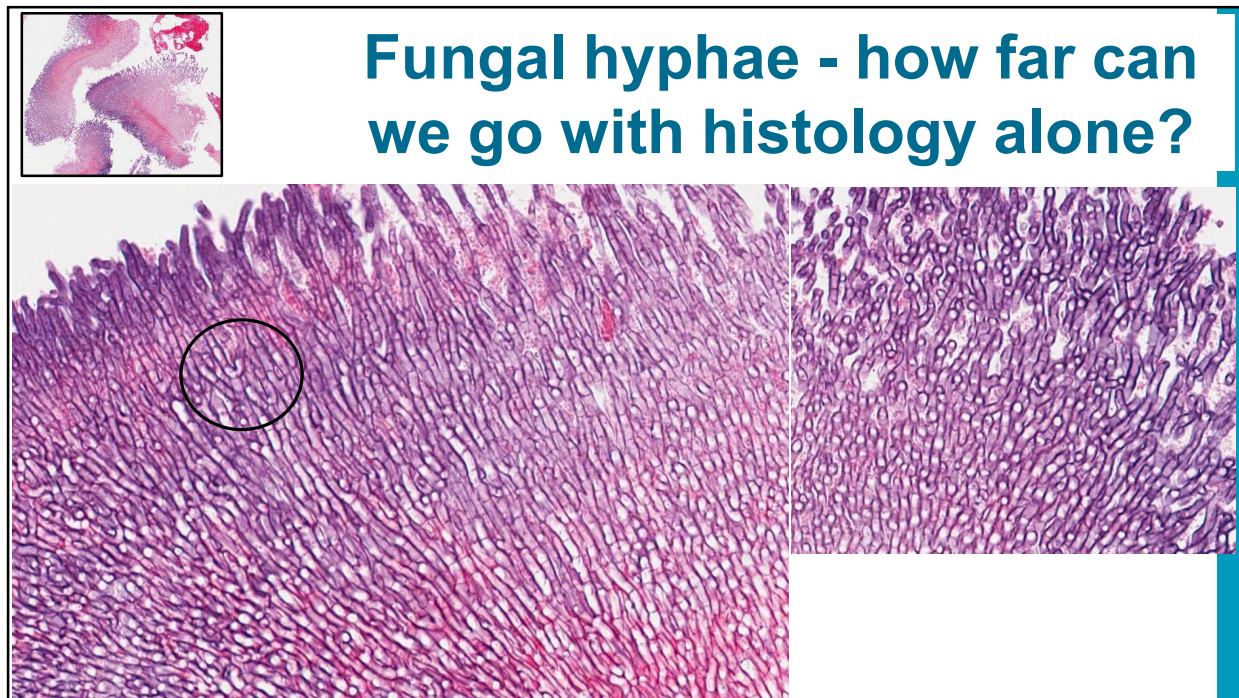
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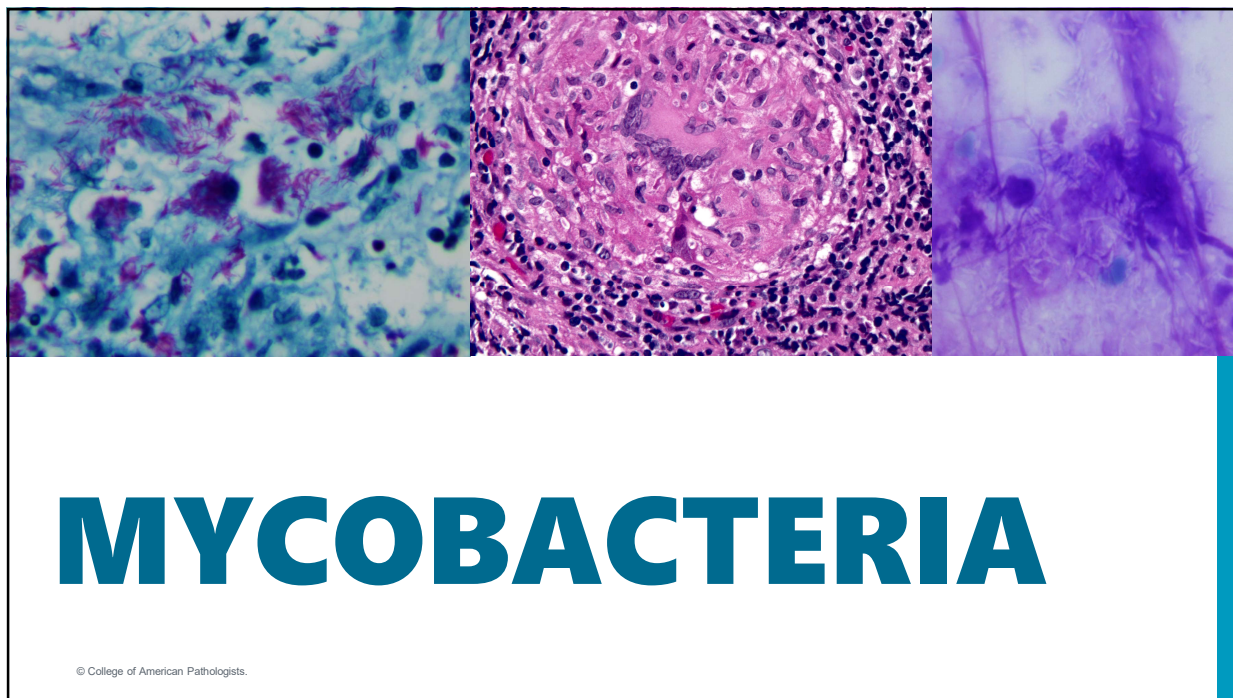
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My approach to reporting fungal hyphae

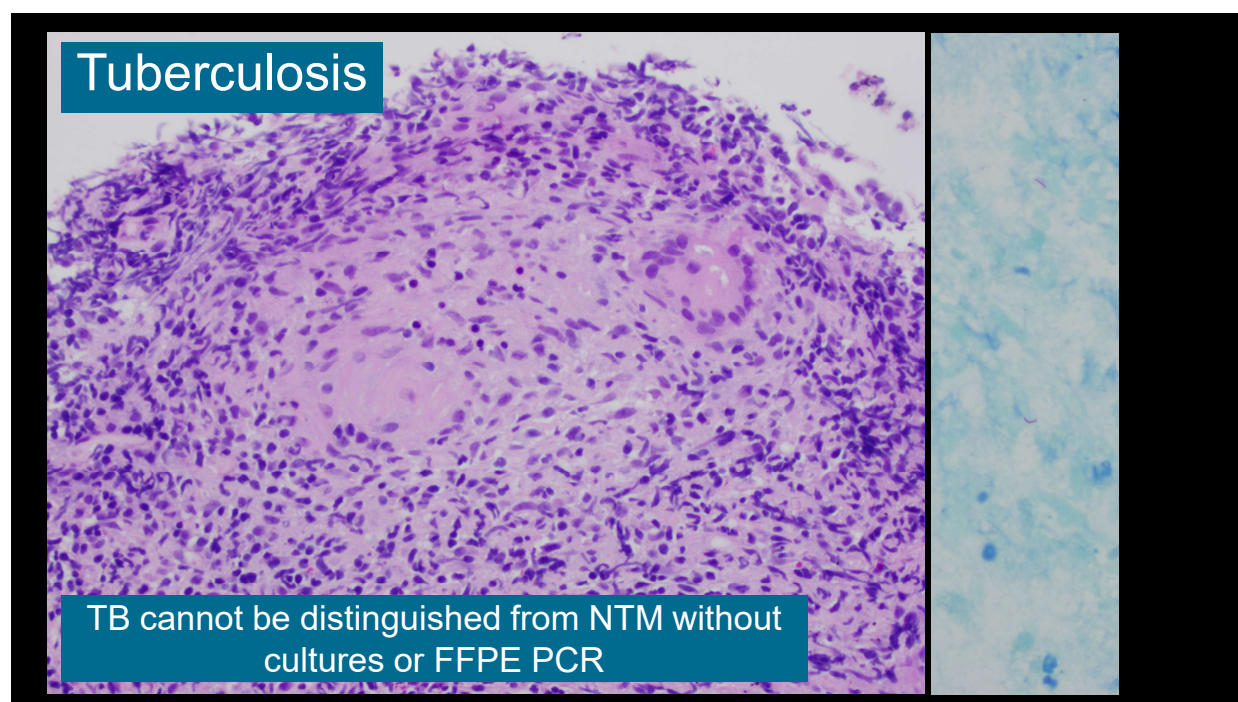
- With fungal hyphae I am never definitive
- Necrosis (fungal hyphae present)
 - Comment: The hyphae are septate and show narrow-angle branching. In the lung, most cases with this morphology represent *Aspergillus*. However, other fungi such as *Scedosporium* and *Fusarium* can appear similar. Results of cultures will be important

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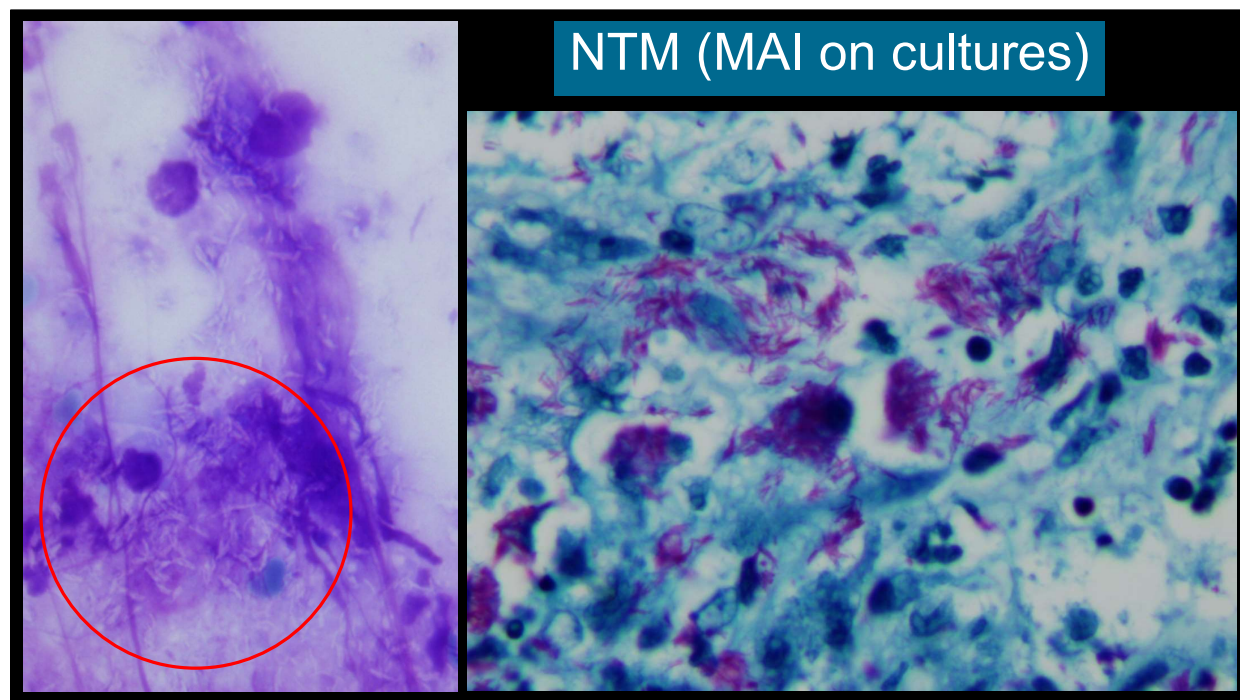
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39

Mycobacterial granuloma

Review article

Pathology of pulmonary tuberculosis and non-tuberculous mycobacterial lung disease: Facts, misconceptions, and practical tips for pathologists

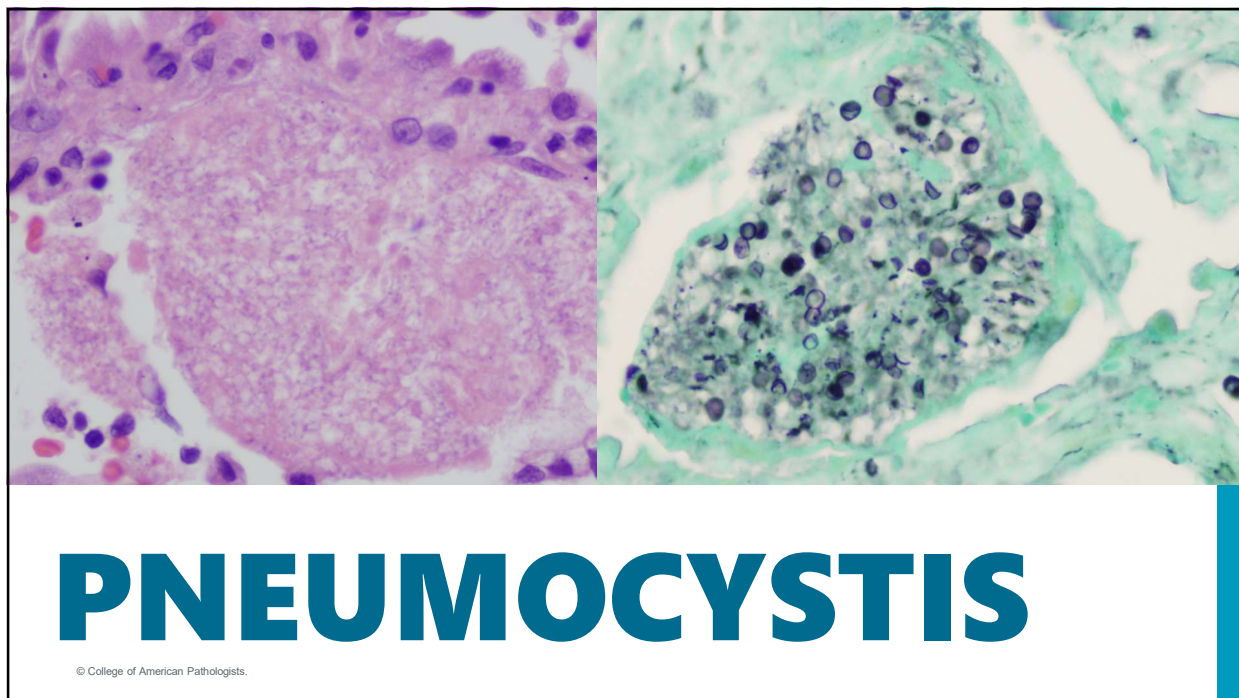
Deepali Jain^a, Subha Ghosh^b, Lucileia Teixeira^c, Sanjay Mukhopadhyay^{d,*}

Table 3
Tips for identifying acid-fast bacteria in necrotizing granulomas.³

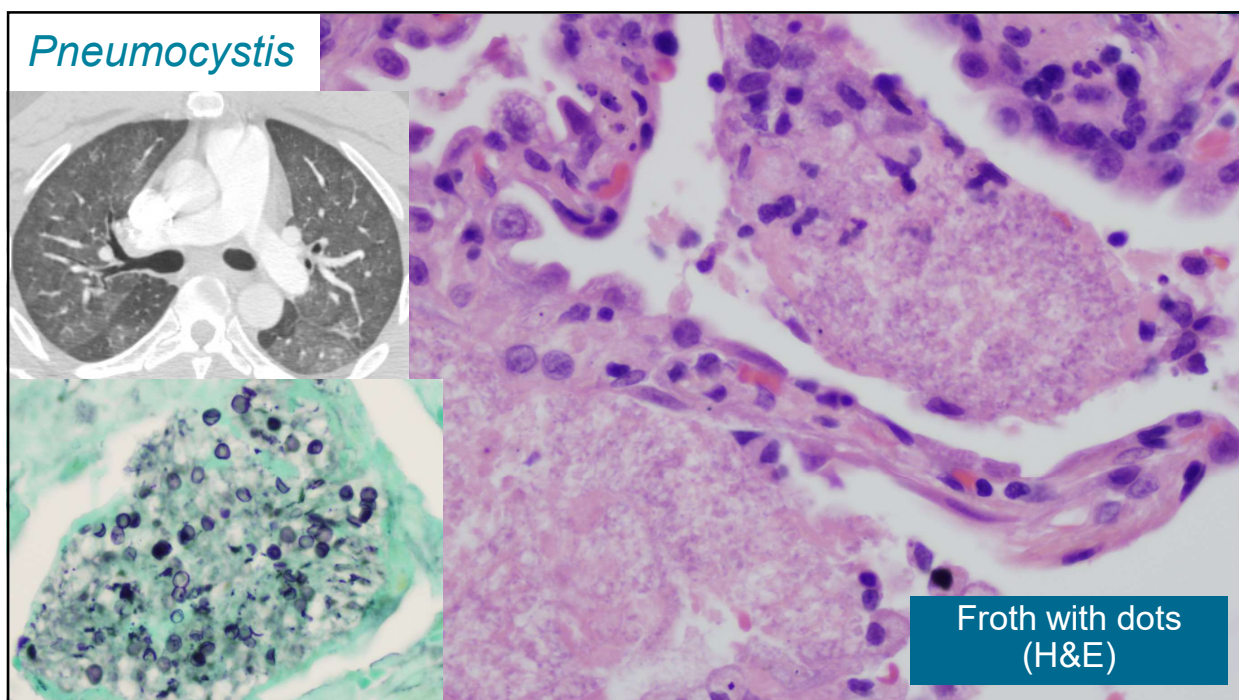
- Do not assume that the entire field will be full of organisms; it is not uncommon to find only a few AFB in a case. In some cases, there may be only 1 or 2 AFB
- After scanning the case briefly at 20x, use either your 40x objective and/or an oil immersion lens to look for AFB
- Focus your search within necrosis (this is where the yield is the greatest)
- AFB may be present in non-necrotic areas in granulomas, but they are usually fewer in number and harder to find
- Spend adequate time (we spend at least 5–10 min per case at high magnification, often much longer). Make sure that you have looked at each field in each necrotic area at high magnification. A few seconds of cursory viewing at low magnification is inadequate
- Constantly changing the fine focus ensures that you don't miss organisms that are in a different plane of section
- Stain at least 2 blocks when multiple blocks have necrotizing granulomas. Choose blocks with the greatest amount of necrosis
- If you practice in an area with an endemic fungus (*Histoplasma*, *Coccidioides*), examine the GMS before the AFB stain. Fungi are often easier and quicker to find than mycobacteria
- If the histologic findings are highly suspicious for infection but you cannot find organisms, show the case to a colleague who is experienced in (or expert at) identifying organisms on special stains
- AFB are often positive on GMS (Fig. 5). If you see bacteria on your GMS stain, spend more time on the AFB stain
- We use the Ziehl-Neelsen as our default stain for AFB
- Remember (and remind your clinicians) that cultures may be positive in cases where AFB stains are negative (see text for references). Mycobacterial cultures can take several weeks to become positive
- Even if cultures are negative, the absence of organisms does not necessarily imply that the etiology is non-infectious. The natural history of mycobacterial and fungal necrotizing granulomas is for the inflammatory infiltrate to destroy the organisms

© College of / Jain D, et al. *Semin Diagn Pathol* 2017;34(6):518-29

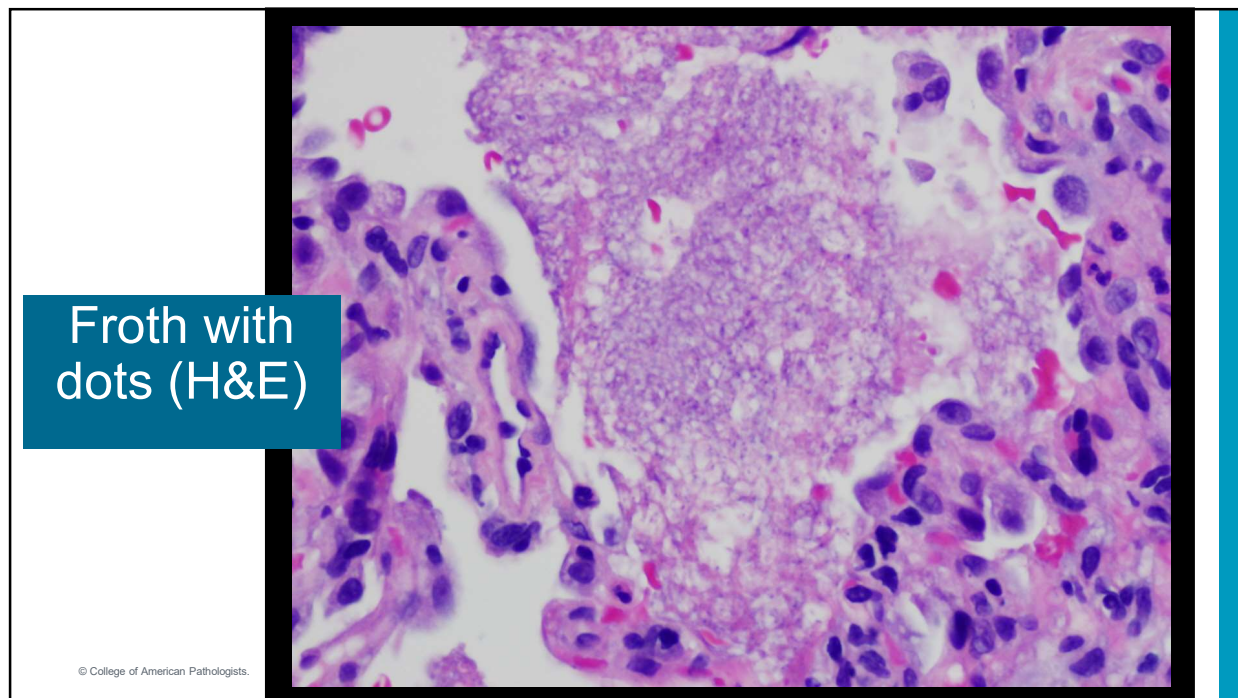
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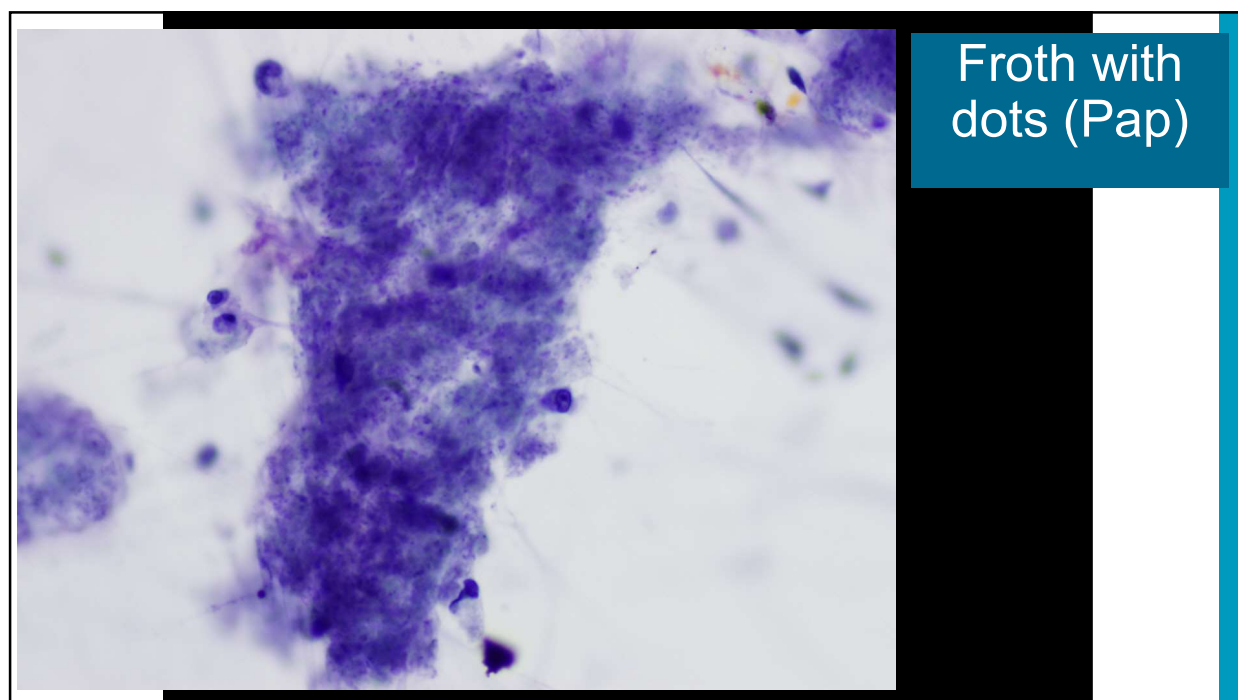
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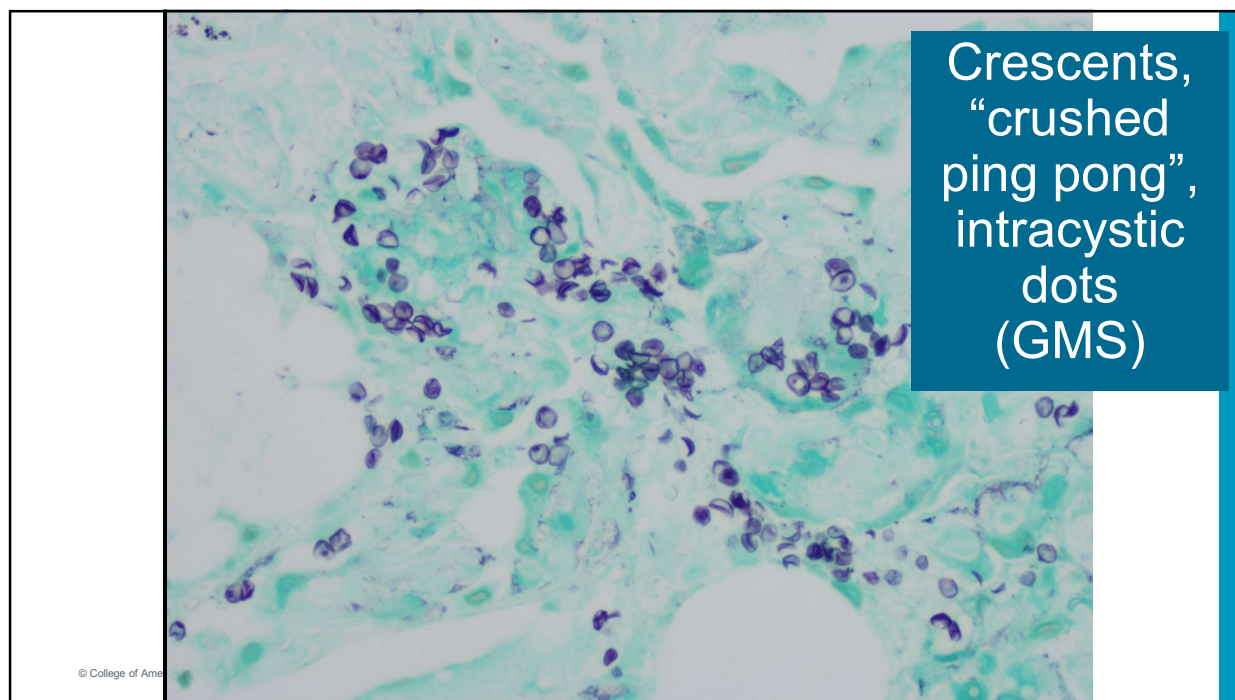
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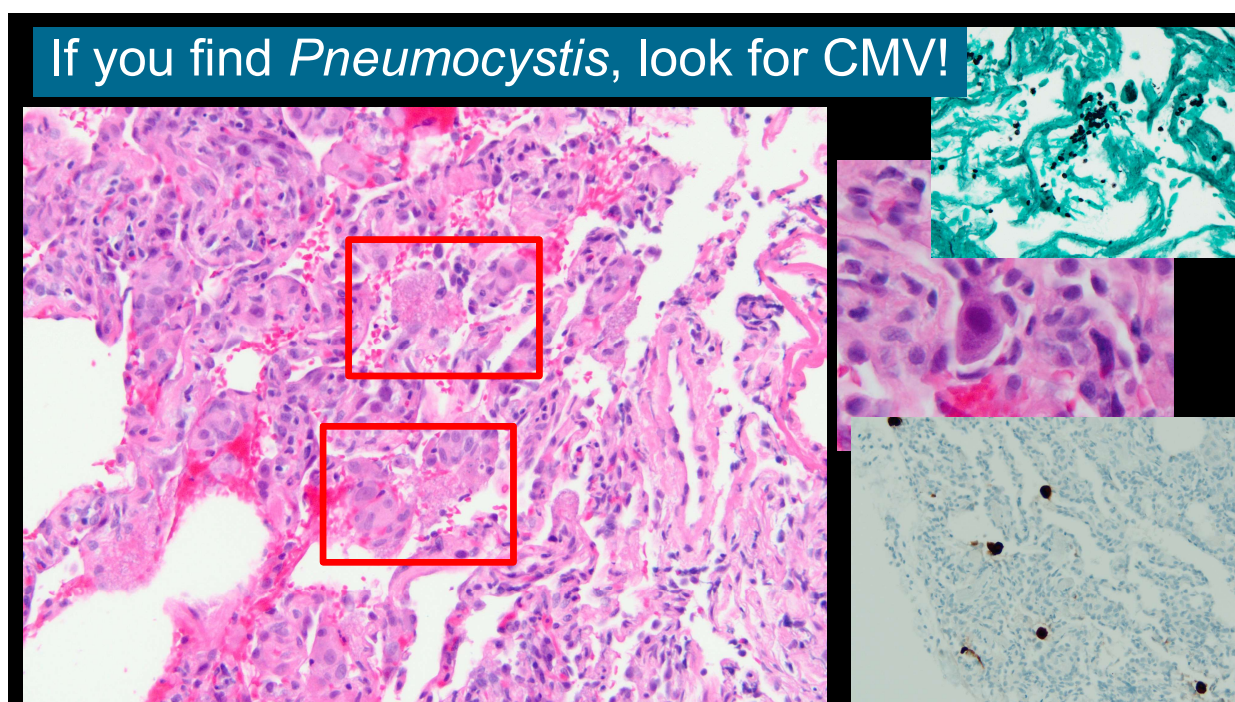
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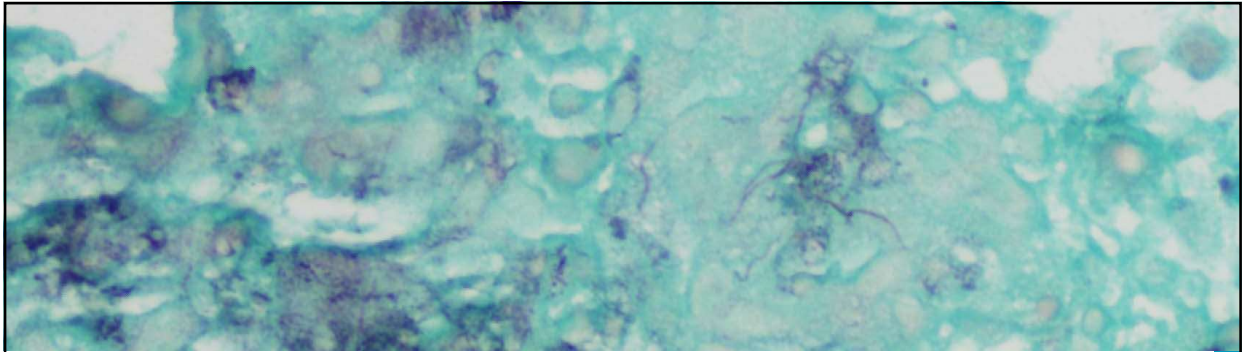
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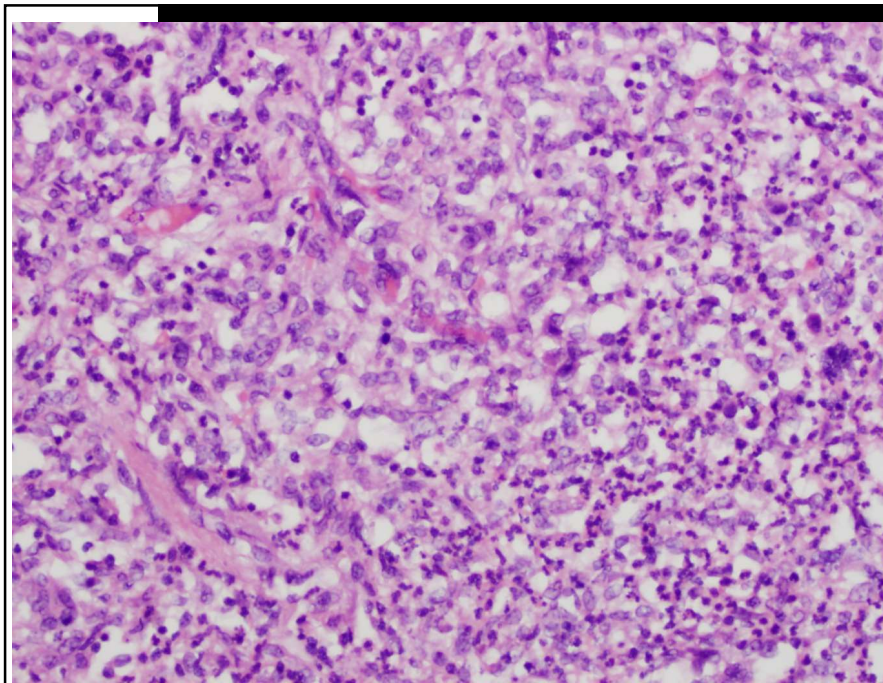
46



NOCARDIA

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47

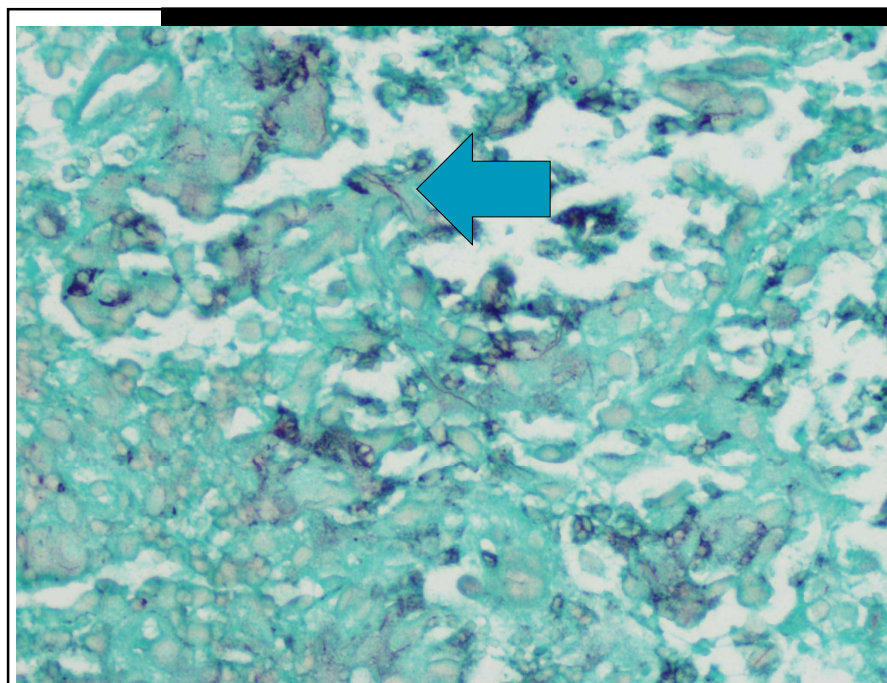


Usual tissue
reaction to
Nocardia:
neutrophils +
histiocytes

Mimics abscess

May be vaguely
granulomatous

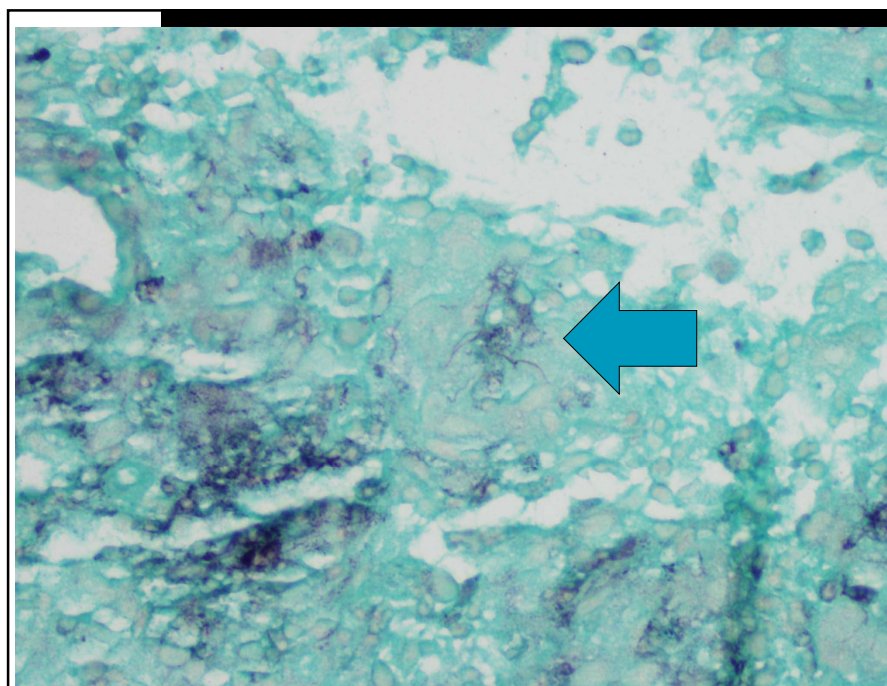
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In my
experience, in
FFPE histology,
GMS is by far
the best stain
for *Nocardia*

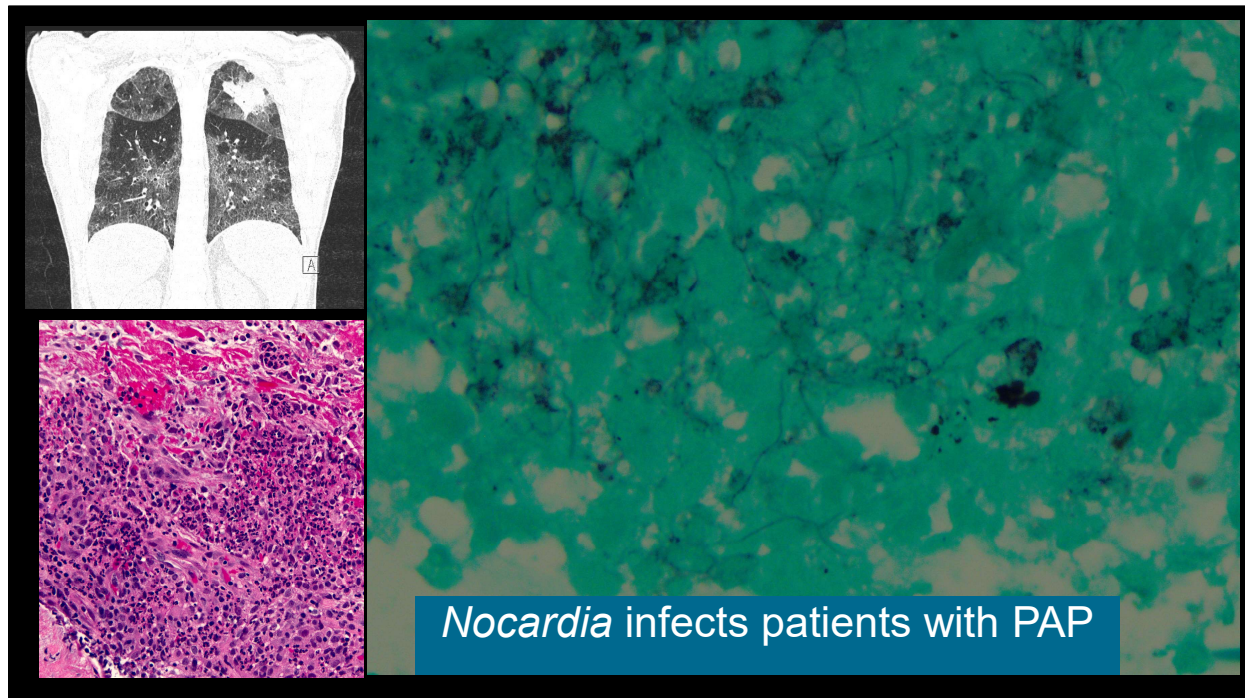
BUT: for boards
and other
exams, it is
AFB-positive

49



Look for
long
filamentous
bacteria

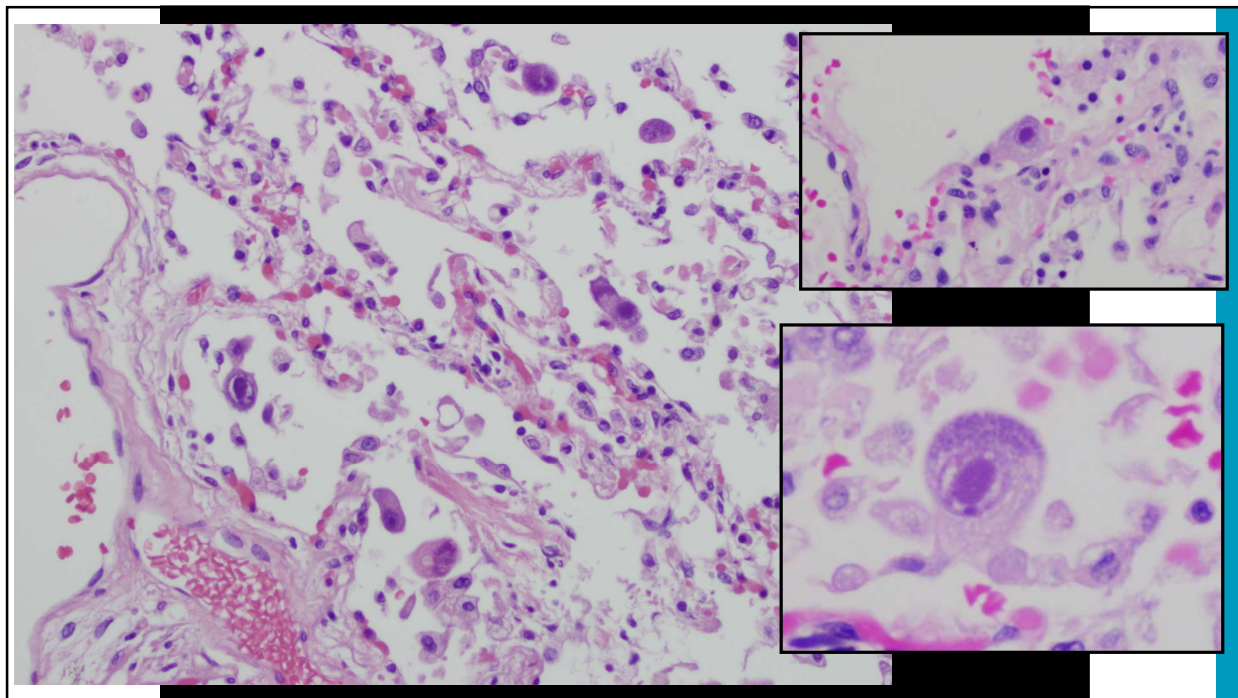
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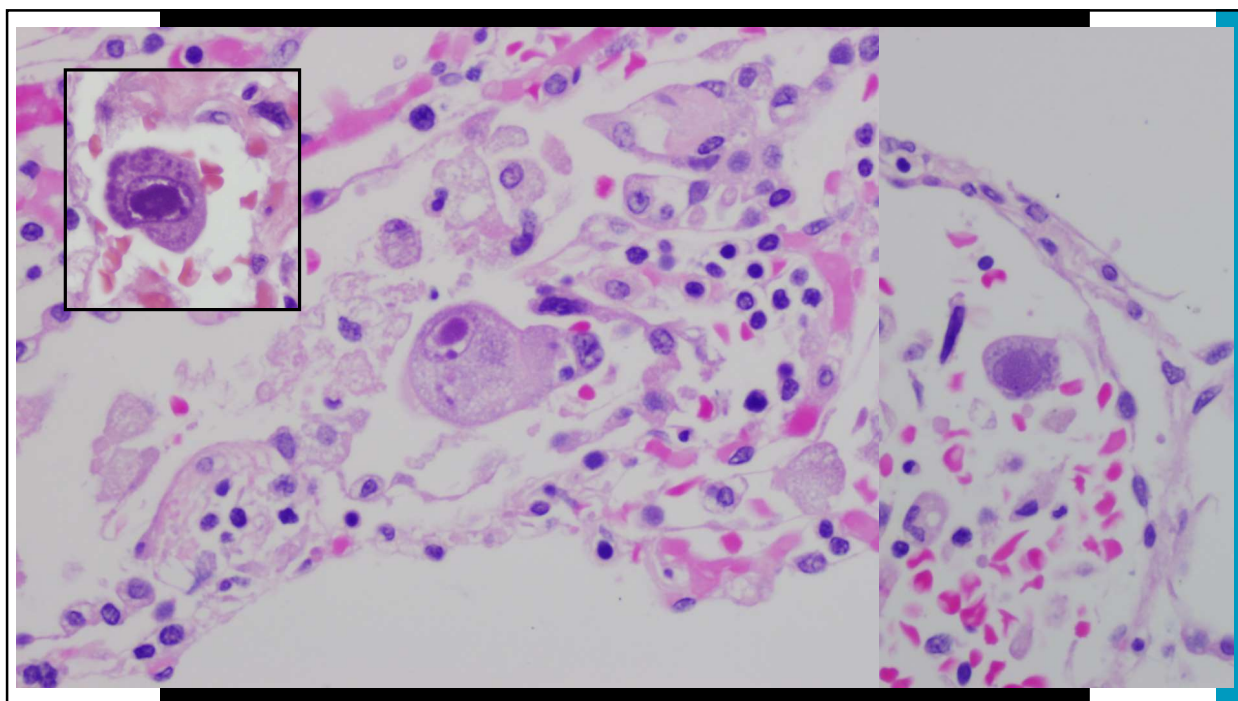
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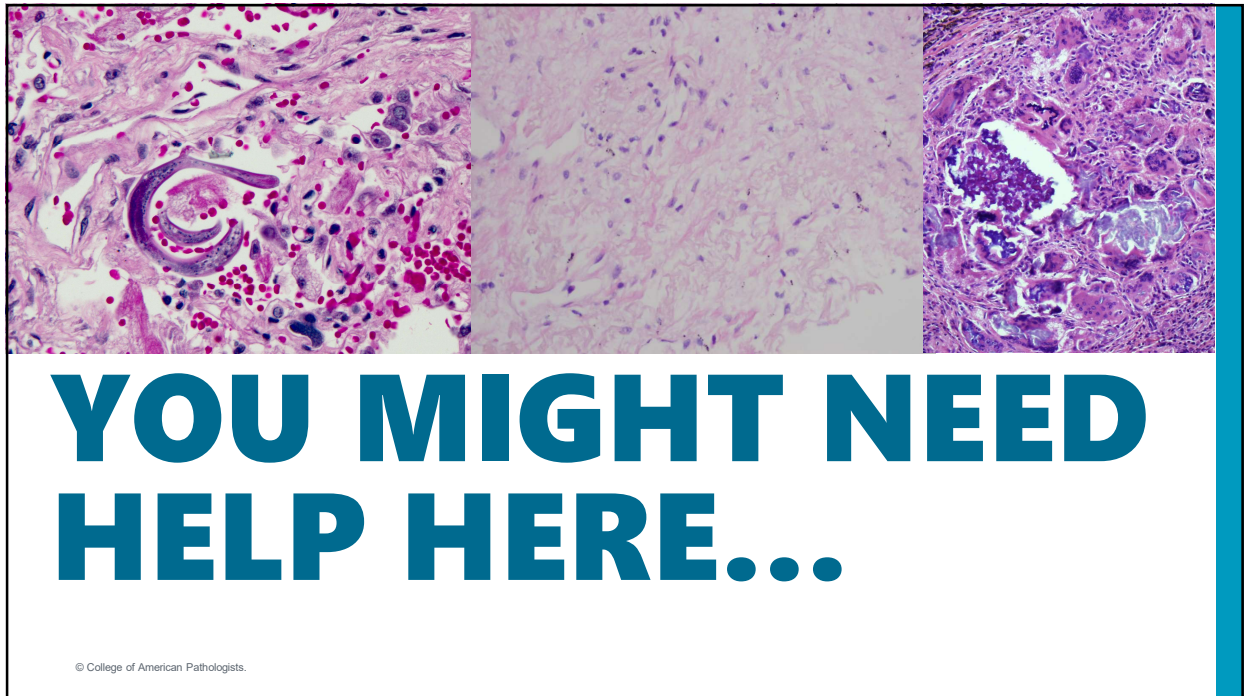
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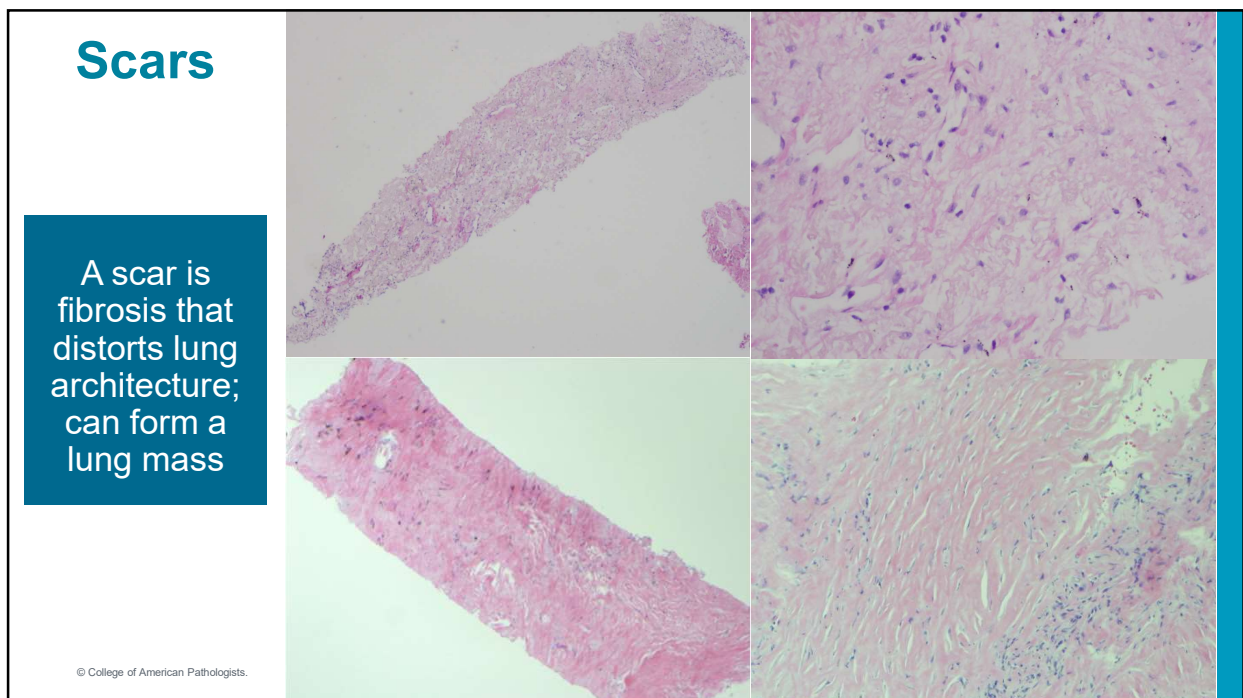
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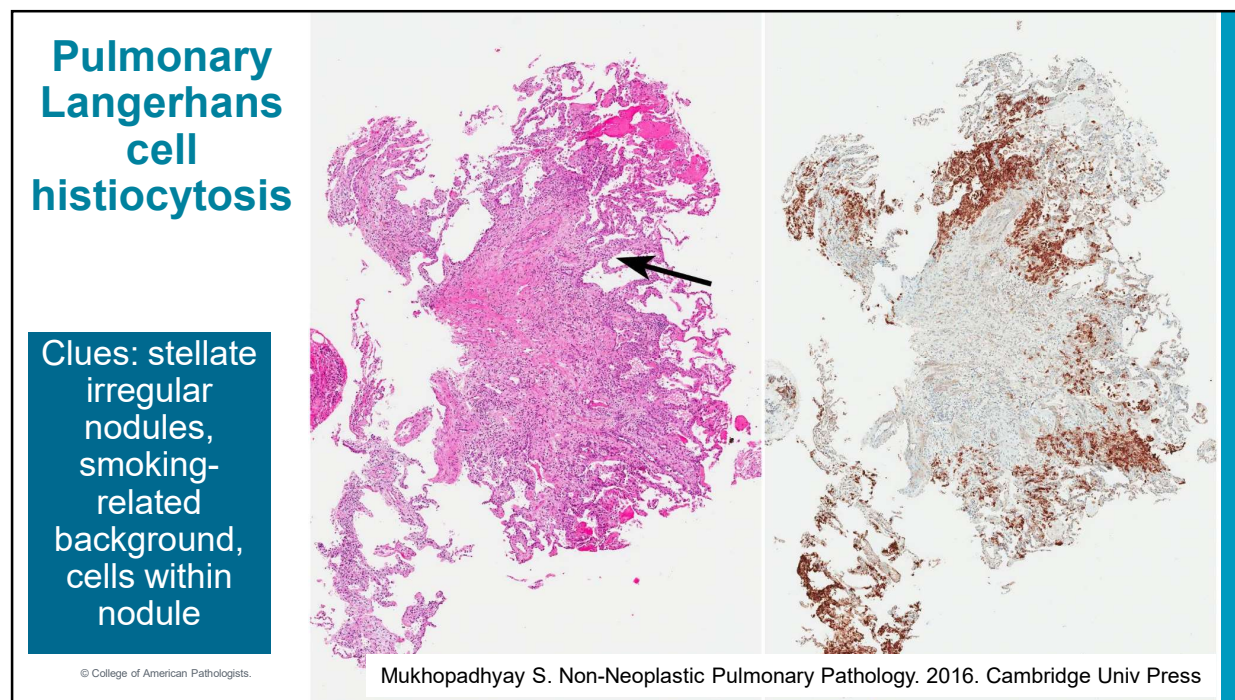
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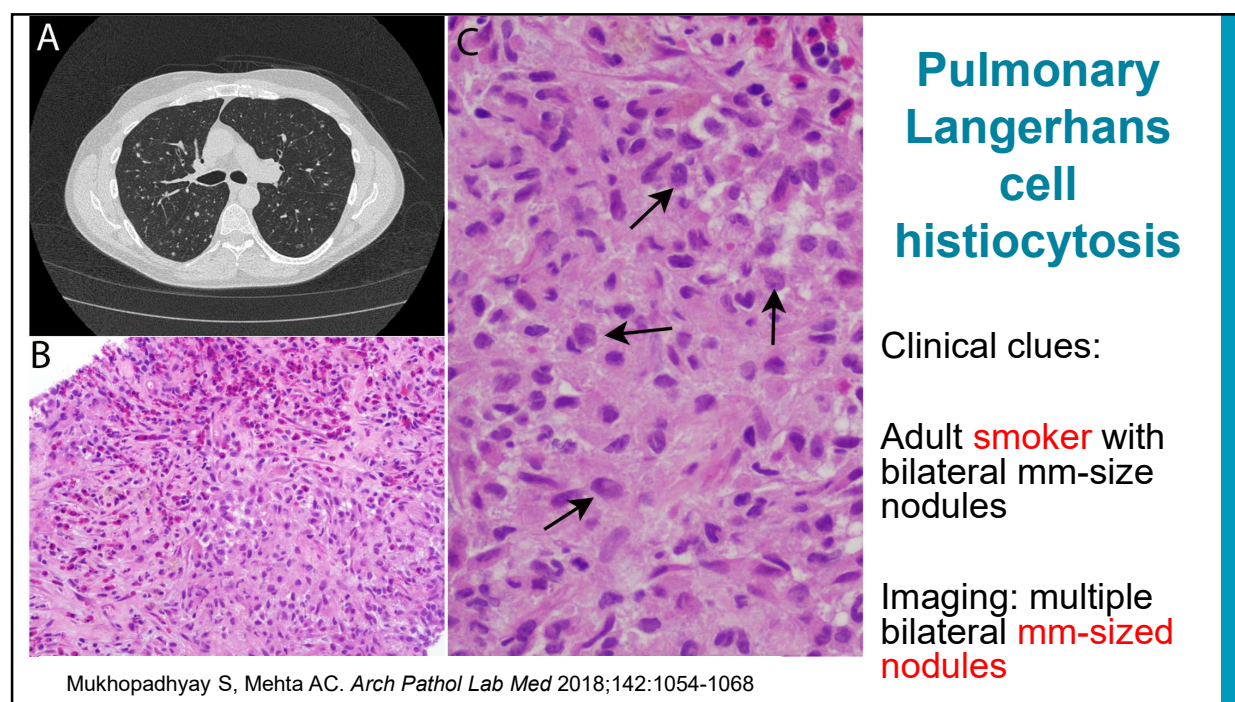
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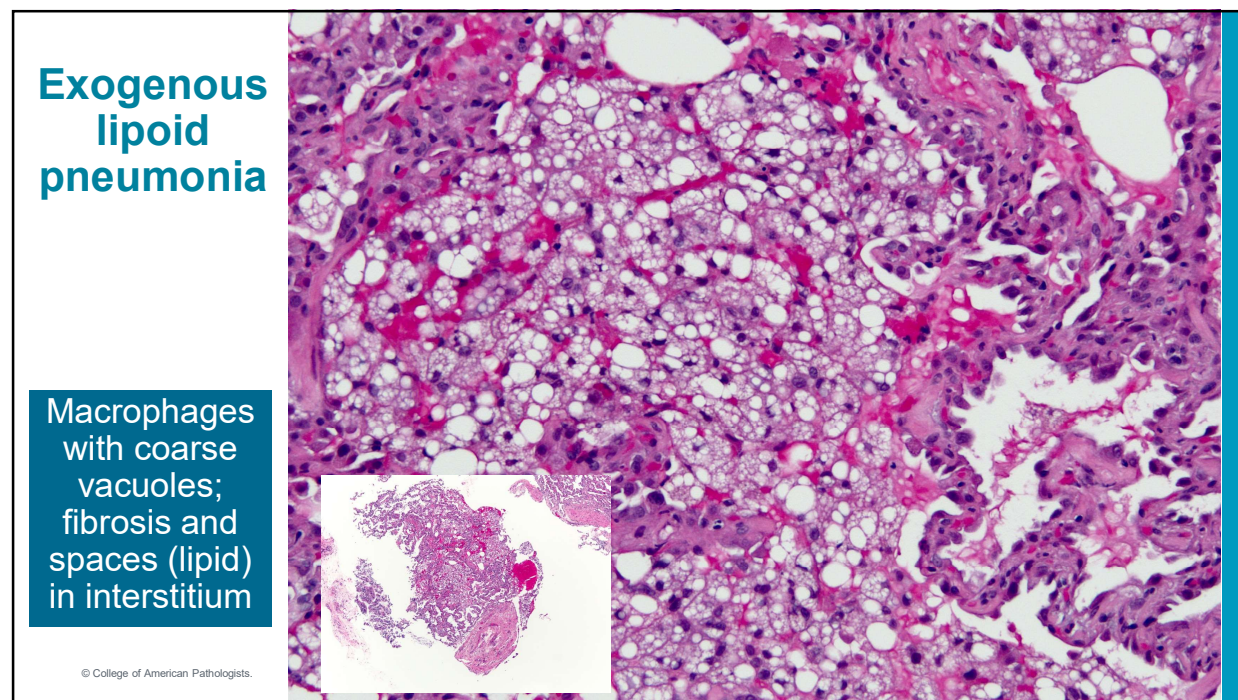
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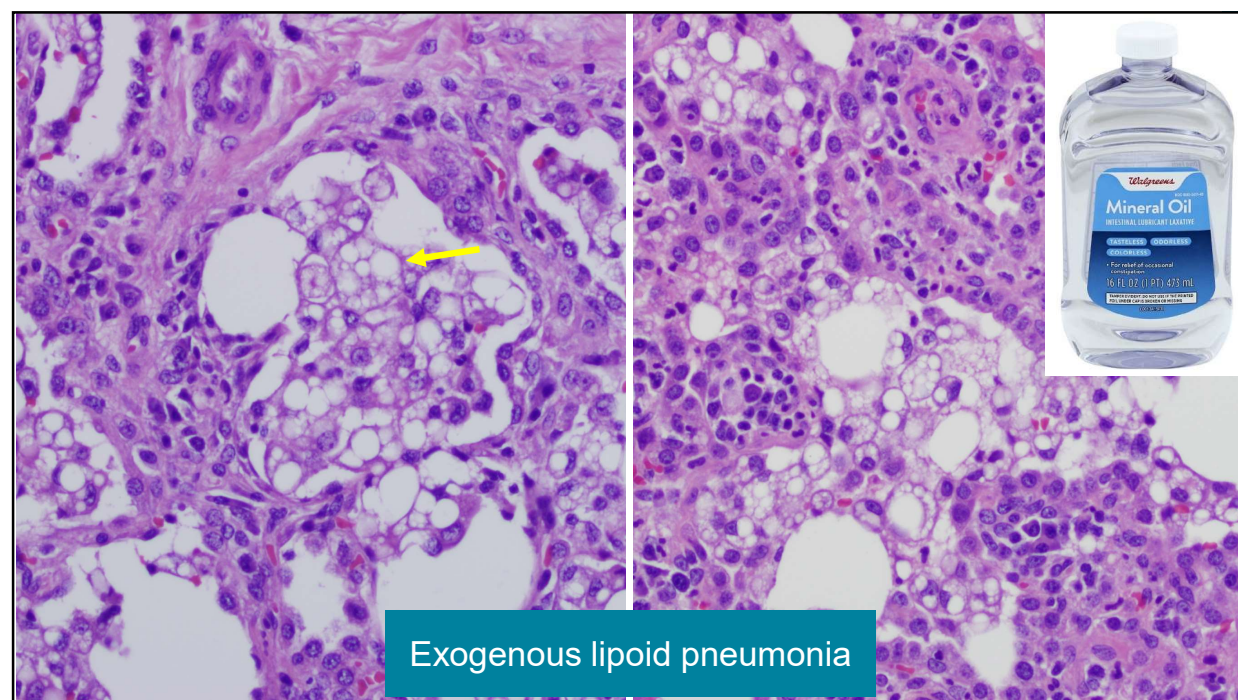
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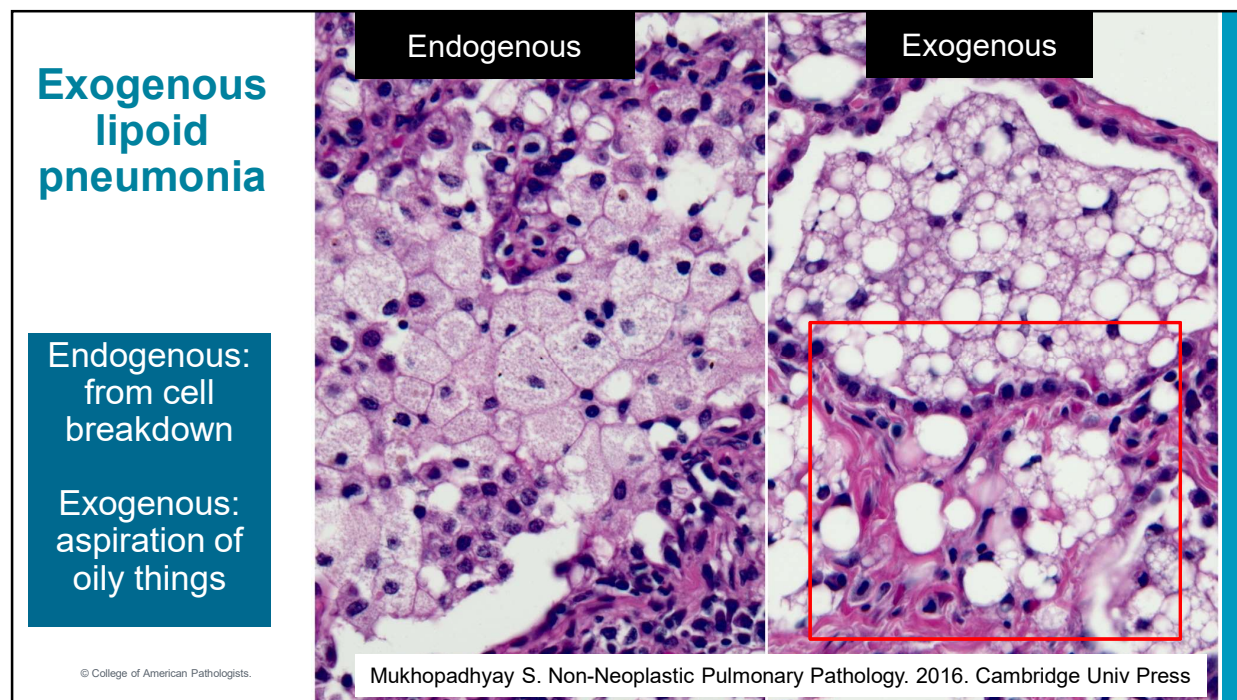
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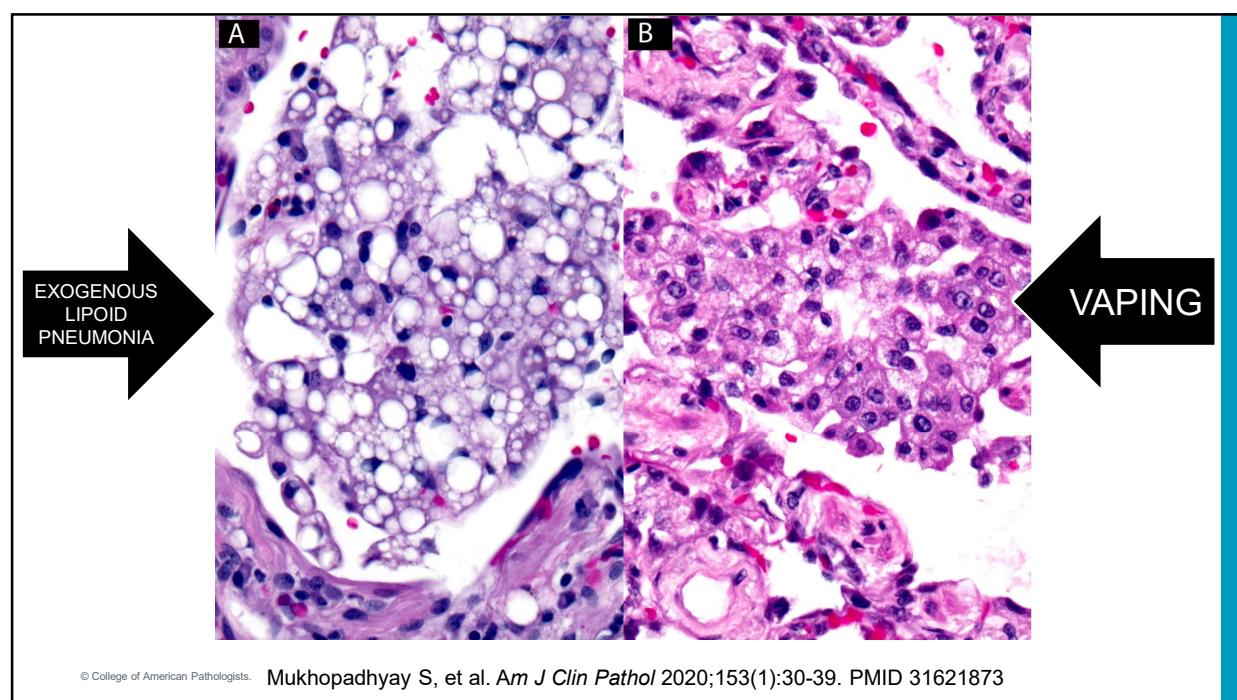
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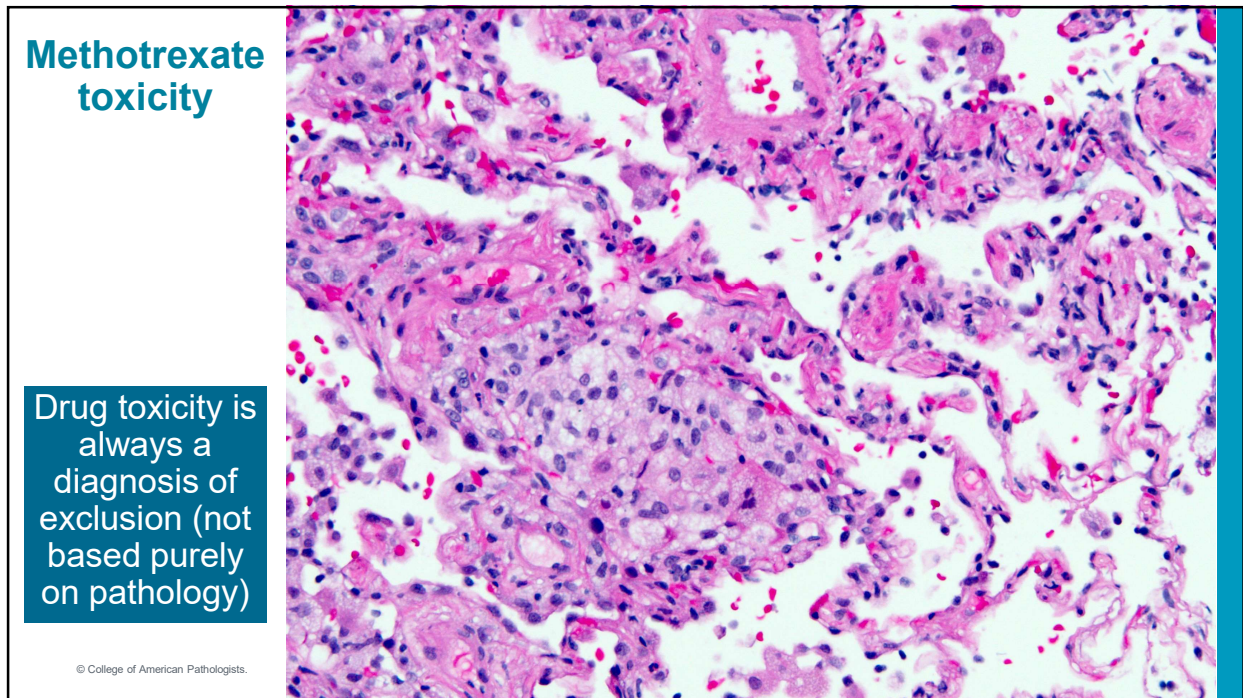
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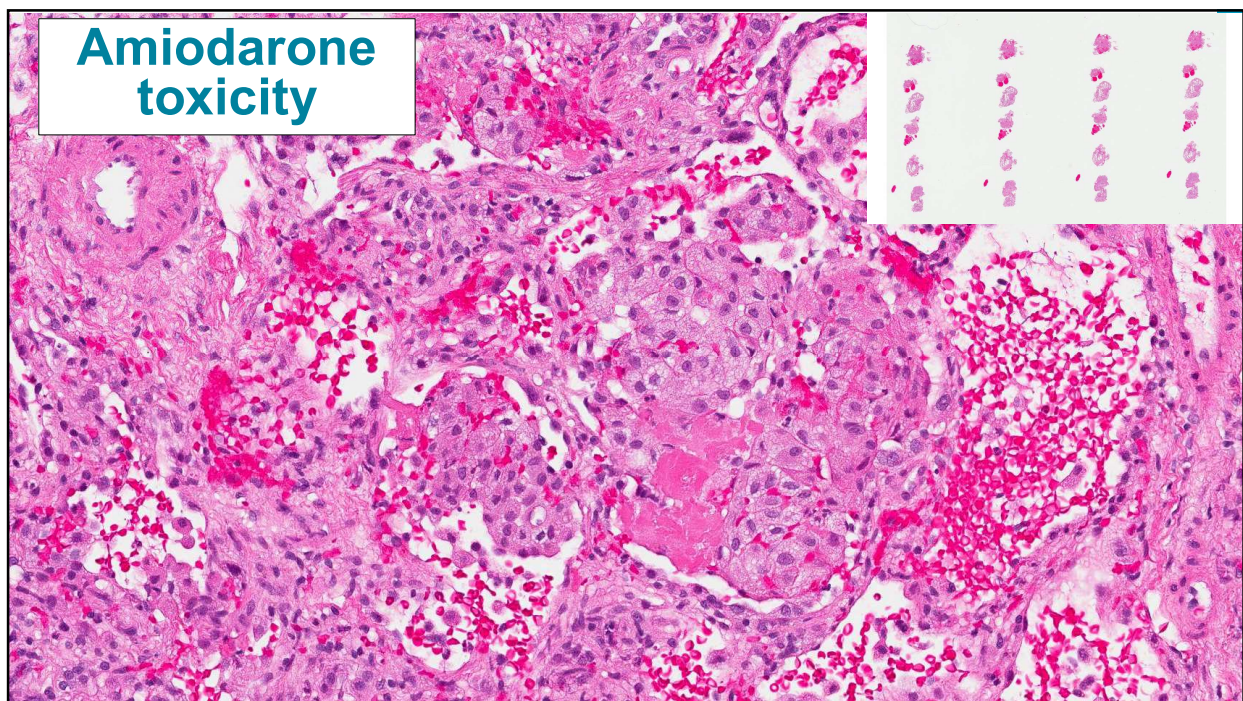
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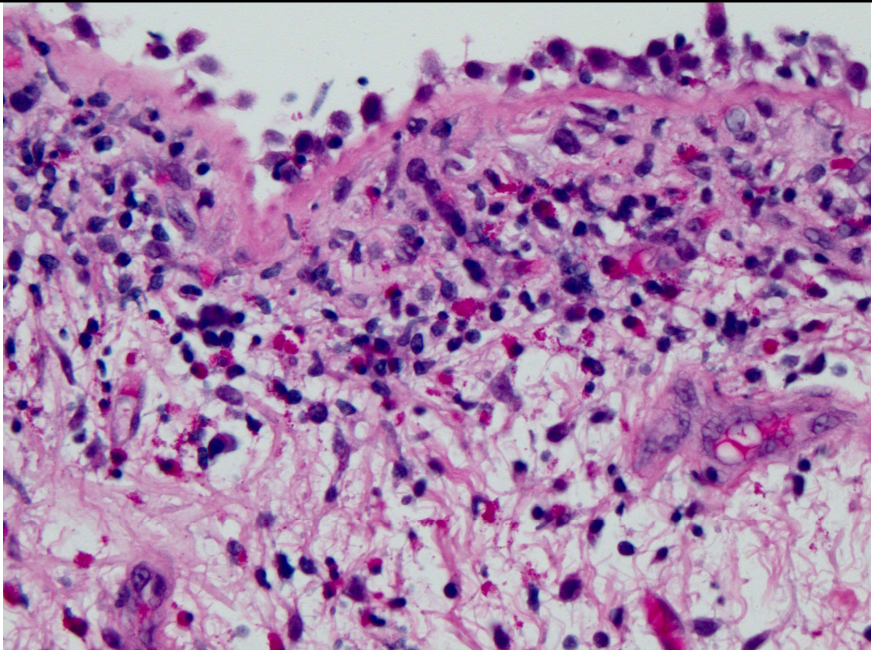
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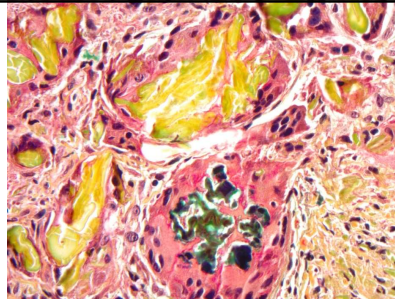
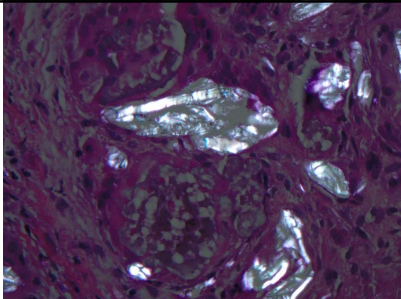
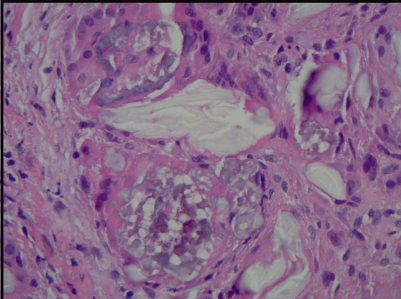
Pembrolizumab toxicity

Immune checkpoint inhibitor toxicity is increasing with increasing use of immunotherapy; organizing pneumonia, vague granulomas, foamy macrophages, eosinophils

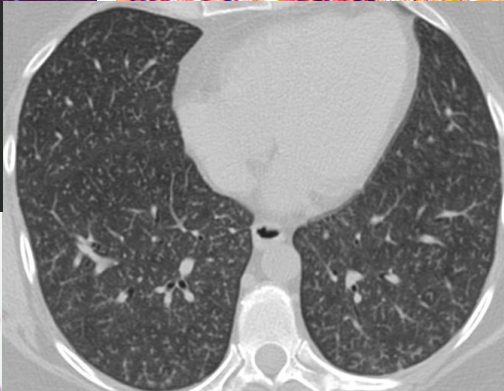
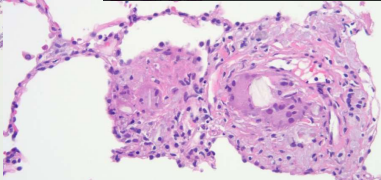
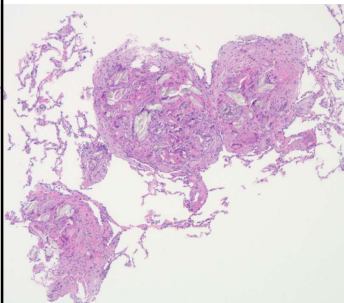


Sehgal S et al. Resp Med Case Rep 2016;19:118-20.

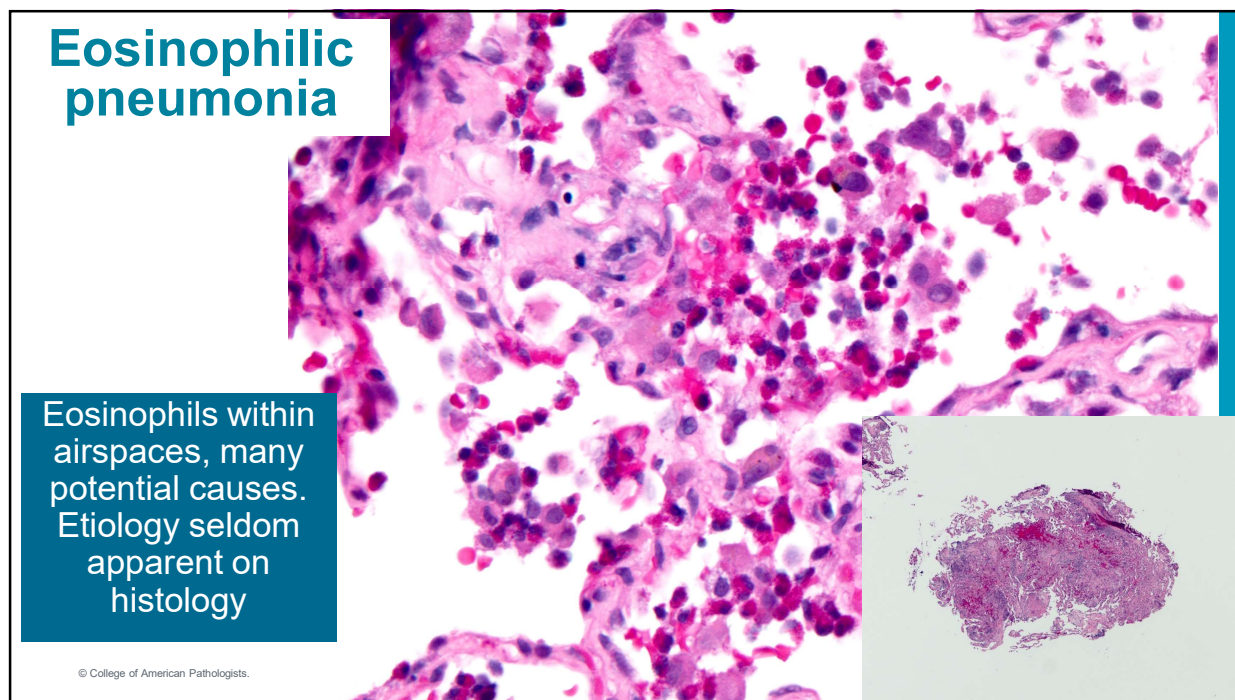
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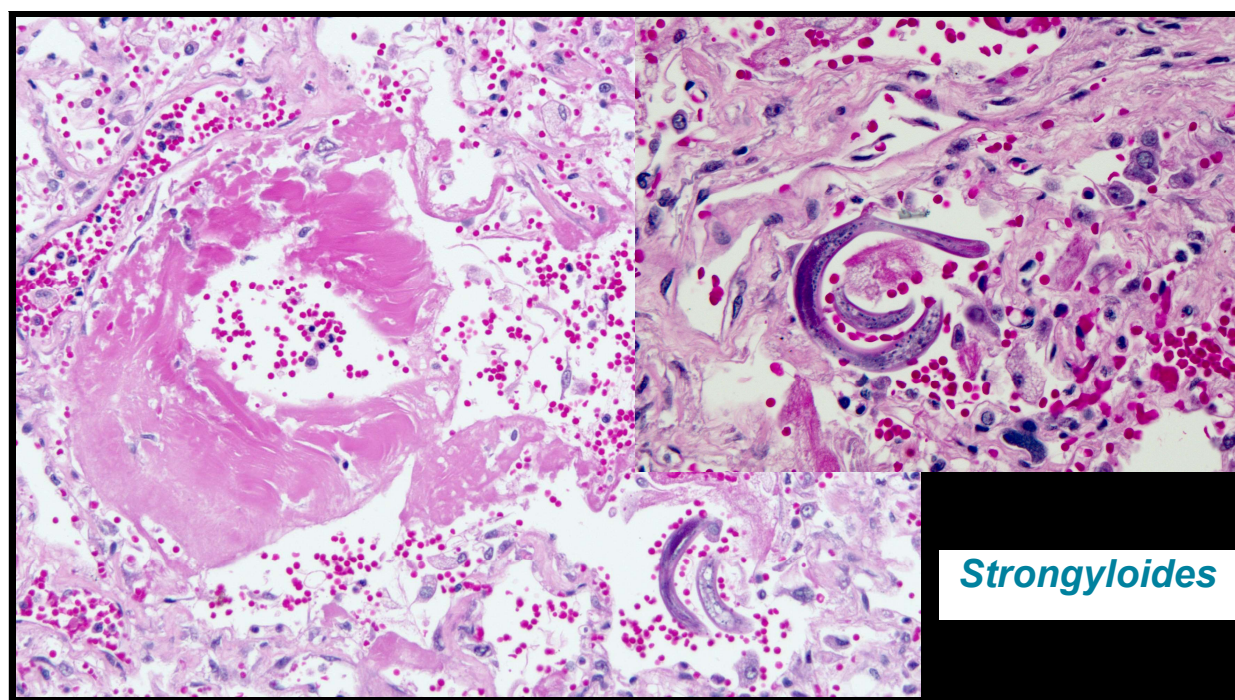
Talc granulomatosis



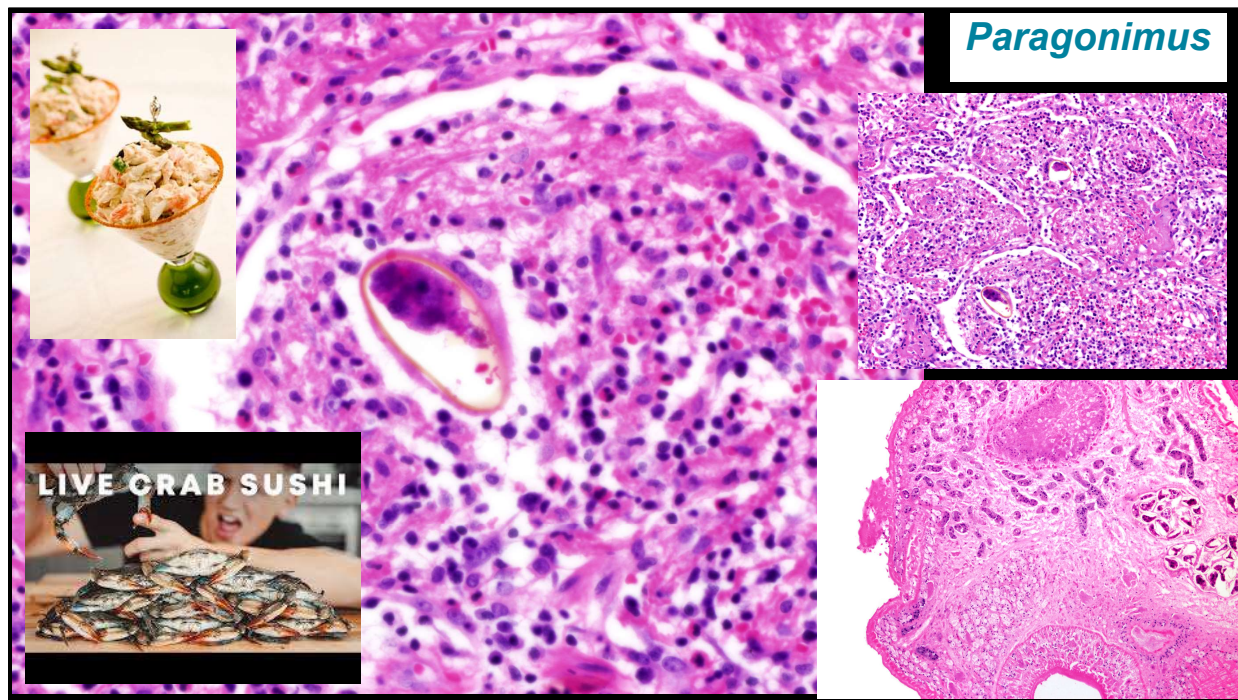
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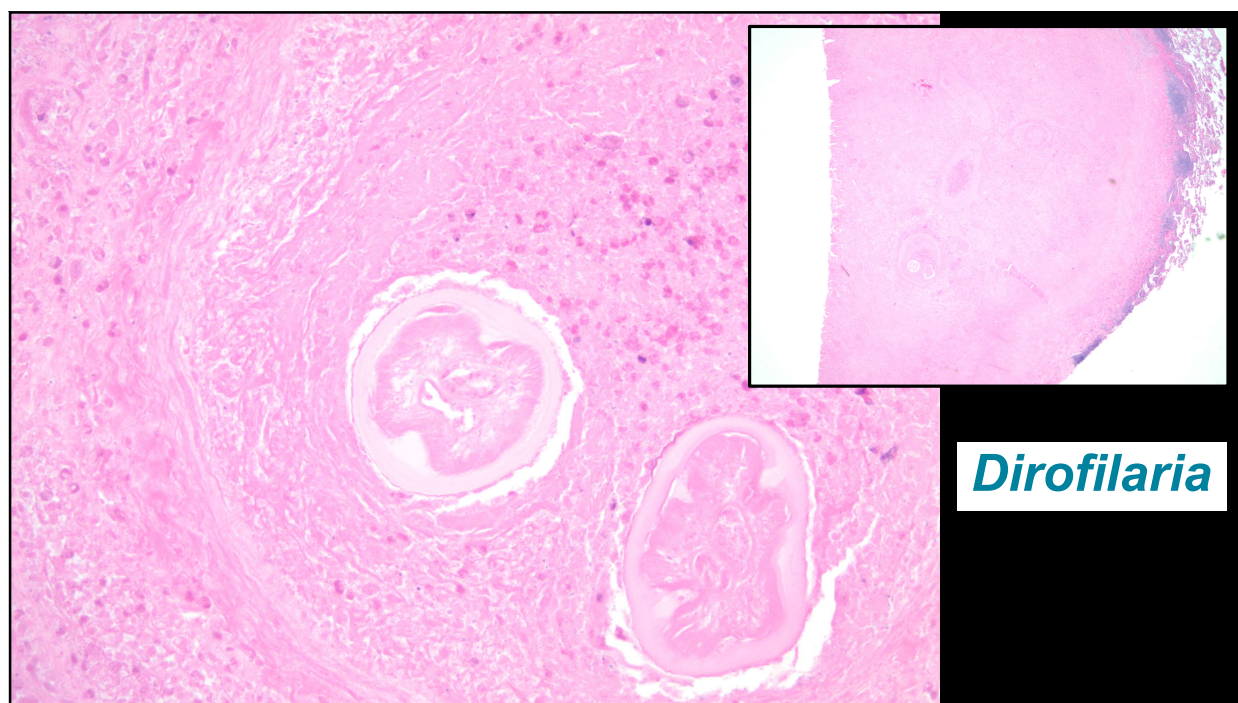
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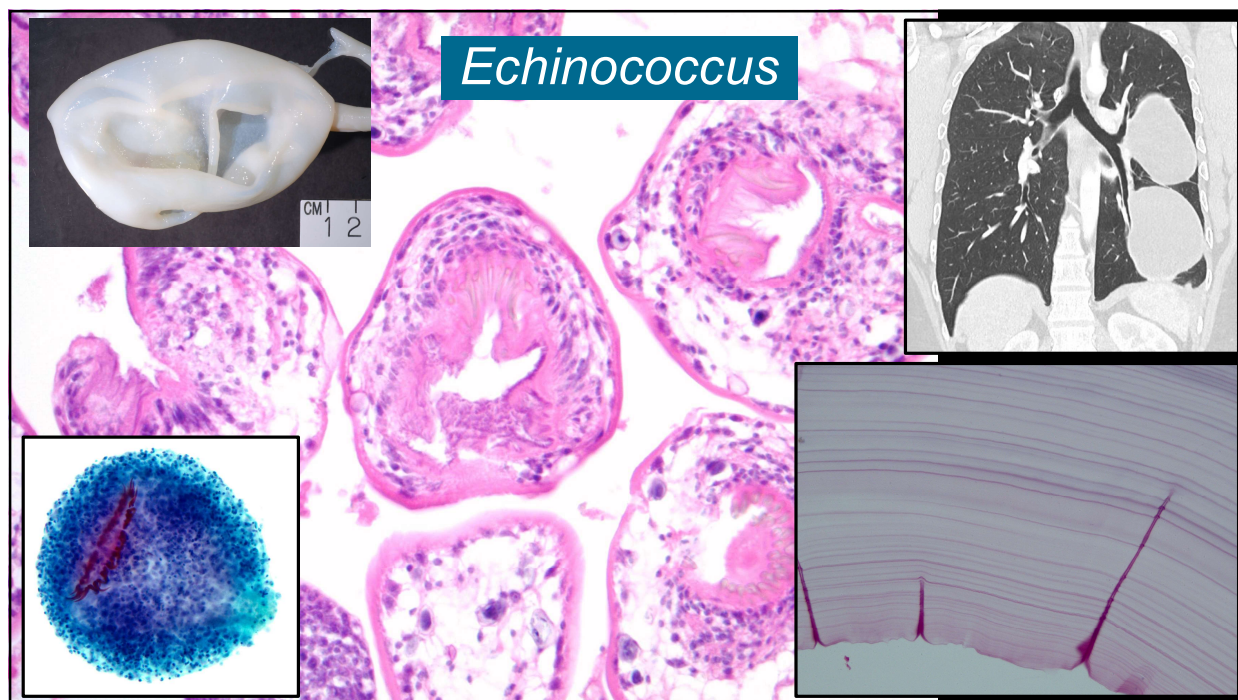
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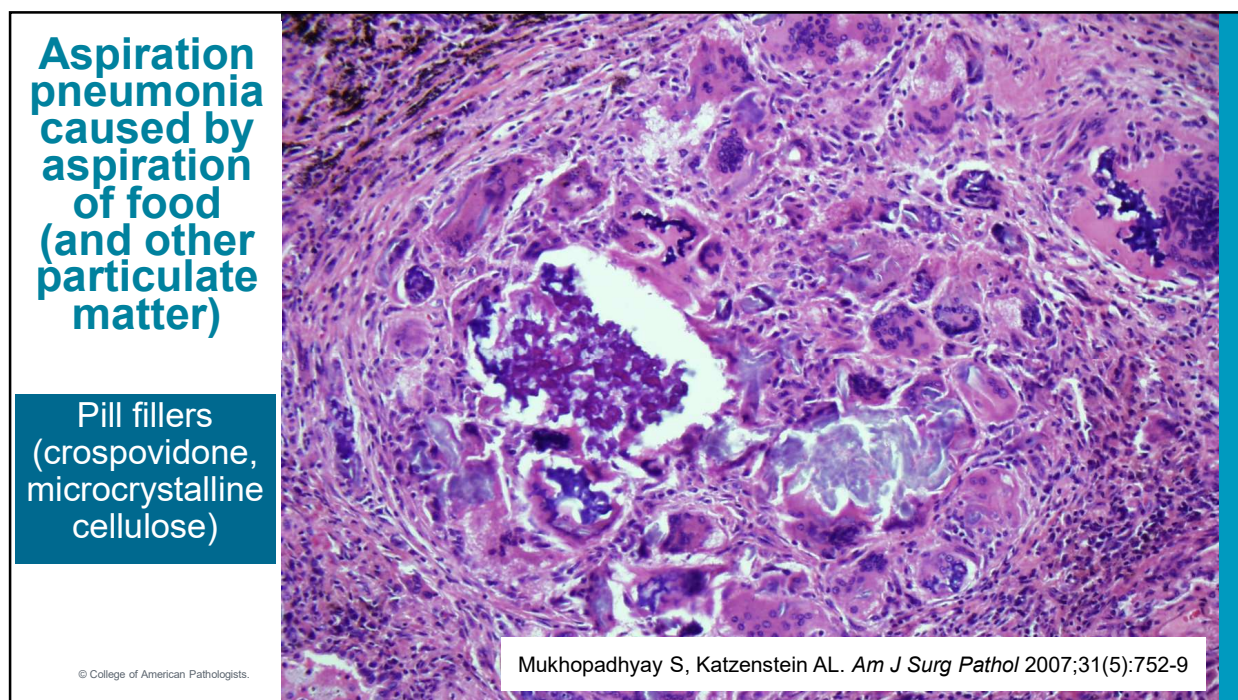
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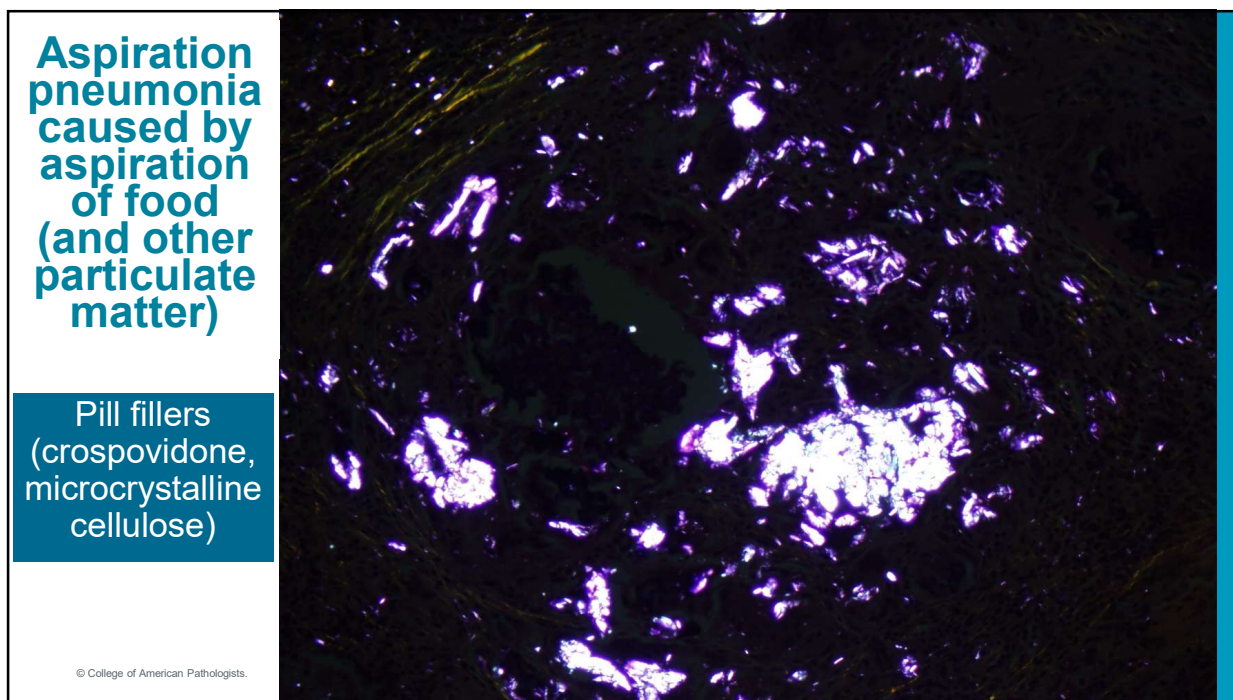
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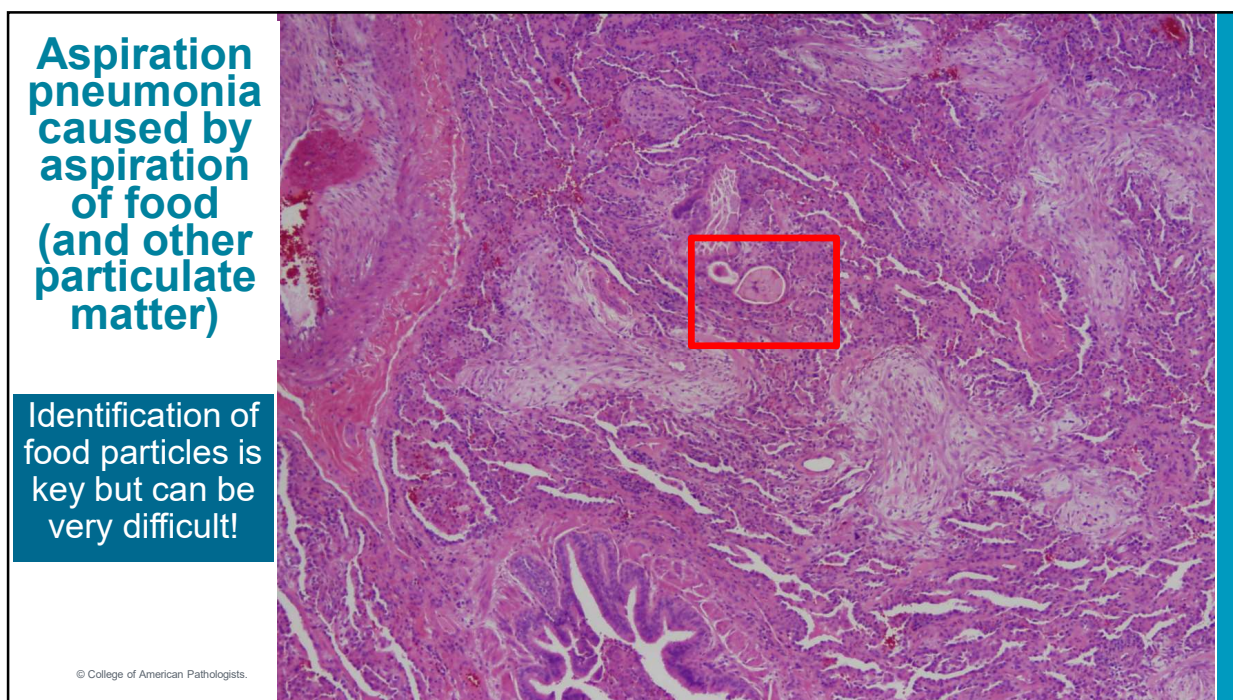
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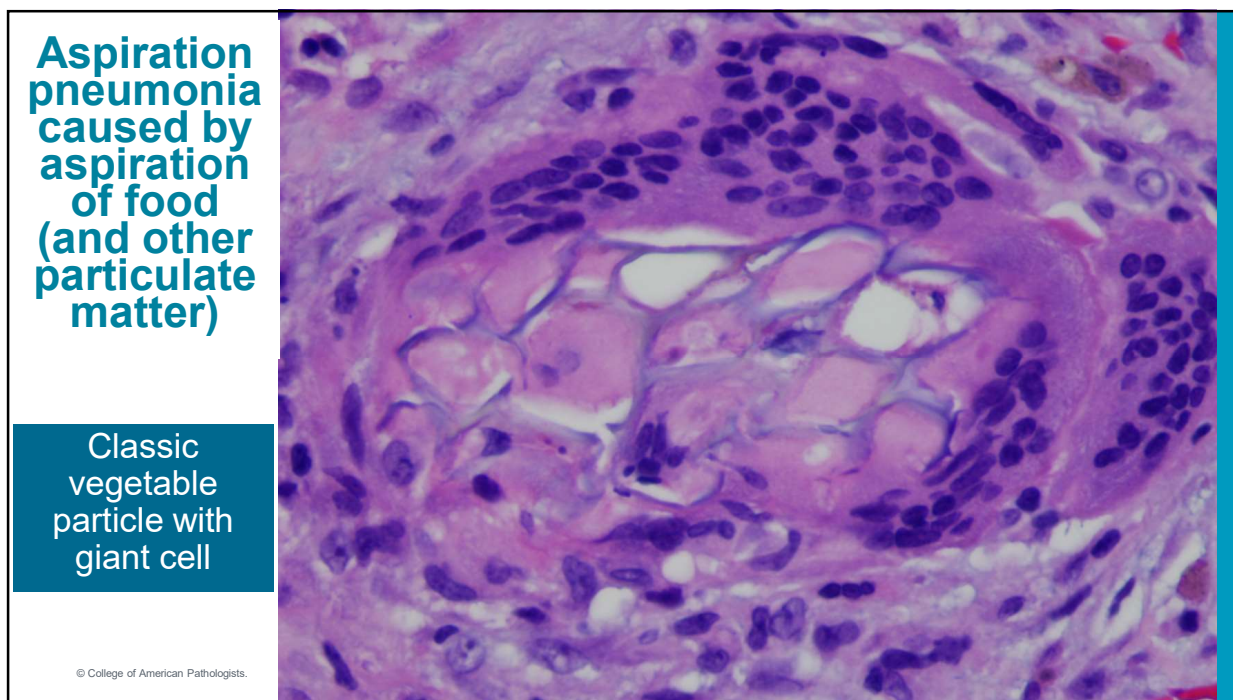
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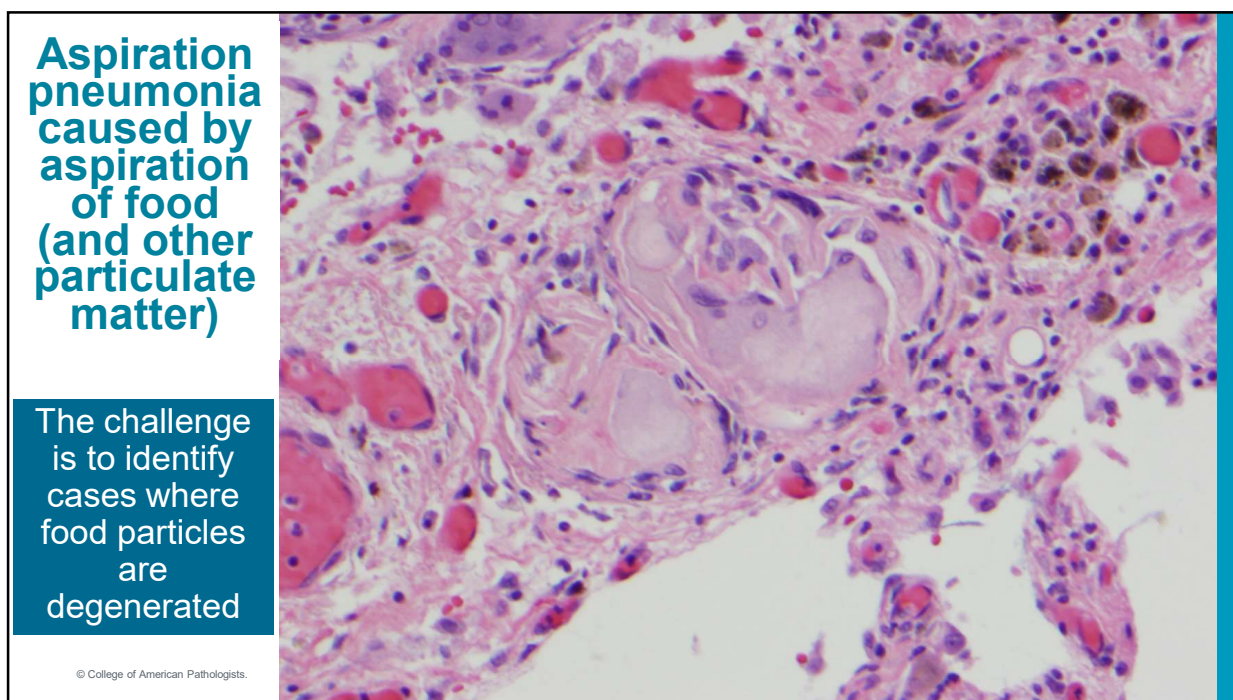
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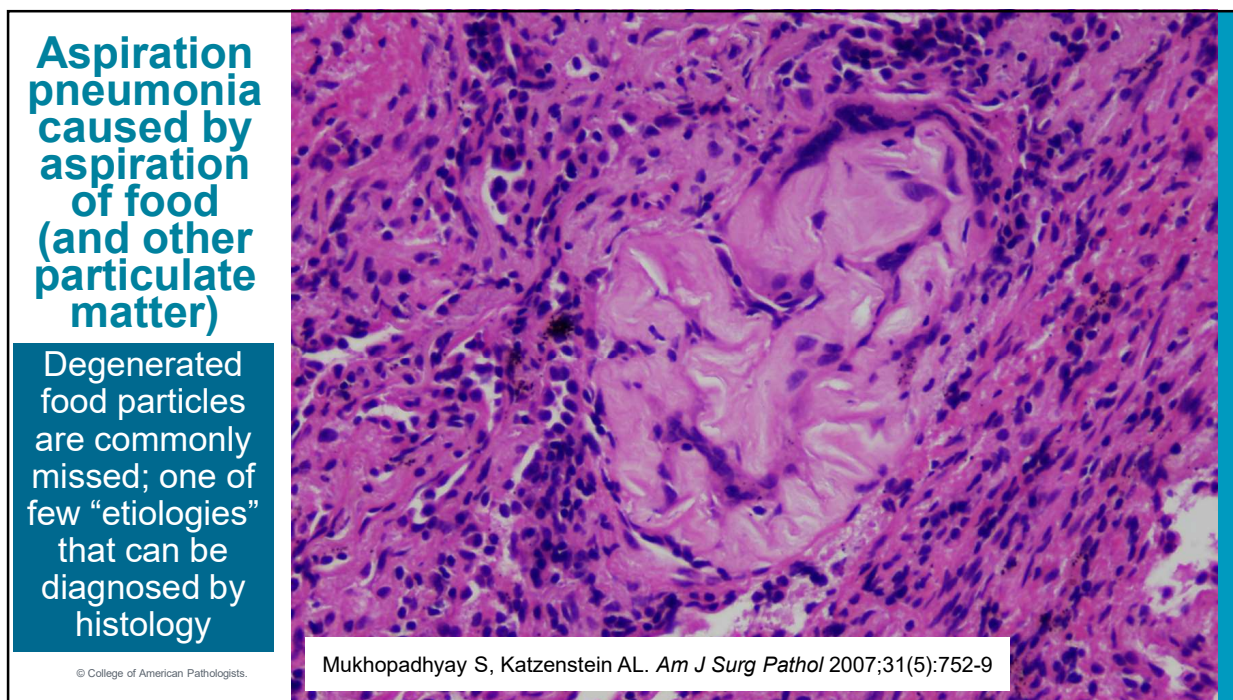
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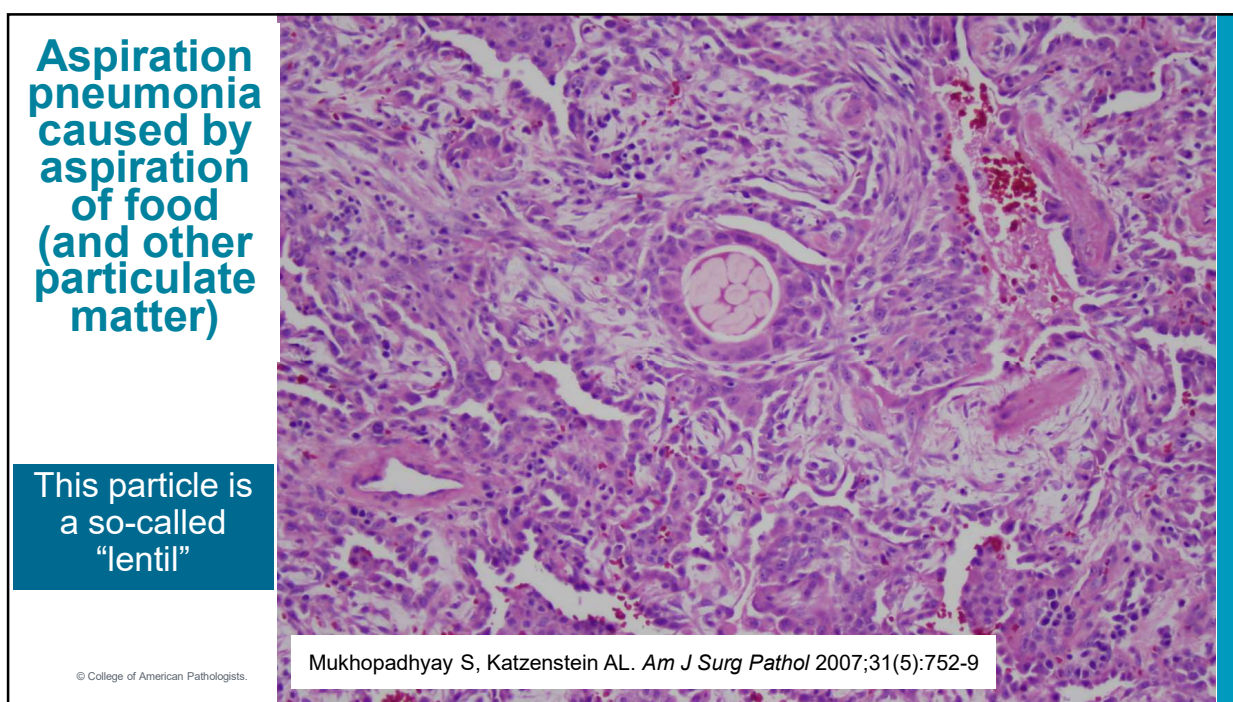
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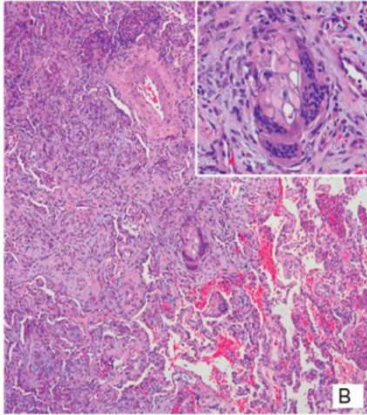
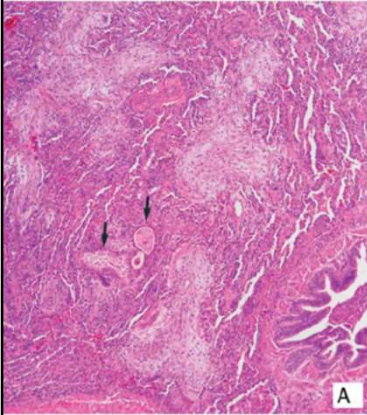
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78

Pulmonary Disease due to Aspiration of Food and Other Particulate Matter: A Clinicopathologic Study of 59 Cases Diagnosed on Biopsy or Resection Specimens

Sanjay Mukhopadhyay, MD and Anna-Luise A. Katzenstein, MD



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TABLE 1. Clinical Features of 59 Patients With Food/Particle Aspiration Pneumonia

Mean age: 57 (range, 26-85)
M/F ratio: 40/19 (2/1)

Presenting complaints (information known for 36)

Dyspnea	14/36 (39%)
Fever	9/36 (25%)
Recurrent pneumonia	9/36 (25%)
Cough	6/36 (17%)
Hemoptysis	4/36 (11%)
Chest pain	3/36 (8%)
Asymptomatic	2/36 (6%)

Radiographic findings (information known for 34)

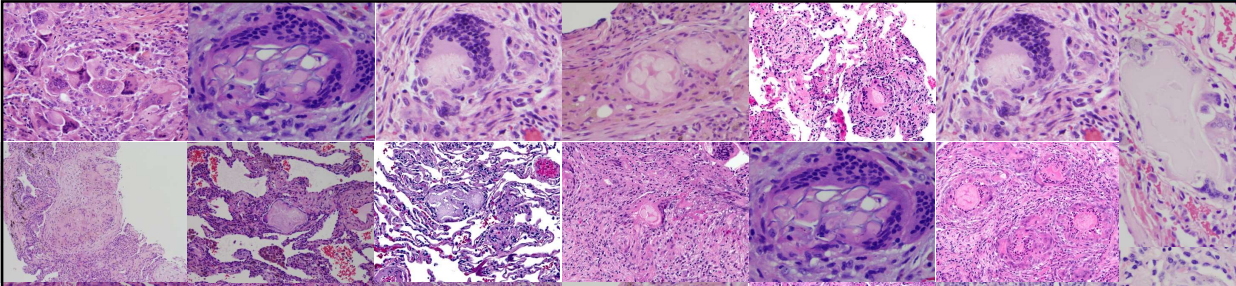
Unilateral	17/34 (50%)
Right/left	15/2
Solitary/multiple	13/4
Nodules/infiltrates	14/3
Bilateral	17/34 (50%)
Nodules/infiltrates/both	4/12/1

Predisposing causes for aspiration (information known for 32*)

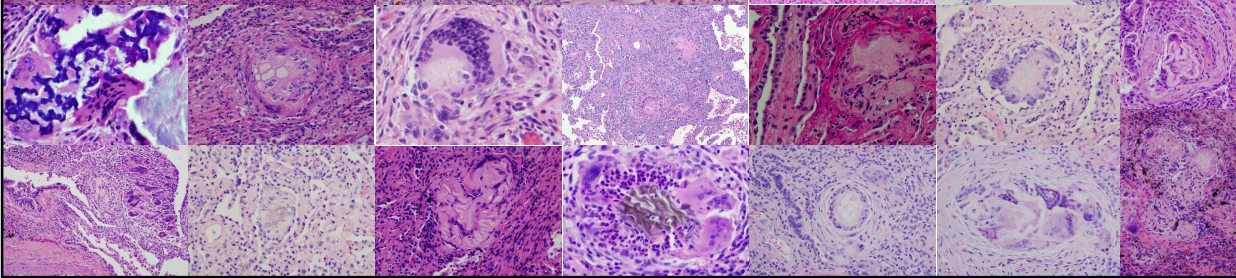
Esophageal	11
Drug use	10
Gastric	8
Neurologic	6

*Total adds up to 35 because 3 cases had more than 1 predisposing factor (see text).

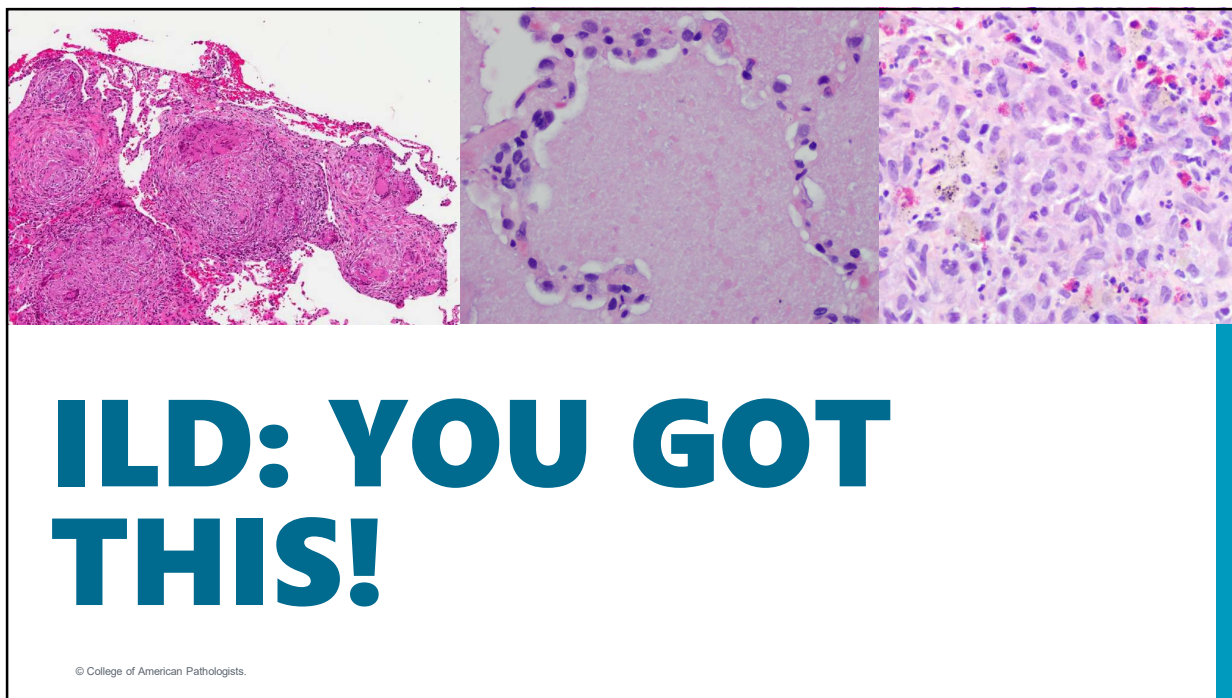
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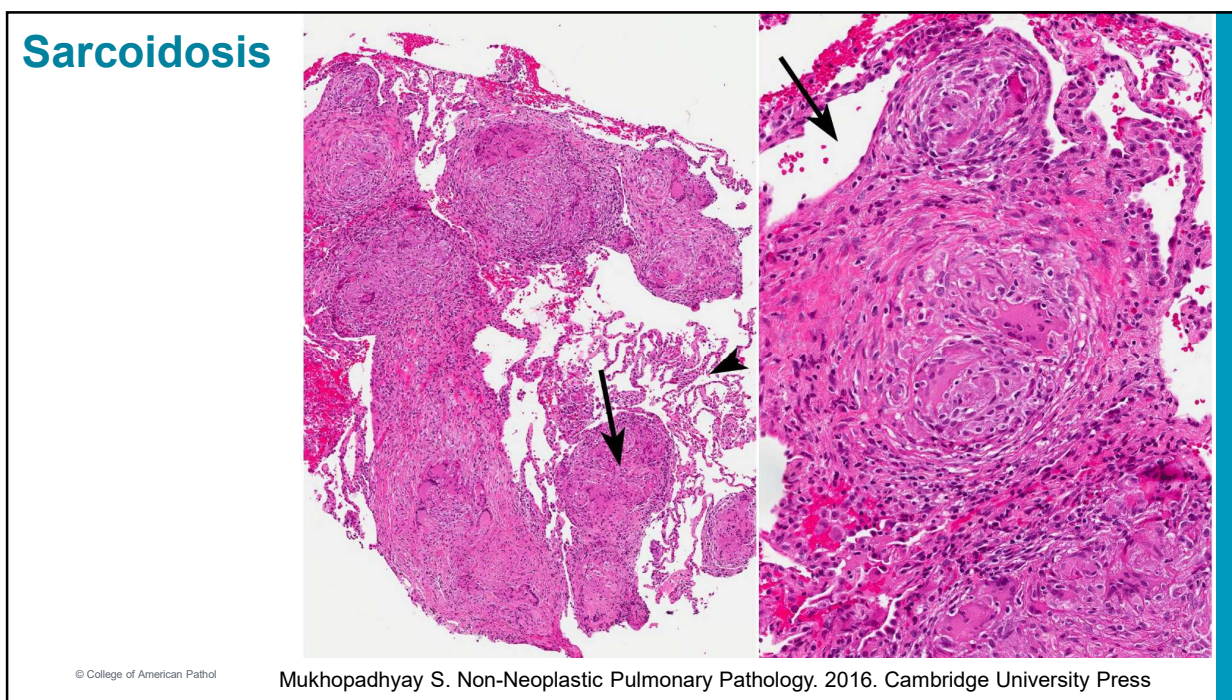
Particulate matter aspiration is one of the few definitive non-neoplastic diagnoses you can make in a lung biopsy



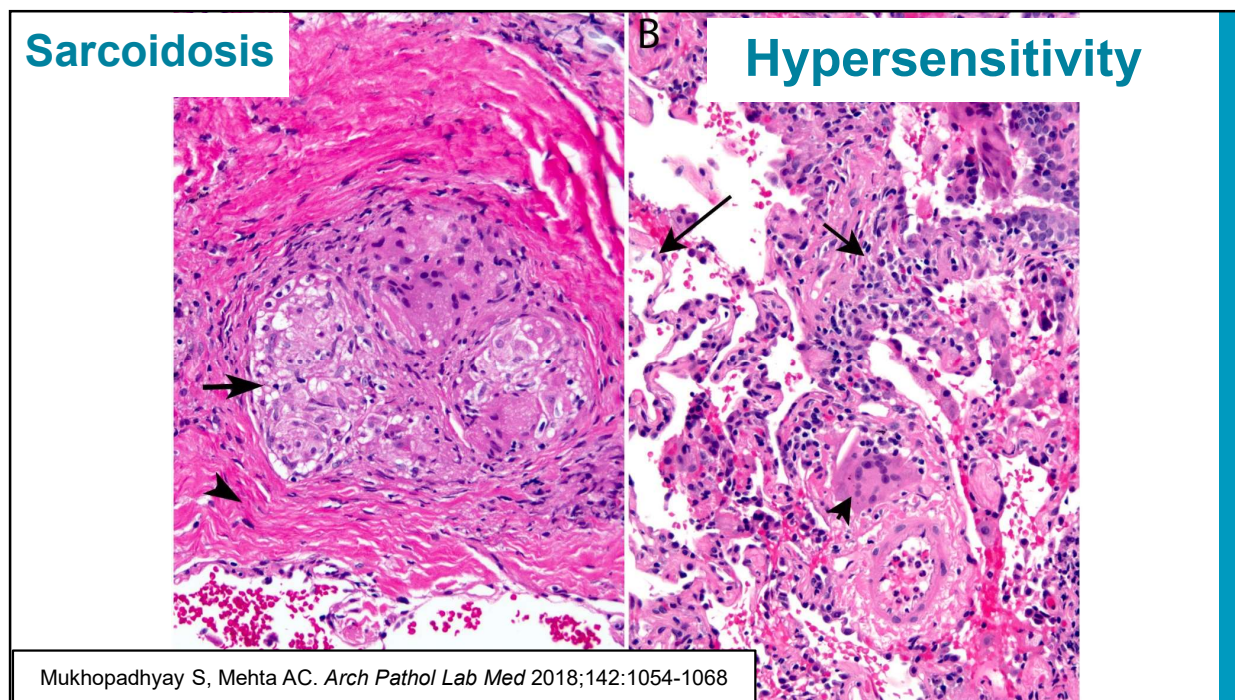
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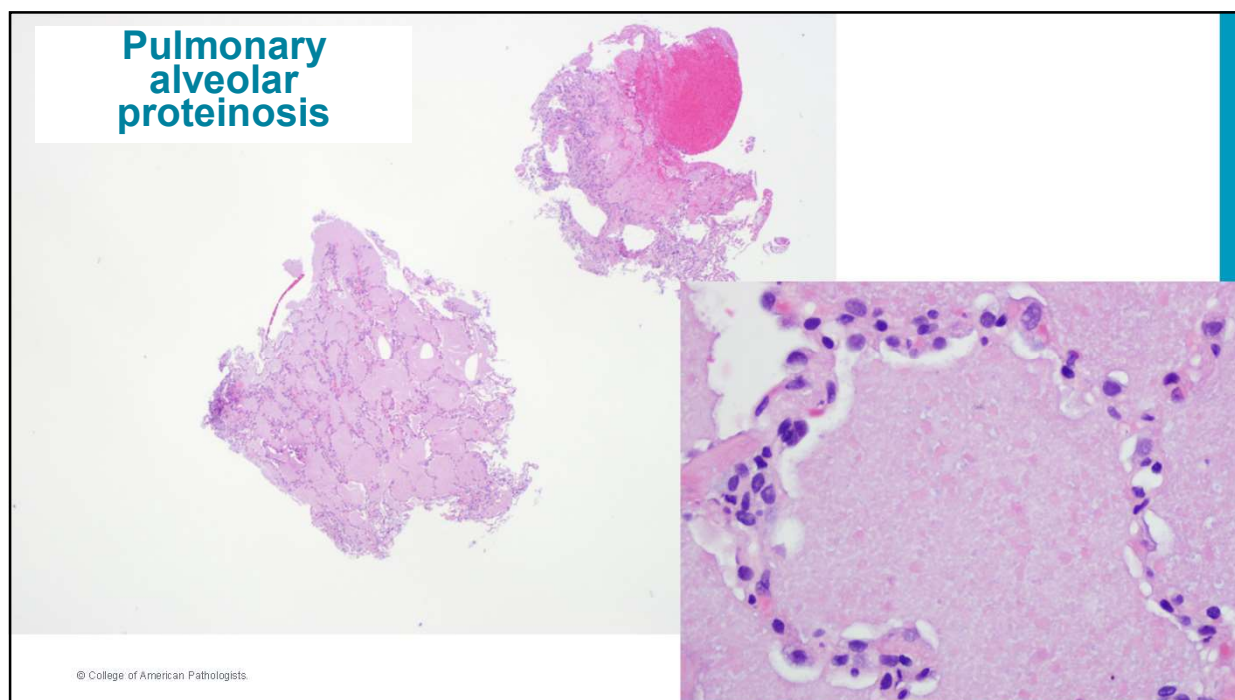
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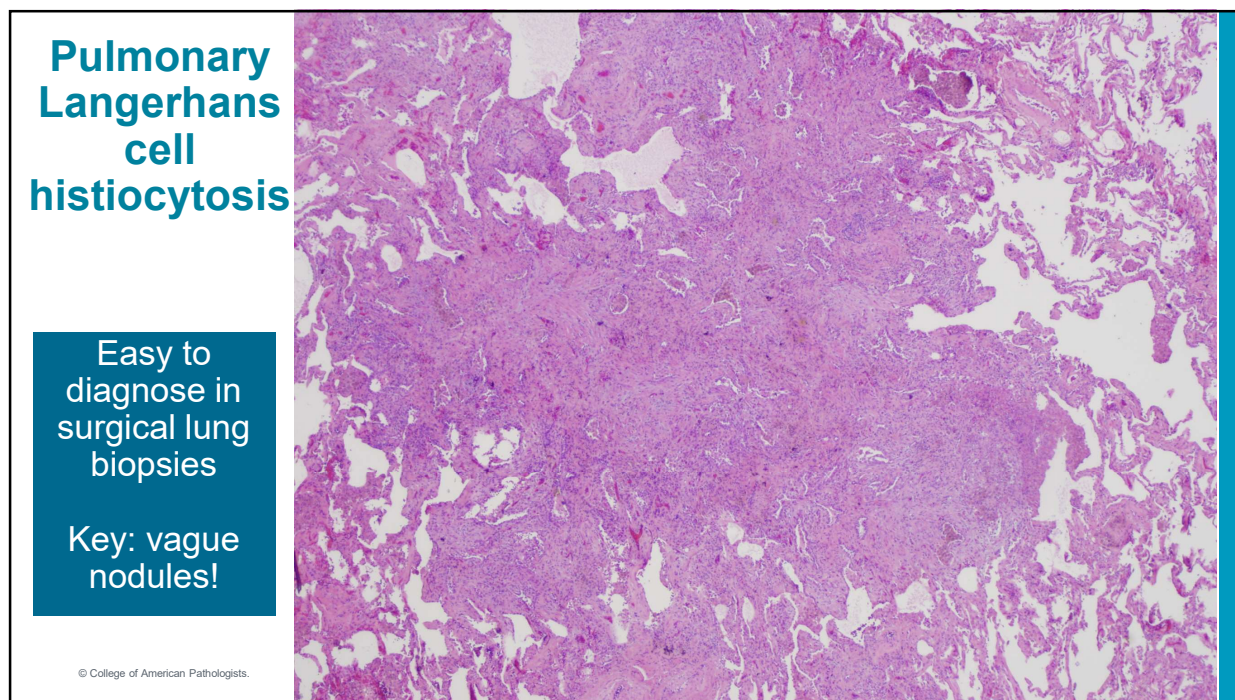
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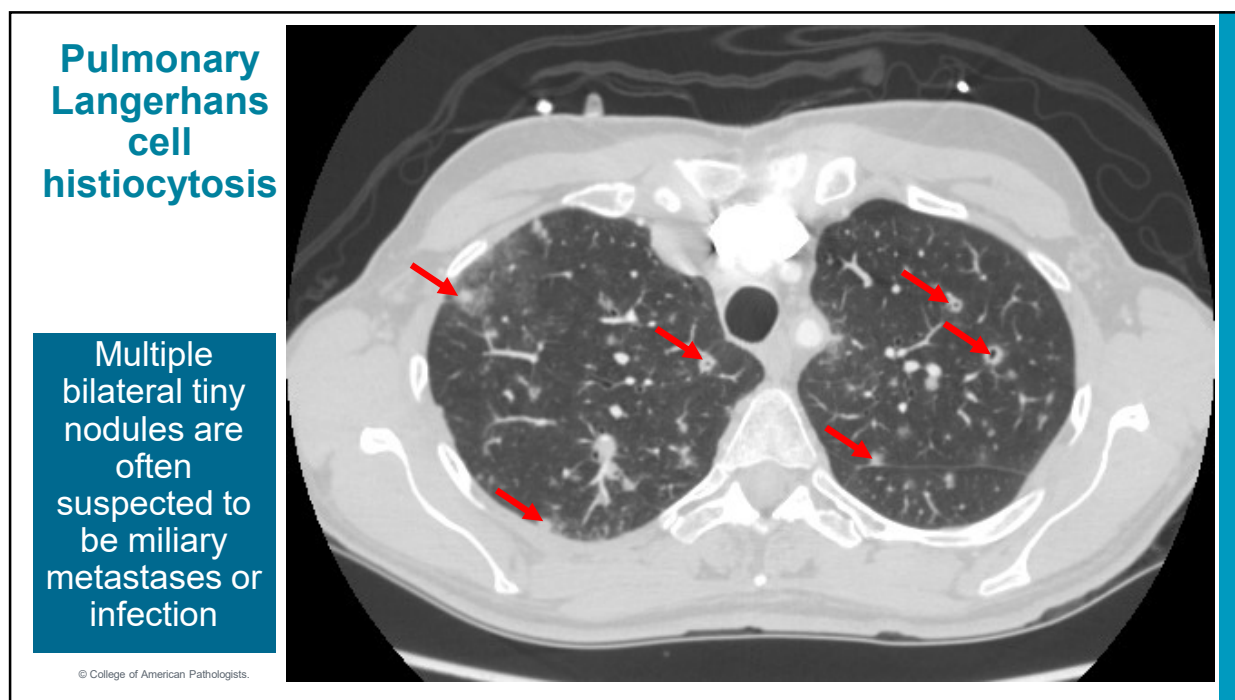
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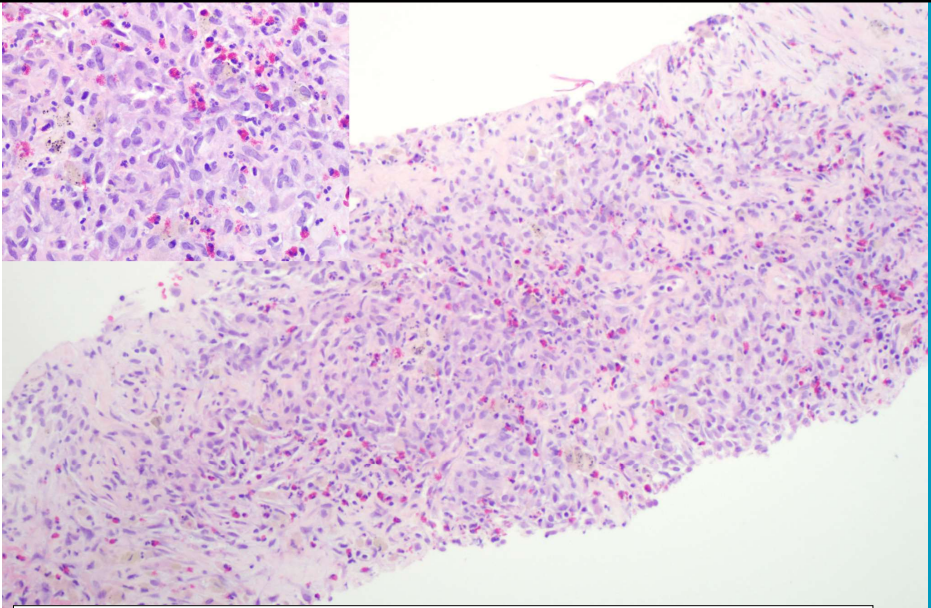


86

**Pulmonary
Langerhans
cell
histiocytosis**

**Diagnosis by
CT-guided
core needle
biopsy is
possible!**

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63/F - h/o SLE, RA, multiple nodules, all <1 cm, some cavitary

87

Diagnosis of pulmonary Langerhans cell histiocytosis by CT-guided core biopsy of lung: a report of three cases

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ABSTRACT
A pathological diagnosis of pulmonary Langerhans cell histiocytosis (PLCH) usually requires a surgical lung biopsy. To date, diagnosis of PLCH by core needle biopsy has not been reported. Three cases are presented of PLCH diagnosed by CT-guided core biopsy in adult female smokers found to have multiple small bilateral lung nodules. The nodules biopsied were 5 mm, 7 mm and 1 cm in size, and showed interstitial expansion by Langerhans cells and eosinophils. CT-guided core biopsy should be considered as one of the less invasive techniques by which a pathological diagnosis of PLCH can be established.

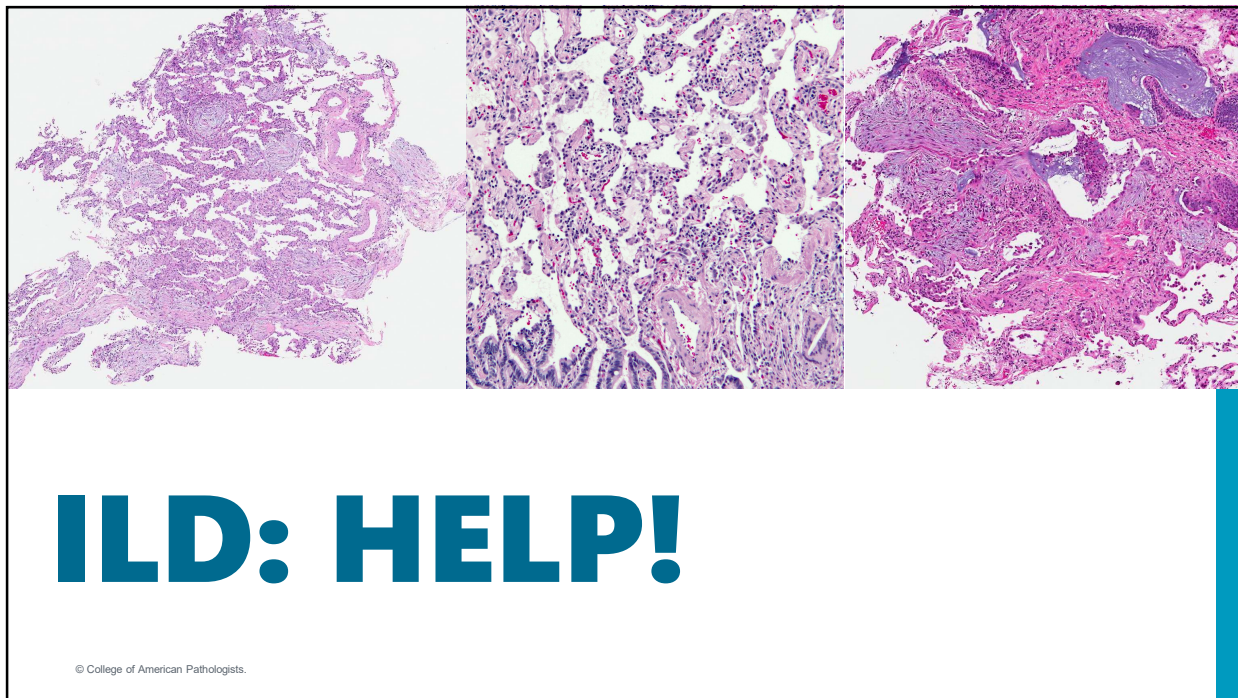
CASE 1
A 68-year-old female 30 pack-year active smoker

noted (figure 3). Pulmonary function tests demonstrated moderate obstruction. The FEV₁/FVC (forced expiratory volume in 1 s/forced vital capacity) ratio was 0.58 and the DL_{CO} (diffusing capacity for carbon monoxide) was 49% of predicted. A metastatic malignancy was suspected. A bone scan performed to evaluate for metastases was negative. CT-guided biopsy of the 1 cm right upper lobe nodule was performed. Cultures were not obtained.

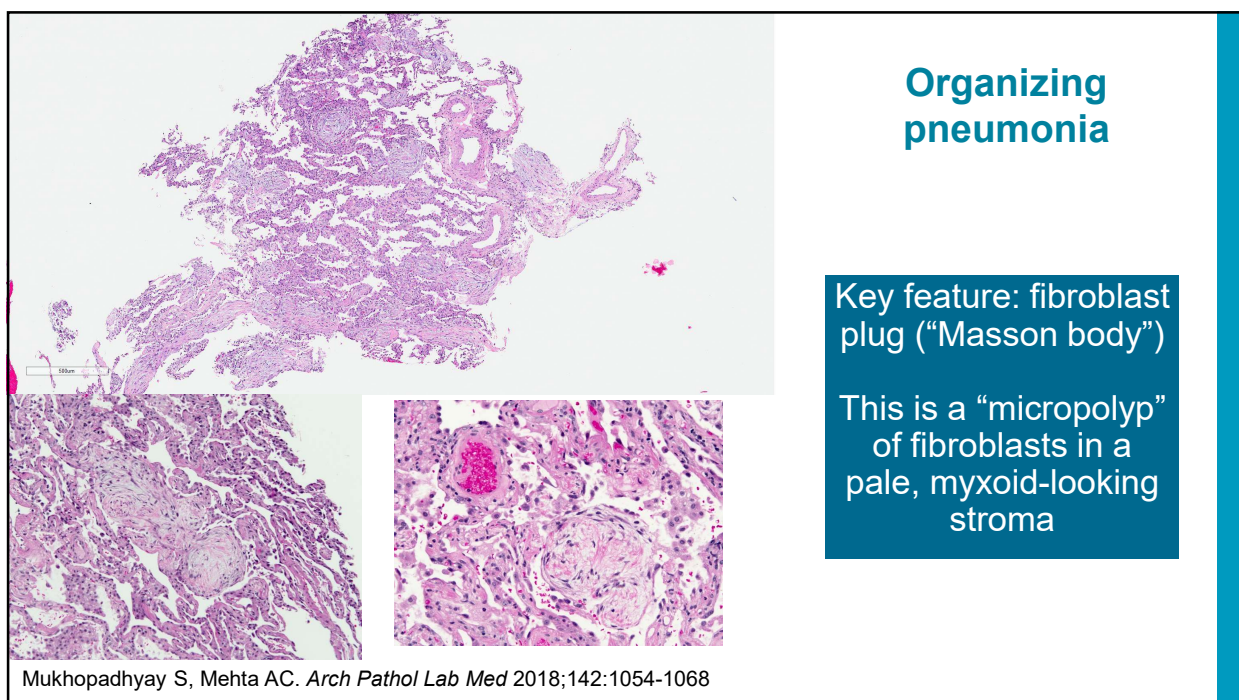
PATHOLOGICAL FINDINGS
Pathological findings were similar in all three cases, showing expansion of fibrotic pulmonary interstitium by Langerhans cells along with pigment-laden histiocytes and scattered eosinophils (figure 1–3). Focal necrosis was additionally

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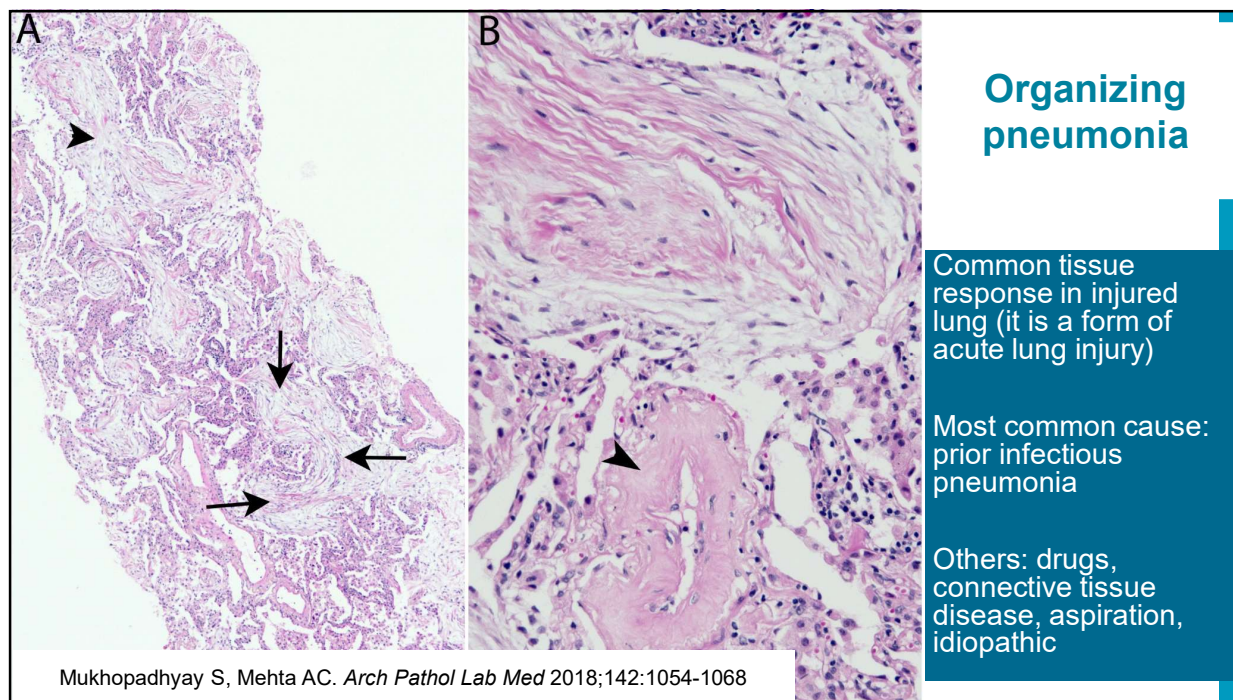
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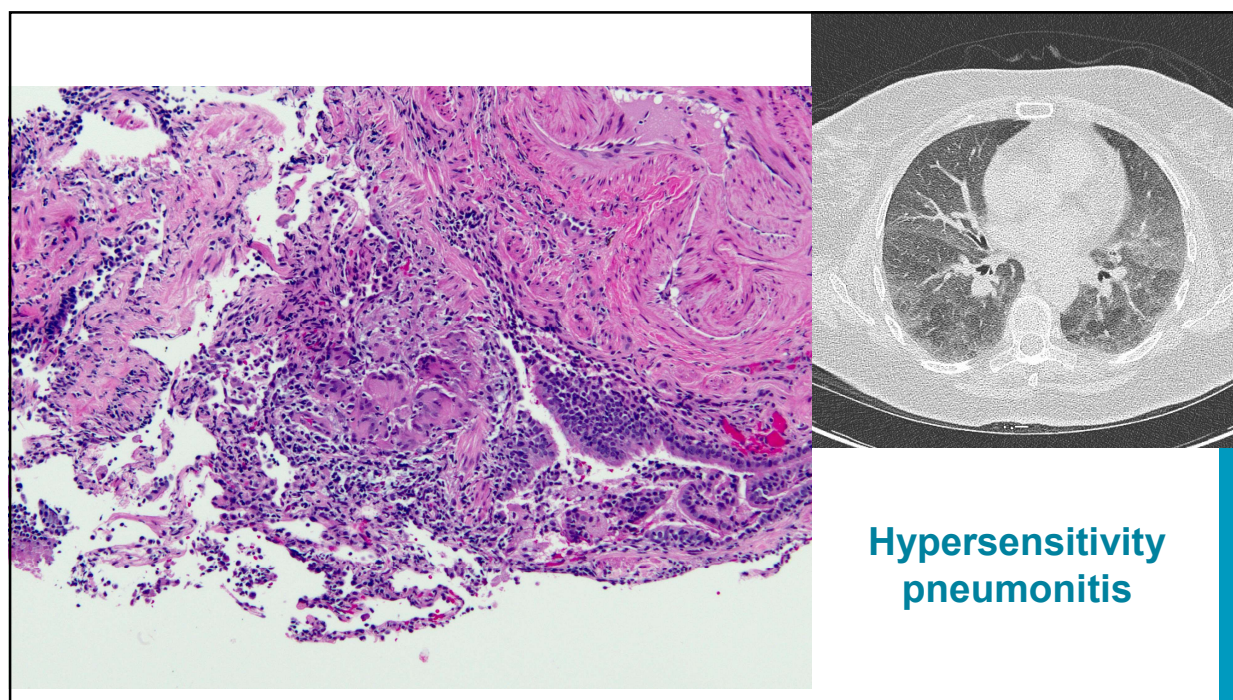
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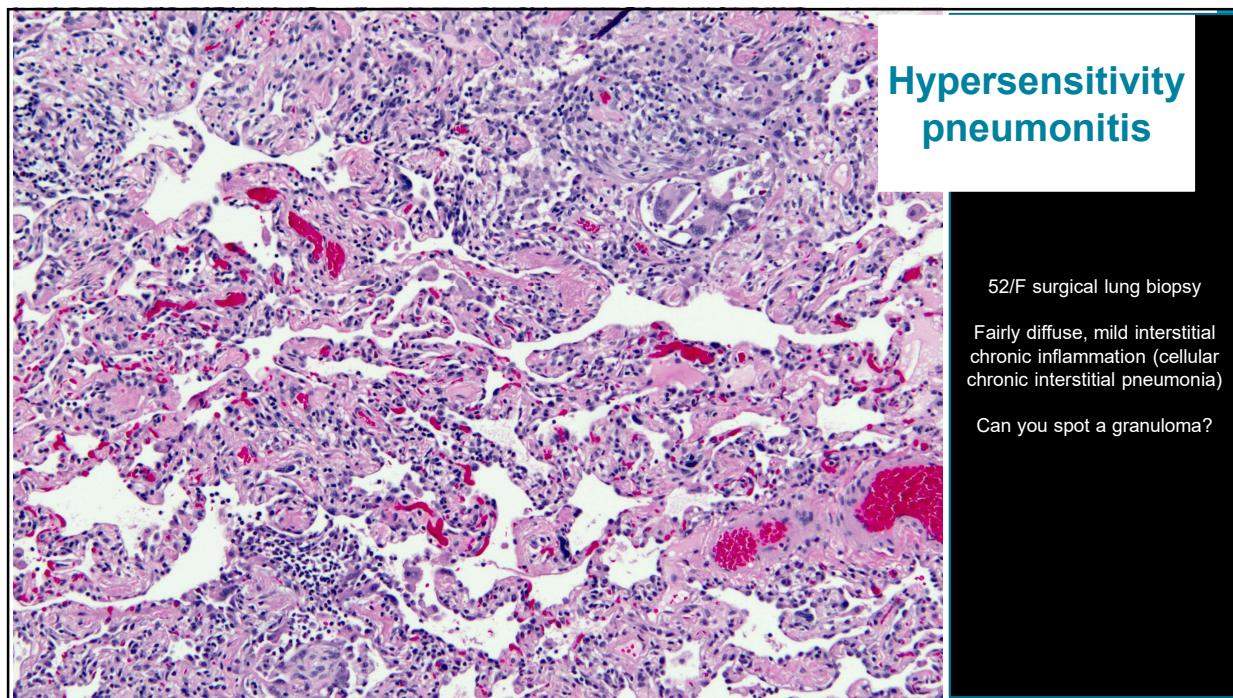
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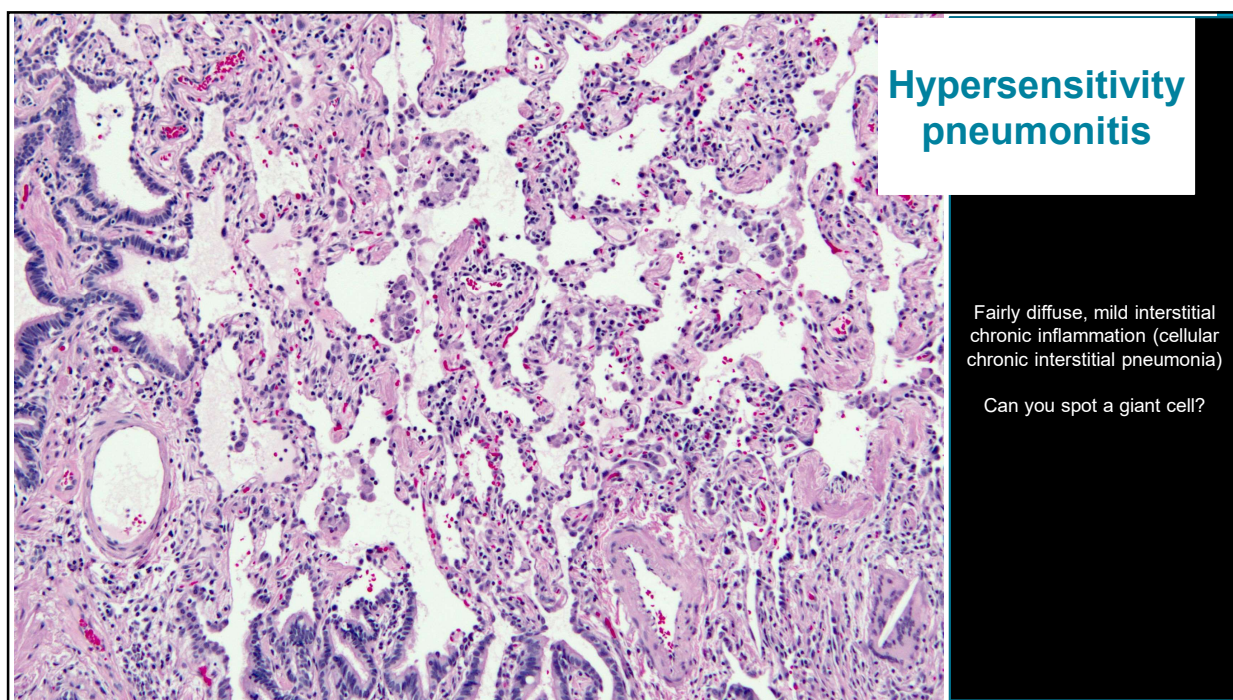
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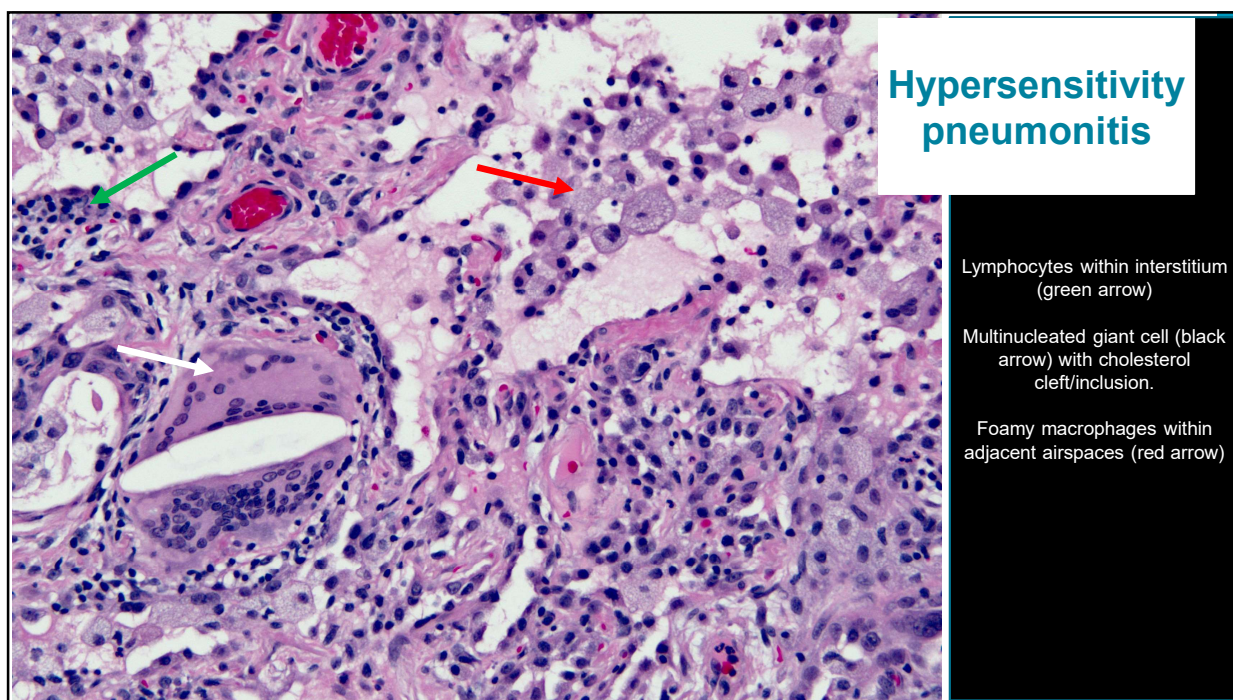
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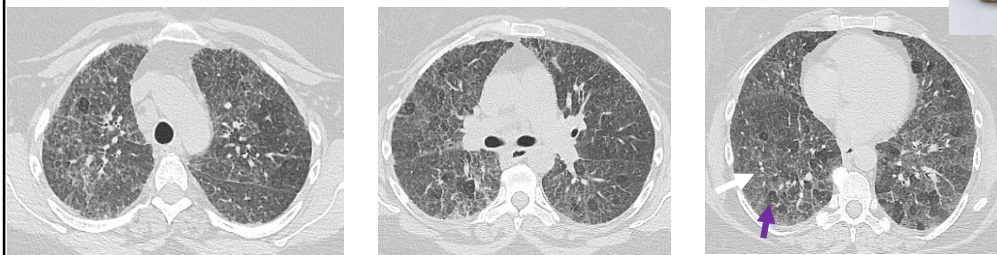


96

Hypersensitivity pneumonitis

Chest CT: axial inspiratory images





Upper, mid and lower lungs): Mosaic attenuation with areas of increased attenuation (ground glass opacity, white arrow) and decreased attenuation (air-trapping, purple arrow) = "head-cheese sign"

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Images courtesy of Rahul Renapurkar, MD, Cleveland Clinic

97

Human Pathology (2008) 39, 1275–1294

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Current topics

Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases

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Keywords:
Idiopathic interstitial pneumonia;
Usual interstitial pneumonia;
UIP;
Nonspecific interstitial pneumonia;
NSIP;
Hypersensitivity pneumonia;
Interstitial fibrosis

Summary Usual interstitial pneumonia is an almost uniformly fatal form of fibrosing interstitial lung disease. It is the most common idiopathic interstitial pneumonia, and currently, there is no effective therapy. Lung biopsy is often needed for diagnosis, and pathologists must be able to recognize its features and distinguish it from other interstitial lung diseases that have a better prognosis and a more favorable response to therapy. This review is an attempt to clarify the diagnostic pathologic features of usual interstitial pneumonia and to provide guidelines for its distinction from other interstitial lung diseases that enter the differential diagnosis.
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Usual interstitial pneumonia (UIP)

REVIEW ARTICLE

Controversies in Pathology

Usual interstitial pneumonia (UIP): a clinically significant pathologic diagnosis

Sanjay Mukhopadhyay^{1,2*}

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This editorial focuses on common issues that surround the diagnosis of usual interstitial pneumonia (UIP), a clinically significant pathologic diagnosis. Most of these issues stem from conflation of the pathologically defined entity UIP with the clinically defined entity IPF. A pathologic or radiologic diagnosis of UIP is required for the clinical/multidisciplinary diagnosis of idiopathic pulmonary fibrosis (IPF) but it has also been described in several other clinical settings. I offer my viewpoint on 5 important questions. 1. Is UIP a diagnosis or a "pattern"? Answer: UIP is a pathologic diagnosis and is better conceptualized as a "pattern" than as a specific clinical entity. Since all cases of UIP require pattern recognition, adding the word "pattern" to UIP is redundant. 2. Is pathology the gold standard for UIP? Answer: Yes. 3. How do you "prove" etiology of a given case of UIP? Answer: "Soft" histologic features can raise the possibility of certain etiologies but the final determination of etiology comes from the multidisciplinary team. With few exceptions, there are no findings pathognomonic for any etiology in UIP. 4. Does UIP imply IPF? Answer: No. 5. What should we do when pathology and HRCT are discordant? Answer: This depends on the specifics of the discrepancy. When HRCT suggests a non-UIP diagnosis such as NSIP and histology shows UIP, histology has been shown to predict prognosis in multiple studies. In other settings, the radiologic impression based on HRCT is often proven to be incorrect by the histologic findings.

Modern Pathology; <https://doi.org/10.1038/s41379-022-01053-3>

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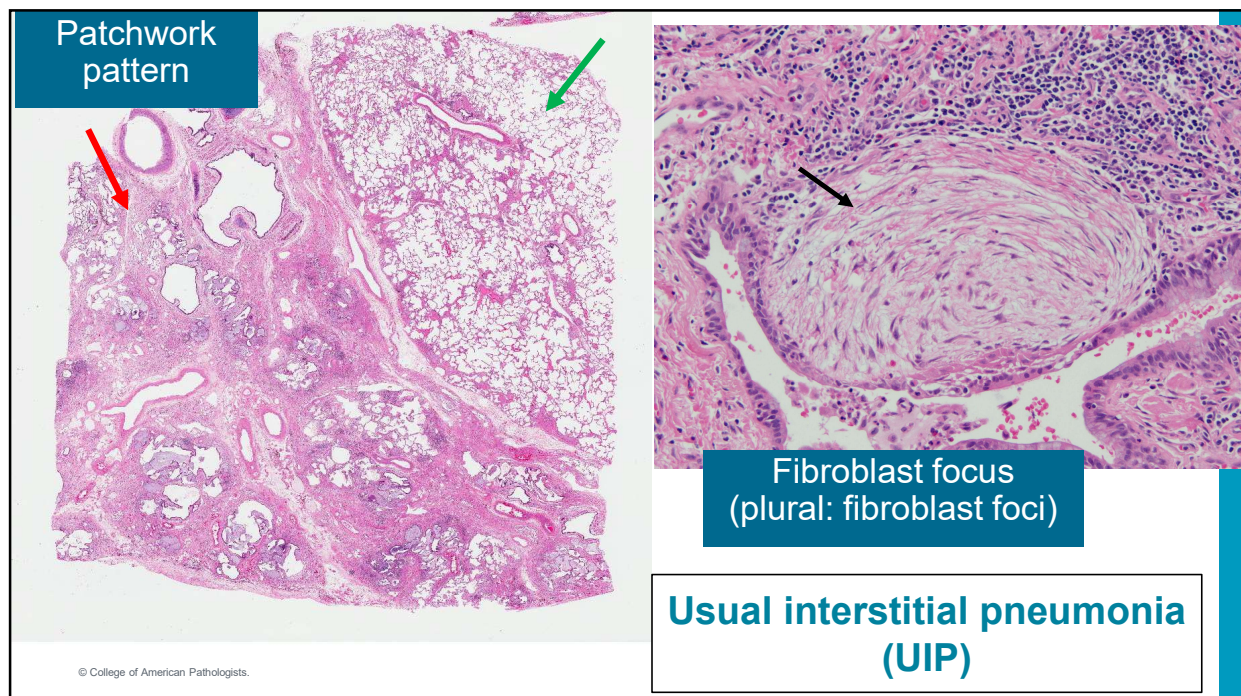
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Basics: Pathology of UIP

- Interstitial fibrosis with scarring and honeycomb change abruptly juxtaposed to normal lung (patchwork pattern)
- Old fibrosis (collagen) + ongoing fibrosis (fibroblast foci)

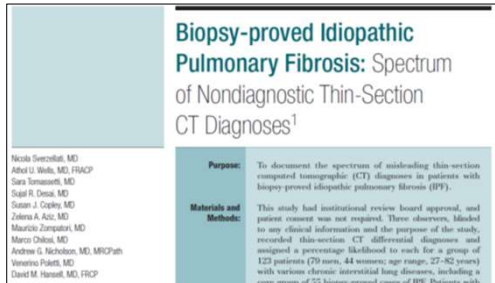
Mukhopadhyay S. *Mod Pathol* 2022;35(5):580-588

99



100

The problem with UIP diagnosis is that imaging is often interpreted as “not UIP”



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UIP Diagnosed at Surgical Lung Biopsy, 2000–2009: HRCT Patterns and Proposed Classification System

James F. Gruden¹
Prasad M. Panse¹
Kevin O. Leslie²
Henry D. Tazelaar²
Thomas V. Colby²

OBJECTIVE. High resolution CT (HRCT) is diagnostic of usual interstitial pneumonia (UIP) if honeycombing is present. However, biopsy-proven UIP also occurs in patients without honeycombing. Identification of specific HRCT patterns may enable specific diagnosis and allow more patients to enter clinical trials. Pattern may also predict prognosis. We sought to identify specific HRCT patterns in patients with biopsy-proven UIP (2000–2009) and to assess outcomes and serial change in pattern.

MATERIALS AND METHODS. We reviewed the HRCT findings in 44 patients with

Radiologic-pathologic discordance in biopsy-proven usual interstitial pneumonia

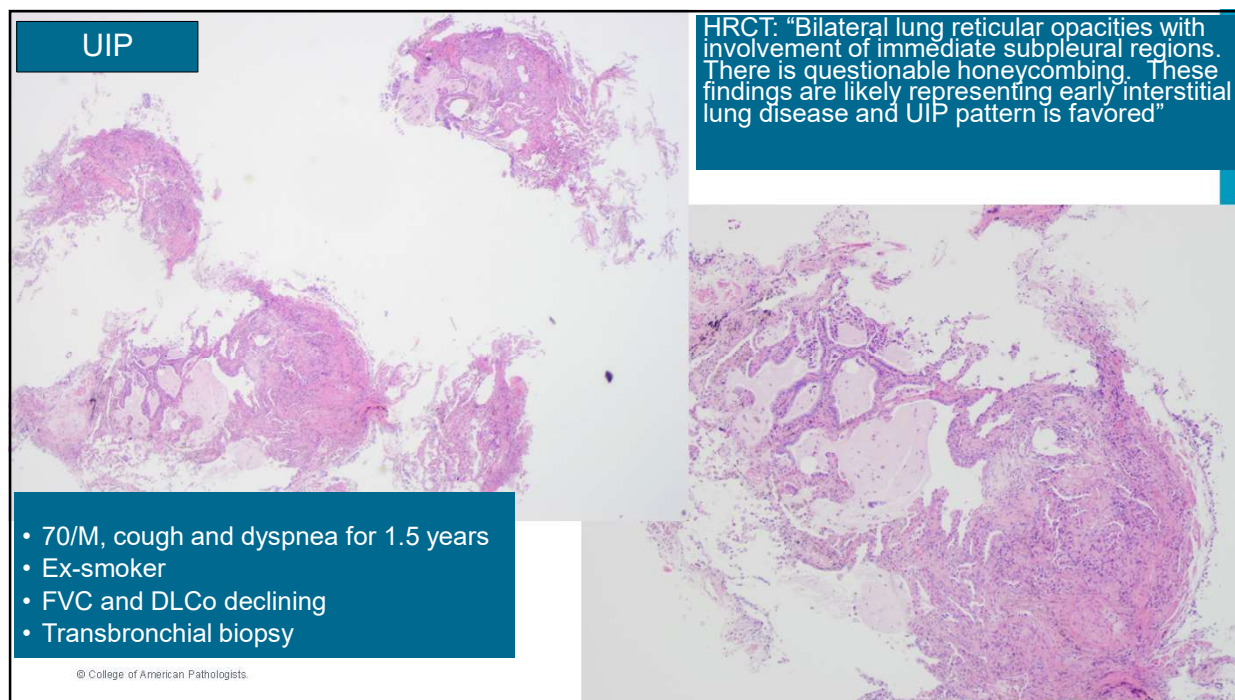
Kunihiro Yagihashi^{1,2,3}, Jason Huckleberry⁴, Thomas V. Colby⁵, Henry D. Tazelaar⁵, Jordan Zach², Baskaran Sundaram⁶, Sudhakar Pipavath⁷, Marvin I. Schwarz⁸ and David A. Lynch² for the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet)⁹

101

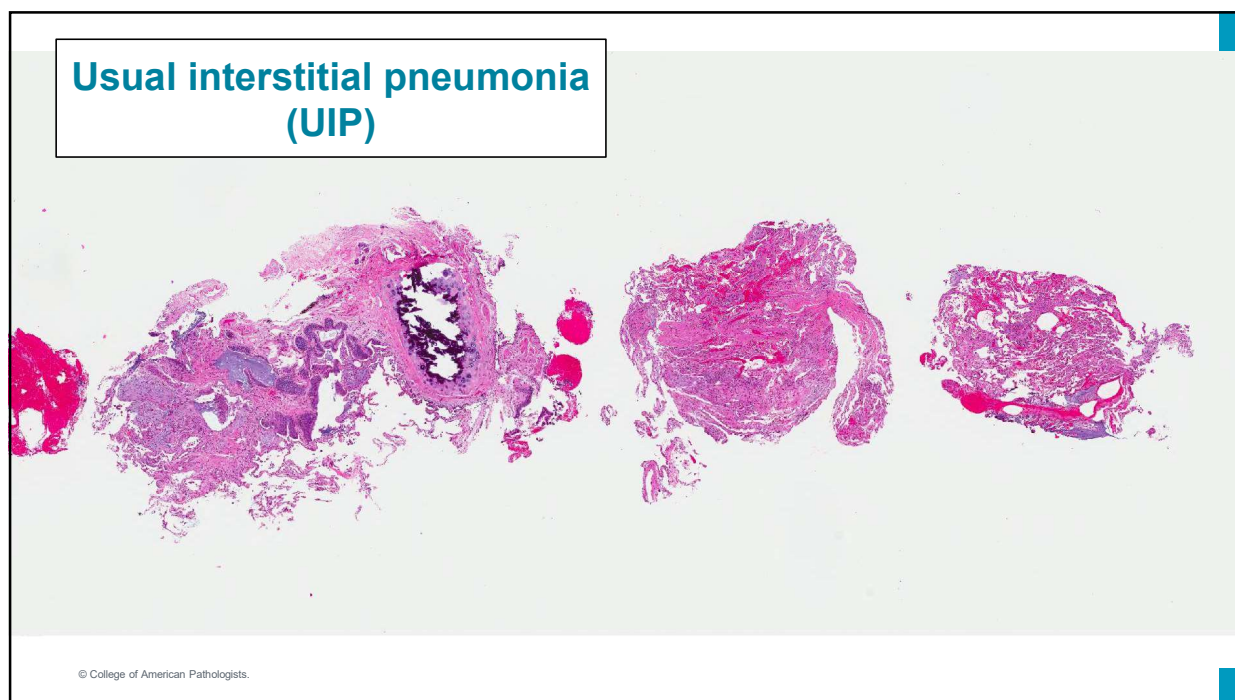


Sverzellati N, et al. *Radiology* 2010;254(3):957-964

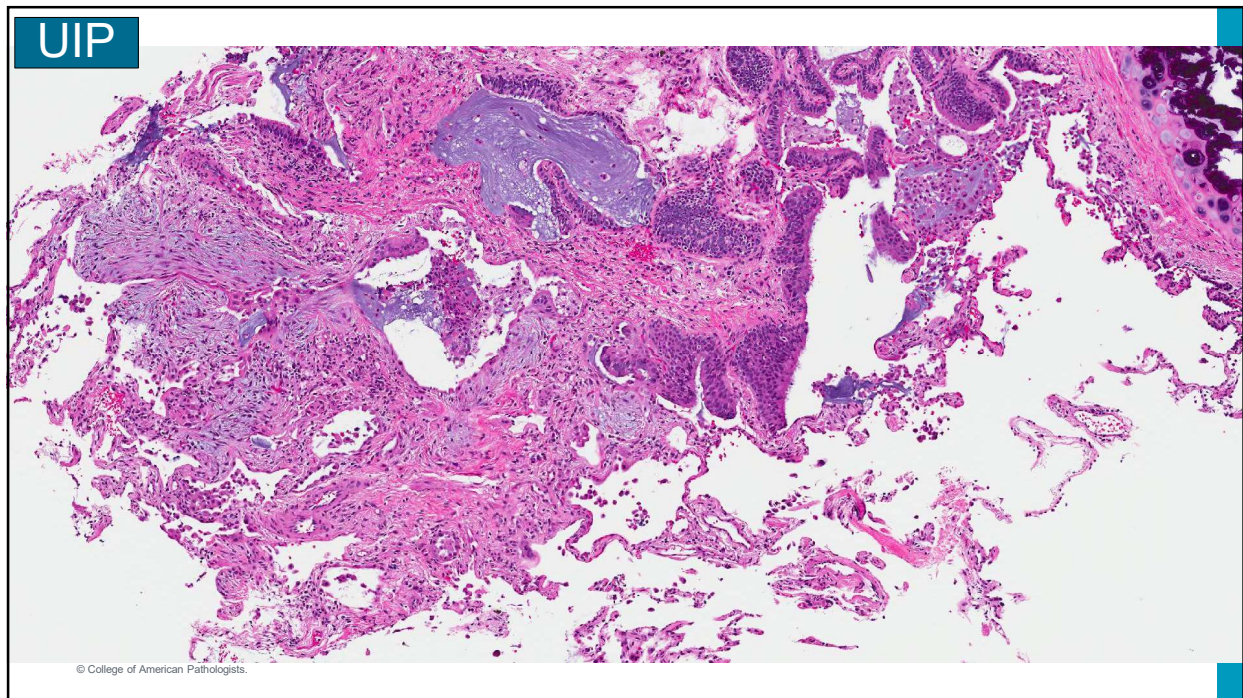
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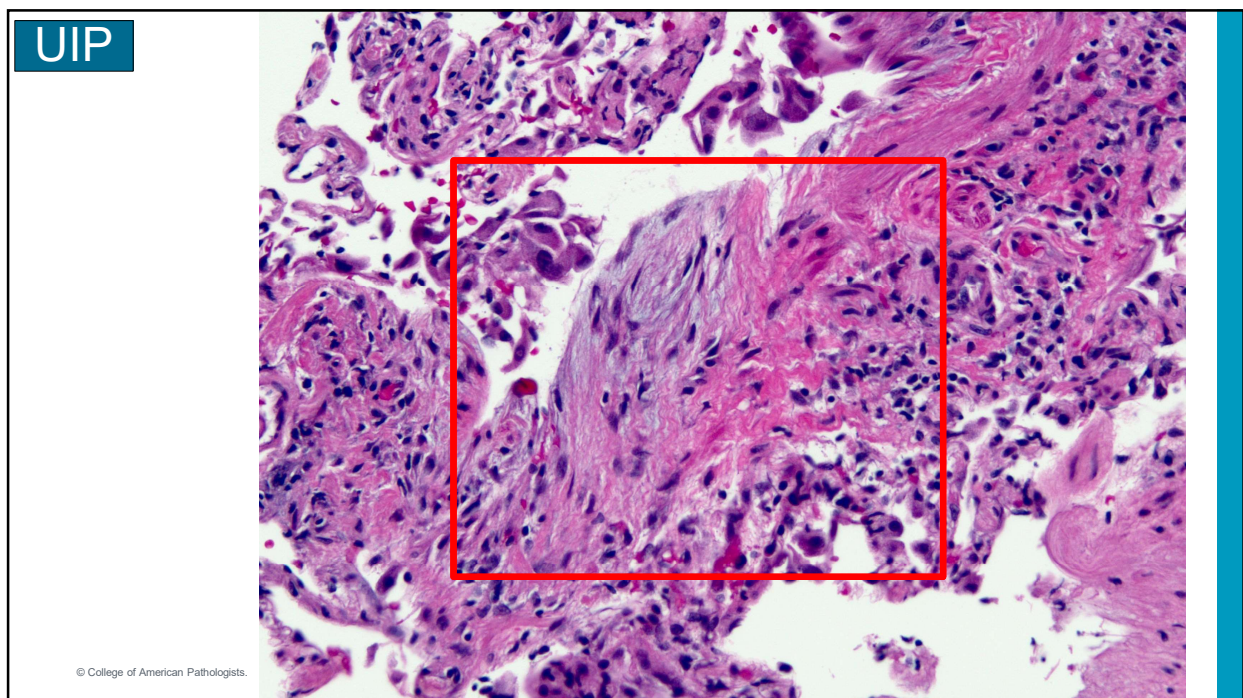
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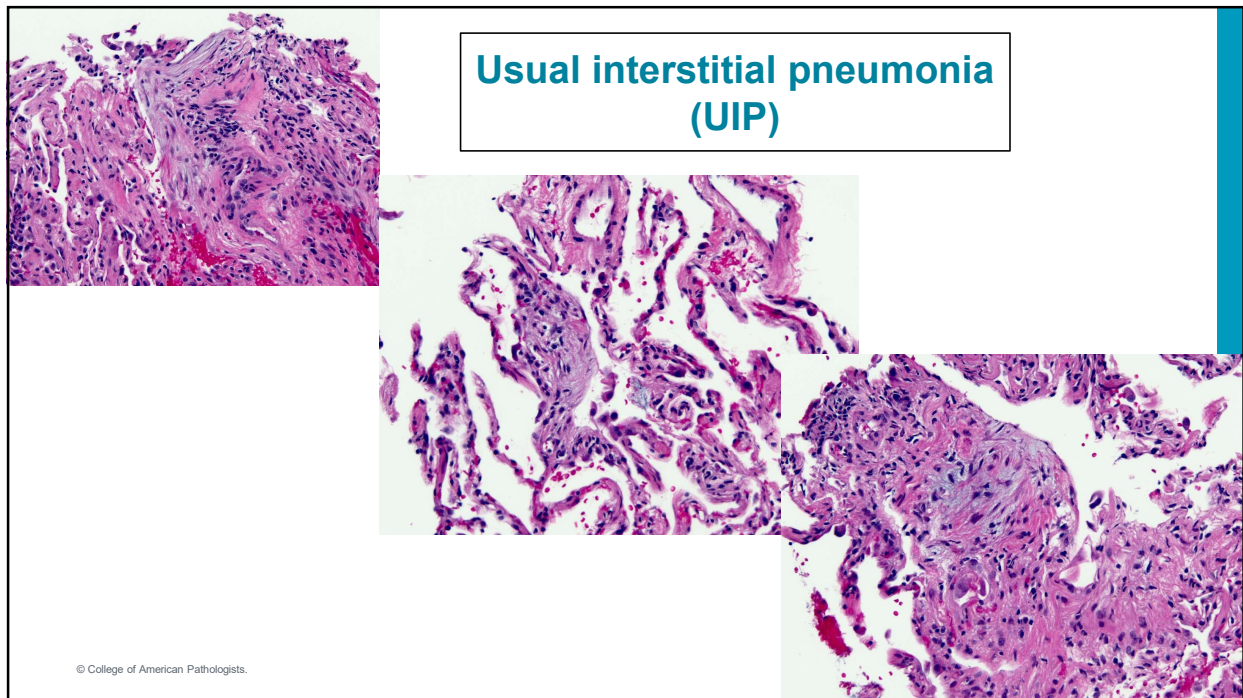
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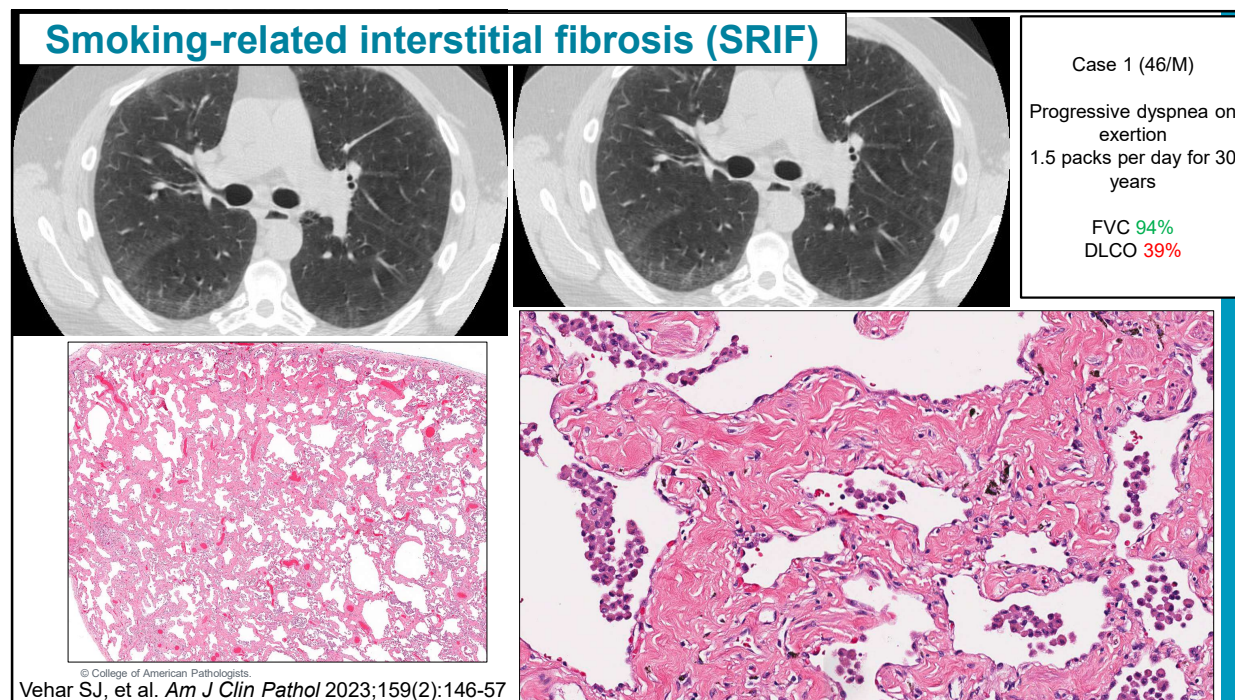
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Diagnosis

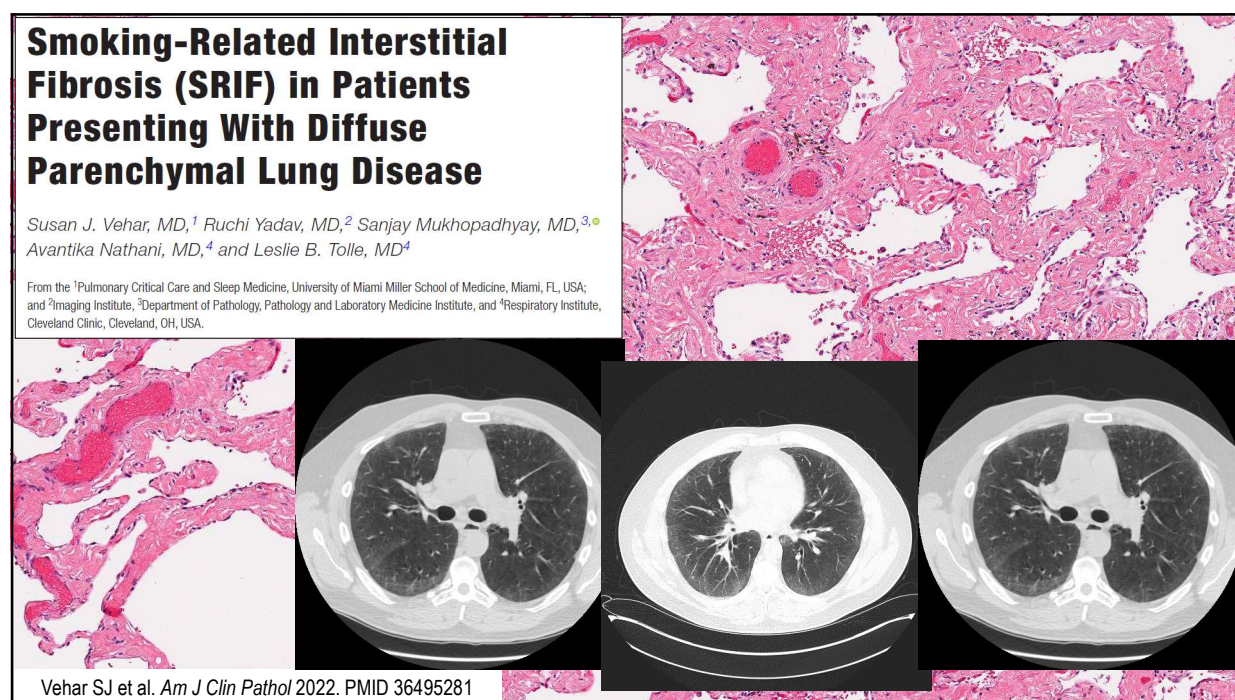
- **Lung, right middle lobe, transbronchial biopsy - Interstitial fibrosis with honeycomb change consistent with usual interstitial pneumonia**
- **Follow-up: Started on pirfenidone**

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108

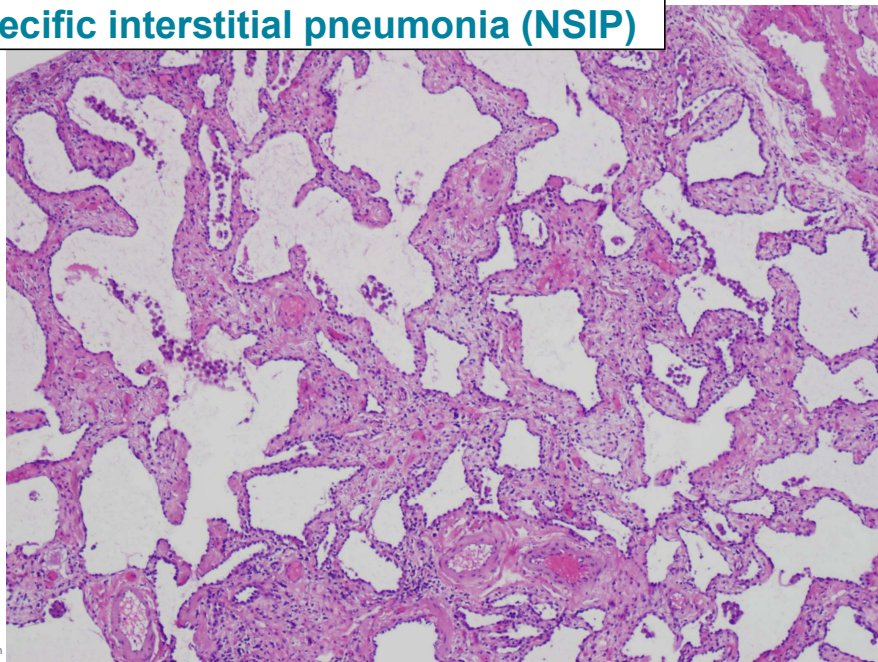


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110

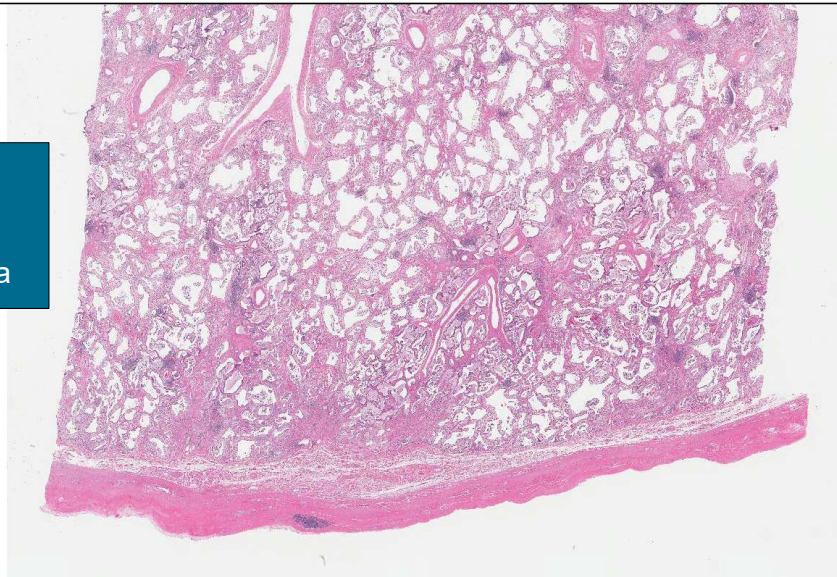
Non-specific interstitial pneumonia (NSIP)



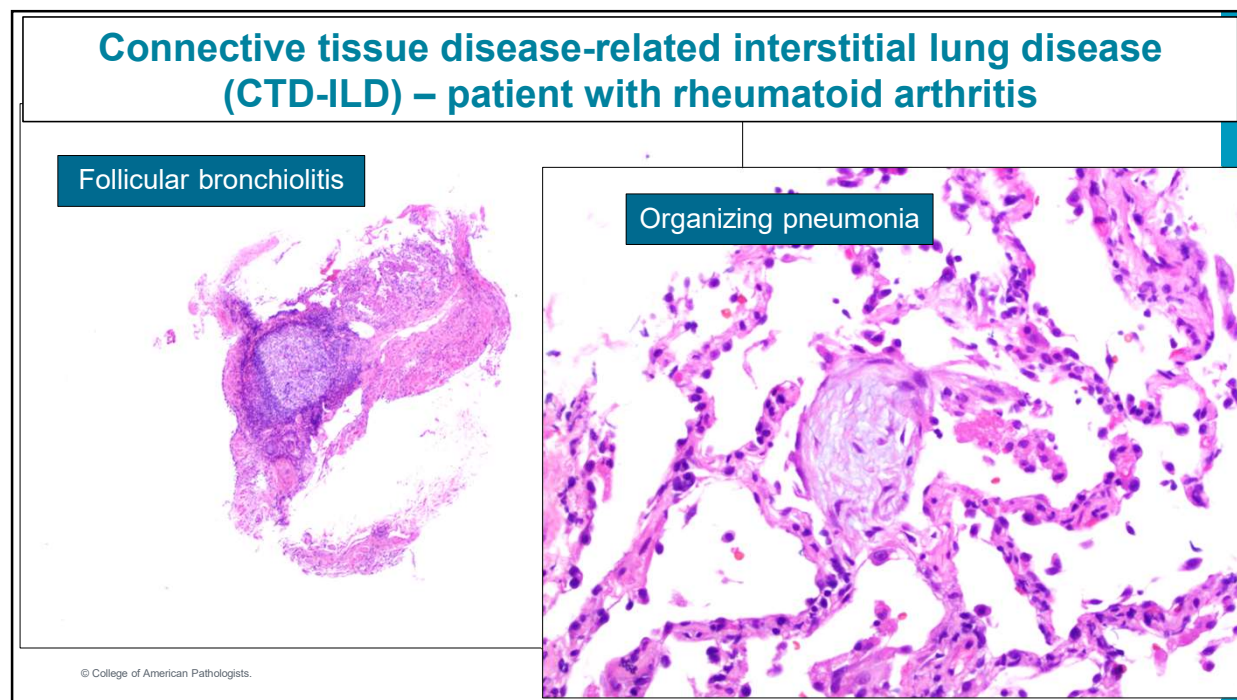
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Connective tissue disease-related interstitial lung disease (CTD-ILD) – patient with scleroderma

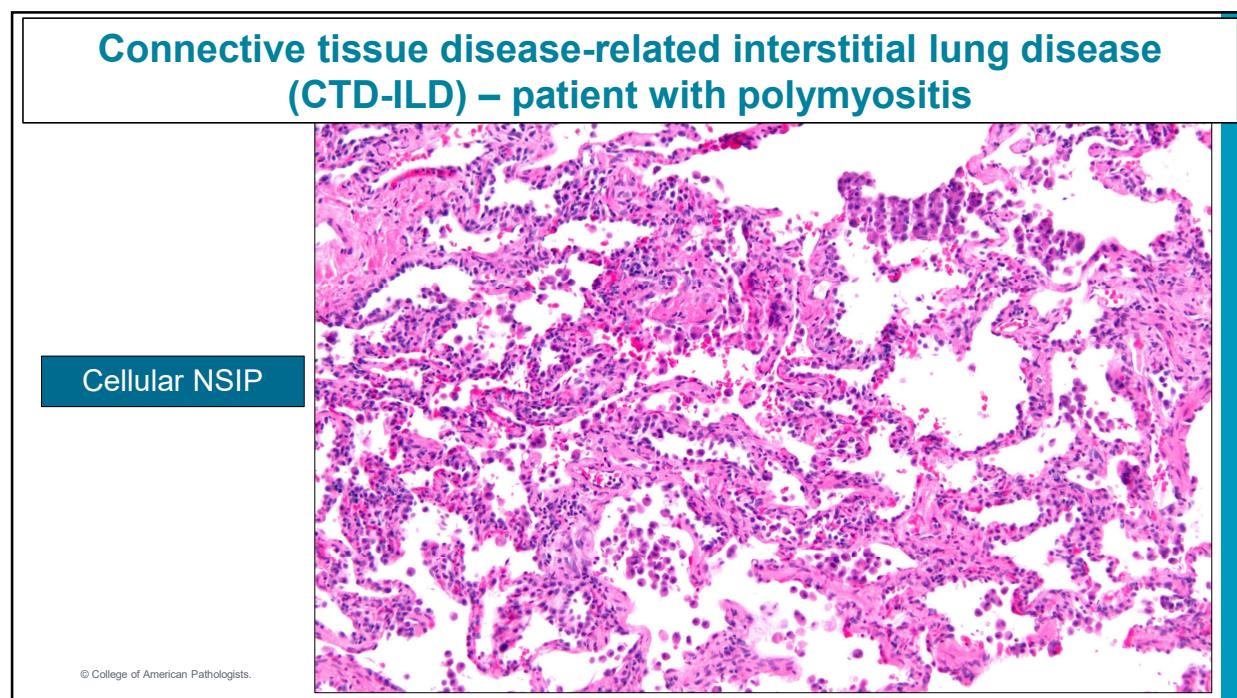
Chronic
fibrosing
interstitial
pneumonia



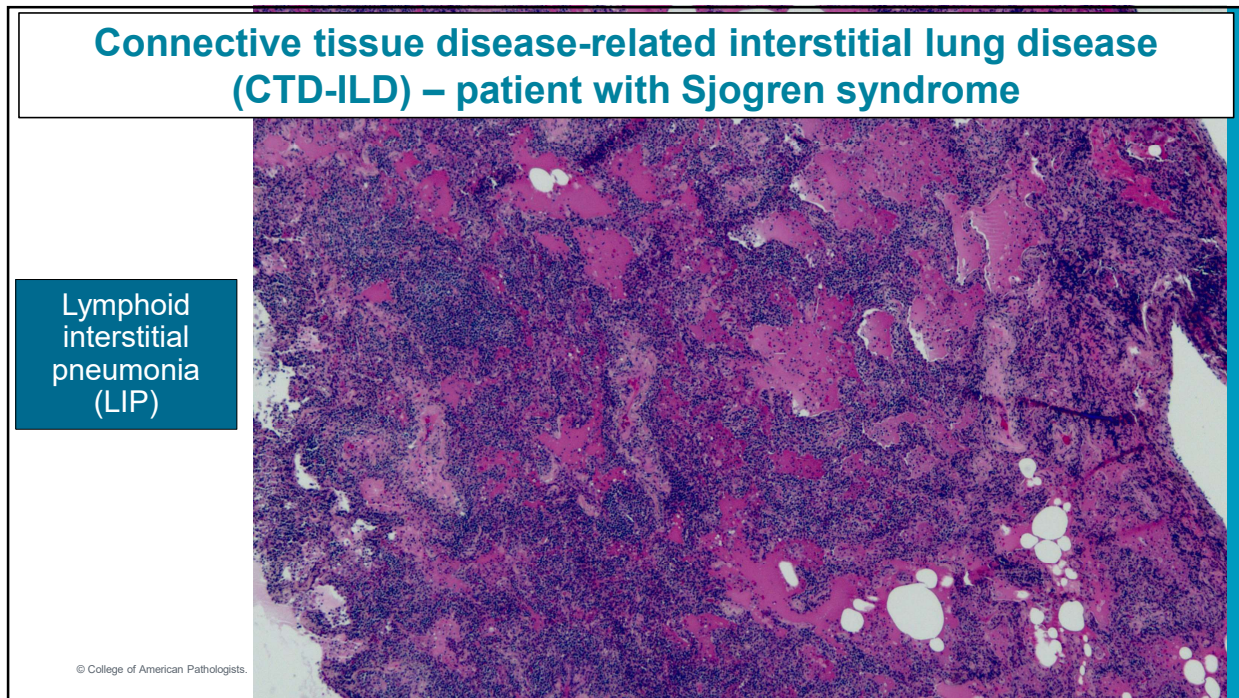
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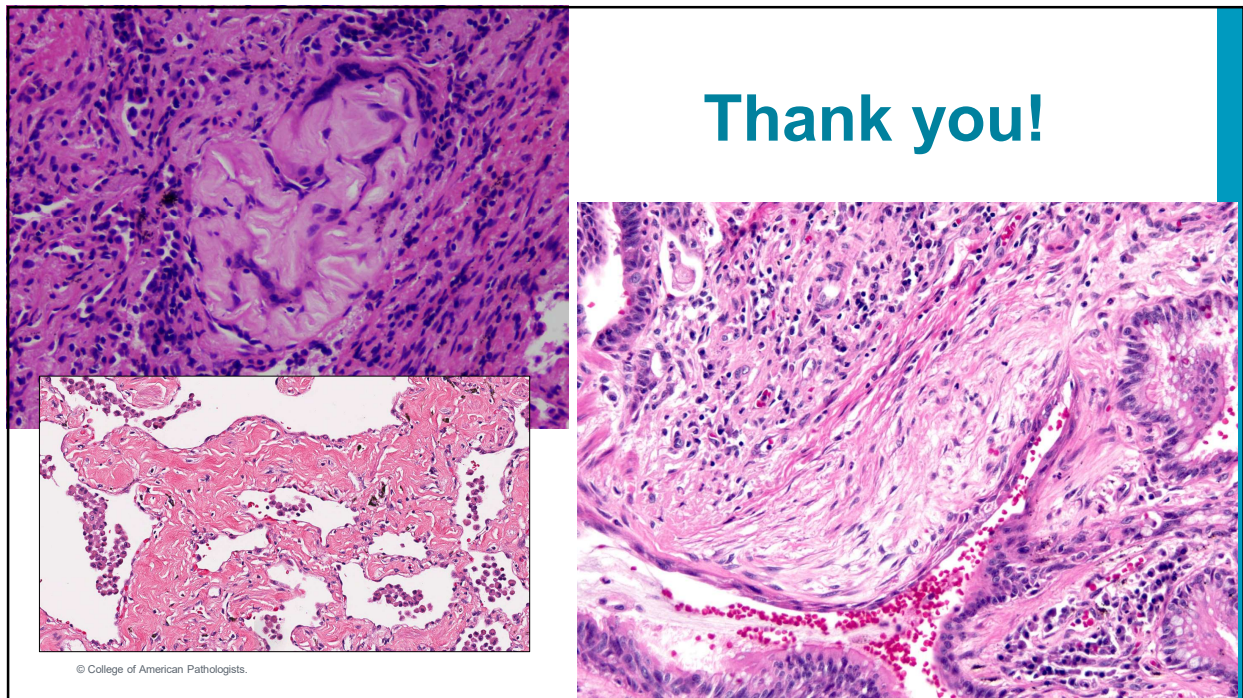
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Do you need to send every nonneoplastic lung pathology case out to an expert?

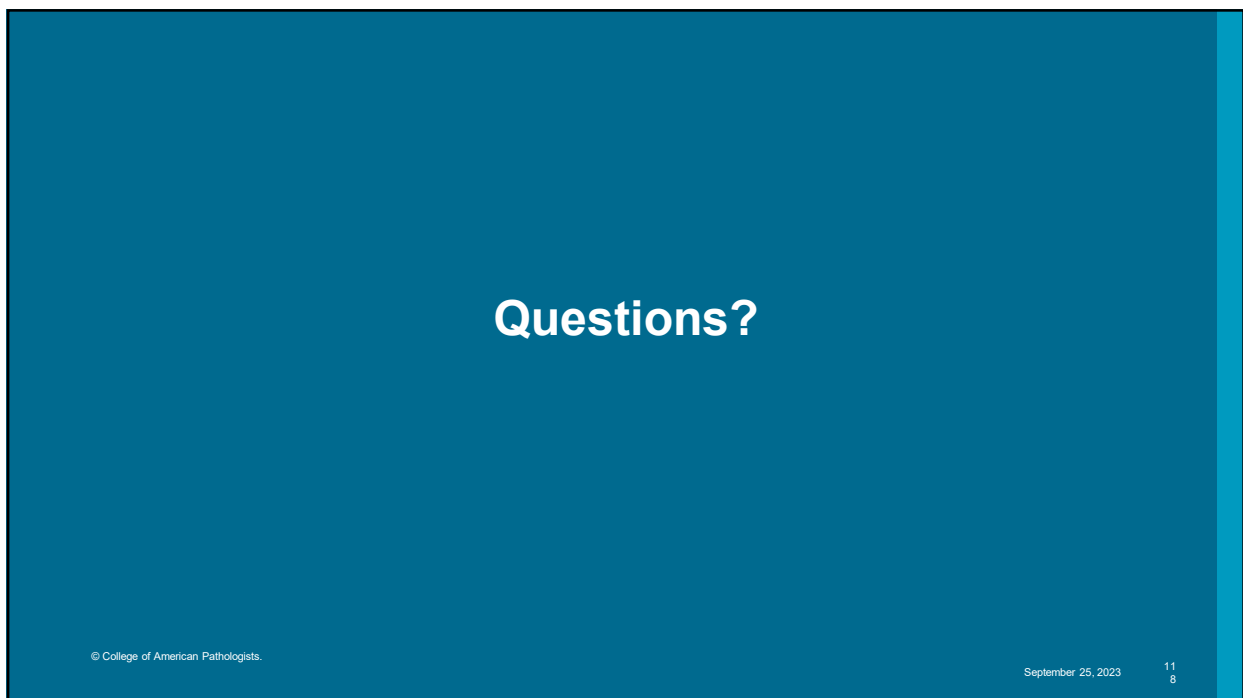
- **Infections can (mostly) be diagnosed by you!**
- **Classic ILDs that fit with the clinical picture can be handled by you**
- **Biggest need to send out: ILDs that do not fit with clinical picture, ILD in cryobiopsies or transbronchial biopsies**

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116



117



118

