

Help! What do I do with those granulomas in the lung?

2019 Anatomic
Pathology Update
University of Utah
Park City, Utah

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Objectives/Outline

At the end of the lecture, participants should be able to...

- **Provide a framework for approaching cases with granulomatous inflammation**
 - **Large granulomas**
 - **Small granulomas**
- **List the features of granulomas associated with infection**
- **List the features of granulomas which favor a vasculitic process**
- **Discriminate between foreign material and endogenous inclusions in the lung**

Radiologic Distribution

Focal/Multi-Focal

Diffuse

Bronchiectasis ?

No

Yes

Infection
Aspiration
GPA
Rheumatoid
Nec/Nodular Sarcoid
Lymphoma

MAC/MLS
IBD

Hypersensitivity pneumonitis
Hot tub lung
Infection
Sarcoid
Lymphoma
Aspiration

Granulomas in Biopsy

Necrotizing

Small

Infection
Sarcoid

Gross nodule(s)

Infection
Aspiration
GPA
Lymphoma
Rheumatoid
Nec Sarcoid

Non-necrotizing

Small

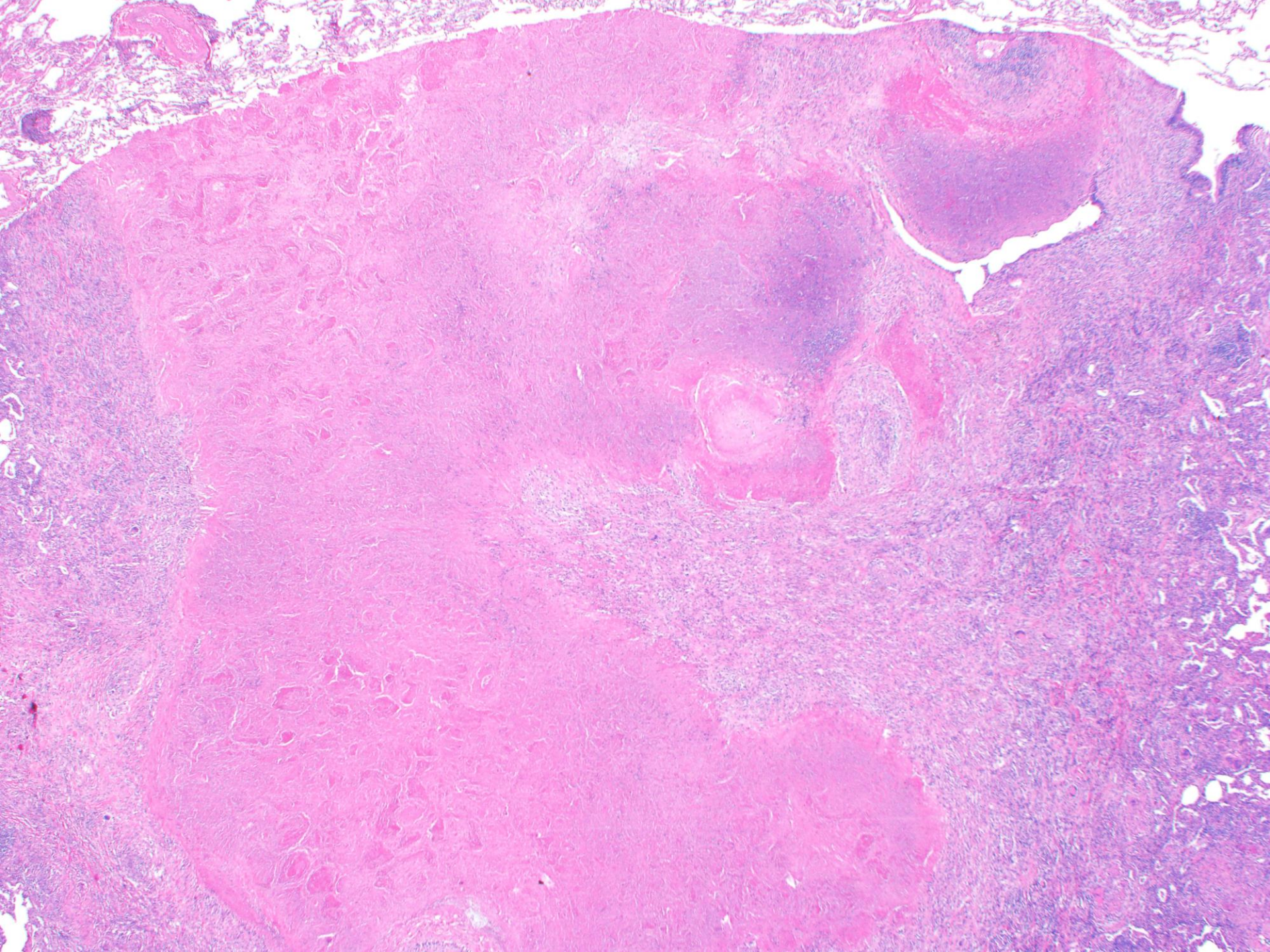
HP
Hot tub
Infection
Drug
Lymphoma
LIP

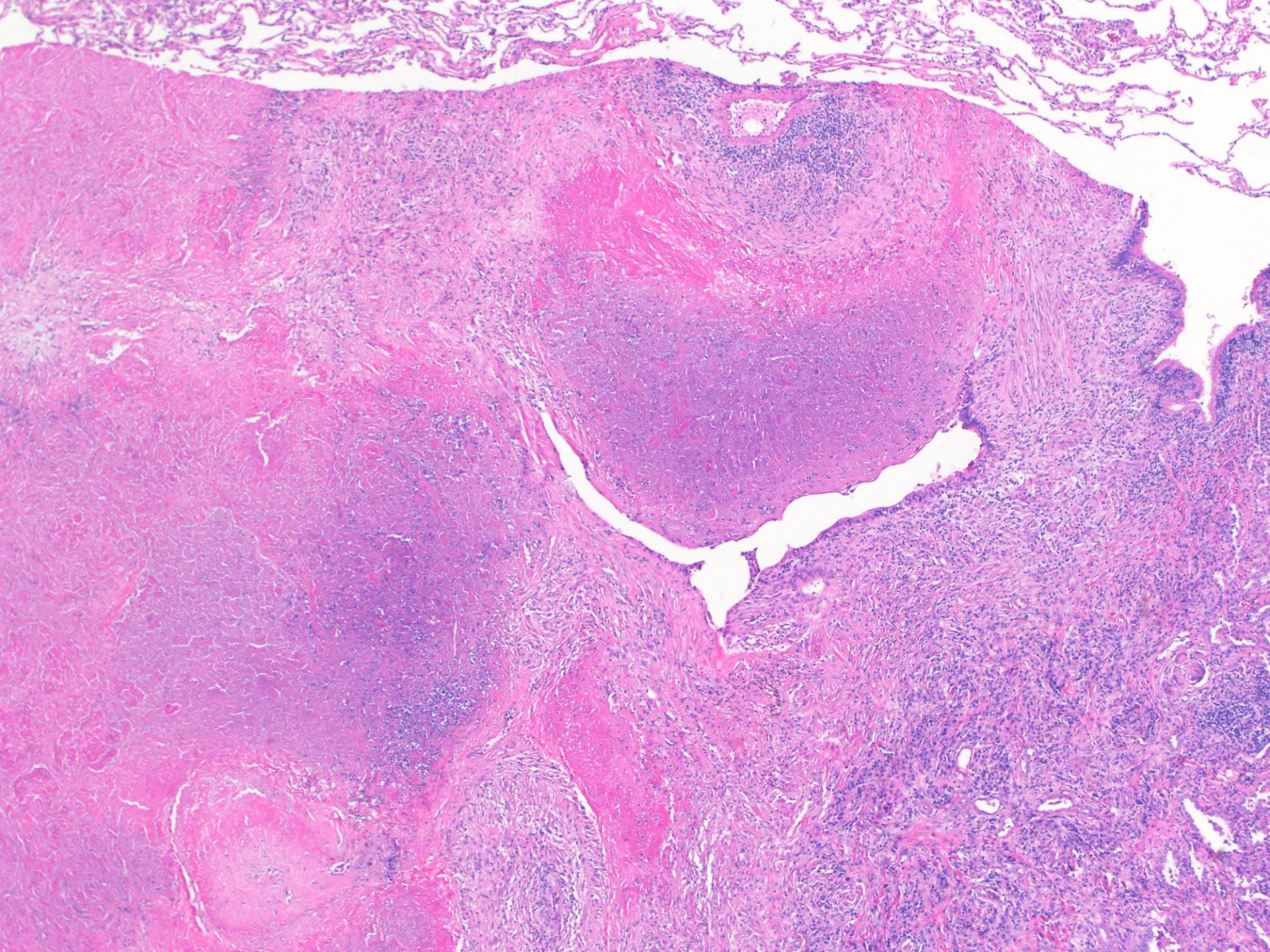
Gross nodule(s)

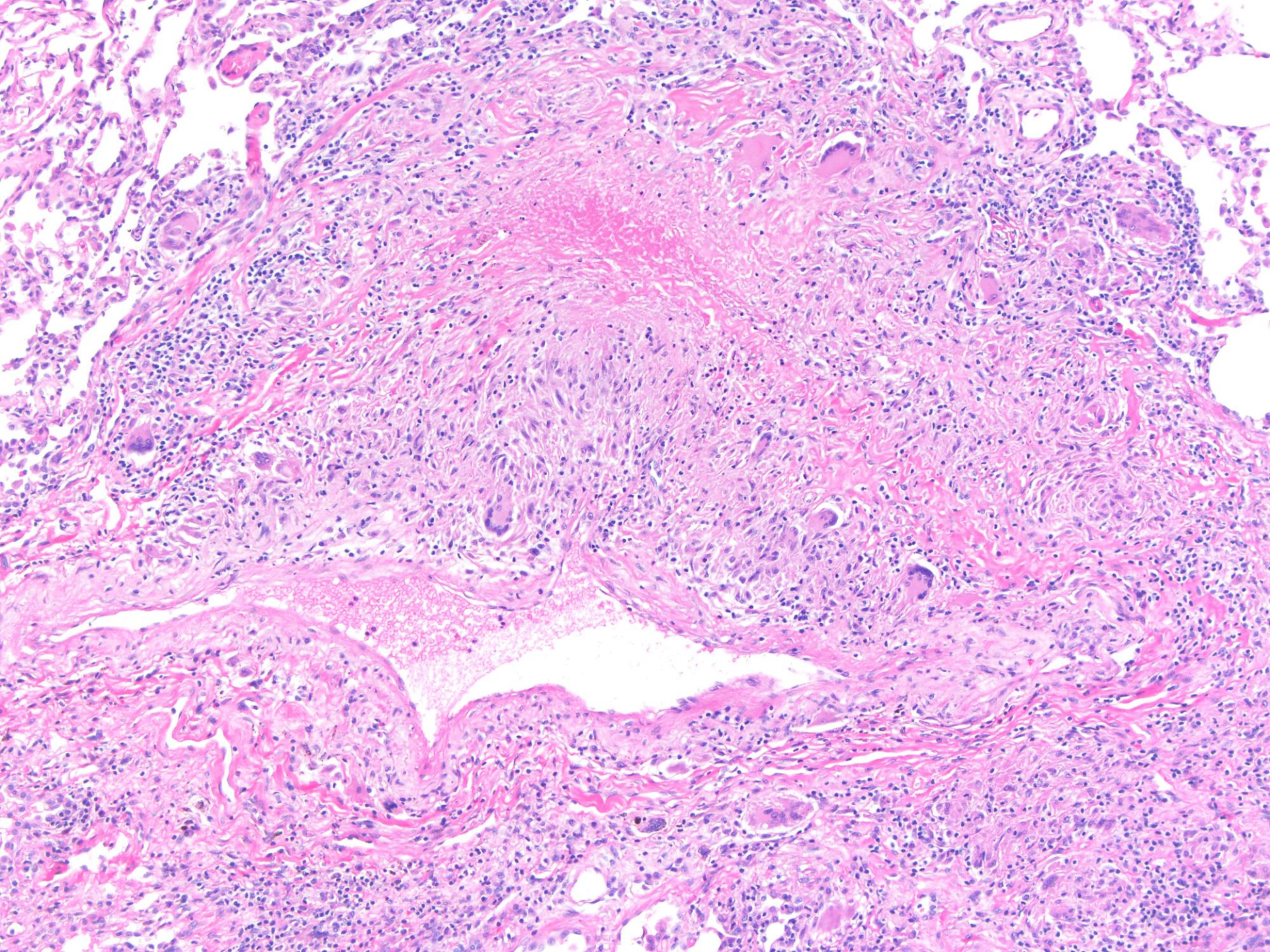
Nodular
sarcoid

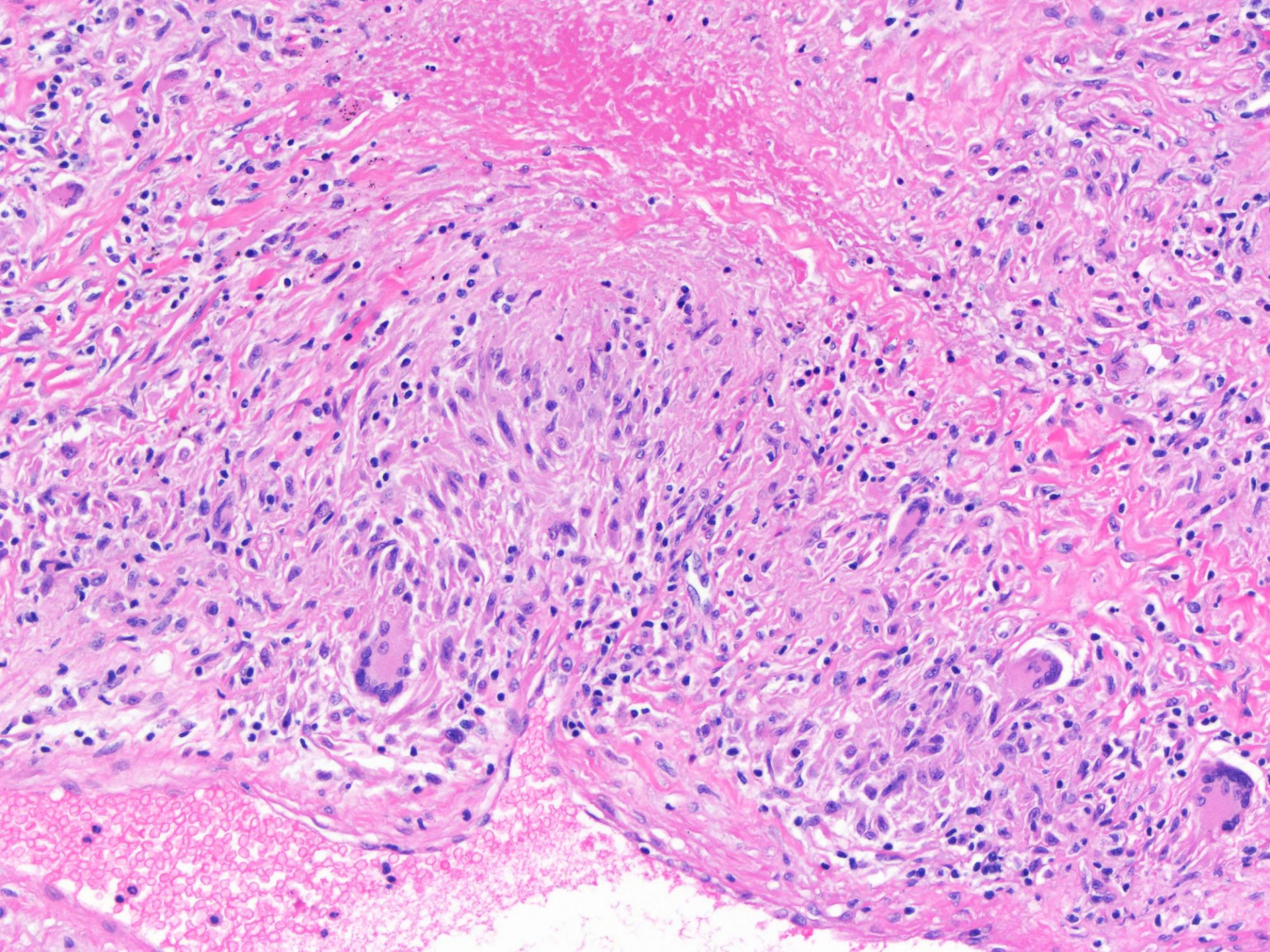
History

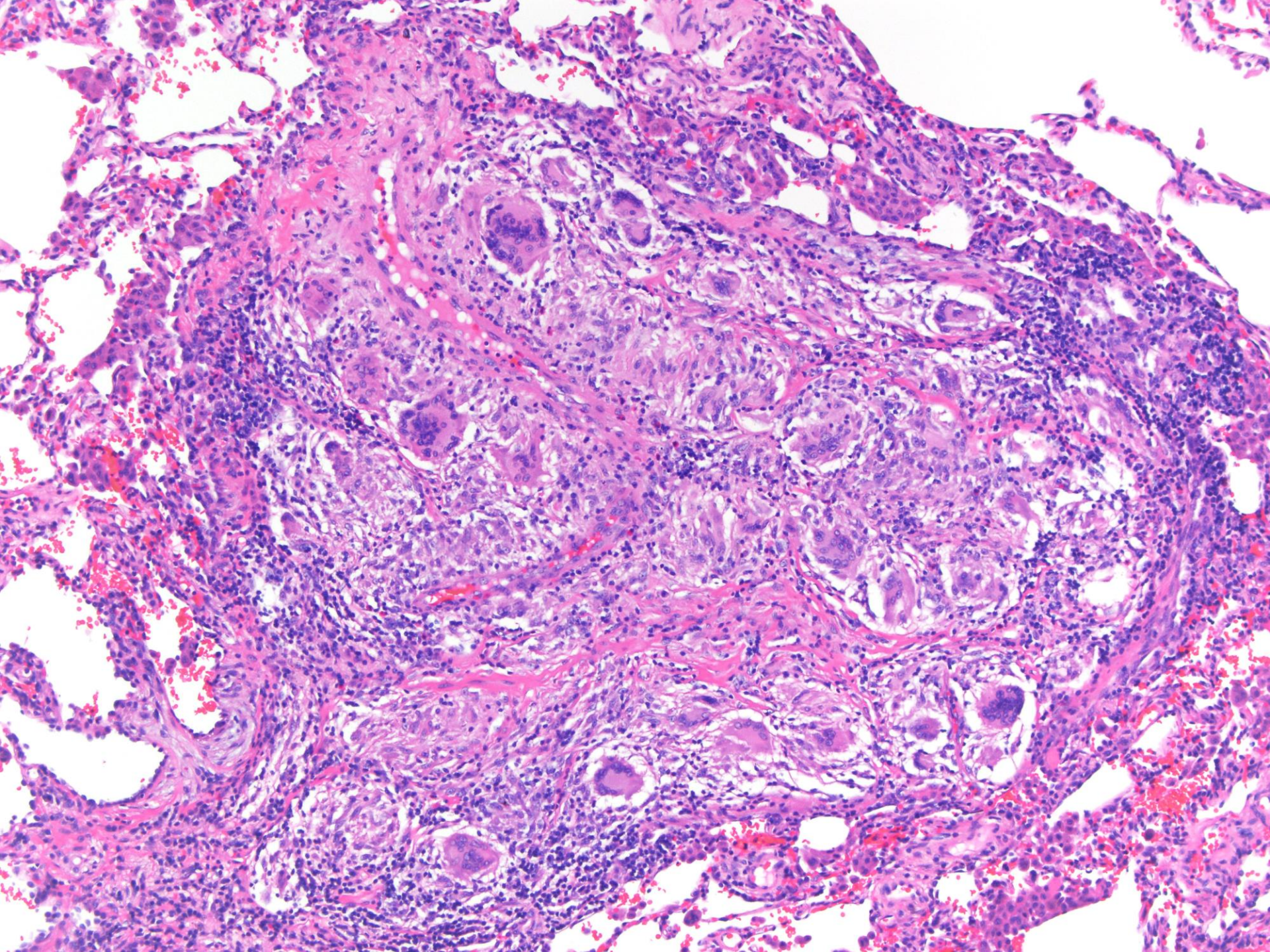
- A 55 yr old man was found to have 2 lung nodules
- History: intercapillary glomerulosclerosis
- Underwent surgical lung biopsy

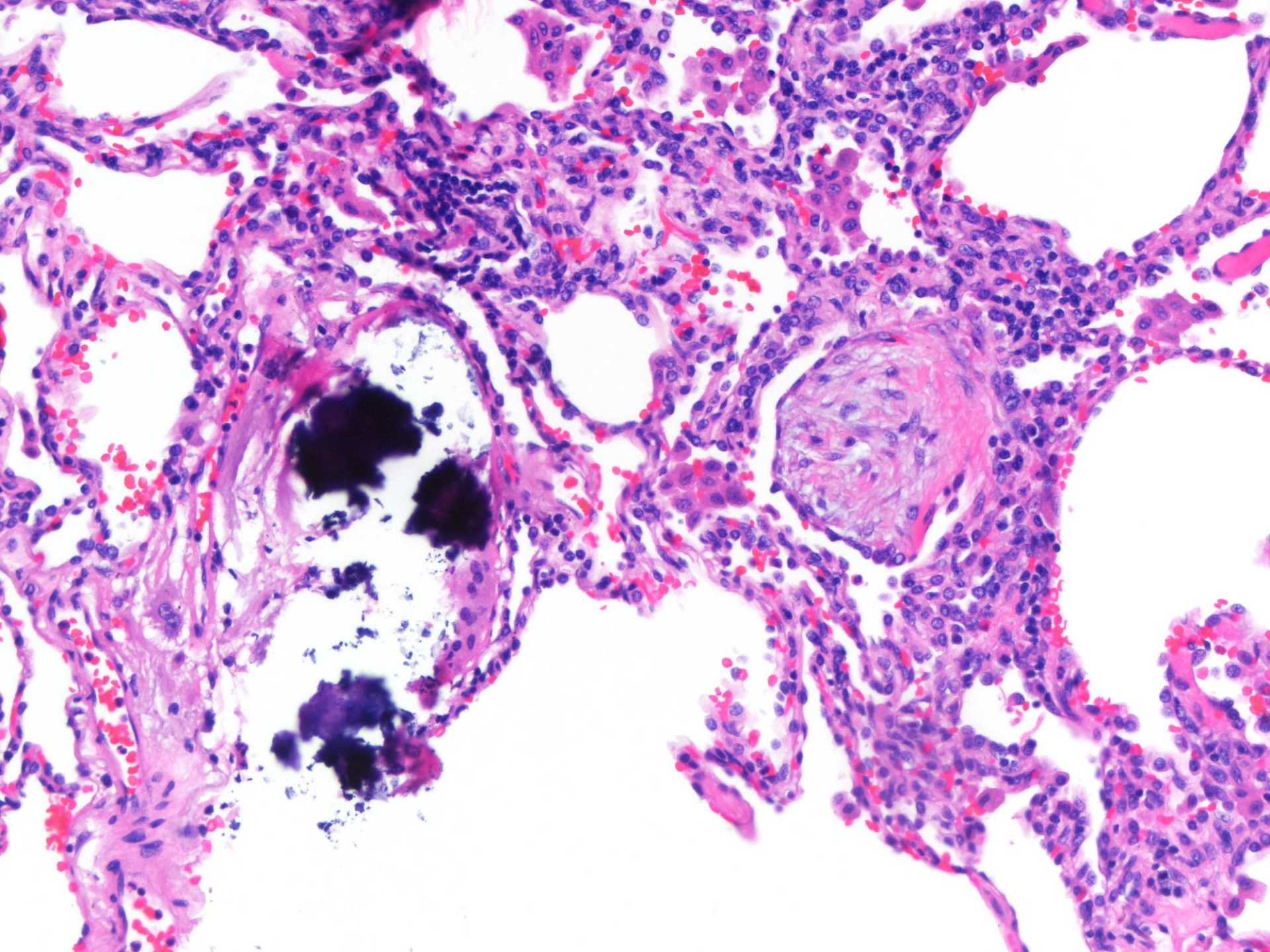












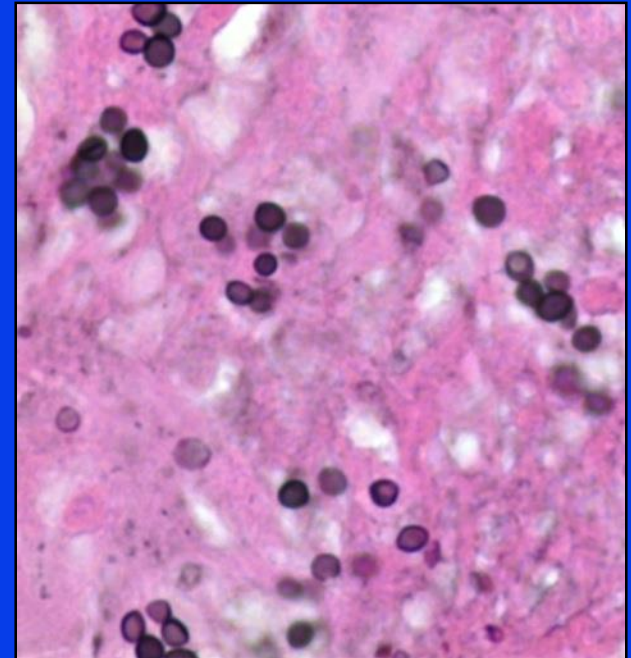
Diagnosis?

Diagnosis?

**Necrotizing Granulomatous
Inflammation most c/w an
Infectious Etiology**

Additional Studies

- Serologies including pANCA and cANCA were negative
- Stains for acid fast neg
- Stains for fungi...



Diagnosis

**Histoplasmosis
characterized by
Necrotizing Granulomatous
Inflammation and Vasculitis**

Key Histologic Features

- Granulomas
 - Necrotizing
 - Round borders
 - Geographic borders
 - Non-necrotizing
 - Surrounded by thin rim of infl'n
 - Some bronchiolocentric
- Vasculitis
- Presence of calcified bodies

Key Histologic Features

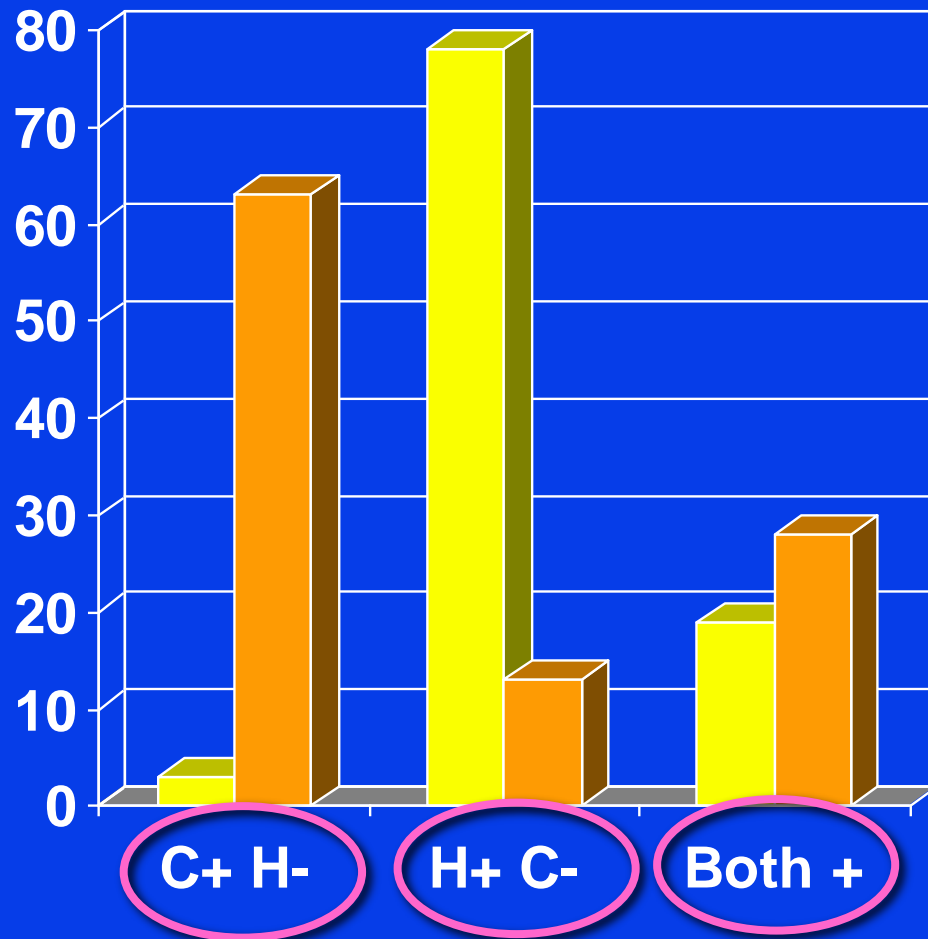
- Granulomas
 - Necrotizing
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 - Non-necrotizing
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- Vasculitis
- Presence of calcific inclusions

Solitary Granulomas

Culture Results for *Histoplasma* Cases

Source	N, Pos/total
Sputum	0/22
Bronchial Wash	0/9
Bronchial Brush	0/3
Needle Aspiration	0/2
Lung Biopsy	0/19

% Yield of Cultures (C) vs. Histology (H)



88 Cases
10 Centers
(7 Countries)

■ Fungi
■ Mycobacteria

Mycobacteria more often
culture positive
Fungi, more often
histology positive

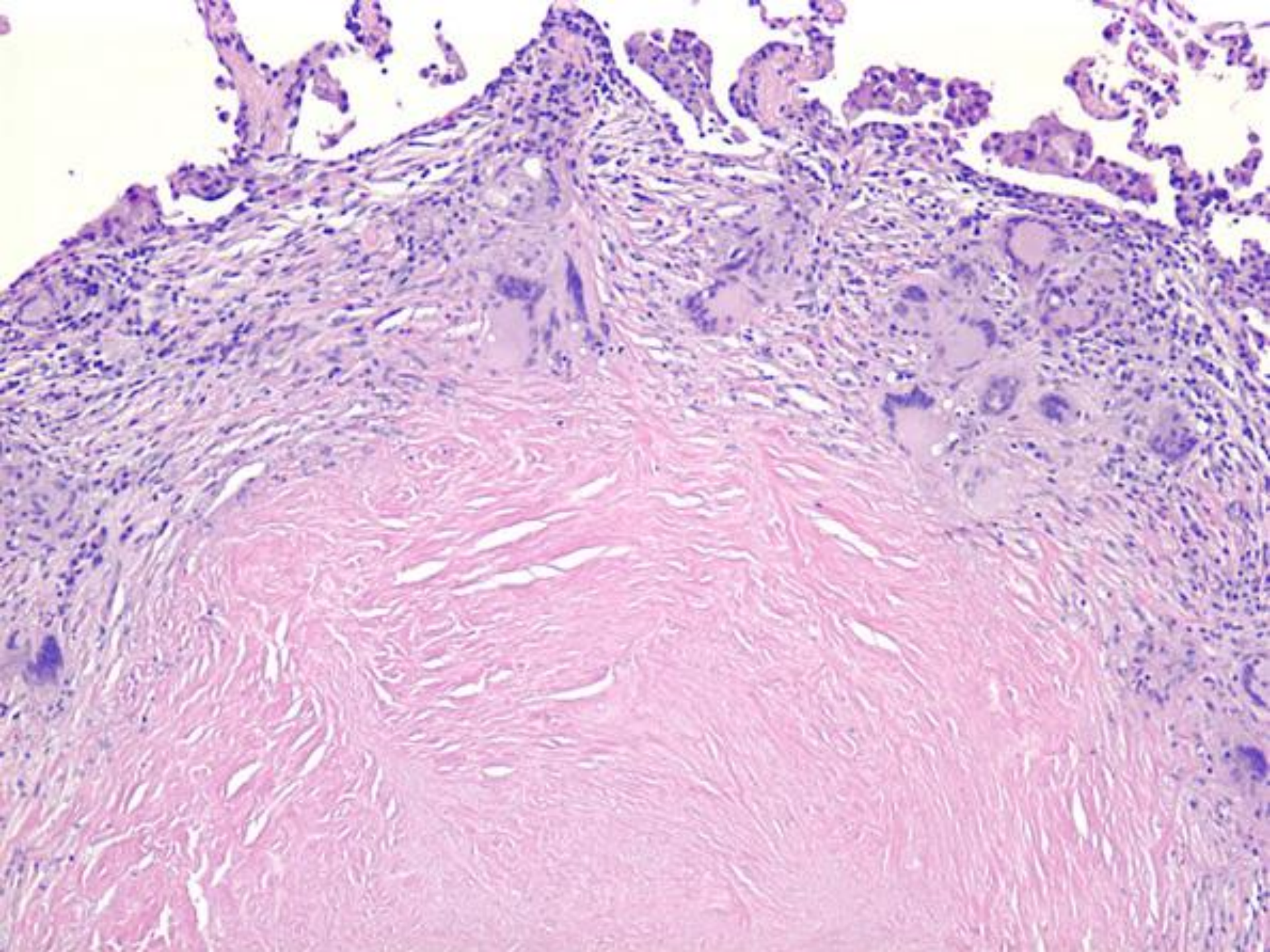
Solitary Granulomas

Importance of Special Stains

- **Among all patients with histoplasmosis, 54 blocks were stained with GMS**
- **Only 74% contained organisms**
- **Organisms “numerous” 58%**
 - **Usually located centrally**

Histol'ic features of Histoplasmosis forming a Solitary Nodule, N=24

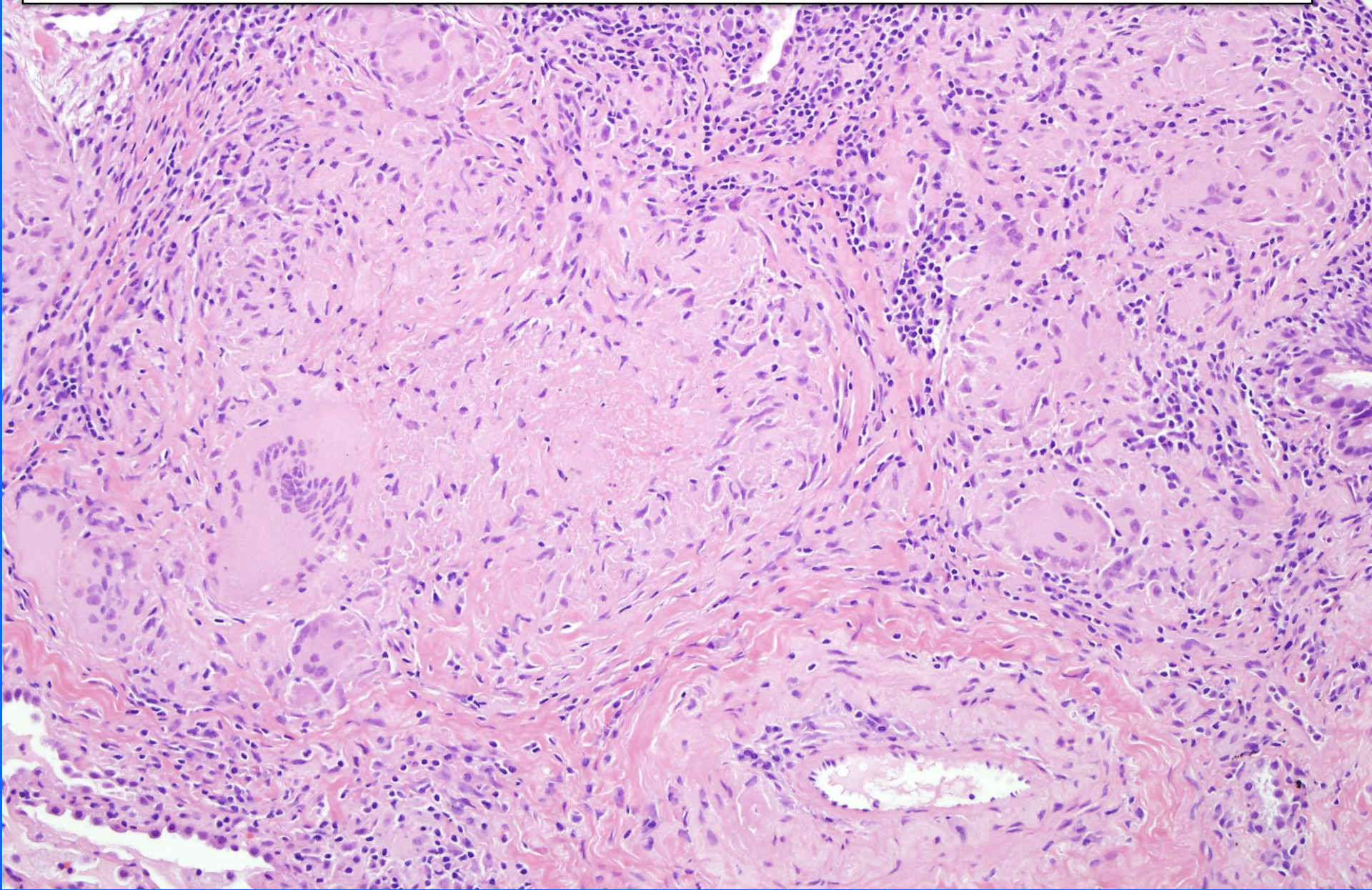
Feature	%
Round borders	79
Geog'ic borders	21



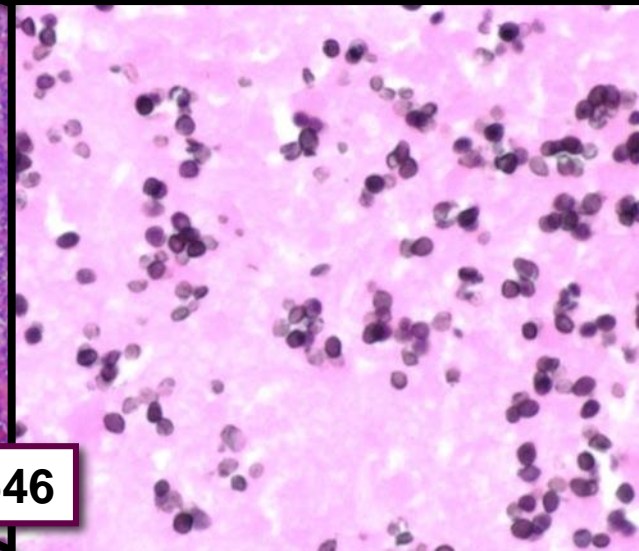
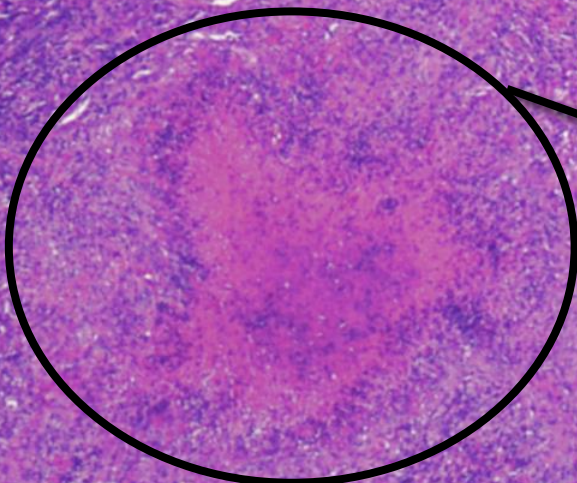
Histol'ic features of Histoplasmosis forming a Solitary Nodule, N=24

Feature	%
Non-nec gran	13
Vasculitis	54 ←

Histo – Well Formed Non-Nec Gran



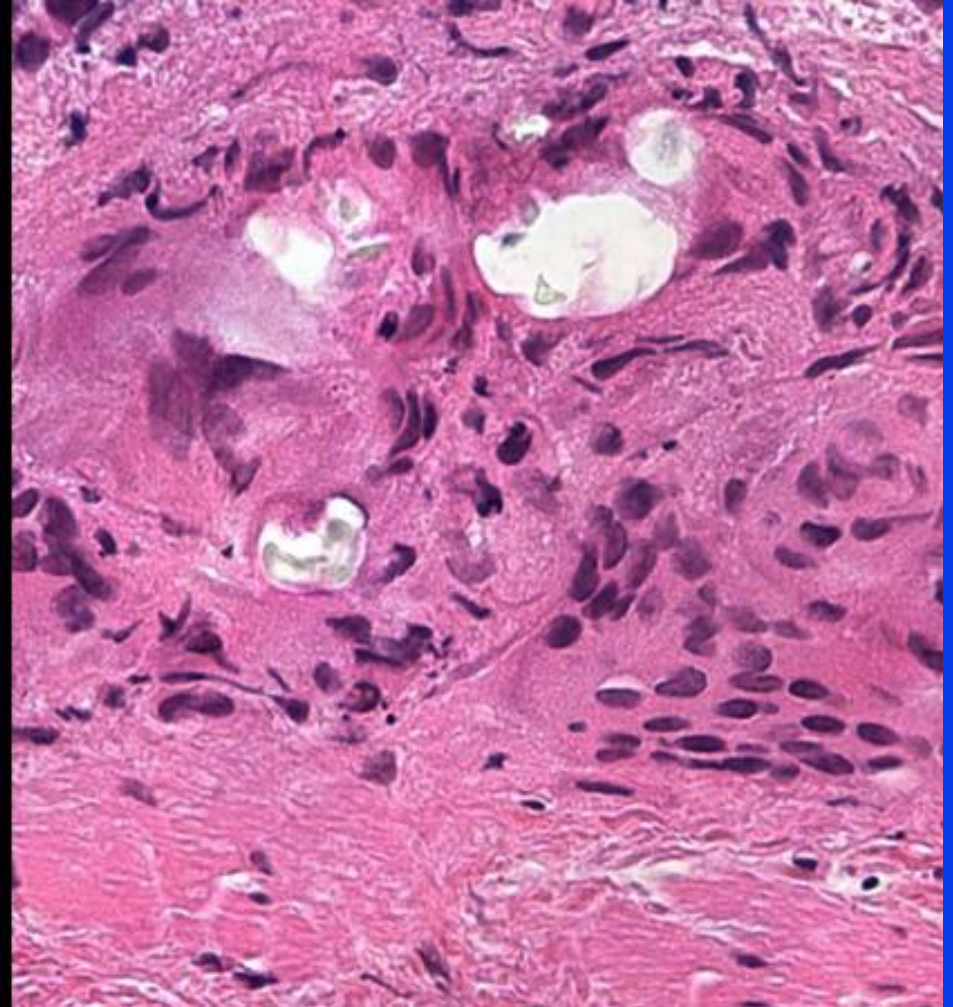
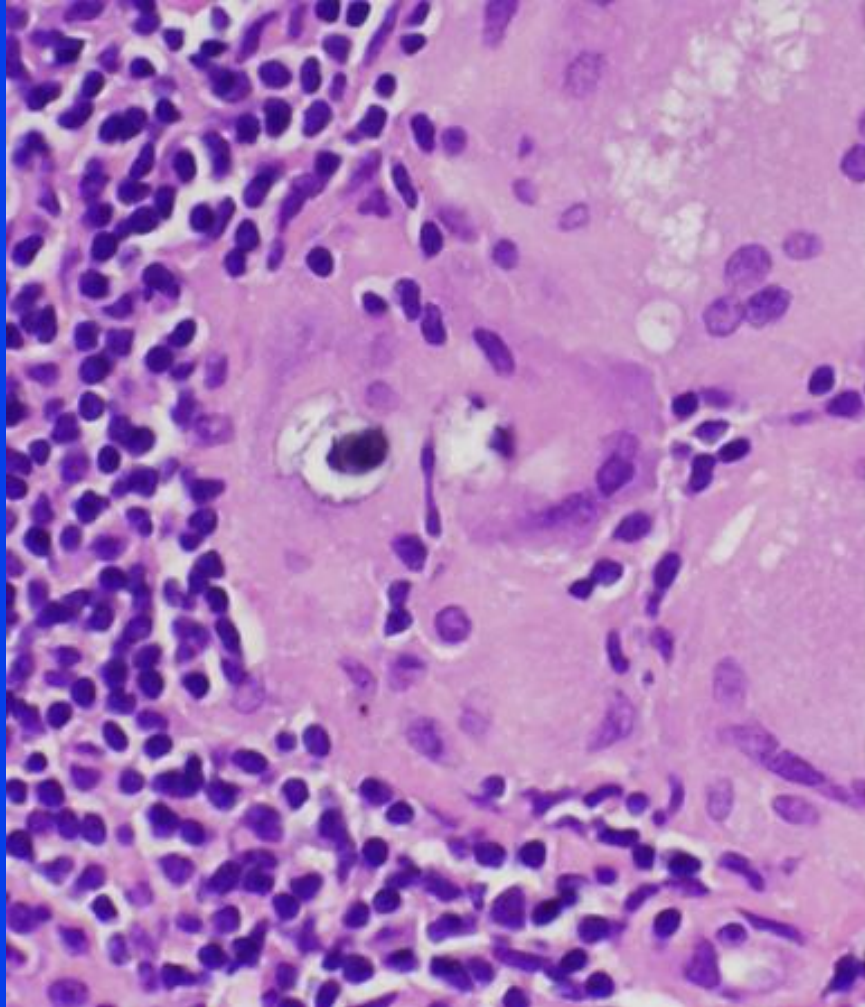
Acute Histoplasmosis



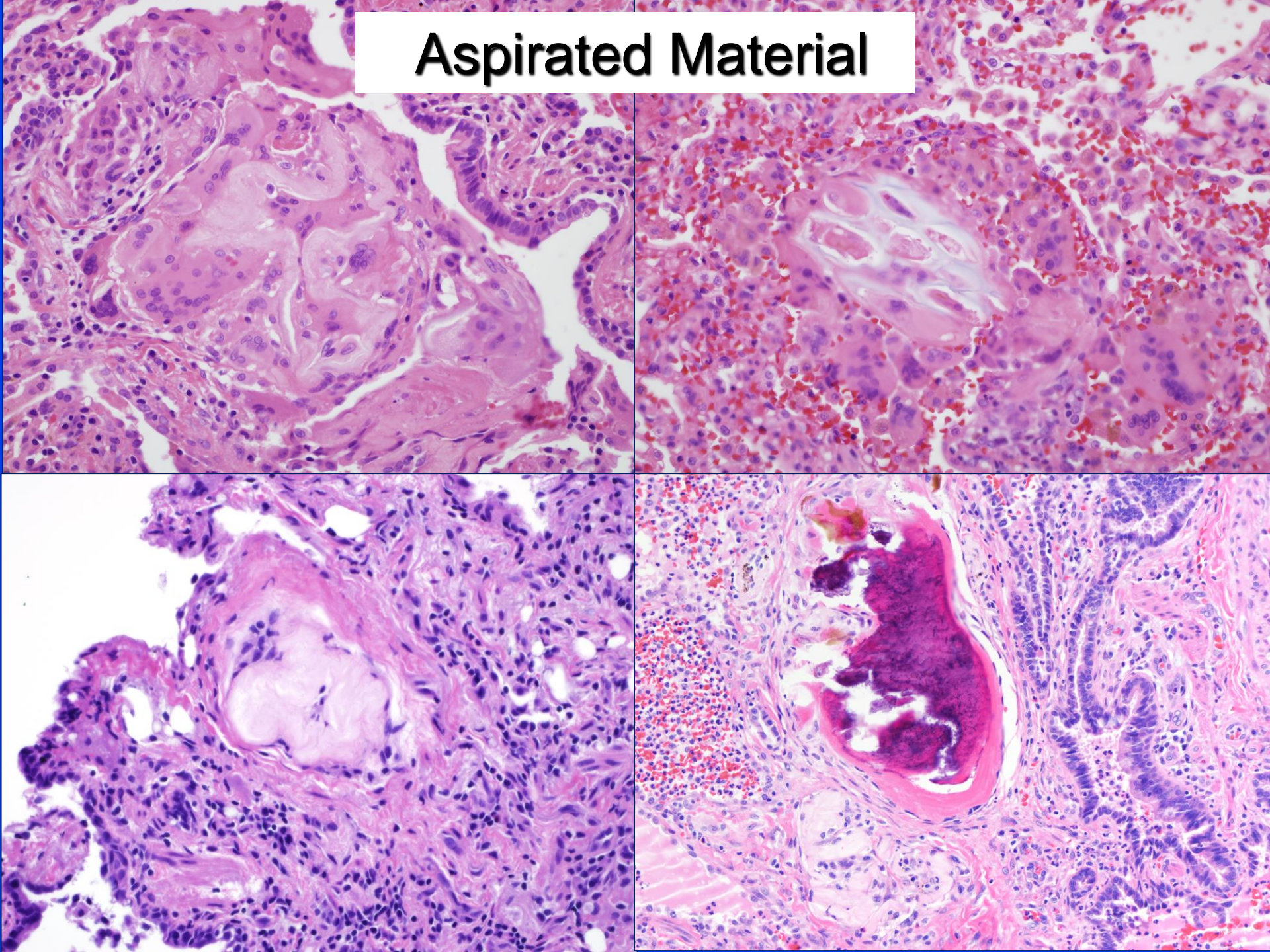
Endogenously-Derived Crystals

Ca carbonate

Ca oxalate



Aspirated Material



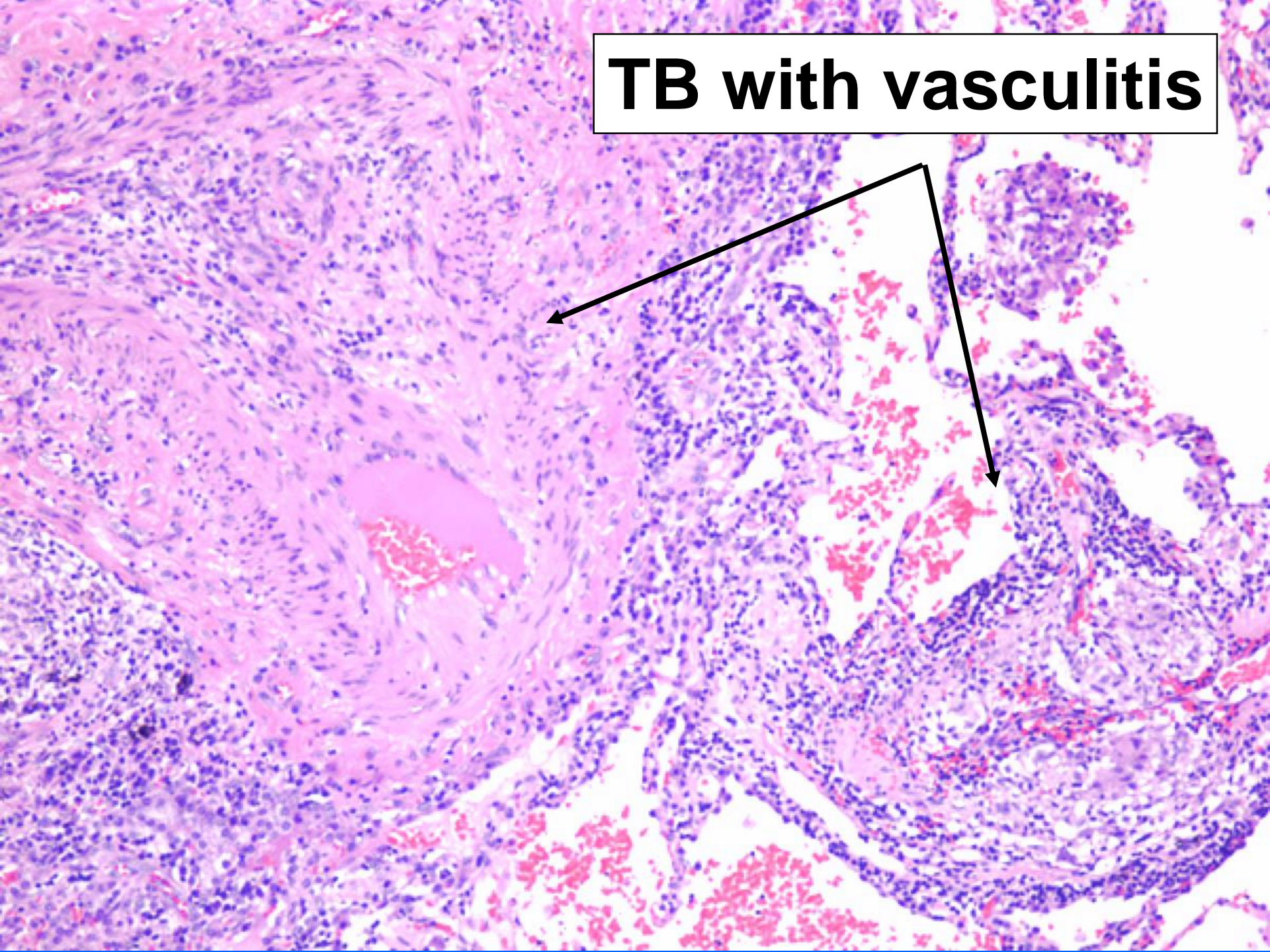
Differential Diagnosis

- Other necrotizing granulomatous infections
- Wegener granulomatosis /Granulomatosis with polyangiitis
- Catheter sheath emboli

Mycobacterium tuberculosis

Histologic Feature	%
— Vasculitis	87
— Geographic necrosis	30
— Non-caseating granulomas	30

TB with vasculitis



Pneumocystis jirovecii



Granulomatous PCP

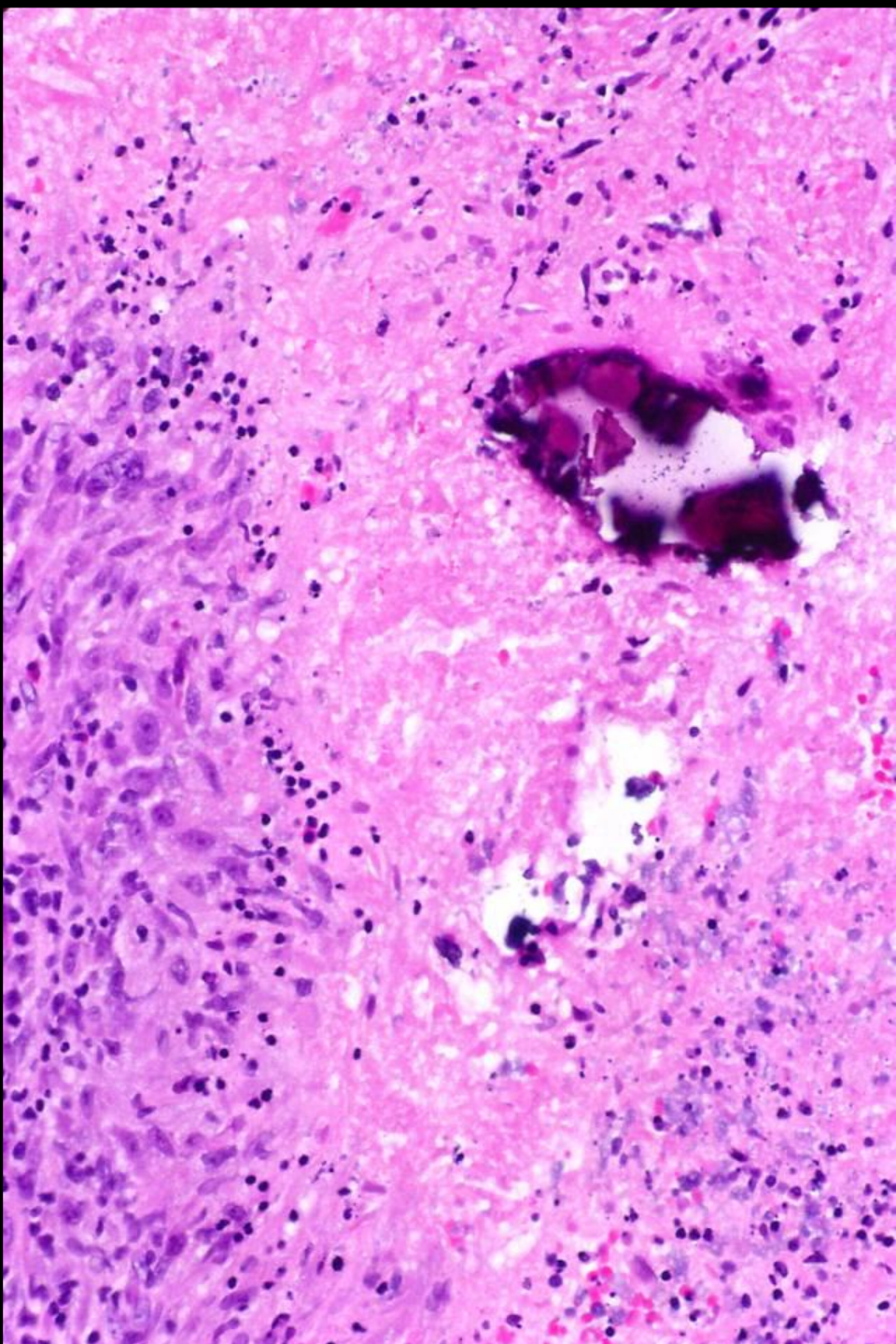
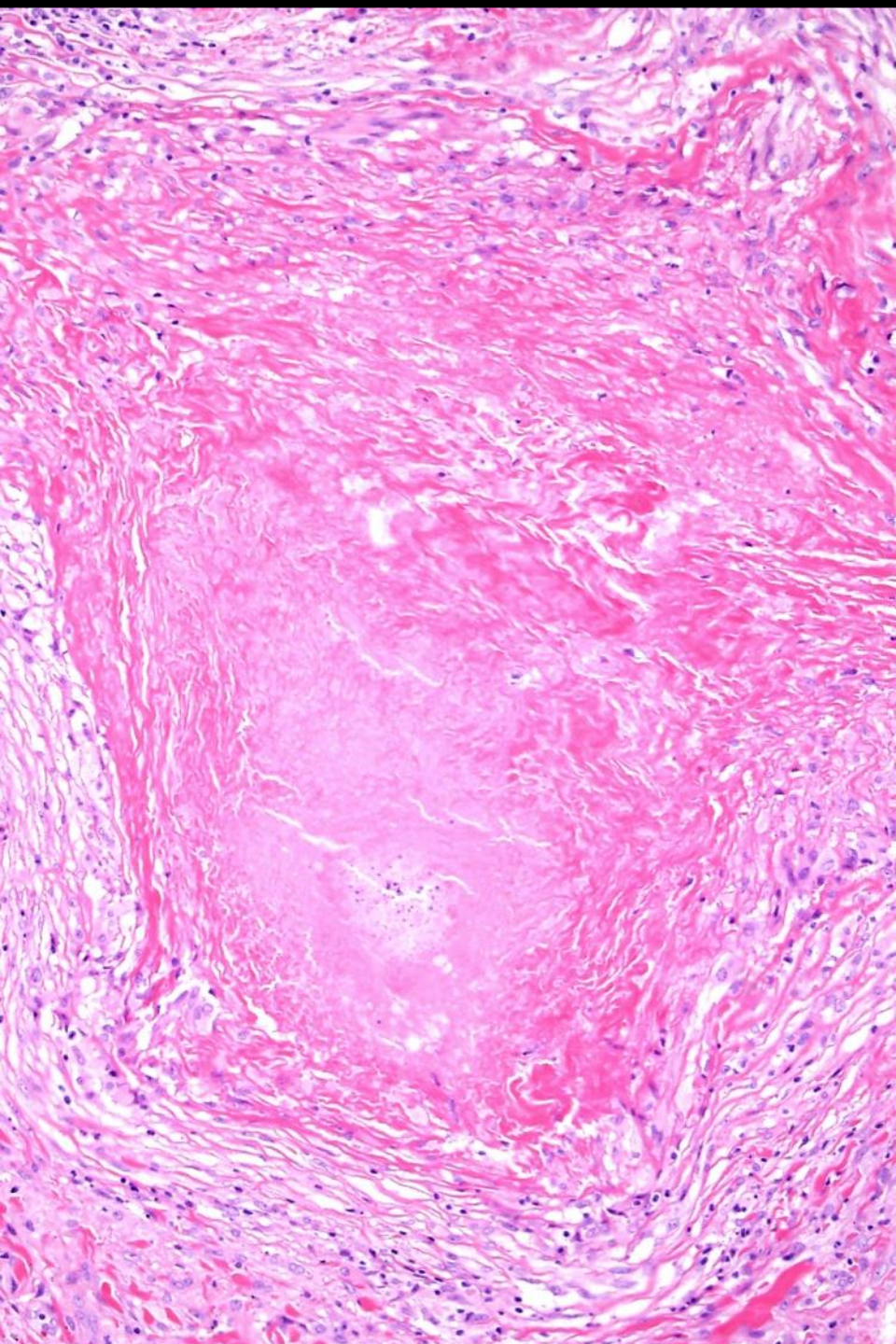
20 Cases

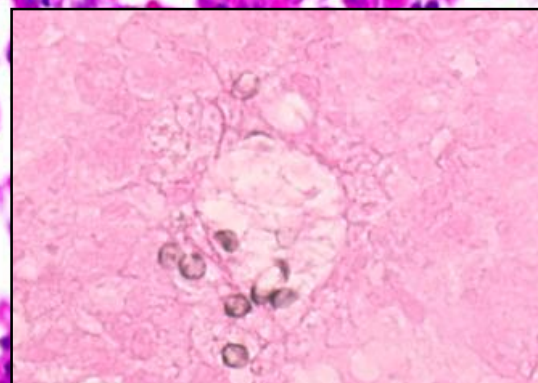
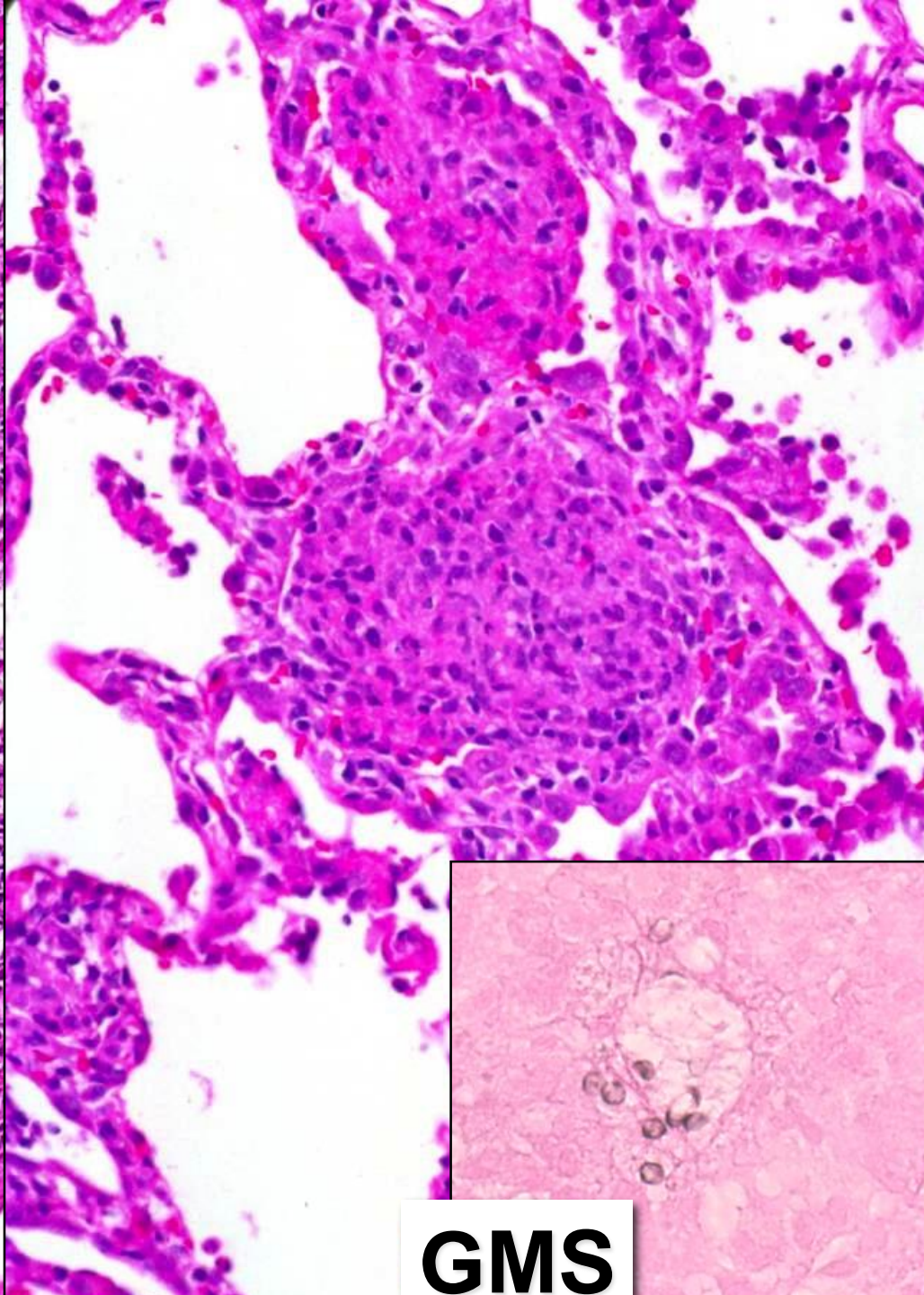
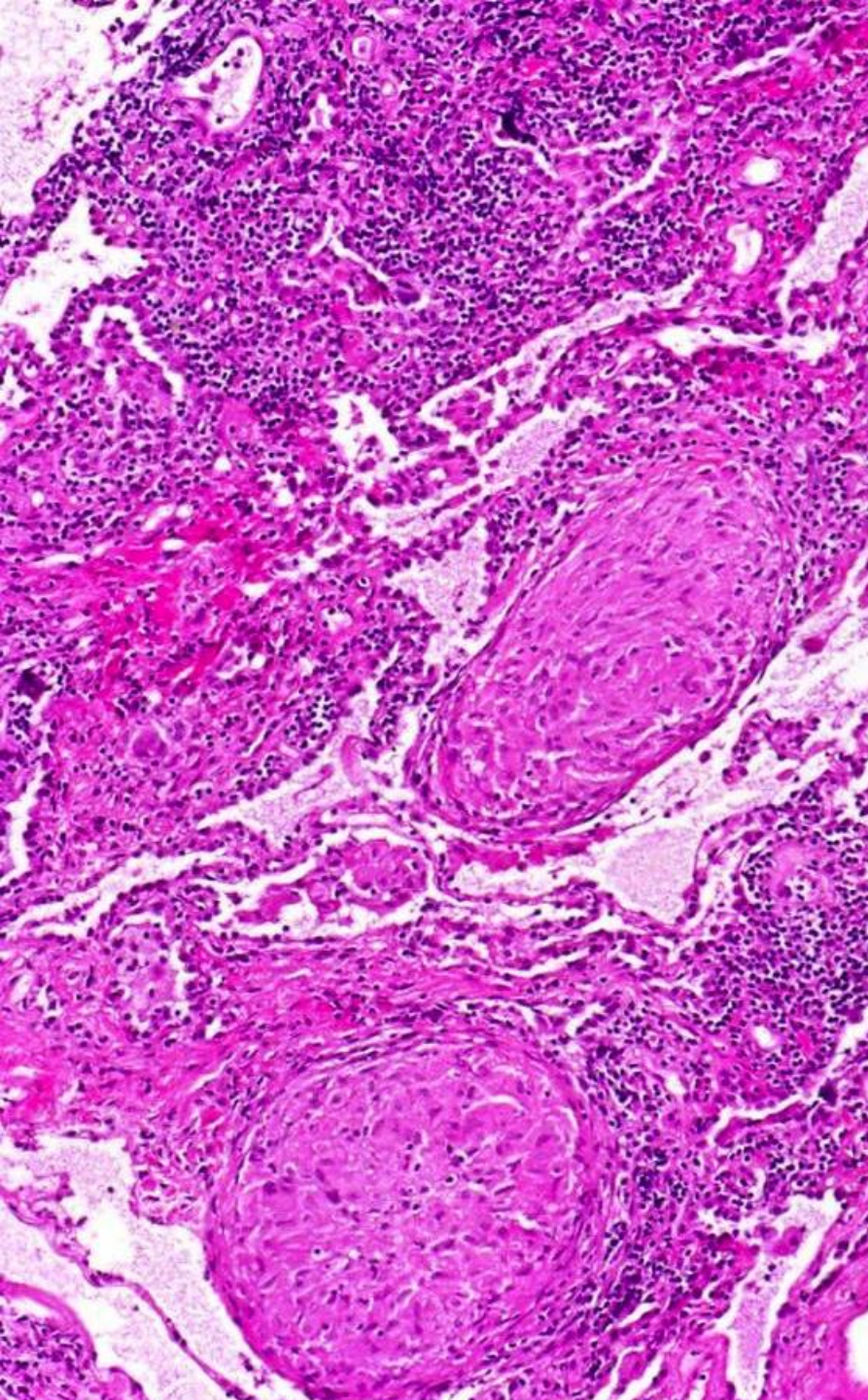
Disease	%
HIV	35
Heme malign.	30
Solid tumor	20
Unknown	15

Granulomatous PCP

20 Cases

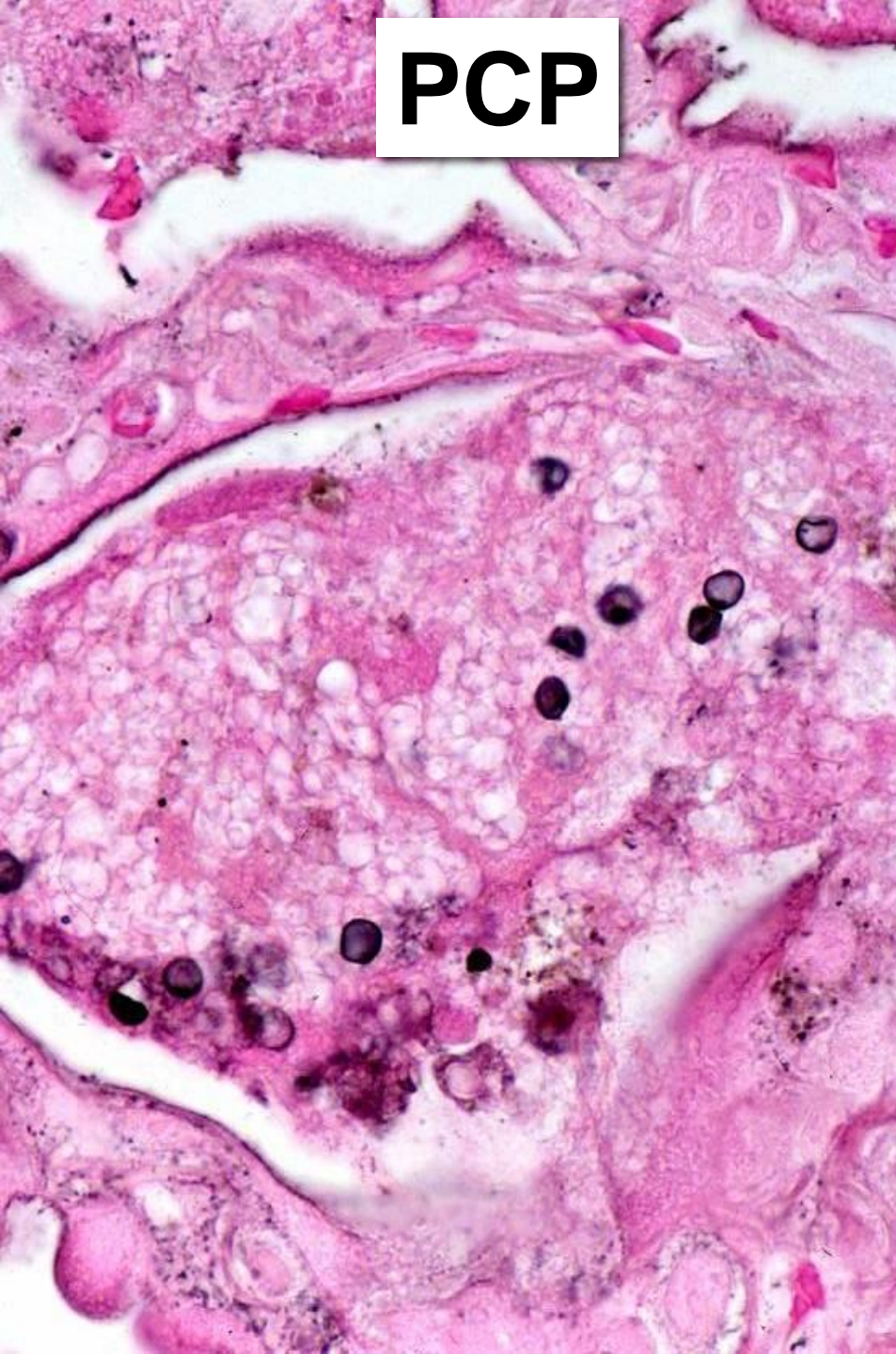
Feature	%
Necrotizing gran	80
Non necrotizing gran	20
Foamy exudate	25
Cystic spaces	5
Calcification	5



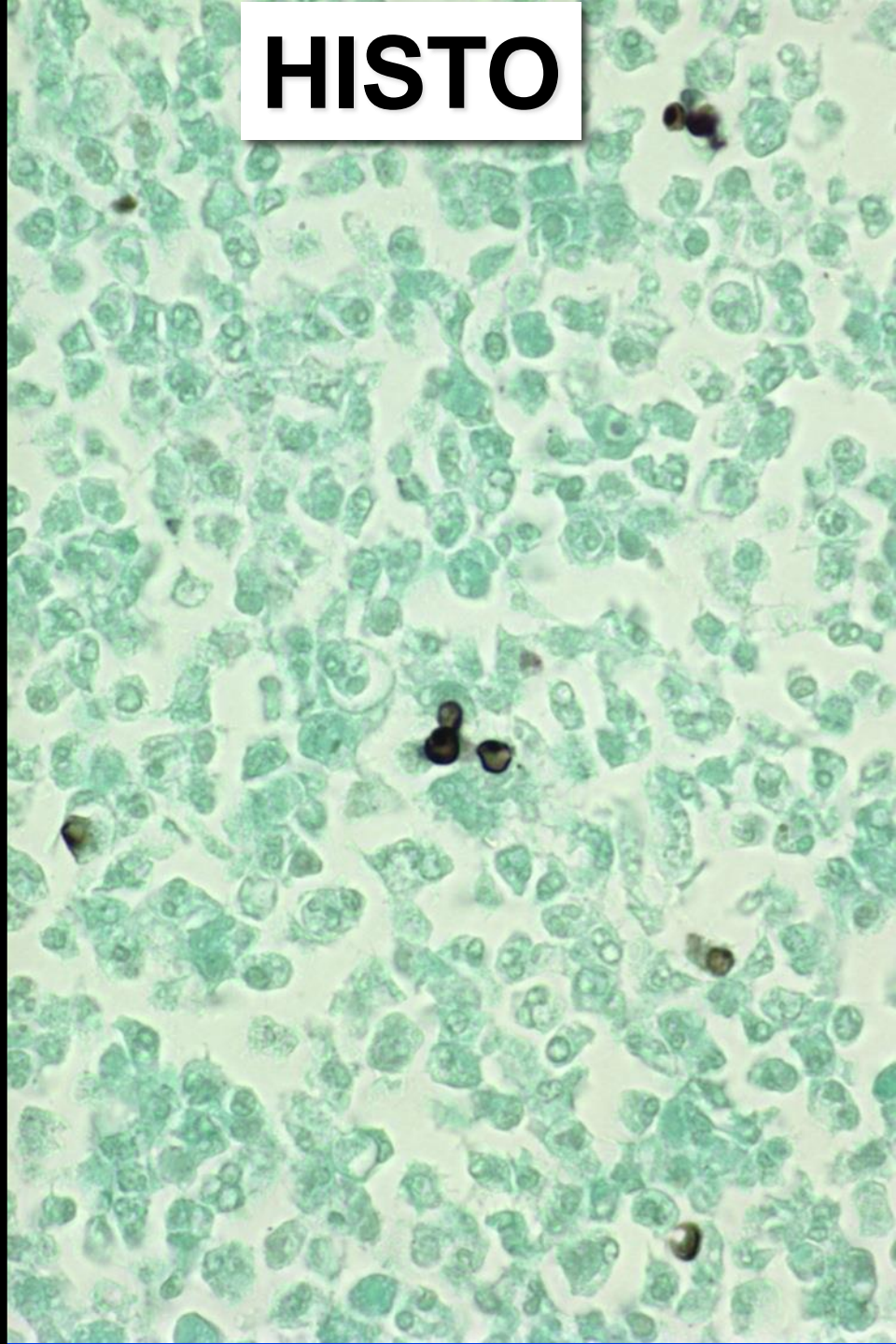


GMS

PCP



HISTO



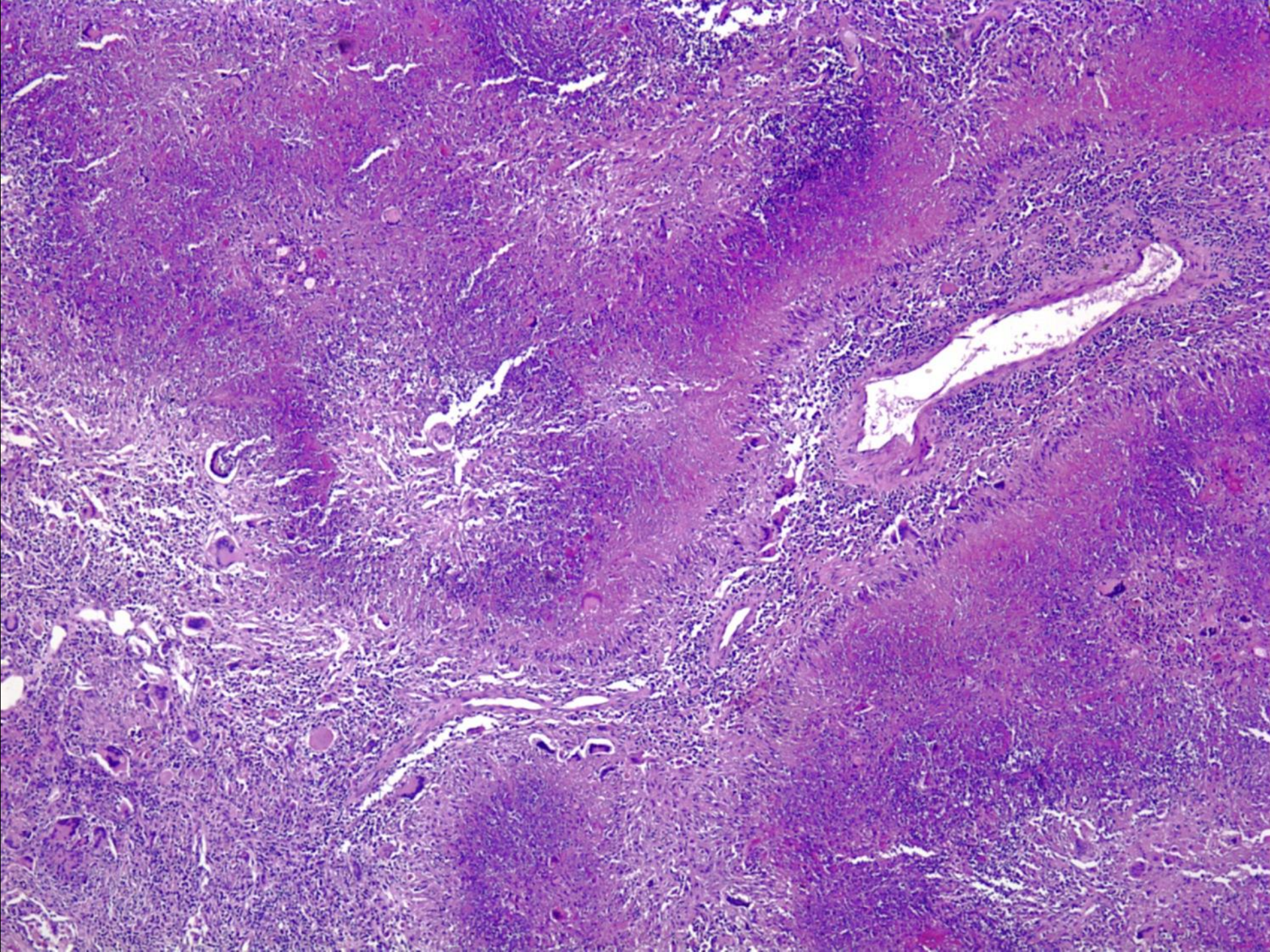
Infectious Granulomas vs Vasculitis

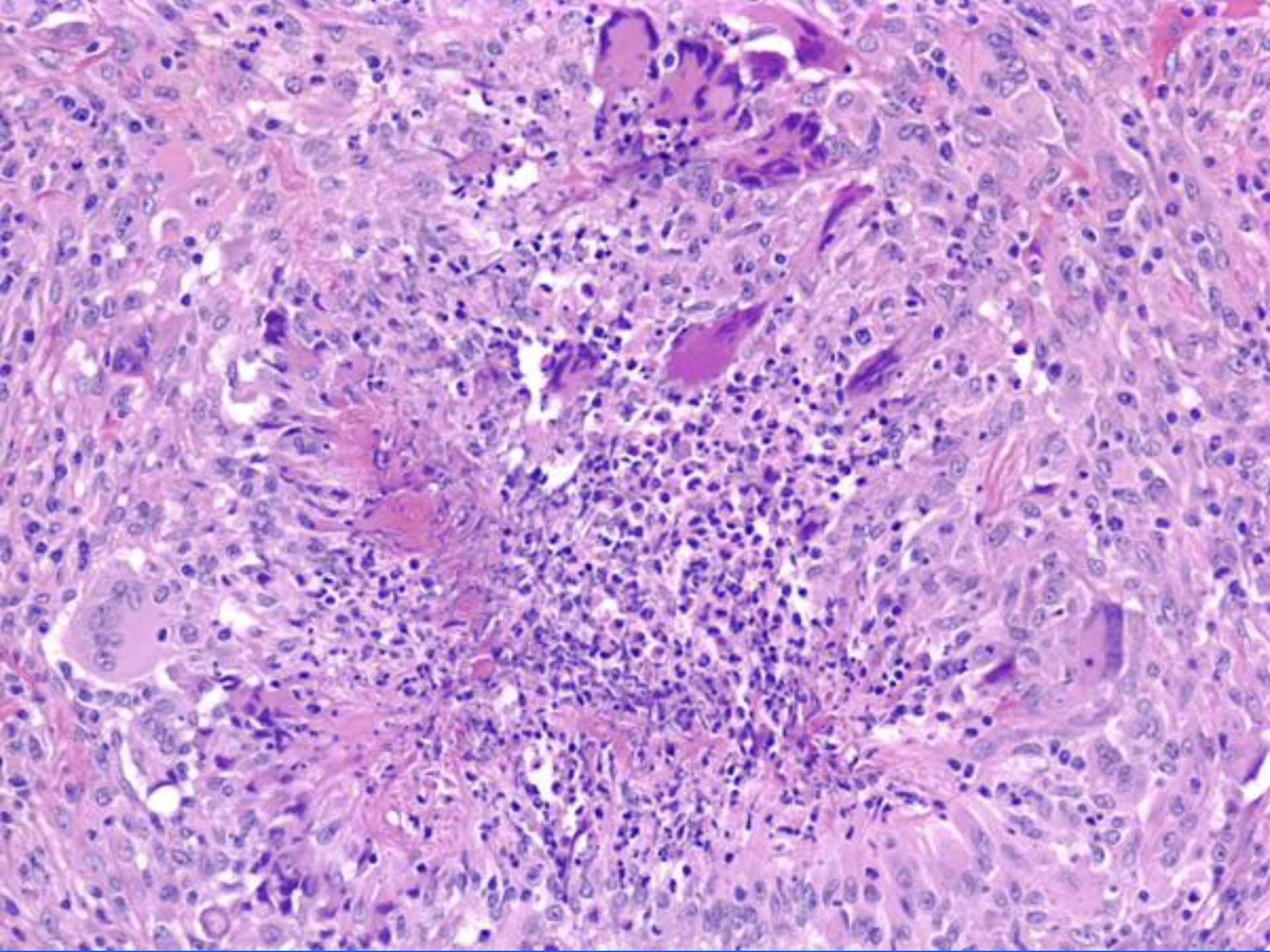
- *Infection* favored
 - Non-necrotizing granulomas
 - Sarcoid-like granulomas
 - Thin rim of inflammation
 - Giant cells that contain inclusions
- Diagnosis of infection may take
 - Repeating special stains
 - Doing stains on more blocks

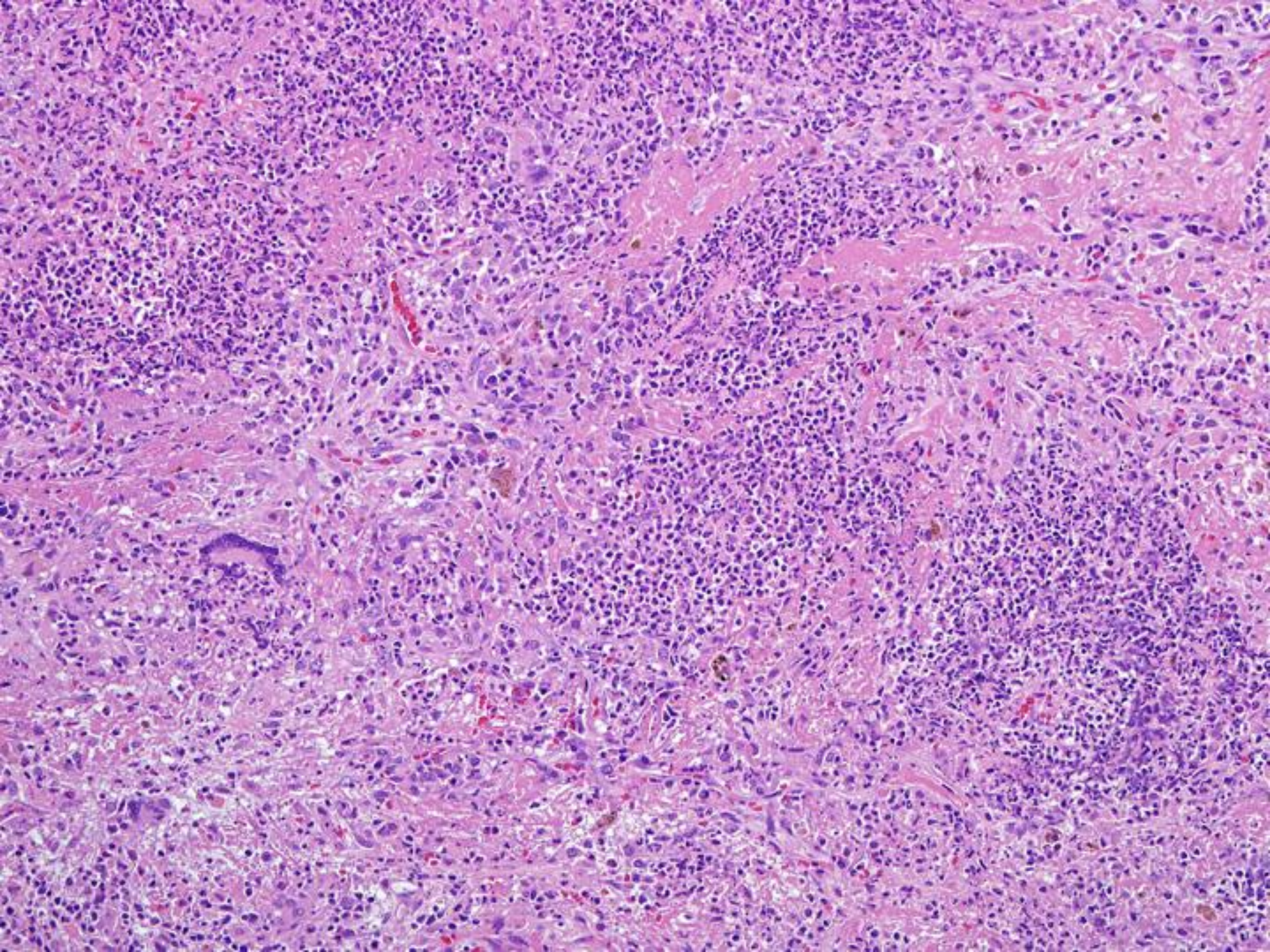
Vasculitis and Geographic Necrosis not helpful

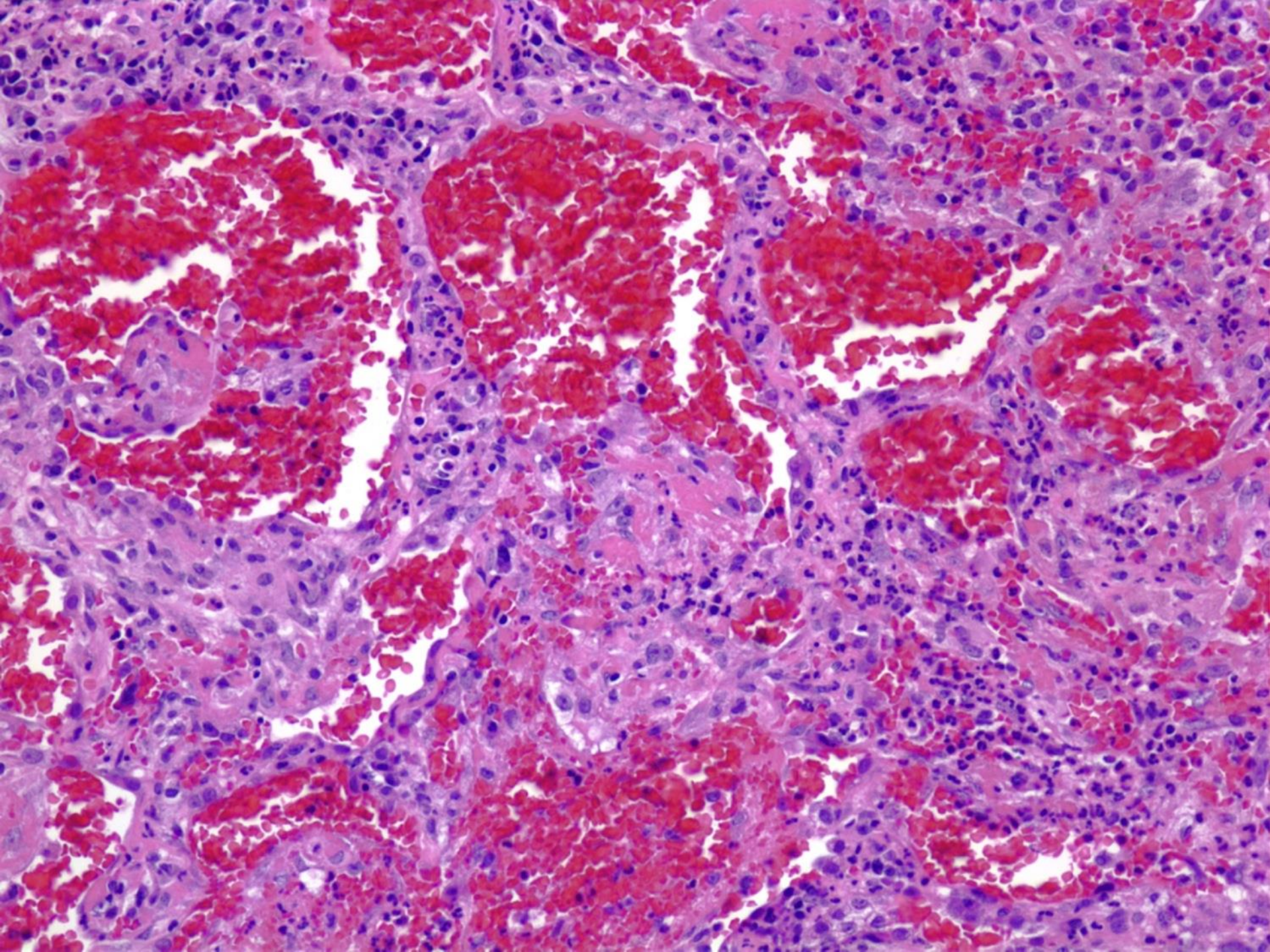
Infectious Granulomas vs Vasculitis

- ***Vasculitis* favored**
 - Only necrotizing granulomas
 - All granulomas have geographic necrosis
 - Granulomas/necrosis set in inflammatory background
 - Microabscess-like foci
 - Bizarre hyperchromatic nuclei in GC's
 - NO inclusions in GC's
 - Foci of alveolar hemorrhage or capillaritis









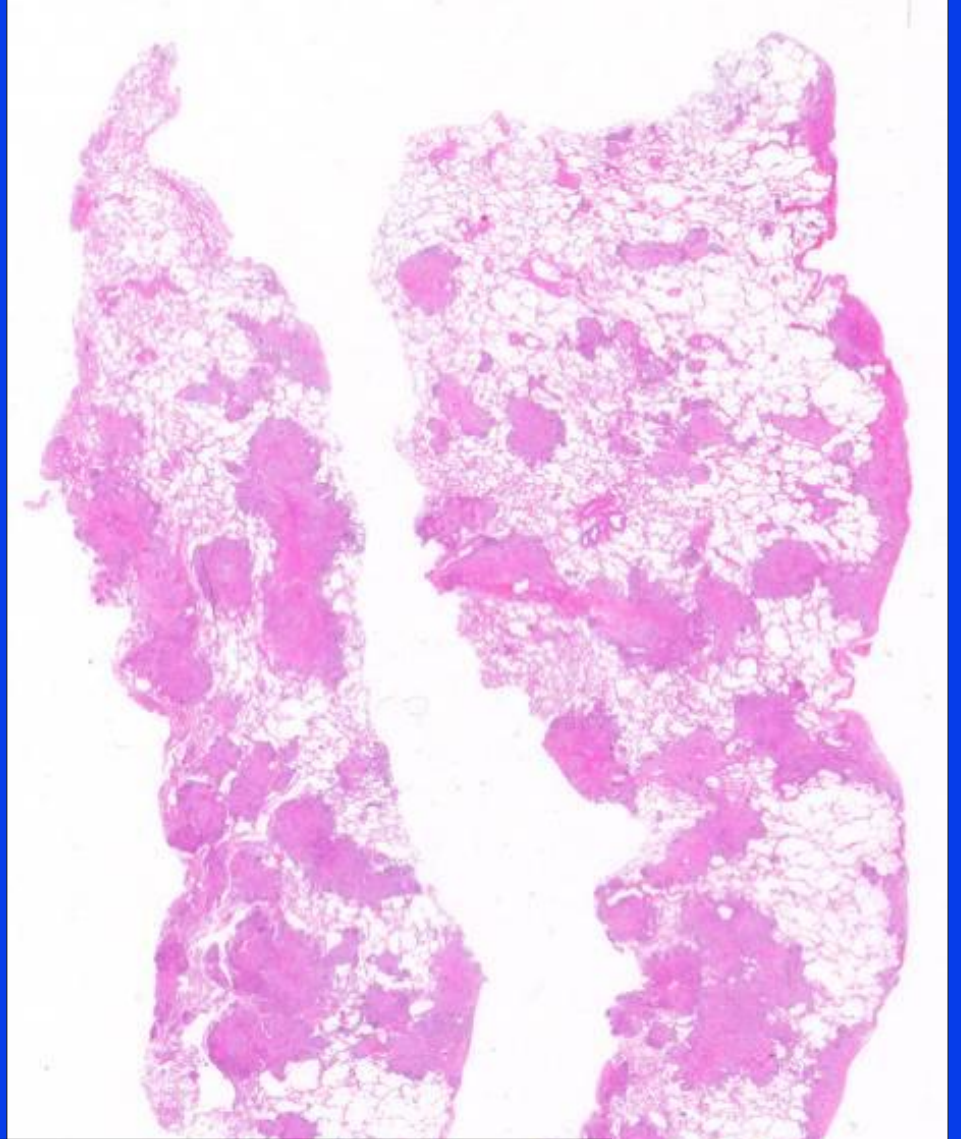
Wegener Granulomatosis /Granulomatosis with Polyangiitis

- **May present as solitary pul nodule**
- **cANCA negative in ~ 30% of patients with limited disease**

Pulmonary Sarcoidosis

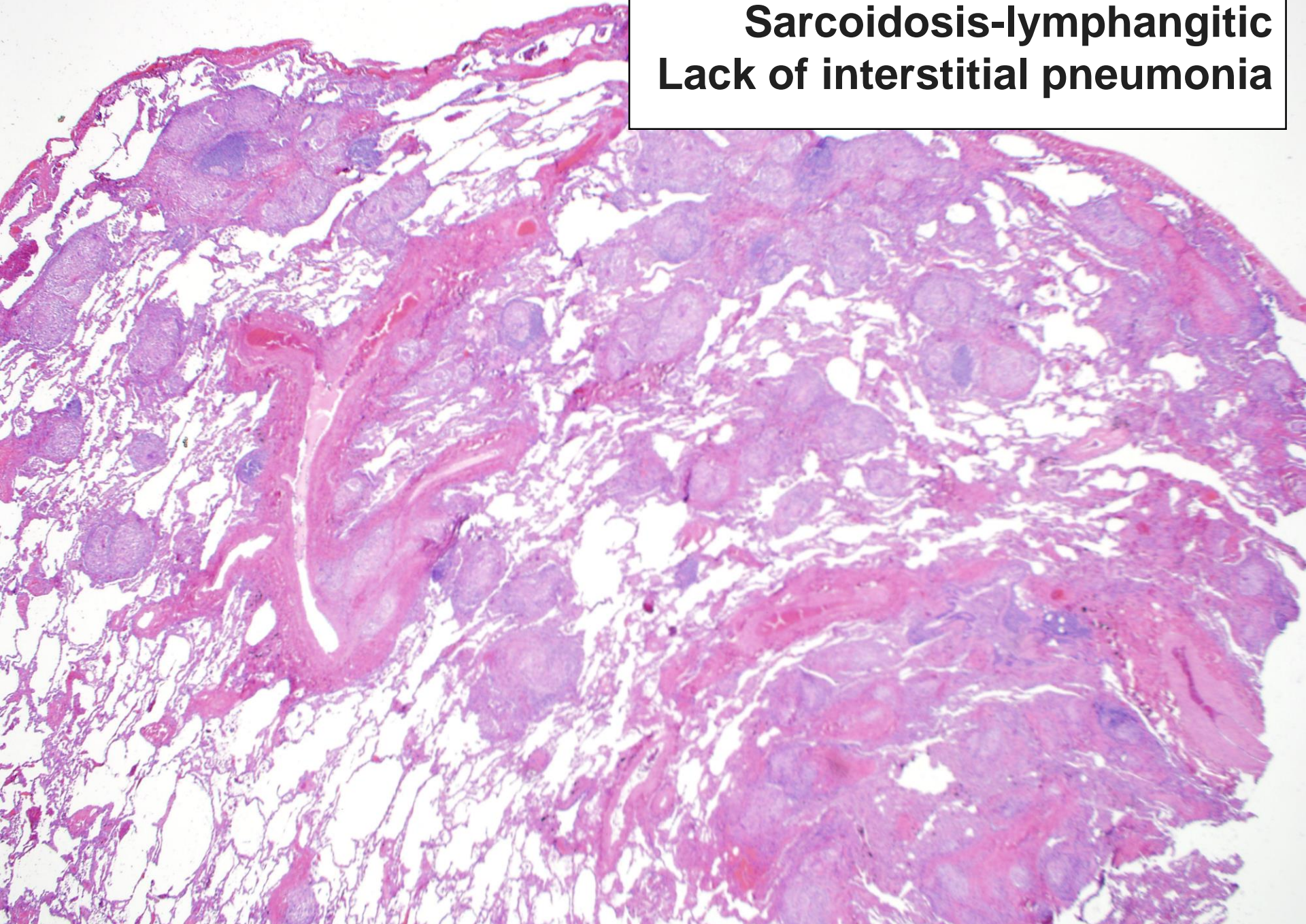
Histology

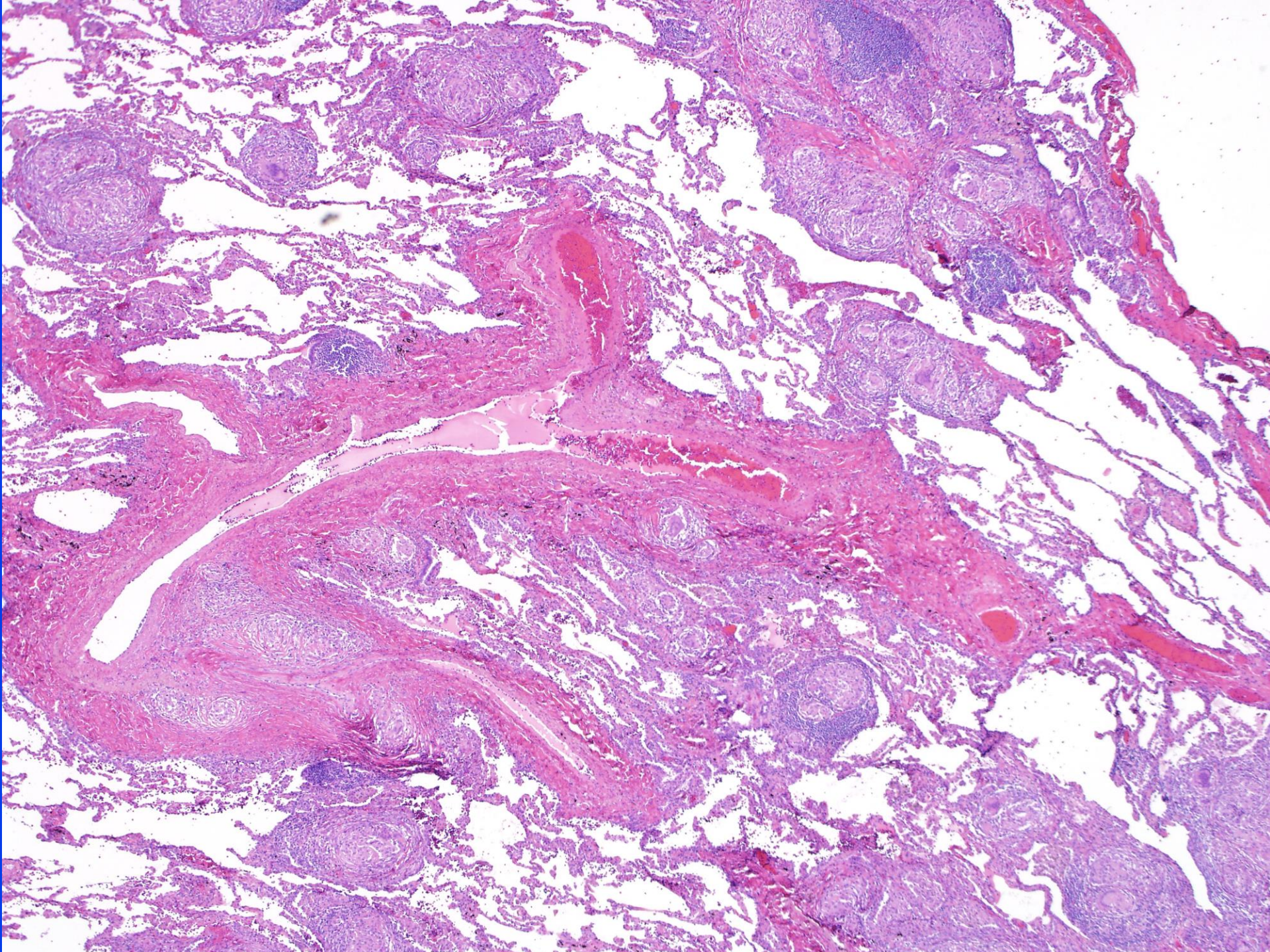
- **Granulomatous inflammation**
 - **Lymphangitic**
 - **Well-formed**
 - **Often hyalinized**
- **Rare**
 - **Isolated giant cells**
 - **Interstitial and organizing pneumonia**



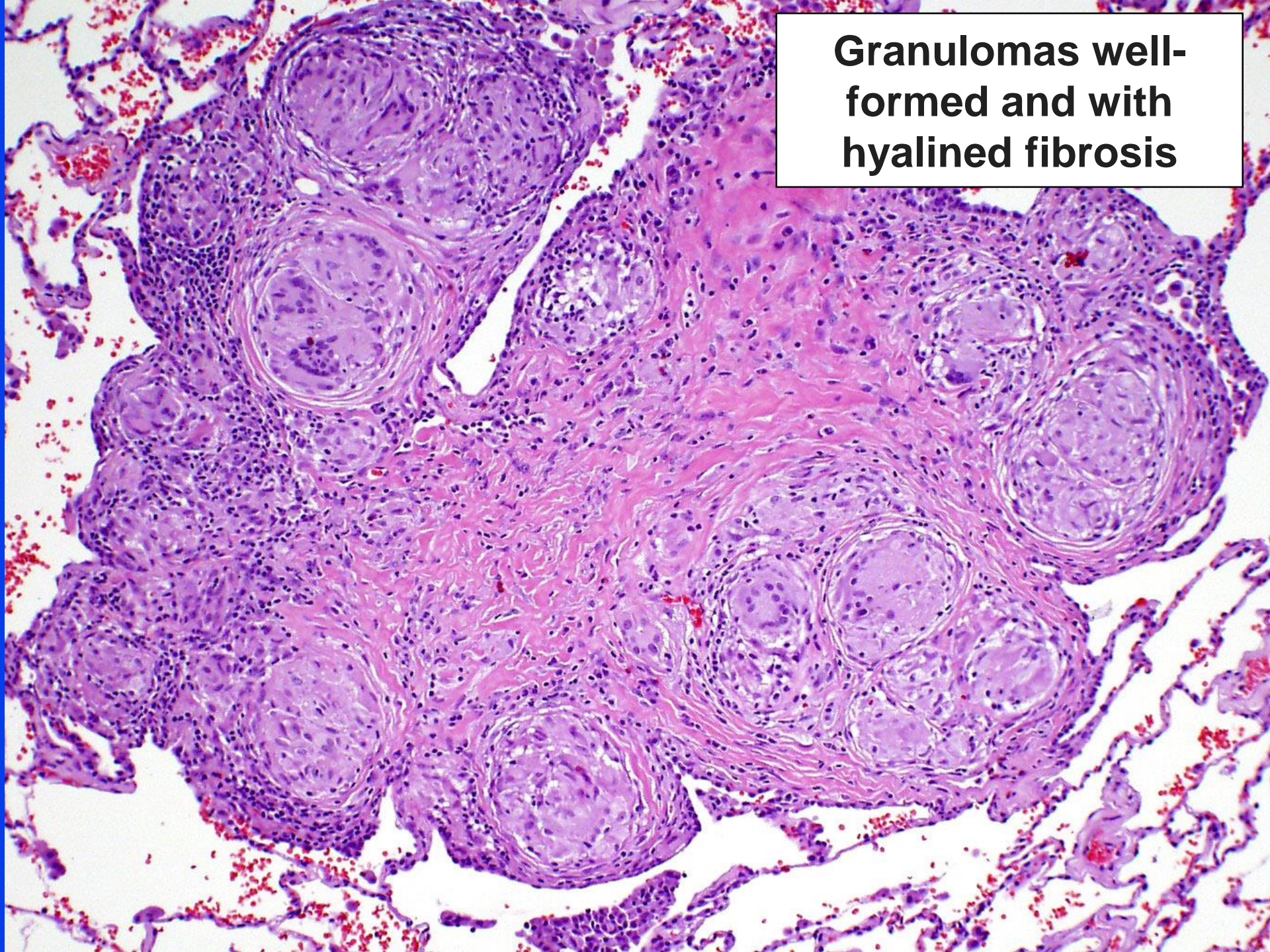
Sarcoidosis-lymphangitic

Sarcoidosis-lymphangitic
Lack of interstitial pneumonia

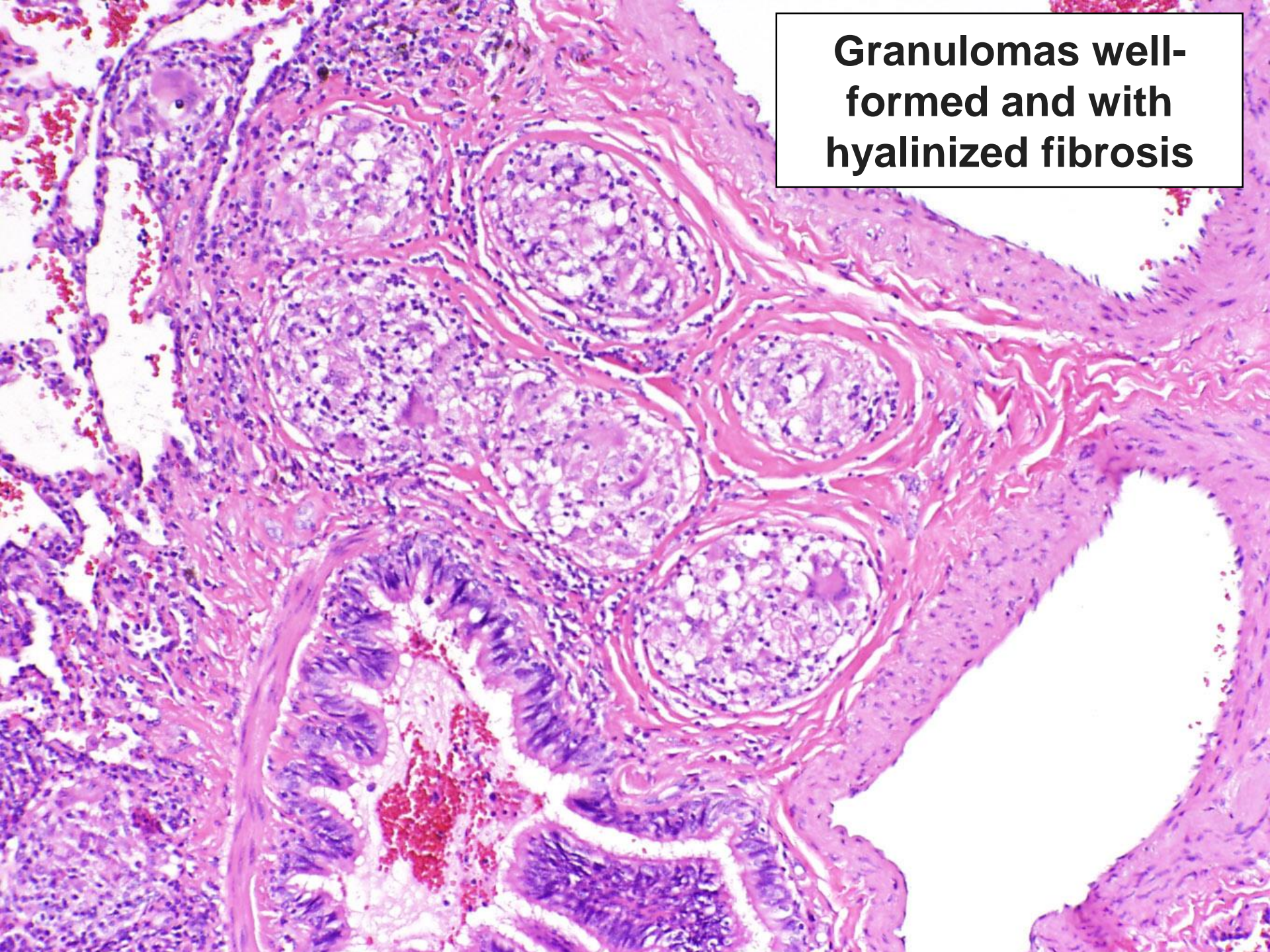




Granulomas well-formed and with hyalined fibrosis



**Granulomas well-
formed and with
hyalinized fibrosis**



Sarcoid :



Features

- **Non-necrotizing granulomatous inflammation without**
 - **Chronic interstitial pneumonia**
 - **Organizing pneumonia**
- **Inclusions usually endogenous**

Pulmonary Sarcoid

Differential Diagnosis

- **Hypersensitivity pneumonitis**
 - **Hot tub lung**
- **Infection**
 - **MAC: bronchiectasis**
- **Berylliosis**

Hypersensitivity Pneumonitis

Diagnosis?

- **Exposure history? only in 50%**
- **Antibodies testing?**
 - **Antibodies not available for many antigens**
 - **Many “exposed” but not ill patients antibodies +**
 - **Currently NOT recommended in work up**

Hypersensitivity Pneumonitis

Diagnosis?

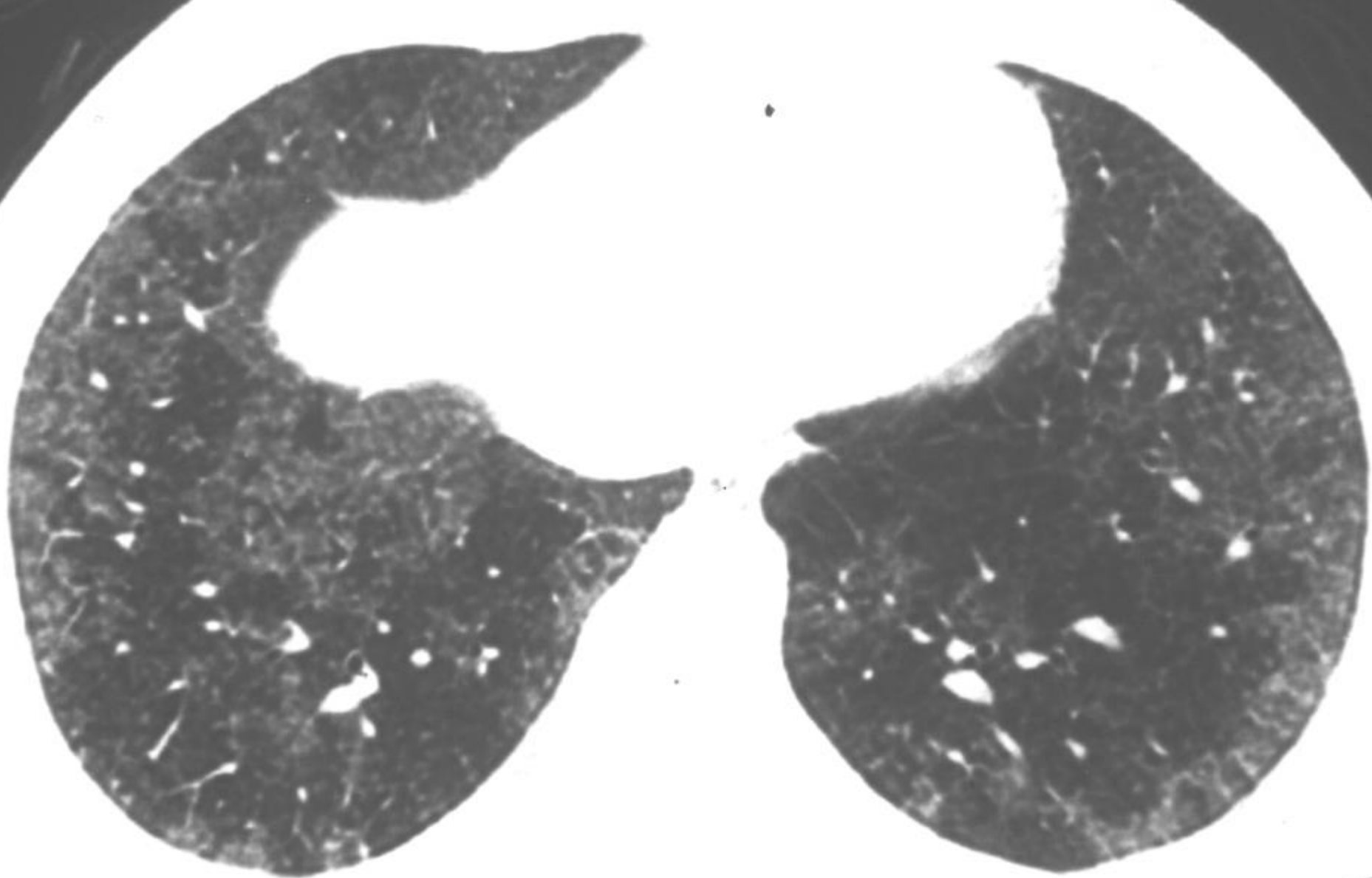
- **A difficult clinical challenge**
- **Compatible clinical, radiographic or physiologic findings**
- **BAL with lymphocytosis (low CD4:8)**
- **Histopathology**

Hypersensitivity Pneumonitis

Clinical Presentations*

- **Acute: dyspnea, cough, myalgias, chills etc.**
 - **2- 9 hours after exposure**
 - **Resolves without specific therapy**
- **Subacute/Chronic: dyspnea, cough, weight loss, anorexia**
 - *depends on intensity and duration of exposure**

Extrinsic Allergic Alveolitis



Hypersensitivity Pneumonitis

Histologic Features

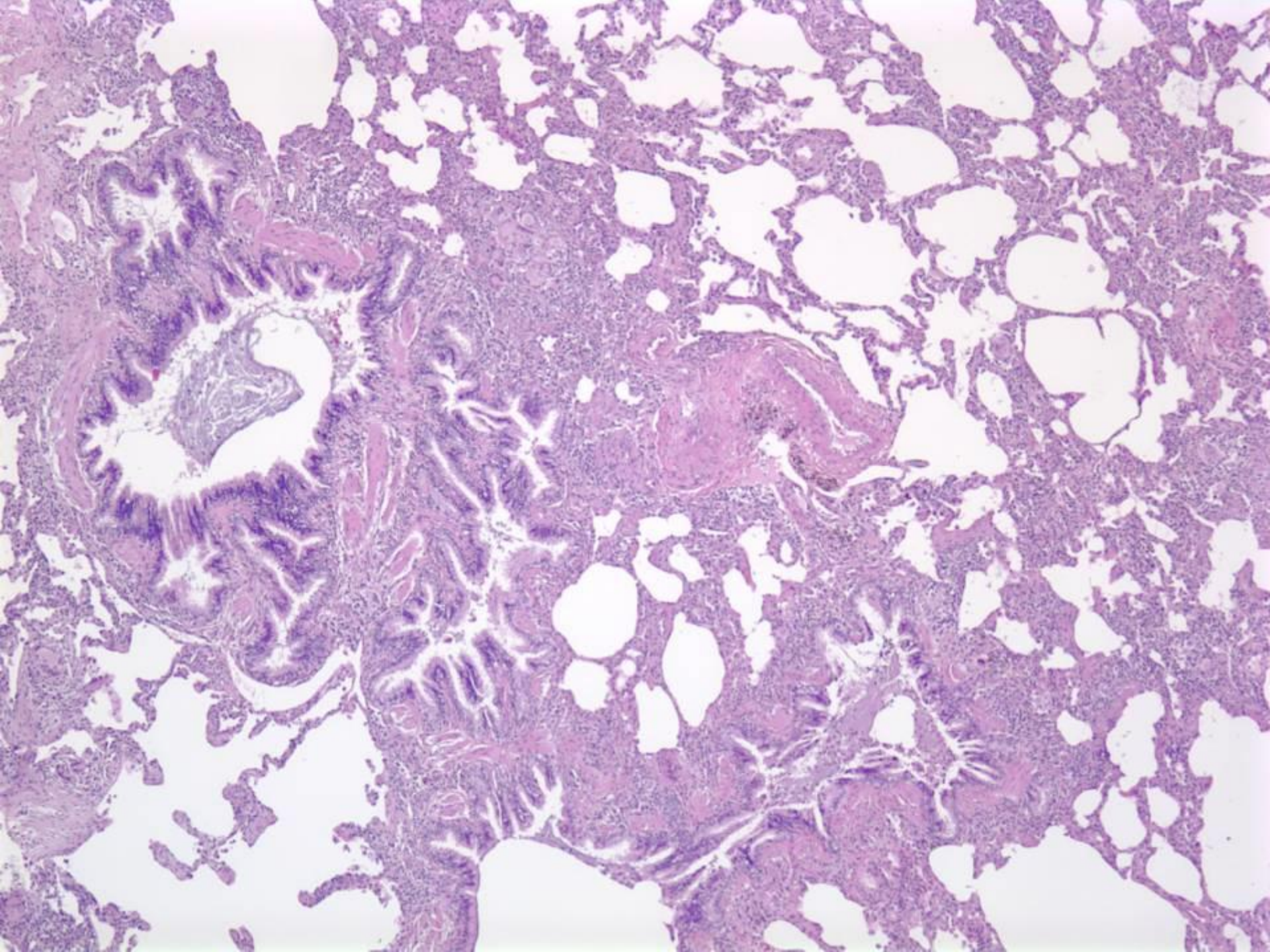
- Non-nec granulomatous inflamm and giant cells
 - Airway-centered *and random*
 - Interstitial *and airspace*
- Interstitial pneumonia
- Chronic bronchiolitis

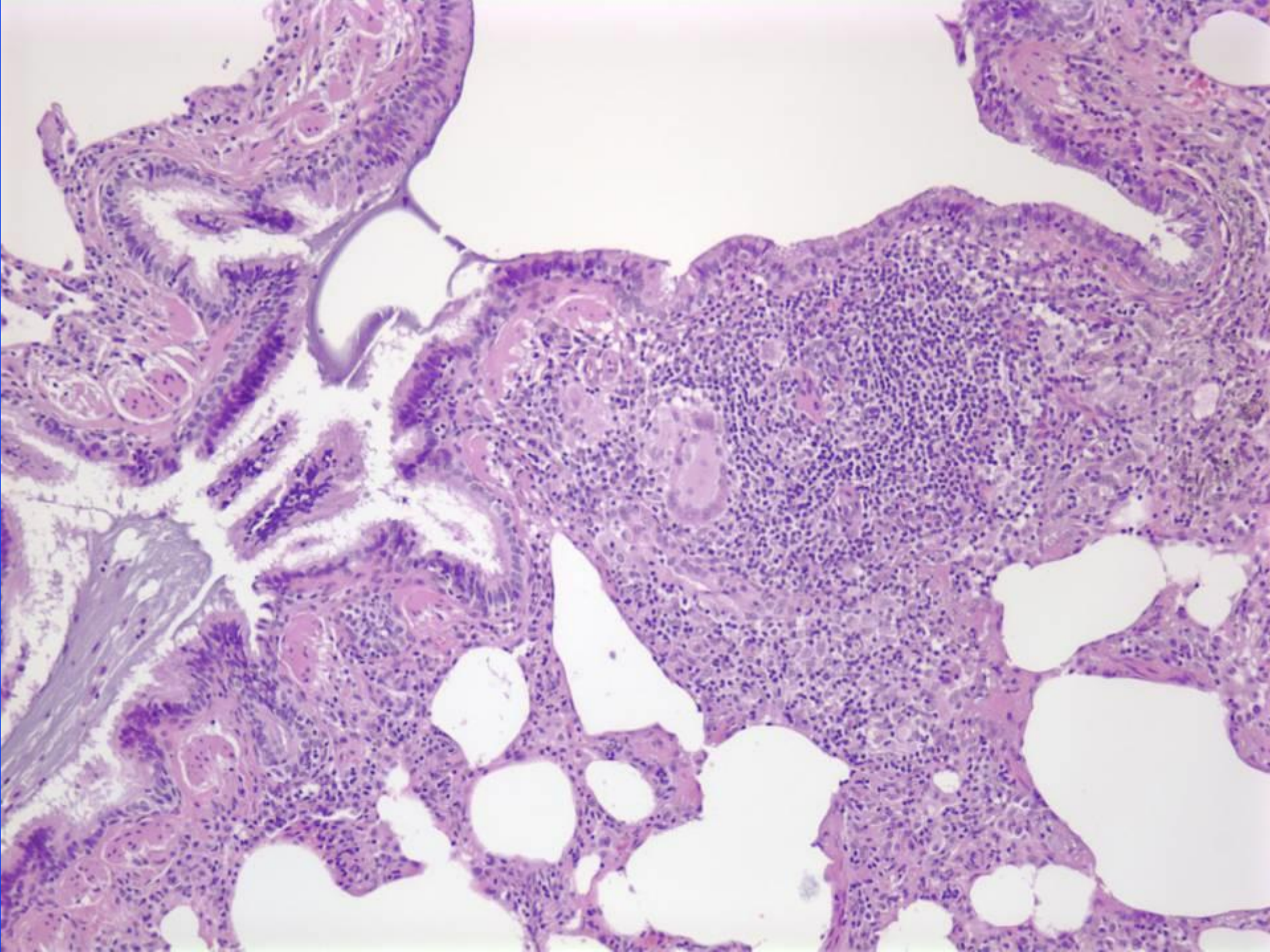
Hypersensitivity Pneumonitis

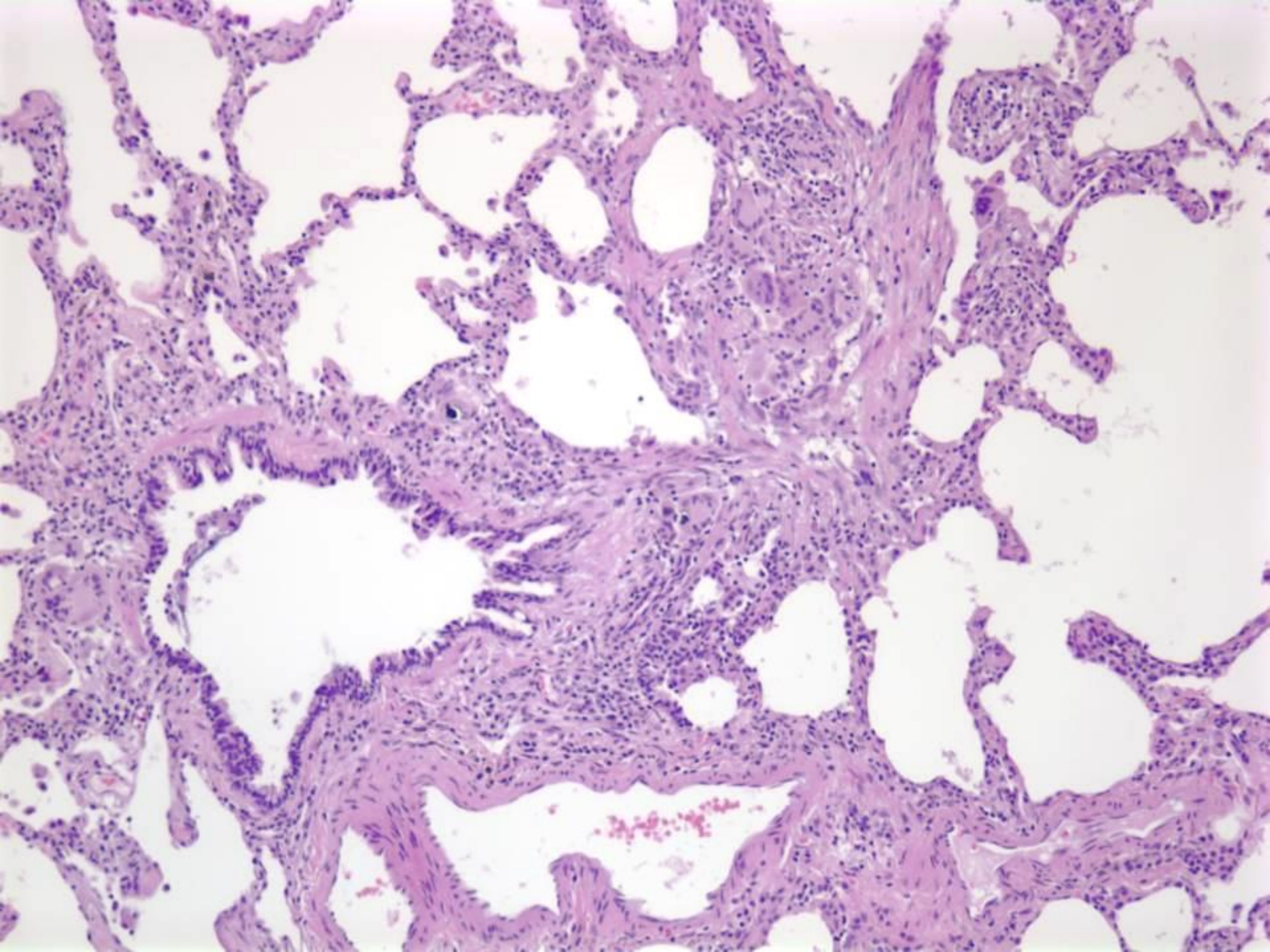
Variable Histologic Features

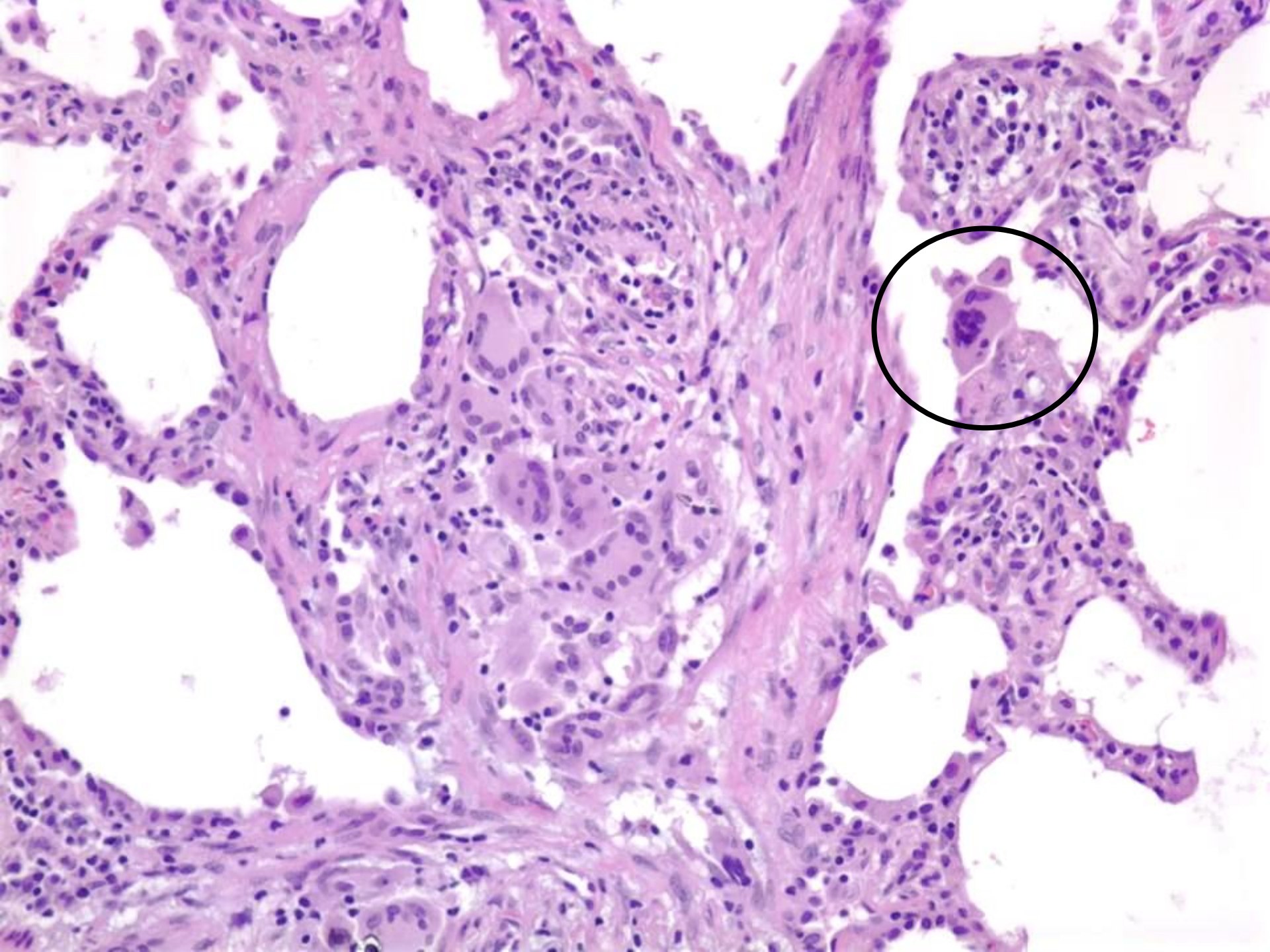
- Prominent centrilobular airspace foam cells
- Organizing pneumonia
- Interstitial fibrosis
- Honeycomb change/ UIP-like features

Eosinophils uncommon
Only 20%







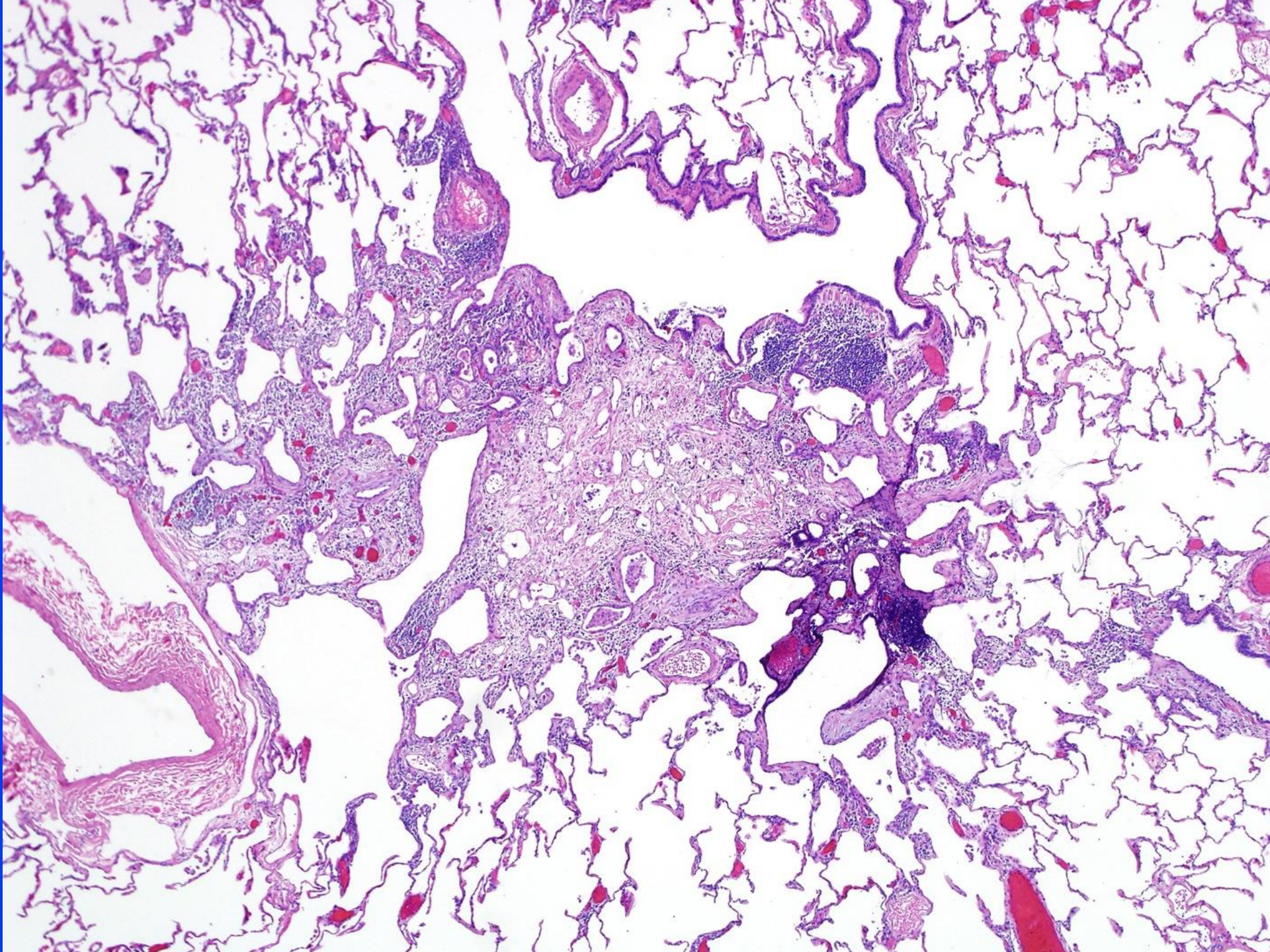


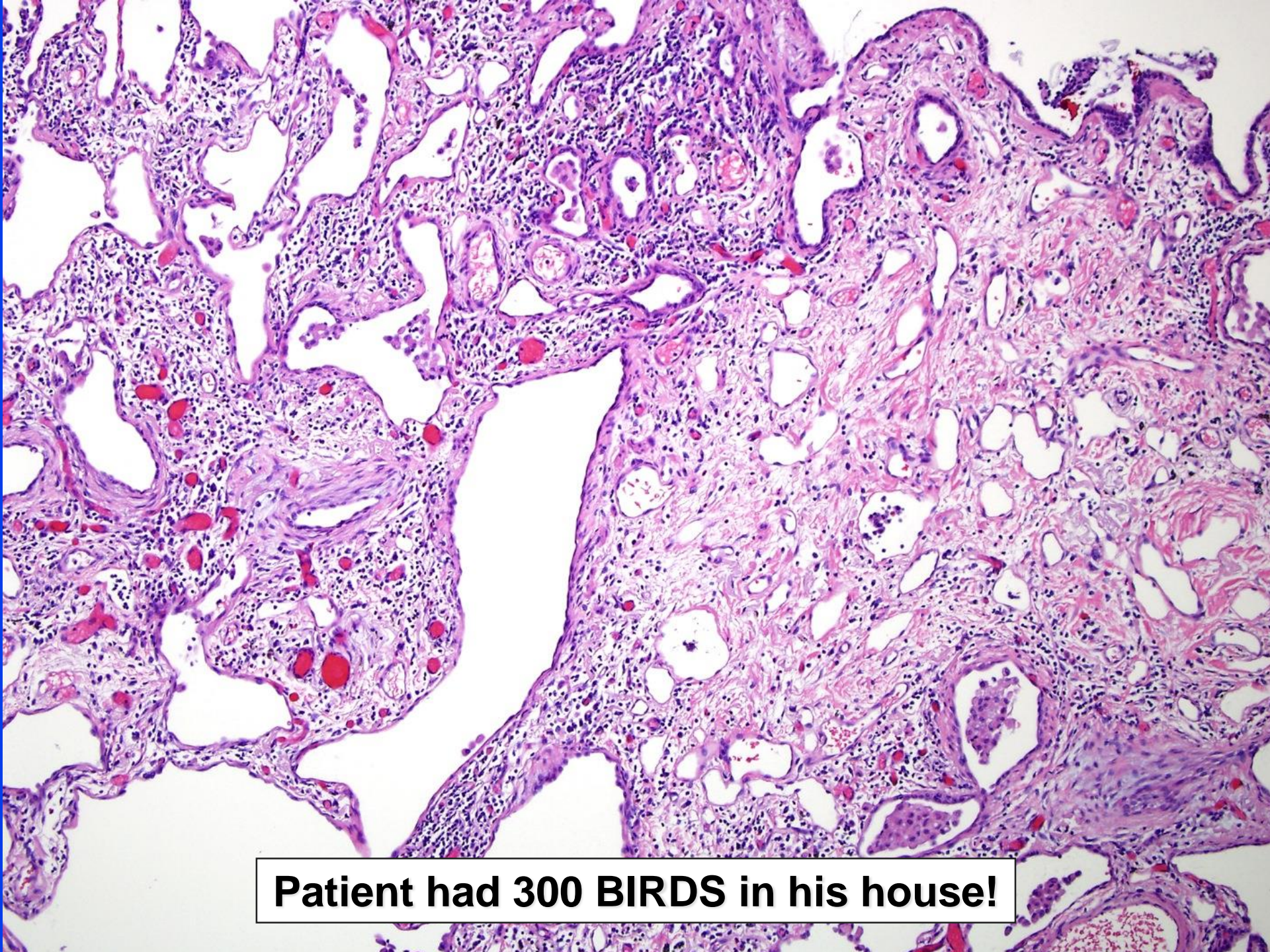
Major Histologic Patterns in HP

n=110 (%)

Cell. NSIP	F NSIP	UIP	Peribronchiolar inflamm with grans	Bronchiolocentric fibrosis
45	20	6	20	9

- 19% of cases had no granulomas or giant cells
- Granulomas and giant often absent in cases with fibrosis





Patient had 300 BIRDS in his house!

Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis

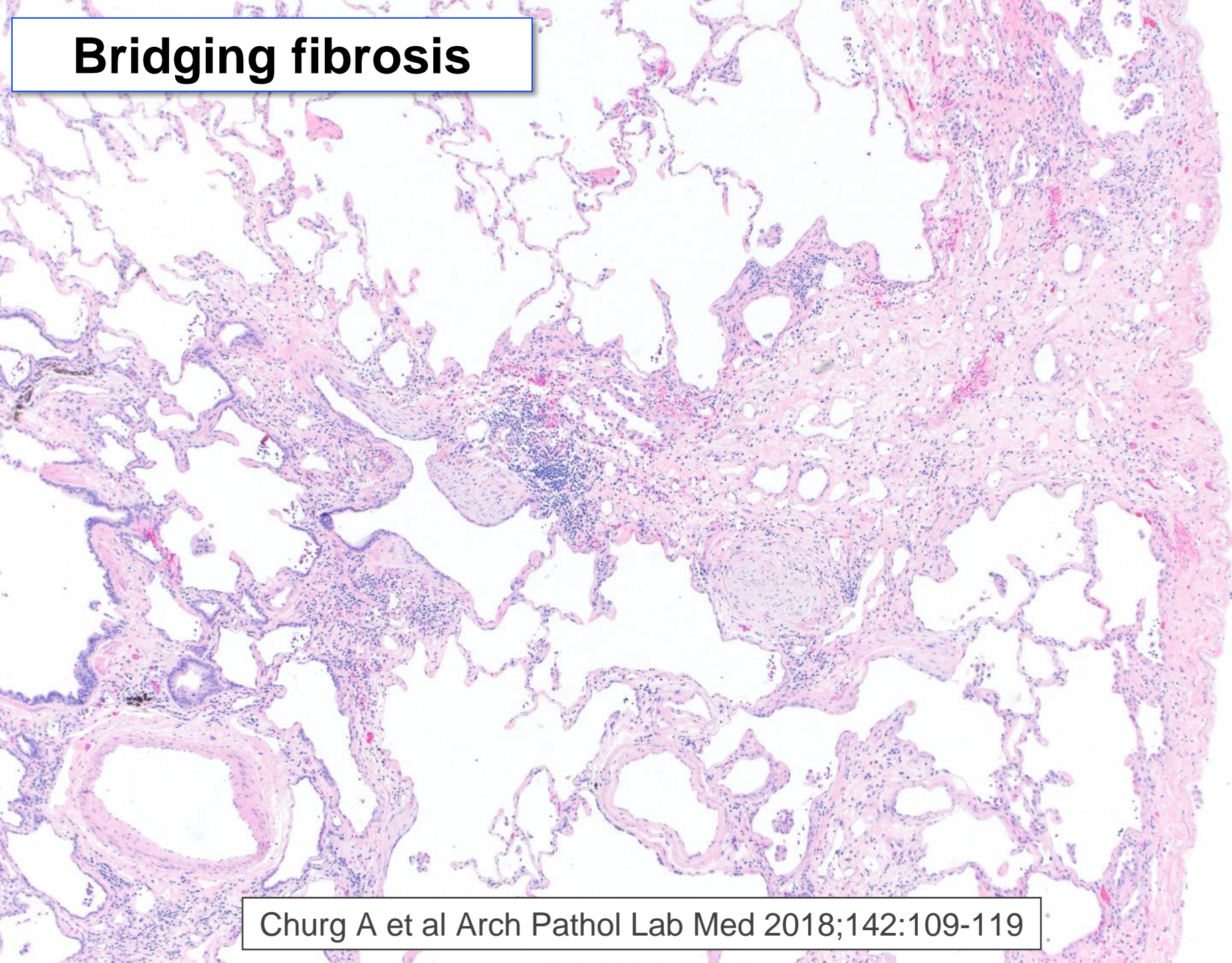
- 20/46 pts with IPF according to 2011 ATS/ERS guidelines were subsequently diagnosed with chronic HP
- Bronchial challenge, lung biopsy and serum precipitins
- Most attributed to occult avian antigen exposure from...
down bedding



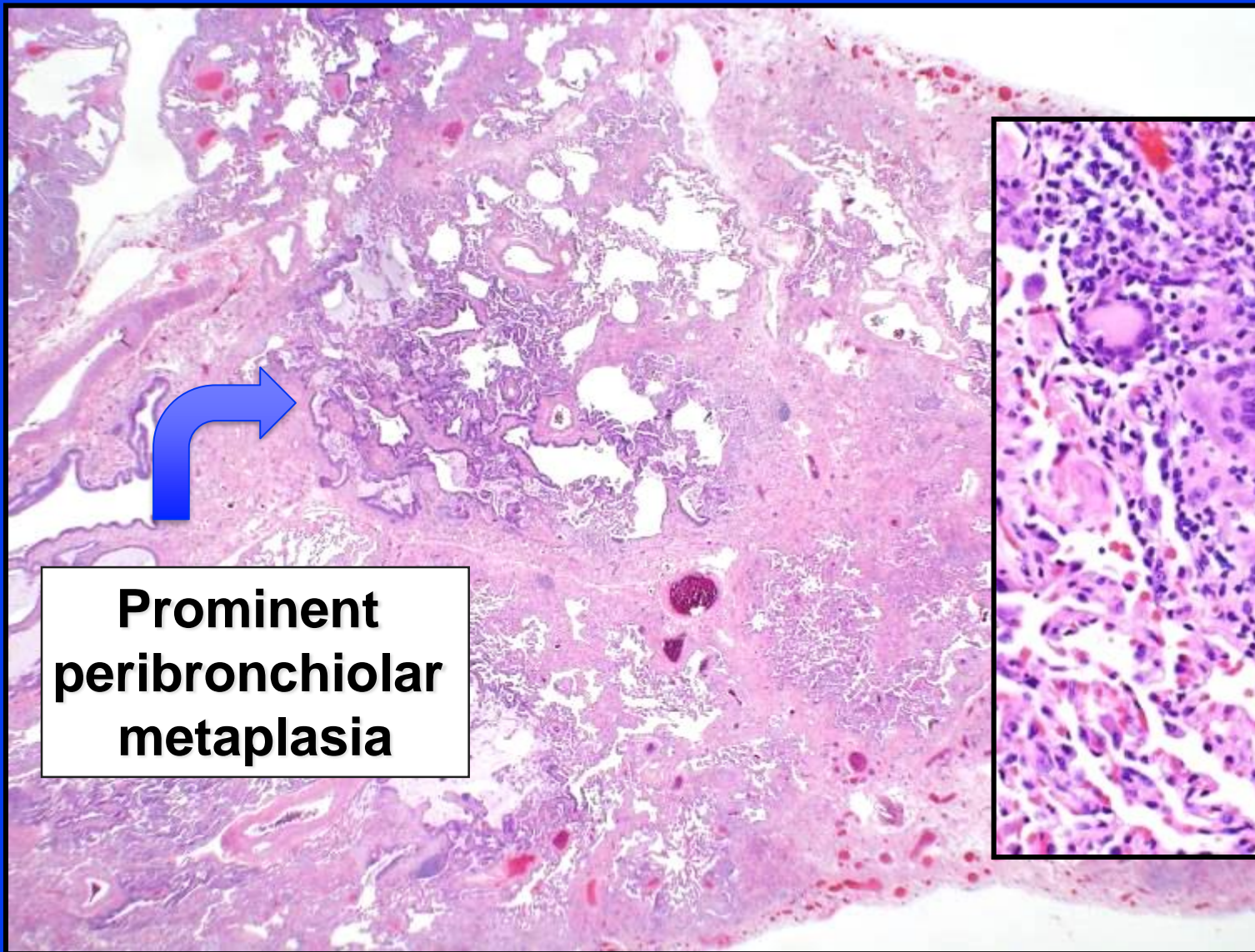
Clues to the Diagnosis of HP

Feature	Pattern	
	UIP	NSIP
Mosaicism/air trapping	++	++
Granulomas and giant cells	++	++
Bronchiolocentric inflammation	++	++
Peribronchiolar metaplasia	++	+
Bridging fibrosis	+	+

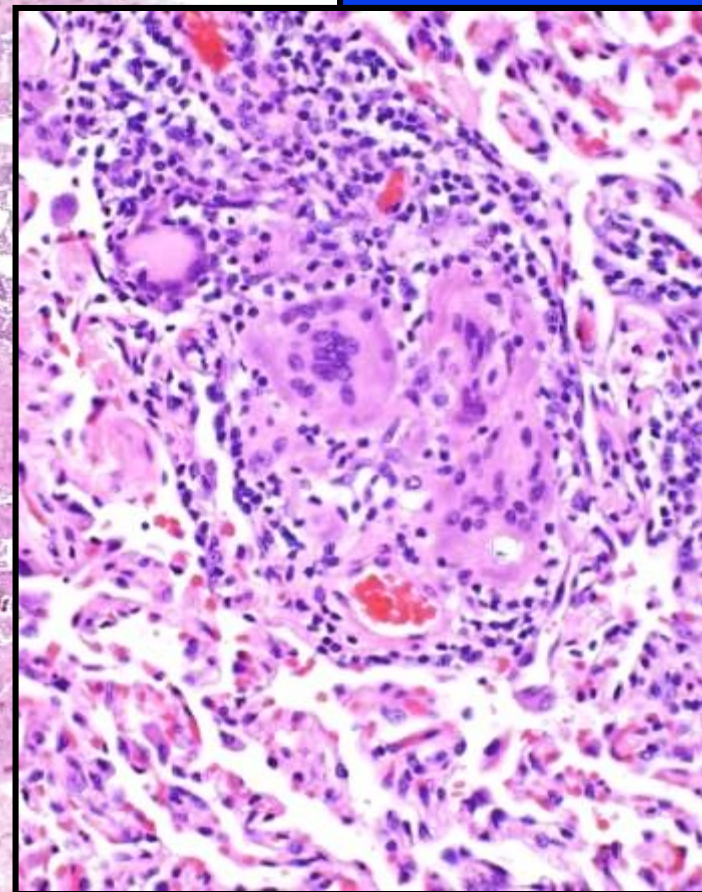
Bridging fibrosis



Chronic HP with UIP pattern



**Prominent
peribronchiolar
metaplasia**



CHP with UIP vs IPF

Does the diagnosis matter?

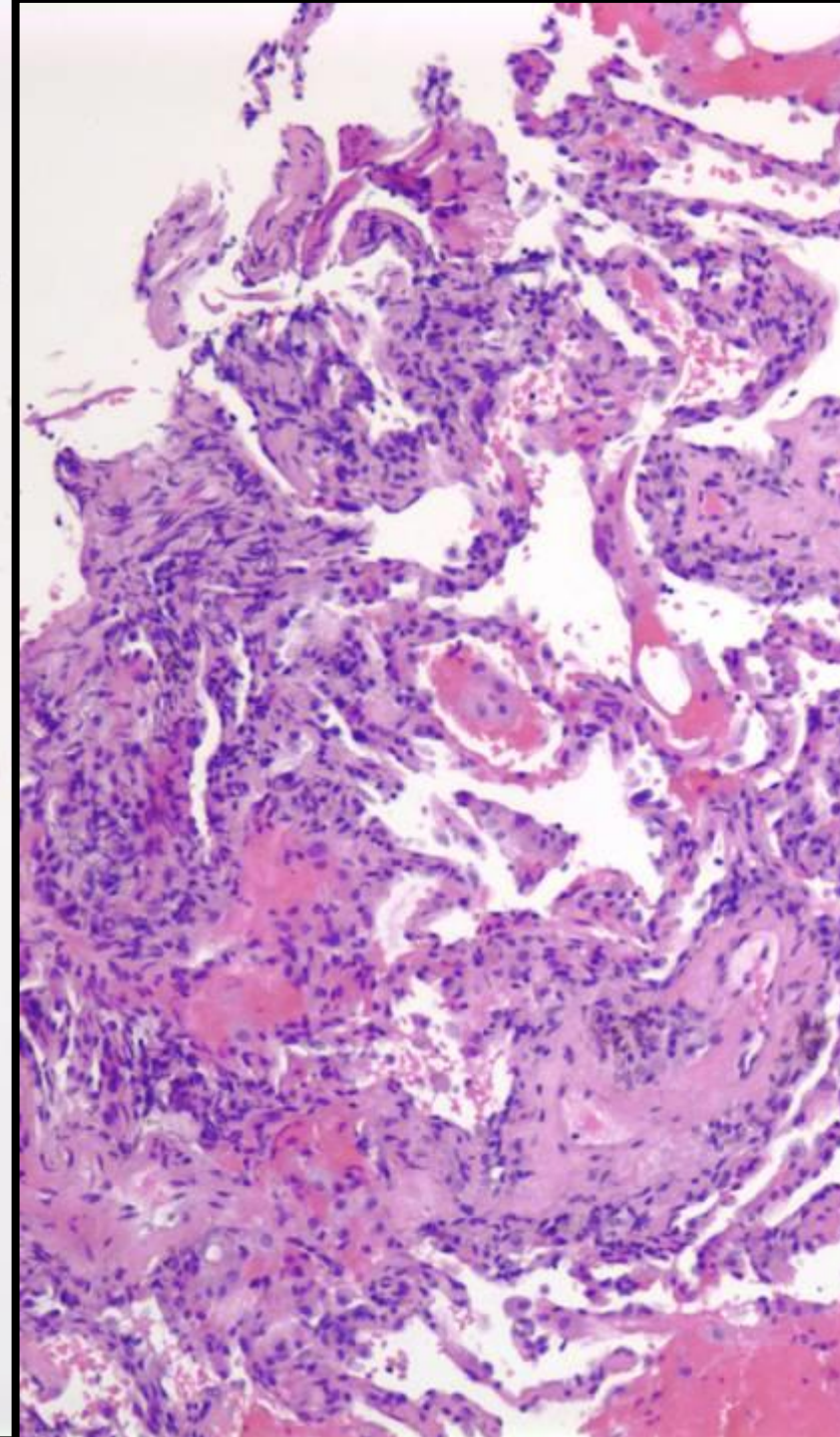
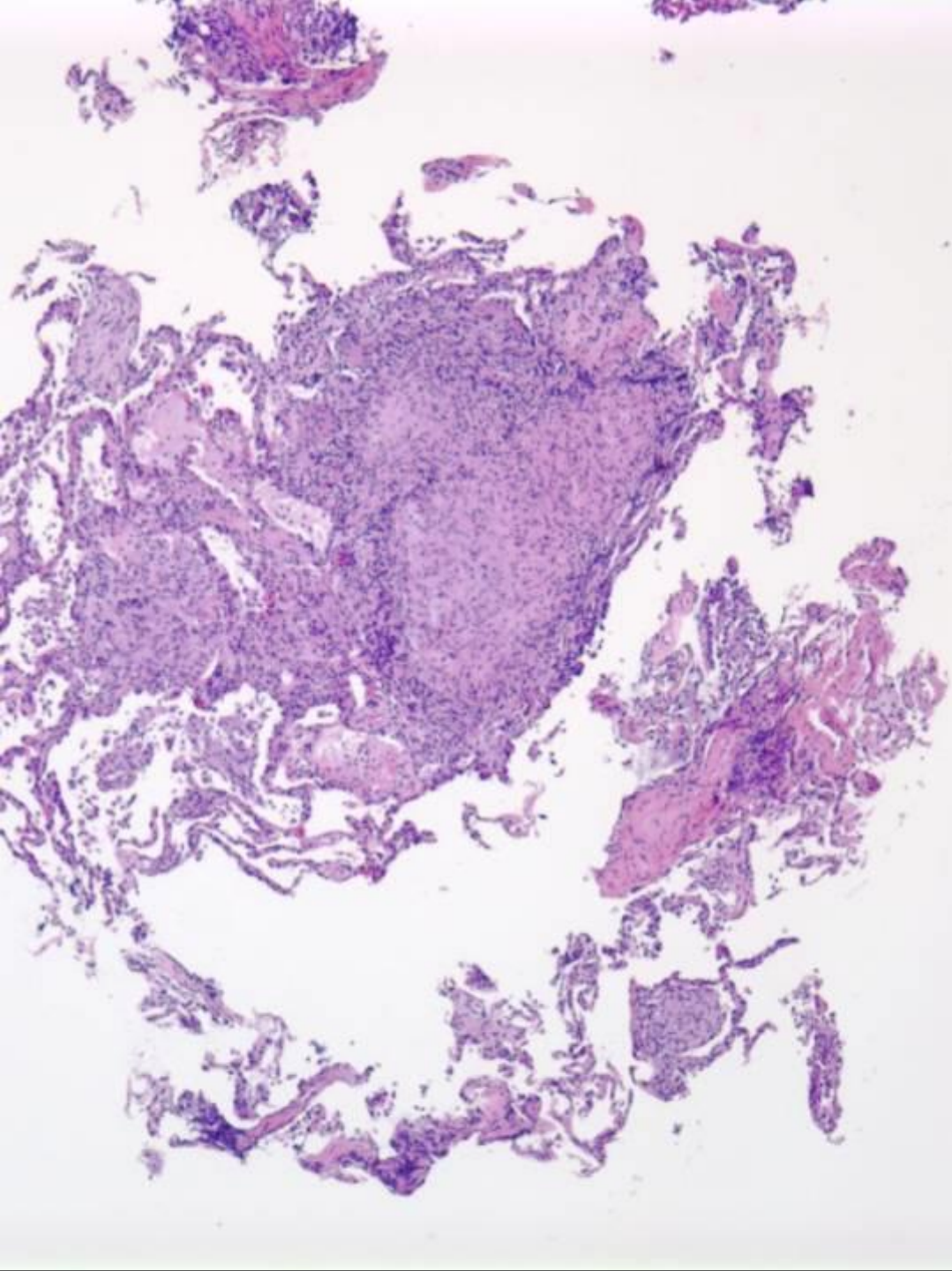
- **Differences in survival-IPF still worse in most studies**
- **Differences in treatment-possible benefit of antigen avoidance**
- **Differences post lung transplant-
CHP may do better than IPF patients**

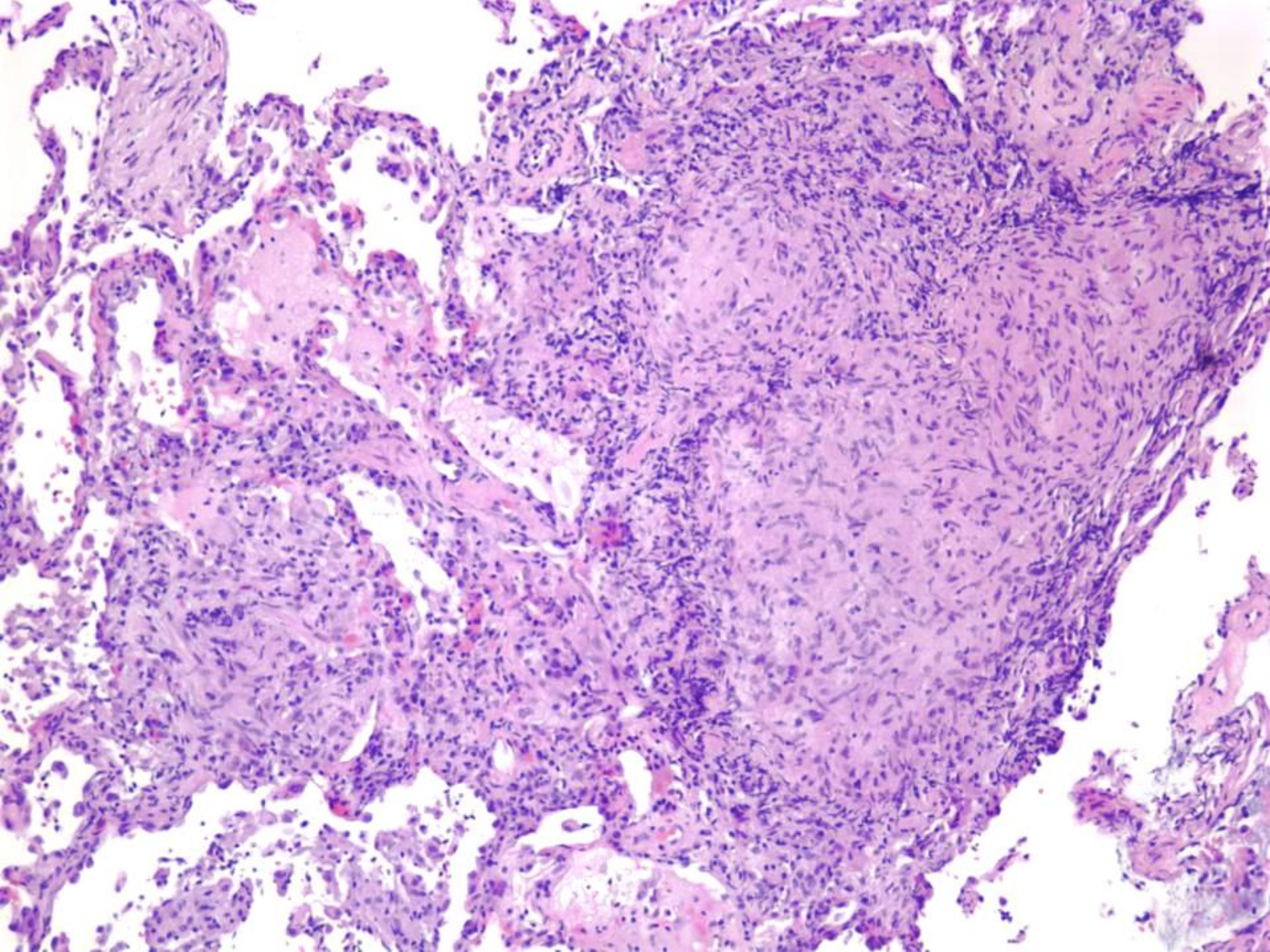
Chronic Hypersensitivity Pneumonitis

- **Increasingly recognized as a cause for non-fibrotic and fibrotic diffuse lung disease**
- **Still no gold standard for diagnosis**
- **Must always be in the differential diagnosis for UIP and NSIP patterns**
- **Subtle clues**

“Hot Tub” Lung

- **Granulomatous lung disease due to exposure to water contaminated with atypical mycobacteria (MAC)**
- **Flu-like illness after exposure**
- **CT: Interstitial and nodular miliary infiltrates**
- **Other water sources: Showers, faucets, saunas**





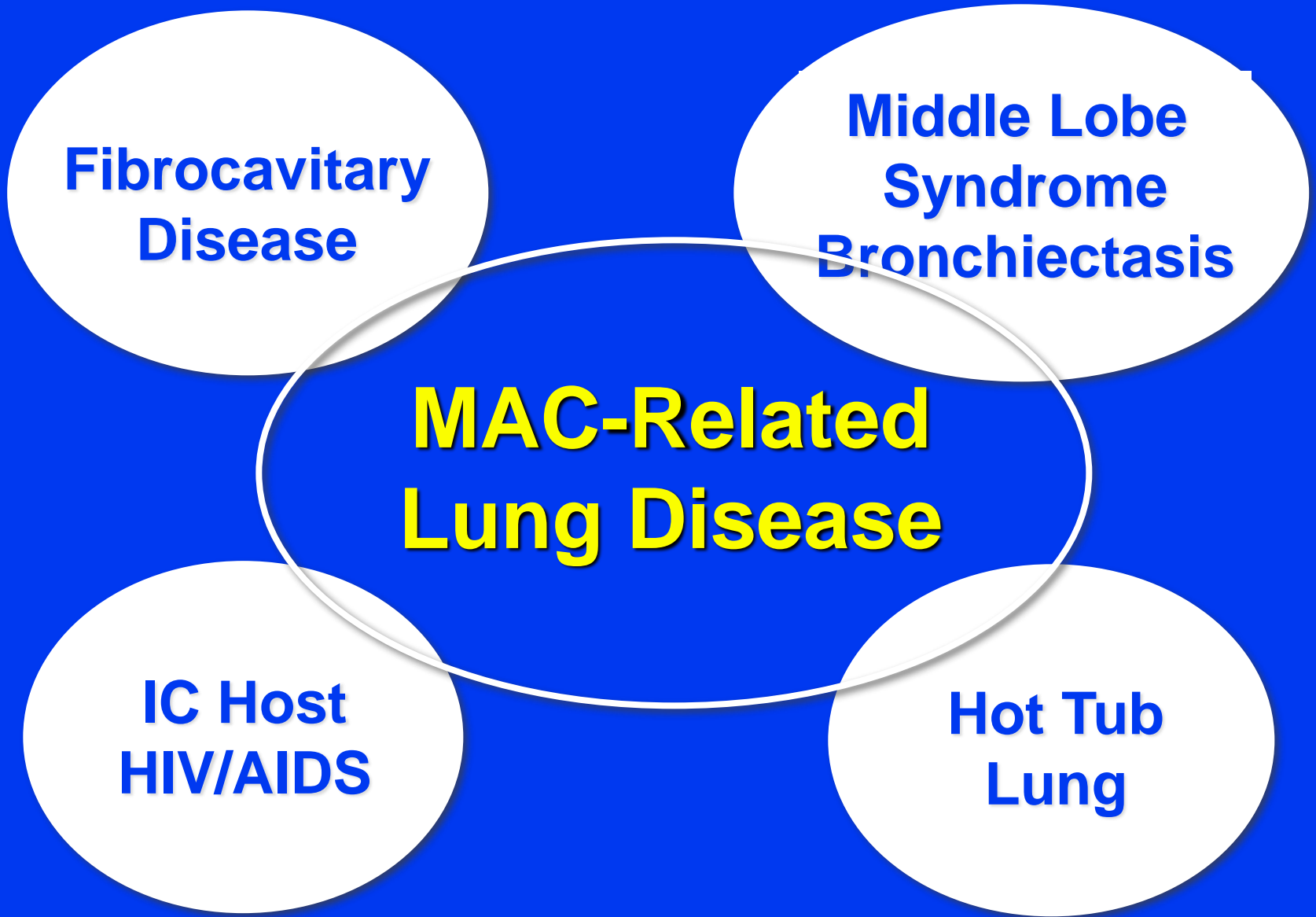
**Fibrocavitary
Disease**

**Middle Lobe
Syndrome
Bronchiectasis**

**MAC-Related
Lung Disease**

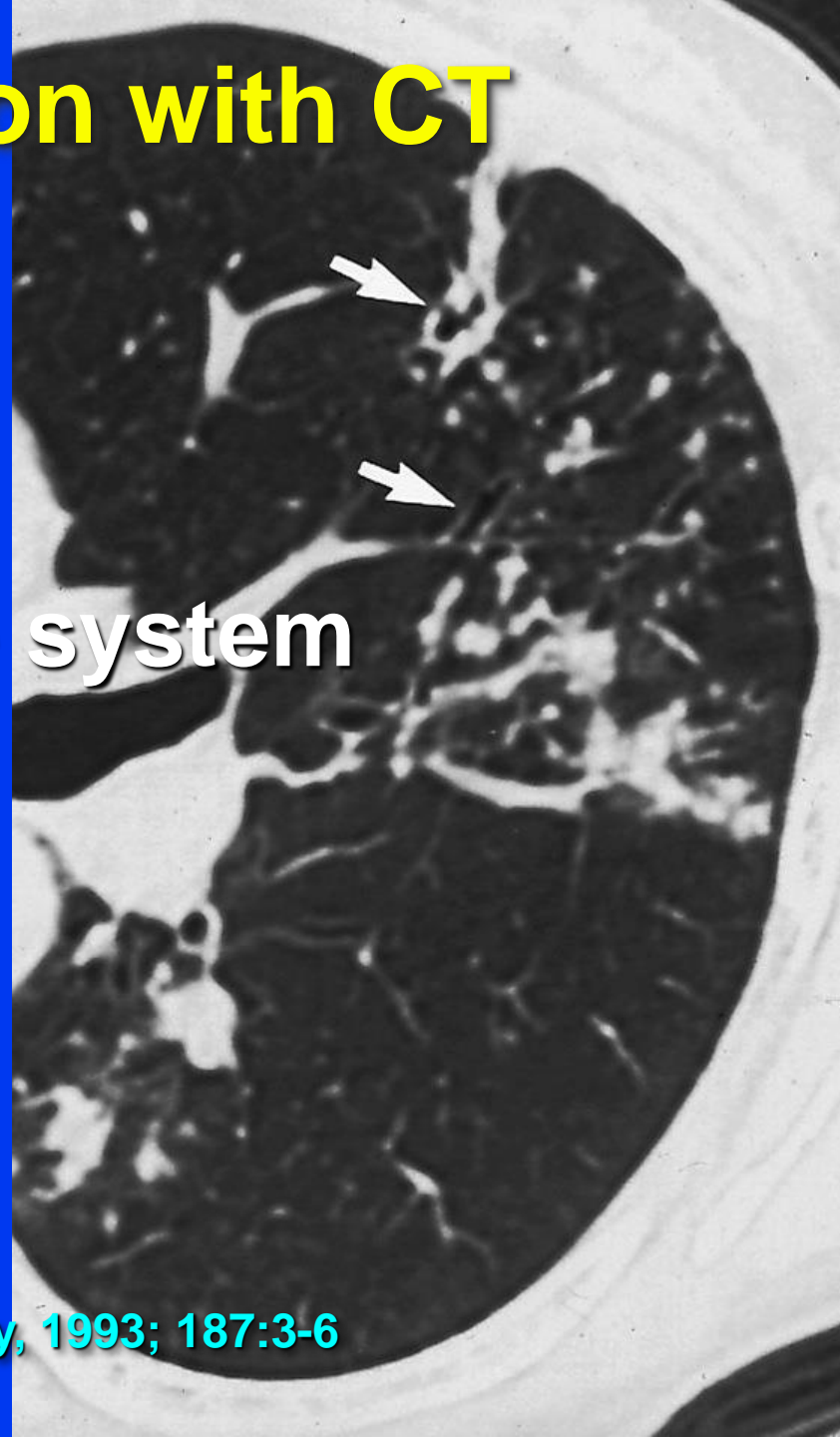
**IC Host
HIV/AIDS**

**Hot Tub
Lung**



MAC: Evaluation with CT

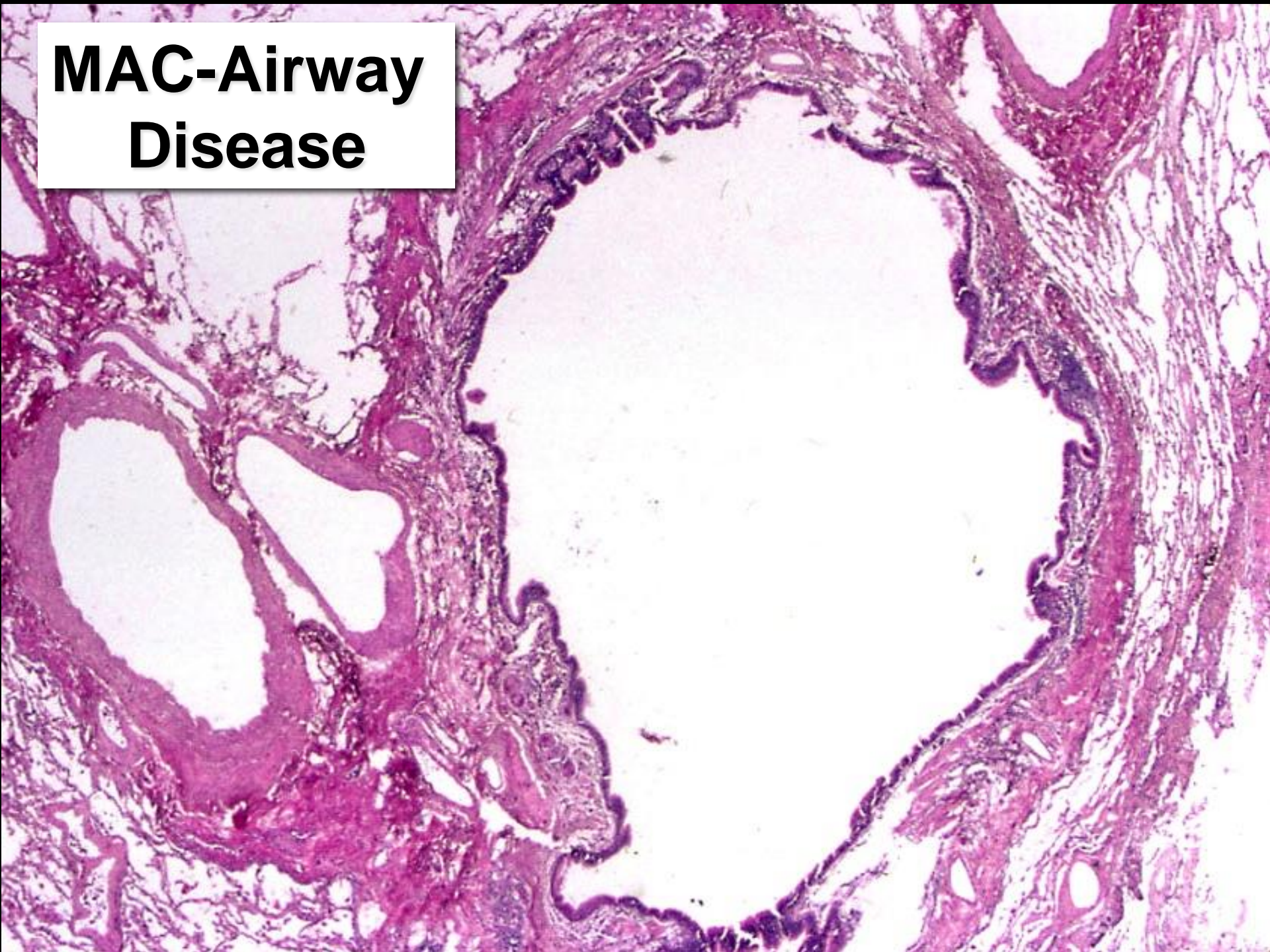
- N=62
- 56 % intact immune system
- Nodular infiltrates
- Bronchiectasis



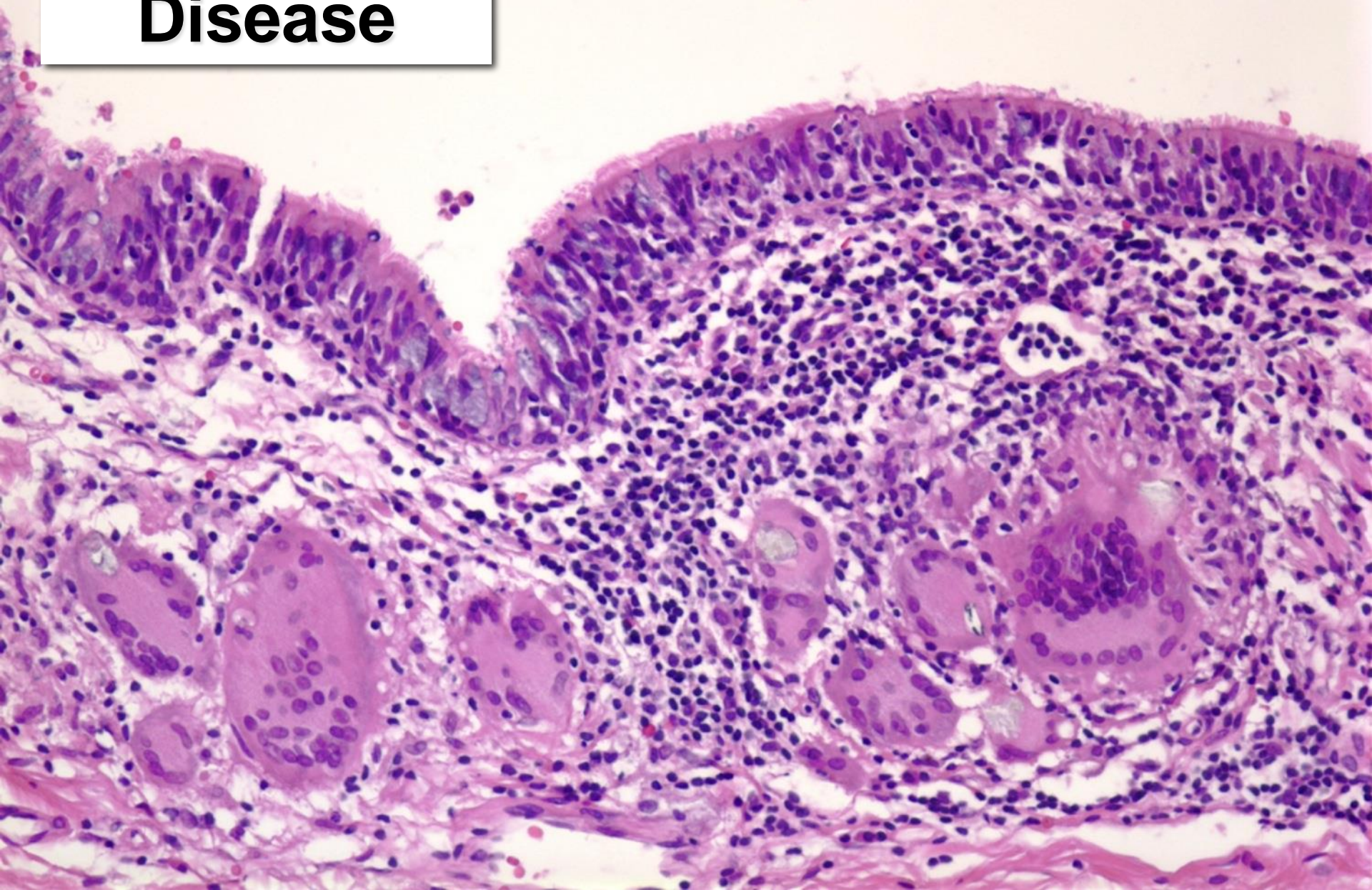
Atypical Mycobacterial Infections with Bronchiectasis/ Airway Disease

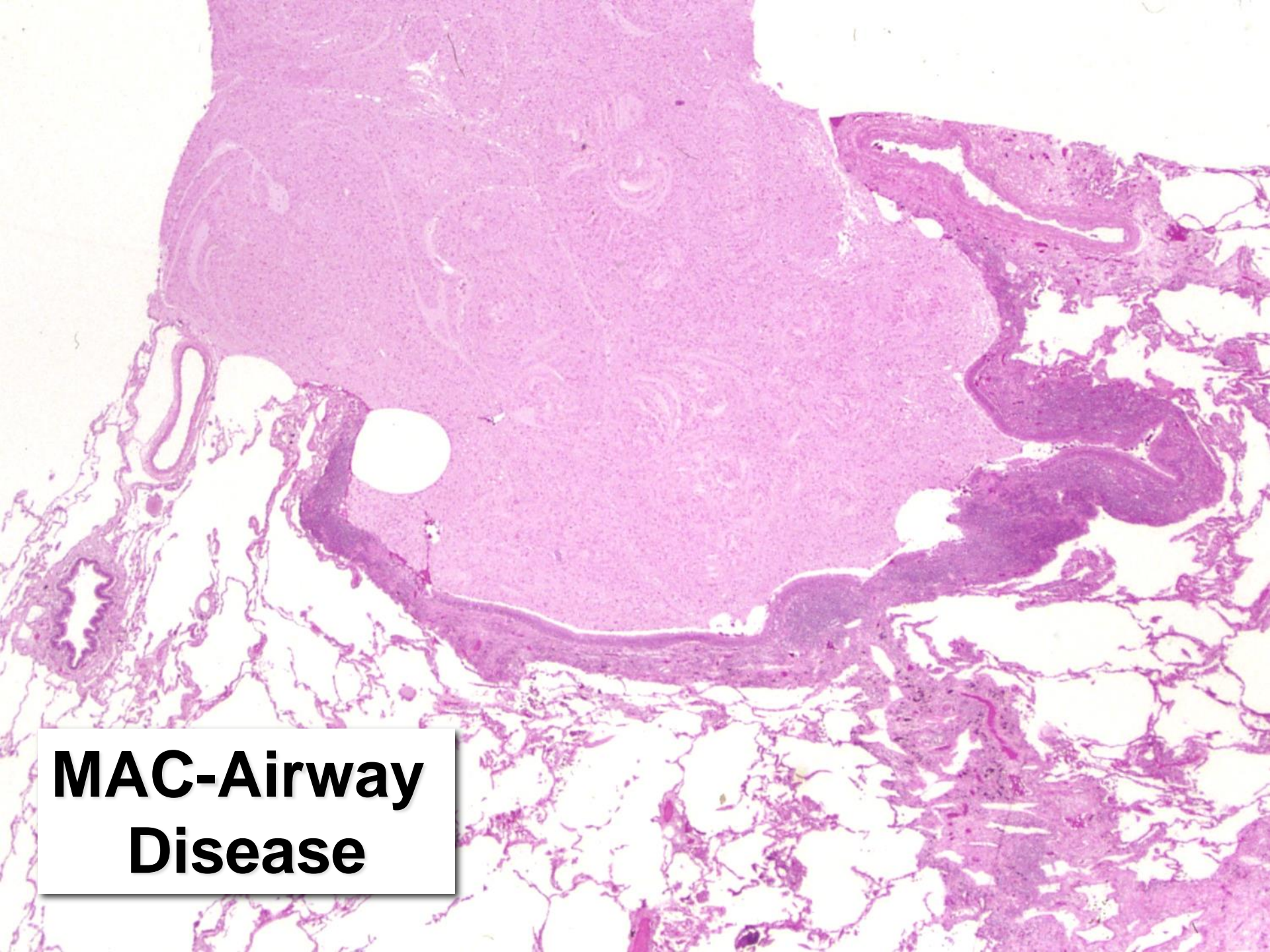
- **Nec and non-nec. granulomas
+ Airway disease
+/- Interstitial pneumonia**

MAC-Airway Disease



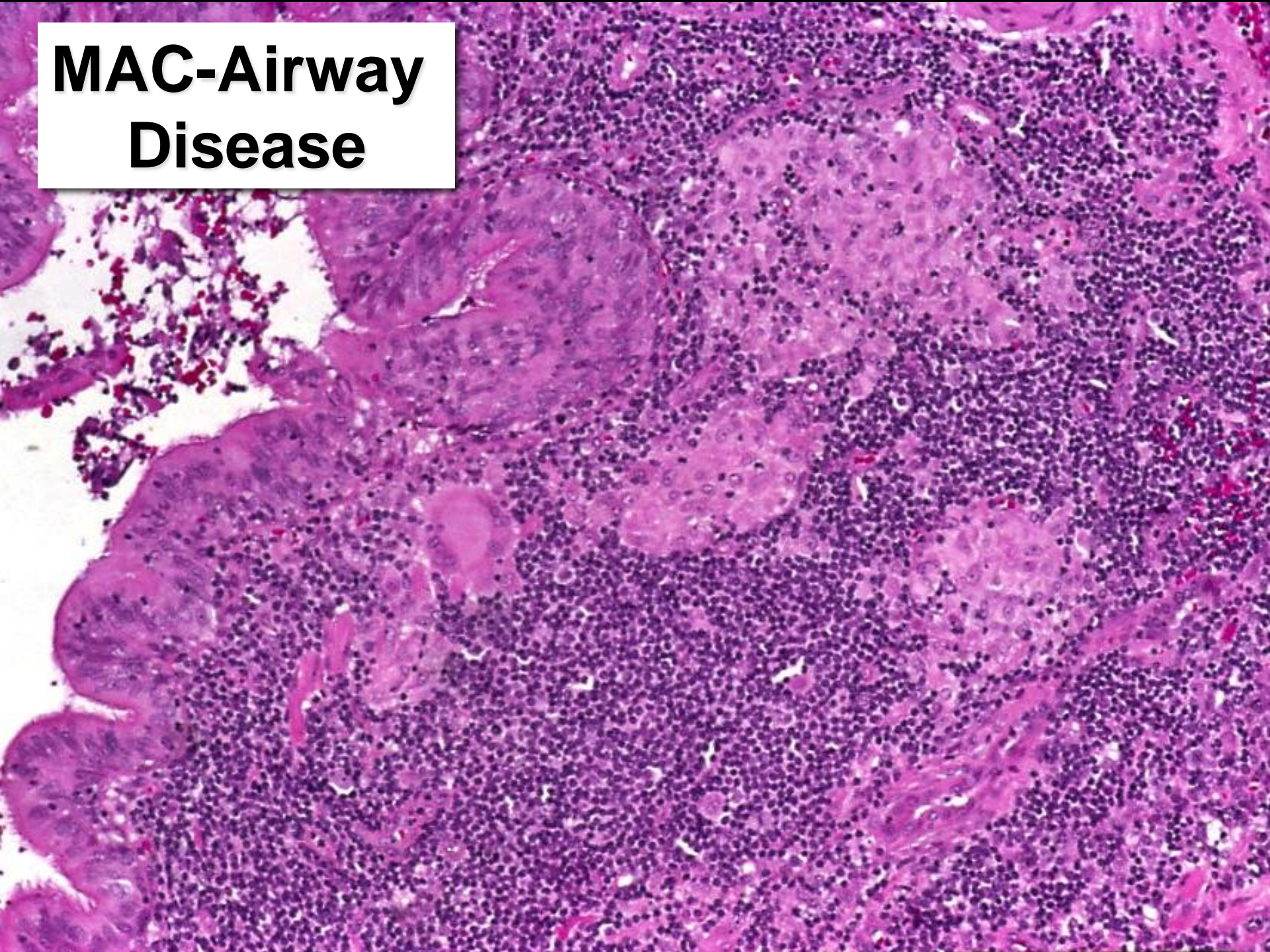
MAC-Airway Disease





**MAC-Airway
Disease**

MAC-Airway Disease



**Lady Windermere, my dear
You haven't been coughing, I fear.
After careful inspection
You have an infection
That will be very difficult to clear**

David Berkely, M.D.

South Bay Pathology Society

May 6, 2000

CF Transmembrane Regulator (CFTR) Mutations in Adults with B'ectasis or Non-Tuberculous Mycobacteria (NTM)

- Prospective analysis, n=50, 42 F
ages 28-82 yrs, mean 61 yrs

	%
• B'ectasis + NTM	60
B'ectasis	34
NTM	6

CF Transmembrane Regulator (CFTR) Mutations in Adults with Br'ectasis or Non-Tuberculous Mycobacteria (NTM)

- Prospective analysis, n=50, 42 F
ages 28-82 yrs. mean 61 yrs

<i>De novo</i> CF	20
-------------------	----

- B CFTR mutations 50

B'ectasis	34
-----------	----

NTM	6
-----	---

Pulmonary Nontuberculous (NTM) Mycobacterial Disease, n=63

Characteristic	%
Women	95
White	91
Scoliosis	51
Pectus excavatum and Mitral Prolapse	10
Mutation in CFTR gene	36
Taller and thinner than those with disseminated NTM dis	P < 0.002

Genetic Variation in NTM Infection

- **Have more low frequency protein-affecting variants of immune, CFTR, ciliary and connective tissue-associated genes than family members or controls**
- **NTM infection is multi-genic predisposition in combination w/ exposure**

What do I do with those pesky little granulomas?

Hutton Klein J et al Am J Surg Pathol 2010;34: 1456

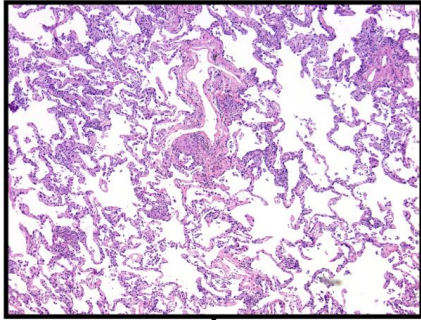
Chronic Interstitial Inflammation
± Organizing Pneumonia?

HP
Infection
Hot Tub

Yes

No

Sarcoid
Infection



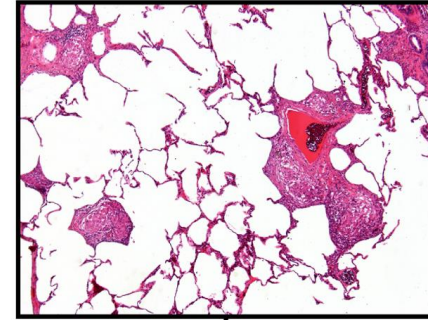
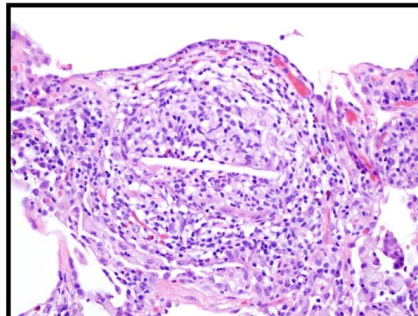
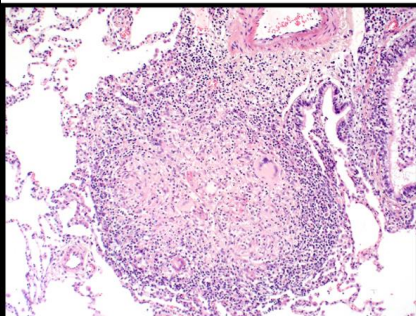
Well-formed?

Yes

No

Infection/Hot Tub

Hypersensitivity



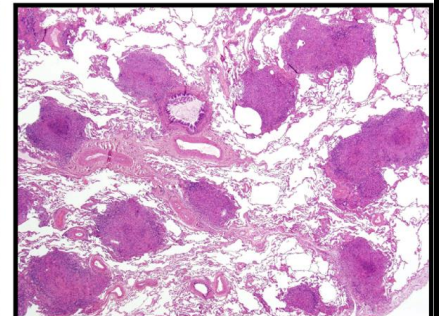
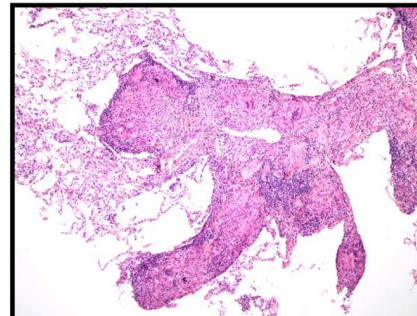
Lymphangitic
Distribution?

Yes

No

Sarcoid

Infection



Granulomatous Infections

- Vasculitis a common feature
- Differentiate between inclusions and true foreign material
- MAC becoming an increasingly important pathogen with complex pathophysiology and settings



Thank you!



MAYO CLINIC