

# 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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Mayo Clinic Arizona

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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

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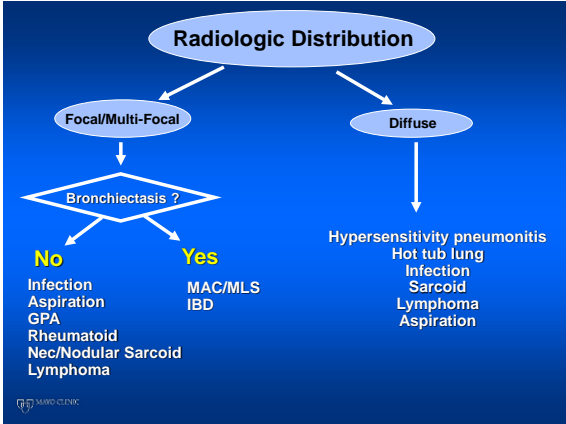
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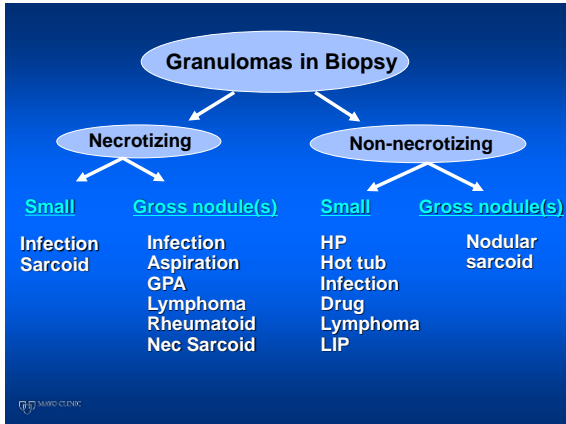
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**History**

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

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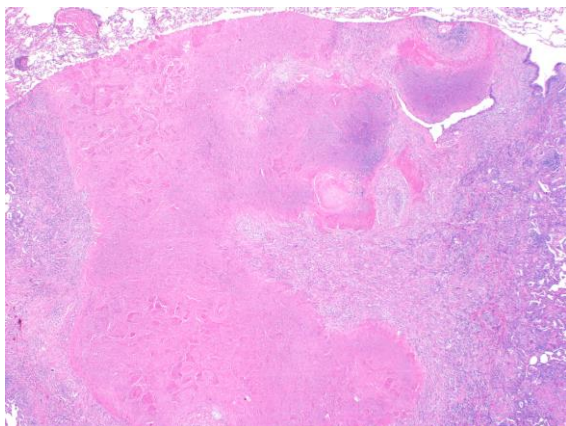
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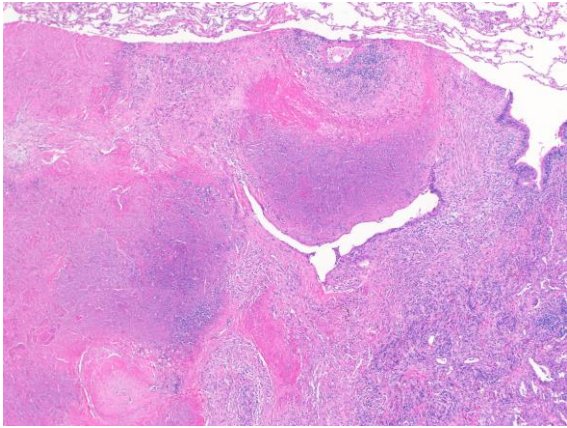
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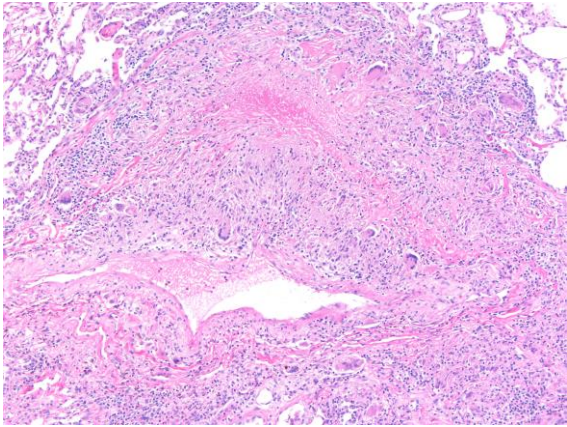
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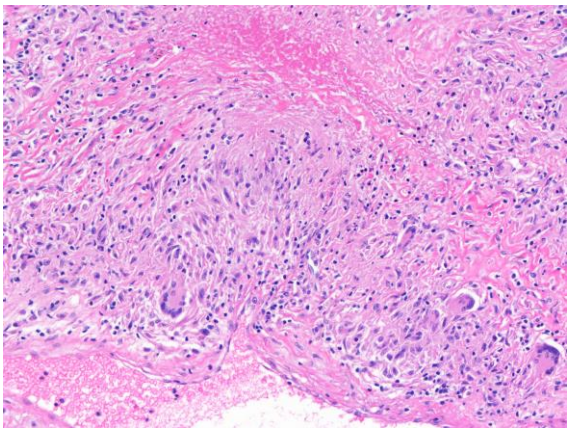
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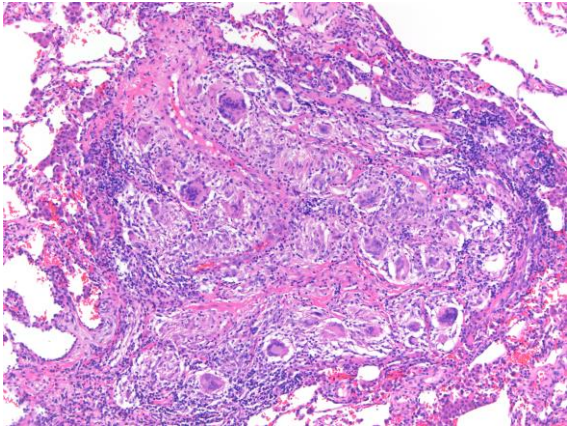
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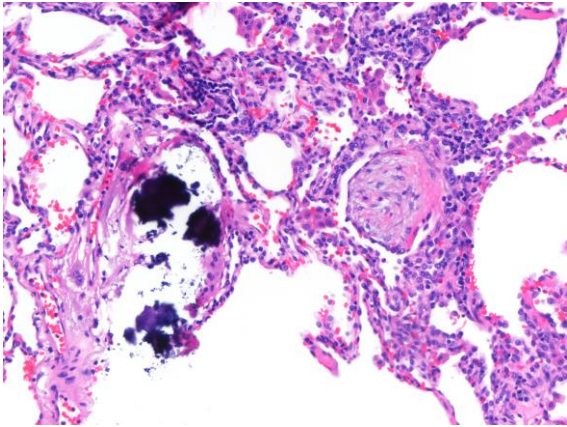
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**Diagnosis?**

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## Diagnosis?

Necrotizing Granulomatous Inflammation most c/w an Infectious Etiology

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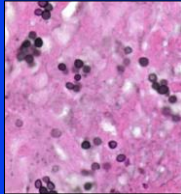
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## Additional Studies

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



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## Diagnosis

Histoplasmosis characterized by Necrotizing Granulomatous Inflammation and Vasculitis

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## 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

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## Key Histologic Features

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- Presence of calcific inclusions

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## 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

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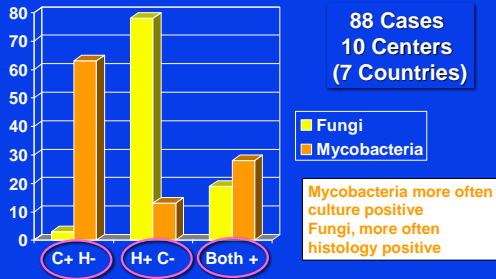
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## % Yield of Cultures (C) vs. Histology (H)



Mukhopadhyay S et al. J Clin Pathol 2012; 65:51-7

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## 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

Ulbricht and Katzenstein, Am J Surg Pathol 1980; 4:13-28

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

Feature	%
Round borders	79
Geog'ic borders	21

Ulbricht and Katzenstein, Am J Surg Pathol 1980; 4:13-28

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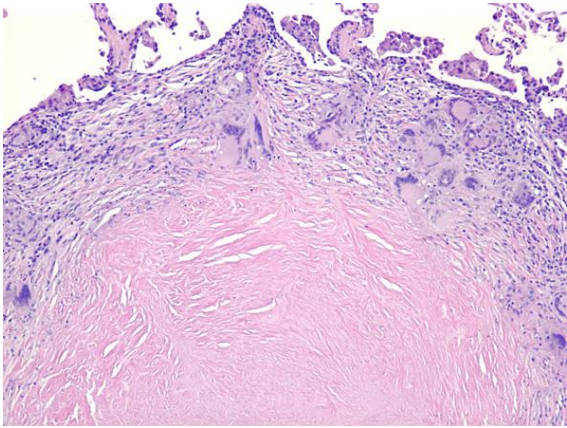
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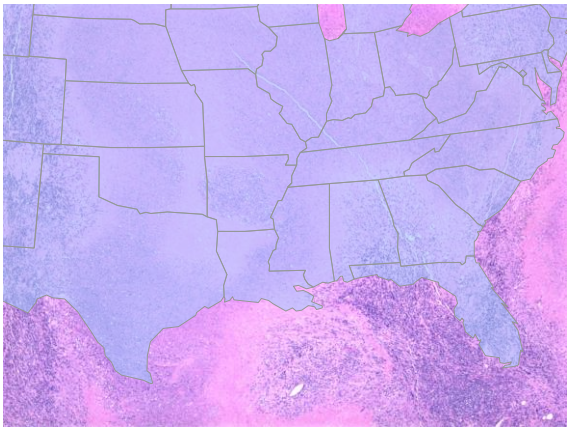
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### Histologic features of Histoplasmosis forming a Solitary Nodule, N=24

Feature	%
Non-nec gran	13
Vasculitis	54 ←

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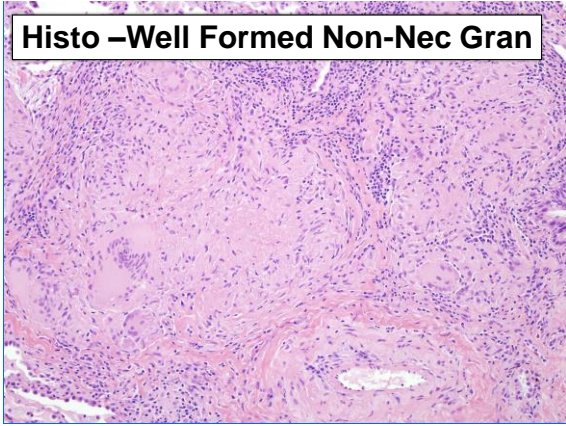
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**Histo –Well Formed Non-Nec Gran**



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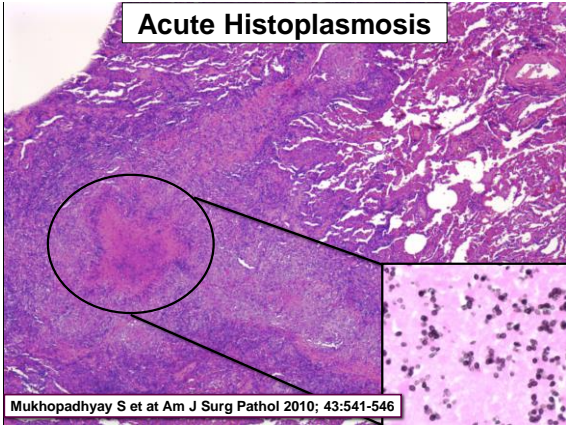
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**Acute Histoplasmosis**



Mukhopadhyay S et al Am J Surg Pathol 2010; 43:541-546

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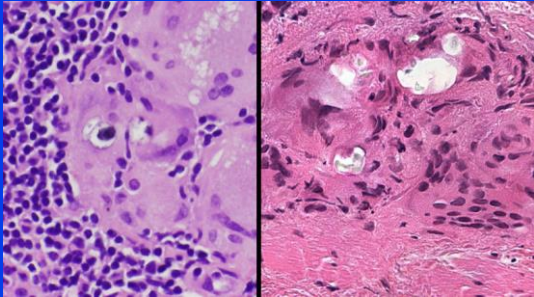
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**Endogenously-Derived Crystals**

Ca carbonate

Ca oxalate



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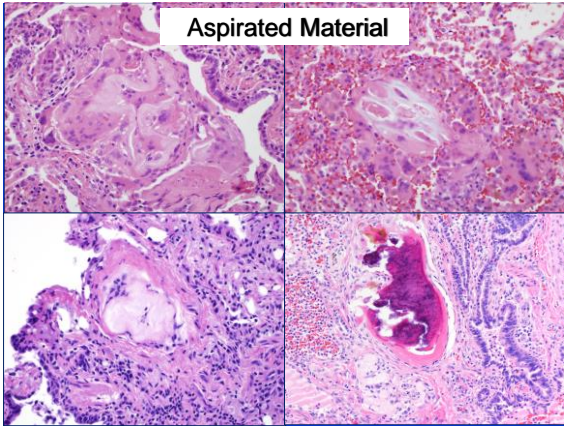
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Aspirated Material

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### Differential Diagnosis

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

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### *Mycobacterium tuberculosis*

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

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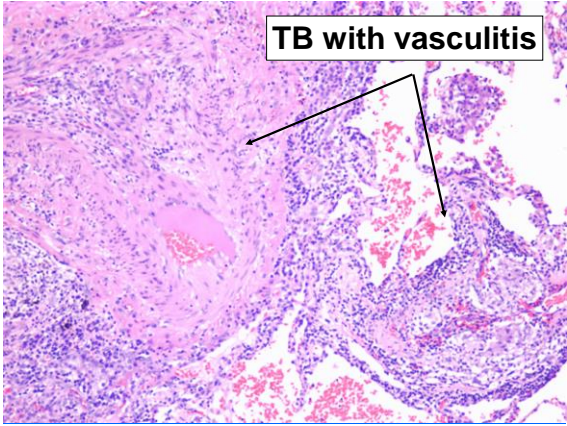
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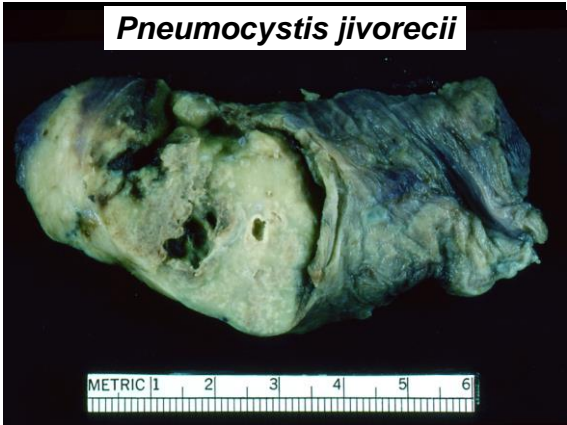
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**Granulomatous PCP**  
20 Cases

<b>Disease</b>	<b>%</b>
HIV	35
Heme malig.	30
Solid tumor	20
Unknown	15

Hartel PH et al Am J Surg Pathol 2010; 34:730-4

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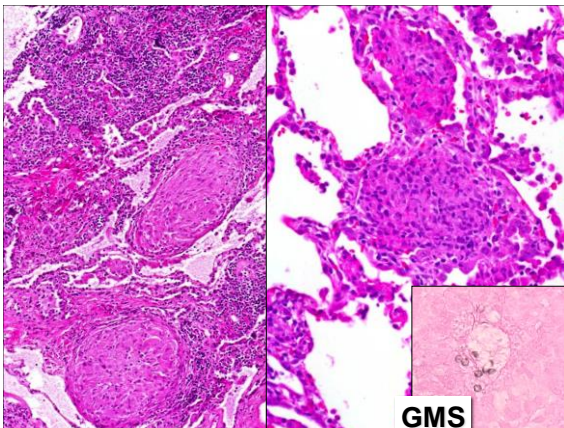
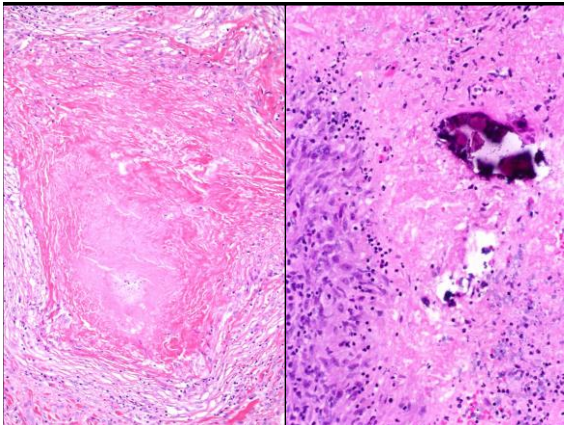
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## Granulomatous PCP

20 Cases

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

Hartel PH et al Am J Surg Pathol 2010; 34:730-4



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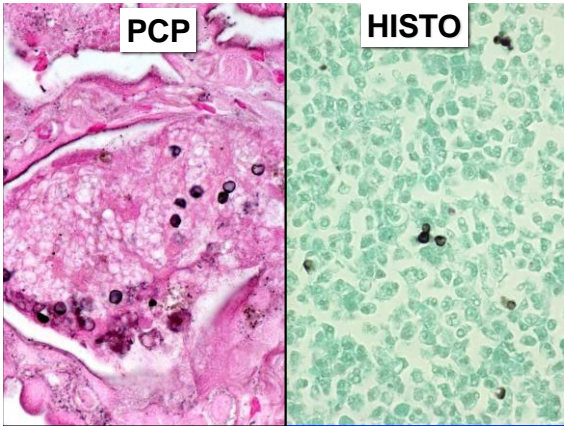
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### Infectious Granulomas vs Vasculitis

- *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***




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### 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




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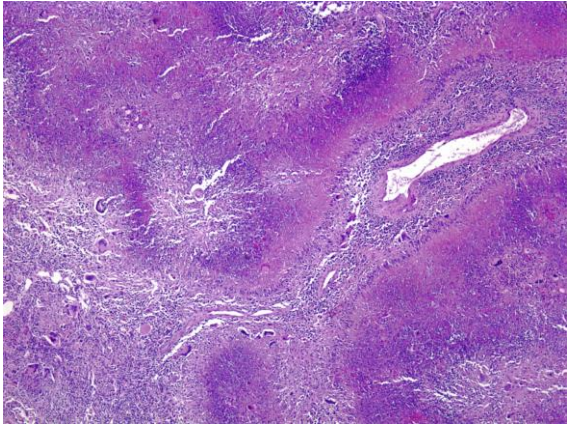
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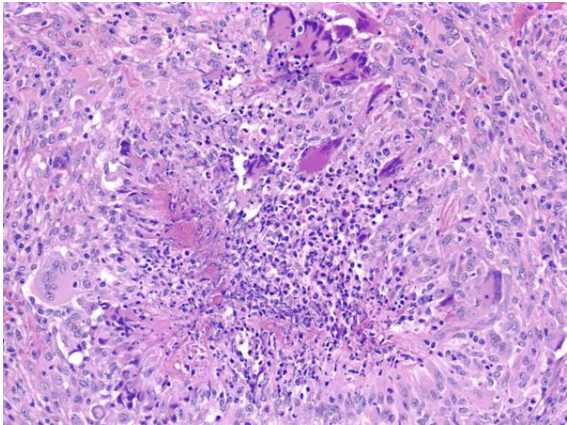
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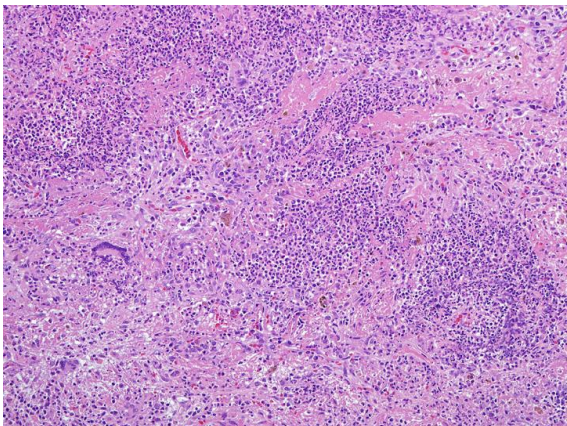
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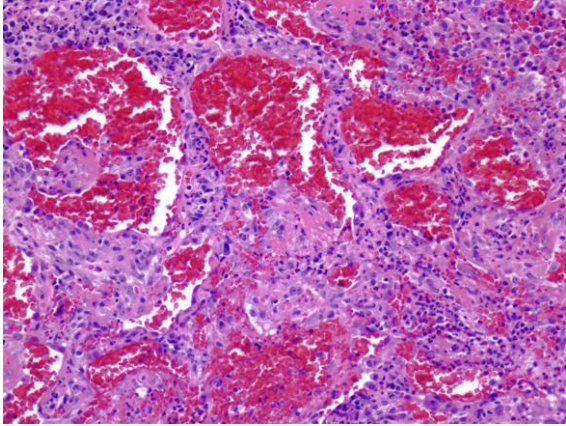
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### **Wegener Granulomatosis /Granulomatosis with Polyangiitis**

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

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### **Pulmonary Sarcoidosis**

#### **Histology**

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

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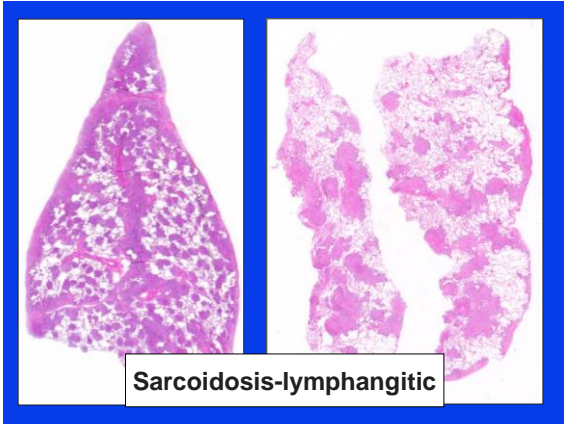
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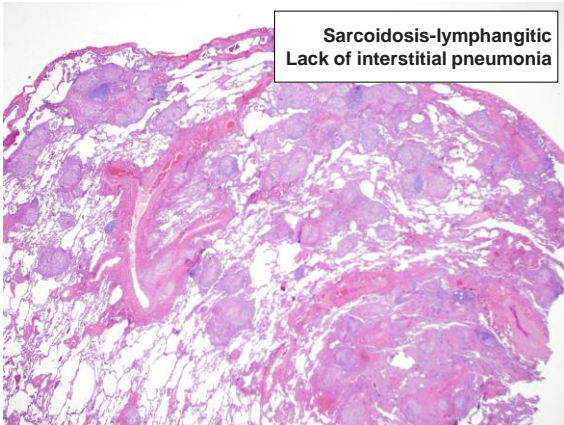
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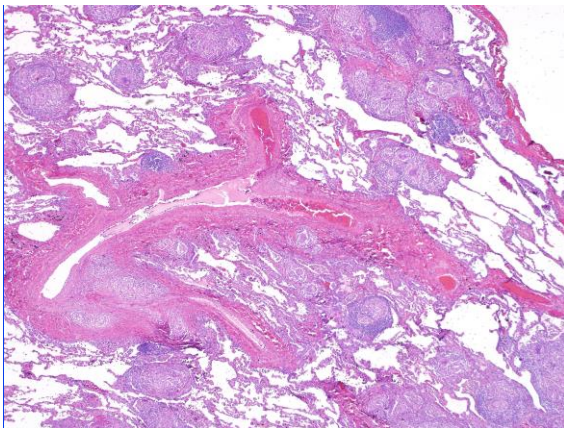
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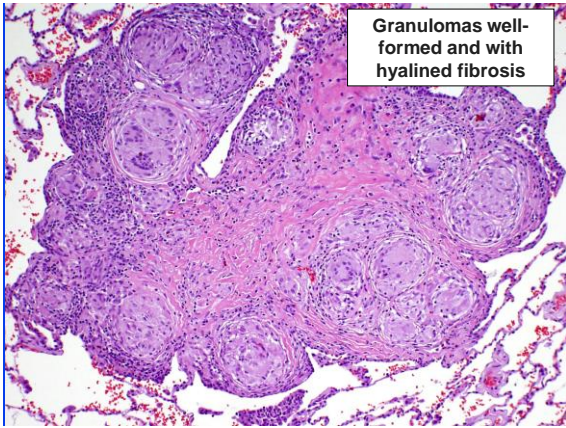
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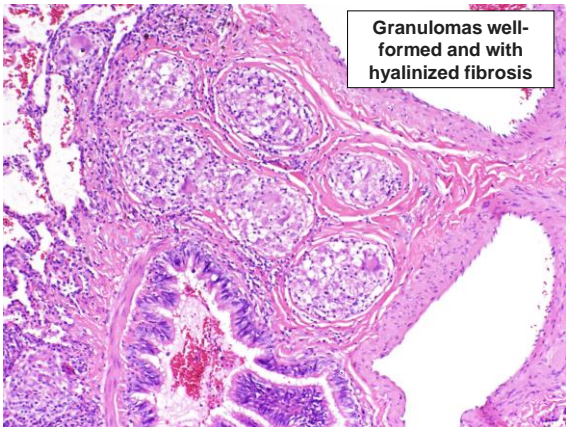
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**Sarcoid :**  **Features**

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

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## **Pulmonary Sarcoid**

### Differential Diagnosis

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

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## **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

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## **Hypersensitivity Pneumonitis**

### Diagnosis?

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

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## 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

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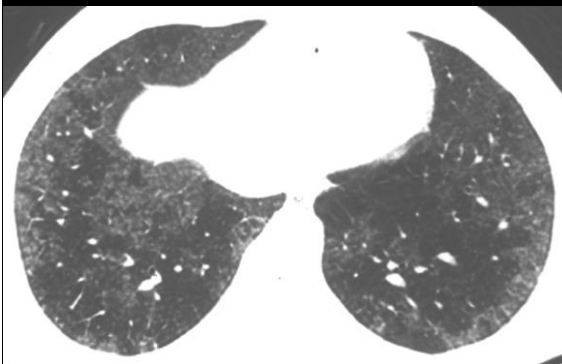
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## Extrinsic Allergic Alveolitis



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## Hypersensitivity Pneumonitis Histologic Features

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

Castonguay M et al Human Pathol 2015;46:607-131

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## Hypersensitivity Pneumonitis

### Variable Histologic Features

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

Eosinophils uncommon  
Only 20%

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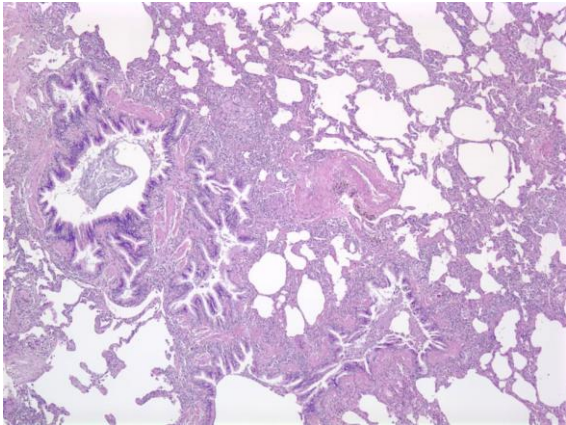
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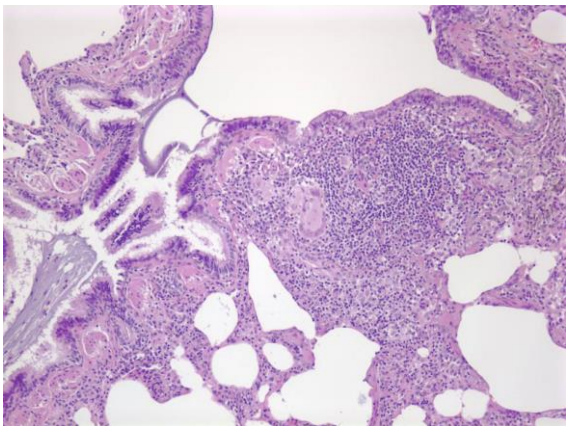
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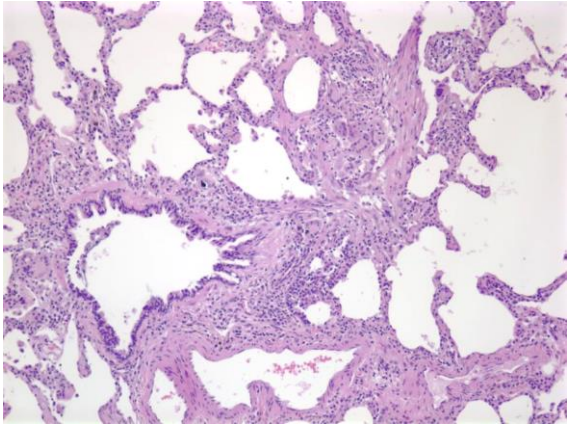
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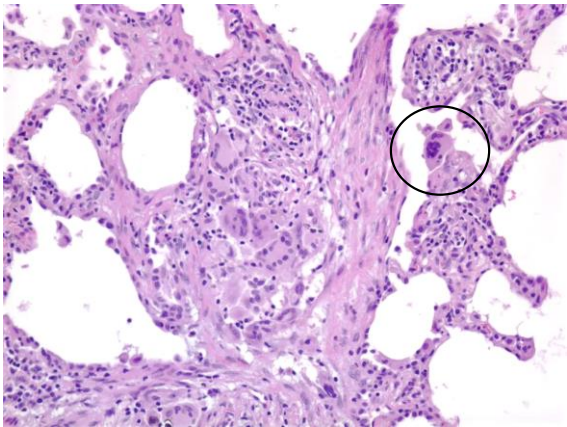
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### Major Histologic Patterns in HP n=110 (%)

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

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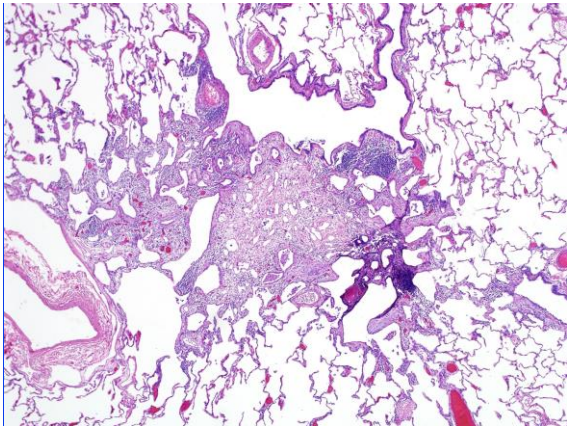
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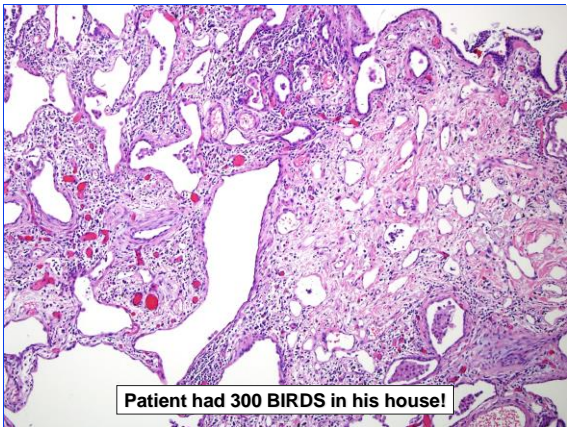
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**Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis**

- 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



Morell F et al. Lancet Resp Med 2013; 1:685-94

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### Clues to the Diagnosis of HP

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

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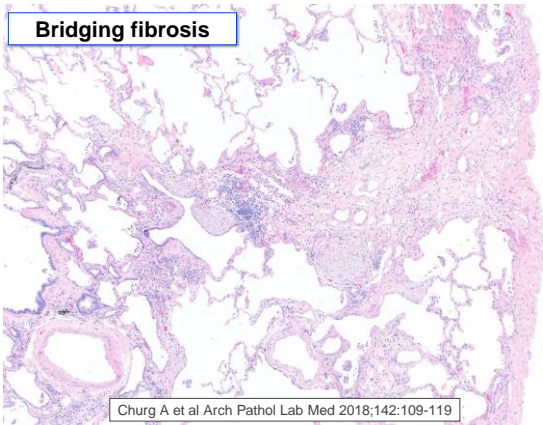
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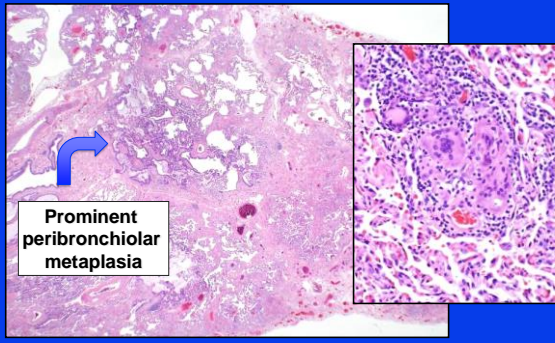
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### Chronic HP with UIP pattern




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### **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

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### **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

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### **“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

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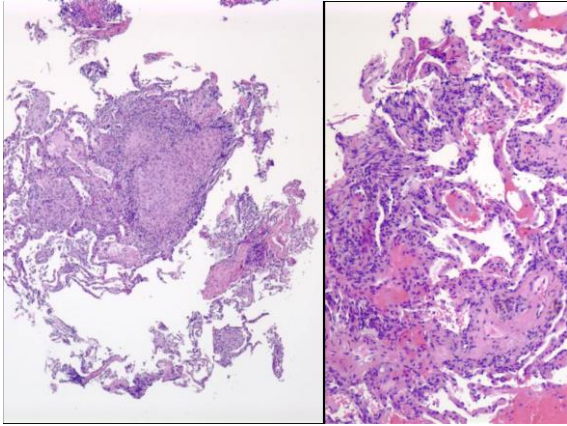
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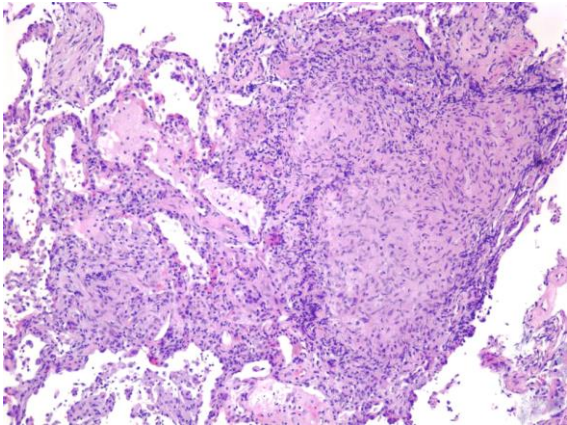
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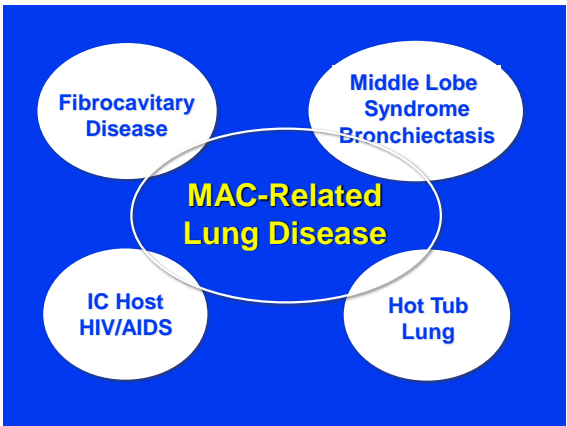
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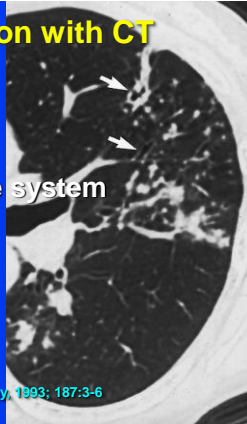
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## MAC: Evaluation with CT

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



Hartman TE et al. Radiology, 1993; 187:3-6

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## Atypical Mycobacterial Infections with Bronchiectasis/ Airway Disease

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

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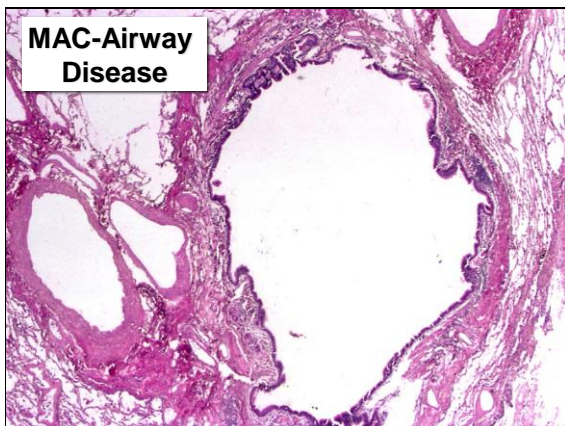
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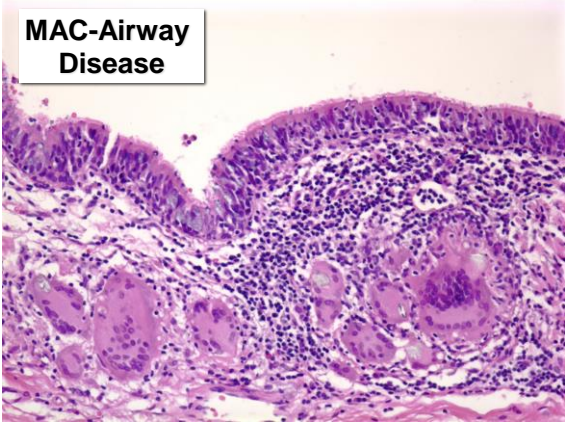
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**MAC-Airway  
Disease**



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**MAC-Airway  
Disease**



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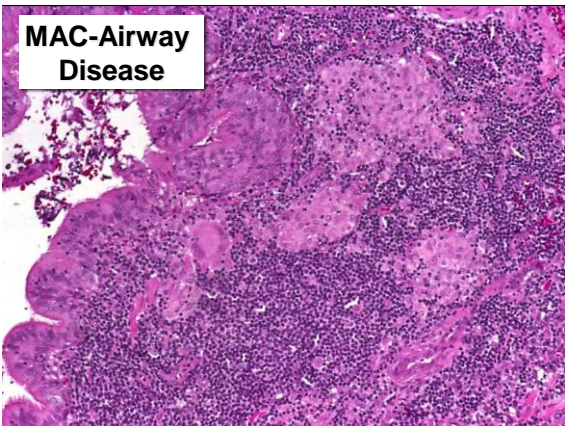
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**MAC-Airway  
Disease**



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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

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### 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

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

Ziedalski et al Chest 2006;130: 995

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### 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'ectasis + NTM	50
B'ectasis	34
NTM	6

Ziedalski et al Chest 2006;130: 995

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## 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

Kim RD et al. Am J Resp Crit Care Med 2008; 178:1066-74

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## 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

Szymanski EP et al Am J Resp Crit Care Med 2015;192:618-28

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What do I do with  
those  
pesky little  
granulomas?

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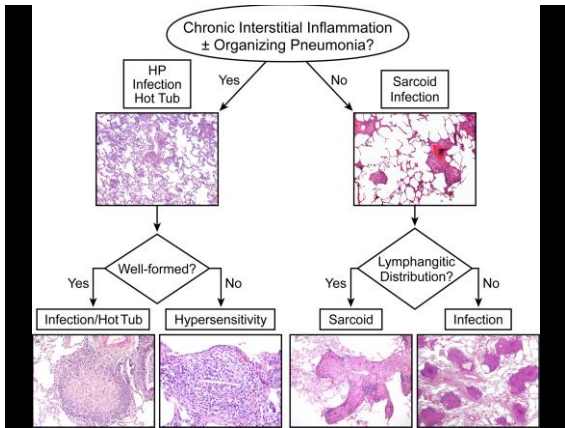
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## Granulomatous Infections

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

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**Thank you!**

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