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

2019 Anatomic Pathology Update
University of Utah
Park City, Utah
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
- Bronchiectasis?
  - No
    - Infection
    - Aspiration
    - GPA
    - Rheumatoid
    - Nec/Nodular Sarcoid
    - Lymphoma
  - Yes
    - MAC/MLS
    - IBD

Diffuse
- 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
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

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# Solitary Granulomas

## Culture Results for *Histoplasma* Cases

<table>
<thead>
<tr>
<th>Source</th>
<th>N, Pos/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td>0/22</td>
</tr>
<tr>
<td>Bronchial Wash</td>
<td>0/9</td>
</tr>
<tr>
<td>Bronchial Brush</td>
<td>0/3</td>
</tr>
<tr>
<td>Needle Aspiration</td>
<td>0/2</td>
</tr>
<tr>
<td>Lung Biopsy</td>
<td>0/19</td>
</tr>
</tbody>
</table>

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


88 Cases
10 Centers
(7 Countries)

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round borders</td>
<td>79</td>
</tr>
<tr>
<td>Geog’ic borders</td>
<td>21</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-nec gran</td>
<td>13</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>54</td>
</tr>
</tbody>
</table>

Histology: Well-Formed Non-Necrogranuloma
Endogenously-Derived Crystals

Ca carbonate

Ca oxalate

Visscher D et al Mod Pathol 1988;1:415
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 jivorecii
# Granulomatous PCP

## 20 Cases

<table>
<thead>
<tr>
<th>Disease</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>35</td>
</tr>
<tr>
<td>Heme malig.</td>
<td>30</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>20</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
</tr>
</tbody>
</table>

Granulomatous PCP
20 Cases

<table>
<thead>
<tr>
<th>Feature</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing gran</td>
<td>80</td>
</tr>
<tr>
<td>Non necrotizing gran</td>
<td>20</td>
</tr>
<tr>
<td>Foamy exudate</td>
<td>25</td>
</tr>
<tr>
<td>Cystic spaces</td>
<td>5</td>
</tr>
<tr>
<td>Calcification</td>
<td>5</td>
</tr>
</tbody>
</table>

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 pulmonary 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 inflammation 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 (%)

<table>
<thead>
<tr>
<th>Cell. NSIP</th>
<th>F NSIP</th>
<th>UIP</th>
<th>Peribronchiolar inflamm with grans</th>
<th>Bronchiolocentric fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>20</td>
<td>6</td>
<td>20</td>
<td>9</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pattern</th>
<th>Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosaicism/air trapping</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Granulomas and giant cells</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Bronchiolocentric inflammation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Peribronchiolar metaplasia</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bridging fibrosis</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Bridging fibrosis

Churg A et al Arch Pathol Lab Med 2018;142:109-119
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
MAC-Related Lung Disease

- Fibrocavitary Disease
- Middle Lobe Syndrome Bronchiectasis
- IC Host HIV/AIDS
- Hot Tub Lung
MAC: Evaluation with CT

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

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

  *De novo* CF 20
  CFTR mutations 50

  Br’ectasis 34
  NTM 6

Ziedalski et al Chest 2006;130: 995
### Pulmonary Nontuberculous (NTM) Mycobacterial Disease, n=63

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>95</td>
</tr>
<tr>
<td>White</td>
<td>91</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>51</td>
</tr>
<tr>
<td>Pectus excavatum and Mitral Prolapse</td>
<td>10</td>
</tr>
<tr>
<td>Mutation in CFTR gene</td>
<td>36</td>
</tr>
</tbody>
</table>

*Taller and thinner than those with disseminated NTM disease, 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?

**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!