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

2019 Anatomic Pathology Update
University of 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

Hypersensitivity pneumonitis
Hot tub lung
Infection
Sarcoid
Lymphoma
Aspiration

MAC/MLS
IBD

No
Infection
Aspiration
GPA
Rheumatoid
Nec-Nodular Sarcoid
Lymphoma

Yes

Bronchiectasis?
Granulomas in Biopsy

Necrotizing

Non-necrotizing

Small Gross nodule(s)

Infection Aspiration GPA Lymphoma Rheumatoid Nec Sarcoid

Small Gross nodule(s)

Infection HP Hot tub LIP

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

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Key Histologic Features

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- Presence of calcified inclusions

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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)

- Fungi
- Mycobacteria

Mycobacteria more often culture positive
Fungi, more often histology positive

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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

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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>
Histo –Well Formed Non-Nec Gran

Acute Histoplasmosis


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**

<table>
<thead>
<tr>
<th>Histologic Feature</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
<td>87</td>
</tr>
<tr>
<td>Geographic necrosis</td>
<td>30</td>
</tr>
<tr>
<td>Non-caseating granulomas</td>
<td>30</td>
</tr>
</tbody>
</table>

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>


![Histological images of granulomatous PCP](image)
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
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

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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
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

Castonguay M et al Human Pathol 2015;46:807-13
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 (%)

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

<table>
<thead>
<tr>
<th>Cell. NSIP</th>
<th>F NSIP</th>
<th>UIP</th>
<th>Peribronchiolar inflamm with gran</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>

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>UIP</th>
<th>NSIP</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>

Chung 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

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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
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
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 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

Ziedalski et al Chest 2006;130: 995

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**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
  - De novo CF 20
  - CFTR mutations 50
  - B’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>
<tr>
<td>Taller and thinner than those with dissemination NTM dis</td>
<td>P &lt; 0.002</td>
</tr>
</tbody>
</table>


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!