CASE 4

53 year old woman smoker complained of chest pain
Chest CT showed a 2.2 cm left lower lobe nodule with spiculated margins
A wedge resection was performed
Special stains negative for organisms
Case 4 - Diagnosis

Necrotizing Granulomatous Inflammation
Diagnosis of Necrotizing Granulomatous Inflammation

Marie-Christine Aubry, MD
Mayo Clinic
Rochester, MN
Case 4 - Questions

• What is the significance of a necrotizing granuloma that looks infectious, but in which no organism is identified?

• What features are most helpful in separating infectious granulomas from other lesions such as Wegener’s granulomatosis?

• Are there newer techniques besides special stains and cultures to identify infectious agents?
Necrotizing granuloma
Special stains negative

What does it mean?
What does it mean?

- Of 86 cases of necrotizing granulomas
  - 61 (71%) infectious
  - 3 (3%) specific dx (1 WG, 2 HG)
  - 22 (26%) unexplained

- Of 132 cases of necrotizing granulomas with negative stains
  - 64 (48%) infectious
  - 17 (13%) specific dx
  - 51 (39%) unexplained

Any features to distinguish infectious from others?

- Yes
- But challenge is overlap
Differential diagnosis of necrotizing granulomas

- Infection
- Wegener’s granulomatosis
- Necrotizing sarcoid granulomatosis
- Infarct
- Aspiration pneumonia
- Rheumatoid nodule
- Bronchocentric granulomatosis
- Lymphomatoid granulomatosis
Infectious granuloma
Infectious granuloma
Wegener’s granulomatosis

Geographic necrosis
“Dirty” blue necrosis
Wegener’s granulomatosis

Necrotizing vasculitis

Dark single giant cells
Wegener’s granulomatosis

- Geographic necrosis
- Dirty necrosis
- Granulomatous inflammation
- Vasculitis i.e. necrotizing vasculitis

Combination of all these findings
Granulomas in a lymphangitic distribution
Necrotizing sarcoid granulomatosis

• Sarcoidosis
  – Non necrotizing granulomas
    • “Naked”
    • Fibrosis
  – Lymphangitic distribution

• Granulomatous “vasculitis”
  – Not a true necrotizing vasculitis

• Necrosis

Combination of all these findings
Infarct

A
Necrotizing granuloma

B
Infarct
Infarct

- No rim of epithelioid histiocytes
  - “pseudogranulomatous” in 74%
- Thromboembolic lesion
  - In 100%
- Small biopsy (TTBX, TBBX)
  - Sampling

Yousem *Mod Pathol* 2009
### Histologic overlap

<table>
<thead>
<tr>
<th></th>
<th>Infectious</th>
<th>Unexplained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic necrosis</td>
<td>23-30%</td>
<td>18%</td>
</tr>
<tr>
<td>“Dirty” necrosis</td>
<td>8%</td>
<td>36%</td>
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<tr>
<td>Vascular inflammation</td>
<td>59%</td>
<td>41%</td>
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## Histologic overlap

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<tbody>
<tr>
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<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Dirty necrosis</td>
<td>8</td>
<td>11</td>
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<tr>
<td>Vascular (gr.) inflammation</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>Lymphangitic</td>
<td>8</td>
<td>11</td>
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### Histologic overlap

<table>
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<tr>
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<tbody>
<tr>
<td>Geographic necrosis</td>
<td>35</td>
</tr>
<tr>
<td>Dirty necrosis</td>
<td>52</td>
</tr>
<tr>
<td>Vascular inflammation</td>
<td>56</td>
</tr>
</tbody>
</table>

Yousem *Mod Pathol* 2009
Summary

• Any single histologic feature by itself is not entirely specific
  – Exception necrotizing vasculitis

• Association of several histologic features that leads to the specific diagnosis
Back to our case…

No specific diagnosis
Other tests?

- **A few pointers for fungi**
  - Look at H&E, in areas of necrosis
  - Necrosis present on special stains
    - Histoplasmosis 59% (10/17) \cite{Goodwin1980}
  - Look at the stains twice
    - Histoplasmosis 81% in our study
    - All fungi 90% (27/30) \cite{Ulbright1980}
  - Stain more than one block
    - Histoplasmosis 10% in our study
    - Ulbright et al recommended average 2 blocks
Rare and pale staining Histoplasma
Our case

One block completely negative
Second block strongly positive
Other tests?

• Antibody test (Immunodiffusion)
  – 24% in our study
  – 80% reported sensitivity

• Cultures for fungi variably sensitive
  – 4% (1/23) on non lung tissue
  – 2% (5/42) on lung tissue
Other techniques?

- On frozen tissue
  - Real time PCR for Histoplasma
- On paraffin embedded tissue
  - No PCR test commercially available
  - ISH for speciation not detection
    - False negative (sensitivity 75-95%)

Hayden et al *Diag Mol Pathol* 2001
Other tests?

- **A few pointers for mycobacteria**
  - **Mycobacteria on stains**
    - 93% (28/30), numerous  
    - 23% (5/22), rare
      - Non tuberculous mycobacteria now more common
  - **Auramine (IF) more sensitive than ZN**
    - Fite, ZN and AR
      - 0/5 with 3 +
      - 2/5 with 2 + (ZN and Fite, ZN and AR)
      - 3/5 with 1 + (1 of each stain)
    - Easier to see on AR
    - Fewer organisms - level

Other techniques?

• Increasing sensitivity of routine stains
  – Computer assisted screening
  – Screening by cytotechnicians
    • 1 false negative
    • False positive not issue

Tadrous PJ *Am J Clin Pathol* 2010
Other techniques?

• QuantiFERON-TB GOLD
  – FDA approved in 2004
  – ELISA - Quantifies IFN-\(\gamma\) release after stimulation with \textit{M. tuberculosis}
  – No cross immunoreactivity with BCG
  – Some false + with non MTB
Other techniques?

• Commercially available PCR for TB
  – GenProbe or AMPLICOR
    • Many false +
    • Sensitivity 50-100% Nyendak et al Curr Opin Infect Dis 2009

• Commercially available Real time PCR for TB
  – On paraffin embedded tissue
    • Sensitivity 65%
    • Specificity 99%
  – On all other specimens (BAL, CSF, urine, stool…)
    • Sensitivity >90%
Other tests?

• Culture
  – 50% (6/12)
  – 100% (22/22)
    • Culture only test positive in 77% (15/22)
      – 15 tissue
      – 5 other than tissue (BAL, sputum)
  – Remains the gold standard
    • Sputum preferred specimen
    • However diagnosis not always suspected before the surgery and collection of tissue

Necrotizing granuloma

Culture
Frozen tissue

Specific diagnosis other than infection

Yes
Specific Dx

No
Special stains

Positive
Infection

Negative

Additional studies?

Negative Correlation

Undetermined

Look again stain >1 block
Necrotizing granulomas

Unexplained – Clinical significance

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Necrotizing granulomas
Unexplained - Clinical significance

- FU in 4/22
  - No additional treatment
  - All alive and well

- FU 34/51 (1-141 mos)
  - No additional treatment
  - 2 with new nodules but no additional treatment
  - 2 decrease/resolution of nodule(s)

Necrotizing granulomas

Infectious - Clinical significance

• All cases not diagnosed initially as infectious (54/64, 84%) were not treated
• No significant impact on outcome
  – 5 had new nodules but no additional treatment
Summary

• What is the significance of a necrotizing granuloma that looks infectious, but in which no organism is identified?
  – Specific diagnosis : WG, NSG, LYG, Asp...
  – Undetermined
    • No treatment
    • Good outcome
Summary

• What features are most helpful in separating infectious granulomas from other lesions such as Wegener’s granulomatosis?
  – Overlapping histologic features
  – Combination of features
  – Necrotizing vasculitis = vasculitis - WG
Summary

• Are there newer techniques besides special stains and cultures to identify infectious agents? On tissue:
  – Real time-PCR for TB
    • Poor sensitivity
References


2- Hayden RT, Qian X, Roberts GD, Lloyd RV. In situ hybridization for the identification of yeast-like organisms in tissue section. Diag Mol Pathol 2001; 10:15-23

3- Jarzemowski JA and Young MB. Nontuberculous mycobacterial infection. Arch Pathol Lab Med 2008; 132: 1333-41


11- Tadrous PJ. Computer-assisted screening of ZN-stained tissue for mycobacteria. Algorithm design and preliminary studies on 2,000 images. Am J Clin Pathol 2010; 133: 849-858


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