Granulomatous Lung Disease: How Pathologic Findings Add Value to Clinical and Radiologic Information

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Standard teaching often highlights pitfalls in pathologic interpretation and emphasizes the benefits of correlating pathologic findings with clinical and radiologic features. This presentation aims to provide a different perspective; i.e., it will attempt to highlight the value of histologic findings in the diagnosis of granulomatous lung disease, and illustrate cases in which excessive reliance on clinical or radiologic features would lead to misdiagnosis. Throughout the presentation, the approach to the differential diagnosis of granulomas in the lung will be emphasized (Table 1).

Table 1: Differential diagnosis of granulomatous inflammation in the lung (for details of individual entities, see Mukhopadhyay and Gal in References)

<table>
<thead>
<tr>
<th>Entity</th>
<th>Necrotizing granulomas</th>
<th>Non-necrotizing granulomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Typical</td>
<td>Common, usually mixed with necrotizing granulomas</td>
</tr>
<tr>
<td>Non-tubercular mycobacterial</td>
<td>Typical</td>
<td>Common, usually mixed with necrotizing granulomas</td>
</tr>
<tr>
<td>Infection</td>
<td>Typical</td>
<td>Occasional, usually mixed with necrotizing granulomas</td>
</tr>
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<td>---------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Typical</td>
<td>Occasional, usually mixed with necrotizing granulomas</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>Occasional</td>
<td>Common, can be mixed with necrotizing granulomas; pure non-necrotizing granulomatous inflammation with multinucleated giant cells is also fairly common</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Typical, suppurative (neutrophil-rich)</td>
<td>Possible, usually overshadowed by suppurative granulomas</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>Typical</td>
<td>Common, usually mixed with necrotizing granulomas</td>
</tr>
<tr>
<td>Dirofilariasis</td>
<td>Typical, infarct-like</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Other organisms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td>Too few cases</td>
<td>Too few cases</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>May occur, typically with minimal necrosis</td>
<td>Typical</td>
</tr>
<tr>
<td>Granulomatosis with</td>
<td>Invariable, commonly with “dirty” necrosis</td>
<td>Absent</td>
</tr>
<tr>
<td>polyangiitis (GPA; Wegener)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with</td>
<td>Common, with numerous eosinophils</td>
<td>Possible, with numerous eosinophils</td>
</tr>
</tbody>
</table>
In granulomatous pulmonary infections, pathology enhances clinical and radiologic information in the following ways:

1. By definition, pathology is the only way to confirm the presence of a granulomatous inflammatory response. In a lung nodule or mass that is clinically and radiologically suspicious for a neoplasm, pathology is the best means for confirming a benign diagnosis, and is the gold standard against which clinical and radiologic criteria are evaluated.

2. Pathology is typically the first modality to detect an organism within a granuloma. Cultures are usually slower to provide results since the organisms in granulomas are almost always mycobacteria or fungi. The fact that pathology can provide a
rapid diagnosis greatly enhances its clinical utility and its ability to impact therapy in a timely fashion.

3. Although microbiology is the gold standard for definitive identification of most organisms, pathology provides the best means to confirm that an organism is truly pathogenic, based on its presence within a granulomatous inflammatory response.

4. Pathology can identify whether the organisms within a granuloma are mycobacteria or fungi.

5. If the organisms are mycobacteria, pathologists can and should guide clinicians to take appropriate next steps (obtain tissue for cultures or send FFPE tissue for PCR) in order to differentiate *M. tuberculosis* from nontuberculous mycobacteria. This is especially important in countries that are not endemic for tuberculosis, and in patients in whom a mycobacterial infection was not previously suspected.

6. If the organisms are fungi, histopathology easily differentiates hyphae from yeasts, and narrows the differential diagnosis for the former. For the latter, in many cases, a specific organism can be identified based purely on pathologic criteria.

7. Pathology can confirm the presence of an infection when clinical and radiologic findings suggest an alternative diagnosis, such as a neoplasm or interstitial lung disease. The pathologist’s ability to diagnose infections in atypical clinical settings adds great value to clinical and radiologic information.

8. Pathology can detect some organisms that cannot grow in cultures (*Pneumocystis*) or are rendered non-viable by the granulomatous response (*Histoplasma* in pulmonary histoplasmosmas).
9. If, as is often the case, material was not submitted for cultures - pathology may be the only means of identifying an organism.

In non-infectious granulomatous lung diseases, pathology improves upon or enhances clinical and radiologic findings in several ways, a few of which are listed here:

1. In sarcoidosis, pathologic demonstration of granulomas adds to the degree of confidence with which the clinician makes the diagnosis. In cases where sarcoidosis was not suspected clinically or was thought to be unlikely, the identification of typical granulomas by pathology can dramatically alter the diagnostic thought process.

2. In GPA, pathology helps to confirm the diagnosis in suspicious clinical settings. However, the value of pathology is even greater when ANCA serologies are negative or classic multi-system involvement is absent. In patients with suspected diffuse alveolar hemorrhage, pathology is the only means of confirming a diagnosis of capillaritis, with significant therapeutic implications.

3. The role of pathology is perhaps most underappreciated in patients who aspirate particulate matter from gastric contents (food particles or pill fragments). Clinical and radiologic findings in such cases are notoriously non-specific and the possibility of aspiration is often missed by clinicians and radiologists. Clinicians are trained to consider the diagnosis of aspiration pneumonia mainly in debilitated patients with lower lobe infiltrates; thus, they seldom consider this possibility in healthy individuals with upper or middle lobe infiltrates or nodules.
4. Pathology is critical for the diagnosis of talc granulomatosis. This entity is often encountered in individuals who inject crushed narcotic pills intravenously. Since these individuals have an incentive to conceal their illicit activity, a history of drug abuse is often absent, and pathology becomes the only means to make the diagnosis.

5. Pathology plays an important role in confirming the diagnosis of hypersensitivity pneumonitis, particularly in individuals without a classic exposure history and atypical radiologic features.

6. Hot tub lung can be diagnosed clinically if the clinician suspects the diagnosis based on radiologic findings and a careful exposure history. However, if the clinician has not specifically considered the possibility of the diagnosis, the patient might not volunteer a history of hot tub use. In such cases, pathologists may be the first to raise the possibility of the diagnosis, prompting appropriate history-taking and management.

References:


45. Miller K, Harrington SM, Procop GW. Acid-fast smear and histopathology results provide guidance for the appropriate use of broad-range polymerase chain reaction and sequencing for mycobacteria. *Arch Pathol Lab Med* 2015 (Epub ahead of print).


