PULMONARY PATHOLOGY SOCIETY COMPANION MEETING

HANDOUT/SYLLABUS

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)

Entity	Necrotizing granulomas	Non-necrotizing granulomas
Tuberculosis	Typical	Common, usually mixed with necrotizing granulomas
Non-tubercular mycobacterial	Typical	Common, usually mixed with necrotizing granulomas

infection		
Histoplasmosis	Typical	Occasional, usually mixed with necrotizing granulomas
Cryptococcosis	Occasional	Common, can be mixed with necrotizing granulomas; pure non-necrotizing granulomatous inflammation with multinucleated giant cells is also fairly common
Blastomycosis	Typical, suppurative (neutrophil-rich)	Possible, usually overshadowed by suppurative granulomas
Coccidioidomycosis	Typical	Common, usually mixed with necrotizing granulomas
Dirofilariasis	Typical, infarct-like	Uncommon
Other organisms: Candida	Too few cases	Too few cases
Sarcoidosis	May occur, typically with minimal necrosis	Typical
Granulomatosis with polyangiitis (GPA; Wegener)	Invariable, commonly with "dirty" necrosis	Absent
Eosinophilic granulomatosis with	Common, with numerous eosinophils	Possible, with numerous eosinophils

polyangiitis (Churg-Strauss)		
Particulate matter aspiration pneumonia	Reported but uncommon	Common, in the form of foreign-body type giant cells surrounding particulate material
Talc granulomatosis	Rare	Typical, usually perivascular, containing filler materials
Rheumatoid nodules	Typical	Possible
Hypersensitivity pneumonitis	Absent	Typical, poorly formed, or scattered giant cells
Hot tub lung	Possible	Typical

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 histoplasmomas).

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.

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