Inflammatory, Infectious and Indeterminate Lung Nodules

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Disclosures

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Objectives:

• Examine the pathologic differential diagnosis of ground glass nodules and other mass lesions worrisome for malignancy
• Recognize features that discriminate between reactive and neoplastic alveolar proliferations
• Define the features of in situ and invasive adenocarcinomas of the lung
• Examine diagnostic reproducibility
What is a “ground glass nodule”?

“A hazy opacity that does not obscure underlying pulmonary structures on high-res CT.”

Estimated 20% of pure ground glass nodules and 60-90% of GGN with solid component are malignant.

Clinical and radiographic mimics of pulmonary neoplasia

• Ground glass nodule differential diagnosis:
  • Tumor
    • Lung adenocarcinoma/AIS/MIA
    • Invasive mucinous adenocarcinoma
    • Metastatic carcinoma
  • Inflammatory
    • Organizing pneumonia
    • Drug reaction
  • Infection
Case 1.

• 70 year old nonsmoking man with systemic amyloidosis with cough and hemoptysis, lower lobe opacity. No resolution following antibiotic therapy.

• Proceeded to surgical resection due to concern for primary malignancy.
Pulmonary wedge resection:

Diagnosis: Pneumocystis pneumonia
Fluffy pink proteinaceous debris filling airspaces
Black speckles (organisms) may be evident on H&E
Clusters of organisms are evidence on silver stain
5-8 micron cysts resemble cups, or contact lenses
Pneumocystis pneumonia:

- Results from infection with Pneumocystis jirovecii
- Considered a fungus
- Cysts and trophozoites visible in infected tissue
  - Cysts- visible on silver stain/5-8 microns
  - Trophozoites- visible on geimsa stained cytology preparations/1-5 microns
- Most people are exposed by early childhood
- Becomes clinically significant in immunosuppressed patients

https://www.cdc.gov/dpdx/pneumocystis/index.html
Patient follow-up:

• Subsequent testing revealed that the patient was HIV+
Case 2:

- 38 year old man with Crohn’s disease on TNF-inhibitor
- Tore down a 100 year old farmhouse one month prior
- Two week history of fever/malaise
- CT shows pulmonary GGOs and mediastinal lymphadenopathy
Lymph node biopsy:
Disseminated histoplasmosis

• A disease of the immunocompromised

• In immunocompetent hosts, inhaled organisms lead to asymptomatic development of solitary lung/lymph node granuloma

• Slowly enlarged pulmonary granuloma may mimic primary malignancy

• Self-contained pulmonary infection is observed in majority of adults from endemic areas in autopsy series

• Our patient: treated with antifungals and recovered
Cryptococcus neoformans
Ubiquitous - Birds/pigeons
4-7 micron round yeasts with surrounding clear space
Narrow-based budding
Alcian blue/Mucicarmine+ mucinous capsule

Histoplasma capsulatum
Ohio/Mississippi river valley - Bird/bat droppings
5 micron ovoid yeast forms
Narrow-based budding
Invisible when dead (old granulomas)
Basophilic on H&E when alive
Aggregate in macrophages

Coccidioides immitis
Southwestern US- “valley fever” – soil
5 to 60 micron spherules containing endospores
Small immature spherules mimic other yeasts
Occasional hyphal forms
May form a cavitary mass- especially in diabetics
Risk of rupture into pleura
Neutrophils or eosinophils may be prominent

Blastomyocosis dermatitidis
South central US, Great Lakes -soil
Can present with acute pneumonia
8-15 micron yeast forms, occ. mycelial forms
Broad based budding
Basophilic on H&E with refractile cell wall
Endemic mycoses

• An important differential diagnosis for granulomatous disease in the lung
• Chronic/resolved infection is a frequent incidental finding in immunocompetent hosts in endemic regions
• Endemic regions are not necessarily well-defined, e.g. Histoplasma infection very common in New England; Cocci outbreaks observed in pacific northwest
• May be clinically significant in some patients, especially the immunocompromised host
Case 3.

70 year old man with metastatic melanoma status post left pneumonectomy now with new right sided consolidation with ground glass components.
Core needle biopsy performed:
Diagnosis

• Sarcoid-like granulomatosis of the lung
• A recognized sequelae of immune checkpoint blockade therapy in multiple tumor types

• Usually presents as lymphadenopathy, reported in 5-7% of patients
• Patients are usually asymptomatic (distinct from therapy-related pneumonitis)
• Holding immune checkpoint therapy leads to clearance of the radiographic abnormalities

Case 4. 57 year old man with metastatic melanoma, undergoing treatment with PD-1 inhibitor.

March 2017  
September 2017  
July 2018
Resected left lower lobe mass:
Differential diagnosis

- Infection
  - Mycobacterial (tuberculosis vs. atypical)
  - Endemic mycosis
  - Aspergillus
  - Bacterial
- Treated tumor
- Vasculitis
  - granulomatosis with polyangiitis
Special stains performed

- Gram, silver and AFB stains all negative.
Mycobacterial immunohistochemistry

PCR sequencing sent: Mycobacterium avium complex identified.
Pulmonary mycobacterial infection

- Reactivation of mycobacteria (including Mycobacterium tuberculosis and atypical species) described in the setting of immune checkpoint blockade.
  - Unrestrained T-cell effector response → florid necrotizing granulomatous inflammation

Special stains for mycobacterium:
- Traditional AFB staining is relatively insensitive
- Two or more blocks may require staining
- Organisms enriched at interface of necrosis and viable tissue
- Mycobacterial IHC is more sensitive than AFB- organisms visible at low power
  - bright signal, “leaking” of antigen increases the size of the organisms
  - increased number of organisms stained
  - Can cross-react with Nocardia and Candida

Case 5:

- 57 year old man with severe right-sided chest pain
- Chest CT scan showed bilateral pulmonary masses
- PET/CT showed significant uptake in lung and prostate
  - (SUV max 10-11)
- Lung wedge biopsy performed
CT scan; Lung wedge biopsy obtained.
Obliterative vasculitis

Prominent giant cells
Granulomatosis with polyangiitis (formerly known as Wegener’s)

- ANCA associated vasculitis
  - Anti-PR3 ANCA positivity (C-ANCA) in 66%
  - P-ANCA in 24%
- May lead to life-threatening pulmonary hemorrhage or kidney failure
  - 28% 5-year fatality
- Significant genetic component
- Responsive to immune suppression

Lyons PA et al. NEJM 2012.
Case 6: 55 year old man, incidental lung mass, growing on repeat CT scans over 6 months

At followup #1

Three months later
Lung core needle biopsy:

- LUNG ADENOCARCINOMA, lepidic pattern in this limited specimen
Lung lobectomy performed.

• Gross examination reveals 5.4 cm ill-defined mass
Lung Lobectomy, final diagnosis:

• Organizing pneumonia with atypical alveolar pneumocytes consistent with reactive changes

• The mass was entirely submitted for histologic evaluation.
Reactive pneumocyte proliferation

- Polyclonal population
- Variable to high N:C ratio
- Variable amounts of cytoplasm
- May have prominent nucleoli
- May have coarse, open chromatin

Atypical adenomatous hyperplasia

- Clonal population
- High N:C ratio
- Cytoplasmic vacuoles
- Multinucleation
- Intranuclear inclusions
- Gaps between cells
Reactive pneumocyte proliferation

- Architectural complexity
- Subtle interstitial thickening
- Difficult-to-define boundary
- Associated inflammation/organization

Adenocarcinoma in situ

- Architectural complexity
- May have striking interstitial thickening
- Distinct boundary
A core biopsy overcall leading to unnecessary surgery: How can you avoid this outcome?

• Correlate with clinical history (recent infectious pneumonia) and radiology (radiographic impression of inflammatory vs malignant?) but this exercise is not always helpful.

• Consider the pathologic features of reactive vs neoplastic proliferations – reactive proliferations may be MORE atypical than atypical adenomatomous hyperplasia or adenocarcinoma in situ
  • On cytology, reactive vs. malignant alveolar proliferations may be nearly impossible to distinguish

• Hedge: “Atypical pneumocyte proliferation” and discuss obtaining additional biopsies if clinically indicated/feasible
Best practices in pulmonary pathology

• Clinical and radiographic correlation are often essential
• Keep an open mind about the infectious and inflammatory differential in masses resected for suspicion for malignancy

• Stay up to date on the bread and butter and the unusual:
• Pulmonary Pathology Society case of the month (coordinated by Sanjay Mukhopadhyay and Sinchita Roy-Choudhuri)
• https://www.pulmonarypath.org/cotm/
PPS Biennial Meeting
June 26, 27, 28, 2019
Dubrovnik, Croatia
Registration details:
www.pulmonarypath.org