Medical Lung Diseases

Understanding Fibrosis:
- Dominant finding is fibrosis. Appears “Pink” (from collagen) at low magnification.

Usual Interstitial Pneumonia (UIP)/Idiopathic Pulmonary Fibrosis (IPF):
- Usual Interstitial Pneumonia (UIP) is a histologic pattern, which can be idiopathic (and therefore called Idiopathic Pulmonary Fibrosis, IPF), or due to connective tissue disease, chronic hypersensitivity pneumonitis, or a drug reaction.
- IPF→ Clinical Dx after excluding other etiologies
- Typical IPF presentation: Older male with gradually increasing shortness of breath → eventually fatal!

Histologic pattern findings: Temporally and spatially heterogeneous (the disease is patchy, with some advanced areas and early areas). Minimal inflammation.

Classic findings: fibroblastic foci (immature fibroblastic areas) and honeycombing (architecturally distorted cystic spaces with respiratory epithelium and surrounding fibrosis)

Fibrosis is worst in lower lobes adjacent to pleura and septae. (So can’t Dx on transbronchial biopsy!)

Asbestosis:
- Caused by inhalation of silicate mineral fibers (not just asbestos!)
- Often occupational exposure (e.g., miner, construction, shipyards...)

Key finding: 1) Interstitial fibrosis, 2) Asbestos bodies (however, diagnosis often made clinically)
- Minimal associated inflammation. Fibroblastic foci are absent.

Asbestos bodies: dumbbell-shaped iron deposits (highlight with iron stains)
- Often also see pleural plaques.
- Increased risk of lung cancer and mesothelioma.
Hard Metal Pneumoconiosis

Caused by inhalation of hard metals, usually cobalt.
Other metals: tungsten, titanium.
Occupational exposure: manufacturing, drilling/sawing.

**Histologically:** Giant cell interstitial pneumonia (GIP)
Intra-alveolar giant cells and fibrosis with variable inflammation. Frequent emperipolesis.

Erdheim-Chester Disease

Multisystemic histiocytosis that can involve any organ.
(Frequently involves long bones also)

*In lung:** Broad fibrotic bands with intermixed foamy to pink histiocytes. Scattered Touton-type giant cells.

IHC: Macrophages stain with CD68, FactorXIIIa. S100 +/-.
Some show BRAF V600E gene mutations.

Pleuroparenchymal Fibroelastosis

Early: Upper lobe predominant subpleural fibrosis with mostly elastic fibers (Highlight with elastin stain. Smaller, lighter-colored, kinkier fibers than collagen).

Rare diffuse interstitial disease that can be idiopathic or associated with stem cell transplantation, medications, exposures, etc...
Minimal to no: inflammation, granulomas, fibroblastic foci.

*If localized apical mass lesion:* consider “Apical cap” (common pleural-based fibroelastotic lesions, which can mimic malignancy).

Other Fibrotic Diseases

Many diseases (that may initially start out in a different pattern) can become fibrosis-predominant if the become advanced enough, so be sure to look for clues to other etiologies!

*Smoking-related Interstitial Fibrosis:* Hyalinized ropey fibrosis, respiratory bronchiolitis (smokers’ macrophages), and emphysema.

*Chronic Hypersensitivity Pneumonitis:* Cellular infiltrates, particularly near airways. Loosely formed non-necrotizing granulomas and/or giant cells.

*Chronic Nonspecific Interstitial Pneumonia (NSIP):* Histologic pattern with relatively homogenous thickening of alveolar septae by fibrosis of the same age (as opposed to heterogeneity of UIP). Can be due to hypersensitivity pneumonitis, drugs, connective tissue disease, DAD, etc...
Nonspecific Interstitial Pneumonia (NSIP)

Hypersensitivity Pneumonitis

Due to inhalation of small organic or chemical antigens → stimulate immune response.

Airway-centric inflammation with:
1) Peribronchiolar granulomas/giant cells
2) Peribronchiolar interstitial chronic inflammation
3) Chronic bronchiolitis
Also often see: Peribronchiolar metaplasia (“Lambertosis”), organizing pneumonia, cholesterol clefts,

If fibrosis → consider chronic hypersensitivity pneumonitis

Nonspecific Interstitial Pneumonia (NSIP)

Pattern of inflammation with homogeneous, diffuse thickening of alveolar septae by chronic inflammatory infiltrates.
Can see associated homogenous fibrosis → chronic NSIP. Better prognosis than UIP/IPF.

Can be idiopathic, medication-related, hypersensitivity pneumonitis, or, most commonly, due to Connective Tissue Disease.

Connective Tissue Disease (CTD)-associated interstitial lung disease:
Common findings to suggest this diagnosis:
-Prominent lymphoid follicles +/- germinal centers
-Pleuritis
-Inflammation/patterns that are hard to explain/classify
If suspicious → consider suggesting Rheumatology evaluation

Rheumatoid arthritis
Can see rheumatoid nodules.

Systemic Lupus Erythematosus
Can have pretty much any pattern/appearance

Scleroderma
Polymyositis/Dermatomyositis
Sjogren’s syndrome
Mixed Connective Tissue Disease
Lymphoid Interstitial Pneumonia (LIP)

Diffuse, dense interstitial lymphoplasmacytic infiltrate. Mostly polymorphous T cells.

Rare, idiopathic. Must exclude other conditions, particularly Autoimmune diseases, HIV/AIDS, and immunodeficient states (e.g., CVID). Also, must exclude lymphoma (esp. MALT lymphoma)!

If lots of large lymphoid follicles centered around airways, consider “Follicular bronchiolitis” (on a spectrum with LIP with similar DDX)

Hot Tub Lung

Hypersensitivity pneumonia-like reaction to mycobacterium avium complex (MAC), which is common in water (like indoor hot tubs, saunas, pools, etc...)

Similar appearance to HP (peribronchiolar chronic inflammation), but more prominent and better-formed granulomas, which can be necrotizing.

Alveolar Filling Pattern

Diffuse Alveolar Damage

Histologic manifestation of Acute Respiratory Distress Syndrome (ARDS) → Bilateral diffuse infiltrates, often requiring ventilation.

Can be seen in a variety of settings (common endpoint) including: Infection, sepsis, drug reactions, toxins, and shock. If idiopathic → “Acute Interstitial Pneumonia” (AIP)

Endothelial/epithelial injury → leakage of serum proteins → Hyaline membranes (fibrinous exudate). Particularly with infection also see necrosis, and acute inflammation.

Organizing Pneumonia

Nonspecific pattern of lung injury/repair. Can be seen after recent infection/injury, aspiration, connective tissue disease, etc..

If idiopathic → “Cryptogenic Organizing Pneumonia” (COP)

Accumulation of immature myxoid material and fibroblasts within airspaces.

In airspaces can see fibroblastic plugs (branching→) /polyps (floating). Intact alveolar septae.

Often resolves after removing inciting agent.
**Desquamative Interstitial Pneumonia (DIP)/Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD)**

*Spectrum* of disease highly associated with smoking.

**RB:** Pigmented “smoker’s macrophages” (→) in respiratory bronchioles and adjacent alveoli. Often with associated adjacent mild fibrosis. Need clinical symptoms/findings to label as RB-ILD.

**DIP:** Filling of alveoli by pigmented macrophages. Often associated fibrosis and mild chronic inflammation.

*Note:* It can be challenging to distinguish these “smoker’s macrophages”, which have fine, powdery anthracotic pigment, from hemosiderin-laden macrophages (seen with hemorrhage/congestion), which is more chunky and refractile. Both contain iron.

**Alveolar Hemorrhage**

Hemosiderin-laden macrophages and fresh blood in alveoli.

Can be secondary to Trauma, Cardiac disease, Vascular disease, Medications, etc..

**Diffuse Alveolar Hemorrhage (DAH)** is often a result of vasculitis → be sure to look for capillaritis!

**Anti-Glomerular Basement Membrane Disease (Goodpasture Syndrome).** Autoantibodies to collagen IV in basement membrane. Impacts capillaries in kidney, lung, or both. In lung → hemorrhage. In kidney → crescentic glomerulonephritis.

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**Eosinophilic Pneumonia**

**Acute Eosinophilic Pneumonia:**

Presents with fever and dyspnea of <1 month duration. Essentially, Diffuse Alveolar Damage with the addition of eosinophil-rich inflammation. Peripheral eosinophilia and Eos on BAL. DDX: Infection (parasites), Medications, Cigarettes, Pneumothorax, Idiopathic.

**Chronic Eosinophilic Pneumonia:**

Insidious onset, relapsing. Responds to steroids. Intra-alveolar collections of Eosinophils, macrophages, and proteinaceous edema. Also, organizing pneumonia. DDX: When idiopathic often associated with asthma, medications, allergies, etc...
Alveolar Proteinosis

Filling of alveoli by amorphous eosinophilic, granular proteinaceous material. Occasional crystals and cholesterol clefts. PASD+ (vs edema, which is PAS negative) “Crazy Paving” appearance on CT.

Three forms:
Congenital: Due to mutations of genes encoding surfactant or GM-CSF
Primary: autoantibodies against GM-CSF → abnormal macrophage function → accumulation of proteinaceous material.
Secondary: A variety of causes including stem cell transplantation, solid organ transplantation, etc...

Key histologic DDX: Pneumocystis pneumonia → be sure to get fungal stains, especially if immunocompromised!

Alveolar Microlithiasis

Microliths of calcium phosphate within alveoli with characteristic circular lamellations
(similar to psammoma bodies)

Autosomal recessive disorder: Mutations in SLC34A2 gene → dysfunctional sodium phosphate transport. Usually causes disease in middle-aged adults, respiratory failure, but usually indolent with slow-progression.

“Sandstorm” appearance on radiology.

DDX: corpora amylacea (normal), dystrophic calcifications, ossification

Lipoid Pneumonia

Lipid-rich material and inflammatory cells filling alveolar spaces.

Endogenous/Post-obstructive: Proximal airway obstruction → inability to clear secretions → accumulation of finely vacuolated macrophages in distal airways.

Exogenous/Aspiration: Aspiration of lipid-rich material (e.g., mineral oil) Accumulation of multinucleated giant cells containing large lipid vacuoles within alveoli.
Nodules

Aspiration

Due to aspiration of food particles.
Can be single or multiple.
Risk factors: Stroke, GERD, obesity, epilepsy, Alcohol.
Airway-centered inflammation with giant cells and organizing pneumonia.
Classically: degenerating food particles (→) (but may be focal)
  → may be polarizable, especially some pill particles.
Can also see lipoid pneumonia (see separate section)
Can see abscess formation if superinfected.

Sarcoidosis

Systemic idiopathic granulomatous disease with frequent pulmonary involvement.
Dx requires clinical correlation.
Starts centrally in lung with large airways and hilar lymphadenopathy→ extends outward with progressive fibrosis.
Classic finding: tightly formed (mostly) non-necrotizing granulomas with giant cells → eventually become more confluent and mass-like with increased hyalinized fibrosis.
Follows lymphangitic distribution (bronchovascular bundle, interlobar septae, pleural). NOT in airspaces.
Sparse lymphoid inflammation at periphery.
No organizing pneumonia or interstitial inflammation.
Extensive necrosis→ favors infectious etiology.
Note: Giant cells can produce some endogenous polarizable material (calcium oxalate)→ don’t mistake as foreign material!

Silicosis

Caused by inhalation of Silica and related minerals.
Risk factors: construction, manufacturing, mining, etc.
Inhale silica → engulfed by macrophages → form aggregates that increasingly fibrose/hyalinize and coalesce into nodules.
Silica is birefringent if polarized.
Coal Workers’ Pneumoconiosis

“Black Lung Disease”

Caused by exposure to Coal dust. Common to see concurrent silica/silicosis (‘mixed dust,’ similar exposure while mining).

**Dust-laden macrophages** in/around terminal bronchiovascular bundles → Mild haphazard fibrosis and emphysema → can progress to large nodules with fibrosis.

**Vasculitis**

Dx often involves clinical/serologic correlation. Often ANCA positive.

**Granulomatosis with Polyangiitis (Wegner’s)**
Necrotizing granulomatous inflammation. Commonly impacts lung, nasal cavity, and kidney. In lung/head see granulomas with geographic central necrosis and associated vasculitis → form ulcers and cavitating nodules. In kidney can see crescentic glomerulonephritis.
PR3-ANCA positive (c-ANCA).

**Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)**
Eosinophil-rich and necrotizing granulomatous inflammation. Often impacts the lung. Associated with asthma and eosinophilia.
MPO-ANCA usually positive (p-ANCA).

**Rheumatoid Nodule**

Granulomatous nodules with central fibrinoid necrosis. Palisading histiocytes with lymphoplasmacytic inflammation.

Most **specific** pulmonary findings for Rheumatoid arthritis. (Can see diverse other finding including pleuritis, follicular bronchiolitis, NSIP, UIP, etc...)

Can see both in lung and pleura.

DDX: Granulomatosis with Polyangiitis, Infection. → be sure to get bug stains, etc...
Fungal Infections

Often diagnosed based on imaging and lab studies. May be focal or diffuse (particularly if immunocompromised). Often cause granulomatous response (+/- necrosis). Have a low threshold to get a GMS/PAS!

Regardless of immune status:

**Coccidioidomycosis**: Southwestern US in dry soil. See spherules +/- endospores. “Valley Fever.”

**Histoplasma Capsulatum**: Mississippi/Ohio River valley in soil/caves (bat droppings). Narrow based buds. Small, oval size. Common to have subclinical infection with burnt out hyalinized granulomas. If disseminated → see in macrophages

**Blastomycosis**: Mississippi/Ohio River valley and Northeast in soil. Broad based buds, round, uniform thick double wall.

**Paracoccidioides**: South and Central America. Radial pattern.

Often immunocompromised:


**Aspergillus**: Ubiquitous in soil. Septae hyphae with 45° branching. Can colonize pre-existing cavity → Aspergilloma (fungus ball). Can also cause allergic response or be tissue/vascular invasive.

**Candida**: Ubiquitous in skin (can be oral contaminate in BAL). Budding yeast and pseudohyphae.

**Mucormycosis**: Ubiquitous. Broad “Ribbon-like” hyphae with irregular branching and inconspicuous septae.

Bacterial Infections

Often diagnosed clinically based on radiology and lab findings, esp. usual bacterial pneumonia.

**Mycobacterium tuberculosis**: Worldwide, many people are asymptomatically infected leaving behind calcified nodules/lymph nodes (Ghon complex). This can reactivate leading to active cavitating infection, often in the upper lobes. Can disseminate more widely if immunocompromised. Histologically, mostly see necrotizing granulomas and fibrosis. Have a low threshold for getting AFB!

**Nocardiosis**: Gram-positive filamentous bacteria. Infect immunocompromised. Highlighted by both AFB and GMS. Look like slender tangled strings.

Pulmonary Hyalinizing Granuloma

Often considered an exaggerated response to a remote infection, most often histoplasmosis. Can also be associated with IgG4-related disease.

Single or multiple slow-growing nodules. **Well-circumscribed, acellular hyalinized collagen.** Scattered foci of chronic inflammation.

Metaplastic Ossification

**Mature lamellar bone.** Often incidental finding. Frequently **response to injury**: scar, aspiration, granulomas, apical caps, etc...

Apical Cap

**Subpleural fibroelastotic scars** seen most commonly in the apices of the upper lobes.

Unclear etiology. Predominantly elastotic fibers with intermixed collagen. Triangular-shape (with broad pleural base). Can radiographically mimic malignancy. 

**If diffuse** → Pleuroparenchymal fibroelastosis (rare type of interstitial lung disease discussed separately)

Pulmonary Langerhans Cell Histiocytosis

aka “Eosinophilic granuloma”

Considered a **reactive proliferation** (as opposed to extrapulmonary LCH, which is neoplastic)

Strongly associated with **smoking** (so often see other smoking-related changes). Stellate nodules centered around airways with surrounding cystic areas.

Early → **Numerous Langerhans cells** (greyish cytoplasm with groove coffee bean nuclei; Stain with S100, Langerin, CD1a) **with associated eosinophils.** Late → Increased fibrosis

Other Non-Neoplastic Mass-forming Lesions

Berylliosis
Amyloidosis
Light-chain deposition disease
Parasitic infections

Vaping (can cause nodular injury)
Ehler-Danlos Syndrome (from spontaneous vascular injury)
**Round Atelectasis**

*In folding of lung* into underlying parenchyma caused by pleural fibrosis/retraction → can *simulate* a “Mass.”

Most common in lingula. Requires radiographic correlation.

Histologically: **Normal-appearing lung tissue with overlying pleural fibrosis** (no obvious mass-forming lesion).

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**Near Normal**

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**Emphysema**

Airspace enlargement due to alveolar septal destruction without significant fibrosis.

Common “background” (incidental) finding in lung.

*Often classified by location:* **Centrilobular**: Destruction near small airways. Classically associated with smoking and upper lobe predominant. Emphysema + Chronic Bronchitis = Chronic Obstructive Pulmonary Disease (COPD). Also see with Coal workers’ pneumoconiosis. Eventually expands to panlobular/acinar.

**Panacinar**: Involves entire lobule from beginning. Classically associated with α1-antitrypsin deficiency. Lower-lobe predominant. Also risk of liver disease.

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**Pulmonary Hypertension**

*Clinical diagnosis!*

Increased pulmonary vascular pressure.

Common causes: Heart failure, Lung disease (e.g., UIP)

Can be primary/idiopathic.

Pathologic findings may not correlate with symptoms.

**Medial hypertrophy** of arteries and veins,

**Intimal proliferation/fibrosis,**

**Plexiform lesions**, fibrous webs/plugs (“colander-like”), emboli/thrombi.

*Note*: Recanalized thrombi (from a PE) are also plexiform.

If the lesion is in a large elastic artery → think pulmonary embolism!
**Birt-Hogg-Dubé Syndrome**

Autosomal Dominant.
Mutations in folliculin gene (FLCN).

**Multi-organ manifestations:**

**Lung:** Variably sized thin-walled cysts underneath pleura near septae or lower lobes → can rupture → pneumothorax

Skin: Fibrofolliculomas

Kidney: hybrid oncocytic neoplasms (chromophobe renal cell carcinoma + oncocytoma)

**Constrictive (Obliterative) Bronchiolitis**

*(mainly say Obliterative bronchiolitis in transplant setting)*

**Fibroinflammatory scarring of bronchioles.**

Scarring between epithelium and smooth muscle → can eventually obliterate lumen.

Elastin stain can highlight elastic layer of obliterated airway and confirm it was there, usually with a remaining paired artery.

Possible causes: Infection, fumes/toxins, medications, connective tissue disease (especially RA), etc..

**Amyloidosis**

Can be localized (just lung) vs systemic.

Localized amyloidosis can be nodular or diffuse.

Regardless, appears similar to elsewhere: Waxy pink protein deposition. (+) Congo Red stain with “Apple green” birefringence

**Foreign Material Emboli**

With intravenous drug use, there can be microcrystalline cellulose emboli: refractile under polarized light → causes pulmonary hypertension.

Can also see bone marrow/fat emboli from bone fractures (including after CPR).
Acute Cellular Rejection

For adequate sensitivity, need 5 pieces of expanded alveolated lung, and multiple levels.

Acute cellular rejection is based on the presence of perivascular and interstitial T-cell-rich infiltrates.

Can also see lymphocytic bronchiolitis with a band-like T-cell-rich chronic inflammatory infiltrate in the submucosa of bronchioles (which have no cartilage in the walls) (vs BALT, which is well-circumscribed and B-cell rich)

**Note:** Perivascular/interstitial and bronchial chronic inflammation is *NOT* specific for rejection!
Infection (e.g., CMV, PCP) and PTLD can look similar, so consider other options, particularly if there are lots of neutrophils or plasma cells (features that favor infection).

(See grading on next page)

Chronic Rejection

**Obliterative Bronchiolitis:** Progressive airway lumen obliteration by inflammation and fibrosis.
Hard to see on surveillance biopsies → often a clinical diagnosis with reduced FEV$_1$.
Elastic stains can be used to highlight obliterated bronchioles.

*(synonymous with constrictive bronchiolitis in nontransplant setting)*

**Chronic Vascular Rejection:** Myointimal thickening and fibrosis within arteries and veins. Not often seen in biopsies.

Antibody-Mediated Rejection

Less well-defined than in other organs.

**Requires:** 1) Clinical dysfunction, 2) Positive circulating donor-specific antibodies (DSA), and 3) C4d immunoreactivity.

On H&E: Neutrophilic capillaritis and neutrophilic septal margination.
IHC/IF: C4d strong, linear/donut pattern of staining in septal capillaries.
### Transplant Acute Rejection Grading

**Alveolar Rejection**

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<th>Description</th>
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<tr>
<td>A2</td>
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**Bronchiolar Rejection**

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### Transplant Chronic Grading

**Obliterative Bronchiolitis**

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**Chronic Vascular Rejection**

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### Histologic Findings of Idiopathic Interstitial Pneumonias

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nonspecific Interstitial Pneumonia (NSIP)</th>
<th>Usual Interstitial Pneumonia (UIP)</th>
<th>Desquamative Interstitial Pneumonia (DIP)</th>
<th>Acute Interstitial Pneumonia (AIP)</th>
<th>Lymphocytic Interstitial Pneumonia (LIP)</th>
<th>Cryptogenic Organizing Pneumonia (COP)</th>
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<tbody>
<tr>
<td>Temporal appearance</td>
<td>Uniform</td>
<td>Varied</td>
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<td>Interstitial inflammation</td>
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<td>Interstitial fibrosis: collagen</td>
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<td>Variable, diffuse</td>
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<td>Interstitial fibrosis: fibroblasts</td>
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<td>OP pattern</td>
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<td>Honeycomb areas</td>
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<td>Intra-alveolar macrophages</td>
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### Diseases with Bronchocentric Granulomas

<table>
<thead>
<tr>
<th>Disease</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration</td>
<td>History of stroke, epilepsy, GERD, etc..., Degenerating food/pill particles</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Tightly formed granulomas, usually non-necrotizing. Also along pleura and septae.</td>
</tr>
<tr>
<td>Infection</td>
<td>Positive cultures or special stains.</td>
</tr>
<tr>
<td>Hypersensitivity Pneumonitis</td>
<td>Peribronchiolar chronic inflammation, Chronic bronchiolitis, Peribronchiolar metaplasia (“Lambertosis”), relevant exposure history (e.g., Birds, molds...)</td>
</tr>
<tr>
<td>Allergic Bronchopulmonary Aspergillosis (ABPA)</td>
<td>Allergic mucin (Charcot-Leyden crystals and eosinophils), Eosinophilic pneumonia, asthma/asthmatic airway changes, rare fungal elements.</td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis</td>
<td>Vasculitis, capillaritis, Diffuse Alveolar Hemorrhage, Positive ANCA, relevant history/clinical findings.</td>
</tr>
<tr>
<td>Middle Lobe Syndrome</td>
<td>Limited to middle lobe.</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Rheumatoid nodules. Relevant clinical history (arthritis, RF+, etc...)</td>
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