Interstitial Lung Disease

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Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

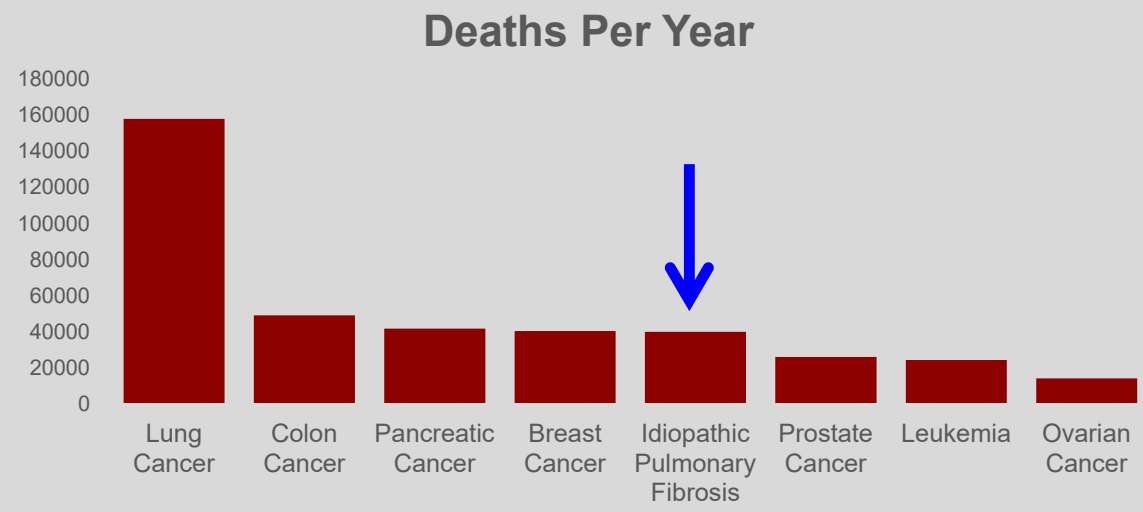
ILD: The 10,000 Foot View

Which of the following are the leading causes of death?

1. Lung cancer
2. Breast cancer
3. Colon cancer
4. Prostate cancer
5. Ovarian cancer
6. Leukemia
7. Pancreatic cancer
8. Idiopathic pulmonary fibrosis

Which of the following are the leading causes of death?

1. Lung cancer: 158,080 deaths per year
2. Breast cancer
3. Colon cancer
4. Prostate cancer
5. Ovarian cancer
6. Leukemia
7. Pancreatic cancer
8. Idiopathic pulmonary fibrosis



Interstitial Lung Disease

- Accumulation of scar and/or inflammation in the lung
- PFTs show restriction and low diffusing capacity
- High resolution chest CT
  - Ground glass infiltrates: inflammation
  - Honeycomb infiltrates: scar
  - Reticular markings: inflammation or scar

Interstitial Lung Diseases

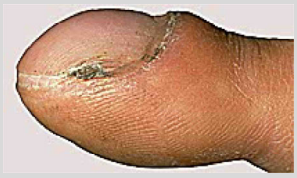
- Desquamative Interstitial Pneumonitis
- Lymphocytic Interstitial Pneumonitis
- Eosinophilic pneumonia
- Alveolar Proteinosis
- Amyloidosis
- Lymphangitic Carcinomatosis
- Radiation Pneumonitis
- Langerhan's Cell Granulomatosis
- Lymphangioleiomyomatosis
- Tuberous Sclerosis
- Neurofibromatosis
- Hypersensitivity Pneumonitis
- Sarcoidosis
- Berylliosis
- Ankylosing Spondylitis
- Rheumatoid Arthritis
- Silicosis
- Asbestosis
- Lymphoma
- IgG4 disease
- Hard metal disease
- Crohn's disease
- Ulcerative collitis
- Idiopathic inflammatory myopathy
- Familial idiopathic pulmonary fibrosis
- Hermansky-Pudlak syndrome
- Gaucher's disease
- Goodpasture's syndrome
- Nitrofurantoin
- Methotrexate
- Amiodarone
- Talc granulomatosis
- Siderosis
- Tannosis
- Coal worker's pneumoconiosis
- Sulfasalazine
- Minocycline
- Idiopathic pulmonary fibrosis
- Bleomycin
- Mixed dust pneumoconiosis
- Hard metal disease
- Hemosiderosis
- Granulomatosis with polyangiitis
- Drug-Induced Fibrosis
- Systemic Sclerosis
- Systemic Lupus Erythematosus
- Sjogren's Syndrome
- Mycobacterial Infection
- Histoplasmosis
- Aspiration
- Lipoid Pneumonia
- Diffuse pulmonary neuroendocrine hyperplasia
- Polymyositis
- Mixed Connective Tissue Disease
- Microlithiasis
- Churg-Strauss Syndrome
- Pneumocystis carinii
- Oxygen Toxicity
- Cryptogenic Organizing Pneumonia
- Non-Specific Interstitial Pneumonitis

Initial work-up of interstitial lung disease:

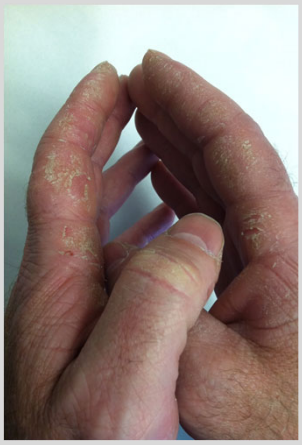
- Thorough history and physical exam
- Autoimmune screen
  - Serologies
- Pulmonary function tests
- High resolution chest CT

Physical Examination:

- Crackles present:
  - IPF
  - Asbestosis
- Crackles absent:
  - Sarcoidosis
  - Langerhan's cell histiocytosis
  - Chronic eosinophilic pneumonia



Digital clubbing:



Mechanic's Hands

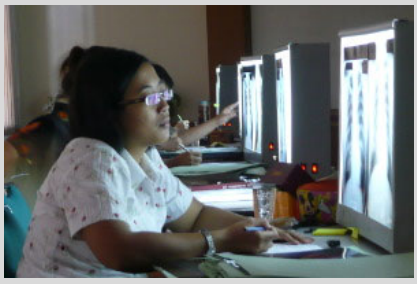
Clues From Infiltrate Locations:

- Upper lobes:
  - Silicosis
  - Sarcoidosis
  - Hypersensitivity pneumonitis
- Lower lobes:
  - IPF
  - Asbestosis
- Peripheral infiltrates
  - Chronic eosinophilic pneumonia

Second-line tests in interstitial lung disease:

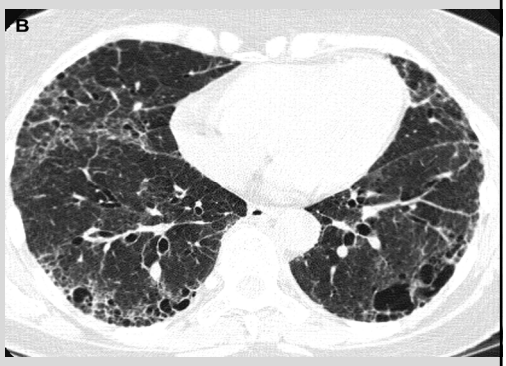
- Bronchoalveolar lavage
  - Primarily useful when chronic eosinophilic pneumonia, infection, or malignancy is suspected
- Transbronchial biopsy
  - Primarily useful when infection, malignancy, or sarcoidosis is suspected
- Bronchoscopic cryobiopsy
  - Role still not defined
- Surgical lung biopsy
  - When ground glass infiltrates predominate
  - When the CT scan is not typical for UIP
  - When there remains diagnostic uncertainty after initial work-up

Interstitial Lung Disease Diagnosis Requires A Multi-Disciplinary Approach



Get to know your radiologist

- Agree on definition of radiographic descriptions
- Presence or absence of honeycombing
- Presence or absence of ground glass infiltrates
- Anatomic location of infiltrates



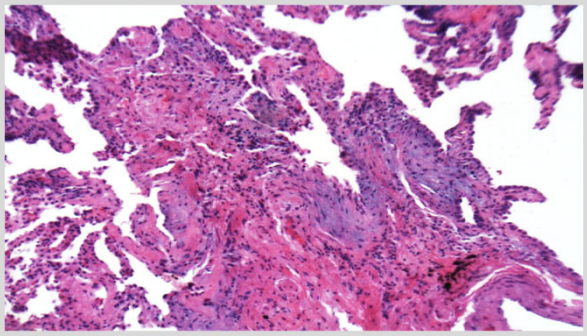
**Diffuse interstitial infiltrates ≠ IPF

Get to know your thoracic surgeon

- 2 or 3 lobe deep biopsies
- Avoid the tips of the lingula, middle lobe, or lower lobes
- Target ground glass infiltrates or transition zones

Get to know your pathologist

- Presence or absence of fibroblastic foci?
- Temporal heterogeneity?
- Presence or absences of microcystic changes?
- Presence or absence of collagen deposition?
- Granulomas?



**End stage fibrosis ≠ IPF

Interstitial Lung Diseases

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Idiopathic Pulmonary Fibrosis

- Most common ILD of unknown etiology
- Mainly affects people > 50 years, most are over the age of 60 years
- Incidence is estimated at 7-16 cases per 100,000 per year
- The incidence is increasing
- Possible risk factors for developing IPF include cigarette smoking, occupational/environmental exposures

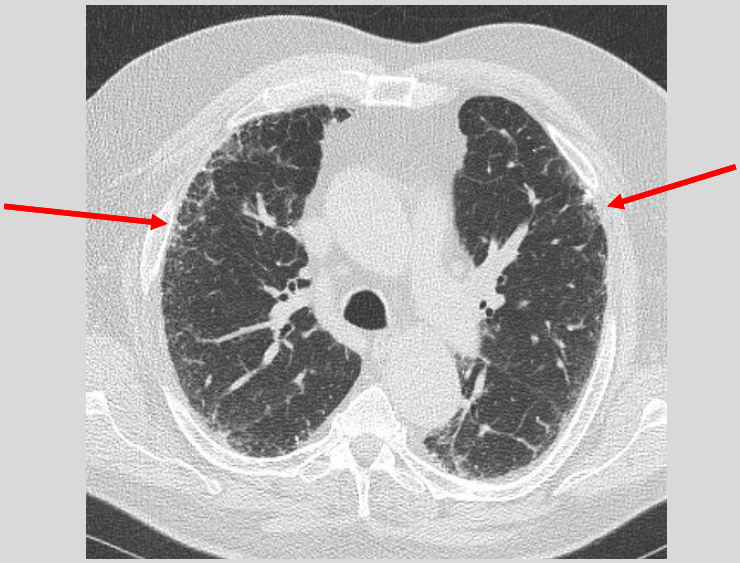
Idiopathic Pulmonary Fibrosis

- History/Exam
  - Gradual onset and progressive dyspnea and/or a nonproductive cough
  - Bibasilar inspiratory crackles (Velcro crackles)
  - Clubbing is common
- PFTs show restriction, low diffusing capacity and desaturation with exertion

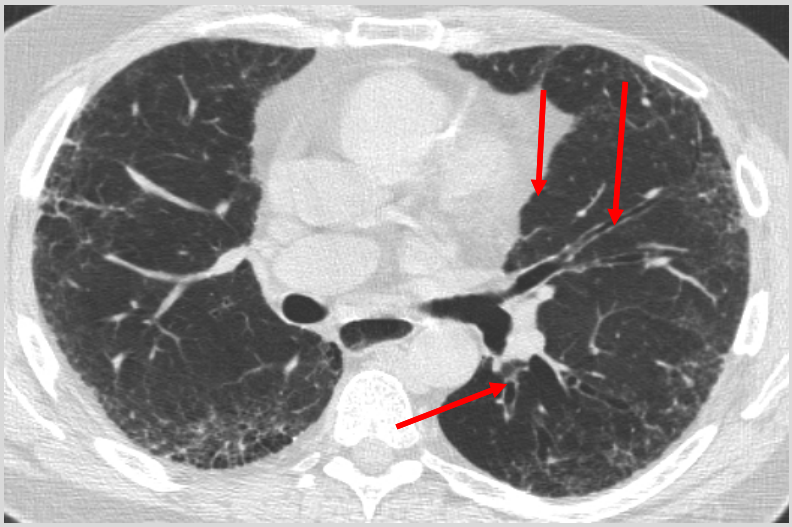
Idiopathic Pulmonary Fibrosis

- Diagnosis confirmed by imaging, lung biopsy
- CT findings: usual interstitial pneumonitis (UIP)
  - Subpleural, basal predominance interstitial/reticular infiltrates
  - Honeycombing with or without traction bronchiectasis
  - Minimal ground glass infiltrates
- Biopsy findings: usual interstitial pneumonitis (UIP) pathologic pattern
  - Temporal & geographic heterogeneity
  - Collagen deposition
  - Fibroblastic foci

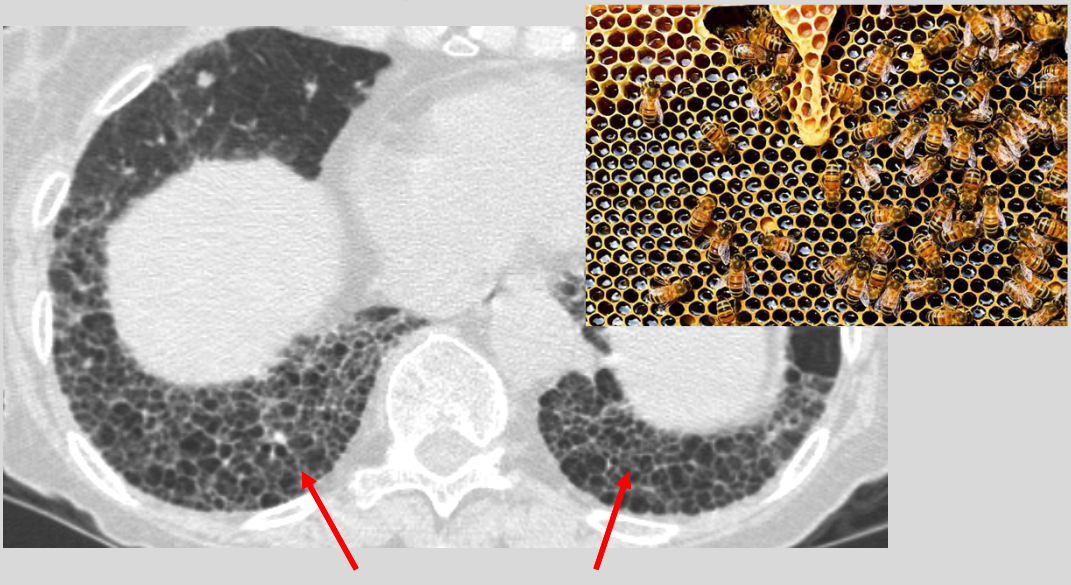
UIP: Peripheral reticular infiltrates



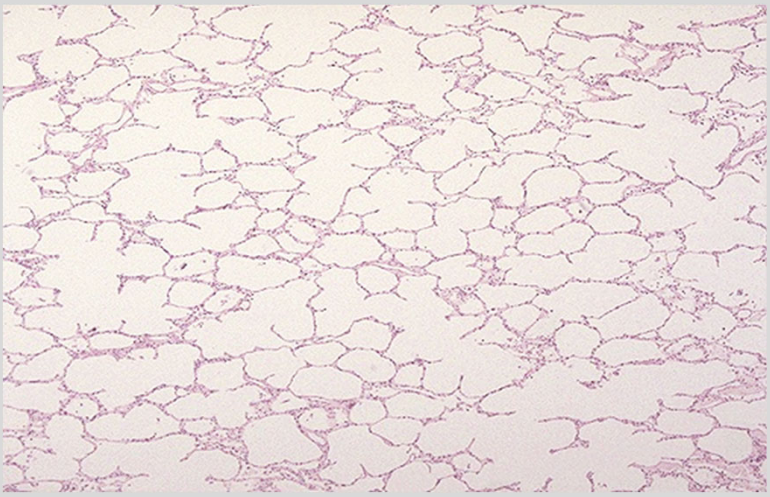
UIP: Traction bronchiectasis



UIP: Basilar honeycomb infiltrates



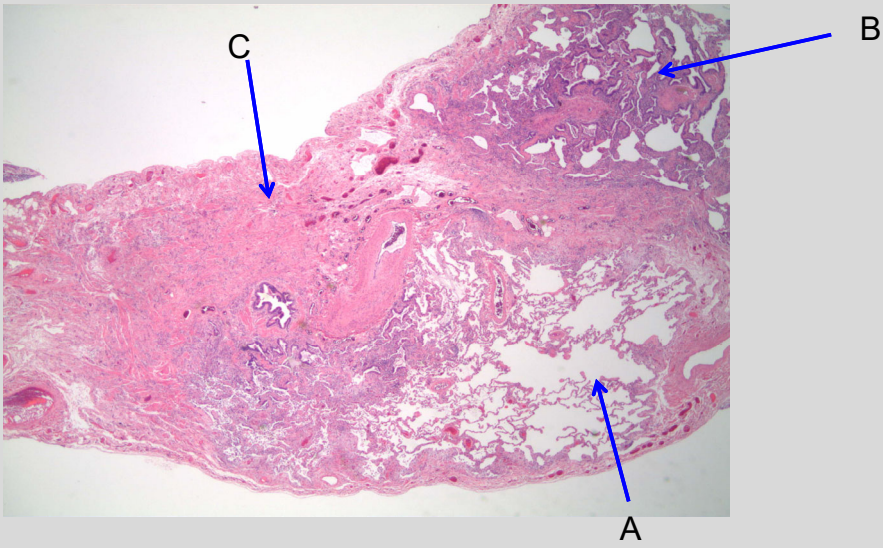
Normal lung alveoli: medium power



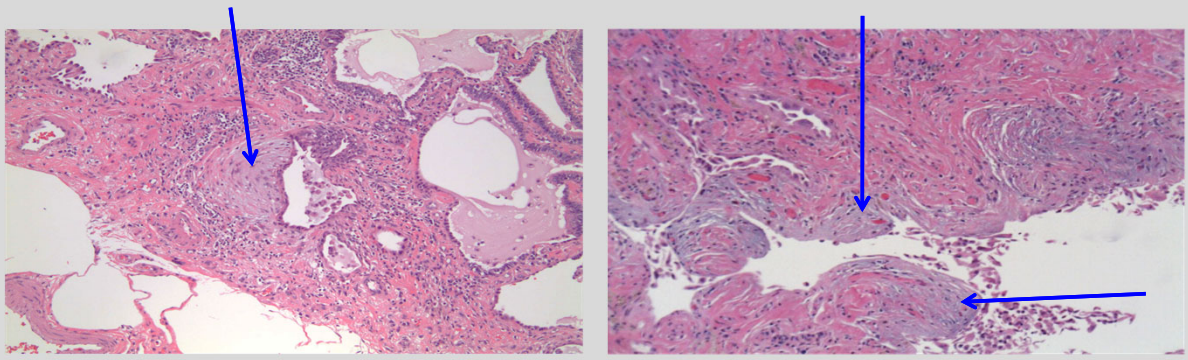
The histologic finding in IPF is usual interstitial pneumonitis (UIP):

1. Temporal & geographic heterogeneity
2. Fibroblast foci
3. Prominent collagen fibrosis
4. Microcysts

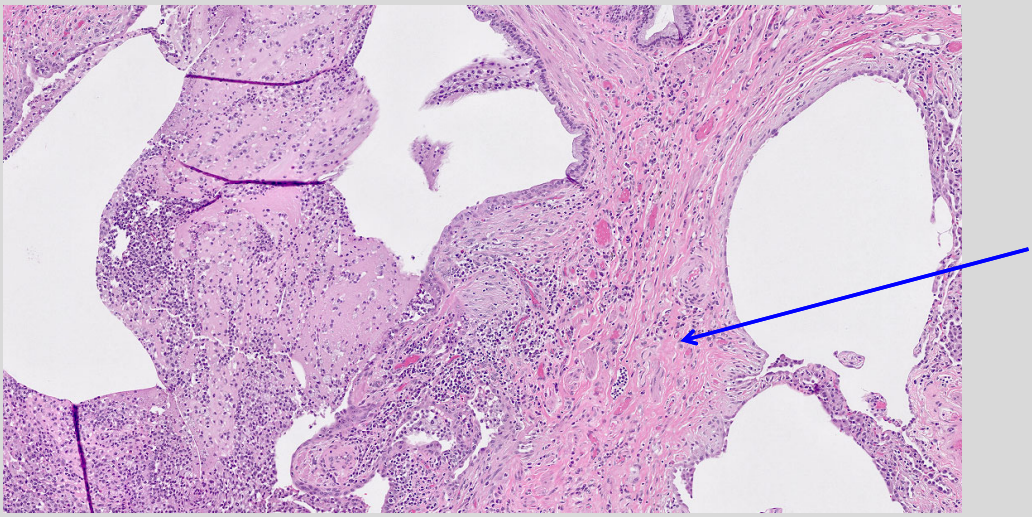
Temporal & Geographic Heterogeneity in UIP



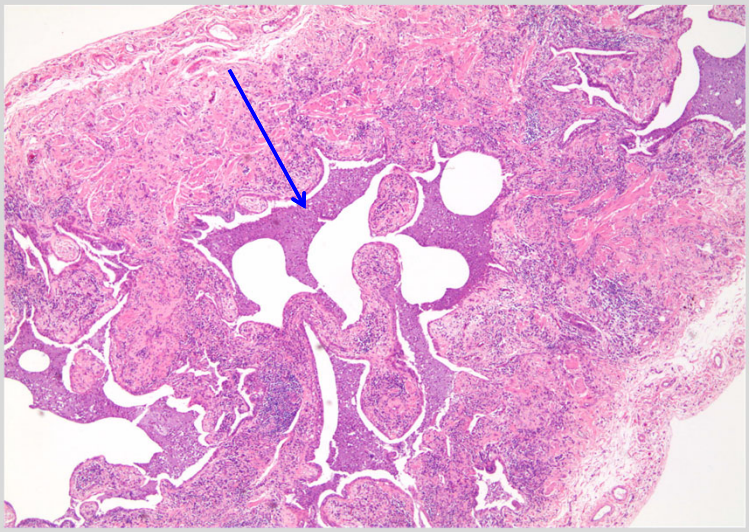
Fibroblastic foci in UIP



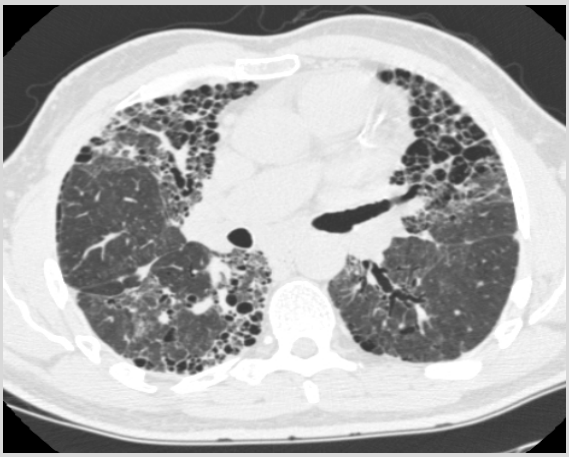
Collagen deposition in UIP

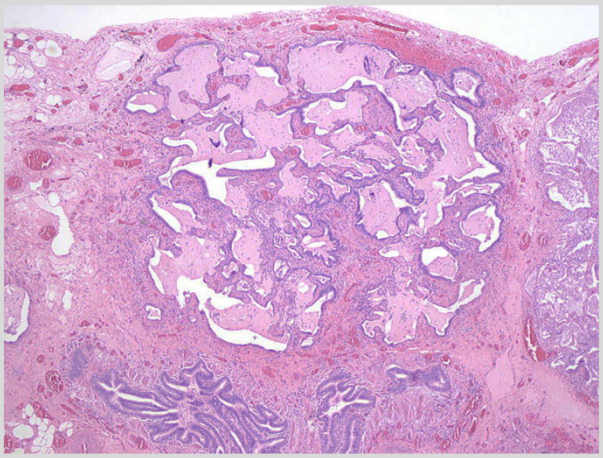


Microcysts in UIP



IPF: Honeycombing





Usual Interstitial Pneumonitis ≠ IPF

Causes Of Usual Interstitial Pneumonitis*

- Rheumatoid-associated
- Scleroderma-associated
- Chronic hypersensitivity pneumonitis
- Radiation-induced
- Drug-induced
- "Post-inflammatory pulmonary fibrosis"
- **Idiopathic pulmonary fibrosis**

*Different causes of UIP have very different prognoses and treatments

What causes IPF?

- #1 Genetic Predisposition
- Surfactant protein C
- Surfactant protein A2
- TERT
- TERC
- MUC5B

- #2 Epithelial Injury
- Dusty environment
- Tobacco smoke
- Viruses
- Acid reflux/aspiration

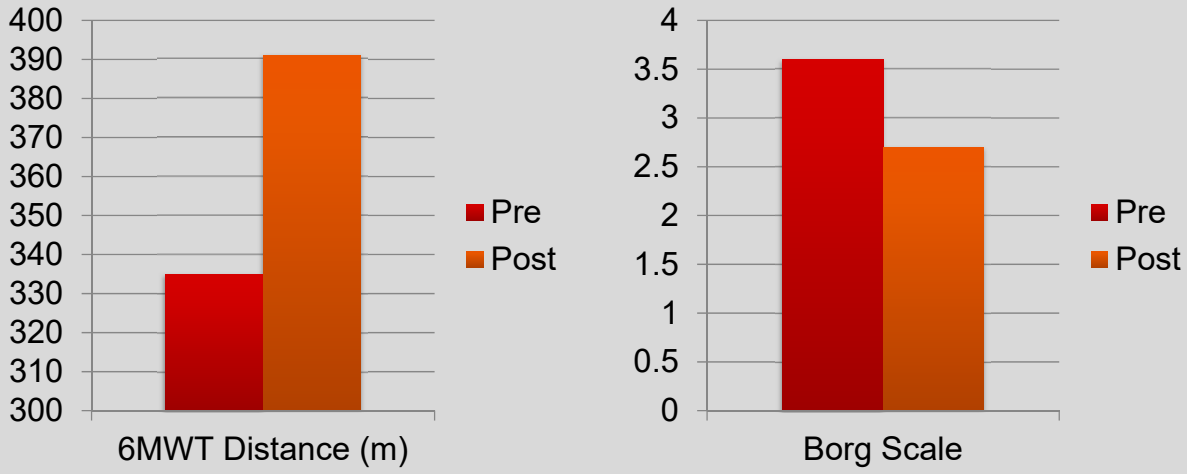
Familial pulmonary fibrosis:

- Accounts for 5-10% of patients with IPF
- Patients look just like IPF
- Typically ages 50-70
- Definition: first degree relative with IPF
- Probably autosomal dominant with variable penetrance
- Genetic cause found in about 10% of familial pulmonary fibrosis
- Treatment is the same as IPF

IPF Treatment: What Works?

- Oxygen
- Pulmonary rehabilitation
- Anti-fibrotic drugs:
  - Pirfenidone
  - Nintedanib
- Lung transplant

Effect of pulmonary rehabilitation on interstitial lung disease



Collard et al. Chest 2009; 135:442-7

What medications do work for IPF?

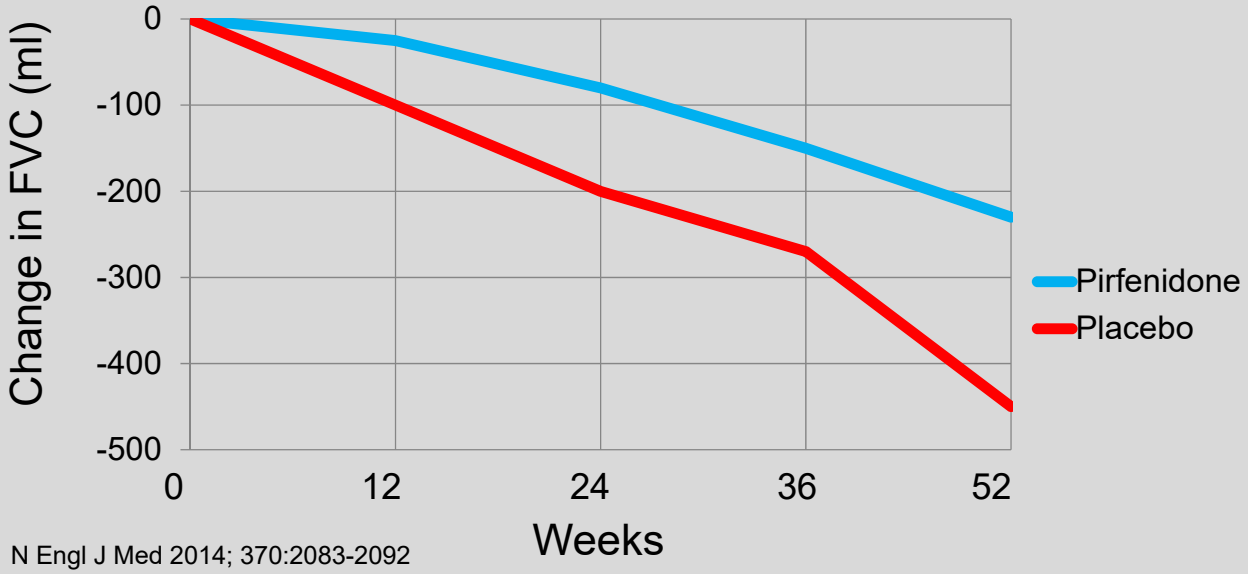
Pirfenidone (Esbriet)

- Anti-fibrotic TGFβ inhibitor
- Slows rate of progression by about half
- 3 capsules three times daily
- Side effects:
  - Sun sensitivity
  - Nausea, weight loss
  - Increased liver enzymes
- $90-100,000 per year

Nintedanib (Ofev)

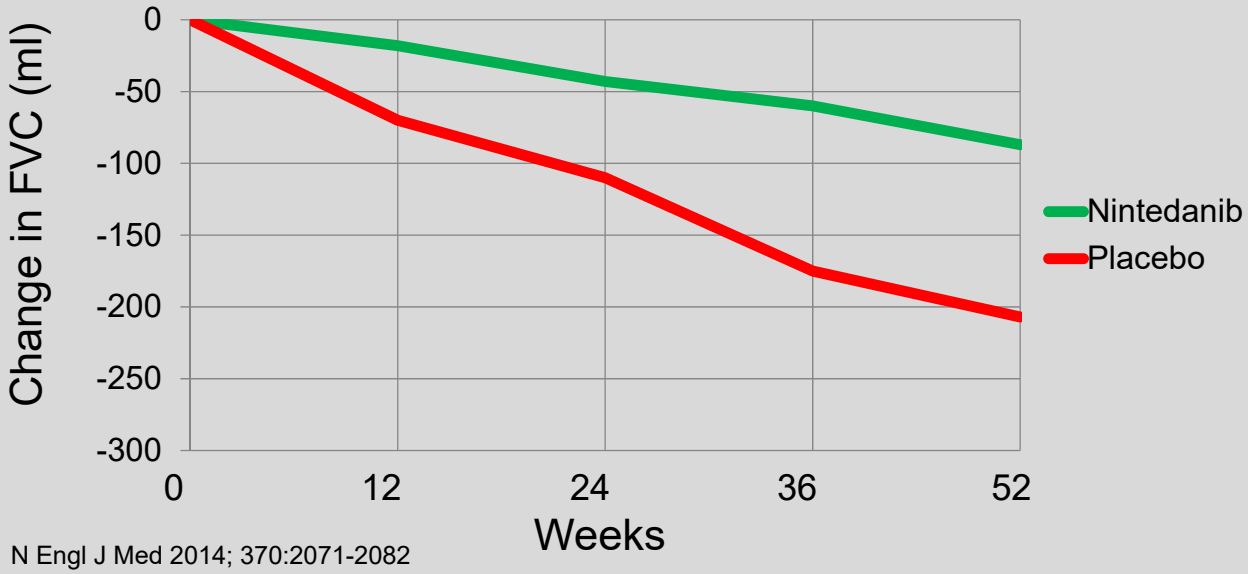
- Tyrosine kinase inhibitor
- Slows rate of progression by about half
- 150 mg twice daily
- Side effects:
  - Diarrhea
  - Nausea, weight loss
  - Increased liver enzymes
- $90-100,000 per year

Pirfenidone versus Placebo



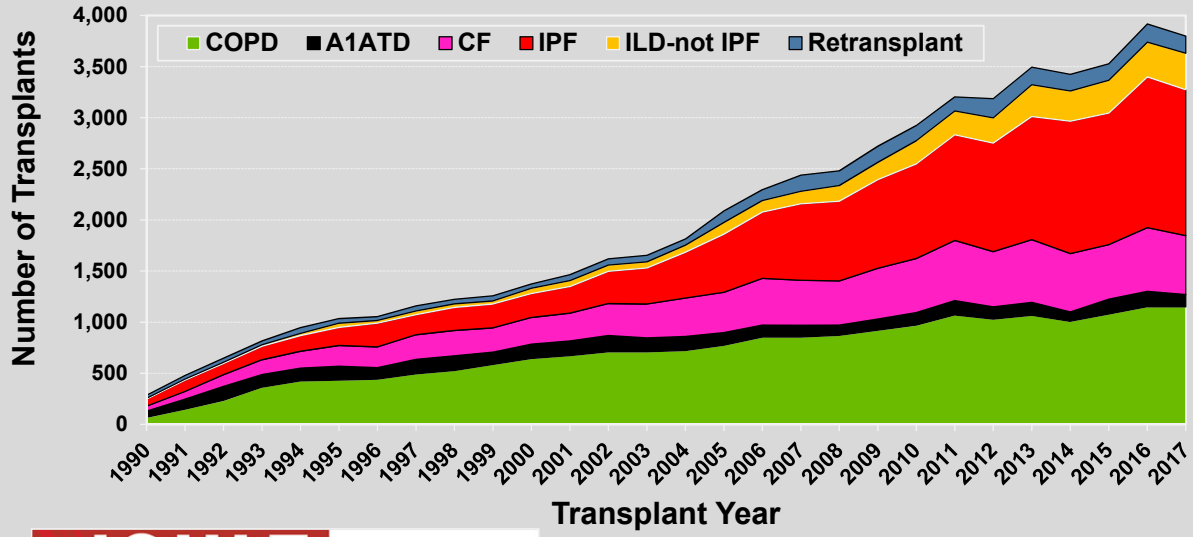
N Engl J Med 2014; 370:2083-2092

Nintedanib versus Placebo



N Engl J Med 2014; 370:2071-2082

Adult Lung Transplants Major Diagnoses by Year



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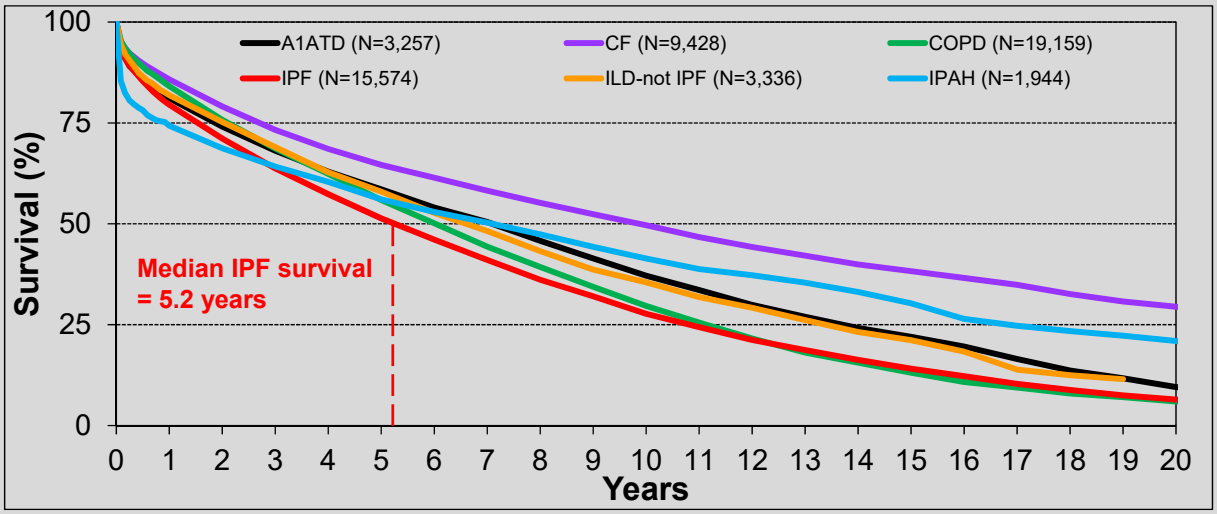
Adult Lung Transplants Survival by Major Diagnosis



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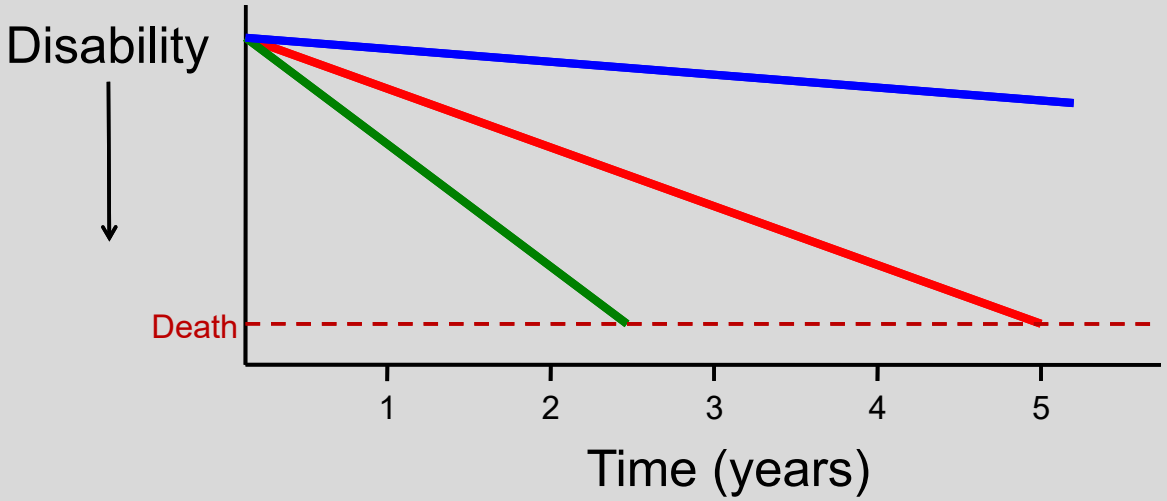
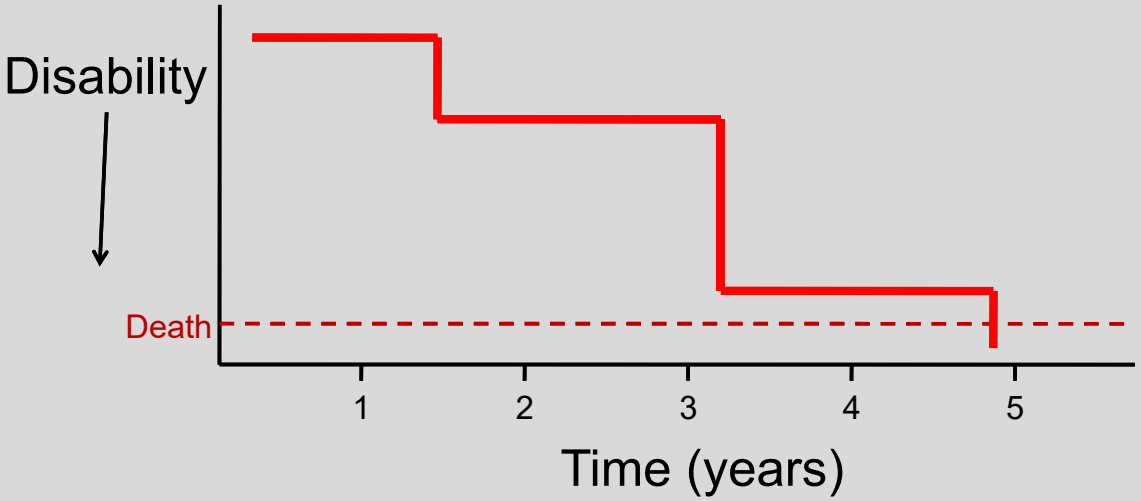
Typical Clinical Course



"Stair-Step" Clinical Course (exacerbations of IPF)



When patients with IPF are worse:

- Progression of IPF
- Acute interstitial pneumonitis
- Anemia
- Heart failure
- Pulmonary embolism
- Lung cancer
- Infection
- Pneumothorax

Clinical approach to IPF:

1. Establish a **confident** diagnosis
2. Search for non-IPF contributors of dyspnea
   - Heart failure
   - Anemia
   - Infection
   - Thyroid disease
3. Assess candidacy for transplant early

Clinical approach to IPF (continued):

4. Stop smoking
5. Assess for esophageal reflux
   - GERD
   - Hiatal hernias
6. Monitor disease progression
   - FVC
   - TLC
   - DLCO
   - Oxygen saturation with exercise
7. Start home oxygen early

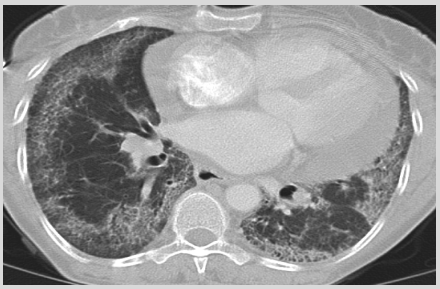
Clinical approach to IPF (continued):

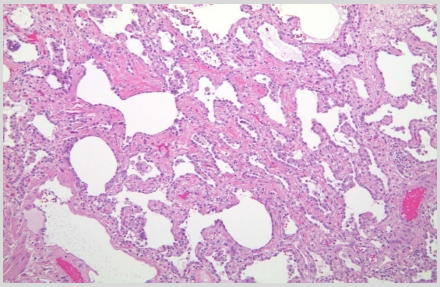
8. Pulmonary rehabilitation
9. Assess for & treat depression
10. Regular vaccinations
11. End of life discussions early

And some other interstitial lung diseases…

Non-Specific Interstitial Pneumonitis

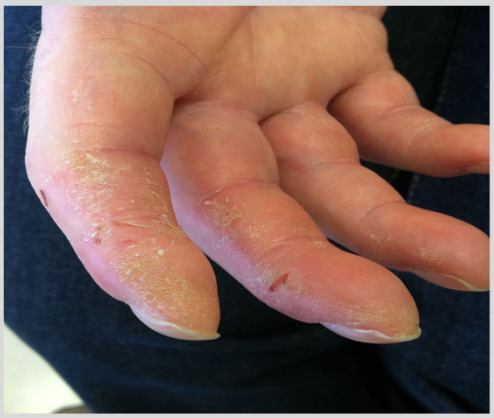
- Second most common idiopathic interstitial pneumonia
- Affects men and women equally with an average age about 10 years younger than IPF
- *Almost always* seen in the setting of rheumatologic disease
- Shortness of breath and dry cough
- Physical findings include inspiratory crackles, ± clubbing





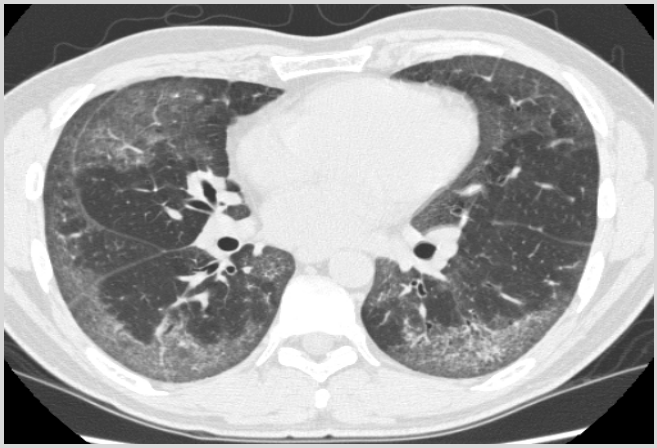
Non-Specific Interstitial Pneumonitis

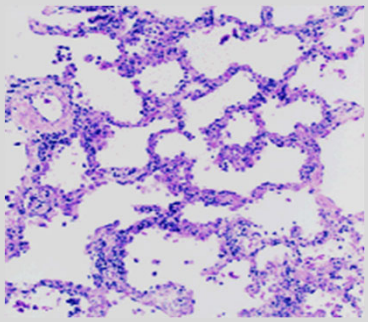
- Important to differentiate from IPF
  - NSIP 5 year mortality <10%
  - Survival > 6-10 years
- Treatment
  - Prednisone
  - Mycophenolate
  - Azathioprine
  - Cyclophosphamide

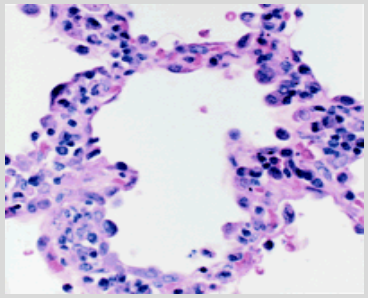


"Mechanic's Hands"

Non-specific interstitial pneumonitis: Ground Glass Infiltrates







Non-specific interstitial pneumonitis (NSIP) pathology:

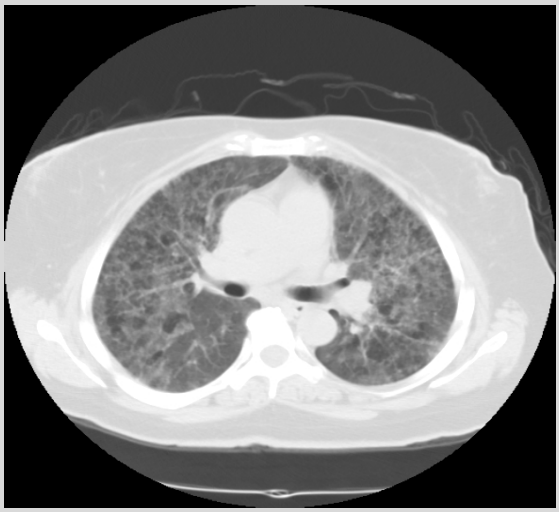
- Alveolar wall inflammatory cells
- Temporal homogeneity
- No fibroblast foci
- Minimal collagen fibrosis

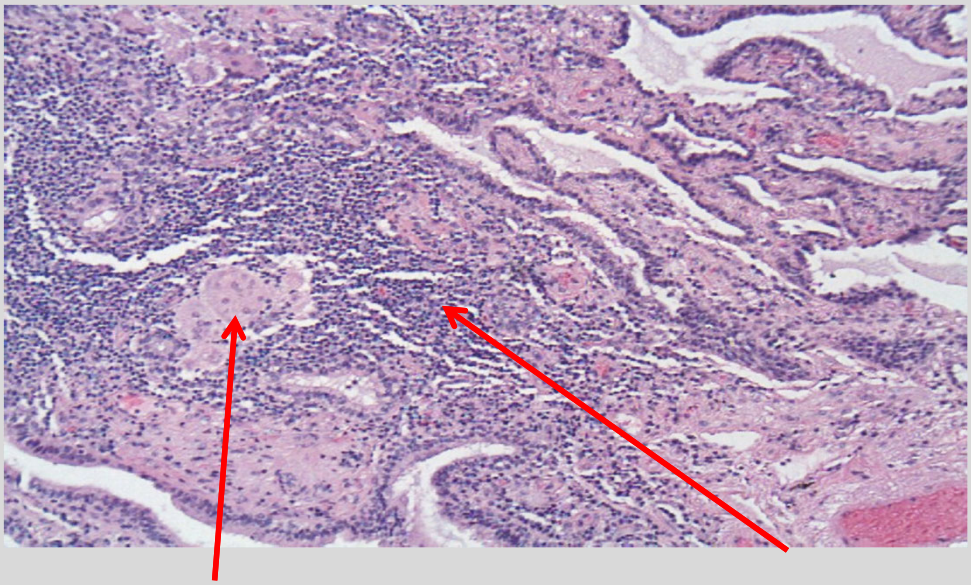
Hypersensitivity Pneumonitis

- Etiology often hard to identify
  - Birds, feathers, down
  - Hot tubs
  - Occupation
  - Drugs
- Pathology:
  - T-suppressor cell alveolitis
  - Poorly formed granulomas
- Treatment:
  - Remove offending antigen
  - Prednisone
- Outcome:
  - Complete resolution
  - Chronic fibrosis

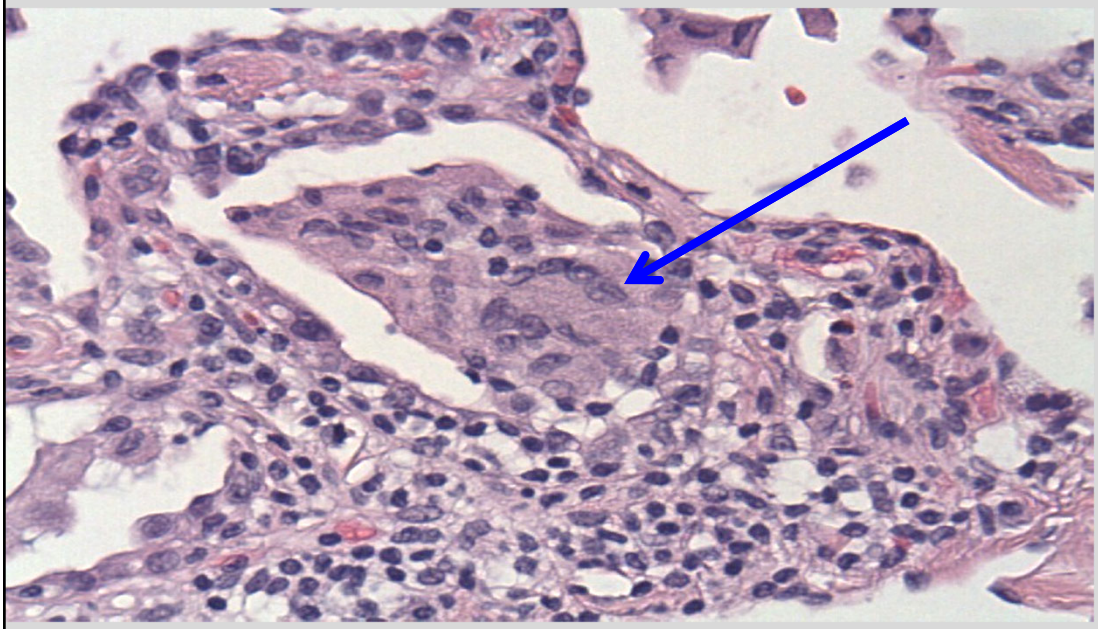
Hypersensitivity Pneumonitis Radiology

- Frequently upper lobe dominant infiltrates
- Ground glass infiltrates
- Nodular infiltrates



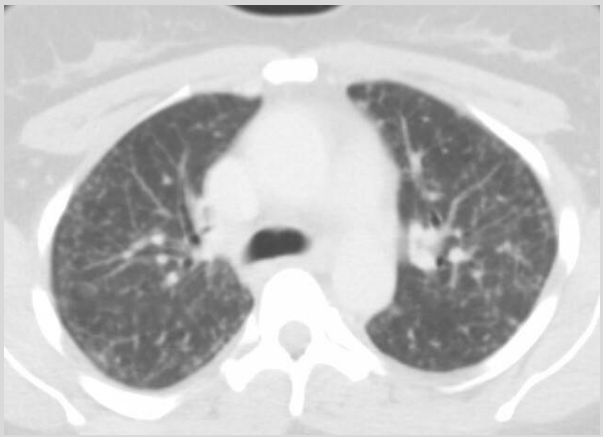


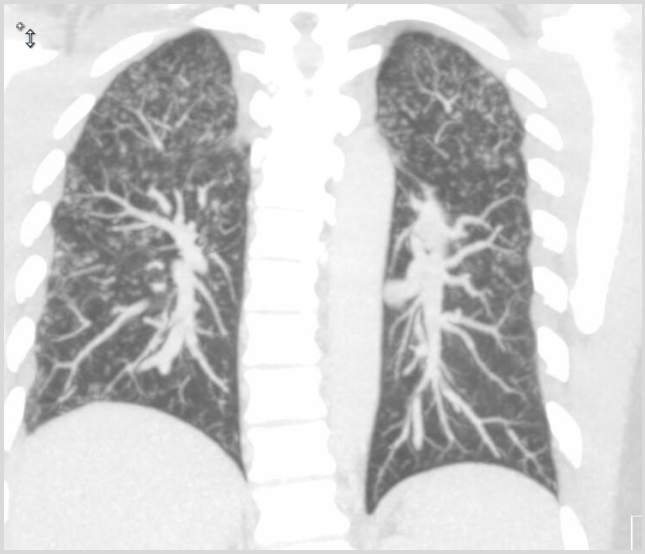
Multinucleated Giant Cell Lymphocytic infiltrates



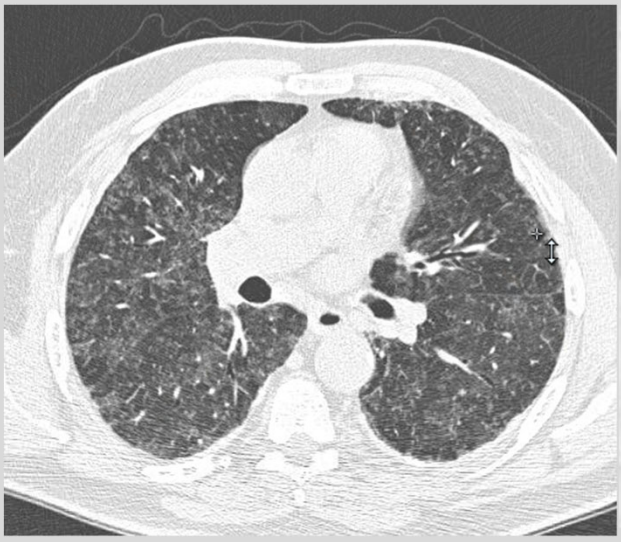
Poorly-formed granuloma

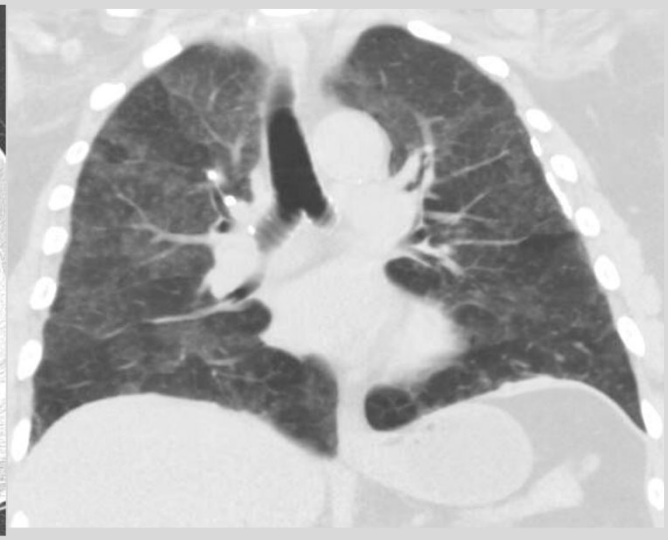
Lettuce farm worker with dyspnea



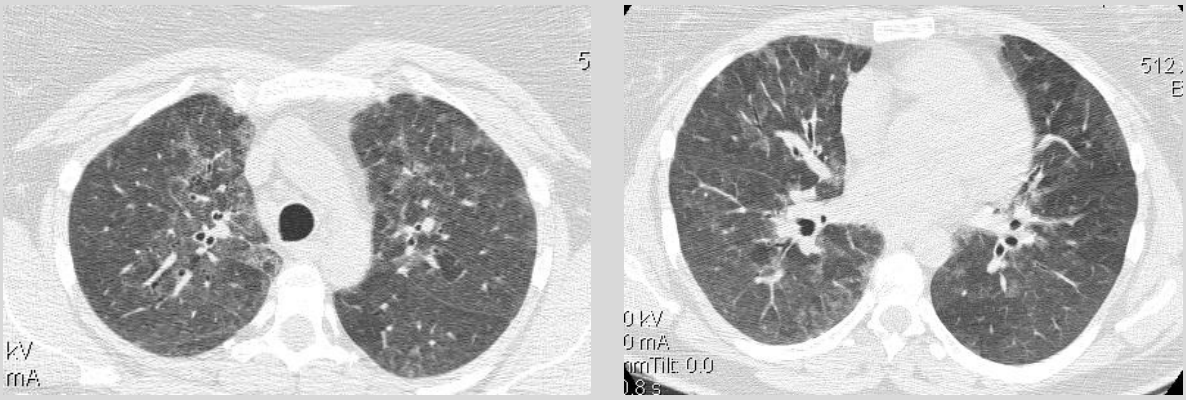


Hot Tub Lung



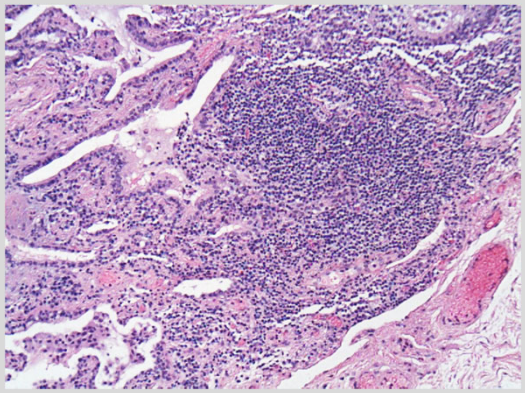


41 year old woman referred for suspected idiopathic pulmonary fibrosis



And then she said…

- "And oh by the way, did I tell you that we raise goats and donkeys in the barn in our back yard?"
- "And oh by the way, did I tell you we have a Quacker Parrot? And Cockatiels? And Parakeets?"
- "And oh by the way, did I tell you we have birds living in our attic and there's a hole in my closet ceiling so that my clothes are covered with bird feathers and bird poop?"

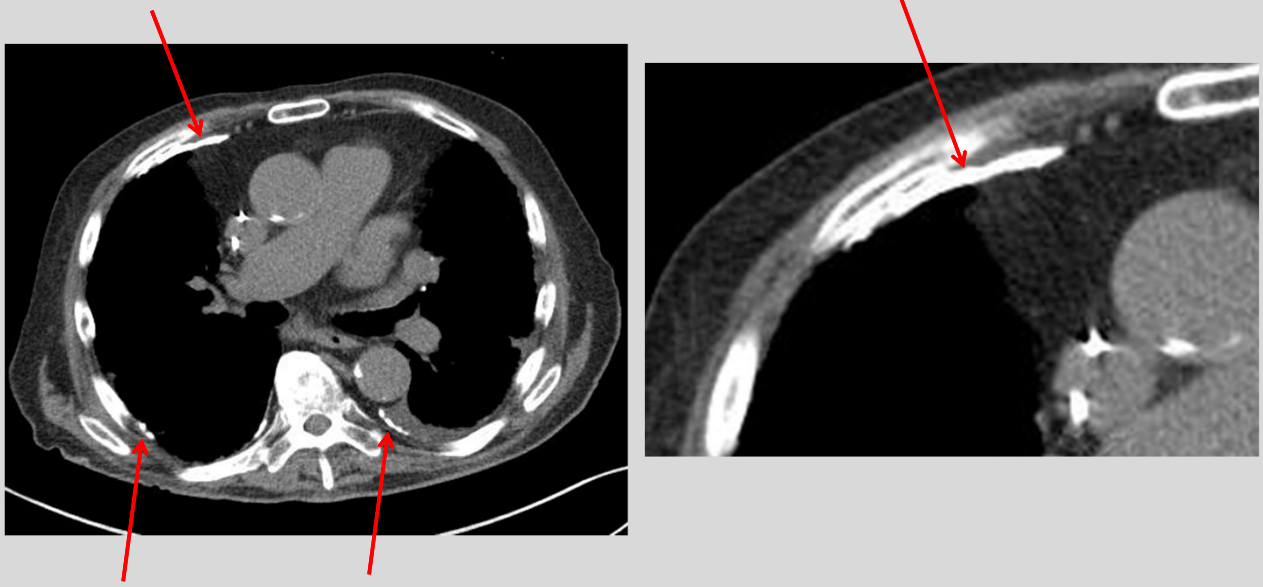


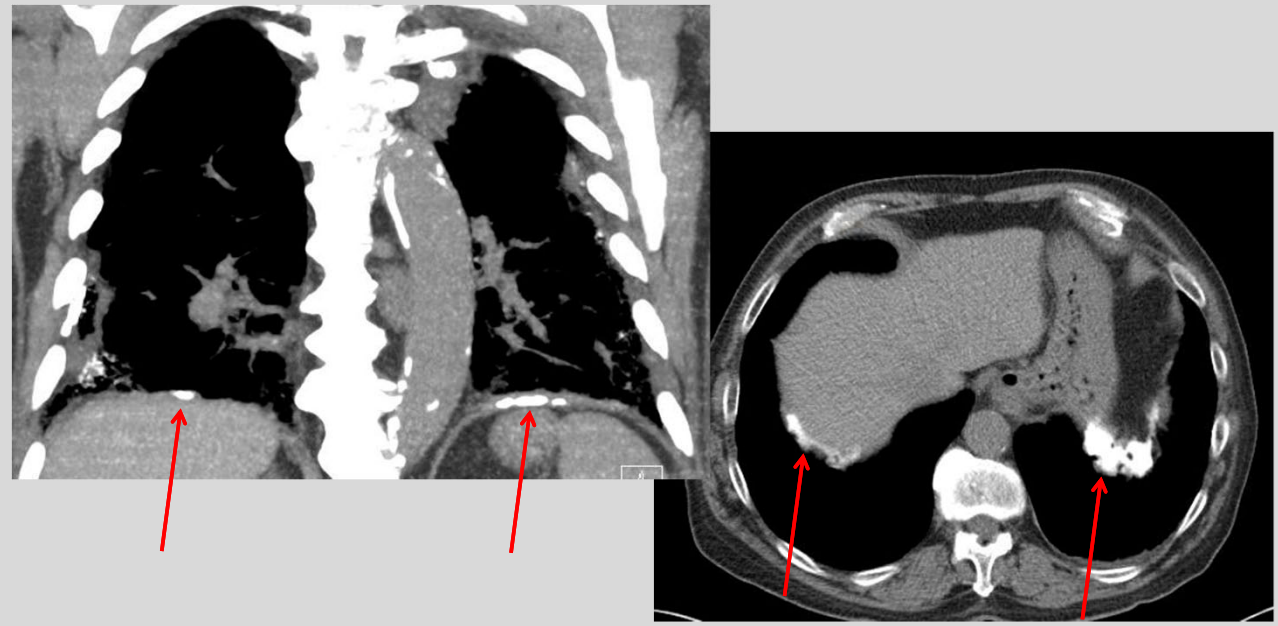
Common Occupational Lung Diseases

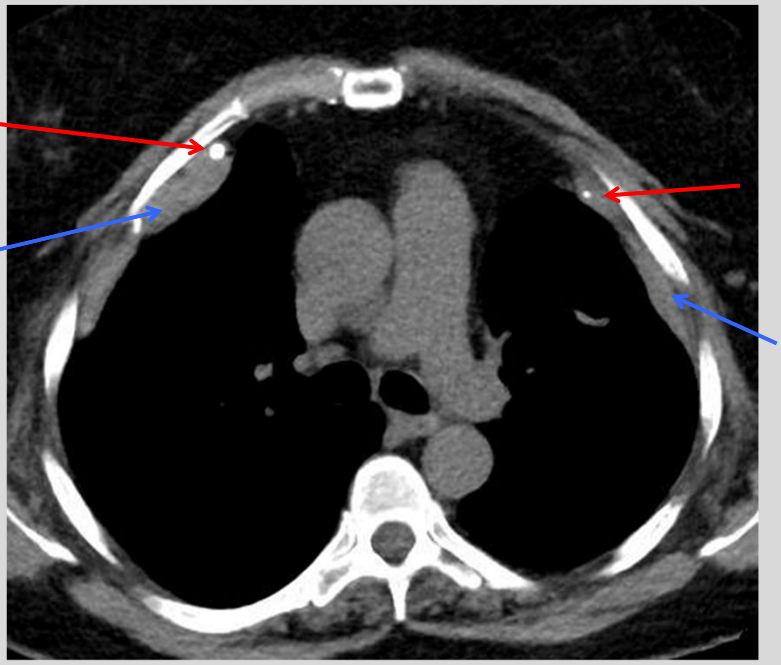
- Asbestosis: boilermakers, plumbers, pipefitters
- Silicosis: miners, quarry workers, sandblasters, foundry workers, many others

Asbestosis

- CT appearance resembles UIP
- Pathology resembles UIP
  - May see ferruginous bodies
- Diagnosis usually made based on occupational history
- Bilateral calcified pleural plaques strongly supports exposure
  - However plaques ≠ asbestosis

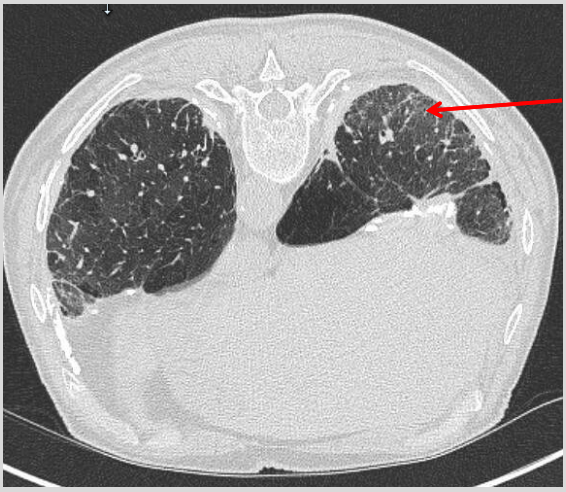


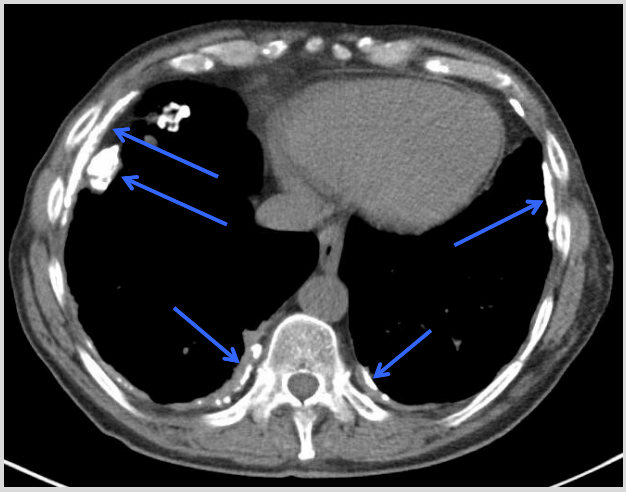




60 year old woman whose father was an pipe-fitter; her mother laundered his dusty work clothes. Both her mother and father died of asbestosis

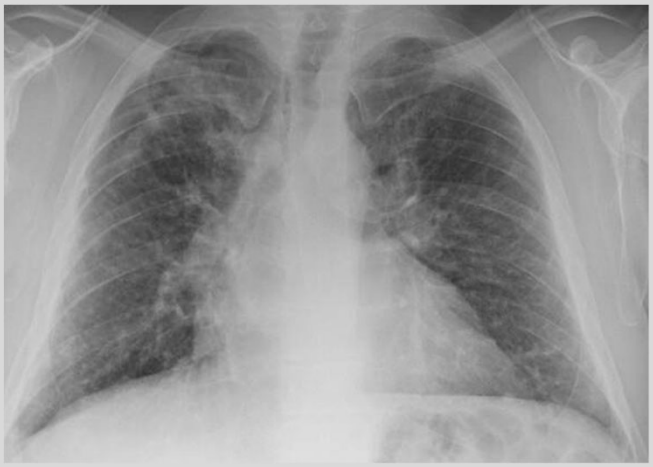
78 year old man with dyspnea for 10 years. Formerly worked in construction

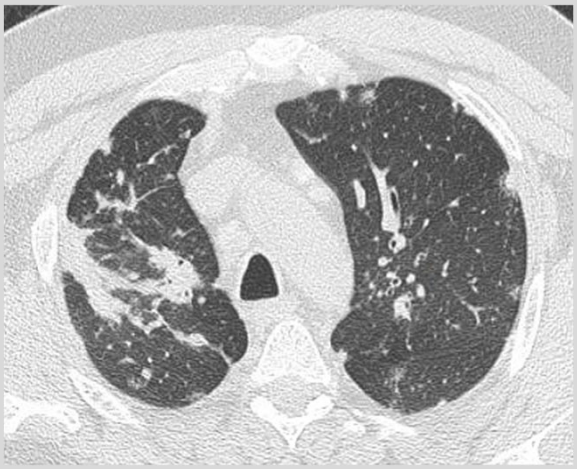




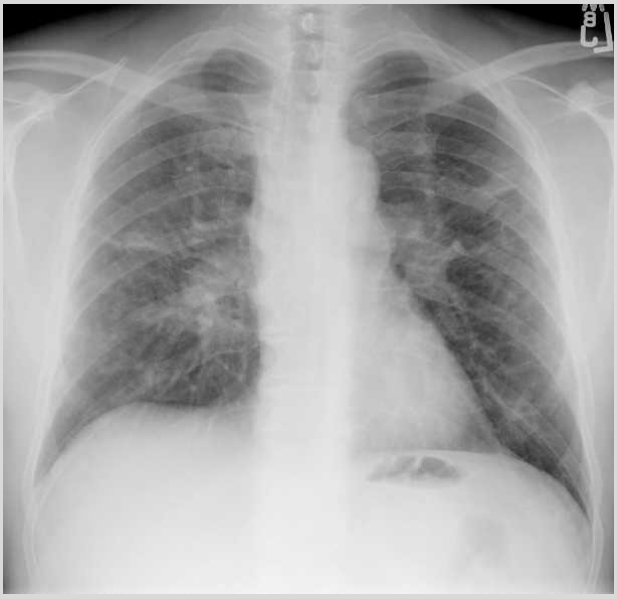
Silicosis

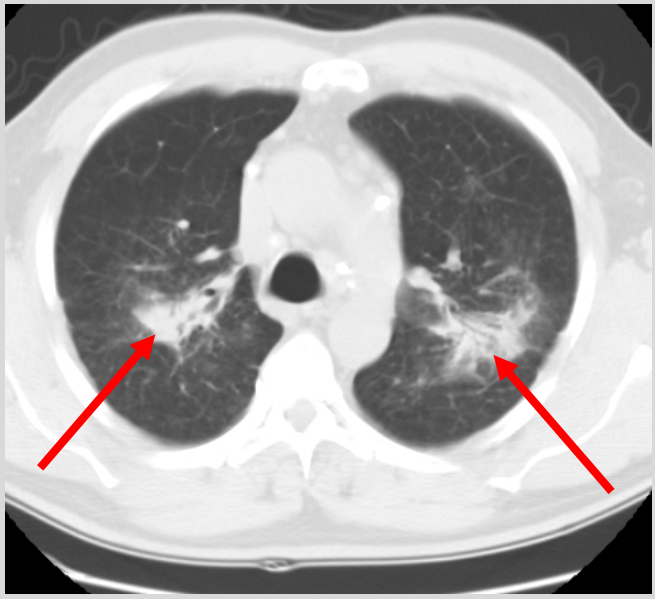
- Upper lobe predominant pulmonary nodules
- Upper lobe progressive massive fibrosis
- Calcified mediastinal lymph nodes

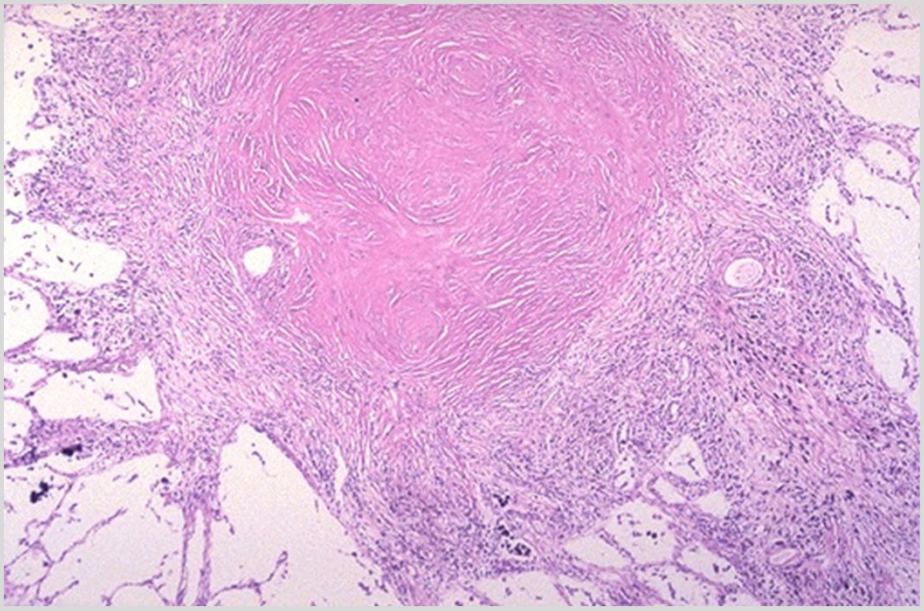




Foundry Worker With Dyspnea



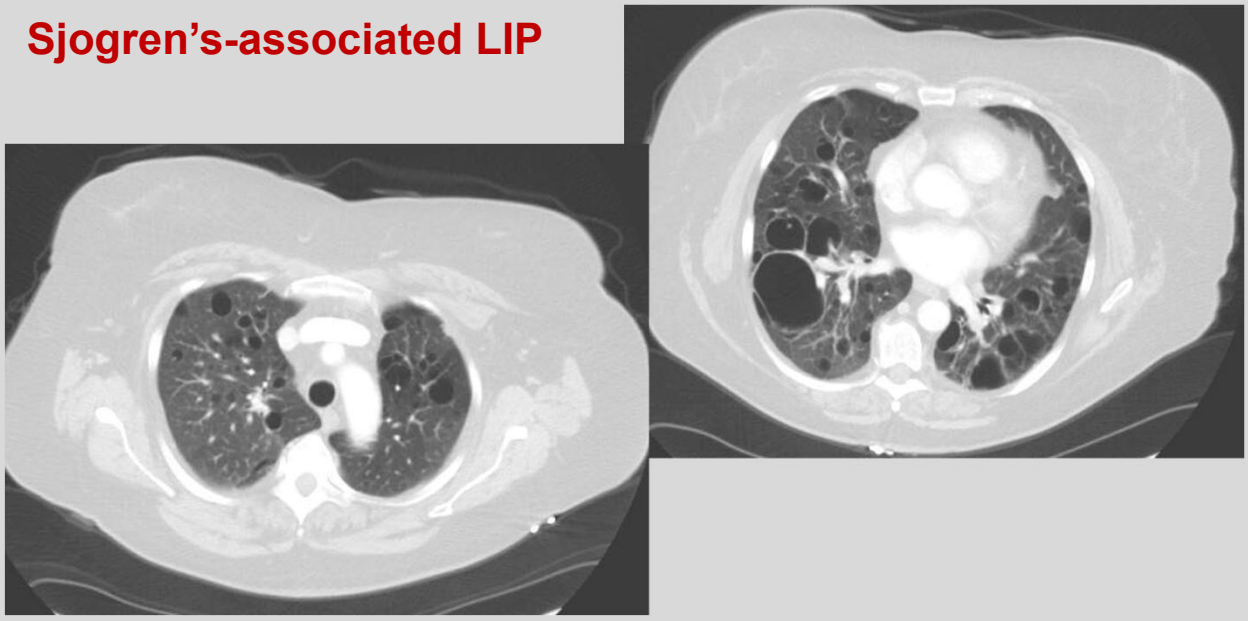




Lymphocytic Interstitial Pneumonitis

- Most commonly seen with Sjogren's
  - Presents with multiple bilateral thin-walled cysts
- Can be seen with HIV, lupus, autoimmune myositis, rheumatoid arthritis
  - Presents with diffuse interstitial/alveolar infiltrates
- Treatment = steroids, mycophenolate, or azathioprine
- Need to watch for evolution into lymphoma

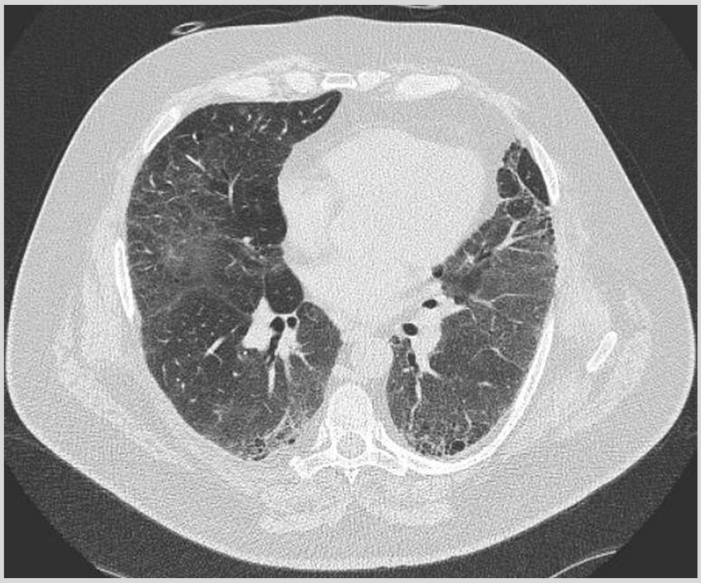
Sjogren's-associated LIP



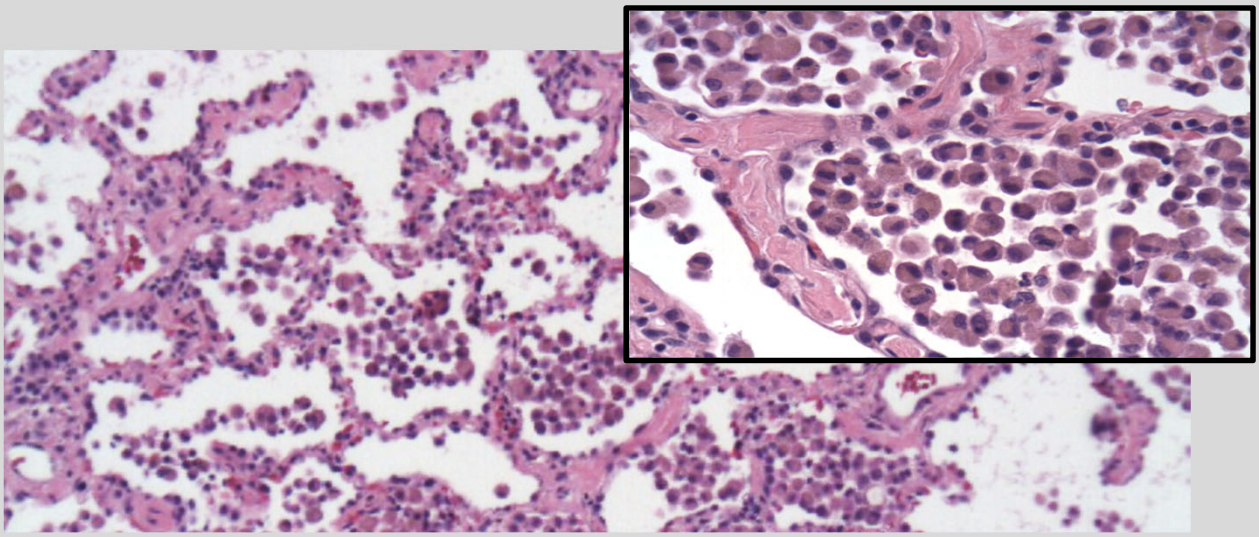
Desquamative Interstitial Pneumonitis

- > 90% are smokers
  - Rarely associated with collagen vascular disease
- Typical age = 30-50
- Chest CT:
  - Ground glass infiltrates
  - CXR may be normal
- Pathology:
  - Abundant smoker's macrophages
  - Little alveolar wall inflammation
  - Little fibrosis

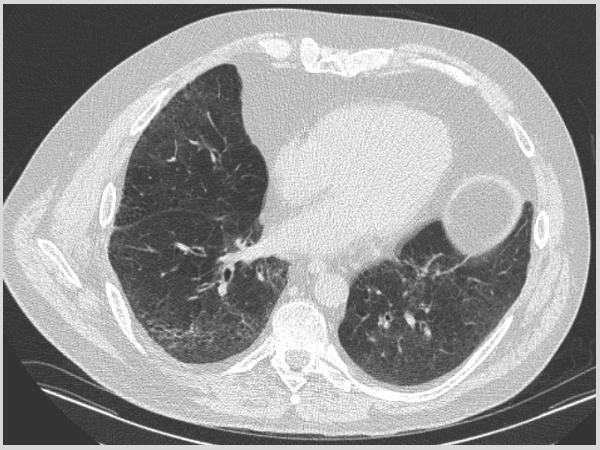
Desquamative Interstitial Pneumonitis

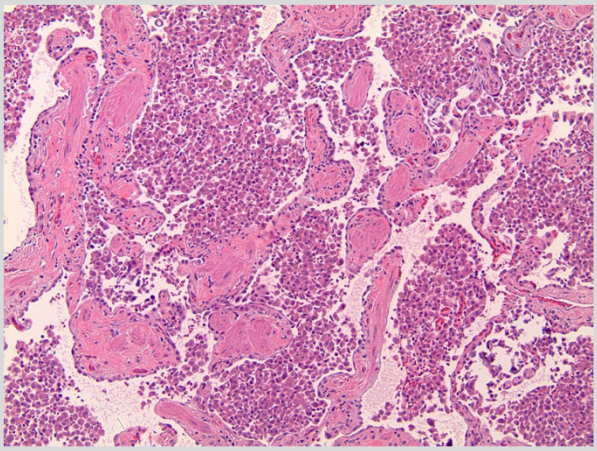


Desquamative Interstitial Pneumonitis

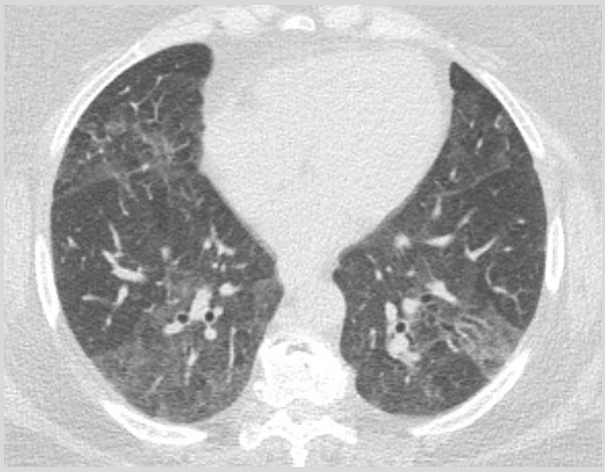


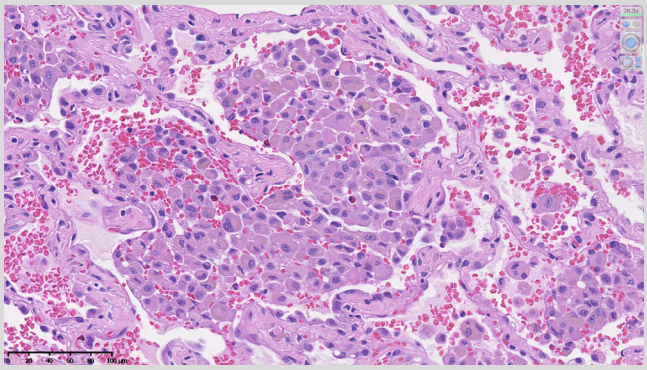
Desquamative Interstitial Pneumonitis





Desquamative Interstitial Pneumonitis



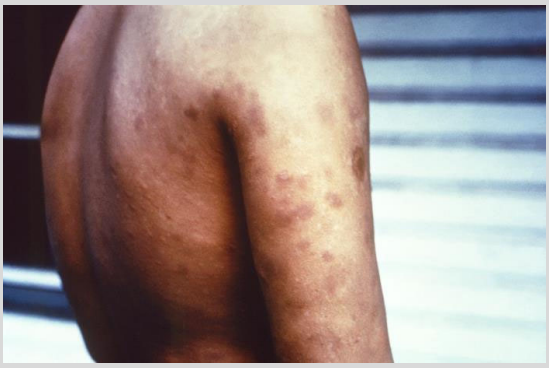


Desquamative Interstitial Pneumonitis:

- Treatment:
  - Smoking cessation!!!!
  - Steroids
  - Occasionally immunosuppressive medications
- Prognosis:
  - Excellent if treated early

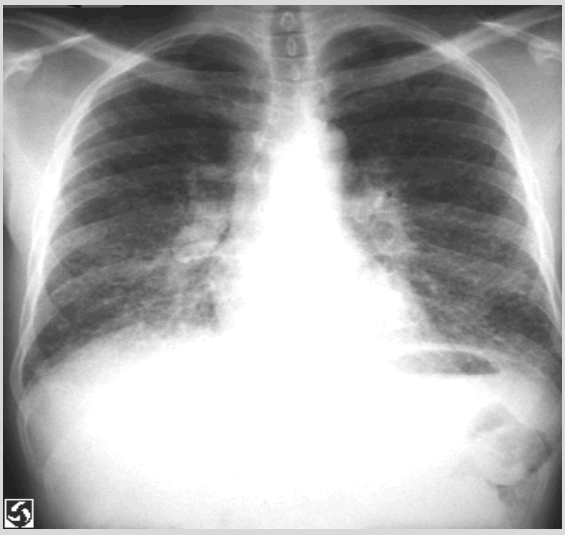
Sarcoidosis

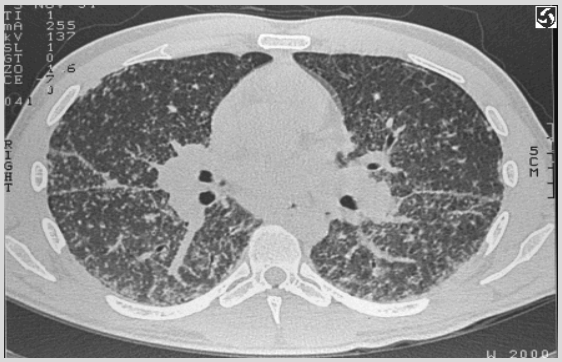
- Multi-organ disease
- High incidence in young African Americans & Scandinavians
- Exam = normal lung auscultation; +/- erythema nodosum
- Chest x-ray = adenopathy and/or nodular infiltrates
- BAL = increased lymphocytes (T helper)



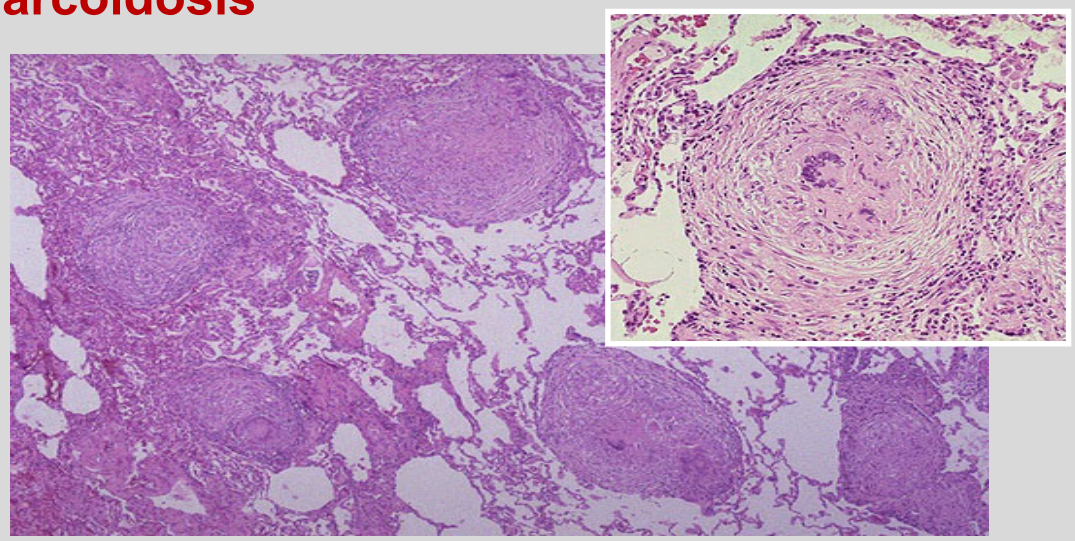
Erythema Nodosum

Sarcoidosis





Sarcoidosis



Sarcoidosis

- Diagnosis based on finding granulomatous inflammation in a patient with a compatible clinical history
- Rule out other cause of granulomas
  - Infections such as mycobacterial and fungal infections
  - Beryllium exposure
  - Foreign body granulomas
- Differentiate from granulomas related to hypersensitivity pneumonitis

Sarcoidosis

Evaluation:

- Pulmonary function tests
- Eye exam
- EKG
- Calcium level
- Liver function tests

Treatment:

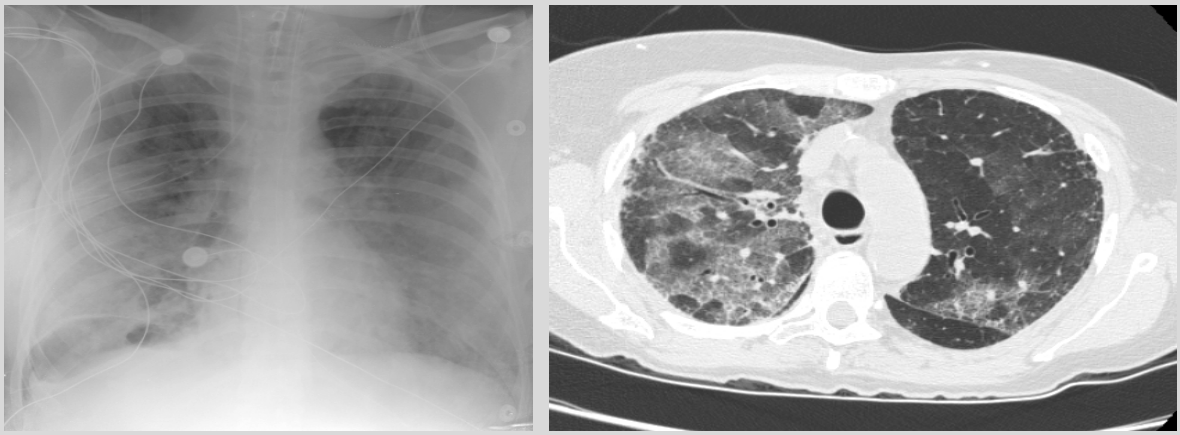
- Prednisone
  - Methotrexate second line
- Mild cases may resolve without treatment
- Prognosis for recovery is generally good

Watch the May 2020 MedNet webcast on Sarcoidosis!

Acute interstitial pneumonitis

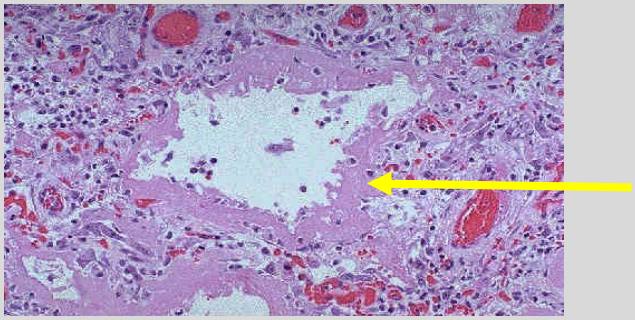
- Diagnosis of exclusion
- Sudden-onset of worsened oxygenation and ground glass infiltrates
- Can occur as:
  - With underlying IPF
  - Idiopathic
  - With underlying rheumatologic disease
- Lung biopsy = diffuse alveolar damage (identical to ARDS)
- Steroids *may* help

Acute interstitial pneumonitis



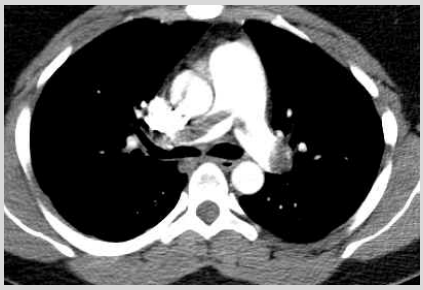
Acute Interstitial Pneumonitis

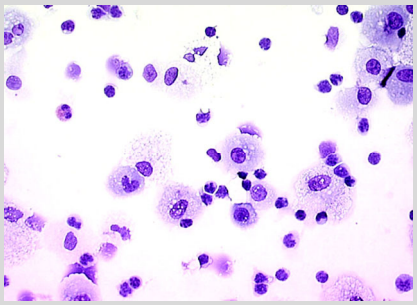
- Acute lung injury
- Pathology = diffuse alveolar damage
  - Indistinguishable histologically from ARDS

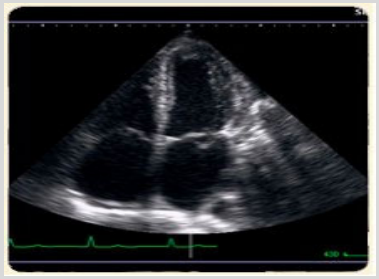


Acute interstitial pneumonitis is a diagnosis of exclusion

- Heart failure
  - Consider BNP
  - Consider cardiac echo
- Pulmonary embolism
  - Consider CT-PA
- Infection
  - Consider BAL



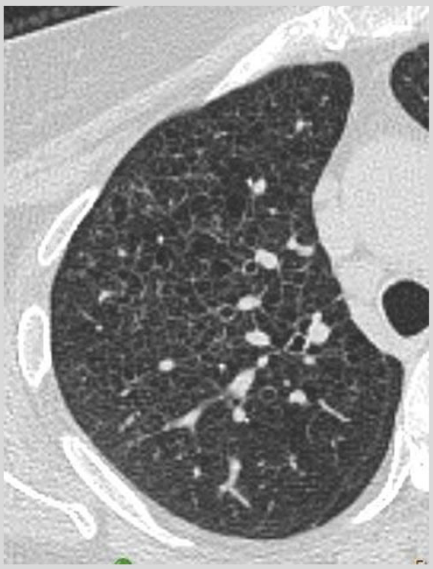


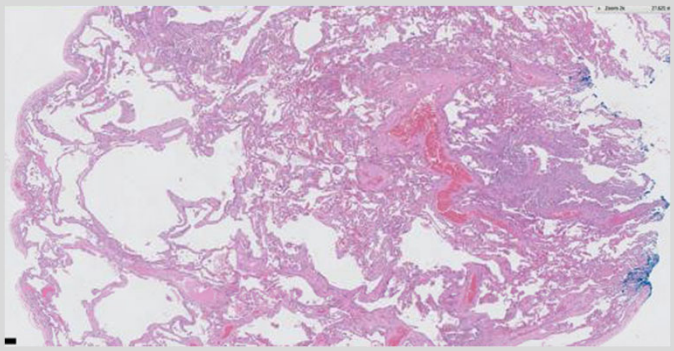


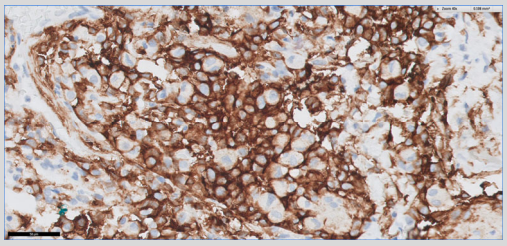
Langerhan's Cell Histiocytosis

- Adult form: generally limited to lung involvement
  - Childhood form is a multisystem malignancy of Langerhan's cells
- Primarily occurs in smokers
- Chest CT shows multiple small thin-walled cysts plus nodules
- Biopsy shows stellate nodules staining for Langerhan's cells
  - CD1a stain
  - S-100 stain

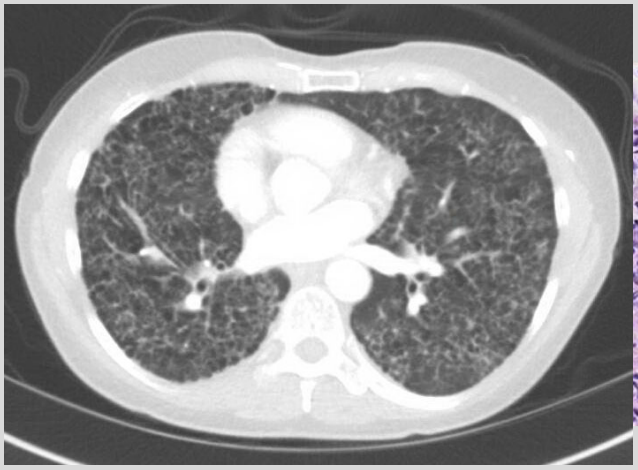
Langerhan's Cell Histiocytosis: 65 year old woman with dyspnea for 6 months

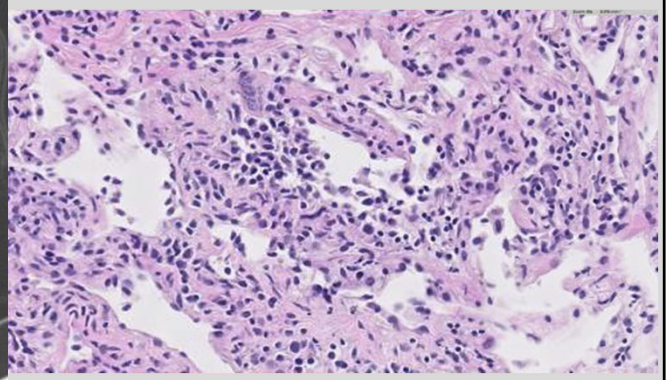






Langerhan's Cell Histiocytosis: 57 year old woman with dyspnea for 1 year

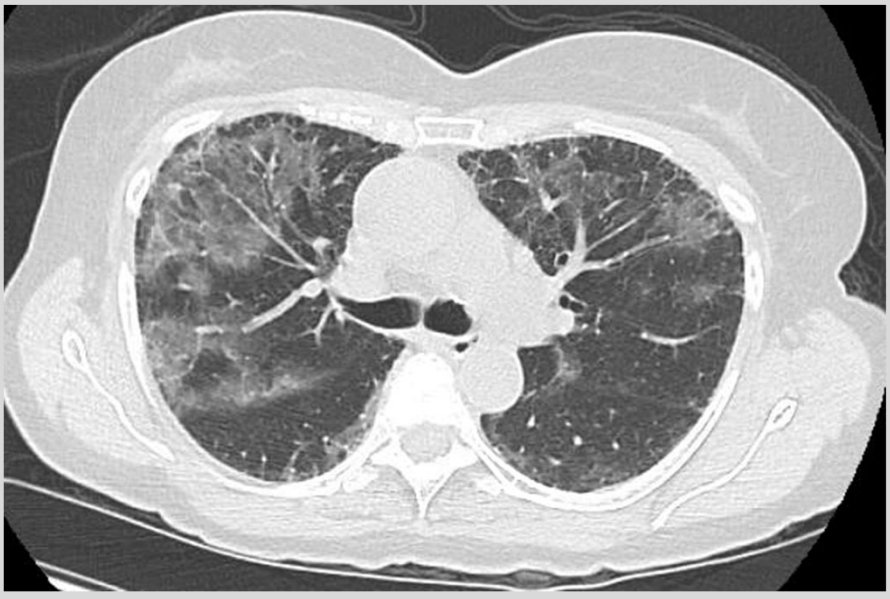




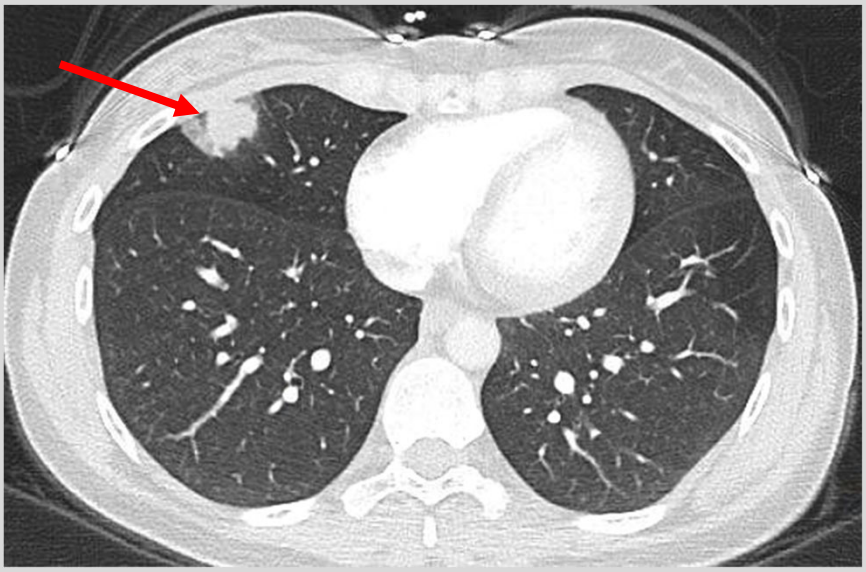
Cryptogenic Organizing Pneumonia

- Initially present with a subacute flu-like syndrome that lasts for a few weeks
- Physical examination, laboratory testing is nonspecific
- Lung biopsy is diagnostic
- Usually responds to corticosteroids
- Good prognosis is caught early
- Can be idiopathic or can be the initial presentation of underlying rheumatologic or autoimmune disease

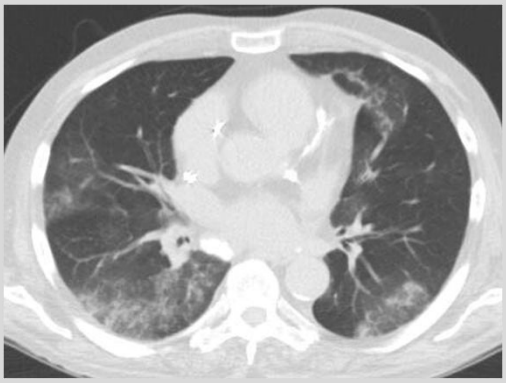
64year old woman with “inflammatory arthritis”

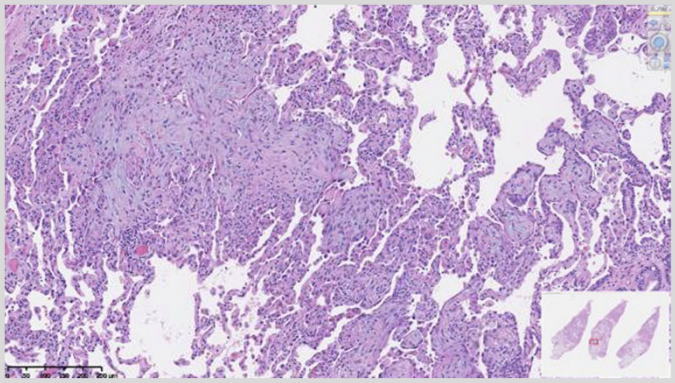


46 year old woman with well-controlled Crohn's disease

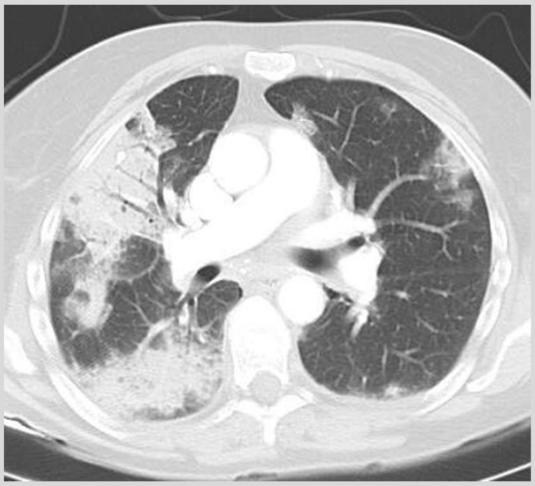


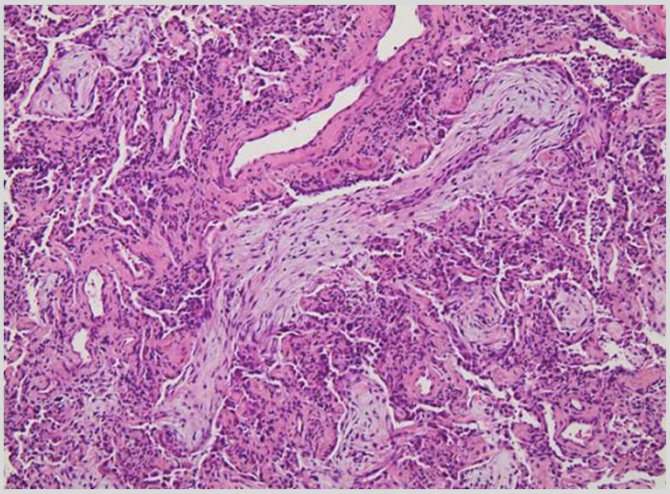
71year old man with worsening cough and dyspnea





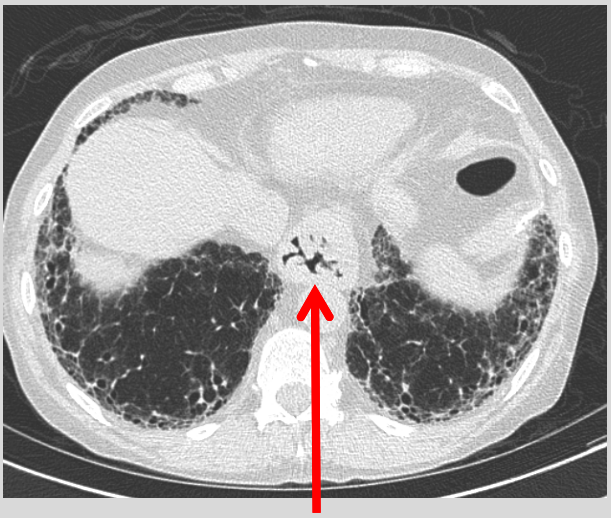
61 year old woman otherwise healthy woman with non-resolving pneumonia



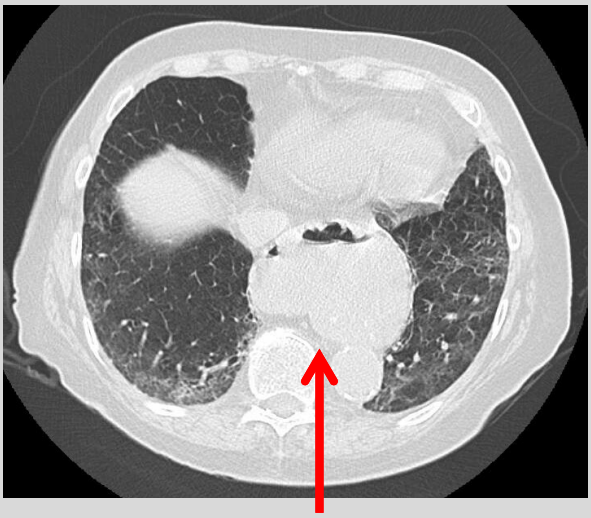


Hiatal hernias and interstitial lung disease

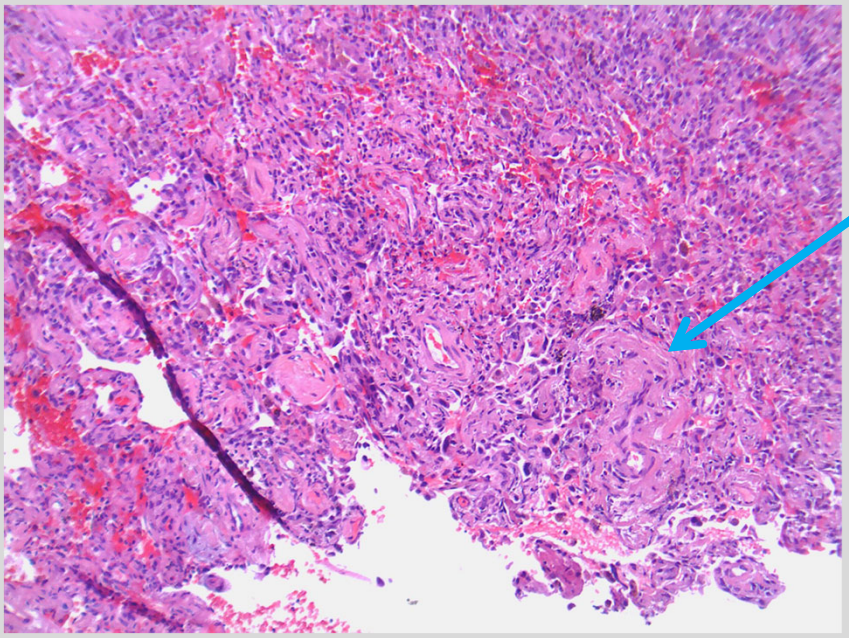
- Chronic aspiration and/or GERD can cause interstitial lung disease
- Chronic aspiration and/or GERD can worsen pre-existing interstitial lung disease
- Consider when patients have aspiration symptoms or hiatal hernia
- Treatment:
  - Stomach acid suppression
  - Surgical repair of hiatal hernias
  - Speech therapy for dysphagia



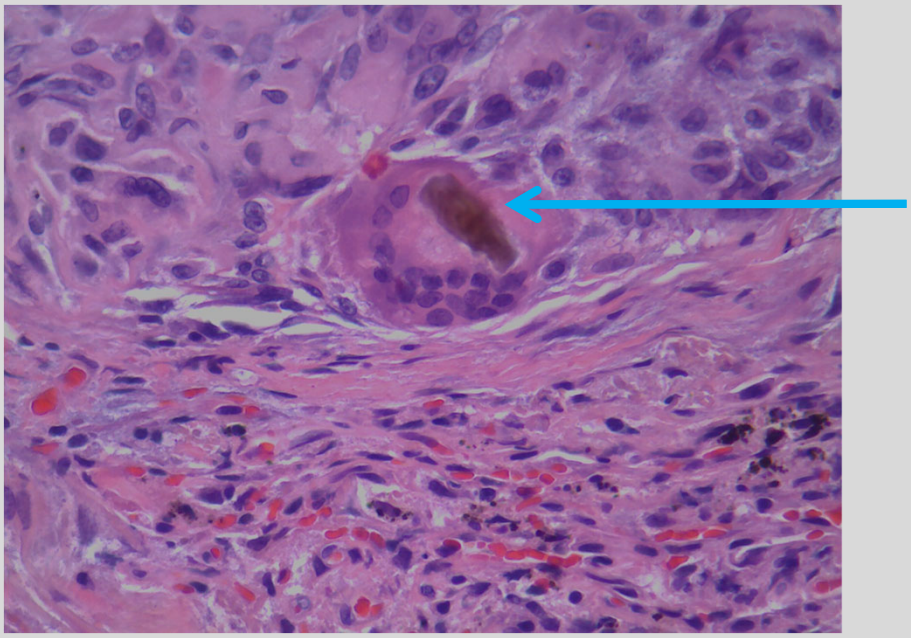
Moderate-Sized Hiatal Hernia



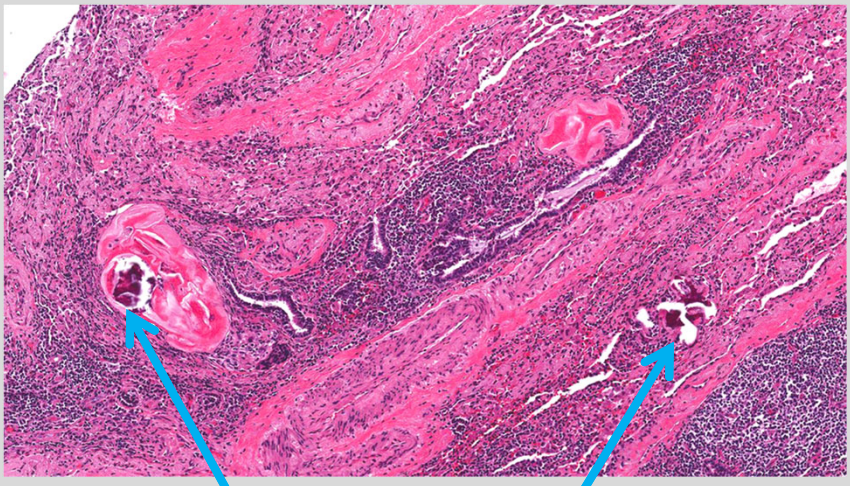
Large-Sized Hiatal Hernia



Granulomatous inflammation



Foreign body in multi-nucleated giant cell



Vegetable material

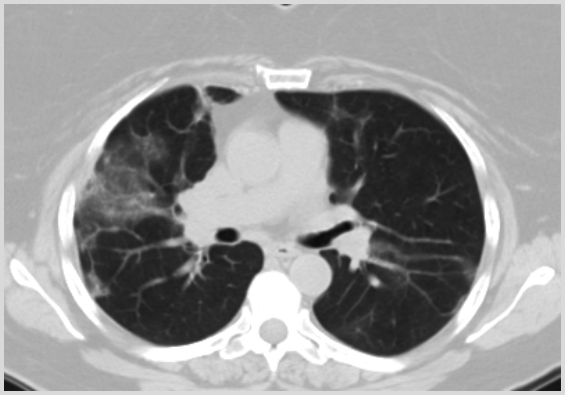
Drug-induced lung disease

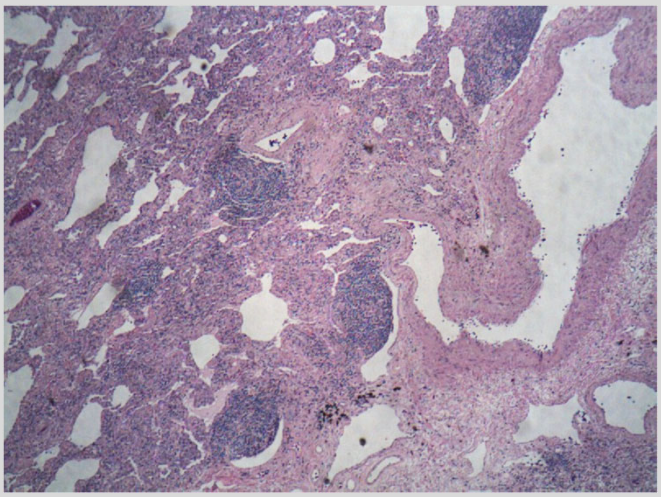
- Difficult to diagnose
- No reliable clinical, imaging, bronchoalveolar lavage (BAL), or histopathologic feature that is specific of, or diagnostic for drug-induced ILD
- Establish a definite temporal relationship between exposure to the agent and the onset of the lung disease
- Stop the drug, consider corticosteroids

Drug-induced lung disease

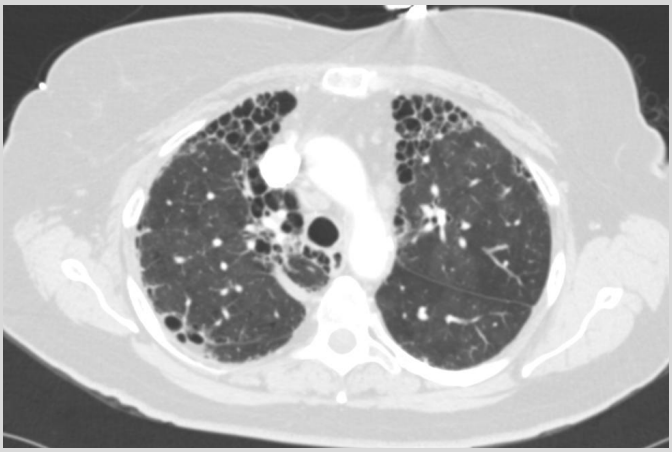
- Dozens of drugs implicated
- Common drugs:
  - Minocycline
  - Nitrofurantoin (macrodantin)
  - Amiodarone
  - Methotrexate
  - Chemotherapy drugs
- www.pneumotox.com is a great reference

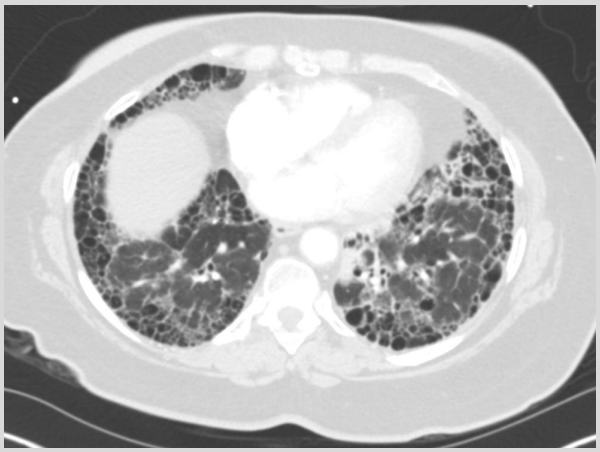
Macrodantin-induced lung disease



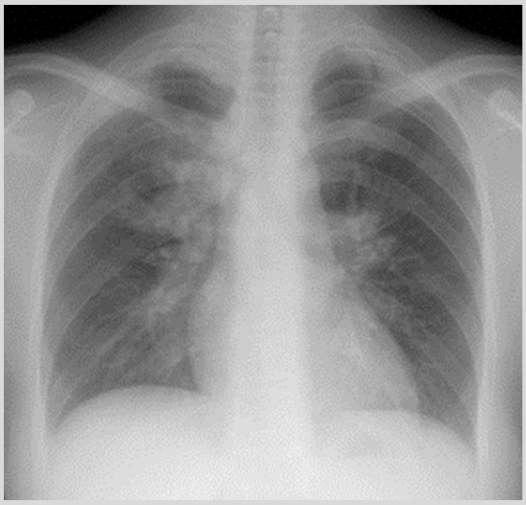


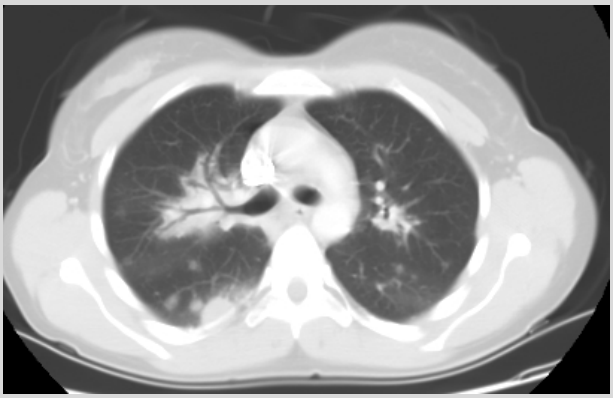
70 year old woman who was told she had IPF12 years ago.
She took macrodantin daily from 1996 - 1999





Sulfasalazine-induced lung disease

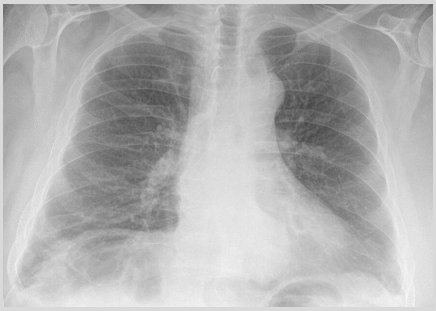


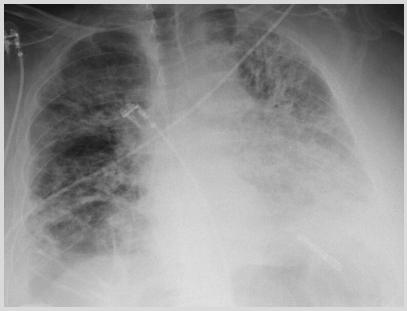


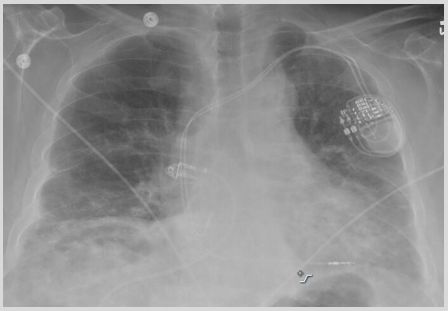
February 2017
Pre-Amiodarone

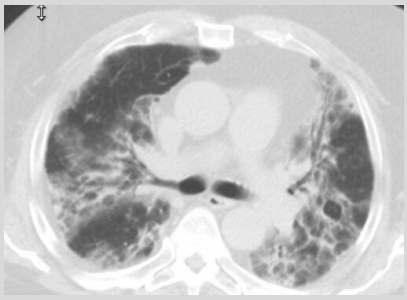
May 2017
During Amiodarone

June 2017
Post-Amiodarone



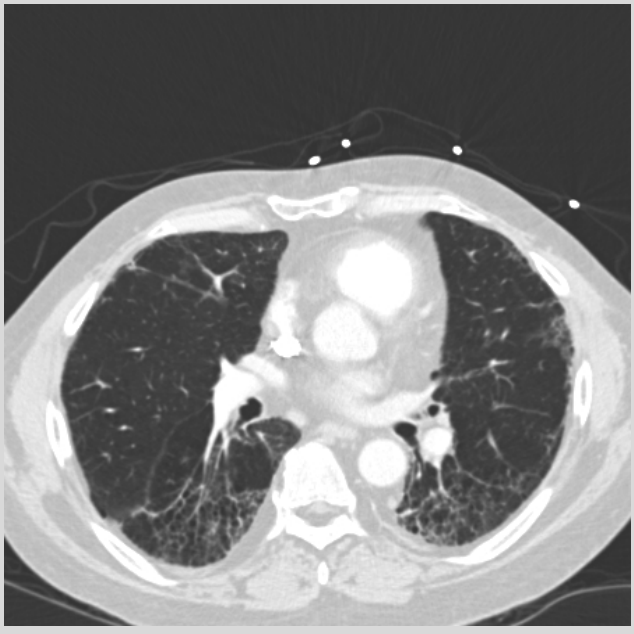


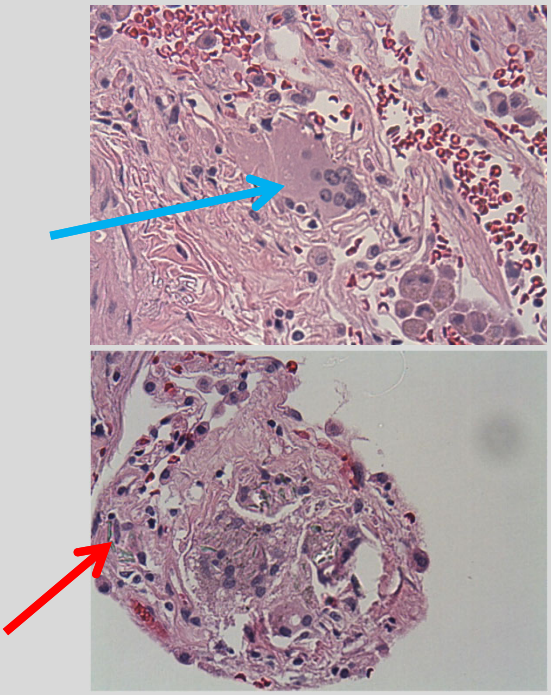




Talc Granulomatosis

- History = remote IV drug use (especially Ritalin)
- Exam = soft basilar crackles
- PFTs = resemble emphysema
- HRCT = may be normal
- Biopsy = polarizable foreign body material
- Treatment = none





Interstitial Lung Disease: Summary

- Your history is the most important diagnostic tool
- A confident diagnosis requires a multidisciplinary approach
- “UIP” is a CT pattern and a histologic pattern, it is not a disease