Interstitial Lung Disease

Monday, May 13, 2019

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Objectives

- **Define the most common types of interstitial lung disease.**
- **Recognize examples of radiographic images and patterns to help assess for interstitial disease.**
- **Identify treatment options for interstitial lung disease.**

Definition

- Interstitial lung disease is a term that broadly describes a diverse collection of more than 200 lung disorders.
- Classified together because they all affect the tissue and space around the alveoli
- Other compartments of the lung, including the alveoli, trachea, bronchi, and bronchioles, blood vessels, and pleura(outside lining of the lung), may also be affected.
- Four manifestations:1) respiratory symptoms such as shortness of breath and cough, 2) specific chest radiographic abnormalities, 3) typical changes on pulmonary function tests in which the lung volume is decreased, and 4) characteristic microscopic patterns of inflammation and fibrosis. *American Thoracic Society*

Epidemiology

- Both prevalence and incidence increase with advancing age, with presentation commonly occurring in the sixth and seventh decades.
- Rarely is IPF seen in patients aged less than 50 years.
- Prevalence and incidence are higher in men than women.
- In the United States, IPF incidence estimates range from 7 to 16 cases per 100,000. In contrast, among a random sample of Medicare beneficiaries (largely ≥ 65 years old), the prevalence of IPF was 494 cases per 100,000
- Certain risk factors have been identified. Cigarette smoking is most strongly associated with IPF. Exposure to stone, metal, wood, and organic dusts has also been suggested as a risk factor.
- Gastroesophageal reflux may contribute to lung injury via microaspiration
- Most cases of IPF are sporadic, but familial/genetic cases have been escribed

History

- Four patients who succumbed to respiratory insufficiency between 1931 and 1943 at the Johns Hopkins Hospital
- Dr. Louis Hamman (an internist) and Dr. Arnold Rich (a pathologist)
- Case reports in literature for the next 46 years
- The Hamman-Rich syndrome is now reclassified as acute interstitial pneumonia rather than usual interstitial pneumonia. However, for several decades the Hamman-Rich Syndrome was often described associated idiopathic pulmonary fibrosis

Symptoms

- Patients with idiopathic pulmonary fibrosis (IPF) typically present in their sixth and seventh decades of life.
- The majority of patients have a history of cigarette smoking
- Dyspnea on exertion and nonproductive cough over several months.
- Fatigue, fever, myalgia, and arthralgia are rarely reported.
- Questions about any family history of lung disease, symptoms suggestive of rheumatic disease (e.g., arthralgia, dry eyes, dry mouth, muscle weakness, numbness, Raynaud phenomenon, tingling), current and recent medications, and exposure fumes, dusts (e.g., asbestos, silica), or therapeutic irradiation.
- Bibasilar crackles are usually audible
- Advanced disease may have end-inspiratory "squeaks" due to traction bronchiectasis.
- Clubbing in 45 to 75 percent of patients. Usually, manifestation of advanced IPF

Diagnostic Studies

- PFTs typically demonstrate a restrictive pattern
- Normal ratio of forced expiratory volume in one second [FEV_1]/FVC)
- Reduced DLCO
- Decrease in the six-minute walk distance
- Characteristic HRCT features of IPF include peripheral, bibasilar reticular opacities associated with architectural distortion, including honeycomb changes and traction bronchiectasis
- Honeycombing refers to clusters of cystic airspaces approximately 3 to 10 mm in diameter. Subpleural distribution

Prognosis

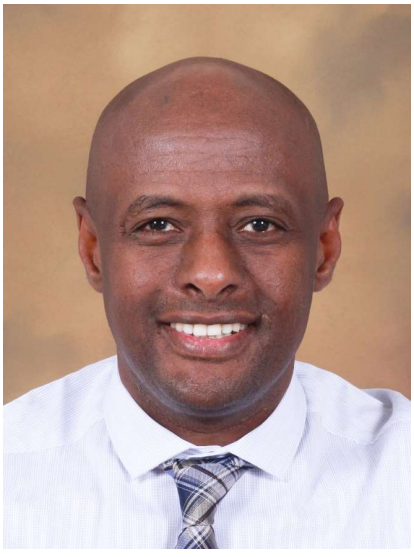
- NSIP RB ILD < 5% at 5 yr.
- DSIP < 10 at 5 yr.
- RBILD Rate < 5% at 5 yr.
- UIP 60% at 3-5 yr.
- AIP 60% mortality rate in 6 months

Causes

Occupational, Environmental, and Therapeutic Exposures	Systemic Disease	Idiopathic Interstitial Pneumonia	Specific Pathology	Miscellaneous Interstitial Lung Diseases
Occupational or Environmental ***Inorganic exposure*** Asbestosis Coal dust Silica Beryllium Aluminum Barium Clay Iron Certain talcs ***Organic exposure*** Hypersensitivity pneumonitis Moldy hay Silage Moldy sugar cane Mushroom compost Barley Cheese Wood pulp, bark, dust Cork dust Bird droppings Paints **Medications and Illicit Drugs** Antibiotics Antiinflammatory agents Cardiovascular agents Chemotherapeutic agents Drug-induced systemic lupus erythematosus Illicit drugs Miscellaneous agents	Connective tissue disease Scleroderma Rheumatoid arthritis Sjögren's syndrome Polymyositis or dermatomyositis Systemic lupus erythematosus Sarcoidosis	Idiopathic pulmonary fibrosis Nonspecific Cryptogenic-organizing pneumonia Lymphocytic interstitial pneumonia	Lymphangioleiomyomatosis Pulmonary Langerhans cell histiocytosis Pulmonary alveolar proteinosis Pulmonary vasculitides Wegener's granulomatosis Churg-Strauss syndrome Lymphomatoid granulomatosis	Goodpasture's syndrome Idiopathic pulmonary hemosiderosis Chronic eosinophilic pneumonia
Radiation Therapy				
Irritant Gases				

Most Common Types

- UIP (Usual Interstitial Pneumonia)
- DSIP (Desquamative Interstitial Pneumonia)
- NSIP (Nonspecific Interstitial Pneumonia)
- RBILD (Respiratory Bronchiolitis Interstitial Lung Disease)
- AIP (Acute Interstitial Pneumonia)



UIP

- Sixth and seventh decades of life.
- Majority of patients have a history of cigarette smoking .
- Patients commonly report a gradual onset of dyspnea on exertion and nonproductive cough over several months.
- Fatigue, fever, myalgia and arthralgia are rarely reported.
- Family history of lung disease.
- Symptoms suggestive of rheumatic disease (e.g., arthralgia, dry eyes, dry mouth, muscle weakness, numbness, Raynaud phenomenon, tingling)
- Current and recent medications, and exposure fumes, dusts .
- Physical examination bibasilar crackles are usually audible, but rarely they may be absent or only heard unilaterally in early disease.
- Patients with more advanced disease may have end-inspiratory "squeaks" due to traction bronchiectasis.
- 5 to 75 percent of patients, our clinical impression is that clubbing is a manifestation of advanced IPF

Laboratory

- Antinuclear antibodies, anti-cyclic citrullinated peptide, and rheumatoid factor.
- Antisynthetase antibodies (eg, anti-Jo-1), creatine kinase, aldolase, Sjögren's antibodies (anti-SS-A, anti-SS-B), and scleroderma antibodies (anti-topoisomerase [scl-70], anti-PM-1), are of unclear benefit, but may be helpful in selected cases
- Circulating antinuclear antibodies (≥1:40) are present in 17 to 25 percent.
- Positive rheumatoid factor in 5 to 18 percent, depending on the population studied.
- For patients with suspected IPF, the utility of screening panels for hypersensitivity pneumonitis is unclear. Base on clinical history.

PFT

- PFTs typically demonstrate a restrictive pattern .
- Reduced forced vital capacity, but normal ratio of forced expiratory volume in one second [FEV_1]/FVC).
- Reduced DLCO, and, as the disease progresses, a decrease in the six-minute walk distance.

Diagnosis

- Exclusion of identifiable causes of interstitial lung disease (ILD) based on the history and physical and laboratory testing.
- An assessment of the pattern and severity of respiratory impairment on pulmonary function testing.
- Confirmation of the presence of ILD by high resolution computed tomography.
- A multidisciplinary clinical, radiologic, and pathologic correlation is useful in arriving at the most accurate final diagnosis [26-29].
- Lung Biopsy?

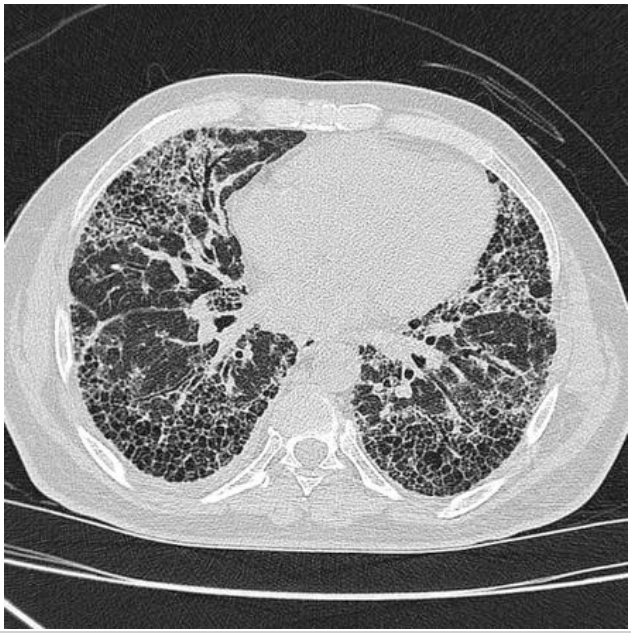
Imaging

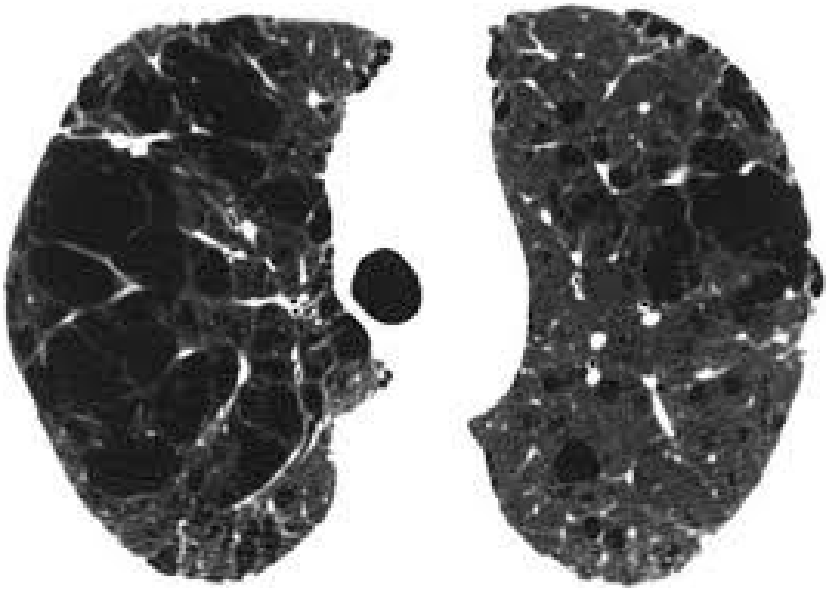
Chest imaging

- **Chest radiograph** – Increase in reticular markings, although this is a nonspecific finding also associated with other interstitial lung diseases or heart failure.

High Resolution Computed Tomography

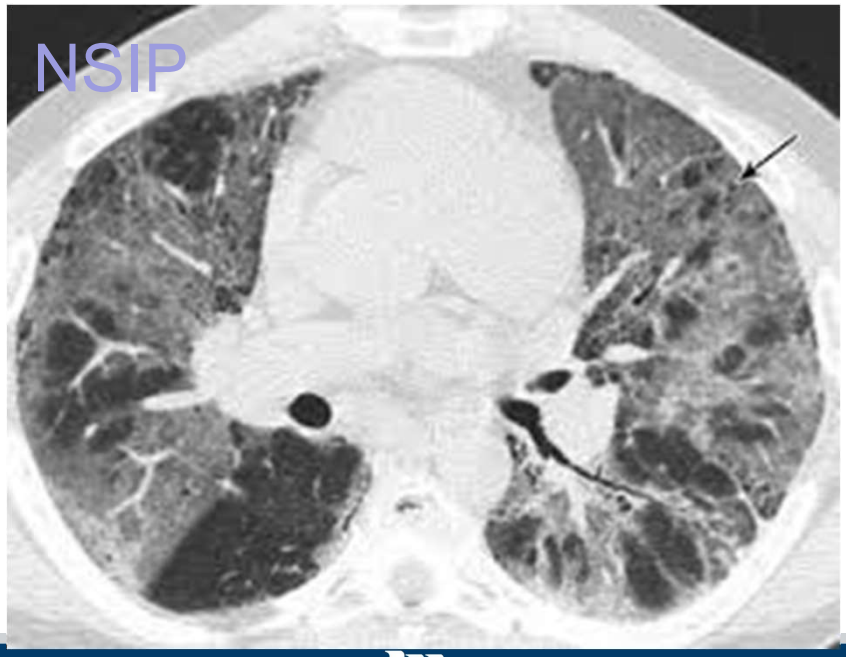
- HRCT should be obtained in all patients suspected of having IPF. The presence of certain specific HRCT features of IPF include peripheral, bibasilar reticular opacities associated with architectural distortion, including honeycomb changes and traction bronchiectasis
- Honeycombing refers to clusters of cystic airspaces approximately 3 to 10 mm in diameter, usually in a subpleural location. Can be absent and still have UIP.
- 30 percent of cases with a pathological diagnosis of definite UIP may have HRCT findings more consistent with an alternate diagnosis





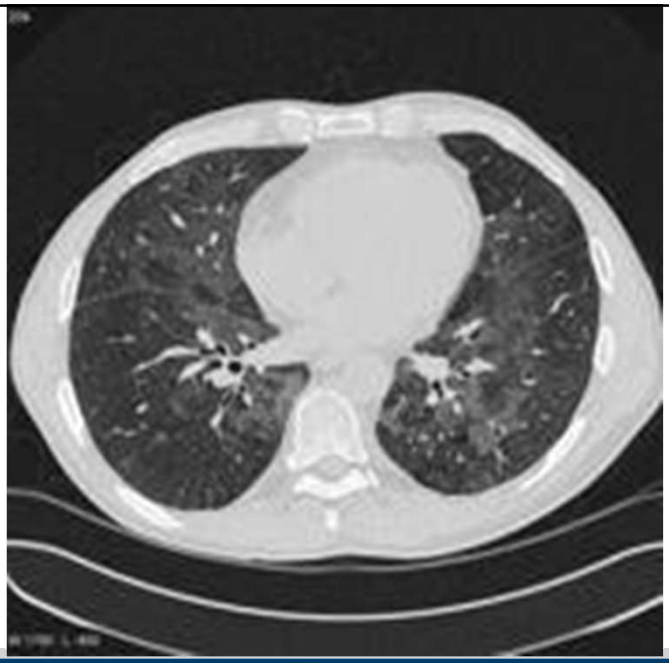
NSIP

- Lacks the histopathologic features typical of usual interstitial pneumonia, desquamative interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, or acute interstitial pneumonia.
- Lesions are often characterized by a relatively uniform appearance at low magnification due to a cellular interstitial infiltrate of mononuclear inflammatory cells associated with varying degrees of interstitial fibrosis.
- Second most common histological category.
- Subacute rather than insidious onset of symptoms.
- Associated fever in about one-third of patients.
- Lack of a strong male predominance, relative absence of clubbing in NSIP.
- Frequency of features suggestive of connective tissue disease.



DSIP

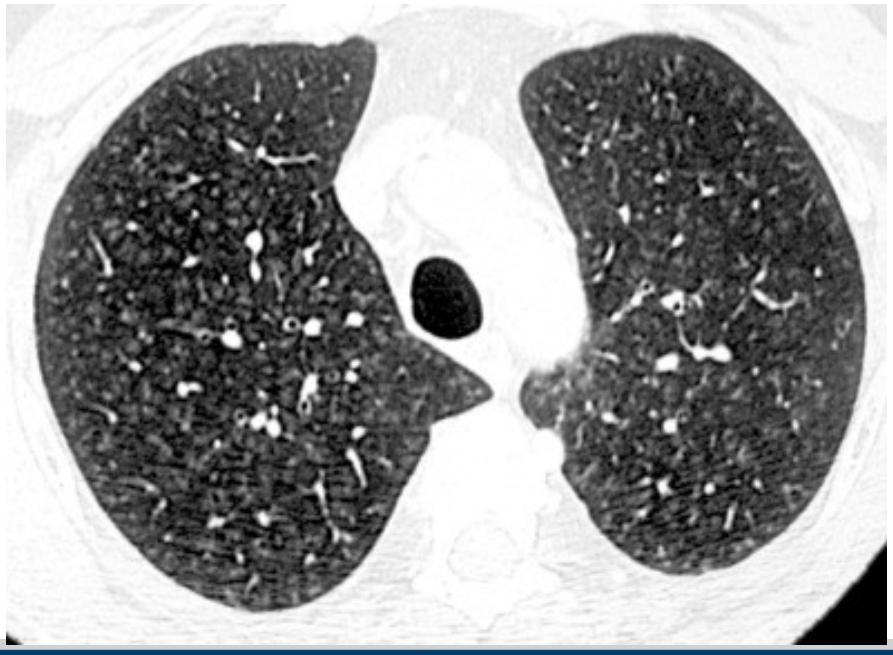
- Uncommon, comprising 3-16 percent of biopsies.
- DIP typically affects cigarette smokers in their fourth or fifth decades of life.
- Vast majority (>90 percent) of patients with DIP are smokers.
- Small percentage of cases are associated with connective tissue diseases.
- PFT shows mild reduction in lung volumes associated with a moderate decrease in diffusing capacity.
- The radiographic abnormalities tend to be less severe than those seen in UIP.
- High resolution computed tomography shows ground glass opacities without the peripheral reticular and reticulonodular opacities.
- One review of HRCT findings found no evidence of progression from DIP to UIP. Separate entities.



RB-ILD

- Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP) share several overlapping clinic pathologic features.
- Better prognosis than usual interstitial pneumonia (UIP).
- Overlap with DSIP.
- Respiratory bronchiolitis was defined in 1974 as a distinct histopathologic entity characterized by the presence of pigmented intraluminal macrophages within first and second-order respiratory bronchioles.
- Small airways dysfunction in cigarette smokers.
- The clinical features of RB-ILD are nonspecific.
- RB-ILD typically occurs during the fourth or fifth decades of life and almost always affects current smokers with average exposures of over 30 pack-years of cigarette smoking (table 10) [33].

- Men are affected more often than women by a ratio of almost 2:1. Symptoms are usually mild and not disabling.
- Nearly all patients present with nonspecific respiratory complaints; these include the insidious onset of dyspnea and a new or changed cough
- Chest radiographs are abnormal in 80 percent of patients and show diffuse fine reticular or reticulonodular opacities in a bibasilar distribution



AIP

- Explosive onset of respiratory symptoms and is characterized by rapidly progressive respiratory failure.
- Diffuse opacities on chest radiographs.
- Analogous to the acute respiratory distress syndrome (ARDS), differing only in that it is not preceded by a catastrophic event.
- Hamman-Rich syndrome and accelerated interstitial pneumonia.
- AIP should be distinguished from the group of chronic interstitial pneumonias.
- AIP has the same poor prognosis as ARDS, and the majority of patients die of respiratory failure

Other Types

LYMPHOID INTERSTITIAL PNEUMONIA

- Uncommon histopathologic entity characterized by infiltration of the interstitium and alveolar spaces of the lung by lymphocytes, plasma cells, and other lymphoreticular elements.

CRYPTOGENIC ORGANIZING PNEUMONIA

- Inflammatory pneumonia rather than a primary airway disorder.
- Excessive proliferation of granulation tissue within small airways associated with chronic inflammation in the surrounding alveoli.

Treatment Options

- For patients with mild or moderate IPF based on pulmonary function tests.
- No underlying liver disease a Pirfenidone or nintedanib is available, we recommend initiating therapy with the available agent [4].
- Current data are insufficient to direct a firm choice between pirfenidone and nintedanib.
- Diarrhea and liver function abnormalities with nintedanib
- Nausea and rash with pirfenidone.
- For patients with more advanced IPF, a diffusing capacity <35 percent of predicted, echocardiographic evidence of right ventricular dysfunction, consider trial of sildenafil may be a reasonable option.
- Glucocorticoids. For AIP, guidelines suggest prednisone1 mg/kg per day orally to methyldprednisolone 1 gram per day intravenously for three days followed by a taper
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Tx Options

- DSIP, RB ILD- Quit smoking
- NSIP- Tx connective tissues disorder. May be steroid responsive

Newer Agents

- Nintedanib: Receptor blocker for multiple tyrosine kinases that mediate elaboration of fibrogenic growth factors (eg, platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor)
- Pirfenidone: Antifibrotic agent inhibits transforming growth factor beta (TGF-b)-stimulated collagen synthesis, decreases the extracellular matrix, and blocks fibroblast proliferation.
- Slow the rate of disease progression in IPF as measured by FEV1 and FVC
- For pts not interested in participating in a clinical trial or transplant
- Questionable mortality benefit

Transplant Referral

- Severe symptoms
- Forced vital capacity (FVC) <80 percent predicted
- Diffusion capacity for carbon monoxide (DLCO) <40 percent predicted
- Requirement for supplemental oxygen, at rest or with exertion
- Clinically and physiologically severe disease for which medical therapy is ineffective or unavailable
- The risk of death from lung disease without transplantation is >50 percent within two years
- The likelihood of surviving at least 90 days after lung transplantation is >80 percent

Contraindications

- Uncontrolled or untreatable pulmonary or extra-pulmonary infection
- Active *Mycobacterium tuberculosis* infection
- Malignancy in the last two years
- Significant dysfunction of other vital organs (eg, heart, liver, kidney, brain)
- Significant coronary heart disease not amenable to revascularization
- Uncorrectable bleeding diathesis
- Significant chest wall/spinal deformity expected to cause severe restriction after transplantation
- Class II or III obesity: body mass index (BMI) ≥35 kg/m^2
- Active tobacco smoking
- Drug or alcohol dependency
- Unresolved psychosocial problems or noncompliance with medical therapy

Relative Contraindications

- Age >65 years in association with low physiologic reserve or other relative contraindications.
- Class I obesity: BMI 30 to 34.9 kg/m^2
- Severe or progressive malnutrition
- Severe symptomatic osteoporosis
- Extensive prior thoracic surgery with lung resection
- Colonization or infection with highly resistant or highly virulent bacteria, fungi, and certain strains of mycobacteria
- HIV infection
- Ongoing hepatitis B or C viral infection
- Absence of a consistent or reliable social support system

Sources

- Up to Date - Slides-6, 11-25
- ACCP- Slides-5,7, 26, 27
- CHEST Pulm Board Review Book- Slides-8,9,28-30
- www.clinicalgate.com- Slide 10

Questions and Discussion