Interstitial lung disease

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What is Interstitium

- The interstitial space is defined as continuum of loose connective tissue throughout the lung
- It is the tissue between the air sacs of the lungs
Subdivisions of lung interstitium

Axial interstitium (peribronchovascular)
Surrounding the bronchi, arteries, and veins from the lung root to the level of the respiratory bronchiole;

Peripheral interstitium
Contains the pulmonary venules, lymphatics and interlobular septae

Centrilobular interstitium
Situated between the alveolar and capillary basement membranes
• Centrilobular bronchus (single wide white arrow) and artery (double white arrow, 1-mm size)
• Interlobular septa (single arrowhead, 0.1-mm thickness)
• Pulmonary vein (double arrowheads, 0.5-mm size)
• Visceral pleura (single black arrow, 0.1-mm thickness)
• Pulmonary acinus (single thin white arrow, 5–10 mm size)
Introduction

• There are >200 disorders
• Can classified into
  – known vs unknown with subcategory of granulomatous and nongranulomatous. OR
  – occupational vs nonoccupational
  – Acute vs Chronic
Classification of idiopathic interstitial pneumonia

<table>
<thead>
<tr>
<th>Clinical-radiologic-pathologic diagnosis</th>
<th>Histopathologic pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>Usual interstitial pneumonia</td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonia</td>
<td>Nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia</td>
<td>Organizing pneumonia</td>
</tr>
<tr>
<td>Acute interstitial pneumonia</td>
<td>Diffuse alveolar damage</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonia</td>
<td>Lymphocytic interstitial pneumonia</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
<td>Desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>Respiratory bronchiolitis interstitial lung disease</td>
<td>Respiratory bronchiolitis interstitial lung disease</td>
</tr>
</tbody>
</table>
Classification

Interstitial Lung Diseases

Sarcoidosis
Hypersensitivity Pneumonitis

UIP/IPF
AIP
LIP
COP
NSIP
DIP
RB-ILD

1970s
Asbestosis
LAM
etc

2007

Fibrosis

Inflammation

“IIP”

Ips=Interstitial pneumonias
LAM=lymphangioleiomyomatosis
Adapted from ATS/ERS. Am J Respir Crit Care Med. 2002;165:277-304.
Distribution

- Pulmonary Fibrosis: 52%
- Occupation: 11%
- Sarcoidosis: 8%
- CTD: 9%
- DILD: 5%
- DAH: 4%
- Other: 11%
Common features in ILD

- Dyspnea
- Diffuse disease on X ray
  - Often the first suggestion of disease but correlates poorly with severity of disease
- Restrictive PFTs
  - Restrictive intrathoracic pattern: Normal airway flow rates but low FVC
- Elevated A-a gradients
History

• 1935, Hamman and Rich described “diffuse interstitial fibrosis of the lungs”. It was rapidly progressive and all patients died within a few weeks or months
• Cases with chronic diffuse pulmonary fibrosis with a much slower progression- “Idiopathic Pulmonary Fibrosis”.
• Based on *pathological* concept -in 1960s and 70s, the concept of diffuse interstitial pneumonitis was developed or IIP
• Liebow’s Classification (1975) - based on cases which had been classified as IPF and 5 pathological subgroups
Idiopathic Pulmonary Fibrosis
PATHOGENESIS AND COURSE OF UIP / IPF

UIP / IPF

*Multiple microscopic foci of injury leading to inflammation (stage of alveolitis)*

- Focal fibroblast proliferation (fibroblastic foci)
- Collagen deposition (Stage of fibrosis)

*Recurrent microscopic injury*

Progressive clinical course

Death

Clinical context

- **Idiopathic Pulmonary Fibrosis (IPF)** affects predominantly middle-aged and older subjects.
- Subacute to chronic dry cough, progressive breathlessness.
- The “Velcro” crackles is nearly universal with IPF.
- Digital *clubbing* - in up to two thirds of patients with IPF but is rare in patients with sarcoidosis.
Approach to Diagnosing diffuse lung disease

Clinical Evaluation: **History**, PE, CXR, PFTs, 6MWT

- Not IIP
- Potential IIP
  - HRCT
    - Diagnostic of diffuse lung disease
    - Diagnosis uncertain
      - Transbronchial Bx or BAL
        - Diagnostic
        - Nondiagnostic
          - Surgical lung biopsy
            - Not IPF
            - IPF

Approach to the diagnosis

- **Thorough medical history is a must**
  - age
  - duration
  - symptoms
  - smoking history
  - occupational and environmental exposures
  - medications and drugs
  - family medical history
  - signs and symptoms of connective tissue disease should be carefully elicited
Patterns of ILD on X-ray

A) Linear
B) Reticular
C) Reticular, honeycomb
D) Nodular
E) Reticulonodular
Typical Features of IPF on Chest X-Ray

Normal CXR

Abnormal CXR
Chest Radiograph

- Abnormal >90%
- Peripheral reticular opacities
- More profuse at lung bases
- Bilateral
- Asymmetrical
- Commonly associated with decreased lung volumes
- Confluent alveolar opacities, lymphadenopathy and pleural involvement uncommon
HRCT Chest

- More sensitive and specific
- Better diagnostic accuracy
- Assessment of disease activity
- May obviate need of biopsy
- Site for biopsy
- Follow up
- Prognosis

INITIAL DIAGNOSTIC MODALITY OF CHOICE
Pattern

- Patchy, peripheral, subpleural, bibasal reticular opacities
- limited areas of ground glass opacities
- traction bronchiectasis and/or subpleural honeycombing suggests severe involvement
Early HRCT Findings in IPF
Subpleural and Basal Predominance

Slide courtesy of W. Richard Webb, MD.
Honeycombing
“Traction” Bronchiectasis
### Common abnormal findings found on HRCT and associated diseases

<table>
<thead>
<tr>
<th>Abnormal HRCT Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reticular Opacities</strong></td>
</tr>
<tr>
<td>• UIP</td>
</tr>
<tr>
<td>• NSIP</td>
</tr>
<tr>
<td>• Collagen vascular disease</td>
</tr>
<tr>
<td>• Asbestosis</td>
</tr>
<tr>
<td>• Drug-related pulmonary fibrosis</td>
</tr>
<tr>
<td><strong>Ground-Glass Opacities</strong></td>
</tr>
<tr>
<td>• NSIP</td>
</tr>
<tr>
<td>• AIP (acute, subacute)</td>
</tr>
<tr>
<td>• DIP</td>
</tr>
<tr>
<td>• RB-ILD</td>
</tr>
<tr>
<td>• LIP</td>
</tr>
<tr>
<td>• COP</td>
</tr>
<tr>
<td>• Subacute HP</td>
</tr>
<tr>
<td>• Acute exacerbation of ILD</td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
</tr>
<tr>
<td>• COP</td>
</tr>
<tr>
<td>• Polymyositis/dermatomyositis</td>
</tr>
<tr>
<td>• Acute exacerbation of ILD</td>
</tr>
<tr>
<td>• AIP</td>
</tr>
<tr>
<td>• Acute HP</td>
</tr>
<tr>
<td>• Drugs</td>
</tr>
<tr>
<td>• Sarcoidosis</td>
</tr>
</tbody>
</table>
High resolution CT

• Differential diagnosis of HRCT pattern
  Connective tissue diseases
  Asbestosis
  Hypersensitivity pneumonitis
  Sarcoidosis

• Extensive **GROUND GLASS OPACITIES** on CT of lung should prompt alternative diagnosis such as DIP, RBILD, NSIP, idiopathic BOOP, hypersensitivity pneumonitis etc.
Approach to the diagnosis of IPF
Pulmonary function testing

• LUNG VOLUMES
  TLC, FRC, RV are decreased

• AIRWAY MECHANICS
  FVC, FEV1, PEFR are often decreased
  FEV1/FVC is maintained or increased
# Pattern of PFT abnormalities in ILD

<table>
<thead>
<tr>
<th>Diseases</th>
<th>FVC</th>
<th>FEV1/FVC</th>
<th>DLco</th>
<th>TLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF</td>
<td>↓↔</td>
<td>↓↔</td>
<td>↓</td>
<td>↓↔</td>
</tr>
<tr>
<td>Connective tissue diseases</td>
<td>↓↔↑</td>
<td>↓↔↑</td>
<td>↓</td>
<td>↓↔</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>↓↔</td>
<td>↓↔↑</td>
<td>↓↔</td>
<td>↓↔</td>
</tr>
<tr>
<td>Hypersensitivity pneumonia</td>
<td>↓↔</td>
<td>↓↔↑</td>
<td>↓↔</td>
<td>↓↔↑</td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>↓↔</td>
<td>↓↔</td>
<td>↓↔</td>
<td>↓↔</td>
</tr>
<tr>
<td>Langerhans’s cell histiocytosis</td>
<td>↓↔</td>
<td>↓↔↑</td>
<td>↓</td>
<td>↔↑</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>↓↔</td>
<td>↓↔</td>
<td>↓</td>
<td>↔↑</td>
</tr>
<tr>
<td>Cryptogenic organic pneumonia</td>
<td>↓</td>
<td>↓↔↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

# Role of BAL vs Biopsy in IPF

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brochoalveolar Lavage (BAL)</td>
<td>• May rule out alternate diagnoses but not diagnostic of IPF</td>
</tr>
<tr>
<td>Transbronchial Biopsy (TBLB)</td>
<td>• May rule out alternate diagnoses but not diagnostic of IPF</td>
</tr>
<tr>
<td></td>
<td>• Often abnormal in IPF but does not confirm diagnosis</td>
</tr>
<tr>
<td>Video-assisted Thoracoscopic Biopsy (VATS)</td>
<td>• Preferred technique</td>
</tr>
<tr>
<td></td>
<td>• Provides best tissue samples</td>
</tr>
<tr>
<td></td>
<td>• Excludes other processes that mimic IPF</td>
</tr>
<tr>
<td></td>
<td>• Biopsies should be obtained from more than one lobe of the lung</td>
</tr>
</tbody>
</table>

# CONTRASTING PATHOLOGIC FEATURES OF IIP

<table>
<thead>
<tr>
<th>Feature</th>
<th>UIP</th>
<th>DIP/RBILD</th>
<th>AIP</th>
<th>NSIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal appearance</td>
<td>Variegated</td>
<td>Uniform</td>
<td>Uniform</td>
<td>Uniform</td>
</tr>
<tr>
<td>Interstitial inflammation prominent</td>
<td>Scant</td>
<td>Scant</td>
<td>Scant</td>
<td>Usually</td>
</tr>
<tr>
<td>Collagen fibrosis diffuse</td>
<td>Patchy</td>
<td>Variable, diffuse in DIP; focal, mild in RBILD</td>
<td>No</td>
<td>Variable,</td>
</tr>
<tr>
<td>Fibroblast proliferation diffuse, or fibroblastic foci</td>
<td>Fibroblastic foci</td>
<td>No</td>
<td>Diffuse</td>
<td>Occasional, rare</td>
</tr>
<tr>
<td>Organizing pneumonia focal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Occasional,</td>
</tr>
<tr>
<td>Honeycomb changes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Intraalveolar macrophage patchy accumulation</td>
<td>Occasional, focal</td>
<td>Diffuse in DIP; peribronchiolar in RBILD</td>
<td>No</td>
<td>Occasional,</td>
</tr>
<tr>
<td>Hyaline membranes</td>
<td>No</td>
<td>No</td>
<td>Occasional,</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>focal</td>
<td>focal</td>
</tr>
</tbody>
</table>
ATS/ERS diagnostic criteria for IPF

Major criteria

Exclusion of other known causes of interstitial lung disease, including environmental exposures, connective tissue diseases and drug toxicities.
Abnormal pulmonary function tests consistent with restrictive and/or impaired gas exchange (increased A-aPO$_2$ with rest or exercise or decreased DLCO).
Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans.
Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis.
ATS/ERS diagnostic criteria for IPF

Minor criteria

Age >50 years.

Insidious onset of otherwise unexplained dyspnoea on exertion.

Duration of illness ≥3 months.

Bibasilar inspiratory crackles (dry or ‘Velcro’ type in quality).
TREATMENT OF IPF

RATIONALE FOR TREATMENT

- Treatment is based on concept that inflammation leads to injury and fibrosis.

- Most treatment strategies have been based on eliminating the inflammatory component.

- Little information has appeared to support the theory that fibrosis can be reversed.
TREATMENT OF IPF

CONVENTIONAL TREATMENT OPTIONS

- CORTICOSTEROIDS
- IMMUNOSUPPRESSIVE / CYTOTOXIC AGENTS
  - AZATHIOPRIM
  - CYCLOPHOSPHAMIDE
- ANTI FIBROTIC AGENT
  - COLCHICINE
  - PI RFENI DONE
  - D-PENICILLAMINE
RECOMMENDATIONS FOR TREATMENT

Initiation of therapy

- CORTICOSTEROIDS (PREDNISONE)

  0.5 mg/kg/day orally for 4 weeks then
  0.25 mg/kg/day for 8 weeks then
  0.125 mg/kg/day or
  0.25 mg/kg every alternate day
TREATMENT OF IPF

CONVENTIONAL TREATMENT OPTIONS

- CORTICOSTEROIDS
  - Maintenance steroid therapy to be reserved for patients exhibiting stabilization or objective improvement
  - Relapses or deterioration warrant escalation of dose or addition of an immunosuppressive agent
TREATMENT OF IPF

CONVENTIONAL TREATMENT OPTIONS

CYTOTOXIC AGENTS (Steroid sparing)

Indications

- steroid non-responders
- patients experiencing serious adverse affects from steroids
- patients at high risk of steroid complications (age > 70 years, poorly controlled diabetes mellitus or hypertension, severe osteoporosis, or peptic ulcer disease)

TREATMENT OF IPF

CONVENTIONAL TREATMENT OPTIONS

AZATHIOPRIM

- combination with steroids was associated with modest improvement and enhanced survival in some patients

- 2-3 mg/kg (LBW)/day (max. 150 mg/day)

- begin at 25-50 mg/day increase by 25 mg every 7-14 days
TREATMENT OF IPF

POTENTIAL ALTERNATIVE TREATMENTS

Possible future therapeutic strategies include

- agents that inhibit cytokines, proteases, oxidants, or fibroblast growth factors
- antifibrotic agents
- dietary modifications
- diphosphonates
- antioxidants
- gene therapy
TREATMENT OF IPF

POTENTIAL ALTERNATIVE TREATMENTS

OTHER ANTIFIBROTIC AGENTS

Interferon Y
Interferon B
**Pirfenidone**
Halfuginone
Suramin
Prostaglandin E2
TREATMENT OF IPF

POTENTIAL ALTERNATIVE TREATMENTS

- OTHER NOVEL AGENTS
  - Antioxidant
  - Glutathione
  - Niacin
  - N-acetylcysteine
STAGING AND PROGNOSIS

INDICATORS OF GOOD PROGNOSIS

- Younger age < 50 years
- Female
- Shorter symptomatic period (<1 year) with less dyspnea, relatively preserved lung function
- Presence of ground glass and reticular opacities on HRCT
RECOMMENDATIONS FOR TREATMENT

Length of therapy

- Objective response to therapy may not be evident until the patient has received $\geq 3$ months of therapy.
- In absence of complications or adverse effects the therapy should be continued for at least 6 months.
RECOMMENDATIONS FOR TREATMENT
Pulmonary Rehabilitation Program

- For motivated patients a combination of exercise training, education, and psychological support may help, not by improvement in lung function, but by improvement in exercise tolerance, decreased symptoms of breathlessness, improved quality of life, and less need for health care services.

_Chest.1998;113:263S-268S_
RECOMMENDATIONS FOR TREATMENT

Lung Transplantation

**INDICATIONS**
- Severe functional impairment
- Oxygen dependency
- Deteriorating course

**CONTRAINDICATIONS**
- Unstable psychosocial profile
- Significant extrapulmonary disorders
- Age > 60 years

*Am J Respir Crit Care Med. 1998; 158:335-339*
RISK FACTORS FOR PROGRESSIVE DISEASE

- Age: >50 yr
- Gender: male
- Dyspnea: moderate to severe with exertion
- History of cigarette smoking
- Lung function: moderate to severe loss (especially gas exchange with exercise)
- BAL fluid: neutrophilia or eosinophilia at presentation
- HRCT scan: reticular opacities or honeycomb changes
- Response to corticosteroids: poor
- Pathology: more fibrosis, fibroblastic foci
CONCLUSIONS (Treatment of IPF)

- Till date insufficient clinical evidence to conclude that any treatment improves survival or quality of life for patients with IPF.
ILD secondary to Connective tissue diseases

- Rheumatoid arthritis
- Systemic sclerosis
- Sjogren syndrome
- Systemic lupus erythematosus
- Idiopathic inflammatory myopathies
General approach

- ILD is often asymptomatic at presentation
- Rarely, it may be the first sign of presentation of disease
- Systemic disease so disease usually has features in joints, skin, etc
- Difficulty in swallowing, Raynaud’s phenomena, proximal muscle weakness.
- Restrictive pattern on PFT
## Serological tests

### Autoantibody testing in the evaluation of ILD

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Type</th>
<th>Association with CTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>ANA</td>
<td>May be seen in various CTDs (SLE, SS, SSc, PM/DM) Nucleolar staining suggests SSc</td>
</tr>
<tr>
<td>dsDNA</td>
<td>Anti-dsDNA antibody</td>
<td>Highly specific for SLE</td>
</tr>
<tr>
<td>SSA</td>
<td>Anti-Ro antibody</td>
<td>SLE, SS, myositis associated</td>
</tr>
<tr>
<td>SSB</td>
<td>Anti-La antibody</td>
<td>Common in SS, 15% in SLE</td>
</tr>
<tr>
<td>Scl-70</td>
<td>Anti-DNA topoisomerase 1</td>
<td>Common in SSc (70% prevalence); high association with ILD</td>
</tr>
<tr>
<td>RF</td>
<td>RF</td>
<td>Sensitivity 60%–80% and specificity 60%–85% for RA</td>
</tr>
<tr>
<td>CCP</td>
<td>Anti-CCP antibody</td>
<td>Sensitivity 68% and specificity 96% for RA</td>
</tr>
<tr>
<td>RNP</td>
<td>Anti-U1 small nuclear RNP</td>
<td>High titer seen in MCTD</td>
</tr>
<tr>
<td>Jo-1, EJ, PL7, PL12, OJ</td>
<td>Anti-tRNA synthetases</td>
<td>Seen in DM/PM/antisynthetase syndrome</td>
</tr>
</tbody>
</table>
Treatment principles

- Treatment of underlying disease
- Steroids and immunosuppressive agents
- Multi-disciplinary approach
- Long duration of treatment
- Supportive treatment and pulmonary rehabilitation
- Treat co-morbidities and limit treatment related side effects
- Lung transplantation
<table>
<thead>
<tr>
<th>Drug</th>
<th>HRCT Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>NSIP; diffuse ground-glass; multiple areas of organizing pneumonia; diffuse reticular opacities</td>
</tr>
</tbody>
</table>
| Bleomycin       | Early: reticular or nodular opacities involving the bases and costophrenic angles  
                             Late: diffuse fibrosis                                                          |
| Cyclophosphamide| Basal reticular or nodular opacities; pleural thickening                       |
| Methotrexate    | Hilar lymphadenopathy; basal reticular or nodular opacities                     |
| Nitrofurantoin  | Early: basal opacities; diffuse ground-glass                                   
                             Late: basal reticular or nodular opacities along with fibrosis                  |
| Nitrosoureas    | Patchy or diffuse ground-glass abnormalities                                    |
Thank You