Non-IPF Interstitial Lung Disease

Tom Schaumberg, M.D.
Pulmonary & Critical Care Medicine
The Oregon Clinic

Disclosures
- PI for Intermune trials for Perfenidone
- PI for Boeringenlehlm trial of Nintedanib
- PI for Gilliad trial for Sustimamab
- Investigator for Genentech for Lebrikizumab
- Investigator for Bristol-Meyers Squibb for Lysoposhatidic Acid Receptor Antagonist
- Contractual agreements for recruiting, screening and conducting clinical trials with patients who have IPF
- I do not receive any money for services that are not directly related to patient care.
Non-IPF Interstitial Lung Disease
IPF: 3-5 year 50% mortality from the time of diagnosis
6.7 years from onset of symptoms

IPF vs Non-IPF ILD

IPF
- IPF is fatal with a 50% mortality in 3-5 years
- IPF is fibro-proliferative lung disease
- IPF is limited to the lungs

Non-IPF ILD
- The prognosis is good
  - Dependent on the specific diagnosis
- Inflammatory conditions
- Often associated with systemic conditions
IPF vs Non-IPF ILD

- Steroids and immunosuppressive medications cause harm
- Pirfenidone and Nintedanib slow the progression of IPF
  - Small treatment effect
  - The results are not predictable
  - Cost $90,000-95,000/year

- Steroids and immunosuppressive can have dramatic benefit in some forms of ILD
  - The type and duration of immunosuppression depends on the diagnosis
- Pirfenidone and Nintedanib are of no benefit in Non-IPF diseases

Clinical Presentation of Interstitial Lung Disease

- Prevalence of all ILD 74/100,000
  - 3,000 Oregonians
  - 42/100,000 new colorectal cancers per year

- 35% of all ILDs are secondary to IPF

Clinical Presentation of Interstitial Lung Disease

- Chronic unexplained cough
- Unexplained dyspnea
- “Velcro” rales on exam
- Abnormal CXR or CT scan
  - Beware of the term “Stable fibrosis”

68 y/o man referred for second opinion regarding IPF

- Sub-acute DOE now at < 50 yards
- NP Cough
- Hx GERD, OSA, TIA with + anticardiolipin antibody
- 22 p/y smoking D/C 1985
- Retired general contractor
  - Incidental asbestos exposure
- Rales at bases
- NI CBC, BMP, EKG, Echo
- FEV1/FVC .71, FVC 83%, TLC 79%, DLCO 38%
High Resolution CT Scan Patterns

- Ground glass opacities
- Reticular "fibrotic" changes
- Honey combing
- Cysts
- Nodules/Micro-nodules
- Mosaic attenuation

Location

- Diffuse
- Focal
- Patchy
- Upper lobe predominant
- Lower lobe dominant
- Peripheral
- Peribronchovascular

Bronchiectasis

"Causes" of Interstitial Lung Disease

Exposures

- Extrinsic Allergic Alveolitis
  - reactions to organic materials
  - Hypersensitivity pneumonitis (bird fanciers, humidifier lung, occupational exposures)
  - Eosinophilic pneumonia

- Minerals (Inorganic)
  - Pneumoconiosis
  - Silicosis, asbestosis, Coal workers, berylliosis

- Drug induced disease
  - Chemotherapy, Nitrofurantoin, Amioderone
  - Biologicals
    - Monoclonal antibodies
    - DMARDS
  - Pneumotox.com

Intrinsic

- Connective tissue diseases
  - RA, polymyositis, SLE, systemic sclerosis, ankylosing spondylitis, sjogrens syndrome, IBD, etc
  - ANCA associated vasculitis;
    - Granulomatosis with Polyangiitis (GPA/Wegeners)
    - Microscopic Polyangiitis (MPA)
    - Eosinophilic granulomatosis with polyangiitis EGPA (Churg-Strauss)

- Idiopathic Interstitial Pneumonias
  - Well defined disorders of unknown cause
    - Sarcoidosis, LAM

- Smoking related
  - RBILD, DIP, Langerhans histiocytosis

- Unknown causes (Idiopathic Interstitial Lung Disease)
  - IPF, AIP
“Treatments” for Interstitial Lung Disease

- Allergic “type” Hypersensitivity
  - Avoidance
  - Steroids
  - Steroid sparing agents
    - Azathioprine, Mycophenolate
    - Avoid MTX

- Chemical/Drug induced disease
  - Withdrawal of the agent
  - +/- Steroids

- Inorganic minerals (Pneumoconiosis)
  - Avoidance

- Connective tissue diseases
  - Steroids
  - Azathioprine, Mycophenolate
  - Cyclophosphamide
  - Rituximab
  - DMARDs

- ANCA associated vasculitis
  - Cyclophosphamide
  - Rituximab
  - Prednisone
  - Azathioprine

- Eosinophilic pneumonia
  - Avoidance
  - Brief steroids

- Idiopathic Interstitial Pneumonias
  - Sarcoïdosis
    - Steroids and steroid sparing agents
  - LAM
    - Sirolimus
  - Langerhans cell histiocytosis, RBILD, DIP
    - Smoking related
    - +/- Steroids
  - (Unknown causes)
    - NSIP, COP, LIP - Steroids & steroid sparing agents
    - AIP +/- Steroids & supportive care
    - IPF - Nintedanib or Pirfenidone

Diagnosis

- Clinical context
  - Exposures
    - Environmental at work and home
    - Drugs
  - Systemic diseases known to cause ILD e.g connective tissue disease

- Diagnostic testing
  - High Resolution CT Scan
    - Pattern recognition
      - No 1:1 correlation with a specific diagnosis
      - IPF has a “typical” CT pattern but is a diagnosis of exclusion
      - The CT appearance of advanced forms of other ILD’s is similar to IPF
  - Lab tests in the setting of systemic diseases
  - Pulmonary Function Test (disease severity)

- Pathology
  - Bronchoscopy is diagnostic in a few disorders
    - Sarcoïdosis, eosinophilic pneumonia, +/- hypersensitivity pneumonitis
    - Exclude infection
  - Surgical lung biopsy
High Resolution CT Scan

- HRCT alone cannot provide a diagnosis
  - Pattern
    - Ground Glass, linear reticulation, micro-nodular, “tree-in-bud”, consolidation, cysts
  - Location
    - Peripheral, peri-bronchial, basilar, sub-pleural, diffuse
  - Airway involvement
    - Traction bronchiectasis, peri-bronchial
  - Lack of effusions
    - Except LAM
  - Lack of enlarged lymph nodes
    - Except Sarcoidosis and Lyphangitic spread of cancer

High Resolution CT Scan

- IPF
  - Reticular opacities
  - Peripheral and basilar predominance
  - Honey combing
  - Traction bronchiectasis
  - Also seen in end-stage NSIP and hypersensitivity pneumonitis
High Resolution CT Scan

- Reticular opacities
- Peripheral and basilar predominance
- Honey combing
- Traction bronchiectasis
- Also seen in end-stage NSIP and hypersensitivity pneumonitis

HRCT Scan

IPF vs Non-IPF

- Characteristic not found in IPF
  - Ground glass opacities > reticular “fibrotic” changes
  - Prebronchovascular
  - Upper lobe predominance
  - Focal consolidation
  - Lymphadenopathy
  - Pleural plaques
  - Cysts
  - Pleural effusions
  - Nodules/Micronodules
  - Mosaic attenuation
HRCT “Ground Glass”

- Hypersensitivity pneumonitis
- Desquamative interstitial pneumonitis (DIP)
- Respiratory bronchiolitis associated ILD (RB-ILD)
- Drug toxicity
- Pulmonary hemorrhage

Nodules

- Sarcoidosis
- Hypersensitivity pneumonitis
- Respiratory bronchiolitis associated ILD (RB-ILD)
- Pulmonary histiocytosis X
- Silicosis
- Pneumoconiosis
- Metastatic cancer
Focal Consolidation

- Cryptogenic Organizing Pneumonia (COP, formally known as BOOP)
- Infection

Cysts

- Pulmonary Histiocytosis X
- Lymphangioleiomyomatosis (LAM)
- Birt Hogg Dube
- Chronic PCP
Serologic Testing

- The ATS recommends screening all patients with ILD
  ANA
  RF, Anti-CCP

- Additional testing based on Systemic symptoms
  Aldolase
  CPK
  Anti-synthitase antibodies (e.g. Jo-1)
  Sjogren’s Antibodies SS-A, SS-B
  Scleroderma Antibodies (scl-70, PM-1)

PFTs

- Disease severity
- Restrictive physiology
  - Spirometry
    • NL or increased FEV1/FVC ratio
    • Decreased FVC
    • FEV1 decreased but in proportion to FVC
  - Lung Volumes
    • Decreased TLC
    • Decreased RV
  - DLCO
    • Decreased
Pathology

Pathology alone does not provide a specific diagnosis/etiology

- Interstitial Pneumonias
  - Usual interstitial pneumonia (UIP) = IPF (Occasionally with hypersensitivity pneumonitis, rheumatoid arthritis, scleroderma, and asbestosis)
  - Nonspecific interstitial pneumonia (NSIP) often associated with connective tissue diseases, occasionally with viral pneumonias, hypersensitivity pneumonitis, and drug-induced toxicity
  - Respiratory bronchiolitis (RB): Cigarette smoke, inhaled minerals, viral infections, connective tissue disease
  - Desquamative interstitial pneumonia (DIP): Associated with smoking
  - Organizing pneumonia: Cryptogenic organizing pneumonia (COP)/BOOP: Connective tissue disease, infections, drug reactions
  - Lymphoid interstitial pneumonia (LIP)
  - Diffuse alveolar damage (DAD): Any form of acute lung injury, e.g., ARDS
- Granulomatous lung diseases
  - Sarcoidosis
  - Vasculitis GPA (Wegener's), MPA, EGPA (Churg-Strauss)
  - Hypersensitivity pneumonitis - environmental exposures and Drugs
  - Langhans cell granulomatosis: associated with smoking
  - Foreign body granulomatosis
  - Chronic beryllium disease
  - Bronchocentric granulomatosis
- Alveolar filling parenchymal lung diseases
  - Eosinophilic pneumonia
  - Pulmonary hemorrhage syndromes
  - Pulmonary alveolar proteinosis
- Proliferative lung diseases
  - Pulmonary amyloidosis
  - Smooth muscle proliferation (LAM)
Diagnosis

• Clinical context
  – Exposures
    • Environmental at work and home
    • Drugs
  – Systemic diseases known to cause ILD e.g connective tissue disease
• Diagnostic testing
  – Lab tests in the setting of systemic diseases
  – High Resolution CT Scan
    • Pattern recognition
    • IPF is a diagnosis of exclusion and a “typical” CT pattern
    • The CT appearance of advanced forms of other ILD’s is similar to IPF
  – Pulmonary Function Test (disease severity)
• Pathology
  – Bronchoscopy is diagnostic in a few disorders
    • Sarcoidosis, eosinophilic pneumonia, +/- hypersensitivity pneumonitis
    • Exclude infection
  – Surgical lung biopsy

Connective Tissue Disease Related ILD

• General Principles
  – ILD rarely presents prior to systemic symptoms
  – No CT pattern or pathologic finding is specific to ILD related to connective tissue diseases
  – Serositis > Interstitial Lung Disease
  – Infections are common with immunosuppressive therapy
  – Methotrexate is associated with the development of ILD independent of underlying Dx
  – Hydroxychloroquine, sulfasalazine are not effective in treating ILD
  – Aspiration is common with scleroderma/Systemic sclerosis

Drug Induced Lung Disease

• http://www.pneumotox.com
4/26/2016

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- ANA (-)
- RF (-)
- CCP (-)
- SCL-70 (-)
- JO-1 Ab
- CK NI
- Aldolase NI
- UA NI
68 y/o man referred for second opinion regarding IPF

- Extensive woodwork with exotic woods
- Humidifier in his bedroom

<table>
<thead>
<tr>
<th>Wood Species</th>
<th>Reaction</th>
<th>Area(s) Affected</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abura</td>
<td>irritant, nausea, giddiness, and vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African Blackwood</td>
<td>irritant, sensitizer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African Boxwood</td>
<td>irritant, headache, asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afrormosia</td>
<td>irritant, nervous system effects, asthma, splinters go septic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afzelia</td>
<td>irritant, sneezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agba</td>
<td>irritant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allanthus</td>
<td>irritant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albizia</td>
<td>irritant, nausea, pink eye, giddiness, nose bleeds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alder (Alnus genus)</td>
<td>irritant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alligator Juniper</td>
<td>irritant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mulga (Acacia aneura)</td>
<td>irritant, headache, nausea, wood contains a virulent poisonous principle used for spear heads by aboriginals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sneeze wood</td>
<td>irritant, oils within the wood cause violent sneezing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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- (+) Hypersensitivity pneumonitis panel
  - Aureobasidium Pullulan
- VATS Biopsy
  - UIP and Hypersensitivity pneumonitis

- Avoidance
- Prednisone and Mycophenolate
- FVC 79% => 100%
- DLCO 38% => 53%
Non-IPF Interstitial Lung Disease

Conclusions

• You will see patients with ILD
  – Cough, SOB, Abnl CT

• IPF is only one type of ILD
  – Progressive, fatal, treated with Pirfenidone or Nintedanib

• The prognosis and treatment of other types of ILD depends on the specific diagnosis

Conclusions

• Consider medications
  – Pneumotox.com
  – “Biologic Agents”
    • Immunosuppression
    • Biologic effect
    • Drug Rxn

• Environmental exposures work and home
  – Intense or highly repetitive exposures; birds, decaying organic materials

• Underlying diseases and systemic symptoms
  – Connective tissue disease
  – Cancer and its treatments

• Consider non-bacterial infections
  – Viruses, PJP
  – Molds rarely cause infections in NI hosts, may cause hypersensitivity reactions
Non-IPF Interstitial Lung Disease

Conclusions

• Avoid “Therapeutic/Diagnostic trials” of steroids
  – Dysphoria
  – Delay in diagnosis
  – Duration?
  – Dose?
  – Which steroid sparing agent is most appropriate?