ACCME/Disclosures

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Dr. Andrew Tager and Dr. Lida Hariri declare they have no conflict(s) of interest to disclose.

Dr. Lynette Sholl declares she was on the Genetech Advisory Board.
Interstitial Lung Diseases: Why The Diagnosis Matters

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Pulmonary and Critical Care Unit
Massachusetts General Hospital

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Department of Pathology
Brigham and Women’s Hospital

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Department of Pathology
Massachusetts General Hospital
Overview: Revisiting IPF

• Diagnostic approaches
• Revisiting therapeutic approaches
  – New concepts of pathogenesis →
    new therapeutic targets for clinical trials
  – Positive Phase III trial results for pirfenidone and nintedanib
• Differential diagnosis
• Future assessments on the horizon for IPF
Clinical Case Presentations

Case 1

56 year old man with 4 month history of shortness of breath and suspected ILD.

Case 2

52 year old woman with interstitial lung disease of unclear etiology, longstanding “chronic organizing pneumonia” for 13+ years.
Revisiting Diagnostic Approaches to IPF: ATS / ERS / JRS / ALTA 2011 Statement

Suspected IPF

Identifiable causes for ILD?

Yes

No

HRCT

UIP *

Possible UIP *
Inconsistent w/ UIP *

Surgical Lung Biopsy

UIP †
Probable UIP † / Possible UIP †
Non-classifiable fibrosis †

MDD

IPF

IPF/Not IPF per Table 6

Not UIP †

Not IPF
IPF Diagnosis: Exclusion of Other ILD

- IPF diagnosis requires exclusion of other causes of ILD
  - Environmental exposures
    - Pneumoconioses
    - Hypersensitivity Pneumonitis
  - Systemic diseases
    - Connective tissue disease
    - Sarcoidosis
  - Drug toxicities
Diagnostic Algorithm for IPF

Suspected IPF

Identifiable causes for ILD?

No

HRCT

~ 50% of cases!

Possible UIP *
Inconsistent w/ UIP *

Surgical Lung Biopsy

Not UIP †

 UIP †
Probable UIP † / Possible UIP †
Non-classifiable fibrosis †

MDD

IPF

IPF/Not IPF per Table 6

Not IPF
### HRCT Criteria for UIP Pattern:

**ATS / ERS / JRS / ALTA 2011 Statement**

<table>
<thead>
<tr>
<th><strong>UIP Pattern</strong></th>
<th><strong>Possible UIP</strong></th>
<th><strong>Inconsistent with UIP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(all 4 features)</td>
<td>(all 3 features)</td>
<td>(Any of 7 features)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subpleural, basal predominance</td>
<td>Subpleural, basal predominance</td>
<td>Upper or mid-lung predominance</td>
</tr>
<tr>
<td>Reticular abnormality</td>
<td>Reticular abnormality</td>
<td>Peribronchovascular predominance</td>
</tr>
<tr>
<td><strong>Honeycombing With Or without Traction bronchiectasis</strong></td>
<td>Absence of Inconsistent features</td>
<td>Extensive ground-glass abnormality</td>
</tr>
<tr>
<td>Absence of Inconsistent features</td>
<td></td>
<td>Profuse micronodules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discrete cysts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mosaic attenuation or air-trapping</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consolidation in bronchopulmonary segments(s) or lobe(s)</td>
</tr>
</tbody>
</table>
HRCT: UIP Patterns

- UIP Pattern with Extensive Honeycombing
- UIP Pattern with Less Severe Honeycombing
- Possible UIP Pattern

Clinical Case 1: HRCT

56 year old man with 4 month history of shortness of breath

Bilateral subpleural reticular opacities, mild bronchiectasis, ground glass changes, and possible honeycomb

Suggestive of fibrosing NSIP or early UIP
Clinical Case 2: HRCT

52 year old woman with ILD of unclear etiology

Bilateral subpleural reticular opacities, with bronchiectasis and honeycombing in the left lower lobe

Stable findings of pulmonary fibrosis
Clinical Case 2: HRCT

52 year old woman with ILD of unclear etiology

Bilateral subpleural reticular opacities, with bronchiectasis and honeycombing in the left lower lobe

*Stable findings of pulmonary fibrosis*
Diagnostic Algorithm for IPF (Con’t):

Suspected IPF

Identifiable causes for ILD?

Yes

No

HRCT

UIP *

Possible UIP *

Inconsistent w/ UIP *

Surgical Lung Biopsy

Not UIP †

UIP †

Probable UIP † / Possible UIP †

Non-classifiable fibrosis †

MDD

IPF

IPF/Not IPF per Table 6

Not IPF
Pathology Criteria for UIP Pattern

**Spatial heterogeneity**
Alternating areas of:
- Honeycomb change
- Fibrosis / distorted architecture
- Normal lung

**Subpleural / paraseptal predominance**

**Temporal heterogeneity**
Fibroblastic foci

Pathology Criteria for UIP Pattern: Fibroblastic Foci

- Small aggregates of actively proliferating fibroblasts/myofibroblasts
- Sites of active collagen synthesis
- Not pathognomonic for UIP, but necessary for the diagnosis
- Number of fibroblastic foci inversely correlates with survival

**Clinical Case 1: Lung Biopsy**

56 year old man with 4 month history of shortness of breath

Architectural distortion with subpleural fibrosis, spatial and temporal heterogeneity, and microscopic honeycombing

*Usual Interstitial Pneumonitis*
Clinical Case 2: Lung Biopsy

52 year old woman with ILD of unclear etiology

Chronic organizing pneumonia with elements of interstitial pneumonitis and fibrosis, unclassified

The pathology is not that of Usual Interstitial Pneumonitis
Clinical Case 2: Lung Biopsy
52 year old woman with ILD of unclear etiology

Chronic organizing pneumonia with elements of interstitial pneumonitis and fibrosis, unclassified

*The pathology is NOT that of Usual Interstitial Pneumonitis*
Diagnostic Algorithm for IPF

Multidisciplinary Conference - Both Cases

Suspected IPF

Identifiable causes for ILD?

Yes

No

HRCT

UIP *

Possible UIP *

Inconsistent w/ UIP *

Surgical Lung Biopsy

Not UIP †

UIP †

Probable UIP † / Possible UIP †

Non-classifiable fibrosis †

MDD

IPF

IPF/Not IPF per Table 6

Not IPF
MDD Discussion about Cases

Case 1: 56 year old man with 4 month history of shortness of breath and suspected ILD.

*Patient has UIP/IPF*

Case 2: 52 year old woman with interstitial lung disease of unclear etiology, longstanding “chronic organizing pneumonia” for 13+ years.

*Patient does NOT have UIP/IPF*

But we’re not entirely sure how to classify her ILD.
Phew, that was a lot of work...

Is this all just academic exercise, or does distinguishing IPF from other ILDs really matter?
Diagnosis stratifies prognosis

Well known that IPF has a significantly worse prognosis than other ILDs

< 3 years

King TE et al, Am J Respir Crit Care Med 2001
What about therapy for IPF and other ILDs?

- IPF thought to result from unremitting inflammation
  - Lymphocyte driven (Adaptive Immunity)

- As a result, IPF therapies targeted inflammation
  - Corticosteroids
  - Cytotoxic agents

- However, these cytotoxic agents / corticosteroids did not seem to impact disease progression
Major Change in Pharmacologic Approach to IPF from 2012 to 2014

PANTHER-IPF Trial 2012

Probability of death

Prednisone/Azathioprine/NA C arm terminated early because had shorter time to death and hospitalization compared to placebo

(Azathioprine / Prednisone / NAC)

Now diagnosis also stratifies therapy!

**IPF**: Immunosuppression now contraindicated

**Non-IPF ILDs**: Immunosuppression often first line therapy

---

*But wait!*  
*If we can’t give IPF patients immunosuppressive drugs, then what are we going to give them?*
Injury / Abnormal Repair Paradigm of IPF

IPF pathology suggests:

- Repetitive / recurrent injury

**Effective repair**

- Restoration of normal structure and function

**Ineffective repair**

- Pulmonary fibrosis and loss of function

- What injures the lung in IPF?
  - Unknown / may be different in different patients

- Why are repair responses ineffective in IPF?
  - Recurrent nature of injury may overwhelm repair mechanisms
  - Repair mechanisms may be abnormal / overly exuberant

Moisés Selman M, King TE, Pardo A, Ann Intern Med 2001
Injury / Abnormal Repair Paradigm of IPF

- Lung Injury
- Fibroblast Recruitment, Invasion, Proliferation, and Persistence
- Vascular Leak and Extravascular Coagulation
- Matrix Accumulation and Cross-Linking
- Alveolar Collapse and Re-Epithelialization
- Epithelial Cell Senescence/Apoptosis
- Macrophage Activation and Polarization
- Fibrin Clot
- Myofibroblast Activation and Myofibroblast Differentiation

Pirfenidone
Nintedanib

Ahluwhalia N, Shea BS, Tager AM, AJRCCM 2014
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*
Primary ASCEND Endpoint Achieved

Patients with ≥ 10% FVC Decline or Death (%)

Week

- Pirfenidone (N=278)
- Placebo (N=277)

Primary Endpoint

P<0.001

48% Relative Reduction

Pirfenidone Reduced Loss of FVC

Mean Change (ml)

Week

Pirfenidone (N=278)

Placebo (N=277)

P-value < 0.00001
By Rank ANCOVA at each time point

235 ml

428 ml

## ASCEND Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pirfenidone (%) (N = 278)</th>
<th>Placebo (%) (N = 277)</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>36</td>
<td>13.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Rash</td>
<td>28.1</td>
<td>8.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>17.6</td>
<td>6.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15.8</td>
<td>6.5</td>
<td>9.3</td>
</tr>
<tr>
<td>GERD</td>
<td>11.9</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>12.6</td>
<td>7.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2</td>
<td>6.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17.6</td>
<td>13</td>
<td>4.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9</td>
<td>8.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Cough</td>
<td>25.2</td>
<td>29.6</td>
<td>-4.4</td>
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<tr>
<td>IPF</td>
<td>9.4</td>
<td>18.1</td>
<td>-8.7</td>
</tr>
</tbody>
</table>

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*
Primary INPULSIS Endpoint Achieved

Annual Rate of Change of FVC

INPULSIS-1

INPULSIS-2

52% Relative Reduction

45% Relative Reduction

## Common Nintedanib Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>INPULSIS-1</th>
<th></th>
<th>INPULSIS-2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib (n = 309)</td>
<td>Placebo (n = 204)</td>
<td>Nintedanib (n = 329)</td>
<td>Placebo (n = 219)</td>
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<tr>
<td>Any (%)</td>
<td>96</td>
<td>89</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>62</td>
<td>19</td>
<td>63</td>
<td>18</td>
</tr>
<tr>
<td>Nausea(%)</td>
<td>23</td>
<td>6</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>

Approaches to Develop New Therapies for IPF

Protect the Epithelium
- Lung Injury
- Capillary
- Epithelial Cell Senescence/Apoptosis
- Fibroblast
- Macrophage
- Innate Immune Activation and Polarization
- Vascular Leak and Extravascular Coagulation
- Fibrin Clot
- Fibroblast Recruitment, Invasion, Proliferation, and Persistence

Rein in Repair Responses
- Alveolar Collapse and Re-Epithelialization
- Matrix Accumulation and Cross-Linking
- Myofibroblast
- Fibroblast Activation and Myofibroblast Differentiation

Ahluwhalia N, Shea BS, Tager AM, AJRCCM 2014
What Drives AEC Senescence and Apoptosis?

- OXIDATIVE STRESS
- ER STRESS
- DNA DAMAGE
- Epithelial Cell Senescence/Apoptosis
- Fibroblast Recruitment, Invasion, Proliferation, and Persistence
- Myofibroblast Activation and Differentiation
- Fibrin Clot
- Vascular Leak and Extravascular Coagulation
- Innate Immune Activation and Polarization
- Lung Injury
- Matrix Accumulation and Cross-Linking
- Alveolar Collapse and Re-Epithelialization
Protecting AECs from Oxidative Stress: Supplementing Anti-Oxidant Defense with NAC

FVC Decline in Panther-IPF:
All subjects

Endpoint-free survival in Panther-IPF:
Subjects with TT genotype at Rs3750920 (TOLLIP)


Justin Oldham . . . Imre Noth, AJRCCM 2015
Protecting AECs from ER Stress: Reducing Production of Unfolded/Misfolded Proteins

- What produces ER stress?
  - Genetic factors: Surfactant protein mutations
  - Environmental exposures: Tobacco smoke / Particulate matter
  - Viruses: Herpesviruses

- Colocalization of XBP-1 and CMV late antigen in IPF AECs

![Image of colocalization]


- Open Pilot Study of Ganciclovir Antiviral Therapy in Advanced IPF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre</th>
<th>Post</th>
<th>P value</th>
<th>Pre</th>
<th>Post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (litres)</td>
<td>1.70</td>
<td>1.85</td>
<td>.046</td>
<td>1.76</td>
<td>1.37</td>
<td>.08</td>
</tr>
<tr>
<td>DTPA (minutes)</td>
<td>22.4</td>
<td>28.2</td>
<td>.001</td>
<td>25.2</td>
<td>17*</td>
<td>.01</td>
</tr>
<tr>
<td>Shuttle (meters)</td>
<td>286</td>
<td>307</td>
<td>.08</td>
<td>260</td>
<td>273</td>
<td>.52</td>
</tr>
<tr>
<td>Prednisolone (mg)</td>
<td>19</td>
<td>10</td>
<td>.02</td>
<td>21</td>
<td>13.5</td>
<td>.95</td>
</tr>
</tbody>
</table>

Innate Immune Activation and Polarization in IPF

- Innate Immune Activation and Polarization
- Lung Injury
- Capillary
- Macrophage
- Fibrin Clot
- Vascular Leak and Extravascular Coagulation
- Epithelial Cell Senescence/Death
- Myofibroblast
- Fibroblast
- Fibroblast Recruitment, Invasion, Proliferation, and Persistence
- Alveolar Collapse and Re-Epithelialization
- Matrix Accumulation and Cross-Linking
- Myofibroblast Activation and Myofibroblast Differentiation

Lung Injury
Capillary
Macrophage
Fibrin Clot
Vascular Leak and Extravascular Coagulation
Epithelial Cell Senescence/Death
Myofibroblast
Fibroblast
Fibroblast Recruitment, Invasion, Proliferation, and Persistence
Alveolar Collapse and Re-Epithelialization
Matrix Accumulation and Cross-Linking
Myofibroblast Activation and Myofibroblast Differentiation
Immune Activation in Response to Injury

Tom Wynn

Macrophage Polarization in Response to Injury

**Signals driving differentiation**
- Infection, DAMPs, PAMPs, TNF-α, IFN-γ

**Monocyte-derived cell phenotype**
- Proinflammatory macrophages (M1)

**Secreted cytokine profile**
- IL-1, IL-6, IL-12, MCP-1, MMPs, ROS, TNF-α

**Cellular effect**
- Induces apoptotic/necrotic cell death

**Fibrosis impact**
- Tissue damage

**Monocytes**

**Apoptotic cells and Pentraxin-2 IL-10**

**Regulatory macrophages (M_{reg})**
- IL-10
- Inactivates myofibroblasts
- ↓ Collagen, ↓ TIMP, ↑ MMP

**Therapies in Trials**
- Recombinant Pentraxin-2

**Apoptotic cells, TGF-β, M-CSF, IL-4, IL-13**

**Profibrotic macrophages (M2a)**
- TGF-β, CTGF, VEGF, PDGF, IL-13, CCL-18, galectin-3

**Fibrocytes**
- Activates myofibroblasts
- ↑ Collagen, ↑ TIMP, ↑ MMP

**Therapies in Trials**
- Anti-IL-13 mAbs
- Anti-IL-4/13 mAb

Duffield JS, Lupher M, Thannickal VJ & Wynn TA
Annu Rev Pathol Mech Dis 2013
Fibroblast Recruitment, Invasion, Proliferation, and Persistence

- Lung Injury
- Capillary
- Macrophage
- Innate Immune Activation and Polarization
- Vascular Leak and Extravascular Coagulation
- Fibrin Clot
- Epithelial Cell Senescence/Death
- Myofibroblast
- Alveolar Collapse and Re-Epithelialization
- Matrix Accumulation and Cross-Linking
- Fibroblast Recruitment, Invasion, Proliferation, and Persistence
Fibroblast Recruitment in IPF is Mediated by LPA (Lysophosphatidic Acid)

• BAL Fibroblast chemotactic activity
  – Present in IPF, SSc-ILD (Behr J, Thorax 1993)
  – Correlates with disease severity/progression (Selman M, PLoS One 2007)

• Activity mediated by LPA-LPA₁ signaling (Tager AM, Nature Med 2008)

BAL LPA levels

LPA receptor expression on IPF BAL fibroblasts

LPA₁ mediates IPF BAL fibroblast CTX

• Therapies in trials
  – LPA₁ receptor antagonist
**Innate Immune Activation and Polarization in IPF**

- **Fibroblast Activation and Myofibroblast Differentiation**
- **Matrix Accumulation and Cross-Linking**
- **Vascular Leak and Extravascular Coagulation**
- **Fibrin Clot**
- **Fibroblast Recruitment, Invasion, Proliferation, and Persistence**
- **Alveolar Collapse and Re-Epithelialization**
- **Macrophage Innate Immune Activation and Polarization**
- **Epithelial Cell Senescence/Death**
- **Lung Injury**
- **Capillary**
- **ALVEOLUS**
Drivers of Fibroblast Activation / Myofibroblast Differentiation in IPF

**Biochemical Signals**
- Mediators from stressed epithelial cells
  - e.g. TGF-β, CTGF
- Mediators from extracellular matrix
  - e.g. EDA fibronectin
- Therapies in trials
  - Anti-ανβ6 mAb (inhibits TGF-β activation)
  - Anti-CTGF mAb

**Biomechanical Signals**
- Increased matrix stiffness
Fibrosis Increases Lung Stiffness

Lung tissue from a healthy control

Lung tissue from a person with IPF

AFM topography

AFM topography

kPa

0 2 4 6 8 10

0 20 40 60 80

Distance (µM)

Distance (µM)

Dan Tschumperlin

Fei Liu

David Lagares
Stiffness Promotes Myofibroblast Differentiation

Actin αSMA DAPI

Soft Stiff

Normal Tissue Fibrotic Tissue

Stiffness (KPa)
Determinants of Tissue Stiffness in Fibrosis

- Tissue stiffness increased by cross-linking of matrix proteins
- Cross-linking enzymes
  - Lysyl oxidases
  - Transglutaminases
  - Prolyl hydroxylases


Novel Targets For The Future: What’s Promising?

A LOT!!!

- Lung Injury
- Fibroblast
- Capillary
- Epithelial Cell
- Epithelium
- Macrophage
- Innate Immune Activation and Polarization
- Matrix Accumulation and Cross-Linking
- Fibroblast Activation and Myofibroblast Differentiation
- Alveolar Collapse and Re-Epithelialization
- Fibrin Clot
- Vascular Leak and Extravascular Coagulation
- Fibroblast Recruitment, Invasion, Proliferation, and Persistence
- NAC
- Nrf2 activators
- NOX4 inhibitors
- Chemical chaperones
- eIF2α phosphorylators
- BiP enhancers
- Gancyclovir
- GSE24-2 peptides
- Anti-IL-13 mAb
- Anti-IL-13/IL-4 mAb
- Pentraxin-2
- LOX inhibitors
- TG2 inhibitors
- Anti-ανβ6 mAb
- LPA₁ antagonist
- Anti-CTGF mAb
- Anti-IL-13 mAb
- Anti-IL-13/IL-4 mAb
- Pentraxin-2
- Nintedanib
- Pirfenidone
- Nintedanib
- Anti-ανβ6 mAb
- LPA₁ antagonist
- Anti-CTGF mAb
- LOX inhibitors
- TG2 inhibitors
- Nintedanib
- Pirfenidone
- Anti-ανβ6 mAb
- LPA₁ antagonist
- Anti-CTGF mAb
IPF… The Great Imitator?

Exploring the differential diagnosis of idiopathic pulmonary fibrosis
I. Chronic hypersensitivity pneumonitis

- Clinically difficult to differentiate from UIP/IPF
- Associated with environmental exposure (molds, organic particulates and dusts)
- Avoiding exposure may limit disease progression
- 30% of patients have no identifiable exposure
- Immunosuppression may be helpful
Chronic HP: Pathologic features

- Morphology may resemble UIP
- Upper lobe-predominant distribution
- Bronchiolocentric distribution
- Loosely-formed granulomas
Hypersensitivity Pneumonitis

Loosely formed non-necrotizing granulomas
Hypersensitivity Pneumonitis

Fibroblast tufts in terminal airways
Chronic Hypersensitivity Pneumonitis

- Granulomas in >75% of cases
- Prominent bronchiolocentric fibrosis
- Cases that present with fibrotic NSIP or UIP pattern associated with ~2 year median survival

Churg et al. AJSP 2009.
II. Connective tissue disease (CTD)-related ILD: lung disease may be the first or only manifestation

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Common patterns of lung pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Usual interstitial pneumonia (UIP)</td>
</tr>
<tr>
<td>Systemic lupus erythematosis</td>
<td>Cellular nonspecific interstitial pneumonia (NSIP)</td>
</tr>
<tr>
<td></td>
<td>Lymphoid interstitial pneumonia (LIP) pleuritis</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>Cellular NSIP</td>
</tr>
<tr>
<td></td>
<td>LIP</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Fibrotic NSIP</td>
</tr>
<tr>
<td>Anti-synthetase syndrome/Inflammatory myopathies</td>
<td>NSIP + organizing pneumonia</td>
</tr>
<tr>
<td>Mixed connective tissue disorders</td>
<td>Diverse</td>
</tr>
</tbody>
</table>
Connective tissue disease-related ILD

• Correlation with autoimmune serologies, physical examination
• Diverse radiographic findings
• Immunosuppression typically recommended
  – Prednisone
  – Steroid-sparing agents
  – Biologic agents (TNF-inhibitors, rituximab)
55 year old woman with chronic cough, bronchiectasis, RF>1400, +ANA

Subpleural and centrilobular inflammation and fibrosis
Rheumatoid arthritis-associated ILD

Subpleural architectural distortion
50 year old woman with pulmonary infiltrates, history of systemic sclerosis
Additional history of esophageal dysmotility and GERD

Dense centrilobular inflammation and giant cells
CTD-associated ILD

• Diverse pathologic manifestations
• Look for multi-compartment involvement
  – Airways
  – Interstitium
  – Vessels
  – Pleura
• Both primary involvement and sequelae of systemic disease may manifest in lung
  – Drug effects
  – Infection
  – Aspiration
III. Respiratory Bronchiolitis/Smoking-related lung diseases

• RB demonstrated in 100% of current smokers and rarely in nonsmokers
• Physiologically undetectable or associated with obstruction

Niewoehner et al. NEJM 1974
Low power histology: airway-centered disease
Respiratory bronchiolitis

**Airway-centered inflammation +/- fibrosis

*** Pigmented “smoker’s” macrophages
26 year old smoker with spontaneous pneumothorax
Subpleural fibroblast proliferation
Pulmonary manifestations of connective tissue disease

Abundant intraalveolar pigmented macrophages
55 year old man with history of TB and lung cancer, multiple new lung nodules
Langerhans cell histiocytosis

Nodular/stellate scars containing eosinophils, Langerhans cells, “dust” cells
RB + Emphysema + Fibrosis

• Respiratory bronchiolitis-Interstitial lung disease (RB/RB-ILD)
  (Yousem SA. Mod Path 2006)
• Airspace enlargement with fibrosis (AEF)
  (Kawabata et al. Histopathology 2008)
• Smoking related interstitial fibrosis (SRIF)
  (Katzenstein et al. Hum Path 2010)
Emphysema, "smokers" macrophages, hyalinized interstitial fibrosis
Reporting on these entities in lung resections for NSCLC

- No clear consensus
- Wright, Tazelaar and Churg (Histopathology, 2011) advise against commenting on emphysema or RB
  - Significant interstitial fibrosis should trigger closer examination of medical record and correlation with radiology
  - Discourage use of the term “smoking related interstitial lung disease”
    - No clear clinical correlate
- Patients with emphysema + fibrosis on HRCT may have more significant disease than apparent based on pulmonary function tests (Washko et al. NEJM 2011)
Revisiting Diagnostic Approaches to IPF: ATS / ERS / JRS / ALTA 2011 Statement

Suspected IPF

Identifiable causes for ILD?

Yes

No

HRCT

UIP *

Possible UIP *

Inconsistent w/ UIP *

Surgical Lung Biopsy

Not UIP †

UIP †

Probable UIP † / Possible UIP †

Non-classifiable fibrosis †

MDD

IPF

IPF/Not IPF per Table 6

Not IPF
Barriers to getting the best diagnosis in patients with ILD

• High perioperative morbidity in patients with UIP
  – Comorbidities
    • Pulmonary hypertension
  – Acute exacerbation

• Inadequate sampling
“End stage lung”

Honeycomb change
Optimizing diagnostic biopsies

• Standard transbronchial biopsies are inadequate for diagnosis of UIP in most hands
• Open lung biopsies preferred modality
  – Work with surgeons who are experienced with this population
  – Obtain biopsies from multiple sites, preferably upper and lower lobes
  – Capture areas with greater and lesser involvement
• Consider alternative/novel approaches to biopsy
  – Cryobiopsy
Thanks!

Questions?