Exploring the Pathophysiology and Burden of IPF

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Idiopathic Pulmonary Fibrosis: Reading Between the Lines to Expedite Diagnosis and Management

Outline

- Pathophysiology of idiopathic pulmonary fibrosis (IPF)
- Importance of accurate diagnosis
- Emerging concepts in pathogenesis of IPF

Idiopathic Pulmonary Fibrosis

- Progressive disease of unknown etiology
- >100,000 patients in the United States
- 2 FDA-approved medical therapies

Idiopathic Pulmonary Fibrosis

- Men > women
- Typical presentation in patients’ 60s
- Therapy will likely be lifelong
- Challenging diagnosis
- Lung transplant is only therapy to prolong life

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Idiopathic Pulmonary Fibrosis: Reading Between the Lines to Expedite Diagnosis and Management

“Classic” Idiopathic UIP

Early HRCT Findings in IPF

HRCT = high-resolution computed tomography.

Early HRCT Findings in IPF
Usual Interstitial Pneumonia

Rapidly Progressive IPF

Is All Fibrotic Lung Disease the Same?

Progressive disease leading to transplant within 3 years

Alive and well without oxygen for 3 years with judicious immunosuppression
65-Year-Old Man with Progressive Symptoms

ANA 1:640
Aldolase 12
Anti-Jo-1+

Chronic Hypersensitivity Pneumonitis

• Mosaic
• Ground glass
• Air trapping
Essential Components in the Pathobiology of Unrelenting Pulmonary Fibrosis

- Epithelial injury/dysfunction/apoptosis
- Transforming growth factor beta (TGFβ) activation
- Fibroblast recruitment and expansion
- Myofibroblast recruitment
- Matrix production
- Matrix (basement membrane) degradation
- Fibrocystic destructive lung disease

Epithelial Dysfunction in the Pathogenesis of Pulmonary Fibrosis

- Familial pulmonary fibrosis
  - Surfactant protein gene mutations
  - Mucin gene polymorphisms
  - Telomerase mutations
- Misfolded proteins

BiP Protein Expression in IPF/UIP
Epithelial Dysfunction in the Pathobiology of Progressive Fibrosis

Environmental insults  
Viral infection  
Smoking  
Genetic predisposition  
Mutations in surfactant protein genes, telomerase, mucin genes  
Epithelial cell dysfunction  
Misfolded proteins in the ER  
Sensory  
UPR  
ER stress  
Impaired progenitor cell renewal and reprogramming  
Apoptosis  
Fibrosis

What Makes Fibrosis Severe and Irreversible?

Schematic of Invasion Assay

Cell suspension placed in upper chamber  
Invasive cells pass through Matrigel layer and cling to the bottom of the Boyden chamber membrane. Non-invasive cells stay in the upper chamber.  
After removal of non-invasive cells, invasive cells are stained and quantified.  
Invasive capacity = # cells invaded Matrigel/20x hpf
Fibroblasts from IPF Patients Spontaneously Invade Matrigel and Express HAS2 During Invasion

HAS2 = hyaluronan synthase 2; NHF = normal human fibroblasts.


Paradigm for the Development of Severe Pulmonary Fibrosis


Management of Fibrotic Lung Disease

IPF/UIP
- Pulmonary rehab
- Transplant evaluation
- Antifibrotic therapy

Not IPF/UIP
- Immunosuppressive therapy

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Idiopathic Pulmonary Fibrosis: Reading Between the Lines to Expedite Diagnosis and Management

Monday, April 18, 2016

Activity Chair
Gregory P. Cosgrove, MD

Reading Between the Lines: The Differential Diagnosis of Idiopathic Pulmonary Fibrosis

Jonathan H. Chung, MD
Associate Professor of Radiology
Associate Section Chief, Thoracic Radiology
University of Chicago Medical Center
Chicago, IL

Outline

• Discuss proper high-resolution computed tomography (HRCT) technique
• Usual interstitial pneumonitis (UIP) pattern on HRCT
  – Honeycombing
• Atypical UIP cases on HRCT
• Other typical high confidence patterns
HRCT technique

- Proper technique essential in interstitial lung disease (ILD) diagnosis
- Myriad protocols
- Essentials
  - Thin reconstruction/collimation (less than 2 mm)
  - High spatial algorithm
  - Prone imaging
  - Expiratory imaging

Accuracy of CT Diagnosis of UIP

<table>
<thead>
<tr>
<th>Study</th>
<th>Correctness of first choice diagnosis of UIP</th>
<th>Correctness of confident first choice diagnosis</th>
<th>% cases of UIP without confident CT diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunningenkake</td>
<td>85%</td>
<td>96%</td>
<td>52%</td>
</tr>
<tr>
<td>Flaherty</td>
<td>100%</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>Tsubamoto</td>
<td>100%</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>Elliot</td>
<td>88%</td>
<td>88%</td>
<td>50%</td>
</tr>
<tr>
<td>Johkoh</td>
<td>71%</td>
<td>76%</td>
<td>44%</td>
</tr>
<tr>
<td>Silva</td>
<td>84%</td>
<td>100%</td>
<td>67%</td>
</tr>
</tbody>
</table>

UIP

- UIP pattern on HRCT (All 4)
  - Basal/subpleural preponderance
  - Reticulation
  - Honeycombing with or without traction bronchiectasis
  - Absence of features listed as inconsistent with UIP
Confident Diagnosis UIP

• Honeycombing
  – 70%-80% of cases of UIP
  – Strongest indicator of UIP on HRCT
  – Survival prognosticator
  ▪ No honeycombing: 3.7 years longer median survival


Honeycombing

• Honeycombing: clustered cystic air spaces, typically of comparable diameters on the order of 3–10 mm, but occasionally as large as 2.5 cm.
  – Subpleural
  – Well-defined walls

Honeycombing on HRCT

Honeycombing versus Bronchiolectasis

UIP

- Possible UIP pattern on HRCT (All 3)
  - Basal/subpleural preponderance
  - Reticulation
  - Absence of features listed as inconsistent with UIP
  - No honeycombing

Possible UIP

- Inconsistent with UIP pattern (any of the 7 features)
  - Upper or mid-lung predominance
  - Peribronchovascular predominance
  - Extensive ground glass abnormality (extent > reticular abnormality)
  - Consolidation in bronchopulmonary segment(s)/lobe(s)
  - Profuse micronodules (bilateral, predominantly upper lobes)
  - Discrete cysts (multiple, bilateral, away from areas of honeycombing)
  - Diffuse mosaic attenuation/air trapping (bilateral, in 3 or more lobes)


The Bad News
Inconsistent with UIP

• Inconsistent with UIP does NOT mean the underlying diagnosis is not UIP/IPF
• Uncommon presentation of a common condition

Atypical UIP on HRCT

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Radiologic and Histologic Classification of UIP, Observed (and Expected) Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP on CT Scan</td>
<td>Not Consistent</td>
</tr>
<tr>
<td>Inconsistent</td>
<td>24 (7.8%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>11 (3.1%)</td>
</tr>
<tr>
<td>Probable</td>
<td>18 (5.6%)</td>
</tr>
<tr>
<td>Definite</td>
<td>17 (5.3%)</td>
</tr>
</tbody>
</table>

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Atypical UIP on HRCT

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Radiologic and Histologic Classification of UIP, Observed (and Expected) Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP on CT Scan</td>
<td>Definite</td>
</tr>
<tr>
<td>Inconsistent</td>
<td><strong>21 (26.1%)</strong> 30%</td>
</tr>
</tbody>
</table>

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HRCT: NSIP; Path: UIP; Clinical: IPF

HRCT: HP; Path: UIP; Clinical: IPF

Atypical UIP on HRCT

- Most commonly mimic NSIP; chronic HP; and, less commonly, sarcoidosis
  - Sverzellati Radiology 2010:
    - 34/55 (62%) patients with biopsy-proven UIP/IPF, scored as low probability UIP on HRCT
    - NSIP (53%), chronic HP (12%), and sarcoidosis (9%) first-choice diagnoses
  - Silva Radiology 2008:
    - 23 cases of histopathologically proven UIP/IPF, observers chose NSIP or chronic HP as a first-choice diagnosis 25.7% of the time
Multidisciplinary review of ILD: Why the combination of radiographic, pathologic, and clinical patterns matters

Multidisciplinary Approach to IIP Diagnosis

- 58 cases with suspected IIP
- Independent review followed by clinical-radiology-pathology (CRP) consensus
- After CRP consensus, changes occurred in:
  - 53% of radiologist diagnoses: NSIP to UIP, HP and RBILD/DIP to NSIP
  - 34% of clinician diagnoses
  - 19% of pathologist diagnoses
- Pathologist is not always right!
- Clinical-radiologic-pathologic review is very important

IIP = idiopathic interstitial pneumonia; RBILD/DIP = bronchiolitis-associated interstitial lung disease.

Take-home Points

- Confident UIP pattern on HRCT highly accurate for UIP/IPF
- Many cases of ‘inconsistent with UIP’ on CT patterns are also UIP/IPF
- Radiology, pathology, clinical correlation paramount to diagnosis
I would like to thank Dr. David A. Lynch for his contributions to this presentation.

Thank you!
ATS Criteria for UIP on Pathology

- Subpleural/paraseptal advanced fibrosis with or without honeycombing
- Patchy, temporally heterogeneous fibrosis
- Fibroblastic foci
- Absence of features against UIP

ATS = American Thoracic Society; UIP = usual interstitial pneumonia.

Honeycombing

Microscopic Honeycombing
Temporally Heterogeneous Fibrosis

Patchy fibrosis where regions appear to have occurred at different times.

Past fibrosis

Temporally Heterogeneous Fibrosis
Temporally Heterogeneous Fibrosis

- Today's fibrosis

- Tomorrow's fibrosis

Features Inconsistent with UIP

- Granulomas
- Organizing pneumonia
Clinical Cases

Case 1

Clinical History

- 69-year-old man
- Dyspnea with exertion and nonproductive cough
- PFT: TLC 68%, FVC 60%, and DLCO 46%
- Reflux with aspiration
- No clinical or serologic evidence of collagen vascular disease
- No environmental or occupational exposures

DLCO = diffusing capacity of the lungs for carbon monoxide; FVC = forced vital capacity; PFT = pulmonary function tests; TLC = total lung capacity.
Pathology

- Subpleural fibrosis with honeycombing
- Fibroblastic foci
- Heterogeneous, patchy fibrosis
- No findings that preclude a diagnosis of UIP
- Diagnosis: Case meets ATS criteria for UIP

Consensus Diagnosis

- UIP on radiology and pathology, without a clear clinical etiology
- Idiopathic pulmonary fibrosis

Case 2
Clinical History

- 42-year-old man
- Shortness of breath and exercise limitation
- PFT: TLC 58%, FVC 48%, DLCO 34%
- Sister with RA and grandmother with scleroderma
- Treated by PCP with antibiotics without improvement
- Abnormal chest x-ray, leading to chest CT

CT = computed tomography; PCP = primary care provider; RA = rheumatoid arthritis.

Chest CT
Pathology

- Diffuse involvement of the lung by inflammation and fibrosis
- No subpleural accentuation
- No microscopic honeycombing
- No fibroblastic foci
- No granulomas

- Diagnosis: Mixed cellular/fibrotic Nonspecific Interstitial Pneumonia (NSIP), not consistent with UIP
**Consensus Diagnosis**

- NSIP on radiology and pathology
- Clinical concern for an underlying collagen vascular disease
- **Interstitial pneumonia with autoimmune features (IPAF)**

**Case 3**

**Clinical History**

- 68-year-old woman
- Developed shortness of breath and wheeze over several months
- Symptoms were somewhat improved when on vacation visiting her sister
- PFT: TLC 81%, FVC 41%, DLCO not performed
### Pathology

- Patchy airway-centered inflammation with minimal scarring
- Numerous poorly-formed granulomas and multinucleated giant cells
- No advanced fibrosis, fibroblastic foci, or honeycombing
- Diagnosis: Hypersensitivity Pneumonia, inconsistent with UIP

### Consensus Diagnosis

- Radiology and pathology consistent with hypersensitivity pneumonia
- Clinically consistent with HP but without a clear antigen exposure
- Hypersensitivity Pneumonia

### Case 4
Clinical History

- 60-year-old man with a history of mild asthma
- Increasing dyspnea with exertion and cough over the past few years
- No history of collagen vascular disease or unusual exposures
- Patient sees PCP for an upper respiratory tract infection, and following an abnormal chest x-ray has a chest CT

Chest CT

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Pathology

- Marked subpleural fibrosis WITHOUT honeycombing
- Numerous fibroblastic foci
- Heterogeneous, patchy fibrosis
- No findings that preclude a diagnosis of UIP

- Diagnosis: Case meets ATS criteria for UIP, even without honeycombing

Consensus Diagnosis

- Radiology not consistent with UIP due to the absence of honeycombing
- Pathology also does not show honeycombing but does meet ATS criteria for UIP
- No clinical etiology

- Idiopathic Pulmonary Fibrosis
Emerging Trends in the Treatment of IPF

Gregory P. Cosgrove, MD
Associate Professor of Medicine
National Jewish Health & University of Colorado-Denver
Chief Medical Officer
Pulmonary Fibrosis Foundation

Interstitial Lung Disease

Interstitial Lung Disease

Idiopathic Pulmonary Fibrosis

Interstitial Lung Disease

Pulmonary Fibrosis
Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Effects of IPF on Patients’ Lives

• “There’s nothing I can do for you.”
• “See you in a year.”

“We have nothing to offer patients with pulmonary fibrosis.”
“We have nothing to offer patients with pulmonary fibrosis.”

**FDA-approved Therapies for the Treatment of IPF**

**Pirfenidone**
- Approved October 15, 2014
- Indicated for the treatment of IPF
- Mechanism of action: Modulator of cytokines and growth factors, including TGF-β1, TNF-α, bFGF, IFN-γ, IL-1β, and IL-18
- Dosage and administration
  - 801 mg (three 267-mg capsules) three times daily with food
  - Doses should be taken at the same time each day
  - Initiate with titration
  - Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions
- Prior to treatment, conduct liver function tests

**Nintedanib**
- Approved October 15, 2014
- Indicated for the treatment of IPF
- Mechanism of action: Inhibits a number of key receptors, including PDGF, VEGF, and FGF
- Dosage and administration
  - 150 mg twice daily approximately 12 hours apart, taken with food
  - Consider temporary dose reduction to 100 mg, temporary interruption, or discontinuation for management of adverse reactions
- Prior to treatment, conduct liver function tests

**Pirfenidone Reduces Loss of FVC**

- ANCOVA = analysis of covariance; FVC = forced vital capacity
Pirfenidone Increased Progression-free Survival


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>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14.7</td>
<td>17.7</td>
<td>-3.0</td>
</tr>
<tr>
<td>Cough</td>
<td>25.2</td>
<td>29.6</td>
<td>-4.4</td>
</tr>
<tr>
<td>IPF</td>
<td>9.4</td>
<td>18.1</td>
<td>-8.7</td>
</tr>
</tbody>
</table>


Nintedanib Reduces Loss of FVC

INPULSIS-1

INPULSIS-2

### Common Nintedanib Adverse Events

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


Fibrogenic Pathways and Therapeutic Targets

Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis


This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1939 – October 23, 2014).

The official Clinical Practice Outline of the American Thoracic Society (ATS) was approved by the ATS, May 2015, the European Respiratory Society (ERS), April 2015, the Japanese Respiratory Society (JRS), April 2015, and the Latin-American Thoracic Association (ALAT), April 2015.


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**Official ATS/ERS/JRS/ALAT Clinical Practice Guideline:**
**Treatment of Idiopathic Pulmonary Fibrosis**

### Table 1: Interpretation of Strong and Conditional Recommendations for Stakeholders (Patients, Clinicians, and Health Care Policy Makers)

<table>
<thead>
<tr>
<th>Implications for:</th>
<th>Strong Recommendation</th>
<th>Conditional Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>The majority of individuals in this situation would want the recommended course of action, but only a small number would. Recognize that different choices will be appropriate for different patients, and that you may help each patient select a management decision consistent with their values and preferences. The recommendation can be adopted as policy in most situations.</td>
<td></td>
</tr>
<tr>
<td><strong>Clinicians</strong></td>
<td>The majority of individuals in this situation would want the recommended course of action, but many would not. Recognize that different choices will be appropriate for different patients, and that you may help each patient select a management decision consistent with their values and preferences. The recommendation can be adopted as policy in most situations.</td>
<td></td>
</tr>
<tr>
<td><strong>Policy makers</strong></td>
<td>The majority of individuals in this situation would want the recommended course of action, but many would not. Recognize that different choices will be appropriate for different patients, and that you may help each patient select a management decision consistent with their values and preferences. The recommendation can be adopted as policy in most situations.</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 6: Comparison of Recommendations in the 2015 and 2011 IPF Guidelines

<table>
<thead>
<tr>
<th>Agent</th>
<th>2015 Guideline</th>
<th>2011 Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>New and revised recommendations</td>
<td>Strong recommendation against use</td>
<td>Conditional recommendation against use</td>
</tr>
<tr>
<td>Combination prednisone + azathioprine + N-acetylcysteine</td>
<td>Strong recommendation against use</td>
<td>Conditional recommendation against use</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>Conditional recommendation for use</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Conditional recommendation for use</td>
<td>Not addressed</td>
</tr>
</tbody>
</table>

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**Comorbidities in IPF**

- **GERD**
  - Very common
  - 80% to 94% of IPF patients have GERD
  - Often asymptomatic
  - 53% to 75% without symptoms
  - Restrictive lung disease may promote reflux
  - Likely contributes to symptoms and pathogenesis

GERD = gastroesophageal reflux disease.


**Comorbidities in IPF**

"Gastroesophageal Reflux Therapy Is Associated with Longer Survival in Patients with IPF"

- **Conclusions**
  - Individuals with IPF and reflux that were treated for GERD with a proton pump inhibitor appeared to have a larger survival advantage from reflux


**Comorbidities in IPF**

- **Obstructive Sleep Apnea**
  - Exceedingly common
  - 88% of 50 patients had OSA (68% had AH1 > 15)
  - Sleepiness scales perform poorly
  - Poor sleep quality = greater fatigue and poor QOL
  - Untreated OSA may worsen reflux and cause PH

AHI = Apnea Hypopnea Index; PH = pulmonary hypertension; OSA = obstructive sleep apnea; QOL = quality of life.


Comorbidities in IPF

- Pulmonary Hypertension
  - Occurs in 20% to 40%
  - Increased mortality
  - Echo can be misleading

Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>2015 Guideline</th>
<th>2011 Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacid therapy</td>
<td>Conditional recommendation for use</td>
<td>Conditional recommendation for use</td>
</tr>
<tr>
<td>N-acetylcysteine monotherapy</td>
<td>Conditional recommendation against use</td>
<td>Conditional recommendation against use</td>
</tr>
<tr>
<td>Antipulmonary hypertension therapy for IPF-associated pulmonary hypertension</td>
<td>Reassessment of the previous recommendation was deferred</td>
<td>Conditional recommendation against use</td>
</tr>
<tr>
<td>Lung transplantation: single vs. bilateral lung transplantation</td>
<td>Formulation of a recommendation for single versus bilateral lung transplantation</td>
<td>Not addressed</td>
</tr>
</tbody>
</table>