Update on Idiopathic Pulmonary Fibrosis

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Disclosures

♦ Dr. Swigris is a consultant for:
  ♦ Boehringer Ingelheim, Inc.
  ♦ Genentech/Roche/InterMune
Objectives

♦ Define IPF

♦ Clinical Presentation

♦ Clinical evaluation
  ♦ How to arrive at a diagnosis of IPF

♦ Theory around pathogenesis
ILD

- Inflammation and/or scar
- In the INTERSTITIUM
To an ILD doc, the interstitium is located...

- Along BV bundles
- In the subpleural region
- In interlobular septae
- Within alveolar walls (largest area)
Within alveolar walls
Etiology-based classification scheme

ILD

Exposure-related
- mold, bacteria, birds
- medications
- XRT
- dusts
- cigarette smoke

Genetic
- FPF

Autoimmune-related
- RA
- Systemic sclerosis
- PM/DM
- Sjögren’s syndrome
- MCTD
- MCTD
- IBD

Idiopathic
- Sarcoidosis
- LAM
- IIP
Idiopathic interstitial pneumonias (IIP)

**Major IIP**
- Idiopathic pulmonary fibrosis (IPF)
- Idiopathic nonspecific interstitial pneumonia (NSIP)
- Respiratory bronchiolitis-ILD (RB-ILD)
- Desquamative interstitial pneumonia (DIP)
- Cryptogenic organizing pneumonia (COP)
- Acute interstitial pneumonia (AIP)

**Rare IIP**
- Idiopathic lymphoid interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (IPPFE)

**Unclassifiable IIP**
Histology-based classification scheme
Etiology-based classification scheme

ILD

Exposure-related
mold, bacteria, birds
medications
XRT
dusts
cigarette smoke

Genetic
FPF

Idiopathic
Sarcoidosis
LAM
IIP

Autoimmune-related
RA
Systemic sclerosis
PM/DM
Sjögren’s syndrome
MCTD

SCAR

NFLAMMATION
ILD → IIP → IPF

- IPF: specific type of ILD within the IIP
- IPF: Diagnosis of exclusion
  - Rule out...
    - Exposure (environment, Rx, occupational)
    - Connective tissue disease
- IPF: specific type of pulmonary fibrosis
  - UIP-pattern on HRCT or SLBx
What to do when you have a patient in front of you and you are considering the possibility of IPF as the clinical summary diagnosis
Making the diagnosis of IPF

You have to be a detective

- History
- Exam
- Pulmonary physiology
- Radiography
- +/- surgical lung biopsy
History
History

- Typically... IPF presents with:
  - Dyspnea—subacute, insidious onset
  - “I thought it was just that I was a year older, 5# heavier, and out of shape”
  - +/- dry cough
  - Fatigue/low stamina
  - Not wheeze, pain, swollen joints, rash
What is the focus of our history-taking?

Identify features that suggest NOT idiopathic
History

Exposures

- Bioaerosols
  - M/M/B
  - Hot tubs (indoor/enclosed)
  - Basement shower
  - Swimming pools
  - Free-standing humidifiers
  - Water damage to home
  - Cooling systems (swamp cooler)
History

♦ Exposures
  ♦ Birds (proteins) / feathers
    ♦ Bloom on feathers
    ♦ Mucin in excrement
    ♦ Feather pillow/down comforter
  ♦ Fumes, dusts, gases
    ♦ Asbestos
    ♦ Beryllium
History: connective tissue diseases

Eyes, skin, joints, muscles, esophagus
Physical Exam
Physical examination
Physical examination

- Hands
- Chest
  - Crackles
    - MAKE SURE YOU LISTEN AT THE BASES
- Joints
- Skin
Laboratory
Laboratory assessment

- Serologies
  - ANA—the pattern matters (nucleolar)
  - RF/anti-CCP
  - Scl-70
  - SSA/SSB
  - anti-Jo-1/myositis panel

- What to do with positive???
Pulmonary Physiology and Gas Exchange
Pulmonary physiology

- Pulmonary function testing
- Measures of resting and exercise-related gas exchange
Patients with ILD have Restrictive Physiology

- Low static lung volumes
- Low forced volumes
  - Low FVC
  - Low FEV1
- Normal FEV1/FVC
- Supranormal velocities
Impaired Gas Exchange
Patients with IPF usually desaturate with exertion

- ABG
- Exercise oximetry
  - Resting SpO2 might be normal
- 6-minute walk test
Radiology

- “ILD protocol” HRCT
  - No IV contrast
  - Supine and prone
  - Inspiratory and expiratory images
  - Reconstruction algorithm—1-1.5mm thick
UIP-pattern HRCT

- Basilar (lower zone)
- Peripheral
- Subpleural
- Patchy
- Reticular opacities
- Traxn b’ectasis
- Honeycombing

- Minimal ground glass
- No nodules, consolidation, air-trapping
UIP-pattern HRCT Scan
Lung Biopsy
Lung biopsy

- Transbronchial biopsy
  - Sarcoidosis
  - Lymphangitic carcinomatosis
  - Subacute HP

- Surgical
  - Thorascopic, multiple lobes
  - When “classic” HRCT pattern absent
Pathologic correlate of IPF is a pattern called usual interstitial pneumonia (UIP)
Usual Interstitial Pneumonia (UIP)

- UIP is a non-specific histological pattern
- Can occur in these settings:
  - Idiopathic (IPF or idiopathic pulmonary fibrosis)
  - CTD (particularly RA)
  - Chronic hypersensitivity pneumonia
  - Exposures
    - Asbestos
    - Drug-induced

AJRCCM 2011
Putting it all Together

- History
- Exam
- Labs
  - ANA, RF, anti-CCP
- Physiology
  - Full PFTs
- Gas exchange
  - 6MWT
- Radiology
  - HRCT
- Pathology

Integrate to get “summary diagnosis”
Idiopathic disease
+ UIP-pattern
_____________________
IPF
Natural History of IPF
Acute Exacerbations Punctuate Slow Decline


(5-10% of patients per year)
What about prognosis?

Strand et al. Chest 2014
IPF: Cause of Death

- Pulmonary Fibrosis, 60.0%
- Ischemic Heart Disease, 8.5%
- Lung Cancer, 2.9%
- Pneumonia, 2.4%
- Congestive Heart Failure, 1.1%
- Cerebrovascular Disease, 1.3%
- Other, 23.4%

Olson et al. *Am J Respir Crit Care Med* 2007
What’s the Diagnosis?
2014

- 2 drugs approved by FDA for IPF
NAC Does Not Reduce FVC Decline

Pirfenidone


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

Week

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

P<0.001
P<0.001
P<0.001

Primary Endpoint

48% Relative Reduction
# Pirfenidone: adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pirfenidone (%) (N = 278)</th>
<th>Placebo (%) (N = 277)</th>
<th>Δ (%)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>36</td>
<td>13.4</td>
<td>22.6</td>
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<tr>
<td>Rash</td>
<td>28.1</td>
<td>8.7</td>
<td>19.4</td>
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<tr>
<td>Dyspepsia</td>
<td>17.6</td>
<td>6.1</td>
<td>11.5</td>
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<tr>
<td>Anorexia</td>
<td>15.8</td>
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<td>GERD</td>
<td>11.9</td>
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<tr>
<td>Weight Loss</td>
<td>12.6</td>
<td>7.9</td>
<td>4.7</td>
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<tr>
<td>Insomnia</td>
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<tr>
<td>Dizziness</td>
<td>17.6</td>
<td>13</td>
<td>4.6</td>
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<tr>
<td>Vomiting</td>
<td>12.9</td>
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<tr>
<td>Dyspnea</td>
<td>14.7</td>
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<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>
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Nintedanib

**INPULSIS-1**

- Nintedanib, 150 mg Twice Daily (N=309)
- Placebo (N=204)
- Adjusted Annual Rate of Change in FVC (ml/yr)
- Difference, 125.3 (95% CI, 77.7–172.8)
- P<0.001
- 52% Relative Reduction

**INPULSIS-2**

- Nintedanib, 150 mg Twice Daily (N=329)
- Placebo (N=219)
- Adjusted Annual Rate of Change in FVC (ml/yr)
- Difference, 93.7 (95% CI, 44.8–142.7)
- P<0.001
- 45% Relative Reduction

### Nintedanib: Adverse Events

<table>
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<tr>
<th>Event</th>
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<th>INPULSIS-2</th>
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<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>
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<td>Diarrhea (%)</td>
<td>62</td>
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<tr>
<td>Nausea (%)</td>
<td>23</td>
<td>6</td>
<td>26</td>
<td>7</td>
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</table>

Main Points

- All ILD is not fibrosing
- All fibrosis is not IPF
- All UIP-pattern lung injury is not IPF
- IPF is a diagnosis of exclusion
- You have to be a detective to diagnose IPF
- Integrate history, exam, objective data
- Requires multidisciplinary approach/communication