Challenges in the Diagnosis of Interstitial Lung Disease

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Overview

• New Classification of IIP
  – Prior classification
  – Modifications for new classification
• Diagnosis of UIP/NSIP
  – Clinical, radiologic, pathologic findings
  – Significance of diagnoses
• Differentiation of mimics
  – Clinical and radiologic clues
  – Multidisciplinary discussion
Classification of Idiopathic Interstitial Pneumonias

• 1969: Liebow
• Muller/Colby, Katzenstein
• 2001: ATS/ERS
  – Patterns
  – OP
• Papers modifying
  – Tentative idiopathic NSIP
  – Diagnosis of UIP
• Current ATS

William D. Travis, Ulrich Costabel, David M. Hansell, Talmadge E. King, Jr., David A. Lynch, Andrew G. Nicholson, Christopher J. Ryerson, Jay H. Ryu, Moisés Selman, Athol U. Wells, Jurgen Behr, Demosthenes Bouros, Kevin K. Brown, Thomas V. Colby, Harold R. Collard, Carlos Robalo Cordeiro, Vincent Cottin, Bruno Crestani, Marjolein Drent, Rosalind F. Duddon, Jim Egan, Kevin Flaherty, Cory Hogaboam, Yoshikazu Inoue, Takeshi Johkoh, Dong Soon Kim, Masanori Kitaichi, James Loyd, Fernando J. Martinez, Jeffrey Myers, Shandra Protzko, Ganesh Raghu, Luca Richeldi, Nicola Sverzellati, Jeffrey Swigris, and Dominique Valeyre; on behalf of the ATS/ERS Committee on Idiopathic Interstitial Pneumonias

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Current Classification

• Some diseases demoted
  – LIP

• Introduction of “rare” categories
  – Rare IIP’s: LIP, PPFE
  – Rare patterns: AFOP, bronchiolocentric

• NSIP officially an IIP
  – Previously given temporary status

• Categorize some entities
  – Idiopathic, mmm not so much
Pattern that has been demoted

- Lymphoid interstitial pneumonia
  - Histology shows broad expansion of the interstitium by chronic inflammation
  - Often a lymphoma
  - When not a lymphoma – CTD vs CVID
  - Now a “rare IIP”
Added Entities

• Rare IIP
  – Idiopathic pleuroparenchymal fibroelastosis
  – LIP (as mentioned in demoted)

• Rare patterns
  – Acute fibrinous organizing pneumonia
  – Bronchiolocentric interstitial fibrosis
Pleuroparenchymal Fibroelastosis

- Pleural and subpleural fibrosis
- Upper lobes show consolidation with traction bronchiectasis
- Described in Japan by Amitani
- Progression in majority, death in 40%
- Unknown cause
- Don’t mistake an apical fibrous cap for PPFE!
Acute Fibrinous Organizing Pneumonia

- Pattern of acute lung injury
- Likely lies along spectrum from DAD to OP
- Polypoid plugs of fibrin with early organization

- Poor prognosis in original series
  - Most referred to AFIP – referral bias
Bronchiolocentric Fibrosis

• Histologic changes with fibrosis centered on small airways
• “Bronchiolization” of alveolar ducts
• Many cases may have either HP or CTD
New Categorization

• Chronic fibrosing
  – Usual interstitial pneumonia
  – Non-specific interstitial pneumonia

• Smoking-related
  – Desquamative interstitial pneumonia
  – Respiratory bronchiolitis

• Acute/Subacute
  – Diffuse alveolar damage
  – Organizing pneumonia
<table>
<thead>
<tr>
<th>Major idiopathic interstitial pneumonias</th>
<th>Rare idiopathic interstitial pneumonias</th>
<th>Unclassifiable idiopathic interstitial pneumonias*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>Idiopathic lymphoid interstitial pneumonia</td>
<td>Interstitial fibrosis, difficult to classify</td>
</tr>
<tr>
<td>Idiopathic nonspecific interstitial pneumonia</td>
<td>Idiopathic pleuroparenchymal fibroelastosis</td>
<td></td>
</tr>
<tr>
<td>Respiratory bronchiolitis–interstitial lung disease</td>
<td></td>
<td></td>
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<tr>
<td>Desquamative interstitial pneumonia</td>
<td></td>
<td></td>
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<tr>
<td>Cryptogenic organizing pneumonia</td>
<td></td>
<td></td>
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<tr>
<td>Acute interstitial pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LIP</td>
<td></td>
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<tr>
<td></td>
<td>Elastotic fibrosis</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis of Usual Interstitial Pneumonia

- Hey, let’s be like radiologists!

**TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN**

<table>
<thead>
<tr>
<th>UIP Pattern (All Four Criteria)</th>
<th>Probable UIP Pattern</th>
<th>Possible UIP Pattern (All Three Criteria)</th>
<th>Not UIP Pattern (Any of the Six Criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution</td>
<td>Evidence of mixed honeycombing</td>
<td>Diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation</td>
<td>Hyaline membranes*</td>
</tr>
<tr>
<td>Presence of patchy involvement of lung parenchyma by fibrosis</td>
<td>Absence of either patchy involvement or fibroblastic foci in other lobules</td>
<td>Absence of other criteria for UIP (see UIP PATTERN column)</td>
<td>Organizing pneumonia*†</td>
</tr>
<tr>
<td>Presence of fibroblast foci</td>
<td>Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) OR</td>
<td>Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>Granulomas†</td>
</tr>
<tr>
<td>Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>Honeycomb changes only‡</td>
<td></td>
<td>Marked interstitial inflammatory cell infiltrate away from honeycombing</td>
</tr>
</tbody>
</table>

Fibrosis - with “temporal heterogeneity”

- Pathologic Findings - Temporal Heterogeneity
  - Honeycomb fibrosis
  - Old collagenous fibrosis
  - Recent (fibroblastic) fibrosis
  - Normal lung
Words to the clinician

• I don’t make a diagnosis of:
  – Definite, Probable, Possible, Not…UIP

• I do put it in the comment:
  – Reasons for – describing histology
  – Reasons against – describing the features against
Significance of a UIP Diagnosis

• Don’t treat with the usual agents!
  – Prednisone and azathioprine shown to be bad
  – PANTHER study
    • Increased deaths (8 vs. 1)
    • Increased hospitalization (23 vs. 7)
  – NAC vs placebo no difference

• Novel antifibrotics and TKI’s
  – ASCEND trial
  – INPULSIS trial
ASCEND Trial (Pirfenidone)

A Decreased FVC or Death

B Change in FVC

C Decreased Walk Distance or Death

D Progression-free Survival

INPULSIS 1 and 2

Diagnosis of UIP

• Be aware of clinical and radiologic findings
  – Idiopathic pulmonary fibrosis usually age 50+
    • Some exceptions
    • If younger, consider UIP pattern in CTD, HP, familial fibrosis, drug reaction
  – UIP shows basilar and subpleural distribution
    • If prominent upper lobe disease, consider PPFE, HP
• Look for classical histologic findings with spectrum from scarred to normal (HORN)
Diagnosis of Nonspecific Interstitial Pneumonia

• Clinical findings may be as nonspecific as its name:
  – Dyspnea, cough

• May have some findings to suggest etiology
  – Exposures, drugs, serologic studies, systemic symptoms

• Some radiologic clues
  – Subpleural sparing
  – Traction bronchiectasis without honeycombing
Diagnosis of NSIP

• Pathologic findings are:
  – Diffuse alveolar septal thickening by inflammation and/or fibrosis
  – “Variable but diffuse”
    • Similar fibrosis in different zones of the pulmonary lobule
Differential Diagnosis

• Usual interstitial pneumonia pattern
  – Idiopathic pulmonary fibrosis
  – Chronic hypersensitivity pneumonia, connective tissue disease, other rarities (asbestosis, drug reaction, PPFE)

• Nonspecific interstitial pneumonia
  – “Other” far exceeds “idiopathic”
  – CTD, HP, drug most common
  – Rarely see other mimics of NSIP – amyloid, PVOD
If my pathologist tells me the biopsy shows NSIP, then my job has only just begun.
Case 1

• 50-year-old male with chief complaint of worsening shortness of breath over 1-2 years
• Travels extensively with entertainment commitments
Case 1 - Diagnosis

• Cellular interstitial pneumonia with foreign-body giant cell reaction
  – Aspiration
  – Drug injection
  – Toxic inhalation

• Occupational hazard of rock and roll?
Case 1 - Diagnosis

• Hypersensitivity pneumonia
Hypersensitivity Pneumonia

• Reaction of the lung to inhaled antigen
• See characteristic CT findings
  – Centrilobular ground glass nodules
  – The “head cheese” sign
    • GGO, normal, air-trapping = triple density
HP - Histology
The Four-Part Triad

• Diffuse lymphoplasmacytic interstitial infiltrate
  – With bronchiolocentric accentuation
• Poorly-formed granulomas
• Foci of organizing pneumonia
Case 1 - Diagnosis

• Traveled with same pillow for 15 years
  – Down pillow
  – Typical exposure

• Other cases we have observed:
  – Feathers: Pets, Farm animal, Duvet, Pillow, Jacket.
  – Molds: Work freezer, Man-Cave, Sleep number mattress
  – Mycobacteria: Indoor spa, shower
  – ? Central valley: Almond dust?
Case 2

- 24-year-old woman with interstitial lung disease.
- Dry cough, Raynaud’s phenomenon, possible feather exposure, arthralgias.
- CT shows patchy ground glass opacities with a peripheral predominance.
Case 2 - Diagnosis

- Cellular and fibrosing interstitial pneumonia (non-specific interstitial pneumonia pattern).
- Found to have a CK of 1108 (nl = 39-189)
- Autoimmune myositis
- Improved with mycophenolate

- In our practice, patients with clinical symptoms get a large panel of serologic studies and likely won’t be biopsied.
Clues for CTD

• Connective tissue diseases, due to their immune activation, often affect several compartments of the lung (i.e. alveolar septa, small airways, vessels, pleura).

• Prominent lymphoid aggregates

• Pleuritis

• UIP pattern with lack of central normal lung
  – UIP/NSIP overlap
Case 3

• 73-year-old woman with a six month history of shortness of breath.
Case 3 - Diagnosis

• Cellular nonspecific interstitial pneumonia with prominent lymphoid aggregates and organizing pneumonia
  – I would probably be thinking connective tissue disease, but it looked like a prior case of a man with BPH.
Case 3 - Continued

• Missing drug history.
  – Medicine note: no drugs of concern.
  – Surgeon’s pre-op note: Nitrofurantoin.
    • “It wasn’t me.”

• On nitrofurantoin for 1-1/2 years.
  – Stealth drug (post-coital UTI’s)

• [www.pneumotox.com](http://www.pneumotox.com)
Case 4 – MDD Illustrated

- 62-year-old man with severe pulmonary fibrosis
- Prior biopsy with UIP pattern
- Now undergoing bilateral lung transplant
Subpleural honeycombing

Fibroblast foci

Normal-appearing lung
Pathologic Pattern

• Usual interstitial fibrosis
  – Marked fibrosis with honeycombing
  – Patchy involvement of lung
  – Fibroblast foci present
  – ?Features suggesting alternate diagnosis?
Bronchiolocentric Fibrosis

Poorly-formed granuloma
Pathologic Diagnosis

• Interstitial fibrosis, UIP pattern, with bronchiolocentric fibrosis and chronic inflammation, and poorly-formed granulomas.

• Most consistent with chronic hypersensitivity pneumonia.
Final Diagnosis

• Familial Interstitial Fibrosis
  – Telomerase mutation (TERT gene)
• With superimposed hypersensitivity pneumonia
Conclusions

• There is a new classification of IIP’s
  – Not much has changed – an “update”
  – Recognition that not all are idiopathic
  – Stressing importance of multidisciplinary discussion
References

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international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013
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