Challenges in the Diagnosis of Interstitial Lung Disease

Kirk D. Jones, MD
UCSF Dept. of Pathology
kirk.jones@ucsf.edu

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

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
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

• PANTHER Study
  – Efficacy of Prednisone, Azathioprine, N-acetylcysteine (NAC) vs. NAC alone vs. placebo
• Patients in the prednisone, aza, NAC arm
  – Increased deaths (8 vs. 1)
  – Increased hospitalization (23 vs. 7)
• NAC vs placebo still accumulating data
  – mucolytic agent used often used in CF patients

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.

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
Pathologic Pattern

- Usual interstitial fibrosis
  - Marked fibrosis with honeycombing
  - Patchy involvement of lung
  - Fibroblast foci present
  - ?Features suggesting alternate diagnosis?

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

• Katzstein AL, Mukhopadhyay S, Myers JL. Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. Hum Pathol. 2008 Sep; 39(9): 1275-94. PMID: 18706349.