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

American Thoracic Society Documents


This official statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) was approved by the ATS Board of Directors, June 2013, and by the ERS Steering Committee, March 2013

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”
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!

Added Entities
- Rare IIP
  - Idiopathic pleuroparenchymal fibroelastosis
  - LIP (as mentioned in demoted)
- Rare patterns
  - Acute fibrinous organizing pneumonia
  - Bronchiolocentric interstitial fibrosis
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

Diagnosis of Usual Interstitial Pneumonia

- Hey, let’s be like radiologists!

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)

- Increased PTC or death
  - Pirfenidone (N=217)
  - Placebo (N=217)
- Changes in PTC
- Increased WBC or death
  - Pirfenidone (N=217)
  - Placebo (N=217)
- Prostate-specific 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

Courtesy of Rick Webb, MD
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
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