Fibrotic Interstitial Lung Disease:
A Pathologist’s Perspective

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No disclosures

Objectives
1. Recommend appropriate biopsy for suspected condition diagnosis
2. Differential diagnosis of UIP – pathologist perspective
3. Understand the difference between IPF/NSIP and UIP/NSIP-like pattern
4. The pathologist report and the importance of pathologist’s case discussion/comments

Types of Lung Biopsy and Condition Dx

CT-Guided Needle Core Biopsy:
- Peripheral inflammatory process/infection
- Malignancy
- Pleural process evaluation

Transbronchial Biopsy:
- Airway infection/periairway infection
- Transplant rejection
- Bronchiolitis obliterans
- Sarcoïdosis, LCH

Transbronchial Cryobiopsy - everything TBBx plus:
- Cryptogenic organizing pneumonia (former BOOP)
- Organizing pneumonia, Acute lung injury
- Eosinophilic pneumonitis

VATS/Open Biopsy - everything CT-NB/TBBx/TBCx plus:
- Fibrotic and nonfibrotic interstitial lung disease (UIP, NSIP, RB-ILD etc.)
- Pneumonia, Acute exacerbation
- Other primary lung conditions (LAM, primary pulmonary hypertension, Hermansky-Pudlak syndrome etc.)

Interstitial Lung Disease (ILD)

- Usual Interstitial Pneumonia (idiopathic pulmonary fibrosis)
- Nonspecific Interstitial Pneumonia
- Chronic Hypersensitivity Pneumonitis
- Superimposed lung injury: COP, Aspiration, Infection, Acute lung injury, Acute exacerbation of underlying chronic fibrotic condition

Usual Interstitial Pneumonitis (UIP)

- Progressive fibrosing disorder of unknown cause
- Adults >50 years old
- Respiratory and heart failure (cor pulmonale) ~ 3 years

UIP - Temporal and Spatial Heterogeneity
UIP – Fibroblastic Foci

1. Temporal and spatial heterogeneity (patchy areas in various stages of fibrosis; characteristic subpleural accentuation of fibrosis with central more preserved areas; fibrosis more prominent in the lower than upper lobes)

2. Fibroblastic foci (predominant interstitial subpleural in early phase, than periarway in advanced stage of disease)

3. Honeycomb change (nonspecific)

IPF – Definite, Probable or Possible?

2011 ATS/ERS/JRS/ALAT guidelines

HRCT criteria for pattern of UIP in the appropriate clinical setting = NO biopsy performed

HRCT pattern of “possible UIP” or “inconsistent with UIP” = consider lung bx

IPF is less often biopsied with current guidelines!

Histopathologic Criteria for UIP

<table>
<thead>
<tr>
<th>UIP Pattern</th>
<th>Probable UIP</th>
<th>Possible UIP</th>
<th>Not UIP</th>
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</thead>
<tbody>
<tr>
<td>1. Marked fibrosis/architectural distortion, 2. honeycombing in a predominantly subpleural/paraseptal distribution</td>
<td>1. Marked fibrosis/architectural distortion, 2. honeycombing</td>
<td>1. Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation</td>
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<tr>
<td>2. Presence of patchy involvement of lung parenchyma by fibrosis</td>
<td>2. Absence of either patchy involvement or fibroblast foci, but not both</td>
<td>2. Absence of other criteria for UIP (see UIP pattern column)</td>
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<td>3. Presence of fibroblast foci</td>
<td>3. Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
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<td>4. Absence of features against a diagnosis of UIP (see fourth column)</td>
<td>4. Honeycomb changes only</td>
<td>4. Marked interstitial inflammatory cell infiltrate distant from honeycombing</td>
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<tr>
<td>OR</td>
<td>4. Honeycomb changes only</td>
<td>5. Predominant airway centered changes</td>
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<td>6. Other features suggestive of an alternate diagnosis</td>
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Nonspecific Interstitial Pneumonia (NSIP)

Pathology:
- Idiopathic interstitial lung injury demonstrating temporal uniformity and lacking diagnostic features of other diseases

Two types:
- **Cellular type**: changes are predominantly cellular, with scant fibrosis; better prognosis
- **Fibrotic type**: changes are predominantly fibrotic, with less cellularity
Nonspecific Interstitial Pneumonia (NSIP) - Cellular

Nonspecific Interstitial Pneumonia (NSIP) - Fibrotic

NSIP Is A Diagnosis of Exclusion!

The following features should not be seen:
- Granulomas or giant cells
- Bronchiolocentric distribution
- Acute lung injury pattern / hyaline membranes
- More than rare eosinophils
- Evidence of infection

The following must be ruled out in every case
- Connective tissue disease
- Other ILD with NSIP-like areas (UIP!)
- Drug reaction
- Chronic hypersensitivity pneumonitis
- Giant cells and/or granulomas
- Predominantly bronchiolocentric distribution
- Immunodeficiency related changes
- Infection
- Slowly resolving acute interstitial pneumonia

What does it signify:
1. Primarily a diagnosis of exclusion in pathology
2. Is it true NSIP? What is the pattern – cellular, fibrotic, mixed?
3. Is there an underlying systemic disease? (exclude other possible etiologies – autoimmune disease, CHP)

NSIP-like pattern may be present in UIP (patchy)
Chronic Hypersensitivity Pneumonitis

- Immunologically mediated disorder affecting airways and interstitium
- Prolonged exposure to inhaled organic antigens

Farmer's lung
Thermophilic actinomycetes in hay

Pigeon breeder's
Air-condition lung
Thermophilic bacteria

What is Pathologist's Message to Pulmonologist?

UIP – may have all of the following:

- **Fibrosis** - Therapy: Pirfenidone, Nintedanib, Transplant
- **Inflammation** (chronic) - Therapy: Corticosteroids
- **Organizing pneumonia**: Corticosteroids?
- **Infection** - Therapy: Antibiotics/Antifungals

Therapy may accelerate progression of disease!

Pathology Report

Pathology Report: Pertinent Positives/Negatives

- **Fibrosis** - pattern (UIP, NSIP, CHP etc.)?
- **Granulomatous inflammation** – necrotizing or not?
- **Infection** - viral cytopathic effect, what type of inflammatory infiltrate (neutrophils, lymphoplasmacytic, eosinophil-rich); consider role of ongoing steroid therapy
- **Vasculitis** associated process? Is vasculitis primary or secondary? Is capillaritis also present?
- Is there toxic **drug effect** present?

Granulomatous Inflammation

- **Infection**
- **Hypersensitivity pneumonitis**
- **Drug reaction**
- **Aspiration**
- **Recreational drug use – intravascular talcosis**
- **CTD/Autoimmune – Sjogren’s, RA, IBD**
- **Sarcoidosis**
Organizing Pneumonia

- Infection
- Acute lung injury component
- Connective tissue disease with lung involvement
- Inflammatory bowel disease with lung involvement
- Drug toxicity
- Hypersensitivity
- Eosinophilic pneumonia
- Vasculitis? (granulomatosis with polyangiitis, Churg-Strauss)

NSIP-like Pattern Associated With...

- Fibrosis: Chronic process, diffuse interstitial fibrosis
- Neutrophils: Infection
- Airspace fibrin: Acute lung injury, infection?, drug toxicity, CTD
- Granulomas: Infection, hypersensitivity, sarcoidosis, autoimmune disease; location is very important:
  1. Bronchiolocentric: Hypersensitivity, infection
  2. Vasculitic/lymphangitic: Sarcoidosis, infection, primary vasculitis syndrome
  3. Pleural involvement: Connective tissue disease
- Eosinophils: Drug toxicity, eosinophilic pneumonia, Churg-Strauss, hypersensitivity
- Granulomas with giant cells/foreign material: Aspiration, hypersensitivity/pneumoconiosis

UIP-like Histologic Pattern – Differential Diagnosis

- Idiopathic pulmonary fibrosis
- Nonspecific interstitial pneumonitis
- Chronic hypersensitivity pneumonitis
- Pneumoconioses (asbestosis, silicosis, berilliosis, siderosis, hard metal exposure)
- Drug toxicity
- Radiation therapy for malignancy
- IgG4-related lung disease
- Connective tissue disease
- Other autoimmune processes (IBD)

UIP-like Histologic Pattern – Clinician’s View

- Is it indeed UIP (IPF)?
- Consider immunosuppression?
- Eliminate offensive drug, inhalant/exposure
- Reversibility
- Explain rapid progression/exacerbation
- Refer to rheumatologist, infection disease specialist
- Transplant work-up

Pathologist Report Should Comment About...

- Exacerbation: Acute lung injury, organizing pneumonia
- Infection: Acute? Granulomas present?
- Aspiration: location of granulomatous inflammation, presence of foreign body giant cell reaction, foreign material
- Pneumoconiosis: Specific deposits, foreign material in multinucleated giant cells
- Immunosuppression: Nature and extent of chronic inflammatory infiltrate
- Reversibility: Is fibrosis present? what is the extent? What is the amount of functional alveolated lung tissue?
- Drug toxicity: presence and number of eosinophils distribution
- CTD pattern: distribution of lymphoid infiltrate/aggregates, pleuritis, vasculitis, presence/number of plasma cells

I Get NSIP-like Pattern, But What Is UIP-like Pattern?

Honeycomb Change
Honeycomb Change: “All Roads Lead To Rome”

End-Stage Lung Disease: “All Roads Lead To Rome”

Common Entities That Lead To End-Stage Fibrosis
- Usual Interstitial Pneumonia
- Nonspecific Interstitial Pneumonia
- Connective Tissue Disease
- Hypersensitivity Pneumonitis
- Sarcoidosis

Correlate Pathologic Finding with Disease!

Questions?