APPROACH TO NON-NEOPLASTIC LUNG DISEASE IN TRANSBRONCHIAL AND SURGICAL BIOPSIES

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TOPICS TO BE COVERED

Bronchoscopic biopsy interpretation
  General approach
Surgical lung biopsies
  General approach
Acute lung injury
Granulomatous interstitial pneumonias
Idiopathic interstitial pneumonias
  ILD from Drugs, Connective tissue disease

BIRCHIAL/TRANSBRONCHIAL BIOPSY DIAGNOSTIC ACCURACY

Visible localized mass  >90%
Acute diffuse disease  35-75%*
Chronic interstitial disease in the immunocompetent  30-35%*

*Remember these numbers!

BASIC QUESTION FOR ALL LUNG BIOPSIES

Can I answer the clinical question??
That presupposes that we know the clinical question…and…
That we know something about clinical and pathologic correlation (including the radiologic findings)

First: Transbronchial biopsy (TBBx)
DOES THE TBBx ANSWER THE CLINICAL QUESTIONS?
It may allow a specific diagnosis...or...
It may be abnormal but nondiagnostic...or...
It may identify unrelated findings...or...
It may be normal/negative/inadequate

APPROACH TO BRONCHOSCOPIC BIOPSIES
What do I see?
1. A specific diagnosis is obvious
2. List of abnormal findings present
3. Nothing/normal tissue

A tabulation of findings is not a specific diagnosis
These both show: type 2 cell proliferation, inflammation, septal widening, and increased macrophages

APPROACH TO BRONCHOSCOPIC BIOPSIES
Necessity of a dynamic interactive diagnostic process
You have a list of abnormalities...but...
You have decided you can't make a diagnosis....
What additional information is needed?
Deeper levels, special stains, clinical-radiologic information, laboratory values, etc.

Specific clinical diagnosis possible with clinical and radiologic correlation

Capillaritis!!
Diffuse infiltrates
MPO-ANCA + Hematuria
Clin-path diagnosis:
Microscopic polyangiitis
APPROACH TO BRONCHOSCOPIC BIOPSIES
3 basic conclusions:
1. There is a specific diagnosis that explains the clinical and radiologic findings
2. The clinical and radiologic findings explain the pathologic findings (i.e. a descriptive diagnosis) in the absence of a specific pathologic diagnosis
3. The biopsy findings are inadequate to explain the clinical and radiologic findings

Unique histology of LAM

HMB

TBBx showing only normal alveoli

APPROACH TO BRONCHOSCOPIC BIOPSIES
3 basic conclusions:
1. Diagnostic of . . .
2. Histologic changes c/w . . .
3. Nonspecific histologic abnormalities (e.g. focal inflammation, scarring, alveolar macrophages, et al.)
4. Normal/negative/inadequate

Can move from 3 → 2 with clinical-radiologic-pathologic correlation
Sometimes can move from 2 → 1 with special studies (e.g. IPOX, PCR)

TBBx has a limited role in chronic ILD in the immunocompetent host

Little usefulness in diseases recognized by pattern: UIP, NSIP, others

Useful for:
Diseases with peribronchovascular or lymphangitic distribution
Conditions with unique or (nearly) specific histology

Dx Rate: *35-75% in Acute ILD, 30-35% in Chronic ILD

Noninformative/nondiagnostic bronchoscopic biopsy in non-neoplastic lung disease are common* and no amount of clinical and radiologic information will allow a specific histopathologic diagnosis!
Transbronchial Biopsy in Sarcoidosis

Sarcoidosis follows lymphatic routes

TBBx in:
26F smoker
Asymptomatic
Diffuse infiltrates
PFT's: Mixed obstruct/restrict

Unique diagnostic histology: PLCH

S-100 +
CD1a +

TBBx in Diffuse Lung Disease
Acute and Chronic

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnostic Bx</th>
<th>Nonspec - 44%</th>
<th>Normal/Inad - 25%</th>
<th>c/w Clin Dx - 37%</th>
<th>Nonspec - 34%</th>
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<td>N=603</td>
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</tbody>
</table>

Ensminger 2006
N=603
38%
TBBx helpful - 76%
Not helpful - 24%

WHAT IS AN ADEQUATE TBBx?

One that can answer the clinical question!
Some have criteria of adequacy: e.g. >50 alveolar spaces, >4 pieces, et al.
These criteria are not always relevant
Adequacy has to be assessed in the individual case setting

LIMITATIONS OF TBBx

Size
Difficult to see patterns of injury
Distortion of tissue

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LIMITATIONS OF TBBx

Size
Difficult to see patterns of injury
Distortion of tissue
How do you get good at interpreting TBBx’s?

Know lung pathology as seen in SLBx’s, resections and at autopsy
Know something about clinical pulmonary disease*
Know something about HRCT of the lung*
Trust your brain!

*Or someone who does!

Surgical lung biopsy allows pattern recognition (and correlation with HRCT)

Diagnostic Usefulness:
~95% fit with clinical findings
~90% diagnostic in chronic diffuse disease
~35-75% Dx rate in acute diffuse disease

1. The larger the specimen the greater the likelihood of diagnosis
   Additive information from cytology/ BAL, culture
2. Addition of clinical and radiologic information increases the likelihood of diagnosis
3. An experienced (pulmonary) pathologist increases the likelihood of diagnosis

The clinician affects #1
The pathologist can address #’s 2 + 3
TOPICS TO BE COVERED

- Bronchoscopic biopsy interpretation
- Surgical lung biopsies
- Acute lung injury
- Granulomatous interstitial pneumonias
- Idiopathic interstitial pneumonias
  
  *Drugs, Connective tissue disease*

ACUTE LUNG INJURY PATTERNS

(Concept introduced by Katzenstein)

- Diffuse alveolar damage – acute and organizing
- Organizing pneumonia (BOOP pattern)

“Acute” here means injury days to weeks in age

Represent the most common findings in biopsy material

DAD

Uniform temporal appearance
Alveolar septal thickening
Airspace organization
Hyaline membranes

Organizing

Acute

DAD and OP represent.....

DIFFERENTIAL DIAGNOSIS OF DAD

- Infections
- Toxic inhalations
- Drug reactions
- Collagen Vascular Dis
- Radiation
- Diffuse alveolar hem

- Shock
- Acute allergic rxns
- Neurologic disease
- Miscellaneous
- Idiopathic (ie. AIP)

“Swine” Flu 2009

Rheumatoid arthritis
**Organizing pneumonia**

- Intraluminal organization
- Patchy distribution
- Preserved architecture
- Uniform age of lesions
- Mild cellular infiltrates

**DIFFERENTIAL DIAGNOSIS OF OP** (i.e., Lesions with a BOOP Pattern)

- Organizing infections (especially influenza)
- Allergic reactions: Eosinophilic pneumonia, extrinsic allergic alveolitis
- Collagen vascular disease
- Drug reactions
- Organizing diffuse alveolar damage
- Aspiration
- Distal to: Obstruction, bronchiectasis, COPD
- Association with/proximity to other lesions: Abscess, vasculitis (WG)
- Idiopathic
- Localized: Focal organizing pneumonia
- Widespread: COP

**ACUTE FIBRINOUS AND ORGANIZING PNEUMONIA (AFOP)**


A form of acute lung injury dominated by airspace fibrin and organization

Overlaps with DAD and OP patterns

A recognizable pattern of acute lung injury

Key feature is recognizing the ALI and considering the differential

**Acute lung injury** represents a starting point from which a differential diagnosis can be generated (based on clinical, radiologic, and histologic information)
Is TBBx useful in ALI?

Transbronchial biopsies

Not very specific- could be infectious or noninfectious

Let’s add some history….

OP pattern

45M with known Churg-Strauss disease on steroid therapy had pulmonary infiltrates and mediastinal adenopathy

Transbronchial biopsy taken at the time of mediastinoscopic biopsy

Diagnosis: Organizing pneumonia consistent with organizing eosinophilic pneumonia in Churg-Strauss syndrome

Caveat: Patient on steroids…therefore exclude infection

DIFFERENTIAL DIAGNOSIS OF OP
(i.e., Lesions with a BOOP Pattern)

Organizing infections (especially influenza)
Allergic reactions: Eosinophilic pneumonia, extrinsic allergic alveolitis
Collagen vascular disease
Drug reactions
Organizing diffuse alveolar damage
Aspiration
Distal to: Obstruction, bronchiectasis, COPD
Association with/proximity to other lesions
Abscess, vasculitis (WG)
Idiopathic
Localized: Focal organizing pneumonia
Widespread: COP

WHAT IS A GRANULOMATOUS INTERSTITIAL PNEUMONIA?

An interstitial pneumonia in which granulomas comprise (at least a portion of) the histologic findings
Commonly encountered: sarcoidosis, infections, hypersensitivity pneumonitis

GRANULOMATOUS INTERSTITIAL PNEUMONIAS

Commonly Encountered

Sarcoidosis
Granulomatous infections
Hypersensitivity pneumonitis
Aerosolized mycobacteria ("hot tub lung")

Infrequently Encountered
(Granulomas Inconsistent)
Berylliosis/other pneumoconioses
Drug reactions
Collagen vascular diseases (esp. Sj)
Intravenous talcosis
Bronchiectasis/bronchiolitis with secondary infection
Vasculitis
Eosinophilic pneumonia
Aspiration pneumonia
Immunoglobulin deficiency
Diffuse lymphoid hyperplasia
Giant cell interstitial pneumonia
Diffuse neoplasms (esp. lymphomas)
Inflammatory bowel disease
Incidental/unclassifiable
SARCOIDOSIS

Granulomas along lymphatic routes

The CT findings in some cases are virtually diagnostic

SARCOIDOSIS: Coalescing granulomas; vascular involvement

SARCOIDOSIS

Aspects for the Pathologist

Confirm the presence of granulomas
Appreciate the distinctive features of the granulomas in sarcoid (naked, confluent, lymphangitic)
Exclusion of infection: cultures and special stains
A clinicopathologic diagnosis

HYPERSENSITIVITY PNEUMONITIS
(Extrinsic Allergic Alveolitis)

A diffuse lung disease . . . “resulting from repeated inhalation of and sensitization to a wide variety of organic aerosols and low molecular weight chemical antigens”

(Murray and Nadel; Textbook of Respiratory Medicine, 3rd Edition; 2000)

Causes of Hypersensitivity Pneumonitis

Fungal antigens
Bacteria antigens
Amebae
Animal proteins
Insect proteins
Chemicals
Unknown

(From Schwarz+King 4th ed)
Hypersensitivity Pneumonitis

Primarily caused by exposure to organic antigens

Hypersensitivity Pneumonitis

"Air conditioner" lung

Centrilobular inflammatory infiltrate
Overshadows fibrosis
Overshadows granulomas
Scattered small non-necrotizing granulomas
Cellular bronchiolitis
Airspace organization, fibrosis (variable)

Granulomas in Hypersensitivity Pneumonitis

Small, single, loose, scattered, and without fibrosis

Chronic HP
HYPERSENSITIVITY PNEUMONITIS
Aspects for the Pathologist

Appreciate the many components of the histology: granulomas, airway-centered, inflammation, fibrosis
Qualitative features of the granulomas
Some cases lack the classic histology
Eg. Look like NSIP or even UIP

INFECTIOUS AGENTS CAUSING GRANULOMATOUS INTERSTITIAL PNEUMONIAS

1. Miliary infections: mycobacterial (eg. TB), fungal, and many others
2. Reactions to aerosolized mycobacteria (eg. “Hot tub lung”)

Miliary Tuberculosis

Miliary Coccidioidomycosis

Diffuse Lung Disease resembling HP from aerosolized mycobacteria*
Organisms aerosolized from:
- Metal working fluids, indoor swimming pools, hot tubs, water-damaged buildings, household water, unknown


Other implicated Mycobacteria:
- Mycobacterium avium
- Mycobacterium immunogenum
- Mycobacterium terrae

Identified by culture of the suspected source of the aerosol
**This is a hot tub!**

Lots of aerosolized Ag from *Mycobacterium avium* growing the water!

**Hot Tub Lung**

Histologically and conceptually these cases include some features of infection and some features of HP

Clinically considered a form of HP

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**HISTOLOGIC APPROACH TO GRANULOMATOUS INTERSTITIAL PNEUMONIAS**

- **Anatomic distribution of the granulomas:** Airway-centered, along lymphatics, angiocentric, randomly distributed
- **Quantitative features of the granulomas:** How many?, coalescing?
- **Qualitative features of the granulomas:** Well-formed, loose, giant cells, necrosis, birefringent material, perigranuloma fibrosis, perigranuloma infiltrate
- **Lung tissue away from the granulomas:** Minimal pathology, interstitial infiltrates, bronchiolitis, organizing pneumonia, fibrosis, eos, foreign material

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**ANATOMIC DISTRIBUTION OF THE GRANULOMAS**

**LUNG PATHOLOGY AWAY FROM THE GRANULOMAS**

- Sarcoid
- Hypersensitivity pneumonitis

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**TBBx in Granulomatous IP’s**

Apply the same principles as with SLBx’s

- Anatomic distribution
- Quantitative features
- Qualitative features
- Findings in the adjacent lung tissue

Of course some cases are not soluble!
SARCOIDOSIS: TBBx’s

With 4 or more TBBx’s 80% of cases have granulomas identified.

TBBx: most consistent with Hypersensitivity Pneumonitis

Idiopathic Interstitial Pneumonias

Classification
Histologic patterns
Diagnosis
Similar patterns associated with connective tissue diseases and drug reactions

2002 ATS/ERS CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS*

<table>
<thead>
<tr>
<th>Clinicopathologic Diagnosis</th>
<th>Pathologic Pattern</th>
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</thead>
<tbody>
<tr>
<td>Idiopathic pulmonary fibrosis (IPF)</td>
<td>UIP</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia (DIP)</td>
<td>DIP</td>
</tr>
<tr>
<td>Respiratory bronchiolitis interstitial lung disease (RBILD)</td>
<td>RB</td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia (COP)</td>
<td>OP (BOOP)</td>
</tr>
<tr>
<td>Acute interstitial pneumonia (AIP)</td>
<td>DAD</td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonia (NSIP)</td>
<td>NSIP</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonia (LIP)</td>
<td>LIP</td>
</tr>
</tbody>
</table>

UIP/IPF is the most important of these

*ATS/ERS International Consensus Panel; Am J Respir Crit Care Med 2002; 165:277

KEY FEATURES OF UIP

Dense fibrosis/remodeling
Patchy involvement
Fibroblast foci
Subpleura/paraseptal

KEY FEATURES OF UIP

Fibroblast foci
DIP vs RB-ILD

Cryptogenic Organizing Pneumonia (COP)

BO

OP

BO+OP= BOOP

Pattern of Acute interstitial Pneumonia: Diffuse Alveolar Damage

Hyaline membranes

Organizing DAD

NSIP: HISTOLOGIC FEATURES

Key features:
- Temporally homogeneous*
- Uniform involvement of tissue*
- Spectrum from cellular to fibrotic

* In contrast to UIP

Lymphocytic Interstitial Pneumonia

LIP: A diffuse bilateral process, polyclonal. Two overlapping patterns: dense diffuse infiltrates, diffuse lymphoid hyperplasia

DIAGNOSIS OF UIP

Surgical lung biopsy is necessary to identify patterns of inflammation and fibrosis

Is biopsy always necessary?

NO! HRCT is an acceptable surrogate in some situations
Usual Interstitial Pneumonia (UIP)

In ~50% of cases IPF can be diagnosed with HRCT

CAN OTHER IIP’s BE DIAGNOSED BY HRCT?

- OP/COP RBILD: Yes - in some cases with clinical-radiol correlation*
- DAD/AIP NSIP LIP: Generally not*

*Personal observations

UIP vs NSIP

For clinicians, radiologists, and pathologists UIP vs NSIP causes the most problems.

Pathologically.....

Inflammation and Fibrosis in UIP and NSIP

NSIP: Spatially uniform Temporally uniform

UIP: Spatially and temporally heterogeneous

DO NSIP AND IPF OVERLAP?

OF COURSE!

NSIP vs UIP: there are significant survival differences

Many other studies have confirmed these findings

DO NSIP AND IPF OVERLAP?

OF COURSE!

UIP

Clinically

Radiologically

Pathologically

NSIP
HOW DOES ONE DEAL WITH OVERLAP CASES?

Individualize each case
Clinical-radiologic-pathologic correlation

“The essential assumption... is that there is no gold standard for ... diffuse lung disease, merely the silver standards of clinical, radiologic, and histopathologic evaluation...”

(Wells AU. In Am J Respir Crit Care Med 2004;170:827-831)

HRCT TRUMPS HISTOLOGY
(Sampling error has occurred)

Diagnosis = UIP (IPF)

Histology=NSIP

Why isn’t this UIP?

Scarring is stellate and centrilobular

Healed Pulm Langerhans cell histiocytosis

Why isn’t this UIP?

Central scar with peribronchiolar metaplasia, granulomas

Chronic hypersensitivity pneumonitis

Why isn’t this UIP?

It is UIP (pattern)! Clinically Chr HP to birds

FEATURES TO ADDRESS IN FIBROSING INTERSTITIAL PNEUMONIAS

Extent of fibrosis/honeycomb change
Distribution of the fibrosis (esp. central vs peripheral)
Evidence of active fibrosis (e.g. fibroblast foci)
Associated findings (e.g. dust, granulomas, foreign material)
Pertinent history (e.g. CVD, radiation, birds?, chemotherapy)
Is TBBx useful in IIP’s?

The idiopathic interstitial pneumonias represent histologic patterns of inflammation and fibrosis.

Transbronchial biopsies are usually too small to allow recognition of patterns of injury.

Transbronchial biopsies do not allow confident diagnosis of UIP or NSIP (the major problem area)

TBBx is of limited value in the IIP’s

Inflammation and Fibrosis in UIP and NSIP

TBBx-sized foci may be identical in NSIP and UIP

DAD c/w AIP  TBBx’s  OP c/w COP

It could be incidental or part of RBILD or DIP

TBBx in the diagnosis of Idiopathic Interstitial Pneumonias (IIP’s)

UIP/IPF …… Not recommended
DIP .......... Insufficient data
RBILD …… Possible with clin-radiol correlation
COP .......... Possible with clin-radiol correlation
DAD/AIP .... Possible with clin-radiol correlation
NSIP .......... Not recommended
LIP .......... Insufficient data

INTERSTITIAL PNEUMONIAS IN OTHER CLINICAL SETTINGS

Patients with connective tissue disease
ILD is a common problem in patients with CTD that may lead to a biopsy
Drug reactions
A drug reaction is always in the differential in a patient with interstitial lung disease
Often there are clues that a CTD is present

Increased inflammation
Fibr. focus

Pulmonary Drug Reactions: many recognized patterns

<table>
<thead>
<tr>
<th>Pulmonary Drug Reaction</th>
<th>LIP</th>
<th>GIP</th>
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<tbody>
<tr>
<td>Edema</td>
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<tr>
<td>Hemorrhage</td>
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<td>Alveolar proteinosis</td>
<td>Lymphoid hyperplasia</td>
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<tr>
<td>Diffuse alveolar damage</td>
<td>Granulomatous IP</td>
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<tr>
<td>Organizing pneumonia</td>
<td>Eosinophilic IP</td>
<td></td>
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<tr>
<td>NSIP</td>
<td>Calcification</td>
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<tr>
<td>UIP</td>
<td>Emphysema</td>
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Pathologic and Radiologic Differences Between Idiopathic and CTD-Related UIP

(Song JW et al. Chest 2009; 136: 23)

<table>
<thead>
<tr>
<th>Category</th>
<th>CVD-UIP Patients</th>
<th>IPF/UIP Patients</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Fibroblastic foot</td>
<td>1.56 ± 0.74</td>
<td>2.01 ± 0.81</td>
<td>0.007</td>
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<tr>
<td>Germinal centers</td>
<td>1.04 ± 1.07</td>
<td>0.33 ± 0.61</td>
<td>&lt; 0.001</td>
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<tr>
<td>Total inflammation</td>
<td>2.10 ± 0.60</td>
<td>1.74 ± 0.68</td>
<td>0.010</td>
</tr>
<tr>
<td>HC (size)*</td>
<td>1.71 ± 1.09</td>
<td>2.20 ± 1.09</td>
<td>0.034</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>1.72 ± 0.98</td>
<td>1.43 ± 0.71</td>
<td>0.044</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>0.33 ± 0.53</td>
<td>0.38 ± 0.60</td>
<td>NS</td>
</tr>
<tr>
<td>Intraalveolar macrophages</td>
<td>0.70 ± 0.54</td>
<td>0.85 ± 0.45</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fibrosis, % of affected cases</td>
<td>4 (10.5%)</td>
<td>7 (11.5%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Chemotherapy related DAD (multiagent)

This would obviously be a diagnosis of exclusion
Methotrexate reaction in RA

This could be cryptogenic organizing pneumonia

Chemotherapy-related UIP (multiple agents)

Could this be UIP in a patient with IPF?

PULMONARY DRUG REACTIONS

Role of the Pathologist

Define the histologic pattern(s) present
Correlate with the drug history and known patterns caused by the drugs
Exclusion of other possible causes...... especially infection
Final diagnosis rests with the clinician; usually retrospective and presumptive

Note: The pathologist does not make this diagnosis!

Thank-you For Your Attention