PATHOLOGIST’S ROLE IN THE DIAGNOSIS OF INTERSTITIAL LUNG DISEASE

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WHAT SHOULD THE CLINICIAN EXPECT FROM THE PATHOLOGIST?

- A diagnosis
- A diagnosis that fits with the clinical-radiologic findings
- An engaged pathologist
- A dynamic interchange of ideas
- Confidence in the pathologist

As an aside….

- Are you a technician or a consultant?
  - Dx = nonnecrotizing granulomas.
  - Dx = nonnecrotizing granulomas with a discussion of the possible diagnoses

- As physicians we should be consultants whenever we can.

WHAT IS THE ROLE OF PATHOLOGY IN THE DIAGNOSIS OF ILD?

- In some cases, no role.
- In some cases, the pivotal role.
- In most cases, part of the data base that must be correlated with the clinical and radiologic features.
WHAT IS THE ROLE OF SPECIMEN TYPE IN PATHOLOGIC DIAGNOSIS AND CLINICAL MANAGEMENT OF ILD?

- Expectations of TBBx
- Expectations of SLBx (VATS)

**TBBx**

**VATS Bx**

1X Magnification

- Some guidelines for TBBx and SLBx

INTERSTITIAL LUNG DISEASES (ILDs): Background

> >100 are recognized with a diversity of pathologic features...... that can be grouped as follows:

- Histologically unique (No Dx/Dx)
- Histologically characteristic (small Dx/Dx)
- Patterns of injury (much larger Dx/Dx)

- Clinical and radiologic correlation is most important in the last group

HISTOLOGICALLY UNIQUE ILD’S: Examples

- Pulmonary Langerhans Cell Histiocytosis (PLCH)
- Lymphangioleiomyomatosis (LAM)
- Diffuse Alveolar Septal Amyloidosis
- Infections (eg. pneumocystis)
- Neoplasms (many types)

HISTOLOGICALLY UNIQUE ILD’S (No Dx/Dx)

1. Small specimens may be adequate for diagnosis (eg. TBBx)
26F Asymptomatic smoker with “diffuse infiltrates”
PFT’s: Mixed obstructive/restrictive

Unique diagnostic histology: PLCH

S-100
CD1a

DIAGNOSTIC TBBx
HMB45

“cyst”

Unique histology of Lymphangioleiomyomatosis/LAM

2. ILD’S WITH CHARACTERISTIC HISTOLOGY (relatively small Dx/Dx)

- Examples
  - Sarcoidosis
  - Pulmonary Alveolar Proteinosis

Correlation of Clinical, Radiologic, and Pathologic findings is important ...
And a small Bx (eg TBBx) may be adequate

SARCOIDOSIS
Granulomatous inflammation

But there are many causes of granulomas...
3. ILD’s WITH NON-SPECIFIC PATTERNS OF LUNG INJURY (and a larger Dx/Dx)

- **Acute Lung Injury:** Diffuse Alveolar Damage (DAD), Organizing pneumonia (OP/BOOP pattern)
- **Chronic inflammation and interstitial fibrosis:** seen in the chronic interstitial pneumonias, especially UIP and NSIP.

These cases have a larger differential diagnosis, and Clinical-Radiologic correlation is necessary for diagnosis.

**Often require SLBx to identify the pattern**

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SARCOIDOSIS
Granulomas along lymphatic routes

This distribution is very characteristic (and correlates with HRCT)

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TBBx
c/w Sarcoidosis

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**THE IDIOPATHIC INTERSTITIAL PNEUMONIAS FALL INTO THIS CATEGORY OF NONSPECIFIC REACTION PATTERNS**

<table>
<thead>
<tr>
<th>Clinicopathologic Diagnosis</th>
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*ATS/ERS International Consensus Panel; Am J Respir Crit Care Med 2002; 165:277*
Inflammation and Fibrosis in chronic IP’s: UIP and NSIP

**NSIP:**
- Spatially uniform
- Temporally uniform

**UIP:**
- Spatially and temporally heterogeneous

**Fibroblast Foci**

**UIP vs NSIP is the major clinical problem - we will come back to this**

FOR THE CLINICIAN Faced a Choice of Biopsy in ILD

- **Consider TBBx**
  - Histologically unique ILD - small specimens may suffice.
  - Histologically characteristic - small specimens may suffice with Clin-Radiol correlation

- **Consider SLBx**
  - Non-specific patterns of lung injury individualize each case, eg.
    - TBBx is sufficient in COP with typical Clin-Rad
    - SLBx required to distinguish NSIP from UIP if radiology not diagnostic

**CHOICE OF BIOPSY IN ILD**

**Radiologic patterns**
- Lymphangitic: consider TBBx
- Ground glass: SLBx
- UIP-like: SLBx

“High yield” TBBx’s (from Churg):
- Suspected malignancies, sarcoidosis, infections, transplant rejection

**APPROACH TO BRONCHOSCOPIC BIOPSIES**

(from TV Colby MD in Pathologica 2011)

<table>
<thead>
<tr>
<th>Disease Entity</th>
<th>Unique/Specific Histology</th>
<th>Characteristic Histology</th>
<th>Lymphangitic Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Lymphoid cell hyperplasia (PLCH)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphangioleiomomatosis (LAM)</td>
<td>X</td>
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<td></td>
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<tr>
<td>Sarcoidosis</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Cellular phase of silicosis alveolitis</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy, especially lymphangitic</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse lymphoid and histiocytic</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypereosinophilic pneumonia</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary alveolar macrophages</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Capillititis</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>IV drug abuse</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Transplant rejection</td>
<td>X</td>
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</tbody>
</table>
**SILICOSIS IDENTIFIED ON TBBx**

Silicosis often follows lymphatic routes and has unique histology.

**TBBx: DIAGNOSIS CATEGORIES**

1. Diagnostic of . . .
2. Histologic changes consistent with . . .
3. Nonspecific histologic abnormalities (e.g. focal inflammation, scarring, alveolar macrophages, et al.)
4. Normal/negative/inadequate (Note: negative information may be useful!)

How can we improve the usefulness of TBBx ??

**NONDIAGNOSTIC TBBx’s**

Abnormal but not diagnostic

A list of pathologic findings (i.e. a descriptive diagnosis) is not a clinicopathologic diagnosis.

From a case of PLCH From a case of COP

**The Pathologist and ILD**

- Even when you cannot make a specific diagnosis you can still be a consultant.
- Be part of the discussion
TBBx: DIAGNOSIS CATEGORIES

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
   (Note: negative information may be useful!)

Can move from 3 → 2 with clin-rad-path correlation and/or additional studies
Can move from 2 → 1 or 3 → 1 with special studies (e.g. IPOX, PCR, genetics, et. al.)

TBBx IN ILD

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnostic Bx</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 1978 N=939 (rev’d by Churg)</td>
<td>31%</td>
<td>Nonspec- 44% Normal/Inad- 25%</td>
</tr>
<tr>
<td>Poletti 1988 N=801</td>
<td></td>
<td>37%</td>
</tr>
<tr>
<td>Ensminger 2006 N=603</td>
<td>38%</td>
<td>TBBx “helpful” in 76% Not “helpful” in 24%</td>
</tr>
</tbody>
</table>

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!
HISTOLOGIC DIAGNOSIS OF LUNG 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 can affect #’s 1 and 2
The pathologist can affect #’s 2 and 3

SURGICAL LUNG BIOPSIES

SURGICAL LUNG BIOPSY (VATS AND OLBx)

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

SURGICAL LUNG BIOPSY (VATS AND OLBx)

Diagnostic Usefulness:
~95% fit with clinical findings
~90% diagnostic in chronic diffuse disease
~35-75% rate of specific diagnosis in acute diffuse disease (most of these show DAD)
Nondiagnostic SLBx done for “pulmonary fibrosis”

Problem Cases
- Radiologic and pathologic interpretation are not black and white.
- Interpretations are subjective and there are shades of gray.
- Your clinician is always assessing your confidence and the specificity of pathologic interpretations.

SELECTED ILD’s
- Acute lung injury
- Alveolar hemorrhage
- Idiopathic interstitial pneumonias

DAD and OP represent….. 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
**Acute Lung Injury:**
Overlap of Organizing DAD and OP

**DAD**
- Uniform temporal appearance
- Alveolar septal thickening
- Airspace organization
- Hyaline membranes

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

**DIFFERENTIAL DIAGNOSIS OF:**

<table>
<thead>
<tr>
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<th>OP</th>
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<tr>
<td>Infections</td>
<td></td>
<td>Organizing infections</td>
</tr>
<tr>
<td>Toxic inhalation</td>
<td></td>
<td></td>
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<tr>
<td>Drug reactions</td>
<td></td>
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<tr>
<td>Collagen Va.</td>
<td></td>
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<tr>
<td>Radiation</td>
<td></td>
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<tr>
<td>Diffuse alveo.</td>
<td></td>
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<tr>
<td>Shock</td>
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<tr>
<td>Acute allergy</td>
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<tr>
<td>Neurologic</td>
<td></td>
<td></td>
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<tr>
<td>Miscellaneus</td>
<td></td>
<td></td>
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<tr>
<td>Idiopathic (ie. AIP)</td>
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*Main Lesions to consider:
- Infection
- Connective tissue disease
- Drug reaction
- Allergic/hypersensitivity
- Idiopathic

*Many unsolved*
**Is TBBx useful in ALI?**

**Cryptogenic Organizing Pneumonia (COP): TBBx**

TBBx findings can be used to support the diagnosis

**DIFFUSE ALVEOLAR HEMORRHAGE (DAH)**

- Pulmonary hemorrhage not due to trauma, airway disease, tumors, or heart failure
- Usually recurrent; may be acute or chronic
- Typically with dyspnea, hemoptysis, airspace infiltrates, and anemia
- Associated renal disease common

This is a medical emergency

**Diffuse Alveolar Hemorrhage (DAH)**

*Specific histologic diagnosis may not be possible!*

- RBC’s, fibrin, hyaline membranes
- Hemosiderin deposition
- Airspace organization
- When chronic
  - Interstitial thickening/slight fibrosis
  - Type II cell proliferation

+/- other changes (e.g. WG); +/- positive immunofluorescence
**Diffuse Alveolar Hemorrhage**

(Anti-GBM Disease)

Organizing alveolar hemorrhage overlaps with OP

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**CAPILLARITIS IN DAH**

- Capillaritis is common in DAH
- Lung capillaritis is analogous to leukocytoclastic vasculitis
- Capillaritis is not specific
- Capillaritis is not a disease

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**AN IMMUNOLOGIC CLASSIFICATION OF DAH IS CONCEPTUALLY USEFUL**

- **ANCA-associated:** WG, MPA, pulmonary renal syndromes, isolated alveolar hemorrhage
- **Antibasement membrane antibody:** Goodpasture's syndrome, isolated alveolar hemorrhage
- **Immune complex deposition:** Collagen vascular diseases, IgA disease, pulmonary renal syndromes, isolated alveolar hemorrhage
- **Immunologic mechanism not identified:** IPH, isolated alveolar hemorrhage

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**HISTOLOGIC EVALUATION OF DAH**

- Confirm presence of alveolar hemorrhage
- Histologic analysis often stops here!
- Look for histologic features of WG
- Correlate with serology, clinical pattern of disease, EM/IF studies (if done)
- Clinicopathologic diagnosis
- Be a consultant.
Diffuse Alveolar Hemorrhage in WG
(91F with fulminant course)

Granulomatous foci diagnostic of WG
(91F with fulminant course)

Is TBBx useful in DAH?

Transbronchial biopsy
Let's add some history....
20F with dyspnea, hemoptysis, patchy radiologic infiltrates, and + c-ANCA

She also had hematuria

- **Diagnosis:** ANCA positive diffuse alveolar hemorrhage (compatible with WG)
- **Follow-up:** The patient responded to therapy for WG and was well several years later

### 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

### THE IDIOPATHIC INTERSTITIAL PNEUMONIAS FALL INTO THE CATEGORY OF NONSPECIFIC REACTION PATTERNS

(2002 ATS/ERS CLASSIFICATION OF IIPs*)

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### Usual Interstitial Pneumonia (UIP)

In ~50% of cases IPF can be diagnosed with HRCT
For clinicians, radiologists, and pathologists UIP vs NSIP causes the most problems.

NSIP vs UIP: there are significant survival differences

Many other studies have confirmed these findings

DO NSIP AND IPF OVERLAP? OF COURSE!

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)
Histology = NSIP

Diagnosis = UIP (IPF)

HRCT TRUMPS HISTOLOGY
(Sampling error has occurred)

Biopsy is not the Gold Standard

HRCT = UIP

Histology = NSIP

Why isn’t this UIP?

Scarring is stellate and centrilobular

Healed Pulm Langerhans cell histiocytosis

Why isn’t this UIP?

Central scarring with peribronchiolar metaplasia, granulomas

Chronic hypersensitivity pneumonitis

FEATURES TO ADDRESS IN FIBROSING INTERSTITIAL PNEUMONIAS

- 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**

RB on TBBx

- It could be incidental or part of RBILD or DIP

DAD c/w AIP  TBBx’s  OP c/w COP

DAD

UIP as seen on trichrome stained section

Potential TBBx Sites

Fibroblast focus

Normal

Scar
**TBBx IN USUAL INTERSTITIAL PNEUMONIA**  
(Berbescu et al. in Chest 2006;129:1126-1131)

Summary: “...histologic features of UIP can be identified on TBBx specimens...and...  
...support the diagnosis of UIP in the appropriate clinical and radiographic setting.”
But not proven useful in prospective studies

**TBBx is not currently accepted for the diagnosis of UIP**

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**WHAT TO EXPECT FROM THE PATHOLOGIST IN ILD CASES?**

On a transbronchial biopsy?
- ~35% Dx rate in chronic diffuse disease

On a surgical lung biopsy?
- ~90-95% diagnosis in diffuse disease

On agreeing with his colleagues?
- Kappas from 0.4 - 0.8

On agreeing with himself/herself?
- Kappas from 0.4 - 0.9

---

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

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<th>Recommendation</th>
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<td>UIP/IPF</td>
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<td>DIP</td>
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**ROLE OF THE PATHOLOGIST IN ILD’s?**

- Be part of a dynamic interchange of ideas and observations with clinical-pathologic-radiologic correlation
- Report a pathologic diagnosis that fits with the clinical and radiologic findings!
  - *Does the Bx answer the question??*
- Be a consultant
THANK-YOU FOR YOUR ATTENTION!