INTERSTITIAL LUNG DISEASE IN PATIENTS WITH CONNECTIVE TISSUE DISEASE (CTD/ILD)

CTD/ILD shows a number of patterns, paralleling those seen in the idiopathic interstitial pneumonias.

Overall CTD/ILD has a favorable prognosis compared to IPF.

The frequency of NSIP pattern is more common in CTD/ILD than IIP.

UIP pattern in some CTD’s has a better prognosis than IPF.

The exception may be RA.

ILD PATTERN IN CTD’s

High frequency of NSIP which varies among CTD’s.

Different frequencies compared to IIP’s:

IPF/UIP = 55%
Idiopathic NSIP = 25%

Prognosis of Fibrotic IPs (NSIP and UIP): Idiopathic vs CTD-Related
(Park JH et. Al AJRCCM 2007; 175: 705)

IIP 269 pts (203 UIP, 66 NSIP)
CTD-IP 93 pts (36 UIP, 57 NSIP)

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</th>
<th>IPF/UIP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblastic foci</td>
<td>1.56 ± 0.74</td>
<td>2.01 ± 0.81</td>
<td>0.007</td>
</tr>
<tr>
<td>Germinal centers</td>
<td>1.04 ± 1.07</td>
<td>0.33 ± 0.61</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total inflammation</td>
<td>2.10 ± 0.69</td>
<td>1.74 ± 0.66</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 ± 0.68</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>0.76 ± 0.54</td>
<td>0.85 ± 0.45</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fibrosis, % of</td>
<td>4 (10.5)</td>
<td>7 (11.5)</td>
<td>NS</td>
</tr>
<tr>
<td>affected cases</td>
<td></td>
<td></td>
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</table>

Sjogren’s
RA

Germinal Centers are the most common clue to a CTD
AKA: “undifferentiated CTD associated ILD”
  “lung-dominant CTD”
  “autoimmune-featured ILD”
IPAF concept provides standardized, multidisciplinary assessment criteria
IPAF is not a clinical diagnosis

**Definition**

Patients with idiopathic interstitial lung disease having combined clinical, laboratory and morphologic attributes suggesting a systemic autoimmune disorder, but who fail to meet criteria for a defined connective tissue disease.

*A priori* requirement: HRCT and/or lung biopsy documenting the presence of ILD.

**Clinical Domain**

1. Distal digital fissuring (i.e. “mechanic hands”)
2. Distal digital tip ulceration
3. Inflammatory arthritis or polyarticular morning joint stiffness $\geq 60$ min
4. Palmar telangiectasia
5. Raynaud’s phenomenon
6. Unexplained digital edema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron’s sign)
**Serologic Domain**

1. ANA >1:320 titre, diffuse, speckled, homogeneous patterns or
   a. ANA nucleolar pattern (any titre) or
   b. ANA centromere pattern (any titre)
2. Rheumatoid factor >2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (eg. Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

**Morphologic Domain**

1. Suggestive radiology patterns by HRCT (see text for descriptions):
   NSIP, OP, NSIP with OP overlap, LIP
2. Histopathology patterns or features by surgical lung biopsy:
   NSIP, OP, NSIP with OP overlap, LIP, Interstitial lymphoid aggregates with germinal centers, Diffuse lymphoplasmacytic infiltration (with/wo lymphoid follicles)
   {UIP may be seen but it is not a suggestive pattern by itself}
3. Multi-compartment involvement (in addition to interstitial pneumonia):
   Unexplained pleural or pericardial effusion or thickening
   Unexplained intrinsic airways disease (by PFT, imaging or path)
   Unexplained pulmonary vasculopathy

AKA: “undifferentiated CTD associated ILD”
“lung-dominant CTD”
“autoimmune-featured ILD”

IPAF concept provides standardized, multidisciplinary assessment criteria
IPAF is not a clinical diagnosis
SMOKING, FIBROSIS, AND ILD

Well-known conditions associated with smoking:
- PLCH, RBILD, DIP, eos pneumonia

Histologic changes associated with smoking:
- Airspace enlargement with fibrosis (AEF)
- Smoking-related interstitial fibrosis (SRIF)
- RBILD with fibrosis

Subclinical interstitial radiologic abnormalities (ILA) in ~10% of smokers

RBILD

An exaggerated RB reaction with increased airspace macrophages and greater extent of lung tissue affected

Desquamative Interstitial Pneumonia (DIP)
Pulmonary Langerhans Cell Histiocytosis LCH

“HEALED” PLCH
Langerhans’ Cell Histiocytosis

<table>
<thead>
<tr>
<th>Previous Names</th>
<th>Proposed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized eosinophilic granuloma (variety of sites)</td>
<td>Single organ involvement</td>
</tr>
<tr>
<td></td>
<td>Lung, bone, skin, pituitary, lymph node, other</td>
</tr>
<tr>
<td>Hand-Schuller-Christian disease</td>
<td>Multisystem disease</td>
</tr>
<tr>
<td></td>
<td>Multiorgan (+lung)</td>
</tr>
<tr>
<td></td>
<td>Multiorgan (-lung)</td>
</tr>
<tr>
<td>Letterer-Siwe disease</td>
<td>Multiorgan histiocytic disorder</td>
</tr>
</tbody>
</table>


PULMONARY LANGERHANS CELL HISTIOCYTOSIS (PLCH)

Current evidence strongly supports an association with cigarette smoking (i.e. inhalation)

*BRAF V600E mutation (25-50%)

Early lesions frequently show an airway-centered distribution
Eosinophilic pneumonia in a young man who recently started smoking

**SMOKING AND SUBCLINICAL CHANGES**

Histologic changes associated with smoking:
- Smoking-related interstitial fibrosis (SRIF)
- Airspace enlargement with fibrosis (AEF)
- RBILD with fibrosis

Subclinical interstitial radiologic abnormalities (ILA) in ~10% of smokers
MICROSCOPIC FIBROSIS CAN BE RELATED TO SMOKING

Pathologic studies

(Yousem SA. Mod Pathol 2006;19:1474)
30 lobectomies from smokers: 13 (43%) with some fibrosis (No fibrosis in 16 nonsmokers)

(Katzenstein et al in Hum Pathol 2010)
20 lobectomies from smokers: 9 (45%) with fibrosis labelled:
Smoking-related interstitial fibrosis

Can this smoking-related fibrosis be clinically recognized ??

Interstitial lung abnormalities (ILA) in CT studies

Study of lung cancer resection specimens

(Kawabata et al. Histopathology. 2008 53:707)
Resections: 587 smokers and 230 nonsmokers.
CLE and airspace enlargement with fibrosis (AEF) were assessed grossly and histologically.

Frequency and degree of AEF

Histopathology, 2008 Dec;53(6):707-14
HRCT IN ASYMPTOMATIC SMOKERS

<table>
<thead>
<tr>
<th>Finding</th>
<th>Smokers (n=144)</th>
<th>Non-Smokers (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill-defined micronodules</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>Ground glass opacities</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>Emphysema</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>33%</td>
<td>2%</td>
</tr>
</tbody>
</table>

RB/DIP likely cause these findings

Mastora et al. Radiology 2001;218:695-702

SUMMARY

We have a lot to learn about the subclinical radiologic (ILA) and pathologic changes (eg. SRIF) in the lungs of smokers.

Are they incidental findings or something that can progress to clinical disease....like IPF ??

HYPERSENSITIVITY PNEUMONITIS UPDATE

Two-hit hypothesis: 1. Genetic predisposition;
2. Exposure to sensitizing antigen
Atypical mycobacteria in aerosolized water as an inciting antigen with better defined granulomas
Usefulness of BAL in cases of HP: lymphocytosis
Some antigens are associated with more aggressive disease (esp. bird fancier's lung)
Chronic HP can have a UIP pattern
Is IPF a form of Chr HP ??

Aerosolized Mycobacteria and HP

The prototype in the USA is “hot tub lung.” This produces a granulomatous interstitial pneumonia distinct from classic HP.

For the pathologist the granulomas in hot tub lung differ from typical HP:

Perhaps this is related to antigenicity?

Chronic HP

Chronic HP with UIP pattern

Fibroblast foci

Clues to Chr. HP: Incr. inflammation, centrilobular inflam/fibrosis, granulomas
THE EFFECT OF FIBROSIS ON SURVIVAL IN PATIENTS WITH HP
(Voulekis in Am J Med 2004; 116: 662)

46 of 72 pts identified were classified as “fibrotic”
No correlation of degree of fibrosis with implicated antigen

![Graph showing survival probability over years after lung biopsy]

How common is Chr HP ??

Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study

Ferran Morell, Ana Villar, Maria-Angelies Montoro, Xavier Murtra, Thomas V Colby, Sadhakar Piperno, Maria-Jesus Cruz, Ganesh Bagghu

46 consecutive pts diagnosed with IPF (2011 guidelines)
20/46 reinterpreted as Chr HP (details available)
The study implicated....

...Feathers pillows and bedding

What does this mean for pathologists?

Chr. HP should be on your radar
How to recognize?

Radiologic clues (upper lobe, centrilobular nodules, air trapping)
Histologic clues (granulomas, centrilobular changes)
Airway centered changes

Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia


N= 22 Chr HP and 13 UIP/IPF

**DISCRIMINATORS**
- Bronchiolitis: 0.0003
- Centrilobular fibrosis: 0.0003
- Bridging fibrosis: 0.0042
- Org pneumonia: 0.0006
- Granulomas: 0.0002
- Giant cells: < 0.0001
- Lymphocytic alveolitis: 0.002

**BRONCHIOLAR CHANGES**
- Lymphocytic infiltr.: 0.0003
- Fibrosis of RB: 0.0011
- Fibroblast foci: 0.0013
- Lymphoid follicles: 0.0091
- Granuloma/giant cell: 0.0077

**LYMPHANGIOLEIOMYOMATOSIS (LAM) UPDATE**

Paradigm shift in the conceptual approach to LAM. It is considered a low-grade destructive metastasizing neoplasm:
- Loss of heterozygosity TSC genes
- Similar clonality of lesions at multiple sites
- Uncontrolled growth
- Ability to recur (“metastasize to”) in allografts
- Invasion
- Angiogenesis, including lymphangiogenesis
- Ability to disseminate via blood stream and lymphatics
Lymphangioleiomyomatosis (LAM)

Affects almost exclusively women in the childbearing years:

- Chylous effusions, pneumothoraces, hemoptysis
- Hormonally sensitive
- Sporadic cases and those in TSC
- Morbidity related to the lung disease

Radiologic manifestations of LAM

McCormack, F. X. Chest 2008;133:507-516

Lymphangioleiomyomatosis (LAM)

VEGF-D levels in the serum (>600 pg/mL) and LAM cell clusters in effusion as new means of diagnosis
Studies suggest that the recurrent LAM lesions derive from recipient cells that have migrated (metastasized) to the allograft. This supports the concept of LAM as a low grade malignancy.
LAM involving LN’s

LAM: Aspects for the Pathologist

Distinctive features of the lesional cells:
- HMB45 + , SMA + , ER/PR +
Some cases are diagnostically subtle

Pathologist Diagnosis of LAM
(In patients with cystic lung disease)

Diagnostic lung biopsy (TBBx, SLBx)
Explanted lungs
Review of “blebs” for pneumothorax
   In real time or retrospectively
Extrathoracic tissues
   eg. Retroperitoneal lymphangiomyoma
Cytologic analysis of pleural/peritoneal fluids

In all of these situations we are aided by knowledge that LAM is suspected.
OVERLAP OF AIRWAY DISEASE (BRONCHIOLITIS) WITH ILD

SMALL AIRWAYS

Small airways are ≤ 2 mm
Unless abnormalities are present, small airways are not visible on HRCT.
Abnormal small airways often apparent on HRCT

BASIC AIRWAY PATHOLOGY

Inflammation is associated with a cellular reaction (acute, chronic, mixed, etc.) and a mesenchymal (fibroblastic, fibrotic) reaction.
BRONCHIOLITIS
(inflammation of bronchioles)

1. Cellular infiltration
(+/- fluid, mucus)

2. Mesenchymal reaction

The clinical, radiologic and functional effects of these lesions vary from case to case

BRONCHIOLAR PATHOLOGY
Major Pathologic Groups

Cellular/exudative reaction dominates
Mesenchymal reaction predominates with:

1) Organization with intraluminal polyps
2) Subepithelial fibrosis and scarring with partial or complete luminal compromise
3) Peribronchiolar scarring with luminal patency

Mixed patterns (are actually most common)

BRONCHIOLAR PATHOLOGY

Cellular/exudative reaction dominates
Descriptively: Cellular bronchiolitis (acute/chronic)
- Follicular bronchiolitis

- Infections (viral, bacterial, et.al.)
- Aspiration
- Collagen vascular diseases
- Lung/bone marrow transplantation
- Inflammatory bowel disease
- Idiopathic
- As part of interstitial pneumonia

Respiratory bronchiolitis associated

Luminal compromise may or may not be present
**FOLLICULAR BRONCHIOLITIS**

**Definition:** Lymphoid hyperplasia along bronchioles (a reflection of BALT hyperplasia)

**Causes and Associations:**
- Connective tissue disease (especially RA)
- Immunoglobulin deficiencies (including HIV infection and acquired Ig deficiencies)
- Hypersensitivity reaction
- Chronic infection/inflammation

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**Respiratory bronchiolitis (RB)**

A universal finding in smokers

A form of cellular bronchiolitis

* + Iron stain

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**Two Forms of Bronchiolitis Obliterans are Recognized Histologically**

1) **With intraluminal polyps**
   - Common reparative reaction
   - Associated with organizing pneumonia (e.g. BOOP)
   - Infiltrative lung disease clinically

2) **Constrictive form** (constrictive bronchiolitis)
   - Uncommon
   - Usually “pure” (restricted to membranous bronchioles)
   - Obstructive disease clinically
BRONCHIOLITIS OBLITERANS WITH INTRALUMINAL POLYPS (OP/BOOP)

A reflection of the mesenchymal reaction in airway injury with intraluminal organization

Organizing infections
Eosinophilic pneumonia
Hypersensitivity pneumonitis
Collagen vascular diseases
Drug reactions
Organizing diffuse alveolar damage
Aspiration
Distal to: obstruction, bronchiectasis
Association with/proximity to other lesions (e.g., abscess, WG)
Idiopathic:
  Localized: focal organizing pneumonia
  Widespread: COP

Bronchiolitis obliterans with intraluminal polyps
(“BOOP”)

Organizing pneumonia (OP)
Bronchiolitis obliterans (BO)

Organizing pneumonia
Cryptogenic Organizing Pneumonia (COP)

Airway pathology is part of patchy consolidation

CONSTRUCTIVE BRONCHIOLITIS

The mesenchymal reaction narrows the lumen

A useful histologic term to identify a histologic lesion commonly associated with airflow obstruction in the small airways

Distinct from bronchiolitis obliterans with intraluminal polyps

CONSTRUCTIVE BRONCHIOLITIS - Causes -

- Post infectious (e.g. adenovirus)
- Fume exposure-related
- Transplantation (lung, GVH in BM Tx)
- Collagen vascular disease-associated
- Drug reaction (e.g. penicillamine)
- Inflammatory bowel disease-associated
- Bronchiolar NE cell hyperplasia
- Idiopathic
- Secondary (e.g. bronchiectasis)
**BRONCHIOLAR PATHOLOGY**

Mesenchymal reaction predominates with:

3) Peribronchiolar scarring with luminal patency (Terms: peribronchiolar metaplasia, Lambertosis)

**Lumenal patency**

**PERIBRONCHIOLAR METAPLASIA:**

the mesenchymal reaction is peribronchiolar

**PERIBRONCHIOLAR METAPLASIA (PBM)**

Peribronchiolar Metaplasia in ILD:
- Bronchiolitis with Interstitial Pneumonia (Mod Pathol 2002)
CAUSES OF PERIBRONCHIOLAR METAPLASIA (PBM)*

Prior infection
Hypersensitivity pneumonitis
Healed ARDS
Unknown/incidental finding (the majority of cases)

*From personal experience

Because of the Interplay Between the Cellular and the Mesenchymal Reaction, Pathologic Changes in the Bronchioles Produce Clinically Diverse Syndromes

Distinction from Interstitial Lung Disease may be difficult and arbitrary

Lumenal patency is often maintained in small airway pathology

SUMMARY

Bronchiolitis – means many things to many observers. Be precise with the terminology you use.

Pathologic changes in the small airways produce many clinical effects, some obstructive, some restrictive, some

THANK-YOU FOR YOUR ATTENTION!
Thank you for your attention!