The Pathologist’s Approach to Diffuse Lung Disease

Kirk D. Jones, MD
UC San Francisco
Department of Pathology
kirk.jones@ucsf.edu

Teaching Lung Pathology

- Deciding to practice pulmonary pathology
- Signouts in Scottsdale
  - The encyclopedic knowledge
  - The gestalt diagnosis
- Pushing glass
Teaching Lung Pathology

• Structures of the Lung
• Zones of the Lung
  – The pulmonary lobule
• Kevin Leslie’s Six Patterns
  – As seen in Leslie and Wick’s “Practical Pulmonary Pathology”

Processing Specimens

• Endobronchial and Transbronchial
  – Shaking and swirling is the inflater of the small specimen
  – Don’t crush the tissue (again)
  – Are any stains or levels needed up front?
    • Transplants get 3 levels, EVG, GMS
    • Rule out sarcoid - probably want levels
Processing Specimens

• Wedge and VATS biopsies
  – Inflating the specimen, the agony of choices
  – Clip the staple line and “shake it like a salt shaker” take a peek then “shake the hell out of it”.
  – Needle and small syringe with formalin
  – Soda and formalin - ol’ bubbly
  – The big syringe vacuum
How to Slice?
Essential Facts

From Katzenstein

• 1. Arteries with Airways - the pulmonary arteries and bronchioles course together.

• 2. Pulmonary veins lie in interlobular septa.

Essential Facts

From Katzenstein

• 3. Pulmonary arteries have two distinct elastic tissue layers while pulmonary veins have only one.
Essential Facts
From Katzenstein

• 4. Lymphatics course in the broncho-vascular bundles, the interlobular septa, and the pleura.

Essential Facts
From Katzenstein

• 5. Alveolar epithelium is not normally detectable by light microscopy.
  – Most of the cells you notice are endothelial, otherwise it is too cellular.
The Pulmonary Lobule

Three Patterns by Distribution

Peripheral Lobular  Bronchiocentric  Diffuse
Patterns of Lung Injury

• 1. Acute lung injury
• 2. Interstitial fibrosis
• 3. Interstitial inflammation
• 4. Alveolar filling
• 5. Pulmonary nodules
• 6. Minimal changes

From Kevin Leslie, MD

Case 1

• 59 year old man vacationing at Lake Tahoe
• Brought to hospital with shortness of breath
• Condition worsened and patient needed to be intubated
• Biopsy performed
Case 1

- Organizing acute lung injury
- Usual interstitial pneumonia
- Organizing pneumonia
- Hot tub lung (M. avium reaction)
Case 1 - Followup

- Patient transferred to hospital in Visalia
- Two weeks later transferred to UCSF
- Died
- Friend admitted they had been snorting cocaine in the hot tub at Tahoe
- Not AIP, probably drug + altitude

Acute Lung Injury

- There is a reason why it is pattern 1
  - Can mimic inflammatory or fibrotic lesions
- Features of pattern
  - Interlobular edema
    - Granulation tissue-like fibrosis
    - Edematous fibrosis without inflammation
  - Increased airspace fibrin
  - Type 2 pneumocyte hyperplasia
  - Hyaline membranes – defn. of DAD
Phases of ARDS

![Graph showing the phases of ARDS: Exudative, Transition, Proliferative, and Fibrotic phases with corresponding events like Edema, Hyaline membranes, Inflammation, and Fibroplasia.]

Slide courtesy of Kevin Leslie
Useful Findings for ALI

• Distal airway squamous metaplasia
  – Do not mistake for tumor on cytology
• Small vessel thrombi
  – Cause or effect? Normally effect – and usually less than 1-2 mm vessels.
DAD – Clues for Etiology

- Often the clinician will want information on the cause of the acute lung injury.
- Neutrophils
  - Infection, sepsis, trauma, TRALI
- Viropathic changes
  - Use of DFA, PCR tests on lavage fluid
- Eosinophils
  - Acute eosinophilic pneumonia, infection
Case 2

- 29-year old man with dyspnea.
- Surgical biopsy – no initial history.
Case 2

- Usual interstitial pneumonia
- Familial interstitial fibrosis
- Apical pleural fibrosis
- Hypersensitivity pneumonia
Case 2 – Apical Bleb

- The case lacks history of distribution.
- Pleural and subpleural fibrosis with bleb formation and reactive fibroplasia from healing.
- Not usual interstitial pneumonia despite good temporal heterogeneity.

Pattern 2 - Fibrosis

- Increased collagenous fibrosis within interstitium.
- Broken down by distribution pattern
Three Patterns by Distribution

- Peripheral Lobular
- Bronchiocentric
- Diffuse

2 Fibrotic Characters

- Destructive
- Non-destructive
<table>
<thead>
<tr>
<th>Peripheral</th>
<th>Destructive</th>
<th>Non-Destructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular</td>
<td>UIP pattern</td>
<td>?UIP vs NSIP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider CVD</td>
</tr>
<tr>
<td>Bronchiolocentric</td>
<td>Oblit. Bronchiolitis</td>
<td>Smoking –RB, LCH</td>
</tr>
<tr>
<td></td>
<td>LCH</td>
<td>Chronic HP, CVD</td>
</tr>
<tr>
<td>Diffuse</td>
<td>“Endstage Lung”</td>
<td>“Dusty Cobweb”</td>
</tr>
<tr>
<td></td>
<td>“Honeycomb Lung”</td>
<td>NSIP Pattern</td>
</tr>
<tr>
<td></td>
<td>Marked interstitial fibrosis</td>
<td></td>
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**Peripheral Destructive Fibrosis**

**UIP Pattern**

- Most common cause of peripheral destructive fibrosis is UIP
- “Temporal heterogeneity”
- For accurate diagnosis, should see chronic active disease
  - Chronicity - Microscopic honeycombing
  - Activity - Fibroblastic foci
Honeycomb vs. Honeycomb
### OP or FF?

<table>
<thead>
<tr>
<th>Organizing Pneumonia</th>
<th>Fibroblastic Foci</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rounded (usually)</td>
<td>• Crescentic or bulge-like</td>
</tr>
<tr>
<td>• Air on most sides</td>
<td>• Collagen on one side</td>
</tr>
<tr>
<td>• Location - airspace</td>
<td>• Location - interstitium</td>
</tr>
<tr>
<td>• Polypoid</td>
<td>• Sessile</td>
</tr>
<tr>
<td>• Branching</td>
<td>• Reactive epithelium</td>
</tr>
<tr>
<td>• Haphazard fibroblasts</td>
<td>• Fibroblasts often parallel</td>
</tr>
</tbody>
</table>

- [Image of Organizing Pneumonia](image1)
- [Image of Fibroblastic Foci](image2)

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**Diagram:**

- Temporal heterogeneity

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What to expect from good “temporal heterogeneity”

• Pathologic Findings - Temporal Heterogeneity
  – Honeycomb fibrosis
  – Old collagenous fibrosis
  – Recent (fibroblastic) fibrosis
  – Normal lung
UIP Pattern

- Think before diagnosing if:
  - Patient under 50
  - Acute onset
  - Radiographically localized lesion

- Try and require HORN before making dx

Diffuse Nondestructive Fibrosis
NSIP Pattern

- Diffuse widening of alveolar septa
  - Without significant architectural destruction
  - Can be cellular (inflammatory) or fibrotic
  - “Dusty Cobweb Fibrosis”
Dusty Cobweb Fibrosis

Photo by Roger Smith

Term by Kevin Leslie
NSIP Pattern

• Many different diseases can show an NSIP pattern:
  – Idiopathic NSIP
  – Hypersensitivity pneumonia
  – Collagen vascular diseases
  – Drug reactions
  – Smoking-related injury (LCH)
NSIP Pattern

- Make the diagnosis when there is diffuse alveolar septal thickening.
- Look out for cases with acute onset.
  - Consider acute interstitial pneumonia
- Check CT to exclude focal lesions.
- If has honeycombing - think about UIP.

Bronchiolocentric Fibrosis - Nondestructive pattern

- Destructive bronchiolocentric fibrosis results in a scar adjacent to the pulmonary artery and can be nearly invisible – obliterative bronchiolitis.
- Nondestructive fibrosis results in subtle small airway changes:
  - Lambertosis (peribronchiolar metaplasia)
  - Mucostasis
  - Stellate scars
Bronchiolocentric Fibrosis

• Large differential diagnosis
  – When present with interstitial inflammation...
    • Hypersensitivity pneumonia
    • Collagen vascular disease
  – Think about airway irritants
    • Aspiration
    • Fume inhalation
    • Asbestos
    • Smoking-related (LCH or RB)
    • Healed viral pneumonia (especially children)
  – Some rare diagnoses
    • Pulmonary neuroendocrine cell hyperplasia
    • Diffuse panbronchiolitis

Idiopathic Bronchiolocentric Fibrosis

• 3 groups published series of patients with central fibrosis of unknown etiology
  – Sept 2002 - De Carvalho et al - “Centrilobular fibrosis”
  – Nov 2002 - Yousem and Dacic - “Idiopathic bronchiolocentric interstitial pneumonia”
  – Jan 2004 - Churg et al - “Airway-centered interstitial fibrosis”
Idiopathic Bronchiolocentric Fibrosis

- Bronchiolocentric inflammation and fibrosis
- Prominent bronchiolar metaplasia
- Poor prognosis
  - Yousem - 33% dead, 33% progressed
  - Churg - 50% progressed (40% dead)

Case 3

- 73-year-old woman real estate agent with shortness of breath and interstitial lung disease on CT scan.
Case 3

• Organizing acute lung injury
• Hypersensitivity pneumonia
• Cellular nonspecific interstitial pneumonia
• Usual interstitial pneumonia

Pattern 3 – Cellular Infiltrates

• Increased interstitial lymphocytic or histiocytic inflammation.

• Modifiers:
  – With granulomas.
  – Dense infiltrates or germinal centers
Case 3 - Encore

- Patient had been complaining of increasing shortness of breath for around 9-12 months.
- Started nitrofurantoin around 18 months ago.
- Stealth drug
  - Post coital UTI
  - UTI from BPH
- [www.pneumotox.com](http://www.pneumotox.com)

Cellular NSIP

- Or “cellular interstitial pneumonia”
- Differential diagnosis is similar to fibrotic NSIP
  - Drug reaction
  - Connective tissue disease
  - Hypersensitivity pneumonia
  - Infection
  - Idiopathic NSIP
If my pathologist tells me the biopsy shows NSIP, then my job has only just begun.

**Cellular with granulomas**

- Hypersensitivity pneumonia
  - Triad of four things.
- Hot tub lung and relatives
- Sarcoidosis and its mimics
Hypersensitivity Pneumonia

- Triad of four histologic findings:
  - 1/4. Lymphocytic interstitial inflammation - with bronchiolocentric accentuation.
    - Composed of a couple histiocytes and giant cells, often with cytoplasmic cholesterol clefts.
  - 3. Foci of organizing pneumonia.
Things we’ve seen recently

• Hypersensitivity pneumonia from...
  – Down pillows
  – Sleep number mattresses
  – Freezer in research lab
  – Chicken ranch
  – Parakeet breeder
  – Pet parrot
  – Down in couch cushions
  – Possibly almond dust
Hot Tub Lung

- Reaction of immunocompetent host to Mycobacterium avium.
- Strong resemblance to hypersensitivity pneumonia.
  - Clinical treatment is often antigen removal only
- Need to understand other causes of MAC disease
  - Small airway disease in COPD patients
  - Middle lobe sx (“Lady Windemere’s Sx”)
Sarcoidosis

- Non-necrotizing, tightly formed, “naked” granulomas in a lymphangitic pattern.
- Diagnosis of exclusion:
  - Idiopathic sarcoidosis
  - Metal related sarcoid reactions
  - Drug reactions
  - Infection
CIP with Dense Infiltrates

- Lymphocytic interstitial pneumonia
- Lymphoma
Dense infiltrates often with germinal centers

- Connective tissue disease
  - Especially Sjogren syndrome
- Immune deficiencies
  - Congenital HIV
  - Hypogammaglobulinemia
- Lymphoma
  - Usually low-grade marginal zone
  - See lymphangitic extension from nodule
  - Use flow cytometry or PCR for clonality
Case 4

- 65-year-old man with one week history of shortness of breath and hemoptysis.
- CT shows bilateral nodular infiltrates.
- Positive proteinase-3 antibody.
Case 4

- Acute and organizing alveolar hemorrhage.
- Wegener’s granulomatosis.
- Goodpasture’s syndrome
- Diffuse alveolar damage

Pattern 4 – Alveolar Filling

- Consolidation of the alveolar spaces by cellular or acellular material.
Filling - Modifiers

• Organizing pneumonia
  – With dense collagen or bone
• Macrophages
  – Smoker’s: DIP, RB
  – Hemosiderin: DAH
  – Lipid-filled
• Eosinophilic material
  – Pneumocystis
  – Alveolar proteinosis
  – Pulmonary edema
BOOP

Granulation tissue polyp

Bronchiolitis obliterans
Organizing Pneumonia
OP with Dense Collagen or Bone

- Persistence of collagenization – nonspecific finding of chronicity, in my experience this is often observed in aspiration.
- Bone in airspaces – also most commonly seen in aspiration, also can be observed in chronic left heart failure.
Acute Fibrinous Organizing Pneumonia

- Another pattern of acute lung injury.
- Plugs of fibrin within airspaces.

Smoking-related ILD

- Desquamative interstitial pneumonia
  - Diffuse alveolar septal thickening
  - Hyperplasia of BALT
  - Filling with lightly-pigmented macrophages
    - Prussian blue dusty positive
  - Often a mild increase in eosinophils
- Respiratory bronchiolitis
  - Ubiquitous in smokers
  - Dusty brown macrophages in peribronchiolar alveoli
  - Often associated with Lambertosis
Hemosiderin-Filled Macrophages

• “Acute and organizing alveolar hemorrhage”
  – Red cells accompanied by fibrin
  – Clinical history of hemoptysis
  – Beware of artifact

• Wide differential of diseases with capillaritis
  – Goodpasture, Lupus, anti-PL, WG, drug reaction

• Increased pulmonary venous pressures
  – CHF, mitral valve disease, sclerosing mediastinitis, occlusive venopathy

• Diffuse or focal? - Aspiration
Filling with Eosinophilic Material

- Edema
  - CHF, CVD, Drug
- Fibrin
  - Infection, CVD, Angiitis, Drug
- Granular protein
  - Pulmonary alveolar proteinosis
- Froth and dot
  - Pneumocystis
Case 5

• 28-year-old woman with multiple bilateral lung nodules, progressive over 6 months.
• Unresponsive to antibiotic treatment.
Case 5

- Wegener’s granulomatosis
- Necrotizing granulomatous infection
- Venous infarct
- Lymphomatoid granulomatosis
Pattern 5 – Nodular disease

• Discrete regions of consolidation from solid growth, filling, or necrosis, surrounded by lung tissue.
• Common manifestation of tumor and infection.
• Less common:
  – Lymphomatoid granulomatosis
  – Wegener granulomatosis

Lymphomatoid granulomatosis

• Nodules of mixed chronic inflammatory cells with prominent vascular infiltration and regions of necrosis.
• Larger cells mark as B-cells with CD20 and are often EBV positive.
• Graded by number of larger cells and number of EBV positive cells.
  – Most grades 2 and 3 are lymphomas
  – Grade 1 LYG is more mysterious

• Superb review as an e-article by Katzenstein
Wegener’s Granulomatosis

- Systemic disease with granulomatous inflammation and vasculitis.
- In Classical form, affects lungs, kidneys, and sinonasal tract.
- Limited form which spares the kidneys
- Antineutrophil Cytoplasmic Antibodies (C-ANCA, anti-proteinase 3)

WG - Diagnostic Criteria

- Triad of findings
  - Vasculitis
    - Arteries, Veins, Capillaries
  - Parenchymal necrosis
    - Geographic basophilic necrosis
  - Mixed inflammatory infiltrate
    - Neutrophilic microabscesses
    - Palisading histiocytes
    - Scattered giant cells
WG - Histologic Clues

• Vasculitis
  – The vasculitis occurs outside of the region of inflammation.
  – The vessel frequently is involved eccentrically
  – While different types of inflammatory cells may be involved in the vasculitis, granulomatous inflammation is rare.
WG - Histologic Clues

• Parenchymal Necrosis
  – Basophilic necrosis “blue cheese”
  – Geographic necrosis
  – Frequently leaves no structures behind
WG - Histologic Clues

• Mixed Inflammatory Infiltrate
  – Just as we think of “a good background” for other diseases, there is a good background for WG.
  – Neutrophilic microabscesses
  – Palisading of histiocytes around necrosis
  – Scattered single giant cells in parenchyma
Rheumatoid Nodule

- Close mimic of WG
- Shows basophilic necrosis, vasculitis, histiocyte palisading
- Almost always subpleural or paraseptal and frequently CROSSES pleura
- Get history (RA and pleural nodule)
Case 6

- 26-year-old man with prior lung transplant for cystic fibrosis. Now with marked air-trapping and dyspnea.
Case 6

- Normal lung
- Acute rejection
- Pneumocystis pneumonia
- Obliterative bronchiolitis

Pattern 6 – Minimal Change

- On low power, the lung looks nearly normal.
- The differential includes regions often neglected:
  - Small airway disease
  - Vascular disease (arterial or venous)
  - Cystic diseases
- Sampling error
Obliterative bronchiolitis
(constrictive bronchiolitis)

• Concentric constrictive scarring which eventually obliterates small airways

• Seen in:
  – Connective tissue disease
  – GVHD and lung transplant
  – Status post infection (esp. adenovirus)
  – Fume or dust inhalational injury
  – Idiopathic
Obliterative bronchiolitis

- The segmental nature of the sclerotic lesion sometimes requires multiple level sections and EVG stains to see.
- Use CT (particularly with dynamic expiratory views) to see air-trapping.
Primary Pulmonary Hypertension

- Plexogenic arteriopathy
- Thrombotic arteriopathy
- Medial and intimal thickening

- May be able to separate on H&E
- Can use EVG stain to help with evaluation
Secondary Pulmonary Hypertension

- COPD
- Collagen vascular diseases
  - Scleroderma, CREST Sx, Lupus
- Congenital heart diseases
- Chronic pulmonary thromboembolism
- HIV infection
- Liver disease
- Methamphetamines and other “uppers”
Pulmonary Veno-Occlusive Disease

- Sclerosis of veins -
  - Large veins in interlobular septa
  - Smaller post-capillary venules
- Frequently see associated
  - Interstitial thickening (cellular NSIP pattern)
  - Siderophages in alveolar spaces
Minimal Changes - Cysts

- Lymphangioleiomyomatosis
- Pulmonary Langerhans Cell Histiocytosis
- Emphysema

Lymphangioleiomyomatosis

- Cystic disease in women
  - Cysts lined by atypical smooth muscle
  - Estrogen receptor positive
  - HMB-45 positive
    - Perivascular epithelioid cell
  - TSC-1 and 2 mutations
Atypical Cells

- Lymphangitic or Intravascular Malignancy
  - Thyroid cancer
  - Renal cell carcinoma
  - Lymphoma
  - Breast carcinoma
Pattern 6 - Minimal Changes

- Small airway disease - Constrictive bronchiolitis
- Vascular disease - PHTN, PVOD
- Cystic diseases - LCH, LAM, Emphysema
- Atypical cells - Lymphangitic or intravascular malignant cells
- Sampling error

Making a Diagnosis

- Structures
- Zones
- Patterns

- Using examination of the pulmonary structures, zone of involvement, and pattern of injury, one can render a pathologic diagnosis.
The Hard Truth

• There are things the clinician knows…
  …that I want to know.
  – Duration of disease.
  – CT findings. Distribution of disease.
  – Medications, drugs, exposures.
  – Occupation. Hobbies.
  – Pulmonary function tests.

The Hard Truth about DLD

• If you want to be a great pathologist, radiologist, or pulmonologist, you need to interact and learn from each other.

• A non-specific pathologic diagnosis can become a specific diagnosis with interaction.