An Update on Inflammatory and Fibrotic Lung Diseases

Henry D. Tazelaar, M.D.
Chair and Geraldine Zeiler Colby Professor of Cytopathology
Department of Laboratory Medicine and Pathology
Alix College of Medicine and Science
Mayo Clinic Arizona

Outline

• Organizing pneumonia
• Small granulomas in new places
  – Connective tissue disease vs. hypersensitivity pneumonitis
  – Immunodeficiency
  – Primary biliary cholangitis
• Check point inhibitor lung toxicity

Not pure bronchiolitis obliterans (obliterative bronchiolitis)
Not idiopathic pulmonary fibrosis
Good prognosis with steroids
CRYPTOGENIC ORGANIZING PNEUMONIA

Cryptogenic organizing pneumonia (COP) is a clinicopathologic entity described by Davidson and coworkers in 1983 (38). In 1988, Epler and colleagues described the same entity under the term bronchiolitis obliterans organizing pneumonia (BOOP), and that latter term came into common usage (sometimes referred to as idiopathic BOOP) (37). The term cryptogenic organizing pneumonia (COP) is preferred because it conveys the essential features of the syndrome described below and avoids confusion with airway diseases such as constrictive bronchiolitis obliterans, which can be problematic with the term BOOP. Features of the organizing pneumonia pattern are organization.

Bronchiolitis obliterans a.k.a Constrictive bronchiolitis

UIP
**Bronchiolitis Obliterans with Organizing Pneumonia**

- Despite sometimes long history, changes were of “same age”
- Some alveolar interstitial fibrosis-peribronchiolar
- Honeycombing never seen

---

**Hyalinized Organizing Pneumonia**

Yousem SA et al Med Pathol 1997;10:864-871
Hyalinized/Cicatricial/Fibrosing Organizing Pneumonia

• 12 pts with cryptogenic disease
• 55% had progressive or persistent CT infiltrates
• 25% assoc. osseous metaplasia
• Contribution of pre-existing non fibrotic lung ds, like emphysema which impairs healing?
• Suggested poor steroid response

Yousem SA Hum Pathol 2017; 64:76-82

Hyalinized/Cicatricial/Fibrosing Organizing Pneumonia

• 10 pts identified by pattern
• 20% assoc with radiologic ossification
• Mimic of fibrotic NSIP
• Non-progressive disease
• Ehlers Danlos-1 pt

Churg A et al Histopathol 2018; 72:846-854

The image contains histological sections of tissue, possibly related to the content discussed.
Ehlers Danlos Syndrome
Patient History

- 41-year-old male real estate broker
  - CC: Cough and hemoptysis
- Past Medical History
  - Asthma
  - Recurrent pneumothorax
    - Unilateral January 2016
    - Bilateral October 2016
  - Autoimmune serologies negative
**Ehlers-Danlos Syndrome**

<table>
<thead>
<tr>
<th>Villefranche classification</th>
<th>Prior Nomenclature</th>
<th>Inheritance Pattern</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Type I and II</td>
<td>AD</td>
<td>COL5A1 and COL5A2</td>
</tr>
<tr>
<td>Hypermobility</td>
<td>Type III</td>
<td>AD (likely)²</td>
<td>Unknown²</td>
</tr>
<tr>
<td>Vascular</td>
<td>Type IV</td>
<td>AD¹</td>
<td>COL3A1</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>Type VI</td>
<td>AR</td>
<td>PLOD1</td>
</tr>
<tr>
<td>Arthrochalasia</td>
<td>Type VIIA and B</td>
<td>AD</td>
<td>COL1A1 (VIIA) COL1A2 (VIIIB)</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>Type VIIIC</td>
<td>AR</td>
<td>ADAMTS2</td>
</tr>
</tbody>
</table>

Differential Diagnosis for Hyalinizing OP

- Ehlers Danlos syndrome
- OP in NSIP
- Fibroblast foci of UIP
- Aspiration pneumonia with OP pattern and ossification
Hyalinized/Cicatricial/Fibrosing Organizing Pneumonia

- New pattern to recognize
- Prognostic significance unclear
- Likely also occurs in association with other disease e.g. CTD
- Other features may point to etiology - EDS, aspiration

Churg A et al Histopathol 2018; 72:846-854

Q. A 58 year old woman with a history of Sjogren syndrome, gastroparesis, MALT lymphoma (treated with Ruxinab and radiation) presented with a two day history of increasing shortness of breath. A CT about 1 month prior (done for cough and dyspnea) showed a stable infiltrate or scarring in the lingula.

a. Aspiration bronchiolitis
b. CTD related changes
c. Drug toxicity
d. Hypersensitivity pneumonitis
e. Non specific interstitial pneumonia
Q. A 58 year old woman with a history of Sjogren syndrome, gastroparesis MALT lymphoma (treated with Ruxinib) presented with a two day history of increasing shortness of breath. A CT about 1 month prior (done for cough and dyspnea) showed a stable infiltrate or scarring in the lingula.

- a. Aspiration bronchiolitis
- b. CTD related changes
- c. Drug toxicity
- d. Hypersensitivity pneumonitis
- e. Non specific interstitial pneumonia
Diagnosis

Chronic bronchiolitis with features of follicular bronchiolitis with non-necrotizing granulomatous inflammation, and patchy mild cellular and fibrotic interstitial pneumonia, most consistent with underlying connective tissue disease

Chronic Hypersensitivity Pn’itis (CHP, n=16) vs. Fibrotic Disease due to Connective Tissue Disease (CTD, n=12)

- Reviewed 15 parameters
- Germinal centers, prominent lymphoid aggregates and plasma cells favor CTD
- Peribronchiolar metaplasia favors HP
- Features that did not help: giant cells, granulomas, distribution of FiFo, pattern of fibrosis

* Churg A et al Am J Surg Pathol 2017; 41:1403-1409
Favor Chronic HP

Chronic Hypersensitivity Pn‘it is (CHP) vs. Fibrotic Disease due to Connective Tissue Disease (CTD)

- Challenging differential diagnosis
- Other features
  - Favor CHP: air trapping on HRCT, identifiable antigen
  - Favor CTD: multi-compartment disease e.g. pleuritis, vasculopathy
## Lung in Primary Biliary Cholangitis

**n=16, 94% women**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic inflammation</td>
<td>94</td>
</tr>
<tr>
<td>Mainly peribronchiolar</td>
<td></td>
</tr>
<tr>
<td>Non necrotizing granulomas</td>
<td>81</td>
</tr>
<tr>
<td>UIP/NSIP patterns</td>
<td>52</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>44</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>33</td>
</tr>
<tr>
<td>MALT lymphoma with light chain deposition</td>
<td>6</td>
</tr>
</tbody>
</table>

Lee HE et al Hum Pathol 2018;82:177-186
Common Variable Immunodeficiency (CVID)

- Global immune dysfunction
- B cells, T cells, cytokines
  - Explains combination of infectious, inflammatory, autoimmune, and neoplastic conditions
  - Significantly reduced serum IgG
  - Low serum IgA and / or IgM

CVID Pulmonary Manifestations

- Infection-pneumonia, bronchitis
- Bronchiectasis
- Asthma
- Interstitial lung disease
  - Granulomatous-lymphocytic interstitial lung disease (GL-ILD)*
  - Organizing pneumonia

So-called GL-ILD

- Dyspnea
- Restrictive PFT's
- HRCT: consolidation, ground-glass opacities, reticular opacities
- Various histologies

So-called GL-ILD
Histologic Features

- Lymphocytic infiltrates/LIP
- Non necrotizing granulomas (most, but not all)
- Follicular bronchiolitis
- Diffuse lymphoid hyperplasia
- Prominent organizing pneumonia
- Fibrosis (including honeycomb)

Rao N et al Hum Pathol 2015;46:1306-1314
So-called GL-ILD
Histologic Features

• Wide spectrum of histologies
• Possibly useful as a clinical term, but very confusing for pathologists!
• Always need to exclude lymphoma
• Granulomas don’t exclude lymphoma (20% of pulmonary MALT lymphomas)

History

• 76 yr. old M 10 pack yr smoker
• Referred for possible bronchoscopy
• History of metastatic melanoma
• Started on Immunotherapy with Pembrolizumab 10 months ago
History
Hospitalized
• Weight loss of 6-8 lbs. over the last 4 weeks
• Noted dyspnea on exertion for 4 weeks
• Dry cough for 3 weeks
• Low grade fever and chills for the past 10 days

CT 3 Months Prior
Transbronchial biopsy
**Pathologic Diagnosis?**

- **Organizing Pneumonia**
  - DDx: infection, drug reaction, connective tissue disease, aspiration, and as an idiopathic entity (cryptogenic organizing pneumonia)

---

**Final Clinical Diagnosis**

- BAL and special stains negative for infection
- **Pembrolizumab-induced organizing pneumonia**
- Pt started on 60 mg of prednisone
- Improved over the next few weeks with tapering of steroids over 2 months

---

**Check Point Inhibitor- Assoc ILD, n=64**

<table>
<thead>
<tr>
<th>Radiologic Patterns</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organizing pneumonia (OP)</td>
<td>23.4</td>
</tr>
<tr>
<td>Hypersensitivity Pneumonia</td>
<td>15.6</td>
</tr>
<tr>
<td>NSIP plus OP</td>
<td>9.4</td>
</tr>
<tr>
<td>NSIP</td>
<td>7.8</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>6.3</td>
</tr>
<tr>
<td>NSIP plus bronchiolitis</td>
<td>1.6</td>
</tr>
<tr>
<td>Not classified</td>
<td>35.9</td>
</tr>
</tbody>
</table>

Check Point Inhibitor - Pathology Patterns

- Diffuse alveolar damage
- Organizing pneumonia (OP) +/- fibrin
- Hypersensitivity pneumonitis/granulomatous pneumonitis
- NSIP-cellular interstitial infiltrates
- Bronchiolitis
- Fibrosis
- Eosinophilic pneumonia
- Granulomatous lymphadenitis

TBBX from 68 year old man on 6th cycle of Pembrolizumab

Courtesy of Dr. Masahara Nemeto, Kameda, Japan
Summary

- Spectrum of OP histology broad
- CTD related lung disease and hypersensitivity pneumonitis have significant overlaps
- PBC and CVID can both cause granulomatous lung disease
- Immune check point inhibitors can cause variety of toxicity patterns

Thank you!