The Pathologic Manifestations of Small Airway Disease

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Small Airway Disease (SAD)

A clinicopathologic syndrome reflecting a CHRONIC inflammatory and cicatricial process primarily affecting the bronchioles (airways <2 mm) that results in obstructive lung disease.

Synonyms: bronchiolitis obliterans, obliterative bronchiolitis, constrictive bronchiolitis.

SAD

As a CHRONIC clinical syndrome, it needs to be separated from acute forms of SAD e.g. acute neutrophilic bronchiolitis however . . .

Acute SAD can cause such severe airway injury that the patient is left with a permanent airflow deficit/irreversibly scarred airways e.g. RSV in infants.
There is a disconnect between the histologic presence of SA inflammation and the diagnosis of SAD.

- Bronchiolar inflammation is present in many diseases but it does not mean that the patient has clinical SAD e.g. many interstitial lung diseases have airway inflammation.
- To make a diagnosis of SAD, the clinical context, radiologic findings and PFTs must support a diagnosis of SAD- irreversible obstructive disease.

The likelihood of SAD is related to the
- # of airways affected (diffuse disease).
- Severity of airway damage.
- Irreversibility of injury – scarring/ luminal compromise.

* you must have widespread airway disease to fall into this CPC diagnosis.

The classification of SAD is confusing. . . . .sometimes the SAD is defined by the clinical scenario. . .other times by the histology. . .and of course, there is histologic and clinical overlap of many of these conditions.
Classification of SAD

1. Bronchiolar involvement in bronchial disease.
   - Asthma.
   - Bronchiectasis.
   - Cystic fibrosis.
   - Aspiration.
   - Bronchial obstruction.

2. Bronchiolar involvement in parenchymal lung disease.
   - Bronchopneumonia.
   - Eosinophilic pneumonia.
   - Cryptogenic organizing pneumonia (idiopathic BOOP).
   - Extrinsic allergic alveolitis.
   - Langerhans cell histiocytosis.

3. Disorders in which bronchiolitis is the predominant abnormality.
   - Follicular bronchiolitis.
   - Respiratory bronchiolitis.
   - Diffuse panbronchiolitis.
   - Mineral dust bronchiolitis.
   - Constrictive obliterative bronchiolitis.

Primary Bronchiolar Disorders Classification

- Bronchiolitis obliterans/obliterative bronchiolitis
- Respiratory bronchiolitis
- Follicular bronchiolitis
- Diffuse panbronchiolitis
- Autoimmune bronchiolitis
- Mineral dust airway disease
- Aspiration bronchiolitis

Bronchiolitis Obliterans

- Synonym: constrictive bronchiolitis/obliterative bronchiolitis.

- Usually defined as a small airway inflammatory process with irreversible scarring of the airways (that correlates with fixed and progressive functional deficits); no unique histologic features.
Bronchiolitis Obliterans/Obliterative Bronchiolitis

Histopathology

1. Cellular bronchiolitis – inflammatory infiltrate around airways; may include intraluminal granulation tissue polyps ("proliferative" phase). DISEASE AT THIS STAGE IS REVERSIBLE

2. Constrictive bronchiolitis – irreversible scarring of submucosa or obliteration of the airway lumen; may also have a peribronchiolar collar of collagen; usu. seen w/ active injury (#1)

3. Remember the functional impact of the inflammatory changes:
   - Mucus/fibrosis – physical obstruction.
   - Epithelial hyperplasia, squamous and goblet metaplasia – ↓ luminal clearance.
   - Cells – cytokines/edema of airway wall.
   - Smooth muscle – spasm/constriction.
   - Scar/metaplasia – disrupted airflow dynamics.
Histology ≠ Etiology
Potential Causes of Constrictive/Obliterative Bronchiolitis

1. Idiopathic
4. Toxic fume exposure – NO₂, sulfur dioxide, ammonia, chlorine, nitrogen, mustard, phosgene, 9/11 lung.
6. GVHD-bone marrow transplant recipients.
7. Lung allograft recipients.
8. Tobacco.
9. UC/CD.
12. Others.

Respiratory Bronchiolitis

RB is a ubiquitous finding in cigarette smokers – when patients present with clinical ILD and no other cause is identified, we place these patients into the category of RB/ILD.

Summary of findings in 156 patients

<table>
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<th>Current smokers</th>
<th>Ex-smokers</th>
<th>Never smokers</th>
<th>Total</th>
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<tr>
<td>RB present</td>
<td>83</td>
<td>24</td>
<td>2</td>
<td>109</td>
</tr>
<tr>
<td>RB absent</td>
<td>0</td>
<td>25</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>49</td>
<td>24</td>
<td>156</td>
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Ref: Fraig, AJSP, 2002
RB Histopathology

- Mild patchy lymphocytic bronchiolitis with luminal and centrilobular aggregates of finely pigmented macrophages, sparing of distal airspaces.
- Mild centrilobular alveolar septal collagenosis with lymphs.
- Associated changes – mucous plugging, atelectasis.
- Excellent 10 year prognosis with smoking cessation with intermittent steroid therapy although recent studies question this benign course.
Diffuse Panbronchiolitis

- East Asians with predisposing HLA genotype (Japanese-B 54; Korean-A 11) with minority presence in Western world.
- 4th-5th decades; M>F; non-smokers.
- Subacute onset of productive cough with purulent sputum; dyspnea: repeated Hemophilus/Staph infections that change to Pseudomonas; clubbing.
- History of chronic sinusitis.
- Bilateral small nodular opacities in bases; bronchiectasis.
- Prognosis: 80% DOD (untreated), 30% (treated with macrolides), at ten years.

Panbronchiolitis – Diagnostic Criteria of Ministry of Health and Welfare of Japan

- Persistent cough, sputum and exertional dyspnea.
- Past history of/or current chronic sinusitis.
- Bilateral diffuse small nodular shadows on a plain chest film or centrilobular nodular shadows on chest CT images.
- Coarse crackles.
- FEV₁/FVC <70% and PaO₂ <80 mm Hg.
- Titre of cold hemagglutinins equal to or higher than 64.

Definite cases should fulfill the first three criteria and at least two of the last three criteria.
**Diffuse Panbronchiolitis**

**Gross:** 4 mm yellow granular nodules.
1. Acute neutrophilic bronchiolitis with mucopurulent exudate.
2. Background chronic bronchiolitis involving RBs with peribronchiolar scarring, ectasia, lymphoid aggregates.
3. Luminal and interstitial aggregates of foamy macrophages.
Follicular Bronchiolitis
• A chronic bronchiolitis characterized histologically by the presence of hyperplastic lymphoid follicles with germinal centers distributed along the bronchioles.
• May be seen with diffuse lymphoid hyperplasia of the BALT, and as part of the LIP/DLH complex.

Follicular Bronchiolitis
• Subacute onset of COE, SOB, occasional wheeze.
• HRCT – small centrilobular nodules with patchy areas of ground glass opacity.
• Four clinical presentations.
  1. Chronic infection – mycoplasma, chlamydia, CF with bacterial colonization.
  2. Autoimmune disease – RA, SS.
  3. Immunodeficiency states – AIDS, CVID, B cell disorders.
  4. Hypersensitivity reactions often associated with PB eosinophilia.
• Prognosis: poor in young; immunodeficiency group.
Bronchiolitis in Autoimmune Disease

- Rheumatoid arthritis/Sjögren’s: approximately 30%.
  - Follicular bronchiolitis.
  - Chronic bronchiolitis.
  - Granulomatous bronchiolitis.
- SLE/PSS/Pemphigus.
  - Chronic bronchiolitis.
  - Cicatricial/constrictive bronchiolitis.
- Ulcerative colitis.
  - Suppurative bronchitis/bronchiectasis with small airway damage.
- Crohn’s disease.
  - Chronic bronchiolitis with or without granulomas.
Bronchiolitis in Autoimmune Disease

Many of the drugs used to treat CVD may independently cause or amplify the risk of developing SAD.
- Penicillamine
- Gold
- Methotrexate

What if we classified SAD solely based on histopathologic changes. . . . . .
Granulomatous SAD

Etiologies:
1. Autoimmune – RA, SS, ABPA.
2. Sarcoidosis.
5. Hypersensitivity pneumonitis.
Eosinophilic SAD

Etiologies:
1. Asthma.
3. Allergic – drug induced, ABPA.
4. Churg-Strauss syndrome.
5. Leukemic infiltrates/hypereosinophilic syndrome.
6. NSHD.
Asthmatic Granulomatosis

• Definition: subset of severe steroid resistant asthmatics who manifest with asthmatic small airway disease with interstitial poorly formed granulomas.


Asthmatic Granulomatosis

• F/M = 9; middle aged with severe nonsteroid responsive asthma; sinus disease; non-smokers.
• Cough, wheeze, chest tightness and SOB.
• PFTs – reversible airflow limitation.
• HRCT – 50% normal; dilation, bronchial wall thickening.
• PB – eosinophilia; normal IgE, negative HSP panel; + atropy (60%).
• 60% self/family history of autoimmune disease.
• + response to non-steroid immunosuppressors

Asthmatic Granulomatosis

• Asthmatic bronchiolitis – mixed infiltrate with eosinophils with mucus plugging with eosinophils, Charcot Leyden crystals; BM thickening; smooth muscle hypertrophy.

• Interstitial pneumonitis – patchy mild alveolar septal mononuclear infiltrate with poorly formed granulomas or giant cells.
1. The diagnosis of SAD/bronchiolar disease is a clinicopathologic one where the histologic SAD is validated for significance by clinical S&S, PFTs and HRCT.

2. Classification of SAD is clinical and/or pathologic – R/O large airway disease.

3. Remember histology ≠ etiology and consider the many possibilities.