The Broad Spectrum of Small Airways Disease

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Aims

Å To review the spectrum of SAD

Å To present the pathologist’s viewpoint

Å To discuss new entities (DIPNECH, NEHI, IBIP, ACIF, ETCé)
SAD — Anatomic definition
CLINICAL AND PATHOLOGIC SETTINGS ASSOCIATED WITH BRONCHIOLAR PATHOLOGY

Asthma
Infections/postinfections
Allergic reactions (eosinophilic pneumonia, hypersensitivity pneumonitis)
Chronic obstructive pulmonary disease
Respiratory (smoker’s) bronchiolitis
Respiratory bronchiolitis-associated interstitial lung disease
Bronchopulmonary dysplasia
Bronchiectasis (regardless of cause)
Collagen vascular diseases
Fume/toxic exposure
Drug reactions
Transplant-associated
Lung transplant rejection
Graft versus host disease following bone marrow transplantation
Conditions associated with cryptogenic organizing pneumonia (Table 8-3)
Aspiration
Diffuse panbronchiolitis
Inflammatory bowel disease
Mineral dust exposure/cobalt lung/nylon flock worker’s lung
Vasculitis (esp. Wegener's granulomatosis)
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (multiple carcinoid tumorlets)
Idiopathic bronchiolitis (including constrictive bronchiolitis)
Miscellaneous: Stevens-Johnson syndrome, neoplasms, thyroiditis, primary biliary cirrhosis, irradiation, lysinuric protein intolerance, ataxia-telangiectasia
How do we classify

* Clinician
* Radiologist
* Pathologist
SAD ï Clinician
Causes

- Infectious bronchiolitis and post-infectious constrictive bronchiolitis
- RB (ILD)
- Diffuse panbronchiolitis
- Asthma
- Mineral dust airways disease
- Fume-related bronchiolar injury
- Idiopathic bronchiolitis (including constrictive obliterative bronchiolitis)

Clinical relevance...
Constrictive (obliterative) bronchiolitis
- Indirect signs on HRCT

“Exudative” bronchiolitis
- Direct signs on HRCT
SAD ï Pathologist

Patterns of tissue damage (distribution/acute v chronic/specific features)

Â NON-SPECIFIC
Â Cellular bronchiolitis (acute, chronic, follicular)
Â (Bronchiolitis obliterans) organising pneumonia
Â Constrictive bronchiolitis
Â Peribronchiolar fibrosis and bronchiolar metaplasia

Â SOME SPECIFIC FEATURES
Â Mineral dust airways disease
Â Asthmatic changes
Â Bronchiolocentric nodules
Â ? SPECIFIC
Â Diffuse panbronchiolitis
Â Respiratory (smokerâ€™s) bronchiolitis
Acute bronchiolitis

- Infection (bacterial and viral)
- Acute fumes/toxins
- Acute aspiration
- Wegener's granulomatosis
Acute and chronic bronchiolitis

- Infection: bacterial/viral
- Distal to bronchiectasis
- Allergic
- Inflammatory bowel disease
- Diffuse panbronchiolitis
- Collagen vascular disease
- Aspiration
- Transplantation
- Wegener's granulomatosis
- Idiopathic
Chronic bronchiolitis

- Distal to bronchiectasis
- Collagen vascular disease
- Inflammatory bowel disease
- Allergic (Asthma, EAA)
- Transplantation
- Lymphoproliferative disease
- DPB and RB
- Chronic aspiration
- Idiopathic
Peribronchiolar fibrosis and bronchiolar metaplasia

- Growth of bronchiolar epithelium along alveoli
- Manifestation of chronic scarring
- Multiple aetiologies
- May be incidental to cause of symptoms
(Bronchiolitis obliterans) organising pneumonia

- Usually minor component of the interstitial pattern of Organising Pneumonia (ATS/ERS Consensus Classification, 2002)
- Varied clinical associations (Organizing diffuse alveolar damage, Organizing drug reactions, fume, and toxic exposures, Connective tissue disease, EAA, Eosinophilic lung disease, Inflammatory bowel disease, secondary or reparative reactions)
- Idiopathic = Cryptogenic
- Occasionally may be BO-OP predominant, ? Significance.
Constrictive obliterative bronchiolitis

- Healed infection
- Healed fume/toxin exposure
- Connective tissue disorders
- Transplantation
- Drug reaction
- Inflammatory bowel disease
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNEH)
- Asthma/EAA
- IDIOPATHIC
Pneumoconiosis/occupational small airways disease

Dusts – talc, asbestos, iron oxide, aluminium oxide, silica, silicates, coal, mixed dust
Asthma and small airways disease

- Not usually biopsied
- Similar features to those in larger airways
- May be complicated by constrictive obliterative bronchiolitis.
- May see follicular bronchiolitis
Follicular bronchiolitis - Part of the spectrum of diffuse pulmonary lymphoid hyperplasia

- Collagen Vascular Diseases
- Immunodeficiency syndromes
- ? Allergic background

LIP
Bronchiolocentric nodules

- Primary cellular (acute, chronic, follicular, DPB, RB, EAA)

- Cellular and fibrotic (HX, Hard metal disease, dust macules, Granulomatous disease (Sarcoid, BCG, Wegener’s, infectious))

- Miscellaneous: DIPNEH, Lymphangitic neoplasms
Bronchocentric Wegener’s granulomatosis
Diffuse panbronchiolitis
Most Western cases are secondary to other pathologies
Respiratory Bronchiolitis-associated Interstitial Lung Disease (RBILD)

- Virtually all smokers.
- A mix of obstructive and restrictive patterns
- May need steroids.
- Good prognosis.

IS THE HISTOLOGY CLINICALLY RELEVANT?
Disorders where bronchioles are primary site of pathology

A  Non-specific features
   • Cellular changes (Acute/acute and chronic/chronic)
   • Fibrotic changes (Peribronchiolar/intraluminal/constrictive)

B  Features suggestive of diseases
   • Follicular bronchiolitis
   • Eosinophilic bronchiolitis
   • Granulomatous bronchiolitis
   • Mineral dust airway disease

C  Disease with specific features
   • Diffuse panbronchiolitis (DPB)
   • Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)
   • Neuroendocrine cell hyperplasia of infancy (NEHI)
   • Other
Disorders where bronchiolar pathology is secondary to other lung disease

Associated with proximal airway disease
- Bronchiectasis
- Asthma
- Chronic obstructive pulmonary disease (COPD)

Associated with interstitial/diffuse lung disease
- Respiratory bronchiolitis
- Extrinsic allergic alveolitis
- Organising pneumonia
- Sarcoidosis
- Langerhans cell granulomatosis
- Wegener's granulomatosis
- **Airway centred interstitial fibrosis (ACIF), centrilobular fibrosis and idiopathic bronchiolocentric interstitial pneumonia (IBIP), Peribronchiolar metaplasia and fibrosis (PBMF)
- Other

** controversy over whether this is a true entity
Key considerations when reviewing a biopsy

1. Multiple patterns of disease may occur
54 year old with rheumatoid arthritis and obstructive LFTs
1. Multiple patterns of disease may occur (eg CTD)

2. Pathologic changes may be primary or secondary
Pathologic changes may be primary or secondary

synchronous secondary changes...
1. Multiple patterns of disease may occur
2. Pathologic changes may be primary or secondary (eg bronchiectasis)
3. Dramatic clinical changes can show minor pathologic features
Indirect changes

Early changes
SAD ë A PATHOLOGISTë VIEWé

1. Multiple patterns of disease may occur (eg CTD)
2. Dramatic clinical changes can show minor pathologic features (eg obliterative bronchiolitis)
3. Pathologic changes may be primary or secondary (eg bronchiectasis)
4. Dynamic process, so acute disease may present in different fashion to chronic disease. The lung may show varied features in active and inactive disease
1. Multiple patterns of disease may occur (eg CTD)
2. Dramatic clinical changes can show minor pathologic features (eg obliterative bronchiolitis)
3. Pathologic changes may be primary or secondary (eg bronchiectasis)
4. Dynamic process, so acute disease may present in different fashion to chronic disease. The lung may show varied features in active and inactive disease

**Clinical and imaging correlation**

**Essential for final clinicopathologic diagnosis and selection of biopsy site**
New entities

Å DIPNECH

Å NEHI

Å IBIP, ACIF
DIPNECH ï Review of 18 cases

• 9 symptomatic cases (Group 1)

• 9 cases as an incidental finding during investigation for another disorder, most frequently malignant disease (Group 2)

• Most patients were female (n=14) and non-smokers (n=15), aged 31-67.
### DIPNECH ï Clinical data

<table>
<thead>
<tr>
<th>Presenting complaints:</th>
<th>Group1</th>
<th>Group 2</th>
<th>Group 1</th>
<th>Group 2</th>
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</thead>
<tbody>
<tr>
<td>Cough</td>
<td>4/9</td>
<td>0/9</td>
<td>4/18</td>
<td></td>
</tr>
<tr>
<td>Increasing dyspnoea</td>
<td>6/9</td>
<td>0/9</td>
<td>6/18</td>
<td></td>
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<tr>
<td>Pleuritic chest pain</td>
<td>2/9</td>
<td>0/9</td>
<td>2/18</td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1/9</td>
<td>1/9*</td>
<td>2/18</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0/9</td>
<td>8/9*</td>
<td>8/18*</td>
<td></td>
</tr>
<tr>
<td>Previous malignancy</td>
<td>0/9</td>
<td>7/9</td>
<td>7/18</td>
<td></td>
</tr>
<tr>
<td>History of asthma</td>
<td>3/9</td>
<td>2/9</td>
<td>5/18</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung function (n=15)</th>
<th></th>
<th></th>
<th>8 : 3 : 4</th>
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<tbody>
<tr>
<td>(Obstructive : Mixed : Normal)</td>
<td>5 : 3 : 0</td>
<td>3 : 0 : 4</td>
<td>8 : 3 : 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean duration of illness before diagnosis</th>
<th>Group1</th>
<th>Group 2</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.6 years</td>
<td></td>
<td>NA</td>
<td>13 years</td>
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<table>
<thead>
<tr>
<th>Bronchoalveolar lavage</th>
<th></th>
<th></th>
<th>Lymphocytosis 2/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytosis 2/2</td>
<td></td>
<td></td>
<td>Lymphocytosis 2/2</td>
</tr>
</tbody>
</table>

** Does not include immunosuppression post transplant (n=1, Group1) and chemotherapy for carcinoma (n=2, Group 2) and chemotherapy for metastatic atypical carcinoid (n=1, Group 2);
*** One patient died of chronic rejection post transplant;
**** One patient died of carcinoma of large bowel at 5 years
# DIPNECH

<table>
<thead>
<tr>
<th>CT findings</th>
<th>Group 1*</th>
<th>Group 2**</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of nodules</td>
<td>4/6</td>
<td>6/6</td>
<td>10/12</td>
</tr>
<tr>
<td>Airway dilatation</td>
<td>2/6</td>
<td>0/6</td>
<td>2/12</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>2/6</td>
<td>0/6</td>
<td>2/12</td>
</tr>
<tr>
<td>Air trapping +/- mosaicism</td>
<td>4/6</td>
<td>0/6</td>
<td>4/12</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1/6</td>
<td>0/6</td>
<td>1/12</td>
</tr>
<tr>
<td>Normal</td>
<td>1/6</td>
<td>0/6</td>
<td>1/12</td>
</tr>
</tbody>
</table>

* One other patient had chest radiograph only, which showed a single nodule
** One other patient had a chest radiograph only, which showed multiple nodules
DIPNECH - Histopathology

<table>
<thead>
<tr>
<th>Histopathological features</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine cell hyperplasia</td>
<td>9/9</td>
<td>9/9</td>
<td>18/18</td>
</tr>
<tr>
<td>Tumourlets</td>
<td>9/9</td>
<td>9/9</td>
<td>18/18</td>
</tr>
<tr>
<td>Typical carcinoid</td>
<td>4/9</td>
<td>5/9</td>
<td>9/18</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>0/9</td>
<td>2/9</td>
<td>2/18</td>
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<tr>
<td>Bronchiolitis</td>
<td>9/9</td>
<td>9/9</td>
<td>18/18</td>
</tr>
<tr>
<td>Obstructive bronchiolitis</td>
<td>7/9</td>
<td>7/9</td>
<td>13/18</td>
</tr>
<tr>
<td>Peribronchial fibrosis</td>
<td>6/9</td>
<td>7/9</td>
<td>12/18</td>
</tr>
<tr>
<td>Bronchiolectasis</td>
<td>4/9</td>
<td>1/9</td>
<td>5/18</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>5/9</td>
<td>4/9</td>
<td>9/18</td>
</tr>
<tr>
<td>TTF-1 staining of NEH/TL</td>
<td>5/5</td>
<td>5/5</td>
<td>10/18</td>
</tr>
<tr>
<td>TTF-1 staining of TC</td>
<td>N/A</td>
<td>3/3</td>
<td>3/3</td>
</tr>
<tr>
<td>TTF-1 staining of AC</td>
<td>N/A</td>
<td>1/2</td>
<td>1/2</td>
</tr>
</tbody>
</table>

NE: neuroendocrine; TTF-1: Thyroid transcription factor-1; NEH: Neuroendocrine cell hyperplasia, TL Tumourlet; TC: Typical Carcinoid; AC: Atypical carcinoid
DIPNECH ï Review of 18 cases

• More common than previously thought

• Increased recognition in part due to increased usage and accuracy of investigative imaging.

• Independent of presentation, most cases remain stable over many years - ? Watch and wait

• Those that show progression - ? Steroid therapy
Deutsch G et al. AJRCCM Dec 2007 - chILD project 1999-2004
Neuroendocrine cell hyperplasia of infancy (NEHI)

Study Population
All diagnostic lung biopsies in children <2 years of age, performed July 1999-July 2004 from 11 children’s hospitals in North America

Excluded case types
Focal lesions
Lobectomies
Segmental resections
Transbronchial biopsies
Needle biopsies
Consultative cases

Study Cohort
187 patients

Review Process
Group review of each case by members of Pathology and Clinical Working Groups

Excluded (n=22)
Inadequate biopsy
Insufficient clinical information
End-stage lung disease

Proposed Classification of Diffuse Lung Disease in Childhood

Disorders more prevalent in infancy (n=59)
- Diffuse developmental disorders (n=11)
  - Alveolar dysplasia (n=10)
  - Congenital alveolar dysplasia (n=2)
  - Alveolar capillary dysplasia with misalignment of pulmonary veins (n=9)
- Growth abnormalities reflecting deficient alveolarization (n=46)
  - Pulmonary hypoplasia (n=7)
  - Chronic neonatal lung disease (n=20)
  - Related to chromosomal abnormalities (n=13)
  - Related to congenital heart disease (n=4)
- Specific conditions of undefined etiology (n=24)
  - Neuroendocrine cell hyperplasia of infancy (n=18)
  - Pulmonary interstitial glycosaminoglycanosis (n=6)
- Surfactant dysfunction disorders (n=18)
  - Surfactant protein B (SP-B) mutations (n=7)
  - ARDS (n=6)
  - Pulmonary alveolar proteinosis (n=2)
  - Chronic interstitial pneumonitis (n=1)
  - Desquamative interstitial pneumonitis (n=1)
  - Nonspecific interstitial pneumonitis (n=1)

Disorders related to systemic disease processes (n=4)
- Immune-mediated collagen vascular disorders (n=4)
- Storage disease (n=1)
- Sarcoidosis (n=1)
- Langerhans cell histiocytosis (n=1)

Disorders of the normal host - presumed immune intact (n=23)
- Infectious/post-infectious processes (n=17)
  - Related to environmental agents
  - Hypersensitivity pneumonitis (n=2)
  - Toxic inhalation (n=8)
  - Aspiration syndromes (n=3)
  - Eosinophilic pneumonitis (n=1)
- Diffuse alveolar damage, unknown etiology (n=5)

Disorders of the immunocompromised host (n=28)
- Opportunistic infections (n=20)
  - Related to therapeutic intervention (n=3)
  - Related to transplantation and rejection (n=4)
- Diffuse alveolar damage, unknown etiology (n=5)

Disorders masquerading as ILD (n=8)
- Arterial hypertension vasculopathy (n=5)
- Congestive changes related to cardiac dysfunction (n=1)
- Veno-occlusive disease (n=2)
- Lymphatic disorders (n=2)
Bronchiolocentric interstitial pneumonias vs SADé

• Bronchiolitis with peribronchiolar organising pneumonia  Thivolet F et al. ERJ 1999;14:272S (Abstract)
• Idiopathic Bronchiolocentric Interstitial Pneumonia (Yousem SA et al. Mod Pathol 2002;15:1148-1153)
• Centrilobular fibrosis  (Pilotto de Calabho et al. Pathol Res Pract 2002;198:577-83)
Airway-centered interstitial fibrosis: a distinct form of aggressive diffuse lung disease

IDIOPATHIC BRONCHIOLOCENTRIC INTERSTITIAL PNEUMONIA (BrIP)
(Yousem and Dacic in Mod Pathol 2002; 15:1148-1153)
PERIBRONCHIOLAR METAPLASIA
(Fukuoka et al. in AJSP 2005;29:948-954)
In the UK, é

Others, including ðOrphan lung diseasesò
10 patients where ðOTHERò was diagnosed by more than one observer.

Problems integrating airway damage into DPLD classification

<table>
<thead>
<tr>
<th>O.L.D. DIAGNOSIS</th>
<th>PATIENTS</th>
<th>NUMBER OF BIOPSIES</th>
<th>ALTERNATE DIAGNOSES</th>
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<tbody>
<tr>
<td>HX (4)</td>
<td>n=1</td>
<td>1</td>
<td>DIP, DAD (2), Non Dx, NSIP</td>
</tr>
<tr>
<td>Epn (5)</td>
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<td>1</td>
<td>DAD (2), OP (2), DIP (1)</td>
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<tr>
<td>LS/e (6)</td>
<td>n=1</td>
<td>1</td>
<td>UNCL (2), FB (1), RB (1)</td>
</tr>
<tr>
<td>IPH (6)</td>
<td>n=1</td>
<td>1</td>
<td>NSIP (2), DIP (1), FB (1)</td>
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<td>AMYLOID (10)</td>
<td>n=1</td>
<td>1</td>
<td>-</td>
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<tr>
<td>LAM (17) EMPHY (2)</td>
<td>n=1</td>
<td>2</td>
<td>NORMAL (1)</td>
</tr>
<tr>
<td>CB (6)</td>
<td>n=1</td>
<td>3</td>
<td>UNCL (9), NSIP (11), Non Dx (2), EAA (2)</td>
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<tr>
<td>BO, Br, PPH</td>
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<td>FB (7)</td>
</tr>
<tr>
<td>BPN(3) EPN(2) BO(1)</td>
<td>n=1</td>
<td>1</td>
<td>NSIP (2), UIP (1), EAA (2), UNCL (1)</td>
</tr>
<tr>
<td>BO (1) HX (1)</td>
<td>n=1</td>
<td>1</td>
<td>OP (5), UIP (1), NSIP (2)</td>
</tr>
</tbody>
</table>
Bronchiolocentric interstitial pneumoniasé
Colby synopsis (USCAP 2008) and critical review

- Female predilection and most patients in their 50s and 60s
- Mortality between series is variable (0% - 45%). No statistical differences in follow-up between series
- None ready for "prime time"
- OR
- Should we have an agreed amalgamated histopathological term?
- Should we remain descriptive with a final CPC term?
- How confident do we need to be to call these hypersensitivity pneumonia (granulomas, evidence of exposure, HRCT) or CTD-related?

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>F</th>
<th>Age</th>
<th>F/U</th>
<th>DOD</th>
<th>Stable</th>
<th>Improved</th>
<th>AWPD</th>
<th>Died</th>
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</thead>
<tbody>
<tr>
<td>Yousem et al.</td>
<td></td>
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<td>Churg et al.</td>
<td>4</td>
<td>8</td>
<td>54</td>
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<td>Fukuoka et al.</td>
<td>2</td>
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<td>57</td>
<td>11</td>
<td>0</td>
<td>6</td>
<td>5</td>
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</tbody>
</table>

Yousem et al. IBIP 2 8 47 9 3 2 1 3 3
Churg et al. ACIF 4 8 54 9 4 2 3 1 4
Fukuoka et al. PBM 2 13 57 11 0 6 5 0 0
Small Airways Disease
Summary \(\text{ï} \) A pathologist’s view

- Method of classifications differ between clinicians, radiologists and pathologists
- *No single view suffices*… Pathology alone will not necessarily provide the *final* diagnosis
- Small airways involvement may only be a component of patient’s disease \(\text{ï} \) are the changes on the biopsy clinically relevant?

- *Gold standard is a multidisciplinary approach.*
Thank you for your attention