Pulmonary manifestations of systemic inflammatory disease

Andrew G Nicholson FRCPath DM

Consultant Histopathologist, Royal Brompton Hospital, London, UK and Professor of Respiratory Pathology, Imperial College School of Medicine, London, UK
AIMS

- To present how specific connective tissue disorders affect the lung and their clinical relevance
- To provide an overview of the spectrum of histological patterns seen in the lung in relation to systemic inflammatory disease
- To discuss the approach to biopsy when a systemic disease affecting the lung is suspected.
<table>
<thead>
<tr>
<th>HISTOLOGIC PATTERN</th>
<th>CLINICOPATHOLOGIC DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual interstitial pneumonia</td>
<td>Idiopathic Pulmonary Fibrosis (CFA)</td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia</td>
<td>Non-specific interstitial pneumonia*</td>
</tr>
<tr>
<td>Respiratory Bronchiolitis (RB)</td>
<td>RB-associated ILD (RB-ILD)</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
<td>Desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>Acute interstitial pneumonia</td>
</tr>
<tr>
<td>Organising pneumonia</td>
<td>Cryptogenic organising pneumonia</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia</td>
<td>Lymphoid interstitial pneumonia</td>
</tr>
</tbody>
</table>

**Consensus classification for idiopathic interstitial pneumonias**

Can these patterns be applied to CTDs?

Do they have the same prognostic significance?
Fibrosing alveolitis in systemic sclerosis

- Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. Wells AU et al. AJRCCM 1994:149;1583-1590

Fibrosing alveolitis in systemic sclerosis

- Histologically identical to lone CFA
- **Pre-recognition of NSIP as a pattern of interstitial pneumonia.**
In 2002 - SScï NSIP (80%)
Interstitial lung disease in PM/DM.

- 14 patients
- UIP was the most common.
- Organising pneumonia (OP) was more favourable prognosis than Usual interstitial pneumonia (UIP).
- DAD had a uniformly poor prognosis.
- One patient with cellular interstitial pneumonia (?NSIP) did well.
Polymyositis-dermatomyositis-associated interstitial lung disease.

- 70 patients with ILD and either PM or DM.
- Jo-1 antibody present in 38%.
- Synchronous associated malignancy in 5.7%.
- **NSIP in 18 of 22 patients (82%)**
- DAD in 9%, OP in 4.5%, UIP in 4.5%.
- Survival was significantly better than that observed for historical control subjects with idiopathic UIP, and was more consistent with survival previously reported in idiopathic NSIP.
Intersitial pneumonias in patients with Sjogren’s syndrome


- 31 cases - **NSIP was the major pathological finding (68%).** Other various pathological findings such as lymphoid hyperplasia (29%), bronchiolitis (16%), lymphoma (13%), amyloid (6%), OP (3%), DAD (3%) and LIP (3%) were seen. *Clinical-Radiological-Pathological Features of Lung Diseases in Patients with Primary Sjogren’s Syndrome* I. Ito et al. AJRCCM
Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease

- UIP: 10, NSIP: 6, and airway disease/OP: 2.
- In three patients, ILD preceded RA; 3 simultaneous diagnosis
- NSIP more frequent in other series (Tansey et al. Histopathology, 2004)
Interstitial pneumonias in connective tissue disorders

- The same spectrum of patterns exists in CTDs as for idiopathic disease
  - Howeveré
  - The prevalence differs overall
  - The prevalence of IP patterns differs for each CTD
The prevalence of interstitial pneumonias in patients with connective tissue diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>RA</th>
<th>SLE</th>
<th>SSc</th>
<th>PM/DM</th>
<th>SjS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UIP</strong></td>
<td>++?</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>NSIP</strong></td>
<td>++?</td>
<td>+?</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>LIP/FB</strong></td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>OP</strong></td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>DAD</strong></td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td><strong>DIP/RB</strong></td>
<td>+/-*</td>
<td>-</td>
<td>+*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

++ = frequent, + = not infrequent, +/- = rare; ? = prevalence currently uncertain; * = Probable incidental to pulmonary symptoms
Overlap states:

- Sameness
- Coexistence
- Transformation**

**may not be readily appreciated by histopathological study
In isolation of CT and clinical data...
Methotrexate-induced hypersensitivity pneumonia

Lymphoid interstitial pneumonia
Pulmonary manifestations of systemic lupus erythematosus

- Pleuritis, pleural effusion (commonest)
- Acute lupus pneumonitis
- Organising pneumonia
- Fibrosing alveolitis (said to be of NSIP pattern)
- Lymphoid interstitial pneumonia
- **Pulmonary thromboembolism**
- **Pulmonary hypertension**
- **Pulmonary vasculitis**
- **Pulmonary haemorrhage**
- **Myopathy in respiratory muscles**
Vasculitis and systemic diseasesé

Patient with SLE
Rheumatoid disease and the lung

- Cricoarytenoid arthritis
- Bronchitis
- Bronchiectasis
- Bronchocentric granulomatosis
- Diffuse panbronchiolitis
- **Follicular bronchiolitis**
- **UIP/NSIP/LIP**
- **Bronchiolitis obliterans**
- Involvement by systemic amyloidosis
- Necrobiotic nodules
- Pulmonary hypertension
- Pulmonary vasculitis
- Carcinoma of the lung
- Lymphoma of the lung
- Pleurisy
- Empyema
54 year old with rheumatoid arthritis and obstructive LFTs

Coexistent pathologies in same anatomic compartment
Remember RA when confronted by a granulomatous nodule

Look for coexistent pathologies in other compartments.
Other connective tissue disorders and the lungé

- Behçet's syndrome and Hughes-Stovin syndrome
- Cutis laxa
- Relapsing polychondritis
- Ehlers-Danlos syndrome
- Pseudoxanthoma elasticum
- Marfan's syndrome
- Hyalinising granuloma/IgG4 disease
Relapsing polychondritis

- Affects connective tissue with high content of GAGs (cartilage, aorta, cornea, sclera)
- 20% associated with rheumatoid arthritis
- Usually involves ears and nose, but may involve respiratory tract (though rarely in isolation)
- Erosion of cartilage plates with chronic inflammatory cell infiltrate and granulomatous inflammation.
- Deformity and scarring of plates
Histopathological spectrum of relapsing polychondritis

Clinical correlation is important***

- e.g. histologic features similar in post-intubation stenosis
EHLERS-DANLOS SYNDROME
Pulmonary manifestations of connective tissue disorders

- **Ehlers-Danlos syndrome:**
  - Haemorrhage,
  - Tracheobronchomegaly,
  - Pneumothoraces,
  - Fibrous scars and pseudotumours (? due to tearing of lung)

- **CAUSE OF SUDDEN DEATH**

- Lung pathology may be the point of diagnosis
Other organ systems and associated lung diseases

- Skin disease
  - Cutaneous manifestations of malignant lung disease
  - Skin disease associated with non-malignant lung disease
- Vascular disease
  - Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu disease)
  - Klippel-Trenaunay syndrome
  - Idiopathic arterial calcification of infancy
  - Blue rubber bleb disease
- Gynaecological and obstetric conditions
  - Meig's syndrome
  - Pregnancy
  - Thoracic endometriosis
- Neuromuscular disease
  - Neurogenic pulmonary oedema
  - Tuberous sclerosis
  - Neurofibromatosis
- Renal disease
  - Renal failure
GI disorders

- Disorders of the upper alimentary tract
- Coeliac disease
- Inflammatory bowel disease
- Whipple's disease
- Pneumatosis coli
- Hepatic disease
- Pancreatic disease
Disorders of the upper alimentary tract associated with aspiration syndromes

- Dental sepsis
- Neuromuscular disease
- Congenital oesophageal atresia
- Congenital tracheo-oesophageal fistula
- Pharyngeal diverticulum
- Aplasia of the oesophagus
- Oesophageal stricture
- Hiatus hernia with gastro-oesophageal reflux
### Pulmonary manifestation of inflammatory bowel disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Granulomatous bronchitis/bronchiolitis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bronchial stenosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Organising pneumonia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fibrosing alveolitis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary eosinophilia (drug related)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pyogenic nodules</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Apical fibrosis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypoproteinaemic oedema</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Many more systemic associations with lung disease than we initially think. Histological patterns are not specific for 'primary vs systemic' association.
Metabolic and endocrine disorders

- Obesity
- Hypercalcaemia and metastatic calcification
- Systemic amyloidosis and systemic light chain deposition
- Storage disorders
- Xanthogranulomatosis
- Alkane lipogranulomatosis
- Erdheim-Chester disease
- Acromegaly
- Thyroid disease
- Diabetes mellitus
- Hypovitaminosis A
Metabolic and endocrine disorders

- Obesity
- Hypercalcaemia and metastatic calcification
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- Erdheim-Chester disease
- Acromegaly
- Thyroid disease
- Diabetes mellitus
- Hypovitaminosis A
Case example

- 44 year old female
- Symptoms of diffuse lung disease
- Possible collagen vascular disease not fitting specific disease pattern.
- Working diagnosis of LAM but slightly atypical HRCT scan
Managing cystic lung disease

- Clinical (CTM)
  - Solitary cyst, Multicystic, Large/hyperlucent, Solid, Otheré
  - Adult versus Paediatric

- Imaging
  - Distribution: ++++
  - Ancillary features: +++
  - Shape of cysts: ++
  - Wall characteristics: (+)
  - Size of cysts: +
  - Profusion of cysts: +
  - **Obvious versus Impossible**

- Pathological
  - Various
  - Neoplastic versus Non-neoplastic

- Pathological
  - Lymphangioleiomyomatosis
  - Langerhans cell histiocytosis
  - Lymphoid interstitial pneumonia
  - Centrilobular emphysema
  - Pulmonary metastases
  - Subacute hypersensitivity pneumonitis
  - Barotrauma / ARDS
  - Desquamative interstitial pneumonia
  - Necrobiotic nodules (late stage)
  - Birt Hogg Dubé syndrome
  - Amyloidosis/Light chain disease
  - Tracheal papillomatosis
  - Neoplasmsé
  - ETC
Amyloidosis, Sjogren’s and lymphoid hyperplasia
Pulmonary amyloidosis

- Symptomatic patients are nearly all of AL-type.
- Other subtypes may involve the lung, but what clinical relevance?

CLASSIFICATION

- A) Anatomical (laryngeal, tracheobronchial, parenchymal)
- B) Local or Systemic
Clinicopathologic approach to pulmonary amyloidosis

- COMPLETE SCREENING
- SAP scan
- CT
- Echocardiography
- Bone marrow investigation
- Serum and urine studies
- Immunohistochemical analysis of biopsy samples

- More accurate prognostic data
May be easier to biopsy site other than the lung.
Storage disorders

- 48 male from Libya.
- Presented with inferior MI, followed by exertional chest pain. Found to have blocked RCA, complex lesion in LAD and severe stenosis in LCxA.
- Episode of possible contamination of oxygen cylinders during initial admission in Libya.
- Noted to have bilateral ground glass shadowing during assessment for CABG.
Uncertain about diagnosis.

- Four relatives with a history of coronary artery disease.
- Smoked commercially available cigarettes (37.5 pack years).
- Heavy exposure to chickens.
- On GTN, omeprazole and dipyridamole at the time of presentation.
- Underwent triple bypass grafting and transfer to ICU. Open lung biopsy taken at the time of surgery.
- Problems weaning from ventilation due to poor gas transfer (22% predicted value).
- Slow recovery with steroid treatment (TLCO up to 33% predicted value).
Lipoid pneumonia

- Aspiration
- Inhalation
- Obstruction
- Drug toxicity

Review of biochemistry on admission showed low HDL level (0.7 [1.1-2mmol/l]).
DIAGNOSIS

NIEMANN-PICK TYPE B

Knowledge of one form of orphan lung disease may help in the treatment of other rare disorders.

- Sequential washout of both lungs leading to an improvement in symptoms, CT scan appearances and LFTs.
Whole lung lavage
Before
After
Pulmonary involvement by inborn errors of metabolism

- **Lysinuric protein intolerance** - Pattern of alveolar proteinosis.
- **Niemann-Pick disease A and B** - only Type B are symptomatic, but both will have pulmonary infiltrates.
- **Fabry’s disease** - Vacuolisation of the intima and media of pulmonary vessels. Rarely presents with COPD.
- **Cholesterol ester storage disease** - May have pulmonary infiltrates and involvement of vessels, but generally no symptoms.
- **Hermansky-Pudlak syndrome**
- **Morquio’s disease**
Drug reactions

- Very rarely is a histologic pattern specific for a drug reaction (eg amiodarone)
- May however be pointers
  1. Eosinophilia
  2. Cytologic atypia within epithelial cells
  3. Variability in patterns may not always be pure and DPLDs may only be one component.

www.pneumotox.com
The features are not classical, but are closest to those of usual interstitial pneumonia, with quite a prominent adjacent DIP-like pattern.

Mixed histological patterns, not classical

Nitrofurantoin therapy

Synergismé ?
Conclusions

- If the patient has a systemic disorder, review the possible pulmonary patterns of disease (a lot more than you think!)
- Clinical correlation essential - may be easier to biopsy other sites, or even not at all.
- Iatrogenic lung disease in relation to treatment of other organ systems

- A few have specific features
- Most overlap with primary pulmonary diseases
- Some overlap with drug reactions
- Involvement of multiple anatomic compartments is a useful histologic feature
- One histologic pattern of disease may progress to another - longitudinal behaviour
- ? Synergism between systemic inflammatory diseases and other disorders
Thank you for your attention
Case example

- 54 year old lady
- Initial presentation with oral ulceration
- Subsequent skin lesions biopsied show small artery vasculitis suggestive of PAN
- Then develops pulmonary mass lesion with marked deterioration of symptoms.
- Serology negative
- Surgical lung biopsy
Case

- ? Behcet’s
- ? Necrotising sarcoidosis
- ? Polyarteritis nodosa
- ? Wegener’s

Diseases do not read textbooks.

Many vasculitides do not fit criteria.
Cases will still undergo biopsy when there is a mass-like lesion mimicking malignancy.

- when there is systemic disease involving the lung and a vasculitic component is suspected
- when there is extreme rarity/atypical presentation leading to a lack of confidence in diagnosis without biopsy
Erdheim-Chester disease


- Histiocytic infiltrates in a lymphangitic pattern with associated fibrosis and lymphoplasmacytic inflammation.
- S-100, CD68, Factor X111a +ve. CD1a negative.
- Electron microscopy studies performed on specimens from two patients showed phagocytic lysosomes but no Birbeck granules.

- Five patients died of disease; one patient with severe respiratory compromise at 4 years.
Look at all anatomic compartments
4 year old with DPLD
Diffuse large B-cell NHL (DLBCL)

DLBCL can occur in FA + CTD but not always carcinomas
Case exampleé

- 36 year old man with congenital lymphoedema who presented with pulmonary lymphangiectasia and alveolar proteinosis.
- ? abnormality of T-cell function in addition. Bone marrow – no significant abnormality.
- After 2 years, he was admitted with right sided scapular pain. CT showed consolidation and sputum grew Aspergillus fumigatus.
- Developed septicaemia and suffered an asystolic cardiac arrest.
Pulmonary disease due to occult systemic disease - longitudinal behaviour

- 1a Septicaemia.
- 1b Invasive aspergillosis.
- 1c Acute myeloid leukaemia.

- 2 Congenital lymphoedema/ alveolar proteinosis
Pulmonary manifestations of polymyositis and dermatomyositis.

- Fibrosing alveolitis
  - 10% in patients with polymyositis (associated with anti-Jo1 antibody)
  - 47-61% in patients with dermatomyositis
- Diffuse alveolar damage
- Organising pneumonia

- Pulmonary haemorrhage
- (Carcinoma/Lymphoma)
- Aspiration pneumonia
- Respiratory muscle weakness
  - Respiratory failure
Pulmonary manifestations of connective tissue disorders

- **Systemic sclerosis**
- NSIP (UIP, sarcoid-like)
- Diffuse alveolar haemorrhage
- Pulmonary hypertension (concentric intimal fibrosis)
- **Associated malignancies**

Biopsies generally only be undertaken for atypical features