Interstitial lung disease in Rheumatology

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  - Boheringer Ingelheim
  - HUB Health Research Solutions
  - Innomar Strategies
Learning Objectives

• Identify clinically significant ILD secondary to rheumatoid disorders.

• Describe management and treatment strategies for ILD in this setting.

• Describe the differential diagnosis of drug-induced lung toxicity.
Interstitial Lung Disease

Diffuse interstitial lines on CXR/chest CT scan

Restrictive ventilatory defect ± desaturation on exertion

Exertional dyspnea ± dry cough
Interstitial Lung Disease

- DPLD of known cause eg, drugs or association eg, collagen vascular disease
  - Idiopathic pulmonary fibrosis
  - Acute interstitial pneumonia
  - Nonspecific interstitial pneumonia (provisional)

- Idiopathic interstitial pneumonias

- Granulomatous DPLD eg, sarcoidosis

- Other forms of DPLD eg, LAM, PLCH, etc.

  - Respiratory bronchiolitis interstitial lung disease
  - Cryptogenic organizing pneumonia
  - Lymphocytic interstitial pneumonia
ILD in rheumatic disorders

• Lung involvement is frequent, but not always clinically significant.

• Lung involvement is a major cause of death in rheumatic disorders.

• Virtually all complications can occur with any of the connective tissue diseases.

• ILD may even present prior to the diagnosis of the underlying connective tissue disease.
Which patients should be screened to identify ILD?

- **Newly diagnosed patients**: baseline lung function testing and CXR are useful to screen and to distinguish drug-induced toxicity from rheumatoid lung.

- **Patients with new opacities on CXR**, especially if the duration of systemic disease is <5 ys.

- **New onset of dyspnea/hypoxemia**, in the absence of infection.
Dole TJ et al. Chest 2014;146:41-50

- 91 (48%) BRASS subjects included in the study

- 41 (45%) had interstitial lung abnormalities (ILA)
  - 7 (8%) had a history of pulmonary fibrosis
  - 38 (45%) had no ILA
  - 34 (40%) had ILA and no history of pulmonary fibrosis
  - 12 (14%) had radiologically severe ILA

Spirometry tables:

- **D**: Spirometry, Pre Bronchodilator
  - FEV\textsubscript{1} L 2.59 100
  - FVC L 3.44 113
  - FEV\textsubscript{1} / FVC % 69 88

- **E**: Spirometry, Pre Bronchodilator
  - FEV\textsubscript{1} L 2.76 70
  - FVC L 3.32 67
  - FEV\textsubscript{1} / FVC % 83 105

- **F**: Spirometry, Pre Bronchodilator
  - FEV\textsubscript{1} L 1.97 56
  - FVC L 2.58 58
  - FEV\textsubscript{1} / FVC % 77 98
Incidence of ILD depends on criteria used

- By HRCT and pulmonary function tests: asymptomatic/preclinical RA-ILD, detectable in 55% of RA patients.

- By consensus forming discussions among 2 respirologists and 2 rheumatologists: 10-, 20- and 30-year cumulative incidence rates for RA-related ILD were 3.5%, 6.3% and 7.7%.
Clinical evaluation

• Ascertainment of dyspnea may be complicated, due to arthritis and immobility as confounding factors.

• Dry cough, inspiratory crackles may be present.

• The 6-minute walk test provides a combined assessment of desaturation during exercise ($O_2$ requirements) and exercise capacity.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I only get breathless with strenuous exercise.</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on level ground or walking up a slight hill.</td>
</tr>
<tr>
<td>2</td>
<td>On level ground, I walk slower than people of the same age because of breathlessness.</td>
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<tr>
<td>3</td>
<td>On level ground, I have to stop for breath when walking at my own pace.</td>
</tr>
<tr>
<td>4</td>
<td>I stop for breath after walking about 100 m or after 5 minutes on level ground.</td>
</tr>
<tr>
<td>5</td>
<td>I am too breathless to leave the house or I am breathless when dressing.</td>
</tr>
</tbody>
</table>
Functional evaluation

• Abnormal pulmonary function may be found in individuals with normal chest x-rays.

• Conversely, the pulmonary function tests may be normal despite the radiographic presence of ILD.

• A mild reduction of DLCO may be the only abnormality.
The role of HRCT

- Patients with functional impairment should undergo HRCT.

- HRCT is very useful in the identification of reversible disease: organizing pneumonia or prominent GG attenuation without associated fibrotic abnormalities.

Clinical relevance and follow-up

- Radiographic progression was observed in 34% to 57% of subjects with subclinical RA-ILD after a mean follow-up of 1.5 to 2 years.

- There should be a high suspicion of ILD in any patient with RA who has respiratory symptoms or functional decrements, especially if the patient has more severe RA.

- Some patients with RA may not have sufficient joint functionality to develop respiratory symptoms, and, thus, the diagnosis of ILD may be missed.

Doyle T et al. CHEST 2014; 146:41-50
Pathologic pattern in CTD-ILD: does it matter?

<table>
<thead>
<tr>
<th>Pathologic pattern</th>
<th>Rheumatoid arthritis</th>
<th>Systemic lupus erythematosus</th>
<th>Systemic sclerosis</th>
<th>Sjögren’s syndrome</th>
<th>Polymyositis/dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ILD: histological patterns</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Usual interstitial pneumonia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(Most common ILD pattern)</td>
<td></td>
<td></td>
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<tr>
<td>Nonspecific interstitial pneumonia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(Rare)</td>
<td>(Most common ILD pattern)</td>
<td>(Most common ILD pattern)</td>
<td>(Most common ILD pattern)</td>
<td>+</td>
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<tr>
<td>Organising pneumonia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>(Rare, but has been reported)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diffuse alveolar damage</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Parenchymal disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>+</td>
<td></td>
<td>(Rare, but has been reported)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td><strong>Pleural disease</strong></td>
<td></td>
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</tbody>
</table>
Usual interstitial pneumonia
Non-specific interstitial pneumonia
Cryptogenic organizing pneumonia
Lymphocytic interstitial pneumonia
Pathologic pattern in CTD-ILD: does it matter?

Park JH et al. Am J Respir Crit Care Med 2007;175:705-11
Lung dominant CTD

- Forty-four patients with biopsy-proven ILD and **serologic** evidence of CTD, but in the absence of **clinical** evidence.

Omote N et al. Chest 2015; published online May 7
The role of BAL

- Patients with RA-ILD had significantly increased numbers of neutrophils recovered in BAL fluid compared with those without ILD.

- A lavage lymphocytosis was found in a subset of patients with normal lung function and chest roentgenogram.

- Marginal role in routine practice.

**BAL**

An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease

<table>
<thead>
<tr>
<th>Lymphocytic cellular pattern</th>
<th>Eosinophilic cellular pattern</th>
<th>Neutrophilic cellular pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;15% lymphocytes</td>
<td>&gt;1% eosinophils</td>
<td>&gt;3% neutrophils</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Drug-induced pneumonitis</td>
<td>Collagen vascular diseases</td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonia (NSIP)</td>
<td>Drug-induced pneumonitis</td>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Bone marrow transplant</td>
<td>Aspiration pneumonitis</td>
</tr>
<tr>
<td>Drug-induced pneumonitis</td>
<td>Asthma, bronchitis</td>
<td>Infection: bacterial, fungal</td>
</tr>
<tr>
<td>Collagen vascular diseases</td>
<td>Churg-Strauss syndrome</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Asbestosis</td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia (COP)</td>
<td>Bacterial, fungal, helminthic, Pneumocystis infection</td>
<td>Acute respiratory distress syndrome (ARDS)</td>
</tr>
<tr>
<td>Lymphoproliferative disorders</td>
<td>Hodgkin’s disease</td>
<td>Diffuse alveolar damage (DAD)</td>
</tr>
</tbody>
</table>

b. Abnormal BAL differential cell patterns that suggest specific types of ILD

A lymphocyte differential count ≥25% suggests granulomatous disease (sarcoidosis, hypersensitivity pneumonitis, or chronic beryllium disease), cellular nonspecific interstitial pneumonia, drug reaction, lymphoid interstitial pneumonia, cryptogenic organizing pneumonia, or lymphoma. CD4+/CD8+ >4 is highly specific for sarcoidosis in the absence of an increased proportion of other inflammatory cell types.

A lymphocyte differential count >50% suggests hypersensitivity pneumonitis or cellular nonspecific interstitial pneumonia.

A neutrophil differential count >50% supports acute lung injury, aspiration pneumonia, or suppurative infection.

An eosinophil differential count >25% is virtually diagnostic of acute or chronic eosinophilic pneumonia.

A cell differential count of >1% mast cells, >50% lymphocytes, and >3% neutrophils is suggestive of acute hypersensitivity pneumonitis.
ILD in rheumatoid arthritis

- In contrast to the predilection of RA for women, RA associated with pulmonary disease is more common in men (ratio of 3:1).

- Smoking and exposure to MTX represent additional risk factors for the development of ILD.

- More frequent in patients with late-onset RA.

- Prevalence is as high as 58%, mostly between the ages of 50 and 60 years. Older age is also a risk factor.

Gabbay E at al. Am J Respir Crit Care Med 1997;156:528-35
Prognostic factors in RA-ILD

- Median survival ranged from 3.2 to 8.1 years.
- Significant predictors of mortality on multivariate:
  - older age
  - male gender
  - lower DLCO
  - extent of fibrosis
  - presence of UIP pattern
- Most studies are of low quality
ILD in scleroderma

- A reduction of the total lung capacity has been noted in 32 to 67%.

- The degree of pulmonary involvement is **not** correlated with the extent of extrapulmonary involvement.

- The greatest rate of decline in lung function occurs in early disease after which the rate of further decline slows.

Tashkin DP et al. Chest 1994;105:489-95
ILD in polymyositis

- Twenty % of patients developed ILD prior to the rheumatologic disease diagnosis.
- Some patients may present with rapidly progressive illness and their muscle disease may be completely missed because of the severity of the lung impairment.

Which patients should be treated?

- **The duration of systemic disease is <5 ys**, indicating a higher risk of clinically significant progression of lung disease.

- **Disease is severe**: many clinicians view a DLCO level <65% as indicative of moderate (as opposed to mild) functional impairment.

- **There is evidence of recent deterioration** - symptomatic, radiographic or functional worsening.
Which treatment should be used?

- Historically, high doses of prednisone have been used, but there is a extreme paucity of outcome data.

- 1\textsuperscript{st} line: prednisone

- 2\textsuperscript{nd} line: azathioprine, mychophenolate mofetil or methotrexate

- 3\textsuperscript{rd} line: cyclophosphamid (1\textsuperscript{st} line in SSc?)
Cyclophosphamide in SSc

- **Scleroderma Lung Study** - 12 months of oral cyc. versus placebo: beneficial effect on FVC, symptoms, skin thickening and health-related quality of life.

Tashkin DP et al. Am J Respir Crit Care Med 2007;176:1026-34
Cyclophosphamide in SSc

- **FAST** study - 6 months of IV cyc. and corticosteroids followed by oral azathioprine versus placebo: trend towards improvement of FVC.

<table>
<thead>
<tr>
<th>Lung function, % predicted</th>
<th>Baseline</th>
<th>1-year followup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment group (n = 22)</td>
<td>Placebo group (n = 23)</td>
</tr>
<tr>
<td>FVC</td>
<td>80.1 ± 10.3</td>
<td>81.0 ± 18.8</td>
</tr>
<tr>
<td>DLCO$_{c}$</td>
<td>52.9 ± 11.5</td>
<td>55.0 ± 12.9</td>
</tr>
<tr>
<td>TLC</td>
<td>81.8 ± 10.1</td>
<td>76.8 ± 16.9</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>79.6 ± 11.5</td>
<td>79.7 ± 19.1</td>
</tr>
<tr>
<td>Kco</td>
<td>71.3 ± 13.4</td>
<td>82.7 ± 19.1</td>
</tr>
</tbody>
</table>

Baseline HRCT‡:
- Disease extent, mean (range) % 20 (6–40) | 19 (5–40) | – | – | – | –
- Ground-glass attenuation, mean (range) % 50 (15–91) | 47 (0–95) | – | – | – | –

Improvement on serial HRCT, no (%)‡: 6 (40) | 3 (20) | 0.39

Dyspnea score, mean (range)§: 7.7 (2–14) | 7.2 (0–18) | 8.75 (0–14) | 7.80 (2–14) | 0.23

Hoyles RK et al. Arthritis Rheum 2006;54:3962-70
MMF in SSc

- Small, retrospective studies (41 pts in total) show stabilization or improvement of FVC after 12 months of therapy.

- MMF was safe and well tolerated.

- Scleroderma Lung Study II (SLS II) is being completed in June.
Pirfenidone in RA and SSc

• Open phase II clinical trial in SSc - safety and tolerability

• An RCT is being planned for RA.
This is a deluxe anti-rheumatic drug!

Why?

It may cost you your lungs!
Drug-induced Lung Disease

- Pulmonary drug complications make up to 7.7% of all adverse reactions. They can mimic acute and chronic pulmonary diseases as clinical, radiographic and histologic characteristics are non-specific.

- They include DAD, diffuse alveolar hemorrhage, NSIP, OP, HP, eosinophilic pneumonia.
43 ys old, seropositive RA, 2 months htx of dyspnea and cough, on MTX for 10 months (switched to s.c 5 months earlier). Hypoxemia (FiO$_2$ 40%), WBC 7, eosinophils 0
Bronchoscopy

- All cultures negative
- Airways looked normal
- Diff. cell count:
  - 76% monocytoid
  - 20% lymphocytes
  - 2% neutrophils
  - 2% eosinophils
Why is it MTX-induced lung toxicity?

• Time line is compatible
• BAL is negative for infection
• No previous evidence of RA-related ILD
• BAL lymphocytosis
History

- Generally, drug-induced ILD develops after a few weeks to a few months.

- Diagnosis is made by excluding other causes.

- Being aware of drug-induced ILD enables the diagnosis to be suspected early and the causative drug withdrawn, which should translate into an improved prognosis.
Risk factors

- Prior lung disease
- Current smoking
- Age >60 years (for MTX)
- Prior reactions to anti-rheumatic drug
- The situation is complex in patients exposed to several drugs capable of causing lung damage.
Dose-related?

• For a few agents (amiodarone, bleomycin, the nitrosoureas, and radiation therapy), dose-related toxicity has been demonstrated.

• However, several ILDs occur after lower doses of these agents.

• Most cases occur unexpectedly as an idiosyncratic reaction in individual receiving relatively long-term treatments with regular does of the causal drug.
Patterns

- **Interstitial** changes, as occur in methotrexate pneumonitis or in eosinophilic pneumonia

- **Alveolar** changes, as occur in drug-induced pulmonary edema or hemorrhage, diffuse alveolar damage, amiodarone pneumonitis.

- **Vascular** changes, as occur in drug-induced angiitis involving either large or small lung vessels.
Methotrexate-induced Lung Disease

- Methotrexate pneumonitis commonly occurs during the first 6 months of therapy.
- No correlation between dose and severity.
- In a recent 2-yr prospective study, incidence was only 1% and there were no late (>6m.) cases.

Sathi N et al. Clin Rheumatol 2012; 31:79-83
72 ys old, seropositive RA diagnosed 2 ys prior, on MTX for 1 year, 1 week htx of fever and cough, presents with dyspnea and hypoxemia (FiO₂ 50%). WBC 12, eosinophils 0
Why it may not be MTX-induced lung toxicity?

- Time line is questionable.
- There is evidence of previous, significant ILD.
- Onset of RA is still relatively recent.
- Acute exacerbations of RA-related ILD are described.

Hozumi H et al. BMJ Open 2013 Sep;3:e003132
38 yrs old, seropositive RA, no improvement with MTX and leflunomide, started on Humira 2 months prior. Four days htx of dyspnea, cough WBC 2.7, eosinophils 0
Bronchoscopy

- All cultures negative

- Transbronchial biopsies: interstitial inflammatory infiltrates with lymphocytes and histiocytes. PJP and fungal stainings negative

- Diff. cell count:
  - 64% monocyctoid
  - 27% lymphocytes
  - 2% neutrophils
  - 4% eosinophils
Why is (probably) it Humira-induced lung toxicity?

- Time line is compatible
- BAL/TBBs are negative for infection
- No previous evidence of RA-related ILD
- BAL lymphocytosis, with eosinophils
61 ys old, pulmonary and cardiac sarcoidosis, LVEF 30-35%. On tacrolimus for 2.5 years. Acute hypoxemic respiratory failure, on MV WBC 9.6, eosinophils 0
Why is infection a primary concern in this case?

- Patient is significantly immunosuppressed
- Patient is not on PJP prophylaxis
- No definite response to diuretic
- Pulmonary acute exacerbations of sarcoidosis are rare.
Differential diagnosis: infection

- Regardless of the pattern of drug-induced ILD, it is important to exclude opportunistic pneumonias: methotrexate, corticosteroids, immunosuppressives, and anti-TNF-α have been associated with the development of bacterial, fungal, and viral infections.
Differential diagnosis: hemodynamic

- Diuresis is usually performed to evaluate the hemodynamic hypothesis. However, diuretic therapy may attenuate the density of nonhemodynamic ILD.

- Therefore, opacities should clear completely for the diagnosis of pulmonary edema to be considered.
Management

- Removal of a drug is generally followed by improvement of symptoms.

- Patients with mild-to-moderate inflammatory ILD will respond quickly, whereas this may not be the case with drugs that cause acute interstitial reactions (e.g., methotrexate pneumonitis) or pulmonary fibrosis.
Management

- Drug removal alone may not be effective in acute drug-induced ILD - once initiated, severe drug-induced reactions may progress at their own pace.

- Methylprednisolone for acutely ill patients, 60-240 mg BID, or steroid pulse

- Prednisone 1 mg/kg
Rechallenge

• Rechallenge of patients with known drug-induced pulmonary fibrosis is generally considered unethical as the pulmonary changes are largely irreversible, and this increases the risk to the patient.

• Rechallenge is also problematic in patients with acute ILD as the relapse may be more severe.
• Rechallenge may be considered if four conditions are present:

(1) there remains a doubt as regards the role of the drug;
(2) the drug is essential to the management of the patient;
(3) no other drug can be used as a substitute;
(4) no reported adverse effects following rechallenge with the drug are known.
Drug-induced lung toxicity: summary

- Clinical, histopathologic and radiographic characteristics are non-specific
- Obtain baseline lung function
- Awareness is the key for diagnosis
- Diagnosis of exclusion
- Drug withdrawal is often followed by improvement

www.pneumotox.com is a valuable source of information.
ILD in rheumatic disorders: summary

- Virtually all ILD complications can occur with any of the connective tissue diseases.
- ILD may present prior to the diagnosis of the underlying connective tissue disease.
- Reduction of DLCO is the first functional abnormality.
- ILD involvement is not always clinically significant, but some patients deserve follow-up.
ILD in rheumatic disorders: summary

- The identification of the histology pattern is not as important as in idiopathic conditions and, on average, the outcome is better.

- Due to the resultant morbidity and mortality from these processes, pulmonary involvement needs to be recognized early, diagnosed accurately and treated aggressively.

- Clinical trials are urgently needed.
Thank you! London