ILD and systemic disease

Dr. med. Manuela Funke-Chambour

Oberärztin I
Female patient, born 1945

- Portuguese

- Presented with cough and dyspnea, no other symptoms

- Non-Smoking

- Reflux

- Medication: PPI

- Comorbidities
  - OSA (under CPAP)
Female patient, born 1945

- Clinical status: bibasal inspiratory crackles

- Lung function 2011:
  - FVC 1.85 l (107%)
  - FEV1 1.31l (94%)
  - DLCOc 60%

- 6 MWT: 295 m (66%), minimal Saturation 89%
- aBGA: normal
Female patient, born 1945
Female patient, born 1945

- **Bronchoscopy 2012:**
  - Normal cell distribution (90% macrophages, 2% lymphocytes, 3% granulocytes)
  - No pathogens
  - TBB: unspecific findings

- **Heart ultrasound:** normal, no PH

- **Laboratory 01.2012:**
  - RF <11 IU/ml
  - ANA 1:80
  - SS-A (Ro) negative
  - SS-B (La) negative
  - p/c ANCA negative

- **Steroidtrial 01/2012-06/2012-** no improvement
What is your diagnosis?
Female patient, born 1945

- Diagnosis IPF (progressive within 6 months)
- treatment with nintedanib (2x150mg/d) initiated
Female patient, born 1945

2015
Female patient, born 1945

2015

- Lung function 2015:
  - FVC 1.44 l (88%)
  - FEV1 1.31l (100%)
  - DLCOc 32%

- Heart ultrasound: normal, no PH

- new joint pain

- Laboratory 05.2015:
  - RF : 586 IU/ml, anti CCP: 198 U
  - ANA 1:80
  - SS-A (Ro)negative
  - SS-B (La) negative
  - p/c ANCA negative

- Revised diagnosis of ILD due to rheumatic disease
- Stop nintedanib after upper GIT bleeding
### RA and lung

#### Table 1: Respiratory complications of rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Lung structure</th>
<th>Disease manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung parenchyma</td>
<td>- Interstitial lung disease (ILD)</td>
</tr>
<tr>
<td></td>
<td>- Usual interstitial pneumonitis (UIP)</td>
</tr>
<tr>
<td></td>
<td>- Nonspecific interstitial pneumonitis (NSIP)</td>
</tr>
<tr>
<td></td>
<td>- Bronchiolitis obliterans with organizing pneumonia (BOOP)</td>
</tr>
<tr>
<td></td>
<td>- Lymphocytic interstitial pneumonitis (LIP)</td>
</tr>
<tr>
<td></td>
<td>- Desquamative interstitial pneumonitis (DIP)</td>
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<tr>
<td></td>
<td>- Diffuse alveolar damage (DAD)</td>
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<tr>
<td></td>
<td>- Drug-induced pneumonitis</td>
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<tr>
<td></td>
<td>- Rheumatoid nodules (necrobiotic nodules)</td>
</tr>
<tr>
<td></td>
<td>- Caplan's syndrome (silicosis associated with RA)</td>
</tr>
<tr>
<td></td>
<td>- Infectious complications</td>
</tr>
<tr>
<td>Airways</td>
<td>- Chronic obstructive pulmonary disease (COPD)</td>
</tr>
<tr>
<td></td>
<td>- Bullous emphysema</td>
</tr>
<tr>
<td></td>
<td>- Bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>- Obliterative bronchiolitis (Constrictive bronchiolitis)</td>
</tr>
<tr>
<td>Pleura</td>
<td>- Pleuritis</td>
</tr>
<tr>
<td></td>
<td>- Pleural effusion</td>
</tr>
<tr>
<td></td>
<td>- Spontaneous pneumothorax</td>
</tr>
<tr>
<td>Vascular</td>
<td>- Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>- Diffuse alveolar hemorrhage</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>- Diaphragm weakness</td>
</tr>
<tr>
<td></td>
<td>- Cricoarytenoid arthritis with extrathoracic obstruction</td>
</tr>
</tbody>
</table>

ILD in RA

• 50% of RA patients will develop lung involvement


• 10% of RA patients will develop ILD with additional 33% with undiagnosed ILD


• ILD counts for 7-20% mortality of RA patients


Specific risk factors:

- RF > 100IU/ml associated with RA-ILD

- Anti-CCP antibodies increase risk for RA-ILD

- High anti-CCP2 levels are associated with ILD in RA patients
ILD in RA - autoimmunity

Restrepo JF et al. Clinical and laboratory factors associated with interstitial lung disease in rheumatoid arthritis
Clinical Rheumatology. September 2015, Volume 34, Issue 9 pp 1529-1536
Pathogenesis of rheumatoid arthritis associated-interstitial lung disease (RA-ILD)

Environmental/epigenetic factors

Genetic predisposition

Increased citrullination of proteins

Epithelial damage

Autoimmunity

Inflammation
- TNF-α, TNF-β, VEGF
- PDGF, IL-1, IL-4, IL-5, IL-13, chemokines

Fibrosis
- Fibroblast proliferation/differentiation

Proliferation

Synthesis

Degradation

Antiprotease

Protease

ECM

MMP

Higher levels of CCP antibodies

RA-ILD

Rheumatoid arthritis

HLA-B54, HLA-DQ1B*0601, HLA-B40, HLA-DR4 Men [RA-ILD]

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Megan Shaw et al. Eur Respir Rev 2015;24:1-16
Pathogenesis of rheumatoid arthritis associated-interstitial lung disease (RA-ILD)

1. Immune response against citrullinated peptides in the joints
   • NSIP pattern

2. Immune response against citrullinated peptides in the lung
   • UIP pattern

Lung biopsy specimens of RA-associated interstitial pneumonia (IP) and idiopathic IP, stained using an anti-modified citrulline antibody.
Usual interstitial pneumonia pattern RA

Megan Shaw et al. Eur Respir Rev 2015;24:1-16
Why does clinical diagnosis matter for UIP?

- Anti-fibrotic drugs are only tested and approved for IPF
- Off-label use should be avoided and be monitored in clinical study settings/registries
Example: UIP pattern

- Specific criteria for radiological UIP
- Specific criteria for histopathological UIP
- But not a clinical diagnosis!!
UIP pattern – exclusion of other causes

- chronic HP
- asbestosis
- drug-induced lung diseases
- IPF
- familial pulmonary fibrosis
- Hermansky-Pudlak syndrome
- rheumatic disease (rheumatoid arthritis, systemic sclerosis)
Suspected IPF
- Dyspnea, therapy resistant cough
- Velcro-like crackling upon lung auscultation
- O₂-Desaturation, restrictive lung function, chest X-ray

Pulmonological evaluation
- Clinical symptoms, laboratory screening
- Bodyplethysmography with diffusion capacity
- Chest scan (HRCT)
- Bronchoscopy with bronchoalveolar lavage
  +/- transbronchial Biopsies

Not consistent

Alternative Diagnosis

Consistent

multidisciplinary ILD Board

Not determined

Alternative Diagnosis

Consistent

Further investigations (e.g. Wedgebiopsy)

Idiopathic pulmonary Fibrosis

Signs for Connective tissue disease in ILD patients

Specific clinical features
- Distal digital fissuring (i.e. “mechanic hands”)
- Distal digital tip ulceration
- Inflammatory arthritis or polyarticular morning stiffness
- Palmar and face teleangiectasie
- Raynaud's phenomenon
- Unexplained digital edema
- Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

Basic laboratory analysis:
- complete blood count
- inflammatory markers
- liver and kidney function
- CK, LDH, aldolase
- urine analysis

Auto-antibody testing in ILD

Basic laboratory testing and Follow-up

ANA (IF)

positive

Signs and symptoms suspicious of:
- MCTD
- SLE
- Systemic Sclerosis
  - CREST

Advanced laboratory testing

- U, RNP
- Sm
- ds-DNA
- Topo-I, Th/To, CENP-B
- RNA Polymerase III

Chronic HP
- UIP
- IPF
- Rheumatic disease (rheumatoid arthritis, systemic sclerosis)
- Familial pulmonary fibrosis
- Asbestosis
- Drug-induced lung diseases
- Hermansky-Pudlak syndrome

Auto-antibody testing in ILD
ANA fluorescence pattern and related auto-antibodies.

<table>
<thead>
<tr>
<th>ANA Pattern</th>
<th>Antibody</th>
<th>CTD</th>
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</thead>
<tbody>
<tr>
<td><strong>Nuclear (most frequent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-homogeneous</td>
<td>dsDNA</td>
<td>SLE</td>
</tr>
<tr>
<td>-speckled</td>
<td>U₁-RNP</td>
<td>MCTD</td>
</tr>
<tr>
<td></td>
<td>Ro/SSA, La/SSB</td>
<td>Sjögren Syndrome</td>
</tr>
<tr>
<td></td>
<td>SmD</td>
<td>SLE</td>
</tr>
<tr>
<td></td>
<td>Mi-2</td>
<td>Myositis (DM)</td>
</tr>
<tr>
<td>-centromeric</td>
<td>CENP-B</td>
<td>SSc</td>
</tr>
<tr>
<td>-nucleolar</td>
<td>RNA-Polymerase III</td>
<td>SSc</td>
</tr>
<tr>
<td></td>
<td>Topoisomerase I (SCL70)</td>
<td>SSc</td>
</tr>
<tr>
<td></td>
<td>Th/To</td>
<td>SSc</td>
</tr>
<tr>
<td></td>
<td>PM-SCL 75/100</td>
<td>Overlap Syndrome</td>
</tr>
<tr>
<td><strong>Cytoplasmatic (less frequent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-speckled</td>
<td>t-RNA synthetase (Jo-1, PL-7, PL-12)</td>
<td>ASS/Myositis</td>
</tr>
<tr>
<td></td>
<td>mitochondrial, ribosomal, cytoskeletal, Golgi apparatus, lysosomes</td>
<td></td>
</tr>
<tr>
<td><strong>Mitotic (rare)</strong></td>
<td>mitotic spindle (tubulin), centrosomes (enolase), NuMA, CENP-F</td>
<td></td>
</tr>
</tbody>
</table>

Auto-antibody testing in ILD

Basic laboratory testing and Follow-Up

ANA (IF)
AND
Jo-1
Myositis / ASS
AND
SSA (Ro52 Ro60)
SSB (La)
Sjögren Syndrome
AND
RF
CCP
RA
AND
ANCA (IF)
MPA

Signs and symptoms suspicious of:

positive

• MCTD
• SLE
• Systemic Sclerosis
• CREST

Advanced laboratory testing

• U, RNP
• Sm
• ds-DNA
• Topo-I, Th/To, CENP-B RNA Polymerase III

Signs and symptoms suspicious of:

negative

• ASS
• Myositis
• Overlap Syndrome

advanced laboratory testing

PL 7, PL 12
OJ, EJ, KS,
Mi-2, MDA-5

PM/Scl-75
PM/Scl-100

MPO-ANCA (EIA)

Positive Results
Rheumatologist and Multidisciplinary Approach
Negative Results
Follow-Up

Conclusion

- Search for systemic disease is crucial for ILD diagnosis
- One time antibody titer might be insufficient
- ILD can be present before systemic symptoms
Thank You!
Grazie!
Merci!
Vielen Dank!