Pulmonary Fibrosis and Inflammation

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Pulmonary research laboratory, DBMR
Overview

1. Overview lung and lung parenchyma
2. Pulmonary Fibrosis
3. Acute exacerbation
4. Treatment options
1. Conclusion
The healthy lung

Nose, Pharynx:
Warming, humidification

Trachea, Bronchi:
Transportation,
Immunological functions

Alveoli:
Gas exchange
Immunological functions
Function of the Lung

- Lung is responsible for gas exchange

- Respiration:
  - Inspiration of Oxygen
  - Expiration of CO₂

- Gas exchange
  - in alveoli
  - depends on lung parenchymal surface and thickness
Air-blood barrier

Inflammation in parenchymal lung diseases

PD Dr. med. Manuela Funke-Chambour
Interstitial lung diseases (ILD)

- Thickening of interstitial tissue
- Impairs gas exchange and oxygenation

Dr. S. Berezowska, Pathologie Uni Bern
Risk factors for ILD

Infection and microbiome

Smoking

Occupational exposure

Underlying Systemic Diseases

http://www.bioedge.org/bioethics/th-case-for-banning-smoking/11668

http://www.who.int/topics/environmental_pollution/en/
Classification of interstitial lung diseases

- Known cause or association:
  - Connective tissue diseases
  - Occupational causes
  - Drug side-effects
- Granulomatous:
  - Sarcoidosis
  - Hypersensitivity pneumonitis
  - Infections
- Other forms, e.g.:
  - Lymphangioleiomyomatosis
  - Histiocytosis X

Major
- Chronic fibrosing
  - Idiopathic pulmonary fibrosis
- Smoking related
- Acute and subacute

Unclassifiable

Rare
- Idiopathic pleuroparenchymal fibroelastosis
- Idiopathic lymphocytic interstitial pneumonia

Acute interstitial pneumonia

Non-specific interstitial pneumonia

Respiratory bronchiolitis-ILD

Cryptogenic organising pneumonia

Desquamative interstitial pneumonia


Idiopathic pulmonary fibrosis

- Fatal lung disease
- Prognosis is extremely poor, no cure available
- The cause is not known
- Unpredictable decline of lung function due to fibrosis

1) ATS/ERS/JRS/ALAT. Am J Respir Crit Care Med 2011;183:788-824
2) Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68
Idiopathische Lungenfibrose - Definition

Usual Interstitial Pneumonia- UIP

Hansell D M et al. Radiology 2008;246:697-722

Idiopathic Pulmonary Fibrosis.

Table 2. Fibrotic Interstitial Lung Diseases (ILDs) of Known Cause That Mimic IPF. *

<table>
<thead>
<tr>
<th>Condition</th>
<th>Examples or Causes</th>
<th>Clues from the Patient History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hypersensitivity</td>
<td>Mold, avian antigens, mycobacteria, isocyanates (specific exposures are often</td>
<td>Microbes in the home or workplace from forced-air heating,</td>
</tr>
<tr>
<td>pneumonitis</td>
<td>not identifiable)</td>
<td>humidifiers, hot tubs, water damage, or visible mold; indoor or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>caged birds, down or feather bedding, agricultural exposure</td>
</tr>
<tr>
<td>Connective-tissue disease-related</td>
<td>Rheumatoid arthritis, systemic sclerosis, idiopathic inflammatory myopathy (e.g.,</td>
<td>Joint pain, stiffness, or swelling; skin thickening or tightening;</td>
</tr>
<tr>
<td>ILDs</td>
<td>anti-synthetase syndrome, Sjögren's syndrome</td>
<td>rash; dry eyes; dry mouth; heartburn; muscle pain or tenderness;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>Drug-induced ILDs</td>
<td>Amiodarone, methotrexate, nitrofurantoin, chemotherapeutic agents</td>
<td>Medication history</td>
</tr>
<tr>
<td>Pneumoconiosis (occupational</td>
<td>Asbestos, coal workers’ pneumoconiosis, silicosis, berylliosis</td>
<td>Occupational history and exposures</td>
</tr>
<tr>
<td>ILDs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ANA denotes antinuclear antibodies, anti-CCP anti–cyclic citrullinated peptide antibodies, CK cm
† Crackles are noted on lung examination in nearly all cases. Reticulation with or without traction
Classification of interstitial lung diseases


Hypersensitivity pneumonitis - HP
Exogen allergic alveolitis - EAA

• Results from repeated exposure to various organic particles
• acute, subacute, chronic forms

### Etiological agents of HP

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungal and bacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer’s lung</td>
<td>Saccharopolyspora rectivirgula</td>
<td>Moldy hay, grain, silage</td>
</tr>
<tr>
<td>Ventilation pneumonitis; humidifier lung; air conditioner lung</td>
<td>Thermoactinomyces vulgaris, Thermoactinomyces sacchari, Thermoactinomyces candidus, Klebsiella oxytoca</td>
<td>Contaminated forced-air systems; water reservoirs</td>
</tr>
<tr>
<td>Bagassosis</td>
<td>T. vulgaris</td>
<td>Moldy sugarcane (i.e., bagasse)</td>
</tr>
<tr>
<td>Mushroom worker’s lung</td>
<td>T. sacchari</td>
<td>Moldy mushroom compost</td>
</tr>
<tr>
<td>Enoki mushroom worker’s lung (Japan)</td>
<td>Penicillium citrinum</td>
<td>Moldy mushroom compost</td>
</tr>
<tr>
<td>Suberosis</td>
<td>Thermoactinomyces viridis, Aspergillus fumigatus, Penicillium frequentans, Penicillium glabrum</td>
<td>Moldy cork</td>
</tr>
<tr>
<td>Detergent lung; washing powder lung</td>
<td>Bacillus subtilis enzymes</td>
<td>Detergents (during processing or use)</td>
</tr>
<tr>
<td>Malt worker’s lung</td>
<td>Aspergillus fumigatus, Aspergillus clavatus</td>
<td>Moldy barley</td>
</tr>
<tr>
<td>Sequoiosis</td>
<td>Graphium, Pullularia, and Trichoderma spp., Aureobasidium pullulans</td>
<td>Moldy wood dust</td>
</tr>
<tr>
<td>Maple bark stripper’s lung</td>
<td>Cryptostroma corticale</td>
<td>Moldy maple bark</td>
</tr>
<tr>
<td>Cheese washer’s lung</td>
<td>Penicillium casei, A. clavatus</td>
<td>Moldy cheese</td>
</tr>
<tr>
<td>Woodworker’s lung</td>
<td>Alternaria spp., wood dust</td>
<td>Oak, cedar, and mahogany dust, pine and spruce pulp</td>
</tr>
<tr>
<td>Hardwood worker’s lung</td>
<td>Paecilomyces</td>
<td>Kiln-dried wood</td>
</tr>
<tr>
<td>Paprika slicer’s lung</td>
<td>Mucor stolonifer</td>
<td>Moldy paprika pods</td>
</tr>
<tr>
<td>Sauna taker’s lung</td>
<td>Aureobasidium spp., other sources</td>
<td>Contaminated sauna water</td>
</tr>
<tr>
<td>Familial HP</td>
<td>B. subtilis</td>
<td>Contaminated wood dust in walls</td>
</tr>
</tbody>
</table>

| **Animal proteins** | | |
| Animal protein's lung; pigeon fancier's lung | Avian droppings, feathers, serum | Parakeets, budgerigars, pigeons, chickens, turkeys |
| Pituitary snuff taker's lung | Pituitary snuff | Bovine and porcine pituitary proteins |
| Fish meal worker's lung | Fish meal | Fish meal dust |
| Bat lung | Bat serum protein | Bat droppings |
| Furrier's lung | Animal fur dust | Animal pelts |
| Animal handler’s lung; laboratory worker’s lung | Rats, gerbils | Urine, serum, pelts, proteins |

### References
Hypersensitivity pneumonitis: pathogenesis

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-Mediated Hypersensitivity</td>
<td>IgG-Mediated Cytotoxic Hypersensitivity</td>
<td>Immune Complex-Mediated Hypersensitivity</td>
<td>Cell-Mediated Hypersensitivity</td>
</tr>
<tr>
<td>Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators</td>
<td>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC</td>
<td>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils</td>
<td>Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage</td>
</tr>
</tbody>
</table>

**Type I**
- Allergen
- Fc receptor for IgE
- Allergen-specific IgE
- Degranulation

**Type II**
- Fc receptor
- Cytotoxic cell
- Surface antigen
- Target cell
- Immune complex

**Type III**
- Immune complex
- C3b
- Complement activation
- Neutrophil

**Type IV**
- Antigen
- Sensitized T_{DTH}
- Cytokines
- Activated macrophage
Pulmonary Lungenfibrose - Pathogenesis

Courtesy of Sabina Berezowska
Lung injury and normal wound healing
Dysregulation of any of these responses can contribute to fibrosis.
CAUSES OF LUNG FIBROSIS
Unpredictable clinical course of IPF

Median survival after diagnosis (years)

Lung function / Symptoms

Rapid decline

Slow decline

Acute exacerbation, embolism and pulmonary infections

PD Dr. med. Manuela Funke-Chambour
Acute IPF exacerbationen

• Steroids without scientific proof

Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75.
Idiopathic pulmonary fibrosis (IPF) - patient 1

- Male patient, born 1960
- Diagnosed with IPF 2015 (Wedge Biopsy)

Nintedanib

PD Dr. med. Manuela Funke-Chambour
Idiopathic pulmonary fibrosis (IPF)- patient 1

Died Mai 2017 due to respiratory failure

Pneumonia (left)
Idiopathic pulmonary fibrosis (IPF)- patient 2

Male, born 1945

09/2016 03/2017 04/2017
Fibrosis progression after pneumonia in IPF

Pulmonary infections (Pneumonia)

Pneumonia patient

Usually no fibrosis

IPF patient

Fibrosis progression

Why is the response different?
TLR4 activation by LPS reduces profibrotic markers in fibroblasts from controls via Smad3

TGF-β receptor expression is reduced after TLR4 stimulation in controls and depends on TLR4

Viral infections can increase risk for pulmonary fibrosis


<table>
<thead>
<tr>
<th>Study</th>
<th>All Viruses</th>
<th>OR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasithiotaki et al (2011)</td>
<td></td>
<td>0.38 (0.10-1.41)</td>
<td>6.03</td>
</tr>
<tr>
<td>Lok et al (2001)</td>
<td></td>
<td>51.00 (2.57-1,011.25)</td>
<td>3.49</td>
</tr>
<tr>
<td>Calabrese et al (2013)</td>
<td></td>
<td>8.44 (2.32-30.78)</td>
<td>6.08</td>
</tr>
<tr>
<td>Tang et al (2003)</td>
<td></td>
<td>56.89 (6.62-489.06)</td>
<td>4.66</td>
</tr>
<tr>
<td>Folcik et al (2014)</td>
<td></td>
<td>1,849.00 (35.06-97,503.81)</td>
<td>2.49</td>
</tr>
<tr>
<td>Tang et al (2001)</td>
<td></td>
<td>82.50 (8.38-812.63)</td>
<td>4.45</td>
</tr>
<tr>
<td>Tsukamoto et al (2000)</td>
<td></td>
<td>6.40 (0.65-62.84)</td>
<td>4.46</td>
</tr>
<tr>
<td>Stewart et al (1999)</td>
<td></td>
<td>5.57 (1.52-20.45)</td>
<td>6.07</td>
</tr>
<tr>
<td>Bando et al (2008)</td>
<td></td>
<td>0.80 (0.14-4.48)</td>
<td>5.36</td>
</tr>
<tr>
<td>Pozharskaya et al (2009)</td>
<td></td>
<td>19.00 (0.83-434.45)</td>
<td>3.32</td>
</tr>
<tr>
<td>Wootton et al (2011)</td>
<td></td>
<td>0.53 (0.19-1.51)</td>
<td>6.46</td>
</tr>
<tr>
<td>Pulkkinen et al (2012)</td>
<td></td>
<td>41.67 (1.96-887.56)</td>
<td>3.40</td>
</tr>
<tr>
<td>Lawson et al (2008)</td>
<td></td>
<td>38.29 (1.99-737.37)</td>
<td>3.52</td>
</tr>
<tr>
<td>Kelly et al (2002)</td>
<td></td>
<td>1.26 (0.35-4.56)</td>
<td>6.10</td>
</tr>
<tr>
<td>Miyake et al (2005)</td>
<td></td>
<td>1.01 (0.28-3.60)</td>
<td>6.11</td>
</tr>
<tr>
<td>Dwomiczak et al (2004)</td>
<td></td>
<td>1.36 (0.29-6.42)</td>
<td>5.66</td>
</tr>
<tr>
<td>Rabea et al (2015)</td>
<td></td>
<td>1.08 (0.41-2.84)</td>
<td>6.58</td>
</tr>
<tr>
<td>Santos et al (2013)</td>
<td></td>
<td>0.73 (0.15-3.47)</td>
<td>5.64</td>
</tr>
<tr>
<td>Ushiki et al (2014)</td>
<td></td>
<td>0.42 (0.03-6.06)</td>
<td>3.89</td>
</tr>
<tr>
<td>Saraya et al (2018)</td>
<td></td>
<td>0.93 (0.28-3.07)</td>
<td>6.24</td>
</tr>
<tr>
<td>Overall ($I^2 = 76.0%$, $P = .000$)</td>
<td></td>
<td>3.48 (1.61-7.52)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
CAUSES OF LUNG FIBROSIS
Treatment of fibrotic lung diseases

Pirfenidone

CAPACITY

ASCEND


Treatment of fibrotic lung diseases

Nintedanib

New treatment approaches

Azithromycin has enhanced effects on lung fibroblasts from idiopathic pulmonary fibrosis (IPF) patients compared to controls. Resp Res 2020 Jan 15;21(1):25.

New treatment approaches

Azithromycin has enhanced effects on lung fibroblasts from idiopathic pulmonary fibrosis (IPF) patients compared to controls. Resp Res 2020 Jan 15;21(1):25.
Azithromycin has enhanced effects on lung fibroblasts from idiopathic pulmonary fibrosis (IPF) patients compared to controls. Resp Res 2020 Jan 15;21(1):25.
Conclusions

• Inflammation and infection influence disease course in lung fibrosis

• Inflammatory receptors and regulators are involved in fibrosis development and progression

• New approaches are needed to improve mortality, specifically after pulmonary infection in patients with pulmonary fibrosis
Sprechstunde für interstitielle Lungenerkrankungen und Sarkoidose