Immunological lung diseases
Hypersensitivity pneumonitis and sarcoidosis

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Aims

• Understand the immunological mechanisms of hypersensitivity pneumonitis

• Understand the immunological alterations in sarcoidosis

• Understand that inflammation leads to fibrosis in some individuals
Overview

• Hypersensitivity pneumonitis
• Sarcoidosis
• Inflammation and fibrosis
Hypersensitivity pneumonitis

- acute, subacute or chronic lung disease
- Lymphocytic and granulomatous inflammation
- Affects peripheral airways, alveoli and surrounding interstitial tissue (alveolobronchiolitis)
- Lymphocytic alveolitis in BAL (CD4/CD8 ratio may be decreased)
- Non-IgE mediated allergic reaction

Hypersensitivity pneumonitis

- Induced by variety of organic materials or low-molecular weight agents
  - Bacteria
  - Fungi
  - animal proteins
  - plant proteins
  - low-molecular weight chemicals
  - metals

# 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>Wood trimmer’s lung</td>
<td>Rhizopus spp., Mucor spp.</td>
<td>Contaminated wood trimmings</td>
</tr>
<tr>
<td>Composter’s lung</td>
<td>T. vulgaris, Aspergillus</td>
<td>Compost</td>
</tr>
<tr>
<td>Basement shower HP</td>
<td>Epicoccum nigrum</td>
<td>Mold on unventilated shower</td>
</tr>
<tr>
<td>Hot tub lung</td>
<td>Mycobacterium avium complex</td>
<td>Hot tub mists; mold on ceiling</td>
</tr>
<tr>
<td>Wine maker’s lung</td>
<td>Botrytis cinerea</td>
<td>Mold on grapes</td>
</tr>
<tr>
<td>Woodsmen’s disease</td>
<td>Penicillium spp.</td>
<td></td>
</tr>
<tr>
<td>Thatched roof lung</td>
<td>Saccharomonospora viridis</td>
<td>Dead grasses and leaves</td>
</tr>
<tr>
<td>Tobacco grower’s lung</td>
<td>Aspergillus spp.</td>
<td>Tobacco plants</td>
</tr>
<tr>
<td>Potato riddler’s lung</td>
<td>Thermophilic actinomycetes, S. rectivirgula, T. vulgaris, Aspergillus spp.</td>
<td>Moldy hay around potatoes</td>
</tr>
<tr>
<td>Summer-type pneumonitis</td>
<td>Trichosporon cutaneum</td>
<td>Contaminated old houses</td>
</tr>
<tr>
<td>Dry rot lung</td>
<td>Merulius lacrymans</td>
<td>Rotten wood</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Aspergillus fumigatus; T. actinomycetes</td>
<td>Esparto dust</td>
</tr>
<tr>
<td>Machine operator’s lung</td>
<td>Mycobacterium immunogenum; Pseudomonas fluorescens</td>
<td>Aerosolized metalworking fluid</td>
</tr>
<tr>
<td>Residential provoked pneumonitis</td>
<td>Aureobasidium pullulans</td>
<td>Residential exposure</td>
</tr>
<tr>
<td>Amebae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humidifier lung</td>
<td>Naegleria gruberi, Acanthamoeba polyphaga, Acanthamoeba castellani, Bacillus sp., others</td>
<td>Contaminated water from home humidifier, ultrasonic misting fountains</td>
</tr>
<tr>
<td>Shower curtain disease</td>
<td>Phoma violacea</td>
<td>Moldy shower curtain</td>
</tr>
<tr>
<td><strong>Animal proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigeon breeder’s or pigeon fancier’s disease</td>
<td>Avian droppings, feathers, serum</td>
<td>Parakeets, budgerigars, pigeons, chickens, turkeys</td>
</tr>
<tr>
<td>Pituitary snuff taker’s lung</td>
<td>Pituitary snuff</td>
<td>Bovine and porcine pituitary proteins</td>
</tr>
<tr>
<td>Fish meal worker’s lung</td>
<td>Fish meal</td>
<td>Fish meal dust</td>
</tr>
<tr>
<td>Bat lung</td>
<td>Bat serum protein</td>
<td>Bat droppings</td>
</tr>
<tr>
<td>Furrier’s lung</td>
<td>Animal fur dust</td>
<td>Animal pelts</td>
</tr>
<tr>
<td>Animal handler’s lung; laboratory worker’s lung</td>
<td>Rats, gerbils</td>
<td>Urine, serum, pelts, proteins</td>
</tr>
<tr>
<td><strong>Insect proteins</strong></td>
<td></td>
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<tr>
<td>Miller’s lung</td>
<td>Sitophilus granarius (i.e., wheat weevil)</td>
<td>Dust-contaminated grain</td>
</tr>
<tr>
<td>Lycoperdonosis</td>
<td>Puffball spores</td>
<td>Lycoperdon puffballs</td>
</tr>
<tr>
<td><strong>Familial HP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td><strong>Antigen</strong></td>
<td><strong>Source</strong></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>


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Hypersensitivity pneumonitis: pathogenesis

Hypersensitivity pneumonitis: pathogenesis

- Activated B-lymphocytes release IgG antibodies (contribute to disease or marker of exposure?)
  

- increased IL-17 production with defective Treg-cell function
  

Hypersensitivity pneumonitis - HP

- HRCT scan
- bronchiolocentric granulomatous lymphatic alveolitis

Hypersensitivity pneumonitis - HP

Diagnosis of acute/subacute occupational HP

Predictors of HP
1. Exposure to known offending antigen at workplace
2. Recurrent symptoms 4-8h after exposure
3. Positive specific IgG (precipitating) antibodies
4. Inspiratory crackles
5. HRCT pattern compatible with acute/subacute HP

Possible substitute for missing feature
1. Lymphocytosis in BAL
2. Signs of acute/subacute HP in lung pathology
3. Positive inhalation challenge test or improvement after avoidance


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Chronic occupational HP Diagnosis

4 or more criteria
1. Exposure to known offending antigen at workplace
2. Positive specific IgG (precipitating) antibodies

Or
1. Lymphocytosis in BAL
2. Reduced DLCO and/or hypoxemia at rest or exercise
3. HRCT pattern compatible with chronic HP
4. Signs of chronic HP in lung pathology
5. Positive inhalation challenge test or improvement after avoidance

Hypersensitivity pneumonitis – HP: Identification of possible Antigens

Antigen exposure
- Serological confirmation of exposure
  - Precipitines
  - Specific antibodies (IgG)


- Antigen challenge
Surgical lung biopsy in HP

- Airway-centered, variably cellular chronic interstitial pneumonia
- Lymphocyte-rich chronic bronchiolitis
- Poorly formed non-necrotizing granulomas

X20: UIP pattern

X200: peribronchiolar lymphocyte infiltrate with multinucleated giant cell

Pathological criteria for HP

<table>
<thead>
<tr>
<th>Classic Features of Hypersensitivity Pneumonitis</th>
<th>Additional Features or Clues</th>
<th>Correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolocentric chronic interstitial pneumonia</td>
<td>Organizing pneumonia (may or may not be present)</td>
<td>Correlate histology with clinical and radiographic findings whenever possible</td>
</tr>
<tr>
<td>Chronic bronchiolitis</td>
<td>Airway-centered interstitial fibrosis</td>
<td>Incomplete or unknown clinical information: suggest a thorough clinical investigation</td>
</tr>
<tr>
<td>Peribronchiolar interstitial giant cells with or without vaguely formed nonnecrotizing granulomas (giant cells and granulomas can be in airspaces only)</td>
<td>Suspect when NSIP or UIP pattern is associated with interstitial giant cells or vaguely formed nonnecrotizing granulomas</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

Multidisciplinary approach to HP

- Helpful as > 50% of patients with HP have no clear exposure
- Multidisciplinary discussion helps to distinguish HP from idiopathic ILD

Identification of antigen is crucial

- Directly linked to mortality
  

- Continued exposure can lead to chronic fibrosing forms
Bird fancier disease - Lovebirds

Current precipitins, including parrots negative.

Individual prepared precipitins positive!

Diagnosis HP - example

• Bird fancier disease
  • Most common HP
  • Lovebirds- parrots species (Psittacidae)
  • Psittacidae
    1. Lovebirds (genus agapornis)- Africa
    2. Budgerigars (genus Melopsittacus)- Oceania
    3. Macaws (genus ara)- Südamerika
Lovebirds fancier disease

Lovebirds

Budgerigars

Macaws

Fossil evidence of the Triassic land reptile Lystrosaurus.

Fossil remains of Cynognathus, a Triassic land reptile approximately 3m long.

Fossil remains of the freshwater reptile Mesosaurus.

Fossils of the fern Glossopteris, found in all of the southern continents, show that they were once joined.
Sarcoidosis: Patient 1965

- dyspnea (mMRC 2)
Bronchoscopy (before referral):

Cytology: no malignant cells, lymphocytic alveolitis

Mucosal biopsy:
no malignant cells,
no granuloma
Sarcoidosis: Patient 1965

Mediastinoscopy (before referral)

- 2/4 LK non-necrotising lymphnodes
- no mycobacteria (Ziehl-Neelsen), negative fungus staining
Sarcoidosis: Patient 1965

- **Heart Ultrasound:** EF 35%

- **Cardiac MRI:**

  compatible with cardiac sarcoidosis

**Diagnosis:** Sarcoidosis Stage I with cardiac involvement
Sarcoidosis: Clinical Symptoms

- Weight loss (20 %)
- Eye or skin involvement
- Acute form „Löfgren Syndrome“ (20 %)
- (fever, erythema nodosum, lymph nodes, arthralgia)
# Sarcoidosis: Organs involved

<table>
<thead>
<tr>
<th>Organ</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal lymphnodes</td>
<td>95-98%</td>
</tr>
<tr>
<td>Lung</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Liver</td>
<td>50-80%</td>
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<tr>
<td>Spleen</td>
<td>40-80%</td>
</tr>
<tr>
<td>Eye</td>
<td>20-50%</td>
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<tr>
<td>Peripheral Lymphnodes</td>
<td>30%</td>
</tr>
<tr>
<td>Skin</td>
<td>25%</td>
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<tr>
<td>Nervous system</td>
<td>10%</td>
</tr>
<tr>
<td>Clinical heart involvement</td>
<td>5%</td>
</tr>
</tbody>
</table>

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Sarcoidosis: Silzbach/Scadding Stages

BRITISH MEDICAL JOURNAL
LONDON SATURDAY NOVEMBER 4 1961

PROGNOSIS OF INTRATHORACIC SARCOIDOSIS IN ENGLAND
A REVIEW OF 136 CASES AFTER FIVE YEARS' OBSERVATION
BY
J. G. SCADDING, M.D., F.R.C.P.
Director of Studies, Institute of Diseases of the Chest, Brompton

I  II  III  IV
Sarcoidosis: Diagnosis

- 90% diagnosis with BAL, TBB and EBUS
  Prasse A. Sarkoidose – was ist neu? Dtsch Med Wochenschr 2017;142:825-828.

- Lymphocytosis marked by elevated BALF CD4/CD8 ratio (>3.5) supports diagnosis

- Bronchoscopy - EBUS
Sarcoidosis

Noncaseating granulomata

T cell mediated disease

bronchocentric

Courtesy from Dr. Sabina Berezowska, Pathology Department University of Berne, Switzerland
Granuloma

Sarcoidosis: Risk factors

• Genetic predisposition

- HLA-DRB1*03
- MHC2TA rs3087456
- HLA-DRB1*12
- HLA-DRB1*14
- HLA-DRB1*15

SNPs
- CCR2 haplotype 2
- BTN2L rs3117099T
- BTN2L rs2076530A
- NOTCH4
- ANXA11 rs230C
- XAF1
- IL23R rs12069782
- rs11209026A
- TNF

Prasse A. Sarkoidose – was ist neu? Dtsch Med Wochenschr 2017;142:825-828.


Sarcoidosis: Risk factors

- **Infectious agents**
  - Mycobacteria (past infections?)
  - Propionibacteria
  - Fungals, others

- **Self antigen**
  - vimentin

- **Environmental factors** - World trade center collapse

Prasse A. Sarkoidose – was ist neu? Dtsch Med Wochenschr 2017;142:825-828.


Sarcoidosis: Immunological dysfunction

- CD4+ T cells, Th1 polarised disorder
- T cells dysfunction (Th1, Th17, Treg)
- exaggerated immune response to a specific antigen (Kveim)
Pathogenesis of sarcoidosis – historical view

Pathogenesis of sarcoidosis – new insights

Pathogenesis of sarcoidosis
- New concept of T-cell plasticity


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Pathogenesis of sarcoidosis
- double trouble

Treatment of sarcoidosis

- Immunosuppressive/cytotoxic
  - Prednison
  - Azathioprin
  - Mycophenolat mofetil

- Modulation of cytokines
  - Methotrexat
  - Leflunomid
  - Cyclosporamine
  - TNF-alpha Antagonists

- Other (Hydroxychloroquin)

Baughman RP et al. A Concise Review of Pulmonary Sarcoidosis
Treatment of sarcoidosis: New approaches

Sarcoidosis: Monitoring of Treatment Response

• Improved symptoms, functional improvement

• Inflammatory markers:
  • Soluble Interleukin-2-Receptor (sIL-2 or sCD25)
  • Neopterin
  • Angiotensin- Conversions Enzym (ACE)

• Activity measurements (PET)
Acute vs chronic sarcoidosis

Sarcoidosis - fibrotic pulmonary disease

CAUSES OF LUNG FIBROSIS

FIBROSIS

INFLAMMATION
Pulmonary Fibrosis - example IPF

Pathomechanism of fibrotic sarcoidosis

Pathomechanism of fibrotic sarcoidosis

TH-17 in IPF

Celada LJ et al. PD-1 up-regulation on CD4+ T cells promotes pulmonary fibrosis through STAT3-mediated IL-17A and TGF-β1 production. Sci Transl Med. 2018 September 26; 10(460).
PRO-FIBROTIC MECHANISMS

Lung Injury (known or unknown) combined with Tissue Response (normal or abnormal)

- Inflammation
- Oxidative Stress
- Coagulation disturbances

Resident fibroblasts: proliferation, resistance to apoptosis, differentiation into myofibroblasts, collagen production
Bone marrow-derived fibroblast precursors: homing to the lungs, differentiation into myofibroblasts
Epithelial injury and apoptosis: disturbed interaction with mesenchymal cells, epithelial-mesenchymal transition (EMT)

Excess deposition and/or reduced turnover of extracellular matrix (ECM)

PULMONARY FIBROSIS

Todd NW et al. Molecular and cellular mechanisms of pulmonary Fibrosis. Fibrogenesis & Tissue Repair 2012, 5:11
Chronic forms of sarcoidosis - fibrotic forms

- Fibrotic lung disease is difficult to treat and most often irreversible
Fibrosis in HP and sarcoidosis
- Gene expression profiles of patients

Analysis of genes differentially expressed between:

- idiopathic pulmonary fibrosis (IPF)
- hypersensitivity pneumonitis (HP)
- Sarcoidosis (self-limiting: N-SL and fibrotic P-F)

Key messages

- Hypersensitivity pneumonitis is an immune mediated disease upon antigen exposure

- Sarcoidosis is an exaggerated immune response with unclear agents

- Sarcoidosis has a defective Th17 and Treg response

- Hypersensitivity pneumonitis and sarcoidosis present with acute and chronic forms

- Chronic inflammation can lead to currently irreversible fibrosis
Vielen Dank

Pneumologie Inselspital
Oberarzt-Sucher

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