Fibrosing interstitial lung diseases of idiopathic and exogenous origin. Phenotype approach.

Conference, Postgraduate and Scientific Course

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Rare exogenous ILDs. (ILDs caused by metals, organic dusts toxic syndrome, et al).
Fibrosing interstitial lung diseases of idiopathic and exogenous origin.
Prague – 20.06.2014

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Organic dust toxic syndrome (ODTS)

- Acute febrile reaction following **single** heavy exposure to (mould contaminated) organic dust
  - “silo unloader’s syndrome”
  - “pulmonary mycotoxicosis”
  - grain fever
  - (cotton) mill fever
  - intensive pig farming

= non infectious, non allergic “toxic alveolitis”
≠ acute Hypersensitivity Pneumonitis
≠ acute Extrinsic Allergic Alveolitis, i.e. ≠ ILD!
ODTS

• 4 to 8 h after exposure:
  • flu-like symptoms
    • fever
    • malaise
  • muscle & joint aches
  • (moderate) respiratory symptoms
  • massive influx of polymorphonuclear cells in BAL
  • peripheral leukocytosis
ODTS

• spontaneous resolution in 24 to 48 h
• cause: bacterial endotoxin ?
• tolerance
  • does not occur in chronically exposed
  • occurs after exposure-free period
• no sequelae (?)
• frequent, but unreported, overlooked or misdiagnosed
ODTS

- all jobs or circumstances with potential heavy exposure to organic dusts or bioaerosols
  - agriculture & horticulture
  - transportation, storage & handling of food stuffs
  - textile & wood industry
  - garbage treatment, sewage & composting
  - old buildings, archives, ...
  - humidifiers
  - swimming pools, ...
“Inhalation fevers”

- Organic Dust Toxic Syndrome (ODTS)
- Metal Fume Fever (MFF)
- Polymer Fume Fever (PFF)
Metal fume fever

- Single exposure to high concentrations of some metal oxides (ZnO, CuO, ...)
  - smelting
  - welding (galvanized metal)
  - galvanizing
  - brazing
  - metallizing (gun-spraying Zn)

- in enclosed spaces or poorly ventilated conditions

- CdO, Os₃O₄, V₂O₅, MnO: more severe pneumonitis (life-threatening pulmonary oedema)
Polymer fume fever

- Exposure to heated F-containing polymers, typically: polytetrafluoroethylene (PTFE) > 300°C
  - PTFE resin moulding & extrusion
  - welding of PTFE-coated metal
  - high-speed machining of PTFE
  - smoking cigarettes contaminated with PTFE
- also heated Cl-containing polymers (PVC)?
- also heated polymers containing Br-based flame retardants?

! May be severe (pulmonary oedema → †)
- No tolerance, possible sequelae (fibrosis)
Inhalation fevers

• 4 - 8 h after exposure influenza-like reaction
  • fever, chills, malaise, g-i upset, muscle pains
  • [metallic taste]
  • mild respiratory symptoms
  • chest x-ray: transient infiltrates possible
    + features of pulmonary oedema if severe
  • LFT: VC (↓), DLco (↓), PaO₂ (↓)
  • pmn ↑↑ in blood and BAL

• self-limited: usually resolution in 24 - 48 h
• tolerance ("Monday fever"), except in PFF
Inhalation fevers

- pathogenesis:
  - non allergic
  - non infectious
  - massive influx of pmn in lung

- “toxic alveolitis”

- activation of cytokine networks
  - macrophages - epithelium?

- switch-off mechanism? tolerance?

- long-term effects? “no sequelae”
Zinc Fume Fever

  • 26 volunteers welding on galvanized steel (15-30 min)
  • BAL 3, 8 or 22 h later
  • pmn 2%, 12 %, 37 %  // ZnO in air
  • ↑TNF (↑↑ 3 h), (IL-1), IL-6, IL-8
• Larsson et al. AJRCCM 1994, 150, 973-7
  • 14 previously unexposed volunteers weighing swines in swine-confinement building (700 pigs) for 2-5h
  • BAL 2 wk before & after 24 h
  • total BAL cells x4
  • BAL pmn x 75 (1% → 28%)
    ↑ // dust & endotoxin
  • blood WBC & CRP
Inhalation fevers

Differential diagnosis

• Other causes of FUO
• Infections (viral, ...)
• Pulmonary oedema (CdO, PTFE, ...)
• Hypersensitivity pneumonitis
• Occupational asthma
Case

- Man, 43 y, smoker, no previous disease
- Visit to Emergency Department:
  - fever, malaise, dry cough, dyspnoea
  - evening: WBC 17,200 (82% pmn), CRP 7 mg/L
  - morning: WBC 11,800 (69% pmn), CRP 53 mg/L, PaO₂ 63 mmHg
- Chest X-ray:
« atypical respiratory infection »
R/ clarithromycin
Case

• Second visit to ED 10 days later:
  • similar symptoms
  • WBC 21,400 (81% pmn), CRP 11 mg/L, PaO₂ 74 mmHg
  • Chest X-ray and HRCT
«sprayed an aerosol to prepare new cars (1 can/car)» Fluorocarbon-containing spray

Toxic alveolitis caused by fabric protection spray
Case

- no infectious organisms detected
- R/ methylprednisolone
- rapid improvement, discharged after 5 days
  - normal pulmonary function, including DLco
  - normal chest X-ray
- 4 months follow-up: further symptomatic improvement
Fabric protection sprays

- Sprays for impregnation of leather or fabrics (shoes, jackets, furnishings, …) (water/dirt repellant, waterproofing, “anti-rain”, …)
  - Fluorine-containing hydrocarbons
  - + propellant (organic solvents)

→ severe pulmonary damage in consumers, domestic animals, workers

Fabric protection sprays

• 2002-2003 reports of (severe) pulmonary injury in users of fabric & leather protection sprays

• The Netherlands
  Bonte et al. *Ned T Geneesk*, 2003, 147, 1185-8
  • Rotterdam, 5 patients [~70 cases reported to PCC]

• Switzerland
  • Lausanne, 6 patients [153 cases reported to PCC]
  • Switzerland: 102 cases

• Belgium
  • Leuven, 3 men (36-43 y)
Change in propellant (solvent with more pleasant smell)
Take home messages

• Not all clinical pictures of acute respiratory infection are due to infection
• Acute lung injury may occur following use of commonly available consumer products
• Old materials in new formulations!
• Take an occupational history in all patients!
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Exposure to metals

- is not confined to metal mining and metallurgy
- the respiratory tract is not necessarily the primary target
- respiratory disease in metal-exposed workers may be due to non-metallic agents
  - other minerals (crystalline SiO$_2$, asbestos, …)
  - gaseous agents (CO, SO$_2$, NO$_x$, …)
  - organic chemicals (solvents, resins, …)
  - Metal Working Fluids (= mineral oil + water + …)
  - microbiological agents (mycobacteria, fungi, …)
### “Pneumoconioses” caused by metals

- Siderosis & welders’ pneumoconiosis (Fe)
- Dental technician’s pneumoconiosis
  - SiO$_2$, Be, Vitallium (Cr-Co-Mo), …
- Aluminium (Al)
  - “aluminosis” is rare and controversial
  - granulomatous reactions (DD sarcoidosis)
- Stannosis (Sn)
- Barytosis (Ba)
- Rare earth / cerium pneumoconiosis (Ce, lanthanides)
- Carborundum pneumoconiosis (SiC)
Metals and diseases of the lung parenchyma (3 specific examples)
ILD due to “hypersensitivity”

low “intrinsic” toxicity

x

immune sensitization

“Low” Dose

Susceptibility
Chronic Beryllium lung Disease (CBD, Berylliosis)

- Be used in (light) alloys (aerospace, electronics, dental, ...), ceramics, nuclear weapons, ...
- Granulomatous lung disease ( = sarcoidosis)
- Cellular (type IV) immune response to Be
- Diagnosis: Be Lymphocyte Proliferation Test
  Ex vivo incubation of lymphocytes with Be salt
  If proliferation (SI > 3): proof of sensitization to Be
- High susceptibility if HLA-DPβ1 glu69
- Also other metals: Zr, Al, Ti, Cr?
Sarcoidosis and CBD


- 84 sarcoidosis patients with possible exposure to Be were re-evaluated for Be exposure (1997-2005; Borstel, Freiburg, Tel Aviv)
  - detailed occupational history
  - 2 Be-LPT with blood lymphocytes
  - 34 diagnosed with CBD
## TABLE 2

Workplaces and occupational settings with beryllium exposure identified by occupational case history

<table>
<thead>
<tr>
<th>Occupational beryllium exposure</th>
<th>CBD</th>
<th>Exposed sensitised healthy</th>
<th>Exposed nonsensitised healthy</th>
<th>Sarcoidosis exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals</td>
<td>34</td>
<td>7</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Dental technician/dentist</td>
<td>13 (7/6)</td>
<td>1 (1/0)</td>
<td>4 (4/0)</td>
<td>10 (6; 4)</td>
</tr>
<tr>
<td>Engine development/mechanics/ automobile industry</td>
<td>2 (1/1)</td>
<td>2 (2/0)</td>
<td>1 (1/0)</td>
<td>7 (7/0)</td>
</tr>
<tr>
<td>Brass alloys, beryllium-containing alloys*</td>
<td>4 (4/0)</td>
<td>1 (1/0)</td>
<td></td>
<td>14 (8/6)</td>
</tr>
<tr>
<td>Metallurgic factory</td>
<td>2 (1/1)</td>
<td></td>
<td></td>
<td>4 (1/3)</td>
</tr>
<tr>
<td>Aircraft production and maintenance</td>
<td>3 (2/1)</td>
<td></td>
<td></td>
<td>2 (2/0)</td>
</tr>
<tr>
<td>Nonsparking tools</td>
<td>1 (1/0)</td>
<td></td>
<td>1 (1/0)</td>
<td>1 (1/0)</td>
</tr>
<tr>
<td>Radiation shielding</td>
<td>1 (0/1)</td>
<td></td>
<td>1 (1/0)</td>
<td></td>
</tr>
<tr>
<td>Military vehicle armour</td>
<td>2 (1/1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescent lamps</td>
<td>2 (1/1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microelectronics/electrical relays</td>
<td>1 (1/0)</td>
<td></td>
<td>1 (1/0)</td>
<td>8 (6/2)</td>
</tr>
<tr>
<td>Chemical industry†</td>
<td>1 (1/0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engraving of gems</td>
<td>1 (1/0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ore mining</td>
<td>1 (1/0)</td>
<td></td>
<td></td>
<td>1 (1/0)</td>
</tr>
<tr>
<td>Grinding of optical lenses for precision instruments</td>
<td></td>
<td>1 (1/0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect‡</td>
<td></td>
<td></td>
<td>1 (1/0)</td>
<td>2 (2/0)</td>
</tr>
</tbody>
</table>

Data are presented as total n (patients in Germany/patients in Israel). CBD: chronic beryllium disease. *: galvanic industry, ship yards, metal processing; †: additive to glass, ceramics, plastics/catalyst; ‡: i.e. contaminated garments.
Take home message

- Sarcoidosis is a diagnosis of exclusion!
- always evaluate the possibility of an exogenous cause
  - silica
  - talc
  - beryllium (Be-LPT)
  - other metals (aluminium, zirconium, …)
  - “inorganic particles” (WTC)
  - atypical mycobacteria

Cobalt (Co)
ILD due to “hypersensitivity”

low “intrinsic” toxicity

“idiosyncracasy”

“Low” Dose

Susceptibility
“Hard metal”

- Man-made composite material
  - 85-95% tungsten carbide (WC) + 5-15% Co + Ni, Cr, carbides of Ta, Ti, Nb
  - “cemented carbides” or “cermets”
- produced by sintering
  = conversion of compacted powder into a polycrystalline material
  - “sintered carbides”

≠ “heavy metal” (Cd, Pb, Hg)
“Hard metal”

• Properties
  • high heat resistance → hardness almost like diamond (“Widia”)

• used for
  • drilling rocks, cement, bricks, glass, ...
  • cutting wood, ceramics, foodstuffs, ...
  • machining, grinding, polishing metals, etc
  • specialised tools & machine parts
Hard metal
Diamond-cobalt

- “Diamond tools”
  - microdiamonds bonded with Co (up to 90%) (also other metals used for bonding)

- used for
  - cutting stone, marble, glass, crystal, roads, …
  - grinding & polishing various materials
  - polishing (faceting) diamonds
Diamond tooling
Diamond polishing with diamond-cobalt disks
Hard metal lung disease
Cobalt lung
Giant Cell Interstitial Pneumonia (GIP)

Clinical presentation

± similar to hypersensitivity pneumonitis

• subacute alveolitis

± work-related:

• dry or productive cough
• dyspnoea, chest tightness
• flu-like symptoms
+ asthenia, fatigue, weight loss
+ nasal & upper airway symptoms
possibly + asthma
Clinical presentation

± similar to hypersensitivity pneumonitis

• **fibrotic lung disease**
  
  with or without prior subacute manifestations:
  
  • gradual dyspnoea
  
  • weight loss
  
  • digital clubbing
  
  • cyanosis
  
  • fine crackles
  
  ➢ cor pulmonale
Clinical presentation

± similar to hypersensitivity pneumonitis

- fibrotic lung disease
  with or without prior subacute manifestations:
  - gradual dyspnoea
  - weight loss
  - digital clubbing
  - cyanosis
  - fine crackles
  - cor pulmonale
F - 24 y - NS
diamond polisher
TLC 49% pred
DLco 27% pred
Thermal spraying of hard metal

Hard facing
giant cell interstitial pneumonia (GIP) = specific feature of HMD, but not always present
also other features:
- lymphoplasmocytic infiltration (no granulomas)
- hyperplasia alveolar epithelium
- cell desquamation in alveoli (DIP)
- BOOP pattern possible
bronchiolocentric distribution
various stages: normal / inflammation / fibrosis
BAL
GIP - cobalt lung
Pathology

Naqvi et al. Pathologic spectrum and lung dust burden in Giant Cell Interstitial Pneumonia (Hard Metal Disease/ Cobalt pneumonitis). Arch Environ Occup Health 2008, 63, 51-70

- 100 cases of HMD (1958-2002)
  - 59 with GIP
  - 41 with $>2.10^6$ particles containing W /cm$^3$ lung (SEM/EDS)

- Co detected in only 6%
Multinucleated giant cells showing cannibalism

Naqvi et al.
Arch Environ Occup Health 2008, 63, 51-70

Figs. 2a-2e. Characteristic MGCs showing “cannibalism.” Semithick plastic section (Figure 2d) reveals incorporation of individual macrophages not yet fused into canniblastic pattern. Typical canniblastic MGC found in BAL (Figure 2e) also shows contained fine opaque particles.
GIP

Naqvi et al.
Arch Environ Occup Health
2008, 63, 51-70

Fig. 3. MGCs conforming to the shape of the alveoli.

Figs. 4a, 4b. Multinucleated alveolar lining epithelium.
Moriyama et al. Two-dimensional analysis of elements and mononuclear cells in hard metal lung disease. AJRCCM 2007, 176, 70-77

- 17 patients with HMLD (13 GIP, 4 “atypical” GIP)
- Electron probe microanalysis (EPMA) with wavelength-dispersive spectrometry (WDS)
- Immunohistochemistry (CD8\(^+\), CD163\(^+\))

[+ editorial by Nemery & Abraham]
Moriyama et al. AJRCCM 2007, 176, 70-7
Pathogenesis?

- immunologic mechanisms?
- genetic susceptibility? HLA-DPβ glu69

- synergy Co + other particles (WC)
  - no ILD reported if exposure to Co only
  - animal studies & *in vitro* studies

- pro-oxidant mechanisms?
Cobalt
(e^- donor)

Tungsten Carbide
(e^- carrier)

Co^{x+}

Active oxygen species!

Indium - Tin Oxide (ITO)
Indium-Tin Oxide (ITO)

Homma S. et al. Pulmonary fibrosis in an individual occupationally exposed to inhaled indium-tin oxide. *ERJ* 2005, 25, 200-4

- Man, 30 y, light smoker (3 cig/d for 3 y)
- Exposure for 4 y to ITO (90% \( \text{In}_2\text{O}_3 \) / 10% \( \text{SnO}_2 \))
  - Manufacture of flat-panel displays (LCD, plasma screen)
- Dry cough and exertional dyspnoea; normal PFT
- Chest x-ray: reticulonodular shadows (right upper f)
Indium-Tin Oxide (ITO)

Homma S. et al. *ERJ* 2005, 25, 200-4

- CT
• VATS
Homma S. et al. ERJ 2005, 25, 200-4

- Electron probe X-ray microanalysis

+ SEM with EDX
  In 61%, Sn 4%
ITO plant
- 108 male workers (24 ex-workers)
- mean age: 34 y [20-60 y]
- mean duration of exposure: 3.6 y [0.8-17 y]
- serum Indium: GM 8 ng.mL$^{-1}$ [0-127] ↑ with exposure duration; (control: GM 0.3 ng.mL$^{-1}$)
- exposure to Indium: GM 0.01 – 0.05 mg.m$^{-3}$ (max: 0.36); (particles Ø 2.5 µm [0.1-11 µm])

- HRCT: interstitial changes in 23 subjects
- Serum KL-6 > 500 U.mL-1 in 40 subjects Related to serum Indium
  More disease in wet-surface grinding of ITO
Facility producing ITO (USA) (~ 15 workers)

2 cases of Pulmonary Alveolar Proteinosis

A. Male, nonsmoker, 49 y
   - September 2000 (after 9 month): dyspnea + dry cough
   - Diagnosis of PAP (HRCT, pathology)
   - October 2006: death in respiratory failure

B. Male, smoker, 39 y
   - 2005 (6 to 9 months after hire): dyspnea, dry cough, chest tightness
   - Diagnosis of PAP (HRCT, pathology)
   - 2009: partial improvement after bilateral whole lung lavage; autoAB against GM-CSF +
Pathology

Cummings et al. AJRCCM 2010, 181, 458-64
Background: Reports of pulmonary fibrosis, emphysema, and, more recently, pulmonary alveolar proteinosis (PAP) in indium workers suggested that workplace exposure to indium compounds caused several different lung diseases.

Methods: To better understand the pathogenesis and natural history of indium lung disease, a detailed, systematic, multidisciplinary analysis of clinical, histopathologic, radiologic, and epidemiologic data for all reported cases and workplaces was undertaken.

Results: Ten men (median age, 35 years) who produced, used, or reclaimed indium compounds were diagnosed with interstitial lung disease 4-13 years after first exposure (n = 7) or PAP 1-2 years after first exposure (n = 3). Common pulmonary histopathologic features in these patients included intraalveolar exudate typical of alveolar proteinosis (n = 9), cholesterol clefts and granulomas (n = 10), and fibrosis (n = 9). Two patients with interstitial lung disease had pneumothoraces. Lung disease progressed following cessation of exposure in most patients and was fatal in two. Radiographic data revealed that two patients with PAP subsequently developed fibrosis and one also developed emphysematous changes. Epidemiologic investigations demonstrated the potential for exposure to respirable particles and an excess of lung abnormalities among coworkers.

Conclusions: Occupational exposure to indium compounds was associated with PAP, cholesterol ester crystals and granulomas, pulmonary fibrosis, emphysema, and pneumothoraces. The available evidence suggests exposure to indium compounds causes a novel lung disease that may begin with PAP and progress to include fibrosis and emphysema, and, in some cases, premature death. Prospective studies are needed to better define the natural history and prognosis of this emerging lung disease and identify effective prevention strategies.
Take home message

• Indium Tin Oxide is a new cause of pulmonary alveolar proteinosis (in addition to SiO$_2$, ...)

• Hi-tech materials are not necessarily produced or applied with hi-tech safety and hygiene!
Final Take Home Messages

Clinicians, radiologists, pathologists,

• Use « idiopathic » or « cryptogenic » with care (diagnosis of exclusion)
• Keep searching for possible environmental causes of lung disease
• Ask advice from experts

Old and new causes of disease may occur even in modern industry
Contrary to this drawing, there is no simple test. The suspicion and the determination of work-relatedness depend primarily on a careful occupational history.

From LEVY BS, WEGMAN DH. Occupational health (3d ed), p.60
When you find one case of occupational disease, there are likely more around ...

In occupational medicine, n is nearly always >1

Modified From LEVY BS, WEGMAN DH. Occupational health (3rd ed), p.60
Thank you for your attention

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