Recently emerging occupational lung disorders due to chemicals and their mixtures

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Contrary to this drawing, there is no simple test. The suspicion and the determination of work-relatedness depend primarily on a careful occupational history.
However, 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
Emerging lung diseases

- some examples of “new” occupational diseases
- a few take-home messages

1. Ardystil syndrome
2. Flock worker’s lung
3. Popcorn worker’s lung
4. Jeansblasting lung
5. Indium Tin Oxide
Ardystil syndrome
Ardystil syndrome

• Severe organising pneumonia in textile workers exposed to high levels of air-sprayed paints
    Solé et al. Thorax 1996, 51, 94-95
    Romero et al. ERJ 1998, 11, 265-71
    ERJ 1999, 13, 940-1
Ardystil syndrome


Moya et al. (Lancet, 1994, 344, 498-502)

- survey of 257 workers from 8 factories (incl. Ardystil)
- on the basis of chest x-ray & lung biopsy:
  - 22 cases of organising pneumonia (~ BOOP)
  - (6 fatal)
Ardystil syndrome

Moya et al. (Lancet, 1994, 344, 498-502)
Organizing pneumonia in textile printing workers: a clinical description

S. Romero*, L. Hernández*, J. Gil*, I. Aranda**, C. Martín*, J. Sanchez-Payá†


ABSTRACT: In April 1992 an outbreak of severe respiratory illness occurred among aerographic textile workers in the area of Alcoi, Autonomous Community of Valencia, Spain. An epidemiological study linked this outbreak to the use of a reformulated aerosolized product, Acramin-FWN.

We analyzed clinical, laboratory, and pathological data of the first 14 patients with confirmed organizing pneumonia (OP) secondary to this newly recognized occupational toxicant.

The mean age of the patients was 30 yrs. The most common clinical findings were cough (86%), epistaxis (71%), dyspnoea (64%), oppressive chest pain (57%), and crackles (50%). A restrictive functional pattern was evident in 64%. Radiographic findings consisted predominantly of patchy infiltrates in 65% and a micronodular pattern in 35%. Treatment with corticosteroids did not prevent initial progression in 11 of the 14 patients and development of irreversible respiratory failure in five patients. At necropsy, besides features of OP, interstitial fibrosis and diffuse alveolar damage were evident. A low total lung capacity, the presence of crackles at admission, and increases in the alveolar-arterial oxygen difference were predictive of death.

The organizing pneumonia caused by the inhalation of Acramin-FWN is characterized by a tendency to evolve into progressive interstitial fibrosis despite the use of corticosteroids. The illness is restricted to the respiratory system and once respiratory failure has developed the prognosis is poor.


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Fig. 3. – Polypoid plugs of immature-appearing fibroblastic tissue within peripheral air spaces. Haemotoxylin and eosin stain. Internal scale bar = 100 μm.

Fig. 4. – Loose connective tissue incorporated into an alveolar wall. Haemotoxylin and eosin stain. Internal scale bar = 50 μm.

Fig. 5. – Fibrous tissue proliferation partially occluding the lumen of a bronchiole. Orcein-van Gieson stain. Internal scale bar = 50 μm.

Fig. 6. – Autopsy lung specimen showing organizing pneumonia associated with diffuse alveolar damage, prominent hyperplasia of type II pneumocytes and hyaline membranes. Masson’s trichrome stain. Internal scale bar = 50 μm.
Ardystil syndrome

- Late 1992 - Tlemcen (Algeria):
  - 5 cases of interstitial lung disease among 12 textile printing workers (1 fatal)
  - air-spraying with “products from Spain”

Ardystil syndrome

Ould Kadi et al. [Lancet, 1994, 343, 962-3]
Ardystil syndrome

Ould Kadi et al. [Lancet, 1994, 343, 962-3]
Ardystil syndrome (Tlemcen, 1994 & 1997)

B
FVC
27%
66%

C
FVC
23%
71%

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>32</td>
<td>35</td>
<td>32</td>
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<tr>
<td>Chest tightness, cough,</td>
<td>+</td>
<td>+</td>
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<td>dyspnea on exercise</td>
<td></td>
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<tr>
<td>Clubbing</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>61</td>
<td>67</td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (% pred)</td>
<td>63</td>
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<td>SaO&lt;sub&gt;2&lt;/sub&gt; at rest (%)</td>
<td>97</td>
<td>98</td>
<td>97</td>
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<td>SaO&lt;sub&gt;2&lt;/sub&gt; after 6 min walk (%)</td>
<td>91</td>
<td>94</td>
<td>92</td>
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</tbody>
</table>
Ardystil syndrome

Dyspnea, clubbing
FVC 61%, FEV₁ 63%
SaO₂ 97% → 92%

30.06.2005

Dyspnea
FVC 67%, FEV₁ 77%
SaO₂ 98% → 94%

30.06.2005
Ardystil syndrome - etiology

• epidemiological investigation (Moya et al. 1994)
  ➢ 20/22 cases came from 2 factories
  ➢ May 1991: a change in paint formulation (to facilitate air-spraying) in these 2 factories only:
    
    Acramin FWR + water → Acramin FWN + solvent

+ bad hygiene conditions
Toxicity of Acramin FWR & FWN

Acramin FWR = polyurea
Acramin FWN = polyamideamine
- both are polymers
- no “structural alerts”
- “non toxic” (rat oral LD$_{50}$ > 2000 mg/kg)
- non irritant for skin or eyes
- “used in screen-printing for many years without adverse health effects”
- inhalation toxicity : unknown
“Ardystil syndrome” - etiology

• toxicological investigations *in vivo* and *in vitro* (Clottens *et al.* 1997, Hoet *et al.* 1999, 2001)

  “is Acramin FWN more toxic than Acramin FWR?”

  NO

  but

  both proved to be surprisingly toxic for the lungs

  [Acramin FWN presumably more respirable (role of solvents?)]
Take home messages

Contrary to the “dogma” that polymers are innocuous, some polymers may exhibit a high respiratory toxicity when they are inhaled

- potentially inhaled materials must be tested by inhalation (“guilty until proven safe”)
- physicians and health authorities must be vigilant
Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma

Y. Song*, X. Li# and X. Du*

- Beijing
- 7 women (18-47 y) working in small print plant (5-13 months)
- Workplace 70 m², no windows, exhaust broken down, no PPE
- 1 machine to airspray coating material onto polystyrene boards
  - Coating material = “mixture of polyacrylic ester”: GC/MS “butanoic acid, butyl ester, N-butyl ether, acetic acid, toluene, di-tert-butylperoxide, 1-butanol, acetic acid ethenyl ester, isopropyl alcohol, ethylene dioxide”
  - Electron microscopy of paste and accumulated dust: “nanoparticles ~ 30 nm”
Song et al. ERJ 2009, 34,559-67

- Dyspnoea
- Itching rash on face & hands + forearms
- Mild to severe restrictive impairment
- Hypoxaemia (4/7)
- Pleural fluid: exudate (amber); pericardial effusion
- Chest CT: interstitial disease + fibrosis (rapid progression in 2)
- No infectious agents detected

- Two died in respiratory failure
Foreign body granulomas

FIGURE 1. a) Aggregation of phagocytes in the alveolar space, swollen and widened alveolar septum, and pulmonary fibrosis were observed (hematoxylin-eosin (HE) stain). b) Infiltration of inflammatory cells was observed in bronchial mucosa, bronchus, and bronchiole (HE stain). c) Pathological examination of the pleura showed foreign body granulomas with fibrous and inflammatory cell effusions (HE stain). Arrows indicate foreign body giant cells (HE stain). d) Pathological examination of the pleural mesothelium 18 months later showed fibrous thickening and swelling, fibroblast proliferation, cellular exudate and lymphocyte aggregation (HE stain). e) Pulmonary pathological examination 18 months later showed the alveolar septum was widened with blood vessel distortion and congestion. Pulmonary alveoli were partly emphysematous with scattered multinucleated giant cells (HE stain). a, d: Scale bars=50 mm. b, c, e: Scale bars=25 mm.

“nanoparticles”

FIGURE 2. a) Nanoparticles (indicated by arrows) in chest fluid. Round nanoparticles ~30 nm in diameter were scattered in the fluid, being wrapped up by fibrous structure, which may have originated from cytolysis in pleural fluid. b) Clusters of nanoparticles (30 nm in diameter) were observed to lodge in the cytoplasm of a pulmonary epithelial cell. c) With nanoparticles lodging in the cytoplasm and eukaryotic cell, the chromatin had condensed and marginalized like a crescent, showing characteristic cell morphology of cells undergoing apoptosis. d) Clusters of nanoparticles were obviously found when the highlighted section of e was enlarged. a, b) Scale bars=200 mm. c, d) Scale bar=500 nm.
Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma

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??? not proven
Engineered nanomaterials

“A cause waiting for a disease”
Flock worker’s lung
“Nylon flock worker’s lung”

- 1994-96: D. Kern: 2 cases of ILD (35y, 28y) in textile workers from a nylon flocking plant, RI
  - hygiene study & survey of workforce (NIOSH)
  - further case-finding
    Health Hazard Evaluation Report 96-0093, April 1998
Nodular, peribronchovascular interstitial lymphoid infiltrates, lymphocytic bronchiolitis, lymphocytic infiltration of alveolar septa, mild fibrosis

Nylon flock microfibres

Scanning electron microscopy of bulk nylon fiber ends
Flock worker’s lung


- No abnormal chest x-ray
- HRCT in 10 subjects with low DLco: suggestive of (mild) ILD or bronchiolitis
Take home message

Synthetic polymeric fibres may cause lung disease if high amounts of very small fragments of microfibres can reach the lung
Popcorn worker’s lung
(Food flavourer’s lung)
Popcorn worker’s lung

• May 2000, USA:
  • report of 8 persons with severe airway obstruction (“bronchiolitis obliterans”)
  • all employed 1993-2000 at microwave-popcorn plant in Missouri:
    • 4 worked in flavor-mixing room
    • 4 worked in packaging areas only
  • no reported incident or apparent overexposure
  • mostly nonsmokers
  • cause ?

- cause = “butter flavor”

predominant compound:

\[
\text{diacetyl} = 2,3\text{-butanedione}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{C} - \text{C} - \text{CH}_3
\end{align*}
\]
Popcorn worker’s lung

  - 9 cases (27-51 y; 1-17 y in popcorn industry)
  - 3 never smokers, five ex-smokers, 1 smoker
  - FEV₁ 14 – 67% pred
  - HRCT bronchial wall thickening, air trapping
  - Lung biopsy: constrictive bronchiolitis
  - Stabilisation after leaving employment
Popcorn worker’s lung

Akpınar-Elçi et al.
Eur Respir J. 2004, 24, 298-302
Popcorn worker’s lung

  - Rats exposed for 6h to vapors of butter flavoring
  - necropsy after 24 h
  - necrosuppurative rhinitis + multifocal, necrotizing bronchitis (diacetyl = 203-371 ppm)
van Rooy FBGJ et al. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavourings. AJRCCM 2007, 176, 498-504

• Retrospective study among 102 process operators in a Dutch chemical plant producing diacetyl (1960-2003)
• 3 (4) cases consistent with Bronchiolitis Obliterans
“Food flavourer’s lung”


- Man, 36 y, nonsmoker
- Exposed to diacetyl in factory producing food flavouring for potato crisps/chips
- Rapidly evolving fixed airways obstruction
Take home messages

• Food ingredients and additives that are GRAS [Generally Regarded as Safe (for use in food)] may be highly toxic when they are inhaled (by workers or consumers)

  ➢ No chemical should be assumed to be safe by inhalation unless this has been tested

• Even in modern industrial societies new occupational (respiratory) diseases may occur

  ➢ Clinicians must remain vigilant for “unusual” presentations of common diseases (e.g. COPD in nonsmokers) or clusters of disease

  ➢ Use “idiopathic” or “cryptogenic” with care
Sandblasting jeans
“Jeans blasting”

Alveolar proteinosis
Acute silicosis

19 y old

18 y old

Courtesy Dr. Akgün, Erzurum
J Occup Health 2005, 47, 346-9
An epidemic of silicosis among former denim sandblasters

M. Akgun*, O. Araz*, I. Akkurt#, A. Eroglu‖, F. Alper†, L. Saglam*, A. Mirici§, M. Gorguner* and B. Nemery†
Akgun et al. ERJ 2008, 32, 1295-1303

- 157 former denim sandblasters
- Mostly unregistered workplaces
- 2-12 sandblasting devices/workplace
- Use of sifted sea sand
- 10-12 h/d (2 shifts, sleeping on premises), 6-7 d/w
- No exhaust ventilation, 1-2 face masks/day
- 250-500 jeans/day, 3,000-5,000 skirts/day
- Apprentices & foremen
• Turkey, Bingöl (near Erzurum)
• 157 former denim sanblasters, all males
• mean age: 23 y [15-44 y]
• start work: 17 y [10-38 y]
• duration: 3 y [1-120 months]
- Respiratory symptoms in 131 subjects (83%)
  - Dyspnea 52%
  - Chest pain 46%

- X-ray silicosis in 77 subjects (53%)
  - ILO Category 0: 68 (47%) [0/- 52; 0/0 3; 0/1 13]
  - ILO Category 1: 35 (24%) [1/0 19; 1/1 9; 1/2 7]
  - ILO Category 2: 16 (11%) [2/1 4; 2/2 2; 2/3 10]
  - ILO Category 3: 26 (18%) [3/2 8; 3/3 6; 3/+ 12]
  - Large opacities: 14 (10%) [A 6; B 3; C 5]
Take home message

- “Sand” is one of the most toxic agents for the lungs
- Exposure to crystalline silica does not occur only in mining, tunnelling, foundries, ... but may occur in the “textile industry”
- Workers may die for futile reasons
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% In₂O₃ / 10% SnO₂)
  - 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
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 +
A

PAS
Cummings et al. AJRCCM 2010, 181, 458-64
em + EDXA

A

B

X-RAY ENERGY

X-RAY INTENSITY

P  S  O  N  Na  Mg  Al  K  Ca
Cummings et al. AJRCCM 2010, 181, 458-64
Pathology

B

PAS
Take home message

• Indium Tin Oxide is a new cause of pulmonary alveolar proteinosis (in addition to SiO\textsubscript{2}, ...)

• Hi-tech materials are not necessarily produced or applied with hi-tech safety and hygiene!
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 (3$^{\text{d}}$ ed), p.60
Thank you for your attention

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