The Natural History and Pathogenesis of Silica Associated Diseases

Monday September 29, 2014

Dr. Francis H.Y. Green
Department of Pathology and Laboratory Medicine
University of Calgary

Location: Erg Chebbi Desert, Hassilabied, Morocco
Photo by Peter Vruggink
Disclosure

• Consultant to Encana Corporation on Silica Toxicity
Overview

• Silica types and mechanisms of toxicity
• Diseases caused by or associated with silica exposure
• The natural history of these diseases and their relationship to intensity of exposure
Diseases associated with silica exposure

- Silicosis
  - Acute
  - Chronic
  - Subacute
- COPD
  - Emphysema
  - Chronic bronchitis
  - Small airway disease
- Lung cancer
- Autoimmune disease
- Infection
  - TB
  - HIV

Remote: Sarcoidosis, Idiopathic pulmonary fibrosis
To understand the risk one needs to know the context

- Silica (silicon dioxide) can range in toxicity from minimal to extreme depending on its chemical composition and structure
- Amorphous silica is the least toxic, crystalline silica much more toxic
- The toxicity of crystalline silica is modified by many factors; particle size and shape, recent fractures, surface modification
- Remember that silica is not a new hazard, it has been around for billions of years
Types of Silica

• Crystalline
  – quartz
  – cristobalite
  – tridymite
  – diatomite

• Amorphous
  – Quenched molten; glass
  – Condensed from vapour phase
CalTech (2013) Optical and SEM Images of silica [$\text{SiO}_2$] polymorphs (and varieties)
http://minerals.caltech.edu/Silica_Polymorphs
In chemistry, a free radical is any atom, molecule, or ion with an unpaired valence electron.
Metal ions

$O_2 \cdot -$ 

$OH \cdot$

Silanol groups

Surface radicals

Silicon Atom

Oxygen Atom

$-SiO(s) + H_2O \rightarrow -SiOH(s) + HO^- \cdot$

Jim Clark (2012) Giant Covalent Structures
http://www.chemguide.co.uk/atoms/structures/giantcov.html
Modified from Borm et al. Critical Reviews in Toxicology 41(2011)756-770
• Silicon Atom
• Oxygen Atom

Modified from Castranova et al. Silica and Silica-Induced Lung Diseases. CRC Press (1996); Fubini & Hubbard Free Radical Biology and Medicine 34 (2003)1507-1516
Silica
Silanol groups
Surface radicals
Free radicals:
$O_2^{•−}$
$HO^{•−}(H_2O_2)$
$ONO^{−}$
Phagocytosis
Lysosome
Nucleus
Free radicals:
$O_2^-$
$HO^-(H_2O_2)$
$ONO^-$

Phagocytosis

Cathepsin D

Proteolytic enzymes

Lysosome

Fibrogenic cytokines:
IL-1β
TNF-α
MIP-1/MIP2
MCP-1
IL-8

Nucleus
Free radicals:
- $\text{O}_2^-$
- $\text{HO}^-$ ($\text{H}_2\text{O}_2$)
- ONO$^-$

Apoptosis (Programmed Cell Death)

Lysosome

Cathepsin D

Proteolytic enzymes

Fibrogenic cytokines:
- IL-1$\beta$
- TNF-$\alpha$
- MIP-1/MIP2
- MCP-1
- IL-8

Nucleus
Video of macrophages with silica
Video of macrophages with asbestos
Silica Toxicity

• Persistent Inflammation
• Cytotoxicity
• Fibrosis
• Emphysema
• Effects on immune function and innate immunity
• Carcinogenicity
Intensity of Exposure

• Low intensity exposure
  → Classic nodular silicosis, 10+ year latency

• High intensity exposure
  → Alveolar lipoproteinosis

• Mixed high and low
  → Rapidly progressive pneumoconiosis with features of low and high intensity plus interstitial fibrosis and granulomatous inflammation
Acute silica Toxicity (Rats)
## Silica Toxicity Cont.

<table>
<thead>
<tr>
<th>Factors that Enhance Silica Toxicity</th>
<th>Factors that Reduce Silica Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Type of silica</td>
<td>• Mixed dusts</td>
</tr>
<tr>
<td>• Particle size/surface area</td>
<td>• Chemical modification of particle surface</td>
</tr>
<tr>
<td>• Fractured crystal planes</td>
<td>• Surfactant</td>
</tr>
</tbody>
</table>
Electron Beam

High Energy (20 keV)

Si X-ray intensity

Low Energy (5 keV)

Al X-ray intensity

Si X-rays

Surface occlusion

Castranova et al. Silica and Silica-Induced Lung Diseases. CRC Press (1996)
Natural history of Silica lung Disease

- Acute silicosis
- Accelerated silicosis
- Chronic (classic silicosis)
- Mineral dust small airway Disease
- Chronic Bronchitis
- COPD
- Lung Cancer
Timelines

Exposure Onset 0 5 10 15 20 25 Years

- Acute Silicosis
- Accelerated Silicosis
- Mineral Dust Small Airway Disease
- Chronic Silicosis
- Emphysema
- Lung Cancer

Timeline between pathologic and clinical presentations
Acute and Accelerated Silicosis
Accelerated Silicosis: Hawks Nest, West Virginia

• 1927 – Construction began
• 700 – 1,000 deaths among 3,000 workers
Small Airway Disease

- Normal respiratory bronchiole
- Coal dust macule with centriacinar emphysema
- Mineral dust small airway disease, airway narrowing, no emphysema
Pneumoconiosis from agricultural dust exposure among young California farmworkers.

<table>
<thead>
<tr>
<th></th>
<th>Farmworkers</th>
<th>Non-farmworkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population*</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Smokers</td>
<td>54%</td>
<td>51%</td>
</tr>
<tr>
<td>Age (25 - 75%ile)</td>
<td>36 (23-40)</td>
<td>30 (21-36)</td>
</tr>
</tbody>
</table>

* Unknown farm working status, n=6

# Quartz in Samples from Three California Crops (%)

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>GRAPE</th>
<th>CITRUS</th>
<th>PEACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soil</td>
<td>20.3</td>
<td>12.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Foliar</td>
<td>18.9</td>
<td>12.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Airborne, total (mg/m$^3$)</td>
<td>20.7</td>
<td>8.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Airborne, resp (mg/ m$^3$)</td>
<td>8-12</td>
<td>3.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Lawson '93
Simple Silicosis

Normal
Simple Silicosis
Evolution of the lesions of silicosis
Silicotic PMF

Lung Biopsy from West Virginia coal miner with rapidly progressive CWP, 2013

"Coupe de poumon atteint de silicose" by Gabacho1ro - Own work. Licensed under Wikimedia Commons
Accelerated Silicosis
(Progressive Massive Fibrosis)

Normal Chest X-Ray

PMF
Eggshell calcification – almost exclusively silicosis
Lung Cancer

• The International Agency for Research on Cancer (IARC) classified crystalline silica as a probable carcinogen in 1987 and in 1997 reclassified it as a group 1 carcinogen
• Weight of evidence is that silica causes lung cancer in humans
• However the evidence is relatively weak and the mechanism is unknown
Rat lung Exposed to Silica Dust for 150 Days Showing Atypical (Pre-Malignant) Epithelial Changes
Atypical pulmonary effects of silica exposure

• Synergism with tuberculosis and HIV infection
• Increased risk for auto-immune, connective tissue and vascular disorders involving the lung
• Relationship to Idiopathic Pulmonary fibrosis (IPF)
• Association with Sarcoidosis
Miner's lung with silicosis and tuberculosis
Silica exposure and tuberculosis
A case of Sarcoidosis?
Interstitial fibrosis due to silica exposure resembling UIP

Silicotic nodule
Weakly-pigmented interstitial fibrosis bridging silicotic nodules
Pathogenesis of Emphysema

ANTI - PROTEASES

PROTEASES
Dust Induced Emphysema

- Cigarette smoke
- Coal mine dust
- Silica
Cumulative Coal Mine Dust Exposure and Predicted Emphysema Index

FEV1 65%
### Relationship between emphysema index and lung dust burden

<table>
<thead>
<tr>
<th>Lung Dust Characteristics</th>
<th>Mg gm(^{-1}) dry lung (mean ± SE) Ever Smokers</th>
<th>Mg gm(^{-1}) dry lung (mean ± SE) Never Smokers</th>
<th>Overall Correlation</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7.1 ± 0.58</td>
<td>6.9 ± 1.5</td>
<td>0.34</td>
<td>0.006</td>
</tr>
<tr>
<td>Coal</td>
<td>4.4 ± 0.50</td>
<td>5.1 ± 1.2</td>
<td>0.46</td>
<td>0.0002</td>
</tr>
<tr>
<td>Total Mineral</td>
<td>2.8 ± 0.31</td>
<td>1.8 ± 0.46</td>
<td>-0.09</td>
<td>0.49</td>
</tr>
<tr>
<td>Silica</td>
<td>0.20 ± 0.02</td>
<td>0.18 ± 0.03</td>
<td>0.09</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Systemic effects of silica exposure

• Scleroderma
• Rheumatoid arthritis
• Chronic renal disease
• Systemic lupus erythematosus
Conclusion: What can pathology say about surveillance programs?

• Important to know the type of silica, its size, freshness and intensity of exposure

• Important to recognize the diverse range of diseases associated with silica exposure and their natural history

• Important to recognize the sensitivity of the tests used to detect early disease
Thank You

• Dr Ken Corbett
• Colleagues at NIOSH
  • Dr Val Vallyathan
  • Dr Eileen Kuempel
  • Dr Vince Castranova

Questions?