General Toxicology

Toxic Responses of the Respiratory System (II)

Lec. 8
4th Year
2020-2021

Lecturer Rua Abbas Al-Hamdy
College of Pharmacy/Al-Mustansiriyah University
Department of Pharmacology & Toxicology

Objectives of this lecture are to:

- determine the pulmonary toxicity caused by some inhalation hazards, &
- explain the pulmonary toxic effects caused by blood-borne agents in humans.

Inhalation hazards:

- Acrolein
- Asbestos
- Silica
- Naphthalene

Acrolein:

- Acrolein is an α–β-unsaturated aldehyde. It is volatile at room temperature & is highly irritating to upper & lower respiratory tract.

- It can be formed by heating cooking oils & fats above 300°C (eg, wok cooking). It also can be formed in cigarette smoke, smoke from fires, & diesel exhaust.

- Acrolein contains a reactive carbonyl group & an electrophilic α-carbon & thus is highly reactive (often forming crosslinks) with biological macromolecules.

- Irritant stimuli, of which acrolein is one of the most potent, activate respiratory sensory nerve endings, especially TRPA1.

- More plentiful in cigarette smoke than polycyclic aromatic hydrocarbons (PAHs), acrolein can adduct tumor suppressor p53 (TP53) DNA.

- Because of its high reactivity, acrolein:
- alters gene regulation,
- increases inflammation,
- decreases mucociliary transport, &
- diminishes alveolar-capillary barrier integrity.

- Acrolein contributes to the morbidly & mortality associated with acute lung injury & COPD, & possibly asthma & lung cancer.

Asbestos:

- Asbestos refers to a group of silicate minerals in fiber form.

- Exposure to asbestos fibers occurs in mining operations & in the construction & shipbuilding industries, where asbestos was at one time widely used for its insulating & fireproofing properties.

- Asbestos causes three forms of lung disease: asbestosis, lung cancer, & malignant mesothelioma.

- Asbestosis is a form of pulmonary fibrosis with characteristically diffuse collagen foci & the presence of asbestos fibers.

- Lung cancer develops in workers in the asbestos mining industry & smoking of cigarettes greatly enhances risk.

- Malignant mesothelioma is a rare form of cancer that develops mainly in the pleural mesothelium, the protective lining that covers the lungs, diaphragm, & interior of the chest wall. Unlike lung cancer, mesothelioma is not associated with smoking history.

Silica:

- Inhaled particles of silicon dioxide (silica) cause a characteristic human lung disease-silicosis. Crystalline silica is a major component of the earth's crust; silicon is only second to oxygen as the most common element.

- Silicosis may be acute or chronic with distinct pathological consequences.

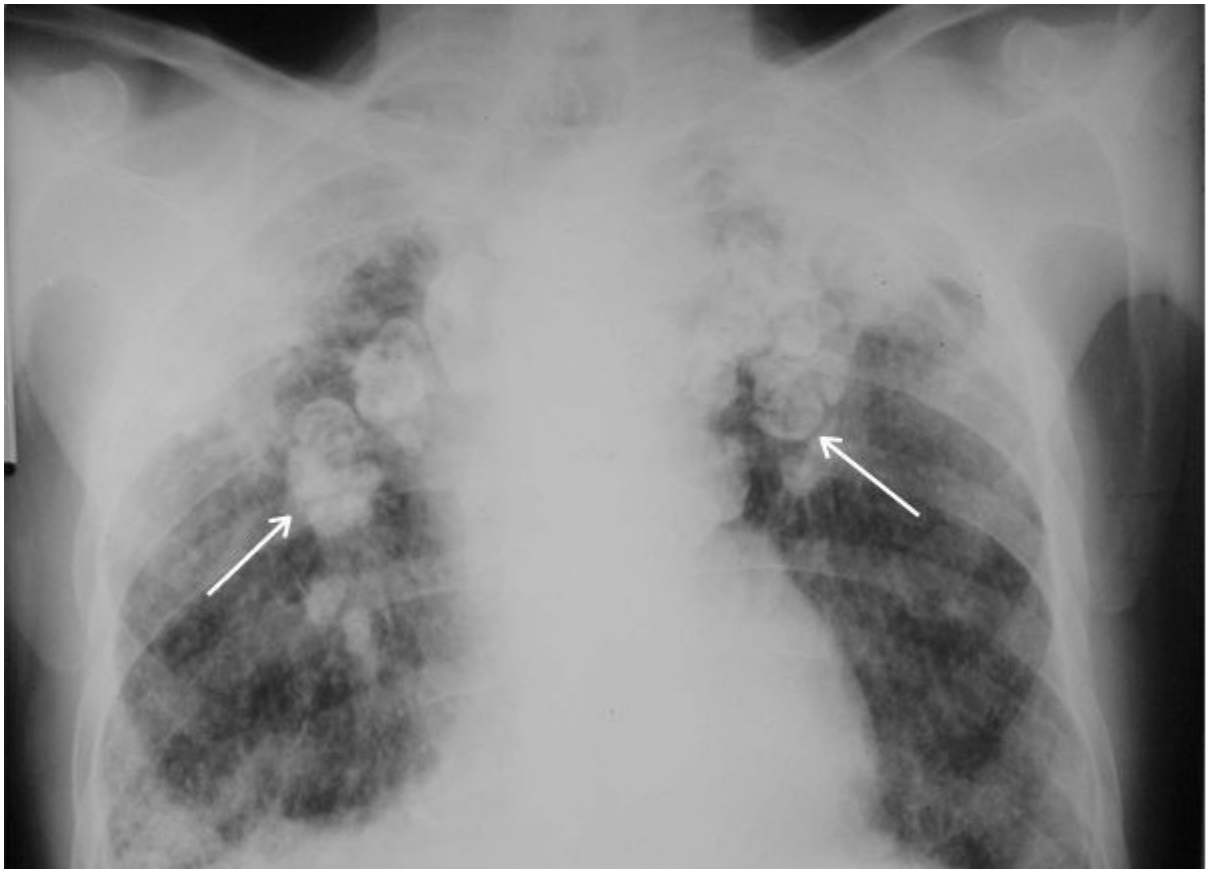
Acute silicosis:

- Acute silicosis occurs:
- only in subjects exposed to a very high level silica (most often quartz or sand) small enough to be respirable (usually <5 µm) over a relatively short period, generally a few months or years.
- patients with acute silicosis have:
- worsening dyspnea,
- fever,
- cough, &
- weight loss.

- The condition can rapidly progress to respiratory failure, usually ending in death within two years.

Chronic silicosis:

- It has a long latency period, usually >10 years & can be divided into simple & complicated silicosis.
- Even after radiographic changes, simple silicosis may be asymptomatic (ie, no dyspnea) with little change in pulmonary function. The x-ray presents fibrotic nodules, generally in the apical portion of lung.
- The hilar lymph nodes have peripheral calcifications known as eggshell calcifications (Fig. 1) .



Figures 1. Egg shell calcifications in hilar lymph nodes (as indicated by arrows) in chronic silicosis.

- Simple silicosis may progress into complicated silicosis, which is defined as the presence of conglomerate nodules larger than 1 cm in diameter.
- These nodules usually occur in the upper & mid-lung zones. In advanced stages, the nodules may be surrounded by emphysematous bullae.
- Chronic silicosis is associated with an increased incidence of tuberculosis.

- Simple silicosis may progress into complicated silicosis, which is defined as the presence of conglomerate nodules larger than 1 cm in diameter.
- These nodules usually occur in the upper & mid-lung zones. In advanced stages, the nodules may be surrounded by emphysematous bullae.
- Chronic silicosis is associated with an increased incidence of tuberculosis.

- The role of pulmonary alveolar macrophages in the ingestion of silica is an initiating event involved in the pathophysiology of the pulmonary fibrosis in chronic silicosis.

- In contrast to microorganisms, silica particles cannot be degraded & macrophages undergo cell death, releasing these particles that are engulfed by other macrophages, thus perpetuating the process of phagocytosis & cell death.
  This leads to elevated mediator release (TGFB1, TNF, etc) & initiates & maintains myofibroblast collagen.

Naphthalene:

- Naphthalene occurs in cigarette smoke, tars, petroleum & is a precursor in the chemical synthesis of tanning agents. It is also used in mothballs.
- In laboratory animals, inhaled or parenterally administered naphthalene produces extensive necrosis in the bronchiolar epithelium of the mouse but much less necrosis in the airways of rats, or monkeys.
- The primary target in the surface epithelium is the bronchiolar secretoglobin cells.

- In mice, naphthalene is metabolized to naphthalene oxide primarily through CYP2F enzymes. In rats & other species, including monkeys, the rates of formation of the epoxide are much slower.
- Naphthalene epoxides may subsequently be conjugated with glutathione & form adducts that are eliminated as mercapturic acids.
- The epoxide can undergo rearrangement to 1-naphthol with subsequent metabolism to quinones, which are potentially toxic compounds.

- Naphthalene metabolites bind covalently to cellular proteins & this may be related to the mechanism of toxicity by this chemical.

Blood-borne agents that cause pulmonary toxicity in humans:

A number of compounds administered systematically can enter the lung through pulmonary circulation & cause lung injury & disease. For example, intraparenteral napthalene has marked lung toxicity in the mouse. Another example is that the ingestion of arsenic has been associated with lung cancer. Below are two more examples that have had toxicological significance in clinical settings:

- Bleomycin, &
- Cyclophosphamide & 1,3 Bis (2-Chloroethyl)-1-Nitrosourea (BCNU)

Bleomycin:

- Bleomycin is a cancer chemotherapeutic drug with a major complication—pulmonary fibrosis that can be fatal.
- Bleomycin produces:
  - necrosis of capillary endothelial cells & alveolar type I cell,
  - edema formation & hemorrhage,
  - apoptosis of alveolar type II cells, &
  - eventually thickening of the alveolar walls by fibrotic changes.

- In many tissues, the cytosolic enzyme bleomycin hydrolase inactivates bleomycin.
  In lung & skin, two target organs for bleomycin toxicity, the activity of this enzyme is low compared with that in other organs.

Cyclophosphamide & Bis (2-Chloroethyl)-1-Nitrosourea (BCNU) :

- Cyclophosphamide is widely used as an anticancer & immunosuppressive drug.
- The undesirable side effects include hemorrhagic cystitis & pulmonary fibrosis.
- Although the exact mechanism of action for causing lung damage has not been established, studies with isolated lung microsomes have shown that cyclophosphamide & its metabolite acrolein initiates lipid peroxidation.

- Another chemotherapeutic drug that has pulmonary fibrosis as a complication is carmustine (BCNU).
- BCNU exerts its antitumor properties by reacting with cellular macromolecules & forms cross-links with DNA.
- In humans, a dose related pulmonary toxicity is often noticed first by a decrease in diffusion capacity, which can develop into fatal pulmonary fibrosis.

- The mechanism of action is not entirely clear. It is possible that BCNU inhibits pulmonary glutathione disulfide reductase, an event that may lead to a disturbed GSH/GSSG state in pulmonary cells. Eventually, this state leaves the cell unable to cope with oxidant stress.


Thank
you