Electron Microprobe Analysis in Metal-Induced Lung Disease

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Introduction.

A variety of pulmonary reactions have been associated with the inhalation of metallic dusts.\textsuperscript{1,2} Some of these result in familiar pneumoconioses, whereas others simply result in intrapulmonary pigment deposition. Some of the metallic materials that can cause disease as well as the typical reaction to deposits of these particulates are listed in Table 1. Electron microprobe analysis can be useful in the identification of these particulates and, in some cases, may clarify the nature of pulmonary disease. The most useful instrumentation for the identification of these particulates consists of a scanning electron microscope (SEM) equipped with a back-scattered electron (BSE) detector and an energy dispersive spectrometer (EDXA).\textsuperscript{3} By means of this methodology, individual particulates may be identified and analyzed for their elemental content. The application of SEM/BSE/EDXA to the diagnosis of metal-induced lung disease is the subject of this presentation.

Welder’s Pneumoconiosis (Siderosis).

The inhalation of iron oxides into the lung results in the peribronchiolar and perivascular deposition of a characteristic pigment that can usually be identified by light microscopy. In the author’s experience, this most commonly occurs in the setting of work as an arc welder.\textsuperscript{4,5} Welding fumes consist of a variety of metal oxides, including iron, aluminum, magnesium and titanium along with various silicates and carbonates. The author has identified more than 100 cases of welder’s pneumoconiosis, nearly half of which occurred as an incidental finding in and individual with lung cancer. Nearly a quarter of the cases also had asbestosis, primarily in the setting of welding in a shipyard.\textsuperscript{6} Miners of hematite ore are also exposed to iron oxides along with varying amounts of silica and silicates. In addition, exposure may occur in the setting of iron smelting operations. In the latter circumstance in particular, the author has observed ferruginous bodies with black cores composed of iron oxide ‘fibers’.\textsuperscript{7}

Welder’s pigment consists of peribronchiolar and perivascular deposition of dark brown to black iron oxide particles. These often have a characteristic golden brown halo giving them a targetoid appearance. This latter finding as well as the primarily interstitial (as compared to intra-alveolar) location permits their distinction from hemosiderin. There is usually very little reaction to the pigment, and the presence of significant fibrosis should lead to the consideration of additional exposures, such as asbestos or silica. The sheet silicates that welders are also exposed to may lead to the formation of non-asbestos
ferruginous (pseudoasbestos) bodies with broad yellow cores, which can usually be
distinguished from true asbestos bodies by their light microscopic appearance. Due
to the characteristic appearance and distribution of the pigment in welder’s pneumoconiosis,
electron microprobe analysis is usually not required to confirm the iron composition of
the particulate material.

**Hard Metal Lung Disease.**

Formerly known as tungsten carbide pneumoconiosis, this disorder is nearly
synonymous with giant cell interstitial lung disease. Tungsten carbide is a hard metallic
material that is utilized in the manufacture and application of cutting tools, drilling
equipment, armaments, alloys and ceramics. It is believed that cobalt, which is used as a
binder, is the causative agent of disease. Tungsten carbide per se is inert in experimental
animal studies, whereas cobalt used as an abrasive for polishing diamonds has been
associated with giant cell interstitial pneumonia in diamond polishers (who have no
exposure to tungsten carbide). The pathogenetic mechanism probably involves a
hypersensitivity response, since fewer than 1% of exposed individuals develop interstitial
lung disease. Furthermore, asthma develops in about 10% of exposed workers. Most
reported cases have occurred in individuals exposed to dust during the manufacturing
process or in the polishing of finished products.

Giant cell interstitial pneumonia (GIP) is an inflammatory and fibrotic reaction in
which there are numerous giant cells within alveolar spaces and lining alveolar walls.
Ultrastructural studies have confirmed the origin of the former from macrophages and the
latter from Type II pneumocytes. This is the typical pattern in individuals with hard metal
lung disease. A pattern resembling hypersensitivity pneumonitis has also been described.
The finding of a GIP pattern or of interstitial lung disease in an individual with a
compelling exposure history is an indication for the performance of SEM/BSE/EDXA on
paraffin sections. The finding of tungsten particles with or without cobalt is considered
confirmatory. Tantalum and titanium may also be identified. Although cobalt is the likely
etiologic agent, it may not be identified due to its solubility in biologic fluids.
Examination of bronchoalveolar lavage pellets for the characteristic multinucleate giant
cells and particulate material may also be useful for confirmation of the diagnosis.

**Berylliosis.**

Chronic beryllium disease is the classic example of a metal-induced pulmonary
granulomatosis. Exposure to beryllium occurs primarily in the aerospace, electronics and
nuclear power industries, where it is used in heat shields, rocket motor parts, guidance
systems, optical devices, thermocouples, ceramics and crucibles. It is also used in the
manufacture of dental prostheses and even some golf clubs. Exposure may also occur
during the mining and extraction of beryllium ores or living in the vicinity of a
The development of hypersensitivity is associated with certain HLA genotypes. The granulomatous reaction seen in patients with beryllium hypersensitivity may be difficult to distinguish from sarcoidosis, and some have advocated the use of lymphocyte blast transformation assays on peripheral blood or bronchoalveolar lavage samples to assist in the differential diagnosis. Identification of beryllium in tissues is problematic on two accounts. As is the case for cobalt, beryllium is soluble in biological fluids, so it may be undetectable in individuals with a prolonged interval since last exposure or in tissue samples that have been in formalin for a considerable period of time. Furthermore, in the past, many energy dispersive spectrometers have used beryllium windows that would filter out the low level x-rays produced by beryllium. Other methodology that has been used to identify beryllium in tissue samples includes electron energy loss spectrometry, laser microprobe mass analysis, and secondary ion mass spectrometry. These techniques are not available in most medical centers where such patients are likely to be seen.

The advent of thin-window detectors (with a proprietary polymeric as opposed to beryllium window) has opened up the possibility of detecting beryllium with traditional SEM/BSE/EDXA technology. Butnor et al reported such a case in which this approach was used to detect beryllium within a granuloma from a wedge lung biopsy specimen of a patient with occupational beryllium exposure. Confirmation of this approach in additional cases is necessary before this methodology can be applied routinely.

**Aluminosis.**

Aluminum is a lightweight metal used extensively in industrial and manufacturing processes. Exposure primarily occurs from aluminum smelting, manufacture of aluminum oxide abrasives, aluminum polishing, and aluminum arc-welding. The particles often occur as fumes, with sizes ranging from 0.1 to 1.0 µm. Pulmonary disease from aluminum exposure is uncommon. In some cases, all that is found is perivascular and peribronchiolar deposits of aluminum particles within macrophages. The dust has a gray-brown granular appearance and is refractile. Disease resulting from exposure to aluminum oxide abrasives (corundum) has been referred to as Shaver’s disease. Corundum consists of aluminum oxide, silica, ferric oxide and traces of titanium. In fatal cases of Shaver’s disease, the lungs are heavy, grayish black, and have dense fibrotic areas scattered throughout, dense pleural adhesions, and subpleural emphysematous bullae. The latter may give rise to spontaneous pneumothorax.

Fibrotic lung disease may also occur as a result of exposure to aluminum among potroom workers (aluminum smelting) or aluminum arc-welders. The fibrotic areas in the lung and regional lymph nodes may have a metallic sheen. Other reactions that have been described among individuals exposed to aluminum dusts include granulomatous reaction resembling sarcoidosis, desquamative interstitial pneumonia and alveolar proteinosis. Analysis by EDXA in these conditions typically demonstrates
particles with a peak for aluminum only. The rarity of these conditions suggests that there may be a hypersensitivity component to the response, similar to that of beryllium or cobalt. ¹

Zirconium Lung Disease.

Zirconium is a grayish metal used in the production of steel, refractory ceramics manufacture, enamels and glasses, as a polishing and abrasive agent, and as a substitute for sand in foundries. ¹ Exposure occurs during the mining or refining of zirconium ore, or in any of the applications noted above. There is generally little pathologic reaction to the accumulation of dust within macrophages in a perivascular or peribronchiolar location. In rare cases, pulmonary fibrosis has been described. ¹⁶ The occurrence of a granulomatous reaction has been suggested but is controversial and unproven. ¹⁷ Analysis by EDXA demonstrates particles with peaks for zirconium (Zr).

Rare Earth Pneumoconiosis.

Rare earths include cerium, lanthanum, neodymium and samarium. They typically occur as the oxides and exposures come from processing of rare earth ores, manufacture or use of carbon arc lamps, and manufacture or use of cerium oxide rouge used for the polishing of glass lenses.⁴ Disease from exposure to rare earths is very uncommon with only about 20 cases having been reported. Reactions include pulmonary fibrosis and granulomatous disease. ¹⁸ Analysis by EDXA primarily demonstrates peaks for cerium although trace levels of other rare earths may be detected as well. Cerium oxide is birefringent with polarizing microscopy.

Silicon Carbide Pneumoconiosis.

Silicon carbide (carborundum) is a synthetic abrasive widely used because of its hardness. It is used for abrasive wheels and in the manufacture of refractory materials for boilers and foundry furnaces.⁴ Silicon carbide is thought to be inert, and only one case with pathologic findings has been described. This showed perivascular and peribronchiolar as well as intraalveolar deposits of pigmented dust with occasional ferruginous bodies formed on silicon carbide ‘whiskers’. ¹⁹ Analysis of dust recovered from lung tissue by x-ray diffraction demonstrated the presence of predominantly silicon carbide with minor traces of silica and tungsten carbide.
**Cadmium-Induced Lung Disease.**

Cadmium is used in the manufacture of alloys and alkaline accumulators and in the control of atomic reactors. Chronic exposure to cadmium results in emphysematous changes. Diagnosis requires a careful occupational exposure history or analysis of lung tissue for cadmium. Cadmium also occurs in cigarette smoke, which is the most common cause of emphysema.

**Other Metals.**

A variety of other metals (Table 1) may accumulate in the lungs with little or no reaction. Some of these are named pneumoconioses (stannosis for tin, baritosis for barium) while others are not. Exposures to these metals manifest as peribronchiolar and perivascular deposits of pigment. Specific identification of these pigment deposits by EDXA is seldom required since there is no clinical symptomatology or impairment associated with the exposures, although they may produce interstitial markings on chest roentgenograms due to impedance of the x-rays by the high atomic number dusts. Exposures to very high levels of metal fumes can cause metal fume fever, which may be associated with a chemical pneumonitis that microscopically has the appearance of diffuse alveolar damage. Finally, it should be noted that metals may be a component of mixed dust pneumoconiosis.

**Dental Technicians’ Pneumoconiosis**

Dental laboratory workers may be exposed to a variety of different particles. Prosthetic devices made of metal alloys are polished with high-speed abrasive wheels which may generate dust composed of silica or silicon carbide. Asbestos molds are used in the process of dental gold casting, and dismantling of the molds may result in substantial exposure to aerosolized asbestos fibers. Furthermore, analysis of lung tissue from some dental technicians has demonstrated the presence of chromium-cobalt-molybdenum alloys which may be a factor in the development of pneumoconiosis. These alloys may cleave into elongated fragments that can be coated with iron to form ferruginous bodies. Dental technicians may also be exposed to acrylic resins (used in the preparation of dental prostheses) or alginate impression powder, which may contribute to the development of pneumoconiosis. The pathologic response is interstitial fibrosis. In cases with significant exposure to silica, silicotic nodules or progressive massive fibrosis may be observed.
References:


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*Includes chromium, copper, nickel, titanium and zinc