Asbestos Associated Lung Disease

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Abstract

Asbestos is a naturally occurring silicate mineral. Its deposition can occur in any portion of the respiratory system. It is known that particles that penetrate to the alveoli are 1 µm or less in diameter, but asbestos fibers are the exception despite their length of 30 µm or more. Interstitial lung diseases (ILD) are a heterogeneous group of lower respiratory tract disorders that share certain pathogenic mechanisms and histopathologic features. The common denominator among ILDs is the widespread disruption of alveolar walls and fibrosis. Asbestosis is the ILD produced by asbestos which affects the alveolar interstitium. The cause of most ILDs is still unknown. Different agents including environmental ones have been implicated, but further studies are necessary to understand and develop preventive measures that will benefit population at high risk to develop ILD.

CROCIDOLITE ASBESTOS

Silicate is chemically defined as a compound with one or more central silicon atoms surrounded by electronegative ligands, most often oxygen atoms. Because the most abundant elements in the continental crust are oxygen (45.2% weight) and silicon (27.2% weight), high silicate abundance (30%) in the Earth's crust is not surprising. Structurally, silicates are classified into six subclasses: Nesosilicates, Sorosilicates, Inosilicates, Cyclosilicates, Phyllosilicates, and Tectosilicates [3031]. Silica belongs to the tectosilicate and the asbestos amphibole crocidolite to the inosilicate sub class.

Asbestos is a naturally occurring fibrous hydrated silicate mineral widely used in the past for commercial applications. In the last century, more than 30 million tons of asbestos have been mined, processed and applied in the United States. [12] Asbestos exposure can be classified into two groups: occupational and non-occupational. Occupational exposure occurs during mining and milling of the fibers, or during industrial application of asbestos in textiles, insulation, shipbuilding, brake lining mechanics, etc. Non-occupational exposure is related to fugitive asbestos fibers released into the environment and material inadvertently brought home and released from contaminated clothing or other asbestos contaminated materials. [3]

Despite the fact that most occupational asbestos exposure ceased in the late 1970's due to governmental legislation, asbestos-related disease is still a public health concern because: a) approximately 27 million workers in U.S. had been exposed, b) the latency period involved between initial exposure and asbestos-related disease which is 20 years or longer, c) the continued presence of construction material containing great amounts of asbestos, and d) the increase in death rate due to asbestos-related disease. [45] Asbestos-related diseases integrate several different kinds of diseases related to previous exposure to asbestos fibers. The spectrum of thoracic diseases includes benign pleural effusion, pleural plaques, diffuse pleural thickening, rounded atelectasis, asbestosis, mesothelioma, and lung cancer. Asbestosis is the ILD produced by the inhalation of asbestos fibers.

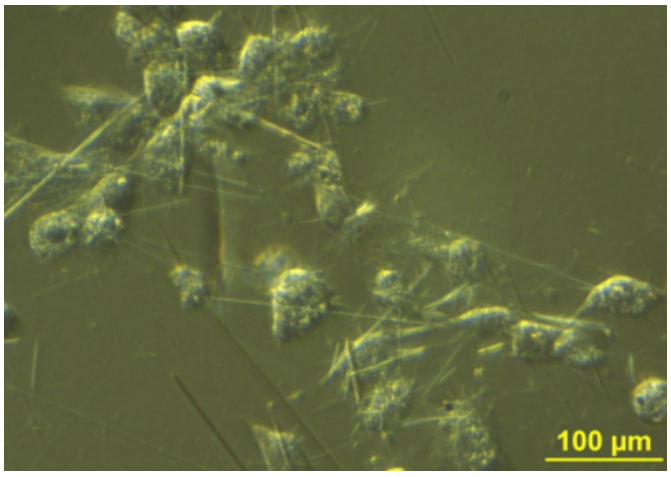
Asbestos forms fine, fibrous crystals and exhibits different properties such as high tensile strength and durability, flexibility and malleability, thermal and chemical resistance, and low electrical conductivity. Due to these properties, asbestos had been used widely in many industrial and commercial applications. There are two primary classes of asbestos: serpentine and amphibole. Serpentine fibers are curly-stranded structures. Chrysotile ($Mg_6Si_4O_{10}(OH)_8$), a white or greenish colored asbestos generally considered to be a less toxic fiber is the only commercial serpentine asbestos and accounts more than 90% of asbestos used in the United States. Amphiboles fibers are straight, rigid and needlelike. Three examples of amphiboles fibers are: crocidolite ($Na_2Fe2+_3Fe3+_2Si_8O_{22}(OH)_2$) a blue sodium iron silicate fiber that may be woven or spun into cloth or tape, tremolite a white to yellowish calcium magnesium silicate that has been a major ingredient in industrial and commercial talc, and amosite ($Fe_7Si_8O_{22}(OH)_2$) a brownish-yellow to white asbestos mineral used for heat insulation. [5]

Despite their differences in physical properties, all types of asbestos fibers are fibrogenic, but crocidolite is considered the most carcinogenic.

In the last 30 years numerous studies have been performed using different kinds of asbestos and cell types. It has been established that alveolar macrophages [6,7,8], alveolar type II cells [9], mesothelial cells [10,11], fibroblasts [12], and endothelial cells [13,14] can generate different responses when exposed to asbestos fibers. These different responses include DNA damage, gene transcription, and expression of proteins modulating cell proliferation, cell death, and inflammation [15,16,17,18]. In addition, several factors had been found related to the pathogenesis of asbestos induced lung injury: a) chemical and structural properties of the fiber, b) fiber burden in the lung, c) uptake by pulmonary epithelial cells, d) iron catalysed free radicals, e) DNA damage, f) induction of cytokines and growth factors, and g) cigarette smoke [19]. All these findings give an idea about the complexity of the lung response after asbestos exposure. In the asbestos related disease literature, approximately 15% of publications are about asbestosis, while most of the published work is about mesothelioma a malignancy associated with asbestos exposure.

Figure 1

Figure 1: LA-4 cells (alveolar type 2 cells like) exposed to Crocidolite asbestos for 24 hours. Photograph taken at Darrell Jackson's laboratory, University of Montana



PARTICLE INHALATION

Every day the respiratory system is exposed to large amounts of air through respiration. The calculated amount of air mobilized by an adult is 15 to 20 m3 per day. Due to this large amount of air volume, a considerable amount of inhaled particles could accumulate in the lungs despite their low concentrations in the environment. The principal mechanisms of inhaled particle deposition in the respiratory tract are impaction, sedimentation, interception, and diffusion [20,21].

Impaction is the dominant mechanism of deposition of particles larger than 3 µm in aerodynamic diameter. It occurs when the particles follow their initial path because of inertia rather than following changes in direction or speed of the airflow, resulting in collision with the wall of the airway usually near a bifurcation.

Sedimentation of particles occurs when the airflow is slow and particle deposition is influenced by gravity. As particles increase in aerodynamic diameter the sedimentation increases.

Interception is a non-inertial incidental contact with the airway wall. It is more important for fibers because their length (not their diameter) increases the probability that the ends of the fiber will deposit by interception on the walls of the airway.

Diffusion is responsible for the deposition of particles smaller than 0.5 µm in diameter. As particle size decreases, diffusion increases. Deposition by diffusion is highest in the alveoli where the airflow is very slow

Particle deposition can occur in any portion of the respiratory system, but for the development of pneumoconioses, the deposit has to occur in the distal regions, such as the terminal bronchioles and alveoli. The great majority of particles that penetrate to the alveoli are 1 µm or less in diameter. Larger particles are deposited on the upper respiratory tract, trachea, and larger bronchi. Asbestos fibers are the exception because they can penetrate the lung parenchyma despite their length of 30 µm or more [22]. After the noxious agent (e.g. silica or asbestos) reaches the lung, several factors in exposed individuals may play a role in their susceptibility to develop ILD. Nemery et al., proposed four factors: First: differences in delivery and/or persistence of the noxious agent could be related to innate anatomical or physiological characteristics, and to acquired changes. Second: genetic or acquired variations in enzymatic and non-enzymatic defense systems mainly related to protection against oxidative stress. Third: the immunological sensitization that is dependent on genetic and environmental factors. And fourth, the propensity to develop particular types of reaction such as granulomas, and the ability to regulate and resolve inflammation and fibrogenesis [23].

INTERSTITIAL LUNG DISEASE

Interstitial lung diseases (ILD) are a large and heterogeneous group of lower respiratory tract disorders that share certain pathogenic mechanisms and histopathologic features. ILD is also known as “Interstitial pulmonary fibrosis” or “Diffuse parenchymal lung disease” [24]. The prevalence of ILD in the general population is estimated to be 20 to 40 per 100,000 and accounts for 100,000 hospital admissions each year. [25] Several factors such as an increase in the use of pneumotoxic drugs prescribed to treat malignancies, cardiovascular diseases, or organ transplantation, and the increase in the identification of occupationally induced ILD have contributed to an increase in its incidence.

The human respiratory system includes the following regions: the nasal cavity, pharynx, larynx, trachea, bronchi and their smaller branches, and the lungs. The histology of the respiratory system is complex in the proximal regions and simple in the distal regions [2627]. The human respiratory tract contains over 40 different cell types, such as epithelial cells lining in the airways, alveoli and blood vessels as well as connective tissue cells. The affected structure in ILD is the alveolar interstitium, which involves the space between the alveolar epithelium and the capillary endothelium including the connective tissues surrounding blood vessels, lymphatic vessels, and airways. Despite the presence of some pathologic differences, the common denominator among ILDs is the widespread disruption of alveolar walls with loss of functional alveolar capillary units and accumulation of collagenous scar tissue also described as fibrosis.

The clinical presentation of ILD includes the triad: progressive dyspnea or shortness of breath, evident radiographic interstitial infiltrates, and pulmonary function tests showing a decrease in volume and gas diffusion. The clinical classification of ILD could be divided into five groups: Primary lung disease, associated with autoimmune disease, associated to drug or treatments, Environmental-Occupational associated, and secondary to inherited disorders. [25] This review focuses in the Environment/Occupation–associated ILD. Occupational diseases affecting the pulmonary interstitium and producing ILD include primarily the pneumoconiosis or dust diseases of the lung, and hypersensitivity pneumonitis. The principal cause of pneumoconioses are asbestos (asbestosis), coal dust (coal workers’ pneumoconiosis), cobalt (hard metal disease), silica (silcosis) and talc (talcosis). [28] The term pneumoconiosis can be defined as “the accumulation of dust in the lungs and the tissue reactions to its presence.” [22] The most prevalent pneumoconioses are the ones caused by silicates such as asbestos and silica. Pneumoconiosis as a consequence of silicate exposure produced significant morbidity and mortality during the early part of the twentieth century. Today silicate exposure in the workplace has been reduced through enforcement of strict regulations in US, but due to the latency period between exposure and disease, new cases of silicate pneumoconiosis are still detected in the general population. [29]

ETIOLOGY

The cause of most ILDs is unknown. Different agents such as bacteria, virus, fungi, toxic agents, and environmental agents have been implicated. It has been proposed that these agents can activate inflammatory or immune cells in the lung, or alternatively these agents could produce direct injury to the resident pulmonary cells leading to an inflammatory response initiated by the injured lung tissue. Because most of the time more than one agent is present, it is possible to conclude that ILD is produced by a combination of factors that induce direct and indirect inflammation, and affect the self-limited inflammatory response. In the past it was proposed that an insult initiated an inflammatory response leading to a cycle of chronic inflammatory injury leading to fibrosis. As a consequence, anti-inflammatory therapy was the primary therapy in the hope that an interruption of the inflammatory cascade before irreversible tissue injury occurred would benefit patients with ILD. However, in many cases, the use of anti-inflammatory agents such as glucocorticoids and cytotoxics failed to improve the outcome. [32] Therefore, a new hypothesis has been proposed focusing on the alveolar surface of the lung. It has been suggested that a stimulus (e.g. asbestos, beryllium) produces repeated episodes of lung injury and the damaged alveolar epithelium induces accumulation and activation of immuno-inflammatory cells, with subsequent migration and proliferation of fibroblasts and extracellular matrix deposition leading to the development of foci of fibroblasts/myofibroblasts in the alveolar interstitium. This wound healing process leads to fibrosis and loss of lung function. [3334]

PATHOGENESIS

The pathogenesis of ILD can be divided into three steps:

1. Epithelial damage: Epithelial cell injury is a hallmark of ILD. In situations of extensive cell damage and/or inappropriate re-epithelialisation of

the lung surface, the normal interaction between alveolar epithelial cells, inflammatory cells and interstitial fibroblasts is altered resulting in an unbalanced production of inflammatory mediators.

2. Intra-alveolar inflammation: Inflammatory exudate accumulates and inflammatory cells such as macrophages, neutrophils and lymphocytes increase in number in the alveolar walls and in the alveolar air spaces. The inflammatory cell recruitment process, which depends on production of cytokines and chemokines, includes the following four steps: sequestration of inflammatory cells in pulmonary vessels, transmigration of the vascular wall, migration through the extracellular matrix, and selective tissue retention.

3. Intra-alveolar fibrosis/alveolar collapse: The local population of fibroblasts and myofibroblasts increases, leading to a progressive aberrant tissue remodeling process with deposition of extracellular matrix components, including fibrillar collagen, elastic fibers, fibronectin and proteoglycans. Under the influence of growth factors and angiogenic molecules, epithelial cells proliferate and convert the fibrin-rich exudate in fibrotic tissue producing scars and changes in the normal lung architecture.

Because ILD is the final outcome of different cellular events, further studies describing the role of each cell type in the respiratory system and their interaction between them are necessary to understand and develop preventive measures that will benefit exposed individuals and population at high risk to develop ILD.

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