Expanding the Spectrum of Particle-and Fiber-Associated Interstitial Lung Diseases

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Abstract

While interstitial lung disease (ILD) is common, less than five percent of diagnoses appear to be related to occupational and environmental exposures to particles and fibers; these injuries are most frequently recognized as pneumoconioses and hypersensitivity pneumonitides. As a result of this small contribution to recognized ILD, the association of particles and fibers with this group of diseases is frequently deemed of little consequence. However, it has been proposed that some portion of ILD without a recognized cause (i.e. idiopathic disease) can also be related to exposures to particles and fibers. Many of these diagnoses are determined without benefit of microscopic examination of lung tissue. Even when tissue is available, the conventional examination for the presence of particles and fibers is used. This approach employing optical microscopy is insensitive and leads to misdiagnosis. A review of previous investigation demonstrates associations of idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, pulmonary alveolar proteinosis, sarcoidosis, and eosinophilic granuloma with particle and fiber exposures. It is recommended that scanning electron microscopy in combination with the use of electron dispersive X-ray analysis be employed whenever the question of a possible relationship between ILD and particle and fiber exposure arises.

INTRODUCTION

Interstitial lung diseases (ILDs), a group also described as diffuse parenchymal lung diseases (DPLDs), includes over 200 distinct diseases in which the interstitium is altered by inflammation and/or fibrosis [1]. The interstitium of the lung is comprised of the alveolar wall (and the lumen), vasculature, interstitial macrophages, fibroblasts, myofibroblasts, and matrix components; the inflammatory and fibrotic disorders encompassed by ILD may affect any of these components. The resulting infiltration by cellular and extracellular elements either causes distortion and destruction of the alveolar and bronchiolar architecture or has little associated damage.

Interstitial lung disease is a diverse group of both acute and chronic disorders. Common clinical, radiographic, and pathophysiologic features form the basis for collectively referring to this massive group of injuries as a single entity. Frequently, the patient with ILD presents with the symptoms of dyspnea and nonproductive cough and crackles particularly “Velcro rales” on physical examination. A chest radiograph shows reticular, nodular or mixed pattern markings and lung function tests demonstrate some loss including decreased volumes and reduced diffusing capacity.

Interstitial lung disease is common and the diagnosis is established in about 70 out of every 100.000 individuals in the United States [2]. About 10.000 Americans die every year from ILD [2]. This group of lung disorders includes disease with both known and unknown causes. Less than five percent of ILD appears to be related to occupational and environmental exposures to particles and fibers [3]. These injuries are most frequently recognized as pneumoconioses and hypersensitivity pneumonitides and are almost always related to occupational exposures to particles and fibers. A diagnosis of work-related ILD is most frequently established on the basis of an occupational history, revealing a pertinent exposure, and an abnormal chest x-ray.

As a result of the small contribution to recognized lung injury, the association of particles and fibers with ILD is frequently deemed of little consequence. In the clinical setting or in the conduct of observational studies, a number of factors may limit recognition of an association between a patient with idiopathic pulmonary fibrosis (IPF) and his or her environmental and occupational exposures. These factors may include diagnostic misclassification, infrequent occurrence of IPF, exposure misclassification, and variation in susceptibility to exposures. However, it has been speculated that some portion of that ILD without a recognized cause (i.e. idiopathic disease, which includes the majority of diagnoses...
of ILD) can also be related to exposures to particles and fibers [4]. Historically, the histopathological assessment of a surgical biopsy specimen has been viewed as the “gold standard” among the diagnostic tests in ILD, especially if IPF. However, in many cases it is seen that either patients are too compromised to undergo such procedures or physicians assume that such a management approach has no practical benefits from surgeries. Furthermore, technological advances of high resolution CT scan and semi-invasive methods of bronchoalveolar lavage, has shifted a focus from histological to the non-pathological mode of management and also in selection of representing groups for epidemiological studies [5]. Most of these diagnoses are determined without benefit of microscopic examination of lung tissue (in two UK surveys of patients with IPF, only 7.5% [33] and 12% [34], respectively, had an open lung biopsies), and, therefore, the issue of a pertinent exposure can sometimes not be introduced. Even when tissue is available, the conventional examination for the presence of particles and fibers uses light microscopy, which is insensitive and leads to misdiagnosis. Scanning electron microscopy coupled with energy dispersive x-ray analysis (EDXA) is more sensitive but is infrequently accomplished. Therefore, the classification of ILD as idiopathic may be made when the detection of particles and fibers responsible for the disease is missed. Evidence supporting a relationship between particles and fibers and idiopathic ILD is herein examined. This review of previous investigations supports associations of idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, pulmonary alveolar proteinosis, sarcoidosis, and eosinophilic granuloma with particle and fiber exposures (Figure 1).

**Idiopathic pulmonary fibrosis**

The term “idiopathic pulmonary fibrosis” (IPF), or lone cryptogenic fibrosing alveolitis, historically has encompassed four separate forms of interstitial pneumonia as well as a number of other conditions, each having a different clinical course and prognosis [6]. According to the current definition, IPF is a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs and associated with a surgical lung biopsy showing a histologic pattern of usual interstitial pneumonia (UIP) [7]. A diagnosis of idiopathic pulmonary fibrosis is made in an estimated 5 out of every 100,000 patients [8]. A more recent population-based study for all interstitial lung diseases in the county population of Bernalillo, New Mexico revealed a prevalence of 20.2 cases per 100,000 for males and 13.2 cases per 100,000 for females with IPF [3]. Incidence estimates for IPF are quite limited. It has been estimated at 10.7 cases per 100,000 per year for males and 7.4 cases per 100,000 per year for females [3]. A majority of these patients present between 40 and 80 years of age, though IPF may occur in children. Patients usually present with insidious onset of otherwise unexplained dyspnea on exertion for ≥3 months and bibasilar, inspiratory crackles (dry or “Velcro” type in quality) on the physical examination. Pulmonary function studies are abnormal with evidence of restriction (reduced vital capacity and forced expiratory volume in one second) and impaired gas exchange (increased A-a PO2 with rest or exercise or decreased DLCO) whereas there are bibasilar reticular abnormalities with minimal ground glass opacities on high resolution CT scans. The pathology of this injury shows the characteristic finding of usual interstitial pneumonia, which includes varying quantities of alveolar inflammation and progressive fibrosis; however, the latter always predominates. Following diagnosis, patients typically survive for four to five years [7].

The diagnosis of IPF requires exclusion of other known causes of interstitial lung diseases such as drug toxicities, environmental exposures, and connective tissue diseases. There are several potential risk factors which have been identified and linked to the development of IPF. In case-control studies, cigarette smoking has been identified as a potential risk factor with the odds ratio (OR) from various regions of the world ranging from 1.6 to 2.9 for the development of IPF in ever-smokers [9-11]. The odds of developing IPF increased with the pack-years of smoking in a study from the United Kingdom, but this effect was not significant [10]. A study in the United States revealed that those with a history of smoking for 21 to 40 pack-years had an OR of 2.3 (95% confidence interval [CI], 1.3 to 3.8) [9]; the OR for ever smoking was 1.6 (95% CI: 1.1 to 2.4). Several viruses have been implicated into the pathogenesis of IPF yet there is no clear evidence of viral etiology [12]. Viruses suggested to potentially have an etiologic relationship with IPF include Epstein-Barr virus (EBV), cytomegalovirus (CMV), influenza, hepatitis C virus, adenovirus, and human immunodeficiency virus type 1 (HIV-1) [13-20]. Hereditary factors may contribute to the risk of developing IPF but no specific genetic markers have been identified [21]. The most compelling evidence for participation of genetic factors is descriptions of familial cases of IPF. Familial IPF is probably inherited as an autosomal dominant trait with variable penetrance [22].

It has been suggested that occupational and environmental exposures to dusts can also be associated with IPF. To evaluate for some relationship between particle and fiber exposures and IPF, differences in mortality attributable to IPF in...
regions of England were examined [8]. Patients with IPF were documented to have basal crackles, restrictive pulmonary function, and an absence of exposure to known fibrogenic agents in the past. There were a greater number of males included in the study, possibly because more men work at “dirty” work sites. Four controls were selected for every subject with IPF; these were obtained from patients provided medical care by the same general practitioner treating that individual diagnosed with IPF. The mortality rate for IPF was highest in industrial zones, suggesting that specific exposures may possibly be related to occupations necessitating dust exposure. A fifty percent increase in the risk of developing IPF was seen in patients who were involved in such activities as carpentry work, stone cutting/polishing, bird raising, or employment in a chemical plant, mining, and the insulation industry [23]. In addition, it was noted that agricultural workers suffered from a greater rate of decreased lung function and fibrosis. These correlations support some relationship of particle- or fiber-exposure with a diagnosis of IPF. A second study similarly noted that the IPF rate was twice as high in patients whose jobs exposed them to dusts and organic solvents [11]. Metal production workers and miners exemplified those individuals at the greatest risk.

In a third investigation, the postulate that deposits of silica/silicates could be increased among patients diagnosed with IPF was tested [24]. Silicon (Si) and sulfur (S) signals from energy dispersive X-ray analysis (EDXA) were measured in the lungs of patients with IPF and control subjects. The median Si/S ratio in the normal lung group was 0.130. Only two of the 25 normal lung samples had Si/S ratios greater than 0.3 (suggesting that a Si/S ratio less than 0.3 could be used to define normality). In a cohort of patients previously diagnosed to have IPF, the Si/S ratio in the lungs was demonstrated to have a median value of 0.330. Fifty percent of IPF patients with high Si/S ratios had a history of dust exposure while only 3 of 13 of those with low Si/S ratios were deemed to have had significant exposures. These results support the contention that individuals diagnosed using conventional methodology to have IPF can demonstrate lung deposits of silica/silicates using a more sensitive approach. Pneumoconiosis is likely to be a more accurate diagnosis in some portion of these patients.

In a fourth study of patients with pulmonary fibrosis, it was demonstrated that examination of tissue by only optical microscopy led to misdiagnosis of IPF in 8.3% of cases (2/24) [25]. These two cases were diagnosed to be asbestosis after using electron microscopy techniques.

Finally, a specific example of a particle-associated lung injury with a clinical presentation comparable to IPF was observed among workers in a chalk plant [26]. Several teachers similarly had a clinical presentation approximating that of IPF but had a significant amount of dust in their lungs [27]. In these cases, silica and alpha-quartz were considered to be a potential etiologic agent.

In addition to silica and asbestos, silicates (Figure 2), coal, wood fires, metals (cobalt, hard metals, aluminum, titanium, nickel and magnesium) (Figures 3, 4), stone and sand dusts, textile dusts, vegetable dusts, wood dusts, animal/livestock dusts, and mildew have been deemed to possibly contribute to IPF diagnoses [2, 8, 10, 11, 23, 28-32]. Pulmonary fibrosis associated with agricultural work and farming is receiving increased attention since it may contribute to over 20% of all idiopathic cases [28]. This is now being defined clinically and the etiology has been suggested to result from inorganic components of soil dust [33-35]. Clerical work may protect against IPF [29].

**Desquamative Interstitial Pneumonia**

Desquamative interstitial pneumonia (DIP) is a form of idiopathic interstitial pneumonia marked by the presence of an increased number of pigmented macrophages in the alveolar spaces. Patients diagnosed with DIP usually present with a mean age of over 40 years and are predominantly male. Chest x-rays and CT scans reveal bilateral ground glass opacities. No specific therapies for DIP have been shown to be effective.

Particle exposure is recognized to be occasionally associated with DIP. At least one study has examined the relationship between DIP and particles [36]. Cases of DIP were diagnosed by light microscopy and later underwent scanning electron microscopy and EDXA. Controls had other air space filling processes with no known association with particles. While individuals who were considered to have DIP had 5.8x10^7 particles/cm^2, controls had 0.8x10^6 particles/cm^2.

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A majority of these patients with DIP had not shown increased numbers of birefringent particles. Almost three-quarters of the cases of DIP with available environmental history had a history of some dust exposure (metal or welding fumes and silicate exposure among them).

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare ILD characterized by an altered surfactant metabolism with a resultant accumulation of granular, acellular material (a phospholipid which is either surfactant or surfactant-like substance) in the alveolar spaces and a lack of inflammation and fibrosis. The accretion is the result of either an over-stimulation of type II pneumocytes or an impairment of a clearance mechanism that removes alveolar phospholipids.

Similar to other injury patterns like diffuse alveolar damage or interstitial fibrosis, PAP is a nonspecific response to lung injury. The histology of this injury is also characterized by accumulation of abnormal alveolar macrophages with surfactant-like material; these phagocytes demonstrate decreased anti-microbial function. In addition, there is cellular hyperplasia, sloughing, and degranulation of type II pneumocytes. Patients may present with some dyspnea, infection, cor pulmonale, or respiratory failure. Therapeutic lavage restores pulmonary function successfully; corticosteroid and immunosuppressive agent regimens show little benefit.

While a majority of PAP diagnoses are considered idiopathic in origin, this ILD can be associated with infections and drugs. Regarding an association with particles, in one study of 139 cases of patients diagnosed to have PAP, approximately half provided a history of exposure to either dusty environments or noxious fumes [37]. This same association of PAP and particulate matter was demonstrated with exposures to respirable agents including cement dusts, oven cleaners, silica from sandblasting, hairsprays, insecticides, and spray paints in 13/37 patients diagnosed to have PAP [38]. In another twenty-four cases of PAP studied by light microscopy and scanning electron microscopy, 78% contained a higher number of birefringent particles compared to the control subjects [39]. The concentration of inorganic particles in PAP patients was between $1.3 \times 10^7$ and $1.02 \times 10^9$ per cm$^3$, while controls all had less than $10^7$ per cm$^3$. These results support some relationship between PAP and exposure to particles.

In a case report, a truck driver presented to medical care providers with PAP [40]. This followed a history significant for exposure to Portland cement dust. The high numbers of inorganic particles (especially particulate matter containing silicon) observed in his lavage fluid supports the hypothesis that this patient developed PAP as a result of an occupational exposure to particles.

Animal studies confirm an association between alveolar proteinosis and particles and fibers. Numerous species demonstrate a PAP-like reaction following exposures to silica, quartz, cristobalite, pyro aluminum powder, and titanium [41-44]. In addition, one model of lung injury developed PAP within several months of exposure to glass fibers [41]. Specific human exposures responsible for PAP demonstrate a relationship with silica. Other causative agents are thought to include asbestos, mineral dusts, glass fiber dust, volcanic ash, metal fumes, welding fumes, cement, titanium dust, aluminum, talc, cadmium, tin, chlorinated resin, molybdenum, kaolin, and bentonite [37-39, 45-47].

Sarcoidosis

Sarcoidosis is a disorder in which multiple organ systems usually have non-caseating granulomas. It is the most common ILD of unknown etiology, with a prevalence of approximately 15 of every 100,000 people in North America [48]. The vast majority of patients present between 20 and 45 years old. The diagnosis is rare in children and the elderly.

The diagnosis of sarcoidosis is one of exclusion and is assigned only after known causes of similar-appearing disease have been eliminated. (Previously, if polarizable foreign matter was found in the granulomata, the patient was immediately deemed not to have sarcoidosis; however, this has changed). Many cases of sarcoidosis have demonstrated that foreign body granulomata and sarcoidosis are not exclusive of each other, and some investigators now contend that the two diseases are one and the same. It has also been proposed...
that sarcoidosis is a disease in which the ability of the immune system to handle particulate foreign matter is altered, therefore providing the stimulus for granuloma formation.

One investigation examined the relationship between occupational and environmental exposures and sarcoidosis [49]. This study was carried out following the development of lung disease in a naval serviceman whose tasks included grinding “non-skid” surface coatings from aircraft carriers. Results support the postulate that environmental exposures can cause or augment sarcoidosis-like disease. However, no such association was found in one large epidemiological study [50].

In a report of a series of cases, six of twelve lung specimens collected from patients diagnosed to have sarcoidosis demonstrated elevated signals for silica, aluminum, and titanium particles [51]. A relationship was suggested between fiber deposits and granulomatous disease with 14/50 cases, providing a history of exposure to man-made mineral fibers (MMMF). A previous study supported such a possible association between inhalation of MMMF and pulmonary fibrosis [52].

Another report noted a chronic pulmonary granulomatous reaction in two patients exposed to talc [53]. While talc pneumoconiosis was diagnosed in one patient, the other, who was exposed to cosmetic talcum powder, was considered to have chronic sarcoidosis. These cases had identical presentations but their separate diagnoses demonstrate how difficult it is to differentiate between chronic sarcoidosis and talc-related lung disease.

In a fourth case report, a patient presented with diffuse pulmonary granulomatosis, with sarcoid-like epithelioid granulomas and helper T-lymphocyte alveolitis [54]. The individual’s occupational history suggested that his illness could be related to his work; he had worked as a chemist for eight years in a catalyst fabrication plant where he was exposed to large amounts of aluminum powders and iron and smaller quantities of copper, zinc, nickel, chromium, manganese, cobalt, molybdenum, vanadium, palladium, and silica. Particles found in the patient’s lung reflected these exact exposures; 42% were aluminum-bearing, 17% were iron oxides/hydroxides, 10% were silica, and the remaining 31% were alumino-silicates, coal or soot dusts, calcium-bearing particles, or titanium oxides.

In addition to those inhalational exposures delineated above, several others are deemed to possibly cause sarcoidosis (cutaneous and systemic). These would include exposures to silica, cristobalite, aluminum compounds, barium compounds, beryllium, cobalt, copper, gold, titanium, zirconium, lanthanide metals, talc, glass fibers, rock wool, mixed dust, woodstoves, and firefighting [28, 53-63].

Cigarette smoking and ILD

Cigarette smoking is the most significant exposure of humans to particles. It is both the most frequent human exposure to particles and that of greatest intensity. Smoking a single cigarette exposes an individual to between 10,000 and 40,000 µg particles. The diameter of these particles is frequently less than a micron and they have a high total deposition rate. Cigarette smoke is made up of more than 4,000-5,000 compounds and has many different pulmonary and systemic effects on individuals. Among these, smoking has been connected with causing several different forms of ILD. These must be included as disease associated with particle and fiber exposure.

Idiopathic pulmonary fibrosis is much more common among smokers relative to lifetime non-smokers. The prevalence of some history of smoking among patients with IPF is estimated to be between 41% and 83% [64]. Cigarette smoking increases the risk of the development of IPF. Carrington’s classic longitudinal study of patients with usual interstitial pneumonitis (that pathology most commonly observed in patients with IPF) showed that 71% of patients with this pathology were smokers [65].

Comparable to IPF, DIP demonstrates a close relationship with cigarette smoking. Case studies have shown that about 90% of patients with DIP smoked cigarettes or had a history of having smoked cigarettes [64].

Eosinophilic granuloma (EG) is an uncommon form of ILD with unknown etiologic but it is likely an inflammatory response by Langerhans cells to some component of tobacco smoke since the diagnosis is very closely associated with cigarette smoking in younger individuals (under 40 years of age). In a study by the National Institutes of Health, 100% of all reported cases were smokers [66]. EG is included in a group of histiocytoses that includes Letterer-Siwe disease and Hand-Schuller-Christian disease. Patients frequently present with respiratory complaints of dyspnea, chest pain, cough, and hemoptysis; in addition, weight loss, fatigue and fever are common. The exam is often unremarkable but occasional wheezing may be present. Pulmonary function tests can show a decrease in lung volumes and diffusing capacity with either normal or reduced expiratory flow rates. Radiographically, there are reticulonodular interstitial infiltrates, changes of honeycombing, and thin-walled cysts; the last are especially prominent in the upper lung fields. Pleural effusions are uncommon, while pneumothoraces occur in approximately 10% of patients. The HRCT scans are highly distinctive, revealing numerous peribronchiolar nodular and cystic lesions. As the disease progresses, the nodules are replaced by cysts which become confluent. EG is characterized by an accumulation of histiocytic cells (Langerhans type). There are also intraluminal fibrosis, stelate nodules, cysts, and parenchymal fibrosis. Corticosteroid therapy does not show a huge benefit but patients rarely die from EG. There are no reported associations of EG with particles (or fibers) other than the absolute relationship with cigarette smoking.

In respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), pigmented macrophages and mild interstitial inflammatory changes are evident. The alveolar septa may thicken but collagen deposition is minimal. There is significant overlap between DIP and RB-ILD patients in terms of pathology as well as in the clinical and radiographical features of the patients. Individuals with RB-ILD are usually 40 to 60 years in age. There is a slight male predominance.
These individuals usually present with respiratory symptoms of cough and dyspnea. The physical exam reveals inspiratory crackles in approximately one-half of the patients. The chest radiographs usually are abnormal with basilar interstitial opacities showing up in over 2/3 of the patients; on the CT scan of the chest, a ground-glass pattern in frequently observed along with focal atelectasis and nodules. Patients almost always recover with cessation of cigarette smoking and corticosteroid therapy is infrequently required.

Finally, there is a more recently described entity of smoking-related interstitial fibrosis [67]. This is characterized by varying degrees of alveolar septal widening by collagen deposition along with emphysema and respiratory bronchiolitis. Smoking-related interstitial fibrosis is observed in subpleural and in deeper parenchyma. It is associated with (and frequently surrounded by) enlarged airspaces of emphysema, but it also involves non-emphysematous parenchyma. It can also be accompanied by respiratory bronchiolitis. Most patients are asymptomatic or only mildly symptomatic, and the clinical course is stable in most.

Features of the clinical presentation, physiologic changes, and pathology of individuals exposed to many disparate particles and fibers can be common. Among these is an ability of the particle and fiber to induce an inflammatory response. An universal event in ILD is an initiation of injury with evidence of an alveolitis/vasculitis. Persistence of this inflammatory lesion affects an alveolar, capillary, and parenchymal cell injury. All particles and fibers can be associated with such a reaction. Abnormal repair leads to mesenchymal cell proliferation with the production of excess collagen (and other extracellular matrix connective tissue elements) and fibrosis. It is plausible, and probable, that many dissimilar particles and fibers contribute to the injuries recognized in humans as ILD. Previous investigation supports such a participation of particles and fibers in several injuries included in ILD. Between 8% and 50% of IPF, a majority of both DIP and PAP, and up to 50% of sarcoidosis demonstrate some association with particle and fiber exposure. In addition, RB-ILD and EG are always associated with particles (specifically cigarette smoking particles). As the majority of particles and fibers can be below the resolution of an optical micro-
scope and are undetected with conventional examination, the association of ILD with both will necessitate examination with scanning electron microscopy in combination with the use of EDXA when the question of this relationship arises. A standardized approach to ILD must emphasize repeated attempts to include all occupational and environmental exposures and the use of electron microscopy techniques (Figure 5).

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