Asbestosis and environmental causes of usual interstitial pneumonia

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Purpose of review
Recent epidemiologic investigations suggest that occupational and environmental exposures contribute to the overall burden of idiopathic pulmonary fibrosis (IPF). This article explores the epidemiologic and clinical challenges to establishing exposure associations, the current literature regarding exposure disease relationships and the diagnostic work-up of IPF and asbestosis patients.

Recent findings
IPF patients demonstrate a histopathologic pattern of usual interstitial pneumonia. In the absence of a known cause or association, a usual interstitial pneumonia pattern leads to an IPF diagnosis, which is a progressive and often terminal fibrotic lung disease. It has long been recognized that asbestos exposure can cause pathologic and radiographic changes indistinguishable from IPF. Several epidemiologic studies, primarily case control in design, have found that a number of other exposures that can increase risk of developing IPF include cigarette smoke, wood dust, metal dust, sand/silica and agricultural exposures. Lung mineralogic analyses have provided additional support to causal associations. Genetic variation may explain differences in disease susceptibility among the population.

Summary
An accumulating body of literature suggests that occupational and environmental exposure can contribute to the development of IPF. The impact of exposure on the pathogenesis and clinical course of disease requires further study.

Keywords
asbestosis, idiopathic pulmonary fibrosis, occupational lung disease, usual interstitial pneumonia

INTRODUCTION

The idiopathic interstitial pneumonias encompass a diverse range of clinico-radio-pathologic disorders. Among the idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) is the most common. Usual interstitial pneumonia (UIP) represents the pathologic pattern seen in IPF. Despite the presumption that no cause exists, several epidemiologic studies implicate exposure risk factors including tobacco smoke, wood and metal dust [1–9]. Given that epithelial injury is likely the initial event, the presence of an inciting exposure is biologically plausible. Genetic susceptibility may explain why exposure elicits disease in only some individuals. Although a UIP pattern is usually presumed to be 'idiopathic', the current literature supports a relationship between exposures, in addition to asbestos and UIP.

Other interstitial lung diseases such as nonspecific interstitial pneumonia and chronic hypersensitivity pneumonitis have been associated with a number of exposures, particularly organic antigens emanating from a variety of sources such as dairy and grain products, animal dander and protein and water reservoir vaporizers. These interstitial lung diseases have distinct radiologic and pathologic patterns and are not addressed in this review.

USUAL INTERSTITIAL PNEUMONIA: OCCUPATIONAL AND OTHER RISK FACTORS

Idiopathic pulmonary fibrosis represents the most commonly identified idiopathic interstitial pneumonia. UIP is the pathologic pattern associated with

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KEY POINTS

- IPF may have known causes and association.
- Asbestosis, a diffuse interstitial lung disease, develops insidiously after years of chronic asbestos exposure and may appear indistinguishable from IPF.
- Several epidemiologic investigations worldwide of IPF have suggested a number of possible occupational and environmental causes such as exposure to cigarette smoke, wood dust, metal dust, sand/silica and agricultural exposures.
- The essential elements of the IPF and asbestosis diagnostic work-up include a high index of clinical suspicion and the HRCT. Histopathologic confirmation is not routinely required.

IPF, but may be seen in association with connective tissue diseases, medication toxicity and occupational exposures such as asbestos [10].

Epidemiology studies of IPF have been hindered by several challenges, including changes in disease classification and diagnostic approaches, and also the many challenges involved in assessing chronic usually mixed exposures over many years. Recent epidemiologic studies suggest an increasing prevalence of IPF. Raghu *et al.* [11], using an administrative dataset, reported a prevalence of interstitial lung disease (ILD) of 14.0 and 42.7 per 100 000 depending on case definition. Increasing age, male sex and smoking increase the risk for ILD [11]. Gastroesophageal reflux disease, a type of 'exposure', also increases risk. Researchers are currently investigating whether aggressive reflux treatment, such as with Nissen fundoplication, alters disease course [12,13▪].

Several studies, mostly case control in design, have demonstrated associations between exposure and IPF [1–4,6–8,14▪▪]. Smoking has consistently been reported as a risk factor for IPF with a population-attributable risk estimated at 49% [9]. For example, in the United States, Baumgartner *et al.* [2] reported an odds ratio (OR) of 1.6 for ever smokers In a recent Swedish study of 181 patients enrolled in a long-term oxygen registry, Ekstrom *et al.* [15▪▪] reported significant interactions between smoking, male sex and occupational exposure, with an OR of 3.0 [95% confidence interval (CI) 1.3–6.5] for exposed IPF patients compared to nonexposed women. Although inconsistently reported in the past, a dose response to smoking was observed [15▪▪].

Several studies have consistently shown an increased IPF risk in association with specific exposures including metal dust, wood dust, stone/silica and farming.

Hubbard *et al.* [6] analyzed data derived from mailed questionnaires and telephone interviews in 218 patients and 569 match-based controls in the United Kingdom. Dose response increases in IPF risk were found in association with metal dust (OR 1.69, 95% CI 1.07–2.65), wood dust (OR 1.71, 95% CI 1.01–2.92), as well as associations with stone/sand (OR 1.76, 95% CI 1.01–3.07) and textile dust (OR 1.80, 95% CI 1.10–2.96) [6].

In Japan, Iwai *et al.* [7] used data from autopsy records in 1311 IPF patients to report an OR of 3.01 (95% CI 1.29–7.43) with agricultural exposures and 1.34 (95% CI 1.14–1.59) among metal workers.

In 2000, Baumgartner *et al.* [1] recruited 248 IPF patients through a random digit dialing method and demonstrated associations with livestock (OR 2.70, 95% CI 1.30–5.50), sand/stone/silica (OR 3.90, 95% CI 1.20–12.70) and metal dust exposures (OR 2.00, 95% CI 1.00–4.00). A dose–response relationship was seen in association with metal dust [1].

Hubbard *et al.* [5] investigated IPF risk in 20 526 workers employed at a major engineering company in the United Kingdom using pension-fund mortality data and historic occupational records to assess exposures. An increased proportional mortality ratio of 1.39 was found in this cohort compared to national data, with a significant dose response seen in workers exposed to metals (OR per 10 years of metal exposure of 1.71, 95% CI 1.09–2.68) [5].

Using extensive occupational data from 181 pulmonary fibrosis patients including 140 with IPF enrolled in a Swedish Oxygen Registry, Gustafson *et al.* [4] demonstrated an increased risk of IPF in men with exposure to birch dust (OR 2.7, 95% CI 1.30–5.65) and hardwood dust (OR 2.7, 95% CI 1.14–6.52).

In a recent Egyptian hospital-based case control study, exposure data from 201 confirmed IPF cases and 205 controls were compared. Carpentry and woodworking (OR 2.56, 95% CI 1.02–7.01), and chemical and petrochemical occupational exposures (OR 6.47, 95% 1.66–25.12) were associated with increased IPF risk [16].

The Korean Interstitial Lung Disease Research Group recently conducted a national cross-sectional survey of 1311 IPF patients, stratified into five occupational groups. Dust-exposed workers showed earlier-onset ILD, and dust exposure occupation was associated with increased mortality (hazard ratio 1.813, 95% CI 1.049–3.133) [14▪▪].

Several novel exposures or novel uses of old exposures have recently been implicated in the development of ILD. Raghu *et al.* [17] reported a case of a 64-year-old male patient who for many years had ground, machined and drilled Corian, a solid surface material composed of acrylic polymer

and aluminum triyhydrate. Pathology revealed birefringent crystals on polarizable microscopy and autopsy revealed evidence of aluminum trihydroxide. Past studies have suggested a link between aluminum and interstitial lung disease [17].

Mineralogic analysis of lung tissue has been used to evaluate exposure in UIP patients. An excess of silica, and metals, including iron and nickel, has been reported in several studies [18–20]. Using scanning electron microscopy and energy dispersive X-ray analysis, Monso *et al.* [20] reported elevated surface silica to sulfur ratios among six IPF patients compared to controls. Postulating that exposures may be concentrated in lymph nodes, a recent Japanese study of 23 IPF cases versus 23 controls demonstrated an excess of silicon and aluminum in the pulmonary hilar lymph nodes [21].

Although familial IPF is rare, investigators have described several genetic associations in patients with sporadic IPF, including genetic variations in surfactant protein C and A, human telomerase reverse transcriptase and more recently MUC5B [22]. The causative contribution of respiratory exposure to IPF is potentially supported by the identification of a MUC5B genetic variant. MUC5B encodes mucin glycoproteins and it is postulated that defects in mucin glycoprotein may make airways more susceptible to injury [22].

ASBESTOSIS

Asbestos refers to a group of naturally occurring fibers composed of hydrated magnesium silicates that are commercially valuable due to its strength, flexibility and resistance to electrical, thermal and chemical degradation. Two categories of asbestos exist: serpentine – long, curly fibers; and amphibole – long straight rod-like structures. Chrysotile is the only significant commercially used serpentine fiber. Amphibole fibers include crocidolite, amosite, anthophylite, actinolite and tremolite. Chrysotile fiber use is more common, whereas amphibole fibers are considered more toxic.

In addition to its association with lung cancer, mesothelioma, small airways disease and pleural disease, asbestos exposure can lead to asbestosis, a form of interstitial lung disease often indistinguishable from IPF [23,24].

The WHO estimates that 1.3 million and 125 million workers in the United States and worldwide, respectively, have experienced asbestos exposure during mining or milling or during its use in several industries such as building and construction, shipbuilding and the automotive industry [25▪]. An estimated 13 885 individuals died of asbestosis between 1994 and 2010 with a potential loss of 180 000 years of life lost [26▪]. In the United States, the number of deaths attributed to asbestos reached 1493 in 2000 and declined to 1470 by 2004 [25▪]. The median age at death is generally 79 years [27▪]. Asbestosis increased the risk for lung cancer as demonstrated from a study of 339 North American Insulator workers who died from lung cancer. The rate ratio for lung cancer for exposed nonsmokers versus smokers was 7.40 (95% CI 4.0–13.7) and 36.8 (95% CI 30.1–45.0) [28▪]. The asbestos exposure that emanated from the collapse of the World Trade Centers was a reminder of the asbestos that still remains in older buildings and that the long-terms effects of such exposure should be monitored over time [29].

Asbestos consumption remains substantial in Eastern European, South American and Asian countries [25▪]. China, for example, is the leading consumer of asbestos and the second largest producer of worldwide asbestosis. The number of asbestosis cases among Chinese miners [30] and factory workers exceed the number of cases found in developing countries. For example, in a cohort study of Chinese asbestos factory workers, 39 of 259 deaths observed in 586 male asbestos workers were due to asbestosis [31▪].

Nonoccupational environmental exposure to asbestos is also a concern. Environmental exposure can occur from exposure to the soiled clothes of asbestos workers. Mining, road construction, agricultural and natural weathering and development may lead to nonoccupational exposures from naturally occurring asbestos, minerals found as natural components of soils and rock. Asbestos-related diseases, predominantly pleural plaques and mesothelioma, have been reported in association with environmental exposures in areas such as China, Corsica, Turkey, Greece, Cyprus and California [32▪]. Asbestos-containing soil has been routinely used in the plastering, whitewashing and roof insulation of houses in countries such as Greece [33]. The use of serpentinite in New Caledonia for road surfacing has been reported as a risk factor for mesothelioma [34]. Erionite, technically not asbestos but similar to a long thin amphibole fiber, found in white stucco and soil, in Turkey, has been associated with mesothelioma [35]. Proximity to industrial sources with some modification of exposure by wind direction has been reported as, for example, in Libby, Montana, the world's largest vermiculite mine and processing operation [36]. Residents of Libby endured exposure to the vermiculite ore contaminated with amphibole asbestos resulting from past industrial production. While pleural disease has been reported most commonly, parenchymal abnormalities have also been reported [37].

Inhaled asbestos fibers deposited at the level of the respiratory bronchiole and alveolar duct bifurcations exert a direct deleterious effect on the lung. Lung deposition stimulates the release of various mediators including cytokines, growth factors, proteases and reactive oxidative species. By impairing mucociliary clearance mechanisms, smoking may increase risk for asbestosis. Gene environment interactions might further influence the development of the disease [38▪]. Franko *et al.* [38▪] reported several gene–gene environment interactions on the risk of asbestosis including a strong interaction between glutathione S-transferase GSTM1-null polymorphism and smoking and iNOS $(CCTTT)_n$ polymorphism and smoking, and between iNOS $(CCTTT)_n$ and cumulative asbestos exposure. A glutathione S-transferase GSTT1 deletion may protect against asbestosis [39].

Work-up of patients with possible asbestosis includes radiographic imaging and requires histopathologic confirmation only when the exposure history is indeterminate. At early stages, chest computed tomography (CT) scans may be more sensitive while at more advanced stages the CT scan is indistinguishable from IPF. Pleural plaques indicate prior exposure [40]. Physiologic testing correlates with radiographic abnormalities, and diffusion capacity is more sensitive at detecting progressive disease [41]. The diagnostic assessment is further reviewed below.

DIAGNOSTIC WORK-UP

The diagnostic work-up of any patient with ILD includes a comprehensive history, radiographic assessment, preferably with high-resolution chest CT scan, and pulmonary function testing. Biopsies are not routinely required.

History

Identifying culprit exposures require a high index of clinical suspicion and a comprehensive history. Given the long latency between exposure and disease, clinicians should inquire about the present and past jobs and employers, as well as the presence of disease among co-workers. Providers should obtain more detailed information such as specific work tasks and workplace materials. For example, workers in the machining trades such as machinists and tool and die operators, and workers in fabricating trades such as welders and blacksmiths may be exposed to metal dust. Clinicians should ask about visible dust exposure, the presence of appropriate engineering controls such as local exhaust ventilation and finally the use of personal protective equipment such as respirators.

Asbestos exposure traditionally has occurred during mining of fibers or industrial applications such as in shipbuilding or insulation work. Non-occupational asbestos-related disease has been reported, such as among individuals with regular exposure to the clothes of asbestos workers and in individuals with environmental exposures to industrial sources as in Libby, Montana [36].

Radiology

Chest radiographs are routinely performed in the diagnostic work-up of dyspneic patients and as part of workplace respiratory surveillance programs such as asbestos surveillance programs mandated by the Occupational Safety and Health Administration. Whereas chest radiographs are often insensitive in detecting the subtle lower lobe reticular abnormalities in early disease, traction bronchiectasis and honeycombing may be evident in the advanced stages.

International Labor Office (ILO) classification of chest radiographs for persons with pneumoconiosis standardizes and grades the presence of radiographic abnormalities including the size, shape and distribution, profusion of small opacities, and presence and type of pleural abnormalities. The use of standard digital images to classify chest radiographs has recently been validated [42,43], facilitating on-going respiratory surveillance of occupationally exposed workers using modern methodology [44]. In addition to the interstitial changes described in UIP, asbestosis patients may also show evidence of pleural plaques.

High-resolution computed tomography (HRCT) provides a more detailed delineation of parenchymal abnormalities with 1-mm slice cuts. Given that subtle abnormalities at the bases may actually represent dependent atelectasis, prone imaging can be quite useful in patients with early disease. As the presence of significant air trapping or mosaic attenuation excludes the diagnosis of usual interstitial pneumonia, inspiratory and expiratory imaging should be part of the standard high-resolution chest CT scan protocol.

Recent data from chest CT scan studies in lung cancer screening have demonstrated that with respect to asbestos patients, chest CT scans detect three to five times more cases of minor disease. Individuals with asbestosis were generally older and had a longer exposure latency period [45▪].

Whereas asbestosis CT scans may appear indistinguishable from patients IPF, the presence of certain radiographic clues may be particularly helpful in patients who have indeterminate or unknown asbestos exposure. Such clues include the presence of pleural disease such as pleural plaques and pleural

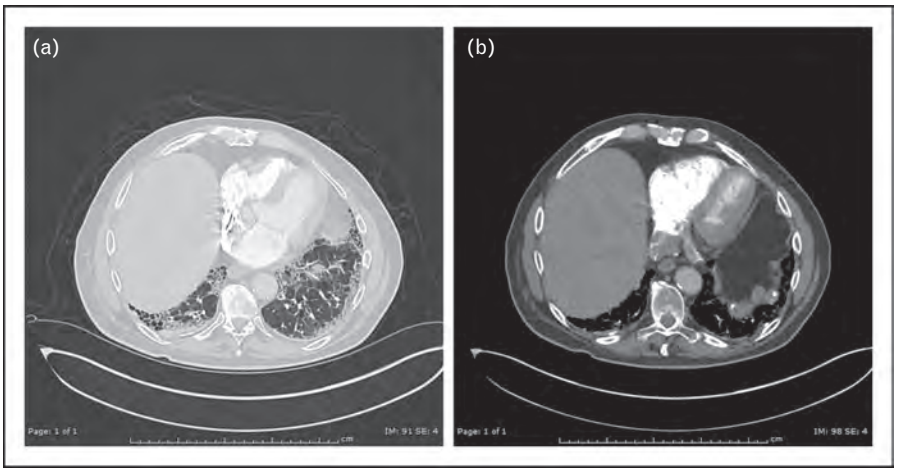

FIGURE 1. Asbestosis high-resolution chest CT scan. (a) HRCT lung windows demonstrate lower lobe predominant disease with evidence of reticular markings and honeycombing. (b) Mediastinal windows reveal evidence of pleural thickening and calcfiications (Courtesy of Jonathan Killam, MD and Ami Rubinowitz, MD). CT, computed tomography.

thickening. Bilateral pleural plaques are pathognomonic for asbestos exposure (Fig. 1). Rounded atelectasis, frequently mistaken for malignancy, is an area of focal lung collapse surrounded by invaginated pleura and is often seen in asbestosis patients. Given the increased risk for lung cancer and mesothelioma, clinicians should scrutinize CT scans for malignancy as well. The severity of radiographic appearance correlates with mortality [46▪,47].

In advanced stages, HRCT is sufficient to document UIP. IPF guidelines delineate three radiographic patterns: a UIP pattern, a possible UIP pattern and a pattern inconsistent with UIP. A UIP pattern is characterized by subpleural basilar predominance, reticular abnormalities and honeycombing with or without traction bronchiectasis. A possible UIP pattern lacks honeycombing, whereas an inconsistent pattern includes features such as upper lobe predominance, ground glass opacities, nodular opacities, bronchovascular predominance, cysts and/or air trapping or mosaic attenuation in three or more lobes [10]. Of note, the presence of upper lobe predominance and air trapping/mosaic attenuation in a patient with fibrotic lung disease suggests chronic hypersensitivity pneumonitis, a disease described in association with a number of organic antigens.

Pulmonary function testing and respiratory surveillance programs

Fibrotic lung disease patients demonstrate a restrictive ventilatory defect accompanied by a reduced diffusion capacity. A reduced forced vital capacity in the absence of obstruction while suggestive of restrictive disease is not diagnostic. Total lung capacity, generally obtained by helium dilution or body plethysmography, is required to officially establish a diagnosis. The presence of a mixed obstructive and restrictive pattern may be due to concomitant emphysema frequently seen in smokers. Given that smoking itself is a risk factor for UIP, the presence of obstruction is certainly seen in clinically practice and the entity of combined fibrosis with emphysema has been described. Mild airflow obstruction in asbestosis workers may alternatively reflect the presence of small airways disease.

Reductions in diffusion capacity are also seen in patients with fibrotic disease. Six-minute walk tests may unmask oxygen desaturation in patients who maintain a normal oxygen saturation at rest. Studies demonstrate that longitudinal changes in lung function as well as the presence of oxygen desaturation portend poorer outcomes. Reductions in diffusion capacity and vital capacity correlate with severity of radiographic abnormalities. Among asbestos workers, recent studies have also demonstrated accelerated declines in lung function during an individual's working life with smoking and exposure having synergistic effects [10,48].

Histopathology

Histopathologic confirmation is not uniformly required in clinical care for UIP or asbestosis patients.

In the absence of a definitive UIP CT scan, video-assisted thoracopically obtained surgical specimens should be considered. Current guidelines delineate four categories of usual interstitial pneumonia – UIP pattern, probable UIP pattern, possible UIP pattern and a not UIP pattern. A UIP pattern includes the presence of marked fibrosis, architectural distortion in a subpleural paraseptal fibrosis, presence of

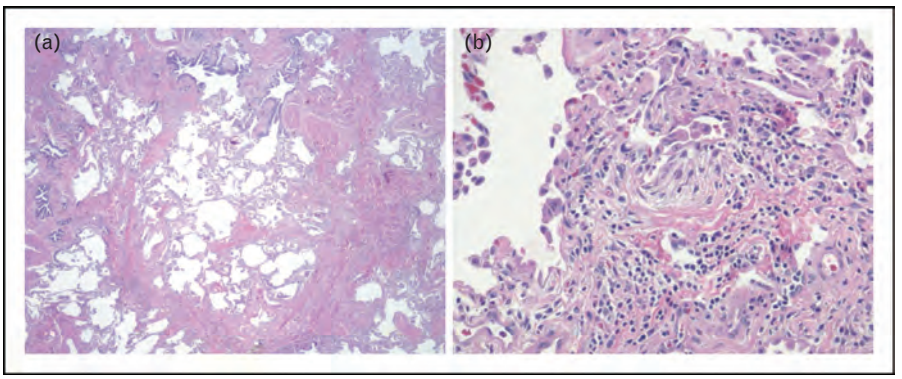

FIGURE 2. Histopathology of usual interstitial pneumonia. (a) Reveals a low-power UIP view showing temporal heterogeneity with areas of abnormal lung alternating with normal lung. (b) Reveals a fibroblast focus representing an area of active fibroblast proliferation typically seen in UIP patients (Courtesy of Robert Homer, MD, PhD). UIP, usual interstitial pneumonia.

patchy involvement, fibroblastic foci and the absence of atypical features (Fig. 2). A final diagnosis requires an overall clinico-radio-pathologic assessment [10] (Fig. 2).

For the asbestosis patient, a strong exposure history in the presence of fibrotic lung disease on HRCT is sufficient for diagnosis. In a patient with an intermediate exposure history or a history of bystander exposure, the presence of pleural plaques is sufficient for diagnosis. Whereas histopathologic findings in advanced asbestosis may resemble UIP, early asbestosis features may reveal only disease centered around the bronchioles. In contrast to UIP, fibroblastic foci are less prominent, whereas mild fibrosis of the visceral pleura is more commonly seen [49].

Lung mineralogic analyses documenting exposure can impact individual patient care and from an epidemiologic perspective provide further evidence of exposure disease relationships [18–20,50] From a direct clinical care perspective, demonstration of asbestos bodies in lung tissue can be quite helpful (Fig. 3). Histopathologic confirmation of asbestos exposure is not uniformly required. For example, an individual with a strong history of exposure in the presence of fibrotic lung disease on HRCT does not require histopathologic confirmation. An individual with an indeterminate history of exposure with fibrotic lung disease who also demonstrates pleural plaques, considered pathognomonic for asbestos exposure, similarly does not require histopathologic confirmation. In comparison to amphibole fibers, chrysotile fibers are more rapidly cleared.

For patients with indeterminate asbestos exposure histories, histopathologic confirmation may be useful. With light microscopy, iron stains should be requested to detect asbestos bodies. Asbestos bodies are golden brown, beaded dumbbell-shaped structures with a thin translucent core. The thin translucent asbestos core is surrounded by an iron protein mucopolysaccharide coating. A similar coating surrounds other particles such a glass, talc, iron or carbon. Accurate identification of asbestos requires scanning electron microscopy with energy dispersive X-ray analysis. Light microscopy generally underestimates the asbestos burden by 10–10 000-fold. Generally, an average concentration of asbestos bodies of at least 2/cm^2 of lung is recommended to make a diagnosis of asbestosis (Fig. 3). The presence of 1 asbestos body/ml of bronchoalveolar lavage fluid is deemed to represent significant asbestos exposure [49].

For UIP patients without a history of asbestos exposure, lung mineralogic analyses can identify possible contributing exposures, such as silicates or metals. From a research perspective, lung mineralogic analyses provide further insight into exposure disease relationships. An excess of silica and metals, including iron and nickel, has been

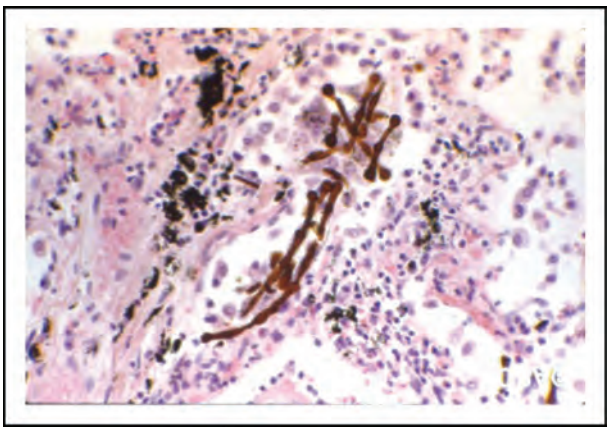

FIGURE 3. Asbestos body. Asbestos bodies seen on iron stained section represent asbestos fibers surrounded by a coating of iron and protein. Definitive identification of the enclosed fibers requires scanning electron microscopy and energy dispersive X-ray analysis (Courtesy Robert Homer, MD, PhD).

reported [18–20]. Postulating that exposures may be concentrated in lymph nodes, a recent Japanese study demonstrated an excess of elemental particles such as silica and aluminum in IPF patients [21].

Prognosis and treatment

For IPF patients, although clinicians generally cite a median survival of 3 years, recent evidence suggests that outcomes are heterogeneous. Patients may decline slowly, rapidly or experience precipitous decline during an acute exacerbation [10,51].

For years, lung transplant with a median survival of 4.5 years remained the only viable treatment option for end-stage IPF. Since the United Network for Organ Sharing issued the lung allocation scoring system in 2005, the proportion of IPF patients on transplant lists has grown and also accounted for the highest percentage of waiting list deaths [52]. Although no strict age cut-off exists, older patients with multiple comorbidities are frequently ineligible.

After years of failed clinical trials, two drugs have emerged as having a modest effect on altering disease course – pirfenidone and nintedanib. Pirfenidone is a small-molecule drug whose antifibrotic effects are likely mediated by the transforming growth factor beta pathway [53▪]. Nintedanib is a triple kinase inhibitor with antifibrotic effects [54▪]. Studies have demonstrated a modest effect on disease progression, particularly on forced vital capacity. A pooled analysis of pirfenidone studies demonstrated improved survival. Immunomodulatory therapy such as with prednisone and azathioprine causes increased harm and should be avoided unless patients are experiencing an acute exacerbation [55].

In a patient with UIP, occupational or environmental exposures that may be contributing should be identified by careful history and on-going exposures eliminated or reduced to the extent possible, including cigarette smoking and workplace exposures such as metal or wood dusts, although exposure intervention studies are limited. On the basis of limited evidence, it is believed that asbestosis progresses more slowly than usual interstitial pneumonia [49]. Lung transplantation may be an option for patients with progressive disease. The efficacy of newly approved IPF drugs nintedanib and pirfenidone in asbestosis patients is unknown. Acute exacerbations have also been reported in asbestosis patients [56]. As demonstrated in a North American cohort of insulators, asbestosis in addition to asbestos and synergistically with smoking increased lung cancer mortality with rate ratio of 7.40 (95% CI 4.0–13.7) among nonsmokers and 36.8 (95% CI 30.1–45.0) among smokers [28▪].

CONCLUSION

While asbestos has often been cited as an example of an exposure that causes disease indistinguishable from IPF, an accumulating body of literature suggests that a number of alternative exposures such as cigarette smoking, metal and wood dust and agricultural exposures may also contribute to the development of IPF. The impact of such exposures on the pathogenesis of disease, outcomes and treatment requires further study.

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Conflicts of interest

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C.A.R. has no conflicts. She has received funding for unrelated research from the CDC-NIOSH.

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