Interstitial Pulmonary Disease After Exposure at the World Trade Center Disaster Site

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Introduction

Exposure to the airborne toxins that resulted from the attack to and subsequent collapse of the World Trade Center (WTC) has been reported to result in development of new-onset and persistent airway disease. This has been well documented by surveillance and clinical and epidemiological data [1–8].

In addition, several case reports and case series in the medical literature document the development of interstitial lung disease (ILD) [9–15] and distal airway disease with evidence of some involvement of the interstitial structures [3, 16] following exposures at the WTC disaster site. To the author's knowledge, no systematic epidemiological review of the incidence or prevalence of ILD in WTC-exposed individuals has been published up to date. This chapter will review the literature that suggests that ILD is likely to occur after exposure at the WTC disaster site. The chapter first discusses issues related to the nature of the WTC dust and which of its components have been causally linked to the development of ILD, subsequently analyzes exposure considerations based on the reported experience with WTC-related ILD conditions, and, finally, reviews the inflammatory response and clinicopathological evidence of WTC-related ILD conditions.

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WTC Dust

The destruction of the WTC towers produced a plume of a complex mixture of chemical agents in different forms. The plume contained the combustion products of jet fuel from the two commercial aircraft that crashed into the towers and the heating, diesel oil, and fuel from the several thousand automobiles and transformers that were destroyed when the towers collapsed, in addition to soot, metals, volatile organic compounds, and hydrochloric acid from the destroyed structures. The plume also contained particulate matter from pulverized building materials such as cement, glass, asbestos, crystalline silica, metals, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated furans, organochlorine pesticides, and dioxins [17]. Lioy et al. [18] and Offenberg et al. [19] have reported on the composition and characteristics of collected settled dust samples in the immediate vicinity of the WTC site. By weight, at least 96% of these samples were composed of particulates larger than 10 μm in mass median aerodynamic diameter (MMAD). Respirable particulates including coarse particulates (PM_{10}: particulates >2.5 μm and <10 μm MMAD) and fine particulates ($PM_{2.5}$: particulates <2.5 μm MMAD) were found at much lower proportions (<1 and 0.5–4%, respectively). However, settled dust may not accurately represent the relative proportions of airborne respirable particulates following the collapse of the towers. Small particulates may coalesce or agglomerate to form larger particulates, altering the relative proportions of fine and coarse particulates. Bulk dust samples collected from the vicinity of the WTC area were composed of both fibrous and nonfibrous materials. Fibrous compounds included chrysotile asbestos, glass fibers, and fibers from cotton, wood, and paper (cellulose). Nonfibrous components included gypsum, calcite, bassanite (calcium sulfate hemihydrate), and quartz [20]. Composition of dust collected from indoor locations adjacent to the WTC site was similar [18, 21, 22]. A total of 287 chemicals or compounds to which people who came in contact with the cloud of dust from the WTC collapse were exposed have been identified. Information on these chemicals is kept by the Contaminants of Potential Concern (COPC) Committee of the World Trade Center Indoor Air Task Force Working Group [17].

There were no air sampling devices operating close to the WTC site at the time of the attacks and collapse of the towers to characterize and quantify the constituents of the dust cloud and smoke plumes. As a consequence, the people's exposures to the specific agents and concentrations in the early moments after the disaster will never be known with certainty [17]. By one estimation, the ambient fine particle mass concentration was approximately 500 $\mu g/m^3$ of air on September 12, 2001 [23], which far exceeds the current US EPA 24-h air quality standard of 65 $\mu g/m^3$ of air [24].

Banauch et al. [25] have classified the chemical toxic components of WTC dust into four categories: (1) particulate matter (calcium carbonate and silica) and fibers (chrysotile asbestos, fibrous glass, gypsum); (2) organic pollutants, including polycyclic aromatic hydrocarbons, other hydrocarbons (naphthalene, fluorine, polychlorinated biphenyl, dibenzo-p-dioxins, and diphenyl ethers), benzene, and Freon; (3)

gases, such as carbon monoxide, hydrogen sulfide, combustion by-products from the fires that burned until mid-December 2001, and diesel exhaust fumes from the vehicle/machinery employed; and (4) heavy metals (calcium, iron, zinc, aluminum, antimony, titanium, and magnesium). Additionally, Wu et al. [15] have identified carbon nanotubes (CNT) in the lungs of WTC patients and in WTC dust samples.

Exposure Categorization

Attempts to categorize the exposure of individuals to the attacks and collapse of the towers and to the efforts of rescue, recovery, and restoration that continued until the end of December 2001, when the fires were finally extinguished, suggest that there were two significant initial time windows for a sufficient exposure that could have resulted in significant health consequences. The first one corresponds to the initial 5–6 h after the actual collapse of the towers, when the earliest release and distribution of the pulverized building materials and plume emissions caused by the jet fuel fires occurred. The second one occurred between September 11 and 14, 2001. During this time, fires were still burning, and the highest levels of re-suspendable particulate mass could be mobilized from surfaces. This period probably ended with the first post-September 11 rains, which may have decreased the intensity of the fires, washed away the settled re-suspendable materials, and thus reduced exposure to ambient background levels [23]. However, during the days that followed September 14, intermittent releases of high concentrations of gaseous substances and particulate matter into the local atmosphere within the Ground Zero area still occurred, caused by uncovered fires and the disturbance of settled dust by rescue workers during debris movement and removal [23]. Smoldering fires continued for some 4 months after the initial attack, during which WTC dust was released and aerosolized [26]. Rescue/recovery efforts finally concluded by the end of May 2002 [26].

Additionally, there was exposure in the indoor environment, in dwellings and offices, and in other commercial buildings in close proximity to the site. Given the facts that conditions of affected residences and buildings were not uniform and that people responded differently in their attitudes to confront such exposures, the estimate of this exposure is virtually impossible in terms of general characterization [23].

Assessment of the exposure during the disaster response has been carried out by a variety of means. Environmental air samples collected between September 18 and October 4, 2001, have been reported [27]. Personal air sample results collected from the breathing zones have been reported in truck drivers [28, 29] and emergency responders [30]. Biomonitoring has been carried out in firefighters [31, 32] and in National Guard and New York State personnel [33, 34]. Measured agents in the different published papers included asbestos, concrete, crystalline silica, carbon monoxide, diesel exhaust, chlorodifluoromethane, heavy metals (e.g., cadmium, mercury), hydrogen sulfide, inorganic acids, particulate matter (including PM_{10} and

$PM_{2.5}$), total dust, volatile organic compounds, perfluorochemicals, polychlorinated aromatic hydrocarbons (such as benzopyrene, hydroxypyrene, xylene), biphenyls (PCB), and dibenzodioxins and dibenzofurans. Overall, these studies show that the levels of measured agents generally remained within NIOSH Recommended Exposure Limits or Occupational Safety and Health Agency (OSHA) Permissible Exposure Limits, with exceptions including perfluorochemicals, polychlorinated aromatic hydrocarbons and dibenzofurans, lead and antimony, and cadmium and carbon monoxide, the two last ones associated mostly with the use of oxyacetylene torches. Measurements show an exposure/response relationship in that the earlier individuals were exposed to the plume or dust, the higher the concentrations found and also a gradient exposure ranging from measurements taken in close proximity to the pile to those taken at the perimeter.

Accounts of the exposure in the published case reports that describe ILD in WTC-exposed individuals show that the vast majority of the cases reported had sustained heavy exposure to the collapse, within the two window periods of heavy exposure as described by Lioy and Georgopoulos [23]. The firefighter who developed eosinophilic pneumonia [13] was present at the site on the day of the collapse of the towers and continued to work for periods of 16 h a day for 13 days. The patient who developed a granulomatous pneumonitis [14] was also exposed on the day of the collapse of the towers and then returned to the area for 1 day on September 14 and later on October 3, on a more regular basis. This patient worked at a building located one block away from the WTC. The NYC highway patrol officer who developed bronchiolitis obliterans [16] was exposed to the WTC dust on the day of the attacks and continued to work for periods of 16 h a day for 3 weeks when he first experienced symptoms. Patients included in the NYC firefighter series of "sarcoid-like" granulomas [11] were all present at the site within the initial 3 days after the collapse of the towers. Ten of the 26 reported patients had arrived in the morning of September 11, 2001, 14 arrived within the next 36 hours, and the last 2 arrived on day 3 after the attack. No specific information as to the duration of the exposure is reported in this article. Of the two cases that reported rheumatologic manifestations in WTC rescue workers with sarcoidosis [35], one was present during day 1 and continued working for some 3 months, while the second patient worked for some 6 months, starting on day 4 after September 11, 2001. The two cases with peripheral airway disease with extension to the parenchyma had worked at the disaster area for over 80 h before November 30, 2001 [3]. Of the 43 patients with sarcoidosis included in the WTC Health Registry report, 34 (79%) sustained their initial exposure within the first 4 days after the attacks. Three of the remainder nine had to evacuate their homes because of the presence of WTC dust. This study documented that working on the WTC debris pile was associated with diagnosis of sarcoidosis [12]. No "statistically significant trend" between level of exposure and diagnosis of sarcoid-like granulomatous disease was found in the series described by Crowley et al. [10]. Finally, only two of the six cases of local residents who underwent pulmonary biopsies and presented with an "interstitial" disease pattern were present in the initial dust cloud; however, no additional information on duration of exposure was provided [9].

Identification of WTC Dust in the Respiratory Tract

There are several reports on the characterization and composition of the WTC dust deposited in the airways or pulmonary tissue of individuals who were exposed and/or developed diseases as a consequence of their exposure.

Rom et al. [13] reported on bronchoalveolar lavage (BAL) analyses in a firefighter hospitalized with acute eosinophilic pneumonitis several weeks after WTC exposure. Significant quantities of fly ash, degraded fibrous glass, and asbestos fibers were found. BAL revealed 305 fibers per million alveolar macrophages. Types of fibers included chrysotile and amosite asbestos, chromium, and predominantly silica-containing fibers that were attributed to degraded fibrous glass. A variety of nonfibrous particles were identified, including fly ash, silica, metal particles, and various silicates. The fact that only uncoated asbestos fibers were found was interpreted as indicative of recent exposure since coated asbestos bodies are expected in more regular, chronic exposure.

A study of induced sputum samples from nonsmoking New York City firefighters exposed to WTC dust (NY-FF), some 10 months after the collapse of the WTC towers, was reported in 2004 [32]. The firefighters' exposure duration varied from 1 to 75 days. Induced sputum is a noninvasive alternative to study inhaled particle matter and the lung's inflammatory response to inhaled toxins and has yielded similar results to BAL in silica and hard metal workers and other patients with occupational lung diseases [36]. Induced sputum findings on NY-FF were compared to those in a control population of Israeli hospital workers free from respiratory disease and also with a group of Tel Aviv firefighters (TA-FF). The study showed that the NY-FF samples contained a higher percentage of particulates of size >2 and >5 μm than TA-FF, but no relationship between particle size and length of stay at the WTC area was found. Particles found in NY-FF were irregularly shaped as compared to the smaller, regularly shaped particles found in TA-FF. Chemical and mineralogical analyses of these particles revealed metal alloys and oxides consistent with the composition of WTC dust and different from that of non-WTC-exposed firefighters. These mineral particles were seen within the macrophages and epithelial cells of the NY-FF. Minerals detected included silica in three out of four samples and aluminum and magnesium silicates in one of the samples, in addition to metals found in the WTC building components, including titanium, iron, calcium, nickel, chromium, and zinc.

Wu et al. [15] described mineralogical findings in seven previously healthy responders who were exposed to WTC dust on either September 11 or 12, 2001, and developed severe respiratory impairment or unexplained radiologic findings. Tissue analyses showed large amounts of aluminum and magnesium silicates in an unusual sheet configuration in all those who had interstitial disease. Four of the seven patients with interstitial lung disease had single-walled CNT of various lengths. Chrysotile asbestos, calcium phosphate and calcium sulfate, and small shards of glass containing mostly silica and magnesium were identified in some cases as well.

More recently, Caplan-Shaw et al. [9] published on scanning electron microscopy of tissue blocks in five of twelve local workers, residents, and cleanup workers exposed to WTC dust who underwent surgical lung biopsy for suspected interstitial lung disease. All had presence of particles on light microscopy, but not an overwhelming number. Silica was detected in individual particles in four of the five patients. Aluminum silicates, titanium dioxide, and talc particles were also found. All cases had metals identified in the particles, including aluminum, steel, zirconium, chromium, copper, zinc, and tin.

Toxicological Effects in Laboratory Animals and Cultured Cells

Mice exposed to oropharyngeal aspiration of 100 μg (microgram) samples of WTC dust particles with a MMAD of less than 2.5 μm ($PM_{2.5}$) exhibited a slight increase in BAL neutrophils. In addition, this exposure caused significant airflow obstruction in response to methacholine challenge. Lower doses administered directly into the airways (32 and 10 μg) or nasal inhalation of 11 mg/m^3 WTC $PM_{2.5}$ for 5 h did not induce significant inflammation or airflow obstruction. These results suggest that there may be a threshold dose for respiratory effects of WTC $PM_{2.5}$ in healthy mice. Theoretical calculations indicate that the 100 μg dose in mice corresponds to inhalation of 425 μg/m^3 WTC $PM_{2.5}$ for 8 h by humans to achieve a comparable dose in the tracheobronchial region. Such exposures likely existed immediately after the collapse of the WTC towers, especially given the lack of sufficient respiratory protection in most rescue personnel. However, most individuals would not be expected to experience such exposures if they were not caught in the dust cloud immediately after the collapse of the towers [37].

Studies in cultured human alveolar macrophages and type II cells exposed to the $PM_{2.5}$ fraction of indoor and outdoor WTC collected settled dust showed dose-dependent increases in pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)-8, and IL-6 and in gamma-glutamyl transpeptidase (GGT), a membrane-bound enzyme that transfers extracellular precursors of the antioxidant glutathione into the cell cytoplasm where it protects against oxidative tissue damage. The coarse and very coarse fractions of WTC PM caused similar though generally lower responses in these cell types [38]. An additional study has shown that the mitogen-activated protein kinase signaling pathway is activated in a dose-dependent manner by WTC dusts, which could play an important role in the production of inflammatory cytokines [39].

Inflammatory Markers in Response to WTC Dust Exposure

Inflammatory markers have been reported in studies of induced sputum and BAL from patients who developed lung disease due to WTC exposure.

The BAL of the NYC firefighter who was hospitalized with acute eosinophilic pneumonitis several weeks after WTC exposure [13] had a significant inflammatory response with elevated number of cells recovered (730,000 compared to a normal of less than 250,000), 70% of which were eosinophils. The eosinophils were not degranulated. Lymphocyte subpopulations (B cells, NK cells, CD8+ cells, and CD4 T cells) were normal, but the alveolar CD4+ lymphocytes exhibited a highly stimulated surface phenotype. IL-5, an eosinophilic chemotactic factor, was elevated.

Inflammatory markers were studied on induced sputum from nonsmoking NY-FF some 10 months after the collapse of the WTC towers and compared with markers in induced sputum of TA-FF and an unexposed control population of hospital workers [32]. NY-FF and TA-FF had significantly more neutrophils, lymphocytes, and eosinophils and fewer macrophages than hospital workers, but differential cell counts were not different between NY-FF and TA-FF. Percentage of neutrophils and eosinophils significantly increased with longer exposure at the WTC area, thus suggesting a dose (exposure)-response (inflammation) relationship. Higher levels of matrix metalloproteinase-9 (MMP-9) were found in NY-FF as compared to TA-FF and to non-firefighters. MMP-9 plays an important role in neutrophil recruitment to the lungs. It is reliably and reproducibly detectable in induced sputum and has been shown to be elevated in workers exposed to hazardous dust. This elevation was interpreted as evidence for exposure-related immune activation in the lungs, which was persistent some 10 months after WTC dust exposure.

Interstitial Lung Disease Due to WTC Exposure: Clinicopathological Responses

Two main clinicopathological responses have been documented in case series of WTC-exposed individuals with ILD reported in the medical literature: a granulomatous response and a “diffuse pulmonary fibrosis”-type response. Other papers have identified single cases with different clinicopathological responses, some of which have been presented above.

Several studies have documented a granulomatous response to WTC exposure. An initial report described a non-sarcoid granulomatous pneumonitis in a WTC-exposed individual [14]. Lung biopsy of this patient demonstrated non-caseating granulomata with silica, silicate, and calcium oxalate particles. The patient was acutely ill and recovered with corticosteroid therapy. Izbicki et al. [11] reporting on surveillance data among NYC firefighters suggested an increased incidence after September 11, 2001, of “sarcoid-like” granulomatous pulmonary disease, in comparison with before that date. This study included 26 NYC firefighters with “sarcoid-like” granulomatous pulmonary disease. Inclusion into this study required pathology finding of non-caseating granulomas without evidence for foreign body reaction, malignancy, or fungal or mycobacterial infection. Nine patients presented with adenopathy only, and the remaining 17 had adenopathy and parenchymal disease. Only three of the cases had a total lung capacity and/or diffusion capacity below 80% of predicted, and extra-thoracic disease was present in 23% of the cases.

Half of the cases were reported within a year after September 11, 2001, and the remaining half over the following 4 years. Bowers et al. [35] reported two cases of WTC rescue workers who presented with extrapulmonary rheumatologic manifestations. The first patient initially presented with shortness of breath on exertion concomitantly with severe joint pain and swelling involving ankles and knees, as well as painful erythematous lesions on his legs consistent with erythema nodosum. The second patient presented with relapsing uveitis followed by swelling of his ankles, left knee, and left elbow. Both patients had hilar adenopathy identified on CT scans, with no reported parenchymal abnormalities. Crowley et al. [10] reported on their findings of sarcoid-like granulomatous pulmonary disease among a population of some 19,756 responders examined through the WTC Medical Monitoring and Treatment Program. Cases were identified by self-report, physician report, and ICD-9 codes and evaluated by three pulmonologists to include only "definite" cases. Thirty-eight patients were classified as "definite" cases of sarcoid-like granulomatous pulmonary disease, with a peak incidence in the year between September 11, 2003, and September 11, 2004. Incidence in black responders was nearly double that of white responders. Nineteen patients had lymphadenopathy only, and 15 had adenopathy and parenchymal disease, with the remaining having normal radiographs (3) or x-rays not available for review (1). Twelve of 26 with acceptable quality spirometry had a low forced vital capacity (FVC), and 14 had normal spirometry. Jordan et al. [12] reported on biopsy-proven sarcoidosis post-9/11 among some 46,322 individuals who are part of the NYS WTC Health Registry. Cases were defined as sarcoidosis if confirmed by demonstration of non-caseating granulomas and the absence of any known granulomagenic organism or particle on tissue biopsy performed after October 2001, as verified by the authors. Forty-three cases fulfilled inclusion criteria, out of 430 who initially reported having been diagnosed with sarcoidosis. Twenty-seven cases had lymphadenopathy only, seven had parenchymal abnormalities by CT (although not necessarily nodules) only, and four had both. The remaining cases were either normal (two) or had radiography not available. Extra-thoracic involvement was present in 44%. Cases were overall evenly diagnosed between 2002 and 2006, with much less proportion of cases diagnosed in 2007 and 2008. There is no mineralogical information reported on the tissue biopsies of these cases, except for the requirements of "non-evidence of foreign body reaction or particles in biopsy." Mineralogical information in granulomatous responses associated with WTC exposure has been reported in an analysis of patients from the World Trade Center Environmental Health Center who were diagnosed with sarcoidosis after their exposure to WTC dust. This abstract reported silica and aluminum silicates in a limited mineralogical analysis of lymph node and parenchymal biopsy specimens (Parsia et al., cited in [9]).

Two case series have reported a "diffuse pulmonary fibrosis"-like response to the WTC exposure. Wu et al. [15] reported seven patients who underwent pulmonary biopsy because of severe respiratory impairment or radiologic findings. Table 1 summarizes the findings of this case series. All the patients except for case 6 are

Table 1 Summary of cases with interstitial findings presented in the Wu et al. paper

Case no.	Clinical history	Pathology findings/ mineralogical findings	PFT findings	Chest CT scan findings
1	Shortness of breath, hoarseness, cough, wheezing, asthma, bronchitis, pneumonia	Interstitial pulmonary fibrosis with subpleural distribution, prominent mediastinal nodules. AS, MS, CNT	Severe restrictive, low DLco	Honeycombing, severe peripheral fibrosis, peribronchiolar Usual interstitial fibrosis (UIP) like fibrosis
2	Dyspnea, cough, throat irritation, wheezing	7 small nodules, prominent interstitial markings, bronchiectasis. CNT, AS, MS, no asbestos	Mild restrictive/ obstructive, O_2 desaturation on exercise	Bronchiolocentric interstitial fibrosis, multiple patterns: UIP. Nonspecific interstitial pneum onia (NSIP), hypersensitivity
3	Cough, dyspnea on exertion	Subpleural interstitial linear and ground glass changes, enlarged lymph nodes. Chrysotile, AS, MS, CNT	Severe restriction, low DLco	Peribronchiolar fibrosis, NSIP type, extensive lymphocytic infiltrates and bronchiolitis
4	Dry cough, sore throat, hoarseness, wheezing, GERD, diarrhea	Mosaic lung. CNT, AS, MS, calcium sulfate, chrysotile	Moderate restriction	Bronchiolitis, mild peribronchiolar fibrosis
5	Shortness of breath on effort, chest pain, wheezing	Peripheral changes suggestive of UIP, lymph nodes mildly enlarged. AS, MS, chrysotile	Mild restriction, low DLco	Focal areas of fibrosis with fibroblastic foci small granulomas, non-necrotizing, peribronchiolar lesions. Airways: mucopurulent
6	Dry cough, wheezing	Marked mosaic pattern. No mineral detected	Normal spirometry and DLco	Small airway disease, respiratory bronchiolitis, peribronchial metaplasia, lung parenchyma unremarkable
7	Dyspnea on exertion, cough, wheezing, chest tightness	Multiple nodules, some calcified, peribronchial interstitial disease. MS, chrysotile	Minimal restriction, positive bronchodilator response	Granulomas non-necrotizing epithelioid

nonsmokers. All the patients with interstitial disease had large amounts of aluminum silicates (AS) and magnesium silicates (MS), in what was described as an "unusual platy configuration." Both the configuration of the silicates and the excessive amount of silicates were not found in a comparison group of construction workers heavily exposed to asbestos in the course of their work. Additionally, the lung specimens of three of the patients with interstitial fibrosis contained CNT that were virtually identical to those identified in samples of settled WTC dust. CNT were not found in lung samples of a control population of construction workers. Small airway disease was present in almost all cases with different degrees of severity. Interstitial disease was present in four cases, characterized by a generally bronchiolocentric pattern of interstitial inflammation and fibrosis of variable degree of severity.

Caplan-Shaw et al. [9] report on 12 patients who underwent surgical lung biopsy for suspected interstitial lung disease or abnormal pulmonary function tests. Table 2 summarizes the findings of this case series. The authors divided their patients into

Table 2 Summary of cases with interstitial disease presented in the Caplan-Shaw paper

Case no.	Pathology findings/ mineralogical findings (MF)	PFT findings	Chest CT scan findings
Interstitial disease on HRCT			
1	Moderate fibrosis, small airway fibrosis. MF not available	Restrictive, low DLco	Mild reticulation and bronchiectasis, mostly subpleural in lower lobes
2	Severe fibrosis, honeycombing, small airway fibrosis. AS, silica, titanium, talc	Restrictive/obstructive, markedly low DLco	Severe reticulation, moderate bronchiectasis, upper and lower lobes, diffuse
3	Moderate fibrosis, cellular infiltrates, granuloma, small airway fibrosis. AS, silica, titanium, talc	Unable to perform	Moderate reticulation, severe bronchiectasis, moderate ground glass opacity and mosaic attenuation, lower lobe, diffuse
4	Granuloma, organizing pneumonia, no fibrosis and no small airway fibrosis. MF not available	Normal, DLco not available	Mild reticulation, mild mosaic attenuation, lower lob, subpleural
5	Severe fibrosis, honeycombing, organizing pneumonia, small airway fibrosis. MF not available	Restrictive, severely decreased DLco	Marked reticulation and bronchiectasis, honeycombing, all lobes, diffuse
6	Severe fibrosis, honeycombing, small airway fibrosis. MF not available	Restrictive, mildly decreased DLco	Moderate reticulation, mild bronchiectasis, all lobes, subpleural

Table 2 (continued)

Case no.	Pathology findings/ mineralogical findings (MF)	PFT findings	Chest CT scan findings
No interstitial findings on HRCT			
7	Small airway fibrosis. MF not available	Restrictive, moderately reduced DLco	Mild mosaic attenuation, upper and lower lobes, air trapping
8	Granuloma, small airway fibrosis. AS, silica, titanium, talc	Restrictive/obstructive, DLco not available	Diffuse bronchial wall thickening, lower lobe
9	Moderate fibrosis, granuloma, small airway fibrosis. AS, titanium, talc, no silica	Restrictive, moderately reduced DLco	Marked ground glass and mosaic attenuation, diffuse bronchial wall thickening and air trapping
10	Granuloma, small airway fibrosis. MF not available	Restrictive/obstructive, mildly reduced DLco	Moderate mosaic attenuation, diffuse bronchial wall thickening and air trapping
11	Moderate fibrosis, no small airway fibrosis. AS, silica, titanium, talc	Restrictive, mildly reduced DLco	Minimal air trapping
12	Emphysema	Restrictive, mildly reduced DLco	None

two groups: those with predominant "interstitial" disease on HRCT and those who had abnormal physiology and HRCT abnormalities but not "interstitial" findings. Authors state that when identified, granulomas were scant and poorly formed. Pathological analysis identified emphysematous changes in all but one patient (case 10) and mild and patchy cellular infiltrates in all but one patient (case 12). All cases had opaque particles consistent with combustion products and birefringent particles containing inorganic compounds, including silica and aluminum silicates, as well as titanium dioxide and other metals identified within macrophages. Their analysis was not able to detect nanotubes or asbestos fibers.

Constrictive bronchiolitis has been documented histologically in three WTC-exposed workers [3, 16] and suggested radiologically in several others [16]. While this entity is excluded from the histological definition of ILD, one case reported in a WTC-exposed worker [16] demonstrated chronic bronchiolitis, focal obliterative bronchiolitis, and rare non-necrotizing granulomas in the parenchyma on open lung biopsy. Histological findings in a second case included focal and mild interstitial fibrosis with lymphocyte aggregates but without fibroblastic foci or honeycombing [3]. In a third case, end-expiratory air trapping was documented together with peribronchiolar fibrosis in association with severe restriction, reduced diffusion capac-

ity, and radiologic and histological interstitial pulmonary fibrotic changes [3]. Thus, in these three cases of primarily distal airway disease, there is histopathological evidence suggesting some degree of extension of the inflammatory process more distally into the interstitial space.

Discussion

The development of environmentally induced pulmonary fibrosis can be conceptualized as starting with the inhalation of the causative agent. Physical characteristics of the inhaled toxin (e.g., dimensions, solubility), chemical composition, dose, and lung clearance mechanisms (including anatomic and physiologic characteristics of the airways, presence of disease, and minute ventilation) all contribute to the delivery of the agent to the alveolar spaces and affect the distribution, uptake and retention of the toxin at the lung parenchyma, and its potential to cause lung injury [40]. Analyses of WTC dust as reviewed above demonstrated that some percentage of the dust was composed of particles small enough to penetrate deep into the pulmonary system and to reach distal airways and alveoli [18, 19, 41]. The presence and retention of such particles has been confirmed in studies of induced sputum and BAL in WTC-exposed firefighters [13, 32] and in pathology studies of lung tissue from individuals involved in rescue and recovery work [14, 15] as well as from community residents [9]. The two main series and the limited review on granulomatous responses that have described mineralogy composition of the pathology samples of the lungs from WTC-exposed individuals consistently report the presence of silica and aluminum and magnesium silicates, in addition to other mineral findings [9, 15]. It appears so far that these silicates may be the primary agents responsible for the generation of the inflammatory response that results in ILD in WTC-exposed patients.

Following their retention in the pulmonary tissue, and either by their chemical and/or physical characteristics, the inhaled toxins injure the alveolar epithelial cell, dysregulating normal homeostatic wound healing and repair pathways mediated by epithelial mesenchymal interaction, resulting in fibroblast activation and proliferation and continued pathologic production of a provisional matrix primarily of interstitial collagens [42]. Variations in the pattern of immunologic response, probably genetically determined, play a major role on the individual's response to the injury and the final development of persistent damage and disease [40]. As previously reviewed herein, animal, in vitro studies, and case reports all suggest that WTC dust is capable of inducing a pulmonary inflammatory response. Animal models [37] and cell culture models [38] have shown the ability of the dust to induce production of inflammatory mediators. Studies of induced sputum and of BAL in firefighters and in patients who developed disease as a result of their exposure confirm the presence of elevated levels of matrix metalloproteinases and interleukins and alteration in the number and the immunologic properties of pulmonary parenchymal inflammatory cells [13, 32]. Two main inflammatory responses have been described in series that

document findings of ILD in individuals exposed to WTC fumes: a granulomatous response [10–12] and a patchy interstitial fibrosis in a predominant bronchiolocentric pattern [9, 15].

In most of the cases in which a clear environmental cause for ILD can be identified, clinical history usually reveals exposure to the toxin for long periods of time before development of symptoms [43–45] or for shorter periods of time (months) if the exposure was unusually heavy [26, 46, 47]. In the case of drug-induced lung disease, for example, fibrotic lung diseases develop after months to years of using the medication and sometimes even years after it has been stopped, except for acute, idiosyncratic reactions [48]. Similarly, in cases of hypersensitivity pneumonitis, exposure to the sensitizing agent usually occurred over a long period of time [49]. Almost all of the pneumoconioses present after long latency periods. These points illustrate the need to accrue and retain significant amounts of toxins in the lung parenchyma in order to trigger clinical disease and to allow for sufficient latency time for symptoms and clinical findings to manifest. The one common denominator in the vast majority of the cases of post-WTC exposure ILD summarized above is the fact that the affected patients were exposed during the period when the environmental concentration of WTC dust was at its highest, i.e., during the day of the attacks and/or up to 3 days after the collapse of the towers, thus allowing for a sufficient dose of inhaled WTC dust to generate a disease response. The one unusual issue in WTC-DPLD is the relative short latency between exposure and disease. Some of the reported cases of ILD related to exposure to WTC dust have been diagnosed within a short latency period after exposure, while others have been diagnosed several years after the attacks.

An additional unusual feature when comparing WTC-DPLD to other more "traditional" environmentally induced ILD is the lack of a common histopathological pattern. As stated in this review, the current literature has identified two major clinicopathological responses: a granulomatous inflammation and a more diffuse, interstitial-type response with a bronchiolocentric pattern, which we have termed "diffuse pulmonary fibrosis"-like in this chapter. Whereas the studies reported in the articles describing a granulomatous response have significant methodological differences, including recruitment, surveillance, and case ascertainment methods, and are all subject to reporting biases, the fact that this finding has been reported in three different populations (although with some overlap in between) gives some consistency to this finding. Similarly, the two case series that described a more diffuse, "diffuse pulmonary fibrosis"-like response to exposure to WTC dust present some similarities: CT images showed findings consistent with interstitial lung disease, and pathology demonstrated histologic patterns of patchy interstitial fibrosis, often in a bronchiolocentric pattern, with bronchiolitis and peribronchiolar fibrosis, and intracellular particles within collections of macrophages. Again, although the two studies had significant differences as to recruitment and surveillance of cases, the fact that similar clinicopathological responses have been reported in these two different populations gives some consistency to this finding as well.

In summary, at present the most frequently reported pulmonary consequence related to WTC exposure is airway disease. However, granulomatous responses,

interstitial-like pulmonary disease, eosinophilic pneumonitis, and bronchiolitis obliterans with elements of extension into the parenchyma have all been reported. Most of these cases were exposed at the WTC site during the first few hours and days after the attack and the collapse of the towers, when the concentrations of inhalable toxicants are presumed to have been highest. Pathology and mineralogy studies have identified particles and toxicants within the macrophages at the distal airway/alveolar level. The presence of aluminum and magnesium silicates appears to be a common denominator in many of these cases. The variability in the reported pathological descriptions remains a challenge.

In conclusion, published reports so far suggest the possibility of development of an inflammatory response to WTC dust with clinicopathological consequences in the pulmonary tissue manifesting as ILD. Ongoing surveillance and follow-up of the cohort of exposed individuals are warranted, especially to allow for a longer latency period for these diseases to occur and to assess the additional potential for cumulative dose over time on the development of ILD.

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