Lung Pathologic Findings in a Local Residential and Working Community Exposed to World Trade Center Dust, Gas, and Fumes

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Objective: To describe pathologic findings in symptomatic World Trade Center–exposed local workers, residents, and cleanup workers enrolled in a treatment program. **Methods:** Twelve patients underwent surgical lung biopsy for suspected interstitial lung disease (group 1, $n = 6$) or abnormal pulmonary function tests (group 2, $n = 6$). High-resolution computed axial tomography and pathologic findings were coded. Scanning electron microscopy with energy-dispersive x-ray spectroscopy was performed. **Results:** High-resolution computed axial tomography showed reticular findings (group 1) or normal or airway-related findings (group 2). Pulmonary function tests were predominantly restrictive. Interstitial fibrosis, emphysematous change, and small airway abnormalities were seen. All cases had opaque and birefringent particles within macrophages, and examined particles contained silica, aluminum silicates, titanium dioxide, talc, and metals. **Conclusions:** In symptomatic World Trade Center–exposed individuals, pathologic findings suggest a common exposure resulting in alveolar loss and a diverse response to injury.

The terrorist attack on the World Trade Center (WTC) resulted in collapse of the towers, deposited over one million tons of debris in one of the most densely populated commercial and residential districts in the world, and ignited fires that smoldered for months. The release of the complex dust and fumes resulted in potential environmental and occupational exposures for hundreds of thousands of individuals who were working (local workers), living (residents), or at school in the area, as well as for people involved in rescue and recovery and cleanup.[1] The dust included a mix of highly alkaline materials (pH 11) composed of pulverized building materials containing silicates and contaminated with asbestos, glass fibers, lead, and polycyclic aromatic hydrocarbons.[2–5] Local workers, residents, and cleanup workers had potential for massive exposure from the dense cloud of pulverized dust as the buildings collapsed (dust cloud) or prolonged exposure from indoor cleanup efforts, resuspended indoor materials, or outdoor particles from the massive cleanup underway for more than 9 months.[6]

Adverse health effects, first reported as "WTC cough" and associated with shortness of breath, wheezing, and airway hyperresponsiveness, were reported in firefighters and in individuals involved in rescue and recovery operations.[7–12] Upper and lower respiratory symptoms have also been described in residential, pediatric, and local working populations.[1,13–17] Although most studies report symptoms and airway hyperresponsiveness consistent with reactive airways dysfunction or irritant-induced asthma, bronchiolitis obliterans,[18] sarcoid-like granulomatous disease,[19] and interstitial lung disease (ILD)[20] have also been documented in WTC responders.

The World Trade Center Environmental Health Center (WTC EHC) was initiated in 2005 to treat local workers, residents, and cleanup workers with persistent symptoms. The absence of detailed dust and fume exposure assessments[6] and clinical information predating the WTC disaster makes the process of attributing illness to WTC dust exposure difficult, particularly in the non–rescue worker populations. In addition, despite a consistency in complaints of persistent upper and lower respiratory symptoms, the disease processes leading to persistent symptoms are unknown. We now describe a case series of lung biopsy specimens obtained from 12 individuals in the WTC EHC who underwent surgical lung biopsy 4 to 6 years after destruction of the towers.

METHODS

Patient Enrollment

Inclusion into the WTC EHC was based on potential exposure to WTC dust, gas, or fumes as a local worker, resident, or cleanup worker in southern Manhattan on or in the months after 9/11 and the presence of any physical symptom that occurred or was exacerbated after 9/11. Inclusion criteria and clinic procedures are described elsewhere.[17] The institutional review board of New York University School of Medicine approved the analytic database (NCT00404898), and only patients who signed consent were used for analysis. Of 2461 subjects enrolled in the program from September 2005 to February 2009, 17 underwent clinically indicated surgical lung biopsy. Five patients who underwent biopsy for evaluation of a localized nodule or mass were excluded from this analysis.

Clinical, Radiologic, and Pathologic Evaluation

All patients provided detailed clinical and exposure information via interviewer-administered questionnaire, as previously described.[17] Pulmonary function testing (PFT), high-resolution computed axial tomography (HRCT) of the chest with inspiratory and expiratory imaging, review of hematoxylin and eosin–stained slides under polarizing and nonpolarizing light microscopy, and particle analysis were performed. Standardized coding systems were used to summarize radiologic and pathologic findings.

Lung Function Testing

Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society standards[21] on a Sensor-medics spirometer (Yorba Linda, CA), and predicted values were derived from National Health and Nutrition Education Survey III.[22] Patients with a reduced forced vital capacity (FVC) or respira-

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Funded by City of New York, American Red Cross Liberty Disaster Relief Fund, CDC NIOSH E11OH009630.

The scanning electron microscopy with energy-dispersive x-ray spectroscopy system received support as a grant from NYSTAR to Upstate Medical University.

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DOI: 10.1097/JOM.0b013e31822fff60

tory symptoms that were unexplained by spirometry underwent measurement of total lung capacity, functional residual capacity (FRC), and residual volume by plethysmography and diffusing capacity of carbon monoxide by single breath methods. All acceptable measures were expressed in absolute values (liters) and as percent predicted of normal.[22–24] Normal limits for forced expiratory volume in one second (FEV_1), FVC, and FEV_1/FVC were based on the lower limits of normal.[25] For clinical reference, the lower limits of normal for white men aged 40 years in this population, calculated using pre–September 11, 2001 data, corresponded to an FEV_1 of 82% predicted, an FVC of 79% predicted, and an FEV_1/FVC of 0.76. Normal limits for total lung capacity, FRC, residual volume, and diffusing capacity of carbon monoxide were 80% or more of predicted.[23–25] In patients with multiple PFTs, the one obtained earliest was used for analysis. If patients had undergone PFT recently at an outside facility and refused or were unable to perform maneuvers on their visit, data from outside pulmonary function laboratories were used, and flow volume loops were examined for reproducibility and quality. Among the 12 patients, seven had PFT performed at our institution; four had PFT performed at other regional laboratories; and one was unable to perform spirometry.

Radiographic Imaging

Patients with abnormal PFT or severe or unexplained symptoms underwent HRCT of the chest with inspiratory and expiratory imaging. Scans were obtained using low-dose technique without administration of intravenous contrast with 1-mm images obtained from the thoracic inlet to the hemidiaphragms on multidetector computed tomographic (CT) scanners (Siemens Definition, Siemens Medical Systems, Erlangen, Germany). If patients had undergone CT scanning within the last 6 months at an outside facility, images were retrieved and reviewed. Among the 12 patients, nine had HRCT scans performed at our institution and three had CT scans performed at other institutions.

A standard graded coding system was developed to describe presence, distribution, and degree of CT scan findings and to determine the predominant abnormality (reticular, nodular, or airway).[26,27] Three radiologists reviewed CT scans using the standard coding system. There were no discrepancies among the three radiologists regarding presence or absence of findings; however, minor disagreements regarding degree or extent of findings were resolved by a fourth reader.

Scan quality was scored on a scale of 0 to 3. Lung aeration was scored on a scale of 0 to 2 (0 = hypoinflation, 1 = normal inflation, 2 = hyperinflation). Emphysema was graded on a scale of 0 to 3, and distribution (bullous, paraspetal, centriacinar) noted. An assessment of inspiratory and expiratory homogeneity was made on a scale of 0 to 3 (0 = most homogeneous, 3 = most heterogeneous), and areas of involvement (upper or lower) noted. Air trapping (AT) was deemed present when there was greater heterogeneity of aeration on the expiratory scan than on the inspiratory scan. Sparing of secondary lobules was noted as present or absent.

Parenchymal findings were graded on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe), and distribution noted as follows: reticulation (diffuse or subpleural, upper or lower lobe), traction bronchiectasis (upper or lower lobe), ground-glass attenuation (diffuse or localized), septal thickening, and focal fibrosis. Architectural distortion and honeycombing were scored as present or absent.

Airway findings were graded on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe), and distribution noted as follows: bronchial wall thickening (BWT; diffuse or localized, upper or lower lobe), bronchial wall dilation (diffuse or localized, upper or lower lobe), and expiratory tracheomalacia. Large airway mucoid impaction, small airway mucoid impaction (tree-in-bud), and endobronchial lesions were scored as present or absent.

The presence of localized (defined as fewer than six nodules) or diffuse nodules (defined as six nodules or more) was noted. If a diffuse nodular pattern was present, distribution (random, centrilobular, or perilymphatic) and density (solid, semisolid, or ground-glass) of the nodules were noted. Adenopathy (mediastinal or hilar), consolidation or atelectasis, pleural effusion, pleural thickening, pleural calcification, and evidence of previous granulomatous disease were noted as present or absent.

Lung Pathology

Patients underwent video-assisted thoracoscopic surgical lung biopsy for CT showing interstitial changes (n = 6) or for unexplained symptoms and abnormal lung function in the absence of any significant interstitial or nodular pattern on CT (n = 6). Six patients had biopsies performed at Bellevue Hospital after referral by WTC EHC clinicians. Six patients had undergone lung biopsy at other institutions before enrollment in the WTC EHC; these pathology slides were obtained and reviewed. Hematoxylin and eosin–stained slides were reviewed independently by three pathologists under light microscopy and assessed for quality of tissue, characterization of lung parenchyma, and characteristics of the vasculature and airways. Slides were also examined using polarized light microscopy to determine the presence of birefringent particles. A standard semiquantitative coding system based on previous studies was developed to describe presence and distribution of pathologic findings.[27,28] Two of the three pathologists were blinded to the clinical history and radiologic findings. A pathologic finding was designated as present if identified by two of the three pathologists. Intracellular birefringent particles were designated as present if they were located within histiocytes and identified by one of the three pathologists. As controls, hematoxylin and eosin–stained slides of nine consecutive patients presented at a clinical case conference with no occupational or WTC exposures who had undergone surgical lung biopsy for suspected ILD were examined by one pathologist using light microscopy for the presence of intracellular birefringent particles using the same microscope and under the same conditions and magnification as were used for the study patients.

Particle Analysis

Scanning electron microscopy with energy-dispersive x-ray spectroscopy was performed on available tissue blocks to identify inorganic particles (silica, aluminum silicates, talc, metals) in the lung parenchyma and to generate a semiquantitative concentration score for each tissue sample. The freshly cut surface of the paraffin block was examined in the variable-pressure mode at constant 3000X magnification. Methods have been previously described.[29] The concentration score for each particle type was calculated by multiplying the light microscopic grade of dust burden on a three-point scale (1–3) by the percentage of each class of particles.

RESULTS

Clinical, Radiologic, and Pathologic Findings

Characteristics of the 12 patients in the WTC EHC cohort who underwent video-assisted thoracoscopic surgical lung biopsy are shown in Table 1. Many (58%) were women and Hispanic (42%). Forty-two percent reported having been caught in the dust cloud on September 11, 2001. Few (25%) had a greater than 10-pack per year tobacco history. The predominant CT findings along with clinical criteria were used to group patients into two clinicoradiologic patterns: group 1 patients demonstrated "interstitial" disease on HRCT defined as predominant reticular densities (n = 6), and group 2 patients had abnormal physiology and either normal HRCT scans or "airway" disease defined as diffuse BWT, AT, or other abnormalities of the airways in the absence of associated "interstitial" findings (n = 6).

TABLE 1. Characteristics of WTC EHC Patients Who Underwent Lung Biopsy

Patient Characteristics	$N = 12$
Age, median (range), yr	53 (40–64)
Women, % (n)	58 (7)
Race, % (n)	
White	41 (5)
Black	8 (1)
Asian	17 (2)
Other	33 (4)
Ethnicity, % (n) Hispanic	42 (5)
Caught in dust cloud, % (n)	42 (5)
Ever smoker >10 pack/yr, % (n)	25 (3)
Clinicoradiologic patterns, % (n)	
Interstitial lung disease (group 1)	50 (6)
Abnormal physiology (group 2)	50 (6)

Although pathologic findings were diverse, there were several common findings across groups. Findings generally failed to meet criteria for known histopathologic entities. When identified, granulomas were scant and poorly formed. Patchy interstitial fibrosis was seen in both groups, although more commonly and to a greater degree among group 1 patients. Emphysematous changes were identified in almost all patients across CT groups despite the absence of radiologic or lung function suggestion of emphysema. Small airway findings with scant lymphoid aggregates were also noted in most patients. All cases had opaque and birefringement particles identified within macrophages.

Findings in Group 1 Patients

Clinical characteristics are summarized in Table 2. Most patients were more than 50 years old. Only two patients had a smoking history, and all were local workers, except for one who was also a resident. Two reported that they were present in the initial dust cloud. No obvious occupational or environmental risks other than the WTC exposures could be identified in these patients. Prebronchodilator lung function is summarized in Table 3. Most patients showed a characteristic restrictive or combined restrictive and obstructive pattern on spirometry, although one patient (case 4) had normal lung function despite mild diffuse reticulation on CT, and another with moderate to severe diffuse reticular changes (case 3) was unable to perform PFT.

Detailed radiologic findings are shown in Table 4. Group 1 patients showed "interstitial" findings, with mild to severe reticulation. Although lower lobe and subpleural in most cases, the findings were diffuse in others. Traction bronchiectasis was noted in five cases. Architectural distortion was milder and less common, and honeycombing was noted in three cases. Four patients had mild concomitant airway findings including BWT or bronchial wall dilation, and two of the four patients with acceptable expiratory images had AT. None had radiologically apparent emphysema. In two patients, moderate to severe interstitial findings were associated with sparing of select secondary lobules (cases 2 and 5). The differential diagnosis based on the CT findings included usual interstitial pneumonia (UIP), fibrotic nonspecific interstitial pneumonia (NSIP), or chronic hypersensitivity pneumonitis (HP) in three (cases 3, 5, and 6, respectively); the milder interstitial patterns suggested early UIP or NSIP (cases 1 and 4); and NSIP with a possible element of organizing pneumonia in case 2, the only patient with a combined restrictive/obstructive defect on PFT.

Pathologic findings for group 1 are summarized in Table 5. Mild to moderate patchy interstitial fibrosis was identified in five patients, with microscopic honeycombing identified in the three biopsies with moderate fibrotic changes. A very mild interstitial cellular infiltrate consisting of lymphocytes and plasma cells was seen in all six patients. Granulomas were seen in only two cases, and when identified (cases 3 and 4), were rare and poorly formed. Focal areas of organizing pneumonia were seen in two of the six cases (cases 4 and 5) but notably not in case 2, in whom organizing pneumonia or NSIP had been suggested by the CT findings. Small airway abnormalities, including bronchiolitis or peribronchiolar fibrosis, were identified in five cases. Peribronchial lymphoid aggregates were described in five and pulmonary arteriopathy in four patients. Goblet cell hyperplasia and basement membrane thickening were absent from all specimens. Remarkably, all six cases demonstrated emphysematous changes. Only two patients had pathologic findings suggestive of a specific diagnostic entity: Case 4 had features resembling HP (although serologies failed to demonstrate a causative agent), and case 6 was suggestive of UIP or fibrotic NSIP. Macrophages containing opaque particulate material were identified in six of the six cases. Within these areas, birefringent intracellular particles were seen.

The radiologic and pathologic findings for case 2 are shown (Fig. 1). The CT and pathologic findings failed to meet criteria for UIP, NSIP, or any defined ILD. A small birefringent particle is shown (Fig. 1D,E). This patient failed all therapy and underwent lung transplantation. The explanted lung (not shown) had similar findings of end-stage fibrosis. The radiologic and pathologic findings for case 6 are shown (Fig. 2). Subpleural reticular opacities were present on CT, although the findings were less severe than in case 2. Pathologic examination revealed interstitial fibrosis. Areas containing opaque particulate material were noted, and a birefringent particle is shown (Fig. 2D,E). This patient is currently stable.

Findings in Group 2 Patients

Clinical characteristics are summarized in Table 2. Only two patients had a greater than 10 packs per year history of tobacco use. Most were local workers, and three reported exposure to the dust cloud. Four had other exposures with potential risk for lung disease. All group 2 patients had abnormal lung function (Table 3), with most showing a mild-moderate degree of restriction and a reduced diffusing capacity of carbon monoxide.

None of the patients had CT findings suggestive of diffuse interstitial disease or fibrosis (Table 4) and none had evidence of emphysema. BWT was seen in three patients. One (case 8), had small airways abnormalities described as mucoid impaction, manifesting as centrilobular nodules (tree-in-bud) in the lower lobes. Mosaic attenuation or AT was seen in three patients. AT was moderate to severe in two cases suggesting small airways disease; or, when secondary lobules were spared (case 9), suggesting an airway process, such as chronic HP, bronchiolitis obliterans organizing pneumonia, cryptogenic organizing pneumonia, or constrictive bronchiolitis. In two cases (cases 11 and 12), CT scans revealed no abnormalities other than minimal or physiologic AT despite mild to moderate restriction on PFT.

Pathologic findings for group 2 are summarized (Table 5). Focal areas of mild interstitial fibrosis were seen in only two patients, and honeycombing was universally absent. Cellular infiltrates were mild and patchy. Very mild patchy lymphoplasmacytic infiltrates and peribronchial lymphoid aggregates were seen in five cases. Goblet cell hyperplasia, basement membrane thickening, and organizing pneumonia were absent in all. Non-necrotizing granulomas, though scant, were seen in three cases: in case 8, they were peribronchial; in case 9, they were interstitial and poorly formed; and in case 10, peribronchial necrotizing and non-necrotizing granulomas were identified. No etiologic infectious agent was identified in any case. Bronchiolitis was identified in four cases. In all, small airways were affected, almost always in association with emphysematous changes, but a precise diagnosis was elusive. Emphysematous changes were

TABLE 2. Clinical Characteristics of Group 1 and Group 2 Patients

Case	Age/Sex	Pack-year	Exposure Category	Dust cloud	Other Exposures
Group 1					
1	63/F	0	Resident /local worker	Yes	None
2	54/F	0	Local worker	No	None
3	64/F	16	Local worker	No	None
4	49/F	0	Local worker	No	None
5	61/F	32	Local worker	No	None
6	64/M	0	Local worker	Yes	None
Group 2					
7	51/F	0	Local worker	No	None
8	49/M	15	Resident	No	IVDA
9	57/F	0	Local worker/resident	No	Pigeons, fabric
10	45/M	19	Local worker	Yes	Jacuzzi
11	44/M	0	Local worker	Yes	None
12	40/M	0	Local worker	Yes	Construction

IVDA, intravenous drug use.

TABLE 3. Pulmonary Function in Group 1 and Group 2 Patients

Case	Physiologic Pattern	FVC% of Predicted	FEV_1/FVC% of Predicted	TLC% of Predicted	D_LCO% of Predicted
Group 1					
1	Restrictive	70	90	70	62
2	Restrictive/obstructive	39	67	48	36
3	Unable to perform	NA	NA	NA	NA
4	Normal	111	75	134	NA
5	Restrictive	77	87	66	29
6	Restrictive	92	81	74	63
Group 2					
7	Restrictive	56	80	60	49
8	Restrictive/obstructive	47	67	77	NA
9	Restrictive	59	88	54	59
10	Restrictive/obstructive	70	58	84	70
11	Restrictive	60	92	62	70
12	Restrictive	77	85	74	65

D_LCO, diffusing capacity of carbon monoxide; FEV, forced expiratory volume in one second; FVC, forced vital capacity; NA, (data) not available; TLC, total lung capacity.

seen in five cases. Pulmonary arteriopathy was seen in three cases. In the two cases with essentially no radiologic abnormalities (cases 11 and 12), the predominant finding was patchy areas of emphysematous change associated with a mild patchy cellular UIP in case 11 and loss of bronchioles in case 12. Collections of macrophages containing mostly opaque particulates, consistent with combustion products, were present in all six cases. In every case, birefringent intracellular particles were seen.

Radiologic and pathologic findings of case 7, who failed to meet criteria for any defined ILD, are shown in Fig. 3. AT was evident on expiratory HRCT (Fig. 3A,B). Pathology included mild interstitial inflammation, chronic bronchiolitis and bronchiolar fibrosis, and subpleural emphysema (Fig. 3C). Again, opaque particulates were seen within macrophages, and intracellular birefringent particles were identified (Fig. 3D,E). A prolonged trial of systemic steroids failed to completely improve symptoms or pulmonary function in this patient. She demonstrated a marked reduction in lung volumes after brief removal of inhaled corticosteroids and bronchodilators; however, on chronic medication, her exertional dyspnea and restrictive lung function have remained stable for the past 3 years. In case 8 (pathology not shown), a lymphocytic bronchiolitis and granulomatous inflammation were identified and sputum culture grew Mycobacterium avium. Despite prolonged antimicrobial therapy, there has been no significant clinical or radiologic improvement. Case 9 (pathology not shown), whose pathology had features suggesting HP with mild fibrosis, remains oxygen dependent. The findings for case 11 are shown in Fig. 4. The HRCT was essentially normal with minimal AT on expiratory HRCT (Fig. 4A,B). The predominant pathologic finding in this patient was emphysematous change with patchy mild cellular interstitial fibrosis. This patient continues to have exertional dyspnea and stable restriction on PFT for more than 5 years.

Findings in Reference Patients

In nine reference patients, examination under polarizing light microscopy by one pathologist revealed birefringent particles in only three of the nine patients, but these had a globular shape and clearly

TABLE 4. Graded Radiologic Findings in Group 1 and Group 2 Patients

	"Interstitial" Findings						Aeration and Airway Findings			
Case	Reticulation (0–3)	Traction Bronchiectasis (0–3)	Septal Thickening (0–3)	Architectural Distortion (0–1)	Honey combing (0–1)	Ground-Glass Opacities (0–3)	BWT/BWD (0–3)	Mosaic Attenuation or AT (0–3)	Emphysema (0–3)	Distribution of Predominant Abnormality
Group 1										
1	1	1	0	0	0	0	0/2	1	0	Lower lobe, subpleural
2	3	2	0	0	0	0	1/0	0	0	Upper and lower lobes, diffuse
3	2	3	1	1	1	2	1/2	2	0	Lower lobe, diffuse
4	1	0	0	0	0	0	1/0	1	0	Lower lobe, subpleural
5	3	3	3	1	1	0	0/0	2	0	All lobes, diffuse
6	2	1	0	0	1	0	0/0	0	0	All lobes, subpleural
Group 2										
7	0	0	0	0	0	0	0/0	1	0	Upper and lower lobe AT
8	0	0	0	0	0	0	1/0	0	0	Diffuse BWT, lower lobe tree-in-bud
9	0	0	0	0	0	3	1/0	3	0	Diffuse BWT and AT
10	0	0	0	0	0	0	1/1	2	0	Diffuse BWT and AT
11	0	0	0	0	0	0	0/0	0	0	Minimal AT
12	0	0	0	0	0	0	0/0	0	0	None

AT, air trapping; BWT, bronchial wall thickening; BWD, bronchial wall dilation.

differed in morphology from those identified in the study cases (data not shown).

Particle Analysis

Specimens were available for mineralogic analysis in five patients. All had a light microscopic grade of dust burden of 1, indicating the presence of particles but not an overwhelming number. Detailed results are shown in Table 6. Silica was detected in individual particles in four of the five patients. The one case without detectable silica also had the fewest particles analyzed. The concentration scores (microscopic dust burden × % of particles with compound) for silica, aluminum silicates, titanium dioxide, and talc particles varied from 3 to 13, 26 to 52, 11 to 22, and 7 to 29, respectively. All cases had metals identified in particles. Approximately 20% of particles in case 8 contained numerous unusual metal particles, consistent with industrial exposures. Most unusual was the finding of metal particles of types not expected in the general population, including aluminum, steel, zirconium, chromium, copper, zinc, and tin. Figure 5 shows scanning electron microscopy images and energy-dispersive x-ray spectroscopy spectra for cases 2 and 11.

DISCUSSION

In a residential and working community with persistent symptoms after exposure to WTC dust and fumes on or after September 11, 2001, a small subset ($n = 12$) proceeded to surgical lung biopsy for evaluation of possible ILD or unexplained lung function abnormalities. Radiologic and clinical findings were diverse and could be categorized into two predominant patterns on the basis of imaging: Group 1 with a pattern suggesting ILD; and group 2, with abnormal lung function but no evidence of ILD on HRCT. Although pathologic findings were diverse, there were some common findings across patients that were unexpected. Emphysematous changes were identified in almost all patients across CT groups despite the absence of radiologic or lung function suggestion of emphysema. Small airway findings with scant lymphoid aggregates were also noted in most patients. Notably, inflammation was minimal, and pathologic findings generally failed to meet criteria for known histopathologic entities. When granulomas were identified, they were scant and poorly formed. All patients had collections of macrophages containing opaque particulates and intracellular birefringent particles. In the limited sample of cases analyzed, these particles included inorganic compounds and metals.

Our findings are remarkably similar to those seen in seven previously healthy rescue and recovery workers exposed to WTC dust during the first 2 days after the disaster.[20] As in our study, the responders generally had findings consistent with ILD or AT on HRCT, and pathology demonstrated mixed histologic patterns consisting predominantly of patchy interstitial fibrosis, often in a bronchiolocentric pattern, and bronchiolitis or peribronchiolar fibrosis. Furthermore, most patients had persistent but stable restrictive abnormalities on PFT.

The finding of birefringent intracellular particles within collections of macrophages containing opaque particulate material was

TABLE 5. Graded Pathologic Findings in Group 1 and Group 2 Patients

Case	Fibrosis (0–2)	Honey combing (0/1)	Cellular Infiltrates (0–2)	Granuloma (0–1)	Organizing Pneumonia (0–2)	Emphysema (0–2)	Bronchiolitis or Small Airways Fibrosis (0–1)	Peribronchial Lymphoid Aggregates (0–2)	Goblet Cell Hyperplasia (0/1)	Basement Membrane Thickening (0–1)	Pulmonary Arteri-opathy (0–2)	Opaque Particu-lates (0–2)	Birefringent Particles (0–1)
Group 1													
1	1	0	1	0	0	1	1	0	0	0	0	1	1
2	2	1	1	0	0	1	1	1	0	0	1	1	1
3	1	0	1	1	0	1	1	1	0	0	1	1	1
4	0	0	1	1	1	1	0	1	0	0	1	1	1
5	2	1	1	0	1	1	1	1	0	0	0	1	1
6	2	1	1	0	0	1	1	1	0	0	1	1	1
Group 2													
7	0	0	1	0	0	1	1	1	0	0	1	1	1
8	0	0	1	1	0	1	1	1	0	0	1	1	1
9	1	0	1	1	0	1	1	1	0	0	0	1	1
10	0	0	1	1	0	0	1	1	0	0	0	1	1
11	1	0	1	0	0	1	0	1	0	0	1	1	1
12	0	0	0	0	0	1	0	0	0	0	0	1	1

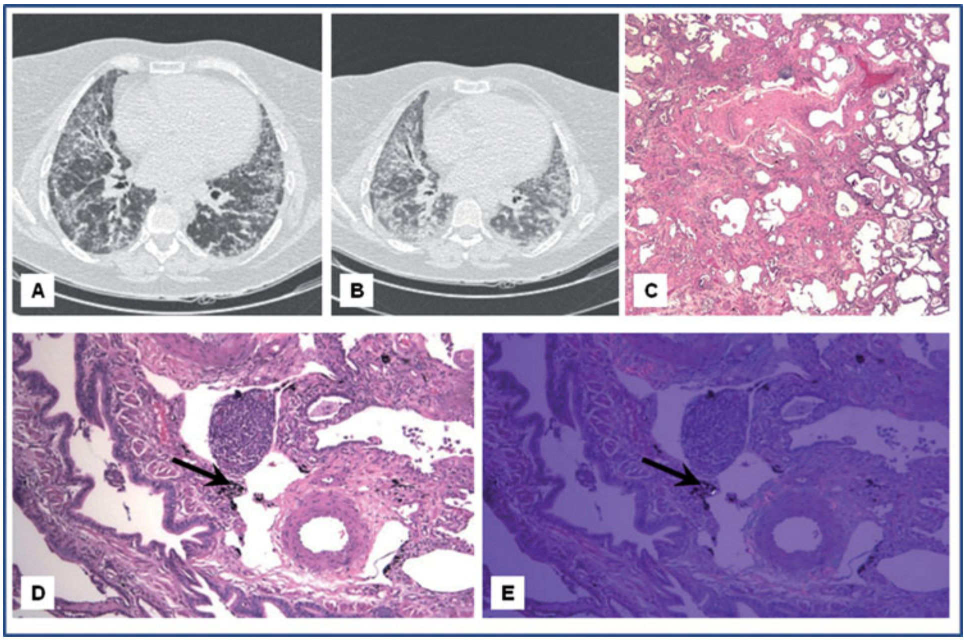

FIGURE 1. Radiologic and pathologic findings for case 2. A, Inspiratory and (B) expiratory high-resolution computed axial tomographic images showing extensive lower lobe reticular and ground glass opacities, (C) low-power hematoxylin and eosin staining showing interstitial fibrosis, (D) high-power hematoxylin and eosin staining showing opaque material in macrophages, and (E) same image with polarizing light microscopy showing a needle-shaped birefringent particle.

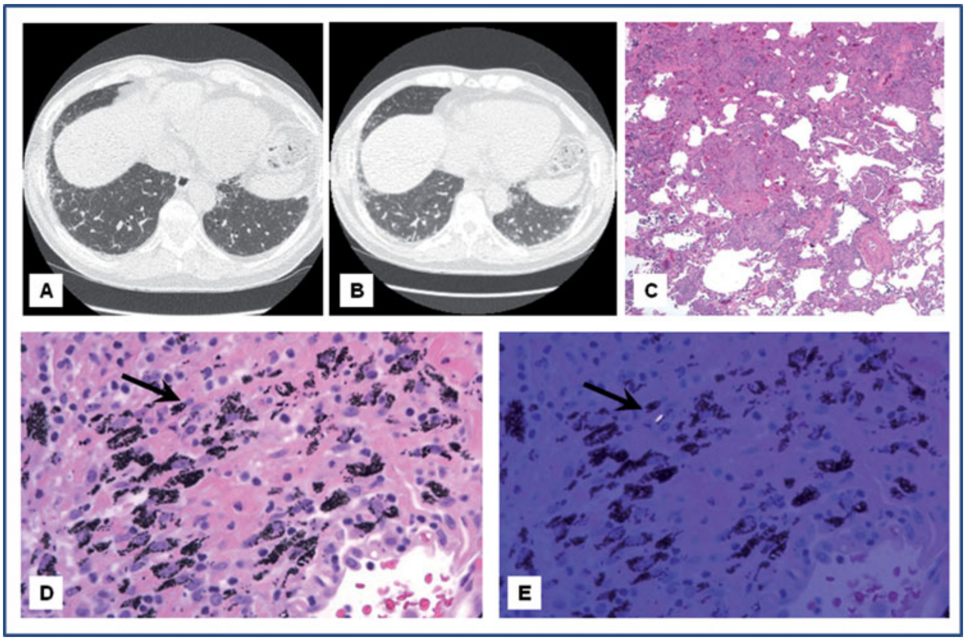

FIGURE 2. Radiologic and pathologic findings for case 6. A, Inspiratory and (B) expiratory high-resolution computed axial tomographic images showing subpleural reticular opacities, (C) low-power hematoxylin and eosin staining showing interstitial fibrosis, (D) high-power hematoxylin and eosin staining showing opaque material in macrophages, and (E) same image with polarizing light microscopy showing a needle-shaped birefringent particle.

a consistent finding across both of our groups. The opaque material is consistent with combustion products. Although birefringent particles were identified in three of the nine of our control specimens, the particles were clearly morphologically different than those identified in the WTC EHC cases. Mineralogic analysis of tissue blocks from the WTC EHC cases revealed the presence of silica and aluminum silicates, with smaller amounts of titanium in the particles. Especially noteworthy is the finding in each case of other metal particle types, including steel (FeCrNi), aluminum, barium sulfate, zirconium silicate, glass, chromium, copper, zinc, and tin. These analyses are consistent

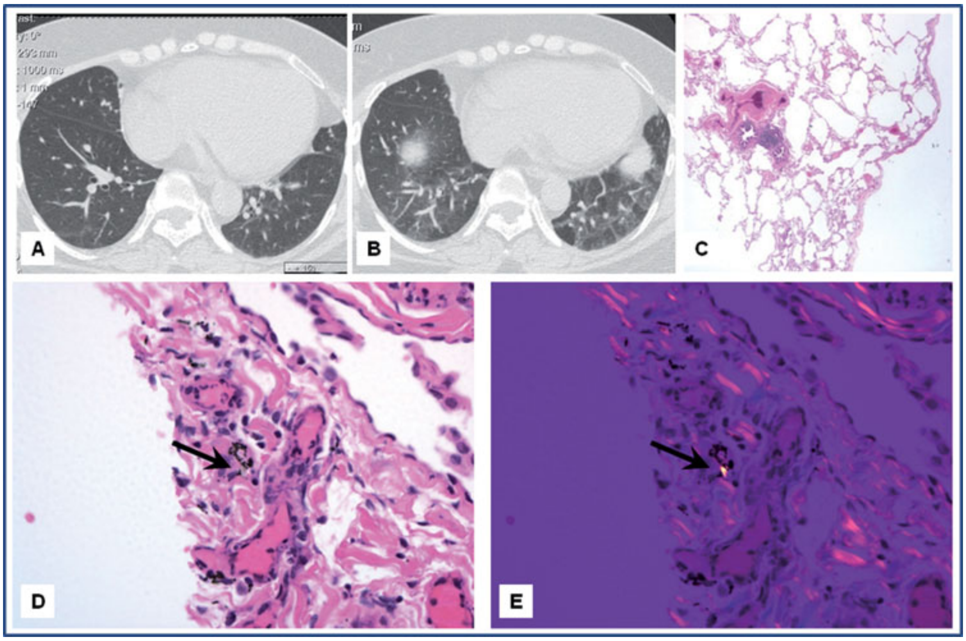

FIGURE 3. Radiologic and pathologic findings for case 7. A, Inspiratory and (B) expiratory high-resolution computed axial tomographic images showing mosaic attenuation, (C) low-power hematoxylin and eosin staining showing emphysematous change, (D) high-power hematoxylin and eosin staining showing opaque material in macrophages, and (E) same image with polarizing light microscopy showing a needle-shaped birefringent particle.

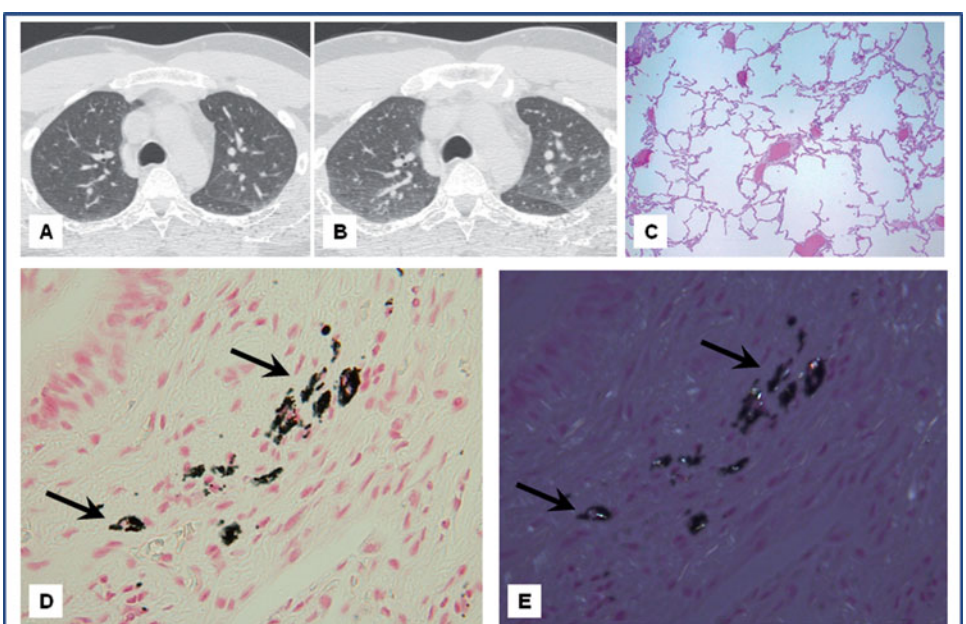

FIGURE 4. Radiologic and pathologic findings for case 11. A, Inspiratory and (B) expiratory high-resolution computed axial tomographic images showing minimal air trapping, (C) low-power hematoxylin and eosin staining showing emphysematous change, (D) high magnification of iron stained section showing numerous macrophages containing a mixture of opaque and birefringent (E) particles.

with mineralogic descriptions of WTC dust. Lioy and colleagues[2] analyzed settled dust from three different locations around the WTC site and documented the presence of large quantities of construction debris including quartz grains and elements consistent with building materials, including chromium, magnesium, manganese, aluminum, and barium, and large signals for iron, calcium, silicon, and titanium.

Furthermore, the ability of WTC particulate matter to be inhaled and retained in the lung is well documented. Mineralogic analysis of bronchoalveolar lavage fluid from a firefighter presenting

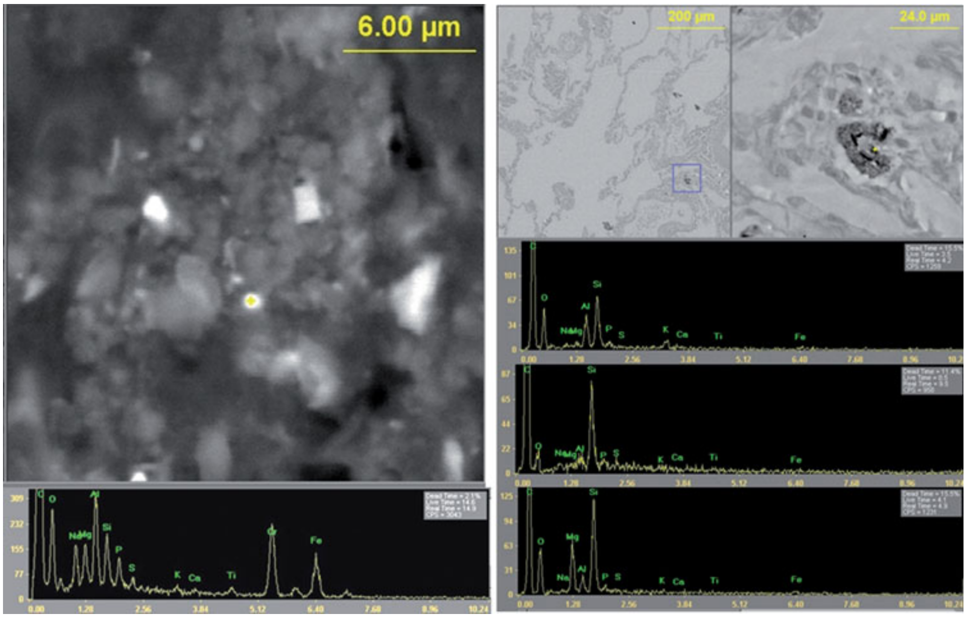

FIGURE 5. Scanning electron microscopy (SEM) with energy-dispersive x-ray spectroscopy (EDS) results. Examples of respirable particulates detected in situ in cases 2 (*left*) and 11 (*right*). SEM images of lung tissue showing macrophages containing numerous particles and a few examples of EDS spectra of individual particles identified. Left: steel particle (Cr with Fe) near other particles; Right: SiAlK (*top*); silica(*middle*); and talc (*bottom*).

TABLE 6. Particle Analysis

Case	Pack/y	Other Exposures	Number of Particles Analyzed	Concentration Scores				
				Silica	Aluminum Silicate	Titanium	Talc	Other Metals
2	0	None	134	13	52	15	7	10 ZrSi
3	16	None	139	9	45	14	10	3 Al; (innumerable tiny Al silicates)
8	15	None (IVDA)	122	8	26	11	29	20 diverse metals:
			59	3	29	22	9	steel, SiZr, Cu, tiny Al silicates
9	0	Pigeons, fabric	21	0	52	14	14	14 steel
11	0	None	119	10	36	20	20	3 Al 8 diverse metals (steel, Cr)

Concentration score = microscopic dust burden × % particle type. All had a microscopic dust burden of 1.
IVDA, intravenous drug use.

with acute eosinophilic pneumonia after WTC dust exposure in the days immediately after 9/11 showed the presence of large Amosite asbestos fibers, fly ash particles, and degraded fibrous glass.[8] Similarly, induced sputum of New York City firefighters after 9/11 demonstrated inflammation and particles with minerals, including titanium, that was different from nonexposed control firefighters, suggesting that these particles can enter and persist in human lung.[30] Most recently, in seven symptomatic WTC responders histopathologic findings of small airways disease, bronchiolocentric parenchymal disease, and non-necrotizing granulomas were identified in the presence of aluminum and magnesium sheet silicates, silicates, chrysotile asbestos, calcium phosphate, and calcium sulfate and, in some cases, carbon nanotubes.[20] A recent analysis of patients from the WTC EHC with post-9/11 sarcoid also showed silica and aluminum silicates in a limited mineralogic analysis of lymph node and parenchymal biopsy specimens.[31] Although attribution remains difficult in our study as in others, our finding of opaque and birefringent particles in macrophages in all specimens coupled with the finding of particles consistent with WTC dust supports an association. Our in situ analytical methodology would not be able to detect nanotubes or asbestos fibers.

Desert dust particles have been shown to cause inflammatory responses in the airways in animal studies, and heavy dust events have been associated with an increased risk of hospitalizations for asthma.[32] Airway hyperreactivity has been well described in WTC responders.[7] Nevertheless, physiologic findings in our study patients were not suggestive of large airways disease, and pathologic findings of asthma, including basement membrane thickening and goblet cell hyperplasia, were conspicuously absent. Pathologic findings were similar, though not identical, to those described for mixed-dust pneumoconiosis, in which macules consisting of interstitial accumulations of dust-laden macrophages, often peribronchiolar or perivascular, can be identified. Numerous birefringent particles can be observed under polarizing light microscopy with mineralogic analysis revealing silica, silicates, and various metal particles. Moreover, these can be associated with centrilobular emphysema, even in the absence of a history of tobacco use.[33] Although several of our patients had some occupational/hobby exposure that might be associated with lung disease, none of our patients had an occupational history that would account for these findings.

The pathologic finding of emphysematous change in all but one case was unexpected because lung function studies and HRCT had not suggested emphysema. Nevertheless, occupational exposures to gas, dust, and fumes are recognized increasingly as a cause of chronic obstructive pulmonary disease[34] and have been described in mixed-dust pneumoconioses[33] or in coal or gold mining.[35,36] Cumulative dust exposure is a significant predictor of emphysema severity in coal miners.[37] Although the time course of dust exposure in our population is shorter than that reported in studies of coal miners, our finding of unsuspected emphysematous change in lung biopsy specimens of symptomatic WTC dust-exposed patients suggests the possibility that one response to WTC dust and fume exposure may be destruction of alveoli accounting for persistent respiratory symptoms many years after the initial injury.

Although pathologic criteria for disease of the small airways are less well defined than for the large airways and parenchyma, the finding of variable small airway abnormalities in our group is instructive. In our WTC-exposed patients with respiratory symptoms, the histologic finding of small airways disease—either in the form of bronchiolitis or peribronchiolar fibrosis—could explain the minimal HRCT abnormalities combined with significant restriction on PFT and certainly could be consistent with an inhalational injury. Furthermore, small airways disease in WTC-exposed individuals has been suggested previously.[20]

In conclusion, asthma-like symptomatology with normal spirometry has been the most commonly described respiratory pattern in all WTC-exposed individuals, including a residential and working community. However, among those with abnormal lung function, a reduced vital capacity has been the most common finding.[17] In the small number of patients with abnormal physiology and HRCT who underwent surgical lung biopsy, pathologic findings included variable interstitial fibrosis and small airways abnormalities with the unexpected finding of emphysema. Samples from every patient had intracellular birefringent particles within areas of opaque particulate material in macrophages, with limited analysis revealing silica, aluminum silicates, and titanium dioxide consistent with exposure to building materials. These findings in individuals who were not involved in rescue and recovery activities suggest the potential for inhalation of pulverized materials and subsequent injury in this additional population. These studies reinforce the heterogeneous response to WTC dust and fume exposure and the need for continued monitoring of these patients to determine the long-term respiratory health effects of WTC exposures.

ACKNOWLEDGMENTS

The authors thank Kymara Kyng, RN, Terry Miles, RN, and Ruchel Ramos, MPA, for their help in administering the WTC EHC. They thank William N. Rom, MD, for his help in review of the manuscript. They also thank the members of the WTC EHC Community Advisory Committee for their commitment to the WTC EHC.

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