Radiologic Features of World Trade Center–related Sarcoidosis in Exposed NYC Fire Department Rescue Workers

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Purpose: An increased incidence of sarcoidosis has been demonstrated in firefighters, supporting the concern that occupational/environmental exposure may pose an etiologic risk factor. This incidence increased further after September 11, 2001 following exposure to World Trade Center (WTC) dust and gases. We review computed tomography (CT) features in this population, comparing the range of findings and physiological correlates with those typically reported in unexposed individuals with pulmonary sarcoidosis.

Materials and Methods: With CT imaging we retrospectively identified 46 patients with WTC-related sarcoidosis, between March 18, 2002 and April 5, 2014. Scans were independently reviewed by 2 dedicated thoracic radiologists and assessed for disease patterns and correlation with pulmonary functions.

Results: The majority (37/46; 80%) had symmetric mediastinal and hilar lymphadenopathy. Similarly, most (38/46; 83%) had perilymphatic nodules. Foci of ill-defined ground glass attenuation were present in 6 (13%). Coalescent nodularity was present in 15 (33%). Only 3 (7%) had parenchymal reticulation. A mixed pattern of lung findings was present in 21 (46%). When all forms of parenchymal disease were scored by zonal distribution, 21 (46%) had parenchymal disease predominantly involving mid and upper lungs; 11/46 (24%) had a random distribution without zonal predominance; 6/46 (13%) demonstrated atypical lower zone predominance. Whereas 15/46 (33%) had obstructive airways disease on pulmonary function tests, there were no CT findings that were predictive of obstructive airways disease.

Conclusions: The majority of cases of WTC-related sarcoidosis demonstrated typical radiographic appearances of sarcoidosis, with symmetric hilar and mediastinal lymphadenopathy and mid to upper lung perilymphatic nodules; these findings were consistent with other previously reported cases of sarcoid-like granulomatous disease in association with various alternate underlying etiologies. There was no correlation between disease patterns or extent on CT and pulmonary function testing, likely at least in part due to the overall mild extent of disease in this population.

Key Words: sarcoidosis, sarcoid-like reaction, World Trade Center

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Sarcoidosis is a multisystem granulomatous disease of unknown etiology. A strong body of evidence supports both occupational and environmental exposures as etiologic factors inducing granulomatous inflammation.[1–4] An increased incidence of sarcoidosis was already recognized in firefighters before September 11, 2001.[5,6] This incidence increased further after September 11, 2001 in rescue/recovery workers (firefighters and emergency medical technicians) from the Fire Department of the City of New York (FDNY) with exposure to World Trade Center (WTC) dust and combustion byproducts and was initially described as WTC-like granulomatous pulmonary disease (WTC-SLGD)[7] and now after confirmation in 2 other large WTC-exposed cohorts[8,9] is described as WTC-related sarcoidosis. Published reports thus far have largely concentrated on clinical findings, documenting associations with obstructive airways, cancer,[10–13] rheumatologic disease, and rarely cardiac disease.[7,14] To date, there has been no detailed description of disease patterns on computed tomography (CT). It is the purpose of this report, therefore, to retrospectively analyze radiologic patterns on chest CT of WTC-related sarcoidosis in FDNY WTC-exposed rescue/recovery workers and correlate these with physiological changes as determined by pulmonary function tests (PFTS).

MATERIALS AND METHODS

Institutional Research Review Board approval was obtained for this retrospective study from Montefiore Medical Center and NYU School of Medicine. FDNY WTC-exposed rescue/recovery workers were screened at the FDNY WTC Health Program for signs, symptoms, or imaging findings suggestive of sarcoidosis. This population is of particular interest as the clinical history, chest radiograph, and laboratory findings are assessed preemployment and then monitored annually, including both before and after the WTC disaster. All patients in this population had negative preemployment chest radiographs and negative pre-September 11, 2001 annual monitoring chest radiographs at outside institutions, as per review of radiograph reports. When sarcoidosis was suspected (either because of patient symptoms or abnormal annual monitoring radiographs), a clinical evaluation was performed, including full medical history, physical examination, blood tests, PFTs (pre-bronchodilator and postbronchodilator measurements, lung

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volumes body plethysmography, and diffusing capacity), cardiac echo, and high-resolution chest CT (HRCT) with inspiratory and expiratory imaging. Pathologic confirmation was obtained in all cases by transbronchial lymph node and transbronchial lung biopsies demonstrating intrathoracic noncaseating granulomas without evidence for foreign body reaction or malignancy by light microscopy or fungus/mycobacterium by culture. From this database, we retrospectively identified 46 patients who had CT imaging and pulmonary function testing at the same institution (NYU) between March 18, 2002 and April 5, 2014 and whose initial HRCT scan with inspiratory and expiratory imaging obtained at the time of diagnosis was digitally available for review (see below).

All scans were performed on Siemens multislice scanners (Siemens Med, Forchheim, Germany) with 5 mm axial B60 (lung) and B40 (mediastinal) images and contiguous 1 mm axial B60 inspiratory HRCT image reconstructions. Select 1 mm low-dose expiratory HRCT images were also obtained every 10 mms for all patients. All scans except 1 were performed without intravenous contrast. All studies were independently reviewed by 2 dedicated fellowship-trained thoracic radiologists (with 30 and 10 y experience) and discordance resolved by consensus.

Scans were assessed for the presence and extent of nodal, parenchymal, and airways disease. Lymphadenopathy was assessed in terms of size (none; shotty—increased numbers of subcentimeter nodes; 1 to <2 cm; >2 cm), distribution (symmetry; hila or mediastinal; atypical nodal groups), and calcification. Lungs were assessed for perilymphatic nodules, ground-glass attenuation, reticulation and honeycombing (on inspiratory HRCT), and mosaic attenuation (on expiratory HRCT), as defined by the Fleischner Society: Glossary of Terms for Thoracic Radiology.[15] In addition, we identified discrete foci of mass-like coalescent nodularity.[16] Each category of parenchymal disease was qualitatively visually graded for extent of involvement (0: none; 1: $\leq$25%; 2: $>$25% to $\leq$75%; 3: $>$75%) for each lung zone (upper, mid, lower), and scores were added to give a global percentage score. Airways were qualitatively visually assessed (on inspiratory HRCT) for evidence of focal or diffuse bronchial wall thickening/narrowing and scored for both extent (0: none; 1: focal; 2: diffuse) and severity (0: none; 1: mild; 2: moderate; 3: severe) by consensus.

Correlations Between CT and Pulmonary Functions

Airflow obstruction on PFTs was defined as: total lung capacity (TLC > 120% predicted); residual volume (RV > 120% predicted); or an RV/TLC ratio >0.45. Bronchial wall thickening on CT was correlated with all of the above pulmonary functions or a forced expiratory volume in 1 second to forced vital capacity ratio <0.70. All percentage predictions were calculated using US reference population equations from NHANES data.[17] Diffusion capacity of the lung for carbon monoxide (DLCO) was calculated using the standard method recommended by the American Thoracic Society.[18,19]

Statistical Methodology

Percentage scores for each category of parenchymal/airways disease on CT were correlated with PFTs. Positive predictive value (PPV) was calculated comparing CT findings with PFT outcomes. PPV was defined as the proportion of patients with a CT abnormality that corresponded to abnormal pathophysiology defined by pulmonary function.

RESULTS

There were 45 male and 1 female patients ranging in age from 29 to 58 years, with an average age of 44 years at diagnosis. For each patient, the first CT available at the time of diagnosis (between March 2002 and April 2014) was reviewed. For 43 of the patients the scan reviewed was performed within 6 months of initial diagnosis, and in 3 cases the available scan was obtained >6 months after diagnosis. Pulmonary function testing and echocardiography were also available on all patients within 6 months of diagnosis and before any treatment, if needed, had been initiated (Tables 1–6).

Nodal Disease

Bilateral, symmetric hilar and mediastinal lymphadenopathy was present in 37 (80%) of 46 patients (Fig. 1), including 25 with nodes measuring 1-2 cm, and 12 with nodes $>$2cm. All patients with lymphadenopathy had both mediastinal and hilar nodes, and all had involvement of typical nodal stations (most commonly right paratracheal and subcarinal). No patients had asymmetric lymphadenopathy or involvement of atypical nodal stations. In 2 patients, there were increased numbers of shotty nodes without frank lymphadenopathy. In 7 (15%) of 46 patients nodal disease was completely absent. Lymph nodes were calcified in 6 (13%), including 1 without lymphadenopathy, 1 with shotty nodes, 2 with nodes between 1 and 2 cm, and 2 with nodes >2 cm. No patients had eggshell calcifications. In 6 patients, there was exclusively nodal disease, with no parenchymal changes of sarcoidosis.

Parenchymal Disease

Characteristic perilymphatic nodules (Fig. 2) were identified in 38 patients, including 25 with <25% involvement, 11 with 25-50%, 2 with 51-75% and none with >75%. All cases with perilymphatic nodules had bilateral lung involvement.

Six (13%) of 46 patients had patchy ground-glass attenuation (Fig. 3) including 5 cases with <25%, 1 case with 25% to 50% lung involvement, and none with >50% lung involvement. Fifteen (33%) of 46 patients had foci of coalescent nodularity (Fig. 4), including 13 cases with

TABLE 1. WTC-related Sarcoidosis—Summary of Main CT Findings

	46 Cases [N (%)]
Typical intrathoracic findings	
Nodal disease	
Bilateral symmetric hilar and mediastinal lymphadenopathy	37 (80)
Parenchymal disease	
Perilymphatic nodules	38 (83)
Ground-glass	6 (13)
Coalescent nodules	15 (33)
Reticular pattern	3 (6)
Mixed pattern parenchymal findings	21 (46)
Airways disease	
Diffuse bronchial thickening	32 (70)
Expiratory mosaic attenuation	33 (72)
Atypical findings	
Lower zone predominance	6 (13)
Cavitation	1 (2)

TABLE 2. Perilymphatic Nodules by Percentage Lung Involvement and PFT Correlation

	Nodules [N (%)]					
OAD by PFT	**None**	**< 25%**	**25%-50%**	**51%-75%**	**76%-100%**	**Total**
No	4 (12.9)	16 (51.6)	9 (29.0)	2 (6.5)	0 (0.0)	31
Yes	4 (26.7)	9 (60.0)	2 (13.3)	0 (0.0)	0 (0.0)	15
Total	8	25	11	2	0	46

For any perilymphatic nodule (present vs. absent), PPV is 11/38 = 29%, negative predictive value is 4/8 = 50%. Overall agreement is (11 + 4)/46 = 33%.
Note: OAD by PFT was defined as TLC > 120% predicted; RV > 120% predicted; or an RV/TLC ratio >0.45.

TABLE 3. Ground-glass Opacity by Percentage Lung Involvement and PFT Correlation

	Ground-glass Opacity [N (%)]					
OAD by PFT	**None**	**< 25%**	**25%-50%**	**51%-75%**	**76%-100%**	**Total**
No	28 (90.3)	3 (9.7)	0 (0.0)	0 (0)	0 (0.0)	31
Yes	12 (80.0)	2 (13.3)	1 (6.7)	0 (0)	0 (0.0)	15
Total	40	5	1	0	0	46

For any ground-glass (present vs. absent) PPV is 3/6 = 50%, NPV is 28/40 = 70%. Overall agreement is (3 + 28)/46 = 67%.
Note: OAD by PFT was defined as TLC > 120% predicted; RV > 120% predicted; or an RV/TLC ratio >0.45.

TABLE 4. Reticular Opacity by Percentage Lung Involvement and PFT Correlation

	Reticular [N (%)]					
OAD by PFT	**None**	**< 25%**	**25%-50%**	**51%-75%**	**76%-100%**	**Total**
No	28 (90.3)	1 (3.2)	1 (3.2)	1 (3.2)	0 (0.0)	31
Yes	14 (93.3)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	15
Total	42	1	1	2	0	46

For any reticular opacity (present vs. absent), PPV is 1/4 = 25%, NPV is 28/42 = 67%. Overall agreement is (1 + 28)/46 = 63%.
Note: OAD by PFT was defined as TLC > 120% predicted; RV > 120% predicted; or an RV/TLC ratio >0.45.

TABLE 5. Coalescent Opacity by Percentage Lung Involvement and PFT Correlation

	Coalescent [N (%)]					
OAD by PFT	**None**	**< 25%**	**25%-50%**	**51%-75%**	**76%-100%**	**Total**
No	20 (64.5)	6 (19.4)	4 (12.9)	1 (3.2)	0 (0.0)	31
Yes	11 (73.3)	2 (13.3)	1 (6.7)	1 (6.7)	0 (0.0)	15
Total	31	8	5	2	0	46

For any coalescent opacity (present vs. absent), PPV is 4/15 = 27%, NPV is 20/31 = 65%. Overall agreement is (4 + 20)/46 = 52%.
Note: OAD by PFT was defined as TLC > 120% predicted; RV > 120% predicted; or an RV/TLC ratio >0.45.

TABLE 6. Mosaic Attenuation by Percentage Lung Involvement and PFT Correlation

	Mosaic [N (%)]					
OAD by PFT	**None**	**< 25%**	**25%-50%**	**51%-75%**	**76%-100%**	**Total**
No	8 (25.8)	10 (32.3)	11 (35.5)	2 (6.4)	0 (0.0)	31
Yes	5 (33.3)	4 (26.7)	4 (26.7)	2 (13.3)	0 (0.0)	15
Total	13	14	15	4	0	46

For any mosaic attenuation (present vs. absent), PPV is 10/33 = 30%, NPV is 8/13 = 62%. Overall agreement is (10 + 8)/46 = 39%.
Note: OAD by PFT was defined as TLC > 120% predicted; RV > 120% predicted; or an RV/TLC ratio >0.45.

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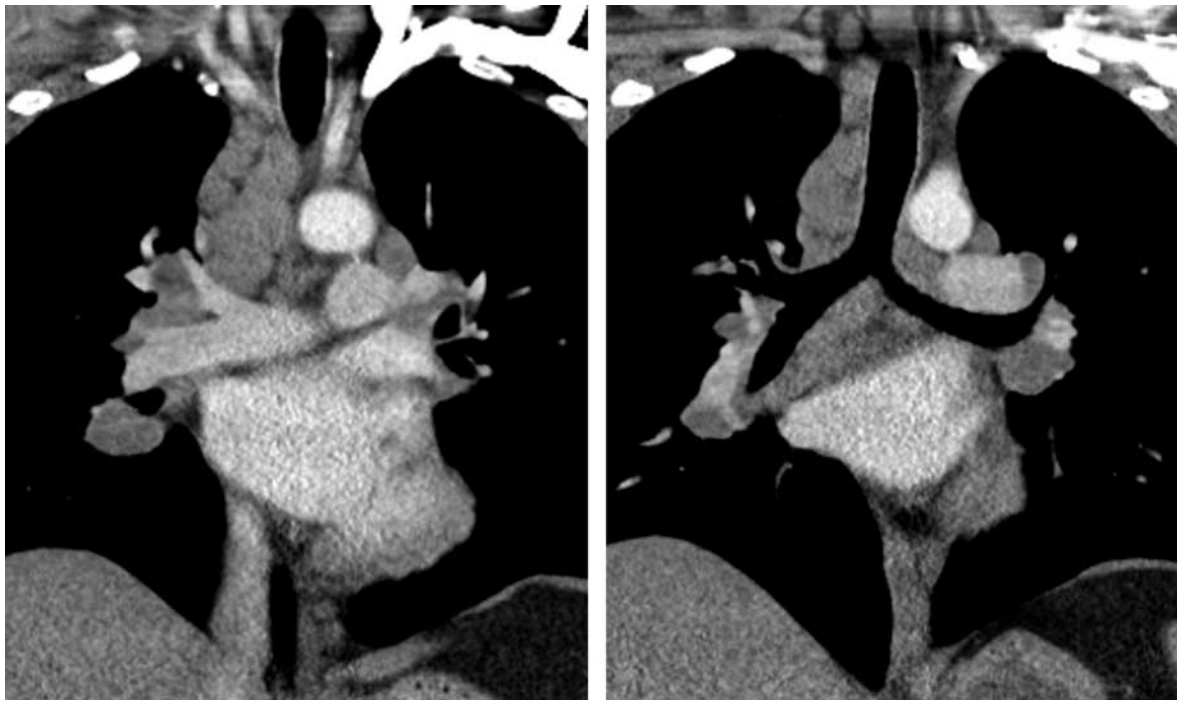

FIGURE 1. Imaging results of a 44-year-old man with WTC-related sarcoidosis. Coronal 5 mm contrast-enhanced CT images showing typical paratracheal, subcarinal, and hilar lymphadenopathy.

<25%, 1 case with 25% to 50%, 1 with 51% to 75%, and none with >75% lung involvement.

Only 3 (7%) of 46 patients had parenchymal reticulation (Fig. 5), including 1 case each presenting with <25%, 25% to 50%, and 51% to 75% involvement. There were no cases of honeycombing.

Only 1 had parenchymal cavitation consistent with presumed necrotizing sarcoidosis given the absence of documented infection or neoplasia by culture or biopsy (Fig. 6). Twenty-one (46%) of 46 patients had a mixed pattern of lung findings involving >1 category of parenchymal disease. Six (13%) had lungs that were entirely clear.

When all patterns of parenchymal disease were included, 21 (45%) of 46 patients had parenchymal disease predominantly involving mid and upper lungs; 11 (24%) had no zonal predominance, and 6 (13%) demonstrated atypical, basilar, lower zone predominance (Fig. 7).

Airways Disease

Bronchial wall thickening/narrowing on imaging was assessed for both distribution (focal or diffuse) and severity (mild, moderate, or severe). In 10 (22%) of 46 patients airways appeared normal; 4 had only focal areas of either mild or moderate airway thickening; 32 (70%) had diffuse airway narrowing including 15 (31%) with mild, 15 (31%) with moderate, and only 2 with diffuse severe airway narrowing. Expiratory mosaic attenuation (Fig. 8) was identified in 33 (72%) of 46 patients, including 14 (30%) with <25% lung involvement, 15 (33%) with 25% to 50% lung involvement, and 4 (9%) with 51% to 75% lung involvement.

Correlations With Pulmonary Functions

In 15 (33%) of 46 patients PFTS showed evidence of obstructive airways disease. None had restrictive physiology or decreased DLCO. There were no parenchymal findings (either by type or extent) that were predictive of OAD on PFTs (Tables 2–6). Of note, even expiratory mosaic attenuation on CT showed poor correlation with OAD, with a PPV of 30%, negative predictive value of 62%, and overall agreement of CT and PFTs of 39%. Bronchial wall thickening on CT was also not well correlated with PFTs with a PPV of 22%.

DISCUSSION

Our study documents that CT findings in WTC-related sarcoidosis demonstrate disease patterns no different than that found with "classic" sarcoidosis[16,20–26] nor in cases of

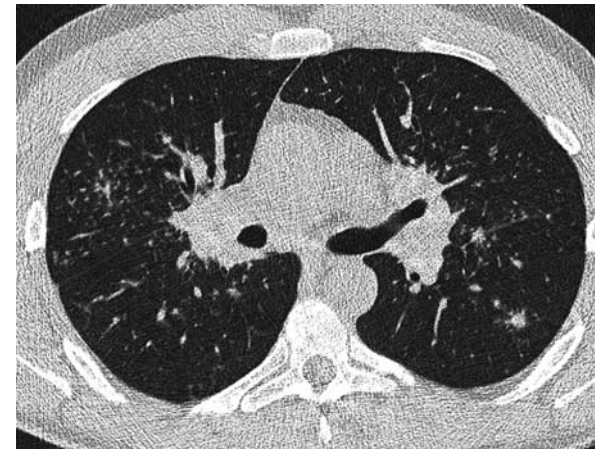

FIGURE 2. Imaging results of a 36-year-old man with WTC-related sarcoidosis. Axial HRCT image showing typical bilateral perilymphatic nodules in the perihilar regions. PFTs were normal.

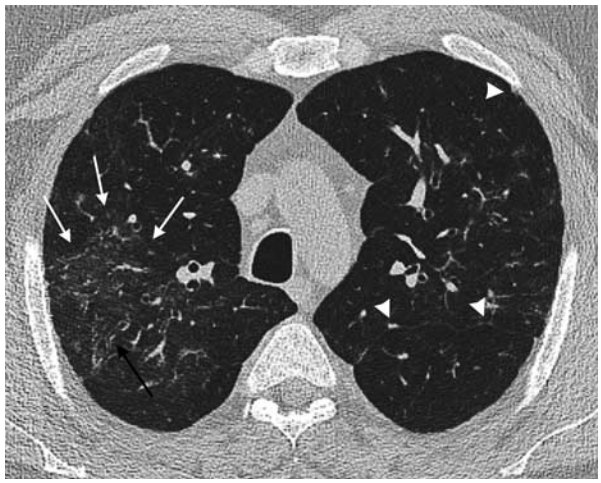

FIGURE 3. Imaging results of a 49-year-old man with WTC-related sarcoidosis. Axial HRCT image demonstrating patchy asymmetric ground-glass attenuation (white arrows) and mild traction bronchiectasis (black arrow). A few small subpleural and perifissural nodules are present (arrowheads). PFTs were normal.

sarcoid-like granulomatous disease previously reported in association with a wide variety of disparate underlying etiologies.[27–32] This includes bilateral mediastinal and hilar lymphadenopathy (Fig. 1) and mid to upper lung zone parenchymal disease including perilymphatic nodules (Fig. 2), patchy ground-glass attenuation (Fig. 3), and coalescent opacities (Fig. 4). Atypical findings were also present, in a similar frequency seen in classic sarcoidosis. Basilar predominant disease (Fig. 7), for example, was present in 13%, consistent with a previous report by Matsui et al[33] who found only 9 (8%) cases of basilar, predominant disease in a review of 119 cases of classic sarcoidosis over a 13-year period. Parenchymal cavitation (Fig. 6) was identified in only 1 case, again consistent with prior reports in

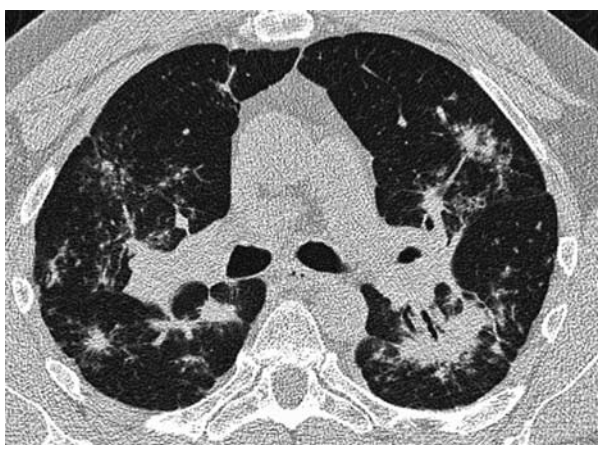

FIGURE 4. Imaging results of a 52-year-old man with WTC-related sarcoidosis. HRCT image demonstrating perilymphatic nodules with multifocal areas of predominantly perihilar coalescence, most pronounced within the superior segment of the left lower lobe. Only 1 patient had coalescent opacities to this extent (51% to 75% lung involvement). PFTs were normal.

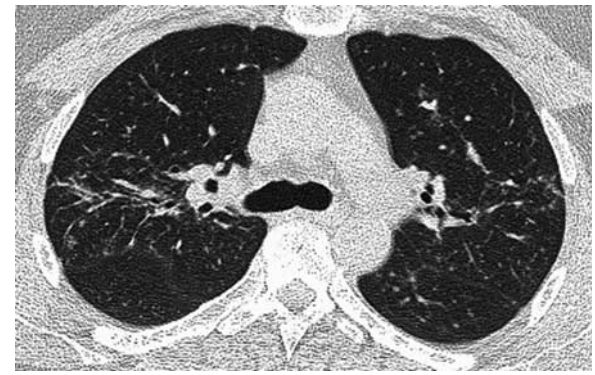

FIGURE 5. Imaging results of a 49-year-old man with WTC-related sarcoidosis. HRCT image demonstrating mild perihilar reticular opacities, right greater than left. PFTs were normal.

unexposed individuals, in which cavitary sarcoidosis proves to be exceedingly rare with a reported frequency of $<1\%$.[21]

Although CT findings in this study mimic those seen in classic sarcoidosis, it is important to emphasize that in these patients with WTC-related sarcoidosis the extent and severity of pulmonary disease on imaging proved remarkably mild. In only a handful of cases were changes including ground-glass attenuation, coalescent nodules, and reticulation present with $>50\%$ lung involvement. Especially notable is the minimal extent of reticulation, complete absence of honeycombing, and absence of any restrictive defect or decreased DLCO on PFTs for all cases.

No patterns of disease on CT were predictive of PFT findings in this population. Even expiratory mosaic attenuation showed poor correlation with obstructive physiology. Of note, reported patterns of PFT abnormality in sarcoidosis are highly variable across studies, with OAD ranging between 4% and 63%, restrictive lung disease between 6% and 100%, and mixed obstructive-restrictive disease between 2% and 19%.[34] The wide range of reported abnormalities likely stems from the clinical heterogeneity of sarcoidosis in different studied populations, inclusion of patients with various stages of disease in separate studies, and different criteria for defining ventilatory defects. Similarly, mosaic attenuation on expiratory CT has a variable reported frequency in sarcoidosis.[22,35] Differentiation of functional versus physiological mosaic attenuation proves challenging, as expiratory mosaic attenuation is also a recognized finding in healthy subjects with normal spirometry.[36,37] Prior radiologic studies have, however, demonstrated positive correlations of various CT patterns with physiological PFT impairments in sarcoidosis.[20,22] Interestingly, Hansell et al[22] found that a reticular pattern, rather than expiratory mosaic attenuation, was the major determinant of airflow obstruction on PFTs in their analysis of 45 patients with sarcoidosis. Only 3 (7%) of the patients in our study population, however, had a reticular pattern, compared with 37 of 45 (82%) in the cohort evaluated by Hansell and colleagues.

Although correlations between morphologic airway changes on CT and airflow obstruction have been reported, in up to 47% of cases in one series,[20] correlation with indices of airflow obstruction were only identified in patients with extensive and diffuse airway distortion. Only 2 of 46 patients in the present study had evidence of both diffuse and severe

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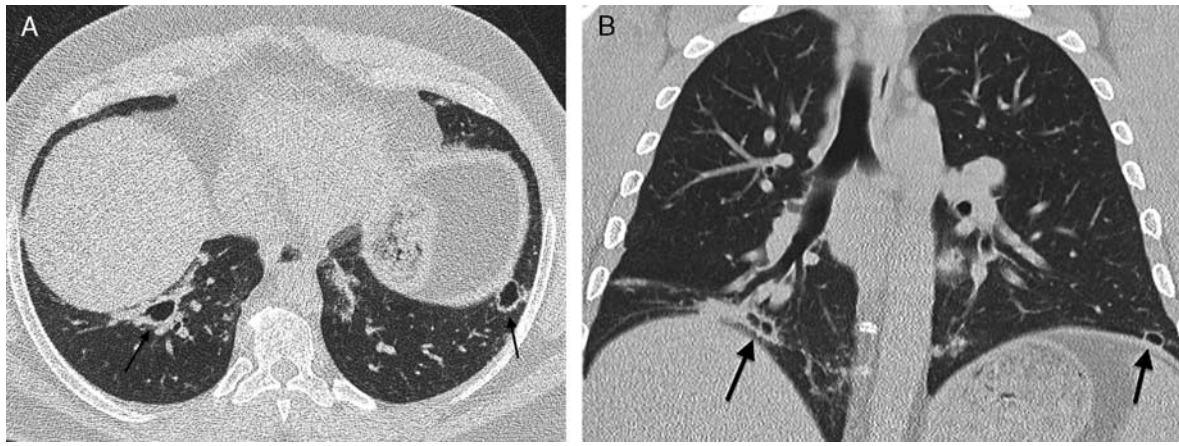

FIGURE 6. Imaging results of a 39-year-old man with WTC-related sarcoidosis. A, Axial 1 mm HRCT image demonstrating small cavities at both lung bases (black arrows). B, Coronal 5 mm CT image demonstrating small cavities at both lung bases (black arrows), in a patient with atypical basilar disease distribution. PFTs demonstrated obstructive physiology.

airway narrowing. In fact, correlation between CT and bronchoscopic findings are limited as mucosal changes are only directly recognized bronchoscopically. This has led to the suggestion that questionable airway morphologic abnormalities on CT require bronchoscopic correlation.[36] Correlations between CT findings and physiological abnormalities are further limited by potential false-positive findings previously reported in up to 15% of cases.[22,38]

Although CT findings in this cohort are comparable to those with classic sarcoidosis, this should not be interpreted as evidence for or against WTC-related sarcoidosis in exposed individuals being a unique granulomatous disease that differs from sarcoidosis in patients without occupational or environmental exposures.[39–41] In this regard it is important to emphasize that, to date, sarcoid-like reactions indistinguishable from generic sarcoidosis have been reported to occur in a wide variety of clinical settings including in association with underlying malignancies, such as colon cancer and melanoma, among others,[29,31] following induction chemotherapy, monoclonal and antiviral antibody therapy,[27,28,30,32] as well as a variety of underlying infections, including nontuberculuous infections.[42]

Our study of CT findings in FDNY rescue/recovery workers with WTC-related sarcoidosis was a clinical study and therefore not without its limitations. Patients were only evaluated with CT when they had either symptoms or reported abnormalities on annual screening chest radiographs; we acknowledge that patients with subclinical disease or radiographically occult disease may not have been included. Air trapping was based on CT images obtained at maximal inspiratory and expiratory effort, but without physiological confirmation that the patients were actually at TLC and RV when these images were obtained. Furthermore, air-trapping was based on visual impressions by 2

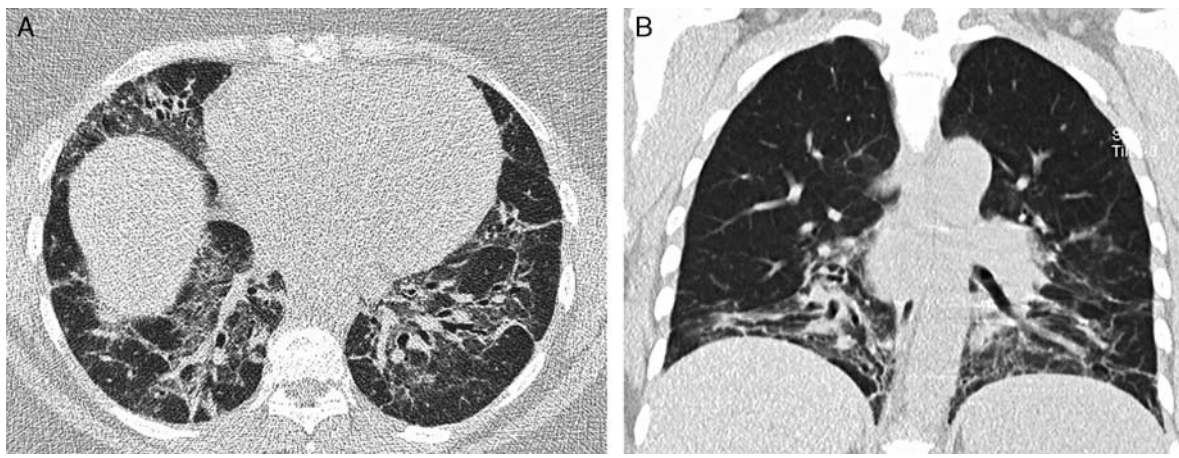

FIGURE 7. Imaging results of a 52-year-old woman with WTC-related sarcoidosis. A, Axial HRCT image demonstrating ground-glass and band-like opacities with traction bronchiectasis and atypical basilar distribution. B, Coronal 5 mm image demonstrating ground-glass and band-like opacities with traction bronchiectasis and atypical basilar distribution. Note complete sparing of the upper lungs. The patient also had symmetric mediastinal and hilar lymphadenopathy, and joint and cutaneous manifestations of sarcoidosis. Diagnosis confirmed by transbronchial biopsies and later by skin biopsy. PFTs were normal.

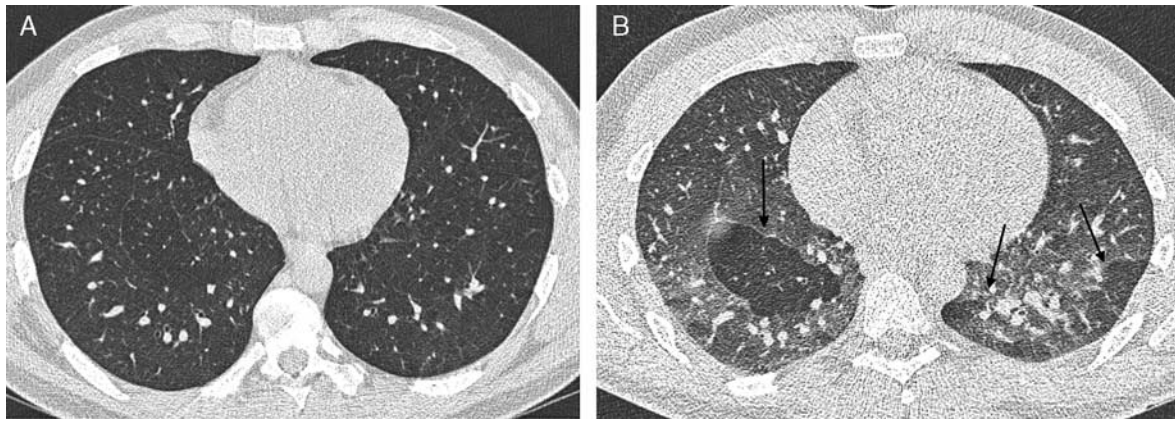

FIGURE 8. Imaging results of a 36-year-old man with WTC-related sarcoidosis. A, Inspiratory HRCT image through the bases demonstrating uniform lung attenuation. B, Expiratory HRCT image at the same level, demonstrating mosaic attenuation in the lower lobes. Opacity within the normal lung has increased on expiration, whereas geographic areas of low attenuation (black arrows) reflect regional air-trapping. PFTs, however, showed no evidence for OAD.

experienced chest CT radiologists, rather than from computer algorithm measurements, as automated quantitative measurements of air-trapping would have required paired volumetric inspiratory and expiratory CT acquisitions.

In conclusion, the majority of cases of WTC-related sarcoidosis, like other etiologies of sarcoid-like reactions, demonstrate typical appearances of classic sarcoidosis on CT imaging. This includes bilateral symmetric hilar and mediastinal lymphadenopathy and mid to upper lung perilymphatic nodules. Parenchymal disease by all patterns was overwhelmingly mild in extent when scored by percentage of lung involvement. The lack of correlation between CT findings and physiological measures likely in part reflects the mild nature of pulmonary disease in most of our cases and suggests that there may be a complimentary role for both modalities in following mild disease. These cases also focus attention on the need for awareness that a pattern of sarcoid-like changes in the thorax may in fact reflect a nonspecific granulomatous response to a number of underlying causes.

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