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Refractory Sarcoid Arthritis in World Trade Center- Exposed New York City Firefighters: a Case Series

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Abstract

Objective—To describe cases of sarcoid arthritis in firefighters from the Fire Department of the City of New York (FDNY) who worked at the World Trade Center (WTC) site.

Methods—All WTC-exposed FDNY firefighters with sarcoidosis and related chronic inflammatory arthritis (n=11) are followed jointly by the FDNY-WTC Health Program and the Rheumatology Division at the Hospital for Special Surgery (HSS). Diagnoses of sarcoidosis were based on clinical, radiographic and pathological criteria. Patient characteristics, WTC-exposure information, smoking status, date of diagnosis and pulmonary findings were obtained from FDNY-WTC database. Joint manifestations (symptoms and duration, distribution of joints involved), radiographic findings, treatment responses were obtained from chart review.

Results—Nine of 60 FDNY firefighters who developed sarcoidosis since 9/11/2001 presented with polyarticular arthritis. Two others diagnosed pre-9/11/2001 developed sarcoid arthritis post-WTC-exposure. All 11 were never cigarette smokers and all performed rescue/recovery at the WTC-site within 3 days of the attacks. All had biopsy-proven pulmonary sarcoidosis and all required additional disease modifying anti-rheumatic drugs (DMARDs) for adequate control (stepwise progression from hydroxychloroquine to methotrexate to anti-TNFα agents) of their joint manifestations.

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Conclusion—Chronic inflammatory polyarthritis appears to be an important manifestation of sarcoidosis in FDNY firefighters with sarcoidosis and WTC-exposure. Their arthritis is chronic, and unlike arthritis in non-WTC-exposed sarcoid patients, inadequately responsive to conventional oral DMARDs, often requiring anti-TNFα agents. Further studies are needed to determine the generalizability of these findings to other groups with varying levels of WTC-exposure or with other occupational/environmental exposures.

Keywords

environmental factors; sarcoidosis; polyarthritis; World Trade Center; firefighters

Introduction

Sarcoidosis is a multi-system disease characterized by non-caseating granulomatous inflammation, which can involve almost any organ system, although the organs most commonly involved include lungs, skin and eyes. Acute arthralgia or inflammatory arthritis occurs in 25–40% of patients and is typically self-limited, presenting as Lofgren's syndrome – arthritis, hilar/mediastinal lymphadenopathy and erythema nodosum. Treatment response is usually excellent, requiring only short-term use of corticosteroids, hydroxychloroquine and/or NSAIDs.[1,2] Chronic sarcoid arthritis, however, is rare, occurring in only 1–4% of patients and may require long-term therapy.[2]

The etiology of sarcoidosis remains unknown, although several studies suggest that environmental or occupational exposure may trigger disease in genetically predisposed individuals. We previously reported a high pre-9/11/2001 point prevalence of sarcoidosis in firefighters from the Fire Department of the City of New York (FDNY) compared with the point prevalence in FDNY Emergency Medical Services (EMS) pre-hospital healthcare workers.[3] More recently, we reported that the prevalence of sarcoidosis among FDNY firefighters further increased after participation in the rescue/recovery effort at the World Trade Center (WTC) site.[4] FDNY firefighters were among the groups of first responders most heavily exposed to the massive amounts of particulate matter and combustion products that the collapse released into the air of lower Manhattan and the first group in which "WTC-Cough Syndrome" (an aero-digestive syndrome consisting of chronic rhinosinusitis, bronchitis, asthma and acid-reflux) was described.[5]

We now describe 11 WTC-exposed FDNY firefighters with multi-system sarcoidosis, chronic inflammatory arthritis as the predominant clinical manifestation and unique treatment requirements. Our report suggests a role for occupational/environmental exposure to the WTC disaster in the pathogenesis of chronic sarcoid arthritis and aims to promote hypothesis-driven research in a field with long term public health implications.

Patients and Methods

The FDNY-WTC Health Program (FDNY-WTCHP) schedules monitoring evaluations of the active and retired workforce approximately every 12–18 months and provides separate visits for treatment, as required. Monitoring evaluations include self-administered questionnaires, spirometry, chest imaging, bloods (chemistries, calcium, liver and kidney

function tests, lipid profile, cell blood counts), urinalysis and physician examinations. Treatment evaluations occur either by physician referral or self-referral. FDNY physicians refer firefighters to physicians outside of the FDNY-WTCHP for specialty care, when indicated.

All FDNY WTC-exposed firefighters with sarcoidosis and associated chronic inflammatory arthritis (n=11) are followed jointly by the FDNY-WTCHP and the Rheumatology Division at the Hospital for Special Surgery (HSS). In all cases, conditions that mimic sarcoidosis, (e.g., granulomatous infections, malignancies) were excluded on the basis of tissue biopsy. Patients had regular follow-up appointments at the FDNY-WTCHP and HSS.

Demographic information, active or retired work status and service (firefighting or EMS) came from the FDNY employee database. Questionnaire data were used to describe WTC-exposure and smoking status prior to the diagnosis of sarcoidosis. Data about disease manifestations (i.e., symptoms and symptom duration, distribution of joints involved, diagnostic tests, radiographic staging[6] and treatment responses) were obtained from HSS and FDNY-WTCHP chart review.

Following a step-wise escalation algorithm, patients were treated with disease modifying anti-rheumatic drugs (DMARDs) to achieve adequate disease control.[2] Response was based on decreased swelling and decreased painful stiffness along with improved exercise tolerance. Using the Visual Analog Scale for Pain (VASP)[7] and the Disease Activity Score for Rheumatoid Arthritis (DASRA),[8] albeit not validated for sarcoidosis. We defined “response” as ≥50% improvement on tender and swollen joint counts, “partial response” was ≥20% but <50% improvement and no response was <20% improvement.

Descriptive analyses including median time and interquartile range (IQR) from WTC exposure to diagnosis, median age (and IQR) at diagnosis, etc. were performed using SAS version 9.4. The study was approved by the institutional review board (IRB) at Montefiore Medical Center (the IRB for the FDNY-WTCHP) and at HSS.

Results

As part of the FDNY-WTCHP, the Bureau of Health Services monitors the health of 13,468 firefighters who worked at the WTC-site. Between 9/11/2001 and 12/31/2013, 60 developed sarcoidosis, 9 (15%) with polyarticular arthritis as part of their clinical presentation. For the 9 presenting with sarcoidosis and polyarticular arthritis, the average time from WTC-exposure to diagnosis was 7.3 years, 1.8 years longer than the time from exposure to diagnosis in the 51 sarcoid patients without polyarticular arthritis (difference not significant, p=0.14). Two others were diagnosed with sarcoidosis pre-9/11/2001 and developed sarcoid arthritis after WTC-exposure.

Patient characteristics are shown in Table 1. All 11 arrived at the WTC-site within the first 3 days after the attack and collapse of the WTC towers, with 7 arriving on day one. All were never cigarette smokers. The median age at diagnosis of sarcoid arthritis was 44 years (IQR= 37.9–47.4) and the median years of FDNY firefighting (hire to diagnosis of sarcoid arthritis or retirement, whichever occurred first) was 15.7 years (IQR= 11.3–17.8).

Sarcoid Diagnosis Characteristics

All 11 patients had biopsy-proven sarcoidosis, 9 by transbronchial or mediastinal biopsy, 1 by both liver and bone biopsies and 1 by Kveim testing. All biopsy specimens were negative for tuberculosis and fungal diseases. All patients had a negative PPD and/or negative Quantiferon serum test for tuberculosis.

Based on chest radiographs, 3 patients presented with stage I, 7 with stage II and 1 with stage IV (cavitary) pulmonary sarcoidosis. In all cases, pre-employment and pre-WTC chest radiographs showed no evidence of sarcoidosis. Ten patients had normal pulmonary function tests (≥80% predicted for all of the following: total lung capacity, forced vital capacity, forced expiratory volume at 1-second and diffusing capacity corrected for alveolar ventilation) while one had mild restrictive pulmonary function (low total lung capacity with normal diffusing capacity corrected for alveolar ventilation). Chest imaging and pulmonary function (adjusted for aging), remained relatively constant throughout follow-up, even during sarcoid arthritis flares, and did not in itself require pharmacologic treatment.

Articular Manifestations

Polyarticular arthritis was part of the initial presentation in all 9 patients who developed sarcoidosis post-9/11/2001. Three of 9 had Lofgren's syndrome, but only 1 presented with arthritis. In the 2 patients with sarcoidosis diagnosed prior to 9/11/2001, polyarticular arthritis occurred after WTC-exposure (4.9 and 10.2 years after initial diagnosis; 3.9 and 4.8 years after WTC-exposure, respectively,) and presented without evidence of disease progression in other organs.

In all 11 cases, polyarthritis was symmetrical, involving swelling and painful stiffness of the small joints in 10 patients (9 involving ankles; 7 involving wrists) and 5 with both small and large joint involvement (Table 1). On exam, no patient had dactylitis or clinically significant joint effusions. In these patients, plain radiographs of symptomatic small joints (hands, wrists, ankles and feet) did not reveal any joint erosions or bone lesions. In one patient, hands x-rays showed the punched out bony lesions typical of sarcoid. In another, x-rays of the hands and wrists were normal, but MRI (obtained for severe pain) revealed erosion in the wrist. One patient had only large joint involvement (bilateral, right greater than left, hip pain). No axial joints were involved. Bone radiographs were not available for this patient but CT and MRI imaging (obtained for severe pain and stiffness) revealed infiltrating bone lesions at the right iliac crest, superior pubic ramus, superior part of the acetabulum and distal shaft of the right femur that on biopsy was positive for culture negative, non-caseating granulomas.

Serum Biomarkers

Patients were tested for serum markers of autoimmune diseases. Four of 10 tested had elevated angiotensin converting enzyme levels; on initial evaluation 9 of 10 had normal sedimentation rates; only 1 of 9 had an elevated C-reactive protein. Anti-cyclic citrullinated peptide (CCP) antibody assay was negative in all 11 patients and rheumatoid factor (RF) was negative in 10 and low positive in 1.

Treatment

Following a step-wise escalation algorithm, patients were treated with disease modifying anti-rheumatic drugs (DMARDs) to achieve adequate disease control of articular symptoms[2]; none of these patients had pulmonary or other organ disease that merited treatment (Table 1). Response was based on decreased swelling and decreased painful stiffness along with improved exercise tolerance as quantified by the VASP[7] and DASRA.[8] Ten were initially treated with hydroxychloroquine, for at least 3 to 4 months, and 8 of the 10 also received corticosteroids at the same time. One patient responded to hydroxychloroquine (corticosteroids eventually tapered to zero), 2 had partial response and 8 had no response, as previously defined. In all 3 patients with Lofgren's syndrome, erythema nodosum did not predict response to therapy with hydroxychloroquine and corticosteroids. Methotrexate was used in 10 patients – 2 responded well, 3 showed partial response and 6 showed no response after 3 to 4 months of therapy. Anti-TNFα agents were eventually started in 8 patients (adalimumab n=5; infliximab n=2; and etanercept n=1) who failed to respond after sequential treatment with hydroxychloroquine for 3 months and then methotrexate for 3 months. In all but 1 case, oral DMARDs were discontinued within 2–3 months of initiating biologic therapy. All 8 patients responded (most >70% improvement) to anti-TNFα agents without complications, although 1 patient discontinued adalimumab despite achieving symptom improvement due to concerns about immunosuppression. All 7 patients have been maintained on anti-TNFα agents for at least 1 year, with continued sustained benefit.

Discussion

Chronic polyarthritis, an important clinical manifestation of sarcoidosis, occurred in 9 of 60 FDNY firefighters who developed post-9/11/2001 sarcoidosis and in 2 additional cases diagnosed pre-9/11/2001 following WTC-exposure. Presentation was symmetrical involving the ankles in all but one case, and was not limited to the ankles, also involving other small joints in all cases and large joints in half of the cases. Radiographic evidence of "punched-out" bone lesions typical of sarcoidosis involvement was evident in 2 of the 11 patients and atypical erosions in one.[9,10] Although we cannot rule out seronegative rheumatoid arthritis with complete certainty, in all 11 cases sarcoidosis was biopsy proven, none had significant elevations in CCP or RF and all lacked the typical erosions of rheumatoid arthritis.

Contrary to previous reports of sarcoid arthritis in non-WTC-exposed patients, we found sarcoid arthritis after WTC-exposure to be chronic [2] and of the 3 cases with Lofgren's syndrome only 1 presented with arthritis and erythema nodosum, which did not predict a favorable outcome with regard to arthritis resolution.[1, 2, 9] Cases with or without Lofgren's syndrome were minimally or nonresponsive to standard therapies such as NSAIDs, hydroxychloroquine, corticosteroids and/or methotrexate.[2] In most cases, adequate control of arthritis required the use of anti-TNFα agents. Furthermore, and of great concern in our patients due to their WTC inhalation exposure, was whether progressive or severe pulmonary sarcoidosis would occur. The literature is mixed on this subject,[2, 10] but in our 11 patients this did not occur, even during arthritis flares.

FDNY firefighters were among the most heavily exposed WTC-rescue/recovery workers because of their early arrival at the disaster site and their prolonged work effort, lasting through July 2002. Before 9/11/2001, previously published data describing a higher incidence of sarcoidosis among firefighters suggested a role for environmental and occupational exposures in the pathogenesis of this disease. [2] After 9/11/2001, sarcoidosis incidence in the same population increased further.[3] Despite concerns about ascertainment bias due to post-exposure screening studies, this did not appear to be a major factor, as FDNY firefighters have regularly received pre-employment and post-employment medical exams which include chest radiographs. The frequency of screening exams with chest radiographs did increase in the first years after 9/11/2001, but even after adjusting for this, incidence rates remained elevated.[3] Two other cohort studies in WTC-exposed non-firefighting groups also reported a higher than expected incidence of sarcoidosis..[11,12] In our original report, extra-pulmonary manifestations of sarcoidosis in WTC firefighters included splenomegaly, renal vein thrombosis, pelvic and abdominal lymphadenopathy, while bone and joint involvement was noted in only one patient. [3] Since our original report, Bowers et al described two WTC-exposed NYC Police Officers with sarcoid arthritis.[13]

Studies have suggested a relationship between the type of environmental exposure and its clinical features, either pulmonary alone or systemic. In a cross-sectional study, pulmonary-only disease was associated with wood burning and dust exposures (metal, organic, wood) while systemic disease was associated with chemical (insecticides and pesticides) exposures.[14] The WTC collapse and the resulting environmental fallout provided exposure to smoke, dust and chemicals and could thus explain both the increased incidence of pulmonary sarcoidosis and its systemic manifestation as sarcoid arthritis. The attacks on 9/11/2001 that led to the collapse of the WTC towers resulted in an unprecedented release of particulate matter, combustion byproducts and toxic substances. Over 400 compounds including soot, heavy metals, volatile organic compounds, pulverized cement, glass fibers, asbestos, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated dibenzodioxins, polychlorinated dibenzofurans, pesticides, and other hydrocarbons have been identified in airborne and settled WTC dust samples.[15,16] WTC dust is pro-inflammatory in tissue culture,[17] which would explain the increased incidence of respiratory disease[2] and its systemic manifestations. Although the connection between inhaled WTC dust particulates and joint disease is speculative, possible immune mechanisms include 1) adjuvant response, 2) autoantibody formation (similar to citrullinization of peptides following cigarette smoking) and/or 3) generation of cytokines leading to joint inflammation.

In conclusion, inflammatory polyarthritis is an important manifestation of sarcoidosis in WTC-exposed firefighters occurring at higher than expected rates. The arthritis is chronic, inadequately responsive to conventional oral DMARDs (even when presenting as Lofgren's syndrome) and in most cases required long-term treatment with anti-TNFα agents. Further studies are needed to determine the generalizability of these findings to other groups with varying levels of WTC-exposure or with non-WTC occupational/environmental exposures. This report demonstrates the need for continued health surveillance of WTC-exposed workers to fully characterize the deleterious systemic health effects following inhalation exposures.

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Significance and Innovation

- The environmental exposure to particulate matter and gases released with the collapse of the World Trade Center on 9/11/2001 provides a unique opportunity to examine the induction of sarcoid arthritis and its unique features in a subset of highly exposed NYC-firefighters.
- Post 9/11 sarcoid arthritis is a chronic, symmetrical non-erosive polyarthritis, which tends to be resistant to traditional treatments.
- These patients had only partial response to oral DMARDs, but responded well to biologic anti-TNF medications.

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Table 1

Patient Characteristics:

PATIENT	Age	FDNY Firefighting (years) to diagnosis of sarcoid arthritis	Time from WTC exposure to diagnosis of sarcoid arthritis (years)	Time from sarcoid diagnosis (pulmonary) to development of arthritis (years)	Pulmonary Involvement: Stage/PFT	Joint Involvement	Other Extra-Pulmonary Involvement	Treatment	Initial Arrival Time at WTC site
1.	49.2	17.8	10.9	0	II/Normal	Hands And Toes	None	HCQ no response; MTX no response; adalimumab effective	Day 1 Afternoon
2.	37.9	14	6.3	1.2	I/Normal	Wrists, Hands, Ankles	Lofgren's Syn, Constitutional symptoms	HCQ no response; MTX no response; adalimumab partial response; infliximab effective	Day 2
3.	39.6	11.3	10.6	0.1	II/Restrictive	Wrists, Hands, Ankles, Feet	Constitutional symptoms, Liver	HCQ no response; MTX partial response, adalimumab effective	Day 1 Afternoon
4.	31.2	5.8	5.5	0	I/Normal	Hands, Ankles, Feet, Back	Lofgren's Syn, Constitutional symptoms	HCQ partial response; MTX effective	Day 1 Afternoon
5.	45.4	12.1	7.7	0	II/Normal	Elbows, Wrists, Knees, Ankles	Constitutional symptoms	HCQ no response; MTX no response; etanercept effective	Day 2
6.	42.7	16.7	1.9	1.5	I/Normal	Shoulders, Elbows, Wrists, Ankles, Back, Hips	Lofgren's Syn, Constitutional symptoms	HCQ no response; MTX no response;	Day 1 Morning

PATIENT	Age	FDNY Firefighting (years) to diagnosis of sarcoid arthritis	Time from WTC exposure to diagnosis of sarcoid arthritis (years)	Time from sarcoid diagnosis (pulmonary) to development of arthritis (years)	Pulmonary Involvement: Stage/PFT	Joint Involvement	Other Extra-Pulmonary Involvement	Treatment	Initial Arri Time at W site
								adalimumab + adalimumab + adalimumab +	HCQ effectiv HCQ effectiv HCQ effe
7.	37.9	10.5	5.9	0	IV/Normal	Shoulders, Elbows, Wrists, Knees, Ankles	Cardiac, Uveitis, Constitutional symptoms	HCQ no response; MTX partial response; adalimumab no response; infliximab effective	Day 1 Morn
8	44	15.7	9.5	0	II/Normal	Wrists, Hands, Ankles, Feet	Constitutional symptoms	HCQ no response; MTX partial response; adalimumab effective	Day 2
9	48.6	21.7	10.6	1.2	II/Normal	Elbows, Wrists, Hands, Knees, Ankles	Small fiber neuropathy	HCQ no response; MTX no response; adalimumab effective	Day 1 Aftern
10	47.4	17.1	3.9	Pre-9/11/01 diagnosis 10.2	II/Normal	Hips And Back	Liver	HCQ + high dose steroids for 1.5 years; now off all medications with minimal pain on exertion	Day 3
11	47.2	22	4.8	Pre-9/11/01 diagnosis 4.9	II/Normal	Hands, Ankles	Unilateral vocal cord paralysis	HCQ partial response; MTX response; off meds with flare	Day 1 Aftern

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PATIENT	Age	FDNY Firefighting (years) to diagnosis of sarcoid arthritis	Time from WTC exposure to diagnosis of sarcoid arthritis (years)	Time from sarcoid diagnosis (pulmonary) to development of arthritis (years)	Pulmonary Involvement: Stage/PFT	Joint Involvement	Other Extra-Pulmonary Involvement	Treatment	Initial Arri Time at W site
								up; restarted HCQ effect	
								up; restarted HCQ effec	
								up; restarted HCQ effec	
								up; restarted HCQ effect	
								up; restarted HCQ effective	

Age = age at diagnosis of sarcoid arthritis. Firefighting years = years from hire to the earlier of date of either diagnosis of sarcoid arthritis (n=10) or date of retirement (n=1). WTC = World Trade Center. Time from diagnosis of sarcoid (pulmonary) to diagnosis of sarcoid arthritis = years from diagnosis of sarcoidosis to diagnosis of sarcoid arthritis (set to 0 if sarcoid arthritis diagnosed at same time). Pulmonary Stage by Chest Imaging: (Stage I = adenopathy; Stage II = adenopathy + parenchymal involvement; Stage III = parenchymal involvement; Stage IV = parenchymal fibrosis or cavities). PFT = Pulmonary function testing including lung volumes, flow rates and diffusion. PFT Normal requires ≥80% predicted for all of the following: Total lung capacity, Forced vital capacity, Forced expiratory volume at 1-second, and Diffusing Capacity corrected for alveolar ventilation. Lofgren's Syndrome = arthritis, hilar/mediastinal lymphadenopathy and erythema nodosum. Constitutional symptoms include any combination of fever, fatigue, night sweats, hot flashes or weight loss, of which fever was the most common. HCQ = Hydroxychloroquine. MTX = Methotrexate