Predictive Biomarkers Of World Trade Center-Related Sarcoid

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RATIONAL: World Trade Center (WTC) particulate matter exposure was associated with an increased incidence of lung disease in Fire Department of New York (FDNY) firefighters, rescue workers, and lower Manhattan residents. FDNY reported increased cases of sarcoid-like granulomatous pulmonary disease (WTC-sarcoid) after 9/11. It is unknown why certain individuals developed WTC-sarcoid, and the natural history of WTC-sarcoid has not been well characterized. Developing biomarkers of WTC-sarcoid diagnosis, progression and response to therapy will improve treatment.
METHODS: Our nested case-cohort study was derived from 801 WTC-exposed FDNY firefighters with normal pre-9/11 lung function who had presented for subspecialty pulmonary evaluation (SPE) for respiratory symptoms after 9/11 and before Mar/2008. We had access to 37 cases with biopsy-proven WTC-sarcoid who had full PFTs and chest CT performed during their SPE. The control group of 171 subjects were derived from the baseline cohort after stratification based on pre-911 forced expiratory volume in 1 second (FEV_1) and BMI. Serum biomarkers obtained within 6 months of 9/11 were available in 7 of the 37 WTC-sarcoid patients and 124 of 171 controls. The serum samples were assayed for chemokines/cytokines by Luminex.
RESULTS: Demographics: Both WTC-sarcoid and control groups had similar WTC exposure, age on 9/11, and years of fire service (data not shown). Sarcoid cases have longer time (months) to SPE (49.4(35-70) vs 34.0(24-55)) and lower BMI(kg/m2) at SPE (29.2(27-32) vs 30(26-30)) than the cohort control (values expressed as Medians (IQR)). Pulmonary Function Test: WTC-sarcoid patients had lower diffusing capacity of carbon monoxide (DLCO) at diagnosis when compared to a representative sub-cohort of WTC dust exposed firefighters, although the DLCO for both groups were in the normal range (Table 1). WTC-Sarcoid cases had similar FEV1, forced vital capacity (FVC), FEV1/VC, functional residual capcity (FRC), methacholine challenge test (MCT) slope and bronchodilator response at time of diagnosis when compared to controls. Serum Biomarkers: Seven WTC-sarcoid patients sera were analyzed and had elevated levels of migration inhibitory factor (MIF) and Eotaxin, and lower levels of interferon (IFN)-gamma, IL-3, IL-4, IL-10, macrophage Inflammatory Proteins (MIP)-1beta, tumor necrosis factor (TNF)-beta and soluble vascular endothelial growth factor receptors (sVEGFRs) when compared to WTC-exposed controls (Table 2).
CONCLUSION: WTC-sarcoid patients had significantly lower DLCO compare to controls. However, this difference was not large enough to be clinically useful for screening. The different biomarker expression pattern in WTC-sarcoid cases versus controls suggests that stored serum could identify a distinct immuno-pathogenic pathway producing WTC-sarcoid.

PFT Result (% predicted)	Sarcoid N=37	Controls N=171	p
FEV_1	92(80-106)	91(80-100)	0.351
FVC	97(84-108)	99(89-107)	0.877
$FEV_1/FVC^{¶}$	78(75-82)	77(73-81)	0.254
TLC	100(88-106)	103(95-108)	0.178
DLCO	104(90-116)	108(101-119)	0.039
Airway Responsiveness			
BD Response*	4(3-8)	6(2-12)	0.213
MCT Slope	0.04(0.02-0.30)	0.05(0.02-0.15)	0.907

Table 1: Pulmonary Function Test. Values Median (IQR)
¶ represented as ratio not % predicted * % change in FEV1

Analyte*	Sarcoid N=7/37	Controls N=124/171	p
MIF	1768 ±1975	827± 1637	0.038
Eotaxin	186± 55	134 ± 62	0.048
IFN-γ	6.81 ±3.22	21.89 ± 45.18	0.001
IL-3	1.25 ± 0.98	2.30± 2.39	0.034
IL-4	1.80 ± 2.57	13 ± 62	0.042
IL-7	6.62 ± 8.41	17± 31	0.022
IL-10	6.10 ± 4.8	17 ± 53	0.042
MIP-1β	33± 24	71 ± 98	0.006
TNF-β	1.00 ± 0.84	11 ± 37	0.005
sVEGFR1	376 ±77	611± 613	0.000
sVEGFR3	1632±995	3336± 4051	0.004

Table 2: Significant WTC-Sarcoid Biomarkers
*Values Expressed as Mean SD

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