Circulating Cytokines in Sarcoidosis

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Background

Sarcoidosis is a systemic granulomatous disease of unknown etiology. The lungs, heart, skin, eyes, liver, and/or nervous system can be affected. While most patients experience resolution of symptoms within a few years of presentation, up to a third have a chronic course of persistent, progressive inflammation. Pulmonary fibrosis and neurosarcoid occur in chronic disease, and both are associated with increased morbidity and mortality. We do not know why some patients with lung involvement develop extensive fibrosis while others do not, although specific immunopathologic features may mediate pulmonary fibrosis. Neurosarcoid tends to be progressive and refractory to treatment. We consider pulmonary fibrosis and neurosarcoid as distinct phenotypes.

The immunopathogenesis of sarcoidosis remains poorly understood. Antigen presenting cells (APCs) present an unknown antigen that is recognized by naïve CD4+ cells, which polarize to a T helper 1 (Th1) phenotype and release a variety of cytokines. Cytokines drive the accumulation and further activation of APCs, which organize to form granulomas. In pulmonary sarcoidosis, many cytokines are up-regulated in lung samples. However, detailed information on circulating cytokines in this systemic condition is lacking.

We evaluate circulating cytokines in sarcoidosis, and assess cytokines in phenotypes anticipated to have distinct immunopathologic features. Confounder effects, correlations among cytokines, and correlations between leukocyte counts and hematopoiesis-associated cytokines are also evaluated.

Methods

Samples and Subjects

IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1β, and TNF-α were measured with Bio-Rad multiplex kits in adults with established sarcoidosis, and in controls matched to age, gender and ancestry. Clinical data and leukocyte differentials (drawn at the time of sample collection) were available for review.

Phenotype definitions

Fibrotic pulmonary: honeycombing and/or traction bronchiectasis on imaging
Non-fibrotic pulmonary: endobronchial and/or non-fibrotic parenchymal imaging abnormalities
Neurosarcoid: positive biopsy and/or MRI findings

Statistical Analysis

The non-parametric data were expressed as medians, and compared using the Mann-Whitney U test. Multi-variate logistic regression evaluated for confounder effects. Spearman's test was used to evaluate correlations among cytokines, and the correlation of cytokines with leukocyte counts. A p-value <0.05 defined statistical significance*.

Table 1 Demographic data

Characteristic	Controls (N = 18)	Sarcoid Subjects (N = 54)	p-value
Age - yr			
Mean	52	50	0.523
Range	37-74	31-75	—
Gender – no. (%)			
Female	13 (72)	40 (74)	1.000
Ancestry – no. (%)			
African American	13 (72)	43 (80)	0.611
European American	5 (27)	10 (10)	
Other	0	1 (2)	
Active Smoking – no. (%)			
Yes	3 (17)	3 (5)	0.100
No	13 (72)	50 (93)	
Unknown	2 (11)	1 (2)	
Neurosarcoid subtype – no.			
CNS	—	5	—
Cranial neuropathy	—	2	
Peripheral neuropathy	—	1	
Immunosuppression* – no. (%)			
Yes	—	27 (50)	—
No	—	21 (39)	
Unknown	—	6 (11)	
Years since diagnosis – no. (%)			
< 2 years	—	2 (4)	—
2-5 years	—	17 (31)	
> 5 years	—	35 (65)	

Figure 1 Median values of cytokines in controls and cases, and by organ phenotype

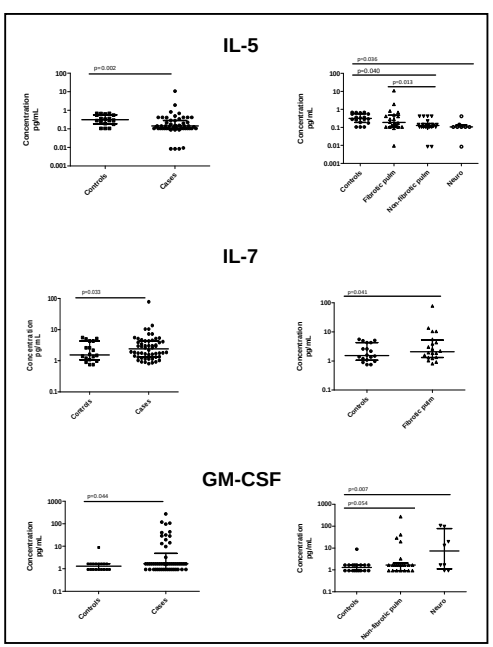

Figure 2 Correlation of cytokines

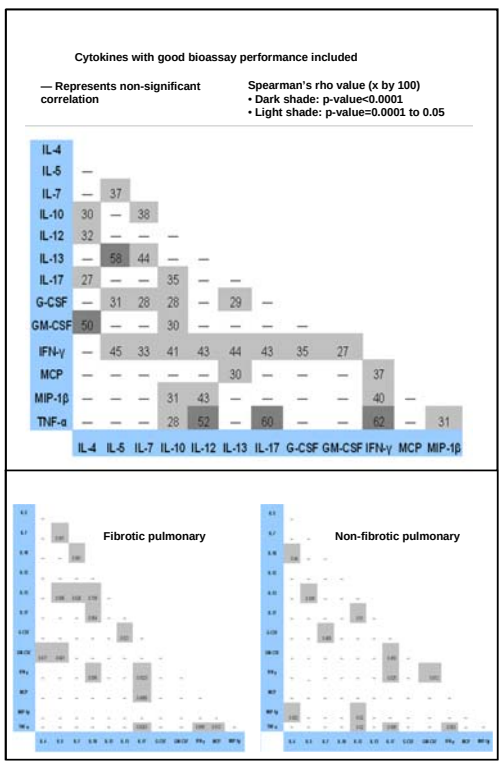

Table 2 Correlation of hematopoietic cytokines and leukocyte counts

	Spearman's rho	p-value
GM-CSF and Monocytes	0.122	0.472
GM-CSF and Granulocytes	-0.031	0.881
IL-7 and Lymphocytes	-0.099	0.566

Conclusions

• IL-5 is *decreased* in sarcoidosis; IL-5 is a T helper 2 cytokine, and low IL-5 in sarcoidosis supports the concept of a Th1 inflammatory process.

•IL-7 is *increased* in sarcoidosis; generally unexplored in sarcoidosis, IL-7 was recently reported to be increased in pulmonary sarcoidosis.

•GM-CSF is *increased* in sarcoidosis; this is similar to findings of increased GM-CSF in lung samples.

•Distinct cytokine patterns exist in fibrotic and non-fibrotic pulmonary disease, and in neurosarcoid.

•Cytokines have a concerted biology, and we detect many correlations among cytokines; however there is no significant change in p-values for IL-5, IL-7 and GM-CSF when cytokines were included in regression analysis (data not shown).

• Increased GM-CSF and IL-7 do not correlate with leukocyte counts. Gender, ancestry, smoking and immuno-suppression are not confounders (data not shown).

The roles of circulating IL-5, IL-7 and GM-CSF in sarcoidosis merit further exploration. Evaluating alterations in immunology by phenotype will contribute to our understanding of the mechanisms of clinical diversity.

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References: available upon request

*** P-value**: significance of p-value<0.05 used in initial uni-variate anlayses; an adjusted p-value of <0.005 to account for multiple comparisons used in regression analysis