Objectives: This cohort study aims to describe the prevalence and features of systemic phenotype of pericarditis characterized by pleurapulmonary involvement, fever, and elevation of C-reactive protein (CRP), comparing this phenotype with other forms of pericarditis.

Methods: All patients in our center were enrolled in a prospectively maintained registry from 2019 to 2022. 412 patients with idiopathic recurrent pericarditis were analyzed. “Systemic” subset was defined as the presence of all of the following criteria: fever > 38 °C, CRP higher than 2 times normal values, pleural effusion detected with any imaging techniques. The absence of any of the 3 criteria was defined as “isolated” subset.

Results: We found that 211 (51.2%) of 412 patients presented the systemic subset and the variables significantly associated with this subset in univariate analysis (p<0.001) were: higher mean age of onset 45.5 (±SD 16.4) years, higher mean CRP values 128.8 (95% CI 117.8-139.8) vs 49.9 (95% CI 41.5-58.3) mg/L, higher proportion of pericardici enosis 40 (19%) vs 3 (1.5%), higher mean leukocyte count 13143.3 (95% CI 12790.4-13496.2) vs 9910.3 (95% CI 9556.2-10264.4)/mm³, higher mean neutrophils number 10402.5 (95% CI 10082.1-10723) vs 6779.8 (95% CI 6505.2-7054.4)/mm³ and lower mean lymphocyte count 1693.9 (95% CI 1621.9-1765.8) vs 2079.3 (95% CI 1979-2179.6)/mm³. As results the neutrophil-to-lymphocyte ratio was higher in systemic phenotype: 6.6 (95% CI 6.2-6.9) vs 3.4 (95% CI 3.3-3.6). Anti-IL1 therapy was started more frequently in the systemic subgroup (55/211, 26%) than in the isolated subset (15/201, 7.5%) (p < 0.001). On multivariate analysis neutrophil count and lymphopenia, were statistically associated with the systemic subset (p < 0.001).

Conclusion: These results demonstrate the clinical relevance of the systemic phenotype in a referral center and confirm its analogy with the autoinflammatory diseases, suggesting a pivotal role of IL1 in the genesis of this subset.


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SOLVING SARCOIDOSIS: A TRANSCRIPTOME-BASED META-ANALYSIS OF CLINICAL SARCOIDOSIS STUDIES ILLUSTRATES SHARED PATHOPHYSIOLOGY, EXAMINES MEDiators OF FIBROSIS, IDENTIFIES CANDIDATE BIOMARKERS AND SUGGESTS A THERAPEUTIC MECHANISM OF JAK INHIBITION

Keywords: -Omics, Biomarkers, Rare/orphan diseases

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Background: Sarcoidosis is a systemic, non-caseating granulomatous disease driven by a dysregulated immune response to environmental antigens. Disease manifestations are driven by both active inflammation and resultant fibrosis in a wide variety of tissues, but the dynamics and mediators of these two states are not well understood. Diagnosis relies on imaging and biopsy and treatment typically includes steroids. JAK inhibitors have been utilized as steroid-sparing therapies for cutaneous and pulmonary sarcoidosis, however the mechanism is unclear.

Objectives: We performed a meta-analysis of 20 transcriptome studies on clinical sarcoidosis to explore perturbed pathways, examine mediators of fibrosis, prioritize candidate biomarkers, and study the JAK/STAT pathway.

Methods: We searched publicly available data repositories for clinical sarcoidosis datasets with healthy controls and at least 3 biological replicates evaluated with transcriptome analysis and found 20 studies (14 microarray and 6 RNAseq), comprising 316 sarcoidosis patients and 383 healthy controls. The majority of samples came from peripheral blood; tissue-based samples included lung, skin, anterior orbit, lacrimal gland and lymph nodes. We performed differential expression on each of the 20 studies independently with Limma (microarray) and DESeq2 (RNAseq). Results were merged for the 17,705 genes that were evaluated by at least 9 of the studies. For microarray studies, data from the probe with lowest adjusted p-value and largest absolute fold change (FC) was selected. Genes were selected for pathway enrichment analysis if at least 10 studies identified them as differentially expressed. Candidate biomarkers were genes that were consistently differentially expressed in both tissue and peripheral samples with a fold change magnitude of at least 1.5x. Pathway enrichment analysis was performed with Reactome. We mined our dataset with 232 fibrosis related genes identified by the FibROAD project and the 11 central genes of the JAK/STAT pathway.

Results: We prioritized 2,349 genes that were differentially expressed in the majority of the datasets. Unsupervised clustering of these studies showed a distinct difference between peripheral and tissue sample types. Of the 15 biomarker candidates, some have been associated with sarcoidosis (e.g STAT1, ITGA6, LEP1) and others have been reported in tuberculosis (e.g GBP5, ANKRD22), however the majority have not been associated with either (e.g RHOD, SPTBN1, UBASH3A). Pathway enrichment identified significant perturbation of interferon signaling and antigen presentation which supports two established mechanisms of sarcoid pathophysiology: an abnormal TH1 response and existence of MHC risk alleles. Qualitative exploration of the JAK/STAT pathway (Figure 1) shows a predominant upregulation of the pathway, most strongly in STAT1 and JAK2. We prioritized 25 fibrosis related genes that were significantly differentially expressed in at least 10 of our studies and included STAT1, HBEFG, FOXP1 and JAK2.

Conclusion: This meta-analysis summarizes the current transcriptional landscape of sarcoidosis, including pathophysiology, mediators of fibrosis, biomarkers and therapeutics targeting the JAK/STAT pathway. We hypothesize that JAK2 may be an important therapeutic target for sarcoid by disrupting the JAK/STAT component of an abnormal TH1 response as well as a possible JAK2/STAT1 associated fibrosis mechanism.

Reference: Cited inline.