A128 **B CELL DISTRIBUTION AND ACTIVATION-INDUCED CYTIDINE DEAMINASE EXPRESSION IN RHEUMATOID SYNOVITIS: CLINICAL AND BIO-MOLECULAR CORRELATES**

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Background and objectives Development of functional B cell niches in peripheral tissues has been associated to chronicity and pathologic severity in different human conditions such as kidney allograft rejection and multiple sclerosis. Ex vivo studies in the rheumatoid arthritis (RA)-severe combined immunodeficiency mouse chimera model advocate a role for the synovial B cell compartment in enhancing local immune responses through production of auto-antibodies and by promoting local T cell activation. The aim of this study was to investigate the relationship between the degree of B cell infiltration and activation in the joint and clinico-pathologic variability in patients with RA.

Methods Synovial tissues from 66 RA patients were evaluated by immunohistochemistry (IHC). 25 paired paraffin and RNA samples were used for comparative IHC and quantitative PCR. B cell infiltration was assessed semi-quantitatively (0–3) based on the size and density distribution of CD20 B cell aggregates and through quantitative evaluation of mRNA expression of activation-induced cytidine deaminase (AID), the enzyme required for immunoglobulin affinity maturation and class switching. B cell scores and AID expression levels were correlated to clinical and bio-molecular parameters of immune cell activation, disease activity and bone remodelling.

Results The IHC CD20 B cell score was significantly related to the expression levels of CXCL13 ($p=0.001$) and lymphotoxin β ($p=0.004$). The degree of B cell aggregation tightly

associated to progressive increase in CD3 lymphocyte and CD138 plasma cell infiltration as well as to *in situ* expression of AID ($p=0.0006$), interferon γ ($p=0.02$) and interleukin 2 ($p=0.001$). Despite signs of lymphoid cell activation, no significant variability in local and systemic markers of disease activity was found. Rather, increasing degrees of B cell aggregation and AID transcripts associated to progressive increase in the receptor activator of nuclear factor- κ B ligand/osteoprotegerin (OPG) ratio primarily due to significantly reduced OPG levels ($p<0.001$). Bone morphogenetic protein-2 and -7 showed similar although weaker reductions. At clinical level, the highest degrees of B cell aggregation were associated to increased prevalence of erosive disease independent of disease duration and serum autoantibodies (OR 6.6, 95% CI 1.7 to 26.3, $p=0.007$).

Conclusions The degree of B cell aggregation in RA joints is characterised by a continuous quantitative spectrum associated to pathologic variability. The highest degrees of the spectrum correspond to an immunologically active pattern of synovial inflammation, not strictly related to increased disease activity, but coupled to clinical and molecular signs of unbalanced bone remodelling. Quantitative assessment of AID+ synovial B cell niches might expand our understanding of pathogenic and response-to-treatment heterogeneity in RA.