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**Background:** Immune checkpoint inhibitors (CI) are monoclonal antibodies that block CTLA-4, PD-1 or PD-L1, resulting in cytotoxic T cell activation in the tumor microenvironment. They have revolutionized the management of metastatic cancer but unleash “immune-related adverse events” in >80% of treated patients, including inflammatory arthritis in ~4–6%. CI-associated arthritis (CI-A) often presents as a symmetrical polyarthritis, phenotypically indistinguishable from rheumatoid arthritis (RA), but whether it shares cellular and molecular features of RA has not been determined.

**Objectives:** To compare synovial fluid (SF) T cell populations from CI-A patients to those in RA, phenotypically and functionally.

**Methods:** We immunophenotyped SF mononuclear cells from patients with CI-A caused by anti-PD-(L)1 therapy (n=9), seropositive RA (n=5), and psoriatic arthritis (PsA) (n=5) using a 39-marker mass cytometry (CyTOF) panel. FlowSOM was used to cluster CD4 and CD8 T cells into 15 ‘metaclusters’ based on multidimensional phenotypes. We used Kruskal-Wallis or Mann-Whitney tests to identify significantly altered populations (p<0.05), which we confirmed by biaxial gating. Flow cytometry was used to confirm SF findings in an independent cohort, and to identify cells of interest in peripheral blood. Cytokine staining was performed on sorted T cells populations after CDCD3/CD28 stimulation for 72 hours, followed by 4 hour PMA/ION+BRA/MON restimulation.

**Results:** In CI-A patients, T cells represented 50% of SF mononuclear cells (33% CD4, 40% CD8), followed by monocytes (24%) and NK cells (8%), comparable to RA and PsA. However, FlowSOM analysis revealed expansion of a distinct population of PD-1+ CD38hi CD127- CD8 T cells (CD8 metacircle2) (Fig 1). These cells comprised 30% of CD8+ T cells in CI-A, a 3.4-fold increase over RA/PsA, p=0.0002 (Fig 2). Over 40% of these cells expressed Ki67 in CI-A, suggesting active proliferation. Flow cytometry on SF cells from an independent cohort of CI-A patients (n=5) and RA/PsA comparators (n=9) confirmed our findings. PD-1+ CD38hi CD127- CD8 T cells were also expanded in the blood of CI-A patients, where they represented 4.6% of CD8 T cells, a 2.8-fold increase over RA, p=0.0057. In addition to expressing high levels of PD-1, CD38hi CD127- these CD8 T cells express other immune checkpoint receptors including CD27 and TIGIT. After in vitro stimulation, CD38hi CD127- CD8 T cells produced granzyme B along with TNF and IFN-γ at comparable levels to other CD8 populations, suggesting that they are not functionally exhausted.

**Conclusion:** CFOT analysis of SF T cells in CI-A patients revealed the expansion of a subpopulation of CD4 cells with a similar surface phenotype of PD-1+ CD38hi CD127- (metacircle2, 10% of CD4s in CI-A, a 2.4-fold increase over RA/PsA, p=0.004). In contrast, RA patients had a significantly expanded population of PD-1+ ICOS+ CD4 T peripheral helper (Thp) cells (metacircle5, 30% of CD4s in RA, p=0.006), but these cells were not expanded in CI-A (Fig 3).

**References:**

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**Figure 1.** Mass cytometry CD8+ T cells (tSNE plots) with FlowSOM metaclusters.
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Figure 2. Synovial fluid PD-1+ CD38hi CD127- CD8+ T cells

Figure 3. Synovial fluid CD4+ T peripheral helper cells

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