Background Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer treatment but is associated with a range of immune toxicities. ICI-associated inflammatory arthritis (ICI-IA) is a complication that affects around 5% of patients on ICI therapy. Clinical manifestations mimic those of rheumatoid arthritis or seronegative spondyloarthopathies and often require treatment with glucocorticoids or other immunosuppressive medications. In severe cases, irArthritis results in interruption or discontinuation of ICI therapy and is a significant cause of morbidity. Understanding why ICI-IA develops and rationalizing our approach to its treatment could improve outcomes for this expanding patient cohort.

Methods Comprehensive clinical and demographic data were collected for patients with malignancy, treated with ICI, and subsequently diagnosed with inflammatory arthritis (n=41). Peripheral blood and synovial fluid were collected and profiled when possible. Presentations of ICI-IA included monoarthritis (n=5 total, n=4 profiled), oligoarthritis (n=10 total, n=5 profiled) and polyarthritis (n=26 total, n=7 profiled). Six additional patients with inflammatory arthritis after ICI that were not checkpoint-related were profiled. Samples were analyzed by paired single cell RNA sequencing, surface proteome of 204 protein targets, and T cell receptor (TCR) sequencing.

Results We captured data from 741,883 cells in total following quality-control (559,251 synovial fluid, 264,997 blood) and identified diverse cell populations in synovial fluid, including rare mast cells, AXL+SIGLEC6+ dendritic cells and cycling lymphocytes. Patients presenting with monoarthritis were ANA negative (0/6) with higher abundance of DC1 and DC2 (Dirichlet regression, p=1.1x10^-3 and p=8.1x10^-5), with DC1 having the highest per cell expression of TNF across all samples. Patients presenting with polyarthritis were significantly more likely to be antinuclear antibody positive (15/26, Fisher’s test, p=0.04) with expansions of a macrophage population enriched for interferon response genes (IFI44L, ISG15) and peripheral helper CD4+ T cells (CXCL13, PDCD1) previously described as expanded in seropositive rheumatoid arthritis. TCR repertoire analysis demonstrated clonal expansion of specific CD8 T cell subsets, including shared clones across patients. Gene set enrichment analysis highlighted upregulation of distinct inflammatory pathways with existing biologic drugs in mono- and oligoarthritis presentations versus polyarthritis.

Conclusions These data demonstrate that ICI-IA is heterogeneous both in terms of clinical presentation and at the cellular and transcriptional level. It is likely that patients will benefit from better targeting of treatments that can simultaneously control arthritis and preserve anti-tumor efficacy and our data support new strategies for developing personalized medicine approaches for this patient population.

REFERENCES

Ethics Approval Patients involved in this study were consented to Dana-Farber Cancer Institute/Harvard Cancer Center collection protocols #11-181 and #13-416.