Background The relationship between severe immune-related adverse events (irAE) and anti-tumor efficacy resulting from the use of immune checkpoint inhibitors (ICI) is poorly understood. ICI-related myocarditis (irMyocarditis) is among the most serious toxicities and is fatal in 25-50% of cases. Reports of shared T-cell clones in irAE and tumor suggest that common antigens or epitopes may couple anti-tumor immunity and irAE biology. To test this hypothesis and account for potential nonspecific “bystander” T cells, we examined the T-cell receptor (TCR) repertoire of matched human heart, tumor, and control tissues to identify T cells enriched in tumor or irMyocarditis.

Methods Five autopsy cases with matched irMyocarditis, tumor, and histologically normal tissue adjacent to tumor (“control”) were identified. FFPE slides were stained for H&E, and marked regions of interest were macroscopically dissected in serial unstained slides to isolate gDNA. Bulk TCRβ chain sequencing of the CDR3 region was performed. Expanded TCRs were defined as those comprising >0.5% of the TCRβ repertoire from a given tissue. For each expanded clone, a Fisher’s exact test was used to determine if the TCRβ sequence was enriched in irMyocarditis tissue compared to control tissue and in tumor tissue compared to control tissue.

Results Four tumor histologies were captured: melanoma (n=2), renal cell carcinoma, cholangiocarcinoma, and prostate cancer. TCRβ sequencing recovered tumor-enriched clones in four of five samples (range: 0-18 clones) and irMyocarditis-enriched clones in all five samples (range: 2-8). Across all patients, 17% (11/63) of tumor-enriched clones and 29% (11/37) of the irMyocarditis-enriched clones were enriched in both tissues. In two patients, the most abundant TCRβ sequence in irMyocarditis was not enriched in tumor tissue.

Conclusions TCRs enriched in ICI-treated tumors and irMyocarditis heart tissue are often distinct, suggesting that T-cell responses causing severe irAEs and anti-tumor immunity may not be driven by common antigens or epitopes, as has been previously suggested in other settings. We are currently analyzing these data together with our unpublished single-cell RNA sequencing and TCR data from peripheral blood and heart, which encompass 25 patients and ~300,000 cells. This effort could identify pathologic T cells that are distinct from tumor-reactive clones or nominate biomarkers for patients with irMyocarditis. Differentiating the T-cells responses driving irMyocarditis and anti-tumor immunity may be the first step towards developing clinical strategies that can maximize ICI efficacy while mitigating irAEs.

Acknowledgements We are grateful to the patients and their families whose generosity with their samples and time have made this study possible.

REFERENCES


Ethics Approval Patients involved in this study were consented to Dana-Farber Cancer Institute/Harvard Cancer Center collection protocols #1-181 and #13-416.