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 made this study possible. Families whose generosity with their samples and time have made this study possible.

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 We are currently analyzing these data together with our unpublished single-cell RNA sequencing and TCR data from peripheral blood and heart, which encompass 25 patients and ~300,000 cells.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.

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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.