Abstract Form

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Project Title:	Immune landscape of resected brain metastases in patients treated with and without immune checkpoint blockade

Research Category (please check one):

☒	**Original Research**	☐	**Clinical Vignette**	☐	**Quality Improvement**	☐	**Medical Education Innovation**

Abstract

Background: The brain metastatic niche has been historically difficult to study and thus poorly understood. Although brain metastases portend high morbidity and mortality, increasing evidence has shown that immune checkpoint blockade (ICB) can confer long-lasting responses in patients. How ICB remodels the brain tumor microenvironment is still relatively unknown. Here, we examine the immune microenvironment of resected brain metastases in a cohort of 19 patients pre-operatively treated with and without ICB using single-cell methods.
Methods: Tumor tissue was obtained from patients who underwent surgical resection of brain metastases at our institution, and single-cell RNA sequencing (scRNAseq) and multiplex immunofluorescence (mIF) analyses were performed, including unsupervised clustering and multivariate regression.
Results: A total of 8 patients with pre-operative exposure and 11 patients without pre-operative exposure to ICB were included. Represented histologies included melanoma, breast, lung, and endometrial cancers. Basic demographic and clinical characteristics, including age, sex, body mass index, performance status, stage at initial diagnosis, and time from initial diagnosis to development of brain metastases were not significantly different between the two groups. mIF revealed an immune exclusion phenotype in ICB naïve samples compared to ICB-treated samples, manifested by the lower density and percentage of lymphoid infiltrate and presence of immune perivascular cuffing. T cells in the ICB-treated group had higher expression of both effector and exhaustion markers (IFNG, GZMH, PDCD1, HAVCR2, TOX, NR4A2, NR4A1); while myeloid cells exhibited increased interferon-stimulated gene expression (CXCL9, CXCL10, STAT1, GBP1, GBP4, GBP5, MHC-II genes). One particular cluster of CD8+ T cells, the TCF and CD226-expressing progenitor population, correlated with overall survival. Furthermore, ICB-treated samples showed decreased CD14+ CD206+ perivascular macrophages, suggesting that these macrophages play a role in restraining immune cell extravasation and tumor infiltration.
Conclusion: This work contributes to the growing understanding of the brain metastatic niche and the impact of ICB on this unique microenvironment. While it is not surprising that we found increased T cell numbers and activation in ICB-treated samples, we also found increased evidence of TIL exhaustion. This may be a result of selection bias, as patients who undergo resection after ICB treatment typically do so due to poor response and intracranial progression, or from chronic antigen stimulation from checkpoint inhibition. Interestingly, our studies suggest that the myeloid populations, particularly the perivascular macrophages, are an important mediator of the brain tumor microenvironment. Further functional studies are needed to investigate the role of these perivascular macrophages and elucidate the cross-talk between these cells, infiltrating lymphocytes, and the brain vasculature.