Abstract

Primary central nervous system lymphoma (PCNSL) is a rare, aggressive type of lymphoma, most often histologically diagnosed as diffuse large B cell lymphoma (DLBCL). Recent advancements in single-cell sequencing have elucidated that the diverse germinal center states in systemic DLBCL manifest as tumor cell diversity, intricately linked to variations in the microenvironment. However, detailed characterization of intratumoral heterogeneity reflecting B-cell states in PCNSL remains elusive. Here, we conducted single-cell and spatial multiomic analyses to elucidate the cellular and spatial heterogeneity and the microenvironment in PCNSL. We identified a distinctive lymphoma subpopulation with gene and protein expression similar to that of plasmablasts (PBL), enriched in some patients with PCNSL. B-cell receptor (BCR) analysis revealed that BCR clonotypes of the PBL signature subpopulation were shared with other subpopulations, suggesting a common origin with other lymphoma cell subtypes. Spatial analysis additionally revealed several localization patterns of PBL signature subpopulations within the tissue, indicating spatial heterogeneity. An expansion study showed that around 40% of patients with PCNSL had a PBL signature subpopulation, as defined by CD138 immunohistochemistry staining. Additionally, patients with a PBL signature subpopulation and low CD3-positive cell infiltration

exhibited a worse prognosis. Finally, intercellular communication analysis suggested that the PBL signature subpopulation had distinct cellular interactions with the microenvironment. In summary, our study identified a tumor subpopulation with a PBL signature in PCNSL, suggesting distinct molecular and spatial crosstalk with the microenvironment. These findings provided new insights into the biological mechanisms of PCNSL.

Key points

- Plasmablast-like lymphoma cell subpopulation is enriched in some patients with PCNSL.
- This study suggests a novel rationale for using the plasmablast-like subpopulation as a potential therapeutic target in patients with PCNSL.