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Diagnosis of Leptomeningeal Disease in Diffuse Midline Gliomas by Detection of H3F3A K27M Mutation in Circulating Tumor DNA of Cerebrospinal Fluid

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Abstract

Introduction: Leptomeningeal disease (LMD) in diffuse midline gliomas (DMGs) can lead to devastating symptoms such as severe pain, urinary incontinence, and tetraparesis, with limited treatment options. We determined whether detecting H3F3A K27M-mutant droplets in cerebrospinal fluid (CSF) circulating tumor deoxyribonucleic acid (ctDNA) could be a biomarker for detecting LMD in DMGs.

Methods: Twenty-five CSF samples were obtained from 22 DMG patients. Histological confirmation of H3F3A K27M mutation was obtained in 10 (45.5%) cases. ctDNA was extracted from CSF, and H3F3A K27M-mutant and wildtype droplets were detected using digital droplet polymerase chain reaction (ddPCR). LMD was diagnosed by CSF cytology and pre- and post-contrast head and spine magnetic resonance (MR) imaging.

Results: The number of H3F3A K27M-mutant droplets (median 27 [range: 1-379] vs. median 0 [range: 0-1]; $p < 0.0001$) and variant allele frequency (VAF) (median 48.9% [range: 7.5%-87.5%] vs. median 0.0% [range: 0.0%-50.0%]; $p < 0.0001$) were significantly higher in the LMD/early-LMD group compared to no-LMD group. In two cases (Cases 4 and 11) without clinical evidence of LMD, multiple H3F3A K27M-mutant droplets were detected in CSF ctDNA. In those cases, extensive spinal dissemination was detected 6 months after the initial liquid biopsy. One case (Case 15) with high Schlafen11 (SLFN11) expression responded well to treatment for LMD and survived for 532 days after the diagnosis of LMD.

Conclusion: This study provides evidence that detecting H3F3A K27M-mutant droplets in CSF ctDNA is diagnostic for LMD and is more sensitive than traditional methods such as CSF cytology and MR imaging.

Keywords: diffuse midline glioma; droplet digital PCR; leptomeningeal disease; liquid biopsy.