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NGS REVEALS MSI-HIGH STATUS IN MMR-PROFICIENT PANCREATIC DUCTAL ADENOCARCINOMA: A RARE CASE REPORT

Background/Aim. Microsatellite instability (MSI) is a predictive biomarker for immune checkpoint inhibitor therapy. In pancreatic ductal adenocarcinoma (PDAC), MSI-H tumors are rare (<2%), and MSI status is commonly assessed by immunohistochemistry (IHC) for mismatch repair (MMR) proteins and molecular methods, including next-generation sequencing (NGS). Although these methods are usually concordant, discordant cases may occur, creating diagnostic and therapeutic challenges. In this study, we aimed to describe a rare phenomenon of discordance between IHC and NGS in determining MSI status in PDAC. **Materials and Methods.** DNA was extracted from FFPE tissue of a moderately differentiated (G2) PDAC (cT2N0M0) collected during patient treatment, in accordance with the Declaration of Helsinki and with informed consent obtained. Genomic DNA was sequenced using the Oncomine Comprehensive Assay Plus on the Ion GeneStudio S5 Plus platform. Data were analyzed using Torrent Suite, Ion Reporter, and Oncomine Reporter Software. **Results.** Previously demonstrated by IHC, preserved nuclear expression of all four MMR proteins (MLH1 (DAKO, clone ES05), PMS2 (DAKO, clone EP51), MSH2 (DAKO, clone FE11), and MSH6 (DAKO, clone EP49), consistent with proficient dMMR (pMMR). Contrastingly, NGS analysis identified an MSI-High phenotype with an MSI score of 30.20. It also detected somatic driver mutations in KRAS p.G12R (c.34G>C), TP53 c.376-1G>A, SMAD4 p.Y412* (c.1236C>G), and a tumor mutational burden of 10 mutations/Mb. These results show an unusual genomic variant of pancreatic ductal adenocarcinoma with MSI. Although the co-occurrence of SMAD4 and TP53 mutations in this case suggests aggressive disease with increased metastatic potential and genomic instability, the MSI-High phenotype supports consideration of immunotherapy. **Conclusions.** The data obtained demonstrate that MSI-H may be identified by NGS even in tumors that show preserved MMR protein expression by IHC. Such discordant cases underscore the complementary value of molecular MSI testing and support comprehensive biomarker assessment in PDAC, particularly when assessing immunotherapy eligibility. Relying solely on IHC can lead to false-negative MSI results, potentially excluding patients from immunotherapy. Despite NCCN and ESMO recommendations to combine IHC with molecular MSI testing, NGS-based assessment is still rarely used in practice.

Keywords: NGS, mismatch repair, MSI, immunotherapy, pancreatic ductal adenocarcinoma.

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