AB039. SOH23ABS_198. MLH1-deficient colorectal carcinoma with wild type BRAF and MLH1 promoter hypermethylation—an understudied molecular phenotype

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Background: Up to 15% of colorectal cancers (CRCs) display microsatellite instability (MSI). MSI is reflective of a deficient mismatch repair (MMR) system (dMMR). dMMR CRC represents a heterogeneous group of diseases with separate tumorigenic pathways. The majority of dMMR CRC is sporadic (>90%) and occurs due to acquired methylation of the MLH1 gene promoter. Sporadic MLH1-deficient CRC is thought to originate in lesions that arise from the serrated neoplasia pathway. Although the presence of the BRAF V600E mutation is characteristic of a sporadic cancer, as many as half of CRCs with MLH1 promoter hypermethylation will lack a BRAF mutation.

Methods: MMR status was determined by immunohistochemistry (IHC) for the MMR proteins hMLH1, hPMS2, hMSH2, and hMSH6. BRAF mutation status of MLH1 +/– PMS2 deficient specimens were evaluated using a mouse monoclonal BRAF V600E mutation-specific monoclonal antibody. The MLH1 promoter methylation status of MLH1-deficient, BRAF wild type CRC was assessed using a direct MLH1 promoter methylation assay.

Results: We report the clinicopathologic and molecular features of MLH1-hypermethylated, BRAF wild-type CRC (n=38) in comparison with MLH1-deficient, BRAF mutated CRC (n=144) and patients with suspected Lynch syndrome-associated CRC (n=56). Both MLH1-hypermethylated, BRAF wild-type CRC and MLH1-deficient, BRAF mutated CRC more commonly occurred in females (P≥0.002), had a tendency for the right colon (86.8% *vs.* 91.7% *vs.* 62.5%, P≥0.010) and had an advanced age at presentation (P<0.000) compared with the suspected Lynch group. In the tumours that had KRAS mutation analysis performed 15.7% (3/19) of the MLH1-hypermethylated BRAF wild type CRC harboured a KRAS mutation. There was no significant difference in mucinous differentiation, signet ring cell differentiation, tumour budding, poorly differentiated cluster grade, tumour-infiltrating lymphocytes or Crohn's-like reaction between the 3 tumour groups. Both MLH1-hypermethylated BRAF, wild-type CRC and MLH1-deficient, BRAF mutated CRC appear to be associated with a poorly differentiated phenotype with loss of CDX2 expression and increased medullary morphology compared to suspected Lynch group (P≥0.046). No significant difference in disease-free survival was observed (P>0.05).

Conclusions: Our results indicate MLH1-hypermethylated, BRAF wild type CRC can harbor KRAS mutations and arise from conventional tubular/tubulovillous adenomas or serrated lesions.

Keywords: Colorectal cancer (CRC); BRAF; Lynch syndrome; microsatellite instability (MSI); mismatch repair (MMR)

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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