Original Article

Mismatch Repair Status and Associated Clinicopathological Factors Among Young-Onset Colorectal Carcinoma

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Abstract

Background: Microsatellite instability (MSI) forms an important pathway in the pathogenesis of colorectal carcinoma (CRC). CRC with MSI is termed MMR-deficient (dMMR), and those with intact MMR genes are termed MMR-proficient (pMMR). The objective of the study is to determine the proportion of pMMR and dMMR among young-onset CRC patients and to evaluate the association of the clinicopathological profile with MMR status.

Materials and Methods: This retrospective cross-sectional study was carried out in the Department of Pathology, RIMS Imphal, among patients diagnosed with CRC below 45 years of age from March 2021 to February 2023. The slides were re-evaluated regarding tumor types, grade, presence of lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes (TILs). IHC staining was performed using antibodies MLH1, PMS2, MSH2, and MSH6. Loss of nuclear expression in all or any one of the antibodies was termed dMMR, whereas intact nuclear expression of all four antibodies was labeled pMMR.

Results: A total of 44 cases were included in the study, of which 36 (81.82%) were pMMR and 8 (18.18%) were dMMR. The dMMR group had a mean age of 37.1 years, with a male preponderance (62.50%). The ascending colon was the most common site (50.00%), 62.50% presented as advanced disease (stage IV), 50.00% were moderately differentiated, 37.50% had mucinous morphology, and 62.50% showed the presence of TILs.

Conclusion: A significant proportion of young-onset CRC in our study population demonstrated dMMR status. dMMR CRC had a higher histological grade, mostly presenting at an advanced stage.

Keywords:

Mismatch repair genes, microsatellite instability, IHC, young-onset CRC

Introduction

Colorectal cancer (CRC) ranks as the third most common cancer worldwide [1,2] and the second most common cause of death [3]. Approximately 10–15% of CRCs show mismatch repair deficiency [4,5]. Of these, 80% are sporadic, owing to MLH1 promoter hypermethylation or v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations, while 20% are linked to autosomal dominant Lynch syndrome (LS)/HNPCC (Hereditary Non-Polyposis Colorectal Cancer) [4].

CRC develops through various pathways, including chromosomal instability (CIN), microsatellite instability (MSI), and CpG

island methylation (CIMP), with some overlap between these mechanisms [2,6]. MSI is a crucial pathway in CRC pathogenesis, commonly found in HNPCC and sporadic CRC. Microsatellites are short tandem DNA repeats [2,4,6,7] that are prone to DNA replication errors [8].

The MMR system, a highly conserved cellular process, corrects these errors by identifying and repairing mismatched bases and insertion-deletion loops [6,7]. Key MMR genes include MutL protein homolog 1 (MLH1), post-meiotic segregation increased 2 (PMS2), MutS homolog 2 (MSH2), and MutS homolog 6 (MSH6) [4,8,9,10]. MSI is due to mutations in the MMR genes (inherited or somatic mutation or epigenetic silencing) [6,11]. Mutations in these genes, either inherited or somatic, or through epigenetic silencing, result in MSI [10,11].

CRCs with intact MMR genes are termed MMR proficient (pMMR) or microsatellite stable (MSS) CRC, while those with deficient MMR genes are termed MMR deficient (dMMR) or MSI-H (high) CRC [4,12]. MSI-H tumors, whether sporadic or germline, are associated with better survival rates compared to MSS tumors of similar stages. They also pose a higher risk for metachronous cancers and may resist conventional chemotherapy [6]. Increased surveillance benefits patients with LS and their families, aiding decisions on surgery extent, prophylactic procedures, therapy choices, and family member screening [6,7].

The 2018 American Cancer Society (ACS) guidelines recommended screening for CRC in average-risk adults at 45 years [13]. MSI, being a key biomarker of CRC, can be a screening tool for detecting LS and a prognostic marker.

Two common tests for MSI or MMR deficiency are polymerase chain reaction (PCR) testing for MSI and immunohistochemical staining (IHC) for altered proteins [2,4,6,7,10]. IHC tests for MMR proteins (MLH1, MSH2, MSH6, PMS2) to indicate functional MMR and, indirectly, MSI, aiding in identifying defective proteins for mutation analysis [2,7,9].

Both IHC and PCR are highly sensitive, specific, and concordant (95%) for dMMR and MSI [7]. Despite genetic testing being the gold standard, the College of American Pathologists (CAP) recommends initial IHC with a four-antibody panel. This study used IHC to evaluate 44 young-onset CRCs for MMR protein status and associated clinicopathological profiles [6].

Due to limited resources, we preferred using IHC as a screening modality. In this study, we aimed to determine the frequency of pMMR and dMMR among young-onset CRC patients and to evaluate the associated clinicopathological profile with the MMR status. The mismatch repair (MMR) status of colorectal cancer (CRC) in young patients is important to consider because it can impact survival and treatment.

Materials and Methods

This retrospective cross-sectional study was carried out in the Department of Pathology, RIMS, Imphal, among patients diagnosed with colorectal carcinomas below 45 years, for a study period of 1 year and 11 months, from March 2021 to February 2023. The sample size was not calculated, but all the patients diagnosed with CRC below 45 years within the study period were included in the study. Patients with prior neoadjuvant therapy or tissue blocks with insufficient material were excluded from the study. Informed consent (written) was obtained. Ethical clearance from the Institutional Ethics Committee was obtained.

Data on the patient's age, gender, clinical details, and reports were retrieved from the department's record section. Histopathological slides and blocks were also retrieved. The slides were re-evaluated by two pathologists regarding the tumor types, grade, presence of lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes (TIL). The presence of tumor-infiltrating lymphocytes was defined as an average of ≥3 lymphocytes between tumor cells per high-power (40× objective) field,

with counts from 5 consecutive high-power fields.

IHC staining was performed for the panel on the representative blocks using the antibodies (clones)—MLH1: ES05; PMS2: 8224R; MSH2: SP46; MSH6: 2D4B5 (Biogenics). Loss of nuclear expression of tumor cells in all or any one of the four antibodies, despite positive staining in the surrounding stromal cells, was termed dMMR, whereas intact nuclear expression of all four antibodies was labeled as pMMR CRC.

Descriptive statistics were used, and the independent variables were expressed as percentages. The chi-square test for larger values and Fisher's exact test for smaller values were applied to determine the association of various clinicopathological features with MMR status. A p-value of ≤0.05 was considered statistically significant.

Results

A total of 51 cases were retrieved within the study period of 1 year and 11 months. Only 44 cases were included in the study, as the other 7 cases were inadequate for IHC evaluation. Out of 44, 25 (56.82%) were male, and 19 (43.18%) were female. Of the 44 cases, 36 (81.82%) were pMMR CRC [Fig-1a & b], and 8 (18.18%) were dMMR CRC [Fig-2a, b & 3a, b]. Males comprised 55.56% (20 cases) of pMMR and 62.50% (5 cases) of dMMR. Females were 44.44% (16 cases) in pMMR and 37.50% (3 cases) in dMMR, which was statistically insignificant (p = 0.071, Fisher's exact test).

The mean age of distribution of dMMR CRC was 37.1 years. The ascending colon was the most common location in both pMMR (21 cases, 58.33%) and dMMR (4 cases, 50%), followed by the rectosigmoid colon in both pMMR (6 cases, 16.67%) and dMMR (2 cases, 25%). In pMMR, CRC in the descending colon was 13.89% (5 cases), and that in the transverse colon was 11.11% (4 cases). Both the transverse and descending colon were equally affected in dMMR (1 case each, 12.50%). It was found that both pMMR and dMMR commonly involved the right-sided colon; hence, the location of CRC was not significant with the MMR status (p = 0.071, Chi-square test) [Table 1].

The most common histologic type of tumor in pMMR was adenocarcinoma NOS (30 cases, 83.33%), while mucinous was the most common in dMMR (3 cases, 37.50%). In pMMR, mucinous tumors comprised only 13.89% (5 cases), followed by medullary with only 1 case (2.77%). In contrast, in dMMR, medullary and signet ring types each comprised 25% (2 cases each), followed by adenocarcinoma NOS (1 case, 12.50%). The mucinous type in dMMR is statistically significant (p = 0.003, Chi-square test).

In both pMMR and dMMR, most CRCs were moderately differentiated (17 cases, 47.22% in pMMR, and 4 cases, 50% in dMMR). Poorly differentiated tumors were more common in pMMR, comprising 36.11% (13 cases), than in dMMR (2 cases, 25%). dMMR had an equal proportion of well- and poorly-differentiated tumors, with 2 cases each (25% each). Well-differentiated tumors were the least in pMMR (6 cases, 16.67%). Moderately differentiated tumors in dMMR are statistically significant (p = 0.005, Chi-square test) [Table 2].

In dMMR, stage IV CRC was predominant, with 5 cases out of 8 (62.50%). It was followed by stage III and stage II, comprising 25% (2 cases) and 12.50% (1 case), respectively. pMMR showed mostly stage III tumors (20 cases, 55.56%), followed by stage IV, stage II, and stage I, with 27.78% (10 cases), 11.11% (4 cases), and 5.56% (2 cases), respectively. dMMR is significantly associated with stage IV (metastasis), while pMMR is associated with stage III (locally advanced disease), which is statistically significant (p = 0.005, Chi-square test).

Lymphovascular invasion was absent in most cases in both pMMR (24 cases, 66.67%) and dMMR (5 cases, 62.50%). Hence, no

strong conclusion could be drawn regarding the association of lymphovascular invasion with MMR status, though the statistical calculation shows a p-value of 0.002 (Fisher's exact test) [Table 2].

Mild to moderate intra-tumoral lymphocytes were noted in 62.50% (5 cases), marked in 25% (2 cases), and absent in 12.50% (1 case) of dMMR. In contrast, most cases of pMMR (77.78%, 28 cases) showed no intra-tumoral lymphocytes, while 22.22% (8 cases) showed mild to moderate intra-tumoral lymphocytes. Tumor-infiltrating lymphocytes are significantly associated with dMMR ($p = 0.005$) [Table 3].

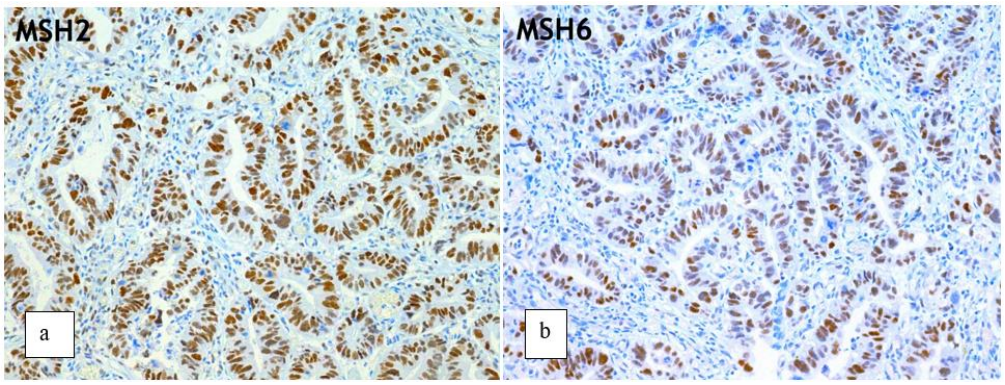

Figure 1: Photomicrograph of ascending colonic tissue showing nuclear positivity for MSH2 (a) & MSH6 (b) from pMMR CRC (IHC stain, 10X)

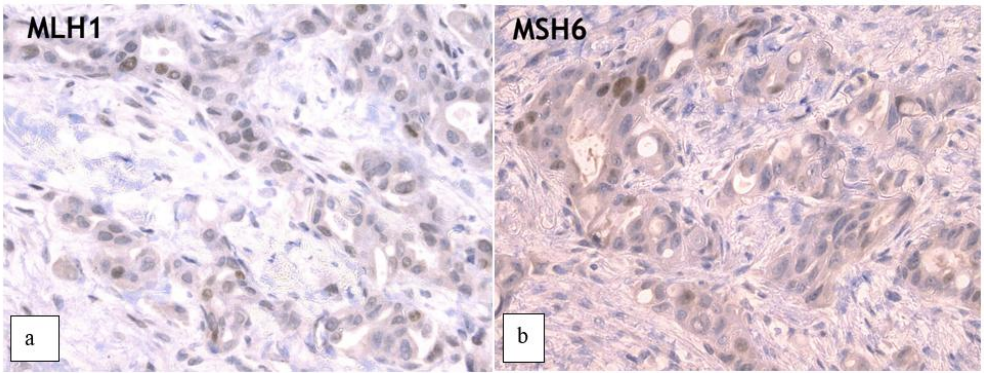

Figure 2: Photomicrograph of rectosigmoid tissue showing a nuclear negativity for MLH1 (a) & MSH6 (b) indicating dMMR case (IHC stain, 40X)

Discussion

Lynch syndrome (LS) is an autosomal dominant disorder that increases the risk of developing CRC and endometrial adenocarcinoma and other malignancies, including those of the small intestine, stomach, ureter, renal pelvis, ovary, brain, and prostate [7]. LS is characterized by germline mutations in DNA mismatch repair (MMR) genes, leading to microsatellite instability (MSI), particularly high levels of MSI (MSI-H). Loss of DNA MMR activity accelerates the accumulation of gene mutations responsible for apoptosis and growth regulation, facilitating the transition from adenoma to carcinoma [14].

PMS2 and MSH6 rely on their primary partners, MLH1 and MSH2, for stable expression. Loss of MSH2 often results in concurrent loss of MSH6, suggesting an MSH2 germline mutation. Similarly, MLH1 loss typically coincides with PMS2 loss,

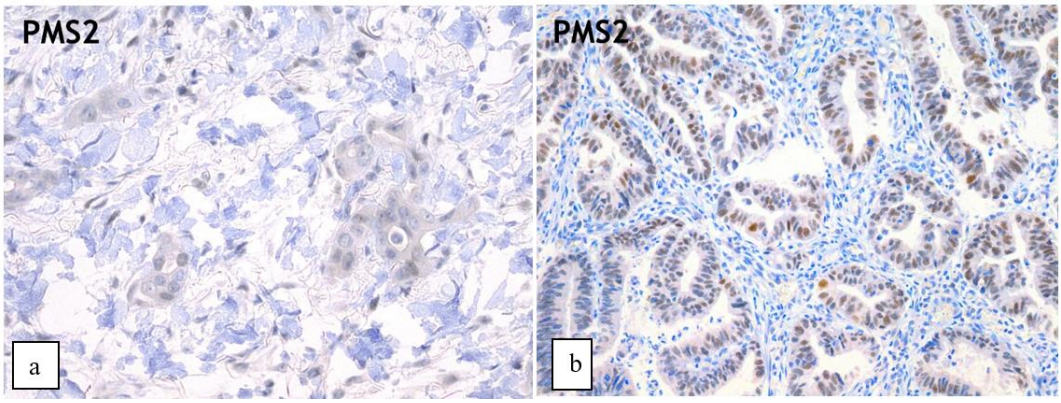

Figure 3: Photomicrograph of descending colonic tissue showing a nuclear negativity for PMS2 (a) and a nuclear positive stain for PMS2 (b) indicating dMMR case (IHC stain, 40X)

Table 1: Showing the distribution of CRC cases according to gender & location of the tumor

Characteristics (N=44)			**pMMR (n=36)**		**dMMR (n=8)**		**p-value**
		Number	Frequency	Percentage	Frequency	Percentage	
Gender	Male	25	20	55.56	05	62.50	0.099*
	Female	19	16	44.44	03	37.50	
	TOTAL	44	36	81.82	08	18.18	
Location	Ascending colon	25	21	58.33	04	50.00	0.071#
	Transverse colon	05	04	11.11	01	12.50	
	Descending colon	06	05	13.89	01	12.50	
	Rectosigmoid colon	08	06	16.67	02	25.00	

Table 2: Showing the distribution of CRC cases according to tumor histologic type & differentiation of the tumor

Characteristics (N=44)			**pMMR (n=36)**		**dMMR (n=8)**		**p-value (Chi-square test)**
		Number	Frequency	Percentage	Frequency	Percentage	
Tumor histologic type	Adenocarcinoma NOS	31	30	83.33	01	12.50	0.003
	Mucinous	08	05	13.89	03	37.50	
	Medullary	03	01	2.77	02	25.00	
	Signet ring	02	00	00	02	25.00	
Differentiation	Well differentiated	08	06	16.67	02	25.00	0.005
	Moderately differentiated	21	17	47.22	04	50.00	
	Poorly differentiated	15	13	36.11	02	25.00	

caused by either MLH1 germline mutations or somatic MLH1 promoter hypermethylation. Germline mutations in MSH6 and PMS2 generally lead to isolated loss of the respective proteins [7]. Loss of one or both markers necessitates MLH1 promoter methylation and BRAF mutation analysis. Absence of BRAF mutation and MLH1 hypermethylation warrants next-generation sequencing to detect potential germline mutations for accurate diagnosis and treatment planning [4].

MSI/dMMR tumors, common in younger patients and the right colon, feature mucinous traits, tumor-infiltrating lymphocytes, poor differentiation with medullary growth, Crohn-like lymphocytic reaction, and a favorable prognosis [4,6,7].

Table 3: Showing the distribution of CRC cases according to tumor stage, lymphovascular invasion & intra-tumoral lymphocytes in the tumor

Characteristics (N=44)			pMMR (n=36)		dMMR (n=8)		p-value
		Number	Frequency	Percentage	Number	Frequency	
Stage	I	02	02	5.56	00	00	0.007#
	II	05	04	11.11	01	12.50	
	III	22	20	55.56	02	25.00	
	IV	15	10	27.78	05	62.50	
Lymphovascular invasion	Present	15	12	33.33	03	37.50	0.002*
	Absent	29	24	66.67	05	62.50	
Intra-tumoral lymphocytes	None		28	77.78	01	12.50	0.005#
	Mild to moderate		08	22.22	05	62.50	
	Marked		00	00	02	25.00	
* Fisher's exact test; # Chi-square test							

In our study, 8 of 44 patients (18.18%) had dMMR CRC, aligning with Sacdalan et al. (16%) [2] and Gaur et al. (18.7%) [14] but lower than Hashmi et al. [6] (34%) and Rios-Valencia et al. [15] (27.1%). The higher rates in some studies may reflect age, selection bias, or other factors. Our rate may be influenced by the small sample size and inclusion of patients under 45 years. The mean age of distribution of dMMR was 37.1 years in this study, as also seen by Sacdalan et al. [2] (37.1 years). Similarly, Park SK et al. [16] and Li C et al. [17] found MSI-high CRC to be common among younger patients. No gender association with dMMR was seen (p = 0.099), as also observed by Hashmi et al. [6] (p = 0.082) and Gaur et al. [14]. However, it was noted that more males had CRC (56.82% vs. 43.18%), similar to the observation of Sacdalan et al. [2] (58.25% vs. 43.75%).

Most dMMR tumors (62.5%) were stage IV and significantly associated (p = 0.007), unlike studies by Sacdalan et al. [2] and Rios-Valencia et al. [15], who found links to locally advanced stages. The ascending colon was the most common site (50%), consistent with Sacdalan et al. [2] (37.5%) and Gaur et al. [14] (57.2%). Studies, including Ye JX et al. [18], Hashmi et al. [6], and Gaur et al. [14], reported a strong association of dMMR with right-sided colon tumors. dMMR status significantly correlates with mucinous histology and tumor-infiltrating lymphocytes (TIL) but not peri-tumoral lymphocytes (PTL). MSI-H mucinous tumors typically have a better prognosis than MSS counterparts [6].

The mucinous phenotype was the most common histological variant of dMMR (37.50%), similar to Sacdalan et al. [2] (50%) and Hashmi et al. [4]. We also observed that most cases of dMMR CRC (50.00%) were moderately differentiated, similar to the findings of Gaur et al. [14] and against Sacdalan et al. [2] (well-differentiated, 37.50%). 62.50% of CRC with MSI had intra-tumoral lymphocytes. Hashmi et al. [6], Hashmi et al. [4], Takemoto N et al. [19], and Smyrk TC et al. [20] noted that MSI is characterized by TILs, as in our case. The frequency of lympho-vascular invasion was lower in dMMR (62.50%, p = 0.002), as also seen by Hashmi et al. [4] (90.9%, p = 0.001).

Our study found significant associations of dMMR with mucinous histology (p = 0.003), moderate differentiation (p = 0.005), stage IV (p = 0.007), and intra-tumoral lymphocytes (p = 0.005). dMMR tumors often display distinct features, including younger age, right-sided location, mucinous/signet ring histology, and TILs, correlating with favorable prognosis and improved survival after adjuvant chemotherapy. While PCR is the gold standard for MSI detection, it is impractical for routine use. Right-sided location and TILs have predictive values (PPV 57%, NPV 95%) but miss up to 40% of MSI-H tumors. IHC is a reliable alternative, with proximal lesions being strong MSI predictors (OR 0.419; P = 0.007) [9].

MSI-H cancers often evoke a host response, resulting in the migration of activated T cells into the neoplastic epithelium. The immune system recognizes neoplasia poorly, but in MSI-H cancers with TILs, the mechanisms of T cell cytotoxicity (CD8+, TCR+) are activated [6]. This is due to the lack of an MMR system with the consequent accumulation of frame-shift mutations that cause the transcription and translation of peptides with altered amino acid sequences (neoantigens), which are presented by HLA class I and recognized by cytotoxic T cells [4,7,9].

The improved prognosis of MSI-H CRCs is attributed to an upregulated immune system and strong antitumoral immune response [6,7]. TILs are independently linked to better survival after curative surgery and are significantly associated with dMMR ($p = 0.007$). Quantifying TILs can serve as a simple criterion for selecting CRC patients for MSI testing, potentially reducing the number of tests by half while still identifying 93% of MSI-H cancers. TILs can classify tumors as MSI-H with about 85% accuracy [6].

New immunologic biomarkers have emerged for predicting prognosis and therapy response [7]. MSI CRCs show highly upregulated expression of immune checkpoints, including PD-1, PD-L1, and CTLA-4, making them more responsive to PD-1 blockade (e.g., pembrolizumab) than pMMR tumors [2,7]. Studies indicate that patients with MSI-H CRCs have a more favorable stage-adjusted prognosis and better overall survival than those with MSS tumors. Two meta-analyses showed improved overall survival in MSI CRC patients compared to MSS tumors, with Popat et al. [23] finding a hazard ratio (HR) of 0.65 (95% CI: 0.59–0.71) and Guastadisegni et al. [22] finding an HR of 0.6 (95% CI: 0.53–0.69; $P < 0.001$).

IHC is more advantageous than PCR testing for several reasons. It is a sensitive (77–100%) and specific (98–100%) method that is less expensive than MSI testing. IHC is more convenient, using resources available in most pathology labs and performed on paraffin-embedded tissue from colectomy samples. Additionally, IHC can identify likely mutated MMR genes, serving as a substitute for molecular MSI testing [2,14]. The sensitivity of IHC is improved when using a four-antibody panel [14].

Histological evaluation is essential for all CRC cases. For right-sided tumors with TILs, MSI screening using a four-antibody IHC panel is recommended, followed by PCR-based MSI testing if Lynch syndrome is suspected. Detecting MSI is vital for Lynch syndrome screening, assessing prognosis, and predicting responses to chemotherapy and immunotherapy. The limitation of the study is the small sample size and lack of stratified analysis by tumor subsite in terms of LVI and intra-tumoral lymphocytes.

Conclusion

A significant proportion of young-onset CRC cases exhibited dMMR status, higher histological grades, mucinous differentiation, and increased TILs, all linked to favorable prognosis and better survival. IHC for MMR proteins is cost-effective and simple, and it should be standard for all CRC evaluations due to its clinical utility. Proper clinical management and genetic counseling are essential for these patients and their families. Further studies and screening for familial CRC are urgently needed.

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