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Molecular and Histopathological Characteristics in Colorectal Cancer Patients with Family History of Cancer: A Case Series of Nine Patients with Review of Literature

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Abstract

Family history of Colorectal Cancer (CRC) is a known risk factor for CRC and holds within both genetic and environmental risk. Limited data from India are available on the patients with family history of cancer which suggests a differential age or stage at cancer diagnosis and also there are mixed evidence on histopathological and molecular characteristics.

This study was aimed to find out the histopathological and molecular characteristics of histopathologically confirmed colorectal cancer patients with familial history of cancer. MSI analysis and immunohistochemical staining were used to detect the mutation in Mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*).

In this study, there were 8 males and 1 female patient. Age range of the patients was 24 years to 77 years. Our study revealed that patients with history of cancer in their families were relatively young had advanced disease (Stage III and IV) and revealed comparatively more Microsatellite instable phenotype, poor degree of differentiation and poorer prognostic factors.

Keywords: Colorectal Cancer (CRC); Family history of cancer; Immunohistochemistry (IHC); Microsatellite Instability (MSI), Histopathological features

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Introduction

Colorectal Cancer (CRC) is the third most deadly and fourth most commonly diagnosed cancer in the world [1-3]. Historically, Colorectal Cancer (CRC) is a disease of older population, with more than 90% occurring after the age of 55 years. Off late, colorectal cancer incidence is increasing in young age patients and is associated with a poor outcome due to presentation at advanced stage at the time of diagnosis and poor degree of differentiation. Hereditary conditions such as Familial Adenomatous Polyposis (FAP) and Lynch Syndrome (LS) confers an extremely high lifetime risk of CRC but accounts for a minority of all CRCs. Early detection of CRC through screening with established modalities beginning at age 50, reduces CRC morbidity and mortality [4,5]. Optimal screening for people with established family history of CRC is not well defined, and screening recommendations vary and focus on earlier initiation of screening [6,7]. If optimal screening strategies could be determined based on evidence-based risk, and adherence to screening, there is significant potential for early detection of young age cancer. This study was aimed to find out the histopathological and molecular characteristic of colorectal cancer with family history of cancer to understand pathobiology which may ultimately allow identifying patients at risk at an earlier stage and may improve the outcome.

Material and Methods

Between 2016 to 2019 one hundred and three patients were admitted for the surgery with the diagnosis of colorectal cancer. Nine patients (8.7%) had family history of cancer, which formed the study group. Patients with presence of Familial Adenomatous Polyposis (FAP) or with any other malignancies were excluded from the study.

After informed consent, clinical data (Age, tumor location, sex, family history), histopathological, molecular findings and survival was recorded on a defined proforma.

Table 1: Clinical and Histopathological features.

Patients No	Age/Sex	Site of lesion	History of cancer in family	Stage/TNM	Histopathological features				
					Degree of Differentiation Well/Moderate/Poor	LVI	PNI	TILS	Mucin Secretion
1	24 Years/ Female	Rectum	Great Grand Mother – Rectum CA	IVC, T4aN0M1c	Poor	Present	Present	-	-
2	35 Years/Male	Rectum	Brother -Abdominal CA	IVA, T2NxM1a	Moderate	-	-	-	Present
3	46 Years/Male	Right Colon	Mother – Endometrial CA, Father – Lung CA	IIIC, T3N1cM0	Poor	-	-	-	Present
4	49 Years/Male	Right Colon	Mother – Lung CA	IIA, T3N0M0	Moderate		Present	-	Present
5	50 Years/Male	Rectum	Uncle – Rectum CA	IIIB, T3N1bM0	Poor	Present	Present	Present	-
6	55 Years/Male	Right Colon	History of cancer was present site not known	IIA, T3N0M0	Poor	Present	Present	-	Present
7	59Years/Male	Right Colon	Father –Colonic/ Rectal CA	IIA, T3N0M0	Well	-	-	Present	-
8	62 Years/Male	Right Colon	Father and Brother- Pancreatic and colonic CA, respectively	I, T2N0M0	Well	-	-	-	-
9	77 Years/Male	Rectum	Great Grand Mother – Gastric CA	IIIC, T4aN2M0	Well	-	-	-	Present

LVI: Lymphovascular Invasion; PNI: Perineural Invasion; TILS: Tumor infiltrating lymphocytes

Table 2: Detailed view of Microsatellite markers and MMR protein expression in patients with family history of cancer.

Patients No	Tumor site	Microsatellite Markers						MMR Protein Expression				
		BAT25	BAT26	D2S123	D5S346	D17S250	Combined Microsatellite markers Phenotype	*MLH1*	*MSH2*	*MSH6*	*PMS2*	Protein Expression
1	Rectum	Instable	Instable	Instable	Stable	Stable	MSI-High	Positive	Positive	Positive	Positive	MMR Intact
2	Rectum	Instable	Instable	Stable	Instable	Stable	MSI-High	Positive	Positive	Positive	Negative	MMR Loss
3	Colon	Instable	Instable	Stable	Stable	Stable	MSI-High	Positive	Positive	Positive	Positive	MMR Intact
4	Colon	Stable	Stable	Stable	Instable	Stable	MSI-Low	Positive	Positive	Positive	Positive	MMR Intact
5	Rectum	Stable	Instable	Stable	Stable	Stable	MSI-Low	Positive	Positive	Positive	Positive	MMR Intact
6	Colon	Instable	Instable	Instable	Instable	Stable	MSI-High	Positive	Positive	Positive	Positive	MMR Intact
7	Colon	Stable	Instable	Stable	Stable	Stable	MSI-Low	Positive	Positive	Positive	Positive	MMR Intact
8	Colon	Stable	Instable	Stable	Stable	Stable	MSI-Low	Positive	Positive	Positive	Positive	MMR Intact
9	Rectum	Stable	Stable	Stable	Stable	Stable	MSS	Positive	Positive	Positive	Positive	MMR Intact

Various histopathological features (stage of disease, degree of differentiation, and other markers of poor prognosis-Lymphovascular/Perineural Invasion (LVI/PNI), Tumor Infiltrating Lymphocytes (TILS) which might affect the prognosis were identified and noted PCR-Fragment Analysis (FA) and IHC for MMR protein detection were done. MMR proteins expression was seen by IHC staining using 4 antibodies (*MLH1*, *MSH2*, *MSH6* and *PMS2*). MSI analysis was performed by using 5 Microsatellite markers (BAT25, BAT26, D2S123, D5S346, and D17S250). Histopathological characteristics were correlated with the results of PCR-FA and IHC.

Results

There were 8 males (88.9%) and 1 female (11.1%) in the age range of 24 to 77 years. There were 5 patients of right sided colon cancer and 4 patients of rectum. None of the patients had left sided or transverse colon cancer. The demographical and various pathological features are presented in Table 1. All patients had advance stage of the disease except one 62 years male patient of right colon cancer. Four out of 9 patients had poor histological features such as poor degree differentiation, presence of Lymphovascular Invasion (LVI), Peri-Neural Invasion (PNI), TILS, etc. Three patients had well differentiated carcinoma; all of them were older (>55 years of age) as compared to those with poorly/mod diff carcinoma (<55 years of age). Out of 9 patients; 8 had Microsatellite Instability (MSI-High histology was in 4 and MSI-Low in 4) and only 1 patient was microsatellite stable. This was a 77 years old male patient of stage III carcinoma rectum with no poor prognostic factors involved. MSI was more frequently found in mononucleotide markers (BAT25 and BAT26); MSI marker D17S250, was found stable in all patients. Contrary to this, MMR expression was constantly expressed as intact except in one patient (11%) (Figure 1). This was a rectal cancer patient with stage IV disease with moderate degree of differentiation with MSI-High. There was no correlation found between MSI and MMR pattern (Table 2).

Discussion

In human colorectal carcinoma, 80% of the tumors are microsatellite stable, which means they have intact Mismatch Repair (MMR) genes which can correct single-bases and small-loop base-pair mismatches present throughout the non-coding and coding regions of the genome. Rest 20% of CRC tumors exhibit MSI due to defects in MMR pathway that corrects small base-pair mistakes in mononucleotide, di-nucleotide, and tri-nucleotide repeat region through-out the genome and are termed as high or low MSI (MSI-H or MSI-L, respectively) [8]. MSI was more frequently found in mononucleotide markers (BAT25 and BAT26) in our patients which were similar to the earlier studies [9] (Figure 2). Earlier publications in young CRC patients have reported advance stages of disease, mucinous histology and a more proximal localization of the tumor in the colon [10]. Our study also revealed the similar findings. In practice, MSI-PCR and IHC testing often act as complementary tests; while both are sensitive and specific for mismatch repair deficiency in patients with family history of cancer. Many studies

Table 3: Clinicopathological comparison with published literature.

Published by	Total Patients with family history	Age Range (in Years)	Gender		Location		Histopathological Features				Other factors	Microsatellite Status			MMR Protein loss
							Stage		Differentiation						
			Male	Female	Colon	Rectum	I/II	III/IV	Well/ Moderate	Poor		High	Low	Stable	
Park et al. [17]	143	28-89	86	56	65	65	77	66	123	5	Presence of Mucin secreting cells	26 (18.2)	3 (2.1%)	114 (79.7%)	47 (32.9%)
Schiemann et al. [18]	25	5-69	11	14	25	25	-	-	-		-	2 (8%)	18 (72%)	5 (20%)	0 (0%)
Ziadi et al. [19]	44	50-70	17	21	21	38	13	25	34	4	Medullary pattern PNI	6 (13.7%)	14 (31.8%)	24 (54.5)	5 (11.4%)
Present Study	9	24-77	8	1	1	8	4	5	5	4	LVI, PNI, TILS and mucin secretion	4 (44.4%)	4 (44.4%)	1 (11.1%)	1 (11.1%)

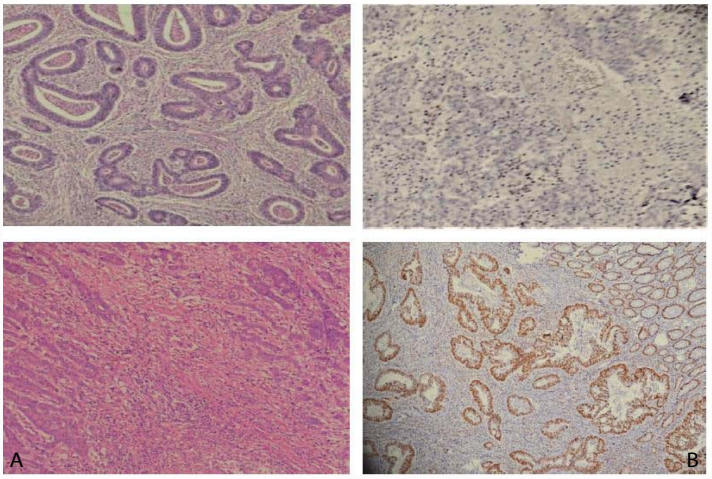

Figure 1: A: H&E stain photomicrographs showing well differentiated (top left; 40x magnification) and poorly differentiated adenocarcinoma (bottom left; 20x). B) Immunohistochemistry photomicrographs; Loss of PMS2 protein showing poorly differentiated adenocarcinoma in group I (top); Intact MSH2 protein showing poorly differentiated adenocarcinoma in group II (bottom) in 20x magnification.

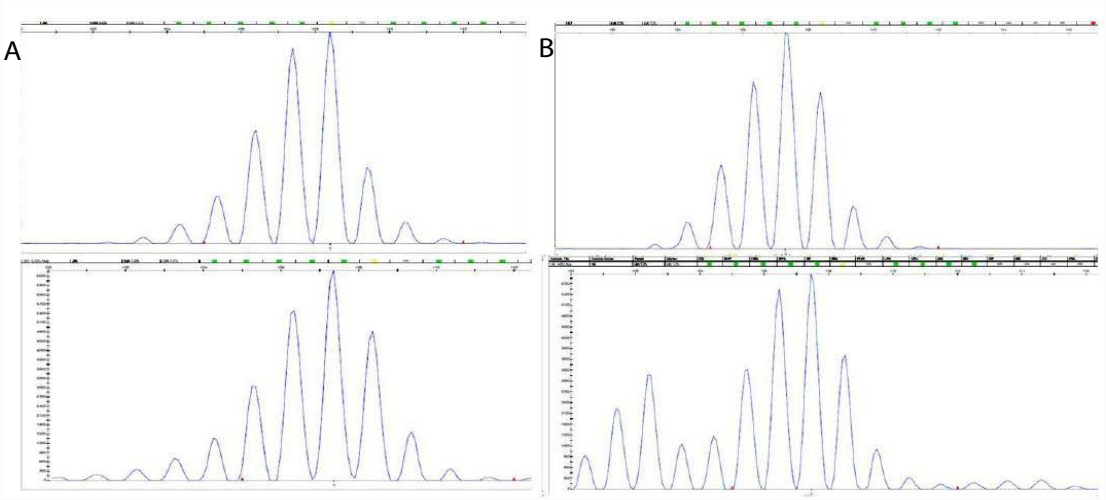

Figure 2: A) The electropherogram of the mononucleotide repeat marker BAT25 in normal sample (top panel). The tumor sample (Bottom) is showing Microsatellite stability. B) BAT25 in normal sample (top panel). The appearance of extra alleles at lower molecular weights in the tumor sample (bottom panel) indicates significant microsatellite instability.

showed the concordance in the results of these 2 techniques [11,12]. But in our study discordances between IHC of MMR proteins and MSI molecular testing results have been reported in the literature which ranges from 1% to 10% [13,14]. This is due to IHC of MMR protein which can be difficult or misleading as it depends on staining processes, which are not standardized and varies from one laboratory to another [15]. The technique can give false positive results as a non-functional MMR protein can remain expressed in tumor tissue and detected by IHC even though the tumor is MSI. In these cases, germ-line mutation testing of the MMR genes must be performed to validate the results (Table 3). The techniques, IHC and MSI analysis, both require accurate interpretation [16]. Our data suggest that MSI analysis has a higher diagnostic accuracy than IHC; therefore, it should be worthwhile to perform it first and consider IHC staining

only in the MSI-H selected cases.

Conclusion

In our study 89% of Microsatellite markers were found instable and majority of patients had poor histopathological features. This data has small sample size and needs further studies on larger no. of patients to validate these findings.

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