Clinicopathologic Characteristics of Left Colon Cancers with High Microsatellite Instability

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Directed by Professor Hoguen Kim

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<ABSTRACT>

Clinicopathologic Characteristics of Left Colon Cancers with High Microsatellite Instability

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A subset of colorectal carcinomas (CRCs) have numerous mutations in the microsatellite sequence and are classified as high microsatellite instability (MSI-H). MSI-H tumors are characterized by right side preponderance, frequent peritumoral and intratumroal lymphocityic infiltration and frequent mucin production. However, the clinicopathologic changes according to anatomic site and type of genetic changes are largely unknown. We analyzed the histopathologic features of 136 MSI-H CRCs and compared them to 140 microsatellite stable (MSS) CRCs. The histopathologic changes in MSI-H were further analyzed according to the

anatomic site and genetic changes.

MSI-H CRCs showed previously reported clinicopathologic findings; right-side preponderance [83/136 (61.0%) in MSI-H CRCs versus 20/140 (14.3%) in MSS CRCs, $p<0.001$], increased number of mucinous carcinoma [83/136 (61.0%) in MSI-H CRCs versus 30/140 (21.4%) in MSS CRCs, $p<0.001$], and peritumoral lymphoid reaction [75/135 (55.1%) in MSI-H CRCs versus 42/140 (30.0%) in MSS CRCs, $p<0.001$]. Increased serum CEA level showed MSS CRC preponderance [range: 0.01-72.50ng/mL (mean: 4.71 ng/mL) in MSI-H CRCs versus range: 0.01-2169.40 ng/mL (mean: 27.19ng/mL) in MSS CRCs, $p=0.009$]. We further analyzed the differences of right- and left-side MSI-H tumors. We found higher stage in left-side tumors [stageⅢ: 14/53 (26.4%) in left-side tumors versus 20/83 (24.1%) in right-side tumors, stageⅣ: 6/53 (11.3%) in left-side tumors versus 6/83 (7.2%) in right-side tumors, $p=0.042$]. We found a trend toward frequent mucin production in right-side tumors ($p=0.054$). We categorized MSI-H and MSS CRCs to the hereditary nonpolyposis colorectal cancers (HNPCCs) according to the Bethesda and Amsterdam criteria II and found right-side preponderance of HNPCCs with MSI-H.

These findings indicate that MSI-H CRCs of the left colon are infrequent and have similar clinicopathologic characteristics, however, left-side MSI-

H CRCs have characteristics of advanced tumor stage, less mucin formation, and infrequent association with HNPCC than MSI-H CRCs of the right side.

Key words: colorectal carcinoma, microsatellite instability, hereditary nonpolyposis colorectal cancer

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I. INTRODUCTION

Colorectal cancer is one of the most common tumors in Western countries and the fourth most common cancer in both sexes in Korea. The molecular pathogenesis of CRC is well explained in two pathways: chromosomal instability (CIN) and microsatellite instability (MSI). [1, 2] The MSI pathway begins with the inactivation of one of a group of genes responsible for DNA nucleotide mismatch repair, which leads to extensive mutations in both repetitive and nonrepetitive DNA sequences with low frequencies of allelic losses and rare alterations of tumor DNA content. [3]

After the discovery of MSI in cancer of the colon, [4] many studies on the genetic,

pathological, and clinical features of MSI colon cancer have been carried out. A National Cancer Institute (NCI) workshop suggested that the form of genomic instability associated with defective DNA mismatch repair in tumors was to be called MSI, and a panel of five microsatellites had been validated by Ruschoff and Fishel. [5] The recommended panel was composed of two mononucleotide repeats (bat26 and bat25) and three dinucleotide repeats (D5S346, D2S123. and D7S250). [6, 7] Tumors had been divided into three groups according to five markers: high-frequency MSI (MSI-H, the majority of markers exhibit MSI); low-frequency MSI (MSI-L, only a minority of markers exhibit MSI); and a group lacking apparent instability (MSS, none of the markers exhibit MSI). [5] Among these groups, MSI-H CRCs comprise 10-15% of all CRCs and most HNPCCs. [5]

MSI-H had characteristic clinical and pathological features compared to MSI-L and MSS CRCs such as an enhanced survival, marked preponderance of tumors proximal to the splenic flexure, preponderance in females, earlier tumor stage, increased diploid status, poor differentiation, extracellular mucin production, Crohn's-like lymphoid reaction, and frequent relation to HNPCC. [11-13]

Until recently, many small-scale studies have been conducted to clarify the biologic nature of the MSI-H CRCs, however, the histological changes according to site and HNPCC versus sporadic MSI-H tumors are largely unknown. In order to identify the clinicopathologic characteristics related to anatomic site and history of HNPCC, we analyzed the histopathologic features of 136 MSI-H CRCs and compared them to 140 MSS CRCs.

II. MATERIALS AND METHODS

1. Case Selection

A total of 136 MSI-H CRCs and 86 MSI-L CRCs that had been operated and diagnosed at Yonsei University Medical Center from 2003 to 2007 were included in this study. One hundred forty MSS CRCs that had been operated and diagnosed from May to October 2005 were used as controls. All cases had been confirmed by histological examination and molecular workup.

2. Microsatellite Instability Analysis

DNAs were extracted from formalin-fixed and paraffin-embedded tissue samples of 1458 cases. Tumor areas and adjacent normal areas were separately marked and collected for DNA extraction. The recommended panel (bat26, bat25, D5S346, D2S123. and D7S250) were used for genetic classification. Fluorescent polymerase chain reaction (PCR) was done and the differences between tumor and normal tissue were detected. MSI-H tumors were defined as having instability in two or more markers, MSI-L tumors as having instability in one marker, and MSS tumors as showing no apparent instability[5] (Table 1). MSI-H CRCs occupied 9.33% and MSI-L CRCs 5.90% of 1458 colorectal specimens that had been submitted for five years.

Table 1. Incidence of MSI of 5 markers according to molecular type of CRCs

Molecular markers	MSI-H (n=136, 9.33%)	MSI-L (n=86, 5.90%)	MSS (n=1,239, 84.98%)
bat26	124	2	0
bat25	126	7	0
D5S346	109	9	0
D2S123	118	20	0
D7S250	122	48	0

3. Analysis of Clinical Features

Clinical features such as sex, mortality, anatomic site, number of tumors, stage, patient survival status, HNPCC association, and carcinoembryonic antigen (CEA) level at diagnosis of CRC patients were obtained from medical records. The anatomic site of the tumor was classified as the ascending, transverse, descending, sigmoid colon, and rectum (Table 2) and divided into right and left side by splenic flexure.

Table 2. Comparison of tumor location in MSI-H and MSS CRCs

Site	MSI-H (%)	MSS (%)	Total (%)
Ascending	72 (52.9)	17 (12.1)	89 (32.2)
Transverse	11 (8.1)	1 (0.7)	12 (4.3)

Descending	15 (11.0)	9 (6.4)	24 (8.7)
Sigmoid	18 (13.2)	40 (28.6)	58 (21.0)
Rectum	20 (14.7)	73 (52.1)	93 (33.7)
Total	136 (100.0)	140 (100.0)	276 (100.0)

The number of tumor masses was counted according to endoscopic and gross findings. For diagnosis of HNPCC, the Bethesda criteria[10] and Amsterdam II criteria[16] presented in 1997 were used in this study. Preoperative serum CEA levels of all patients had been measured at the time of diagnosis (normal range: 0-5 ng/mL). We divided CRCs into two groups, normal (normal range: 0-5.0 ng/mL) and increased (higher than 5.0 ng/mL), and compared serum CEA level with each parameters in MSI-H and MSS CRCs.

4. Analysis of Pathologic Features

The clinicopathologic features of MSI-H and MSS CRCs were further analyzed according to site (right versus left) and history of HNPCC, with the parameters described as follows. The histological type of tumors were subclassified by mucinous carcinoma (carcinoma containing mucin in more than 50% of the tumor area), medullary carcinoma (poorly or undifferentiated carcinoma containing scant tumor stroma with intense peritumoral and intratumoral lymphocytic infiltration) and the other conventional adenocarcinomas[17] (Figure 1).

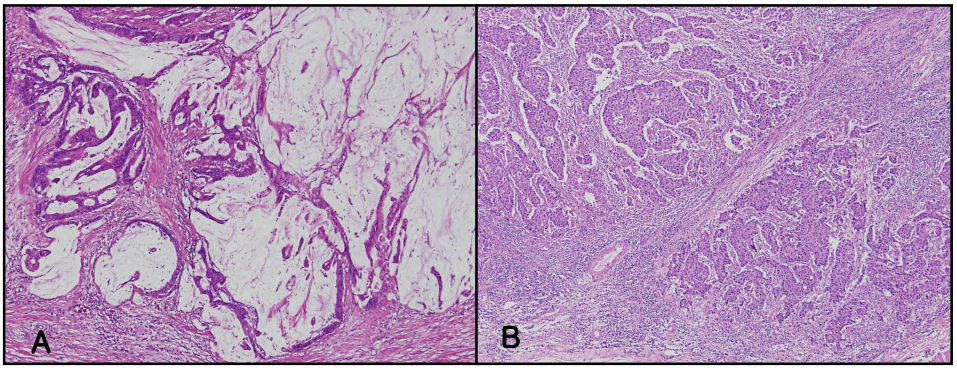

Figure 1. Histological type. Mucinous carcinoma shows extensive extracellular mucin pool formation (A). Medullary carcinoma shows sheets of undifferentiated tumor cells with peritumoral and intratumoral lymphocytic reaction (B). Hematoxylin & eosin stain.

Tumors were graded on the basis of the extent of glandular appearances and divided into well differentiated lesions (glandular structures in more than 95% of the tumor), moderately differentiated lesions (glandular structures in 50-95% of the tumor), and poorly differentiated and undifferentiated lesions (glandular structures in less than 50% of the tumor). Peritumoral lymphocytic reaction and intratumoral lymphocytic reaction (tumor-infiltrating lymphocytes) were estimated when there is mild to moderate peritumoral or intratumoral lymphocytic reaction and/or lymphoid follicles (Figure 2).

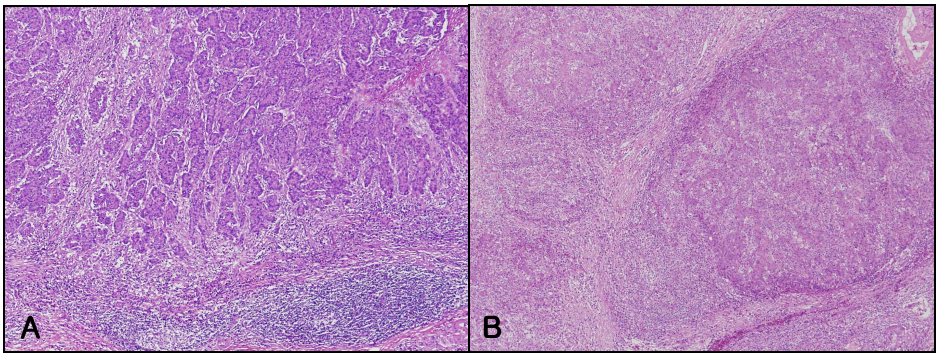

Figure 2. Peritumoral lymphocytic reaction with lymphoid follicle formation (A) and peritumoral and intratumoral lymphocytic reaction (B). Hematoxylin & eosin stain.

Extracellular mucin pool formation was divided into none, focal (less than 50% of the tumor area), and extensive (more than 50% of the tumor area). Tumor necrosis was divided into none, focal (less than 30% of the tumor area), and extensive (more than 30% of the tumor area). The infiltrative tumor borders had been divided into irregular or pushing types (Figure 3).

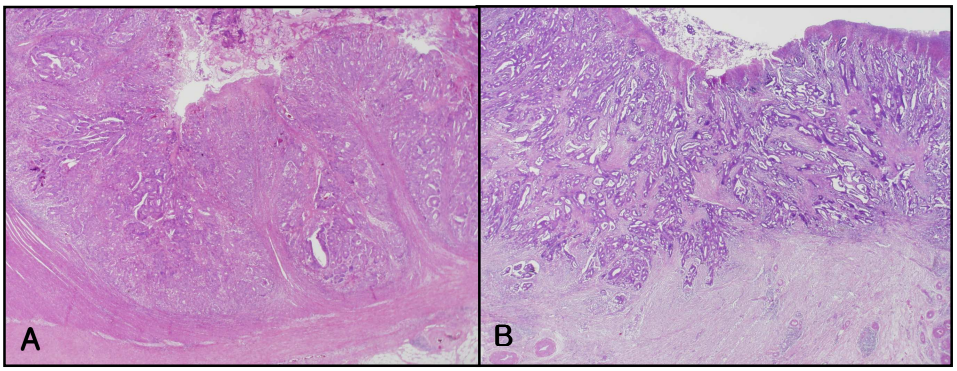

Figure 3. Infiltrating tumors with pushing margin (A) and irregular margin (B). Hematoxylin & eosin stain.

5. Statistical Analysis

Statistical analysis of each parameter was performed to clarify associations with MSI-H and MSS CRCs with chi-square test for categorical variables using SPSS 12.0 program (SPSS Inc., Chicago, IL, USA). All reported p-values are two-sided and p-values of less than 0.05 were considered to indicate statistical significance.

III. RESULTS

1. Different clinicopathlogic features between MSI-H CRCs and MSS CRCs

The clinicopathologic features of 136 MSI-H CRCs with comparison to 140 MSS CRCs were compared (Tables 3, 4). The significantly different clinicopathologic features were mortality, anatomic site, pathologic tumor stage, CEA level, histological type and grade, peritumoral and intratumoral lymphocytic reaction, and mucin formation. However, there was no significant difference in sex, T stage and necrosis between the two groups ($p>0.05$).

Table 3. The comparison of clinical features between MSI-H and MSS CRCs

Variable	MSI-H	MSS	Total	p-value
Category	(n=136)	(n=140)	(n=276)	
Sex				0.659
Male	80 (58.8)*	86 (61.4)	166 (60.1)	
Female	56 (41.2)	54 (38.6)	110 (39.9)	
Mortality†	2/124 (1.6)	13/119 (10.9)	15/243 (6.2)	0.003
Tumor stage				<0.001
I	21 (15.4)	15 (10.7)	36 (13.0)	
II	69 (50.7)	45 (32.1)	114 (41.3)	
III	34 (25.0)	38 (27.1)	72 (26.1)	
IV	12 (8.8)	42 (30.0)	54 (19.6)	
Tumor site				<0.001
Right	83 (61.0)	20 (14.3)	103 (37.3)	

Left	53 (39.0)	120 (85.7)	173 (62.7)	
Mass number				0.182
Single	129 (94.9)	137 (97.9)	266 (96.4)	
Multiple	7 (5.1)	3 (2.1)	10 (3.6)	
CEA‡				0.009
Normal	110 (80.9)	94 (67.1)	204 (73.9)	
Increased	26 (19.1)	46 (32.9)	72 (26.1)	
History of HNPCC	16 (11.8)	0 (0.0)	16 (5.8)	<0.001

*Cell: no. (%)

†Mortality: death/total, 12 MSI-H CRC patients and 21 MSS CRC patients were missing in clinical follow up.

‡Preoperative serum CEA level: normal (0.0-5.0 ng/mL); increased (higher than 5.0 ng/mL)

Table 4. Comparison of pathologic features of MSI-H and MSS CRCs

Variable	MSI-H	MSS	Total	p-value
Category	(n=136)	(n=140)	(n=276)	
Histological type				<0.001
Medullary carcinoma	12 (8.8)*	1 (0.7)	13 (4.7)	
Mucinous carcinoma	42 (30.9)	13 (9.3)	55 (19.9)	
Conventional carcinomas	82 (60.3)	126 (90.0)	208 (75.4)	
Mucin				<0.001
Absence	53 (39.0)	98 (70.0)	151 (54.7)	
Presence	83 (61.0)	42 (30.0)	125 (45.3)	
Histological grade†				<0.001

WD	40 (29.4)	81 (57.9)	121 (43.8)	
MD	31 (22.8)	41 (29.3)	72 (26.1)	
PD	65 (47.8)	20 (12.8)	83 (30.1)	
Peritumoral lymphocytic reaction				<0.001
Absence	60 (44.4)	98 (70.0)	158 (57.5)	
Presence	75 (55.6)	42 (30.0)	117 (42.5)	
Intratumoral lymphocytic reaction				<0.001
Absence	80 (59.3)	131 (93.6)	211 (76.7)	
Presence	55 (40.7)	9 (14.3)	64 (23.3)	
Necrosis				0.121
None	71 (52.6)	66 (47.1)	137 (49.8)	
Focal	52 (38.5)	68 (48.6)	130 (43.6)	
Extensive	12 (8.9)	6 (4.3)	18 (6.5)	
Tumor border				0.002
Irregular	104 (77.0)	127 (90.7)	231 (84.0)	
Pushing	31 (23.0)	13 (9.3)	44 (16.0)	

*Cell: no. (%)

†Histological grade: WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated

2. Comparison of clinicopathologic features of right- and left-side MSI-H CRCs

MSI-H CRCs showed right-side preponderance with statistical significance ($p<0.001$). The differences between right-side and left-side MSI-H CRCs were further analyzed (Table 5). More advanced tumor stage was found in left-side

MSI-H tumors [stage III: 14/53 (26.4%) in left-side tumors versus 20/83 (24.1%) in right-side tumors, stage IV: 6/53 (11.3%) in left-side tumor versus 6/83 (7.2%) in right-side tumor, p=0.042]. However, differences in other clinicopathologic features between the two groups were not statistically significant. There was a trend toward poor survival preponderance [2/49 (4.1%) in left-side MSI-H CRCs versus 0/83 (0.0%) in right-side MSI-H CRCs, p=0.078], less mucin formation [27/53 (50.9%) in left-side MSI-H CRCs versus 56/83 (67.5%) in right-side MSI-H CRCs, p=0.054], and less association with HNPCC [3/53 (5.7%) in left-side MSI-H CRCs versus 13/70 (15.7%) in right-side MSI-H CRCs, p=0.077]. No significant differences in sex, survival rate, histologic type and grade, peritumoral and intratumoral lymphocytic reaction, necrosis, tumor border, CEA level and five molecular markers were found (p>0.05).

Table 5. Comparison of clinicopathologic features of right- and left-side MSI-H CRCs

Variable Category	Right side (n=83)	Left side (n=53)	Total (n=136)	p-value
Sex				0.950
Male	49 (59.0)*	31 (58.5)	80 (58.8)	
Female	34 (41.0)	22 (41.5)	56 (41.2)	
Mortality†	0/75 (0.0)	2/49 (4.1)	2/124 (1.6)	0.078
Stage				0.042

	I	8 (9.6)	13 (24.5)	21 (15.4)	
	II	49 (59.0)	20 (37.7)	69 (50.7)	
	III	20 (24.1)	14 (26.4)	34 (25.0)	
	IV	6 (7.2)	6 (11.3)	12 (8.8)	
Mass number					0.311
	Single	80 (96.4)	49 (92.5)	129 (94.9)	
	Multiple	3 (3.6)	4 (7.5)	7 (5.1)	
CEA‡					0.613
	Normal	66 (79.5)	44 (83.0)	110 (80.9)	
	Increased	17 (20.5)	9 (17.0)	26 (19.1)	
Histological type					0.121
	Medullary carcinoma	7 (8.4)	5 (9.4)	12 (8.8)	
	Mucinous carcinoma	31 (37.3)	11 (20.8)	42 (30.9)	
	Conventional carcinomas	45 (54.2)	37 (69.8)	82 (60.3)	
Mucin					0.054
	Absence	27 (32.5)	26 (49.1)	53 (39.0)	
	Presence	56 (67.5)	27 (50.9)	83 (61.0)	
Histologic grade§					0.627
	WD	22 (26.5)	18 (34.0)	40 (29.4)	
	MD	18 (21.7)	13 (24.5)	31 (22.8)	
	PD	46 (51.8)	22 (41.5)	65 (50.8)	
HNPCC		13 (15.7)	3 (5.7)	16 (11.8)	0.077

*Cell: no. (%)

†Mortality: death/total, 12 MSI-H CRC patients and 21 MSS CRC patients were missing in clinical

follow up.

‡Preoperative serum CEA level: normal (0.0-5.0 ng/mL); increased (higher than 5.0 ng/mL)

§Histological grade: WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated

3. Comparison of clinicopathologic features between MSI-H rectal and MSI-H colon cancers

Twenty out of 136 MSI-H CRCs were located in the rectum (20/136, 14.7%). We compared 20 MSI-H rectal cancers to the other 116 MSI-H colon cancers. We found more earlier tumor stage in rectal cancers [I: 8/20 (40.0%) in MSI-H rectal cancers versus 13/116 (11.2%) in other MSI-H carcinomas, p=0.005] but there were no differences in other clinicopathologic factors.

4. Comparison of clinicopathologic features between HNPCC and sporadic MSI-H CRCs

The clinicopathologic features of MSI-H CRCs were analyzed by comparison of the sporadic tumors and HNPCCs according to the Bethesda[9] and Amsterdam II criteria.[16] HNPCC is a distinct autosomal dominant syndrome accounting for approximately 5–6% of the total colorectal cancer burden with clinical and pathologic features caused by defective mismatch repair genes.[8] In 2004, the revised Bethesda criteria were published, but there have beeb several debates on its utility.[9] Therefore, the Bethesda criteria of 1997 was used for HNPCC in this study.[10] We compared HNPCCs with sporadic MSI-H CRCs in clinicopathologic

features. We found that most of the clinicopathologic features were not different between CRCs from HNPCC and sporadic MSI-H CRCs, although there was a trend toward more proximal location in HNPCC [proximal location: 13/16 (81.3%) in HNPCC versus 70/120 (53.8%), p=0.073] (Table 6).

Table 6. Comparison of clinicopathologic features of HNPCCs and sporadic CRCs with MSI-H

Variable	Category	HNPCC (n=16)	Sporadic CRC (n=120)	Total (n=136)	p-value
Sex					0.445
	Male	8 (50.0)*	72 (60.0)	80 (58.8)	
	Female	8 (50.0)	48 (40.0)	56 (41.2)	
Mortality†		0/15 (0.0)	2/107 (1.8)	2/124(1.6)	0.597
Stage					0.183
	I	4 (25.0)	17 (14.2)	21 (15.4)	
	II	4 (25.0)	65 (54.2)	69 (50.7)	
	III	6 (37.5)	28 (23.3)	34 (25.0)	
	IV	2 (12.5)	10 (8.3)	12 (8.8)	
Site					0.077
	Right	13 (81.3)	70 (53.8)	83 (61.0)	
	Left	3 (18.8)	50 (41.7)	53 (39.0)	
Mass number					0.156
	Single	14 (87.5)	115 (95.8)	129 (94.9)	

	Multiple	2 (12.5)	5 (4.2)	7 (5.1)	
CEA‡					0.163
	Normal	15 (93.8)	95 (79.2)	110 (80.9)	
	Increased	1 (6.3)	25 (20.8)	26 (19.1)	
Histological type					0.653
	Medullary carcinoma	2 (16.7)	10 (83.8)	12 (8.8)	
	Mucinous carcinoma	6 (14.3)	36 (85.7)	42 (30.9)	
	Conventional carcinomas	8 (9.8)	74 (90.7)	82 (60.3)	
Histological grade‡					0.122
	WD	6 (37.5)	34 (28.3)	40 (29.4)	
	MD	0 (0.0)	29 (24.2)	31 (22.8)	
	PD	10 (62.5)	57 (47.5)	65 (47.8)	
Mucin					0.500
	Absence	5 (31.3)	48 (40.0)	53 (39.0)	
	Presence	11 (68.8)	72 (60.0)	83 (61.0)	
Peritumoral lymphocytic reaction					0.589
	Absence	8 (50.0)	51 (42.5)	59 (43.7)	
	Presence	8 (50.0)	68 (57.1)	76 (56.3)	
Intratumoral lymphocytic reaction					0.500
	Absence	5 (31.3)	48 (40.0)	81 (60.0)	
	Presence	11 (68.8)	72 (60.0)	54 (40.0)	
Necrosis					0.409
	None	9 (56.3)	62 (52.1)	71 (52.6)	
	Focal	7 (43.8)	45 (37.8)	52 (38.5)	

Extensive	0 (0.0)	12 (10.1)	12 (8.9)	
Tumor border				0.837
Irregular	12 (75.0)	92 (77.3)	104 (77.0)	
Pushing	4 (25.0)	27 (22.7)	31 (23.0)	

*Cell: no. (%)

†Mortality: death/total, 12 MSI-H CRC patients and 21 MSS CRC patients were missing in clinical follow up.

‡Preoperative serum CEA level: normal (0.0-5.0 ng/mL); increased (higher than 5.0 ng/mL)

§Histological grade: WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated

IV. DISCUSSION

In this study, the clinicopathologic features of MSI-H CRCs were analyzed and compared to MSS CRCs. The differences in mortality, anatomic site, pathologic stage, preoperative serum CEA level, histological type and grade, peritumoral and intratumoral lymphocytic reaction, and mucin formation were significant ($p<0.05$).

Most of the findings in our Korean patients were in concordance with the previously reported characteristics of MSI-H. Our MSI-H CRCs showed previously reported clinicopathologic findings[11, 12]: right-side preponderance [83/136 (61.0%) in MSI-H cancers versus 20/140 (14.3%) in MSS carcinoma, $p<0.001$]; frequent mucin formation [83/136 (61.0%) in MSI-H cancers versus 30/140 (21.4%) in MSS carcinoma, $p<0.001$]; relatively increased number of mucinous carcinoma [42/136 (30.9%) in MSI-H cancers versus 13/140 (9.3%) in MSS carcinoma, $p<0.001$]; and more peritumoral lymphoid reaction [75/135 (55.1%) in MSI-H cancers versus 42/140 (30.0%) in MSS carcinoma, $p<0.001$].

The incidence of MSI-H CRCs was lower than the previously reported incidence of 12-15% in Western countries. [5] This difference might be due to the different preferred location of CRCs in Korean and Western populations. In fact, it is well known that the incidence of rectal cancer in Korean populations (58.0%) is higher than in Western populations (19.3%).[18, 19] The very low incidence of MSI-H in rectal cancer has been reported, [5] and was also confirmed in this study. Therefore, the high preponderance of rectal cancer in the Korean population would explain a slightly lower incidence of MSI-H CRCs in this study (9.3% in this study

compared to 10-15% in Western studies).[5]

One of the characteristic features of MSI-H CRCs is more frequent medullary and mucinous carcinoma than MSS CRCs. We simplified the subclassification of histological type into medullary carcinoma, mucinous carcinoma and other conventional adenocarcinomas, and analyzed the clinicopathologic features. Medullary carcinoma, predominantly presented in MSI-H CRCs, accounted for the smallest number (12/136, 8.8%) among three simplified histological types and showed female predominance although mucinous carcinoma and other carcinomas showed male predominance ($p=0.034$).

We could not find out any other difference between HNPCC-related MSI-H CRCs and sporadic MSI-H CRCs. These findings indicate that although the initiating molecular mechanisms of HNPCC and sporadic MSI-H CRCs are different, the downstream molecular pathways are quite similar, and they share similar pathologic features.

We classified tumor location as ascending colon, transverse colon, descending colon, sigmoid colon, and rectum, and the tumor distribution was divided into right- and left-side from the splenic flexure. We validated right-side preponderance of MSI-H CRCs with statistical significance ($p<0.001$). We further analyzed the difference between right- and left-side CRCs with MSI-H. There were no significant differences in sex, mortality, histological type and grade, peritumoral and intratumoral lymphocytic reaction, necrosis, tumor border, serum CEA level and five molecular markers ($p>0.05$). We found significant differences

in the pathologic tumor stage between right- and left-side MSI-H cancers (p=0.042), however, we could not conclude higher stage preponderance in left-side MSI-H CRCs due to slight differences in the higher stages. We found that right-side MSI-H CRCs had a tendency showing higher proportion of mucinous carcinoma than left-side MSI-H CRCs (p=0.077).

We categorized to HNPCC according to the Bethesda and Amsterdam II criteria and found 16 HNPCCs with MSI-H. Among these, 13 cases (81.3%) were located in the right colon and 3 cases (18.8%) in the left colon. As it is known that the majority of HNPCC is located in the right colon,[5] there was a trend toward right-side preference of HNPCC in this study (p=0.077). We could not find significant differences in the other clinicopathological characteristics of MSI-H CRCs between HNPCC-related MSI-H CRCs and sporadic MSI-H CRCs. These findings indicate that the molecular pathways of MSI-H tumors are homogenous although the inactivating mechanisms of mismatch repair genes were different.

Preoperative serum CEA level is the oldest and best marker for early detection and gives independent prognostic information of CRCs.[15] CEA is a high molecular weight glycoprotein belonging to the immunoglobulin super family of molecules.[14] It is useful in screening for early disease, aiding diagnosis, determining prognosis, predicting likely response to specific therapies, surveillance of patients undergoing curative resection and monitoring the treatment of advanced disease.[15] We examined preoperative serum CEA level at diagnosis. We divided CRCs into two groups according to CEA level, normal

(normal range: 0-5.0 ng/mL) and increased (higher than 5.0 ng/m:), and compared serum CEA level with each parameters of MSI-H and MSS CRCs. Serum CEA levels of all patients were measured at diagnosis (normal range: 0-5 ng/mL). Serum CEA level of MSI-H CRCs ranged from 0.01 to 72.50 ng/mL (mean: 4.71 ug/mL) and CEA level of MSS CRCs ranged from 0.01 to 2169.40 ng/mL (mean: 27.19 ug/mL). In other words, MSS CRCs had a higher CEA level than MSI-H CRCs (p=0.009), and may be used for prediction of MSS CRCs when preoperative serum CEA level is markedly increased.

The decreased preoperative serum levels of CEA in HNPCC have also been reported.[20] In this study, a preponderance to be in normal range of serum CEA level in HNPCC was also noted [normal range in serum CEA level: 15/16 (93.7%) in HNPCC versus 71/189 (72.7%) in sporadic CRC, p=0.050]. However, there was no significant difference in serum CEA level between HNPCC and sporadic MSI-H CRCs (p=0.163). These findings suggest that identification of serologic biomarkers for MSI-H CRCs is necessary.

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V. CONCLUSIONS

We found that MSI-H tumors of the left colon were infrequent and showed the same clinicopathological characteristics as right-side MSI-H CRCs, except less mucin formation and infrequent association with HNPCC. We could not find any significant clinicopathological difference between HNPCC-related MSI-H CRCs and sporadic MSI-H CRCs. These findings indicate that although the inactivating mechanisms of mismatch repair genes were different, the molecular pathways of the MSI-H tumors are homogenous, and these show similar clinicopathological features.

REFERENCES

1. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. Nature 1998;396:643-9.
2. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996;87:159-70.
3. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature 1993;363:558-61.
4. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816-9.
5. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998;58:5248-57.
6. Bocker T, Diermann J, Friedl W, Gebert J, Holinski-Feder E, Karner-Hanusch J, et al. Microsatellite instability analysis: a multicenter study for reliability and quality control. Cancer Res 1997;57:4739-43.
7. Dietmaier W, Wallinger S, Bocker T, Kullmann F, Fishel R, Ruschoff J. Diagnostic microsatellite instability: definition and correlation with mismatch repair protein expression. Cancer Res 1997;57:4749-56.
8. Ponz de Leon M. Descriptive epidemiology of hereditary non-polyposis colorectal cancer. Tumori 1996;82:102-6.
9. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, et al.

Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-8.

10. Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997;89:1758-62.

11. Kim H, Jen J, Vogelstein B, Hamilton SR. Clinical and pathological characteristics of sporadic colorectal carcinomas with DNA replication errors in microsatellite sequences. Am J Pathol 1994;145:148-56.

12. Thibodeau SN, French AJ, Cunningham JM, Tester D, Burgart LJ, Roche PC, et al. Microsatellite instability in colorectal cancer: different mutator phenotypes and the principal involvement of hMLH1. Cancer Res 1998;58:1713-8.

13. Baba S. [Familial cancer: recent advances]. Gan To Kagaku Ryoho 1999;26:735-43.

14. Hammarstrom S. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. Semin Cancer Biol 1999;9:67-81.

15. Duffy MJ, van Dalen A, Haglund C, Hansson L, Klapdor R, Lamerz R, et al. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines. Eur J Cancer 2003;39:718-27.

16. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116:1453-6.

17. Jass JR, Sobin L.H. Histological Typing of Intestinal Tumours. WHO. 2nd ed. Berlin: Springer-Verlag; 1989.

18. Devesa SS, Chow WH. Variation in colorectal cancer incidence in the United States by subsite of origin. Cancer 1993;71:3819-26.

19. Park YJ, Park KJ, Park JG, Lee KU, Choe KJ, Kim JP. Prognostic factors in 2230 Korean colorectal cancer patients: analysis of consecutively operated cases. World J Surg 1999;23:721-6.

20. Schiemann U, Gunther S, Gross M, Henke G, Muller-Koch Y, Konig A, et al. Preoperative serum levels of the carcinoembryonic antigen in hereditary non-polyposis colorectal cancer compared to levels in sporadic colorectal cancer. Cancer Detect Prev 2005;29:356-60.

<ABSTRACT (IN KOREAN)>

좌측 대장에 발생한 고빈도 현미부수체 불안정형 대장암의 임상적 병리적 특징

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대장직장암의 일부는 현미부수체 돌연변이에 의해 발생하며, 고빈도 현미부수체 불안정형 대장암 (high microsatellite instability; MSI-H) 은 전체 대장암의 10-15%를 차지한다. MSI-H 대장암의 임상적, 병리학적 특징은 잘 알려졌으나, 해부학적 위치에 따른 특징이나 유전성 비용종증 대장암 (hereditary non-polyposis colorectal cancer; HNPCC) 과 산발성 대장암에서의 비교는 이루어지지 않았다. 본 연구에서는 MSI-H 대장암 136예와 현미부수체 안정형 (microsatellite stability; MSS) 대장암 140예를 해부학적 위치, 조직학

적 특성, 수술 전 혈청 암배아항원의 수치, HNPCC 여부 등에 따라 비교하고 좌측 대장에서 발생한 MSI-H 대장암의 특징을 규명하였다.

MSI-H 대장암은 MSS 대장암에 비하여 우측 대장에 호발하였고, 점액성 선암의 발생빈도가 더 높았으며 종양주변 림프반응이 더 많이 관찰되었다. 또한 MSS 대장암은 MSI-H 대장암에 비하여 수술 전 혈청 암배아항원의 수치가 유의하게 높았다.

좌측 MSI-H 대장암은 MSI-H 대장암의 특징을 모두 보이나, 우측 MSI-H 대장암에 비하여 HNPCC의 발생빈도가 낮았고 점액성 물질 형성이 적었다. HNPCC은 산발성 대장암에 비해 우측 대장에 호발하였으나 다른 임상적 병리조직학적 특징에 차이를 보이지 않아, 두 군의 MSI-H 대장암은 그 유발원인은 다르나 동일한 분자유전학적 종양발생 경로를 거치고, 이로 인하여 비슷한 임상적, 병리학적 특성을 나타내는 것으로 생각된다.

핵심되는 말: 대장암, 현미부수체 불안정형, 유전성 비용종증