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Clinicopathologic Characteristics of Left-Sided Colon Cancers with High Microsatellite Instability

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Background : High microsatellite instability (MSI-H) colorectal carcinomas (CRCs) with numerous mutations in the microsatellite sequence are characterized by a right-sided preponderance, frequent peritumoral and intratumoral lymphocytic infiltration, and frequent mucin production. However, no study has correlated anatomic site and type of genetic changes with clinicopathologic changes. **Methods :** We analyzed the histopathologic features of 135 MSI-H CRCs and compared them to 140 microsatellite stable (MSS) CRCs. Histopathologic changes in MSI-H were further analyzed according to anatomic sites and genetic changes. **Results :** MSI-H CRCs showed previously reported clinicopathologic findings; a right-sided preponderance, an increased number of mucinous carcinomas, and peritumoral lymphoid reactions ($p<0.001$ for each variable). Increased serum CEA levels showed an MSS CRC preponderance ($p=0.013$). We further analyzed the histologic differences between right- and left-sided MSI-H tumors. We found that MSI-H CRCs on both sides had similar clinicopathologic findings, except for higher tumor stage ($p=0.048$) and less frequent abnormal CEA levels in left-sided MSI-H tumors ($p=0.027$). We found that not all clinicopathologic features were different between hereditary nonpolyposis colorectal cancers (HNPCCs) and sporadic MSI-H CRCs. **Conclusions :** These findings indicate that MSI-H CRCs of the left colon have similar clinicopathologic characteristics as right-sided MSI-H CRCs. We did not find any significant clinicopathological difference between HNPCCs and sporadic MSI-H CRCs.

Key Words : Colorectal neoplasm; Microsatellite instability; Colorectal neoplasms, hereditary nonpolyposis

Colorectal carcinoma (CRC) is one of the most common tumors in Western countries and the fourth most common cancer in both genders in Korea (Korean Statistical Informative Service, 2005). The molecular pathogenesis of CRC is well explained in 2 pathways: chromosomal instability (CIN) and microsatellite instability (MSI).[1,2] The MSI pathway begins with the inactivation of genes responsible for DNA nucleotide mismatch repair, which results in extensive mutations in 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 of the genetic, pathologic, 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 should be called MSI and a panel of 5 microsatellites was validated by Ruschoff and Fishel.[5] The panel was composed of 2 mononucleotide repeats (bat26 and bat25) and 3 dinucleotide repeats (D5S346, D2S123, and D7S250).[6,7] Tumors were divided into 3 groups according to 5 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 any apparent instability (MSS, none of the markers exhibit MSI).[5] Among these groups, MSI-H CRCs comprise 10-15% of sporadic CRCs and most of hereditary nonpolyposis colorectal cancers (HNPCCs).[5]

MSI-H CRCs have characteristic clinical and pathological features compared to MSI-L and MSS CRCs such as enhanced survival, a marked preponderance of tumors proximal to the splenic flexure, earlier tumor stage, increased diploid status, poor differentiation, extracellular mucin production, a Crohn's-like lymphoid reaction, and a frequent relation to HNPCC.[8-10]

Until recently, although many small-scale studies had been conducted to clarify the biologic nature of MSI-H CRCs, there were no reports correlating histological changes according to anatomic site and histological comparison with HNPCC-associated MSI-H tumors versus sporadic MSI-H tumors. In order to identify any clinicopathologic characteristics related to anatom-

ic site and history of HNPCC, we analyzed the histopathologic features of 135 MSI-H CRCs and grouped and analyzed them according to anatomic site and type of genetic change.

MATERIALS AND METHODS

Case selection

A total of 135 MSI-H CRCs and 30 MSI-L CRCs from the 1,460 colon cancers that had been operated and diagnosed at Yonsei University Medical Center from 2003 to 2007 were included in this study. A total of 140 MSS CRCs that had been operated and diagnosed between May and October 2005 were used as controls. All cases had been confirmed by histological examination and molecular workup.

MSI analysis

DNA was extracted from formalin-fixed and paraffin-embedded tissue samples of 1,458 colon cancer cases. Tumor and adjacent normal areas were separately marked and collected for DNA extraction. The recommended panel (bat26, bat25, D5S346, D2S123, and D7S250) was used for genetic classification. PCR was done and differences in amplified PCR fragments between tumor and normal tissue were detected by gene analyzer. MSI-H tumors were defined as having instability in 2 or more markers (Fig. 1A), MSI-L tumors as having instability in 1 marker (Fig. 1B), and MSS tumors as showing no apparent instability (Fig. 1C).[5] MSI-H CRCs accounted for 9.68% and MSI-L CRCs 2.05% of the 1,460 colorectal specimens that had been accumulated over the 5 years of the study (Table 1). This study was approved by the Institutional Review Board and informed consent from all participants was obtained.

Analysis of clinical features

Clinical variables such as sex, mortality, anatomic site, num-

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

Molecular markers	MSI-H (n=135, 9.25%)	MSI-L (n=30, 2.05%)	MSS (n=1,295, 88.70%)
bat26	123	2	0
bat25	125	7	0
D5S346	108	5	0
D2S123	117	6	0
D7S250	121	10	0

MSI, microsatellite instability; MSI-H, high frequency MSI; MSI-L, low-frequency MSI; MSS, microsatellite stable.

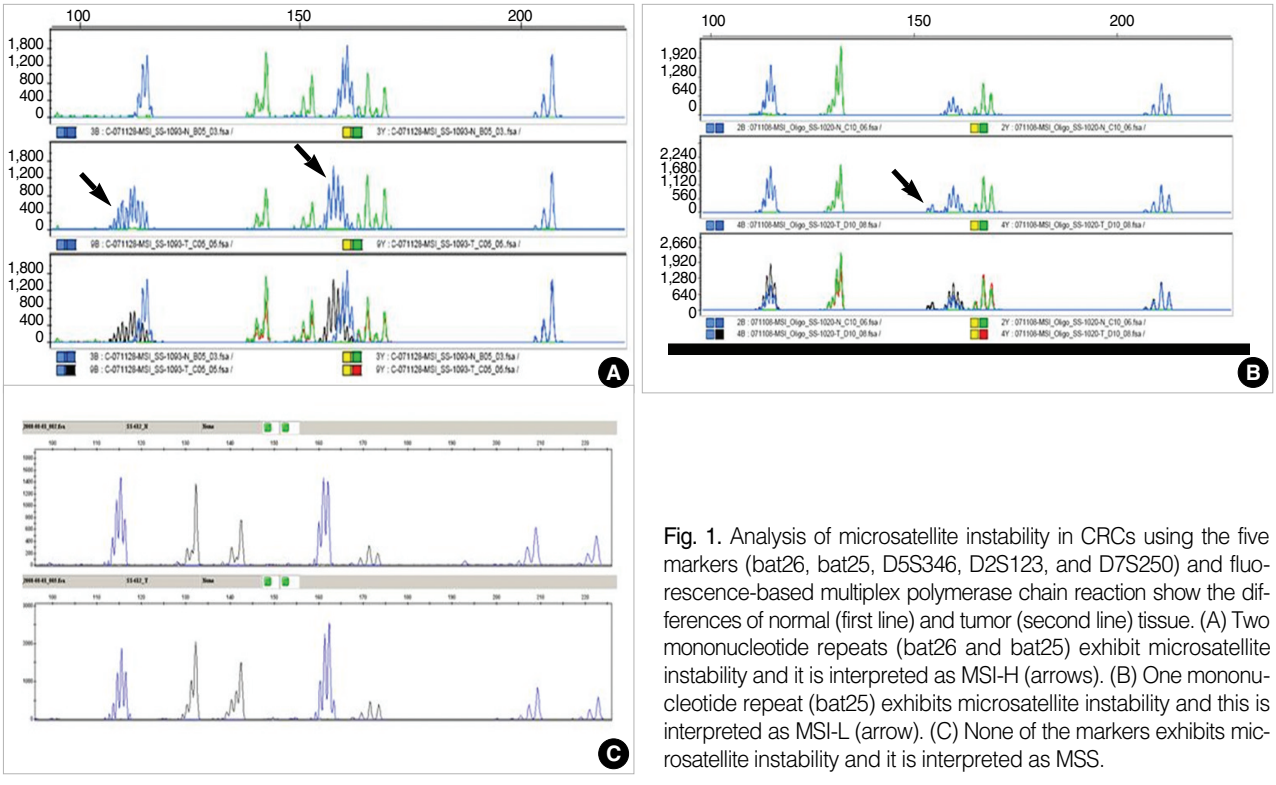

Fig. 1. Analysis of microsatellite instability in CRCs using the five markers (bat26, bat25, D5S346, D2S123, and D7S250) and fluorescence-based multiplex polymerase chain reaction show the differences of normal (first line) and tumor (second line) tissue. (A) Two mononucleotide repeats (bat26 and bat25) exhibit microsatellite instability and it is interpreted as MSI-H (arrows). (B) One mononucleotide repeat (bat25) exhibits microsatellite instability and this is interpreted as MSI-L (arrow). (C) None of the markers exhibits microsatellite instability and it is interpreted as MSS.

ber of tumors, stage, patient survival status, HNPCC association, and CEA level at diagnosis of CRC patients were obtained from medical records. The anatomic site of the tumor was classified as the ascending colon, transverse colon, descending colon, sigmoid colon, or rectum (Table 2) and divided into right and lest-side based on the location with regard to the splenic flexure.

The number of tumor masses was determined according to endoscopic and gross findings. For diagnosis of HNPCC, we used the Amsterdam II criteria[11,12] which were presented in 1999. Preoperative serum CEA levels for all patients were measured at the time of diagnosis (normal range: 0-5 ng/mL), and we divided CRCs into 2 groups; normal (range: 0-5.0 ng/mL) and abnormal ($\geq$5.0 ng/mL).

Analysis of pathologic features

The clinicopathologic features of MSI-H and MSS CRCs were further analyzed according to site (right vs left) and history of HNPCC. The histological type of tumor was subclassified by mucinous carcinoma (carcinoma containing mucin over 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 conventional adenocarcinomas.[13]

Tumors were graded on the basis of glandular appearance and divided into well differentiated (glandular structures in more than 95% of the tumor), moderately differentiated (glandular structures in 50-95% of the tumor), and poorly differentiated lesions (glandular structures in less than 50% of the tumor). Lymphocytic reactions were estimated when there was more than a moderate degree of peritumoral or intratumoral lymphocytic infiltration and/or lymphoid follicle formation.

Extracellular mucin pool formation and tumor necrosis was rated as absent or present. The infiltrative tumor borders were classified as irregular or pushing types.

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

Site	MSI-H (%)	MSS (%)	Total (%)
Ascending	72 (53.3)	17 (12.1)	89 (32.4)
Transverse	10 (7.4)	1 (0.7)	11 (8.1)
Descending	15 (11.1)	9 (6.4)	24 (8.7)
Sigmoid	18 (13.3)	40 (28.6)	58 (21.1)
Rectum	20 (14.8)	73 (52.1)	93 (33.8)
Total	135 (100.0)	140 (100.0)	275 (100.0)

MSI-H, high frequency MSI; MSS, microsatellite stable; CRCs, colorectal carcinomas.

Statistical analysis

Statistical analysis of each parameter was performed to clarify associations between MSI-H and MSS CRCs using the χ^2 test for categorical variables and SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). All reported p-values are 2-sided and p-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Different in clinicopathlogic features between MSI-H CRCs and MSS CRCs

The clinicopathologic features of 135 MSI-H CRCs were compared to 140 MSS CRCs (Table 3, 4). The significantly different clinicopathologic features were mortality (p=0.003), anatomic site (p<0.001), pathologic tumor stage (p<0.001), CEA level (p=0.013), histological type and grade (p<0.001), peritumoral and intratumoral lymphocytic reaction (p<0.001), and mucin formation (p<0.001). However, there was no significant differ-

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

Variable category	MSI-H No. (%)	MSS No. (%)	Total No. (%)	p-value
Sex				0.622
Male	79 (58.5)	86 (61.4)	165 (60.0)	
Female	56 (41.5)	54 (38.6)	110 (40.0)	
Mortality[a]	2/123 (1.6)	13/119 (10.9)	15/243 (6.2)	0.003
Stage				<0.001
I	21 (15.6)	15 (10.7)	36 (13.1)	
II	68 (50.4)	45 (32.1)	113 (41.1)	
III	34 (25.2)	38 (27.1)	72 (26.2)	
IV	12 (8.9)	42 (30.0)	54 (19.6)	
Tumor site				<0.001
Right	82 (60.7)	20 (14.3)	102 (37.1)	
Left	53 (39.3)	120 (85.7)	173 (62.9)	
Mass number				0.211
Single	128 (94.8)	137 (97.9)	265 (96.4)	
Multiple	7 (5.2)	3 (2.1)	10 (3.6)	
CEA[b]				0.013
Normal	109 (80.7)	94 (67.1)	203 (73.8)	
Abnormal	26 (19.3)	46 (32.9)	72 (26.2)	
History of HNPCC	8 (5.9)	0 (0.0)	8 (2.9)	0.003

[a]12 MSI-H CRC patients and 21 MSS CRC patients were missing in clinical follow up; [b]Preoperative serum CEA level, normal (0.0-5.0 ng/mL), abnormal (higher than 5.0 ng/mL).
MSI-H, high frequency MSI; MSS, microsatellite stable; CRCs, colorectal carcinomas; HNPCC, hereditary nonpolyposis colorectal cancers.

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

Variable category	MSI-H No. (%)	MSS No. (%)	Total No. (%)	p-value
Histological type				<0.001
Medullary carcinoma	11 (8.1)	0 (0.0)	11 (4.0)	
Mucinous carcinoma	37 (27.4)	13 (9.3)	50 (18.2)	
Conventional carcinomas	87 (64.4)	127 (90.7)	214 (77.8)	
Mucin				<0.001
Absence	53 (39.3)	98 (70.0)	151 (54.9)	
Presence	82 (60.7)	42 (30.0)	124 (45.1)	
Histological grade				<0.001
WD	40 (29.6)	81 (57.9)	121 (44.0)	
MD	29 (21.5)	41 (29.3)	70 (25.5)	
PD	66 (48.9)	18 (12.9)	84 (30.5)	
Peritumoral lymphocytic reaction				<0.001
Absence	59 (43.7)	98 (70.0)	157 (57.1)	
Presence	76 (56.3)	42 (30.0)	118 (42.9)	
Intratumoral lymphocytic reaction				<0.001
Absence	81 (60.0)	131 (93.6)	212 (77.1)	
Presence	54 (40.0)	9 (14.3)	63 (22.9)	
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)	

MSI-H, high frequency MSI; MSS, microsatellite stable; CRCs, colorectal carcinomas; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

ence in sex, tumor mass number and tumor necrosis between the 2 groups (p>0.05).

Comparison of clinicopathologic features between right- and left-sided MSI-H CRCs

MSI-H CRCs showed a right-sided preponderance (right-sided tumors: 82/135 [60.7%] in MSI-H CRCs vs 18/140 [12.8%] in MSS CRCs, p<0.001). Differences between right- and left-sided MSI-H CRCs were further analyzed (Table 5). More advanced tumor stage was found in left-sided MSI-H CRCs (stage III and IV: 20/53 [37.7%] in left-sided MSI-H CRCs vs 26/82 [31.7%] in right-sided MSI-H CRCs, p=0.022). Serum CEA level, checked before surgery, was higher in right-than left-sided CRCs (increased CEA level: 5/53 [9.4%] in left-sided MSI-H CRCs vs 21/82 [24.7%] in right-sided MSI-H CRCs, p=0.027). There was a trend toward poor survival (mortality: 2/49 [4.1%] in left-sided MSI-H CRCs vs 0/74 [0.0%] in right-sided MSI-H CRCs, p=0.080) and towards less mucin formation (mucin formation: 27/53 [50.9%] in left-sided MSI-H CRCs vs 55/ 82 [67.1%] in right-sided MSI-H CRCs, p=0.061). No significant differences in sex, survival rate, histologic type and grade of tumor, peritumoral and intratumoral lymphocytic reaction, tumor necrosis, tumor border, association with HNPCC, and 5 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 No. (%)	Left side No. (%)	Total No. (%)	p-value
Sex				0.996
Male	48 (58.5)	31 (58.5)	79 (58.8)	
Female	34 (41.5)	22 (41.5)	56 (41.2)	
Mortality[a]	0/74 (0.0)	2/49 (4.1)	2/123 (1.6)	0.080
Stage				0.048
I	8 (9.8)	13 (24.5)	21 (15.4)	
II	48 (58.5)	20 (37.7)	68 (50.7)	
III	20 (24.4)	14 (26.4)	34 (25.0)	
IV	6 (7.3)	6 (11.3)	12 (8.8)	
Mass number				0.552
Single	77 (93.9)	51 (96.2)	128 (94.8)	
Multiple	5 (6.1)	2 (3.8)	7 (5.2)	
CEA[b]				0.027
Normal	61 (75.3)	48 (90.6)	109 (80.7)	
Abnormal	21 (24.7)	5 (9.4)	26 (19.3)	
Histological type				0.201
Medullary carcinoma	6 (7.3)	5 (9.4)	11 (8.1)	
Mucinous carcinoma	27 (32.9)	10 (18.9)	41 (27.4)	
Conventional carcinomas	49 (59.8)	38 (71.7)	87 (64.4)	
Mucin				0.061
Absence	27 (32.9)	26 (49.1)	53 (39.3)	
Presence	55 (67.1)	27 (50.9)	82 (60.7)	
Histologic grade				0.386
WD	22 (26.8)	18 (34.0)	40 (29.6)	
MD	16 (19.5)	13 (24.5)	29 (21.5)	
PD	44 (53.7)	22 (41.5)	66 (48.9)	
HNPCC	6 (7.3)	2 (3.8)	16 (11.9)	0.386

[a]12 MSI-H CRC patients and 21 MSS CRC patients were missing in clinical follow up; [b]Preoperative serum CEA level: normal (0.0-5.0 ng/mL); abnormal (higher than 5.0 ng/mL).
MSI-H, high frequency MSI; CRCs, colorectal carcinomas; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; HNPCC, hereditary nonpolyposis colorectal cancers.

Comparison of clinicopathologic features between HNPCCs and sporadic MSI-H CRCs

The clinicopathologic features of MSI-H CRCs were compared to those of sporadic tumors and HNPCCs with HNPCC being defined as a positive result on the Amsterdam II criteria. We found that not all of the clinicopathologic features were different between CRCs from HNPCCs and sporadic MSI-H CRCs (Table 6).

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

Variable category	HNPCC No. (%)	Sporadic CRC No. (%)	Total No. (%)	p-value
Sex				0.814
Male	5 (62.5)	74 (58.3)	79 (58.5)	
Female	3 (37.5)	53 (41.7)	56 (41.5)	
Mortality[a]	0/7 (0.0)	2/116 (1.6)	2/123 (1.7)	0.726
Stage				0.421
I	1 (12.5)	20 (15.7)	21 (15.6)	
II	3 (37.5)	65 (51.2)	68 (50.4)	
III	2 (25.0)	32 (25.2)	34 (25.2)	
IV	2 (25.0)	10 (7.9)	12 (8.9)	
Site				0.394
Right	6 (75.0)	76 (59.8)	82 (60.7)	
Left	2 (25.0)	51 (40.2)	53 (39.3)	
Mass number				0.495
Single	8 (100.0)	120 (94.5)	128 (94.8)	
Multiple	0 (0.0)	7 (5.5)	7 (5.2)	
CEA[b]				0.635
Normal	6 (75.0)	103 (81.7)	109 (81.3)	
Abnormal	2 (25.0)	23 (18.3)	26 (18.7)	
Histological type				0.602
Medullary carcinoma	0 (0.0)	11 (8.7)	11 (8.1)	
Mucinous carcinoma	3 (37.5)	34 (26.8)	37 (27.4)	
Conventional carcinoma	5 (62.5)	82 (64.6)	87 (64.4)	
Histological grade				0.076
WD	5 (62.5)	35 (27.6)	40 (29.6)	
MD	0 (0.0)	29 (22.8)	29 (21.5)	
PD	3 (37.5)	63 (49.6)	66 (48.9)	
Mucin				0.394
Absence	2 (25.0)	51 (40.2)	53 (39.3)	
Presence	6 (75.0)	76 (59.8)	82 (60.7)	
Peritumoral lymphocytic reaction				0.711
Absence	4 (50.0)	55 (43.3)	59 (43.7)	
Presence	4 (50.0)	72 (56.7)	76 (56.3)	
Intratumoral lymphocytic reaction				0.882
Absence	5 (62.5)	76 (59.8)	81 (60.0)	
Presence	3 (37.5)	51 (40.2)	54 (40.0)	
Necrosis				0.632
None	5 (62.5)	66 (52.0)	71 (52.6)	
Focal	3 (37.5)	49 (38.6)	52 (38.5)	
Extensive	0 (0.0)	12 (9.4)	12 (8.9)	
Tumor border				0.883
Irregular	6 (75.0)	98 (77.2)	104 (77.0)	
Pushing	2 (25.0)	29 (22.8)	31 (23.0)	

[a]12 MSI-H CRC patients and 21 MSS CRC patients were missing in clinical follow up; [b]Preoperative serum CEA level, normal (0.0-5.0 ng/mL); abnormal (higher than 5.0 ng/mL).
HNPCC, hereditary nonpolyposis colorectal cancers; CRCs, colorectal carcinomas; MSI-H, high frequency MSI; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

DISCUSSION

In this study, the clinicopathologic features of MSI-H CRCs were analyzed and compared to thosed of MSS CRCs.

The incidence of MSI-H CRCs (9.25%) was slightly 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. It is well known that the incidence of rectal cancer in the Korean population (58.0%) is higher than in Western populations (19.3%).[14,15] A very low incidence of MSI-H in rectal cancer has been reported,[5] and this was confirmed in our study (incidence of rectal cancer: 20/135 [14.8%] in MSI-H CRCs vs 73/140 [52.1%] in MSS CRCs, p<0.001). Therefore, the high preponderance of rectal cancer in the Korean population would explain a slightly lower incidence of MSI-H CRCs in our study. [5]

Most of the clinicopathologic findings in our patients were in concordance with previously reported characteristics of MSI-H CRCs. Our MSI-H CRCs showed similarities to previously reported clinicopathologic findings[8,9]: right-sided preponderance (82/135 [60.7%] in MSI-H cancers vs 20/140 [14.3%] in MSS cancers, p<0.001); frequent mucin formation (82/135 [60.7%] in MSI-H cancers vs 42/140 [30.0%] in MSS cancers, p< 0.001); relatively greater number of mucinous carcinomas (37/135 [27.4%] in MSI-H cancers vs 13/140 [9.3%] in MSS carcinomas, p<0.001); and more peritumoral lymphoid reactions (76/135 [56.3%] in MSI-H cancers vs 42/140 [30.0%] in MSS carcinoma, p<0.001). Frequent intratumoral and peritumoral lymphoid reactions and mucin formation in MSI-H CRCs are related to the specific subtype of CRCs; medullary and mucinous carcinoma. We simplified the subclassification of histological type into medullary carcinoma, mucinous carcinoma, and other conventional adenocarcinomas,[13] and used this scheme to analyze clinicopathologic features. Medullary carcinomas were present in 11 of 135 (8.1%) MSI-H CRCs and mucinous carcinomas in 37 of 135 (27.4%) MSI-H CRCs. In contrast, no medullary carcinoma and 13 (9%) mucinous carcinomas were present in 140 MSS CRCs. These findings indicate that the histologic type of MSI-H CRCs is different from MSS CRCs, and is related to different biologic features.

CEA is a useful marker in screening for early disease, aiding diagnosis, determining prognosis, predicting likely responses to specific therapies, surveillance of patients undergoing curative resection, and monitoring the treatment of advanced disease.[16,17] We found abnormal CEA level less frequently in MSI-H CRCs than MSS CRCs (abnormal CEA level: 26/135 [19.3%] in MSI-H CRCs vs 46/140 [32.9%] in MSS CRCs, p=0.013). In a previous report that analyzed CEA level according to MSI-H and MSS CRCs, Chang *et al.* compared clinicopathological parameters between 19 MSI-H and 194 MSS CRCs and showed

that MSI-H CRCs had a greater elevation in CEA level than MSS CRCs (CEA level [>5 μg/mL]: 15/19 [78.9%] in MSI-H CRCs vs 97/194 [50%] MSS CRCs, p=0.013).[18] However, they analyzed a smaller number of MSI-H CRCs, and both MSI-H and MSS CRCs showed higher CEA levels than our data did.

We classified tumor location as ascending colon, transverse colon, descending colon, sigmoid colon, and rectum, and tumor distribution was divided into right- and left-sided relative to the splenic flexure. We validated a right-sided preponderance of MSI-H CRCs that was statistically significant (p<0.001). We further analyzed the difference between right- and left-sided CRCs with MSI-H. There were no significant differences in sex, mortality, histological type and grade, peritumoral and intratumoral lymphocytic reaction, necrosis, tumor border, clinical history of HNPCC, and 5 molecular markers. We found a higher tumor stage (stage III and IV: 20/53 [37.7%] in left-sided MSI-H CRCs vs 20/82 [31.7%] in right-sided MSI-H CRCs, p=0.022) and a lower CEA level (increased CEA level: 5/53 [9.4%] in left-sided MSI-H CRCs vs 21/82 [24.7%] in right-sided MSI-H CRCs, p=0.027). These findings suggest that closer surveillance is necessary for the detection of left-sided MSI-H CRCs.

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.[11] We diagnosed HNPCC cased according to the Amsterdam II criteria and found 8 HNPCCs with MSI-H. It is well known that the majority of HNPCCs are located in the right colon.[5] In our study, among these 8 cases, 6 (75.0%) were located in the right colon. However, there was no statistical significance to the difference in tumor location between MSI-H CRCs associated with HNPCCs and sporadic MSI-H CRCs. Decreased preoperative serum levels of CEA in HNPCC have been reported.[19] However, our study found no significant difference in serum CEA level between HNPCC and sporadic MSI-H CRCs (p=0.635). Thus, we did not find any difference in clinicopathological characteristics between HNPCC-related MSI-H CRCs and sporadic MSI-H CRCs. These findings indicate that the molecular pathways involved in the pathogenesis of MSI-H tumors are similar although the initial inactivating mechanisms of mismatch repair genes are different.

CONCLUSIONS

We found that left-sided MSI-H CRCs were infrequent. However, they showed similar clinicopathological characteristics as right-sided MSI-H CRCs, except for less frequent-mucin formation, higher tumor stage and more frequent normal CEA levels. We could not find any significant clinicopathological differences between HNPCC-related MSI-H CRCs and sporadic MSI-H CRCs. These findings suggest that although the initial inactivating mechanisms of mismatch repair genes were different, the molecular pathways involved in the pathogenesis of MSI-H tumors are homogeneous, and show similar clinicopathological features.

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