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Gastric cancer is associated with a high rate of microsatellite instability versus chronic gastritis: A retrospective study

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Abstract

***Objective**: Microsatellite instability (MSI) in gastric cancer contributes to genetic complexities of gastric cancer. In the current study, we employed a panel of mononucleotide and dinucleotide markers to detect MSI in 99 gastric cancer patients and 91 chronic gastritis patients and further analyzed the association of MSI with clinicopathologic variables of the study patients. **Methods**: We retrospectively analyzed the clinicopathologic data of primary gastric cancer patients and chronic gastritis patients. MSI was analyzed using five microsatellite markers, including D2S12, D5S346, D17S799, BAT26, and D18S34. MSI was defined as either a band shift or the appearance of a novel band in DNA. Multivariate logistic regression analysis was used to predict risk of MSI. **Results**: Seventeen (17.2%) gastric cancer patients and 7 (7.7%) chronic gastritis patients were positive for MSI (P=0.012). Multivariate analysis further showed that gastric cancer was associated with a significantly higher likelihood for MSI versus gastritis (OR 3.73; 95% CI 1.19, 11.72; P=0.024) while age, drinking or smoking was not associated with increased MSI. **Conclusion**: Gastric cancer is associated with a high rate of MSI. MSI should be further explored in future studies with a larger sample size for its role in gastric cancer development and as a predictive biomarker.*

***Keywords:** microsatellite instability (MSI); gastric cancer; gastritis; predictive biomarker; clinicopathologic variables*

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Introduction

Gastric cancer accounts for 7% of total global cancer incidence and is the third most common death-causing cancer in the world(1-3). The disease is often diagnosed at an advanced stage as early gastric cancer is often asymptomatic. China is a high risk country for digestive tract cancers; gastric cancer ranks fourth in cancer mortality in the country, with 498,000 gastric cancer deaths reported in 2015 (4, 5).

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Delineation of the landscape of genetic changes in gastric cancer is paving the way for morpho-molecular stratification of gastric cancer (6, 7). The majority of gastric cancer is sporadic and genetic alterations including gene mutations, chromosomal abnormalities, and gene amplifications such as *MET*, *MYC*, and *ERBB2* amplification have been documented (9-12). Somatic mutations in mitochondrial DNA were also reported in gastric cancer in humans (13). Recently, Park *et al.* have shown that accumulation of microsatellite instability (MSI) in gastric cancer further contributes to the genetic complexities of gastric cancer (14). Microsatellites are tandem repeats of short DNA motifs composed of 1–6 nucleotides scattered throughout the nuclear and mitochondrial DNA in both eukaryotic and prokaryotic genomes. MSI results from inactivation of DNA repair proteins and is present in 15–20% of gastric cancer patients (15-20). In a systemic review with meta-analysis, Choi *et al.* analyzed the data of 5,438 gastric cancer patients from 24 studies and found that 13.1% (712) of them had MSI, and MSI was associated with good prognosis of gastric cancer patients (21).

In the current study, we employed a panel of mononucleotide and dinucleotide markers (BAT26, D2S123, D5S346, D17S799, and D18S34(22)) to detect MSIs in 99 gastric cancer patients and 91 chronic gastritis patients and further analyzed the association of MSI with clinicopathologic variables of the study patients.

Material and Methods

Patients

We retrospectively analyzed the clinicopathologic data of chemotherapeutically naïve patients with pathologically proven primary gastric cancer who underwent curative gastrectomy at the Second Hospital of Hebei Medical University (Shijiazhuang, China) between March 2007 and June 2016. Gastric cancer was staged using the American Joint Committee on Cancer stage criteria (AJCC, 8th Edition) (23, 24). We excluded patients with a history of prior gastric surgery or who had a family history of hereditary nonpolyposis colorectal cancer (HNPCC**)**. In addition, patients with chronic gastritis were included as non-cancer control subjects.

The study protocol was approved by the ethics committee of the authors' affiliated hospital. No patient consent was required because of the retrospective nature of the study. Patient data were anonymized in the current paper.

Sequence analysis of MSI

Genomic DNA and mitochondrial DNA were extracted from blood and biopsy samples using the QIAmp DNeasy Blood and Tissue kit (Qiagen, Hilden, Germany) according to the tissue protocol by the manufacturer. MSI was analyzed using five microsatellite markers, including D2S12, D5S346, D17S799, BAT26, and D18S34. The sequences of the primers used in the current study were as follows: BAT26: 5'-TGACTACTTTTGACTTCAGCC-3' (sense) and 5'-AACCATTCAACATTTTTA-ACCC-3' (antisense); D2S123: 5'-AAA-CAGGATGCCTGCCTTTA-3' (sense) and 5'-GGACTTTCCACCTATGGGAC-3' (antisense); D5S346: 5'-ACTCACTCTAGTGATA-AATCGGG-3' (sense) and 5'-CAGATAAGA-CAGTATACTAGTT-3' (antisense); D17S799: 5'-ATTGCCAGCCGTCATT-3' (sense) and 5'-GACCAGCATATCATTATAGACAA-3' (antisense); D18S34: 5'-CAGAAAAT-TCTCTCTCTGGCTA-3'(sense) and5'-CT-CATGTTCCTGGCAAGAAT-3'(antisense). Polymerase chain reaction (PCR) was performed and PCR products were denatured in formamide loading buffer and resolved on 7.5% and 10% polyacrylamide gels. Silver stain was performed to develop bands. MSI was defined as either a band shift or the appearance of a novel band in DNA and direct DNA sequencing was done for

PCR products with altered band patterns including nucleotide 16190-16209 and nucleotide 602-583 using commercially available kit (Applied Biosystems, Foster City, CA, USA) and ABI PRISM Genetic Analyzer 3100 (Applied Biosystems) as instructed by the manufacturer. PCR was performed at least three times independently to rule out any artifacts. No shifted microsatellites were defined as microsatellite stable (MSS).

Statistical analysis

Counting variables were compared between groups using chi-square test or Fisher exact test. For continuous variables, Student's *t*-test was used for normally distributed data; Wilcoxon two-sample test was used for non-normally distributed data. Demographic and baseline variables of gastric cancer patients were all arbitrarily entered into multivariate logistic regression analysis to predict risk of MSI. SAS 9.3 was used as statistical analysis software. The tests were two sided and $P<0.05$ was considered to be statistically significant.

Results

Demographic and baseline characteristics of the study population

We included 99 gastric cancer patients in the current study. The demographic and baseline characteristics of these patients are shown in Table 1. Their median age was 58 years (range 42 to 82 years; 50.7 ± 16.1 years) and 69.7% were male patients. The median duration of history of gastric cancer was 2 months (range 0.07 to 36 months). The median tumor size was 7.00 cm (range 0.50 to 16.00 cm). Thirteen (13.1%) patients had distant metastasis. Adenocarcinoma was the most common tumor in the patients (95.0%). Stage I tumor was seen in 8.1% of the patients, stage II 23.2%, stage III 56.6% and stage IV 12.1%. In addition, 91 gastritis patients were included and they were significantly older (59.3 ± 8.2 years) than the gastric cancer patients ($P < 0.001$).

MSI and gastric cancer characteristics

Seventeen (17.2%) gastric cancer patients were positive for MSI. The demographic and baseline characteristics of gastric cancer patients with or without MSI are shown in Table 2. Patients with and without MSI were comparable in the demographic and baseline variables. Though gastric cancer patients with MSI had a numerically higher rate of positive family history (11.76%) than gastric cancer patients without MSI (1.22%), no statistical difference was observed (P=0.075).

Seven (7.69%) chronic gastritis patients were tested positive for MSI and the positive rate of MSI of gastritis patients was significantly lower than that of gastric cancer patients (P=0.012). Patients with MSI were comparable in age, gender, smoking and drinking variables *versus* those without MSI (Table 3). Gastritis and gastric cancer patients were also comparable in smoking and drinking variables (Table 4). Our multivariate analysis further showed that gastric cancer was associated with a significantly higher likelihood for MSI *versus* gastritis (OR 3.73; 95% CI 1.19, 11.72; P=0.024) while age, drinking or smoking were not associated with increased MSI (Table 5).

Discussion

In this study, we detected the presence of MSIs in patients with gastric cancer or chronic gastritis. Our results showed that gastric cancer patients had a significantly higher rate of MSI than chronic gastritis, and occurrence of MSI was independent of patient clinicopathologic characteristics and unrelated to the drinking or smoking status of the study patients.

The incidence of MSI in gastric cancer patients in the current study was 17.2% and it falls into the range of 13% to 44% for gastric cancer as

Table 1.Demographic and baseline characteristics of gastric cancer patients in this study

Variables	All
N (%)	99 (100)
Age, years	
Mean(SD)	59.26 (8.20)
Median (range)	58 (42,82)
Male gender	69 (69.70)
Drinking (Yes)	18 (18.18)
Smoking^ (Yes)	32 (32.32)
Positive family history[&]	3 (3.03)
Tumor size, cm	
Body	37 (37.37)
Antrum	48 (48.48)
Cardia	16 (16.16)
Fundus	35 (35.35)
Tumor size, cm	
Mean(SD)	7.15 (3.84)
Median(range)	7.00 (0.5,16.0)
Depth of tumor invasion	
T1-3	20 (20.20)
T4	79 (79.80)
Vascular invasion	24 (24.24)
Nerve invasion	5 (5.05)
Invasion of the duodenum	9 (9.09)
Metastasis	13 (13.13)
Pathological type	
Poorly differentiated adenocarcinoma	30 (30.30)
Undifferentiated carcinoma	1 (1.01)
Adenocarcinoma	55 (55.56)
Signet ring cell carcinoma	4 (4.04)
Mucinous adenocarcinoma	8 (8.08)
Mucosal adenocarcinoma	1 (1.01)
Tumor AJCC stage	
IA	3 (3.03)
IB	5 (5.05)
IIA	4 (4.04)
IIB	19 (19.19)
IIIA	29 (29.29)
IIIB	22 (22.22)
IIIC	5 (5.05)
IV	12 (12.12)

*Data are expressed N (%) unless otherwise indicated.

^Smoking is defined as consumption of >100 cigarettes/lifetime or >10 pack year history.

[&]a history of gastric cancer in the immediate familymembers of the patient

Table 2. Demographic and baseline characteristics of gastric cancer patients stratified by MSI status

Variables	MSI	MSS	Statistical tests	P values
No. (%)	17(17.2)	82(82.8)		
Age, years			Student's t-test	0.358
Mean(SD)	57.59(6.17)	59.61(8.56)		
Median(IQR)	57(54,64)	59(54,66)		
Male gender	12(70.59)	57(69.51)	Chi-square test	0.930
Duration, months			Wilcoxon two sample test	0.936
Mean(SD)	5.72(9.79)	4.31(6.37)		
Median(IQR)	2(1,3)	2(1,6)		
Drinking (Yes)	2(11.76)	16(19.51)	Chi-square test	0.683
Smoking (Yes)	4(23.53)	28(34.15)	Chi-square test	0.394
Positive family history*	2(11.76)	1(1.22)	Fisher's Exact Test	0.075
Tumor involvement			Chi-square test	
Body	9(52.94)	28(34.15)		0.145
Andrum	9(52.94)	39(47.56)		0.686
Cardia	2(11.76)	14(17.07)		0.858
Fundus	6(35.29)	29(35.37)		0.996
Tumor size, cm			Wilcoxon two sample test	0.236
Mean(SD)	8.12(4.06)	6.95(3.78)		
Median(range)	8(6,10)	6(4,8)		
Lymph node metastasis, n(%)			Wilcoxon two sample test	0.798
Mean(SD)	3.94(4.07)	3(2,5)		
Median(IQR)	4.9(5.57)	4(0,8)		
Vascular invasion	7(41.18)	17(20.73)	Chi-square test	0.139
Nerve invasion	0(0.00)	5(6.10)	Fisher's Exact Test	0.584
Pathological type			Fisher's Exact Test	0.535
Adenocarcinoma	16(94.12)	79(96.34)		
Signet ring cell carcinoma	1(5.88)	3(3.66)		
Differentiation, n(%)			Chi-square test	0.697
Yes	10(58.82)	44(53.66)		
No	7(41.18)	38(46.34)		
TNM				
T			Chi-square test	0.199
T1-3	1 (5.00)	19 (95.00)		
T4	16 (20.25)	63 (79.75)		
N			Fisher's Exact Test	0.126
N0				
N1	5 (29.41)	22 (27.50)		
N2	6 (35.29)	10 (12.50)		
N3	4 (23.53)	23 (28.75)		
N4	2 (11.76)	25 (31.25)		
M			Chi-square test	1.000
M0	15 (88.24)	72 (87.80)		
M1	2 (11.76)	10 (12.20)		
Stage			Fisher's Exact Test	0.945
I	1(5.88)	10(12.20)		
II	3(17.65)	16(19.51)		
III	10(58.82)	46(56.10)		
IV	3(17.65)	10(12.20)		

*The uncle of one patient with mucinous adenocarcinoma died of gastric cancer; both parents of a patient with low differentiated adenocarcinoma had esophageal cancer; the father of one patient with adenocarcinoma had gastric cancer.

Table 3. Comparison of the study subjects with and without MSI

	MSI	MSS	P values
No.(%)	22(11.58)	168(88.42)	
Age, years			0.759
Mean(SD)	56.68 ± 9.67	54.94 ± 13.73	
Median(IQR)	57.5 (52,64)	56 (47,66)	
Male gender, N(%)	14(63.64)	116(69.05)	0.608
Drinking, N(%)			0.159
Yes	5(22.73)	64(38.10)	
No	17(77.27)	104(61.90)	
Smoking, N(%)			0.519
Yes	4(18.18)	41(24.40)	
No	18(81.82)	127(75.60)	

Table 4. Comparison of gastric cancer patients and gastritis patients in MSI status and drinking and smoking variables

Variables	Gastric cancer	Gastritis	P value
Male gender	69(69.70)	61(67.03)	0.693
MSI			0.012
Yes	17(17.17)	5(5.49)	
No	82(82.83)	86(94.51)	
Drinking			0.233
Yes	32(32.32)	37(40.66)	
No	67(67.68)	54(59.34)	
Smoking			0.063
Yes	18(18.18)	27(29.67)	
No	81(81.82)	64(70.33)	

Table 5. Multivariate logistic regression analysis of risk factors for MSI in the study population

Independent variable	OR(95%CI)	P
Age	0.996(0.954, 1.041)	0.871
Drinking	0.493(0.146, 1.663)	0.254
Smoking	1.162(0.311, 4.345)	0.824
Male *vs*. female	0.975(0.339, 2.806)	0.962
Gastric cancer *vs.* gastritis	3.730(1.188, 11.715)	0.024

earlier reported. Habano *et al.* (25) reported an incidence rate of 16% for MSI in gastric cancer patients while Liu *et al.* reported a noticeably higher rate (58.3%) of MSI in Chinese gastric cancer patients (26). Several factors contribute to differences in the reported rates of MSI including the use of different MSI panels or the number of MSI markers used, or differences in the clinicopathologic features of the patient population. We used a five-marker panel (D2S12, D5S346, D17S799, BAT26, and D18S34) in the current study. Liu *et al.* also used a five-marker panel (Bat25, Bat26, D5S346, D17S250, and D2S123); 3 of their makers are identical to the ones used in our study. Wang *et al.* used a panel of 42 markers and reported a rate of 33.9% for MSI in Chinese gastric cancer patients (27).

We observed that 7.7% of the chronic gastritis patients were positive for MSI. Kashiwagi *et al.* studied MSI in gastritis, adenoma and adenocar-

cinoma retrospectively and found a very low rate of MSI (1.82%, 1/55) in chronic gastritis patients (28). Six (35.2%, 6/17) patients with gastric adenoma or well-differentiated adenocarcinoma had MSI. Interestingly, these patients had MSI when they were at the stage of chronic gastritis. We also observed a higher likelihood of gastric cancer *versus* gastritis for MSI (OR3.73; 95%CI 1.19, 11.72; *P*=0.024). However, currently, any causal role of MSI in gastric cancer remains speculative.

Discovery of predictive biomarkers and gene mutations and other genetic alterations paves the way for morphomolecular stratification of gastric cancer, which allows targeted therapy of gastric cancer patients(6). It remains to be further investigated whether MSI could be integrated into morphomolecular stratification of gastric cancer. A recent integrative genomic analysis has led to the proposal of a molecular classification of gastric cancer into four subtypes, including the MSI subtype (29). Hopefully, a morphomolecular approach to gastric cancer classification could lead to the identification of novel therapeutic targets and biomarkers for screening, prognosis, prediction of response to treatment, and monitoring of gastric cancer progression. The panel o MSI markers (BAT26, D2S123, D5S346, D17S799, and D18S3) used in the current study has been previously described and has been shown to be able to discriminate MSI gastric cancer patients from non-MSI gastric cancer patients with good sensitivity and specificity (22, 30, 31).

The current study has several limitations. The study is retrospective in nature and has a small sample size. We did not carry out immunohistochemistry study of mismatch repair proteins of gastric carcinoma tissues. Furthermore, we did not carry out analysis of histological or molecular subtypes of gastric cancer.

In conclusion, gastric cancer is associated with a significantly higher rate of MSI. MSI should be further explored in future studies with a larger sample size for its role in gastric cancer development and as a predictive biomarker.

Author's contributions

LX and GL contributed to the study design; all authors collected the data and performed the data analysis; all authors prepared the manuscript.

Conflict of interest

All the authors declare that they have no conflict of interest.

Ethics approval and consent to participate

Ethical approval was given by the Ethics Committee of the Second Hospital of Hebei Medical University, Shijiazhuang, China. All patients gave their written information consent.

Data and material availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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