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Expression of Mismatch Repair Proteins in Early and Advanced Gastric Cancer in Poland

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Literature Search F
Funds Collection G

ABCDEF 1 Katarzyna Karpińska-Kaczmarczyk
AC 1 Magdalena Lewandowska
AB 2 Małgorzata Ławniczak
AB 2 Andrzej Białek
ACDE 1 Elżbieta Urasińska

1 Department of Pathology, Pomeranian Medical University, Szczecin, Poland
2 Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland

Corresponding Author: Katarzyna Karpińska-Kaczmarczyk, e-mail: kkarp@pum.edu.pl
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Background: Mutations in DNA of mismatch repair (MMR) genes result in failure to repair errors that occur during DNA replication in microsatellites, resulting in accumulation of frameshift mutations in these genes and leading to DNA mismatch replication errors and microsatellite instability. Gastric cancers (GCs) with high MSI (MSI-H) are a well-defined subset of carcinomas showing distinctive clinicopathological features. In this study we investigated the rate of MSI and the correlation between MSI status and clinicopathological features of GC.

Material/Methods: The study included 107 patients with GCs: 61 with advanced gastric cancers (AGC) and 46 with early gastric cancer (EGC). MSI deficiency in GCs was assessed by the immunohistochemical analysis of expression of MMR proteins – MLH1, MSH2, MSH6, and PMS2 – using formalin-fixed and paraffin-embedded tissue.

Results: A total of 6 (5.6%) MSI-H were observed. The loss of MMR proteins expression was associated with the intestinal type of GC in Lauren classification, and tubular and papillary architecture in WHO classification. There was no statistically significant association between negative MMR expression and other selected clinical parameters: age, sex, tumor location, depth of invasion (EGC and AGC), lymph nodes status, presence of the ulceration, and lymphocytic infiltrate.

Conclusions: In the present era of personalized medicine, the histological type of GC and MMR proteins status in cancer cells are very important for the proper surveillance of patients with familial GC and sporadic GCs, as well as for selecting the proper follow-up and treatment. Larger collaborative studies are needed to verify the features of MSI-H GCs in Poland.

MeSH Keywords: Microsatellite Instability • Neoplasms by Histologic Type • Stomach Neoplasms

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Background

Gastric cancer (GC) is one of the leading causes of death worldwide, although the incidence has gradually decreased in nearly all populations [1,2]. Poland has an average prevalence of gastric cancer, with an incidence rate of 11.8/100 000 for men and 4.6/100 000 for women. It has been estimated that 5000 people in Poland developed gastric cancer in 2012. It is the fifth most common cancer for men and the eighth most common for women [3,4].

The pathogenesis of GC involves multiple genetic and epigenetic alterations, chromosomal instability, microsatellite instability (MSI), and mutations. However, most GCs show chromosomal instability, approximately 10% of GCs appear to have a familial predisposition, and about half of these can be attributed to hereditary germline mutations [5,6]. Mutations in mismatch repair (MMR) genes result in failure to repair errors that occur during DNA replication in microsatellites, resulting in accumulation of frameshift mutations in these genes and leading to DNA mismatch replication errors and microsatellite instability [7–9]. Microsatellites are defined as stretches of DNA sequence where a single nucleotide or units of 2 or more nucleotides are repeated in the genome [10]. MSI are insertion and deletion mutations at microsatellites; these structures are particularly prone to DNA replication errors [10]. The key MMR proteins involved in the process of repair of DNA mismatch replication are MLH1, MSH2, MSH6, and PMS2 [7,8,10,11]. MSI is an extremely useful tool for the detection of families affected by hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, due to a defect in the DNA MMR system [10–12]. MSI occurs in GC associated not only with Lynch syndrome but also in sporadic GCs due to the somatic alteration of MMR genes promoter methylation [9,13]. A standard test for MSI, known as the Bethesda panel, was proposed by the National Cancer Institute. This panel consists of 2 mononucleotide repeats (BAT25 and BAT 26) and 3 dinucleotide repeats (D2S123, D5S346, and D17S250) [10]. Using this panel, instability can be classified as high-level MSI (MSI-H) with instability at the 5 Bethesda panels, and as low-level MSI (MSI-L) with instability at only 1 of the 5 Bethesda panels. Microsatellite stable (MSS) tumors present non-positive markers in the Bethesda panel [14]. The tumor is interpreted as MSI-low (MSI-L) if 1 marker is unstable and MSI-high (MSI-H) if 2 or more markers show instability [9]. The MSI status can also be assessed by immunohistochemistry (IHC) to highlight the expression of MMR proteins in tumor cells [7]. While almost all MSI-H tumors are MMR protein-deficient, most MSI-L tumors have no MMR protein defect [10]. GCs with MSI-H are a well-defined subset of carcinomas showing distinctive clinicopathological characteristics [15,16].

GC is commonly diagnosed at an advanced stage and has extremely poor prognosis. Chemotherapy remains the cornerstone of treatment for GC patients with locally advanced and metastatic disease [17]. Unlike mutations in other DNA repair genes that generally increase sensitivity to drug treatment, defects in MMR genes often confer resistance to cancer therapy [12]. This difference can be attributed to the contribution of MMR proteins to the initiation of apoptosis in response to DNA damage [12]. Assessment of the MSI status in GC may potentially serve as a predictor of chemotherapy response, thereby improving patient stratification in the administration of this otherwise toxic treatment [7].

The aim of the study was to reveal the MSI in tissue samples of GCs, as well as the relation of MSI and clinical characteristics of patients and histological parameters of tumors.

Material and Methods

The study included 107 patients with GC: 61 with AGC and 46 with EGC, diagnosed from 2008 to 2014 at the Department of Pathology, Pomeranian Medical University in Szczecin. Patient characteristics are shown in Table 1. Patients with AGC were treated with total gastrectomy. Patients with EGC were treated with ESD (endoscopic submucosal dissection) (28 cases), polypectomy (7 cases), and partial (5 cases) and total gastrectomy (6 cases). All patients with EGC removed en block by endoscopic submucosal dissection (ESD) or by polypectomy were treated in the Department of Gastroenterology, Pomeranian Medical University (Table 1).

Expression of MMR proteins in gastric tumors was determined by immunohistochemical analysis. Immunostaining was carried out in the paraffin sections using standard techniques. The monoclonal antibodies – mouse anti-MLH1 (Ventana, #7090-4535), mouse anti-MSH2 (Ventana, # 760-4265), mouse anti-MSH6 (Ventana, #790-4455), and rabbit anti-PMS2 (Ventana, #760-4531) – were used for IHC staining. MSI deficiency was determined when the tumor showed loss of expression for the examined MMR proteins. Normal tissue adjacent to the tumor was used as a positive internal control. Evaluation was performed independently by 2 observers. Each case of GC was reclassified on the basis of the available hematoxylin and eosin stained slides according to Lauren and WHO classification for histological type and TNM classification for the depth of invasion (T) and lymph node (N) status [18–20]. A semiquantitative approach was used to score the intensity of lymphocytic infiltrate in the vicinity of the tumor (0=the lack of lymphocytic infiltrate, 1=mild lymphocytic infiltrate, 2=moderate lymphocytic infiltrate, 3=severe lymphocytic infiltrate). Student's t-test or Fisher's exact test were used for statistical analysis. Statistica (version 10, StatSoft, Inc., ww.statsoft.com) was used for statistical analysis and a p value <0.05 was considered statistically significant.

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Table 1. Clinicopathological characteristic of patients (No=107).

Factor	Mean ±SD or n (%)	
Age	65.2±11.4	
Gender		
Male	40	(37.4)
Female	67	(62.6%)
EGC	46	(42.9%)
AGC	61	(57.0%)
Total gastrectomy	67	(62.6%)
Partial gastrectomy	5	(4.7%)
ESD	28	(26.2%)
Polypectomy	7	(6.5%)
Tumour location		
Cardia + corpus	55	(51.4%)
Antrum	52	(48.6%)
Depth of invasion		
T1	46	(42.9%)
T2	11	(10.3%)
T3	33	(30.8%)
T4	17	(15.9%)
Lymph node metastases		
N0	71	(66.4%)
N1+N2+N3	36	(33.6%)
Lauren classification		
Intestinal type	59	(55.1%)
Diffuse type +mixed type	48	(44.8%)
WHO classification		
Tubular adenocarcinoma	47	(43.9%)
Papillary adenocarcinoma	8	(7.5%)
Poorly cohesive carcinoma	30	(28.0%)
Mixed adenocarcinoma	22	(20.6%)
Histological grade		
Grade 1+2	55	(51.4%)
Grade 3	52	(48.6%)
Ulceration		
Present	36	(66.6%)
Absent	71	(66.4%)
Lymphocytic infiltrate		
0+1	82	(76.6%)
2+3	25	(23.4%)

EGC – early gastric cancer; AGC – advanced gastric cancer; ESD – endoscopic submucosal dissection.

Results

A total of 6 (5.6%) MSI-H were observed (Figures 1–3). Four GCs exhibited the loss of MLH1 and PMS2. This group included 1 case of EGC, and in 2 GCs the loss of MSH2 and MSH6 was present (Table 2).

In the present study we analysed clinicopathological features associated with MSI tumor phenotype. Patients with MMR-negative GC did not differ from patients with MMR-positive tumors with respect to age (72.7±4.9 *vs.* 64.8±11.5, p=0.099). Only 1 patient with an MSI tumor was younger than 70 years old. Four patients with MMR-negative GC were females and 2 were males. GCs with MSI did not show any predilection for antral localization. Three tumors with MSI were localized in the gastric cardia (the case of EGC is included in this group), 1 tumor in the gastric corpus, and 2 in the antrum. The depth of invasion of MSI tumors (T category in TNM classification) was T1a for EGC, 1 case of AGC was classified as T2, 2 cases as T3, and the last 2 as T4a. All GCs with MSI were histologically classified as the intestinal type of GCs in Lauren classification. Half of the cases of MSI GC in WHO histologic classification showed a tubular architecture and the other half were papillary tumors. Five tumors with MSI were classified as well differentiated cancers and only 1 tubular AGC was poorly differentiated. Only 1 case of AGC, which was defined above as a poorly differentiated tubular adenocarcinoma, tested positive for lymph node metastatic process (N1). Moderate lymphocytic infiltrate in the vicinity of the tumor was found in half of the cases and weak infiltrate was found in the other half. Correlations between clinicopathological features and MMR proteins expression are summarized in Table 3.

Loss of MMR proteins expression was associated with the intestinal type of GC in Lauren classification, and was associated with tubular and papillary architecture in WHO classification. However, age, sex, tumor location, depth of tumor invasion (T stage in TNM classification), regional lymph node metastases (N stage in TNM classification), grade of histological differentiation, presence of ulceration, and presence of lymphocytic infiltrate in the vicinity of the tumor were not associated with negative MMR proteins immunohistochemical expression.

Discussion

This study investigated the prevalence of MSI-H in GC. Six cases out of 107 (5.6%) examined GCs in immunohistochemical staining revealed the loss of expression of MMR. In other studies, MSI was found in 5.6–30% of GC [15,21–25]. Only 1 case of EGC showed MSI. A limited number of studies have dealt with MSI in EGC and most were focused on AGC [22,26,27]. In many papers significantly lower rates of MSI in EGC were

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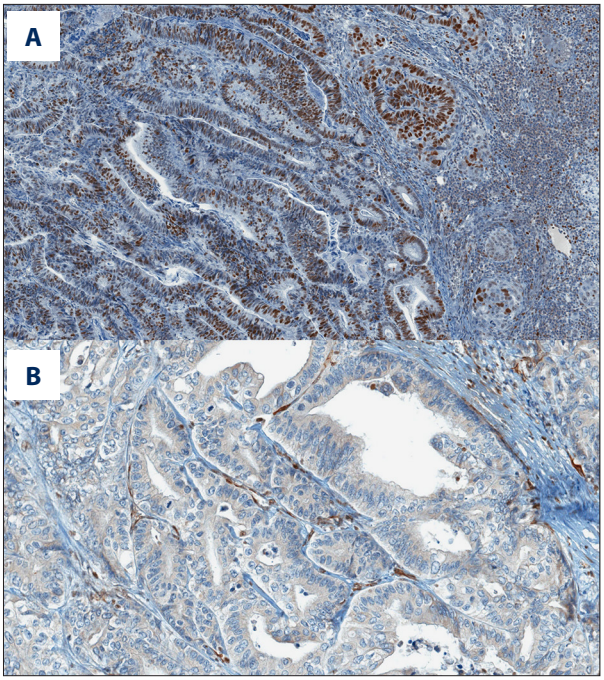

Figure 1. Immunohistochemical staining for MSH6 and MSH2 proteins in AGC. (**A**) Malignant tubules of AGC and benign lymphoid cells showing positive nuclear staining for MSH6 protein. (**B**) MSI-H AGC exhibiting a complete loss of MSH2 expression, with stromal cells showing positive staining.

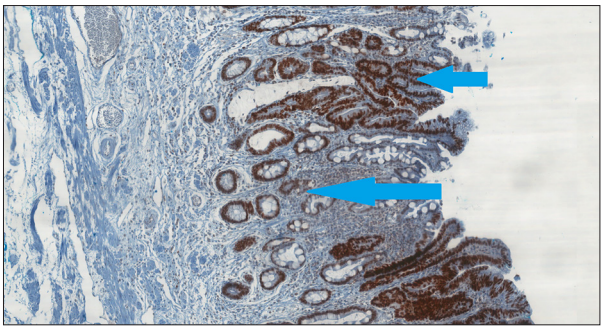

Figure 3. EGC with overexpression of MSH6 (short arrow) and adjacent benign gastric glands displaying normal strength of MSH6 expression (long arrow).

observed [5,16,26]. In the present study and in the literature, the loss of MLH1 in GC was more common than the loss of MSH2 [5,15,23,27]. Hypermethylation of the promoter region of MLH1 is the major causative event in the development of human cancers with MSI phenotype [23].

In most research, GC or colon cancer MSI was analysed using PCR method [5,16,22]. Studies in which MSI was assessed with both methods found 93.3–100% correspondence between PCR and IHC [5,10,16,22]. The sensitivity of IHC for detecting MSI-H tumors was the highest when the expression of 4 MMR

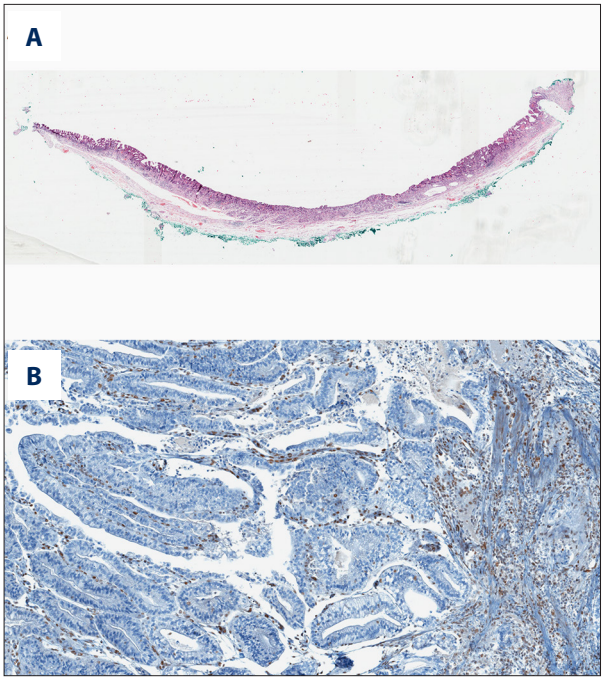

Figure 2. (**A**) Histological slide of EGC removed en block by ESD. (**B**) EGC exhibiting a complete loss of MLH1 expression, with the positive control in the lymphoid cells of adjacent mucosa.

Table 2. Immunohistochemical staining for MLH1, MSH2, MSH6 and PMS2 in GC.

MMR proteins expression	Negative GC	Positive GC
MLH1 PMS2	4 (3.7%)	103 (96.3%)
MSH2 MSH6	2 (1.8%)	105 (98.2%)

GC – gastric cancer; MMR – mismatch repair proteins; MLH1 – Human Mutl Homolog 1; MSH2 – Human MutS Homolog 2; MSH6 – Human MutS Homolog 6; PMS2 – PMS1 homolog 2, mismatch repair system component.

proteins was analyzed [5,22]. In most papers, GCs with MSI were associated with a more favorable prognosis, larger size, female sex, advanced age, less lymph node involvement, intestinal histotype, and distal location [16,28,29]. In the present study, MSI-H tumors were found in patients whose average age was over 70 years and whose history of genetically determined cancer was negative. The age-dependent accumulation of DNA damage seemed to affect the frequency of MSI in older individuals [16]. GCs in older patients were usually sporadic neoplasms, and MSI found in some of them was the result of promotor methylation [30]. The key to any cancer genetics evaluation is a complete 3-generation family history [5]. In patients with positive Amsterdam criteria invoked for Lynch syndrome and with gastric tumors that exhibit MSI

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Table 3. Univariate analysis of clinicopathological characteristics and MMR proteins expression in GC.

Variable	MMR negative (n=6)	MMR positive (n=101)	p
Gender			0.194
Male	2 (3.0%)	65 (97.0%)	
Female	4 (10%)	36 (90.0%)	
Tumour location			0.679
Upper (cardia + corpus)	4 (7.3%)	51 (92.7%)	
Lower (antrum)	2 (3.9%)	50 (96.2%)	
Depth of invasion-T			0.233
T1 (EGC)	1 (2.2%)	46 (97.8%)	
T2+T3+T4 (AGC)	5 (8.2%)	57 (91.8%)	
Lymph node metastases-N			0.661
N0	5 (7.0%)	66 (93.0%)	
N1, N2, N3	1 (2.8%)	35 (97.2%)	
Lauren classification			0.032
Intestinal	6 (10.2%)	53 (89.8%)	
Non intestinal (diffuse, mixed)	0 (0%)	48 (100%)	
WHO classification			0.027
Tubular+papillary	6 (10.1%)	49 (89.9%)	
Others	0 (0%)	52 (100%)	
Histological grade			0.206
G1+G2	5 (9.1%)	50 (90.9%)	
G3	1 (1.9%)	51 (98.1%)	
Ulceration			1.000
Present	2 (5.6%)	34 (94.4%)	
Absent	4 (5.6%)	67 (94.4%)	
Lymphocytic infiltrate			0.138
0+1	3 (3.7%)	79 (96.3%)	
2+3	3 (12.0%)	22 (88.0%)	

EGC – early gastric cancer; AGC – advanced gastric cancer.

in immunohistochemistry, further germline testing is necessary to confirm a molecular diagnosis of Lynch syndrome [5].

In contrast to much previous research, the present study demonstrated that MSI GCs were more commonly localized in the upper part of the stomach than in the antrum. Three of these cancer cases were cardia cancers, whose incidence is rising rapidly in Western countries [30,31]. This result, however, requires further research on larger samples of patients. In the present study there was also a conflicting finding of the relationship between MSI status and gastric cancer aggressiveness, which increases the T stage. In accordance with our data, Kim et al. reported increased aggressive behavior of MSI-H GC [25]. A histological type of GC, in line with WHO and Lauren classifications, was examined, with particular attention focused on the histological structure of cancers with MSI. The histopathological classification of Lauren is one of the most useful classifications, distinguishing 2 main types of GC – intestinal and diffuse

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– which display different clinicopathological profiles and often occur in different epidemiological settings [5,18]. The importance of distinguishing 2 main histopathological types of GC – one with a glandular/intestinal component and the second with diffuse component (isolated cells) – was also highlighted by finding specific genetic changes associated with different types [5,33,34]. MSI-associated GC showed predominantly intestinal histology (more than 90% of cases), which is consistent with our own findings [33]. The intestinal-type carcinoma showed less aggressive behavior than the diffuse type of GC [18,32]. Generally, the intestinal-type carcinoma does not spread more widely in the mucosa than to a point above the infiltrating part of the tumor [18]. The prognosis of patients with intestinal GC is better than that of patients with the diffuse type [32]. A diffuse type of GC was found in hereditary diffuse gastric cancer (HDGC) with E-cadherin (CDH1) mutation [5,33,34]. Although we did not consider E-cadherin expression in the present study, the histological differences between GC with MSI and GC in a patient with HDGC make it worth mentioning. E-cadherin and B-catenin are transmembrane and cytoplasmic proteins, respectively, involved in epithelial cell-cell interactions, and they are abnormally expressed in almost half of GCs [35]. HDGC is an uncommon genetic syndrome [5,33]. Germline mutation of CDH1 was found to be associated with approximately 30% of families with HDGC. About 100 CDH1 mutation-positive families have been reported worldwide [33]. Patients with familial GC syndrome resulting from mutation in the CDH1 gene have up to 80% likelihood of developing GC during their lifetime and up to 60% risk for developing lobular breast cancer in female carriers [5,33]. The loss of E-cadherin may be found by immunohistochemistry [33]. The diagnosis of GC in patients younger than 50 years old should involve a comprehensive analysis of the histological type of cancer, and the clinical examination should be focused on genetically determined cancers. It is possible to use immunohistochemical staining to analyze expression of MMR proteins and CDH1, and the presence of possible mutations can be further confirmed in genetic examination. The EGC cases analyzed in the present study were treated using endoscopy, either ESD or polypectomy. ESD, considered to be a non-invasive therapy of EGC, is mainly used in Japan, Korea, and China [36–38]. The number of subjects with EGC and treated using ESD in our study was very high, given the Polish and European context, and demonstrates that very small lesions may be diagnosed and radically treated. The size EGCs removed with the method did not exceed 2 cm. While diagnosis is based on conventional white light endoscopy findings, the use of dye-based image-enhanced endoscopy (chromoendoscopy) and endoscopic ultrasonography is contributing to improved diagnostic capabilities for EGC [38]. Early detection and early treatment are vital, improving the prognosis of GC, especially in patients with Lynch and HGGC, who need frequent control appointments. ESD is an alternative method of treating early changes for preventive total gastrectomy, which may lead to many complications [33]. The disappointing prognosis of GC calls for the identification of factors predictive of tumor behavior, patient survival, and/or response to treatment [13,39–41]. Many authors have expressed the opinion that in the current era of personalized medicine the histological type of GC and MMR proteins status in neoplastic cells are very important for the proper surveillance of patients with familial GC syndromes and sporadic GCs, and it can be crucial in choosing the proper follow-up treatment [5,13,33].

Conclusions

There is sparse data in the literature on microsatellite instability and gastric cancer Poland [42]. The present study of MSI in GCs used immunohistochemical analysis of MMR proteins expression. To more precisely evaluate the association between GCs and MSI, a more advance molecular examination should be perform using fresh-frozen tumor samples. Our study included 107 patients with GC: 61 with AGC and 46 with EGC. Further collaborative studies with more cases are needed to verify the features of MSI-H GCs in Poland.

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