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ORIGINAL ARTICLE

The Expression of MCM7 is a Useful Biomarker in the Early Diagnostic of Gastric Cancer

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Abstract The aim of this study was to investigate the expression of minichromosome maintenance complex component 7 (MCM7) in gastric mucosal lesions, further to find its potential effect as a biomarker to distinguish intraepithelial neoplasia from gastric mucosal lesions. MCM7 and Ki67 were detected in 93 cases of gastric mucosal lesions by immunohistochemistry. MCM7 and Ki67 expression in GT were lowest compared with other groups ($P<0.001$), meanwhile there were significant differences compared with Group IM and other groups in MCM7 and Ki67 expression ($P<0.001$). MCM7 and Ki67 expression in GSC were highest ($P<0.05$). Groups of LGN, HGN and GIC had no significant differences in MCM7 expression ($P>0.05$), but there was significant difference compared with Group LGN and Group GIC in Ki67 expression ($P<0.05$). MCM7 expression elevated with tumor grade increasing and had positive correlation with Ki67 significantly ($r=0.940$, $P<0.001$). Furthermore, in some cases, some tumor cells were immunoreactive to MCM7 but negative to Ki67. So we concluded that MCM7 is helpful for us to make differential diagnosis in pathological grade, MCM7 combination of Ki67 may serve as more sensitive proliferation markers for evaluation of gastric carcinoma and precancerous lesions.

Keywords MCM7 · Ki67 · Intestinal metaplastic · Gastrointestinal epithelial neoplasia

Introduction

Gastric adenocarcinoma used to be the second leading cause of cancer-related death worldwide in the end of the twentieth century [1]. And China had a high incidence and mortality of gastric cancer in the beginning of the twenty-first century [2]. In 2012, the incidence rates of stomach cancer were highest in Eastern Asia (particularly in Korea, Mongolia, Japan, and China), and in less developed countries, stomach cancer among males was also leading cause of cancer death [3]. Early diagnosis, radical surgery and adjuvant therapy in China has improved the prognosis of patients with gastric cancer, but most patients prognosis is still poor [4, 5]. It is generally admitted that improving the early diagnostic rate of gastric cancer and precancerous is of great significance to the early treatment of gastric cancer.

Once there was large discrepancy between Western and Japanese pathologists in the diagnosis of adenoma/dysplasia versus carcinoma for gastric glandular lesions [6], and the Vienna classification of gastrointestinal epithelial neoplasia has been applied for resolving many discrepancies since 1998. Even though, low grade neoplasia (LGN) is still difficult to differentiate from intestinal metaplastic (IM), and it is

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also difficult to distinguish between high grade neoplasia (HGN) and gastric intramucosal carcinoma (GIC) [7–9].

The occurrence of gastric adenocarcinoma is a complex multistep process, it is accompanied by multiple gene mutation, but the specific mechanism is still unclear. Oncogene, tumor suppressor genes, cell cycle regulation factor, cell adhesion molecules, DNA repair genes, genetic factors such as instability and telomerase activation were involved in the occurrence and progress of gastric cancer. The minichromosome maintenance (MCM) protein family, which consists of six members (MCM2–7), is a highly conserved group of DNA-binding proteins [10]. It has been provided the evidence that MCM7 overexpression is correlated with diffuse-type gastric adenocarcinoma survival and siRNA mediated downregulation of MCM7 in gastric cancer cell lines has anti-oncogenic effect [11]. And recently research had pointed out that MCM7 may serve as more sensitive proliferative markers for the evaluation of esophageal lesions [12]. However, clinical significance of MCM7 in gastric precancerous conditions has rarely been addressed.

In this study, we wanted to evaluate the expression of MCM7 and Ki67 in different pathologic stages and grades of gastric mucosal lesions. Meanwhile, we tried to demonstrate whether the MCM7 expression was correlated with gastric cancer multi-step process.

Materials and Methods

Patients

A total of 93 patients who underwent gastric mucosal lesions at the Second Hospital of Shandong University, between June 1, 2011 and October 31, 2015, were enrolled in the study. The clinical information was obtained from the clinical records. All the diagnoses were made following the Vienna classification of gastrointestinal epithelial [6] with HE staining slices by three pathologists.

This study was approved by the Ethics Committee of our hospital. Written informed consents were obtained from all patients for the subsequent use of their resected tissues.

Immunohistochemistry

Specimens were fixed by 10% neutral formaldehyde, conventionally dehydrated, embedded in paraffin, and sliced in 4 μm sections. The sections were deparaffinized in xylene, and then dehydrated in descending dilution of ethanol. For the antigen retrieval regimen, all slides were microwaved in 10 mmol/L sodium citrate buffer (pH 6.0) at 10 min intervals for a total of 20 min. The endogenous peroxidase activity was blocked 10 min of incubation with 3% hydrogen peroxidase (reagent A) at room temperature. After washing in PBS the sections were incubated with monoclonal mouse anti-human MCM7 (clone 47 DC141, dilution 1:100; Abcam) or Ki67 (clone MIB-1, dilution 1:50; DAKO) overnight at 4 °C. The sections were washed with PBS and incubated with polymerase auxiliaries (reagent B) for 20 min, after washing in PBS the sections were incubated with biotinylated secondary antibody (reagent C) for 30 min, at room temperature and finally DAB was visualized. Tissues were counterstained with hematoxylin. Negative control was designed by using PBS instead of primary antibody.

Sections were scored by light microscopy. The nuclear expression of MCM7 and Ki67 was positive. The percentage of positive cells was expressed as the mean value of counted glandular tube in five fields.

Statistical Analysis

The variables were described as follows: n, proportion, mean and standard deviation. The predominance of each variable among different grades was using χ^2 test for gender and ANOVA for age, MCM7 and Ki67. *Dunnett-t* test was used for MCM7 and Ki67 comparison among grades. Correlation analysis was used for MCM7 and Ki67. All analyses were performed using SPSS 18.0 software package for Windows (SPSS Inc., Chicago, IL). The P value less than 0.05 was statistically significant.

Results

Patient Characteristics and MCM7 and Ki67 Expression in Gastric Mucosal Lesions

According HE staining of the 93 cases in our study, 18 were gastritis with Helicobacter pylori infection (GT) (19.35%), 16 were IM (17.20%), 11 were LGN (11.83%), 8 were HGN (8.60%), 13 were GIC (13.98%), and 27 were gastric submucosal carcinoma /beyond (GSC) (29.03%). The HE staining results were showed in Fig. 1A-F.

The overall mean age was 60.23 years old. 60 were males (64.52%) and 33 were females (35.48%). Age and gender had no significant differences among different grades ($P > 0.05$). MCM7 and Ki67 expression in GT were lowest compared with other groups (46.67 ± 8.22, $P < 0.001$; 43.33 ± 7.67, $P < 0.001$), and there were significant difference compared with Group IM and other groups in MCM7 and Ki67 expression (59.63 ± 14.88, $P < 0.001$; 59.38 ± 8.14, $P < 0.001$). MCM7 and Ki67 expression in GSC were highest (91.19 ± 6.40, $P < 0.05$; 93.19 ± 4.27, $P < 0.05$). Groups of LGN, HGN and GIC had no significant differences in MCM7 expression

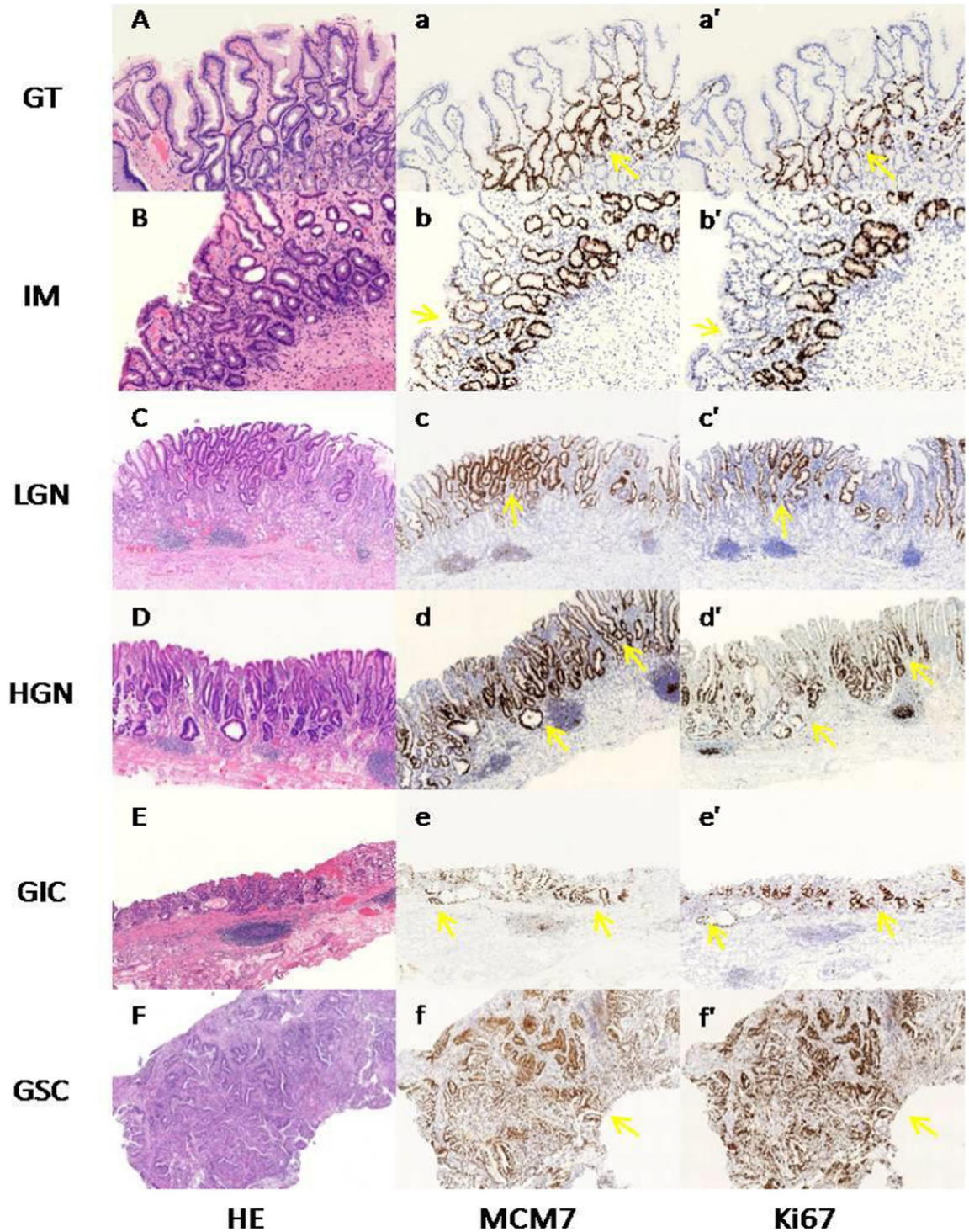

Fig. 1 HE and immunostaining of MCM7 and Ki67 in gastric mucosal lesions. MCM7 and Ki67 showed nuclear staining patterns, *GT* gastritis with Helicobacter pylori infection (**A**, 10×), MCM7 (*a*, 10×) and Ki67 (*a*', 10×) were expressed mildly to moderately in gastric pit neck region cells; *IM* intestinal metaplastic (**B**, 10×), MCM7 (*b*, 10×) and Ki67 (*b*', 10×) were expressed moderately in gastric pit neck region cells; *LGN* low-grade neoplasia (**C**, 4×), MCM7 (*c*, 4×) and Ki67 (*c*', 4×) were expressed strongly in gastric pit neck region and intermediate cells; *HGN* high-grade neoplasia (**D**, 4×), MCM7 (*d*, 4×) and Ki67 (*d*', 4×) showed stronger and diffuser in gastric pit surface mucous cells; *GIC* gastric intramucosal carcinoma (**E**, 4×), MCM7 (*e*, 4×) and Ki67 (*e*', 4×) expressed not only strongly in gastric surface mucous cells, but sporadically and moderately in gastric glands; *GSC* gastric submucosal carcinoma/beyond (**F**, 4×), MCM7 (*f*, 4×) and Ki67 (*f*', 4×) were expressed strongest and extensively in epithelial layers

Table 1 Patient Characteristics and MCM7 and Ki67 expression in different pathologic grades of gastric mucosal lesions

	Group GT (n = 18)	Group IM (n = 16)	Group LGN (n = 11)	Group HGN (n = 8)	Group GIC (n = 13)	Group GSC (n = 27)	F/χ^2	P
Age (years)	58.44 ± 10.00	61.13 ± 9.56	56.91 ± 13.56	64.50 ± 8.60	59.54 ± 11.01	61.30 ± 12.13	0.608	0.694
Gender Male (n, %)	10 (55.56)	11 (68.75)	6 (54.55)	4 (50.00)	8 (61.54)	21 (77.78)	4.183	0.523
Female (n, %)	8 (44.44)	5 (31.25)	5 (45.45)	4 (50.00)	5 (38.46)	6 (22.22)		
MCM7 (%)	46.67 ± 8.22 [a]	59.63 ± 14.88 [b]	79.09 ± 12.41	80.25 ± 8.56	82.31 ± 10.92	91.19 ± 6.40 [c]	50.551	<0.001
Ki67 (%)	43.33 ± 7.67 [a]	59.38 ± 8.14 [b]	77.73 ± 10.57 [d]	82.50 ± 4.63	86.54 ± 9.66	93.19 ± 4.27 [c]	118.488	<0.001

GT gastritis with Helicobacter pylori infection, *IM* intestinal metaplastic, *LGN* low-grade neoplasia, *HGN* high-grade neoplasia, *GIC* gastric intramucosal carcinoma, *GSC* gastric submucosal carcinoma/beyond

[a] meant there were significant differences compared with GT and other groups ($P < 0.001$)

[b] meant there were significant differences compared with Group IM and other groups ($P < 0.001$)

[c] meant there were significant differences compared with Group LGN, HGN, GIC and Group GSC ($P < 0.05$)

[d] meant there was significant difference compared with Group LGN and Group GIC ($P < 0.05$)

(79.09 ± 12.41 vs 80.25 ± 8.56 vs 82.31 ± 10.92, $P > 0.05$), but there was significant difference compared with Group LGN and Group GIC in Ki67 expression (77.73 ± 10.57 vs 86.54 ± 9.66, $P < 0.05$). Moreover, There was a significant and positive correlation between MCM7 and Ki67 in gastric mucosal lesions ($r = 0.940$, $P < 0.001$). The results were included in Table 1.

Immunohistochemistry Characteristics of MCM7 and Ki67 in Gastric Mucosal Lesions

MCM7 and Ki67 expression in Fig. 1a-f and Fig. 1a'-f' were corresponding to different grades of HE staining. MCM7 and Ki67 immunostaining showed nuclear staining patterns. They increased accompanied with the severity of the pathology. MCM7 and Ki67 were expressed mildly to moderately in gastric pit neck region cells of the GT (Fig. 1a, a'), moderately in the same location of the IM (Fig. 1b, b'), and strongly in gastric pit neck region and intermediate cells of the LGN (Fig. 1c, c'). Furthermore, they showed stronger and diffuse in gastric pit surface mucous cells of the HGN (Fig. 1d, d'). In addition, they expressed not only strongly in gastric surface mucous cells, but sporadically and moderately in gastric glands of the GIC (Fig. 1e, e'). Furthermore, in epithelial layers of the GSC, MCM7 and Ki67 expressed strongest and extensively (Fig. 1f, f').

Discussion

MCM mediating regulation of DNA synthesis ensures that DNA replicates only once during each cell cycle and represents a convergence for many signaling pathways involved in cell growth [13]. MCMs are expressed in all cycling cells throughout the cell cycle and are lost in quiescent and differentiating cells [14–17]. They are essential for the initiation of genomic replication. The hexametric protein complex formed by the MCM proteins is a key component of the pre-replication complex (pre-RC) and involved in the formation of replication forks and in the recruitment of other DNA replication related proteins [11, 18, 19]. Dysregulation of MCM, especially MCM7 has been found in neuroblastomas, skin squamous cell carcinoma, colorectal cancer, prostate cancer, medulloblastoma, ovary carcinoma, Hodgkin lymphoma, non-small cell lung cancer and hepatocellular carcinoma, and is associated with tumorigenesis, distant metastasis, advanced disease, relapse and poor clinical prognosis [20–28], And MCM7 has screened by mRNA expression microarray and array-CGH (comparative genomic hybridization) in 9 gastric cancer cell lines [11]. The MCM7 mRNA expression showed positive correlation with DNA copy number change [29]. MCM7 oncogenicity may be linked to over-expression of the hosted miRNAs which targets TGF-β tumor suppressor pathway in gastric cancer [30].

The gastric adenocarcinoma in accordance with Lauren classification is divided into two major histologic subtypes: type one for well-differentiated adenocarcinoma or intestinal adenocarcinoma, another type of poorly differentiated adenocarcinoma or diffuse adenocarcinoma. The intestinal adenocarcinoma is closely associated with atrophic gastritis and intestinal metaplasia [4, 31]. And the intestinal adenocarcinoma can be divided into three steps: intestinal metaplastic, non-invasive neoplasia (LGN, HGN) and gastric invasive neoplasia (GIC, GSC) (Fig. 1b-f). Some reports have indicated that MCM7 was a more reliable and useful biomarker in assessing tumor proliferation, aggression and in the prognosis of patients even than the existing markers such as Ki-67 [32, 33].

In this study, MCM7 was first screened in different pathologic stages and grades of gastric mucosal lesions. We identified that MCM7 was expressed mildly to moderately in gastric pit neck region cells of the GT (46.67 ± 8.22), moderately in

the same location of the IM (59.63 ± 14.88), and there was significant differences compared with GT and IM ($P < 0.001$), which suggesting that the intestinal metaplastic epithelia was more proliferative like as the progenitor/stem cells, it might be the origin of the tumorigenesis. Moreover, it expressed strong in gastric pit neck region and intermediate cells of the LGN (79.09 ± 12.41), stronger and diffuse in gastric pit surface mucous cells of the HGN (80.25 ± 8.56). In GIC, it showed not only strongly in gastric surface mucous cells, but sporadically and weakly in gastric glands (82.31 ± 10.92). In addition, it expressed strongest and extensively in epithelial layers of the GSC (91.19 ± 6.40). These expressions of MCM7 might indicate that it was related to the progression of the tumors. Furthermore, MCM7 fixed in most tumor cells, and had strong staining in the nuclei in GSC, which showed that the initiations of genomic replication were increasing with the regulation of MCM7. In conclusion, The MCM7 expression has showed positive correlation with the occurrence of gastric adenocarcinoma, this indicated that MCM7 expression might promote the tumor progression.

Ki67 is a nuclear proliferation associated antigen expressed in the growth and synthesis phases of the cell cycle but not in the resting phase [34]. Studies have revealed that the Ki67 proliferating index increases in the transformation from IM to gastric carcinoma [35]. And the expression of Ki67 in gastric cancer may provide useful prognostic information for patients [36–38]. A previous study had reported that MCM7 expression had similar distribution as conventional proliferation marker Ki-67 and had significant correlation with Ki-67 in esophageal lesions [12]. Our research also found that MCM7 expression had significantly positive correlation with Ki67 expression in gastric mucosal lesions($r = 0.940$, $P<0.001$). This finding suggested that MCM7 are potential proliferation marker and have potential combined utility in predicting prognosis and behavior in gastric mucosal lesions.

Sometimes, it is hard to distinguish the IM and LGN in our daily work. Our study found that MCM7 and Ki67 were expressed moderately in gastric pit neck region cells of the IM, but strong in gastric pit neck region and intermediate cells of the LGN. In addition, the expression of MCM7 and Ki67 had showed a significant difference between IM and gastrointestinal epithelial neoplasia ($P < 0.001$). These indicated that MCM7 might have potential as a biomarker to separate LGN from IM. However, this study showed there were no significant differences between LGN, HGN and GIC for the expression of MCM7 ($P > 0.05$), But, the expression of Ki67 had significant difference compared with Group LGN and Group GIC ($P < 0.05$). And in some cases, some tumor cells were immunoreactive to MCM7 but negative to Ki67 (Fig. 1c, c', d, d', e, e'). These confirmed that MCM7 combination of Ki67 may be a useful indicator for patients with immunohistochemistry in the early diagnostic of gastric cancer, and LGN and HGN might be the process of the tumorigenesis, but HGN have worse prognosis. In brief, we think that MCM7 is helpful for us to make differential diagnosis in pathological grade of gastric mucosal lesions, and MCM7 combination of Ki67 may serve as more sensitive proliferation markers for evaluation of precancerous lesions and early gastric carcinoma.

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