Micropapillary component in gastric adenocarcinoma: an aggressive variant associated with poor prognosis

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Received: 6 August 2013 / Accepted: 1 February 2014 / Published online: 22 February 2014
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Abstract

Background Adenocarcinomas with a micropapillary component (MPC) have been described as an unusual morphological variant in various organs. However, few reports have described MPCs in gastric carcinomas, and the clinicopathological features of MPC are unclear.

Methods Immunohistochemistry was used to detect the expression of epithelial membrane antigen, CK7, CK20, p53, epidermal growth factor receptor, β -catenin, c-erbB-2, and Ki-67. Correlation of the MPC to tumor stage, lymph node metastasis, and lymphovascular invasion was performed using Fisher's exact test. Kaplan–Meier estimates were used to analyze overall survival.

Results Immunohistochemical staining demonstrated that micropapillary and conventional gastric carcinomas showed similar positivity rates for all markers. However, aberrant expression of E-cadherin was detected in the tumors with MPCs without immunoreactivity in the stroma face. Epithelial membrane antigen showed the

characteristic inside-out staining pattern of MPCs. Lymphatic invasion ($P = 0.003$), venous invasion ($P = 0.017$), lymph node metastasis ($P = 0.014$), and tumor stage ($P = 0.022$) were significantly increased in patients with MPCs when compared with conventional adenocarcinomas. MPC subtype II had a significantly higher frequency of lymph node metastasis than subtype I ($P = 0.014$). However, the proportion of MPC was not associated with lymph node metastases ($P = 0.136$). Overall survival of patients with an MPC was significantly shorter than that of patients with conventional adenocarcinomas ($P = 0.031$). In addition, overall survival was significantly lower in patients with a subtype II MPC growth pattern than in those with subtype I MPC in gastric carcinomas ($P = 0.040$).

Conclusion Gastric adenocarcinomas with MPC appear to be an aggressive variant associated with a poor prognosis. MPCs occurring in gastric adenocarcinomas should be included in surgical pathology reports, even if the proportion of MPC in the lesions is very low in the lesion.

Keywords Micropapillary carcinoma · Lymph node metastasis · Immunohistochemistry

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Introduction

Micropapillary patterns are characterized by morula-like small cell clusters without fibrovascular cores and surrounded by a clear space. Prior studies have found that the micropapillary component (MPC) pattern may occur in various organs, including the breast [1], lung [2], urinary tract [3], ovary [4], parotid gland [5], and colorectum [6]. The micropapillary pattern exhibits biological behaviors associated with unfavorable prognoses, such as high-risk lymph node metastasis and lymphovascular invasion.

Fig. 1 Microscopic features of the micropapillary component (MPC) in gastric carcinoma with MPC. **a** Subtype I MPCs in gastric carcinomas show invasive growth of the micropapillary carcinoma component into fibrous septa. **b** Subtype II MPCs in gastric carcinomas show that most of the MPC lies freely within cystic spaces. **c** The MPC was accompanied by tubular adenocarcinoma. **d** Vascular invasion. **e** Gastric carcinoma with MPC showing tumor-infiltrating neutrophils either intraepithelial or concentrated in the stroma; cholesterol crystals were also observed in tumor stroma. **f** Abundant foam cells are concentrated in the stroma of gastric carcinomas with MPC. Hematoxylin and eosin. $\times 200$. Bar 300 μm

However, data on the clinicopathological and immunohistochemical characteristics of this pathological entity in gastric carcinomas are limited. Gastric carcinoma with micropapillary carcinoma was classified as a subtype of papillary adenocarcinoma in 2010 by the World Health Organization [7]. Gastric carcinomas with invasive micropapillary pattern have been reported to be a variant with poor prognosis and rapid progression. Lymphatic invasions were frequently detected in recent study [8]. Ushiku et al. [9] reported the identification of 17 cases of gastric carcinoma with MPC. In this report, lymphatic and venous invasions were found more frequently than in cases with MPCs, and the presence of MPCs was regarded as an independent predictor of nodal metastasis. Fujita et al. [10] reported 14 cases diagnosed with gastric micropapillary cancer; 3-year disease-free and overall survival rates with an invasive MPC were much lower than the stage-matched controls. A study by Roh and colleagues [11] observed that in 11 cases of gastric carcinoma, micropapillary features were often found at the deep advancing edge of the tumor. However, no significant difference was found in overall survival and the proportion of MPC was not associated with any significant clinicopathological outcome. The objective of this study was to analyze the

clinicopathological features of gastric adenocarcinomas with MPC and compare them with those of gastric tubular or papillary adenocarcinoma without MPC.

Materials and methods

Case selection and clinicopathological features

We identified and retrieved 32 cases of gastric adenocarcinomas (18 cases tubular adenocarcinoma and 14 cases papillary adenocarcinoma) with MPCs of the entire tumors from 2,036 cases (1.57 %) diagnosed during 2004 and 2008 in the First Affiliated Hospital and Shengjing Hospital of China Medical University. The micropapillary component presented with two kinds of growth pattern. One pattern is characterized by most of the MPC (more than 80 %) lying freely within cystic spaces (Fig. 1a; subtype I, 12 cases). The other kind of growth pattern resembles closely that in invasive micropapillary carcinoma of the breast: the micropapillary carcinoma components invade the fibrous septa (Fig. 1b; subtype II, 20 cases).

For comparison, the patients were matched with 98 conventional adenocarcinomas (56 cases tubular

Table 1 Antibodies used

Antibodies	Clones	Dilutions	Sources
CK7	OVT-TL 12/30	1:100	Dako, Carpinteria, CA, USA
CK20	KS20.8	1:500	Dako, Carpinteria, CA, USA
CDX2	CDX-88	1:50	Biogenex, San Ramon, CA, USA
E-cadherin	NCH-38	1:50	Dako, Carpinteria, CA, USA
β-catenin	E247	1:500	Abcam, USA
CD31	JC70A	Ready to use	Dako, Carpinteria, CA, USA
D2-40	D2-40	Ready to use	Dako, Carpinteria, CA, USA
p53	DO-7	1:75	Dako, Carpinteria, CA, USA
Ki67	MIB-1	Ready to use	Dako, Carpinteria, CA, USA
EGFR	31G7	1:50	Invitrogen, Carlsbad, CA, USA
HER2	neu Ab8	1:300	Labvision, Fremont, CA, USA

adenocarcinoma and 44 cases papillary adenocarcinoma) who were diagnosed with non-MPC during the same period. Exact matches were made for age, gender, tumor size, and treatment methods. Two independent, blinded investigators, X.S.Q. and Q.F.Z., examined all tumor slides randomly. The study was approved by the hospital ethical committee.

Histological and immunohistological methods

The surgical specimen was fixed in 10 % buffered formalin solution and embedded in paraffin. Histological sections (4 μm thick) were assessed with hematoxylin and eosin stain. Immunohistochemical staining was performed using the streptavidin–peroxidase system (Ultrasensitive; Mai-Xin, Fuzhou, China) according to the manufacturer's instructions. Heat-induced epitope retrieval was performed. The antibodies used on this study are shown in Table 1; all the internal and external controls worked appropriately. Immunohistochemistry evaluation was separately evaluated by two senior pathologists using a double-blind method. The sections were evaluated at a random ten areas at 400× magnification; positive staining of the tumor cells was defined as a distinct nuclear or membranous pattern in more than 10 % of tumor cells. Ki-67 and p53 expression was evaluated by scoring 10 different tumor fields at 400× magnification and the mean percentage of tumor cells showing nuclear staining.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences Statistical Analysis (version 16.0; SPSS, Chicago, IL, USA). Chi-squared tests were applied to analyze the clinicopathological characteristics between MPC and non-MPC groups. The Kaplan–Meier method was used to estimate the distribution of disease-specific survival times separately for patients with MPC and control groups, and these groups were compared using a log-rank test. All data were represented as mean ± SD. Results were considered statistically significant at $P < 0.05$.

Results

Histological findings

In this study, the micropapillary pattern in gastric carcinomas accompanied tubular adenocarcinoma (Fig. 1c) in 18 cases (53.3 %) and papillary adenocarcinoma in 14 cases (43.7 %). There were no cases of neuroendocrine carcinoma, mucinous carcinoma, or signet-ring cell carcinoma accompanied by MPC. In contrast to gastric carcinoma without MPC, the micropapillary carcinomas were predominantly composed of tumor cells forming a micropapillary pattern surrounded by cleft-like clear spaces. The cells showed abundant eosinophilic cytoplasm and pleomorphic nuclei with clumped chromatin and occasional prominent nucleoli. Vascular invasion was seen in some cases (Fig. 1d; lower right corner). Two cases showed distinct neutrophil infiltration and cholesterol crystal formation (Fig. 1e), and one case showed a large number of foam cells in the tumor stroma (Fig. 1f). Interestingly, neutrophil infiltration and foam cells were still observed in the metastatic lymph nodes.

Immunohistochemical findings

As summarized in Table 2, cases with an MPC showed positive expressions for CK7 (28.1 %), CK20 (56.3 %), epidermal growth factor receptor (EGFR) (18.8 %), HER2 (15.6 %), p53 (mean index, 75 %; Fig. 2a), and Ki-67 (mean index, 64 %). There was no significant difference when compared with those without MPC ($P > 0.05$). Although EGFR was more frequently expressed in the MPC cases (18.8 %, 6/32) than in the cases of the same tumor type without MPC (11.2 %, 11/98 cases), the difference was not statistically significant. CD34 (Fig. 2b) and D2-40 immunohistochemical staining showed no positive endothelial lining in the lacunar-like clear spaces and

Table 2 Summary of immunohistochemical findings of carcinoma with micropapillary carcinoma component (MPC) and conventional adenocarcinoma

Markers	MPC (<i>n</i> = 32) (%)	Non-MPC (<i>n</i> = 98) (%)	<i>P</i> values
CK7	9 (28.1)	34 (34.7)	>0.05
CK20	18 (56.3)	62 (63.3)	>0.05
CDX2	21 (65.6)	69 (70.4)	>0.05
E-cadherin	24 (75.0)	80 (81.6)	>0.05
Aberrant β -catenin	8 (25.0)	16 (16.3)	>0.05
P53	30 (93.8)	95 (96.9)	>0.05
Ki67	32 (100)	98 (100)	>0.05
EGFR	6 (18.8)	11 (11.2)	>0.05
HER2	5 (15.6)	10 (10.2)	>0.05

highlighted the lymphatic and venous invasion of tumor cells. Epithelial membrane antigen (EMA) (Fig. 2c) expression in the stroma-facing surface on the tumorous cell clusters showed the characteristic inside-out pattern of tumors with an MPC. However, the cohort of the same tumor without an MPC showed positive membranous staining patterns. All cases of micropapillary carcinoma and the cohort without MPC of the same tumor type were membrane positive for E-cadherin and showed no difference in stain intensity. However, in micropapillary carcinoma, E-cadherin (Fig. 2d) was highlighted at intercellular cell membranes of the micropapillary tufts but not found in the stroma face. Aberrant β -catenin expression, cytoplasmic, nuclear, or reduced expression was observed both in cases with MPC (25.0 %) and the cohort of the same tumor

type without MPC (16.3 %); however, there were no significant differences between the two groups.

Clinical and pathological characteristics of gastric carcinomas with or without a micropapillary pattern

In the 32 patients, the MPCs occupied 10–90 % of the entire tumors; however, none of the patients showed a pure form of MPC, and 20 cases (62.5 %) contained more than 50 % micropapillary carcinoma component. The mean age of the study population (*n* = 32), which comprised 18 men and 14 women, was 55.4 years (range, 46–72 years). The mean tumor size was 3.4 cm (range, 2.1–6.6 cm). Twenty-six cases underwent postoperative chemotherapy. All the patients had advanced cancer (>T1), and 28 (87.5 %) had lymph node metastasis. TNM stages I, II, III, and IV accounted for 0 % (*n* = 0), 21.8 % (*n* = 7), 62.5 % (*n* = 20), and 15.6 % (*n* = 5), respectively. The clinico-pathological parameters of gastric carcinomas with and without MPC were evaluated (Table 3). Age, sex, tumor size, and histological grade differences between the two groups were not significant. Lymphatic and venous invasion was more frequently observed in cases with an MPC than in the cases of gastric adenocarcinoma without MPC (*P* = 0.003 and *P* = 0.017, respectively). Lymph node metastasis was also more frequently observed in the cases with a MPC (87.5 %) than in gastric adenocarcinoma without a MPC (63.3 %, *P* = 0.014). There was a significantly higher percentage of stage III or IV tumors in the MPC group than in the non-MPC group (78.2 % vs. 54.1 %; *P* = 0.022). Patients with subtype II MPCs showed lymph node metastasis more frequently than

Fig. 2 Immunohistochemical findings. a Expression of p53 in nuclei of neoplastic cells. b CD34 stain shows no positive endothelial lining in the cystic spaces of type I MPCs in gastric carcinomas. c Epithelial membrane antigen (EMA) staining shows characteristic “inside-out” staining pattern in gastric carcinomas with MPC. d Immunohistochemical demonstration of E-cadherin on outer surface of micropapillary tufts of MPCs. $\times 200$. Bar 300 μ m

Table 3 Comparison of clinicopathological findings between gastric carcinomas with MPC and those without MPC

Parameter	MPC (<i>n</i> = 32) (%)	Non-MPC (<i>n</i> = 98) (%)	<i>P</i> values
Age (years)			
<60	22 (68.8)	71 (72.5)	0.822
≥60	10 (31.2)	27 (27.5)	
Gender			
Male	18 (56.3)	59 (60.2)	0.836
Female	14 (43.7)	39 (39.8)	
Tumor size (cm)			
<3	12 (37.5)	45 (45.9)	0.832
≥3	16 (62.5)	53 (54.1)	
Histological grade			
Low or moderate grade	21 (65.6)	56 (57.1)	0.417
High grade	11 (34.4)	42 (42.9)	
Lymph node metastasis			
Negative	4 (12.5)	36 (36.7)	0.014
Positive	28 (87.5)	62 (63.3)	
Lymphatic invasion			
Negative	11 (34.3)	67 (68.4)	0.003
Positive	19 (65.7)	31 (31.6)	
Venous invasion			
Negative	16 (50.0)	72 (73.4)	0.017
Positive	16 (50.0)	26 (26.6)	
TNM stage			
Stage I–II	7 (21.8)	45 (45.9)	0.022
Stage III–IV	25 (78.2)	53 (54.1)	

patients with subtype I MPCs ($P = 0.014$). However, the proportion of MPCs (MPC >50 % and MPC <50 %) did not impact the lymph node metastases ($P = 0.136$) (Table 4).

Survival analyses for other clinicopathological parameters

Follow-up information for 26 cases of gastric carcinoma with MPC was available in 26 cases (range, 2–80 months; mean, 26 months). Twenty-four patients died of disease within 3–80 months, and 2 patients were alive with disease at 48 and 68 months, respectively. The mean follow-up durations were 23 ± 4.5 and 38 ± 3.3 months in patients with and without micropapillary patterns, respectively. A

univariate statistical analysis showed survival differences between invasive micropapillary and gastric adenocarcinoma without an MPC ($P = 0.031$; Fig. 3a). In addition, overall survival was significantly lower in the patients with a subtype II MPC growth pattern than in the patients with a subtype I MPC in gastric carcinomas ($P = 0.040$; Fig. 3b). However, a comparison of the lesions stratified by MPC >50 % and MPC <50 % did not show any statistically significant differences ($P = 0.733$; Fig. 3c).

Discussion

Primary invasive micropapillary carcinoma of the stomach was first reported by Shimoda et al. [12] in 2008. Because of the limited number of gastric carcinoma cases with MPC reported in the literature, the pathological features, immunophenotype, and subtypes are undefined. In this study, by using immunohistochemical staining, we found that the unique “inside-out” pattern of EMA expression in the MPC of gastric cancer was similar to EMA expression in MPC in other organs. Cell membranes at the periphery of tumorous cell clusters were characteristically positive for EMA, indicating an inside-out pattern of reactivity. This distinctive finding is critical for identifying the MPC as confirmed previously [13, 14]. MPC showed immunohistochemical findings similar to the immunohistological findings of the same tumor type without MPC. The proportion of CK7–/CK20+ in the gastric micropapillary carcinomas was 43 %; CDX2 expression was detected in 65.6 % (21/32) of the cases. This immunohistochemical finding (CK7–/CK20+/CDX2+) may be a useful adjunct to discriminate between the diagnosis of the primary gastric origin from intragastric metastasis such as urinary breast, lung, bladder, or ovary metastasis.

The E-cadherin– β -catenin complex plays an integral role in epithelial cell adhesion. Moreover, the aberrant expression of the E-cadherin/ β -catenin complex has been implicated in the invasion and metastasis of carcinoma [15]. Abnormal expression of the E-cadherin–catenin complex occurs frequently in gastric carcinoma and correlates with poor survival [16]. In our study, immunohistochemical staining showed that no significant difference of E-cadherin expression was found between tumors with MPC and those without MPC. However, the expression pattern of E-cadherin was completely different in MPC

Table 4 Nodal metastasis of gastric carcinomas with different percentages and different subtypes of MPC

Parameters	MPC <50 % (%)	MPC >50 % (%)	<i>P</i>	Type I (%)	Type II (%)	<i>P</i>
Negative	3/12 (25.0)	1/20 (5.0)	0.136	4/12 (33.3)	0/20 (0.0)	0.014
Positive	9/12 (75.0)	19/20 (95.0)		8/12 (66.7)	20/20 (100.0)

Fig. 3 a Kaplan–Meier survival curves showed that disease-free survival of gastric carcinoma with micropapillary pattern was worse compared with gastric adenocarcinoma without MPC ($P = 0.031$). b Differences were observed in the two subtypes of MPC of gastric carcinomas. Overall survival of subtype II MPCs (follow-up of 16

cases) was significantly worse than that of subtype I MPCs in gastric carcinomas ($P = 0.040$). c However, no significant differences in survival were found between an MPC component $<50\%$ and an MPC component $>50\%$ ($P = 0.733$)

cases and showed the absence of immunoreactivity in the stroma face. This special expression pattern of E-cadherin could be helpful in distinguishing MPC from the same tumor type without MPC, particularly in cases with limited biopsy samples. In addition, this expression pattern could lead to adherent junction disassembly and consequently to the formation of nonadhesive invasive and metastatic cancer cells, which may be one of the reasons that MPC cells are more aggressive and have higher metastatic potential. Dae-Woon Eom et al. [17] reported that aberrant cytoplasmic and nuclear β -catenin expression was more frequently observed in cases with MPC than in the same tumor type without MPC. However, our study showed no significant difference between the two groups. The differences in these studies may be attributable to different sample sizes and ethnic differences.

The CD44 antigen is another important cell-surface glycoprotein involved in cell adhesion and migration. Regarding human cancers, different research groups analyzing the same neoplastic disease reached contradictory conclusions regarding the correlation between CD44 expression and disease prognosis. In lung adenocarcinoma, the expression of CD44 was found to be similar in the papillary component that generates MPC and in the papillary component without MPC lesions [18]. Simonetti [19] demonstrated that the reduction of CD44 isoforms v5 and v9 in the MPC of breast carcinoma and loss of the CD44 adhesion molecule probably played significant roles in the high incidence of lymphovascular permeation and metastasis in MPC [20]. As for gastric micropapillary carcinoma, the expression of CD44 v9 represents a potential predictive marker for recurrence in early gastric cancers [21]. However, another study of gastric carcinoma found MPC cases with more frequent CD44 v6 expression [17]. Therefore, more variants of CD44 need to be investigated and

evaluated in cases of gastric adenocarcinomas with MPC to reach a precise conclusion.

It has been reported that the micropapillary growth pattern in a gastric carcinoma predicts an increased risk of lymph node metastasis [9]. In recent studies, we demonstrated that lymphatic invasion, venous invasion, lymph node metastasis, and higher tumor stage were significantly increased in gastric adenocarcinoma MPC cases compared to cases without MPC. The published outcome data on MPC in the stomach are limited. In an analysis of 11 cases, Roh et al. [11] showed that micropapillary growth patterns in gastric carcinoma were not found to be associated with survival. In our study, we demonstrated that the survival rate in the patients with gastric cancer and a MPC was significantly lower than that in the patients without a MPC. This observation supports the data reported by Dae-Woon Eom et al. [15]. Moreover, there was no significant difference in survival rate between the patients with an MPC ratio $<50\%$ and those with a ratio $>50\%$. These findings indicate that the MPC may be more likely to metastasize. We recommend that MPC occurring in gastric adenocarcinomas be indicated in surgical pathology reports even if the proportion in the lesion is very low.

In this study, MPC cases were divided into two subtypes based on different growth patterns in the histological features. Our results indicate that the MPC subtype II was more aggressive and increased the risk of lymph node metastasis. Furthermore, survival analysis revealed that the patients with MPC subtype II had worse prognoses than those with subtype I ($P = 0.040$). These findings have not been previously reported, and a larger-scale study is required to understand the mechanisms underlying these processes. Tumor-infiltrating neutrophils may reflect a natural protective cytotoxicity in the host or may be the result of cytokine production by the tumor cells. Several

pieces of evidence indicate that tumor-infiltrating neutrophils may promote tumor progression and a poor prognosis [22, 23]. Poor prognosis and shortened survival associated with micropapillary carcinoma may be in part related to the presence of abundant tumor-infiltrating neutrophils. In this study, two cases showed abundant tumor-infiltrating neutrophils. One case had foam cells and cholesterol crystal formation, which had invaded the lymph nodes with the cancer cells. However, the small sample size in our study limits the applicability of statistical analysis. More studies of tumor-infiltrating neutrophils in micropapillary carcinomas are needed to analyze these relationships.

In summary, gastric carcinoma with MPC is an aggressive variant associated with a poor prognosis. This uncommon variant should be distinguished from gastric adenocarcinoma without MPC and recognized separately. Patients with gastric adenocarcinoma with MPC should be more aggressively treated postoperatively.

Conflict of interest The authors declare that they have no competing interests.

Consent Consent was received from the patient before publication.

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