Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.08.461 2019;26(12):2908-14

Original Article

Evaluation of MUC-1, MUC-4, CDX-2 and OCT-1 expression profiles in gastric carcinomas and precancerous lesions

Yuksel Ulu[1], Seza Umit Tetikkurt[2], Ugur Izol[1], Yunus Donder[3]

[1]Kilis State Hospital, Clinic of Pathology, Kilis, Turkey
[2]Bagcilar Training and Research Hospital, Department of Pathology, Istanbul, Turkey
[3]Kayseri City Hospital, Clinic of General Surgery, Kayseri, Turkey

Abstract

Aim: We investigated the diagnostic and prognostic utility of MUC-1, MUC-4, CDX2 and OCT-1 expression profiles in high-mortality gastric carcinomas and their precancerous lesions.

Material and Methods: Areas in proximity of dysplasias and gastric carcinomas that were suspected of having intestinal metaplasia were stained with PAS / Alcian Blue at pH 2.5 and pH 0.5; Giemsa staining was applied for evaluation of presence of H. Pylori.

Results: Presence of MUC-1 expression may exclude the diagnosis of low-grade dysplasia. MUC-1 and MUC-4 overexpression may be used for determination of groups at high risk of development of carcinomas, primarily in cases of high-grade dysplasia, while overexpression of MUC-1 in gastric carcinomas may be used as a favorable prognostic factor. Presence of CDX2 expression in various histological types of carcinomas gives rise to a suggestion that intestinal differentiation occurs in all histological types at least to some degree. OCT-1 plays a role in CDX2-mediated carcinogenesis and its regulation.

Conclusion: In cases of dysplasia occurring with intestinal metaplasia, CDX2 was found to be expressed at a significantly higher degree (95.5%, p=0.011). Expression of CDX2 and OCT-1 was observed in all high-grade dysplasia cases, and was significantly higher in comparison to low-grade dysplasia cases (p=0.042; p=0.006, respectively). MUC-1 and MUC-4 expression significantly increased with each progressing stage of precancerous lesions in all lesions following low-grade dysplasia (p=0.0001; p=0.027, respectively). MUC-1 expression was the lowest (53.6%) in weak cohesive type carcinomas. Positive immunoreactivity with MUC-1 and CDX2 was higher in cases with a smaller number of metastatic lymph nodes compared to the cases with a larger number thereof.

Keywords: Gastric carcinoma; MUC-1; MUC-4; CDX2; OCT-1

INTRODUCTION

Gastric carcinomas are malignant epithelial tumors. Adenocarcinomas comprise %90-95 of gastric cancers and are the second most common cause of all cancer-related deaths in both men and women (1,2). Diagnosis and follow-up of precursor lesions is vital for early diagnosis, treatment and prognosis of gastric cancers (3). The most important prognostic factor is tumor grade, with life expectancy in patients with untreated advanced-stage gastric cancer varying between 3 to 9 months (4). Despite all advances in diagnostic and treatment modalities of malignant gastric tumors, 5-year survival rate was found to be only 2%, while survival in early- stage gastric cancers approaches 90% (5).

Caudal-related homeobox transcription factor (CDX2) is a homeoboxdomain transcription factor encoded by the CDX2 gene that serves an important function in intestinal development (6,7). Expression of CDX2 has been observed in the nuclei of epithelial cells from the duodenum to the rectum (8). It plays a vital role in cellular differentiation and tumor suppression through activation of cycline-dependent kinase inhibitor p21 (9,10). While CDX2 is heavily stained in early-stage intestinal carcinomas, advanced cancerous lesions with perineural and

Received: 08.08.2019 **Accepted:** 17.12.2019 **Available online:** 09.01.2020
Corresponding Author: Yunus Donder, Kayseri City Hospital, Clinic of General Surgery, Kayseri, Turkey
E-mail: ydonder@hotmail.com

lymphatic invasion exhibit lower degree of staining. These findings may therefore be used as predictors of clinical outcomes in patients with gastric carcinomas (11).

OCT-1 is a transcription factor related to the homeodomain family (12). POU (Pit-1, Oct-1/2, Unc-86) homeodomain proteins play an important role in regulation of CDX2 during development of various organs and systems in early embryogenic stages (13). OCT-1 also plays a role in gastric carcinogenesis of intestinal-type carcinomas (14).

Mucins are high-molecular-weight glycoproteins (15). MUC-1 epidermal growth factor shows its effects through the tyrosine-kinase receptor (16). Its' overexpression has been observed in gastric cells infected with Helicobacter pylori (H. pylori) (17).

MUC-4 is a membrane mucin, first described in tracheobronchial mucosa (18). It is expressed in normal gastric, cervical, intestinal, and lung epithelium cells (19). MUC-4 plays a role in tumor differentiation of gastric mucosal cells through regulation of membrane-localized growth factors and signal pathways related to cell growth (20).

In this study, we aimed to investigate the expression profiles, diagnostic utility and prognostic significance of MUC-1, MUC-4, CDX2 and OCT-1 in gastric carcinomas, which have high mortality rates among cancer-related deaths worldwide, and in the precancerous lesions of these cancers.

MATERIAL and METHODS

Sixty samples of stomach resection materials from patients diagnosed with gastric carcinomas, and 30 gastric biopsy samples defined as low-grade or high-grade dysplasia, obtained in our hospital between the years of 2008 and 2013, were included in the study. Informed consent was obtained from the patients, and Bagcilar Training and Research Hospital Ethics Committee approval was obtained. Hematoxylin and Eosin (H&E) stained preparations obtained from the archived cases were reassessed according to the World Health Organization's histological dysplasia, tumor differentiation grading and histological cancer classification guidelines published in 2010 and AJCC's 2010 TNM Gastric Cancer Staging Manual. The information in the original pathology reports of the samples were used for the pathological and clinical properties of the cases.

Histochemistry

We applied pH2.5 PAS/Alcian Blue stain to the areas with suspected intestinal metaplasia accompanying gastric carcinomas. Endoscopic biopsy materials were interpreted together with previously stained preparations used in routine evaluation. In preparation for staining, deparaffinized and dehydrated 3-4 micron sections were washed with distilled water. Staining was done in the following sequence: 3% aceticacid (3minutes), Alcianblue (30minutes), 3% acetic acid (2seconds), tap water (10minutes), distilled water, nuclear fastred (5minutes), tap water (1 minute). PAS staining was done using periodic acid (5 minutes), Schiff's reagent (20 minutes), running tap water (2 minutes), distilled water, Mayer's hematoxylin (5 minutes), running tap water (2 minutes), and distilled water. After this procedure, the sections were washed with alcohol and xylene, and covered with a sealing substance. We observed magenta staining in neutral mucins, while sialomucin and sulfomucin containing cells were stained blue. Areas with intestinal metaplasia were thereby demonstrated with this staining procedure. In order to differentiate complete and incomplete intestinal metaplasia, PAS/Alcian Blue staining were performed with a pH of 0.5. Sections of 3-4 microns in width were taken from paraffin blocks pertaining to relevant cases and applied onto microscopic slides. Alcian Blue (pH 0.5) Stain Kit by ScyTek Laboratories was used for Alcian Blue staining. After deparaffinization, aceticacid (3minutes), Alcian blue (30minutes), running tap water (2minutes), distilled water (twice) were applied. PAS staining was done using the same protocol as with pH 2.5 PAS/Alcian Blue staining. Sulfomucin cells appeared to be stained in purple-blue, therefore we observed that our intestinal metaplasia areas were incomplete-type intestinal metaplasia.

Giemsa staining was used for evaluation of H.Pylori. Tissue sections of 3-4 microns were placed on the microscopic slides, and following deparaffinization, stained in accordance with the Giemsa protocol using Sakura Tissue-Tek DRS Section Stainer. Xylene, xylene, alcohol, May-Grünwald (5 minutes), water, Giemsa (45 minutes), acetone, acetone, xylene were applied in order, after which the ready preparations were covered with a sealing substance.

Immunohistochemistry

In preparation for histochemical staining of MUC-1 (695 clone, ready-to-use, Biocare), MUC-4 (8G-7 clone, 1:100, Biocare), CDX2 (monoclonal, 1:200, CellMarque), and OCT-1 (polyclonal, 1:100, Gene Tex) antibodies, sections of 3-to-4 micron in width were taken from paraffin blocks and placed on positively charged microscopic slides. After being put in an oven at 60 degrees Celsius for 60 minutes, and then held at room temperature for 10 minutes, the preparations were stained automatically in the Ventana BenchMark XT device with multimer technology according to XT DAB v3 protocol. Following drying and application of 96% alcohol and xylene, the preparations were covered in a sealing substance.

Immunoreactivity Assessment

One hundred cells were selected from the heavily stained areas. For positive internal control, MUC-1 stained cytoplasm and membranes of normal gastric glands, MUC-4 stained membranes of gastric glands and surface epithelial cells, CDX2 stained nuclei of areas of intestinal metaplasia, and OCT-1 stained nuclei of gastric proliferative zones, were used. Zero-to-five percent staining was accepted as negative, 6-25% as mildly

positive (+), 26- 50% as moderately positive (++), and 51-100% as strongly positive (+++). This grading was used for all immunohistochemical staining assessment.

Statistical Analysis

SPSS (Statistical Package for Social Science) version 15.0 was used for the statistical analysis of the acquired data. Aside from using descriptive statistics to illustrate the distribution of the acquired data, Chi-Square and Fisher's exact tests were used for intergroup comparison of categorical variables, and Student T test and Mann-Whitney U test were used for comparison of means between two given groups. Results were assessed based on 95% confidence interval with significance accepted at $p < 0.05$.

RESULTS

30 patients with a diagnosis of dysplasia made by gastric endoscopic biopsies and 60 patients with a diagnosis of carcinoma made with gastric resection were included in the study. Fifty percent of dysplasia cases were identified as low-grade dysplasia, while the other 50% were high-grade dysplasia. Among cases with gastric dysplasia, 11 (%36.7) were women and 19(%63.3) were men, while carcinoma cases included 24 women (%40) and 36 men (%60). Mean age was 63.13±13.69 in patients diagnosed with dysplasia, and 62.57±11.26 in patients with gastric carcinomas. Antrum was the most common location for both grades of dysplasia and carcinomas. In all cases with tubular and papillary-type carcinomas, incomplete intestinal metaplasia was observed in areas neighboring the tumor (Figure-1).

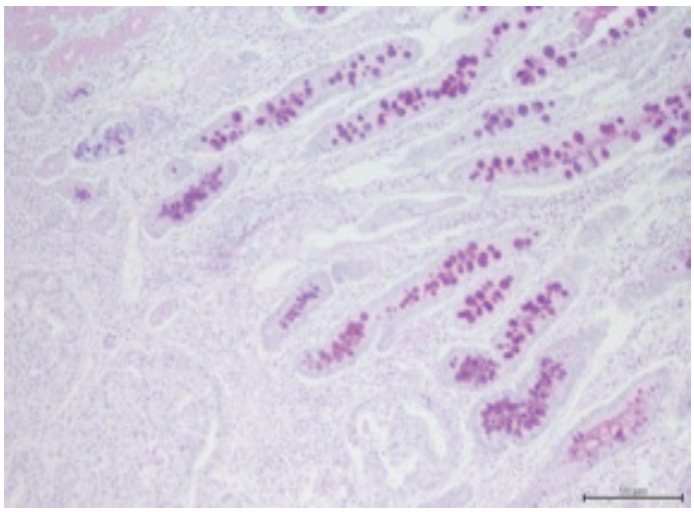

Figure 1. pH 0.5 PAS-AB staining in the area of incomplete intestinal metaplasia adjacent to tubular carcinoma (pH 0.5 PAS/AB x100)

H.Pylori positivity was seenin ~30% (n=9) of cases with observed dysplasia, and in 35% (n=21) of mucosal areas in proximity of carcinomas. Statistical analysis showed no significant difference in H. Pylori positivity between the two groups (p>0.05). Histological typing of carcinomas revealed poorly cohesive gastric carcinoma as the most common (33.3%), mucinous adenocarcinoma as the second most common (23.3%), and tubular adenocarcinoma (20%) as the third most common type of gastric carcinomas. The most commonly observed tumor stage was Stage 3 (81.7%), most common invasion depth type was pT4 (86.7%), and most common metastatic lymph node count was N3 (36.7%). CDX2 and OCT-1 expression was observed in all cases of high-grade dysplasia and in a significant portion of low-grade dysplasia (p=0.042 and p=0.006, respectively) (Figure-2).

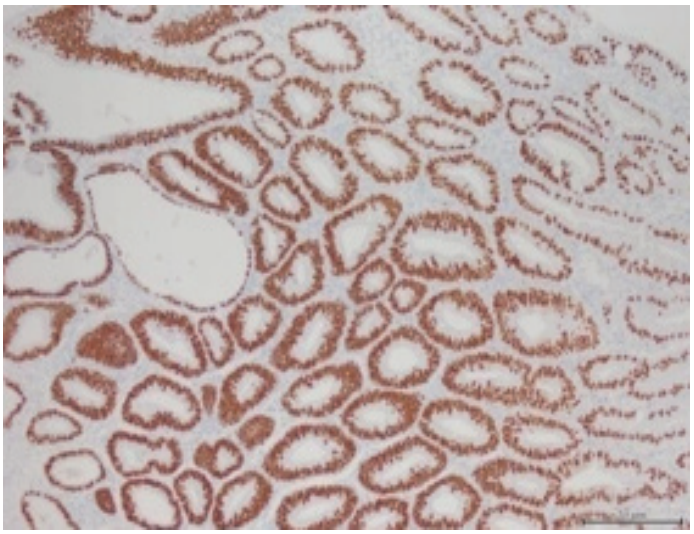

Figure 2. CDX2 immunoreactivity in high-grade dysplasia (CDX2x100)

No significant difference in MUC-1, MUC-4, or OCT-1 positivity was observed between the high-grade and low-grade dysplasia groups (p>0.05). CDX2 positivity was significantly higher in cases with intestinal metaplasia in comparison to those with no observed intestinal metaplasia (p=0.042) among the dysplasia cases. OCT-1 negativity was most commonly observed in low-grade dysplasia group, while positivity was most commonly

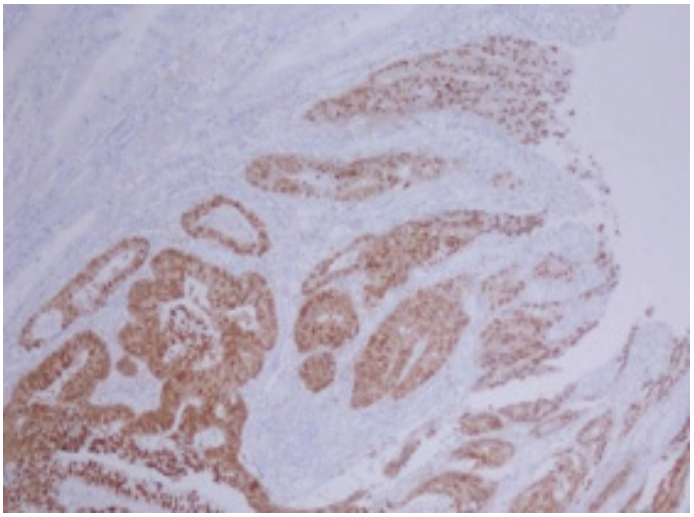

Figure 3. CDX2 immunoreactivity in tubular carcinoma (CDX2x100)

observed in high-grade dysplasia cases, this difference was found to be statistically significant (p=0.007). CDX2 expression was presented in all types of carcinomas in different proportions (Figure-3). No MUC-1 expression was detected in samples with low-grade dysplasia. Significant increase in the expression of MUC-1 and MUC-4 was observed in relation to increasing tumor grade (p=<0.0001, p=0.027, respectively; Table-1, Figure-4 and Figure-5). MUC-1 expression was the lowest in poorly cohesive gastric carcinomas.

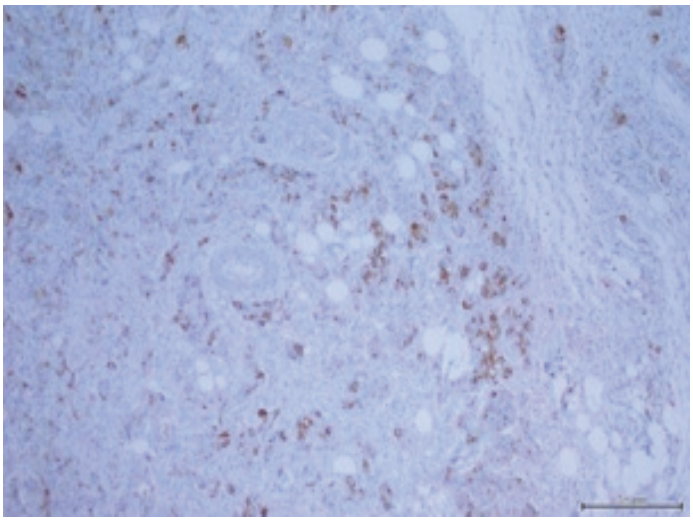

Figure 4.MUC-1 immunoreactivity in tubular carcinoma (MUC-1x100)

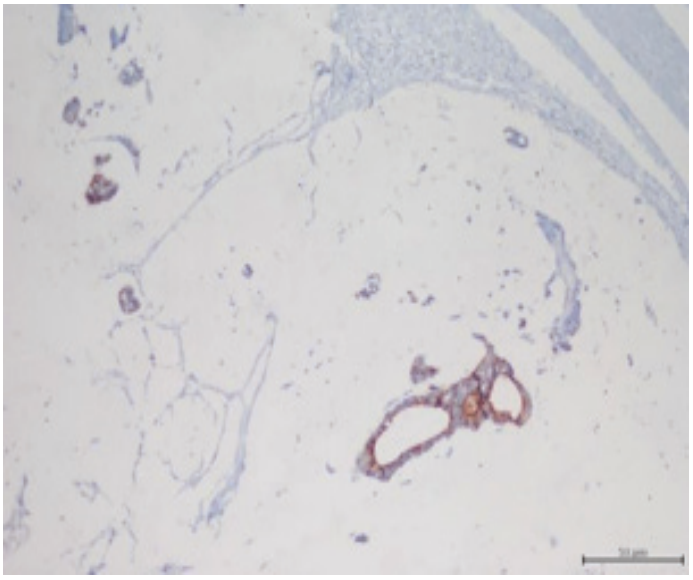

Figure 5. MUC-4 immunoreactivity in mucinous carcinoma (MUC-4x100)

MUC-1 and CDX2 immunoreactivity was significantly higher in those with a low number of metastatic lymph nodes than in those with a higher metastatic lymph node count (p=0.046 and p=0.005, respectively, Table-2). No significant difference was found between expressivity of MUC-4 and OCT-1 and the number of metastatic lymph nodes (Figure-6).

Table 1. Immunohistochemical staining patterns of low/high grade dysplasia and gastric carcinomas

	Low grade Dysplasia		High grade dysplasia		Gastric carcinoma		p
	Number of cases	%	Number of cases	%	Number of cases	%	
MUC-1							
Negative	15	100.0	12	80.0	28	46.7	<0.0001
Positive	0	0.0	3	20.0	32	53.3	
MUC-4							
Negative	11	73.3	6	40.0	21	35.0	0.027
Positive	4	26.7	9	60.0	39	65.0	
CDX2							
Negative	5	33.3	0	0.0	10	16.7	0.054
Positive	10	66.7	15	100.0	50	83.3	
OCT-1							
Negative	7	46.7	0	0.0	17	28.3	0.007
Positive	8	53.3	15	100.0	43	71.7	

Table 1. Comparison of the number and immunohistochemical expressions in metastatic and non-metastatic lymph nodes

	Lymph node without metastasis		Lymph node with metastasis		p
	Med	Sd	Med	Sd	
MUC-1					
+ immunoreactivity	13.09	12.36	7.50	9.31	0.046
- immunoreactivity	17.82	10.75	25.00	17.53	0.202
MUC-4					
+ mmunoreactivity	11.31	10.25	9.83	11.85	0.323
- immunoreactivity	17.62	11.72	23.82	16.34	0.154
CDX2					
+ immunoreactivity	17.83	6.11	9.21	11.42	0.005
- immunoreactivity	26.10	19.90	20.76	14.01	0.545
OCT-1					
+ immunoreactivity	10.50	7.78	10.30	12.33	0.439
- immunoreactivity	22.71	16.30	21.23	14.75	0.706

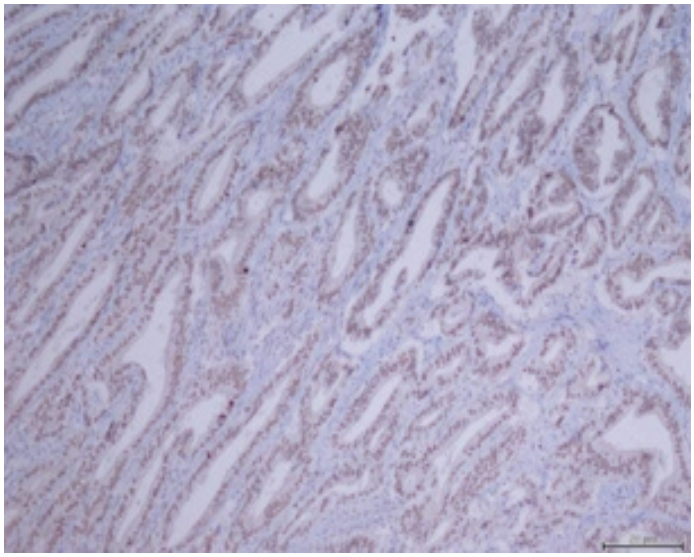

Figure 6. OCT-1immunoreactivity in tubular carcinoma (OCT-1x100)

DISCUSSION

Adenocarcinomas comprise 90-95% of all gastric cancers (1). It is the second most common cause of cancer-related death both among men and women (2). The "Chronic gastritis – atrophic gastritis- intestinal metaplasia-dysplasia-cancer" cascade plays an important role in the pathogenesis of gastric cancers, especially intestinal-type cancers. Identification and follow-up of precursor lesions plays a crucial role in the treatment and prognosis of gastric cancers (3). Intestinal metaplasia is considered a precancerous lesion, the pathogenesis of which is not clearly understood. Jass and Flippe have divided intestinal metaplasia into three different types, of which incomplete type (Type III – colonic type) has been associated with the development of carcinoma (21). In our study, incomplete intestinal metaplasia has been detected in the vicinity of primary tumors in 66.7% of low-grade dysplasia cases, 80% of high-grade dysplasia cases, and all of the tubular and papillary-type carcinomas (n=19). These results were of significance in determining the risk of progression to invasive carcinoma in the range of 10-100%, especially for co-occurrence of intestinal metaplasia with high-grade dysplasia. All of the intestinal metaplasia areas in our study were found to be of the incomplete type, which supports the notion that sulfomucin-secreting columnar cells play an important role in the dysplasia-carcinoma sequence.

Dysplasia of the gastrointestinal system is defined as non-invasive neoplastic epithelium. It is a high-risk precursor lesion for the development of cancer (22). Antrum is considered to be the most common location of gastric dysplasia (23), which is also supported by our study's findings, in which 86.7% of dysplasia was seen in the antrum. Dysplastic lesions were found to co-exist together with intestinal metaplasia in 73.3% of cases of dysplasia in endoscopic biopsy samples. Many studies have been conducted for the early diagnosis, determination of prognostic factors and treatment of gastric cancer. Mucins are high-molecular-weight glycoproteins thought to have a considerable diagnostic and prognostic value in gastric cancers (15). MUC-1 is a transmembrane apomucin, which is a primary component of the mucous membrane in gastric mucosa, and MUC-4 is a membrane-related mucin, first described as a tracheobronchial mucin (24, 25). Among the cases of dysplasia in which incomplete intestinal metaplasia was present, we observed positive immunoreactivity in 3 (13.6%) samples stained with MUC-1 and 8 (26.4%) samples stained with MUC-4.While absent in low-grade dysplasia, MUC-1immunoreactivity was observed in 20% (n=3) of high-grade dysplasia cases and 53.3 % (n=32) of gastric tumors. MUC-4 immunoreactivity was detected in 26.7% (n=4) of low-grade dysplasia, 60% (n=9) of high-grade dysplasia, and 65.5% (n=39) of gastric tumors. Our findings suggest that MUC-1 and MUC-4 overexpression may be a possible determinant of carcinoma progression and may be used for the identification of high-risk groups and for treatment design, especially in case of high-grade dysplasia. However, more research with larger-scale studies are needed to determine the threshold values. One of the studies reported lower occurrence of MUC-1 and MUC-4 immunoreactivity in papillary and tubular-type lesions compared to poorly cohesive-type lesions, in gastric resection samples observed to have adenocarcinomas of the stomach (18). Our study also supports the evidence of significantly lower degree of expression of MUC-1 in cohesive-type carcinomas. We found no significant difference in expression of MUC-4 among different histological types of carcinoma. Some studies point out no correlation between expression of

MUC-1 and MUC-4 and clinicopathological properties of the tumors (26, 27). Our study also shows no difference in expression of MUC-1 and MUC-4 among various stages, degree of lympho-vascular or perineural invasion, depth of invasion, and histological grades. Another study reports inverse correlation between mucin expression and tumor differentiation (28). Our study also established a lower expression of MUC-1 with increasing number of metastatic lymph nodes (p=0.046). Overexpression of MUC-1 therefore appears to be useful as a favorable prognostic factor. In one study, MUC-4 expression was reported to be associated with lymph node metastasis (29). However, expression of MUC-4, on the other hand, does not appear to have a prognostic value.

CDX2 is a homeobox-gene transcription factor that facilitates normal intestinal development. Under normal conditions, CDX2 immunoreactivity is not usually present in gastric mucosa (6,7). We have also not observed any evidence of CDX2 staining in normal gastric mucosa in our study. One study reported increased CDX2 expression in intestinal metaplasia and dysplasia, incomparison to gastric tumors (30). In our study, we observed staining in 66.7% of cases with low-grade dysplasia, 100% of cases with high-grade dysplasia, and 83% of cases of gastric carcinomas. We also noticed significantly higher CDX2 positivity in cases with intestinal metaplasia as opposed to those with no metaplasia among dysplasia samples (p=0.011). Our findings indicate that CDX2 is related to the process of intestinal differentiation in carcinogenesis. In our study, in accordance with the results of other studies, we found no significant difference among different types of histological types, presence of lympho-vascular or perineural invasion, depth of invasion, and histological grades between samples with positive and negative CDX2 expression (31,32). Significantly lower CDX2 expression was demonstrated in cases with 7 or more metastatic lymph nodes (p=0.05). CDX2 expression was associated with increased survival in gastric carcinomas independent of age, sex, and histological type of the tumor.

POU proteins play a role in organ development, cell type formation, growth and cellular differentiation. POU proteins have been reported to have an effect on CDX2 regulation (13). OCT-1 is a POU homeodomain family-related transcription factor (12). OCT-1 plays a role in cellular response to genetic stress, especially in the mechanism of p53-independent gene activation (33). In our study, we demonstrated immune expression of OCT-1 in 53.3% of low-grade dysplasia, 100% of high-grade dysplasia, and 71.7% of gastric carcinomas. OCT-1 negativity was most commonly observed in the low-grade dysplasia group, while positivity was most commonly observed in the high-grade dysplasia group; the difference was found to be statistically significant (p=0.007). These findings support the suggestion that OCT-1 may play a role in the regulation of CDX2. In one study, it was reported that OCT-1 overexpression can be used as a marker of poor prognosis in patients with well-differentiated gastric adenocarcinoma (34). However, we found no evidence for the utility of OCT-1 as a prognostic factor.

CONCLUSION

In conclusion, presence of MUC-1 expression may be used for the elimination of low-grade gastric dysplasia. MUC-1 and MUC-4 overexpression may be used for determination of groups at high risk of development of carcinomas, primarily in cases of high-grade dysplasia. MUC-1 overexpression is seen more frequently in well-differentiated tumors with low potential of metastasis. MUC-1 overexpression may thus be used as a positive prognostic factor. MUC-4, however, does not appear to have any value in the prognosis. CDX2 is associated with intestinal differentiation in the process of carcinogenesis. Lack of significance in expression of CDX2 in gastric carcinomas is thought to be related, to a certain point, with intestinal differentiation. Potential of tumor metastasis seems to rise with the decrease in CDX2 expression. Coexistence of CDX2 and OCT-1 negativity in suspicious samples obtained from endoscopic biopsies may be used in separating high-grade dysplasia from low-grade dysplasia. OCT-1 plays a role in steps CDX2 takes in regulating carcinogenesis. OCT-1 may be a response factor related to unrepairable cell damage and increased cellular proliferation, but does not appear to serve any prognostic value. More large-scale studies are necessary to obtain precise and reliable results to support and expand on ourfindings.

Competing interests: The authors found that the conflict of interest did not fully coincide.
Financial Disclosure: Financial support provided by Bagcilar Training and Research Hospital Non-invasive Clinical Research Board.
Ethical approval: Informed consent was obtained from the patients and Bagcilar Training and Research Hospital Ethics Committee approval was obtained.H&E stained preparations obtained from the archived cases.

Yuksel Ulu ORCID: 0000-0001-7012-6715
Seza Umit Tetikkurt ORCID: 0000-0002-4537-0975
Ugur Izol ORCID: 0000-0002-5862-7178
Yunus Donder ORCID: 0000-0002-0560-1708

REFERENCES

1. Mitrut P, Burada F, Enescu A, et al. The genotoxicity study of resveratrol in primary gastric adenocarcinoma cell cultures. Rom J Morphol Embryol 2009;50:429-33.
2. Mistry M, Parkin DM, Ahmad AS, et al. Cancer incidence in the United Kingdom: projections to the year 2030. Br J Cancer 2011;105:1795-803.
3. JooYE, Park HK, Myung DS, et al. Prevalance and risk factors of atrophic gastritis and intestinal metaplasia: a nationwide multicenter prospective study in Korea. Gut Liver 2013;7:303-10.
4. Chiaravalli AM, Klersy C, Vanoli A, et al. Histotype-based prognostic classification of gastric cancer. World J Gastroenterol 2012;18:538-45.
5. Akyağcı SB, Bağcıvan E, Özgüç H, ve ark. Mide Kanserinde Prognostik Faktörler. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2005;3:113-8.

6. Mutoh H, Hayakawa H, Sakamoto H, et al. Transgenic Cdx2 induces endogenous Cdx1 in istestinal metaplasia of Cdx2 – transgenic mouse stomach. FEBS J 2009:5821-31.
7. Ikarashi S, Nishikura K, Ajoika Y, et al. Re-evaluation of phenotypic expression in undifferentiated – tpye early gastric adenocarcinomas using mucin core protein and CDX2. Gastric Cancer 2013:16;208-19.
8. Werling RW, Yaziji H, Bacchi CE, et al. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. Am J Surg Pathol 2003;27:303-10.
9. Bai YQ, Miyake S, Iwai T, et al. CDX2, a homeobox transcription factor, upregulates transcription of the p21/WAF1/CIP1 gene. Oncogene 2003;22:7942-9.
10. Song JH, Kim CJ, Cho YG, et al. Genetic alterations of the Cdx2 gene in gastric cancer. APMIS 2008;116:74-80.
11. Oz Puyan F, Can N, Ozyilmaz F, et al. The relationship among PDX1, CDX2 and mucin profiles in gastric carcinomas; correlations with clinicopathologic parameters. J Cancer Res Clin Oncol 2011:137;1749-62.
12. Tsukamoto T, Mizoshita T, Tatematsu M. Gastric-and-intestinal mixed-type intestinal metaplasia: aberrant expression of transcription factors and stem cell intestinalization. Gastric Cancer 2006:9;156-66.
13. Jin T, Li H. Pou homeodomain protein OCT1 is implicated in the expression of the caudal-related homeobox gene Cdx-2. J Biol Chem 2001:276;14752-8.
14. Almeida R, Almeida J, Shoshkes M, et al. OCT-l is over-expressed in intestinal metaplasia and intestinal gastric carcinomas and binds to, but does not transactivate, CDX2 in gastric cells. J Pathol 2005;207:396-401.
15. Carvalho F, David L, Aubert JP, et al. Mucins and mucin -associated carbonhydrate antigens expression in gastric carcinoma cell lines. Virchows Arch 1999;435:479-85.
16. Li XH, Zheng HC, Wang ZG, et al. The clinicopathological and prognostic significance of MUC1 expression in Japanese gastric carcinomas: An immunohistochemical study of tissue microarrays. Anticancer Res 2008;28:1061-7.
17. Jia Y, Persson C, Hou L, et al. A comprehensive analysis of common genetic variation in MUC1, MUC5AC, MUC6 genes and risk of stomach cancer. Cancer Causes Control 2010;21:313-21.
18. Tamura Y, Higashi M, Kitamoto S, et al. MUC 4 and MUC1 expression in adenocarcinom of the stomach correlates with vessel invasion and lymph node metastasis: an immunohstochemical study of early gastric cancer. PloS One 2012;7:49251.
19. Senapati S, Chaturvedi P, Sharma P,et al. Deregulation of MUC4 in gastric adenocarcinoma: potential pathobiological implication in poorly differentiated non-signet ring cell the gastric cancer. Br J Cancer 2008;99:949-56.
20. Mejias-Luque R, Peiró S, Vincent A, et al. IL6 induces MUC4 expression through gp130/STAT3 pathway in gastric cancer cell lines. Biochim Biophys Acta 2008;1783:1728-36.
21. El-Zimaity HM, Ramchatesing J, Saeed MA, et al. Gastric intestinal metaplasia : subtypes and natural history. J Clin Pathol 2001;54:679-83.
22. Sharma P, Montomery E. Gastrointestinal dysplasia. Pathology 2013;45;273-85.
23. Spiegel A, Stein P, Patel M. A Report of Fundic Gland Polyps. Gastroenterol Hepatol 2010;6:45-8.
24. Terada T. Human fetal ductal plate revisited: II. MUC 1, MUC5AC, and MUC 6 are expressed in human fetal ductal plate and MUC1 is expressed also in remodeling ductal plate, remodeled ductal plate and mature bile ducts of human fetal livers. İnt J Clin Exp Pathol 2013:6;571-85.
25. Inagaki Y, Xu H, Nakata M, et al. Clinicopathology of sialomucin: MUC1, particularly KL-6 mucin, in gastroistestinal, hepatic and pancreatic cancers. Biosci Trends 2009;3:220-32.
26. Hwang I, Kang YN, Kım JY, et al. Prognostic significance of membrane – associated mucins 1 and 4 in gastric adenocarcinoma. Exp Ther Med 2012:4;311-6.
27. Wang XT, Kong FB, Mai W,et al. MUC1 Immunohistochemical Expression as a Prognostic Factor in Gastric Cancer: Meta-Analysis. Dis Markers 2016;2016:9421571.
28. İlhan Ö,Han Ü, Önal B,et al. Prognostic significance of MUC1, MUC2 and MUC5AC expressions in gastric carcinoma: Türk J Gastroenterology 2010;21:345-52.
29. Boltin D, Niv Y. Mucins in gastric cancer. J Gastrointest Dig Syst 2013;3:15519.
30. Tian MM, Zhao AL, Li ZW,et al. Phenotypic classification of gastric signet ring cell carcinoma and its relationship with clinicopathologic parameters and prognosis. World J Gastroenterol 2007;13:3189-98.
31. Park DY, Sirivastava A, Kim GH, et al. CDX2 expression in the intestinal type gastric epithelial neoplasia: frequency and significance. Mod Pathol 2010;23:54-61.
32. Zhang Y, Wang H ,Bi C, et al. Expression of CDX2 in gastric cardia adenocarcinoma and its correlation with H. pylori and cell proliferation. Oncotarget 2016;7:54973-82.
33. Zhao H, Jin S, Fan F, et al. Activation of the transcription factor Oct-1 in response to DNA damage. Cancer Res 2000:60;6276-80.
34. Jeong SH, Lee YJ, Cho BI, et al. OCT-1 overexpression is associated with poor prognosis in patients with well-differentiated gastric cancer. Tumor Biol 2014;35:5501-9.