Institute of Experimental Morphology, Pathology and Anthropology with Museum
Bulgarian Anatomical Society

Acta morphologica et anthropologica, 19
Sofia • 2012

Expression of MUC 1, MUC2, MUC5AC and MUC6 in gastric carcinoma

*M. Tzaneva, N. Zgurova, V. Tsvetkova**

Departmant of General and Clinical Pathology, Medical University, Varna

Gastric carcinoma is two main histological types: intestinal and diffuse type. The aim of this study was to evaluate the expression and the distribution of MUC1, MUC2, MUC5AC and MUC6 in the tumor and adjacent non-tumor epithelial tissue by immunohistochemistry in twelve cases of gastric carcinomas. MUC1 immunoreactivity in the cytoplasm of tumor cells was variable – from weak to moderate, while in non-tumor tissue it was very weak.

MUC5AC and MUC6 showed a low content in tumor cells as compared to non-tumor tissue. MUC2 expression was observed in seven intestinal and one diffuse carcinoma. In adjacent mucosa MUC2 positive goblet cells had in all intestinal carcinomas.

In conclusion, these results show that during the process of carcinogenesis the expression of gastric mucins MUC5AC and MUC6 is decreased and the expression of MUC2 is aberrant in areas of intestinal metaplasia. An increased MUC1 expression probably plays a role in the development of neoplastic gastric epithelium.

Key words: gastric carcinoma, mucin expression, gastric carcinogenesis

Introduction

Mucus, a gel-like substance that covers the mammalian epithelial surfaces is composed of mucin glycoproteins (10). Mucus acts as both a lubricant and as a protective barrier between the contents of the stomach and the mucosal epithelial surface (7). In human gastric mucosa three mucins have been identified: MUC1, MUC5AC and MUC6 (3). There are two structurally and functionally distinct classes of mucins: secreted gel-forming mucins (MUC2, MUC5AC, MUC5B and MUC6) and transmembrane mucins (MUC1, MUC3, MUC4, MUC12 and MUC17) (10). Alterations of their expression pattern have been described in carcinomas as well as in precursor lesions (2, 6, 8, 11). The aim of this study is to investigate the expression and the distribution of MUC1, MUC2, MUC5AC and MUC6 in tumor tissue and to compare this expression with the MUC profile in tumor adjacent mucosa of gastric carcinoma.

Materials and Methods

Twelve patients carcinoma surgically resected were investigated. The patients were 7 men, and 5 women. The age varied from 36 to 76 years.

Tissue specimens

Three or four tissue specimens were collected from surgically removed tumor and another two or three from adjacent non-tumor epithelial tissue. Paraffin sections were stained with HE, PAS and Alcian blue. A histopathological diagnosis of the carcinoma was made in accordance to Lauren (5). Paraffin sections (5 μm thick) were processed by peroxidase-antiperoxidase technique. The primary antibodies were: MUC1 (RB-9222-R7), Mucin2 Ab.2 (M53) (Ms 1037-R7), Mucin 5AC Ab-2(1-13ML) and MUC-6 Ab-1 (CLH5) (MS-1153-S) (LAB VISION THERMO)

Results

Histology.

Gastric carcinomas were divided into two main histological types (intestinal and diffuse) on the basis of their tendency of glandular formation. Ten of gastric carcinomas were from intestinal type and two had a diffuse growth pattern.

Light microscopic immunohistochemistry.

In non-tumor tissue MUC1 immunoreactivity was weak and was located in the apical membrane and the cytoplasm of parietal cells in the fundic glands It was also occasionally present in cytoplasm of the antral glands and antral surface mucous cells (Fig.1).

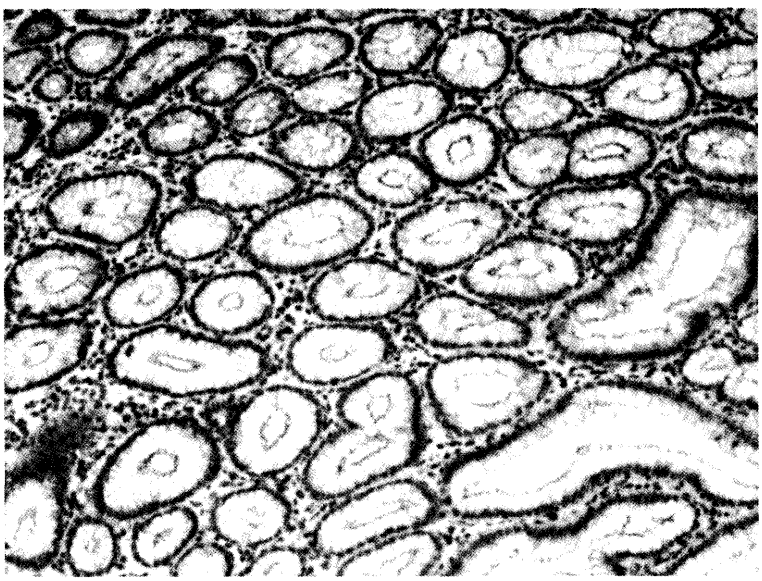

Fig.1. MVD in *JAK2* positive patients with PV

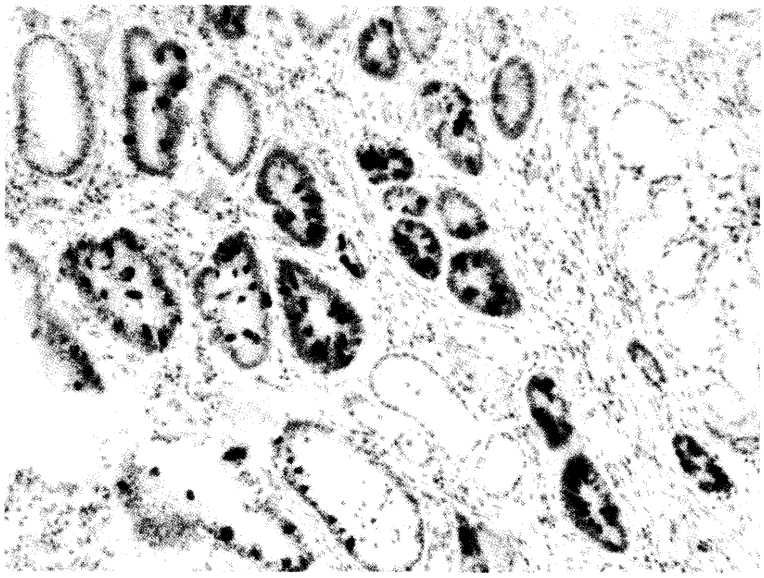

Fig.2. MVD in *JAK2* negative patients with PV

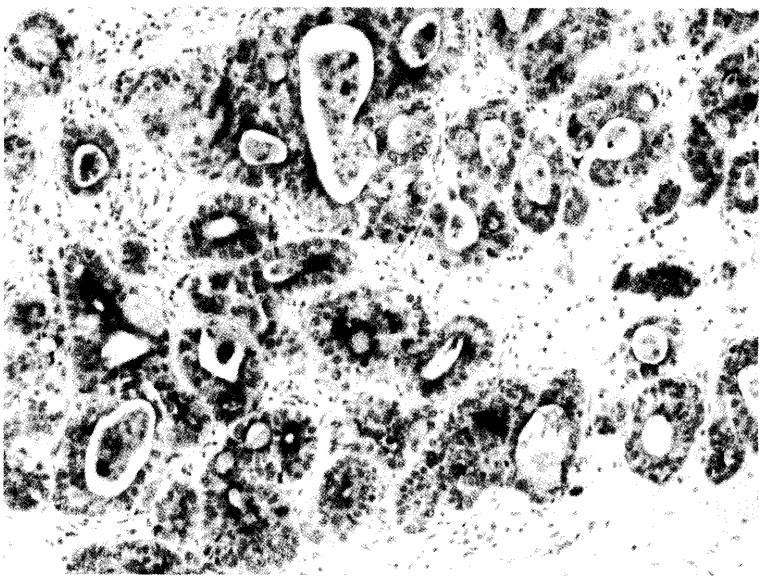

Fig.3. MUC1 in the cell tumor cytoplasm and in the lumen of the tumor glands

MUC5AC was highly expressed in foveolar epithelium and mucous neck cells of antrum. MUC6 was localized in the glands of the antrum and in some mucus neck cells. MUC2 was not detected in normal gastric mucosa. It was observed in goblet cells in intestinal metaplasia next to intestinal carcinoma only (Fig.2). In adjacent non-tumor mucosa MUC2 positive goblet cells had in all intestinal carcinoma.

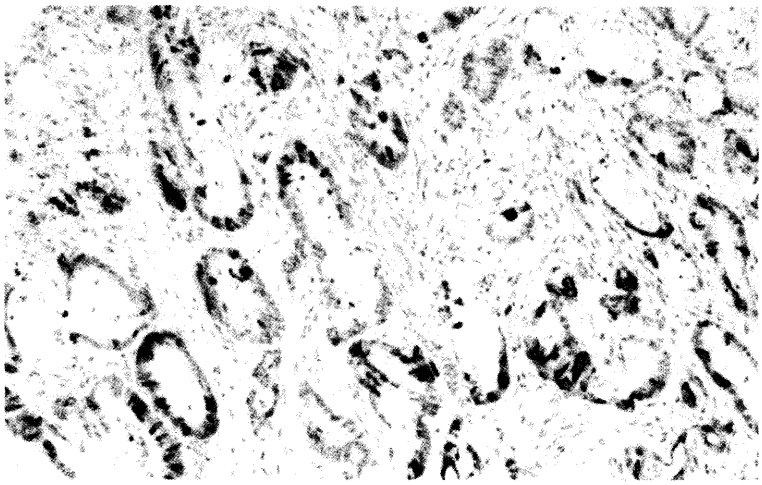

Fig. 4. MUC2 in the cell tumor cytoplasm in intestinal gastric carcinoma

In tumor tissue of the intestinal carcinoma MUC1 expression was weak to moderate and was localized mainly in cell tumor cytoplasm and sometimes in the lumen of the tumor glands (Fig.3). In diffuse carcinoma MUC1 positive expression in the tumor cell was weak, but present in almost all of the tumor cells. In the most of intestinal carcinomas we were not able to find MUC5AC expression in tumor cell or they showed a very weak expression. The tumor cells of the two diffuse carcinomas were moderately positive for MUC5AC. MUC6 expression was weak or lacking. Seven intestinal carcinomas and one diffuse carcinoma were MUC2 positive. MUC2 was found only in tumor cell cytoplasm (Fig.4).

Discussion

In this study, we established an altered expression of the gastric mucins: MUC1, MUC5AC and MUC6 in gastric carcinoma. Our results showed that the process of neoplastic transforwmation in human stomach is associated with a decrease of some gastric mucins: MUC5AC and MUC6 and an aberrant expression of mucins normally expressed by the intestine (MUC2).

Adenocarcinomas of the stomach can be classified into two major types (5). The "intestinal" type is composed of distinct glands with polarized cells resembling colon carcinoma. The "diffuse" type is composed of solitary cells or small clusters of cells. The intestinal type of gastric cancer is the predominant type in elderly populations and is preceded by well-defined precancerous lesions, such as intestinal metaplasia and atrophic gastritis. We found expression of MUC2 in goblet cells in adjacent non-tumor gastric mucosa only in intestinal carcinoma. The most of intestinal carcinomas showed MUC2 positivity in tumor cells. These results support the assumption that the intestinal metaplasia does represent a differentiation of the mucosa toward an intestinal phenotype of gastric carcinoma.

The diffuse carcinoma is not preceded by precancerous lesions (8). It is suggests that MUC2 is not expressed in diffuse carcinomas. We observed MUC2 in one of the two diffuse carcinomas. In the two diffuse carcinomas we did not detect immunohistochemically MUC2 in non-tumor tissue. We considered that MUC2 synthesis in diffuse

carcinomas may be reflects an altered synthetic ability and as a result diverse mucin products may appear in tumor tissue.

We found an increased expression of MUC1 in tumor tissue of all gastric carcinoma. It was localized mainly in tumor cell cytoplasm in contrast to non-tumor tissue, where it was detected in the apical membrane and cytoplasm of parietal cells in fundic glands. MUC1 expression was very weak in antral mucosa. It has been reported that MUC1 molecule participates in cell-cell and cell-substratum interaction (10). It is also known that MUC1 acts as docking protein for some signaling molecules (4). Immunohistochemical studies in human gastric carcinoma have shown that over-expression on carcinoma cells plays a role in metastatic process by inhibiting tumor cell adhesion and in escaping from immune surveillance (1). Our results suggest that the over-expression of MUC1 may be regarded as one of the factors, which play a role in the malignant transformation of gastric epithelial cells.

We found a decreased expression of gastric mucins (MUC5AC and MUC6) in the both types of gastric carcinoma. Similar data were also described (9). The present study shows that expression of MUC5AC and MUC6 is not associated with the histological type of the gastric carcinomas.

In conclusion, our results suggest that there is a decreased expression of gastric mucin MUC5AC and MUC6 together with an abberant expression of MUC2 in intestinal metaplasia, during the process of gastric carcinogenesis. A high MUC1 level probably plays a role in appearance of neoplastic gastric epithelium. The mucin profile in tumor cells is not different in both types of gastric carcinoma.

References

1. Agrawal, B., B.M.Longenecker. MUC1mucin-mediated regulation of human T cells. – International Immunology 17, 2005, 391-399.
2. Babu, S.D., V. Venkataraman, N. Devaraj, C. A. Reis., H. Devaraj. Expression profile of mucins (MUC2, MUC5AC and MUC) in Helicobacter pylori infected pre-neoplastic and neoplastic human gastric epithelium. Molecular Cancer, **5,** 2006, 5-10.
3. Byrd, J., R.S. Bresalier. Alterations in gastric mucin synthesis by Helicobacter pylori. – World J. Gastroenterol., **4**, 2000, 475-482.
4. Huang, L, D. Chen, D. Liu, L. Yin, S. Kharbanda, D. Kufe. Muc1 oncoprotein blocks glycogen synthase kinase 3β-mediated phosphorulation and degradation of β-catenin. – Cencer Res. **65,** 2005, 10413-10422.
5. Lauren, P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma.- Acta Pathol. Microbiol. Scandinavica, **64,** 1965, 31-49.
6. Li, X. H., H.C. Zhen, Z. G. Wang, H. Takahashi, X. H. Yang, Y. F. Guan, Y.Takano. The clinicopathological and prognostic significance of MUC-1 expression in Japanese gastric carcinoma: an immunohistochemical study of tissue microarrays. – Anticancer Res., **28,** 2008, 1061-1068.
7. Magalhäls, A., C.A.Reis. Helicobacter pylori adhesion to gastric epithelial cells in mediated by glycan receptors. – Brazillian J. Medical Biolog. Res. **43,** 2010, 611-618.
8. McGrath, S.C., M. Ebert, C. Röcken. Gastric carcinoma: Epidemiology, pathology and patogenesis. – Cancer Therapy **5,** 2007, 877-894.
9. Reis, C.A., L. David., F. Carvalho., U. Mandel., C. De Bolós., E. Mirgorodskaya., H.Clausen., M.S. Simões. Immunohistochemical study of the expression of MUC6 mucin and co-expression of other secreted mucins (MUC5AC and MUC2) in hunan gastric carcinoma. – J.Histochem. Cytochem. **48,** 2000, 377-388.
10. Sasaki, M., H. Ikeda, Y. Nakanuva. Expression profiles of MUC mucins and trefoil factor family (TTF) peptide in the intrahepatic biliary system: physiological distribution and pathological significance. – Progress Histochem. Cytochem. – **42,** 20007, 61-110.
11. Szachnowicz, S., I. Cecconello., U. Ribeiro, K,Iriya., R.E.Ibrahim., F.R.Takeda., C.E.Corbett., A.V.S.Ribeiro. Mucin pattern reflects the origin of the adenocarcinoma in Barret's asophagus: a retrospective clinical and laboratorial study. – World J. Surg. Oncol. **7,** 2007, 7-27.