Institute of Experimental Morphology and Anthropology with Museum
Bulgarian Anatomical Society

Acta morphologica et anthropologica, 15
Sofia • 2010

Chromogranin A Expression in Diffuse Gastric Carcinoma

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Gastric carcinoma is divided into two main histological types, intestinal and diffuse type on the basis of their tendency of glandular formation. The diffuse type has been further subdivided into three types: desmoplastic, signet ring and anaplastic variant. The aim of this study was to elucidate the morphology of the acinar and ribbon-like structures, appearing in the tumor tissue of some diffuse gastric carcinoma by histochemical, immunohistochemical and electron microscopic techniques. Acinar and ribbon-like structures were found in eight cases (four desmoplastic and four mixed) from out twelve diffuse gastric carcinomas. Immunohistochemistry revealed that these structures were chromogranin A positive and they were localized in the submucosa and mainly in muscularis propria. The tumor cells in the mucosa contained PAS-positive mucus. Electron microscopically, the structures were composed of endocrine cells, which contained numerous pleomorphic or oval endocrine granules. We conclude that some diffuse gastric carcinomas acquire endocrine phenotype in the process of the gastric carcinogenesis.

Key words: diffuse gastric carcinoma, acinar structure, ribbon-like structure, neuroendocrine differentiation.

Introduction

Gastric carcinoma is divided into two main histological types, intestinal and diffuse type on the basis of their tendency of glandular formation. The diffuse gastric carcinoma has been further subdivided into three variants: desmoplastic, signet ring and anaplastic variant. The intestinal type is associated with the appearance of intestinal metaplasia, whereas the origin of diffuse type gastric carcinoma is still unclear. W a l d u m et al. [9] have found ultrastructurally endocrine cells similar to enterochromaffin-like (ECL) cells in the tumor tissue of some diffuse gastric carcinoma and concluded that this carcinoma have neuroendocrine origin.

The aim of this study was to elucidate the morphology of the acinar and ribbon-like structures, appearing in tumor tissue of some diffuse gastric carcinoma by histochemical, immunohistochemical and electron microscopic techniques.

Material and Methods

Twelve gastric carcinoma surgically resected from 2000 to 2003 years were investigated. The patients were 10 men, and 2 women. The age varied from 50 to 80 years.

Tissue specimens

Three or four blocks of surgically resected gastric carcinoma tissue specimens were fixed in 10% buffered formalin solution and embedded in paraffin wax. Paraffin sections were stained with HE and PAS. A histopathological diagnosis of the carcinoma was made in accordance with L a u r e n [4]. Paraffin sections (5μm thick) were processes by peroxidase-antiperoxidase technique. The primary antibody was polyclonal rabbit antibody against human chromogranin A (Code N 1535, Dako).

In seven cases electron microscope study of fresh tumor tissue was performed along with the paraffin sections.

Results

Histology

All twelve gastric carcinoma had a diffuse growth. Four of them were desmoplastic, one – anaplastic and seven – mixed type. Acinar and ribbon-like structures were found in eight cases /four desmoplastic and four mixed – in desmoplastic part of the mixed variant/. They were localized in the submucosa and mainly in muscularis propria (Fig. 1).

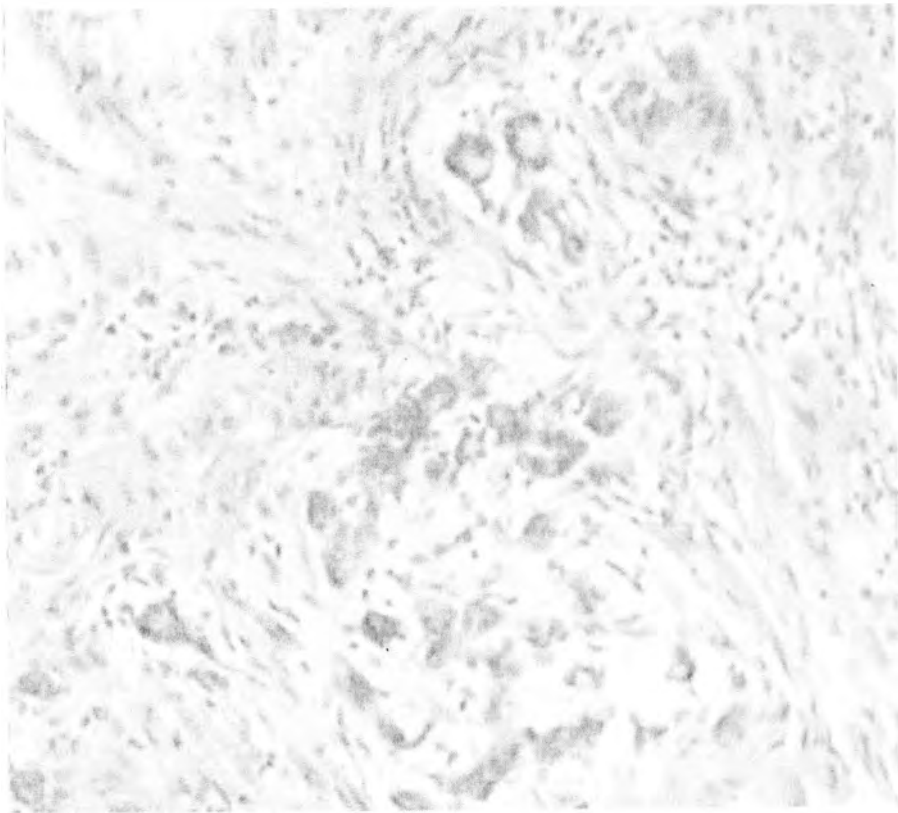

Fig. 1. Acinar structures in muscularis propria. HE, × 100

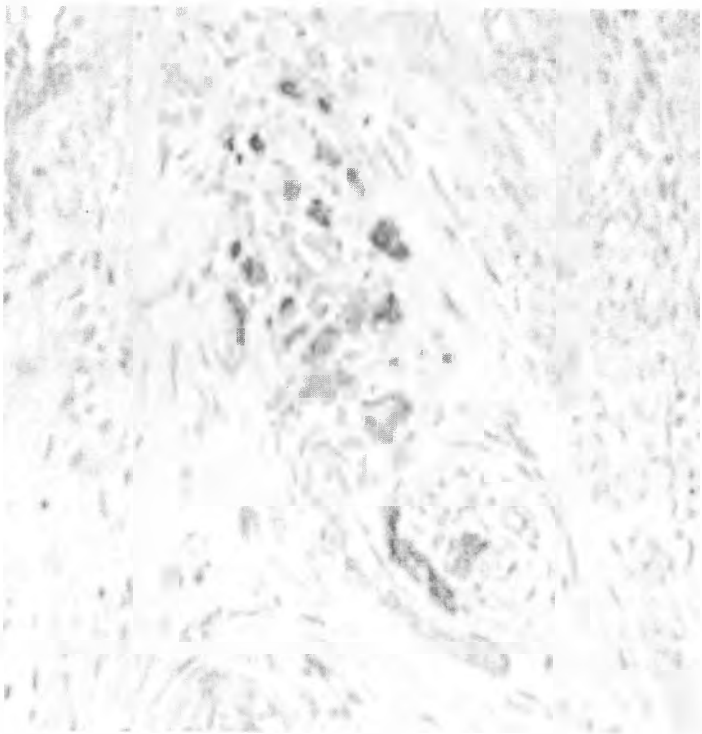

Fig. 2. Chromogranin A positive acinar structures. Immunohistochemistry, × 100

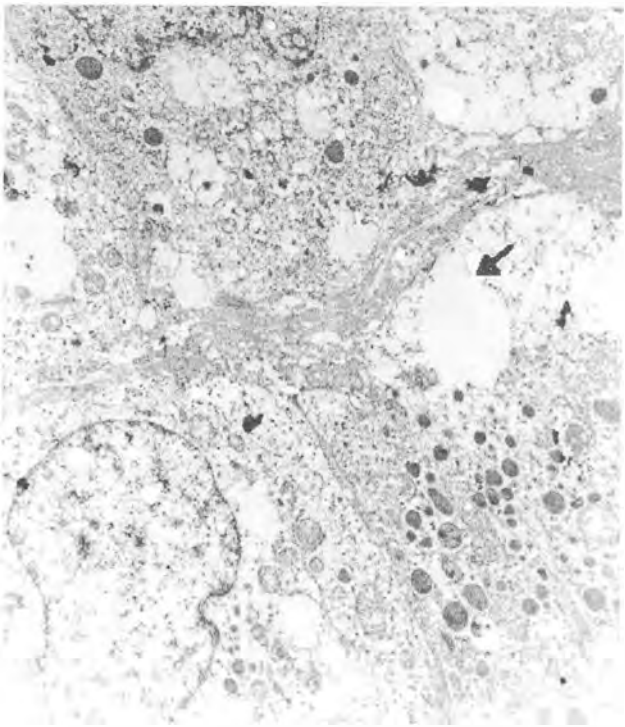

Fig. 3. The structures compose of endocrine cells with pleomorphic or oval granules and mucoid granules (↑). Electron microscopy, × 20 000

The tumor cells in the mucosa did not show glandular differentiation. They often were PAS positive. The mucus content in tumor cells localized in both submucosa and muscularis propria often was scanty and entirely absent in the acinar or ribbon-like structures.

Light microscopic immunohistochemistry

The most acinar or ribbon-like structures and some tumor cells were chromogranin A positive (Fig. 2).

Electron microscopic study

The structures were composed of endocrine cells, which contained numerous granules (Fig 3). The granules were pleomorphic or oval in shape. Some endocrine tumor cells contained electron-lucent, homogeneous mucoid granules, amongst the endocrine granules.

Discussion

In this study, we established that the acinar and ribbon-like structures appearing in some diffuse carcinomas were neuroendocrine structures. Our results corresponded to W a l d u m et al. [9], who found ultrastructurally ECL cells in tumor tissue of some diffuse gastric carcinomas.

We found acinar or ribbon-like structures in both muscularis propria and submucosa. We did not find similar structures in the mucosa where the tumor cells were PAS positive and chromogranin A negative. Our results suggest that some tumor cells in diffuse gastric carcinoma acquire neuroendocrine differentiation in the process of the gastric carcinogenesis.

Endocrine cells have been found in all parts of the gastrointestinal tract [5, 7, 9]. Like many other cells, endocrine cells may undergo neoplastic transformation and are capable to give origin of neuroendocrine carcinoma. In well-differentiated neuroendocrine carcinoma, the endocrine cells are from one type while in poorly differentiated carcinomas they do not show to characteristic ultrastructural appearance [2]. Ultrastructurally, we found that the endocrine structures were composed mainly from well-granulated endocrine cells, which corresponded mainly to ECL cells or enterochromaffin (EC) cells. In our opinion the acinar or ribbon-like neuroendocrine structures are a way of differentiation of the tumor cells in diffuse gastric carcinoma and they do not represent dedifferentiated neuroendocrine carcinoma as considered previously [9].

We found endocrine differentiation in the desmoplastic type and in the desmoplastic part of compound type of diffuse gastric carcinoma. In the murine entero-endocrine cell line STC-1, hormone synthesis is regulated from subepitelial fibroblast cell lines by soluble factors, which inhibit the endocrine cell proliferation and modulate the expression of hormonal peptide genes [6]. It is possible that the fibroblast- or myofibroblast-like cells in sclerotic tumor tissue of diffuse gastric carcinoma do not exert similar effects.

The origin of endocrine cells in gastrointestinal carcinoma has been the subject of debate. Theories include simple entrapment of normal endocrine cells, benign proliferation of endocrine cells, and malignant transformation of two distinct stem cell lines or a single stem cell line with multiple differentiations [1, 3, 10]. The facts that: (1) the acinar or ribbon-like structures location mainly in muscularis propria; (2) the rich of granules and the correspondence of definite endocrine cell type and (3) the dual differentiation of tumor cells (amphocrine cells, which contain endocrine and mucoid granules) support the theory for a single common stem cell origin with multiple differentiations.

In conclusion, the acinar and ribbon-like structures are a manifestation of neuroendocrine differentiation in desmoplastic tumor tissue of diffuse gastric carcinoma.

References

1. Hamada,Y., A. Oishi, T. Shoji, H. Takada, M. Yamamura, K. Hioki, M. Yamamoto. Endocrine cells and prognosis with colorectal carcinoma. – Cancer, **69,** 1992, 2641-2646.
2. Hammond, E. H., R. L.Yowell, R. L. Flinner. Neuroendocrine carcinomas: role of immunocytochemistry and electron microscopy. – Human Pathology, **29,** 1998, 1367-1371.
3. Jonas, L., M. Barten, S. Kunkel. Endocrine cells in adenocarcinoma and their prestage in the glandular stomach and duodenum of rats after MNNG administration. – Acta Histochem. **80,** 1986, 197-204.
4. 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.
5. Potela-Gomes, G. M., M. Stridsberg. Chromogranin A in the human gastrointestinal tractÓ an immunohistochemical study with region-specific antibodies. – J. Histochem. Cytochem., **50,** 2002, 1487-1492.
6. Ratineau, C., M. Plateroti, J. Dumorfier, M. Blanc, M. Kedinger, J. A. Chayuialle, C. Roche. Intestinal-type fibroblasts selectively influence proliferation rate and peptide synthesis in the murine entero-endocrine cell line STC-1. – Differentiation, **62,** 1997, 19-147.
7. Tzaneva, M. Electron microscopic immunohistochemical investigation of chromogranin A in endocrine cells in human oxyntic gastric mucosa. – Acta Histochem., **103,** 2001, 179-194.
8. Tzaneva, M. Endocrine cells in gastric carcinoma and adjacent mucosa. An immunohistochemical and ultrastructural study. – Histochem., J., **34,** 2002, 173-180.
9. Waldum, H. L., S. Aase, I. Kvetnoi, E. Brenna, A. K. Sandvik, U. Syversen, G. Johnsen, L. Vatten, J. M. Polak. Neuroendocrine differentiation in human gastric carcinoma – Cancer, **83,** 1998, 435-444.
10. Маневска, Б., М. Гърдевски. Количествена оценка на ендокринните клетки при карцином на стомаха и дебелото черво. – Онкология, **2,** 1984, 89-93.