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Clinicopathological and Immunohistochemical Analysis of Gastrointestinal Neuroendocrine Neoplasms

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The distribution, the morphology and the expression of chromogranin A and synaptophysin were investigated in tumor tissue and tumor adjacent mucosa of 61 neuroendocrine neoplasms by applied of peroxidase-antiperoxidase technique. On the basis of tumor size and Ki-67, 14 (22.9%) well differentiated neuroendocrine tumors, 10 (16.3%) well differentiated neuroendocrine carcinomas and 37 (60.8%) poorly differentiated ones were identified. The distribution was as follow: stomach, 18 cases (29.5%), small intestine, 10 cases (16.3%), appendix, 16 cases (26.3%) and large intestine 17 (27.9%). The well differentiated neuroendocrine tumors (81.2%) were prevailing in the appendix while in the small intestine all neoplasms were poorly differentiated neuroendocrine carcinomas. The later were prevailing in the stomach and the large intestine, respectively 13 (72.3%) and 14 (82.4%) cases. Our results show that neuroendocrine neoplasms with a wide range of differentiation may originate in different parts of the gastrointestinal tract.

Key words: neuroendocrine neoplasms, chromogranin A, differentiation, distribution.

Introduction

Neuroendocrine neoplasms comprise a family of tumors with a wide range of morphologic, functional and behavioral characteristics [3]. Their diagnostics depends on the recognition of characteristic morphologic features and on the presence of markers indicative of neuroendocrine differentiation [3, 5]. Chromogranin A and synaptophysin are the most used markers for the assessment of both normal endocrine cells and neuroendocrine neoplasms [5].

The aim of this study was to investigate the distribution, the morphology and to compare the expression of both chromogranin A and synaptophysin in tumor tissue and tumor adjacent mucosa of neuroendocrine neoplasms with a different differentiation.

Materials and Methods

Sixty-one patients with neuroendocrine neoplasms were investigated. Clinical records for age, sex and tumor localization in the gastrointestinal tract were available. Three or four surgical specimens were collected from tumor tissue and two or three from adjacent non-tumor tissue. Paraffin sections were processed by peroxidase-antiperoxidase technique [5]. The used primary antibodies were: polyclonal rabbit anti-human

chromogranin A (Code N 1535, DAKO), polyclonal anti-synaptophysin (Syn 38, DAKO) and monoclonal mouse anti-human Ki67 Antigen, Clone MIB-1 (Code N1633, DAKO).

Every neoplasm was graded according to the World Health Organization classification [4]. The tumors were divided according to the embryonal origin of: foregut (stomach, duodenum), midgut (jejunum, ileum, appendix) and hindgut (colon and rectum) [3].

Results

The 61 neuroendocrine neoplasms studied were divided according to their histological features into: 14 (22.9%) well differentiated neuroendocrine tumors; 10 (16.3%) well differentiated and 37 (60.8%) poorly differentiated neuroendocrine carcinomas. The neoplasms were located as follows: stomach, 18 cases (29.5%), small intestine, 10 cases (16.3%) , appendix, 16 cases (26.3%) and large intestine 17 (27.9%) . Eighteen (29.5%) cases originated in foregut, 26 (42.6%) cases in midgut and 17 (27.9%) in hindgut. The gastric neoplasms were as follows: one (5.5%) well differentiated neuroendocrine tumor, 4 (22.2%) well differentiated neuroendocrine carcinomas and 13 (72.3%) poorly differentiated neuroendocrine carcinomas. In the small intestine all neoplasms were poorly differentiated neuroendocrine carcinomas. The neoplasms of appendix were 13 (81.2%) well differentiated neuroendocrine tumors and 3 (18.8%) well differentiated neuroendocrine carcinomas. The neoplasms of large intestine were classified as: well differentiated neuroendocrine carcinomas – 3 (17.7%) cases and poorly differentiated neuroendocrine carcinomas – 14 (82.3%) cases.

Tumor tissue. Histologically, the well differentiated neuroendocrine tumors were strong chromogranin A positive while in the well differentiated neuroendocrine carcinomas chromogranin A was more frequently expressed in their peripheral than in the central part

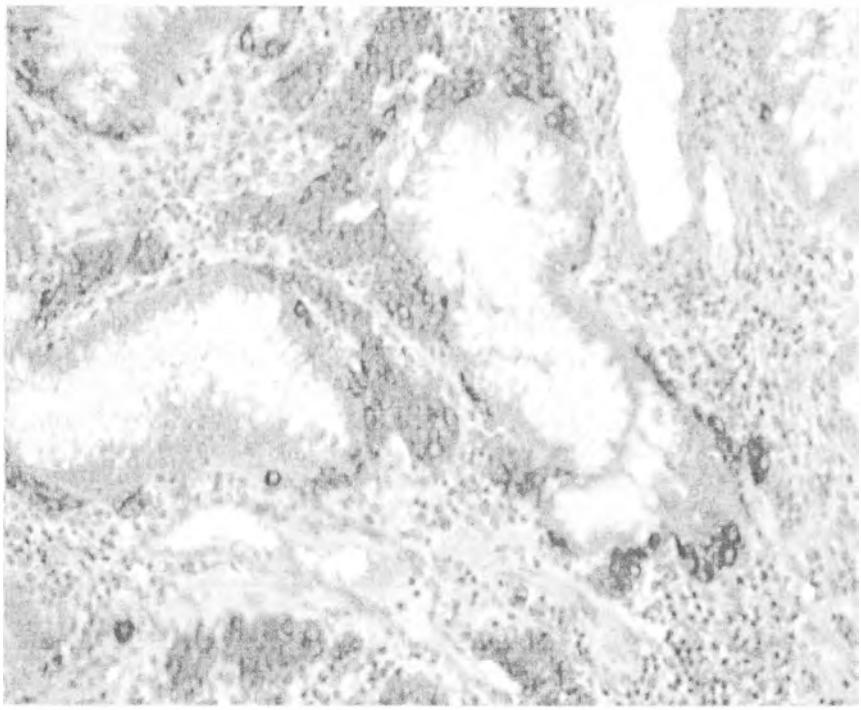

Fig. 1. Nodular hyperplasia of chromogranin A positive cells in adjacent mucosa of gastric well differentiated carcinoma. Immunohistochemistry, × 200

of tumor areas. The expression of chromogranin A was weak and localized in the peripheral part of the tumor areas in poorly differentiated neuroendocrine carcinomas. All neuroendocrine neoplasms showed weak or moderate expression of synaptophysin.

Tumor adjacent tissue. In the adjacent gastric mucosa in most of the cases, linear and nodular hyperplasia of chromogranin A positive cells was established (Fig. 1).

Discussion

Our results show that the distribution of neuroendocrine neoplasms in the gastrointestinal tract is different. The neuroendocrine neoplasms originate mainly in the midgut than in the other parts of gastrointestinal tract. We established also a different differentiation of the neoplasms in midgut. The well differentiated neuroendocrine tumors were prevailing in the appendix while in the small intestine all neoplasms were poorly differentiated neuroendocrine carcinomas. Poorly differentiated neuroendocrine carcinomas were more common in both the foregut and the hindgut. Our results corresponded to others studies, which have examined both well differentiated neuroendocrine tumors and well differentiated neuroendocrine carcinoma in different parts of gastrointestinal tract [3]. In this study, we performed a comparative investigation of the neuroendocrine neoplasms with different grade of differentiations according to the site of embryonal origin of individual parts of gastrointestinal tract.

The origin and development of neuroendocrine tumors or carcinomas has been a matter of debate [5]. It has been suggested that well differentiated neuroendocrine tumors and well differentiated neuroendocrine carcinomas arise from orthotopic neuroendocrine cells of partially differentiated precursor cells while poorly differentiated neuroendocrine carcinomas originate from a stem cell [6]. Our study showed both linear and nodular endocrine cell hyperplasia next to gastric well differentiated neuroendocrine tumors and carcinomas. These results confirm the literature data [4] that the development of gastric well differentiated neuroendocrine neoplasms begins from small neuroendocrine nodules, which represent their precancerous lesions.

The origin of the poorly differentiated neuroendocrine carcinomas in the different locations and well differentiated neuroendocrine tumors and carcinomas outside the gastric mucosa is not clear. Hyperplastic lesions were not found in adjacent mucosa. So, it may be suggest that these tumors probably arise from stem cells.

We found that the expression of chromogranin A decreases in the poorly differentiated neuroendocrine carcinomas, as compared to both the well differentiated neuroendocrine tumors and neuroendocrine carcinomas. Thus, in addition of the tumor size and Ki-67 positive nuclei, the expression of chromogranin A may be used in the valuation of the differentiation of the neuroendocrine neoplasms.

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