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Colonic Adenocarcinoma with Numerous Paneth and Endocrine Cells

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Numerous granular eosinophilic cells corresponding to Paneth cells were unexpectedly revealed in a moderately differentiated adenocarcinoma of the hepatic flexure of the colon in a 76-year-old man. These cells were clearly seen in routine slides and their nature was confirmed by Masson's trichrome stain, by immunohistochemical reaction for lysozyme, and by electron microscopy. The tumor contained also cells intermediate between Paneth and goblet cells (with both supranuclear granules and mucous globules), observed in Masson's trichrome stain and in electron microscope. Additionally, immunohistochemical reaction for chromogranin A was performed and irregularly scattered neoplastic endocrine cells were visualized in the tumor. The light microscopic and ultrastructural features of this rare neoplasm are described together with detailed clinical data. The incidence and significance of the Paneth cell and endocrine differentiation in colorectal carcinomas are discussed with the review of the literature.

Introduction

Epithelial lining of the large intestine consists of several cell types that are thought to differentiate from a common stem cell, according to the unitarian theory proposed by Cheng and Leblond [4]. The most numerous are columnar absorptive cells (enterocytes) and mucus producing goblet cells. Less numerous, but constant elements are entero-endocrine cells. A few Paneth cells, typical of the small intestine, are sometimes observed in the mucosa of the large bowel, mainly in its proximal part [20]. Colorectal adenomas and adenocarcinomas may contain neoplastic counterparts of both entero-endocrine and Paneth cells, which argues in favor of common origin of all cellular elements of the intestinal epithelium. At present, thanks to immunohistochemical methods, the endocrine component is frequently recognized in epithelial colorectal tumors [7, 9, 21]. The incidence of the neoplastic Paneth cells in these tumors is much lower [5, 7].

We report here a rare case of colonic adenocarcinoma containing numerous neoplastic Paneth cells (well seen in routine slides) and dispersed neoplastic endocrine cells (visualized by immunohistochemistry for chromogranin A). In addition, cells intermediate between Paneth and goblet cells were revealed in the tumor.

A Case Description

A 76-year-old man was examined due to hypogastric pain, constipation alternate with diarrhea, distension and loss of body weight about 10 kg for 3 months. His past medical history included hiatal hernia and chronic duodenal peptic ulcer as well as cholecystectomy and appendectomy caused by acute inflammations. He also suffered from diabetes mellitus and ischemic heart disease. Hematological examination showed severe hypochromic microcytic anemia. Ultrasonography revealed enlargement of lymph nodes located near the superior mesenteric artery. Colonoscopy demonstrated a large polypoid and ulcerated tumor of the hepatic flexure of the colon with almost complete bowel obstruction. The biopsy samples taken from the tumor showed adenocarcinoma. The right hemicolectomy was performed. The postoperative course was uneventful and the patient is alive 24 months after operation.

The surgical specimen consisted of a 40 cm-long segment of cecum and colon with a 5 cm cuff of the small intestine. Eleven lymph nodes were found in paracolic adipose tissue. Gross examination showed 8x4x2 cm fungating and superficially ulcerated tumor located 25 cm distally to the ileocecal valve.

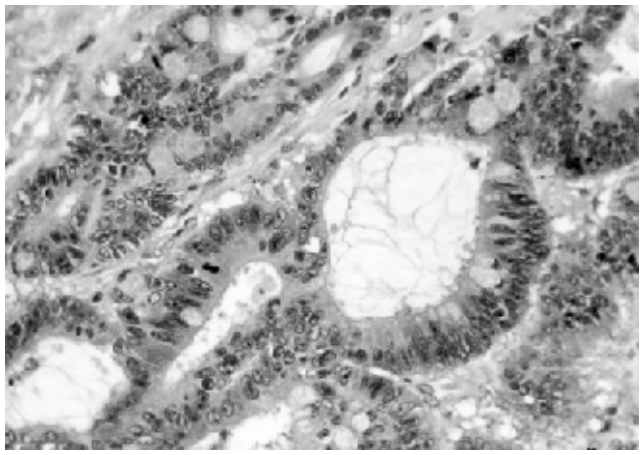

Fig. 1. Colonic adenocarcinoma with various cell populations. HE. Magn. 400×.

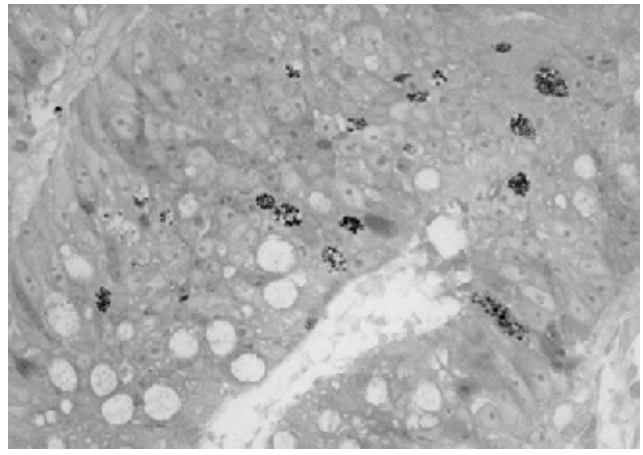

Fig. 2. Paneth cells with cytoplasmic granules. Methylene blue. Magn. 600×.

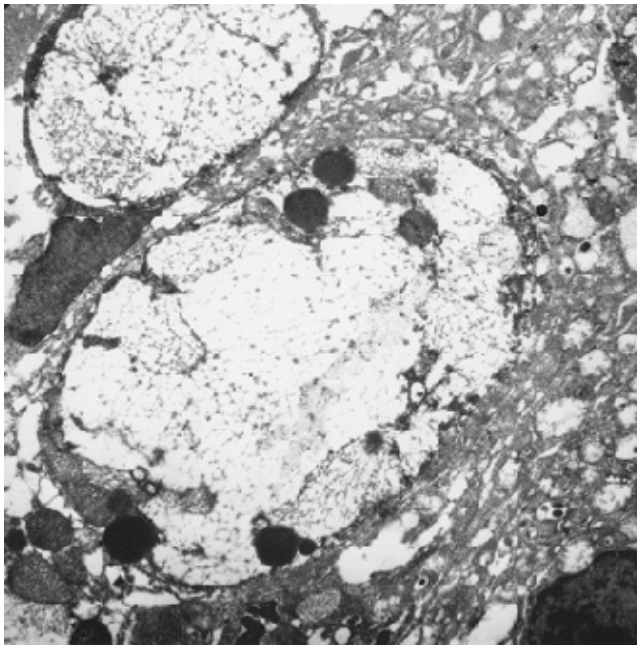

Fig. 3. Intermediate cell containing numerous mucous globules and granules. Magn. 9,000×.

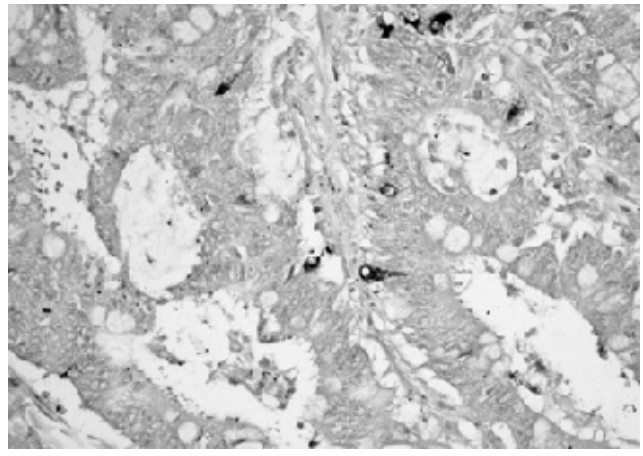

Fig. 4. Endocrine cells exhibiting positive immunohistochemical reaction for chromogranin A. LSAB2/HRP. Magn. 400×.

The tumor was a moderately differentiated adenocarcinoma with a relatively abundant mucinous component (<50%). The neoplastic infiltration extended beyond the muscularis propria of the colon and metastases were present in 2 out of 11 lymph nodes, including the node located near the superior mesenteric artery (pT3N3). All resection margins were free from tumor invasion. The tumor was composed mainly of tubular structures lined with various populations of cells. The commonest were tall columnar cells with large irregular hyperchromatic nuclei with prominent nucleoli as well as goblet cells containing neutral and acidic mucin stained red with mucicarmine, blue with alcian blue/periodic acid Schiff (AB/PAS) and green with Masson's trichrome, but failed to stain with high-iron diamine. Unexpectedly numerous granular cells corresponding to Paneth cells were also revealed. They were interspersed haphazardly, singularly or in small clusters within tumor mass with a tendency to be located in the close vicinity of goblet cells (Fig. 1). The Paneth cells showed marked variation in size and shape. Their characteristic supranuclear granules were pink with routine hematoxylin and eosin (HE) and AB/PAS, reddish with Masson's trichrome, deep blue with methylene blue (Fig. 2) and exhibited strong immunohistochemical reaction for lysozyme. At the ultrastructural level the granules varied greatly in size and osmophilia. Furthermore, existence of cells containing both mucous globules and granules typical of Paneth cells were also revealed. The intermediate cells were seen with Masson's trichrome stain and their presence was confirmed in electron microscope (Fig. 3). The proportion of both intracellular components varied significantly in various cells. The last population of cells found in the tumor were irregularly scattered, single endocrine cells strong immunohistochemical reaction for chromogranin A (Fig. 4), which were not man-

aged to visualize at the ultrastructural level. All types of neoplastic cells were present in the nodal metastases. The normal Paneth and endocrine cells were also noticed at the basis of the crypts of the colonic mucosa around the tumor.

Discussion

We have reported a case of otherwise typical adenocarcinoma of the colon containing minor populations of neoplastic Paneth cells and endocrine cells. The cells corresponding to Paneth cells were clearly seen in routine slides stained with HE because of their characteristic eosinophilic supranuclear granules (this observation drew our attention to the case). Their nature was then confirmed by Masson's trichrome stain, by immunohistochemical reaction for lysozyme and by electron microscopy. There were also cells intermediate between Paneth and goblet cells, observed in Masson's trichrome stain and in electron microscope. The presence of dispersed neoplastic endocrine cells was revealed by immunohistochemistry for chromogranin A.

Neoplastic Paneth cells are occasionally observed as an integral component in tumors of the alimentary tract, most often in adenomas of the large intestine [1, 5, 7, 8]. The first reports of human carcinomas containing neoplastic Paneth cells were given by Stern and Sobel [19] in 1961 (carcinoma of jejunum) and by Holmes [8] in 1965 (carcinoma of sigmoid colon). Since then, such carcinomas have been found in various locations, including the stomach [2, 6, 10, 12], Meckel's diverticulum [15] and even nasal mucosa [16] but the most frequently reported cases involve the large bowel [5, 7, 8, 17, 18]. Serio and Zampatti [17] reported a case of colonic adenocarcinoma with a predominance of neoplastic Paneth cells, representing about 60% of all tumor cells. In 1967 Gibbs [5] examined 150 primary adenocarcinomas of the large bowel, using routine HE stain and stains for Paneth cells (phloxine tartrasine, phosphotungistic acid hematoxylin and Gram method in Weigert's modification). He found Paneth cells in four tumors (2.7%), including three with numerous Paneth cells. Twenty-two years later Ho et al. [7] applied the immunohistochemical method to evaluate the expression of lysozyme as a marker of Paneth cells in 42 colorectal carcinomas and observed a positive reaction in as many as 17 tumors (40.5%). But lysozyme immunoreactivity was not associated with typical Paneth cell characteristics in routine stain, as it was in our case. The authors proposed four possible explanations: 1) neoplastic Paneth cells lose typical morphological features (possibly due to altered packaging and storage of lysozyme); 2) carcinomatous lysozyme-positive cells are not Paneth cells but synthesize an ectopic lysozyme; 3) these cells express a cancer-associated antigen that cross-reacts with antibodies to lysozyme; or 4) these cells adsorb extracellular lysozyme from luminal secretions. Thus, lysozyme immunoreactivity in carcinomas may not be a convincing proof of the Paneth cell differentiation. Wong et al. [18] found the immunohistochemical reaction for lysozyme not selective enough – it stained many cells which were overtly not Paneth cells. Ho et al. [4] compiled the results of five studies based only on histological criteria and reported that Paneth cells were found in only 7 out of 521 colon carcinomas (1.3%). The presence of neoplastic cells with histological features of Paneth cells in carcinomas of the large intestine remains a rare phenomenon.

Features of endocrine differentiation are much more widely recognized in tumors of the alimentary tract and of other systems. Apart from pure "neuroendocrine" tumors and rare mixed exocrine/endocrine tumors, there are conventional adenomas and adenocarcinomas, in which scattered cells with endocrine properties are detected by histochemistry or immunohistochemistry [1, 5, 7, 9, 11, 21, 22, 23]. Reported incidence of this phenomenon in colorectal carcinomas varies greatly and with immunohistochemical methods used reaches maximally 50% of analyzed cases [9]. According to research carried out in our department using various endocrine markers, this incidence is 52.6% (unpublished data). Such scattered endocrine elements in adenocarcinomas are usually invisible in routine stain.

In very few papers the presence of both Paneth and endocrine cells in colorectal carcinomas was investigated systematically. Two studies mentioned above – by Gibbs [5] and by Ho et al. [7], besides Paneth cells, were also concerned with endocrine cells, the former with histochemical methods for argentaffin properties and the latter with immunohistochemistry for chromogranin A. Gibbs found both Paneth and argentaffin cells in only one out of 150 adenocarcinomas (0.67%). Ho et al. observed both cells with lysozyme expression and cells with chromogranin A expression in 7 out of 42 carcinomas (16.7%). This great difference may be explained by the following facts: 1) argentaffin cells constitute only a proportion of all endocrine cells and silver impregnation methods are far less sensitive than modern immunohistochemistry for chromogranin A (Gibbs revealed argentaffin cells in only 2% of carcinomas, whereas Ho et al. observed the expression of chromogranin A in 33% of tumors); 2) lysozyme expression may be of limited value as a marker of Paneth cells as we mentioned before. If we accept the incidence of Paneth cells in colorectal carcinomas given by Gibbs (2.7%) as more reliable, the incidence of both Paneth and endocrine cells should be about two-three times lower, provided that these two features are independent of each other. Such tumors with numerous Paneth cells, well visible in routine stain, as it was in our case, must be still less frequent.

We have also observed neoplastic cells intermediate between Paneth and goblet cells, containing both characteristic granules, and mucous globules in various proportions. These cells were visible in Masson's trichrome stain and in electron microscope. Similar cells were previously reported in a few cases of colorectal carcinomas [17, 18, 20]. Shousha [18] observed them in Paneth cell-rich papillary adenocarcinoma of the colon, in routine and AB/PAS stained slides and in electron microscope. Serio and Zampatti [17] found a large number of such cells (seen again in AB/PAS) in their adenocarcinoma with a predominant Paneth cell differentiation. Ohtani and Sasano [12] observed such cells in three out of five poorly differentiated gastric carcinomas with Paneth-like cells. There is another type of intermediate cells rarely reported in tumors of the alimentary tract: containing both endocrine granules and mucous globules [3, 14]. These cells have been named "amphicrine cells" by Ratzenhofer and Aubock [14]. We failed to reveal such cells in our case. The occurrence of intestinal adenomas and adenocarcinomas containing neoplastic endocrine and Paneth cells, and especially intermediate cell types, argues in favor of a common origin (from the common stem cells) of all cellular elements of the intestinal epithelium, in accordance with the unitarian theory proposed by Cheng and Leblond [4]. Another opinion, developed by Pearse [13] in the APUD concept, postulated a neuroectodermal origin of the endocrine cells of the digestive system ("neuroendocrine cells").

At present, it is not known whether the presence of neoplastic Paneth cells in adenocarcinomas has any influence on prognosis because of the very few reported cases. The presence of dispersed neoplastic cells with endocrine features is much more frequent in colorectal adenocarcinomas, but its prognostic significance is still highly controversial. This is not a homogenous phenomenon: the neoplastic endocrine cells occur in various numbers and express various active products with various biological properties. We suppose that only some of these substances (as β-HCG or gastrin) when produced in significant quantities may worsen prognosis, acting for example as autocrine growth factors.

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