Jpn. J. Cancer Res. 87, 109–112, January 1996

Paneth Cell-rich Flat Adenoma of the Rectum: Report of a Case

Carlos A. Rubio,[1,5] Lena Kanter,[1] Jan Björk,[2] Bertil Poppen[3] and Lynn Bry[4]

[1]Departments of Gastrointestinal Pathology, Karolinska Institute, Department of [2]Gastrointestinal Medicine, [3]Surgery, Karolinska Hospital, 17176 Stockholm, Sweden and [4]Department of Pharmacology, Washington University, St. Louis, Mo. 63110, USA

A patient having familiar adenomatosis polyposis and an ileo-rectal anastomosis developed a flat mucosal lesion in the rectum. A punch biopsy revealed a villous adenoma with high-grade dysplasia. The subsequent surgical specimen indicated that the flat villous adenoma was rich in Paneth cells. Special stains included lysozyme muramidase (to visualize Paneth cells), MIB1 proliferation monoclonal antibody and single and multilabel immunohistochemistry for Paneth cells. Other methods included transmission electron microscopy and quantification with an image quantifier (Program Optilab 2.1) of lysozyme-stained Paneth cells. The subjective evaluation of hematoxylin-eosin-stained preparations demonstrated that the Paneth cells were mainly located in the lower half of the villi. Sections labeled with a specific stain (lysozyme muramidase) revealed more Paneth cells in the villi and electron microscopy showed even more in lysozyme-negative areas. Obviously some migrating dysplastic Paneth cells had retained their characteristic granules on their way towards the tip of the villi. Quantitative studies indicated that the lysozyme muramidase-positive material accounted for 41% of the adenomatous tissue. MIB1 revealed intense cell proliferation at the base of the adenoma and in the entire slopes of the villi. Despite the wide distribution of Paneth cells in intestinal metaplasia of the stomach, in the normal small intestine and in the large bowel with chronic inflammatory diseases, it is surprising that tumors arising in Paneth cells are extremely rare. The causes of the apparent natural resistance of Paneth cells to tumor development deserve to be investigated. This is the first case of Paneth cell-rich flat adenoma of the rectum in the literature.

Key words: Flat adenoma — Paneth cell — Rectum

Since the first description by Schwalbe in 1872[1] of what today are known as Paneth cells,[2] much interest has centered around the role played by these cells in the GI tract.[3,4] Though Paneth cells are widely distributed in intestinal metaplasia of the stomach,[5] in the normal mucosa of the small bowel[6] and in the colorectal mucosa without[7] or with chronic inflammatory diseases,[8] tumors originating in these cells are extremely rare.

As regards the colon, only a few authors have reported the occurrence of Paneth cells in adenomas and adenocarcinomas.[9] We are aware of five cases of exophytic colonic neoplasias in the literature in which Paneth cells have been particularly noted. One case was a villous adenoma of the colon[10] having "shallow crypts lined predominantly by Paneth cells and a few columnar cells." The second a "Paneth cell-rich" papillary adenocarcinoma of the colon with a large number of Paneth and goblet cells dispersed singularly and in small groups.[11] Of the three remaining cases reported by Holmes,[12] two were adenomas and one an adenocarcinoma of the colon. All five neoplasias were exophytic and located in the colon.

The case to be reported here was flat and located in the rectum. The histology revealed a villous adenoma having predominantly Paneth cells. This subjective observation was subsequently validated by analytical quantitation of histochemically labeled preparations.

CASE REPORT

The patient The patient was a 61-year-old male with a family history of familiar adenomatous polyposis. A brother had an ileostomy following proctectomy for colonic adenomatous polyps and a sister having the same syndrome died of a metastatic colonic adenocarcinoma. Our patient had an ileorectal anastomosis performed in 1977. Follow-up with periodic rectoscopies revealed multiple small exophytic polyps which were removed for histologic examination at each endoscopic control examination. The last rectoscopy had been done in August 1989. The patient consulted 5 years later in August 1994 when a new rectoscopy was done. It revealed a flat villous lesion 2 cm in diameter in the anterior wall of the ampulla recti. A biopsy taken from that lesion revealed a villous adenoma with high-grade dysplasia. The rectum was subsequently removed and an ileostomy was performed.

[5] To whom correspondence should be addressed.

Fig. 1. Low-power view of Paneth cell-rich flat adenoma of the rectum (hematoxylin-eosin, enlarged from original).

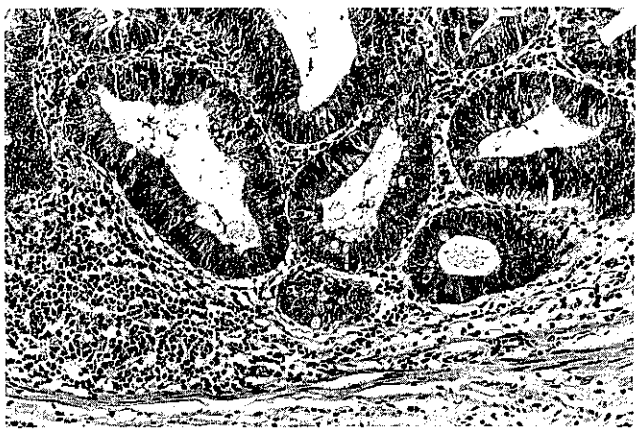

Fig. 2. Detail of Fig. 1, to show dysplastic glands covered with Paneth cells (hematoxylin-eosin, ×100).

Gross examination The surgical specimen measured 17 cm and carried an ileorectal anastomosis. In the rectum a flat lesion 2 cm in diameter with a villous surface was observed. In addition, multiple small exophytic polyps up to 0.5 cm in diameter were found.

Method Sections were stained with hematoxylin-eosin. Special stains included periodic acid Schiff, lysozyme muramidase,[13] acid fuchsin without counterstain, carcinoembryonic antigen, Chromogranin A, tissue polypeptide antigen, *p53* tumor suppressor gene, MIB1 proliferation monoclonal antibody and single and multilabel immunohistochemistry for Paneth cells.[14] A sample of the tumor was cut from the paraffin block and processed for transmission electron microscopy. Lysozyme-stained Paneth cells were quantified using an image quantifier (Program Optilab 2.1).[15]

Histological examination The flat adenoma (Fig. 1) was classified as flat following the criteria of Muto *et al.*[16] and Wolber and Owen.[17] The lesion lacked an exophytic polypoid configuration and consisted of a slightly elevated dysplastic mucosal plaque no greater than two times the thickness of the adjacent nondysplastic mucosal segment (Fig. 1). At histological examination, the flat villous lesion was diagnosed as high-grade dysplasia because the dysplastic nuclei had reached the superficial half of the epithelium in at least three crypts. The lower half of the villi contained predominantly Paneth cells (Fig. 2). Scattered Paneth cells were seen in the slopes of the villous structures in hematoxylin-eosin-stained sections.

Lysozyme muramidase without counterstain (Fig. 3) and acid fuchsin stain, as well as immunohistochemical reactions, revealed the presence of Paneth cells in the tumor. MIB1 showed intense cell proliferation at the base and in the entire slopes of the villi (Fig. 4). Other reactions added little information. Quantitative analysis indicated that 41% of the cell mass was lysozyme muramidase-positive.

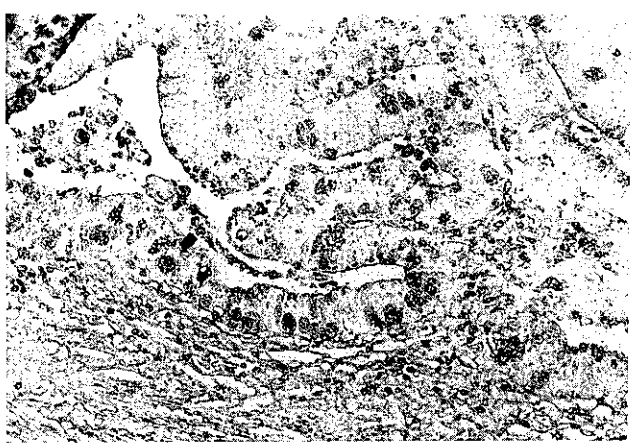

Fig. 3. Immunohistochemical stain showing Paneth cells in flat adenoma (lysozyme muramidase without counterstain, × 120).

Electron microscopy demonstrated characteristic Paneth cell granules not only at the base of the tumor, but also in cells on the slope of the crypts in areas in which the lysozyme assay had been non reactive (Fig. 5). Many cells on the tip of the villi were cylindrical and had an absorptive border with microvilli, similar to the cylindrical absorptive epithelium of the small intestine.[6]

Review of previously removed exophytic polyps revealed tubular adenomas with low-grade dysplasia. Paneth cells were also present.

Fig. 4. Paneth cell-rich flat adenoma of the rectum challenged with a proliferation antibody. Note intense cell labeling of the entire lesion (MIB1 without counterstain, ×25).

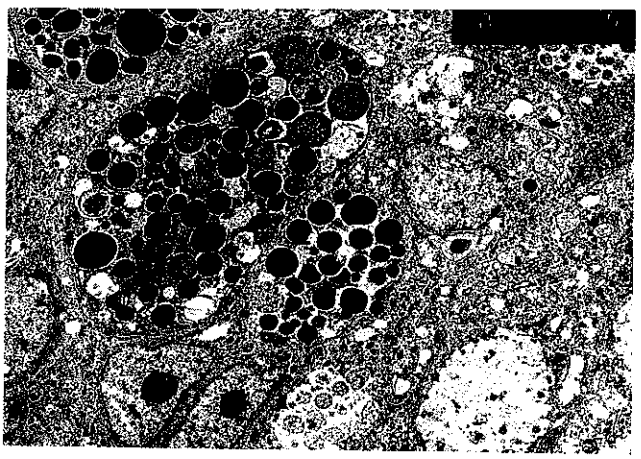

Fig. 5. Transmission electron microscopy to demonstrate the characteristics of the granules in Paneth cells (TEM, × 2895).

DISCUSSION

Morphological, histochemical, immunohistochemical and electron-microscopical studies indicated that the rectal neoplasia described here was a Paneth cell-rich flat adenoma with high-grade dysplasia. Paneth cells predominated in the lower half of the villi in hematoxylin-eosin-stained sections. Scattered Paneth cells were also found in the upper part of the villi. More specific stains (lysozyme muramidase and single and multilabeled immunochemistry for Paneth cells) showed more Paneth cells, and even more were detected with transmission electron microscopy. Obviously some dysplastic Paneth cells had retained their granules while migrating along the slopes on their way to the tip of the villi. The granule-free dysplastic cells of the upper part of the villi adopted a columnar configuration with a brush border. Quantitative studies indicated that lysozyme muramidase-positive material accounted for 41% of the adenomatous tissue.

Considering that the villous architecture of the adenoma resembled that of the small bowel, that the basal aspect of the crypts contained Paneth cells and that the columnar cells of the tip of the villi resembled enterocytes, the adjective "intestinalized" for this adenoma seems appropriate. In recent years, flat adenomas of the colorectal mucosa have received much attention in the literature.[16–18] The presence of occasional Paneth cells has been mentioned in flat adenomas,[9] but no case of Paneth cell-rich flat adenoma of the rectum has previously been reported. Paneth cells are common in gastric intestinal metaplasia of the complete type[5] and in the small intestine under normal conditions. Paneth cells are also present in the colorectal mucosa of patients having chronic inflammatory diseases.[8] Despite the ubiquitous distribution of Paneth cells, it is surprising that Paneth cell-containing tumors have only rarely been reported in the gastrointestinal tract.[10, 11, 19, 20] The causes of the apparent natural resistance of Paneth cells to tumor development remain enigmatic and deserve to be further investigated.

ACKNOWLEDGMENTS

This study was supported by grants from the Karolinska Institute and the Cancer Society, Stockholm.

(Received August 17, 1995/Accepted October 16, 1995)

REFERENCES

1) Schwalbe, G. Beiträge zur Kenntnis der Drusen in der Darmwandungen, in's Besondere der Brunner'schen Drusen. *Arch. Mikrosk. Anat.*, **8**, 97–140 (1872).
2) Paneth, J. Ueber die secernierenden Zellen des Dunndarm-Epitelets. *Arch. Mikrosk. Anat.*, **31**, 113–191 (1888).
3) Garrett, K., Grounds, M. and Beilharz, M. Nonspecific binding of nucleic acid probes to Paneth cells in the gastrointestinal tract with *in situ* hybridization. *J. Histochem. Cytochem.*, **40**, 1613–1618 (1992).
4) Cheng, H. Origin, differentiation and renewal of the four main epithelial cell types in the mouse small intestine. IV

Paneth cells. *Am. J. Anat.*, **141**, 521–535 (1974).
5) Rubio, C. A., Kato, Y., Sugano, H. and Kitagawa, T. Intestinal metaplasia of the stomach in Swedish and Japanese stomachs without ulcers or carcinoma. *Jpn. J. Cancer Res.*, **78**, 467–472 (1987).
6) Ross, M., Reith, E. and Romrell, L. "Histology. A Text and Atlas," pp. 433–434 (1989). Williams and Wilkins, Baltimore.
7) Shethye, J., Rubio, C. A. and Mellstedt, H. Normal colon of Sprague-Dawley rats. An immunohistochemical study. *Anat. Embryol.*, **185**, 69–76 (1992).
8) Whitehead, R. Ulcerative colitis. *In* "Gastrointestinal and Oesophageal Pathology," ed. R. Whitehead, pp. 627–642 (1995). Churchill Livingstone, Edinburgh.
9) Wada, R., Miwa, H., Abe, H., Santo, R., Kitamura, S., Kuwabara, N., Suda, K., Kondo, K., Yamada, S. and Matsukawa, M. Incidence of Paneth cells in minute tubular adenomas and adenocarcinomas of the large bowel. *Acta Pathol. Jpn.*, **42**, 579–584 (1992).
10) Lewin, K. Neoplastic Paneth cells. *J. Clin. Pathol.*, **21**, 476–479 (1968).
11) Shousha, S. Paneth cell-rich papillary adenocarcinoma and mucoid adenocarcinoma occurring synchronously in colon: an electron microscopic study. *Histopathology*, **3**, 489–501 (1979).
12) Holmes, E. Neoplastic Paneth cells. Their occurrence in 2 adenomas and one carcinoma of the colon. *Cancer*, **18**, 1416–1422 (1965).
13) Heitz, P. U. and Wegmann, W. Identification of neoplastic Paneth cells in an adenocarcinoma of the stomach using lysozyme as a marker, and electron microscopy. *Virchows Arch. A Pathol. Anat.*, **386**, 107–116 (1980).
14) Bry, L., Falk, P., Huttner, K., Ouellette, A., Midtvedt, T. and Gordon, J. Paneth cell differentiation in the developing intestine of normal and transgenic mice. *Proc. Natl. Acad. Sci. USA*, **91**, 10335–10339 (1980).
15) Rubio, C. A., Porwit-McDonald, A., Rodensjö, M. and Duvander, A. A method to quantitate Paneth cell metaplasia of the stomach by image analysis. *Anal. Quant. Cytol. Histol.*, **11**, 115–118 (1989).
16) Muto, T., Kamiya, J., Sawada, T., Konishi, F., Sugihara, K., Kubota, Y., Adachi, M., Agawa, S., Saito, Y., Morioka, Y. and Tanpratoon, T. Small "flat adenoma" of the large bowel with special reference to its clinicopathologic features. *Dis. Colon Rectum*, **28**, 847–851 (1985).
17) Wolber, R. and Owen, D. A. Flat adenomas of the colon. *Hum. Pathol.*, **22**, 70–74 (1991).
18) Rubio, C. A., Kumagai, J., Kanamori, M., Yanagisawa, A., Nakamura, K. and Kato, Y. Flat adenomas and flat adenocarcinomas of the colorectal mucosa in Japanese and Swedish patients: a comparative histologic study. *Dis. Colon Rectum*, **38**, 1075–1079 (1995).
19) Rubio, C. A. Paneth cell adenoma of the stomach. *Am. J. Surg. Pathol.*, **13**, 325–328 (1989).
20) Ferrell, L. D. and Beckstead, J. H. Paneth-like cells in an adenoma and adenocarcinoma in the ampulla of Vater. *Arch. Pathol. Lab. Med.*, **115**, 956–958 (1991).