

Paneth Cell Adenoma of the Ileum

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Abstract. *A Paneth cell adenoma of the ileum was recently found in a 47-year-old male with familial adenomatous polyposis (FAP). The patient had years previously been subjected to a total proctocolectomy. Following surgery, endoscopical biopsies were obtained from the duodenum (10 biopsies) in four instances and from the ileal pouch (6 biopsies) in three. All biopsies were taken between 1988 and 2003. Hematoxylin and eosin (H&E) sections from all those 16 biopsies were reviewed. In one biopsy from the ileal pouch, a tubular adenoma carrying 92% dysplastic Paneth cells was found. Paneth cells were more easily singled out when H&E sections were observed in a fluorescent microscope than when using conventional transmitted light, or lysozyme immunostain. Despite a wide distribution of Paneth cells in mucosas with intestinal metaplasia (e.g. Barrett's esophagus and gastric intestinal metaplasia), in the normal small intestine and in the large intestine with chronic inflammatory diseases only a few Paneth cell neoplasias have been reported in the GI tract. The cause of the apparent natural resistance of these specialized cells provided with anti-microbial and growth factors to undergo neoplastic transformation deserve further investigation. A review of the literature indicates that this is the first reported case of Paneth cell adenoma of the small intestine.*

Despite the fact that an increased number of Paneth cells is often reported in duodenal adenomas from patients with familial adenomatous polyposis (FAP), no case of Paneth cell adenoma of the duodenum or the small intestine has been reported in those patients.

Odze *et al.* (1) recently studied 74 periampullary and duodenal adenomas from 30 patients with FAP. They found Paneth cell differentiation in the majority (92%) of the adenomas (average 24.5 Paneth cells/high power field).

Paneth cells were initially discovered by Schwalbe in 1872 (2) and described in more detail by Paneth in 1888 (3). The

cells are normally found at the bottom of the crypts of Lieberkühn in the small intestine and may also be present in the cecum and the proximal colon. As metaplastic cells, Paneth cells may be found in Barrett's esophagus, in gastric intestinal metaplasia (4), in chronic inflammation in the transverse, distal colon and rectum, the gall bladder with cholelithiasis, the urinary bladder, the prostate, the epididymis and the uterine cervix.

Isolated cases of neoplasias containing Paneth cells have been reported in the GI tract, *e.g.* stomach (5-7), jejunum (8), Meckel's diverticulum (9), rectum (10,11), gall bladder (12) as well as at extraintestinal sites, *e.g.* urinary bladder (13), uterine cervix (14) and prostate (15).

In 1981, Reitamo *et al.* (8) reported one case of adenocarcinoma of the jejunum with "areas containing cells resembling Paneth cells". The number of Paneth cells was not reported.

Recently, we found a high number of dysplastic Paneth cells in an adenoma from the ileal pouch in a FAP patient.

Case Report

A 47-year-old male with familial adenomatous polyposis (FAP) had been subjected to a total proctocolectomy 27 years previously. Following surgery, endoscopical biopsies were obtained from the duodenum in four instances and from the ileal pouch in three. Between 1988 and 2003, a total of 10 biopsies were taken from the duodenum and 6 biopsies from the ileal pouch. The hematoxylin and eosin (H&E) sections from all those 16 biopsies were reviewed.

Counting Paneth cells in H&E - or in lysozyme-stained tissue sections may be unreliable (16). In fact, when observing H&E and lysozyme (Muramidase, DAKO, Denmark (17))-stained sections with conventional transmitted light (TL) many Paneth cells are "packed" in tight groups. The cell borders are imprecise and the true number of Paneth cells is impossible to determine. Recently, we described an alternative method to enumerate Paneth cells (16). By observing H&E-stained sections in a fluorescent microscope (*i.e.* with indirect light fluorescent -ILF-460 nm), we found that all Paneth cells become auto-fluorescent. Against the dark, non-auto-fluorescent background, the cell borders are easy to delineate, even when arranged in

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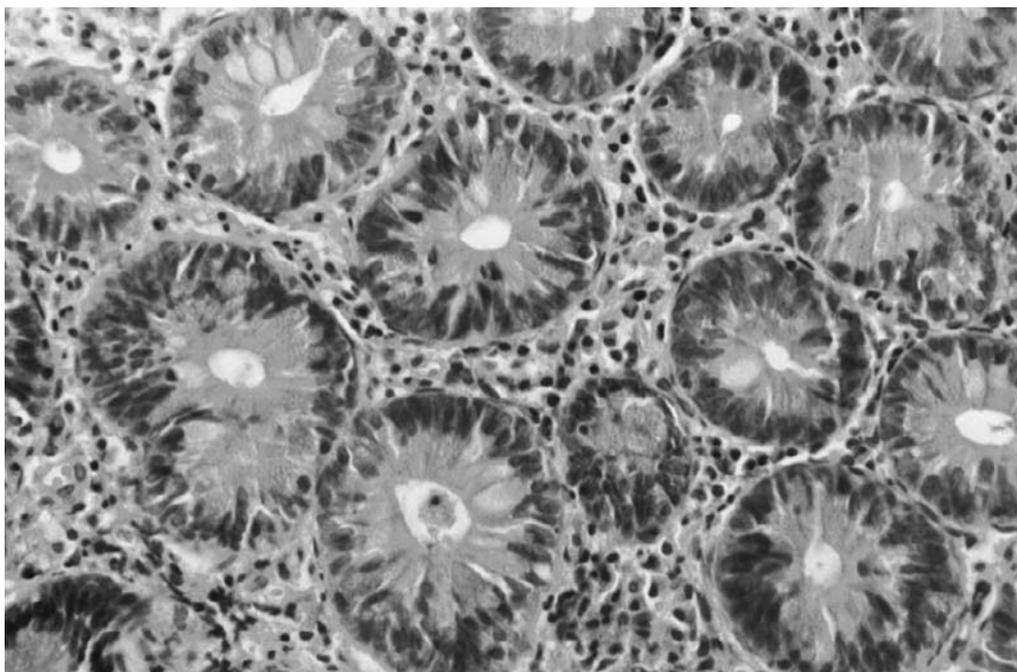


Figure 1. Close view of an H&E-stained section from a Paneth cell adenoma of the ileum. Note that the Paneth cells are difficult to outline (H&E, photographed in transmitted light, 10 x).

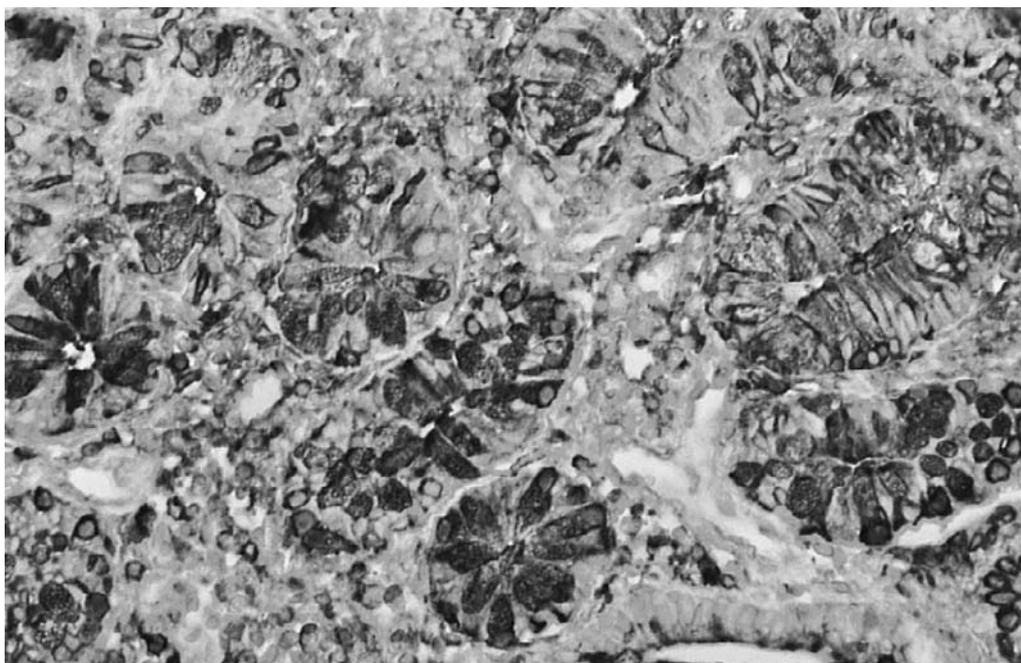


Figure 2. Close view of a lysozyme-immunostained section from a Paneth cell adenoma of the ileum. Note that the Paneth cells are difficult to outline (lysozyme-muramidase, photographed in transmitted light, 10 x).

tight groups. Another advantage of the method is that the auto-fluorescence of the eosin stain does not fade despite long periods of observation in a fluorescent microscope and of exposure-time while photographing. This advantage permits repeated inspections of old archival H&E-stained sections in a

fluorescent microscope. Thanks to this simple procedure (16), special staining procedures recommended for Paneth cells such as phloxine-tartrazine, aldehyde fuchsin, toluidine blue, phosphotungstic acid, Masson trichrome, Verhoeff stains or lysozyme are no longer being used at this laboratory.

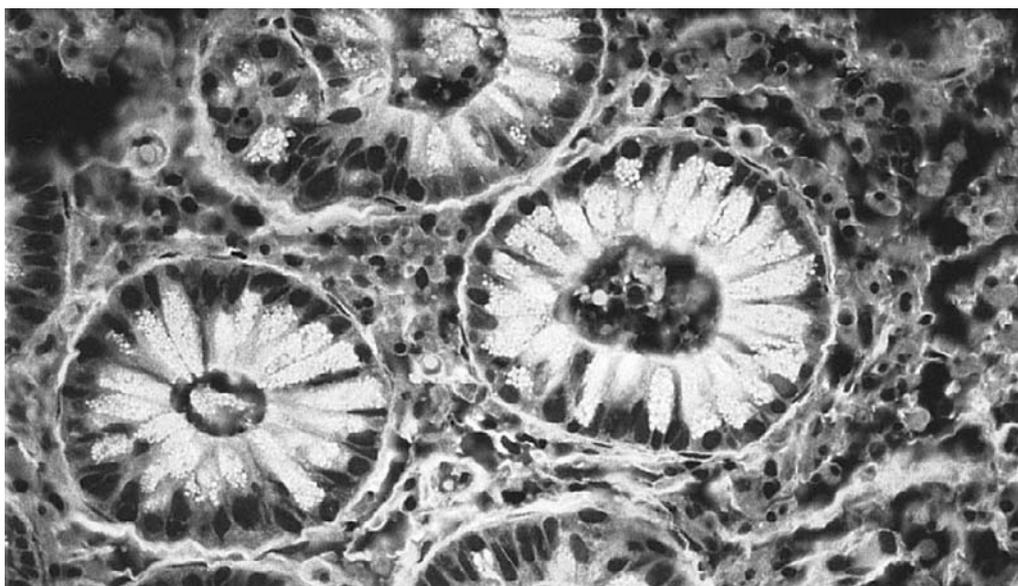


Figure 3. Close view of an H&E -stained section from a Paneth cell adenoma of the ileum. Note auto-fluorescent dysplastic Paneth cells (H&E, photographed with indirect light fluorescent, 460 nm, 10 x).

In the present case, 10 tubular adenomas (all with low grade dysplasia) were found in the duodenum. By the use of a fluorescent microscope, we found in those 10 adenomas that $\leq 18\%$ of the dysplastic cells were Paneth cells. By the same method, we found in one biopsy of the ileal pouch a tubular adenoma carrying 92% dysplastic Paneth cells (case reported here, Figures 1-3) and in the remaining biopsies, 5 tubular adenomas (all with low grade dysplasia) having $\leq 20\%$ dysplastic Paneth cells.

Sections from the ileal pouch adenoma were also stained with lysozyme. That immunostain showed a high frequency of lysozyme-positive cells (Figure 2). The actual number of Paneth cells could not be assessed with that method.

The review of the proctocolectomy specimen revealed multiple tubular and tubulovillous adenomas with occasional Paneth cells.

Discussion

A case of Paneth cell adenoma of the ileal pouch in a FAP patient is reported. Several authors have highlighted the occurrence of Paneth cells in neoplasias of the GI tract, particularly in duodenal adenomas in FAP patients (1,18,19). To describe the presence of Paneth cells in neoplasias, many authors used the following expressions in their reports: "the majority" (20), "occasional" (21), "approximately" (12), "numerous" (22), "as an integrated part of the tumor" (5), "being a significant component" (18), "rich in" (23), or "predominant cell type" (24). Those descriptive terms are a testimony to the difficulties in setting limits in defining the proportion of neoplastic cells required to recognize a tumor

as belonging to a particular predominant histological phenotype.

Using differential cell counting, some workers calculated the percent of neoplastic Paneth cells in GI neoplasias. Iwama *et al.* (25) found 43% of Paneth cells in a cecal adenoma, Sakaki *et al.* (12) "approximately 40% Paneth cells" in a gallbladder adenocarcinoma, Zampatti (26) 60% Paneth cells in a colonic adenocarcinoma, and Rubio (7) 95% neoplastic Paneth cells in a gastric adenoma. With the aid of an image quantifier, we subsequently found that 41% of a rectal flat adenoma tissue was lysozyme muramidase-positive (10). Whereas the gastric lesion was reported as a Paneth cell adenoma (7), the rectal lesion was regarded as a Paneth cell-rich adenoma (10).

The question arises: what is the percentage of Paneth cells required to catalogue a tumor in the GI tract as Paneth cell neoplasia, alternatively as Paneth cell-rich neoplasia?

For breast carcinomas, Weidner (27) considered tumors with a special pattern as those having 90% or more of the special pattern. In the adenoma reported here, 92% of the dysplastic cells were Paneth cells, a percent that satisfies the limit of $\geq 90\%$ proposed by Weidner (27) for breast tumors. If that limit is strictly respected, only four cases of true Paneth cells neoplasia (including the present one) seem to be on record in the literature. However, if that is the case, should tumors having between *e.g.* one-third (*i.e.* 33%) and 89% neoplastic Paneth cells be defined as Paneth cell-rich neoplasias? As regards the lower limit, Bariol *et al.* (28) recently reported that the diagnosis of serrated adenomas of the colon and rectum should include serrated structures in $\geq 20\%$ of the dysplastic crypts. It is apparent that the proportion of differentiated cells required to classify a GI

neoplasia as belonging to a particular histological phenotype remains to be elucidated.

The variety of cellular phenotypes (*i.e.* Paneth cells) and of architectural phenotypes (*i.e.* tubular (1), villous (29) and serrated (30)) in FAP adenomas suggests that the genetic trait that triggers the development of thousands of adenomas may be unrelated to the molecular events that decide the different cellular and architectural dissimilarities of FAP adenomas.

Despite a wide distribution of Paneth cells in mucosae with intestinal metaplasia in Barrett's esophagus, in the stomach, as well in the normal small intestine and in the large intestine with chronic inflammatory diseases, only a few tumors arising in Paneth cells have been reported in the GI tract. The cause of the apparent natural resistance of these cells, carrying antimicrobial and growth factors, to undergo neoplastic transformation deserves to be further investigated.

The review of the literature indicates that this is the first reported case of Paneth cell adenoma of the ileum.

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