

Duodenal adenomas in familial adenomatous polyposis: their structure and cellular composition with particular reference to endocrine hyperplasia

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Summary. 134 duodenal biopsies from 14 patients with familial adenomatous polyposis were evaluated by light microscopy for the presence of adenoma. Staining reactions for endocrine cells were applied. 90 biopsies contained adenoma, almost all of the tubular type (98%) with dysplasia, ranging from mild to moderate. Accompanying hyperplasia of argyrophil and argentaffin endocrine cells was found in 91% and 64% of the adenomas, respectively. Based on histological criteria it is concluded that the risk of carcinoma development in the duodenum could equal that in colon and rectum. The observation of endocrine hyperplasia is new, and further investigations are needed before the significance of this finding can be evaluated.

Key words: Familial adenomatous polyposis – Duodenal adenomas – Endocrine hyperplasia

Introduction

Until 1976 duodenal polyps in patients with familial adenomatous polyposis (FAP) were considered to be very rare. Since then the literature contains many reports on fiberendoscopic examination, revealing duodenal adenomas in more than half of FAP patients. In a Danish study (Bülow et al. 1985) the high frequency of duodenal polyps was confirmed. Histologically the polyps turned out to be adenomas, resembling those in the colon and rectum. The purpose of this paper was to evaluate the adenoma structure, the type of epithelial cells involved and the degree of dysplasia in these duodenal proliferations.

Materials and methods

The material comprised 134 fiberendoscopic biopsies from duodenal polypoid lesions from 14 FAP patients. Seven were men and 7 women, with median age of 43½ years (range 16–69). The frequency of biopsy varied from 1 to 5, and a median number of 6 biopsies (range 3–35) was taken. Histologically the classification for epithelial tumours given by Morson and Dawson (1979) was used.

The biopsies were fixed in 10% formalin and routinely embedded in paraffin. Sections were stained with haematoxylin – eosin, periodic acid – Schiff – Alcian blue, pH 2,5 for mucosubstances, and with the silver method of Grimelius for argyrophil cells (Grimelius 1968). The alkaline diazonium reaction for argentaffin cells (Pearse 1961), employing Fast Garnet GBC in 0,1 M phosphate buffer at pH 7,8 was used.

The biopsies were studied for the presence of adenoma, and the following variables were examined; size of the adenoma measured as a proportion of the total mucosa present in the specimen and categorised as <1/3, 1/3–2/3, >2/3; the histological type of the adenoma (tubular, villous or tubulo-villous); the degree of dysplasia (whether mild, moderate or severe, characterized by cellular atypia, abnormal differentiation and disorganised architecture) and the extent of endocrine hyperplasia, graded as a slightly, moderate or heavily increased number of stained cells, compared with the number of cells in the non-adenomatous mucosa in the biopsy.

Hyperplasia was defined as linear, when sequences of more than 5 cells were lying inside the basement membrane of the crypts; micronodular, when groups of more than 5 cells were found in a non-linear arrangement; and diffuse, when no localized collections of cells were found (Solcia 1988). The number of Paneth cells and of cells in an accompanying eosinophilic granulocyte infiltration was also estimated.

Results

Endoscopically 14 patients had between 10 and approximately 50 yellowish – white sessile polyps with smooth or slightly lobulated surface, measuring from 1 to 10 mm in diameter.

Ninety of the 134 biopsies (67%) contained adenoma, the rest consisted of normal mucosa. The results are given in Table 1. Adenomas were found in 20–100% (median 75%) of the biopsies from

Table 1. Number and histological features of 90 duodenal adenomas from 14 FAP patients

Case	Patient's Sex/Age (YR)	No. of Biopsies	No. of Adenomas	Grade of dysplasia		Argyrophil cells			Argentaffin cells		
				Mild	Moderate	+	++	+++	+	++	+++
1	F/56	4	2	2	0	1	1	0	2	0	0
2	F/41	5	5	2	3	1	1	2	1	2	0
3	F/51	14	10	10	0	0	0	9	0	2	6
4	M/31	14	10	9	1	1	6	2	2	2	0
5	M/47	10	5	3	2	2	1	2	2	1	1
6	M/69	7	6	3	3	2	0	3	0	1	2
7	F/41	4	3	2	1	0	0	3	0	0	3
8	F/42	15	9	7	2	1	1	6	5	1	1
9	M/57	35	27	7	20	2	6	17	2	5	12
10	M/45	8	7	4	3	4	1	1	1	0	0
11	F/24	3	1	1	0	0	0	1	1	0	0
12	M/16	6	3	0	3	1	1	1	2	0	0
13	M/48	4	1	1	0	1	0	0	0	0	0
14	F/20	5	1	0	1	0	0	1	0	1	0

+ Slightly increased number
 ++ moderate increased number
 +++ heavily increased number

each patient. 27 adenomas (30%) involved more than 2/3 of the propria mucosa, 29 (32%) more than 1/3 and less than 2/3, while 34 (38%) comprised less than 1/3. Eighty eight adenomas (98%) were of the tubular type, 2 (2%) of the tubulo-villous type. Mild dysplasia was found in 51 adenomas (57%), moderate dysplasia in 39 (43%) (Fig. 1). None showed severe dysplasia. An obligate loss of goblet cells was noted in all adenomas. With the Grimelius' silver method 82 adenomas (91%) showed an increased number of blackened cells (Fig. 2), the increase being slight in 16 adenomas (20%), moderate in 19 (23%) and heavy in 47 (57%). With the alkaline diazonium reaction 58 adenomas (64%) showed an increased number of stained cells, the increase being slight in 18 adenomas (31%), moderate in 15 (36%), and heavy in 25 (43%). Thus 24 adenomas from 10 patients showed only the argyrophil reaction, while the rest (58) showed a mixed pattern of reaction. The distribution of the endocrine cells was observed to be linear (Fig. 3) in all but 8 adenomas, in which the cells were located in a diffuse manner (Fig. 4). A micronodular pattern was never seen. Extension towards the surface epithelium was often found. Paneth cell hyperplasia, confined to the lower crypt parts, was found in 68 adenomas (76%), the degree being slight in 26 (38%), moderate in 14 (21%), and pronounced in 28 (41%).

In the lamina propria, a high number of eosinophilic granulocytes was noted in all adenomas. The adjacent duodenal mucosa, including the Brünner

glands, present in some of the specimens, was found to be normal in all biopsies.

Discussion

The duodenal polyps in FAP are known to be adenomas, similar to those in the colon and rectum. The frequency with which they are encountered is given to be 33–100% (Watanabe et al. 1977; Järvinen et al. 1983; Sarre et al. 1987). In the Danish study from 1985 (Bülow et al. 1985) on a small group of FAP patients the adenoma frequency was 46%.

Few reports deal with details of the adenoma type (tubular or villous) or degree of dysplasia (Watanabe et al. 1977; Sweeney and Anderson 1982; Järvinen et al. 1983; Burt et al. 1984; Romagnoli et al. 1986). In this study we found tiny adenomas, almost all of the tubular type (98%), the rest being tubulo-villous, and the degree of dysplasia was mild or moderate in all adenomas. If the theory of the adenoma-carcinoma sequence applies to the duodenum, as it does to the colon, (Morson and Dawson 1979) our results show FAP patients to have an increased risk of carcinoma development in the duodenum. This has already been suggested by other authors in clinical series (Melmed and Bouchier 1972; Yao et al. 1977; Bussey 1980; Sugihara et al. 1982; Itoh et al. 1985; Kurtz et al. 1987; Jagelman et al. 1988).

Hyperplasia of argentaffin, and/or non-argentaffin argyrophil endocrine cells in duodenal ad-

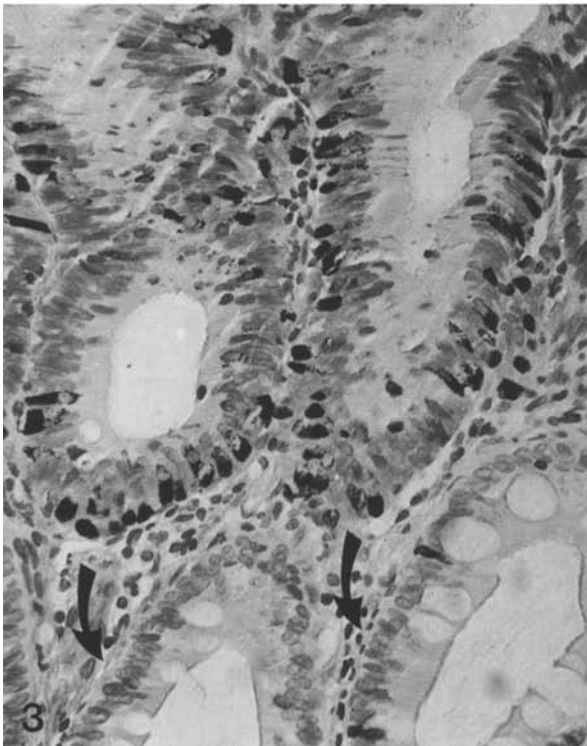
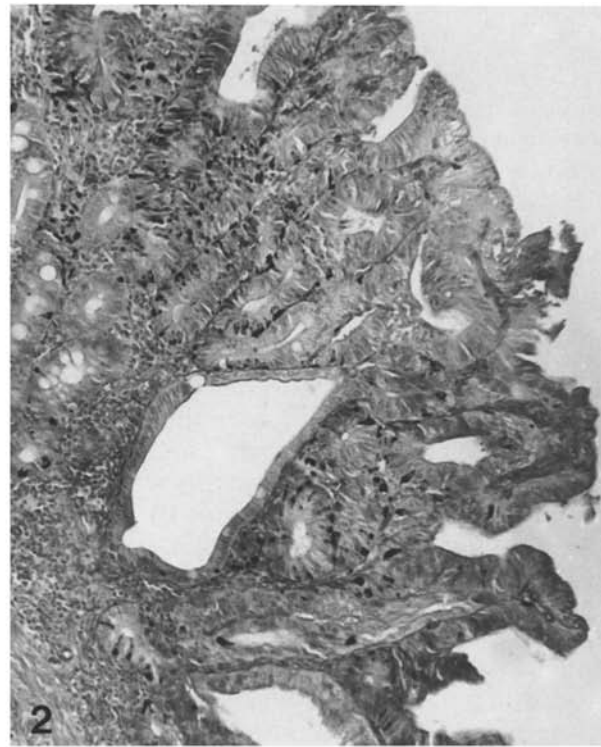
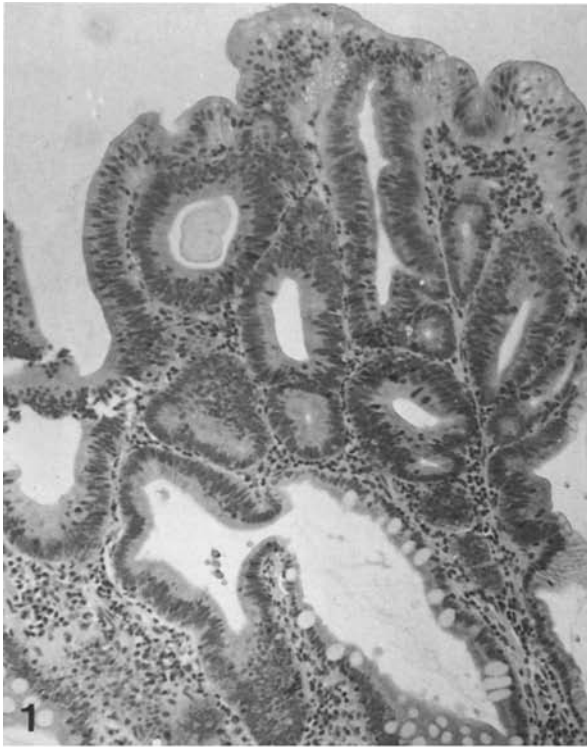


Fig. 1. Tubular adenoma with moderate epithelial dysplasia. Haematoxylin-eosin $\times 110$

Fig. 2. Hyperplasia of argyrophil endocrine cells. The silver method of Grimelius $\times 110$

Fig. 3. Hyperplasia of argyrophil endocrine cells in a linear pattern. Few endocrine cells are seen in the normal intestinal epithelium (arrows). The silver method of Grimelius $\times 560$

Fig. 4. Hyperplasia of argyrophil endocrine cells in a diffuse pattern. No endocrine cells in the normal intestinal epithelium (arrow). The silver method of Grimelius $\times 560$

enomas has not been reported previously. Our investigation revealed endocrine hyperplasia in multiple adenomas; in 24 shown to be of the non-argentaﬀin, argyrophil type, in 58 of a mixed argentaﬀin and argyrophil type. The endocrine cells were found located along the basement membrane of the crypts, often forming a continuous layer, encircling the crypts partly or entirely (linear hyperplasia). This pattern was often seen together with a dispersed, scattered distribution. A tendency for the cells to proliferate up along the crypt walls and, to some degree, to spread over the surface was also noted. Micronodular hyperplasia was not found. The observation of endocrine hyperplasia indicates a possible analogy with the theory of the adenoma-carcinoma sequence; adenomas with endocrine hyperplasia may predispose to development of neuroendocrine tumours. The connection between endocrine cell hyperplasia, formation of micronoduli outside the basement membrane of the epithelial lining and development of endocrine tumours is not known, but has been discussed (Black and Haffner 1968; Mendelsohn et al. 1987). So far however, we have found no evidence suggesting that this occurs in FAP patients, neither in our own experience, nor in the literature.

The finding of only a small number of goblet cells is explained by the loss of differentiation, which goes with the premalignant change. An increased number of Paneth cells occurred in 76% of the adenomas. The cells were located at the bases of the crypts and did not seem to take part in the neoplastic process. This observation is in accordance with that of Watanabe (1972), who found a positive correlation between argentaﬀin cells and Paneth cells in gastric adenomas. However, we consider the interpretation to be different in the duodenum, and thus believe the Paneth cell hyperplasia to be part of a simple crypt hyperplasia. In gastric adenomas Watanabe (1972) also found an almost inverse relation between the number of argentaﬀin cells and the degree of dysplasia. This observation could not be confirmed by our results, since adenomas from only 3 patients showed the tendency. One explanation might be an effect on grading the dysplasia due to the presence of endocrine hyperplasia, in such a way that the dysplasia was "overgraded". In the stroma an eosinophil granulocyte reaction of varying strength was obligatory, possibly as a non-specific reaction.

In conclusion our study demonstrated that the duodenal polyps were adenomas, 98% being tubular with mild or moderate dysplasia in all cases. Based on histological characteristics, the potential risk of carcinoma development in the duodenum

in FAP-patients may equal that of the colorectum. Further, endocrine hyperplasia was found in the great majority of the adenomas. This observation is new and more investigation is necessary in order to evaluate the significance of the observation.

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