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Electron microscopic studies of endocrine hyperplasia in duodenal adenomas in familial adenomatous polyposis

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Summary. Electron microscopical studies on endocrine cell hyperplasia of duodenal adenomas from five patients with familial adenomatous polyposis were performed. All the endocrine cell types normally found in the duodenal mucosa were identified. A constant feature was proliferation of duodenal-enterochromaffin cells but an increase in the number of all other endocrine cell types apart from pyloricgastrin cells and somatostatin cells, was also observed. Certain types of intestinal endocrine cells (the intestinal enterochromaffin cell and the glicentin cell) are rare cells in the normal duodenal mucosa. The finding of these cells may indicate increased biological aggressivity.

Key words: Familial adenomatous polyposis – Duodenal adenomas – Endocrine hyperplasia – Electron microscopical studies

Introduction

In 14 patients with familial adenomatous polyposis (FAP) biopsies from multiple duodenal polyps showed adenomas with a tubular or tubulovillous growth pattern and cytological characteristics of epithelial dysplasia varying from mild to moderate. Endocrine cell hyperplasia was found in 82 of the 90 adenomas removed. In most of the adenomas the endocrine cells were a mixture of argentaffin- and argyrophil non argentaffin cells (Mogensen et al. 1988).

The present investigation was undertaken in order to establish an ultrastructural typing of the various cell types involved in the endocrine hyperplasia.

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Material and methods

The material consisted of fiberendoscopic biopsies from duodenal polyps from 9 patients, 5 men and 4 women. The biopsies were cut into small parts and immediately fixed in cold, cacodylate buffered Karnovsky fixative pH 7.2 (Karnovsky 1965). Subsequently, the specimens were rinsed in 0.1 M cacodylate buffer pH 7.2, post-osmicated and embedded in Epon after dehydration.

Semithin sections were stained with 0.5% toluidine blue for identification of the adenoma and for orientation of the ultrathin sectioning. Adenomas were found in five of the nine patients. The biopsies from four patients were composed of normal duodenal mucosa, and were used as reference material. None of the biopsies included Brünner glands. Ultrathin sections were stained with Zn-uranyle acetate and lead citrate and examined in a Philips 201 electron microscope.

At least 10 ultrathin sections were examined from each biopsy and all endocrine cells were identified and photographed. The photographs were reproduced at a magnification of 27.750 and the morphology of the secretory granules of the various endocrine cell types was determined, according to the "update on Lausanne classification of endocrine cells" (Solcia et al. 1981).

Results

The ultrastructural identification of the various types of endocrine cells was mainly based on the shape, size and texture of their secretory granules. The endocrine cells of the adenomatous epithelium of five patients were compared with the endocrine cells of the normal duodenal epithelium of the four patients without adenomas.

In the normal duodenal mucosa the different endocrine cells were few, and scattered throughout the crypt epithelium, lying at the basement membrane and reaching the lumen in small areas. In the stratified epithelium of the adenomas the endocrine cells were located on or near the basal lamina, often forming a continuous layer along the entire crypt with extension into the surface epithelium, where a few cells occured. The different types of

Table 1. The types of endocrine cells found in the adenomatous epithelium of five patients with FAP. The presumed main product is given in brackets

	PG-cell (gastrin)	D-cell (somatostatin)	Mo-cell (motilin)	TG-cell (gastrin/CCK)	I-cell (CCK)	K-cell (GIP)	S-cell (secretin)	L-cell (glicentin)	D-EC (5 HT)	I-EC (5 HT)
I	N	N	+	+++	+	÷	÷	÷	+++	+++
II	N	N	+	+	+	+++	÷	+	++	÷
III	N	÷	+	÷	÷	++	++	÷	++	+
IV	N	÷	÷	÷	÷	++	÷	++	++	÷
V	N	N	÷	+	÷	÷	++	++	+++	+++

÷: no cells
N: "normal number" compared with the findings in normal duodenal mucosa
+: slightly increased numbers
++: moderate increased numbers
+++: heavily increased number

endocrine cells found in the adenomatous epithelium of the five patients are shown in Table 1. The presumed main product is given in brackets.

With the exception of the intestinal enterochromaffin (I-EC) cell (Solcia et al. 1976) and the L-cell, all endocrine cells identified in the adenomatous epithelium were also present in the non-pathological epithelium, although much more scattered and fewer in number. Proliferation of I-EC cells was found in two cases (I+V) whereas proliferation of duodenal enterochromaffin (D-EC) cells was found in all cases.

The I-EC cell was characterized by large, rod-like-biconcave or kidney shaped granules with closely applied membranes (Fig. 1), while the granules of the D-EC cell were large and irregular, often with a wide space between the eccentrically located core and the enveloping membrane (Fig. 2). A large number of L-cells was noted in two cases (IV+V). The L-cell was characterized by rather large, round to slightly irregular granules with homogeneous, dense cores and closely applied membranes (Fig. 3). Most D-EC cells, I-EC cells and L-cells were situated within the epithelial lining of the base and middle part of the crypt. The other endocrine cell types (Table 1) were more unevenly distributed throughout the crypt, including a few in the surface epithelium. The various endocrine cell types could be grouped together or mixed. Luminal contact was occasionally demonstrated.

K-cell proliferation was observed in one case (II), whereas a substantially higher number was found in two (III+IV). The K-cell was characterized by small round granules with homogeneous and fairly osmophilic cores and closely applied membranes (Fig. 4).

A high number of S-cells (Fig. 4) was present in two cases (III+IV), and a high number of TG-cells in one (I). A slight increase in the number of Mo-cells and I-cells was noted in three and two cases, respectively. The number of PG-cells and D-cells were few in all cases.

Hyperfunction such as enlargement of Golgi complexes or increased granular endoplasmic reticel was not observed in any of the endocrine cell types discovered. Nor did any of the endocrine cells display signs of dysplasia, involving nuclear pleomorphism, less prominent Golgi complexes or few secretory granules, when compared with their normal counterparts in the non-pathological duodenal mucosa.

Discussion

The various types of endocrine cells in the dysplastic epithelium of adenomas from five patients with FAP were studied at the ultrastructural level and compared with the endocrine cell population in the normal duodenal mucosa of four patients with FAP. All the endocrine cell types described in the normal duodenal mucosa (Solcia et al. 1975; Usellini et al. 1984a, 1984b, 1984c, 1985) were identified in the dysplastic epithelium and except for two, the I-EC cell and L-cell, were also seen in the non-pathological duodenal epithelium of another four patients with FAP. It is accepted that the morphology of the dense cored secretory granules permits a prediction of the type of peptide in a particular endocrine cell (Polak and Bloom 1987). However there is considerable interspecies variation (Solcia 1981).

The endocrine cells showed hyperplasia in all parts of the crypts within the dysplastic epithelium of the duodenal adenomas, thus participating in the neoplastic proces, without showing any signs

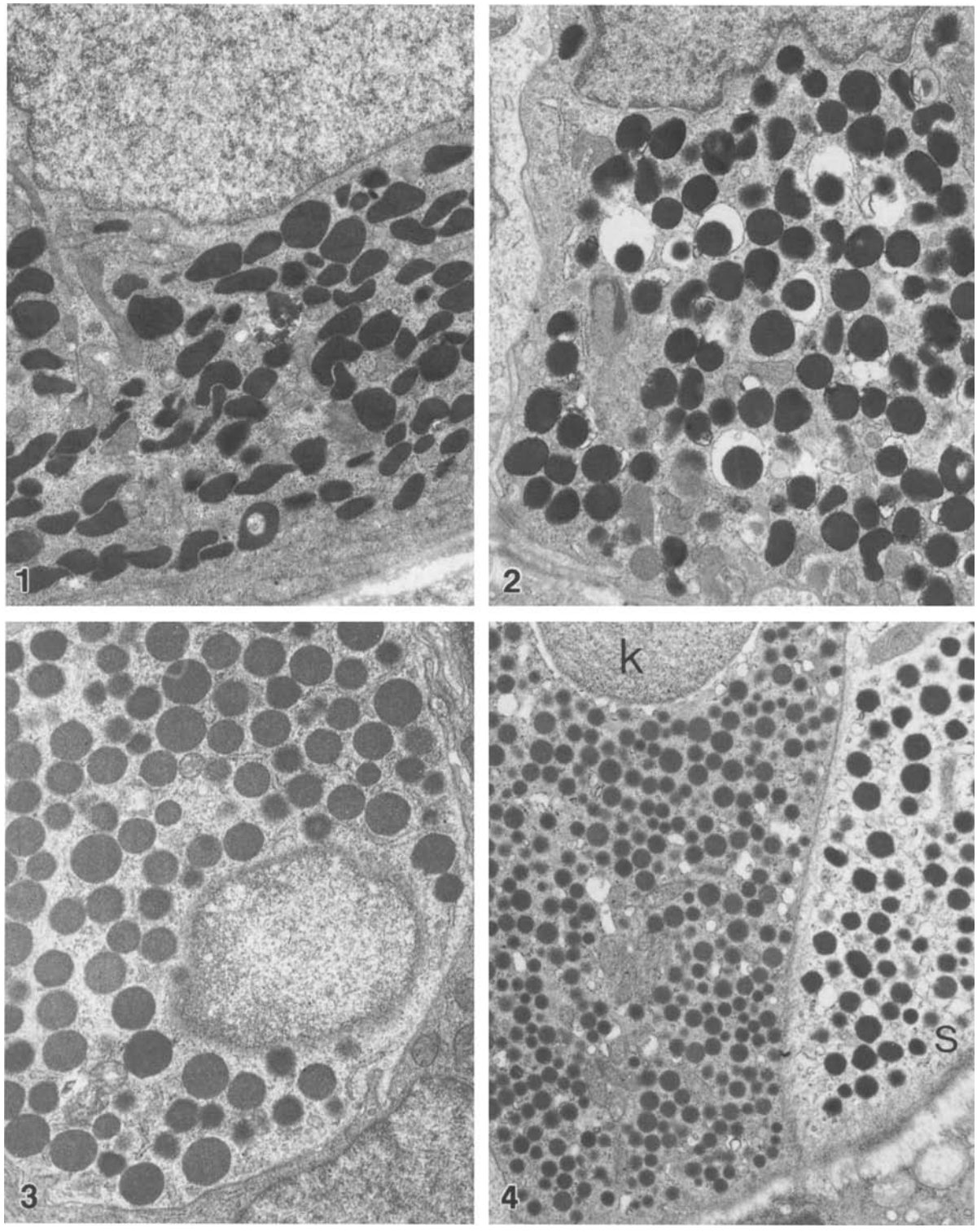

Fig. 1. Intestinal enterochromaffin (I-EC) cell of a duodenal adenoma (I) ×12000

Fig. 2. Duodenal enterochromaffin (D-EC) cell of a duodenal adenoma (V) ×12000

Fig. 3. L-cell of a duodenal adenoma (V) ×12000

Fig. 4. K-cell (*K*) and S-cell (*S*) of a duodenal adenoma (II) ×12000

of dysplasia themselves. This is in contrast with the findings in dysplastic human bronchi, where about 10% of the endocrine cells themselves displayed dysplastic changes (Gould et al. 1978). Although I-EC cells and L-cells are described in normal duodenal mucosa, they seem to be more numerous in the distal part of the smaller intestine and in the large intestine (Solcia et al. 1975). Their occurrence in large numbers in some duodenal adenomas from patients with FAP, as found in our study, may indicate an atypical intestinal endocrine differentiation.

Adenomas in the stomach have been described as being of intestinal type, because they occur in areas where the adjacent mucous membrane is composed of intestinal type epithelium (Morson 1955), or because well differentiated intestinal type EC-cells and Paneth cells have shown up together with atypical columnar cells of intestinal type as part of the adenomatous epithelium (Watanabe 1972). Ultrastructural studies on intestinal metaplasia of the stomach and on intestinal metaplasia in the columnar epithelium in Barretts syndrome revealed only intestinal types of endocrine cells (Hage 1976).

In studying the morphogenesis of gastric adenomatous polyps, transformation into invasive carcinoma of intestinal type has been suggested (Holmes 1966), and an increased risk of developing epithelial dysplasia and adenocarcinoma is believed to exist in areas with intestinal metaplasia in patients with Barrett's syndrome (Monnier et al. 1988). Similarly, large numbers of intestinal EC-cells and L-cells in adenomas of patients with FAP may indicate increased biological aggressivity, possibly necessitating more frequent endoscopic controls.

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