Histologic Classification of Endoscopically Removed Flat Colorectal Polyps: A Multicentric Study

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A total of 594 flat colorectal polyps, removed at endoscopy, were histologically classified into non-neoplastic (n=49) and neoplastic (n=545) polyps. Non-neoplastic polyps were subdivided into metaplastic (n=45) and hyperplastic (n=4), whereas neoplastic polyps were subdivided into adenomas (n=481), intramucosal carcinomas (n=28) and invasive adenocarcinomas (n=36). Several adenoma phenotypes were discerned: tubular (n=375), serrated (n=59), villous (n=39), mixed (n=7) and fenestrated (n=1). Intramucosal carcinomas were subdivided into tubular (n=26) and serrated (n=2), and invasive adenocarcinomas into tubular (n=32), serrated (n=3) and fenestrated (n=1). The microscopic characteristics of each histologic phenotype described in this communication are defined and illustrated.

Key words: Flat polyp — Colon — Classification — Histology

Until a few years ago it was generally accepted that the majority of the colorectal adenocarcinomas originated in exophytic adenomas.[1,2] In recent years, however, the systematic study of the colorectal mucosa by Japanese endoscopists, using improved optical devices complemented by chromography, resulted in the detection of small, flat polyps in that mucosa.[3,4] Japanese pathologists and endoscopists with training in pathology, found those lesions to be either flat (tubular) adenomas or flat adenocarcinomas arising in flat (tubular) adenomas, thus introducing an alternative pathway in the "adenoma-carcinoma sequence" of the colorectal mucosa.[1] Many studies have demonstrated that flat adenomas may attain a considerable size without losing their flat appearance. There are no indications that flat adenomas evolve into exophytic lesions.

The application of the Japanese methodology in Sweden has permitted endoscopists to detect similar small flat colorectal polyps in Swedish patients.[5] These flat polyps were interpreted at histology as flat tubular adenomas or adenocarcinomas arising in flat tubular adenomas,[6] thus confirming the results obtained in Japan.

Recently, while reading histologic sections of endoscopically removed colorectal polyps, we noticed that polyps regarded as flat by the endoscopist could display not only tubular structures but also other histologic phenotypes.[7]

The present work was designed to classify, describe and illustrate the various histologic phenotypes so far noticed in a relatively large number of flat colorectal polyps removed at endoscopy in both Japan and Sweden.

MATERIALS AND METHODS

The histological sections of 594 flat colorectal polyps were reviewed. Sections had been cut at 4 μm and stained with hematoxylin and eosin. All lesions reviewed in this survey had already been considered by the endoscopists as flat polyps following the criteria of Muto et al.[3] and Kudo.[8] Colonoscopically excised lesions which had been endoscopically regarded as pedunculated or exophytic polyps were excluded from the classification of flat polyps, regardless of their histologic features. The endoscopic characteristics of flat hyperplastic and metaplastic polyps, flat serrated adenomas, flat tubular adenomas, flat villous adenomas and flat adenocarcinomas have been presented elsewhere.[3,5,9]

Lesions were removed either by mucosectomy or by forceps. Of the 594 lesions, 319 were from Japanese patients and the remaining 275 from Swedish patients. At histology, the lesions lacked an exophytic polypoid configuration and consisted of slightly elevated mucosal plaques, never greater than two times the thickness of the adjacent normal mucosa.[3,10]

RESULTS

The results are presented in Table I. The table shows that flat colorectal polyps could be classified into the following groups.

Table I. Histologic Phenotypes Found in 594 Endoscopically Removed Flat Colorectal Polyps

Histology	No. of cases
Non-neoplastic polyps	
Hyperplastic	4
Metaplastic	45
Neoplastic polyps	
a) Adenomas	
Tubular	375
Serrated	59
Villous	39
Mixed	7
Fenestrated	1
b) Intramucosal carcinomas	
Tubular	26
Serrated	2
c) Invasive carcinomas	
Tubular	32
Serrated	3
Fenestrated	1
Total	594

Fig. 1. a, Flat hyperplastic polyp (hematoxylin-eosin, ×20). b, Detail of a flat hyperplastic polyp to demonstrate straight crypts (hematoxylin-eosin, ×80).

Non neoplastic flat polyps

Flat hyperplastic polyps: In flat hyperplastic polyps, the crypts of Lieberkuhn were longer than normal, but their normal parallel and straight configuration was retained (Fig. 1). Regular, small nuclei were located at the base of the cells.

Flat metaplastic polyps: In flat metaplastic polyps, the sides of the crypts of Lieberkuhn had a crenated, sawtooth configuration due to scalloped epithelial infoldings (Fig. 2). The cells in those infoldings were cylindrical with or without apical mucin vacuoles alternating with large goblet cells. The regular nuclei were small, and located at the base of the cells.

Neoplastic flat polyps Neoplastic flat polyps were subclassified into flat adenomas, flat intramucosal carcinomas and flat invasive adenocarcinomas.

Degree of cellular dysplasia in flat adenomas: The histologic degree of epithelial dysplasia was determined by the following criteria[11]: Low grade dysplasia (LGD) when the dysplastic nuclei were present in the deeper half of the epithelium and high grade dysplasia (HGD) when the dysplastic nuclei were also present in the superficial half of the epithelium in at least three crypts.

Flat tubular adenoma: In flat tubular adenoma, the dysplastic epithelium (either LGD or HGD) was found initially in the epithelium of the lumen of the crypts of Lieberkhun (Fig. 3). The normal U-shaped configuration of the crypts was retained. Depending upon the topographic distribution of the dysplastic cells along the crypts, flat tubular adenomas were divided into type I when the dysplasti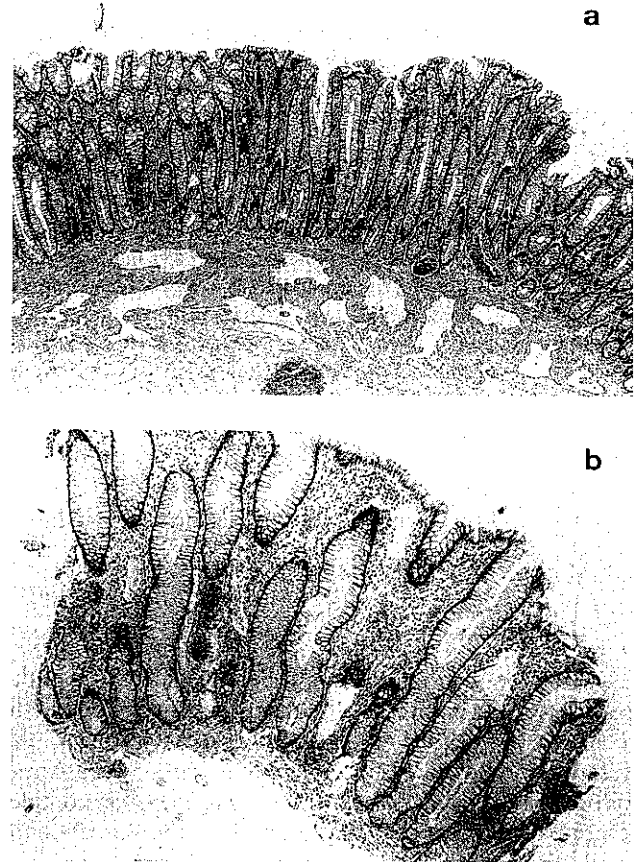c epithelium was limited to the upper half of the crypts and type II when the dysplastic epithelium was present even in the lower half of the crypts.[11] Some flat tubular adenomas exhibited a central depression.

Flat villous adenoma: Flat villous adenoma was composed of finger-like villous formations covered by dysplastic cells, either in the deeper half of the epithelium (LGD) or including the superficial half of the epithelium (HGD) (Fig. 4). The same topographic classification of the dysplastic epithelium as for flat tubular adenomas was applied to flat villous adenomas (i.e., type I and type II). Flat villous (as well as flat tubular adenomas) could contain variable proportions of Paneth cells.[12, 13]

Flat serrated adenoma: In flat serrated adenoma, the epithelium covering the sides of the crypts of Lieberkuhn showed a crenated, sawtooth configuration due to scalloped epithelial infoldings. Initially, only the cells at the lower part of the crypts were dysplastic (Fig. 5). As
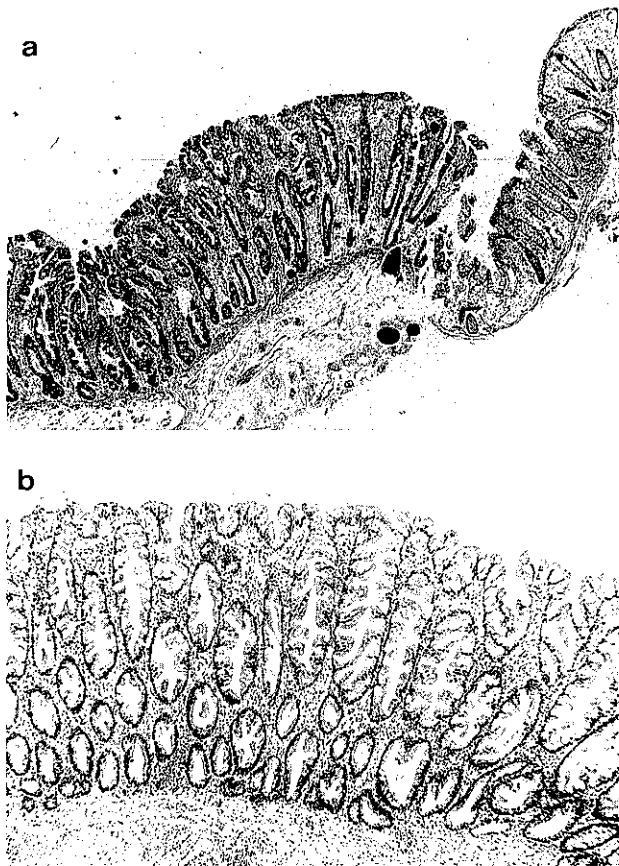
a

b

Fig. 2. a, Flat metaplastic polyp (hematoxylin-eosin, ×20). b, Detail of a flat metaplastic polyp to demonstrate crenated, sawtooth configuration due to scalloped epithelial infoldings (hematoxylin-eosin, ×80).
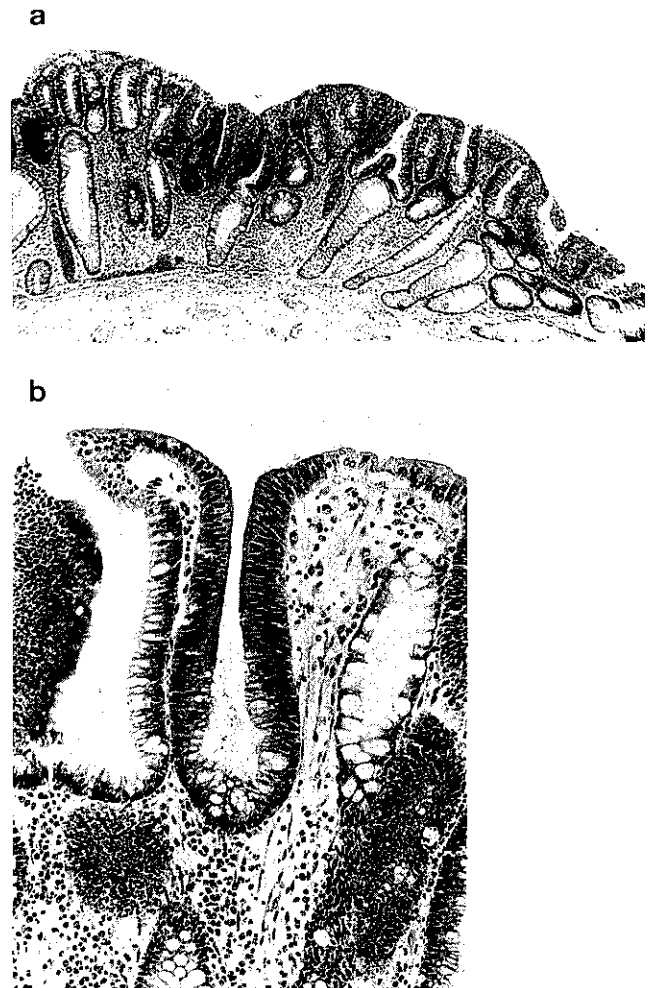
a

b

Fig. 3. a, Flat tubular adenoma showing dysplastic epithelium in the upper part of the mucosa (hematoxylin-eosin, × 20). b, Detail to demonstrate the replacement of the epithelial thickness by dysplastic cells (hematoxylin-eosin, ×300).

Fig. 4. Flat villous adenoma showing finger-like villi (MIB1 to demonstrate cell proliferation along the villi, ×20).

in flat tubular or flat villous adenomas, the dysplasia in flat serrated adenomas was classified into LGD and HGD.[7] Depending upon the topographic distribution of the dysplastic cells in the crypts, flat serrated adenomas were divided into type I when the dysplastic epithelium was limited to the lower half of the serrated crypts and type II when the dysplastic epithelium was present even in the superficial half of the serrated crypts.[7]

Flat fenestrated adenoma: In flat fenestrated adenoma, the single lumen of individual crypts was divided into multiple small, irregular lumina by dysplastic epithelial bridges (compare Fig. 10).

Flat mixed adenoma: In flat mixed adenomas, variable proportions of tubular and villous, or tubular and serrated adenomatous structures were present.

Flat intramucosal carcinomas In flat intramucosal carcinomas the crypts were no longer parallel (as is the case in tubular adenomas), but were architecturally distorted,
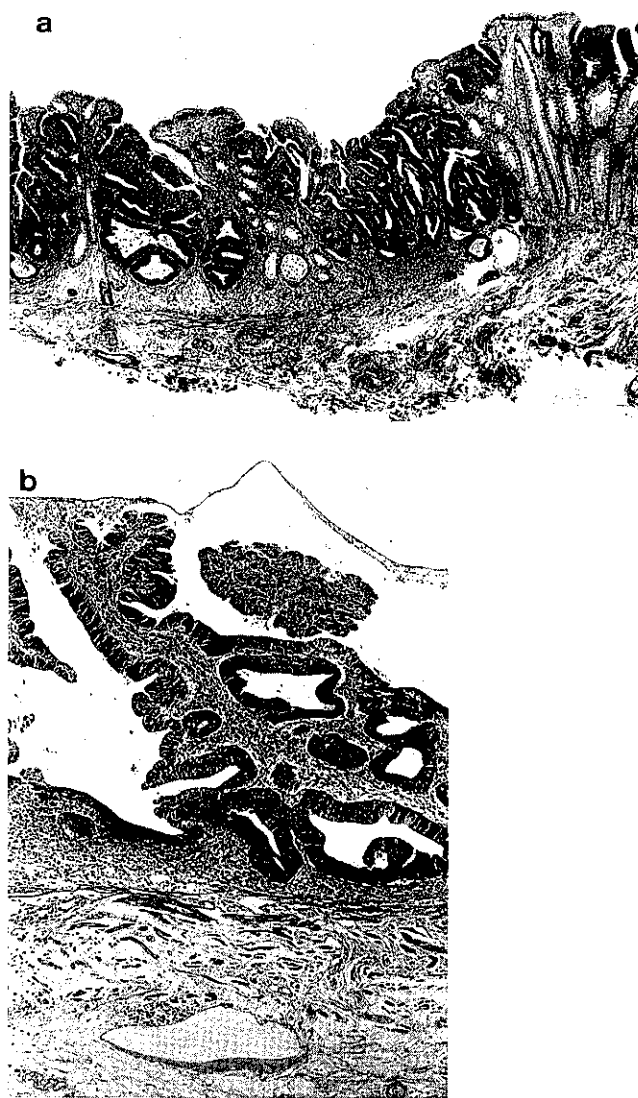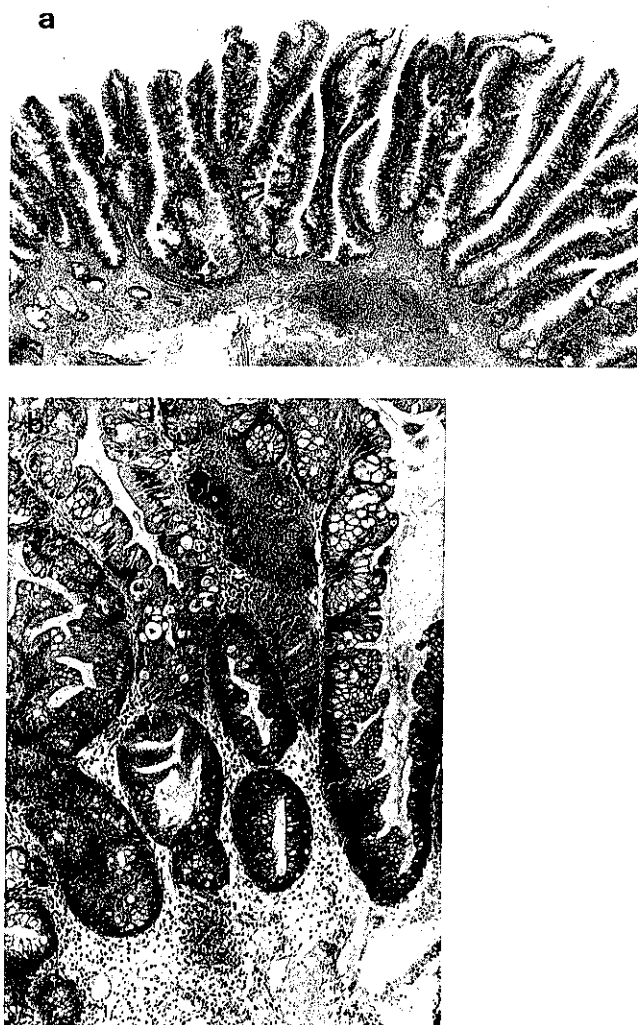
Fig. 5. a, Flat serrated adenoma type II (hematoxylin-eosin, ×20). b, Detail of flat serrated adenoma type I to demonstrate low grade dysplasia in the lower part of the crypts (hematoxylin-eosin, ×75).

Fig. 6. a, Flat tubular intramucosal carcinoma (hematoxylin-eosin, ×20). b, Detail of flat tubular intramucosal carcinoma (limited by the muscularis mucosa), showing distorted, irregular pattern in crypts lined with high grade dysplasia (hematoxylin-eosin, ×300).

with crowding, molding ("back-to-back") and/or lateral buddings.[11] The adenomatous structures were lined by HGD.

Flat tubular intramucosal carcinoma: In flat tubular intramucosal carcinoma, the crowded distorted crypts retained to some extent the tubular configuration (Fig. 6). *Flat serrated intramucosal carcinoma*: In flat serrated intramucosal carcinoma, the crowded distorted crypts retained to some extent the serrated pattern (Fig. 7).

Flat invasive adenocarcinomas Flat invasive adenocarcinomas were considered present when clusters of tumor cells were found in the submucosal tissue or beyond, the luminal parental lesion being a flat adenoma.

Flat tubular invasive adenocarcinoma: In flat tubular invasive adenocarcinoma,[11] clusters of tubuli-forming invading tumor cells were seen to originate from a flat tubular adenoma on top (Fig. 8).

Flat serrated invasive adenocarcinoma: In flat serrated invasive adenocarcinoma,[7] clusters of invading tumor cells adopting a serrated configuration were seen to depart from a flat serrated adenoma on top (Fig. 9).

Flat fenestrated invasive adenocarcinoma: In flat fenestrated invasive adenocarcinoma, the invading clusters of

Fig. 7. Flat serrated intramucosal carcinoma (limited by the muscularis mucosa), showing distorted, irregular serrated crypts lined by dysplastic cells (hematoxylin-eosin, ×20).

a

b
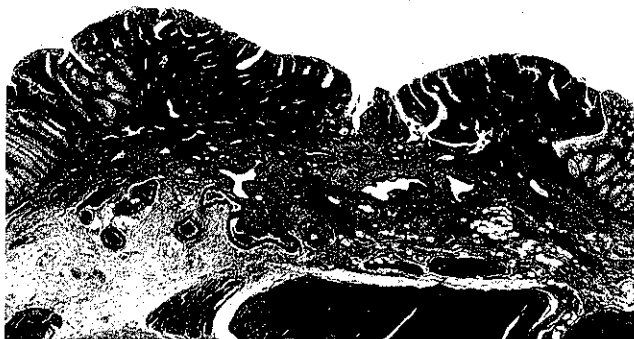

Fig. 8. Flat tubular invasive adenocarcinoma having irregular tubular glands in the submucosa (hematoxylin-eosin, × 20).

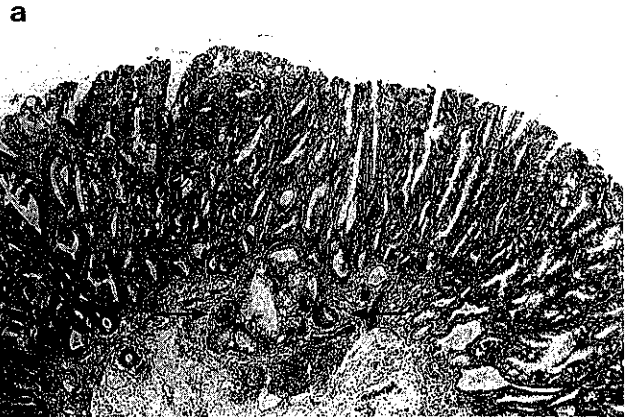Fig. 9. a, Flat serrated invasive adenocarcinoma showing invasion in the submucosa at arrows (hematoxylin-eosin, × 20). b, Another case of flat serrated invasive adenocarcinoma showing invasion in the submucosa at arrows (hematoxylin-eosin, ×20).

tumor cells were seen to originate from a flat fenestrated adenoma on top (Fig. 10).

DISCUSSION

The present classification indicates that those colorectal mucosal changes considered by the endoscopist to be flat polyps may display a wide spectrum of lesions at histology. The histologic spectrum ranged from flat non-neoplastic hyperplastic and metaplastic polyps, through flat adenomas (tubular, villous, serrated, fenestrated and mixed) and intramucosal carcinomas (tubular and serrated), to flat invasive adenocarcinomas (tubular, serrated and fenestrated).

We distinguished between hyperplastic and metaplastic polyps depending upon the architecture of the slopes of the crypts (straight or serrated, respectively).

The common histologic denominator for flat adenomas was the degree of epithelial dysplasia (LGD or HGD). The difference between flat tubular adenomas and flat villous adenomas on the one hand, and flat serrated adenomas on the other depended upon the topographic distribution of the dysplastic cells in the epithelium of the crypts. In tubular and in villous adenomas the dysplastic epithelium was seen initially in the upper part of the crypts (type I) and progressed downwards, eventually replacing even the lower half of the crypts (type II).[11] Contrariwise, in flat serrated adenomas the dysplastic cells were found initially at the lower part of the crypts (type I) and progressed upwards, eventually replacing the upper half of the crypts along the serrated structures (type II).[7, 14] The occurrence of dysplastic cells in up to one half of the crypts (i.e., type I adenomas) or beyond that limit (type II adenomas) was considered the result
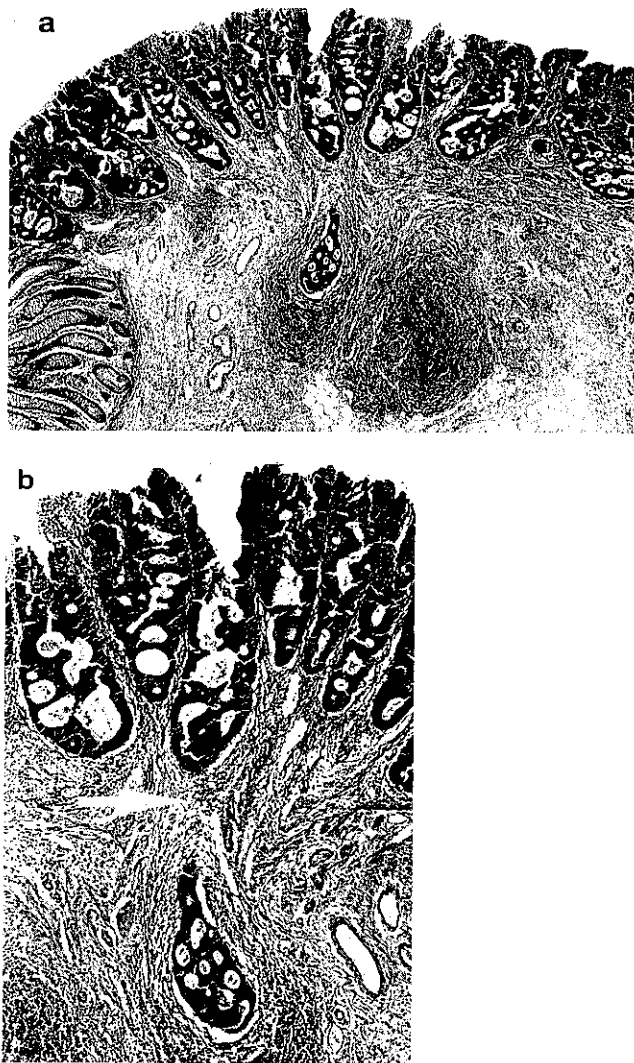
853

a

b

Fig. 10. a, Flat fenestrated invasive adenocarcinoma at arrows. Note adenoma on top (hematoxylin-eosin, ×20). b, Detail from a to demonstrate the fenestrated architecture in the adenoma on top, as well as in the invasive cluster (hematoxylin-eosin, ×80).

of the replacement* of the normal epithelium by proliferating dysplastic cells. This stepwise replacement by dysplastic cells was interpreted as the progression of the neoplastic process. The significance of intramucosal carcinomas remains enigmatic. Some authors consider these lesions to be invasive carcinomas[15] and others believe

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* The term "replacement" is used here as a descriptive, noncommital term meaning "instead of," in preference to the more commital terms: supplant, substitute, displace, supervene, superpose and supersede.

them to be non-invasive neoplasias.[11] The possibility that flat intramucosal carcinoma mirrors one of the essential histologic events in the process of colorectal carcinogenesis must be entertained.

Intramucosal carcinoma may be a "link" between HGD and invasive carcinoma. This view is supported by the following observations: a) all intramucosal carcinomas seen so far have been type II lesions (i.e., lesions occupying topographically the full length of the gland), b) invading cell clusters had the same histologic phenotype as their intramucosal counterpart (tubular or serrated). So far we have not found a case of intramucosal fenestrated carcinoma. The histological differences between flat adenomas, flat intramucosal carcinomas and flat invasive adenocarcinomas in Japanese and Swedish patients were reported elsewhere.[11]

Exophytic as well as flat colorectal adenomas are today considered as precursors of invasive colorectal adenocarcinomas.[2, 16-18] The reasons behind the development of either exophytic or flat adenoma remain enigmatic. Why some patients develop only exophytic adenomas, others develop both exophytic and flat adenomas and a third group develops only flat adenomas ("flat adenoma syndrome" of Lynch[19]) is unclear. Another unclear point is why some flat adenomas display a tubular pattern, others a villous pattern, a third group serrated structures and others a fenestrated pattern. In this connection, it may be of interest to mention that the injection of the colonotropic carcinogen 1,2-dimethylhydrazine into rats[20] evoked colorectal exophytic adenomas, exophytic intramucosal adenocarcinomas, exophytic invasive adenocarcinomas, flat tubular or villous adenomas, flat intramucosal carcinomas and flat invasive adenocarcinomas with tubular structures and mucus-producing signet ring cells, as well as lymphoid-associated invasive carcinomas. In contrast, the injection of another colonotropic carcinogen, a mutagenic compound isolated from a glutamic acid pyrolysate,[21] induced exclusively exophytic neoplasias: exophytic tubular or tubulo-villous adenomas, exophytic intramucosal carcinomas and exophytic invasive tubular adenocarcinomas. None of the rats receiving glutamic acid pyrolysate developed flat tubular or flat villous adenomas, flat intramucosal tubular carcinomas, flat invasive tubular or signet ring cell adenocarcinomas or lymphoid-associated carcinomas.[21] Thus, the animal experiments suggest that different carcinogens may interact with oncogenes in colonic cells in a different fashion. If that is the case, the histologic phenotype of colorectal tumors may be influenced by the type of carcinogen acting in the mucosa.

Not only because of the histologic features, but also because of certain biological properties, it is now possible to differentiate some of the lesions herein described, namely flat tubular from flat serrated adenomas. Recent developments in histochemistry and immunogenetics

have demonstrated intense cell proliferation,[12] increased apoptosis,[22] and overexpression of mutated p53,[23] as well as abrogation of secretion of acidic mucins, in the upper part of the crypts in flat tubular adenomas.[24] In contrast, similar biologic attributes were demonstrated, but at the lower part of the crypts, in flat serrated adenomas.[12, 22-24]

Ongoing studies by this group using other immunogenetic markers aim to detect novel biological properties inherent to the various phenotypes of flat colorectal polyps described in this communication.

ACKNOWLEDGMENTS

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