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Flat Serrated Adenomas of the Colorectal Mucosa

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A total of 47 flat serrated neoplasias of the colorectal mucosa are presented: 44 were flat serrated adenomas and the remaining 3 flat serrated adenocarcinomas arising in flat serrated adenomas. These lesions were found among 600 flat mucosal lesions removed at colonoscopy during a 3-year period (1992 and 1994) at the Karolinska Hospital. Thirty-five of the 47 patients (74%) were males and the remaining 12 (26%), females. Depending upon the degree of cellular dysplasia within the epithelium, serrated adenomas were divided into those with low-grade dysplasia (LGD), when the dysplastic nuclei were present in the deeper half of the epithelium, and those with high-grade dysplasia (HGD), when the dysplastic nuclei were found even in the upper half of the epithelium. LGD was present in 37 (84.1%) of the 44 serrated adenomas and HGD in the remaining 7 (15.9%). Depending upon the topographic distribution of the dysplastic epithelium within 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 even present in the superficial half of the serrated crypts. Of the 44 serrated adenomas, 38 (86.1%) were type I and the remaining 6 (13.9%) type II. The dysplastic epithelium seemed to originate at the base of the crypts and to progress upwards, replacing the scalloped, serrated epithelium of the sides of the crypts. Invasive adenocarcinomas (i.e., with submucosal extension) were seen to arise from flat serrated adenomas with LGD type I (n=2) or with HGD type II (n=1). This preliminary survey suggests that flat serrated adenomas of the colorectal mucosa may be lesions with a propensity to evolve into invasive adenocarcinoma, irrespective of the degree of the epithelial dysplasia or of their extension along the crypts.

Key words: Flat serrated adenoma — Adenocarcinoma — Colon — Rectum

For many years, it has been believed that adenocarcinomas of the colorectal mucosa originate in exophytic mucosal proliferations known as adenomatous polyps.[1,2] The "adenoma-carcinoma sequence" concept for exophytic lesions proposed by Jackman and Mayo in 1951[3] has prevailed in western countries since it has been in accordance with the experience of western endoscopists and pathologists at many hospitals.

In recent years, however, the systematic study of the colorectal mucosa by Japanese endoscopists, using improved optical devices complemented by chromography, has resulted in the detection of small, flat mucosal alterations.[4] Japanese pathologists found that those lesions were either flat tubular adenomas or flat adenocarcinomas, thus introducing a new concept into the "adenoma-carcinoma sequence" of the colorectal mucosa.[5,6]

At the Karolinska Hospital, Stockholm, there was much interest in the results of the Japanese researchers and members of the staff visited Japan to assimilate that knowledge and to incorporate it into routine colonoscopic-histologic work at this hospital. Upon their return from Japan, Swedish endoscopists soon found small flat lesions in the colorectal mucosa of Swedish patients. Based on the histologic findings, these small lesions were interpreted by pathologists here as flat tubular neoplasias (i.e., flat adenomas or flat adenocarcinomas), thus confirming results reported earlier by Japanese pathologists.

More recently, it was noticed that colorectal lesions regarded as flat by the colonoscopists[7] could display histologic features which differed from those recognized for flat tubular adenomas.[4,5] We denominated those lesions flat serrated adenomas to distinguish them from the exophytic serrated adenomas described by Longacre and Fenoglio-Preiser.[8] The difference between flat tubular adenomas and flat serrated adenomas emerges from their histological appearances. In flat tubular adenomas, the mucosa shows straight crypts of Lieberkuhn[9] and the dysplastic cells are found initially in the luminal cells of those crypts, whereas in flat serrated adenomas, the dysplastic epithelium is seen initially in the lower part of the crypts and the epithelium of the sides of the crypts has serrated infoldings without dysplastic cells. The serrated appearance of the sides of the crypts is preserved even when the dysplastic epithelium has replaced the entire crypt. Adenocarcinomas have been found to originate in some flat serrated adenomas.

MATERIALS AND METHODS

From the 3986 patients referred for colonoscopic examination during a three-year period (June 1992 to July 1994), 600 had flat mucosal changes. Some of those

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lesions were punch-biopsied and others were removed by strip-mucosectomy.[4,5]

The endoscopic and histologic characteristics of flat tubular neoplasias, flat or exophytic hyperplastic polyps and exophytic tubular and/or villous neoplasias have been reported elsewhere.[7,10] The endoscopic appearance of the flat serrated adenoma was found to be identical to that of a flat hyperplastic polyp: the surface pattern consists of rather regular, large and stellate pits, which contrasts with the regular pit pattern of the surrounding normal colorectal mucosa. In flat tubular adenomas, the pit pattern is more irregular, often with a shallow or a deep depression. The flat serrated colorectal adenomas were found among lesions considered harmless by endoscopists because of their appearance (small, flat and with a pit pattern identical to that of a hyperplastic polyp).

Strip-biopsies were placed on a Millipore filter (with the submucosal aspect on the filter) and were subsequently (as were punch biopsies) fixed in 10% neutral formalin and processed for histology. All sections were stained with hematoxylin and eosin.

Definitions Serrated adenomas were classified as flat following a modification of the criteria of Muto *et al.*[4] and Wolber and Owen[11] for flat tubular adenomas. The lesions lacked an exophytic polypoid configuration and consisted of slightly elevated mucosal plaques never greater than twice the thickness of the adjacent nondysplastic mucosal segments. Serrated adenomas surpassing twice the thickness of the adjacent nondysplastic mucosa were regarded as exophytic and therefore were not included in this work. The epithelium covering the sides of the crypts of Lieberkuhn showed scalloped infoldings. The dysplastic cells were found at the bottom of the crypts in some cases and in other cases, the dysplastic cells had replaced the entire epithelium of the serrated crypts.

Depending upon the degree of cellular dysplasia within the epithelium, serrated adenomas were divided into those with low-grade dysplasia (LGD), when the dysplastic nuclei were present in the deeper half of the epithelium (Fig. 1) and those with high-grade dysplasia (HGD), when the dysplastic nuclei were found even in the upper half of the epithelium (Fig. 2).

Depending upon the topographic distribution of the dysplastic cells within the crypts, flat serrated adenomas were divided into type I, when the dysplastic epithelium was limited to the lower half of the serrated crypts (Fig. 3), and type II, when the dysplastic epithelium was even present in the superficial half of the serrated crypts (Fig. 4). Lesions having both type I and type II were classified as type II. Invasive flat serrated adenocarcinomas were considered as flat serrated neoplasias extending into the submucosa (Figs. 4, 5 and 6). In the present material, no case with intramucosal carcinoma was found.

While the histologic characteristics of LGD and HGD in these adenomas were similar to those of serrated

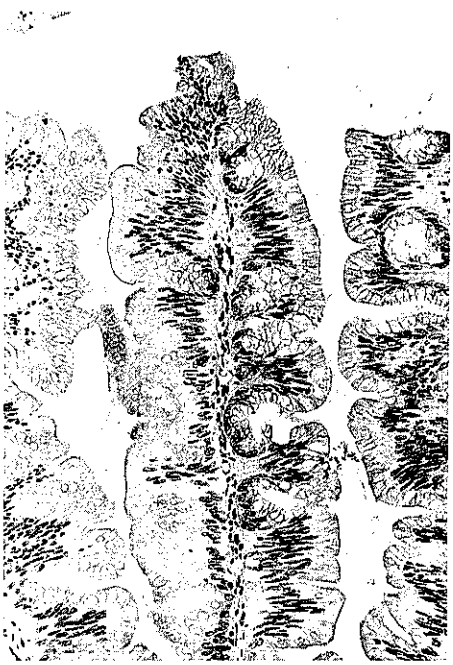

Fig. 1. Flat serrated adenoma with low-grade dysplasia. (Hematoxylin and eosin 200×).

Fig. 2. Flat serrated adenoma with high-grade dysplasia. (Hematoxylin and eosin 200×).

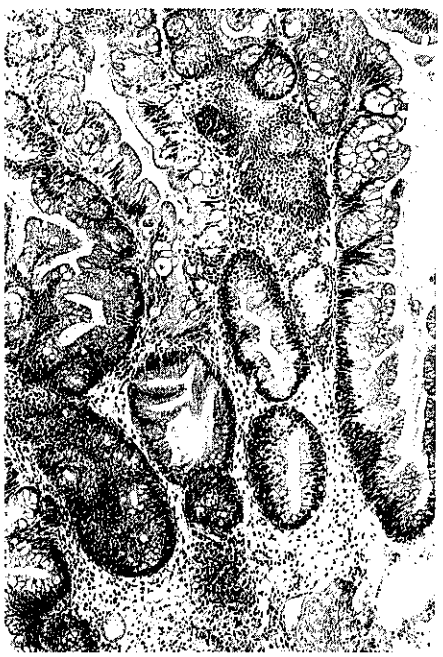

Fig. 3. Detail from a serrated adenoma with low-grade dysplasia in the lower part of the crypts (type I). Note serrated epithelium without dysplasia in the epithelium on top. (Hematoxylin and eosin 100×).

adenomas (see above), the topographic distribution of the dysplastic cells within the crypts in tubular and/or villous adenomas (flat or exophytic) differed. In the tubular and/or villous adenomas, type I lesions were considered to be those having dysplastic cells in the upper half of the crypts and type II lesions those having dysplastic cells even in the lower half of the crypts.[10]

RESULTS

Of the 47 patients included in this study, 35 were males (mean age 65.7 years, range 52–81) and 12 were females (mean age 65.3 years, range 41–79). Of the 47 flat lesions 5 were localized in the transverse colon, 3 in the left colon, 12 in the sigmoid colon and the remaining 27 in the rectum. No apparent differences in localization were found between males and females

In males the mean size of the 35 flat lesions was 6.0 mm (range 2–15 mm). In the 12 lesions found in females, the mean size was 4.9 mm (range 2–18 mm). Of the 47 flat serrated neoplasias, 44 were found at histology to be flat serrated adenomas and the remaining 3 flat invasive adenocarcinomas arising in flat serrated adenomas. LGD was present in 37 (84.1%) of the serrated adenomas and HGD in the remaining 7 (15.9%). Of the 44 serrated adenomas, 38 (86.1%) were type I and the remaining 6 (13.9%) type II lesions.

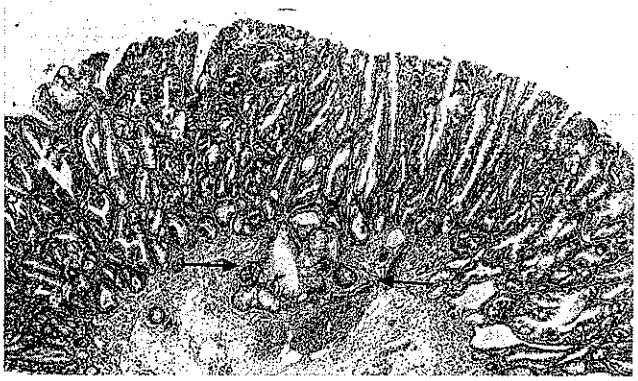

Fig. 4. Serrated adenoma type II with high-grade dysplasia including the upper half of the lesion (type II). Note invading clusters at arrows. (Hematoxylin and eosin 40×).

Fig. 5. Flat serrated adenoma type II with invasive adenocarcinoma. (Hematoxylin and eosin 25×).

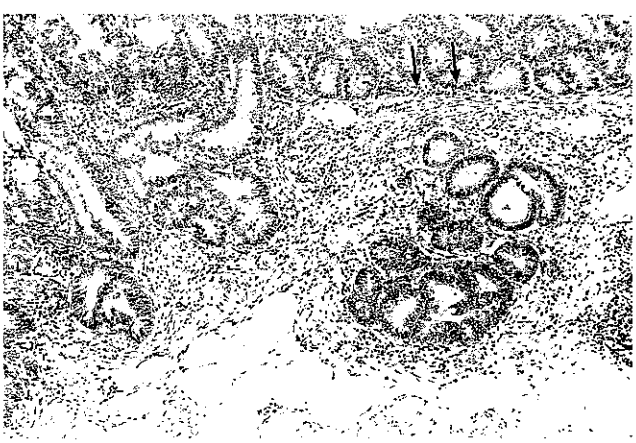

Fig. 6. Close view showing invasion in the submucosa (muscularis mucosae at arrows). (Hematoxylin and eosin 80×).

Invasive adenocarcinomas (i.e., with submucosal extension) were seen to originate in samll (< 10 mm in diameter) flat serrated adenomas with LGD type I (n = 2) or with HGD type II (n = 1).

DISCUSSION

Colorectal exophytic polyps have been defined as lesions protruding into the lumen of the organ. The two most common histologic types of exophytic colorectal epithelial polyps reported in the literature are hyperplastic polyps and adenomas.[12] The first observation that hyperplastic glands and adenomatous structures could coexist in the same polyp was reported by Goldman *et al.*[13] Urbanski *et al.*[14] proposed the term "mixed hyperplastic adenomatous polyps" for these exophytic lesions, while Longacre and Fenoglio-Preiser preferred "serrated adenomas."[8] Invasive adenocarcinomas were shown to originate in these exophytic lesions.[15]

The recent improvement in the optical resolution of the colonoscope, coupled with chromography, has made it possible to detect small non-exophytic (i.e. flat) mucosal lesions.[4,7] The histologic examination of such lesions had previously revealed either flat hyperplastic (metaplastic) polyps, flat adenomas or flat adenocarcinomas.

In a recent publication[7] we reported 200 cases of flat adenomas and flat adenocarcinomas of the colorectal mucosa using the same endoscopic method as the one employed here. The difference between those flat adenomas and the flat serrated adenomas reported herein emerges from their histological appearance. In serrated adenomas the serrated appearance of the slopes of the crypts is preserved even when the dysplastic epithelium has replaced the superficial half of the serrated crypts (type II serrated adenomas).

Regarding the histogenesis of exophytic serrated adenomas, several possibilities have been considered by other authors[8,13,14]: a) secondary dysplastic transformation within a hyperplastic polyp, b) collision of two unrelated, different structures developing synchronously and independently, or c) a histological hybrid containing both hyperplastic and adenomatous structures. It may be speculated that the same histogenetic pathways apply for flat serrated adenomas.

Flat serrated adenomas were often found in men; in fact they were detected 3 times more often than among females. The reasons for this male predominance remain unclear.

In flat serrated adenomas we found that 86.1% were type I lesions (i.e., having dysplastic epithelium in the lower half of the crypts) and the remaining 13.9% were type II (i.e., having dysplastic epithelium even in the superficial half of the crypts). From the histologic evaluation it would appear that in flat serrated adenomas the replacement of the serrated epithelium by dysplastic cells takes place from the base of the crypts towards the superficial aspect of the mucosa (i.e., from type I to type II lesions).

Two of the 3 invasive flat serrated adenocarcinomas arose from type I serrated adenomas having LGD. Apparently the type of lesion (i.e., the topographic location of the dysplastic epithelium within the crypts) or the degree of epithelial dysplasia may not be as significant in the histogenesis of adenocarcinomas from flat serrated adenomas as in exophytic adenomas.[1-3,12]

From the above results, it would appear that to the already known sequence of events in colorectal carcinogenesis (i.e., from exophytic adenomas,[12] from exophytic serrated adenomas[8,13,14] or from flat adenomas,[4-6,10] a new pathway should be incorporated, namely from flat serrated adenomas. This histologic phenotype of colorectal adenoma may be found among lesions considered harmless by endoscopists because of their appearance (small and flat) and size (usually a few millimeters in diameter). The importance of this lesion resides in the fact that despite its size and its low histologic profile, it may evolve into invasive carcinoma.

Recent studies of cell proliferation[16] and *p53* tumor suppressor gene expression[17] demonstrated moderate (++) to intense (+++) expression in 23% and 58% of the flat serrated adenomas, respectively. Those findings suggest that some serrated adenomas may already be committed to independent growth. The intense (+++) *p53* expression in the invading glands militates against the claim that they may be ectopic benign submucosal glands.

It remains unclear at present whether some flat serrated adenomas may increase in size and become exophytic or whether they remain flat and small before invasive growth ensues. From the results presented above it would appear that the latter is the most likely pathway of invasive growth, at least in some serrated adenomas.

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