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Comparison of the clinicopathological features of flat and polypoid colorectal adenomas that are smaller than or equal to five millimeters

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Neşe Arzu Yener[1], Ahmet Midi[1], Çiğdem Ataizi Çelikel[2]

[1]Department of Pathology, Maltepe University Faculty of Medicine, Istanbul, Turkey
[2]Department of Pathology, Marmara University Faculty of Medicine, Istanbul, Turkey

Original Article

ABSTRACT

Background/Aims: Colorectal flat adenomas (FAs) may represent a different histogenesis, since their malignant potential is thought to be higher than polypoid adenomas of the same size. In this study, we classified FAs of ≤5 mm into three subgroups-superficially elevated adenomas (SEAs), completely flat adenomas (CFAs), and depressed adenomas (DAs)-based on their low microscopic shapes and compared their clinicopathological features with polypoid tubular adenomas (pTAs) with the same size.

Materials and Methods: One hundred one pTAs and 46 FAs with tubular morphology with the same size (≤5 mm) were studied.

Results: The percentages of high-grade dysplasia in FAs and pTAs were 19.56% and 12.87%, respectively. The percentages of the high-grade dysplasia were 28.57%, 13.63%, and 20.00% in the DA, SEA, and CFA subgroups, respectively. FAs had a significantly higher number of normal epithelium at the basal crypts of the lesion than the pTAs (p=0.001). The presence of pericryptal mesenchymal cells was higher in pTAs than the FAs (78.21% vs 10.86%) (p<0.001).

Conclusion: Flat adenoma represents a distinct type of colorectal adenoma with special histopathological properties-existence of a normal epithelium at the basal crypts, lack of pericryptal mesenchymal cells, and a high percentage of high-grade dysplasia-especially when it has a depressed shape at low magnification.

Keywords: Flat colorectal adenoma, non-polypoid colorectal neoplasia, colorectal carcinogenesis, colorectal adenoma, colorectal adenomatous polyp

INTRODUCTION

Flat adenoma (FA) of the large bowel was initially described by Muto et al. (1) with distinguishable features, such as slight elevations of the mucosa with a reddish surface displaying high-grade dysplasia, even when they were of a small size. Recognition of FA is important, because there have been numerous reports and debates that the malignant potential of these lesions is considerably higher than that of common sessile or pedunculated polyps of the same size (2). The aim of this retrospective study is to compare the clinicopathologic features of the flat adenomas and the polypoid adenomas that are smaller than or equal to (≤) 5 mm observed in the large bowel and to investigate whether flat adenomas represent a distinct disease with a pathogenetic pathway different from that of the classical adenoma-carcinoma sequence in colorectal tumorigenesis. We also aimed to subclassify the FAs depending on their shape under low-power microscopy and compare the clinicopathologic features of these subgroups.

MATERIALS AND METHODS

We reviewed all surgically and colonoscopically removed specimens of the large bowel that were processed in our department of pathology between January 2000 and December 2005. With respect to their endoscopic similarity and also knowing that the rate of malignancy increases with the size of these lesions, flat

Adress for Correspondence: Neşe Arzu Yener, Department of Pathology, Maltepe University Faculty of Medicine, Istanbul, Turkey
E-mail: nese.yener@maltepe.edu.tr

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Table 1. Clinical features of the lesions

Adenoma type	Patients (n)	Lesions (n) (%)	Mean age	Gender (M:F)	Localization
pTA	79	101 (68.70)	59	32:47	AC: 30.7%, TC: 25.9%, DC: 43.4%
SEA	20	22 (14.97)	68	9:11	AC: 27.3%, TC: 22.7%, DC: 50.0%
CFA	9	10 (6.81)	53	6:3	AC: 39.0%, TC: 34.6%, DC: 26.4%
DA	14	14 (9.52)	63	5:9	AC: 46.7%, TC: 32.6%, DC: 20.7%
Total	122	147 (100.0)		122	

AC: ascending colon; TC: transverse colon; DC: descending colon; pTA: polypoid tubular adenoma; SEA: superficially elevated adenoma; CFA: completely flat adenoma; DA: depressed adenoma

adenomas (FAs) and polypoid tubular adenomas (TAs) ≤5 mm in diameter were included in our study. The clinical and histopathological findings of the removed lesions were recorded.

All biopsy specimens were known to be obtained by using conventional white light colonoscopes. The written informed consent of each patient was taken for the study. If multiple adenomas were identified in a patient, the findings were recorded for each lesion. All macroscopic descriptions were reviewed, and the slides were reexamined. The paraffin blocks were recut when needed. The specimens were processed under standard protocols. The polyp size, which was determined with a ruler directly after polyp removal, was noted. Histopathologically, the lesions in which the thickness of the lesion was no more than twice that of the adjacent normal colonic mucosa were recorded as flat adenoma (3,4). Adenomas with villous features were excluded, and the FAs showing tubular adenoma features were included in the study. All the lesions were reclassified according to the Vienna classification of 1998 for gastrointestinal epithelial neoplasms (5). We searched for the existence of normal epithelium at the basal crypts of the lesion and the presence of pericryptal mesencyhmal cells at the base of each lesion.

Central depression is an important colonoscopic finding for Fas, previously suggested to indicate that these lesions would behave more aggressively than the ones that lack this feature (6). In our study, we subclassified the FAs as completely flat adenomas (CFAs), depressed adenomas (DAs), and superficially elevated adenomas (SEAs), depending on their low microscopic shape, as described in several reports (1,6-8) (Figure 1a-d). Since the SEAs, which are slightly elevated although not polypoid, have similar endoscopic features of a typical small polypoid TA (pTA), we also investigated the clinicopathological differences between them.

The SPSS/PC V16.0 (Chicago, IL, USA) program was used to perform all statistical analyses.

RESULTS

A total of 147 selected lesions from 122 patients were studied. One hundred one lesions (68.70%) were polypoid tubular adenomas, whereas 46 lesions (31.29%) were flat adenomas. The most common type of FA given under low-power microscopy was SEA, with a rate of 47.82%, followed by DA and CFA at 30.43% and 21.73%, respectively.

Overall, the patients ranged in age from 43 to 75 without having any significant difference between the two main groups (mean 61.3 for FAs and 59.0 for pTAs). Among the FA subgroups, the mean age of CFAs was significantly lower than that of the DA and SEA subgroups: 53, 63, and 68, respectively ($p<0.005$). There was not any significant association between the localization and the type of the lesion.

The patients with SEA were about 1 decade younger than the pTA patients (68 and 59, respectively). The localizations, the mean ages, and the number of all the lesions are given in Table 1.

All the lesions were classified histologically as category 3 (non-invasive, low-grade neoplasia-LGN) and category 4 (non-invasive, high-grade neoplasia-HGN). All FAs and TAs showing high-grade dysplasia also had low-grade dysplasia within the lesion. Also, 19.56% of all FAs showed high-grade dysplasia, whereas only 12.87% of TAs showed this feature. High-grade dysplasia was more common in the DA subgroup than in the SEA and CFA subgroups (28.57%, 13.63%, and 20.00%, respectively). When we compared the pTAs and FA subgroups, we found that there was a significantly higher number of normal epithelium at the basal crypts of the adenoma in latter than in the pTAs ($p<0.005$). In contrast, pericryptal mesenchymal cells were significantly higher in pTAs than FAs ($p<0.005$). When we compared the SEAs and pTAs, we found that there was a higher number of normal epithelium at the basal crypts of the SEAs than pTAs. However, this was not statistically significant ($p>0.005$). Pericryptal mesenchymal cells were significantly higher in pTAs than SEAs ($p<0.005$) (Figure 1e). The histopathological features of all groups of adenomas are given in Table 2.

DISCUSSION

In this study, we found that the histopathological findings, such as the existence of normal epithelium at the basal crypts of the adenomas, the presence of pericryptal mesenchymal cells at the base, and high-grade dysplasia, in pTA and FA of the same

size are different from each other. This suggests that these two lesions may represent divergent pathways of neoplastic evolution. Genetic findings, including the incidence of K-ras oncogene mutation (9,10), p53 tumor suppressor gene abnormality (11), and microsatellite instability (12), as well as overexpression of Rb protein and increased frequency of codon 201 Gly of the DCC gene in Fas, also support this view (2,13). In the development of colorectal adenomas, stem cells residing near the bottom of the colonic crypt play a major role (14). They give rise to progenitor cells that are capable of differentiating toward all epithelial lineages (14). Proliferating crypt precursors and differentiated crypt cells form a continuous sheet of cells in perpetual upward motion. Mutations in the components of the pathways that control the proliferation and differentiation cascades lead to the development of colorectal carcinoma, mainly through the adenoma-carcinoma sequence. There are two models for the development of adenomas: the "top-down" model, where the mutant cells penetrate from the surface downwards into the crypt base, with the polyp thus originating in the top of the crypt (15); and also the "bottom-up" model, where a stem cell with a mutational defect is pushed up to the intra-cryptal area, as do all cells between the stem cell at the base of the crypt all the way up to the intra-cryptal area and beyond (16,17). To summarize, in the bottom-up model, both sporadic and FAP adenomas start as unicryptal adenomas and grow initially by crypt-fission in a bottom-up pattern, whereas in the top-down model, the precursors of the dysplastic cells reside on the surface of the mucosa and expand downwards. In our series, we observed normal epithelium at the basal crypts in 62.37% of the pTAs. This was significantly lower than in Fas, in which almost all the crypts at the base were composed of dysplastic epithelium. This result supports the conclusion that the FA is a distinct type of adenoma, probably following a "top-down" model with a pathogenetic pathway different from that of the classic polypoid adenoma, in which we observed the evidence of "bottom-up" histogenesis. However, this result should also be supported by genetic evidence with a large series as well.

Flat adenoma is reported to be seen more frequently than pTAs in proximal than in distal parts of the colon and also in older patients (18). In our study we did not observe any significant difference between the ages of the patients, other than the fact that the patients in the CFA group were 1 decade younger than the other subgroups of FA. We also did not observe any significant relationship between the localization and the types of all the lesions.

The overall percentage of HGD among the flat epithelial colorectal lesions, regardless of their size, was reported as 12%-13% (3,7,19). The striking finding is that they display the features of a histologically advanced epithelial lesion, such as submucosal invasion (20) and high-grade dysplasia (13), even when they are of a small size. The submucosal invasion was observed in 4% of polypoid adenomas and 25% of nonpolypoid adenomas in one large series (20). When small FAs and polypoid adenomas with similar size were compared, the rate of HGD was 2.7%-10.12% in FAs and 2.2-0% in polypoid adenomas (13,18). One of the strong points of our study was that only small FAs and pTAs with similar size (≤5 mm) were studied. We did not observe submucosal invasion in any of the lesions. We observed HGD in 19.56% of FAs and 12.87% of pTAs, which was a far higher percentage than that of the previously reported data. Such discrepancies among pathologists from different countries in the use of criteria to define HGD in gastrointestinal epithelial lesions have been reported (21). Nevertheless, with our high percentage of HGD in Fas, we conclude that there is a higher malignant potential of this type of colorectal adenoma than the polypoid ones.

Table 2. Histopathological features of all lesions

Type	Lesions (n)	I* (%)	II **(%)	HGD (%)
pTA	101	63 (62.37)	79 (78.21)	13 (12.87)
SEA	22	19 (86.36)	2 (9.09)	3 (13.63)
CFA	10	9 (90.00)	1 (10.00)	2 (20.00)
DA	14	13 (92.85)	0 (0.00)	4 (28.57)
TOTAL	147			

HGD: high-grade dysplasia; pTA: polypoid tubular adenoma; DA: depressed adenoma; CFA: completely flat adenoma; SEA: superficially elevated adenoma
*Existence of normal epithelium at the basal crypts of the adenoma (%); **Presence of pericryptal mesenchymal cells at the base (%).

As previously suggested, there are major populations of immunohistochemically distinctive mesenchymal stromal cells in the colonic mucosa-namely, the pericryptal myofibroblasts, lamina propria fibroblasts, and smooth muscle cells of the muscularis mucosae (22). These cell populations are interconnected, forming a complex three-dimensional scaffold. Similarly, pericryptal fibroblasts are shown to gradually decrease in the sequence of adenoma, intramucosal carcinoma, and submucosal invasive carcinoma of mainly non-polypoid type, reflecting a progression in the adenoma-carcinoma sequence (23,24). In our study, we found mesenchymal cells in the lamina propria in only 10.86% of all FA subgroups, whereas 78.21% of the TA group contained these cells. One limitation of our study was that we did not identify the origin of these mesenchymal cells immunohistochemically. The design of our study was to compare their existence rather than their origin; so, we still could conclude that flat adenoma is a distinct type of adenoma based on this certain histopathologic finding.

We also compared the histopathological and clinical features of pTAs and SEAs and found that the patients with SEAs were almost 1 decade older than the pTAs. Histopathologically, there were higher amounts of normal epithelium at the basal crypts of the SEAs than pTAs. There were significantly higher amounts of pericryptal mesenchymal cells at the base of pTAs than SEAs. Although pTAs and SEAs had a similar rate of high-grade dysplasia (12.87% vs 13.63%), we concluded that these two groups are different from each other both clinically and histopathologically.

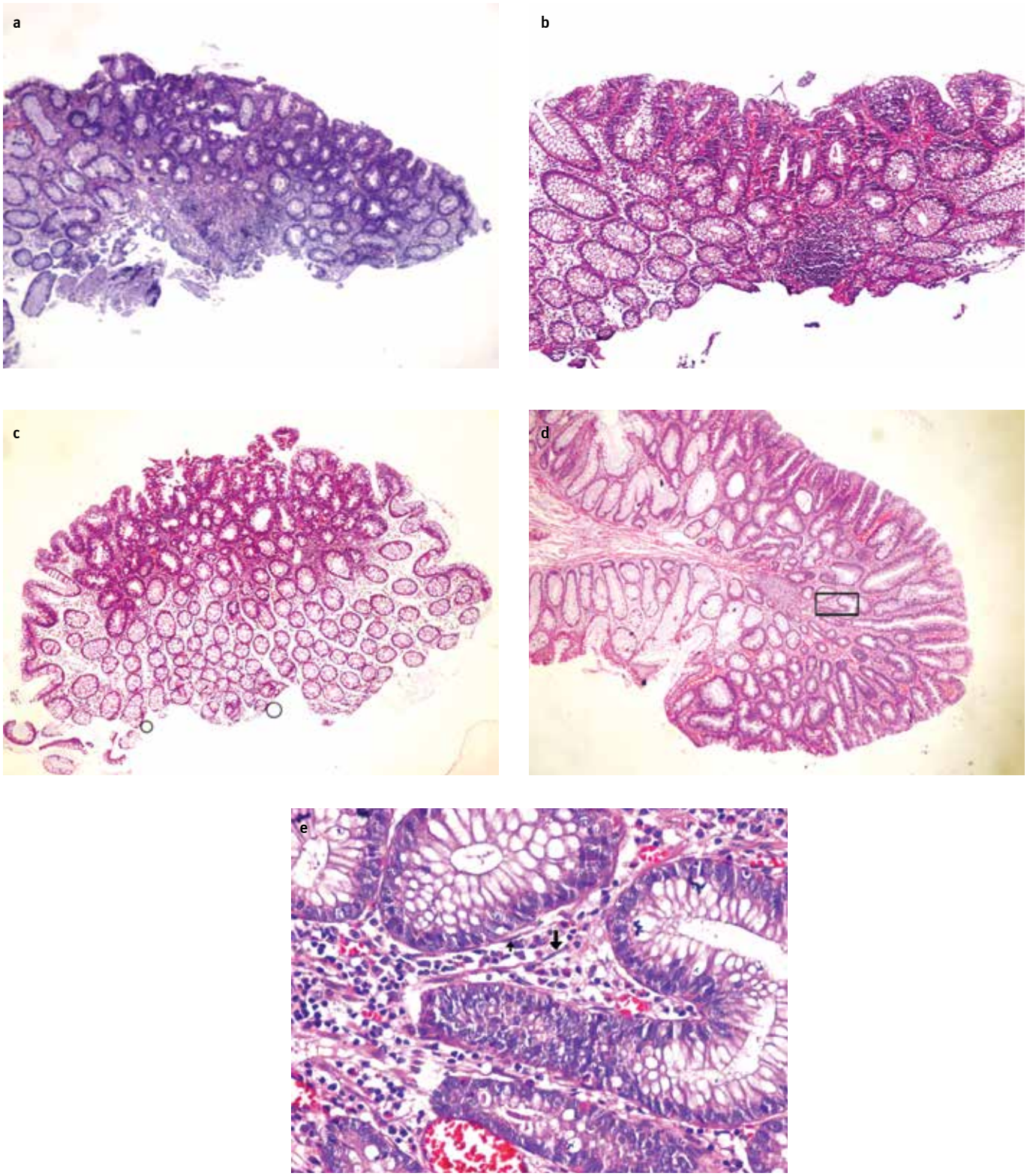

Figure 1. a-e. Completely flat adenoma with low-grade dysplasia, H&E, X100 **(a)**. Depressed adenoma with high- and low-grade dysplasia. Pericryptal mesenchymal cells (arrows) H&E, X100 **(b)**. Slightly elevated adenoma with low-grade dysplasia. Normal epithelium at the crypts of the base of the SEA is also seen. H&E, X100 **(c)**. Tubular adenoma with low-grade dysplasia, H&E, X100 (inset is shown in figure 1e). Pericryptal mesenchymal cells (arrows). H&E, X100 **(d,e)**.

As a conclusion, our results support the view that the FA represents a divergent pathway of neoplastic evolution with distinct histopathological properties: existence of a normal epithelium at the basal crypts of the lesion, lack of pericryptal mesenchymal cells, and a high percentage of high-grade dysplasia, even at a small size. The mesenchymal-epithelial

interactions may be of importance in colonic tumorigenesis, necessitating the requirement of a better understanding of the mucosal mesenchymal matrix. Early detection with intensive treatment and careful follow-up may decrease the chance of development of carcinoma from flat adenoma.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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