ANNALS OF GASTROENTEROLOGY 2010, 23(4):266-269

Current View

Flat adenomas, significance, detection, treatment

K. Geboes,[1] G. De Hertogh,[1] R. Bisschops,[2] K.P. Geboes[3]

SUMMARY

Flat elevated lesions with neoplastic potential can occur in the colon. The detection rate is greatly improved with new endoscopic techniques. Magnifying chromoendoscopy allows frequently a real time diagnosis, based on the pit pattern. Not all flat elevated lesions are adenomas. Small sessile serrated adenomas can mimick flat adenomas. Diagnosis of this lesion thus far implies histology because the pit pattern can mimick that of hyperplastic polyps. Rare non neoplastic lesions can also present as a flat lesion. Flat adenomas comprise from 6.8% to 44.4% of all colorectal adenomas. The exact neoplastic potential of "flat adenomas" remains unclear. A subtype with central depression may be associated with more high-grade dysplasia although the depression may not be a specific diagnostic sign. Studies looking for gene expression profiles demonstrate differences between flat adenomas and normal colon mucosa but confirmation is needed. Early detection, removal and more close follow up (in patients with advanced histology) are indicated.

Key words: Adenomas, flat adenomas, colorectal polyps

INTRODUCTION

Carcinomas (i.e. malignant tumours of epithelial origin) are thought to pass a stage intermediate between normal epithelium and carcinoma. The nomenclature of this premalignant stage is not uniform. For example, dysplasia (=intraepithelial neoplasia) is used in the large intestine, cervix and oesophagus whereas hyperplasia has/is used in the endometrium. In the large intestine, concepts as to the precursor lesions of colorectal cancer have started and have long been dominated by the "polyp-cancer" or "adenoma-cancer" sequence. "Polyps" are elevated – sessile or pedunculated - lesions, protruding in the bowel lumen. Histology reveals a variety of lesions of which the adenomas (tubular, tubulo-villous or villous) correlate with the development of cancer. An important aspect of the (polyp) adenoma-carcinoma sequence hypothesis is the idea that most (if not all) colorectal carcinomas develop from polyps-adenomas. A major argument for this hypothesis was that no cellular neoplastic changes had been observed in non-polypoid mucosa. However, it has been well documented that approximately two-thirds of all colorectal cancer arise from polypoid adenoma. For the remaining cases the mechanism of development remains unclear.

[1]Dept of Pathology, KULeuven, Belgium, [2]Dept of Gastroenterology KULeuven, [3]Division of Gastroenterology, Digestive Oncology UGhent

Author for correspondence:

K. Geboes, Dept of Pathology, KU Leuven, Belgium

Significance of Flat adenomas

The History of Flat Adenomas

In 1985, Muto and Kamiya described an endoscopic lesion in the colon, characterized by a slight elevation and a flat upper surface and with a reddish color. These lesions were generally smaller than 10mm. They were called "flat elevated lesions" (FELs). The occurrence of a central depression was noted, especially when air was properly insufflated. Histologically the lesions were consistent with "adenomas". The thickness of the lesions did not surpass the double thickness of the surrounding mucosa. Therefore they were called "flat adenomas" (FAs).[1] This type of adenomas has been reported to comprise from 6.8% to 44.4% of all colorectal adenomas.[2] Originally it was tought that the "flat adenomas" would at smaller sizes already demonstrate a higher incidence of high grade dysplasia and aneuploidy (abnormal DNA content), as compared to polypoid adenomas of the same size. Earlier studies showed also that small flat adenomas have a higher incidence of submucosal cancer. The grade of atypia seemed to increase with the size of the lesion.[3] Therefore, flat adenomas were considered as the possible precursors of "de novo colorectal cancer". However, this finding was not generally confirmed. In a prospective

French study for instance, 38% of the neoplastic polyps were diagnosed as flat adenomas but the rates of cancer detection in flat adenomas and polypoid adenomas were similar.[4] Nevertheless, studies looking for gene expression profiles showed a total of 180 genes being differentially expressed between flat adenoma and normal mucosa of the colon, including matrix metalloproteinase 7 (MMP7), cadherin 3 (CDH3) and dual oxidase 2 (DUOX2). Immunohistochemical analysis confirmed the differences for CDH3 and MMP7 protein expression.[5]

Evolution in the concept

While FELs were originally described as 10-mm lesions or even smaller in diameter, a precise limit was not stated. In one series lesions were limited to those smaller than 5 mm in their largest diameter showing a central depression in 76%. Whether the central depression is diagnostic or not is controversial but in some studies it was shown to be a sporadic element. The FAs must however be differentiated from the concept of "colon depressed adenoma" which was later developed. Kudo' classification of adenomas distinghuished a protruded type (polypoid lesion), a flat elevated type and a flat type. The flat elevated group is subdivided into two types: the flat elevated and the flat elevated with central depression. The flat type is subdivided into the flat type and the depressed type.[6] In this classification, the flat type would fit the original description of "flat adenoma" while "flat and depressed lesions" would be Thicker.[7] Early flat colorectal cancer is defined as a tumour in which the carcinomatous component is not more than twice the thickness of the surrounding non-neoplastic mucosa.[6] They can be laterally spreading tumours (LSTs). These are subdivided into "granular" and "non-granular" and only the granular correspond to the original concept of the flat lesion.[7] In summary, the introduction of new endoscopic techniques has broadened the concept of flat lesions. This is a heterogeneous group.

Aberrant crypt foci (ACF)

These lesions have first been described in the colonic mucosa from carcinogen treated mice and rats when they were detected at the surface of the mucosa stained with methylene blue. Aberrant crypts are two to three times larger than normal crypts, often show a slit or oval shaped luminal ostium and are microscopically elevated above the surrounding mucosa. Similar lesions, where soon thereafter reported in the colon from patients with FAP. Some ACF have an adenoma-like histology, some are hyperplastic and some just show an upward shift of the proliferative compartment.

Table 1. Comparison of confocal endoscopy images and histology

Parameters		*Normal mucosa*	*Hyperplastic polyp*	*Tubular adenoma*
Architectural criteria				
No crypts/image		8	7,8	9,53
Internal crypt diameter		3.5±0.5 constant	4.25 (highly variable)	5.63 (highly variable)
Intercryptal distance		2.5±0.5 constant	1.81 (moderately variable)	2.16 (moderately variable)
Lumen				
	oval	3	0.37	0.53
	round	3	0	0
	elongated	0	1.81	2.66
	branching	0	0.87	1.5
	star shape	0	0.75	0
	widened	0	0	0.5
Crypts				
	oval	2	0.18	0.46
	Well demarcated	3	0.87	0.8
	crowding	0	0.68	1.9
	elongated	0	1.37	2.6
	branching	0	0.81	0
Cytological criteria				
	Epithelial cellsregular	2	0	0
	long	1	1.75	2.4
	wide	1	0.75	0.73
	homogeneous	2	0	0
	compact	0	0.93	2
Goblet cells		Always present	Presence 1.68	Presence 0.98

Serrated colorectal polyps

Classically, the two most commonly recognized polyps, namely the hyperplastic polyps and the adenomas, are believed to differ in their biological potential. Hyperplastic polyps were considered innocuous. However, recent advances in the understanding of colonic carcinogenesis have led to an increased awareness of the morphological heterogeneity displayed by serrated colorectal polyps and the identification of mixed hyperplastic/adenomatous polyps, traditional serrated adenomas and sessile serrated adenomas or polyps. These three types of serrated lesions have been shown to have a neoplastic potential. While the mixed hyperplastic/

adenomatous polyps and traditional serrated adenomas show signs of "cyotologic dysplasia" on microscopy, the sessile serrated polyps essentially show features of hyperplasia (and no cytologic dysplasia). Serrated polyps are larger than the usual hyperplastic polyps but they may be small. They can appear slightly elevated but have a whitish appearance.[8]

Histology of flat elevated lesions of the colon

In a series of 33 FELs measuring 10 mm or smaller, twelve (36.4%) were found to be neoplastic – adenoma, and 21 (63.6%) did not show the features of an adenoma.[9]

In ten cases a diagnosis of hyperplastic polyp was proposed. Eight cases showed unspecific colitis and one an inflammatory polyp. In this series the lesions were detected using endoscopy with a chromoscopy with spraying of indigo carmine in all suspected lesions. It appears thus that FELs are histologically heterogeneous. The figures of the hyperplastic lesion in the paper look like a sessile serrated adenoma/polyp. It has further been shown that sessile serrated adenoma can mimick flat adenoma endoscopically.[2]

Summary

FLEs can be diagnosed. The macroscopic aspect is variable. Lesions with central depression may have a more prominent malignant potential. Histologically they are also heterogeneous with adenomas and sessile serrated adenomas/polyps, two different lesions with a neoplastic potential. Genuine "flat adenomas" are hence a subtype of FLEs. Proximal right-sided sessile serrated adenomas can also be associated with early cancers (without a component of adenomatous dysplasia). Given the relation with colorectal cancer, early detection of FLEs seems mandatory. This implies appropriate endoscopic techniques.

Detection

The endoscopic diagnosis of FELs used to be difficult because of their small size and scarce luminal protrusion. The original diagnostic endoscopic criteria proposed by Muto and Kamiya1 are not really specific and a high proportion of nonneoplastic lesions are found.

The central depression was revealed to be sporadically present; It may be related to insufflation but also to the leions itself: relation to high grade dysplasia or invasive cancer; it was observed in nonneoplastic and neoplastic lesions. The colour of the lesion was also less reliable, reddish being also sometimes related to colitis.

The introduction of new endoscopic techniques, especially magnifying endoscopy with dye spraying and confocal laser endomicroscopy have greatly improved the detection rate. The pit pattern diagnosis using a magnifying technique is highly accurate; A good correlation is found between the pit pattern diagnosis and histology with the exception of colitis.

Type I is a round opening of a normal gland duct; type II represents a widely dilated opening shaped like a star, triangle or diamond, typical for hyperplastic polyps, but a similar pattern can be seen in traditional serrated adenoma and sessile serrated adenoma. They type IIIL where L stands for long, presents as a long smooth opening of the gland ducts (in protruded lesions) while IIIs where s stands for small is seen in depressed lesions. Type IV and V show long branching and giriform patterns seen in protruding and laterally spreading tumors.[10]

Confocal laser endoscopy (CLE) can be used for the same purposes. We have prospectively analysed CLE images of the colon systematically for different architectural characteristics and correlated these to the final histological diagnosis in 36 patients referred for colonoscopy (surveillance, familial risk, follow-up of colorectal cancer). Lesions were targeted by CLE (Pentax-Optiscan after IV fluorescein injection). Biopsies from the lesions were obtained routinely and targeted to the CLE imaging site. The images were analysed by two pathologists independently using a series of parameters including: number of crypts per image, intercryptal distance, crypt diameter, crypt shape, epithelial cell shape, presence of goblet cells and the vascular pattern. Non quantitative items were scored qualitatively (0 absent, 0.5 partial, 1 discrete, 2 moderate, 3 high). A mean score for each parameter was calculated. CLE images were compared with histology. The analysis shows images of 17 tubular adenomas, 9 hyperplastic polyps and 10 normal colonic sites. Epithelial characteristics are summarized in the ta-

ble. The number of crypts was higher in adenomas (9.53) in comparison to normal mucosa (8+/-2) and hyperplastic polyps (7.8). In normal mucosa, the internal diameter of the crypts is lower (87+/-12 μm) compared with hyperplastic (106 μm) and adenomatous polyps (141 μm). Intercryptal distance and crypt diameter are constant in normal mucosa, but highly variable in hyperplastic and adenomatous polyps. Goblet cells are abundantly present in normal mucosa and hyperplastic polyps. The number of goblet cells is decreased in adenomas. Vascular and stromal features were only assessable in 50% of images. Analysis of confocal images matches routine histology very well (Table 1). These preliminary data confirm that *in vivo* taken CLE images can be used by pathologists in the differential diagnosis of classical polyps and other neoplastic lesions of the colon. Further controlled, prospectively collected data are needed to evaluate sensitivity and specificity. The difference between serrated adenomas and sessile serrated adenomas and hyperplastic polyps is indeed not clear. CLE may however be much more costly and not much superior to magnifying chromoendoscopy.

Treatment

Flat-type colorectal neoplasia itself probably does not imply higher propensity of malignant potential. However, larger size, the presence of a depression and left-sided location may be risk factors. This implies that endoscopists should try to remove these lesions. The presence of advanced histology (villous or serrated histology, high-grade dysplasia or cancer) implies probably a more careful follow up, but this is also true for small elevated lesions with advanced histology.[11]

REFERENCES

1. Muto T, Kamiya J, et al. Small “flat adenoma” of the large bowel with special reference to its clinicopathologic features. Dis Colon Rectum 1985; 28:847-851
2. Park DH, Kim HS, Kim WH. et al. Clinicopathologic characteristics and malignant potential of colorectal flat neoplasia compared with that of polypoid neoplasia. Dis Colon & rectum 2008; 51:43-49
3. Wolber RA, Owen DA. Flat adenomas of the colon Hum pathol 1991; 22:70-74
4. Diebold MD, Samalin E, Merle C, et al. Colonic flat neoplasia: frequency and concordance between endoscopic appearance and histologic diagnosis in a French prospective series. Am J Gastroenterol 2004; 99:1795-1800
5. Kita H, Hikichi Y, Hikami K, et al. Differential gene expression between flat adenoma and normal mucosa in the colon in a microarray analysis. J Gastroenterol 2006; 41:1053-1063
6. Kudo S. Endoscopic resection of flat and depressed types of early colorectal cancer. Endoscopy 1993; 25:455-461
7. Konishi F. Invited commentary. Dis Colon & rectum 2008; 51:49
8. Yantiss R. Serrated colorectal polyps and the serrated neoplastic pathway: emerging concepts in colorectal carcinogenesis. Curr Diagn Pathol 2007; 13:456-466
9. Gualco G, Reissenweber N, Cliche I, Bacchi C. Flat elevated lesions of the colon and rectum: a spectrum of neoplastic and nonneoplastic entities. Ann Diagn Pathol 2006; 10:333-340
10. Yamada T, Tamura S, Onishi S, Hiroi M. A comparison of magnifying chromoendoscopy versus histopathology of forceps biopsy specimen in the diagnosis of minute flat adenoma of the colon. Dig Dis Sci 2009; 54:2002-2008
11. Lieberman D, Moravec M, Holub J, et al. Polyps size and advanced histology in patients undergoing colonoscopic screening: Implications for CT colonography. Gastroenterology 2008; 135:1100-1105