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Original article

Mixed hyperplastic - adenomatous polyps (serrated adenomas). An intermediate step in colorectal carcinogenesis?

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SUMMARY

We compared clinicopathological characteristics of colorectal polyps, in order to investigate the hypothesis of neoplastic transformation of hyperplastic polyps. Of 4723 colonoscopies performed in our department over four years, 22 patients with 23 mixed hyperplastic polyps (MHAP) were found. These were compared with 61 patients with 86 hyperplastic polyps, 40 with 58 tubular adenomas and 27 with 35 villous adenomas. The patients of comparison groups had exclusively one histological type of polyp. A total of 22 synchronous polypoid lesions were found in patients with MHAP; 14 hyperplastic polyps, 6 adenomas and 2 carcinomas. There was a remarkable similarity in the distribution of the four histological types in the colonic regions. The mean age of patients with hyperplastic polyps was 53.7 years, with MHAP 63.2 years ($p=0.0093$), with tubular adenomas 65.2 years and villous adenomas 69.5 years. Considering the size, 87.2% of hyperplastic polyps were less than 5 mm, while the same was true for 17.4% of MHAP, 50% of tubular and 2.9% of villous adenomas. Larger than 10 mm were 3.5%, 56.5%, 24.1% and 37.1% of the polyps respectively. There was a significant difference ($p<0.0001$) between MHAP and hyperplastic polyps in the size classifications. In conclusion, the findings of this study further confirm the hypothesis of a neoplastic transformation of hyperplastic polyps. However, the relationship between hyperplastic polyps and the subsequent development of adenomas and carcinomas remains controversial and further larger studies are warranted to evaluate the proposed hyperplastic polyp - mixed hyperplastic adenomatous polyp - adenoma sequence.

Keywords: Mixed hyperplastic - adenomatous polyps, serrated adenomas, hyperplastic polyps, neoplastic transformation

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INTRODUCTION

The existence of hyperplastic glands in adenomatous polyps was first described by Coldman et al. in 1970.[1] The term mixed hyperplastic-adenomatous polyp (MHAP), was introduced by Estrada and Spjut.[2] Longacre and Fenoglio-Preiser have suggested that MHAP should be considered a distinctive subtype of colorectal epithelial neoplasia and proposed the term «serrated adenoma» to emphasise their neoplastic nature.[3]

The histogenesis of MHAP remains controversial. It is possible, that they derive from an adenomatous transformation of previous hyperplastic polyps (HP), supporting a HP - adenoma sequence.[1] An alternative explanation is that MHAP represent an independent histological type of colorectal neoplasia, originating from a more differentiated cell than the adenoma.[3] The aim of this study is to compare clinical and morphological features in a series of HP, MHAP and adenomatous polyps, in order to investigate the hypothesis of HP - adenoma sequence.

PATIENTS AND METHODS

In this study, all consecutive colonoscopy examinations in which one or more polyps were detected and histologically characterised, over a 4 year period, were included. Endoscopic, histological and clinical data were entered into a precoded database. Patients with inflam-

matory bowel disease and familial polyposis were excluded. We followed an examination protocol with administration of four litres of a polyethylene glycol plus electrolytes solution or liquid diet and 75 ml sennosides syrup plus water enema. In case of insufficient intestinal preparation the examination was repeated. Colonoscopy was performed with conscious sedation using midazolam or diazepam, accompanied by oximetry and blood pressure monitoring. The cecum was reached in 92% of the patients. The rest underwent a barium enema examination. The size of the polyps was estimated by comparing with the known width of an open biopsy forceps. Each polyp was evaluated with respect to size and location by two endoscopists. Polyps measuring >5mm were removed by snare polypectomy, while those <5mm, either by cold snare polypectomy or by hot biopsy forceps. Histopathology was determined by two expert pathologists, according to standard histological criteria. For the definition of MHAP the morphological characteristics proposed by Longacre and Fenoglio-Preiser[3] were used.

Five hundred thirty nine patients, (371 men) with 713 polyps were detected. Of them 22 patients had 23 MHAP. Their characteristics were compared with those of patients exclusively harbouring one histological type of polyp. Thus, all the cases with tubulovillous adenomas (64 patients), with coexistence of hyperplastic and adenomatous polyps (137 patients) and with the presence of a synchronous carcinoma (88 patients) were excluded. In addition, the cases in which the polyps were diagnosed as hamartomas, lymphoid aggregates or mucosal excrescences (105 patients) were also excluded. Finally, 128 patients with 179 polyps meeting the inclusion criteria, formed three comparison groups: 61 patients with 86 HP, 40 with 58 tubular adenomas, and 27 with 35 villous adenomas.

Statistical analysis

In order to facilitate comparison in the four groups, we divided the colon into four regions; rectosigmoid, descending, transverse (including hepatic and splenic flexure) and ascending-caecum area. Considering the size, three groups of polyps were identified; less than 5 mm in diameter, between 5 and 10 mm, and larger than 10 mm. The Fishers' exact test was used to determine differences between the groups. A value of $p<0.05$ was defined as the significance threshold.

RESULTS

Mixed hyperplastic adenomatous polyps comprised 3,2% (23/713) of the removed and histologically examined polyps. A total of 22 synchronous polypoid lesions were detected in 17 patients with MHAP. Eleven patients (50%) harboured 14 HP, four patients had 6 adenomas, while in two patients an invasive carcinoma was discovered.

The table shows the clinicopathological characteristics of the four groups of polyps. The age of patients with HP varied from 20 to 85 years, with MHAP from 39 to 87 years, with tubular adenomas from 52 to 86 years and with villous adenomas from 56 to 90 years. In addition, the mean age was significantly lower in patients with HP than in those with MHAP ($p=0.0093$). A significant male preponderance in patients with MHAP was noticed ($p=0.03$). The anatomical distribution of the four histological types of polyps was almost identical. Regarding size, hyperplastic polyps were significantly smaller than the other groups. In the group of polyps smaller than 5

Table 1. Clinicopathological characteristics of four polyps' groups.

	MHAP	(%)	HP	(%)	Tubular	(%)	Villous	(%)
Mean age		63.2	53.7	65.2	69.5			
Sex (M/F)		20/2	42/19	28/12	17/10			
Distribution								
Rectosigmoid	16	69.6	67	77.9	42	72.4	28	80
Descending	5	21.7	14	16.3	7	12.1	4	11.7
Transverse	2	8.7	3	3.5	5	8.6	2	5.7
Ascending-cecum	0	0	2	2.3	4	6.9	1	2.8
Size								
<5mm	4	17.4	75	87.2	29	50	1	2.9
5-10mm	6	26.1	8	9.3	15	25.9	7	20
>10mm	13	56.5	3	3.5	14	24.1	27	77.1

mm, there was a significant difference in the proportion of HP compared to MHAP (87.2% vs 17.4%, $p<0.0001$), whereas the opposite was observed in polyps larger than 10 mm (3.5% vs 56.5%, $p<0.0001$). Regarding the degree of dysplasia, 8.6% (2 of 23 cases) of MHAP contained areas of severe dysplasia, but no invasive carcinoma was detected.

DISCUSSION

General agreement exists that colorectal hyperplastic polyps are not regarded as neoplastic lesions and do not give rise to colon carcinoma. However, not only do they have qualitative differences that differentiate them from normal mucosa, but also share certain features in common with colorectal carcinomas.[4] Thus in immunohistochemical studies, HP show an increased expression of carcinoembryonic antigen (CEA), depressed IgA secretory activity, reduced secretion of O-acylated sialomucin[5] and disorders of blood group antigen expression.[6] In addition, recent studies examining serrated adenomas, found an increase in markers thought to be associated with neoplasia such us apoptosis, proliferative activity, p53 overexpression,[7] and reduction of acylated mucin secretion.[8]

In addition to these genetic alterations, multiple HP are frequently seen in the vicinity of a rectal carcinoma and are more frequent in gut segments with cancer than in tumour free segments.[9] Furthermore, the coexistence of hyperplastic, adenomatous and carcinomatous components in the same polyp was described in previous reports,[1-3,10-16] indicating a possible relationship between these colorectal lesions. These observations invite a reappraisal of the HP and its role in colorectal carcinogenesis.

In the present study, MHAP comprised 3,2% of the histologically examined polyps. Studies focusing on this aspect have produced various results, depending on the methods and study populations. Estrada and Spjut[2] found that 13% of HP had adenomatous foci. Brady et al.[17] reported that MHAP comprised 7% of the polyps in asymptomatic persons aged over 50. Weston and Campbell[18] found that MHAP comprised 4,3 % of all diminutive polyps, although Pennazio et al.[19] reported a percentage of 2% and Tedesco et al[20] only 0,9%.

The occurrence of MHAP was higher in males than females and this is consistent with other studies.[16-17] Endoscopic studies also show that adenoma prevalence rates are higher in males.[21] A satisfactory explanation for this gender discrepancy remains to be determined. A genetic or a hormonal factor could be postulated for this phenomenon.[22]

It is well documented that age is an important and independent risk factor for polyps and cancer development. The prevalence of adenomas increases with increasing age. In the present study, patients with MHAP are about ten years older than those with HP. This finding supports the concept that HP may transform with age, following the HP-MHAP-adenomatous polyp sequence.

The anatomical distribution of the four groups was virtually identical. The majority of MHAP were located in the left colon area with increased prevalence of HP and adenomas, indicating that these polyps are interrelated. Moreover, MHAP were found to be larger than HP, indicating that going through a transition from hyperplastic to adenomatous histology they enlarge or, alternatively, large HP predispose to adenomatous transformation. The adenomatous potential of large HP has also been observed by other investigators.[2,10,11,16]

Torlakovic and Snover[16] described 6 patients with serrated adenomatous polyposis, distinguishable from true hyperplastic polyposis, indicating a possible association with carcinoma. In addition Longacre and Fenoglio-Preiser[3] showed that intramucosal carcinoma occurs in at least 10% of colorectal MHAP, suggesting that they have a predisposition to malignant transformation in a manner analogous to the adenoma - carcinoma sequence.

In conclusion, the findings of this study further confirm the hypothesis of a neoplastic transformation of HP. However the relationship between HP and the subsequent development of adenomas and carcinomas remains controversial and further larger studies are warranted to evaluate the proposed HP-MHAP-adenoma sequence.

REFERENCES

1. Goldman H, Ming SC, Hickok DF. Nature and significance of hyperplastic polyps of the human colon. Arch Pathol 1970; 89:349-354.
2. Estrada RG, Spjut HJ. Hyperplastic polyps of the large bowel. Am J Surg Pathol 1980; 4:127-133.
3. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/ serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol 1990; 14:524-537.
4. Fenoglio-Preiser CM. When is a hyperplastic polyp not a hyperplastic polyp? Am J Surg Pathol 1999; 23:1001-1003.
5. Jass JR. Relation between metaplastic polyp and carcinoma of the colorectum. Lancet 1983; 1:28-29.
6. Cooper S, Marshall C, Ruggerio F, Steplewski Z. Hyper-

plastic polyps of colon and rectum. An immunohistochemical study with monoclonal antibodies against blood group antigens. Lab Invest 1987; 57:421-428.
7. Kitsanta P, Triantafillou K, Tzathas Ch, Argirakos T, Karavana B, Ladas S, Spiliadi Ch, Raptis S. The role of apoptosis in neoplastic transformation of large bowel adenomas. Annals of Gastroenterology 2000; 13 (Suppl 2), PA056.
8. Kitsanta P, Triantaffilou K, Tzathas Ch, Argirakos T, Karavana B, Ladas S, Spiliadi Ch, Raptis S. Serrated and tubular adenomas of the large bowel. Histopathological study. Annals of Gastroenterology 2000; 13 (Suppl 2), AA 132.
9. Eide TJ. Prevalence and morphological features of adenomas of the large intestine in individuals with and without colorectal carcinoma. Histopathology 1986; 10:110-118.
10. Cooper HS, Patchefsky A, Marks G. Adenomatous and carcinomatous changes within hyperplastic colonic epithelium. Dis Colon Rectum, 1979; 22:152-156.
11. Franzin G, Novelli P. Adenocarcinoma occurring in a hyperplastic (metaplastic) polyp of the colon. Endoscopy 1982; 14:28-30.
12. McCann BG. A case of metaplastic polyposis of the colon associated with focal adenomatous change and metachronous adenocarcinomas. Histopathology 1988; 13:700-702.
13. Heng Teoh H, Delahunt B, Isbister WH. Dysplastic and malignant areas in hyperplastic polyps of the large intestine. Pathology 1989; 21:138-142.
14. Rubio CA, Rodensjo M. Flat serrated adenomas and flat tubular adenomas of the colorectal mucosa: Differences in the pattern of cell proliferation. Jpn J Cancer Res 1995; 86:756-760.
15. Rubio CA, Rodensjo M. p53 overexpression in flat serrated adenomas and tubular adenomas of the colorectal mucosa. J Cancer Res Clin Oncol 1995; 121:571-576.
16. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology 1996; 110:748-755.
17. Brady PG, Straker RJ, McClave SA, Nord HJ, Pinkas M, Robinson BE. Are hyperplastic rectosigmoid polyps associated with an increased risk of proximal colonic neoplasms? Gastrointest Endosc 1993; 4:481-485.
18. Weston AP, Campbell DR. Diminutive colonic polyps: Histology, spatial distribution, concomitant significant lesions and treatment complications. Am J Gastroenterol 1995; 90:24-28.
19. Pennazio M, Arrigoni A, Risio M, Spandre M, Rossini FP. Small rectosigmoid polyps as markers of proximal neoplasms. Dis Colon Rect 1993; 36:1121-1125.
20. Tedesco FJ, Hendrix JC, Pickekns CA, Brady PG, Mills LR. Diminutive polyps: Histology, spatial distribution and clinical significance. Gastrointest Endosc 1982; 28:1-5.
21. Rex DK. Men, women, and colorectal cancer: We are winning the battle. Am J Gastroenterol 1995; 90:840-841.
22. Ponz de Leon M. Genetic basis of tumour development. Ital J Gastroenterol 1996; 28:232-245.