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Neoplasias of the Colorectal Crypts

C.A. RUBIO

Gastrointestinal and Liver Pathology Research Laboratory, Department of Pathology, Karolinska Institute and University Hospital, 17176, Stockholm, Sweden

Abstract. *Colorectal cancers are often preceded by non-invasive neoplasias arising in the surface epithelium, namely tubular, tubulovillous and villous adenomas. That neoplasias may also arise in the colorectal crypts is less well known. Between 1998 and 2002, colonoscopies, rectoscopies and colorectal surgical specimens from 8647 patients were received at this Department for histological diagnosis. The material included 502 adenomas, 865 invasive tumours and 221 cases of ulcerative colitis (UC). The following cryptal lesions were investigated: a) neoplasias arising in the crypts, b) neoplasias possibly arising in the crypts and c) cryptal lesions alleged to be premalignant. Over the 5-year period, the most frequent phenotype encountered was single crypt dysplasia (in all 5 colectomies from familial adenomatous polyposis patients), followed by serrated adenomas (11.2%), hyperplastic polyps (8.4%), dysplasia in UC (6.3%), pure carcinoid tumours (1.7%), signet ring cell carcinoma (1.1%), adenocarcinoid tumours (0.2%) and de novo carcinomas (0.1%). In this survey, no case of Paneth cell adenoma or of cryptal neoplasia in lymphoid-associated mucosa (also known to originate from the crypts) was found. Hence, it was demonstrated that several neoplasia phenotypes actually arise in the colorectal crypts. The awareness that colorectal neoplasias may evolve from that particular cellular domain may cast more light on the understanding of the complex mechanisms of colorectal carcinogenesis.*

The normal colorectal mucosa is built of a single layer of epithelial cells with inward folds called crypts. The vast majority of the surface epithelium is composed of columnar or cuboidal absorptive cells, with closely packed microvilli and a thick glycocalyx (1) and goblet cells. The rest of that surface epithelium is associated with lymphoid aggregates called lymphopatches (2). The function of the surface epithelium of the colonic mucosa is to allow the free passage of water and ions into the host (encouraged by Aquaporin 8, an integral water channel membrane protein) (3).

The surface epithelium is constantly challenged by a series of carcinogens that may generate non-invading neoplasias known as tubular, tubulovillous and villous adenomas (4). The origin of those lesions in the cells of the surface epithelium has been substantiated by cell proliferation studies (4).

The cellular composition of the crypts is more complex; in addition to mature absorptive cells, goblet cells, Paneth's cells (only in the proximal right colon) and endocrine cells, immature and undifferentiated precursor cells are found (1). The function of the crypts is to renew the epithelium *via* the undifferentiated precursor cells and to produce mucins to lubricate the faeces in order to allow their passage through the colon and rectum.

In contrast to the surface epithelium, little is known about the neoplasias that originate in the epithelium of the crypts. In previous studies, we studied in detail neoplasias originating in the surface of the colorectal epithelium (5). The aim of the present work was to investigate the neoplasias originating in the colorectal crypts.

Materials and Methods

During a 5-year period, between 1998 and 2002, colonoscopies, rectoscopies and colorectal surgical specimens from 8647 patients were received at this Department for histological diagnosis. The material included 502 adenomas, 865 invasive tumours and 221 cases of ulcerative colitis (UC). The following lesions were investigated: a) neoplasias arising in the crypts, b) neoplasias possibly arising in the crypts and c) cryptal lesions alleged to be premalignant. Cryptal neoplasias occurring in the natural diverticulum of the colon, (*i.e.* the appendix *vermiformis*) were included in the present study.

Results

Of the 8647 patients registered between 1998 and 2002, 4270 were males and 4377 females. Adenomas were diagnosed in 502 patients (230 males and 272 females). Five of the 502 patients had familial adenomatous polyposis

Correspondence to: C.A. Rubio, MD, Ph.D., Gastrointestinal and Liver Pathology Research Laboratory, Department of Pathology, Karolinska Institute and University Hospital, 17176, Stockholm, Sweden. Fax: 46 8 51774524.2, e-mail: Carlos.Rubio@onkpat.ki.se

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(FAP). Invasive tumours were diagnosed in 865 patients (457 males and 408 females), carcinoid tumours in 16 (8 males and 8 females) and ulcerative colitis (UC) in 221 patients (147 males and 99 females). Six of the 16 carcinoid tumours were localized in the appendix.

The origin of the neoplasias was divided as follows:

Neoplasias arising in the crypts. i) *In ulcerative colitis:* In patients with long-standing UC, biopsies taken from an endoscopically normal colorectal mucosa may show dysplastic cells at the bottom of the crypts (6). The histological detection of epithelial dysplasia in an otherwise apparently normal colorectal mucosa in UC is referred to as dysplasia in *flat mucosa* (Figure 1) and is the base for endoscopical-histological surveillance programmes in UC. In this work, neoplasia in flat mucosa was found in 5 (2.2%) of the 221 specimens with UC.

In other patients with UC, reparative-regenerative changes, induced by the protracted chronic inflammation, lead to focal alterations in the configuration of the crypts. Such areas usually appear irregular. Using endoscopy complemented with chromoscopy (indigo carmine dye spraying), we recently described, in patients with UC, the endoscopical appearance, as well as the histological status in the irregular mucosal areas (7) . Biopsies revealed villous structures, which in reality are the lateral aspects of elongated, architecturally-distorted crypts (Figure 2). In Hamamoto *et al.*'s (7) investigations, irregular endoscopical areas concurred with cryptal dysplasia in 9 of the 18 patients: 7 had low-grade dysplasia (LGD) and 2 high-grade dysplasia (HGD).

In the present survey, cryptal dysplasia in areas with irregular mucosal architecture was recorded in 6 (2.7%) of the 221 specimens with UC.

Lastly, a third group of patients with protracted UC may show more bulky lesions known as *dysplasia-associated lesion or mass* (DALM) (8). The designation DALM agglutinates a series of visible structures telescoping from dysplastic plaques, strictures and pedunculated polyps, to (more commonly) sessile nodules. Many of those lesions (particularly the latter ones) are difficult (or impossible) to differentiate on endoscopic grounds from sporadic adenomas in non-colitic patients (9). In this survey, DALM lesions were found in 3 (1.3%) of the 221 specimens with UC: 1 had LGH and the remaining 2 HGD.

ii) *Single crypt dysplasia* (Figure 3): While studying colectomy specimens from patients with FAP, Bussey (10) found, years ago, not only multiple adenomas, but also dysplasia in single crypts.

In this work, we examined 5 colectomy specimens from FAP patients. All 5 specimens showed, in addition to multiple adenomas, dysplasia in single crypts.

iii) *Serrated adenomas* (Figure 4)*:* As early as 1976, Enterline (11) reported adenomatous changes in hyperplastic polyps and, in 1980, Estrada and Spjut (12) found adenomatous changes in 13% of the hyperplastic polyps. In 1981, Oohara *et al.* (13) illustrated the co-existence of adenomatous and hyperplastic patterns within one colonic gland. They (13) claimed that hyperplastic (metaplastic) polyps are "only an expression of one variant in the growing process of adenomas and that the glands showing these changes most characteristically have a serrated pattern". In 1984, Urbanski *et al.* (14) also investigated mixed hyperplastic adenomatous colorectal polyps, which, years later, were named serrated adenomas by Longacre and Fenoglio (15).

A lesion is classified as serrated adenoma when the epithelium of the crypts of Lieberkühn shows sawtooth-like scalloped infolding with dysplasia in more than 50% of the crypts. Recently, Bariol *et al.* (16) reported that the diagnosis of serrated adenomas of the colon and rectum should include lesions having serrated structures in ≥20% of the dysplastic crypts. We have used a limit of more than 50% (4, 5).

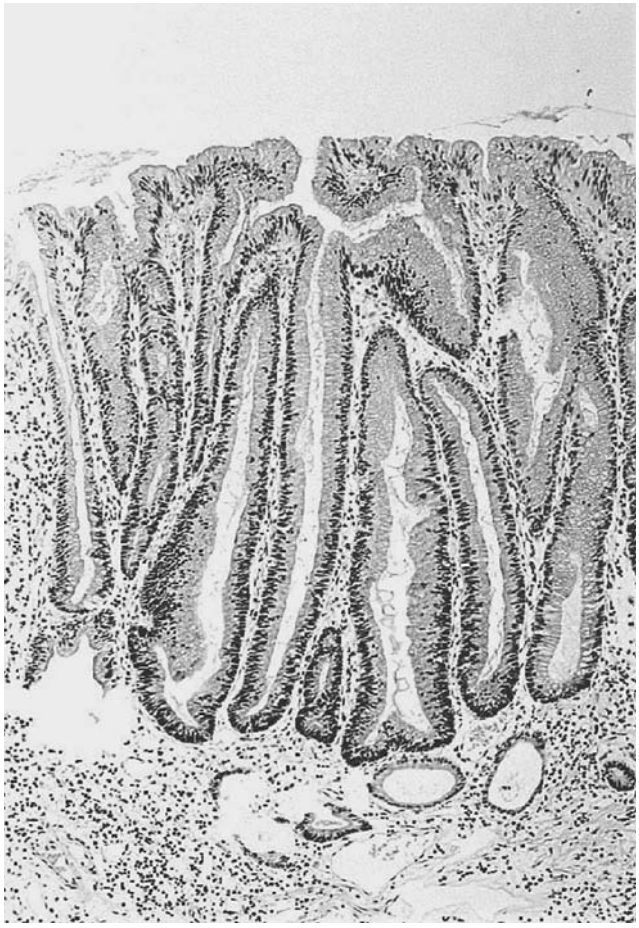

Figure 1. *Low-grade dysplasia at the base of the crypts in "flat mucosa" in a patient with long-standing ulcerative colitis (colon, H&E 50x).*

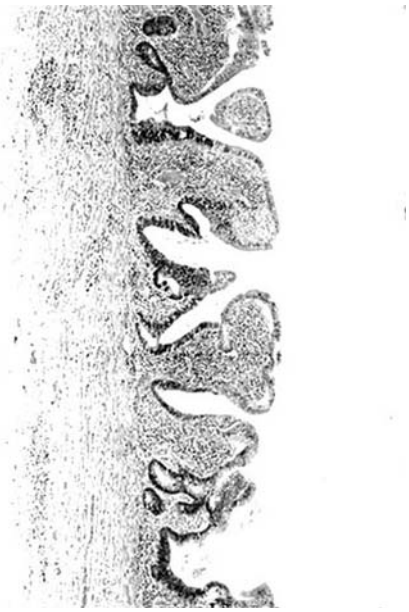

Figure 2. *High-grade dysplasia at the base of the crypts in an area with irregular mucosal architecture. Long-standing ulcerative colitis (colon, H&E 50x).*

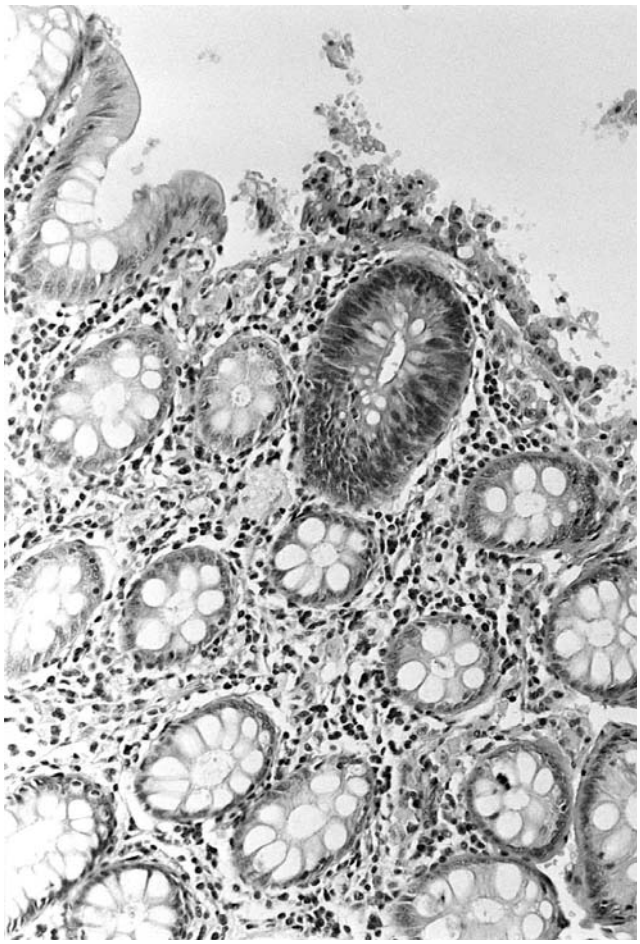

Figure 3. *Single crypt dysplasia in a patient with FAP (colon, H&E 50x).*

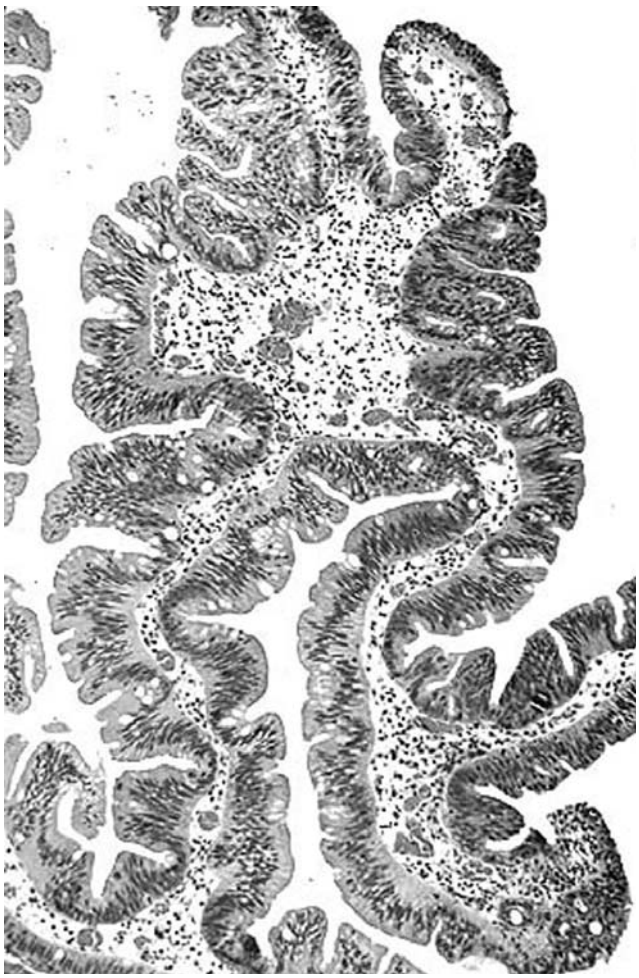

Figure 4. *Serrated adenoma. Note sawtooth-like indentations with dysplastic cells (colon, H&E 50x).*

Dysplasia in serrated adenomas arises in the lower aspect of the crypts. When the dysplastic cells are confined to the lower half of the crypts, the lesion was classified as serrated adenoma Type I (17), while when the dysplastic cells occupy both the lower half of the crypts as well as part or the entire superficial second half of the crypts, they are termed serrated adenomas Type II (17). That pathway of dysplasia progression was disclosed on studies of cell proliferation using Ki67 (Clone MIB1) (18), which showed an increased number of DNA-synthesizing dysplastic cells, initially in the basal half of the serrated crypts. The DNA-synthesizing dysplastic cells progressed upwards, towards the superficial aspect of the crypts of serrated adenomas (18). The kinetic progression of DNA-synthesizing dysplastic cells in serrated adenomas contrasted with that found in tubular and villous adenomas, where DNA-synthesizing dysplastic cells were initially found in the

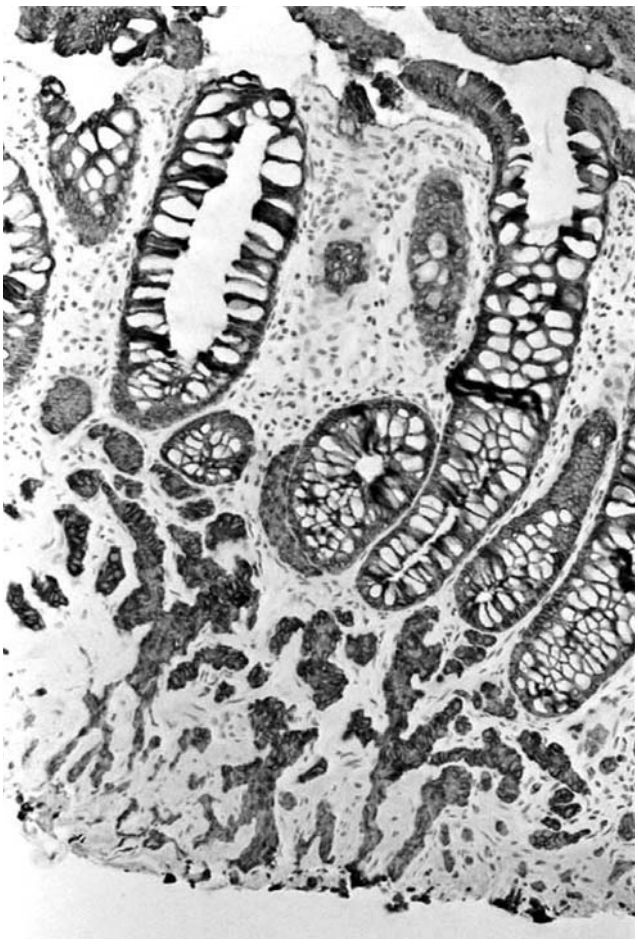

Figure 5. *Carcinoid showing endocrine cells arising at the base of the crypts (rectum, Chromogranin A 50x).*

Figure 6. *Goblet cells with neuroendocrine expression arising in a deformed crypt (appendix, Chromogranin A 50x).*

superficial (*i.e.* luminal) epithelium and progressesed downwards (4) towards the basal aspect of the crypts.

Serrated adenomas were recorded in 53 (10.6%) of the 502 colorectal adenomas.

Four of the 53 serrated adenomas were located in the appendix (19).

iv) *Paneth cell neoplasias:* Similar to normal Paneth cells, the cytoplasm of neoplastic Paneth cells contains eosinophilic granules rich in lysozyme. Albeit Paneth cells are normally found only in the proximal colon (1), cases of Paneth cell adenomas and carcinomas have been found in the colon and rectum (20-22). It is logical to assume that those neoplasias have originated in metaplastic Paneth cells in the lower aspect of the colorectal crypts. In this survey, no single case of Paneth cell adenoma was found among the 502 colorectal adenomas.

Endocrine tumours: v) "Pure" carcinoid tumours (Figure 5)*:* Endocrine tumours of the colon and rectum have been classified by the WHO (23) into carcinoid (well-differentiated endocrine neoplasm), small cell carcinoma (poorly-differentiated neuroendocrine neoplasm) and large cell neuroendocrine carcinoma. The endocrine tumours constitute a small proportion of all gastrointestinal carcinoids and behave in a similar fashion as small intestine carcinoids, where malignancy correlates with the size of the tumour. Carcinoid tumours evolve from the endocrine cells normally present in the lower aspect of the colorectal crypts.

"*Pure*" *carcinoid neoplasias* were found in 15 (1.7%) of the 865 tumours. Of the 15 carcinoids, 6 were found in the colon, 6 in the rectum and the remaining 3 in the appendix.

vi) *Adenocarcinoid tumours (also called mixed carcinoid tumours and goblet-cell carcinoid)* (Figure 6): These tumours are usually found in the appendix (23); only isolated cases have been reported in the colon (24). The tumours are built of nests of neoplastic cells resembling goblet cells or signet-ring cells, as well as of endocrine cells containing mucin globules and/or endocrine-like secretory granules (*i.e.* components also

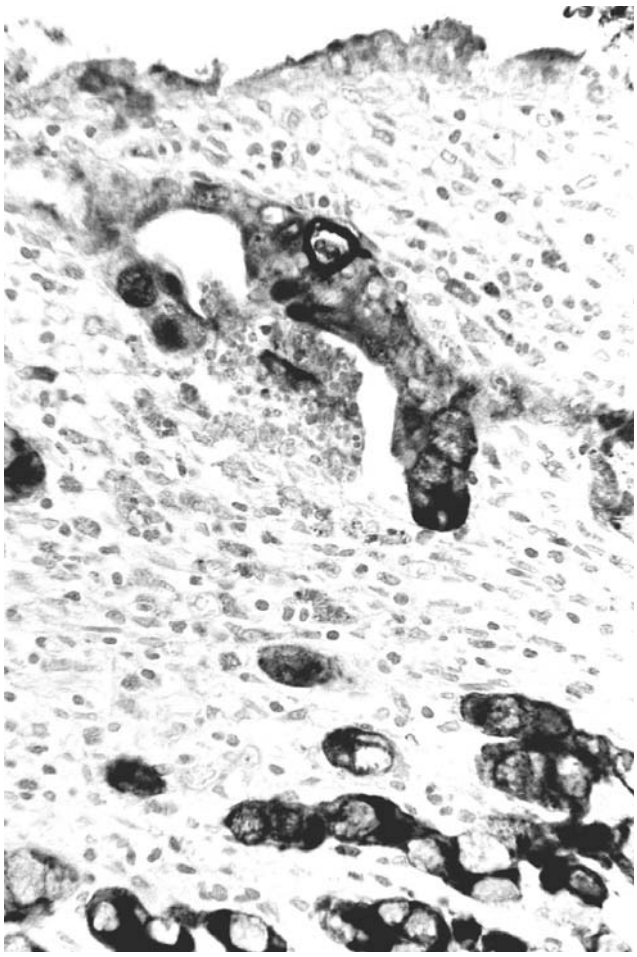

Figure 7. *Signet-ring cell adenocarcinoma arising in a deformed crypt (colon, PAS.100x).*

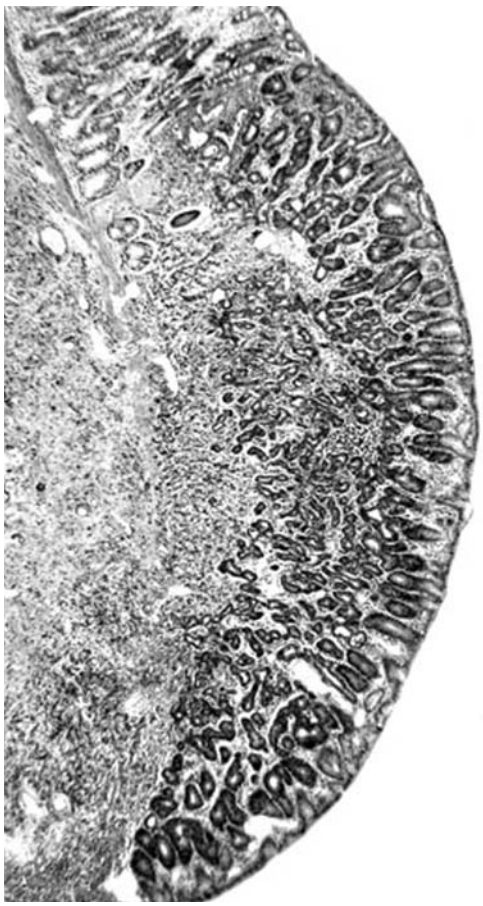

Figure 8. *Cancer "de novo" invading the submucosa. The invasion seems to have originated from the crypts. Despite its minute size, no remnant adenoma was found (colon, H&E.12.5x).*

found in ECL (endocrine-like) or D (somatostatin) cells). The tumour nests may include Paneth cells; for this reason, Isaacson (25) called these lesions *crypt cell carcinoma*. Goblet-cell carcinoids arise from the base of the crypts (Figure 5).

One goblet-cell carcinoid (0.12%) was found among the 865 tumours.

vii) *Tumours in lymphoid-associated herniated mucosa:* In 1954, Dukes (26) described lymphoid-associated mucosal misplacements (later called mucosal herniations) in colectomy specimens from colitic patients, that he claimed were a consequence of mucosal repair following regeneration of ulcers. Dukes (20) believed that the buried epithelium could encourage cancer development. In later years, particular attention was focused on that lymphoid-associated herniated colonic mucosa in UC patients. Quantitative studies of surgical resections (27) indicated that foci of lymphoid-associated herniated colonic mucosa are more common in UC (716/22 colectomies) than in Crohn's colitis (11/20 colectomies). On the other hand, none of the 20 colectomies with sporadic colorectal cancer (CRC) without inflammatory bowel-colorectal-disease (IB-CR-D) had herniated mucosa.

So far, 2 neoplasms arising in lymphoid-associated herniated mucosa have been recorded in patients with UC (27, 28) (Figure 7). The deep location of these 2 tumours strongly underlines their cryptal origin.

In this survey, no single case of neoplasia in lymphoid-associated herniated mucosa was found among the 221 specimens with UC.

Neoplasias probably originating in the crypts. i) *Signet-ring cell carcinomas* (Figure 7)*:* Neoplastic signet-ring cells resemble the goblet cells of the colorectal mucosa. They contain intracytoplasm mucin and are usually arranged as single cells or in clusters, surrounded or not by lakes of mucin. Many incipient cases of signet-ring cell carcinoma show no

Figure 9. *Hyperplastic (metaplastic) polyp showing serration of the crypts (colon, H&E.12.5x).*

adenomatous changes on the surface (luminal) epithelium, suggesting that the invading signet ring cells have originated in the crypts.

Colorectal adenocarcinomas of signet-ring cell type are rare; in a survey (29) of 424 surgical specimens from Swedish (n=223) and Japanese (n=201) patients with a colorectal adenocarcinoma, signet-ring cell carcinomas was found in only 0.8%.

In this work, signet-ring cell carcinomas were found in 9 (1.04%) of the 865 invasive mucosal tumours.

ii) *De novo carcinomas* (Figure 8)*:* Pathologists, particularly in Japan, have the notion that colorectal carcinomas may arise "*de novo*" from normal crypts of Lieberkühn without an adenomatous stage. *De novo* carcinomas are seen at endoscopy as slightly elevated lesions, usually with a central depression, occupying less than one low-power field (20x) (30). Despite the small size of these aggressive neoplastic lesions, no remnant adenomatous structures can be discerned either to the side or on the top (30). The invading tumour cells reach the domains of the *lamina propria* or of the submucosal layer. One (0.12%) *de novo* carcinoma was found among the 865 tumours.

Cryptal lesions alleged to be potentially preneoplastic. Hyperplastic (metaplastic) polyps (Figure 9)*:* These non-neoplastic proliferations of the cryptal epithelium are included here since they have repeatedly been alleged to be potentially pre-neoplastic (31). Schmieden and Westhaus (32) described hyperplastic polyps in the rectal mucosa as early as 1926. Hyperplastic (metaplastic) polyps are foci of cryptal mucosal hyperplasia, characterized by lengthening and dilation of the Lieberkühn's crypts, with a serrated configuration, and lined by a greater proportion of absorptive cells to goblet cells than normal mucosa. The basement membrane does not participate in this infolding. The columnar cells have an abundant, pale, eosinophilic cytoplasm, with or without apical mucin droplets. The base of the crypt is lined with regular cells with small, round nuclei. Araki *et al.* (33) studied the histogenesis of hyperplastic polyps by isolating single colorectal crypts. They found that hyperplastic polyps originate by the apparent fusion of single abnormal crypts within a small region of mucosa, the growth being achieved by fission of the crypts showing hypermaturation; in hyperplastic polyps, they found a slow cell migration from the basal crypts to the mucosal surface (33). Hyperplastic (metaplastic) polyps were found in 726 (8.4 %) of the 8647 colorectal specimens received at this Department between 1998 and 2002.

Discussion

In the present survey, we classified and illustrated various neoplastic phenotypes arising, probably arising and alleged to be preneoplastic in the colorectal crypts. Over a 5-year period, the most frequent phenotype encountered was single crypt dysplasia (in all 5 entire colectomy specimens with FAP), followed by serrated adenomas (11.2%), hyperplastic polyps (8.4%), dysplasia in UC (6.3%), pure carcinoid tumours (1.7%), signet-ring cell carcinoma (1.1%), adenocarcinoid tumour (0.2%) and *de novo* carcinoma (0.1%). In this survey, no case of Paneth cell adenoma or of cryptal neoplasia in lymphoid-associated mucosa (27, 28) was found.

In order to detect dysplasia in flat mucosa in patients with long-standing UC, annual colonoscopic-histological surveillance programmes were advocated years ago at the St. Mark's Hospital in London (6). In so doing, many cases of LGD have been detected worldwide. Notwithstanding, the premalignant significance of LGD in flat mucosa in colitis remains a matter of debate: some gastroenterologists (34) consider LGD to be a high-risk factor that requires colectomy; others, however, found no tumour development in long follow-up studies of up to 10 years (35).

Dysplasia in flat mucosa occurs not only in UC patients, but also as "single crypt dysplasia" in patients with FAP (10). It is currently unknown whether single crypt dysplasia is an

alternative pathway for the development of some colorectal adenomas in FAP patients, or whether single crypt dysplasia remain as such without further progression.

In patients with UC, endoscopical surveillance may be improved with the aid of chromoscopy. In this manner, areas of irregular architecture of the crypts, often showing architecturally-distorted crypts with epithelial dysplasia, can be identified. The development of serrated adenomas proposes an independent pathway in the histogenesis of colorectal carcinoma, that is hyperplasia of the crypts–dysplasia of the crypts (*i.e.* serrated adenoma)–carcinoma sequence. Transitional forms, from hyperplastic polyps to serrated adenomas and carcinomas, have been demonstrated even in the appendix *vermiformis* (19). Serrated adenomas seem to evolve through a genetic pathway that is at variance with that of tubular, tubulo-villous and villous adenomas (4).

Paneth cell metaplasia in the crypts is often present in patients with long-standing UC. However, as none of the reported Paneth cell adenomas or carcinomas has been reported in patients with UC, it may be deduced that Paneth cell metaplasia is not a predisposing condition leading to neoplastic transformation in patients with chronic coloproctitis. This is unexpected, considering that epithelial metaplasias in other organs (*e.g.,* gastric intestinal metaplasia and bronchial squamous metaplasia) are known to promote neoplastic transformation. Paneth cell metaplasia in the colonic mucosa has an antimicrobial task that is exerted *via* the lysozyme-rich granules (36) contained in and released from their cytoplasm. The cause for the apparent natural resistance of Paneth cells, which are provided with anti-microbial and growth factors, to undergo neoplastic transformation, remains poorly understood.

Despite the relative high frequency of lymphoid-associated herniated mucosa in patients with UC, only 2 cases of neoplasia in such mucosa in UC are on record (27, 28). The deep location of those 2 tumours strongly suggested a cryptal origin, thus contrasting with the tumours reported by Petris and Lev (37) in a case of hereditary nonpolyposis colorectal cancer and by Jass *et al.* (38) in a patient with a family history of colorectal carcinoma. Those authors (37, 38) found that the tumour had originated in the dome epithelium of gut-associated lymphoid tissue (*i.e.* from superficially located normal cryptopatches (3)). Neither of the 2 patients (37, 38) had UC.

In cases of incipient signet-ring cell carcinoma, the surface (luminal) epithelium appears unaffected without adenomatous changes. In such cases, the origin of the tumours can be traced to the cryptal epithelium. In other cases of signet-ring cell carcinoma, however, a villous adenoma may be found on top, suggesting that the carcinoma has originated in that adenoma. The question arises: can non-mucin producing dysplastic columnar cells abruptly transform, at the time of invasion, into neoplastic mucin-producing signet-ring cells? Or does the adenoma on top and the signet-ring cell carcinoma underneath represent two independent lesions, one originating in the surface epithelium and the other in the epithelium of the crypts (*i.e.* collision neoplasias)? These important questions remain to be explored.

Although *de novo* carcinomas are often reported by Japanese pathologists, the concept of the *de novo* carcinoma as a pathway of colorectal carcinogenesis remains a controversial issue among Western pathologists. However small, no remnant adenomatous structures (sidewise or on top) can be discerned. It is reasonable to assume that, despite the given nomenclature, dysplastic crypts precede *de novo* carcinomas.

In the light of the present results, and although no distinction has been made in the literature between carcinogens battering the surface epithelium *vs.* those assaulting the cryptal epithelium, it would appear that some carcinogens might preferentially target one of both epithelial domains. This possibility appears to be substantiated by the fact that, even in some forms of lymphocytic mucosal inflammation, the lymphocytes accumulate in the surface epithelium (that is lymphocytic colitis), whereas in others the lymphocytes gather in the cryptal epithelium exclusively (that is lymphocytic cryptitis) (39). One of the explanations for the dual behaviour might be that at least some colonotropic carcinogens are probably *surfotropic* and others are *cryptotropic*.

Differences between adherent mucins and the presence of glycocalix on the surface epithelium and of non-adherent mucins in the lumen of the crypts may influence the selection of the various noxious agents presented to the colorectal mucosa in susceptible individuals.

In conclusion, several neoplasia phenotypes were shown to arise in the colorectal crypts. The awareness that colorectal neoplasias may evolve from cryptal cells may cast more light on the understanding of the complex mechanisms of colorectal carcinogenesis.

References

1 Levine D and Haggitt R: Colon. Chapter 22. *In:* Histology for Pathologists, Sternberg SS (ed.). Philadelphia. Lippincott-Raven Pub, pp. 519-537, 1977.

2 O'Leary A and Sweeney E: Lymphoglandular complexes of the colon: structure and distribution. Histopathology *10*: 267-283, 1986.

3 Fischer H, Stenling R, Rubio C and Lindblom A: Differential expression Aquaporin 8 in human colonic epithelial cells and colorectal tumors. BMC Physiology *1*: 1-6, 2001.

4 Rubio CA: Colorectal adenomas: time for reappraisal. Pathol Res Pract *198*: 615-620, 2002.

5 Rubio CA, Nesi G, L Messerini L and Zampi G: Serrated and microtubular colorectal adenomas in Italian patients. A 5-year survey. Anticancer Res *25*: 1353-1359, 2005.

6 Lennart-Jones J, Melville D, Morson B, Ritchie J and Williams C: Precancer and cancer in extensive ulcerative colitis: findings among 401 patients over 22 years. Gut *31*: 800-806, 1990.
7 Hamamoto N, Rubio CA, Befrits R, Toyoda H, Ceballos J and Jaramillo E: Subtle changes detected at endoscopy in patients with inflammatory bowel disease. Digestive Endoscopy *17(Suppl)*: S24-S29, 2005.
8 Blackstone MO, Riddell RH, Rogers BH and Levin B: Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. Gastroenterology *80*: 366-374, 1981.
9 Rubio CA, Befrits R, Jaramillo E, Nesi G and Amorosi A: Villous and serrated adenomatous growth bordering carcinomas in inflammatory bowel disease. Anticancer Res *20*: 4761-4764, 2000.
10 Bussey HJ: Familial Polyposis Coli. Family Studies, Histopathology, Differential Diagnosis and Results of Treatment. The John Hopkins University Press, pp. 20-103, 1975.
11 Enterline HT: Pathology of the gastrointestinal tract: polyps and cancer of the large bowel. Curr Top Pathol *63*: 97-141, 1976.
12 Estrada R and Spjut H: Hyperplastic polyps of the large bowel. Am J Surg Pathol *4*: 127-133, 1980.
13 Oohara T, Ogino A and Tohma H: Histogenesis of microscopic adenoma and hyperplastic (metaplastic) gland in nonpolyposis coli. Dis Colon Rectum *24*: 375-384, 1981.
14 Urbanski S, Kossakowska A, Marcon N and Bruce R: Mixed hyperplastic adenomatous polyps – an underdiagnosed entity Am J Surg Pathol *8*: 551-556, 1984.
15 Longacre TA and Fenoglio-Preiser CM: Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol *14*: 524-537, 1990.
16 Bariol C, Hawkins N, Turner J, Meagher A, Williams A, Williams DD and Ward R: Histopathological and clinical evaluation of serrated adenomas of the colon and rectum. Mod Pathol *16*: 417-423, 2003.
17 Rubio CA and Rodensjö M: p53 overexpression in flat serrated adenomas and flat tubular adenomas of the colorectal mucosa. J Cancer Res Clin Oncol *121*: 571-576, 1995.
18 Rubio CA and Rodensjö M: Flat serrated adenomas and flat tubular adenomas of the colorectal mucosa; differences in the pattern of cell proliferation. Jpn J Cancer Res *86*: 756-760, 1995.
19 Rubio CA: Serrated adenomas of the appendix. J Clin Pathol *57*: 946-949, 2004.
20 Rubio CA, Kanter L, Bjork J, Poppen B and Bry L: Paneth cell-rich flat adenoma of the rectum: report of a case. Jpn J Cancer Res *87*: 109-112, 1996.
21 Nevalainen TJ, Haapanen TJ, Rajala P and Ekfors T: Expression of group II phospholipase A2 in Paneth cells of an adenoma of the rectum. A case report. APMIS *106*: 780-784, 1998.
22 Shousha S: Paneth cell-rich papillary adenocarcinoma and a mucoid adenocarcinoma occurring synchronously in colon: a light and electron microscopic study. Histopathology *3*: 489-501, 1979.
23 Hamilton S, Vogelstein B, Rubio CA, Sobin LH *et al*: Tumors of the colon and rectum. *In:* WHO Classification of Tumours Series, Pathology and Genetics of Tumours of the Digestive Tract. Hamilton SR and Aaltonen LA (eds.). WHO Lyon, pp. 104-119, 2000.
24 Jiao YF, Nakamura S, Arai T, Sugai T, Uesugi N, Habano W, Suzuki M, Tazawa H and Goukon Y: Adenoma, adenocarcinoma and mixed carcinoid-adenocarcinoma arising in a small lesion of the colon. Pathol Int *53*: 457-462, 2003.
25 Isaacson P: Crypt cell carcinoma of the appendix (so-called adenocarcinoid tumor). Am J Surg Pathol *5*: 213-224, 1981.
26 Dukes C: The surgical pathology of ulcerative colitis. Ann R Coll Surg Engl *14*: 389-400, 1954.
27 Rubio CA: Ectopic colonic mucosa in ulcerative colitis and in Crohn's disease of the colon. Dis Colon Rectum *27*: 182-186, 1984.
28 Rubio CA and Talbot I: Lymphoid-associated neoplasia in herniated colonic mucosa. Histopathology *37*: 187-194, 2000.
29 Rubio, CA, Yanagisawa A and Kato Y: Histologic phenotypes of colonic carcinoma in Sweden and in Japan. Anticancer Res *18*: 2649-2656, 1998.
30 Kurisu Y, Shimoda T, Ochiai A, Nakanishi Y, Hirata I and Katsu KI: Histologic and immunohistochemical analysis of early submucosal invasive carcinoma of the colon and rectum. Pathol Int *49*: 608-616, 1999.
31 Jass J: Hyperplastic polyps and colorectal cancer: is there a link? Clin Gastroent Hepatol *2*: 1-8, 2004.
32 Schmieden V and Westhaus H: Zur klinik und pathologie der ickdarmpolypen und deren klinischen und patologisch-anatomischen beziehungen zum dickdarm karzinom. Dtsch Z Chir *202*: 1-125, 1926.
33 Araki K, Ogata T, Kobayashi M and Yatani R: A morphological study on the histogenesis of human colorectal hyperplastic polyps. Gastroenterology *109*: 1468-1474, 1995.
34 Ullman T, Croog V, Harpaz N, Sachar D and Itzkowitz S: Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. Gastroenterology *125*: 1311-1319, 2003.
35 Befrits R, Ljung T, Jaramillo E and Rubio CA: Low-grade dysplasia in extensive, long-standing inflammatory bowel disease: a follow-up study. Dis Colon Rectum *45*: 615-620, 2002.
36 Rubio CA: Paneth cell adenoma of the ileum. Anticancer Res *24*: 4187-4190, 2004.
37 De Petris G and Lev R: Adenocarcinoma of colon associated with gut-associated lymphoid tissue. Histopathology *37*: 566-573, 2000.
38 Jass J, Constable L, Sutherland R, Winterford C, Walsh M, Young J and Leggett B: Adenocarcinoma of the colon differentiating as dome epithelium of gut-associated lymphoid tissue. Histopathology *36*: 116-120, 2000.
39 Rubio CA and Lindholm JP: Cryptal lymphocytic coloproctitis: a new phenotype of lymphocytic colitis? J Clin Pathol *55*: 138-140, 2002.

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