Commentary

Flat colorectal neoplasia: identification, pathogenesis and clinical significance

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In this issue, Kim et al. \cite{1} have described their experience in Korea in identifying and classifying flat colorectal neoplasia. Over a 5-year period, they found that the ratio of flat colorectal neoplastic lesions to the total number of colonoscopies performed increased every year from 0.13\% to 1.61\%. During this period, they used video endoscopy, sprayed a 0.2\% indigo carmine solution to facilitate detailed observation, photographed and measured each lesion and removed most by endoscopic polypectomy or mucosal resection. They then used standard Western pathology classification of the histological material \cite{2}.

By definition, all their studied lesions were $\leq 5$ mm in diameter and their definition of a ‘flat’ adenoma was as accepted in the literature \cite{1}. They found that the rectum was the most common site for flat adenomas and that the risk for advanced neoplasia (amount of villosity and degree of dysplasia) increased with the size of the flat neoplastic lesion. In fact, 23.5\% were ‘advanced’ neoplasia and they noted that these lesions were more likely to have an irregular surface and a central depression.

It was suggested that the 12-fold increase in the number of flat neoplasia patients identified over 5 years was most probably due to their increased clinical awareness, even though they did not describe any change in endoscopic examination technique, so a true increase in incidence cannot be excluded. It should also be noted that 47\% of their study population had a past or family history of colorectal neoplasia and, therefore, cannot be regarded as representative of the general population. Even so, they have again brought to our attention the necessity to recognize the possibility of alternative genetic and morphologic pathways to colorectal neoplasia.

In this editorial, we will not attempt to review the topic of flat colorectal neoplasia in full, as this is done by Kim et al., but to address specific clinical and pathological aspects and recent publications that provide further knowledge and understanding on the topic. It was almost 20 years ago that Muto et al. \cite{3} described ‘flat’ adenomas in an English language publication. At that time, the general response in European/American literature was that of skepticism, as the accepted pathway to colorectal cancer (CRC) was through the adenomatous polyp—a lesion that gastroenterologists and surgeons could see and remove with the then evolving technique of colonoscopy, and thereby prevent CRC! At that time, both adenomatous polyps and CRC were being identified endoscopically in clinically significant numbers in the American and affluent Westernizing populations, while the incidence of large bowel cancer was only starting to rise in increasingly affluent and Westernizing Asian countries such as Japan. Further endoscopic studies in European populations, using chromoendoscopy and techniques as described by Japanese endoscopists, eventually confirmed that flat adenomas were rare, but could be identified in Western patients, and confirmed as previously described, but ignored, European experience \cite{4}. Western endoscopists had ignored the fact that pathologists, using a magnifying glass to examine the large bowel, had frequently identified small polyps at post mortem and in surgical specimens \cite{5}. The general impression was, and still is, that flat adenomas and cancer do occur, but are not of a high clinical significance in affluent Western countries \cite{6}. This was based on the extensive clinical and follow-up colonoscopy experience from the American National Polyp Study \cite{6} and the UK St. Marks experience of follow-up after rectal-sigmoid polypectomy \cite{7}. In both series, post-polypectomy patients had a significantly reduced risk for CRC, but not an absolute absence of risk for cancer.

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Cooperative studies with Japanese and European researchers confirmed the occurrence of flat colorectal neoplasia in the Swedish population [8], infrequent but identified in a large sigmoidoscopy screening study [9] and in about 1% of a colonoscopy-examined population in the UK [10], and found in 22.7% of high-risk and symptomatic US patients examined by a team of Japanese and American endoscopists using chromoendoscopy [11].

Several issues became clear from these cooperative studies. There was a difference in how Japanese and European pathologists classified colorectal neoplasia and especially flat neoplasia. Most, but not all of studies reporting these lesions come from Japan, using histological criteria differing from those used in Western pathology to diagnose both high-grade dysplasia and invasive colorectal carcinoma [12–14]. For the western pathologists, the presence of submucosal invasion is mandatory for the diagnosis of carcinoma, while in Japan severe cytologic and structural atypia is sufficient for such a diagnosis. Consequently, some Japanese intramucosal carcinomas would be diagnosed in the West as adenoma with high or even low-grade dysplasia [13,14]. Differences in classification were cleared up by joint international meetings of these pathologists and their agreeing on terminology [14–16]. However, if only ‘submucosal carcinomas’ are taken into consideration (there are no differences of diagnostic criteria between Japanese and western pathologists for this category), the incidence of the superficial type still ranges from 32 to 41% [12,13], indicating that the superficial type of carcinoma is not rare in Japan. In a large prospective colonoscopy study in the UK, Rembacken et al. [10], reported the presence of early cancer in 29% (14/49) of flat lesions >10 mm. Furthermore, the high rate of submucosal invasion by these lesions, as compared to the polypoid type, is characteristic of lesions with a central depression [12,13]. Therefore, not all flat lesions have the same risk of submucosal invasion. Central depression is an important macroscopic (and endoscopic) sign with regard to their invasiveness and this sign may have important therapeutic implications. A series of studies demonstrated that both the non-flat and type of flat neoplastic lesions also had specific differences in their proliferative activity [17], apoptosis [18,19] and distribution of acid mucin staining [20]. There was also a marked difference noted in the incidence of those flat lesions depending on ethnicity of the population examined, the use of chromoendoscopy or even a dissecting microscope in surgical specimens to detect minute adenomas [8,9,11,21]. The impression of Western pathologists was that the Japanese lesions had a more advanced degree of dysplasia than those described in Western populations [22,23]. It was suggested that this might reflect ethnic and/or environmental differences between populations [22].

In order to explain this dichotomy of clinical, histological and biological findings in the different ethnic groups, it required a postulation that flat neoplastic lesions represented a mixture of at least two neoplastic pathways. One pathway being the intramucosal adenomas that might or might not progress to adenomatous polyps or remain flat adenomas that might grow into larger, but still non-polypoid adenomas and might progress through dysplasia to flat, invasive cancers [24]. A further pathway could be that of flat, but eventually invasive colorectal carcinoma without histological evidence of initial or residual adenomatous tissue [24,25].

Supportive evidence for these different pathways comes from cooperative, multi-centre, genetic studies of the different lesions: flat adenoma, flat carcinoma, polypoid adenoma and polypoid carcinoma [26–30]. To summarize these studies, there is consistent evidence of a significantly lower incidence of K-Ras mutations in flat adenomas or carcinoma as compared to polypoid adenomas or carcinomas; APC mutations were significantly less common in flat adenomas than in flat carcinoma, polypoid adenomas or cancer; flat cancers had significantly more loss of heterozygosity (LOH) at chromosome 3p as compared to polypoid cancers; LOH at 17p and 18q were uncommon in benign lesions, but occurred in almost 50% of all cancers. These findings suggest that K-RAS and APC gene mutations are associated with exophytic growth of neoplasia—benign or malignant; while almost half of cancers lose chromosomes 17p and 18q probably at the time there is transition from benign to malignant neoplasia; while 3p loss occurs in non-polypoid cancers during their evolution, but not in polypoid cancers. There was no consistent association with microsatellite instability, which is probably a further independent pathway to carcinogenesis [30].

These diverse genetic perturbations are confirmation of the clinical impressions that there are several diverse pathways to CRC. We may now be able to address several clinical observations that, until now, have remained unexplained. The American National Polyp Study demonstrated a significant reduction in CRC incidence after colonoscopic polypectomy and follow-up by expert endoscopists, but not an absolute absence of cancer [6]. Furthermore, in our own country, which has a high incidence of CRC, large and multiple adenomatous polyps are not commonly found during screening. In an audit 10 years ago of a multi-centre screening program using mainly flexible sigmoidoscopy and fecal occult blood testing, neoplastic lesions were found in fewer than 3% of 3000 average-risk screenees [31]. Since then, the incidence of CRC has not increased. However, a recent audit of average-risk screening by colonoscopy (N=688) has now demonstrated neoplasia in 24.1%, still significantly less, with smaller polyps and less likely to be multiple, than found in a US study of Veterans (personal communication, Dr. H. Strul, Tel Aviv) [32]. Possible explanations for these observations includes a pathway to cancer that is not always associated with a polypoid lesion, and that the recent increase in polypoid neoplasia is a consequence of westernized life-style promoting polyp growth [33].

In conclusion, there are several diverse pathways to
CRC and each one will need to be addressed in order to provide an adequate answer to CRC prevention and early detection.

Conflict of interest statement

None declared.

References