Ulcerative colitis and malignancy

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Abstract

Ulcerative colitis is associated with an increased risk for colorectal cancer. The increase is approximately six to ten times the expected in the general population. Disease duration and extension are the major risk factors. Concomitant primary sclerosing cholangitis is an additional independent risk factor. The relative risk is approximately 14.8 for patients with pancolitis while it is 1.7 for patients with disease restricted to the rectum. The risk increases rapidly after 20 years of disease evolution. Active treatment might decrease the risk. The increased cancer risk is a major problem for longterm management of patients with ulcerative colitis. It is the rationale for various surveillance programs and the search for dysplasia. Two major types of dysplasia must be distinguished in ulcerative colitis : sporadic adenomas and ulcerative colitis-associated dysplasia. Sporadic adenomas can be treated by simple polypectomy. The diagnosis of dypsplasia relies mainly on microscopic analysis of biopsy samples. Additional techniques, including flow cytometry and the search for DNA abnormalities and immunohistochemistry or molecular techniques looking for genetic defects can help to improve the diagnostic yield. (Acta gastroenterol. belg., **2000**, 63, **279-283**).

Key words : ulcerative colitis, cancer, dysplasia.

Introduction

Patients suffering from ulcerative colitis (UC) have a higher risk to develop cancer when compared with the general population. Colorectal cancer in UC has been recognized already in 1928 (1). The increased cancer risk is one of the major problems in longterm management of patients with UC. It is important to identify the cancer types which can occur — intestinal or extra-intestinal — the size of the risk, the major risk factors and a strategy for (secondary) prevention.

Cancer types

From larger, population based studies performed in Sweden and the UK it appears that the elevated cancer risk among patients with inflammatory bowel diseases (ulcerative colitis and Crohn's disease) is due predominantly to an increase of intestinal cancer (2- 4). It seems that there is a predominance for distal cancers (sigmoid and rectum) which represents about two thirds of the cases. Although the absolute numbers are small, a subgroup of patients with UC and the hepatobiliary complication primary sclerosing cholangitis (PSC) runs a significantly increased risk of developing carcinoma of the bile ducts (5).

Cancer risk

Several larger population-based studies from different geographical regions have assessed the cancer risk appropriately (taking into account disease duration, using actuarial life-table methods, calculation of the absolute cumulative risk). They provided consistent, independent results regarding the cumulative colorectal cancer-risk in UC. A study of 486 patients with extensive UC (i.e. involvement proximal to the splenic flexure) from three different areas in England and Sweden, followed for a minimum of 17 years, estimated the risk to be 11.6% (CI : 6.4 - 16.8) after 25 years from disease onset. This increase is approximately six to ten times the expected in the general population. In non-extensive UC (left-sided, distal) the risk is only marginally raised or not increased at all (proctitis). Similar results were obtained from a large epidemiological study from Uppsala, Sweden including 679 patiens having extensive colitis. After 25 years the cumulative risk was 12% among patients aged 15-39 years at disease onset. The cumulative cancer risk in patients with left-sided colitis, at time of diagnosis was less than 5% after 30 years, except for those patients who got the disease between 15-29 years of age who had a 12% risk. In a population study from Israel the cumulative risk was 13.8% in total colitis after 20 years of duration. A prospective Danish study could not confirm these data but another study covering the entire country has provided CRC-risk estimates in line with those reported from other countries (6-9).

Risk factors

The increase in risk is mainly related to *the duration* (> 8 years) and to *the extension* of the disease (Table I). In case of pancolitis, the absolute risk for colorectal cancer after 35 years of evolution is estimated at 30%. This risk becomes 40% if the disease started before the age of 15 (6). A recent large prospective study of 2509 UC-patients showed that death due to colorectal cancer in fact is the main cause of the excess long-term mortality found among patients with UC (2). In patients with

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extensive UC, the presence of *concomitant PSC* is an independent risk factor, also for colorectal neoplasia (10).

Young age at onset of UC is associated with a high cumulative colorectal cancer risk, but this risk may not be an independent factor as such but rather interrelated to long duration. Patients in a state of *chronic continuous disease activity* might run a higher risk for colorectal cancer but this is not unequivocally confirmed.

The risk for colorectal cancer appears after a decade of evolution and quickly increases after 20 years of evolution.

Table I. — **Disease extension and cancer risk in ulcerative colitis**

disease restricted to the rectum	: relative risk 1.7 (CI at 95% : 0.8-3.2)
disease restricted to left colon	: 2.8 (CI = 1.6-4.4)
pancolitis	: 14.8 (CI = 11.4-18.9)

Prognosis

The prognosis of colorectal cancer when it occurs seems similar to the one found in the general population. The tumour stage is essential for the prognosis (1 1,12).

Treatment and cancer risk

Active treatment may influence the colorectal cancer-risk in UC. A study including a cohort of 1,161 patients showed that the risk for colorectal cancer was not different from the one in the general population (cumulative incidence at 25 years : 3.5% in ulcerative colitis and 3.7% for the general population) in case of "active treatment" for relapses, followed by long-term maintenance treatment and surgery in case of failure of medical treatment. The protective value of medical treatment was confirmed by a Swedish case control study and in some studies from England (13,14,15,16).

Dysplasia

As early as 1949, Warren and Sommers recognised the presence of a precancerous lesion in the colon of patients with chronic ulcerative colitis. They postulated that a structural precursor to carcinoma existed in long-standing ulcerative colitis and that carcinoma does not arise de novo from morphologically normal mucosa (17). The nature of the precursor lesion was however unclear at that time. The authors suggested that cancer of the colon could develop either from preexisting adenomatous polyps or from loci of regenerative epithelial hyperplasia (18). The presence of a precursor lesion was confirmed in 1959 (19) and in 1967 "precancerous" changes were described in the mucosa of colectomy specimens of 23 patients who underwent resection for carcinoma in ulcerative colitis. The changes occurred in flat mucosa as well as in polypoid lesions and were often widespread (20). The lesion is however often not identifiable at gross examination or during endoscopy (21). The occurrence of "precancer" was confirmed in retrospective studies and was later referred to as "dysplasia" (22). A precise definition and classification for "dysplasia" have been proposed for lesions observed in patients with IBD by an international "Inflammatory Bowel Disease-Dysplasia Morphology study group". According to this definition, which is now generally accepted, dysplasia is used only for lesions showing "Unequivocal, noninvasive (confined within the basement membrane), neoplastic transformation of the epithelium excluding all reactive changes" (23). This definition stresses the nature and origin of the lesion but its identification still relies upon the recognition of morphologic features resulting from cytological and architectural changes in routinely processed and Haematoxylin and Eosin stained sections. Identification of dysplasia is the basis of many surveillance programs that have been proposed.

Macroscopically, dysplasia is categorized broadly as either flat or associated with a raised lesion or mass. The latter is commonly referred to as a dysplasia- associated lesion or mass (DALM) (24). It is however extremely difficult to make the diagnosis on macroscopy because of the common irregular appearance of the mucosa. The diagnosis of ulcerative colitis-associated dysplasia relies on microscopy. When a biopsy is diagnosed as negative for dysplasia, it must be realised that dysplasia in UC usually shows a patchy distribution. Even if 20 - 40 biopsies are taken, less than 0.1% of the colorectal mucosa is covered (25). Still, accumulated experience from several prospective studies shows that 6 - 10 different biopsies from different sites might be sufficient to detect significant dysplasia (26,27).

Differential diagnosis

Surveillance studies have shown that a distinction has to be made between UC-related dysplasia, especially the polypoid or raised type, and sporadic adenoma occurring in UC. While the latter is unequivocally a neoplastic and hence a dysplastic lesion, its development is unrelated to the underlying UC. The clinical distinction between UC-associated dysplasia, especially the polypoid dysplastic lesions on the one hand, and sporadic adenomas on the other hand, is extremely important because the former occur as a result of UC, and their presence is an indication for colectomy because of higher association with cancer, whereas the treatment of sporadic adenomas is simple polypectomy. The differential diagnosis between these two types of neoplastic lesions which both can occur in UC is based upon a variety of clinical and pathologic features. Sporadic adenomas are more common in older patients, having no disease activity and a relatively short disease history. Histologically

there is often a mixture of normal and dysplastic crypts at the surface of the polyps in UC-associated polypoid dysplasia. The presence of stalk dysplasia, if the lesion is pedunculated and the presence of dysplasia in flat mucosa adjacent to a dysplastic polyp are more in favour of IBD-associated polypoid dysplasia as is inflammation of the lamina propria which is uncommon in sporadic adenomas (28,29,30). Pedunculated lesions found in a dysplasia-free surrounding mucosa should be handled as in non-colitic patients (30,31).

The differential diagnosis between polypoid IBD-associated dysplasia and inflammatory pseudopolyps or dysplasia in inflammatory pseudopolyps is another problem. In general, dysplasia in inflammatory polyps is rare. The major problem is that these polyps frequently contain areas of residual regeneration and it may be difficult to make a clear distinction between unequivocally neoplastic changes and regeneration. The presence of a mucosal defect (erosion or ulceration) close by can suggest regeneration. In cases of doubt, multiple biopsies from the lesion and the surrounding mucosa can help to solve the problem.

UC is characterized by frequent recurrences (32). A reduction in the amount of inflammation and restoration of the goblet cell population are observed during remission (33). So there are some features such as mucus depletion of epithelial cells which are associated with active and regenerating disease and with dysplasia. Given the recurrent nature of the disease, healing (both epithelial regeneration and connective tissue repair) is an essential component of IBD and reparative epithelial changes are common in active and resolving colitis. The differential diagnosis between reparative lesions and "genuine" dysplasia may thus be difficult. Whereas high-grade dysplasia can usually reliably be distinguished, the distinction between repair and low-grade dysplasia may present a serious problem. It is important to solve this properly given the clinical consequences. A better knowledge of the repair phenomena occurring in the intestine can be of great help. In the colon, as in other segments of the gastrointestinal tract, the repair of injured surfaces can occur rapidly and does not necessarily require increased proliferation. This process, sometimes called "restitution" involves active migration of cells from the crypts onto the surface. Migrating cells appear at first flattened, and subsequently increase in height from flattened to cuboidal to columnar. Absence of mucus and a low number of goblet cells are common as the cells are not yet fully differentiated and migration is accelerated (34,35). Promotion of cell migration occurs also in IBD, as illustrated by the reduced expression of e-cadherins, adhesion molecules involved in cell migration and polarity (36). The process can be regarded as an exaggeration of the normal migration.

More in general it appears that although the distinction between reparative phenomena and genuine dysplasia can be difficult in UC, usually the cytologic alterations due to reparative phenomena can be readily correlated with a marked increase in inflammatory cells such as neutrophils, lymphocytes and plasma cells. This may however be a problem when the patient receives active treatment. Some of the more recently developed treatment modalities may indeed decrease the inflammatory reaction before completion of reparative phenomena. This discrepancy can result in follow up biopsies showing little or no inflammatory activity and marked regeneration. The latter represents pseudodysplasia and should not be mistaken for dysplasia (37).

Ancillary techniques and the diagnosis of dysplasia in Ulcerative colitis

Because of the diagnostic problems, related with dysplasia other markers have been examined and tested for their possibility to improve the reliability of the diagnosis. These include carcinoembryonic antigen (CEA), changes in mucin pattern and proliferation markers such as proliferating nuclear antigen (PCNA), a nuclear protein involved in the regulation of the cell cycle and Ki-67. The value of staining for CEA seems limited. Using refined methods, eg detection of Sialosyl-Tn antigen, a shift in mucinous production has been demonstrated to precede the occurrence of dysplasia in ulcerative colitis by several years. This marker may become a valuable adjunct to dysplasia in identifying high-risk individuals but further prospective studies are needed to confirm the findings. Monoclonal antibodies against PCNA have been shown to be able to delineate dysplastic from non-dysplastic lesions in ulcerative colitis but the results are influenced by inflammation making the utility of the test in clinical practice uncertain (38-54).

Ancillary techniques can be very useful for the solution of differential diagnostic problems between "genuine" dysplasia and reparative phenomena. Yet, at present molecular techniques offer no alternative for the microscopic diagnosis of dysplasia. A search for genetic alterations in order to better define dysplasia can offer support for the diagnosis if positive, but a negative finding does not exclude the possibility of dysplasia. Furthermore the results obtained with ancillary techniques must be interpreted with caution. Absence or decrease of e-cadherin protein expression occurs in ulcerative colitis-associated CRC and in sporadic CRC. However it is not constantly present in all ulcerative colitis-associated cancers and has been observed also in benign ulcerative lesions in UC. Aneuploidy can be present before the appearance of dysplasia, but, as for dysplasia, its natural history is not known. I may however be a more objective marker than dysplasia. Dysplasia and the genetic defects associated with cancer development are different phenomena identified with entirely different techniques. Dysplasia is a complex phenomenon in the development of which multiple factors are being included. The search for the genetic defects using

additional techniques is usually limited to one specific marker. While a combination of routine morphology and new techniques for additional markers can help to identify dysplasia, the search for additional markers on itself can only support a diagnosis of dysplasia if positive, or help for the identification of a cancer risk in patients in whom routine morphology fails to detect dysplasia. How important the cancer risk is when aneuploidy is found or when p53 overexpression is detected remains however to be determined.

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