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Ulcerative Colitis and Colon Cancer: Biology and Surveillance

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Abstract The risk of colorectal carcinoma is increased among patients with longstanding ulcerative colitis and Crohn's disease. The development of cancer in inflammatory bowel disease is hypothesized to evolve by a multistep process involving genetic instability, clonal expansion and the development of a malignant phenotype. The contribution of nutritional factors such as folate deficiency is of great interest; molecular genetic mechanisms are under study. In contrast to sporadic colorectal carcinoma, carcinomas in ulcerative colitis are associated with a long prior history of chronic inflammation and the subsequent development of epithelial dysplasia. Dysplasia is defined as an unequivocal neoplastic alteration of the colonic mucosa. The object of surveillance is prevention of death from cancer by detection at a premalignant or early curable stage. Patients at greatest risk of cancer who customarily undergo endoscopic surveillance are those with extensive colitis of more than 8 years duration. Dysplastic epithelium may occur in flat mucosa, and may produce a plaque or a nodular/villiform appearance. Dysplasia is not present in all patients with cancer in colitis. It is important to develop more sensitive and specific markers for the presence of precancer or cancer in colitis. Under study are proliferation-associated markers detected by immunohistochemistry, lectin binding, flow cytometry and laser-induced fluorescence coupled with endoscopy.

Key words: clonal expansion, colorectal cancer, endoscopic surveillance, epithelial dysplasia, flow cytometry, intermediate biomarker, ulcerative colitis

The increased risk of cancer in chronic ulcerative colitis (UC) is related to the anatomical extent and the duration of the disease [1–5].

The cause of the increased incidence of colorectal cancer in chronic inflammatory bowel disease is unknown but may be associated with repeated episodes of chronic inflammation and repair of the colonic epithelium. Environmental, particularly nutritional, as well as genetic factors may also be important. A recent hypothesis suggests that nitrites formed by activated macrophages and neutrophils coupled with diminished bicarbonate production by impaired colonocytes facilitate the formation of carcinogenic N-nitroso compounds [6]. In patients with ulcerative colitis, epidemiologic studies have suggested an association between low folate status and an increased risk of colonic neoplasia [7]. Experimentally, folate deficiency enhances the development of colonic neoplasia in dimethylhydrazine (DMH)-treated rats through the formation of hypomethylated DNA which may be an early event in tumorigenesis [8]. However, recent studies have not shown cytosine hypomethylation in the decorin gene in chronic ulcerative colitis [9]. Decorin is a small proteoglycan involved in the regulatin of matrix formation and cell proliferation.

In contrast to sporadic colon carcinomas where 52% contained mutations in codon 12 of the c-Ki-*ras* protooncogene, only 4% of colitis associated carcinomas displayed this phenomenon in one study [10]. More recently, it was shown that 42% of sporadic colorectal carcinomas contained c-Ki-*ras*-codon 12 mutations in contrast to 24% (8/33) of ulcerative colitis carcinomas [11]. Interestingly, a significantly higher c-Ki-*ras* mutation rate was observed in rectal carcinomas (72%) in comparison to colonic carcinomas (28%) in control patients ($p<0.04$), while the opposite was observed in ulcerative colitis patients. The difference be-

tween the incidence of c-Ki-*ras* mutations in rectal carcinomas in UC (9%) and in sporadic rectal carcinomas (72%) was also significant ($p<0.01$). This lower prevalence rate and different site distribution of c-Ki-*ras* mutations in cancers associated with ulcerative colitis compared to sporadic carcinomas suggests that a different genetic pathway may be responsible [10]. Meltzer *et al.* [12] have also identified *ras* mutations in only 2/6 (33%) areas of high grade dysplasia in UC.

INCIDENCE AND RISK FACTORS

The cumulative risk of colorectal cancer varies considerably in various series. Study populations within a defined geographic area are more likely to yield a more accurate result. Recent reports give a cumulative incidence of 5%–10% at 20 years and 12%–20% at 30 years [4,13–17].

PATHOLOGIC FEATURES

Carcinoma complicating ulcerative colitis can assume a polypoid, nodular or plaquelike appearance. Flat, ulcerated tumors with poorly defined margins are common. Multicentricity is a common feature. Strictures, an uncommon complication of ulcerative colitis, may be associated with an infiltrating tumor.

PATHOGENESIS OF CANCER IN ULCERATIVE COLITIS

Dysplasia

In the non-colitis population most, if not all, adenocarcinomas arise from a pre-existing adenoma. Adenomas are characterized by a cytological change (dysplasia) and a proliferative change which results in a polypoid projection into the lumen. In chronic ulcerative colitis the mucosa undergoes analogous changes with development of cytological or architectural abnormalities although a surface projection is unusual. Dysplasia is defined as an unequivocal neoplastic alteration of the colonic epithelium and dysplastic epithelium not only may be a marker or precursor of carcinoma but may overlie an area of malignancy; this lesion has been called the dysplasia associated lesion or mass (DALM) [18–21].

Patient Management

The management possibilities for patients at high risk for colorectal cancer include prophylactic proctocolectomy, periodic endoscopic surveillance or routine clinical care [16,22].

The aim of the surveillance program in chronic ulcerative colitis is not to detect early cancer but to detect premalignancy at an early curable stage. Colonoscopy is used initially during the early years of the disease to determine the extent of colonic involvement; subsequently, surveillance colonoscopies are performed in those with 8–10 years of symptoms and extensive colitis (extending to at least the hepatic flexure). In those with left-sided colitis it is probably reasonable to begin surveillance after 15 years of the disease. Multiple biopsies are obtained at 10–12 cms throughout the colon including the cecum, ascending colon, hepatic flexure, sigmoid and rectum. Particular attention should be paid to areas of mucosal irregularity and plaque-like lesions which may represent macroscopic areas of dysplasia or overlie carcinomas.

In the absence of conclusive data and while waiting for better predictors of risk, the following approach to patient management is followed by many but not all clinicians and pathologists. If the biopsies are classified as negative or indefinite, continued surveillance at 1–2 year intervals is advised. If low grade dysplasia is found, follow-up in three to six months is strongly suggested. Colectomy is indicated (a) for a macroscopic lesion with overlying low grade dysplasia, (b) for low grade dysplasia in multiple foci, (c) possibly for persistent unifocal low grade dysplasia found on repeated examinations, or (d) high grade dysplasia. Expert pathological consultation is essential.

Clinical Interpretation

Skepticism exists in some centers about the benefits of surveillance in chronic ulcerative colitis [23–25]. This criticism maintains that surveillance is unlikely to be cost effective and that properly constructed randomized controlled studies have not proven its usefulness in reducing mortality from cancer. Nevertheless, in the largest British series, the authors considered that surveillance for carcinoma in

over 400 patients prevented the development of carcinoma in 12 patients and permitted the diagnosis of carcinoma at a curable stage in another 17 [16].

Dysplasia may not be present in all patients with cancer in colitis. In a retrospective study of resected colons, some patients with proximal carcinomas did not have rectal dysplasia and dysplasia was sometimes not present (27%) or was limited to the immediate vicinity of the carcinoma [26].

NEW BIOMARKERS

It is important to develop more sensitive and specific markers for the presence of precancer or cancer in colitis because our current methodology is too imprecise and costly. These include proliferation-associated markers detected by immunohistochemistry (bromodeoxyuridine and proliferating cell nuclear antigen [27]), lectin binding [28], molecular genetic probes [29] and flow cytometry [30–32]. At present the clinical usefulness of flow cytometry is still under study but areas of abnormal DNA content may carpet the cancer-prone colon and may overlap with dysplastic patches. Laser induced fluorescence coupled with endoscopy could facilitate the detection of areas of mucosal dysplasia [33].

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