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Endoscopic Appearance of Dysplasia and Cancer in Inflammatory Bowel Disease

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Dysplastic alteration of mucosa may occur in flat or raised mucosal lesions. Over 95% of dysplastic foci occur in flat mucosa. Flat dysplasia is occasionally visible macroscopically as areas of discolouration, velvety - villous appearance, or peculiar fine nodular thickening. The prevalence of macroscopically visible flat dysplasia is unknown. Raised dysplasia or DALM (dysplasia associated lesion or mass) occurs in less than 5% of patients with dysplasia. DALMs are polypoid structures of firm consistency, discoloured mucosa and irregular nodularity. DALMs cannot be distinguished endoscopically from early malignancy. The presence of DALMs has an ominous significance.

Key words: ulcerative colitis, dysplasia, flat dysplasia, raised dysplasia, DALM
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INTRODUCTION

THE FIRST association of ulcerative colitis (UC) and colorectal cancer was demonstrated by Crohn and Rosenberg in 1925 when they showed a rectal carcinoma complicating UC [1]. A few years later Bargen reported further cases [2]. In subsequent years, it was proved that colorectal cancer is a complication of UC. Neoplastic progression in UC is probably a multistep process that begins with inflammation, leading to dysplasia and culminating in carcinoma. Although no precise data are available, epithelial dysplasia would probably progress to cancer in 50–75% of patients with long-standing UC who develop this lesion and are not treated by colectomy. The risk increases with the duration and extent of the disease. Early studies tended to overestimate the degree of risk, with cumulative cancer rates of 16–43% [3, 4]. More recent studies are methodologically sounder and suggest that the cumulative cancer risk is approximately 7–14% at 20 years after the onset of the disease [5, 6]. Prophylactic colectomy was initially advocated for patients with pancolitis of 10 years duration because carcinomas were frequently inoperable at the time of diagnosis. However, most such patients were young and had quiescent disease. Hence, this recommendation was not widely accepted. In contrast to UC, the association of cancer with Crohn's disease was not thought to be significant until lately. Since the first description of colon cancer arising in a patient with Crohn's colitis in 1948 [7], approximately 150 patients have been described with this association. A recent article found the cancer risk to be equal in Crohn's colitis and UC of similar extent and duration [8]. Surveillance has been advocated by some authors, along the lines of UC.

In the late 1950s interest was focused on precarcinomatous changes or dysplasia in the epithelium of the large bowel, as a histological marker for increased cancer risk, and thus as a potential indicator for colectomy in patients with UC. Flat dysplasia was first postulated to be a precursor of carcinoma in UC by Warren and Sommers [9]. However, it was not until 1967 that Morson and Pang demonstrated that flat dysplasia is often widespread, and can be detected on biopsy, thereby identifying patients who are likely either to have or to develop carcinoma [10]. Based on this landmark observation, many surveillance programmes were initiated. The results of many prospective studies have been published [11–13] and critically reviewed [14–16]. However, this article is not intended to cover the pros and cons of such surveillance programmes. Suffice to say that the policy of surveillance is undergoing careful scrutiny at present, and many more answers will be needed before its cost-effectiveness is established. Currently, it is recommended to start surveillance in patients with pancolitis of 8–10 years duration.

In 1959, Dawson and Pryse-Davies described polypoid lesions in 9 of 17 operation or autopsy specimens with a carcinoma complicating ulcerative colitis [17]. Morson and Pang also recognised [10] and illustrated precancerous polypoid changes in operative specimens. They commented that these polyps tended to be few in number compared with inflammatory polyps, were usually sessile and covered a relatively large field of mucosa, and commonly had a papillary or villous configuration. Since then, the endoscopic appearances of dysplastic lesions and cancer complicating UC have been described in many studies [18–20], and the term DALM (dysplasia associated lesion or mass) has been coined. It is very important for the endoscopist to be familiar with the recognition and management of such lesions.

This article will only discuss the endoscopic appearances of dysplasia and carcinoma complicating inflammatory bowel disease. Macroscopically detectable dysplastic changes may occur either in flat mucosa or in raised lesions (Table 1).

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Table 1. Endoscopic appearance of dysplasia in ulcerative colitis

I. Flat dysplasia
  A. Endoscopically undetectable alterations
    ? Magnification endoscopy
    ? Chromoscopy
    ? Endoscopic ultrasonography
    ? Autofluorescence tissue spectroscopy
  B. Suspicious endoscopically visible alterations
    Discolouration
    Velvety appearance
    Irregular nodularity—wart-like thickening

II. Raised dysplasia
  A. Plaque-like dysplasia
  B. Polypoid excrescences

FLAT DYSPLASIA IN ULCERATIVE COLITIS

Dysplasia is defined as an unequivocal neoplastic transformation of the epithelium. The nomenclature and grading of dysplasia was standardised in 1983 [21]. Dysplasia is found in approximately 20% of UC patients undergoing surveillance. Approximately 15–18% of patients with dysplasia will develop cancer. The propensity for development of cancer increases with the grade of dysplasia. Low grade dysplasia can be detected in up to 17% of patients during surveillance colonoscopy. The prevalence of high grade dysplasia is approximately 5%. Although dysplasia may be associated with endoscopically visible mucosal alterations, the majority of dysplastic foci have been detected following random biopsy at regular intervals along the entire length of colon. Raised dysplasia has been documented in <5% of patients with dysplasia. Thus >95% of patients with dysplasia have flat dysplasia on colonoscopy. It should be stressed that colonoscopy should preferably be performed during quiescence, as during the acute attack, it is very difficult to differentiate dysplastic lesions from inflammatory lesions. Dysplasia can be localised or widespread. The entire colon should, therefore, be carefully inspected.

Endoscopic appearance

It is important to recognise that flat dysplasia most often occurs in colonoscopically non-suspicious appearing mucosa. Dysplasia is usually not found in almost normal looking shiny mucosa with a highly visible, only slightly distorted, vascular pattern. Whenever macroscopically detectable, the mucosal alterations are subtle and easily overlooked. Suspicious mucosal changes may take the form of mild discolouration, velvety or villous alteration of the relief, and irregular fine or coarse nodularity. The mucosa may appear mildy thickened upon careful inspection. These mucosal abnormalities often appear as patches of varying sizes and irregular boundaries. Perhaps the commonest macroscopic change in flat dysplasia is a somewhat thickened mucosa with a finely nodular or velvety surface configuration.

Problems and pitfalls

Meticulous cleaning and absence of iron staining of the mucosa are essential for proper inspection of the mucosa. Despite careful scrutiny, dysplastic areas can be missed. Dysplastic areas detected during one colonoscopy may not be found during a follow-up colonoscopy. The suspicious mucosal alterations have never been properly validated with respect to their usefulness. Moreover, it is not known to what extent flat dysplastic changes are unequivocally detectable at endoscopy. The available literature does not allow a reasonable estimate. Failure of a biopsy from one wall to show dysplasia, does not guarantee that dysplasia is absent from the opposite wall at the same site in the colon. In short, the procedure requires a dedicated endoscopist and a dedicated pathologist who are ready to accept failure. Much has been written about low grade dysplasia and interobserver interpretative variation. The interpretation has become more uniform after the introduction of the classification in 1983 [21]. Connell and associates [22] studied the effect of introducing the inflammatory bowel disease Dysplasia Morphology Study Group (IBD–DMSG) modifications. As a result of blinded review using modified criteria, the number of biopsy sets considered indicative of definite dysplasia was reduced by 69%. Thus, the diagnosis of dysplasia has been made more stringent.

RAISED DYSPLASIA IN ULCERATIVE COLITIS

Blackstone and associates [18] found 12 patients with macroscopically raised dyplastic lesions in a 4 year follow-up study of 112 patients. Of the 12, 2 had severe, 5 mild, and 5 moderate dysplasia. 7 of 12 patients with DALM had a carcinoma. They also found 27 instances of flat dysplasia. Of the 12 patients, 5 had single polypoid lesions, 5 multiple polypoid lesions, and 2 had plaque-like lesions. These polypoid lesions were called dysplasia associated lesion or mass (DALM), a terminology which is still in use.

Rosenstock and associates [19] reported results of 248 UC patients. They stressed that DALM was the most consistent indicator of cancer. Of their 7 patients with cancer, 5 had DALM. Of the 17 patients operated on because of a mass lesion at colonoscopy, 13 had DALM. Of these 13, 6 had high grade dysplasia and 2 low grade.

In Lennard-Jones' study of 401 patients, 12 patients had high grade dysplasia. 6 had an associated endoscopic lesion. In 5 of the 6 patients found to have cancer, a raised lesion was noted on endoscopy [11].

In a recent article, 10 prospective surveillance studies were analysed [14]. DALM was found in 40 patients out of 1225 studied. This gives a prevalence of 3.2%. Of those 40, 17 (43%) already had cancer at colectomy. During follow-up, low grade dysplasia was found in 210 (17%) patients while high grade dysplasia was found in 47 of 1104 patients (4.3%).

It should be realised, however, that dysplasia is not universally present in colitic cancer. In a blinded study of colectomy specimens, only 73% of the specimens with UC and cancer had dysplasia at a site distant from the cancer, and distant high grade dysplasia was only seen in 50% [23]. Thus, approximately a quarter of the cancers occur with associated dysplasia.

Endoscopic appearance of raised dysplasia

According to Blackstone and associates [18], DALM can present with the following appearances: a single discrete polypoidal or nodular mass; a discrete plaque-like lesion in which abnormal looking mucosa appears as a raised irregular or nodular area extending over a finite distance; a conglomerate of sessile polyps of variable size appearing in a finite segment of colon. The polypoid lesions are usually sessile, cover a relatively large field of mucosa and commonly have a villous or papillary surface configuration. Another distinctive feature of such polypoid lesions is the presence of an obvious inflammatory component, which is in continuity with the inflammation in the surrounding mucosa.

In a retrospective study [20], the St. Mark's group, London,

U.K., studied colectomy specimens of four groups of patients. Of the specimens, 34 had colitis with cancer, 28 had only flat dysplasia, 32 had ulcerative colitis without dysplasia or cancer, and 77 had cancer without ulcerative colitis. In the 34 specimens with UC-associated malignancy, there were 52 cancers, and 64 dysplastic lesions without cancer. Of the latter, 18 lesions were polypoid, and 47 were elevated. Of the 28 UC specimens with flat dysplasia, 20 contained 40 polypoid or elevated dysplastic lesions. Thus, it can be safely deduced that in long-standing UC, flat dysplasia, raised dysplasia, and cancer often co-exist together. Furthermore, not all raised dysplastic lesions have cancer and a large number of them have dysplasia only.

Problems and pitfalls

The presence of inflammatory polyps or adenomatous polyps is obviously a major confounding factor. Inflammatory pseudopolyps can acquire a size of up to 2 cm, and it may be impossible to differentiate them from DALMs on the basis of their appearance alone. A biopsy showing dysplasia is the only definite proof. In contrast, the usual appearance of the small filiform pseudopolyps is quite distinctive. Adenomatous polyps cannot be differentiated from dysplasia. The IBD–DMSG [21] suggested that in a younger patient (<40 years), the presence of a polyp should be taken as a part of the IBD spectrum, while in older patients, a polyp should be seen as a separate pathology.

Early carcinoma can be grossly indistinguishable from raised dysplasia alone based on endoscopy. The St. Mark's group [20] attempted to differentiate cancer from dysplastic lesions based on appearance. They found that the mean diameter of the polypoid cancer was 4.8 ± 0.4 cm and of the dysplastic lesion 1.4 ± 0.2 cm. Of the patients with DALM, 80% had high grade dysplasia and the rest low grade. In the absence of any endoscopic abnormality, suspicious enough to alert the endoscopist to target his biopsy specimens, it is usually advisable to sample mucosa randomly at 10 cm intervals. However, pinch biopsies sample only a small area. Moreover, there are problems with proper orientation of the specimens. Even if multiple biopsies are taken at 10 cm intervals, 0.05% of the entire area of the colon is sampled [19]. The site of each biopsy sample should be carefully recorded and separate bottles should be used for each sample.

COLORECTAL CANCER COMPLICATING ULCERATIVE COLITIS

The basic growth pattern of cancer in UC tends to be infiltrative, complicating accurate endoscopic diagnosis. The typical apple-core neoplasm seen in non-colitic mucosa may occur, but is uncommon. Synchronous colorectal neoplasms are noted in 12–28% of tumours in UC [24]. In contrast, multicentricity is seen in only 3% of cancers in the non-colitic populations [24].

An early carcinoma may present with several morphological appearances, as described by Riddell [25], such as a polypoidal mass that may cover a large area of mucosa; a flat, plaque-like lesion several centimetres in diameter; a small nodular or polypoid lesion; a verrucous excrescence associated with a conglomerate of polyps. The frequency of strictures in UC varies between 3 and 10% [26, 27]. Malignant strictures constitute 12–29% of all strictures in UC [28, 29]. In one study of a total of 70 strictures, 61% of strictures occurring after 20 years duration of the disease were malignant. One-third of 17 malignant strictures were proximal to the splenic flexure, and 41% presented with complete or partial large bowel obstruction [29]. Benign and malignant strictures may be difficult to differentiate. Endoscopically, malignancy may be suggested by an abrupt luminal narrowing. The stricture mouth may not be typically ulcerated, but may be nodular and friable, and have a firm consistency on biopsy. Multiple biopsies should be taken.

Problems and pitfalls

Repeated episodes of inflammation and mucosal regeneration may produce a wide variety of nodular deformity with irregular tissue excrescences which may complicate accurate recognition of pathology. Giant inflammatory polyps may be mistaken for a polypoid carcinoma and may be large enough to encroach on the lumen. Macroscopically benign post inflammatory changes, adenomas, dysplasia and cancer may all be indistinguishable. As discussed in the section on raised dysplasia, adenomatous polyp may confound the endoscopist, and multiple biopsies or snare excision with multiple biopsies of the surrounding mucosa are usually required to provide the correct interpretation.

DYSPLASIA, COLORECTAL CANCER IN CROHN'S DISEASE

There have been several reports associating colorectal cancer with long-standing Crohn's disease of the large intestine [30–32]. In a recent study from Birmingham, cancer risk was compared in two cohorts of patients with extensive UC and equally extensive colonic Crohn's disease. The relative risk and the absolute 20 year cumulative incidences of cancer were the same in both cohorts [8].

The association of dysplasia with Crohn's disease has been studied by several investigators. Richard and associates [33] found areas of high grade dysplasia adjacent to cancer in all 5 patients with colonic Crohn's disease and colorectal cancer. Hamilton [34] found contiguous high grade dysplasia in all 10 resected specimens with Crohn's disease and cancer. Moreover, these authors found evidence of dysplasia at a distance from the cancer in 7 of 10 patients. In a study from the Cleveland clinic, U.S.A. [35], dysplasia was seen adjacent to cancer in 6 of 7 patients, and at a distance from the tumour in 4 of 7 patients with colonic Crohn's disease and cancer. However, the authors found dysplasia in Crohn's disease to be less extensive than that in UC, and questioned the validity of dysplasia as a useful marker for surveillance studies.

Not all studies point to increased colorectal cancer in Crohn's disease. Of 1251 Crohn's disease patients diagnosed from 1955 to 1984, 69 malignancies occurred among 67 individuals as compared with 59.8 expected cancers, which led to the conclusion that the occurrence of colorectal cancer was not increased [36]. Finally, in a review of Crohn's disease not complicated by carcinoma, Warren and Barwick [37] reported a prevalence of 2% for focal mild dysplasia.

Thus, it appears that patients with Crohn's disease of the colon may have a higher risk of developing colorectal cancer. The development of cancer probably follows the dysplasia cancer sequence as seen in UC. Current experience points towards a possible benefit of surveillance in a carefully selected subgroup of CD patients. To identify this subset of patients who are at higher risk and who may benefit from surveillance remains a challenge. Cost–benefit studies will be needed before a final conclusion is reached.

DISCUSSION

Dysplasia in IBD is considered to be a genuine precursor lesion to cancer. In the colitic mucosa, there may be a spectrum of changes from quiescent mucosa to frank carcinoma. Standard-

ised definitions have helped reduce interobserver variation in the interpretation and reporting of pathology. The growth pattern of neoplastic lesions tends to be intramural and infiltrating, and some lesions may be mimicked by benign colitic changes, making detection difficult. The large variety of mucosal changes occurring with cycles of inflammation and regeneration may further contribute to diagnostic confusion. Dysplastic alterations of the mucosa are usually macroscopically undetectable. Only occasionally are dysplastic alterations endoscopically visible as flat dysplastic lesions (discolourations, irregular nodularity) or raised dysplastic lesions called DALM. Careful examination of well prepared mucosa and noting subtle differences is necessary. Multiple biopsies of suspicious lesions and surrounding mucosa increase the possibility of accurate diagnosis. There may be a role for dye staining to accentuate mucosal differences, examination under endoscopic magnification or endoscopic ultrasound probes to enhance detection and evaluation of suspicious lesions.

To enhance the visualisation of mucosa, supravital dye staining may be attempted, perhaps coupled with endoscopes that can magnify the mucosa up to 40 times [38]. A recent study from Sweden utilised scanning immersion electronic video endoscopy to visualise the epithelial surface of the colon [39]. Endoscopic ultrasonography, whether by an ultrasound probe that may be passed down the biopsy channel of a conventional endoscope or by dedicated echocolonoscope, may perhaps aid in the evaluation of submucosal changes [40]. Autofluorescence tissue spectroscopy may prove to be valuable for detection of dysplasia [41]. The role of this modality is presently exploratory.

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