The histological diagnosis of dysplastic and neoplastic lesions in inflammatory bowel disease: a pathological perspective

Patients with inflammatory bowel disease (IBD), both ulcerative colitis (UC) and Crohn’s disease (CD), are at an increased risk for developing colorectal carcinoma (CRC). The accurate diagnosis of dysplasia in biopsies taken during periodic surveillance of long-standing IBD patients is most important in prevention of UC and CD related cancer. Distinction of low from high grade IBD-related dysplasia and differential diagnosis between IBD-related dysplasia and dysplasia in sporadic adenoma as well as distinction from pseudodysplastic lesions in inflammatory pseudopolyps or reparative lesions is often very subtle and difficult and demands expertise of second experienced gastrointestinal pathologist. Although surveillance colonoscopy with multiple biopsies does not reduce the cancer mortality, it offers a reasonable chance of detecting pre cancer and performed prophylactic colectomy. Novel methods of detecting dysplasia are continuously being evaluated, including chromoscopy and molecular biology markers. In the future, one may expect, from these new markers to detect the dysplasia in IBD patients before development of histological evidence of neoplastic changes.

Key words: inflammatory bowel disease, ulcerative colitis, Crohn’s disease, colorectal carcinoma

INTRODUCTION

Crohn’s disease (CD) and ulcerative colitis (UC) are two distinct but similar diseases, marked by chronic and relapsing inflammation of the gastrointestinal tract. It is well known that both, CD and UC are associated with an increased risk for developing colorectal cancer and precancerous dysplastic epithelial lesions, but still remains controversial the magnitude of this risk. The first case of UC associated with colorectal cancer (CRC) described Crohn and Rosenberg in 1925. Carcinoma occurring in association with CD was described in 1948. Although there are no large controlled trials that definitively prove a benefit for surveillance colonoscopy, it is widely used and recommended by the American Gastroenterological Association (AGA), the American College of Gastroenterology (ACG), the American Society for Gastrointestinal Endoscopy (ASGE) and British Society of Gastroenterology (BSG). The primary aim of those surveillance programmes has been to reduce the overall mortality rate due to CRC in patients with inflammatory bowel disease (IBD). This is based on the finding that pre cancerous lesions, called dysplasia, can be identified in biopsies. There is general consensus that low-grade dysplasia (LGD) warrants long-term colonoscopic surveillance whereas the high-grade dysplasia (HGD) is best controlled by prophylactic proctocolectomy. Despite the existence of guidelines for the diagnosis and grading of UC-related dysplasia, considerable interobserver variability can demonstrate in the evaluation of both these morphological categories. The optimal surveillance system remains controversial. The debate revolves around sensitivity of the detection system, the predictive value of dysplasia for assessing the risk of CRC, and in the most of country about the cost. Due to limitations of surveillance strategies based upon the detection of dysplasia, newer techniques involving the detection of alterations in mucosal antigens and genetic abnormalities are being investigated.

EPIDEMIOLOGY OF DYSPLASIA AND COLORECTAL CANCER IN IBD

Several factors have been suggested to be associated with increased risk of CRC in patients with IBD, both UC and CD. The extent of the disease is an important risk factor in most studies. The risk of colorectal cancer increases in patients with left sided colitis after 15 to 20 years duration, approximately one decade later than in patients with pancolitis. In the later, the magnitude of risk is 20-fold that in general population. Patients with ulcerat-
tive proctitis and proctosigmoiditis are probably not at increased risk for CRC. A recent meta-analysis of 116 studies by Eaden et al. showed that the prevalence of CRC in patients with UC is approximately 3.7%, which increases to 5.4% for those with pancolitis. The approximate cumulative incidence of CRC increased with duration of the disease from 2% after 10 years of disease, 5-10% after 20 years, to 12-20% cancer incidence after 30 years of disease. The development of CRC accounts for one third of deaths related to UC. The magnitude of risk varied from 3-fold to 30-fold the risk of the general population and increases approximately from 1-2% per year after the first ten years of disease. The risk was increased in those with onset of symptoms prior to age 15, but the other reports didn't confirm this finding after adjusting for the longer period of time that young patients were at risk and the extent of the disease.

Increasing data demonstrate a similar risk for CRC in CD and UC. In population based study from Sweden, the relative risk of colon cancer was 2.5 overall in patients with CD and 5.6 in those with disease restricted to the colon. Despite the increased risk of CRC in CD, the absolute number of patients at risk is relatively small. Many of these patients undergo colectomy early in the course of disease. Patients have increased risk of small intestinal cancer, 50 to 100-fold greater then in general population.

An increased risk of CRC has been found in UC patients with primary sclerosing cholangitis, probably in relation to role of bile acids in colorectal carcinogenesis.

In a cohort study with 590 UC patients undergoing surveillance program, those with pancolitis and "backwash" ileitis were up to 19 times more likely to develop colon cancer than patient without "backwash" ileitis and patients with left-sided colitis only.

It is widely accepted that CRC in IBD progresses through a step-wise process from inflammation to dysplasia and carcinoma. Dysplasia was defined by an international Inflammatory Bowel Disease Dysplasia Morphology Study Group as "unequivocal, non-invasive, neoplastic transformation of the epithelium excluding all reactive changes." Most studies support the dysplasia-carcinoma sequence in CD. The reported frequency of dysplasia in CD patients with colorectal carcinoma ranges from 40-100%. In contrast, dysplasia is present in only 2% of colectomy specimens from patients with CD without colorectal carcinoma. The incidence of dysplasia in UC is difficult to estimate. Most studies found 5% of dysplasia incidence after 10 years duration of UC and 25% incidence after 20 years of disease.

**PATHOHOISTOLOGICAL FEATURES OF DYSPLASIA IN IBD**

Morson and Pang described in 1976 flat dysplasia in colon of patients with long-standing UC and Craft et al in 1981 described dysplasia in colon mucosa in CD patient. Dysplastic areas are often difficult to recognize on endoscopy. Grossly, there are two general patterns: flat and...
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in the right colon in patients with ulcerative proctitis is not a DALM). If a DALM is pedunculated, one should make a biopsy around the base of pedunculated lesion. If these biopsies show a dysplasia, this suggests that the lesion is not a sporadic adenoma. In addition, mucosa of the stalk and mucosa away from the "adenoma" usually lack dysplasia in sporadic adenoma, but not in colitis associated DALM. Polypoid dysplastic lesions have higher degree of inflammation within the lamina propria and usually show a mixture of normal and dysplastic crypts at the surface of the polyp.

Riddell and Goldman proposed at 1983 classification of dysplasia as negative, indefinite for dysplasia and positive (Table 1). They subdivide category indefinite for dysplasia into three groups: probably positive, probably negative and unknown. The category indefinite dysplasia is the consequence of limitations of routine histological techniques. There is a problem of subjectivity and reproducibility of this subclassification. In the most commonly used classification, proposed by the International Study Group, there are two histological grades of dysplasia: low and high, always determined by the features of the most dysplastic area. The morphologic criteria for dysplasia reviewed by Riddell et al. are based on combination of microscopic features including:

- Architectural alterations, often resembling the glandular arrangement of adenomas and
- Cytological abnormalities, e.g. cellular and nuclear pleomorphism, nuclear hyperchromasia, loss of nuclear polarity and marked stratification of nuclei (Figure 2).

Some of the problems encountered in the evaluation of dysplasia include sampling error and interobserver variability in interpretation of dysplastic features. Areas of controversy are difficulty to distinguish dysplasia from reactive and regenerative changes on histological sections, lesions indefinite for dysplasia, probably positive, as well as lesions indefinite of dysplasia, unknown. In general, interobserver agreement is better for HGD (Figure 3), and distinction between LGD and repair may be a serious problem. These interpretations require a familiarity with the spectrum of reactive and neoplastic changes that may be encountered in IBD. The presence of dysplasia should be confirmed by an experienced gastrointestinal pathologist. Histological features of dysplasia in comparison with repair are showed at the Table 2. It is accepted that dysplastic features have to be present at least in 3-4 crypts. In addition of the shapes of the dysplastic cells (high columnar and crowded) and mucus depletion, the paucity of inflammation orients to dysplastic changes. If one dysplastic lesion is villous, there is a tendency toward a tall, slim villous instead of broad and leaf-like. The general recommendation is to make biopsy during the remission of UC to eliminate the difficulty of differentiating reactive change from dysplasia on endoscopic biopsy.

Dysplasia in inflammatory polyps is rare. They begin as pseudopolyps- mucosal islands in area of the ulceration. With regeneration of mucosa across the ulcers, the islands of original mucosa protrude above the regenerated mucosa in form of inflammatory polyps. The major problem is that these polyps may contain areas of residual regeneration and it may be difficult to make a clear distinction between unequivocally neoplastic changes and regeneration (Figure 4).

Post inflammatory (filiform) polyps are finger-like projections of submucosa covered by mucosa on all sides reflecting healing of undetermined mucosal and submucosal remnants and ulcers.

Giant polyps are extremely large inflammatory polyps that are segmental and circumferential, and involve a short segment of colon. They may mimic neoplasm on barium enema.

NEW MARKERS

Due to difficulty in establish diagnosis of dysplasia in IBD patients some new markers has been investigated. Odze has been shown that IBD-associated polyposal dysplasia express a different pattern of genotypic abnormali-
ties, including p53, beta catenin, Adenoma Polyposis Coli (APC) gene, compared to sporadic adenomas, and they may be useful markers for distinguish these lesions.

Loss of p53 function occurs early in the pathways of progression toward dysplasia and cancer in UC patients and it is not the final step as in sporadic CRC. A recent study of adenoma-like polyoid dysplastic lesions by Odze et al supports the concept that these lesions have a different molecular genotype than non-adenoma-like DALMs. It has been shown that adenoma-like dysplastic polyoid lesions in UC regardless of their location (within or outside to area of UC) showed similar prevalence of 3p, APC and p16 mutations as sporadic adenomas. However, non adenoma-like DALM from UC patients showed a significantly higher prevalence of p16 and p3 mutations indicating a different timing of molecular events in these lesions. Odze found that adenoma-like polyoid dysplastic lesions in UC and sporadic adenoma represent the same pathobiological entity.

Beta catenin is a cell membrane protein that accumulates more frequently in nuclei of cells within sporadic colon cancer compared to DALM. In comparison, mutations of p53 gene are more frequently in DALM than in sporadic adenomas. Both, p53 protein expression and nuclear accumulation of beta catenin can be useful for correct diagnosis. Recently, Ezaki et al identified high frequency of loss of heterozygosity (LOH) on chromosome 6 in UC associated CRC and dysplasia. There was no LOH in this region in sporadic CRC as well as in inflamed mucosa of longstanding and extensive UC without cancer. Sialosyl-Tn is a mucin-associated carbohydrate antigen that may precede the development of dysplasia and CRC by several years and may be useful in surveillance of UC patients. DNA content is detectable earlier than histological signs of premalignancy. Detection of DNA aneuploidy by flow cytometry of mucosal specimens in UC may be more objective than dysplasia. However, the predictive value of aneuploidy is uncertain. Carcinoma can arise without preexisting aneuploidy, as well as aneuploidy may exist many years without progression to malignancy. Wang et al found that restriction of Ki67 staining to the basal third of the crypt appears to exclude a diagnosis of dysplasia whereas strong intensity p53 staining suggests a diagnosis of dysplasia. Restriction of Ki67 or p53 staining to the basal two-thirds of the crypt appears to exclude a diagnosis of HGD.

However, at this time, assessment of cancer risk in UC by histochometical (mucin), immunohistochemical (Sialosyl-Tn, p53 protein, Ki 67 for assessment of proliferative activity) or molecular methods (K-ras, APC, p16, aneuploidy) have not been shown to be more effective than histological evaluation of dysplasia.

Clinicopathological and molecular characteristics of IBD associated colorectal carcinoma

Development of carcinoma in IBD appears to progress through dysplasia-carcinoma sequence that involves the same protooncogenes and tumor suppressor genes present in the sporadic and familial CRC. Colorectal carcinoma

<table>
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<th>TABLE 1</th>
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<tr>
<td>CLASSIFICATION OF UC ASSOCIATED DYSPLASIA</td>
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<tr>
<td><strong>Negative for dysplasia</strong></td>
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<tr>
<td>probably negative</td>
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<tr>
<td>unknown</td>
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<tr>
<td><strong>Positive for dysplasia</strong></td>
</tr>
<tr>
<td>low grade</td>
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<td>high grade</td>
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<th>TABLE 2</th>
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<tr>
<td>HISTOLOGICAL FEATURES OF UC ASSOCIATED DYSPLASIA AND REPAIR LESIONS*</td>
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<td>Histological features</td>
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<tr>
<td>Distortion of mucosal architecture</td>
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<tr>
<td>Villous configuration</td>
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<tr>
<td>Crypt and surface dysplastic change</td>
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<tr>
<td>Maturation toward crypt surface</td>
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<tr>
<td>Back to back glandular formation</td>
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<tr>
<td>Increased epithelial proliferation and mitoses</td>
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<tr>
<td>Nuclear nuclear/cytoplasmic ratio</td>
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<td>Nuclear pleomorphism</td>
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<tr>
<td>Nuclear hyperchromatism</td>
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<tr>
<td>Irregular nuclear contour</td>
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<td>Prominent nucleoli</td>
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<tr>
<td>Loss of nuclear polarity</td>
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<tr>
<td>Inflammatory milieu</td>
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<tr>
<td>Decreased intracellular mucin</td>
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<td>Cytoplasmic eosinophilia</td>
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* Petras RE et al31 modified by Usaj S et al

genesis is multistep process involving genomic instability and progressive accumulation of genetic alterations, similar to that seen in sporadic CRC.

However, there are several lines of evidence suggesting that pathobiology of IBD associated colon cancer are different from pathobiology of sporadic CRC:

The mean age of patients with IBD associated colon cancer is about 10 years lower than in sporadic carcinoma (between 40 and 50 years).
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**PATHOLOGY OF IBD ASSOCIATED CANCER**

Colorectal carcinoma in IBD arises as polyoid, nodular, ulcerated or plaque-like lesion. Most lesions are adenocarcinomas. Poorly differentiated, anaplastic and mucinous carcinomas are more common in UC associated carcinoma than in sporadic carcinoma

Most UC associated carcinomas are located in the rectum and sigmoid colon whereas CD associated tumors are evenly distributed between the right colon and rectosigmoid. In colitis associated carcinoma synchronous tumors are much more common (in 10-20%) than in sporadic carcinoma of the colon. Patients with CD are at an increased risk for the development of perianal squamous carcinoma and for small intestinal carcinoma. Both, UC and CD appear more than usually susceptible to malignant lymphoma.

**SURVEILLANCE STRATEGY IN IBD**

The identification of well-established risk factors for the development of CRC in IBD has lead to the widely adopted practice of surveillance colonoscopy and biopsy in IBD patients with extensive colitis lasting longer than 8-10 years. The goal of surveillance is to identify dysplasia in IBD patients before cancer develops with expecting that the removal of dysplastic lesions will prevent the appearance of cancer.

The optimal surveillance strategy is controversial. There is no consensus regarding the sensitivity of the detection system, the predictive value of dysplasia for assessing the risk of CRC and the cost benefit.

Periodic colonoscopy should begin 8 to 10 years after the onset of disease for extensive colitis and 15 to 20 years for left sided disease. In the second decade, colonoscopy should be performed every three years, in third decade every two years, and yearly in the fourth decade. Patients who had undergone surveillance had earlier stage carcinomas and significantly longer five-year survival in comparison with control group (77% vs. 36%).

Data supporting the effectiveness of surveillance of dysplasia in patients with IBD are not uniform, but suggest a reduction in mortality from CRC in those patients undergoing surveillance and prophylactic colectomy.

In patients with left-sided disease, colonoscopy should be performed every 5 years.

The efficacy of any surveillance strategy depends on the 1. method of surveillance, 2. the frequency of surveillance, 3. the number of biopsy specimens taken. Recently it has been introduced a novel colonoscopy method - High-magnification-photomicroscopic-colonoscopy (HMCC) which permits the differentiation of neoplastic from non-neoplastic tissue by colonoscopy. During colonoscopy the gastroenterologist have to perform full inspection of entire colon mucosa with representative number of biopsy samples. There is no consensus regarding the optimal
number of biopsies. Surveillance biopsies cannot take only from visible lesions because dysplasia and early carcinoma are frequently found in flat mucosa and may be unrecognizable on colonoscopy. It would seem likely that the more biopsies, the higher likelihood of finding dysplasia and carcinoma. It was found that a total of 33 and 56 biopsy specimens were required for 90% and 95% confidence to detect the dysplasia. In the current practice two common ways of biopsies are followed; 4 quadrant biopsies from every 10 cm segment of colon and every 5 cm of rectum or 8 biopsies from each 4 segment of colorectum (32 total biopsies). Particular attention require a DALK as this type of lesions may be associated with dysplasia or carcinoma. Extra specimens should be taken from any irregular plaques, unusual ulcers, or strictures.

Current concept of surveillance practice is different in different American and European gastrointestinal societies. These recommendations are differ from each other, regarding beginning of the surveillance, frequency of colonoscopy and treatment of low-grade dysplasia.

Total proctocolectomy should be consider in patients with UC in whom there is: (1) HGD found without a mass lesion (flat lesions), (2) LGD or HGD associated with gross lesion, (3) dysplasia proven by biopsy in multiple different sites, (4) adenocarcinoma or (5) LGD found on several consecutive examinations. In all cases, dysplasia should be confirmed by second experienced pathologist who is familiar with this pathology.

The approach to the patients with DALK has begun to change. Rubin et al. and Engelsfeild indicate that adenoma-like DALK observed in colorectal mucosa of IBD patients without any flat dysplasia in colonic mucosa can be treated by colonoscopic resection just as like sporadic adenoma. In those two studies, the mean follow-up of duration was 4.1 and 3.6 years respectively. In no one patient, CRC developed during the study period.

Most patients with flat low-grade dysplasia are treated with increases surveillance. However, recent data showed that five-year predictive value of low-grade dysplasia for the development of HGD or cancer might be 54%-58%. Many gastroenterologists now recommended colectomy for patients with LGD. Patients with flat HGD are generally treated with colectomy, because they have higher probability of coexistent cancer at the time of colectomy.

Surveillance of patients with CD until now is controversial. No standard practice has been established despite the increased cancer risk in these patients. AGA recommends the same surveillance strategy as for UC. In contrast, ACG found insufficient evidence to provide guidelines for surveillance. The ASGE suggests the surveillance colonoscopy and biopsy in CD patients with long standing disease. The BSG suggests that recommendations for UC surveillance should also be apply to CD patients.

CONCLUSION

It is generally accepted that IBD-related dysplasia is premalignant condition but the likelihood of progression to cancer is difficult to predict. Although a reduction in mortality due to surveillance has not been established, there is consensus that patients with long standing UC should undergo surveillance colonoscopy with multiple biopsies. This offers a reasonable chance for detecting precancerous condition or symptomless cancer. In the future one may expect progress in molecular pathology and development of new techniques that will be able to detect neoplastic changes before their histological progression.

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