Natural history of low grade dysplasia in patients with primary sclerosing cholangitis and ulcerative colitis☆☆☆

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Flat dysplasia; Low grade dysplasia; Ulcerative colitis; Primary sclerosing cholangitis

Abstract

Background and Aim: Patients with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) are at increased risk of colon cancer. The aim of this study was to determine the natural history of LGD and its progression to high grade dysplasia (HGD) or colorectal cancer (CRC) in PSC–UC patients.

Methods: Ten PSC–UC patients with LGD who underwent surveillance colonoscopy from 1996 to 2011 were evaluated. Raised dysplasia was defined as a discrete raised lesion located in an area involved by either quiescent or active colitis that was endoscopically resected, while flat dysplasia was defined as the absence of documentation of a raised lesion.

Results: Of the 10 patients with LGD, 3 (30%) progressed to raised HGD over a mean follow-up of 13±11 months. Three of 10 patients had initial raised LGD while 7 had flat LGD. The location of HGD was in the proximal colon in all 3 patients. However, all 3 patients who progressed to HGD had initial dysplasia located in the distal colon and had flat morphology. The incidence rate for detection of HGD/CRC was 9.4 cases per 100 person years at risk. Patients with LGD with flat morphology had an incidence rate of 17.8 cases per 100 person years at risk. HGD occurred more frequently within the first year of initial detection of LGD (23.5 per 100 patient years of follow-up).

Abbreviations: ACG, American College of Gastroenterology; 5-ASA, 5-aminosalicylic acid; CD, Crohn’s disease; DALM, dysplasia associated lesion or mass; IBD, inflammatory bowel disease; IC, indeterminate colitis; HGD, high grade dysplasia; LGD, low grade dysplasia; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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1. Introduction

Ulcerative colitis (UC) patients with concomitant primary sclerosing cholangitis (PSC) are at increased risk for developing colorectal cancer (CRC). The 10-year and 20-year risks of developing colorectal neoplasia have been reported as 14% and 31% respectively in PSC–UC patients in contrast to 4.4% and 8.6% in UC alone. Colonoscopy with biopsy needs to be performed at the time of diagnosis in patients with PSC-inflammatory bowel disease (IBD) with yearly surveillance thereafter. Surveillance to detect early dysplasia to prevent colon cancer in IBD patients is recommended. Dysplasia in UC patients can be classified as low grade dysplasia (LGD) or high grade dysplasia (HGD).

For patients with HGD, colectomy is recommended because of increased risk of detecting synchronous adenocarcinoma. Also the risk of progression to cancer over time is significantly elevated to 35%. However the risk of progression of LGD is very variable. In particular, there is no consensus whether monitoring with endoscopic surveillance or surgery after a diagnosis of LGD is recommended in patients with PSC. In another study from our institution, we found a low rate of progression of LGD to HGD or cancer in UC patients without PSC on a surveillance program. Patients with distal flat LGD were at highest risk of progression. However the literature in PSC–UC patients is very limited with variable risks of progression and studies have clumped both PSC and non-PSC patients together.

The major inclusion criterion was presence of LGD on surveillance colonoscopy. Patients with Crohn’s disease (CD) and indeterminate colitis (IC) were excluded. Patients who had insufficient follow-up after the diagnosis of LGD or underwent immediate colectomy within 1 month were excluded. Patients with lesions classified as indefinite for dysplasia and as non-dysplastic lesions were also excluded. It is a routine recommendation that patients with LGD in the setting of PSC–UC undergo colectomy in our institution. Patients who had lesions or mass which were not endoscopically removable went directly to colectomy and did not undergo follow-up surveillance at our institution were excluded. However, patients who were not willing for colectomy in the setting of flat LGD or raised LGD which was endoscopically removed get follow-up surveillance colonoscopy in our institution.

2. Patients and methods

2.1. Patients

The Cleveland Clinic electronic medical record database was queried for patients with UC and concomitant PSC who underwent two or more surveillance colonoscopies and diagnosed with low grade dysplasia (LGD) from January 1996 to December 2011. Demographic, clinical, and procedural data and adverse events were collected. The study was approved by the Cleveland Clinic Institutional Review Board.

2.2. Inclusion and exclusion criteria

The major inclusion criterion was presence of LGD on surveillance colonoscopy. Patients with Crohn’s disease (CD) and indeterminate colitis (IC) were excluded. Patients who had insufficient follow-up after the diagnosis of LGD or 20-year risks of developing colorectal neoplasia have been reported as 14% and 31% respectively in PSC–UC patients in contrast to 4.4% and 8.6% in UC alone. Colonoscopy with biopsy needs to be performed at the time of diagnosis in patients with PSC-inflammatory bowel disease (IBD) with yearly surveillance thereafter. Surveillance to detect early dysplasia to prevent colon cancer in IBD patients is recommended. Dysplasia in UC patients can be classified as low grade dysplasia (LGD) or high grade dysplasia (HGD).

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2.3. Demographic and clinical variables

PSC was diagnosed based on the finding of intra- and/or extra-hepatic bile duct abnormalities such as beading, duct ectasia, and structuring of the intra- or extrahepatic bile ducts based on the review of endoscopic retrograde cholangiopancreatography and/or magnetic resonance cholangiopancreatography. Patient and disease characteristics including age, gender, age at PSC and UC diagnosis, and duration of UC were evaluated. Information on smoking history, and family history of IBD or colon cancer in first degree relatives was also obtained. Information regarding the type of UC treatment used (steroids, azathioprine, biologics) was also obtained, with patients having to use this medication continuously for at least 6 months for this to qualify as medication use.

All histopathology slides, including biopsies from colonoscopies performed elsewhere, were examined by at least two experienced gastrointestinal pathologists at our institution in order to confirm the diagnosis of dysplasia. Proximal location of dysplasia was defined as dysplasia location anywhere proximal to the splenic flexure, while distal dysplasia was defined as dysplasia location distal to the splenic flexure. Flat dysplasia was defined as the absence of documentation of a raised mass, lesion, or polyp in endoscopy or pathology reports. Raised dysplasia was defined as a discrete raised lesion located in an area involved by either quiescent or active colitis that was endoscopically resected with biopsy confirmation of dysplasia. Raised lesions at endoscopy that were felt to be irregular or unamenable to excision and hence more suggestive of mass or plaque-like lesion i.e. DALM were excluded as these patients automatically underwent colectomy. Thus, only raised lesions that could be endoscopically removed completely and without any evidence of surrounding flat dysplasia were included. Surveillance for dysplasia in our institution involves 4 quadrant biopsies every 10 cm of the colon as recommended by the American College of Gastroenterology (ACG). A complete colonoscopy was done in all cases, without finding dysplasia in the proximal colon in...
cases that evolved to HGD in our study cohort. We use white light endoscopy for dysplasia surveillance in our institution. Chromoendoscopy is not used for cancer surveillance in our institution. Surgical reports and findings during colectomy and in the specimen as noted by the surgeon and the attending pathologist were evaluated.

2.4. Outcome measurement

The primary outcome of interest was the presence of HGD or CRC. Progression was defined as the development of HGD or CRC during surveillance colonoscopy or detected at colectomy. The time of last surveillance colonoscopy without any HGD/CRC detected or colectomy performed for any indication was regarded as the censoring time. The secondary outcome was to identify the time of detection of HGD/CRC after LGD diagnosis.

2.5. Statistical analysis

Descriptive statistics were computed for all factors. These include medians, 25th and 75th percentiles, range or mean and standard deviation for quantitative variables and frequencies and percentages for categorical factors. Normally distributed continuous variables were analyzed by using a t test, and continuous variables that were not normally distributed were analyzed by using the nonparametric (Wilcoxon) rank sum test. Comparisons between categorical variables were performed by Pearson’s chi-square test. The log-rank test was used to compare the Kaplan–Meier curves. Censoring was performed at the time of proctocolectomy, or death. R 2.10.1 software (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

3. Results

Query of the electronic medical records yielded 10 patients who satisfied the inclusion criteria. Table 1 highlights the characteristics of the entire cohort.

### Table 1: Demographics and clinical variables for patients with initial low-grade dysplasia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire cohort N=10</th>
<th>Flat LGD N=7 (70%)</th>
<th>Raised LGD N=3 (30%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, no. (%)</td>
<td>8 (80%)</td>
<td>5 (71.4%)</td>
<td>3 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>Median body mass index (g/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[[median (interquartile range)]</td>
<td>26.5 (23.5–31.8)</td>
<td>25.6 (22.8–25.3)</td>
<td>27.3 (25.3–28.1)</td>
<td>1</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (10%)</td>
<td>1 (14.3%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1 (10%)</td>
<td>1 (14.3%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Family history of IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (20%)</td>
<td>2 (28.6%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1 (10%)</td>
<td>1 (14.3%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Family history of colon cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (10%)</td>
<td>1 (14.3%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Median age at UC diagnosis (yrs)</td>
<td>38.5 (26–39)</td>
<td>39 (26–39)</td>
<td>38 (27.5–45)</td>
<td>0.73</td>
</tr>
<tr>
<td>Median duration of UC at LGD diagnosis (yrs)</td>
<td>15.9 (10–16)</td>
<td>10 (10–15)</td>
<td>13 (8–22)</td>
<td>0.64</td>
</tr>
<tr>
<td>Median age at initial dysplasia (yrs)</td>
<td>49 (44.3–50)</td>
<td>49 (42–49.5)</td>
<td>51 (49.5–53)</td>
<td>0.3</td>
</tr>
<tr>
<td>5-ASA exposure, no. (%)</td>
<td>5 (50%)</td>
<td>4 (57.1%)</td>
<td>1 (33.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Thiopurine exposure no. (%)</td>
<td>2 (20%)</td>
<td>1 (14.3%)</td>
<td>1 (33.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Median duration of follow-up (IQR), months</td>
<td>33 (20.4–36.6)</td>
<td>27 (10.6–34.3)</td>
<td>36.7 (35.2–73.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Progression to advanced neoplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGD, no.</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CRC, no.</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

3.1. Demographic and clinical characteristics

The basic demographic and clinical information of our cohort is summarized in Table 1. There were 8 males (80%) with a median age at UC diagnosis of 38.5 years (IQR, 26–39). The median age at LGD diagnosis in this cohort was 49 years (IQR, 44.3–50) while the median duration of UC at the time of LGD diagnosis was 11.5 years (IQR, 10–16). The patients with LGD were followed for a median duration of 33 months (interquartile range 20.4–36.6 months) from the time of LGD diagnosis. Five (50%) patients were on 5-aminosalicylic acid treatment, 2 (20%) patients on either azathioprine or 6-mercaptopurine, while 2 (20%) patients were on biologics like infliximab for treatment of their UC during follow-up. Three (30%) of the patients required corticosteroids for treatment of acute flares during follow-up. There were no statistically significant differences in any of these clinical parameters between patients with raised and flat LGD (Table 1).

3.2. Progression to HGD/CRC

Of the 10 patients with LGD, 3 (30%) progressed to raised HGD over a mean follow-up of 13±11 months. 3/10 patients had raised LGD while 7 had flat LGD. Initial location of dysplasia was in the proximal colon in 5 and distal colon in 5 patients. The location of HGD was in the proximal colon in all 3 patients. However all 3 patients with HGD had initial dysplasia located in the distal colon and had flat morphology. The incidence rate for HGD/CRC in our entire cohort was 9.4 cases per 100 person years at risk. Patients with LGD with flat morphology had an incidence rate for HGD/CRC in our cohort that was 17.8 cases per 100 person years at risk. Fig. 1 shows the Kaplan–Meier curves for progression to HGD/CRC for our entire cohort.
Of these 3 patients with HGD on surveillance colonoscopy, one patient underwent surgery at 4 months after the initial diagnosis of LGD and the surgical specimen confirmed HGD in the proximal colon. Another patient underwent surgery for HGD detected in the proximal colon 29 months after the initial diagnosis of LGD and the surgical specimen confirmed carcinoma in the proximal colon in the same site as HGD. The third patient also had HGD detected on colonoscopy after 4 months of initial diagnosis of LGD and underwent surgery at 5 months and had carcinoma in the proximal colon in the same site as HGD. Thus 2 patients with initial HGD diagnosis had cancer in their colectomy specimen. Both patients with colon cancer were classified as Dukes A classification (T1N0M0) in our study. Both patients are doing well without any recurrence of cancer 14 and 2 years following surgery.

When evaluating the association between the type of LGD and AN, 0/3 patients with raised LGD progressed to HGD/CRC as against 3/7 (42.9%) patients with flat LGD. Fig. 2 shows the Kaplan–Meier curves relating to the development of HGD/CRC for patients based on the type of LGD. Patients with LGD were followed for a median period of 33 months (interquartile range 20.4–36.6 months). During this time, regular surveillance colonoscopy was performed, with a mean of 5 examinations per patient. The progression occurred more frequently within the first year of initial detection of LGD (23.5 per 100 patient years of follow-up). In fact, 2/3 patients progressed within the first year.

Five patients underwent colectomy in our cohort. Three patients underwent colectomy for HGD on surveillance colonoscopy, while 2 patients underwent colectomy for medically refractory disease and persistent flat LGD. Among these 2 patients who underwent colectomy for medically refractory disease, one patient did not have any dysplasia in his colectomy, while the other patient had persistent LGD.

4. Discussion

The appropriate management of UC patients with dysplasia on colonoscopy is controversial. However UC patients with concomitant PSC are at significant risk of colon neoplasia and the usual recommendation in our institution is to do colectomy. In patients who did not elect to colectomy, we observed that one-third of patients with LGD progressed to HGD/CRC. Flat dysplasia appeared to be at higher risk with 3/7 patients with flat dysplasia progressing. We also observed that most patients progress within the first year of diagnosis of LGD supporting early colectomy with LGD diagnosis in these patients.

The rate of progression of LGD to HGD/CRC has been previously studied with varying reported results. Some studies have suggested this rate as 10–12.4%. In contrast, several studies have reported a significantly higher rate of LGD progression of 30–33%. However, all of these studies have clumped PSC and non-PSC patients together. PSC–UC patients are at specifically higher risk (more than 4 times) for colon neoplasia than UC patients alone. This led to recommendation that colonoscopy with biopsy should be performed at the time of diagnosis in patients with PSC–IBD with yearly surveillance thereafter. However, they identified PSC as the only risk factor that increased the risk of progression to HGD/CRC. In fact, the incidence rate for HGD/CRC in our cohort of PSC patients was 9.4 cases per 100 person years at risk which was similar to the Chicago study in which the incidence rate in PSC patients was 10.5 cases per 100 person years at risk. In an earlier study from Chicago including all UC patients with LGD, the authors reported a risk of progression of 11%. However, they identified PSC as the only risk factor that increased the risk of progression to HGD/CRC. In fact, the incidence rate for HGD/CRC in the Chicago study in which the incidence rate in PSC patients was 10.5 cases per 100 person years at risk was similar to the Chicago study in which the incidence rate in PSC patients was 10.5 cases per 100 person years at risk.

Our results are also similar to a prospective study in which the progression of LGD in all UC patients was studied. The study included 42 UC patients of which 11 had concomitant PSC. When these 11 patients with LGD were followed up, 4 developed HGD/CRC. Thus 36.4% progressed to HGD/CRC which is similar to 30% reported in our study.
We also found that LGD was equally distributed throughout the colon on colonoscopy. Although the colon neoplasms on colonoscopy were equally distributed, when the lesions were identified during colectomy, all 3 patients with HGD/CRC had right sided colon neoplasia consistent with prior studies in PSC–UC patients.\textsuperscript{1, 3} We had also shown a similar distribution on colectomy in our previous study.\textsuperscript{21} Changes in bile acid composition in PSC patients have been hypothesized for the increased risk of right sided colon neoplasia in these patients.\textsuperscript{21}

We also evaluated the association of type (flat vs. raised lesions that could be removed endoscopically) of LGD with the risk of HGD/CRC in the colon and rectum. Dysplasia with a flat morphology appears to more likely progress to HGD/CRC similar to previous studies.\textsuperscript{17–20} Although a large population based study from Denmark reported the decreasing incidence of CRC in UC patients over the last decade, UC diagnosis at a young age, associated PSC, long disease duration continued to remain risk factors for CRC.\textsuperscript{22} The results of our study reinforce that flat LGD in the setting of PSC requires serious consideration for colectomy. In fact, the current ACG guidelines prompt consideration of surgery in patients with flat LGD in all UC patients to prevent progression to a higher grade of neoplasia.\textsuperscript{23}

In addition, we have observed that HGD was detected in the proximal colon in patients who had flat LGD in the distal colon. The possibility is that random biopsies during the index LGD colonoscopy might have not sampled the area where HGD was diagnosed or in the presence of PSC, these might have rapidly evolved to HGD which was detected in the subsequent colonoscopy.

The findings of our study are clinically important. This study highlights that one-third of UC patients who develop LGD in the setting of PSC progress to HGD/CRC; flat LGD appears to be at a higher risk of progression and strongly supports colectomy in the setting of flat LGD in PSC–UC patients.

There are certain limitations of the current study. The study population was recruited from a subspecialty tertiary care referral center. Further the study is retrospective with its inherent limitations. The other major drawback of the study is the small numbers of patients with LGD included in this study and we could not study the determinants of progression of LGD in our cohort. However, colectomy is recommended in our institution for UC patients with PSC who are diagnosed with LGD limiting our sample size to study the natural history. The other major limitation is that we defined flat dysplasia retrospectively from the records and was diagnosed based on absence of confirmation of raised dysplasia on reports on endoscopy and pathology. There might be misclassification bias because of this retrospective analysis overestimating the significance of flat dysplasia or underestimating the risk of raised dysplasia.

In conclusion, one-third of patients with LGD progressed to AN in PSC–UC. Flat dysplasia appears to be at higher risk. Most patients progress within the first year of diagnosis of LGD supporting early colectomy in patients with PSC–UC and LGD.

Conflict of interest

The authors declared no financial conflict of interest.

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References


