

Histological healing favors lower risk of colon carcinoma in extensive ulcerative colitis

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severity in each of 6 segments when endoscopic appearance is normal. Two subgroups of patients were compared: group 1 patients who developed CC/HGD and group 2 patients who did not develop CC/HGD.

RESULTS: Of 115 patients with longstanding UC reviewed, 68 patients met the inclusion criteria. Twenty patients were in group 1 and 48 in group 2. We identified the number of times for each patient when the endoscopic appearance was normal but biopsies nevertheless showed inflammation. Overall, histological disease activity in the absence of gross/endoscopic disease was found in 31.2% (95%CI: 28%-35%) of colonoscopies performed on the entire cohort of 68 patients. Histological disease activity when the colonoscopy showed an absence of gross disease activity was more common in group 1 than group 2 patients, 88% (95%CI: 72%-97%) vs 59% (95%CI: 53%-64%). Only 3/20 (15%) of patients in group 1 ever had a colonoscopy completely without demonstrated disease activity (*i.e.*, no endoscopic or histological activity) as compared to 37/48 (77%) of patients in group 2, and only 3.3% (95%CI: 0.09%-8.3%) of colonoscopies in group 1 had no histological inflammation compared to 23% (95%CI: 20%-27%) in group 2.

CONCLUSION: Progression to HGD or CC in extensive ulcerative colitis of long standing was more frequently encountered among those patients who demonstrate persistent histological inflammation in the absence of gross mucosal disease. Our findings support including the elimination of histological inflammation in the definition of mucosal healing, and support this endpoint as an appropriate goal of therapy because of its risk of increasing dysplasia and colon cancer.

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Key words: Histological inflammation; Risk; Colon cancer; Ulcerative colitis; High grade dysplasia

Abstract

AIM: To search for the answer in extensive ulcerative colitis as to whether histological inflammation persisting despite endoscopic mucosal healing serves to increase the risk of colon cancer (CC) or high grade dysplasia (HGD).

METHODS: This is a single center (Lenox Hill Hospital) retrospective cohort and descriptive study of extensive ulcerative colitis (UC) for 20 years or more with a minimum of 3 surveillance colonoscopies and biopsies performed after the first 10 years of UC diagnosis. Data analyzed included: duration of UC, date of diagnosis of (CC) or (HGD), number of surveillance colonoscopies, and biopsies showing histological inflammation and its

Core tip: Patients with long standing and extensive ulcerative colitis who develop colon cancer rarely have histological healing despite gross endoscopic healing. The persistence of histological inflammation is common in those who develop colon cancer (CC) or high grade dysplasia (HGD). When surveillance colonoscopies in ulcerative colitis of 20 years duration reveal persistent histological inflammation, patients are at high risk for the development of CC/HGD. Consideration of increasing drug therapy should arise, and the patient is entitled to share in this knowledge and contribute to the decision.

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INTRODUCTION

Ulcerative colitis (UC) is one of the two major chronic inflammatory bowel diseases, almost always involving the rectum and any or all segments of the colon proximally in continuity. It is recognized that long-standing UC carries an increased risk for the development of colorectal carcinoma (CC) and high grade dysplasia (HGD), with estimates of risk as high as 20% following 30 years of diagnosis^[1]. This risk appears to be especially prominent in cases of universal UC, which has traditionally been defined by endoscopic evidence of disease proximal to the mid-transverse colon on at least one occasion following diagnosis. Chronic macroscopic disease activity has also been implicated as a risk factor for the development for CC^[2]. These observations have led to the practice of surveillance by colonoscopy in cases of universal UC. Current practice guidelines recommend that surveillance be performed every 1-2 years in these patients beginning 8-10 years after the initial UC diagnosis^[3]. Surveillance typically involves four-quadrant biopsies of the colon, either every 10 cm during withdrawal from the cecum, or by colonic segments (*e.g.*, cecum, ascending colon, *etc.*) as well as biopsies of specific lesions when encountered.

While it is generally accepted that extent, duration and chronicity of inflammation directly impact cancer risk, less well studied is the role of the PERSISTENCE of microscopic inflammation after gross inflammation has subsided in the pathogenesis of colon cancer^[4-6]. Recent case control and cohort studies have shown that the severity of microscopic inflammation is also associated with an increased risk for colorectal neoplasia^[7,8]. Rutter *et al*^[7] noted that both endoscopic and histological severity of disease impacted cancer risk on univariate analysis, only histological severity continued to show an increased

risk for neoplasia following multivariate analysis.

In patients with inflammatory bowel disease (IBD), clinical remission is valuable for quality of life but does not necessarily correlate with “mucosal healing”^[9]. Increasingly, disease and treatment outcomes for IBD are being assessed in terms of mucosal healing, which in most trials is defined by the normal appearance of the colonic mucosa as described by the endoscopist at colonoscopy^[10-13]. Nevertheless, histological inflammation of varying degrees is common even when the mucosa appears normal. Though some may consider normal appearing mucosa as healed, it is unknown whether histological disease activity even in the absence of gross disease carries an increased risk for the development of CC or HGD.

To help answer this question we conducted a retrospective cohort descriptive study of long-standing universal UC patients. Our primary goal was to determine if there was a relationship between histological disease activity and risk for CC and HGD in the absence of gross inflammation. Our secondary goal was to define the incidence of histological disease activity in the absence of gross disease activity, possibly predisposing to the later development of high grade dysplasia or colon cancer.

MATERIALS AND METHODS

This is a study of UC patients utilizing the inflammatory bowel disease data base of over 3000 patients followed by the senior investigator Korelitz BI at Lenox Hill Hospital over a 50 year period. Inclusion criteria required a diagnosis of universal UC defined by the presence of endoscopically active disease proximal to the mid-transverse colon on at least one colonoscopy following the date of UC diagnosis.

Candidates were only included if they had at least 3 surveillance colonoscopies performed following 10 years of UC diagnosis and a minimum of an additional 10 years (total \geq than 20 years of disease). Data recorded included gender, age at diagnosis, year of diagnosis, and disease duration. A Microsoft excel spreadsheet was constructed documenting each surveillance colonoscopy, recording the presence or absence of gross endoscopic disease, and the presence or absence of microscopic inflammation in those macroscopically normal in each colonic segment to include the cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum. No specific index system for histological inflammation was used since none was available during most of the study period. The slides had been read by the institutional pathologists who all had extensive experience with surveillance biopsies in ulcerative colitis. All cases of dysplasia were reviewed by a second pathologist specializing in gastrointestinal diseases. Each subject's follow-up continued until either colectomy, the finding of CC/HGD, or a duration of at least 10 additional years of surveillance after the first 10 years of disease up until

Table 1 Demographics, decades of surveillance, and probable influence of advances in drug therapy

Characteristics	Group 1 CA/HGD	Group 2 Non-CA/HGD
n = 68	20	48
Gender (% female)	50%	46%
Age at diagnosis (yr), range	27.3 (8-51)	25 (6-61)
Disease duration (yr), range	27.3 (12-54)	29.6 (16-48)
Treatment with 6 MP/IFX		
Subjects/decades of diagnosis of UC	Subjects received ¹	Subjects received ²
1930-1949	1	0
1950-1959	1	0
1960-1969	7	5
1970-1979	9	17
1980-1989	2	16
1990-1999	0	10

¹1970-1989, 6-mercaptopurine (6MP) = 55%, infliximab (IFX) = 0%;

²1960-1999, 6MP = 79%; 1980-1999, IFX = 27%. CA: Carcinoma; HGD: High-grade dysplasia; UC: Ulcerative colitis.

the final documented surveillance examination. All colonoscopies were performed by the Senior Author alone or with Fellows in Gastroenterology.

Ethical considerations

This study received approval of the Institutional Review Board of Lenox Hill Hospital on September 15, 2009.

Statistical analysis

This is a retrospective cohort and descriptive study, of greater than 20 year duration, which was undertaken to assess the frequency and extent to which histological inflammation is present in the absence of gross endoscopic findings amongst patients with long-standing ulcerative colitis and whether this observation is more prevalent amongst patients who later develop colon cancer or high grade dysplasia. We report the observed prevalence of histological inflammation and its associated 95%CI in the total cohort and the two groups; the group which later developed colon cancer/dysplasia and the group which did not.

These important observations result from a study the strength of which is its long standing duration and the relative limited variation associated with a single practice. Obviously, its retrospective nature places the usual number of anticipated limitations so that the conclusions must be viewed with caution and taken to generate a hypothesis. Due to the long standing duration required to develop such a study, a prospectively controlled examination of this question in order to confirm these observations is not feasible.

RESULTS

Of 115 patients with longstanding UC reviewed, 68 patients met the inclusion criteria. 47 were excluded either for lack of the minimum of 20 years of surveillance or

less than 3 documented colonoscopies during the second 10 years of ulcerative colitis. Patients were subsequently divided into two groups, group 1 which was comprised of 20 patients who developed CC and/or HGD, and group 2 comprised of 48 patients who did not. Demographic data are summarized in Table 1. Overall, groups 1 and 2 were similar in terms of gender, age of UC diagnosis and disease duration. More of the patients in group 2 were diagnosed and treated in recent decades than those in group 1.

Table 1 notes the decade during which the diagnosis of extensive ulcerative colitis was recognized and records the percentage of patients treated with immunosuppressives and/or biological during these decades.

Table 2 charts the number of surveillance colonoscopies done after 10 years of disease for Groups 1 and 2 and identifies the number of times for each when the endoscopic appearance was normal but biopsies nevertheless showed inflammation. The 20 patients in group 1 had 120 surveillance colonoscopies, range 3-14, median 4. Of the 48 patients of group 2, 550 surveillance colonoscopies were performed, range 3-28, median 8.5. Overall, histological disease activity in the absence of gross/endoscopic disease was found in 31.2% (95%CI: 28%-35%) of colonoscopies performed on the entire cohort of 68 patients. Histological disease activity when the colonoscopy showed an absence of gross disease activity was more common in group 1 than group 2 patients, 88% (95%CI: 72%-97%) *vs* 59% (95%CI: 53%-64%). Only 3/20 (15%) of patients in group 1 ever had a colonoscopy completely without demonstrated disease activity (*i.e.*, no endoscopic or histological activity) as compared to 37/48 (77%) of patients in group 2.

Among the 20 patients who developed CC/HGD, 17 (85%)(95%CI: 62%-98%) were found distal to the splenic flexure, including 11 (55%)(95%CI: 31%-77%) which developed in the rectum. In only 2 of the 20 cases (10%)(95%CI: 1%-32%) was carcinoma (CA)/HGD found isolated proximal to the descending colon. In no case was CA/HGD found in a colonic segment without prior histological inflammation. Table 3 shows the segments of the colon involved with histological inflammation when the colonic mucosa appeared normal and the degree of inflammation on a progressive scale of 1-5. The severity of inflammation was much more marked in group 1 than group 2. In these 20 patients of group 1 who did develop neoplasia, both the persistence of histological inflammation and its severity was most marked in the rectum and sigmoid where 12 of the cases of cancer (70.6%) and 10 with severe dysplasia were found. This finding was similar to that reported by Goldstone *et al*^[14] In only 2 of the 20 patients was CC/HGD found isolated proximal to the descending colon and in no case was it found without there having been previous inflammation. The severity of inflammation was greater in all segments of group 1 than group 2. Features of the 20 patients with high grade dysplasia and/or colon cancer are shown in Tables 4 and 5.

Table 2 Summary of colonoscopic outcomes with and without neoplasia *n* (%)

Colonoscopic outcome	Group 1 (<i>n</i> = 20)	Group 2 (<i>n</i> = 48)	Total (<i>n</i> = 68)
Colonoscopies after 10 yr of UC	120	550	670
	Range 3-14 median 6	Range 3-28 median 11.5	
Colonoscopies with endoscopically active colitis	87 (72.5)	243 (44.2)	330 (49.2)
Colonoscopies without endoscopically active colitis but with histological inflammation ¹	29 (24.2)	180 (32.7)	209 (31.2)
Colonoscopies without gross/endoscopic or histological inflammation	4 (3.3)	127 (23.1)	131 (19.6)
% of endoscopically negative colonoscopies with histological inflammation ²	29 (88)	180 (59)	

¹Prevalence in all colonoscopies; ²Prevalence in all colonoscopies. UC: Ulcerative colitis.

Table 3 Segments of colon showing histological inflammation and its degree when endoscopically normal

Case-index	Cecum	Asc colon	Trans colon	Desc colon	Sigmoid	Rectum
1N	2	2	2	2	2	2, 4, 5
2N	2, 4	2, 4	2	2, 4	2, 4	2, 4
3N	3	3	3	3	3	3, 4
4N	1	1	1	1	1, 5	1, 5
5N	3	3	3	3, 4	3, 5	3, 4, 5
6N	2	2	3, 5	3	3, 5	2
7N	1	1	1	1	2, 4, 5	2, 4
8N	2	2	3, 5	3	3, 5	2
9N	2	2	2	2	2, 4	2, 4
10N	3	3	3	3, 4	3	3
11N	3	3	3	3	3, 5	3
12N	1	1, 5	1, 4, 5	2	2	2
13N	3, 5	3, 5	3	3	3	3
14N	1	2, 5	2, 4	2, 4	1, 4	1
15N	2	2	2	2, 5	2	2
16N	2	2	2	3	3, 4, 5	3, 5
17N	2	2	2	3	3	3, 5
18N	1	1	1	1	2, 4, 5	2
19N	3	3	3	3	3	3, 5
20N	3	3	3	3	3, 4, 5	3, 5
1	1	1	3	2	3	3
2	0	0	0	0	0	1
3	0	0	1	1	0	1
4	2	0	1	1	0	3
5	1	0	2	2	2	2
6	3	3	0	0	1	2
7	0	0	0	0	0	0
8	2	2	0	0	1	1
9	0	0	1	1	1	1
10	1	1	1	1	1	1
11	1	1	1	1	1	1
12	0	1	2	2	2	1
13	1	1	3	2	2	0
14	0	0	0	0	0	0
15	1	0	0	1	1	1
16	0	0	2	1	1	0
17	1	2	2	2	2	2
18	0	0	0	0	0	0
19	1	1	1	1	1	1
20	2	2	0	2	2	0
21	2	0	2	2	1	2
22	0	0	1	1	1	1
23	1	1	1	1	0	0
24	1	1	1	1	1	0
25	0	0	1	1	2	2
26	1	1	1	3	0	2
27	0	0	2	2	2	2
28	1	1	1	2	1	1
29	1	1	2	1	1	3
30	1	1	1	1	1	1
31	0	0	0	1	1	1

32	2	0	2	2	1	1
33	2	2	0	2	2	2
34	0	0	0	1	0	0
35	1	1	1	3	1	1
36	1	1	1	2	3	2
37	1	1	0	0	2	2
38	0	0	1	1	1	0
39	1	1	1	1	1	0
40	1	1	1	1	2	2
41	0	0	3	0	0	0
42	1	0	2	2	2	2
43	1	1	1	0	1	1

Group 1 = 1N→20N (29 colonoscopies); Group 2 = 1→43 (180 colonoscopies). Degree of inflammation: 0, none; 1, mild; 2, moderate; 3, severe; 4, dysplasia; 5, cancer.

DISCUSSION

Our study demonstrates an incidence of CC/HGD of almost 30% following average disease duration of over 27 years. While this finding in a tertiary care/IBD specialty practice may not reflect community norms, it is clearly in line with the incidence in prior observations^[1,6]. While others have examined the risk of CC and dysplasia as a function of duration, extent and severity of inflammation, our goal was to examine whether the persistence of microscopic inflammation was itself a risk factor. We found that microscopic disease in the absence of macroscopic disease was a common finding on surveillance in the group who developed CC/HGD as well as the group who did not. However, a finding of both endoscopic and histological healing was a rare event in the CC/HGD group (3.3% of colonoscopies) *vs* the non-CC/HGD group (23% of colonoscopies), and that few patients in group 1 would ever demonstrate microscopic mucosal healing (15%), while a majority of those in group 2 would at some point during their follow up (77%). Furthermore, the severity of inflammation was much greater for all biopsied segments for group 1 than group 2. These findings add to those earlier observations by reinforcing the prognostic benefits of histological mucosal healing in addition to gross mucosal healing.

Additionally, we sought to determine the incidence of histological disease activity when gross mucosal healing was observed. Overall, we found that 31.2% (95%CI: 28%-35%) of all colonoscopies that demonstrated grossly normal appearing colonic mucosa also

Table 4 Features of 20 patients with high grade dysplasia or carcinoma of colon

Case	High grade dysplasia	Multiple sites of dysplasia	Low grade dysplasia	Colon cancer	Location of cancer
1	+	1	0	0	¹
2	+	1	0	0	¹
3	+	0	0	0	¹
4	+	0	0	+	Recto-sigmoid
5	+	1	0	+	Sigmoid
6	+	1	0	+	Sigmoid
7	+	1	0	+	Sigmoid
8	0	0	0	+	Distal transverse
9	0	1	1	+	Ileo-Anal pouch
10	+	1	0	+	Sigmoid
11	0	0	0	+	Sigmoid
12	0	0	0	+	Prox transverse
13	+	1	1	+	Cecum
14	0	0	1	+	Ascending
15	0	0	0	+	Descending
16	+	0	1	+	Recto-sigmoid
17	+	1	1	+	Rectum
18	0	0	0	+	Sigmoid
19	0	0	0	+	Rectum
20	+	0	0	+	Sigmoid
Totals	12	9	5	17	

¹High grade dysplasia at multiple sites, not cancer.**Table 5** Features of the patients with carcinoma of colon

Features	Colectomies
Cancer discovered at endoscopy led to colectomy	8
Colectomy for high grade dysplasia also disclosed cancer	8
Colectomy for high grade dysplasia did not disclose cancer	3
Cancer discovered by metastases (no colectomy)	1
Most cancers in sigmoid and rectum	12/17
Multiple areas of dysplasia	6
Low grade as well as high grade dysplasia	6
Alive in 2012	9
High grade dysplasia at multiple sites, not cancer	3/20

demonstrated evidence of microscopic inflammation. To the experienced IBD gastroenterologist this finding will come as no surprise. The persistence of histological inflammation in ulcerative colitis without evident clinical activity or abnormal endoscopic appearance was reported over 50 years ago by Truelove and Richards^[15], Dick and Grayson^[16] and Matts^[17]. Later Morson^[18] and Dick *et al*^[19] further popularized the value of rectal biopsies and Sommers *et al*^[20] and Korelitz *et al*^[21] introduced the technique of mucosal cell counts for evaluating persistence of inflammation and for response to specific drug therapy. Their findings were based mostly on finding an excess of chronic inflammatory cells including plasma cells and an apparent increase in polymorphonuclear leukocytes. Riley *et al*^[22] reported the risk of relapse in UC when biopsies showed any acute inflammatory infiltrate histologically and Bitton *et al*^[23] showed that the findings of plasmacytes on biopsy specifically increased the likelihood of relapse. Bessissow *et al*^[24] suggested optimizing medical therapy when this finding is disclosed.

Discussion on the value of surveillance for ulcerative colitis provides a wide range of opinions. Higgins *et al*^[25] and Dhanda *et al*^[26] raise the option of eliminating colonoscopy entirely since it contributes little to the degree of ulcerative colitis activity beyond clinical activity as reported by the patient; we feel that this should pertain only to an index of activity but not to surveillance for dysplasia and cancer. Rutgeerts *et al*^[27], Regueiro *et al*^[9], and Pineton de Chambrun *et al*^[13] emphasize the lack of correlation between clinical and endoscopic findings and support endoscopic healing for clinical trials but do not include histological healing as a component of mucosal healing for surveillance purposes. Baars *et al*^[28] found an incidence of histological inflammation of 49% when the mucosa appeared endoscopically normal. Rutter *et al*^[7], Gupta *et al*^[8] and Mathy *et al*^[29] have recognized the importance of histological inflammation in providing a risk factor for colon cancer in long-standing ulcerative colitis and propose the inclusion of microscopic inflammation in a grading system for risk stratification. Such histological grading scales have been proposed by Geboes *et al*^[30] and Korelitz^[31].

The most notable drawback to our own analysis is the discrepancy between the numbers of surveillance colonoscopies performed between the two groups, with a median number of examinations more than double in group 2 who did not develop HGD/CC. While more examinations decreased the chance of missing HGD/CC, it also increased the number of opportunities for the patients in the non-CC/HGD group to show histological mucosal healing. As such, it is likely that the percentage of individuals who had a colonoscopy with complete mucosal healing would have been less if this groups' surveillance frequency was closer to the HGD/CC group.

Also, our comparison of the two groups does not account for possible treatment differences. It is notable that most of the patients in the non-CC/HGD group were diagnosed and received treatment during an era of increasing use of immunosuppressive and then biologics to treat UC, suggesting a beneficial effect of such therapy. We have previously shown a trend toward a reduced risk for colon cancer in IBD patients treated with 6-mercaptopurine (MP)^[32] but were unable to confirm this statistically though a more recent analysis of the CESAME cohort has shown a significant decrease in the incidence of colon cancer in patients with extensive colitis^[33] treated with thiopurines. In the present study, we show that the decades of treatment with 6 MP alone coincide with reduced risk of neoplasia (6 MP used in 79% of group 2 *vs* 55% in group 1) and similarly with infliximab (27% in group 2 *vs* none in group 1). Though others have observed an association between CC and decade of disease diagnosis, the relationship of treatment with 5-amino salicylic acid preparations and CC/HGD rates in UC remains controversial, as the continuing pro and con debate surrounding their role in CC prevention bears out^[34-37].

In conclusion, our findings clearly add to the argument in favor of defining mucosal healing not only by endoscopic findings, but by histological healing as well. Confirmation of gross mucosal healing has been advocated as an appropriate and objective measure of successful treatment in clinical trials^[38,39], but this definition of mucosal healing remains controversial^[10,11,39,40]. Our findings confirm previously reported high rates of CC/HGD in patients with longstanding extensive colitis. We show that progression to CC/HGD appears to be less common in those patients who demonstrate histological mucosal healing compared to those who persistently show microscopic disease activity. The endoscopist should acknowledge that endoscopic healing and histological healing are not synonymous and surveillance biopsies should be performed even when the endoscopic appearance is normal, and the results should be a part of patient counseling regarding the goals and expected outcomes in this high risk group.

COMMENTS

Background

Ulcerative colitis (UC) is one of the two major chronic inflammatory bowel diseases, almost always involving the rectum and any or all segments of the colon proximally in continuity. It is recognized that long-standing UC carries an increased risk for the development of colorectal carcinoma (CC) and high grade dysplasia (HGD), with estimates of risk as high as 20% following 30 years of diagnosis.

Research frontiers

This risk appears to be especially prominent in cases of universal UC, which has traditionally been defined by endoscopic evidence of disease proximal to the mid-transverse colon on at least one occasion following diagnosis. Chronic macroscopic disease activity has also been implicated as a risk factor for the development for CC. These observations have led to the practice of surveillance by colonoscopy in cases of universal UC. Current practice guidelines recommend that surveillance be performed every 1-2 years in these patients beginning 8-10 years after the initial UC diagnosis.

Innovations and breakthroughs

Progression to HGD or CC in extensive ulcerative colitis of long standing was more frequently encountered among those patients who demonstrate persistent histological inflammation in the absence of gross mucosal disease. Their findings support including the elimination of histological inflammation in the definition of mucosal healing, and support this endpoint as an appropriate goal of therapy because of its risk of increasing dysplasia and colon cancer.

Peer review

This is an interesting manuscript investigating the importance of histologic inflammation in the development of HGD/CRC in UC. The evidence presented here adds support to the fact that persistence of microscopic inflammation increases the risk of colon cancer in ulcerative colitis.

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