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Severity of Inflammation as a Predictor of Colectomy in Patients With Chronic Ulcerative Colitis

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Abstract

PURPOSE—We evaluated a large cohort of patients with longstanding ulcerative colitis in a colonoscopic surveillance program to determine predictors of colectomy.

METHODS—We queried a retrospective database of patients who had symptoms of ulcerative colitis for seven years or more. Histologic inflammation in biopsies was graded on a validated four-point scale: absent, mild, moderate, severe. We performed a multivariate analysis of the inflammation scores and other variables to determine predictive factors for colectomy. Patients who underwent colectomy for neoplasia were censored at the time of surgery; those who did not undergo colectomy were censored at the time of last contact.

RESULTS—A total of 561 patients were evaluated, with a median follow-up of 21.4 years since disease onset. A total of 97 patients (17.3 percent) underwent surgery; 25 (4.5 percent) for reasons other than dysplasia. These 25 constitute events for this analysis. For univariate analysis, mean inflammation ($P < 0.001$) and steroid use ($P = 0.01$) were predictors of colectomy. For multivariable proportional hazards analysis, mean inflammation ($P < 0.001$) and steroid use ($P = 0.03$) were predictors of colectomy, whereas salicylate use ($P = 0.007$) was protective.

CONCLUSIONS—Higher median inflammation scores and corticosteroid use were predictors of colectomy in this patient population. The overall rate of colectomy during a long period of follow-up was low (<1 percent per year).

Keywords

Ulcerative colitis; Colectomy; Dysplasia; Inflammation

Colon resection is a common outcome in patients with ulcerative colitis (UC). Overall, 30 percent of patients diagnosed with UC will at some point undergo colectomy—a rate that has not changed significantly during the last 50 years.^{1,2} Importantly, resection of the colon and rectum, with or without creation of an ileal pouch as a neorectum, can have significant morbidity. Therefore, identification of patients with UC who will ultimately require colectomy is of great clinical value, in that this knowledge may spare some patients the complications of prolonged medical management while avoiding premature or unnecessary surgery in others.

There is considerable literature about factors that predict urgent or emergent colectomy in patients with acute UC flares. Lack of response to steroids, continued diarrhea and bloody bowel movements, and persistently elevated inflammatory markers all have been shown to predict colectomy in hospitalized patients with UC.³⁻⁶ However, there are few data concerning predictive factors for colectomy in patients with longstanding disease.⁷ There is broad agreement in most studies that patients with pancolitis at diagnosis are more likely to require colectomy than those with more limited disease.⁸⁻¹¹ Various genetic markers, including certain HLA haplotypes, also have been shown to contribute to increased risk of colectomy.¹²⁻¹⁴ Evidence for other potential predictive factors, such as malnutrition, inability to wean steroids, or chronic symptoms is unclear and limited. The natural history of patients who enter a dysplasia surveillance program, usually after eight years of disease in patients with left-sided or proximal disease, is unknown. Under what circumstances these patients might be at risk for colectomy is not well understood.

Therefore, we evaluated a cohort of patients with longstanding UC and long-term follow-up enrolled in a program of dysplasia surveillance with long-term follow-up to identify factors predictive of colectomy.

PATIENTS AND METHODS

The Mount Sinai Ulcerative Colitis Surveillance Database was created to explore predictors of neoplasia in a cohort of patients at risk for UC-related neoplasia. This project has been approved in numerous formats by our Institutional Review Board and is presently HIPAA compliant. The inclusion criteria are: 1) a minimum of seven years of ulcerative colitis, 2) no previous history of colectomy, and 3) at least one surveillance colonoscopy. Each surveillance colonoscopy consisted of random four-quadrant biopsies every 10 cm. Patients with visibly abnormal areas received additional directed biopsies.

Demographic information, data on exposure to IBD medications, clinical history, and extent of disease were abstracted from patients' charts, colonoscopy reports, surgical notes, and pathology reports. Extent of disease at diagnosis was categorized as pancolitis or limited disease. Other variables of interest included presence of extra intestinal manifestations (primary sclerosing cholangitis (PSC), erythema nodosum, arthritis, pyoderma gangrenosum (PG), uveitis/episcleritis), presence or absence of exposure to 5-aminosalicylic acid (5-ASA), 6-mercaptopurine (6-MP), azathioprine (AZA), and steroids. Each patient's first colorectal procedure for management of UC also was recorded. Pathologic data included all examinations of biopsies or surgical specimens. Number of biopsies and the grade of any inflammation or dysplasia from each anatomic site separately examined also were recorded.

Inflammation was graded by a validated system developed by one of the authors (NH) and used since 1988. All pathology reports included in this study were issued by NH or pathologists directly trained by him. Each biopsy was graded as inactive/absent (0), mild (1), moderate (2), or severe (3). The criteria for each are summarized in Table 1. This scale has been shown to be highly reproducible among pathologists with different levels of training ($\kappa = 0.9$).¹⁵ These scores were summarized as the patient's mean inflammation score across all colonoscopies, maximum inflammation score (the highest site score at any examination), and as a binary measure (any site score greater than 0 vs. all sites equal to 0).

Patients with previous colon resection, Crohn's colitis, or indeterminate colitis were excluded from the study, as were any patients with a history of colorectal carcinoma or dysplasia on initial colonoscopy. Because we have previously reported that inflammation is a predictor of dysplasia and malignancy in this cohort, we censored patients at the time of surgery if dysplasia

or malignancy was the recorded indication, or in unclear cases, if the colonoscopy immediately before surgery showed dysplasia or colorectal cancer.¹¹

Descriptive variables are summarized as means $\pm$ standard deviation or as percentages. A univariate proportional hazards analysis was performed, including all candidate variables. Variables with $P < 0.2$ on univariate testing were included in a multivariable model. The analysis was repeated using each of the three ways of summarizing the inflammation score. All analyses were performed by using OpenStat for Windows. $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

The database included 724 patients of whom 564 had recorded inflammation scores and anatomic extent. Three patients were excluded because of previous surgery, leaving 561 patients eligible for analysis. Demographic information is shown in Tables 2 and 3, and the study population is summarized in Figure 1. The median follow-up for these patients was 21.4 (range, 0–65) years since disease onset. During surveillance, which started after their first dysplasia surveillance examination, 97 patients (17.3 percent) underwent colectomy. Indications for colectomy included neoplasia or dysplasia ($n = 72$, 74 percent), medically refractory disease ($n = 20$, 21 percent), toxic megacolon or fulminant colitis ($n = 3$, 3 percent), appendiceal mucocele ($n = 1$, 1 percent), and unknown/nondysplasia ($n = 1$, 1 percent). The 25 patients with colectomies for indications other than neoplasia constitute the events for the purpose of this analysis. In this group, procedures performed included total colectomy ($n = 24$, 96 percent) and removal of the cecum and appendix ($n = 1$, 4 percent). The ten-year actuarial rate of colectomy was calculated to be 20 percent per year overall. Broken down, this was 6 percent for nonneoplastic reasons and 15 percent for neoplasia.

The univariate Cox regression of predictors of colectomy is summarized in Table 4. Mean inflammation score ($P < 0.001$) and steroid use ($P = 0.01$) were determined to be significant predictors of colectomy in our patient population. There was a trend toward a protective effect of 5-ASA ($P = 0.11$). Curiously, exposure to azathioprine, extensive disease, and extraintestinal manifestations were not predictive of colectomy. On multivariate analysis, mean inflammation ($P < 0.001$) and steroid use ($P = 0.03$) remained significant predictors of colectomy; 5-ASA ($P = 0.007$) also was demonstrated to be protective in multivariable proportional hazards modeling (Table 5).

DISCUSSION

We report a large population of patients with chronic ulcerative colitis in a colonoscopic surveillance program with a long follow-up interval since disease diagnosis (median, 21.4). This population had a colectomy rate of 17.3 percent, or 4.5 percent for reasons other than dysplasia or malignancy at a median of 18.2 years after disease diagnosis. In addition, the low number of colectomies performed for toxic megacolon, fulminant colitis, or perforation suggests that most surgeries were performed electively, and that once entered in a program of surveillance, this patient population has relatively mild, medically manageable disease flares. Most patients not undergoing surgery for dysplasia or malignancy underwent colectomy for medical intractability. Within the context of this colectomy rate for nonneoplastic disease, our primary finding was that among patients with chronic ulcerative colitis, those with increased inflammation of the colon have significantly higher rates of colectomy. Our group has previously demonstrated that inflammation was an independent predictor of neoplasia.¹⁶

It is interesting that extent of disease (left-sided vs. pancolitis) was not predictive of colectomy in our study. While this is in agreement with one large scale multivariate analysis,¹⁷ multiple

studies have suggested pancolitis to be a strong predictor of colectomy.^{10,11,18,19} It also has been clearly demonstrated that patients with pancolitis have a higher rate of dysplasia and colorectal cancer.²⁰ Studies also suggest that patients with pancolitis have a higher rate of complications that require emergency surgery and that these tend to occur early in the course of a patient's disease.^{11,21} This suggests that patients with pancolitis may have undergone surgery before becoming eligible for our cohort and, thus, may be underrepresented.

Our study is limited by the retrospective nature of the database, and the fact that data were collected from a single referral center with expertise in the management of ulcerative colitis. It is uncertain whether this selection issue would make patients more likely to undergo colectomy secondary to more severe disease or less likely to undergo colectomy because of more frequent use of cyclosporine A and other therapies. In either event, it is by no means clear whether such biases would modify the independent effects of inflammation, disease extent, or medication use that were examined.

As in any retrospective study, data were derived from patients' medical records. The extensive experience of the involved clinicians makes these records more reliable, and the indications for surgery (dysplasia or other) were verified through biopsy results. The absence of information on dosage and duration of medication exposure did not permit us to include these details in our analysis, and this would be an interesting area of future inquiry. We also were limited by the relatively small number of patients who underwent colectomy, given the low rate of surgery in patients with longstanding disease. Additional studies of this and other measures of histologic inflammation, particularly across multiple centers, might prove valuable in validating their use as predictors of disease course. It would be interesting to compare inflammation to other markers of disease activity, such as number of flares, frequency of hospital admission, or number of courses of corticosteroids.

CONCLUSIONS

In a cohort of patients with longstanding, chronic ulcerative colitis undergoing dysplasia surveillance, a relatively small number of patients undergo colectomy, and the majority of these are for reasons of dysplasia or malignancy rather than disease activity. Although specificity is low, patients with increased inflammation on biopsy are more likely to require colectomy for reasons other than dysplasia or malignancy, as are patients who have received treatment with steroids. This suggests that patients who have retained their colons after seven years of disease have a low likelihood of requiring colectomy, and that increased inflammation on colon biopsy may be helpful in selecting patients for more aggressive medical therapy. In addition, these patients may be selected for more extensive counseling concerning potential future surgical procedures.

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FIGURE 1.
Study population.

TABLE 1

Inflammation score

<i>Score</i>	<i>Description</i>
0 - inactive colitis	No cryptitis
1 - mildly active colitis	Cryptitis in <50% of crypts
2 - moderately active colitis	Cryptitis in >50% of crypts
3 - severely active colitis	Ulcerations or erosions

TABLE 2

Patient demographics

Sex (n = 501)	Male	280 (55.2)
	Female	227 (44.8)
Location of disease (n = 561)	Extensive	283 (50.4)
	Left-sided	278 (49.6)
Extraintestinal manifestations (n = 561)	Any	95 (16.9)
	PSC	14 (2.5)
	Arthritis	63 (11.2)
	Erythema nodosum	16 (2.9)
	Pyoderma gangrenosum	13 (2.3)
	Uveitis/episcleritis	13 (2.3)
	Steroid exposure	324 (57.8)
Medication exposure (n = 561)	5-ASA exposure	391 (69.7)
	6-MP/AZA exposure	151 (26.9)
	Steroid exposure	324 (57.8)

PSC = primary sclerosing cholangitis; 5-ASA = 5-aminosalicylic acid;

6-MP = 6-mercaptopurine; AZA = azathioprine.

Data are number of patients with percentages in parentheses.

TABLE 3

Patient demographics (continued)

Median age (yr)	60.2 (13.8-99.6)
Median follow-up (yr)	21.4 (0-65.5)
Median no. of colonoscopies	5 (1-22)
Median time to colectomy (yr)	
Dysplasia/cancer	18.2 (0-52.4)
Other reasons	18.2 (3.8-58.6)
All	18.2 (0-58.6)

Data are number of patients with ranges in parentheses.

TABLE 4

Univariate regression analysis

		<i>Event</i>	<i>No event</i>	<i>Hazard ratio</i>	<i>P value</i>
Inflammation score	Mean	0.83	0.57	3.1	<0.001
	Max	3	2	1.5	0.07
Medications	Binary	24 (96)	493 (91.9)	2.3	0.4
	Steroids	23 (92)	301 (56.2)	6.1	0.01
	5-ASA	17 (68)	374 (70)	0.5	0.11
	6-MP/AZA	11 (44)	140 (26.1)	2.1	0.08
Extraintestinal disease	Any	7 (28)	88 (16.4)	1.5	0.3
	PSC	1 (4)	13 (2.4)	1.6	0.6
	Arthritis	4 (16)	59 (11)	1.1	0.8
	EN	2 (8)	14 (2.6)	2.2	0.3
	PG	1 (4)	12 (2.2)	1.2	0.8
	Uveitis	1 (4)	12 (2.2)	1.4	0.8
	Pancolitis	11 (44)	272 (51)	0.7	0.5

PSC = primary sclerosing cholangitis; 5-ASA = 5-aminosalicylic acid;

6-MP = 6-mercaptopurine; AZA = azathioprine; EN = erythema nodosum;

PG = pyoderma gangrenosum.

Data are numbers with percentages in parentheses unless otherwise indicated.

TABLE 5

Multivariate regression analysis

	<i>Event</i>	<i>No event</i>	<i>Hazard ratio</i>	<i>P value</i>
Mean IS	0.83	0.57	3.3	<0.001
Steroids	23 (92)	301 (56.2)	5	0.03
5-ASA	17 (68)	374 (70)	0.3	0.007
6-MP/AZA	11 (44)	140 (26.1)	1.7	0.23

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine;

IS = inflammation score.

Data are numbers with percentages in parentheses unless otherwise indicated.