The Clinical Significance of Crohn Disease Activity at Resection Margins

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• Context.—Conflicting data about the clinical significance of microscopic Crohn disease (CD) activity at resection margins have led to varying practice patterns for routine reporting by pathologists.

Objective.—To characterize the association between active disease at resection margins with postoperative CD recurrence and time-to-recurrence in the era of anti–tumor necrosis factor therapy.

Design.—We performed a multicenter retrospective cohort study of 101 consecutive CD bowel resections during 10 years. Margin slides were reviewed, and CD activity at the margins was graded as none, mild, moderate, or severe. The association between microscopic CD activity at the margin with postoperative recurrence and time-to-recurrence were evaluated with logistic regression and Cox regression analyses, respectively.

Results.—Crohn disease activity at resection margins was reported in 43% of pathology reports. Resection margins had CD involvement in 39.6% of cases, 20 of which were classified as mild, 6 as moderate, and 12 with severe CD activity. Although patients with mild (odds ratio, 1.14; 95% CI, 0.40–3.20) and moderate to severe (odds ratio, 1.97; 95% CI, 0.62–6.35) activity were at increased risk of disease recurrence, the differences were not statistically significant. Patients with mild (hazard ratio, 0.97; 95% CI, 0.50–1.91) and moderate to severe (hazard ratio, 1.29; 95% CI, 0.65–2.55) disease activity at margins did not have significantly different time-to-recurrence compared with those without disease activity.

Conclusions.—Our study suggests CD activity at resection margins is not significantly associated with postoperative CD recurrence.

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More than 25% of all patients with Crohn disease (CD) require surgical resection in their lifetime.1 In a large cohort study of adults with CD, surgery was reported in half of all cases within 10 years after diagnosis, with postoperative CD recurrence (defined as histologic, endoscopic, radiographic, clinical, or surgical) occurring in 33% to 40% of patients at 5 years, 44% to 55% at 10 years, and 70% at 20 years.2 Because of these high postoperative CD recurrence rates, predictors of CD recurrence based on histologic, clinical, endoscopic, and surgical features of CD patients are of great interest and have been the subject of several studies.

There are conflicting data regarding the prognostic value of CD histologic features in bowel resection specimens. In the early 1980s, Karesen and colleagues3 reported that the presence of microscopic CD at surgical resection margins was associated with increased postoperative CD recurrence, and a wide resection with frozen section evaluation of the resection margins was recommended. A study by Wolff et al4 drew a similar conclusion and also recommended that frozen sections be performed on grossly normal CD resection margins to rule out microscopic disease. In 1993, Heimann et al5 found that patients with severe CD who needed multiple resections with anastomosis that had microscopic inflammation at the resection margins were at high risk for early symptomatic disease recurrence. However, other studies suggested the presence of microscopic CD at surgical resection margins was not associated with postoperative CD recurrence.6,7 Kotanagi et al8 found that recurrence of CD at the anastomotic site did not correlate with any histologic features at the resection margin, including pyloric gland metaplasia, fibrosis, cryptitis, crypt abscesses, ulcers, granulomas, or transmural inflammation. Finally, a randomized controlled trial of 131 patients who had resections between 1986 and 1993 showed no significant difference in recurrence rates between wide-margin and limited-margin resection or disease activity at time of resection.9

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Abbreviations: HBI, Harvey-Bradshaw Index; TNF, tumor necrosis factor.

| Characteristic | Value |
|---------------|-------|
| Age, median, y | 36 |
| Female, No. (%) | 58 (57.4) |
| Race, No. (%) | 76 (75.0) |
| Hispanic | 25 (25.0) |
| Body mass index, median | 23.6 |
| Location of resection, No. (%) | 73 (72.0) |
| Colonic | 8 (8.0) |
| Terminal ileum | 15 (15.0) |
| Proximal small bowel | 5 (5.0) |
| Indication for surgery, No. (%) | 53 (52.5) |
| Stricture | 24 (23.8) |
| Fistula | 21 (20.8) |
| Other (perforation, abscess) | 3 (3.0) |
| Postsurgical HBI score, median | 6 |
| Score ≤3 | (18.0) |
| Score ≥8 | (39.3) |
| Postsurgical HBI score, median | 3 |
| Score ≤3, % | (57.3) |
| Score ≥8, % | (11.2) |
| Presurgical treatment, %a | 20.2 |
| Immunomodulator | 11.2 |
| TNF inhibitor | 61.8 |
| Postsurgical treatment, %a | 39.3 |
| No treatment | 34.8 |
| Immunomodulator | 14.6 |
| TNF inhibitor | 11.2 |

Abbreviations: HBI, Harvey-Bradshaw Index; TNF, tumor necrosis factor.

| Characteristic | Value |
|---------------|-------|
| Postsurgical treatment, %a | 20.2 |
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Abbreviations: HBI, Harvey-Bradshaw Index; TNF, tumor necrosis factor.

a Of the 89 patients with available complete treatment data.

There have been few recent studies examining the importance of microscopic activity at the resection margins of patients with CD. Currently, academic pathology practices in the United States do not have a consensus regarding reporting histologic findings at resection margins in CD. Therefore, the aim of our study was to characterize the association between CD activity at resection margins with postoperative CD recurrence and time-to-recurrence, particularly in the era of anti–tumor necrosis factor (TNF) therapy.

MATERIALS AND METHODS

This study was approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center (UTSW, Dallas, Texas), the Parkland Health and Hospital System (PHHS, Dallas, Texas), and the University of Washington Medical Center (UWMC, Seattle, Washington).

Study Design

We performed a multicenter retrospective study of CD patients who underwent ileal, ileocolonic, and colonic surgical resections at UTSW, UWMC, and PHHS. Pathology databases at each site were searched for patients with CD who underwent small or large bowel resection between January 2005 and January 2015. We excluded patients who were lost to follow-up after resection because recurrence patterns were unknown, those who did not have resection margins taken for histologic examination, and those who did not have margin slides available for review. Demographic and clinical data were collected for each patient from electronic medical records: age, sex, race/ethnicity, smoking status, body mass index before surgery, location of disease, indication for surgery, CD treatment before and after surgery, preoperative Harvey-Bradshaw Index score, first postoperative Harvey-Bradshaw Index score, first postoperative endoscopic findings, first postoperative computed tomography or magnetic resonance enterography result, date of surgery, date of CD recurrence, presentation of recurrence (clinical, endoscopic, and/or radiologic), and date of death.

Pathologic Examination

A gastrointestinal pathologist reviewed en face, entirely submitted proximal and distal surgical resection margin hematoxylin-eosin slides for each case. The pathologist was blinded to the patient’s clinical and recurrence status. Involvement by CD was graded using a modified version of the grading system as described by Gupta et al9 as none (Figure 1), mild (<50% cryptitis; Figure 2), moderate (≥50% cryptitis/crypt abscesses; Figure 3), or severe (ulceration; Figure 4).

Statistical Analysis

Our outcomes of interest were the proportion of patients with postsurgical CD recurrence and time-to-recurrence. Recurrence was defined by a composite of endoscopic findings, radiologic imaging, or clinical symptoms as defined by Harvey-Bradshaw Index score. We used logistic regression analysis to identify factors associated with any recurrence during the follow-up period. We used Kaplan-Meier analysis to characterize time-to-recurrence and Cox regression analysis to identify factors associated with time-to-recurrence. Follow-up was censored at time of last clinic visit or death for those without recurrence. Statistical significance was defined as P < .05. All data analysis was performed using Stata 14.0 (StataCorp, College Station, Texas).

RESULTS

Patient Characteristics

Between 2005 and 2015, a total of 101 patients with CD underwent bowel resection at UTSW, UWMC, and PHHS. Characteristics of the patients at the time of surgery are shown in the Table. The median age of patients was 36 years (range, 18–78 years); 58 patients (57.4%) were female, and most (n = 74; 73.3%) were non-Hispanic white. More than two-thirds (n = 72; 71.3%) of the patients had ileocolonic disease in resected specimens, with 15 (14.8%) having isolated ileum, 8 (7.9%) isolated colonic, and 5 (4.9%) proximal small bowel involvement. The most common indications for surgery included stricture (n = 53; 52.5%), fistula (n = 24; 23.8%), and both stricture and fistula (n = 21; 20.8%). Median presurgical Harvey-Bradshaw Index score was 6, with 16 patients having scores ≤3 (suggesting remission) and 35 patients having scores ≥8 (suggesting severe disease activity). Of the 89 patients with available complete treatment data, patients (61.8%) were treated with both immunomodulators and anti-TNF therapy prior to surgery; of these patients, only 10 (11.2%) were on combination therapy postoperatively. No treatment was initiated in 35 patients (39.3%), whereas 31 (34.8%) received immunomodulators alone and only 13 (14.6%) were on anti-TNF therapy.

A total of 43% of original pathology reports from all 3 institutions in aggregate mentioned presence or absence of...
CD at the resection margins. Following slide review, we were able to determine margin disease activity for 96 cases (95.0%). Resection margins had CD involvement in 39.6% of cases, of which 20 were classified as mild, 6 as moderate, and 12 as severe activity. Given the small number of patients with moderate or severe disease activity, these groups were combined for all analyses.

Factors Associated With Postoperative Recurrence

After resection, 62 patients (61.4%) had evidence of clinical, endoscopic, and/or radiologic disease recurrence after a median follow-up of 8.2 months. In univariate analysis, the only factor associated with CD recurrence was receipt of postoperative CD therapy, likely related to therapy being started in patients at highest risk for recurrence. Recurrence was observed in 64.8% (35 of 54) of patients treated with immunomodulators, anti-TNF agents, or both, versus 42.9% (15 of 35) in untreated patients ($P = .04$). Postoperative recurrence was not associated with disease activity at surgical margins ($P = .38$). Although patients with mild (odds ratio, 1.14; 95% CI, 0.40–3.20) and moderate to severe (odds ratio, 1.97; 95% CI, 0.62–6.35) activity were at increased risk of disease recurrence, the differences did not reach statistical significance. Proportions of patients with CD recurrence were 56.9% (33 of 58) in those without activity, 60% (12 of 20) in those with mild activity, and 72.2% (13 of 18) in those with moderate to severe activity ($P = .51$).

Median time-to-recurrence was 7.5 months, ranging from 0.35 to 85.2 months. Time-to-recurrence was not associated with patient age, sex, race, CD location, CD complications, or preoperative Harvey-Bradshaw Index scores. Further, we
found no association between disease activity at surgical margins and time-to-recurrence ($P = .71$). Patients with mild (hazard ratio, 0.97; 95% CI, 0.50–1.91) and moderate to severe (hazard ratio, 1.29; 95% CI, 0.65–2.55) disease activity at surgical margins did not have significantly different time-to-recurrence compared with those without disease activity. Median time-to-recurrence was 8.4 months for patients without any disease activity, 9.2 months for patients with mild disease activity, and 5.6 months for moderate to severe activity.

**DISCUSSION**

Conflicting data about the importance of disease activity at CD resection margins has led to varying practice patterns among pathologists in reporting. In our multicenter retrospective cohort study with more than 100 patients, we found that disease activity at the margins was reported as part of routine clinical care in nearly half of all cases, highlighting the current lack of uniformity in CD resection margin reporting among pathologists. On independent review, we found active CD involvement of the resection margins in more than one-third of cases. Although disease activity was associated with numerically higher rates of CD recurrence, particularly when moderate to severe in nature, this difference did not reach statistical significance. Further, patients with active disease at resection margins did not have shorter time-to-recurrence. Overall, our findings suggest there is limited, if any, known clinical importance to routinely reporting disease activity at CD resection margins.

Although older literature suggests microscopic CD activity at the resection margins was associated with increased recurrence, our study findings are consistent with other, more recent reports disputing this claim.8,11 It is possible these discrepant findings relate to improved CD treatment, particularly more aggressive postoperative management of high-risk patients over time. Patients considered at the highest risk of recurrence are often started on empiric treatment with antibiotics or anti-TNF therapy. This hypothesis is further supported by our finding that receipt of postoperative CD therapy was associated with an increased risk of recurrence. This likely highlights a selection bias regarding in whom postoperative therapy was started. Although our data, along with other studies, suggest disease activity at CD margins does not appear to predict CD recurrence, this does not discount any utility if reporting disease activity at resection margins. For example, there are some data from the pediatric literature suggesting microscopic disease activity at resection margins may predict postoperative recurrence,12 raising the possibility that there may be a difference in the significance of CD activity at resection margins between the pediatric and adult populations. Another study has shown CD activity at resection margins in adults to be a risk factor for severe postoperative complications, including intra-abdominal sepsis.13,14

Other studies examining the association between resection margin activity and postoperative CD recurrence suggest the specific pattern or type of inflammation may be more informative than the presence of any inflammation. Ferrante et al15 found the presence of myenteric plexitis in the proximal margin predicted higher endoscopic CD recurrence at 3 months (75% versus 41%) and 1 year (93% versus 59%). A subsequent study also found higher CD recurrence rates at 1 year in patients with myenteric plexitis (30% versus 16%), although this difference did not reach statistical significance, given the small size of the cohort.16 Other studies have described high postoperative CD recurrence rates with the presence of specific types of inflammatory cells, including mast cells, eosinophils, and lymphocytes, involving submucosal nerve plexi at resection margins.17,18 Therefore, future studies should evaluate the association between specific patterns of inflammation, such as myenteric plexitis or the type of inflammatory cells, and clinical outcomes, including CD recurrence.

Our study had notable limitations. First, our study was retrospective, so there was the potential for confounders, missing data, and measurement bias. Most notably, we measured recurrence through a combination of radiographic, endoscopic, and clinical data; however, this was assessed as part of routine clinical care instead of a standardized protocol. Because we used a composite outcome including clinical symptoms, we could not distinguish local versus distant recurrence. Similarly, patients were treated as part of clinical care, so there was variation in postoperative CD treatment, including immunomodulators and anti-TNF therapy. Finally, we evaluated several pathologic features, including disease activity at margins; however, we did not collect data on features such as myenteric plexitis. Overall, we feel like these limitations are outweighed by the multicenter nature of our cohort, with a relatively large sample size, independent review of the hematoxylin-eosin stains blinded to clinical data, and robust assessment for any signs of recurrence.

In summary, we found about half of pathology reports in our cohort described CD activity at the resection margins, highlighting variable practice patterns for margin activity reporting in clinical practice. On independent blinded review of hematoxylin-eosin slides, we found active CD involvement of the resection margins in more than one-third of cases; however, disease activity was not associated with increased odds of CD recurrence or shorter time-to-recurrence. Our study supports findings of studies that were performed prior to the era of anti-TNF therapy, suggesting that CD activity at resection margins does not predict CD recurrence, and reporting margins for the prediction of clinical outcomes may not be necessary. Future studies are needed to evaluate whether patterns of inflammation or types of inflammatory cells at the resection margin may have improved predictive accuracy.

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