Patterns of Colonic Involvement at Initial Presentation in Ulcerative Colitis

A Retrospective Study of 46 Newly Diagnosed Cases

Marie E. Robert, MD,1 Mark Skacel, MD,2 Thomas Ullman, MD,3 Charles N. Bernstein, MD,4 Kirk Easley,5 and John R. Goldblum2

Key Words: Ulcerative colitis; Crohn disease; Rectal sparing; Pathology; Colonic mucosal biopsies

Abstract

Studies have shown that rectal sparing and patchiness develop in treated and longstanding ulcerative colitis (UC), making the distinction from Crohn colitis increasingly difficult after treatment is initiated. However, no histologic studies of the incidence of rectal sparing in adults at UC onset have been performed. Colectomy specimens from 46 patients with classic UC histologic features and no Crohn disease features were identified. Biopsy specimens obtained before medical therapy were retrieved and examined blindly by 2 pathologists, along with appropriate control samples. Slides were scored for chronicity (crypt branching, subcryptal plasma cells, lamina propria plasma cells) and activity (cryptitis, crypt abscesses, epithelial injury). In 28 cases, only rectal biopsy specimens were taken; for 16, rectal and at least 1 proximal biopsy specimen were taken. All cases showed rectal involvement; none had rectal sparing at initial biopsy. Of 16 cases with rectal and more proximal biopsy specimens, 5 (31%) showed relative rectal sparing (lower scores in rectum than in more proximal sites). In 16 cases with rectal and more proximal biopsy specimens, chronicity and activity scores were higher in the rectum than in more proximal sites (P = .01; chronicity and activity). The mean overall chronicity score decreased in a linear manner from rectum to cecum. The rectum is involved and shows evidence of chronicity and activity at disease onset in UC, using colectomy as the gold standard for diagnosis. Because rectal sparing at UC onset has been reported, a prospective study using uniform biopsy protocols is needed to establish the true incidence of rectal sparing at presentation.

It is commonly believed that certain features of ulcerative colitis (UC) distinguish it from Crohn colitis. One such feature etched into the dogma of inflammatory bowel disease diagnosis is the continuity of colonic involvement in UC, beginning in the rectum, without patchiness or skip lesions.1 Indeed, most believe that rectal involvement is a prerequisite for making a diagnosis of UC. In recent years, however, it has become increasingly evident that patchy colonic involvement, proximal greater than distal disease activity, and frank rectal sparing can occur in treated UC or in UC of many years duration, even in the absence of medical therapy.2-9

Because initial medical management often is similar for either disease, many clinicians begin therapy for inflammatory bowel disease on the basis of the pathology evident in limited biopsy specimens obtained during flexible sigmoidoscopy. Some time later, when issues of colonoscopic surveillance or possible colectomy are raised or when newer therapies specific to one disease (such as methotrexate, cyclosporine, or infliximab10) are being considered, pathologists are asked to distinguish unequivocally between UC and Crohn colitis, usually on biopsy specimens obtained while the patient is being treated. If ambiguity exists, it is considered advisable to review the initial set of endoscopic biopsy specimens obtained at disease onset, before the institution of therapy, to distinguish between the 2 diseases. Reliance on initial biopsy specimens assumes that patients have disease distribution at initial examination that conforms to the standard paradigm, in which patchy distribution or rectal sparing denote Crohn disease rather than UC. However, universal involvement of the rectum in UC at disease onset has never been tested rigorously in the era of modern endoscopy. The question...
remains whether rectal sparing and patchy colonic involvement occur at disease onset in UC.

The aims of this study were to determine the prevalence of complete and relative rectal sparing in biopsy specimens obtained at disease onset in UC and to document the distribution of histologic involvement throughout the colon.

Materials and Methods

The pathology files of Yale-New Haven Hospital (New Haven, CT) and the Cleveland Clinic Foundation (Cleveland, OH) were examined for colectomy specimens with a diagnosis of UC. Resection specimens were examined by 1 of 2 gastrointestinal pathologists (M.E.R. or J.R.G.) to confirm the diagnosis of UC and to exclude cases in which histologic features were indeterminate for UC or exhibited features of Crohn disease. Features required for a diagnosis of UC in the resection specimens included diffuse mucosal involvement from the rectum proximally, the absence of chronic ileitis (mild acute ileal inflammation was accepted in cases of pancolitis), the absence of appendiceal involvement as a skip lesion, and the absence of transmural inflammation, fissures, and granulomas. In addition, the medical records of each patient were reviewed to exclude cases with clinical features suggestive of Crohn disease or evidence of pouch failure after colectomy.

In the group of cases with colectomy specimens that met the aforementioned criteria for UC, a search for initial endoscopic biopsy specimens was performed. By definition, all initial biopsy specimens were obtained at the time of initial diagnosis and before therapy. Patient charts were reviewed to make this determination. Cases in which the patients had been taking antibiotics, steroids, aminosalicylic acid compounds, or any other medication for inflammatory bowel disease before or at the time of the initial biopsy were excluded from the study.

To serve as control samples for histologic interpretation, slides from 5 cases each of collagenous colitis, lymphocytic colitis, ischemic colitis, and infectious colitis were retrieved. All case and control group biopsy specimens were coded and randomized by a third party (T.U.) and examined blindly and simultaneously by 2 gastrointestinal pathologists (M.E.R. and J.R.G.). Five histologic features routinely used in the evaluation and study of colitis were evaluated on each slide. Of the 16 rectal biopsy specimens, 3 were excluded from chronicity scoring because of a missing data point (inability to score subcryptal cellularity). The chronicity scores (sum of scores for architectural distortion, cellularity of lamina propria plasma cells, and subcryptal cellularity), activity scores (sum of scores for cryptitis and crypt abscesses and epithelial injury), and overall scores (sum of chronicity and activity scores) were calculated for each slide.

Overall chronicity and activity scores and the scores for individual histologic features were compared between biopsy sites (rectal vs other) and between case and control specimens by performing ordered logistic regression using the proportional odds model. Because each patient could have more than one biopsy specimen, the correlated data were modeled using the methods described by Zeger and Liang. Reported P values are 2-sided with α set at P < 0.05.

Results

We identified 46 patients whose cases met our inclusion criteria and for whom the initial biopsy specimens could be retrieved. The mean age at diagnosis was 39 years (range, 13–74 years). Five patients were younger than 18 years. Of the 46 patients (from whom there were a total of 106 slides from the initial endoscopy procedure), 28 had a rectal biopsy and 16 had a rectal biopsy and at least 1 proximal biopsy (16 rectal and 51 proximal biopsies). In 18 cases, no rectal biopsy specimen was obtained (14 cases) or all biopsy specimens including a rectal biopsy specimen were placed in 1 specimen container (4 cases). In the latter 4 cases, all mucosal biopsy fragments obtained were involved by colitis to the same degree. The statistical analysis was performed first on histologic data from all biopsy sites combined and second on the 16 cases with rectal and more proximal biopsy specimens. Of the 16 rectal biopsy specimens, 3 were excluded from chronicity scoring because of a missing data point (inability to score subcryptal plasma cells owing to poor orientation). All but 1 biopsy specimen were used in the evaluation of activity scores (the excluded specimen consisted of exudate only). The chronicity and activity scores and P values for rectal and more proximal biopsy specimens are shown in Table 1 and Table 2.
Distribution of Chronicity and Activity

The rectal biopsy specimens showed greater scores for chronicity ($P = .04$) and activity ($P = .02$) than the more proximal biopsy specimens in all cases (Tables 1 and 2). Considering the 16 patients with both rectal and more proximal biopsies, the difference between the rectum and more proximal sites was even more pronounced, with greater chronicity and activity ($P = .01$) in the rectum. In addition, when overall chronicity scores were analyzed by specific site, there was a gradual decrease in chronicity scores from the rectum to the cecum Table 3.

Evidence of Rectal Sparing or Patchiness

Complete rectal sparing (defined as normal mucosa) was not seen in specimens from the group of 28 patients. Five (31%) of 16 patients with rectal and more proximal biopsies had relative rectal sparing, with lower scores for branching (3/5), subcryptal plasma cells (1/5), lamina propria plasma cells (4/5), cryptitis (4/5), and epithelial injury (2/5) in the rectum than in more proximal sites in the same patient Image 1.

Considering individual histologic features for all 28 rectal biopsy specimens, 4 (14%) of 28 had no crypt branching, 4 (16%) of 25 had no subcryptal plasma cells (3 biopsy specimens could not be scored owing to poor orientation), 5 (18%) of 28 had a score of 0 or 1 for lamina propria plasma cells, and 1 (4%) of 28 had no evidence of cryptitis or epithelial injury. Although all rectal biopsy specimens received overall chronicity scores of at least 1 (of a possible 9), low overall chronicity scores (1-2) were present in 4 (16%) of 25 cases. Of note, 2 endoscopy reports noted endoscopic...
rectal sparing, but biopsy specimens of the rectum were not obtained in these 2 cases, precluding them from analysis.

Control Group

UC cases had significantly higher chronicity ($P < .001$) and cryptitis ($P = .002$) scores but less epithelial injury ($P = .06$) than control cases.

Discussion

In the present study, rectal biopsies taken from 28 patients at the time of initial diagnosis of UC, before therapy, showed histologic changes characteristic of chronic colitis. There was no histologic evidence of complete rectal sparing. **Relative rectal sparing**, defined as the finding of higher chronicity or activity scores in sites proximal to the rectum in the same patient, was found in 5 of 16 patients who had rectal and more proximal biopsies. This finding has not been shown before in patients newly diagnosed with UC. These results suggest that, while the rectum usually is the most severely involved site, the finding of relative rectal sparing at disease onset should not dissuade the clinician from making the diagnosis of UC.

While the data support the established doctrine of universal rectal involvement (ie, no complete rectal sparing) in UC at disease onset, we are cautious about drawing broad conclusions from a retrospective study of this type. The inclusion criteria might have biased the study against finding an increased rate of rectal sparing or rectal patchiness by including only cases that at colectomy had diffuse involvement including the rectum. Because rectal sparing may occur in up to 40% of treated UC patients, it is possible that the exclusion of cases with rectal sparing at the time of surgery excluded some that also might have had rectal sparing at disease diagnosis.

The literature on rectal sparing at initial diagnosis in UC is scant. In 1980, Burnham et al reported that 11 patients presenting with fulminant UC had endoscopic rectal sparing, but no biopsy specimens were obtained to document this endoscopic observation. In 1987, Spiliadis et al described 12 patients with UC with normal or mildly abnormal rectal mucosa revealed by endoscopy. However, all 12 rectal biopsy specimens showed colitis, although the inflammation was “mild” in 4 cases. Thus, no histologic rectal sparing was documented in either of those studies of adults with UC.

In a study of children, 5 of 12 with UC diagnosed in colectomy specimens had patchy and mild rectosigmoid disease revealed by initial biopsies before therapy, and 1 had a normal rectal biopsy specimen. In addition, Kleer and Appelman reported that rectal sparing at disease onset occurred in 1 of 41 patients. However, the endpoints for the diagnosis of UC and the assurance of lack of therapy at the time of or before biopsy were not provided in that study. More recent studies comparing children with adults found rectal sparing at initial diagnosis in a small proportion (3%-4%) of children. A third study found no evidence of rectal sparing at disease onset in 15 adults and 25 children.

The strengths of the present study are 2-fold. First, colectomy specimens were used as the “gold standard” for...
the diagnosis of UC. Clinical records and colectomy specimens were examined carefully, and cases with an atypical clinical course (such as pouch failure) or atypical histologic features were excluded. This approach to case definition has not been used in previous studies of adults with UC and essentially eliminates the criticism that Crohn disease has not been excluded adequately, a frequent criticism of studies of rectal sparing in UC. Second, great care was taken to ensure that the biopsy specimens retrieved were obtained at disease onset, before the institution of medical therapy. In all cases, the patient’s chart and, in many cases, the endoscopy reports were reviewed to make this determination. Cases in which patients had been taking antibiotics, steroids, aminosalicylic acid compounds, or any other medication for inflammatory bowel disease before or at the time of the initial biopsy were excluded from the study.

The complete lack of uniformity in the clinicians’ approaches to endoscopy and biopsy in patients with symptoms suggestive of colitis limited the study findings. Of 46 cases included in the study, a rectal biopsy specimen was not obtained in 14. In some of these cases, the endoscopy report indicated diffuse involvement of the left colon, including the rectum. However, 2 endoscopists reported endoscopic rectal sparing but failed to biopsy the rectum. The failure to obtain a biopsy specimen of endoscopically normal mucosa is a pitfall to accurate diagnosis, as it is well documented that endoscopically normal mucosa is frequently histologically abnormal in patients with inflammatory bowel disease.23

The distinction between UC and Crohn colitis is more than an academic pursuit. Major patient care decisions are predicated on this distinction, the most significant of which is whether to offer patients a pouch procedure when total colectomy is necessary. The development of new medications such as infliximab that are appropriate for refractory Crohn disease but have a limited role in UC is another reason to be sure of the diagnosis.10 As more disease-specific therapies are developed, the pressure to distinguish between UC and Crohn colitis undoubtedly will intensify.

The impact of our findings is as follows: First, although rectal sparing occurs in the treated setting, complete rectal sparing at disease onset in adults with UC is rare. However, colitis that is less severe in the rectum than in more proximal sites can be seen at initial presentation in UC. Second, there is a lack of uniformity among gastroenterologists in the approach to biopsy in patients who appear to have colitis. Accurate distinction of UC from Crohn colitis may depend on sampling the rectum and using different specimen containers to separate rectal from more proximal biopsy specimens. Any areas of apparent endoscopic sparing should be sampled and separated from involved areas in order to have the best chance at accurately documenting disease distribution. The true incidence of complete and relative rectal sparing at initial presentation in UC remains unknown and will require a prospective study with a uniform biopsy protocol to determine the spectrum of disease patterns that exist. We believe the results of our study suggest that relative rectal sparing occurs. However, complete rectal sparing at disease onset in adults with UC is uncommon.

From the Departments of 1Pathology, Yale University School of Medicine, New Haven, CT; 2Anatomic Pathology, the Cleveland Clinic Foundation, Cleveland, OH; 3Medicine, Mount Sinai New York University Health, New York, NY; 4Medicine, the University of Manitoba, Winnipeg, Canada; and 5Biostatistics, Emory University, Atlanta, GA.

Address reprint requests to Dr Robert: Dept of Pathology, Yale University School of Medicine, 310 Cedar St, PO Box 208023, New Haven, CT 06520-8023.

References


