Best Practice & Research Clinical Gastroenterology 38-39 (2019) 101601

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

What is the role of histopathology in the evaluation of disease activity in Crohn's disease?

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ARTICLE INFO

Article history:
Received 11 December 2018
Accepted 14 February 2019

Keywords:
Crohn's disease
Mucosal healing
Histologic remission
Disease activity

ABSTRACT

Assessment of disease activity is essential for developing and determining appropriate therapy in patients with Crohn's disease. Currently, clinical and endoscopic treatment targets have been proposed, whereas histologic assessment of disease activity is not recommended in expert guidelines. Histologic assessment of disease activity has emerged as an important tool in ulcerative colitis as persistent histological inflammation is associated with clinical relapse, corticosteroid use, hospitalisation, and development of dysplasia. Similar data for Crohn's disease is limited but emerging literature suggests that histologic evaluation of disease activity may have value. This review summarizes the recent literature regarding histologic evaluation of disease activity in Crohn's disease. Correlation between histologic, endoscopic, and other markers of disease activity are discussed. Histologic scoring systems in Crohn's disease are described and practical guidance is provided to gastroenterologists and pathologists on how to report and interpret histologic data.

Introduction

In both ulcerative colitis (UC) and Crohn's disease (CD), histologic evaluation is necessary to establish the diagnosis and is useful to evaluate response to therapy. Histology is also commonly used to confirm the presence of a disease flare and plays an essential role in evaluation for the presence of neoplasia. Emerging data from the UC literature indicates that histology may have other uses [1,2]. In UC, histologic assessment of mucosal biopsies has been shown to predict clinical relapse, corticosteroid use, and hospitalisation better than endoscopy [3–11]. The power of histologic measurements in UC in predicting clinical relapse is supported by a recent meta-analysis of 15 studies that evaluated 1567 patients [7]. The relative risk of histologic remission versus histologic activity for clinical relapse or disease exacerbation was 0.48 (95% CI 0.39–0.60). Histologic remission outperformed endoscopic remission in predicting relapse with a relative risk of 0.83 (95% CI 0.72–0.95). Furthermore, histologic activity has also been shown to better predict the development of dysplasia and carcinoma in UC patients compared to endoscopy [12–14]. For these reasons, the US Food and Drug Administration and the has required histologic evaluation of mucosal biopsies for assessment of mucosal healing [15].

For CD, the role of histological assessment of disease activity is less clear due to the complexities inherent to the heterogeneity of disease location and the patchy nature of microscopic inflammation. However, in principal histologic evaluation may have added value over pure endoscopic evaluation of disease activity. Given the growing interest in histologic measurements of disease activity, this review will summarize the current literature regarding histologic evaluation in CD. In particular, the correlation between different measures of disease activity are discussed. Recent data on the significance of histologic activity in CD is presented and the ability of current therapies to achieve histologic remission is shown. Finally, the various histologic scoring systems in CD are discussed and practical guidance is provided to pathologists and gastroenterologists when evaluating histologic data.

Current treatment targets in CD

Crohn's disease (CD) frequently results in structural damage to the gastrointestinal tract resulting in complications including

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https://doi.org/10.1016/j.bpg.2019.02.003
1521-6918/

stricture, fistula and abscess formation, and impaired health-related quality of life [16,17]. There is unanimous agreement that control of inflammation is the underlying principle that should guide therapeutic strategies. However, management of CD is complicated by the fact that inflammation can be measured by a range of modalities including symptoms, endoscopy, cross sectional imaging and histopathology, meaning that there are several potential targets for control of inflammation. The discordance between symptoms and endoscopic inflammation is well established, thus targeting of clinical symptoms alone does not reliably control endoscopic inflammation. Several observational studies have shown positive associations between endoscopic healing and clinical remission, reduced risk of disease-related complications, lower rates of surgery and hospitalisation [18–21]. However, the endoscopic lesions of CD may not be readily assessable by endoscopy, radiologic measurements are not well validated, and histologic assessment of mucosal biopsies is hampered by the transmural nature and patchiness of disease [22]. Based on the aforementioned observations, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) working group recommends resolution of abdominal pain and normalization of bowel habit, together with endoscopic absence of ulceration as an additional target [23]. Complete endoscopic mucosal healing was not suggested as a target. The STRIDE group felt that histologic remission should not be a target in CD due to the lack of studies evaluating the significance of histologic disease activity in predicting outcomes. However, similar to UC, achieving histologic remission may have additional value.

Pathologic principles in CD

In the untreated setting, mucosal biopsies, although superficial, can show features that are suggestive of CD. Discrete foci of lymphoplasmacytic inflammation often associated with neutrophilic cryptitis and adjacent to histologically normal crypts are common (Fig. 1). The lymphoplasmacytic inflammation may occur deep within the mucosa and separate the crypts from the muscularis mucosae (basal plasmacytosis). Aphthous erosions, characterized by focal surface epithelial injury associated with a mixed inflammatory infiltrate and underlying lymphoid aggregate, are typical early lesions. Variability of inflammation within a single biopsy and among several biopsy fragments from the same anatomic location is also typical. The involved areas typically show architectural distortion, while adjacent crypts may appear normal. Granulomas are infrequently seen in adults, but, when present, are often poorly formed, non-necrotizing, and associated with lymphocytic inflammation.

In resection specimens, the inflammatory process is often multifocal, with areas of submucosal fibrosis and transmural inflammation, including transmural lymphoid aggregates (Fig. 2). Ulcers are typically longitudinally oriented, separated by histologically normal edematous mucosa. Fissures, sinuses, and fistulas with associated abundant inflammation may be seen. Transmural inflammation occurs away from deep ulcers, a feature helpful in distinguishing CD from severe UC. Neural hyperplasia is common in the submucosa and muscularis propria. In both resections and biopsies, the presence of neutrophilic inflammation defines histologic activity.

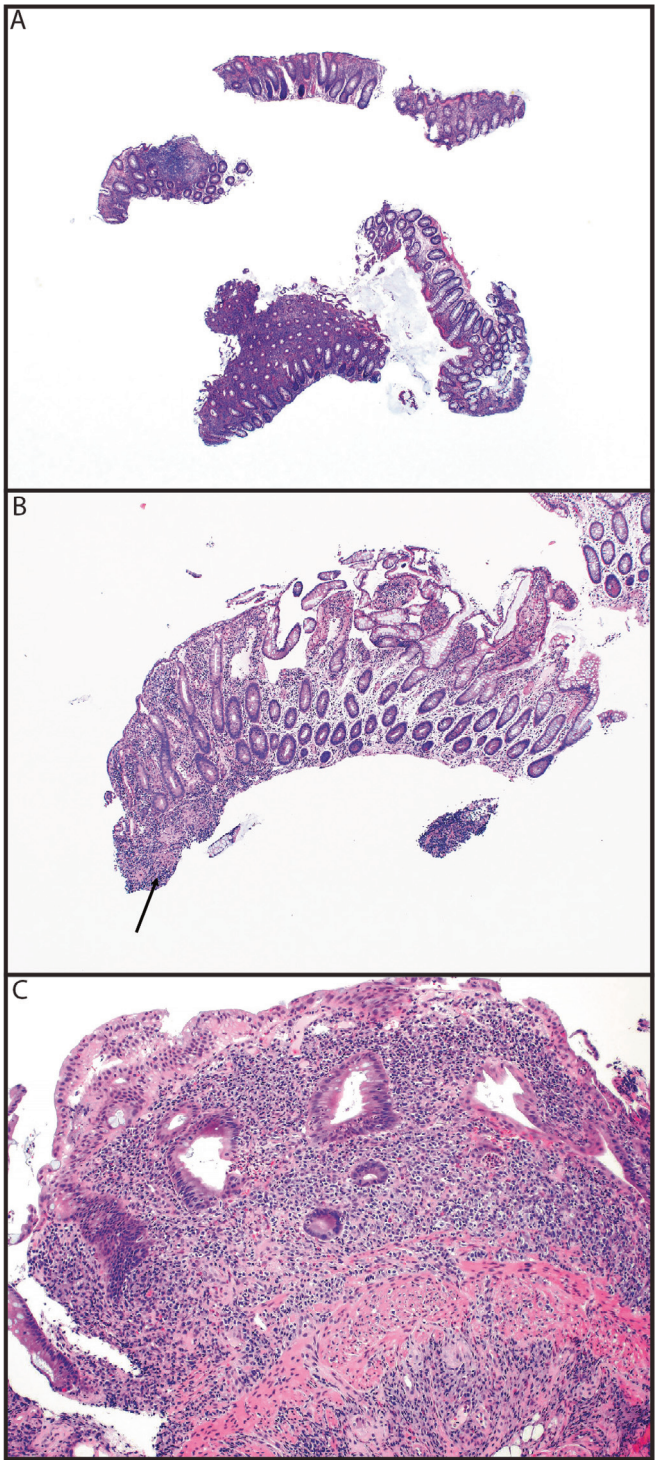

Fig. 1. Pathologic features of Crohn Disease on mucosal biopsies. **A.** Colonic biopsies with varying degrees of involvement by Crohn's disease. Some fragments demonstrate active inflammation and increased lamina propria chronic inflammation whereas other fragments are much less involved. **B.** Ileal biopsy fragment with more severe involvement of only a portion of the biopsy fragment (left). Rare mucosal granulomas are also seen (arrow). **C.** Well-developed features of a chronic active colitis that can be seen in both CD and UC characterized by basal plasmacytosis and mucosal neutrophilic inflammation.

Correlation between different measures of disease activity in CD

Endoscopic evaluation remains the gold standard when assessing disease activity in CD. More recently, imaging studies and biomarkers have been used to assess gut inflammation. However, there have been relatively few studies directly comparing these measures of disease activity with histology in CD.

Molander et al. studied 183 patients with Crohn's disease

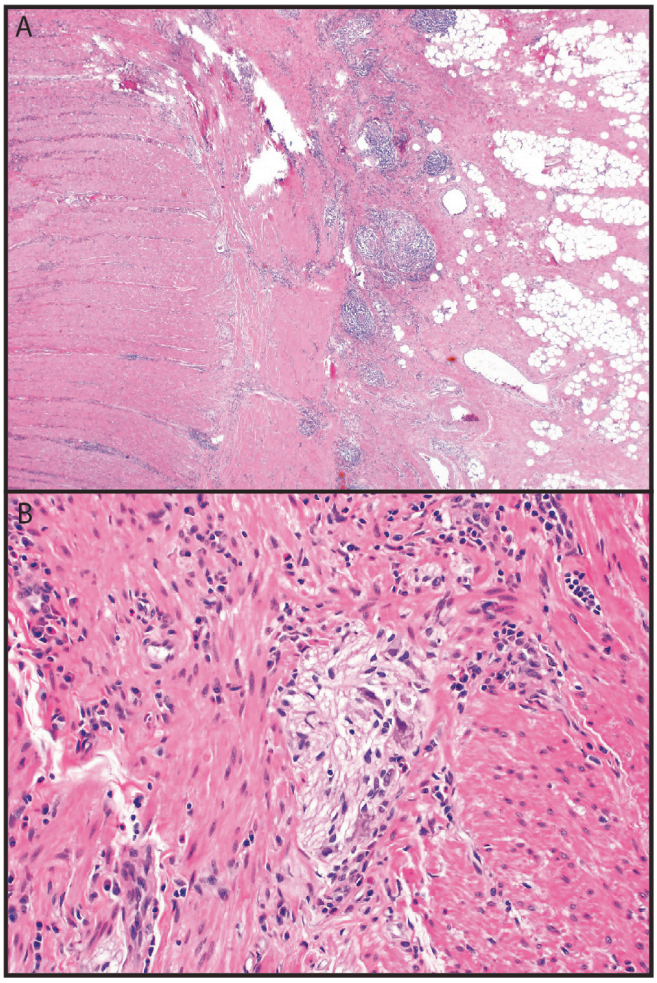

Fig. 2. Pathologic features of Crohn's Disease on resection specimens. **A.** Dense lymphoid aggregates are seen at the interface between the muscularis propria (left) and subserosal adipose tissue (right). **B.** Myenteric plexus (center) with lymphocytes within the ganglion. Lymphoplasmacytic inflammation is also seen surrounding this structure.

treated with infliximab and adalimumab [24]. Histologic activity was simply graded as normal or active. Interestingly, of the 79 patients in endoscopic and clinical remission, 25% had histologic evidence of activity suggesting that endoscopic and clinical measures may not adequately reflect microscopic gut inflammation. Fecal calprotectin (FC) and C-reactive protein (CRP) were also measured in this study. While FC and CRP were higher in those with endoscopically active disease compared to those without endoscopic activity, direct comparison with histology was not performed.

Baars et al. studied 46 patients with Crohn's disease in clinical remission. In this group, 33/46 (72%) patients were in endoscopic remission as measured by the Mayo endoscopic score [25]. Of the 13 patients with endoscopic activity, all but 12 had histologic evidence of active inflammation as defined by neutrophilic cryptitis and crypt abscess. However, 18 of the 33 (54%) patients in endoscopic remission had histologic activity on mucosal biopsies. The histologic activity was predominately mild in these patients characterized by neutrophilic cryptitis without crypt abscesses. In this study, treatment strategies did not change based on the presence of histologic inflammation alone. On a subsequent 2-year follow-up colonoscopy, the majority of those patients with histologic activity at baseline had persistent histologic inflammation. Interestingly, a significant proportion of those patients with both endoscopic and histologic inflammation at baseline, had only histologic inflammation at the 2-year follow-up colonoscopy further highlighting the disconnect between endoscopic and histologic measurements.

A recent study by Santha et al. evaluated the presence of endoscopic and histologic inflammation in 76 pediatric CD patients [26]. Endoscopy was measured by the simplified endoscopic activity score for CD (SES-CD) and histologic inflammation was simply graded as inactive or active (presence of neutrophilic inflammation). The correlation between SES-CD and histologic inflammation was only moderate with kappa of 0.44 (95% CI 0.24–0.65). Agreement was seen in 55/76 patients; however, in 10 patients, endoscopic activity was seen in the absence of histologic inflammation. Similarly, 11 patients had histologic inflammation in the absence of endoscopic lesions.

FC has been extensively studied as a biomarker of gut inflammation in both CD and UC although only a few studies have correlated FC with histology. FC had a strong correlation with histologic inflammation in a small study of 27 IBD patients (15 colonic CD, 12 UC) [27]. In a separate study of 38 patients with small bowel CD, histologic inflammation on resection specimens were evaluated using Chiorean's score which classifies CD into inflammatory and fibrostenotic types [28]. High levels of FC were seen in those patients with moderate and severe inflammatory activity compared to those with none to mild activity. No association with histologic inflammation was seen with CRP and erythrocyte sedimentation rate. Sipponen et al. correlated FC levels with endoscopic activity as measured by SES-CD and histologic disease as measured by the modified global histologic disease activity score (GHAS). In patients with ileocolonic and colonic CD, the colonic SES-CD correlated with FC. For those patients with ileal CD, there was no correlation between ileal SES-CD and FC. These overall results suggest that although there is some correlation between histologic activity and FC, the correlation may not be strong in those with primarily ileal CD.

Histology as a predictor of clinical outcomes

The benefits of achieving histologic remission in CD are less studied than in UC. In 1977 Ward and Webb evaluated 64 rectal biopsies from 27 patients with colonic CD [29]. Ten histologic features were evaluated and correlated to disease outcome including colectomy and death from disease. Histologic activity on the baseline biopsy was more severe in those patients who died from CD. This was the first study to suggest that histologic inflammation may predict outcomes.

More recently, Brennan et al. evaluated 62 CD patients in clinical remission who had a total of 103 colonoscopies over the study period [30]. The majority of the colonoscopic exams (55/103, 53%) revealed an SES-CD score of 0 indicating endoscopic healing. The proportion of patients with endoscopic healing who experienced a disease flare (defined by increased abdominal pain, increased stool frequency, and bloody stools) at 6 months, 12 months, and 24 months was not significantly different from those with endoscopic activity (9% vs. 13% $p = 0.58$, 11% vs. 17% $p = 0.53$, and 21% vs. 28% $p = 0.59$). Ileocolonic biopsies were also evaluated for the presence of active inflammation in these patients. In contrast to endoscopic healing, the absence of histologic activity predicted fewer disease flares at 12 months (2.4% vs. 25.5%, $p = 0.03$) and 24 months (10.5% vs. 37.8%, $p = 0.05$). At 6 months there was a trend towards decreased flares in the group without activity although this did not reach clinical significance (2.3% vs. 16.7%, $p = 0.07$). The presence both endoscopic and histologic remission did not better predict rates of disease flare. Confocal laser endomicroscopy (CLE) allows for in vivo assessment of the mucosa, and in a recent study of 49

patients with CD, the presence of activity on CLE demonstrated complete concordance with the presence histologic activity on mucosal biopsies [31]. The presence of microscopic inflammation correlated with increased CRP as well as the Crohn's Disease Activity Index (CDAI). No correlation was seen between microscopic activity as measured by CLE and the CD endoscopic index of severity (CDEIS). The presence of microscopic inflammation on CLE but not CDEIS or CDAI predicted treatment escalation and transmural adverse events (strictures and perianal disease) at 1 year of follow-up. These studies suggest that persistent microscopic inflammation may be associated with an increased risk of adverse clinical outcomes and may be more predictive than endoscopic measures of disease activity.

The significance of granulomas has been the subject of a few recent studies. Johnson et al. performed a retrospective study of 1466 adult patients with CD of whom 187 (12.8%) had granulomas on mucosal biopsies [32]. Granulomas were associated with increased steroid use, immunomodulators, biologics, narcotics, and higher CRP. Clinical activity and quality of life scores also indicated more severe disease. Finally, mean hospital and emergency department visits per year were higher in the granuloma group (0.49 vs. 0.25 $p < 0.0001$ and 0.60 vs. 0.38 $p < 0.0001$ respectively). Two recent studies have analyzed the significance of mucosal granulomas in pediatric CD. Ideström et al. evaluated 45 pediatric CD patients of which 28 (62%) had granulomas. In this study, granulomas were associated with a shorter time to initiating immune modulating treatment [33]. Rothschild et al. followed 289 pediatric CD patients, of which 99 (34%) had granulomas. Patient's with granulomas were more likely to be hospitalized (HR 1.43, 95% CI: 1.0–2.0) and to receive biologic therapy (HR 1.52, 95% CI 1.1–2.11).

Other studies have evaluated histologic features on resection specimens in order to determine features that predict recurrence [34]. Histologic involvement of the resection margin in the absence of macroscopic involvement appears to have little influence on the course of disease although there is some conflicting literature [35–37]. However, the degree of inflammation within the myenteric plexus or submucosal plexus may have prognostic significance. Ferrante et al. correlated the degree of inflammation within the myenteric plexus at the proximal resection margin in ileocolonic resection specimens with recurrence [38]. As little as one definite inflammatory cell within the myenteric plexus was classified as evidence of plexitis. Of the 32 patients with inflammation of the myenteric plexus at the proximal resection margin, 75% developed endoscopic recurrence at 3 months compared to 41% without this feature [38]. Subsequently, Sokol et al. demonstrated that $\geq$3 mast cells (identified by CD117 immunohistochemistry) within the submucosal plexus at the ileal resection margins was predictive of endoscopic recurrence [39]. Bressenot et al., in 2013 demonstrated that $\geq$1 eosinophil or >6 lymphocytes in the submucosal plexus predicted additional surgery [40]. In 2015, Misteli et al. found that $\geq$10 inflammatory cells within the myenteric plexus correlated with clinical and surgical recurrence [41]. Lastly, Lemmens et al., in 2017 demonstrated that lymphocytes ($\geq$1) within the submucosal plexus as measured on a CD45 immunohistochemical stain correlated with endoscopic recurrence [42].

There is conflicting literature on the significance of granulomas in surgical resection specimens. In one study of 600 adult CD patients that underwent surgery, granulomas were seen in 21% and were associated with repeat surgery during the study period [32]. Similarly, Anseline et al. found that granulomas were associated with recurrent disease necessitating repeat surgery [43]. However, other studies have found no such associations [44,45]. Finally, individual studies have identified decreased lymphatic vessel density at the resection margin [46] or increased abnormal Paneth cells within the ileum (as seen in patients with *NOD2* CD susceptibility variants) [47] with shorter time to disease recurrence.

Histologic response and remission as a treatment target

Only limited studies have assessed the feasibility of achieving histologic remission in CD [48]. In a study of 77 patients with steroid dependent CD treated with azathioprine versus budesonide, histologic improvement was only seen in the azathioprine group although complete remission was not achieved [49]. Patients treated with azathioprine also had improved clinical outcomes. In a retrospective analysis of 183 Crohn's patients treated with anti-TNFα agents, 79 (43%) achieved both clinical and endoscopic remission and 59 (32%) were in histologic remission suggesting that histologic remission is an achievable target [24]. In a single-center pediatric IBD practice, the rates of endoscopic and histologic healing in 76 CD patients treated with various medications was assessed. Endoscopic healing (as defined by SES-CD = 0) and histologic healing (defined as absence of active inflammation in all biopsies) was present in 45% and 46% respectively.

In a recent trial evaluating the efficacy of maintenance therapy with adalimumab, histologic activity was measured using GHAS [50]. Maintenance adalimumab was more effective than placebo at improving endoscopic inflammation, although endoscopic improvement was less pronounced in the right colon and terminal ileum. Histologic remission was identified in the colon in 28.3% of patients treated with adalimumab compared to 8.8% treated with placebo. Similarly, 21.2% of adalimumab-treated patients versus 2.9% of placebo-treated patients had histologic remission in the terminal ileum. In a phase 2a induction trial (the FTZROY study) of the Janus Kinase (JAK) Inhibitor, Filgotinib (GLPG0634, GS-6034), 60 (47%) of 128 patients treated with filgotinib 200 mg achieved clinical remission at week 10 versus ten (23%) of 44 patients treated with placebo (difference of 24% [95% CI 9–39], $p = 0.0077$) [51]. A statistically significant difference between filgotinib 200 mg and placebo was observed in the mean change from baseline in the global GHAS score. These overall results suggest that histologic remission is achievable in a minority of patients with current therapies.

Other studies have correlated the rates of histologic remission with serum concentrations of active drug. In 66 CD patients treated with maintenance adalimumab, 43.9% and 29.9% were in endoscopic and histologic remission respectively [52]. Persistent histologic inflammation was associated with lower serum concentration of adalimumab. Similarly, histologic activity was also associated with lower adalimumab concentrations in another study of 72 CD patients [53]. In a study evaluating the efficacy of infliximab in CD, histologic remission was associated with higher levels of active drug [54].

Histologic assessment of disease activity in CD specimens

Given the patchy nature of CD, using mucosal biopsies to evaluate disease activity can be problematic. Theoretically, mucosal biopsies may not adequately reflect deep inflammation; however, deep inflammation is almost always associated with mucosal disease on resection specimens. To date thirteen histologic scoring indices exist for Crohn's disease [55]. Table 1 provides detail on selected scoring systems in Crohn's. The most widely used is the GHAS which measures epithelial damage (i.e. surface injury, crypt destruction), architectural changes, infiltration of mononuclear cells within the lamina propria, neutrophils within the epithelium, presence of erosions/ulcers, presence of granulomas, and number of biopsy specimens affected [56]. Many studies have modified the GHAS to account for assessments of different segments as well as to

Table 1
Histologic scoring systems in Crohn's disease.

Histologic index	Key Features
Global histologic disease activity score (GHAS), 1998 [56]	Score ranges from 0 to 12 Items scored: Epithelial damage (0–2), architectural changes (0–2), infiltration of mononuclear cells in lamina propria (0–2), infiltration of neutrophils cells in lamina propria (0–2), Neutrophils in epithelium (0–3), Erosions/ulcers (0–1), granulomas (0–1), and number of biopsy specimens affected (0–3)
Naini and Cortina, 2012 [60]	Ileum and colon are scored separately Ileum: Architectural distortion (0–2), increased lymphocytes and plasma cells in lamina propria (0–2), neutrophilic inflammation including erosions/ulcerations (0–2), granulomas (0–1), pyloric gland metaplasia (0–1) Colon: Crypt architectural distortion (0–2), basal plasmacytosis (0–2), cryptitis and crypt abscesses (0–2), ulcers (0–1), granulomas (0–1), increased lamina propria eosinophils (0–2), Paneth cell or pyloric gland metaplasia (0–1), lymphoid nodules at base (0–1), muscularis mucosae hyperplasia and splaying of fibers/adipose tissue in mucosa/base of lamina propria fibrosis (0–1), hyperplasia of endocrine cells (0–1)
Brennan, 2016 [30]	Multiple histologic features evaluated in a semiquantitative manner 1. Epithelium: Paneth cell metaplasia of left colon, mucin depletion, erosion/ulceration 2. Architectural distortion: Crypt drop out or asymmetry,rare angulated crypts (mild), architectural distortion (moderate to severe) 3. Chronic inflammatory components in lamina propria: Increased, heterogeneous (skip); increased, homogenous (diffuse); basal plasmacytosis, basally located lymphoid aggregates 4. Active inflammation of the epithelium: neutrophils in the lamina propria, cryptitis,crypt abscess,increased eosinophils in the lamina propria 5. Granulomas
Robarts Histopathologic index, 2016 [61], used in UC but is likely applicable in CD	Based on the Geboes score. Measures those items that correlate with histologic severity, are reproducible, and respond to therapies. Calculated score that ranges from 0 to 33. RHI = 1 X Chronic inflammatory cell infiltrate (0–3) + 2 X Lamina propria neutrophils (0–3) + 3 X Neutrophils in epithelium (0–3) + 5 X Erosions or ulceration (0–3 [combines Geboes subscores 5.1 and 5.2])
Nancy index, 2016 [63], used in UC but is likely applicable in CD	5-point scale evaluating both chronic lamina propria inflammation and active inflammation Grade 0: No histological significant disease (no or only mild increase in chronic inflammatory cells) Grade 1: Chronic inflammatory cell infiltrate with no acute inflammatory cell infiltrate Grade 2: Mildly active disease Grade 3: Moderately active disease Grade 4: Severely active disease (ulceration)

only assess inflammatory changes [49,57–59]. More recently Naini and Cortina developed a scoring system in order to facilitate the histologic diagnosis of Crohn's disease [60]. However, this scoring system contains many variables that are not indicative of active disease but rather indicate chronic mucosal injury.

In UC, two scores, the Robarts Histopathology Index (RHI) and the Nancy index, have recently been extensively validated although they have not been systematically evaluated or validated in CD [61–63]. Disease activity in both diseases is predominately defined by the degree of neutrophilic inflammation and surface injury (ulcers and erosion). The RHI also assess the degree of lamina propria lymphoplasmacytic inflammation including basal plasmacytosis; features also seen in CD. Thus, from a histologic perspective, it is likely that these scores would have utility in measuring disease activity in CD.

For histologic measurements of disease activity to affect clinical practice, pathologists should agree upon which standardized features to report. Histologic features should correlate with clinical and surgical outcomes, be reproducible, and responsive to therapeutic intervention. Agreed upon definitions of what constitutes histologic healing and remission are also needed. Complete histologic healing could be defined as complete normalization of the mucosa while remission could indicate a mucosa with persistent architectural abnormalities without active (neutrophilic) inflammation (i.e. quiescent disease). In an International Organization of Inflammatory Bowel Disease initiative authored by Bryant et al., the following histologic target was proposed for both UC and CD [1]: absence of neutrophils (both in the crypts and lamina propria) [2], absence of basal plasma cells and ideally reduction of lamina propria plasma cells to normal, and [3] normal numbers of lamina propria eosinophils [64].

Basal plasmacytosis, defined as deep plasma cells separating colonic crypts from the muscularis mucosae, is a well-recognized pathological feature and has been shown to predict clinical relapse in some UC studies [5,10] but has not been evaluated in CD. What constitutes increased mucosal eosinophils is less clear as eosinophils are routinely present within the lamina propria of normal individuals. They tend to be more numerous in the right colon compared to the distal colon [65,66]. Most importantly, there is no agreed upon definition of what constitutes increased lamina propria eosinophils [67]. Furthermore, evaluation of lamina propria eosinophils has only moderate inter-observer agreement [68]. Given the lack of reproducibility and predictive data, reducing eosinophils to normal should not be included in the primary definition of histologic remission at this time.

Assessment of neutrophilic (active) inflammation both within the epithelium and lamina propria has been shown to be reproducible in the setting of UC [68] and is likely to have similar reproducibility in CD although this needs to be proven. Neutrophils are not normally present within the lamina propria or epithelium and have long been used to define active disease. Eliminating neutrophils from the mucosa should be the minimum requirement for histologic remission (Fig. 3).

As histologic disease activity is not currently considered in the management of patient's with Crohn's disease, rigorous assessment of activity using scoring systems in routine practice is not necessary. However, in order for any assessment of histologic disease activity in CD, standardized biopsy procurement protocols are needed. In a surgery naïve patient, this should include biopsies of the rectum, left colon, transverse colon, right colon, and terminal ileum. In patients with prior surgery or in patients with severe strictures, all accessible segments should be biopsied. Further research is needed to determine the optimum number of biopsies that are required per segment to reduce sampling variation.

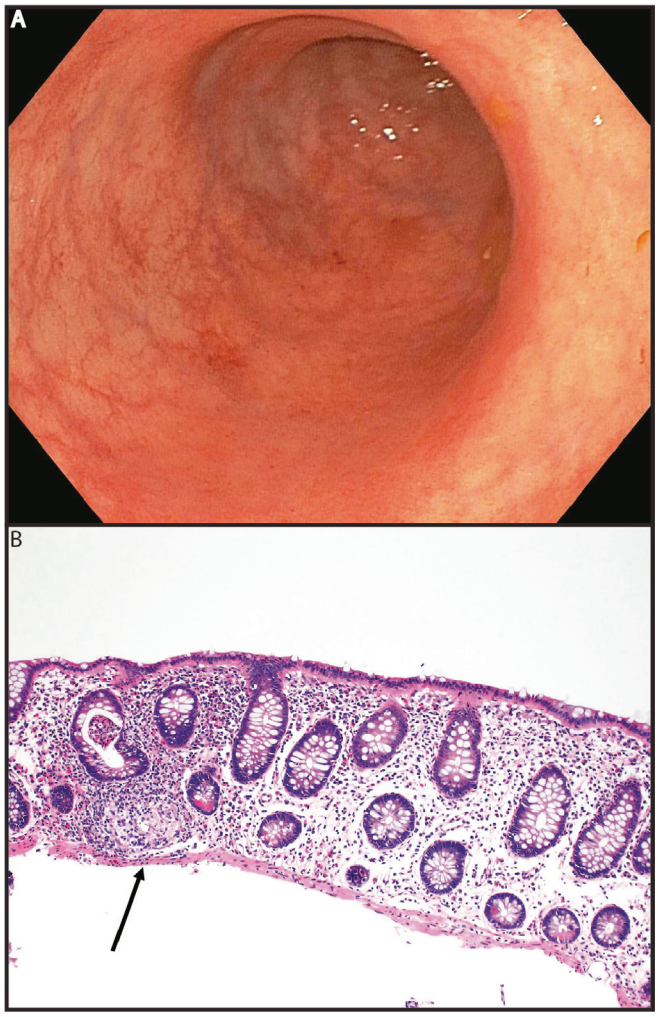

Fig. 3. Persistent histologic disease activity in the setting of normal colonoscopy. **A.** Normal endoscopic appearance of the left colon. **B.** Mild Crohn's colitis with focal crypt abscess and mucosal granuloma (arrow).

Biopsies should be taken from the edge of ulcers if present. If ulcers are not present, biopsies from the most macroscopically abnormal area should be procured. If the colonic mucosa appears normal, random biopsies should be taken. Some measurement of neutrophilic activity should be given in each segment and should be assessed on the most involved biopsy fragment. Basal plasmacytosis if present should be commented upon. Furthermore, the presence or absence of granulomas should be recorded.

Histologic evaluation of resection specimens will depend on the type of specimen received. In all specimens, the number, length, and severity of strictures and fistulas if present should be documented. The presence or absence of granulomas should be recorded. Although data is limited, histologic activity at the resection margins should be documented including presence of inflammation within the submucosal and myenteric plexus.

Conclusions

While current treatment targets in CD are based on symptoms and endoscopy, histologic assessment may have value. Histologic activity persists in CD patients in the absence of endoscopic lesions and, although the data is limited, this histologic inflammation may result in adverse clinical outcomes. Furthermore, histologic features on resection specimens can predict endoscopic recurrence. Histologic data should be collected in clinical practice and correlated with clinical outcomes. Randomized controlled trials are needed to determine whether histologic activity should guide medical therapy and if histologic remission should function as a distinct treatment target.

Practice points

- *Current treatment targets in Crohn's Disease include resolution of abdominal pain, normalization of bowel habit and endoscopic absence of ulceration*
- *An increasingly number of studies indicate that residual histological activity may persist in CD despite normal endoscopic mucosal appearance and is associated with adverse clinical outcome*
- *As a minimum, histopathologists should report on the presence of active inflammation (ulcers, erosion, and/or neutrophils in the lamina propria/ epithelium), basal plasmacytosis, and granulomas on mucosal biopsies.*
- *To assess histological activity in CD, endoscopists should procure biopsies from the ileum and each colonic segment from the edge of ulcers if present, or from the worst affected area, or randomly within each segment if the mucosa appears normal.*

Research agenda

- *A fully validated histological scoring for assessment of CD disease activity is required*
- *Further research is needed to understand the minimum number of biopsies that are required per segment to reduce sampling variation*
- *Prospective studies are required to demonstrate that treatment to resolution of histological inflammation is superior to resolution of endoscopic mucosal appearances only*

Conflicts of interest

RKP received consulting fees from Seres Therapeutics, Eli Lilly, Protagonist, Genentech, and Robarts Clinical Trials.

VJ has received has received consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genetech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert, Celltrion; speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie, Pfizer.

Funding

The authors have received no funding for this work.

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