Research article

The role of the pathologist in the assessment of disease activity in ulcerative colitis

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DOI: *http://doi.org/10.4038/jdp.v13i1.7749*

Submitted on 15.05.2018 Accepted for publication on 28.06.2018

Summary

In order to determine the role of the pathologist in assessing disease activity in UC, clinical and histological correlation of disease activity, correlation between endoscopy and histology and determining the most satisfactory method of scoring histological activity were assessed. A cohort of 41 patients attending a gastroenterology clinic in a tertiary hospital in Sri Lanka was studied. Their clinical activity was determined based on the simple clinical colitis activity index (SCCAI), endoscopically visible inflammation was recorded with reference to the extent of involvement and histology was assessed using three different histological scoring systems. The Spearman rank correlation coefficients between SCCAI and the three histological scoring systems were 0.298, 0.286, and 0.238 respectively denoting poor correlation. The kappa value of agreement between endoscopy and histology was poor (k=0.136). The Spearman rank correlation coefficients between the three histological scoring systems were 0.883, 0.883 and 0.952, reaching a level of statistical significance ($p<0.01$). The clinical activity and histological activity do not correlate and this is especially when assessing the more proximal colon. Endoscopy and histology also shows no correlation highlighting the importance of microscopic assessment of endoscopically normal mucosa. Finally, the histological scoring systems correlate fairly closely with one another enabling histopathologists to choose one that is most practical for routine use.

Key words: ulcerative colitis, disease activity, histological activity assessment

Introduction

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Chronic idiopathic inflammatory bowel disease as the name implies is a chronic inflammatory disorder of the gastrointestinal tract characterized by remissions and relapses. It

encompasses two major disease entities namely ulcerative colitis (UC) and Crohn disease (CD) and a group of conditions with overlapping features of UC and CD termed "Inflammatory bowel disease - unclassified" according to the World Congress in Gastroenterology, Montreal recommendations (1). Since this is a prolonged illness, the pathologist is often called upon to play varying roles during its course. These include the diagnosis of inflammatory bowel disease (IBD) and its differentiation from many other conditions that may mimic IBD on histology, the classification of IBD as UC or CD, the assessment of disease activity especially during exacerbations, and the diagnosis of dysplasia in IBD. In this article, our experience with regard to the role of the pathologist in assessing the disease activity in UC will be discussed. In this study we determined the place of histology, its correlation with other modalities of assessing disease activity such as clinical and endoscopic assessment and the best method of assessing histological activity (HA) in UC.

How is disease activity assessed in UC?

The complete assessment of disease activity in UC involves symptomatic evaluation, physical examination, measurement of laboratory indices, endoscopic visualization and the histological assessment of the mucosal inflammation (2). However, incorporating all these criteria to assess the disease activity is cumbersome and time consuming in practice and will delay therapy.

There are many different methods designed to assess the disease activity in UC, which incorporates the above parameters in different combinations. In routine clinical practice the disease activity and subsequent medical treatment is usually assessed largely by the clinical symptomatology.

Histological assessment (HA) of the degree of inflammation is the gold standard for evaluating the true disease activity. Although the HA may not be important in the everyday management of patients which often depends on the general wellbeing of the patient, it can be important in the choice of drug treatment, monitoring drug therapy and in therapeutic trials (3). The conventional use of histology in assessing disease activity is limited owing to its inconvenience, invasiveness and the cost (4).

Currently there is no gold standard for measuring the HA (3,5,6). Pathologists use different scoring systems depending on the ease of use and preference. These scoring systems combine chronic and acute changes and epithelial as well as inflammatory features. At least 18 HA indices have been described and compared but only a few have been formally validated (7,8).

Comparatively few studies have considered the question of whether histological parameters of disease correlate with clinical disease activity indices which rely heavily on subjective criteria (9).

Therefore, when studying the importance of histology in assessing disease activity in UC, the clinical and histological correlation of disease activity, the correlation between endoscopy and histology and determining the most satisfactory method of scoring histological activity need to be considered.

Hence a cohort of UC patients was studied to ascertain whether there was a correlation between three histological scoring systems and a currently used clinical scoring system in UC in order to determine which of these histological scoring systems correlates best with clinical activity (CA), to compare the extent of disease in UC as seen endoscopically versus that

determined histologically and to evaluate the correlation between these three different - histological scoring systems.

Method

Forty one UC patients attending the gastroenterology clinic at a tertiary referral center in Sri Lanka were studied. Seventeen out of these 41 patients were identified at the time of initial presentation and the remaining 24 patients were those being followed up at the clinic and were on treatment for UC.

The symptomatology and general well-being of the patients were assessed at the time of endoscopy using a patient information sheet, pre-designed to determine the Simple Clinical Colitis Activity Index (SCCAI) (2). The results of endoscopy were also included in this information sheet. The data in the questionnaire were utilized in calculating the SCCAI (Table 1).

17 out of 41 patients underwent sigmoidoscopic examination of the left colon and rectum whilst in 24 patients the entire colon was examined by colonoscopy. The relevant colonoscopic/ sigmoidoscopic series of biopsies stained with Haematoxylin and Eosin, were evaluated for histological scoring. A total of 136 biopsies were examined varying from 1 to 6 biopsy/ biopsies per individual patient (mean 3.2). At least six serial sections of each biopsy were examined. Each biopsy was scored on following histological scoring systems.

1. Histological scoring system A: Bristol histological activity index (5) Table 2
2 Histological scoring system B: by Saverymutty S H et al (6) Table 3
3. Histological scoring system C: by Geboes, et al (3) Table 4

Table 1: Clinical scoring system for the Simple Clinical Colitis Activity Index (2)

Symptom	score
Bowel frequency (day)	
1-3	0
4-6	1
7-9	2
> 9	3
Bowel frequency (night)	
1-3	1
4-6	2
Urgency of defecation	
Hurry	1
Immediately	2
Incontinence	3
Blood in stools	
Trace	1
Occasionally frank	2
Usually frank	3
General well being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extra colonic features	1per manifestation

The histological scoring was performed blind without the knowledge of the CA. The highest grade was considered to be the representative in patients where there is variation in the degree of inflammation. The biopsies were scored separately by two investigators. The cases with discrepancies between histological scores, were reviewed and a consensus score was achieved.

Table 2: Histological scoring index A - Bristol histological disease activity index for ulcerative colitis (5)

Inflammation	Score
Acute	
PMN* cells in lamina propria	1
PMN* cells in crypt wall	2
Crypt abscesses	3
Crypt destruction	4
Chronic	
Mild	1
Severe	2

*PMN-polymorhponuclear

The series of biopsies of individual patients were evaluated for the presence or absence of histological inflammation and were compared with endoscopic evidence of inflammation as recorded in the patient information sheet either as a diagrammatic representation of inflammation or as descriptive terms (proctitis, proctosigmoiditis, left sided colitis, right sided colitis or pancolitis).

The Spearman rank correlation coefficient was used to determine the correlation between the SCCAI and the different histological scoring systems as well as correlation among the three histological scoring systems. The agreement between the extent of disease as seen endoscopically versus that seen histologically was studied using kappa statistics.

Results

Patient characteristics

The age distribution of the population varied from 8 -71 years (mean age 38.4 years (SD 15.9)). Twenty-six out of 41 patients were females (63.5%). Seventeen were identified at the time of initial diagnosis and were not on medication. The other 24 were follow up patients on drug therapy.

Table 3: Histological scoring index B- by Saverymutty SH et al (6)

Histological feature	score
Enterocytes	
Normal	0
Loss of single cells	1
Loss of groups of cells	2
Frank ulceration	3
Crypts	
Normal	0
Single inflammatory cells	1
Cryptitis	2
Crypt abscesses	3
Lamina propria	
Mononuclear cells	
Normal	0
Slightly increased	1
Moderately increased	2
Markedly increased	3
Neutrophils	
Normal	0
Slightly increased	1
Moderately increased	2
Markedly increased	3

A wide range of CA was present in the study sample ranging from 0 – 12. A majority (n=24/41, 58.5%) showed a moderate CA (SCCAI of 5-8), whilst only 5 (20.8%) patients showed a SCAAI of 10 or more.

Table 4 : Histological scoring index C - by Geboes, et al (3)

Grade	Histological feature
Grade 0 Structural (architectural change): Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormality
0.3	Severe diffuse or multifocal abnormality
Grade 1 Chronic inflammatory infiltrate: Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2 Lamina propria neutrophils and eosinophils	
2A Eosinophils	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B.0	No increase
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3 Neutrophils in epithelium	
3.0	None
3.1	<5 % crypts involved
3.2	<50 % crypts involved
3.3	>50 % crypts involved
Grade 4 Crypt destruction	
4.0	None
4.1	Probable- local excess of neutrophils in part of crypt
4.2	Probable-marked attenuation
4.3	Unequivocal crypt destruction
Grade 5 Erosion or ulceration	
5.0	No erosion, ulceration or granulation tissue
5.1	Recovering epithelium +adjacent inflammation
5.2	Probable erosion- focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

Does CA and HA correlate?

The Spearman rank correlation coefficients between SCCAI and histological scoring systems A, B and C were 0.298, 0.286, and 0.238 respectively denoting a poor correlation between the CA and the HA. Therefore, none of the three histological scoring systems correlated with the SCCAI. When the study population was divided into two groups considering whether they are on drugs (n=24) or not (n= 17), a similar result was obtained denoting a poor correlation between CA and HA. (table 5)

Table 5: Spearman rank correlation between SCCAI and the different histological scoring systems in drug treated patients n= 24 and non treated patients n=17

	Spearman rank correlation coefficient	
	Drug treated n=24	Non drug treated N=17
SCCAI Vs histological score A	0.264	0.464
SCCAI Vs histological score B	0.282	0.339
SCCAI Vs histological score C	0.283	0.302

Is there a correlation between endoscopy and histology?

Seventeen patients had undergone sigmoidoscopic examination whilst 24 patients had undergone colonoscopic examination of the entire colon. A total of 136 endoscopic observations were compared with the histological appearance of the relevant site of the bowel. The results of endoscopic observation and the relevant histological appearance for the presence or absence of inflammation are shown in table 6**.**

Table 6: Results of endoscopic observation and the histological examination of the biopsies of corresponding region for the presence of inflammation

		Histology		
		positive	negative	
Endoscopy	positive	68	1	69
	negative	57	10	67
		125	11	136

kappa value of agreement between endoscopy and histology was 0.136 denoting a poor agreement. The kappa value of agreement for the patients on drug therapy and for the patients without drug therapy was 0.184 and 0.044 respectively, again denoting that the agreement between the endoscopic appearance and the presence of histological inflammation was poor.

The sensitivity of endoscopy in detecting the presence of true inflammation was studied for the different regions of the bowel. The results are shown in the Figure 1. Endoscopic examination had a high sensitivity in detecting proctitis. The sensitivity of endoscopic examination has gradually declined in detecting histological inflammation of more proximal colon.

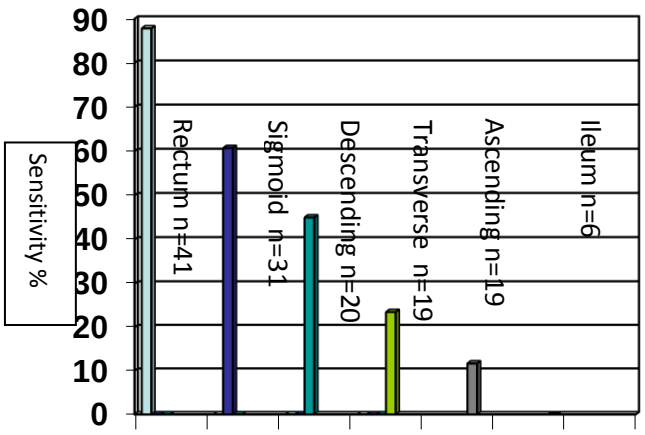

Figure 1: Sensitivity of endoscopy in detecting the presence of true inflammation in the different regions of the colon.

Is there agreement among the different histological scoring systems?

The correlation between the three histological scoring systems reached a level of statistical significance ($p<0.01$). The Spearman rank correlation coefficient between system A and system B was 0.883 (Figure 2), system A vs. system C was 0.883 (Figure 3) and system B vs system C was 0.952 (Figure 4).

Discussion

Assessing colonic mucosal histology obtained by endoscopic biopsy is the most reliable means of diagnosis of UC (10). However, it is an invasive, expensive and contraindicated test in acutely ill patients. Hence the family practitioners and the gastroenterologists use different CA indices to determine the activity of disease and to prescribe appropriate therapy.

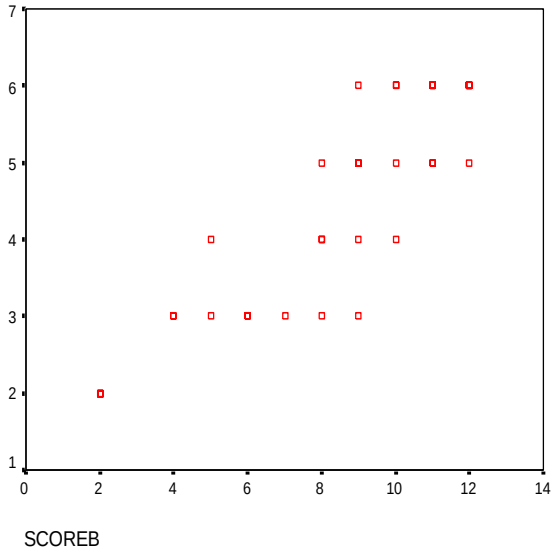

Figure 2: Correlation between histological scoring system A and B Spearman rank correlation coefficient 0.883 (p=0.01)

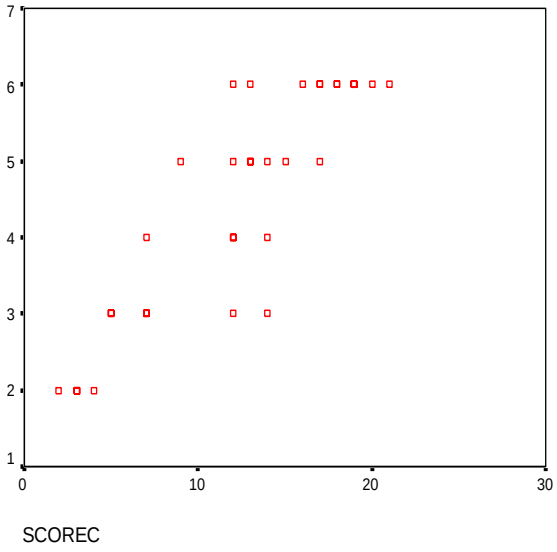

Figure 3: Correlation between histological scoring system A and C Spearman rank correlation coefficient 0.883 (p=0.01)

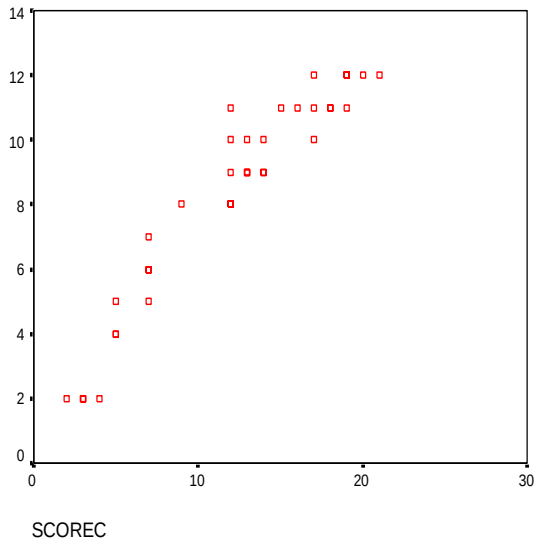

Figure 4: Correlation between histological scoring system B and C Spearman rank correlation coefficient 0.952 (p=0.01)

There is no clear gold standard for measuring disease activity in UC (11). Walmsley and colleagues developed the SCCAI in 1998. This index does not include the endoscopic appearance of the colon and therefore can be used at any level of medical practice (2). How good the SCCAI is, in predicting the underlying mucosal inflammation has not been tested. Our study shows that there is no correlation between the SCCAI and the HA as assessed by three different histological scoring systems. It is known that even in clinically quiescent disease, the mucosa may show features of acute inflammation (12). Riley and colleagues examined 82 patients with chronic quiescent disease over 12 months. The histological examination of the mucosa showed microscopic abnormalities in all specimens. A chronic inflammatory infiltrate was present in all. But in 32% of these there were features of acute inflammation (acute cell infiltration, mucin depletion and crypt abscesses) which were predictive of a relapse in a subsequent one year of follow up.

SCCAI is a survey of six questions about symptoms (2). Each criterion is sub grouped on a numerical scale to minimize the degree of bias towards the subjective component. However, the individual differences in the perception of these symptoms can make the assessment subjective. The patients will assess their general well being depending to large extent on the degree of disturbance to their personal life style.

In UC the intestinal inflammation is confined to the colonic mucosa. In active disease, this results in specific symptomatology with frequent diarrhea and blood loss. The complaints of a patient do not always represent the severity and extent of disease. Severe proctitis of 10cm or less may provoke more complaints than a moderate colitis over more than half of the colon (13). Thus in evaluating activity in UC, the significance of clinical parameters will vary with the anatomical distribution of disease. It has been suggested that anatomical site of involvement should be taken into account when analyzing the disease activity in UC (14). More severe proximal inflammation will possibly give rise to a lower CA.

Endoscopic examination of the colon is valuable in both clinical trials and clinical practice (11). In clinical practice, endoscopy is used in confirming the diagnosis, to evaluate the extent of disease, to evaluate disease that is unresponsive to therapy and to identify complications such as dysplasia or cancer. The histological examination of biopsies obtained at endoscopy yields valuable information that can help in the management.

Very little is known about the extent to which the endoscopy and histology correlate in determining the disease extent. Previous studies have shown that there is a discrepancy between

endoscopy and histology in regards to the extent of the disease (15,16,17). Our study gives similar results showing that there is a poor agreement between endoscopy and histology in UC. Lack of agreement is seen mainly in the endoscopically uninvolved region of the bowel. This is not surprising as endoscopy and histology do not assess the same morphological features. Endoscopic assessment depends mainly on the presence of macroscopic evidence of inflammation such as increased vascularity, oedema, friability and erosions. Focal active inflammation is likely to be missed on endoscopy, thus biopsies contributing additional information regarding the presence of inflammation. Therefore, it is appropriate to sample both abnormal as well as normal appearing mucosa in assessing the true extent of disease in UC.

Furthermore, our results show that the sensitivity of endoscopy in detecting histological inflammation decreases towards more proximal parts of the bowel. This becomes more significant when considering that more severe proximal inflammation gives rise to lower CA, a fact that has been discussed above.

There are many different systems of scoring the HA in UC. Microscopic activity in UC is based primarily on the presence of neutrophils and the amount of crypt and epithelial destruction caused by them (22). Histologically the neutrophil appears to be the effector cell causing the epithelial damage. It has been also shown that the presence of an acute inflammatory cell infiltration, crypt abscesses, mucin depletion and breaches in the surface epithelium is associated with a higher frequency of a relapse. The presence of a chronic inflammatory cell infiltrate or crypt architectural irregularities bear no relation to the frequency of relapse of colitis (19).

The Bristol histological activity system is a simple scoring system useful for the pathologist in routine practice. As most simple scoring systems are found to be highly reproducible this may be an additional advantage of this system. The scoring systems by Saverymutty et al and Gebboes et al are more precise and refined in that, in these systems each histological feature is sub categorized on a numerical scale to give a more objective result. These more complex scoring systems have been designed to aid in the assessing the effectiveness of therapy in UC rather than in the routine assessment of the biopsies (3).

Comparison of the Geboes, Riley, Gramlich and Gupta indexes have shown a good intra-observer reproducibility and a good inter-observer agreement and a strong correlation among these indices (20). Similarly when comparing the Geboes score and modified Riley score a ‘substantial' to 'almost perfect' intra-class correlation coefficients (ICCs) for intra-rater agreement were found in the assessment of histological activity though the corresponding inter-rater ICCs were substantially lower (21).

The current study also shows that there is a good correlation between the simple histological scoring system and the more complex scoring systems. Furthermore, the two complex systems showed excellent correlation with each other. (Spearman rank correlation coefficient 0.952). Therefore, any of these scoring systems may be recommended for use and the choice will depend on the ease of usage and personnel preference.

This study shows that the true disease activity in UC is a combined result of disease evaluation by

the clinician, endoscopist and the pathologist. In clinical practice it may not always possible to assess the involved bowel macroscopically and

microscopically due to inconvenience, invasiveness and cost. However, it is better to observe the changes occurring in the mucosa histologically as it is the most objective assessment of the true disease activity of this chronic relapsing disease (9).

The development of a simple, noninvasive test that accurately reflects HA in UC is clearly of importance in monitoring the disease progression. Thus attempts have been made to gauge disease activity non-invasively, the focus being mainly on inflammatory biomarkers such as Calprotectin and Lactoferrin. These two components of neutrophils when excreted in the faeces, have proven to be reflecting disease activity with good sensitivity and specificity (22). There is also growing evidence for newer biomarkers and it is likely that there is no single biomarker that will reliably measure disease activity in IBD. Much work is being done on a multitude of potential biomarkers, which when combined would likely to be more accurate and sensitive (23).

Conclusion

Our experience has shown that in UC the CA and HA do not correlate especially when assessing disease that involves the more proximal colon. Endoscopy and histology also shows poor correlation highlighting the importance of assessing endoscopically normal or non-inflamed mucosa resulting in the need to biopsy normal colonic mucosa as well. It is also evident that HA scoring systems correlate fairly closely with one another enabling the histopathologists to choose one that is most practical and simple for routine use.

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