Predicting Mucosal Proliferation in Ulcerative Colitis by Assessing Mucosal Vascular Pattern Under Narrow Band Imaging Colonoscopy

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ABSTRACT

Background: *Proliferative abnormalities are believed to represent an early phase of colorectal carcinogenesis. Narrow band imaging (NBI) colonoscopy allows visual assessment of the mucosal vascular pattern (MVP) without dyeing. The aim of this study was to investigate the predictive value of MVP for mucosal proliferation in ulcerative colitis (UC).*

Methods: *A total of 119 colorectal lesions were analyzed from 42 patients with UC who underwent NBI colonoscopy. Both the MVP and the Mayo endoscopic score (MES) were assessed. The mucosal inflammation was histologically graded using a colitis score. The proliferation marker Ki-67 was assessed by immunohistochemical staining.*

Results: *The results showed that MVP correlated well with the MES ($r = 0.796$, $P < .001$). There was moderate correlation between the distribution of Ki-67 staining and MVP ($r = 0.492$, $P < .001$), and the Ki-67 labeling index increased with the orderly patterns of MVP ($P < .001$). An expansion of Ki-67 staining upward from the crypt base may be caused by active inflammation.*

Conclusion: *MVP based on NBI colonoscopy can predict mucosal proliferation which is associated with inflammation in patients with UC.*

Keywords: *Ulcerative colitis, narrow band imaging, proliferation, inflammation*

INTRODUCTION

Ulcerative colitis (UC) is a chronic disorder characterized by relapsing mucosal inflammation of the colon. UC-associated chronic inflammation increases the risk of developing colorectal cancer. The duration, extent, and activity of the disease are the important risk factors for neoplastic transformation.[1] Persistent inflammation may repeatedly damage the epithelial cells, which is compensated by epithelial hyperproliferation. This suggests that long-term inflammation or repetitive renewals lead to epithelial changes that increase the tendency toward inflammation-associated dysplasia.[2,3] Disturbed proliferation is believed to represent an early step of colorectal carcinogenesis. An intensified activity of proliferation from normal colonic mucosa, colonic adenoma, to colonic cancer has been documented.[4] The Ki-67 antigen, which is present in the active phases of the cell cycle, is one of the better-known proliferation markers. An increase in the expression of Ki-67 and an abnormal distribution of Ki-67 staining have been demonstrated both in animal models and in human subjects at a high risk of gastrointestinal cancer.[5,6] The search for abnormalities of Ki-67 expression and distribution can be useful in estimating the risk of dysplasia and colonic cancer in patients with UC.[7,8]

Narrow band imaging (NBI) is an endoscope-based image-enhanced technology that enhances the fine structure of the mucosa without the use of dyes.[9] Because of its shorter withdrawal time and easier applicability compared with chromoendoscopy, NBI is useful for detecting dysplasia, the precursor of colorectal cancer in the colonoscopic surveillance of patients with UC.[10] It has been proposed that NBI colonoscopy is superior to white light endoscopy (WLE) for evaluating the mucosal vascular pattern (MVP) in patients with UC.[11] Previously, we demonstrated that NBI colonoscopy might be a useful tool to assess mucosal angiogenesis according to the MVP in UC.[12] However, there is a lack of studies investigating the correlation between the MVP

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based on NBI colonoscopy and the histological assessment of epithelial proliferation in UC. The aim of the current study is to explore whether mucosal proliferation in UC can be predicted by assessing the MVP under NBI colonoscopy.

MATERIALS AND METHODS

Patients

Between December 2012 and January 2015, patients with UC were considered for recruitment into the study. The diagnosis of UC was made based on symptomatic, endoscopic, and histological criteria. For each patient, the range of colonic involvement was identified by total colonoscopy, and the disease severity was determined using the Mayo score.[13]

Colonoscopy Procedure

For each patient, colonoscopy was performed using an endoscope (CF-H260AI; Olympus, Tokyo, Japan) with a prototype of the NBI system (Evis CV-260; Olympus). The colonoscope was advanced to the cecum and a routine observation was performed during withdrawal. The colorectum was divided into six segments (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum). For each segment, the most severe inflamed area was first identified using WLE, and then the imaging mode was switched to NBI. Both WLE and NBI images were captured and saved for later assessment. From the same lesion observed by WLE and NBI, at least one mucosal specimen was biopsied for histological assessment.

Image Analysis

All WLE and NBI images from the target area were randomly assigned to two experienced endoscopists for evaluation who were unaware of the clinical data. In case of controversy, a consensus was reached after consultation. The endoscopic activity under WLE was classified into 4 degrees from 0 to 3 (0: inactive, 1: mild, 2: moderate, 3: severe) according to Mayo endoscopic score (MES).[13] Based on the previous method,[12] the MVP under NBI was divided into the following 3 types: clear pattern, for a segment with a clear mucosal vascular network; obscure pattern, for a segment with a blurred mucosal vascular network; absent pattern, for a segment with an invisible mucosal vascular network. According to the observation of the surface pattern, the absent vascular pattern was subclassified into the following 2 types: crypt opening pattern, for a segment with whitish round crypts; villous pattern, for a segment with villous structures.[12]

Histological and Immunohistochemical Assessment

Based on a histological colitis score,[12] the grade of inflammation was classified into the following 4 categories: 0, no inflammation; 1, chronic inactive inflammation; 2, mild active inflammation; 3, moderate active inflammation; 4, severe active inflammation. An immunohistochemical assessment of antigen was performed using an Autostainer system (DakoCytomation, Carpinteria, CA) and a Ventana Benchmark XT Autostainer (Ventana Medical Systems Inc., Tucson, AZ). One antibody was used for Ki-67 (Zsbio Commerce Store, Beijing, China). The Ki-67 expression was considered to be a positive reaction when nuclear cell staining was evident with the intensity above background. The results of Ki-67 staining were presented as a percentage of positive cells among 500 counted cells (labeling index) and divided into the following four patterns according to the distribution of Ki-67 staining: basal zone, positive cells confined to the lower third of the crypt; middle zone, positive cells expanded to the middle third; top zone, an expansion to the upper third; surface, positive cells presented on the surface epithelium.[14] In our study, cells were counted along whole crypts up to the mucosal surface. The histological features were analyzed by a veteran pathologist who did not have access to the endoscopic findings.

Statistical Analysis

All statistical analyses were performed using the IBM SPSS Statistics 22 software package (IBM, New York, NY, USA). Wilcoxon Mann–Whitney U tests and Kruskal–Wallis tests were used for nonparametric values and a one-way analysis of variance (ANOVA) was used for the parametric values. For correlations, Spearman's rank correlation coefficient was used. The predictive power of the diagnostic model was evaluated using receiver operating characteristics (ROC) analysis, and the cutoff value was obtained when the Youden index reached the maximum. Sensitivity, specificity, and area under the ROC curve (AUC) were used to assess the prediction accuracy. A two-tailed P value < .05 was defined as statistically significant. The statistical methods of this study were reviewed by a biomedical statistician.

RESULTS

Patient Characteristics

A total of 42 UC patients (aged between 26 and 72 years, median age = 45 years) who underwent colonoscopy were recruited into this study; 25/42 (60%) were male. Clinical characteristics are shown in Table 1. According to

Table 1. Clinical Characteristics of Patients with Ulcerative Colitis (UC)

Clinical characteristics	*n* (%)
Patients with UC	42
Sex	
Male	25 (59.5%)
Female	17 (40.5%)
Age (years), median (range)	45 (26-72)
Disease duration (years), median (range)	4.1 (3-19)
Maximum extent of UC	
Extensive colitis	8 (19%)
Left-sided colitis	27 (64.3%)
Proctitis	7 (16.7%)
Disease severity of UC	
Inactive (Mayo score: 0-2)	9 (21.4%)
Mild activity (Mayo score: 3-5)	18 (42.9%)
Moderate activity (Mayo score: 6-10)	10 (23.8%)
Severe activity (Mayo score: 11-12)	5 (11.9%)

UC, ulcerative colitis.

colonoscopy and Mayo score, both the extent of colonic involvement and the disease activity were assessed.

Colonoscopic Findings

A total of 119 colorectal segments from 42 UC patients were analyzed. Based on the images of WLE and NBI colonoscopy, the MES and the MVP were determined. The endoscopic findings are shown in Table 2.

Correlation Between the MVP and the MES

Table 3 shows the relationship between the MVP and the MES. We observed that in the clear pattern group, 58.8% (20/34) and 41.2% (14/34) of the segments were identified as MES 0 and MES 1. In the obscure pattern group, 56.9% (33/58) and 32.8% (19/58) of the segments were identified as MES 1 and MES 2. In the absent pattern group, 33.3% (9/27) and 66.7% (18/27) of the segments were identified as MES 2 and MES 3. It was shown that the orderly types of MVP correlated well with the grades of MES (r = 0.796, P <.001).

Table 2. Colonoscopic Findings of Patients With Ulcerative Colitis

Colonoscopic findings	*n* (%)
Colorectal segments	119
The MVP assessed using NBI colonoscopy	
Clear	34 (28.6%)
Obscure	58 (48.7%)
Absent	27 (22.7%)
Crypt opening	11 (9.2%)
Villous	16 (13.4%)
The MES assessed using WLE	
MES 0	26(21.8%)
MES 1	47(39.5%)
MES 2	28(23.5%)
MES 3	18(15.1%)

MVP, mucosal vascular pattern; MES, Mayo endoscopic score; NBI, narrow band imaging; WLE, white light endoscopy.

Comparisons of the Ki-67 Staining in the Mucosal Patterns

Table 4 shows the distribution of Ki-67 staining in orderly types of mucosal patterns. We observed that in the clear pattern, there was a predominance (76.5%, 26/34) of Ki-67 positive cells limited to the crypt base, and only 2.9% (1/34) of the specimens showed Ki-67 staining expanded to the top zone, and no staining was noted at the surface. In the obscure pattern, 82.8% (48/58) of Ki-67 staining was confined to the lower two-thirds of the crypts. In the absent pattern, 59.3% (16/27) of the specimens showed Ki-67 staining extended to the middle zone; in addition, 29.6% (8/27) of the specimens moved to the top zone or surface. Compared to the clear pattern, either the obscure pattern or the absent pattern

Table 3. The Correlation Between the MVP and the MES

	Classification of Mucosal Patterns Using NBI				
MES	Clear (n = 34)	Obscure (n = 58)	Absent (n = 27)	Crypt opening (n = 11)	Villous (n = 16)
0	20	6	0	0	0
1	14	33	0	0	0
2	0	19	9	4	5
3	0	0	18	7	11

MVP, mucosal vascular pattern; MES, Mayo endoscopic score; NBI, narrow band imaging.

Table 4. Ki-67 Staining in Mucosal Patterns (Mean ± SD)

		Classification of Mucosal Pattern Using NBI				
		Clear (*n* = 34)	Obscure (*n* = 58)	Absent (*n* = 27)	Crypt opening (*n* = 11)	Villous (*n* = 16)
Distribution of Ki-67 staining	Basal zone	26	18	3	1	2
	Middle zone	7	30	16	7	9
	Top zone	1	8	5	2	3
	Surface	0	2	3	1	2
Ki-67 (labeling index, %)		15.6 ± 7.3	30.3 ± 12.8*	45.9 ± 12.5#	45.5 ± 12.1	46.3 ± 13.1

*P < .001 *vs* clear pattern, #P < .001 *vs* obscure pattern.
NBI, narrow band imaging.

showed an extension of Ki-67 staining beyond the basal zone (P < .001). However, no difference in Ki-67 staining distribution was noted between the crypt opening pattern and the villous pattern (P = .933). In general, a moderate correlation was found between the distribution of Ki-67 staining and the MVP determined under NBI colonoscopy (r = 0.492, P < .001).

With regard to the counting of the Ki-67 positive cells (labeling index), Table 4 shows an increasing change along with the ordered types of the MVP. The Ki-67 labeling index was significantly higher in the obscure pattern compared with the clear pattern (30.3 ± 12.8 vs 15.6 ± 7.3, P < .001), as well as higher in the absent pattern compared with the obscure pattern (45.9 ± 12.5 vs 30.3 ± 12.8, P < .001). However, between the crypt opening pattern and the villous pattern, there was no significant difference in the counting number of Ki-67 staining cells (45.5 ± 12.1 vs 46.3 ± 13.1, P = .741).

Correlation Between the Ki-67 Staining and the Severity of Histological Inflammation

Table 5 shows the staining distribution of Ki-67 in the lesions with orderly grades of histological inflammation. We observed that in the lesions with histological colitis score 1, 70% (28/40) showed Ki-67 positive cells confined to the crypt base and 30% (12/40) extended to the middle zone. In the lesions with score 2, 91.9% (34/37) showed staining limited to the lower two-thirds of the crypts. In the lesions with score 3, 51.9% (14/27) showed staining extended to the middle zone and 37.0% (10/27) moved to the top zone or surface. In the lesions with score 4, 46.7% (7/15) showed staining extended to the middle zone and 40.0% (6/15) moved to the top zone or surface. It was shown that a moderate correlation was detected between the distribution of Ki-67 staining and the severity of histological inflammation (r = 0.555, P < .001).

With regard to the counting of the Ki-67 positive cells (labeling index), an increased tendency along with the severity of histological inflammation was observed in Table 5. The Ki-67 labeling index was significantly higher in score 2 compared with score 1 (28.8 ± 10.9 vs 17.1 ± 8.4, P < .001), as well as higher in score 3 compared with score 2 (40.2 ± 11.6 vs 28.8 ± 10.9, P < .001) and higher in score 4 compared with score 3 (49.5 ± 10.3 vs 40.2 ± 11.6, P < .001). The predictive power of the Ki-67 labeling index for diagnosing severe active inflammation (histological

Table 5. The Correlation Between Ki-67 Staining and the Severity of Histological Inflammation (Mean ± SD)

		Grades of Histological Inflammation (Histological Colitis Score)				
		0 (*n* = 0)	1 (*n* = 40)	2 (*n* = 37)	3 (*n* = 27)	4 (*n* = 15)
Distribution of Ki-67 staining	Basal zone	0	28	14	3	2
	Middle zone	0	12	20	14	7
	Top zone	0	0	3	7	4
	Surface	0	0	0	3	2
Ki-67 (labeling index, %)		0	17.1 ± 8.4	28.8 ± 10.9*	40.2 ± 11.6#	49.5 ± 10.3&

*P < .001 *vs* score 1, #P < .001 *vs* score 2, &P < .001 *vs* score 3.

colitis score 4) was assessed using ROC analysis and AUC was calculated to be 0.883 (95% CI, 0.807-0.960). The optimal cutoff value was obtained to be 35.0 points based on the Youden index, and the lesion with a Ki-67 labeling index (%) ≥35.0 was diagnosed as severe active inflammation. By using the optimal cutoff value, the sensitivity and specificity of the diagnosing model was 86.7% and 71.2%, respectively.

DISCUSSION

Histological disease activity has been suggested as a predictor of early clinical recurrence in patients with UC.[15] Thus endoscopy, with an essential role in identifying the severity of histological inflammation in the intestinal mucosa, is critical for the surveillance and treatment of the disease. The MES based on WLE assessment is widely used as an objective method to describe the degree of endoscopic activity in UC and has been validated to have a significant overall correlation with histological severity.[16] In most studies, the MES was used to evaluate the most severely affected segment of the colon and seldom considered the range of colon involvement. Because of the better visualization of the mucosal surface and vascular patterns, NBI colonoscopy may be more effective in evaluating areas with inflammation in UC in comparison with WLE.[17,18] In our previous study, we first divided the MVP of UC into 3 categories (clear pattern, obscure pattern, and absent pattern) using NBI colonoscopy and demonstrated that the MVP had a good correlation with the severity of histological inflammation.[12] However, it is still unclear whether the MVP based on NBI versus the MES based on WLE can predict mucosal inflammation in clinical practice. In the current study, the MES was modified to evaluate the severity of inflammation in accordance with the multiple involved segments of colon. We compared the capabilities of NBI colonoscopy with WLE in assessing the disease activity in UC, and the result indicated a good correlation between the MVP and the MES.

Previous studies have shown that in normal mucosa of colon, a majority of cell proliferation is confined to the crypt base. For patients with UC, a different Ki-67 staining distribution, with a shift of the positive cells from the basal to the superficial part of the crypts, seems to be a well-recognized finding in areas of dysplasia or carcinoma, which might help to distinguish dysplasia from epithelial regeneration when mutual discrimination is difficult to ascertain by histology alone.[4,7,19] Our study showed that the confinement of Ki-67 staining to the crypt base is a feature of the clear pattern. Furthermore, the obscure pattern was characteristic of the limitation of Ki-67 staining to the lower two-thirds of the crypts. But in the absent pattern, 18.5% (5/27) and 11.1% (3/27) of the specimens showed an extension of Ki-67 positive cells to the top zone and surface, respectively. We further demonstrated that severity of histological inflammation was moderately correlated to the distribution of the proliferative zone. This suggests that an upward expansion of the proliferative zone may be a result of active inflammation. Our data support the results of previous studies that the confinement of Ki-67 staining to the crypt base is not a feature of UC-related dysplasia. In addition, the limitation of Ki-67 positive cells to the lower two-thirds of the crypts might exclude a determination of high-grade dysplasia.[20] However, since we did not identify histological dysplasia in this study, our findings refute the previously demonstrated suggestion that the expansion of Ki-67 staining to the crypt top or surface is a specific sign of UC-related dysplasia.[7,19] It presumably reflects that persistent inflammation and repeated regenerative hyperplasia may eventually result in epithelial abnormalities, which trigger or predispose to dysplasia.

We also found that there was an increase in the total Ki-67 labeling indices from the mucosa of the clear pattern, through the mucosa of the obscure pattern, to the mucosa of the absent pattern. In addition, the total Ki-67 labeling indices and the Ki-67 staining pattern could not show any differences between the crypt opening pattern and the villous pattern, which corresponds with our previous result that there were no differences in the inflammatory degree between the two patterns.[12] Furthermore, our results also showed that the Ki-67 labeling indices increased significantly along with the activity of histological inflammation. The Ki-67 labeling index, with an AUC of 0.883 using ROC analysis, had a good capability to predict severe active inflammation (histological colitis score 4). By using the optimal cutoff value, the sensitivity and specificity of the diagnosing model were 86.7% and 71.2%, respectively. Therefore, we conclude that Ki-67 expression correlates with inflammatory activity and the increased cell proliferation may be due to epithelial hyper regeneration as a result of active inflammation in UC.[20]

There are limitations to our study. First, because the sample size is small and from a single center, this study is regarded as preliminary research. Second, since no dysplasia was identified by histology, we did not assess the ability of NBI colonoscopy to detect dysplasia in UC. Third, no assessment was made on inter-observer variation. Furthermore, during the NBI assessment of mucosal patterns, the

appearance of ulcers or spontaneous bleeding is the main disadvantage to clear observation; therefore, only a few UC patients with severe disease activity were included. To further corroborate our results, prospective multicenter studies involving larger samples, lesions with dysplasia, and inter-observer comparison are required.

In conclusion, our data suggest that the MVP based on NBI colonoscopy correlates well with the MES based on WLE in patients with UC. Based on the types of MVP, NBI colonoscopy can predict the activity of proliferation which is associated with inflammation; furthermore, it may help in the surveillance of lesions that are predisposed to dysplasia.

Ethics Committee Approval: This study protocol conformed to the ethical guidelines of the 1964 Helsinki Declaration and its later amendments and was reviewed and approved by the Ethics Committee of our Medical College Hospital (Protocol number: S-K508).

Informed Consent: Written and verbal informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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