INFLAMMATORY BOWEL DISEASE

Pit patterns in rectal mucosa assessed by magnifying colonoscope are predictive of relapse in patients with quiescent ulcerative colitis

Y Nishio, T Ando, O Maeda, K Ishiguro, O Watanabe, N Ohmiya, Y Niwa, K Kusugami, H Goto

Gut 2006;55:1768–1773. doi: 10.1136/gut.2005.086900

See end of article for authors' affiliations

Correspondence to:
T Ando, Department of
Gastroenterology, Nagoya
University Graduate
School of Medicine, 65
Tsurumai-cho, Showa-ku,
Nagoya 466-8550,
Japan;
takafumia-gi@umin.ac.jp

Revised 30 March 2006
Accepted 5 April 2006
Published Online First
8 May 2006

Background: Relapse of ulcerative colitis is difficult to predict by routine colonoscopy. A high-resolution video-magnifying colonoscope with chromoscopy enables the observation of colorectal mucosal pit patterns.

Aims: To investigate the association of pit patterns as assessed by magnifying colonoscopy (MCS) with histological inflammation and mucosal chemokine activity in patients with quiescent ulcerative colitis, and to prospectively analyse the prognostic factors that may predict exacerbations.

Methods: MCS was performed in 113 patients with ulcerative colitis in remission. Pit patterns in the rectal mucosa were classified into four MCS grades on the basis of size, shape and arrangement. Mucosal interleukin (IL) 8 activity was measured in biopsy specimens of rectal mucosa and the specimens were assessed for histological disease activity. The patients were then followed until relapse or for a maximum of 12 months. Multivariate survival analysis was carried out to determine the independent predictors of clinical relapse.

Results: A positive correlation was identified between MCS grade, histological grade ($p=0.001$) and mucosal IL8 activity ($p<0.001$). Multivariate proportional hazard model analysis showed that MCS grade was a significant predictor of relapse (relative risk 2.06, $p=0.001$). Kaplan–Meier estimate of relapse during 12 months of follow-up was found to increase with increasing MCS grade, with values of 0% for grade 1, 21% for grade 2, 43% for grade 3 and 60% for grade 4.

Conclusion: MCS grading is associated with the degree of histological inflammation and mucosal IL8 activity in patients with quiescent ulcerative colitis, and may predict the probability of subsequent disease relapse in patients with ulcerative colitis in remission.

Ulcerative colitis is a chronic inflammatory bowel disorder characterised by exacerbations and remissions. Endoscopic study is an important means of assessing the severity of ulcerative colitis and predicting the efficacy of treatment.¹ Although the degree of inflammation as assessed by routine colonoscopy is a reliable parameter of disease activity, discrepancies between colonoscopic appearance and histopathological abnormalities are sometimes seen in patients with clinically inactive disease. Even when routine colonoscopy suggests remission and a normal mucosal appearance, microscopic abnormalities may persist^{2–3} and relapse may occur later.⁴

A recently developed high-resolution video-magnifying colonoscope has enabled the observation of pit patterns on the surface of the colorectal mucosa. This in turn allows an understanding of the morphological relationship between the pit patterns detected colonoscopically and the crypts observed histopathologically.^{5–9} The purpose of this technology is to provide an *in vivo* optical biopsy that can be used at the time of colonoscopy to enhance diagnostic precision and guide subsequent therapeutic strategies. In particular, a magnified view of the diseased colon and rectum may be useful in predicting exacerbations of the disease and in deciding whether medical treatment should be maintained. As far back as 1980, Poulsen *et al*¹⁰ examined biopsy specimens from the rectal mucosa of patients with ulcerative colitis under a stereomicroscope and found microstructural abnormalities in the mucosal surface in almost every patient, as well as a close correlation between stereomicroscopic features and clinical

disease activity, sigmoidoscopic findings and histological activity of the disease.

Among other activities, cytokines have a role in modulating the immunopathogenesis of inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease, and are rapidly synthesised and secreted by inflammatory cells.^{11–12} Interleukin (IL) 1, IL6, IL8, tumour necrosis factor α and growth-related gene product α have all been described as major factors increasing the inflammatory response in intestinal tissue in patients with IBD.^{11–14} Recent studies^{15–19} have shown that cytokine measurement can detect subtle but ongoing escalation of the inflammatory process in the mucosa of patients with IBD before clinical symptoms and endoscopic inflammation are apparent.

To help more accurately identify disease activity in patients with ulcerative colitis with clinically inactive disease, we examined pit patterns in the rectal mucosa with a high-resolution video-magnifying colonoscope after spraying with methylene blue and compared the findings with laboratory test results for inflammation, histopathological findings and mucosal IL8 activity. We also prospectively analysed prognostic factors that might predict exacerbations in patients with ulcerative colitis, including the pit patterns observed with high-resolution video-magnifying colonoscopy.

Abbreviations: CRP, C reactive protein; DAI, disease activity index; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; MCS, magnifying colonoscopy; WBC, white cell count

Figure 1 Grading of pit structures in the colorectal mucosa of patients with inactive ulcerative colitis. (A) Magnifying colonoscopy (MCS) grade 1: pits small, round and regularly arranged. (B) MCS grade 2: pits rather large, oval and somewhat irregular in arrangement. (C) MCS grade 3: pits of various shapes and sizes and irregularly arranged. (D) MCS grade 4: dispersed pits varying in morphology associated with the presence of small erosions.

MATERIALS AND METHODS

Participants

The study was conducted according to a prospective design in patients with clinically inactive ulcerative colitis, who underwent high-resolution video-magnifying colonoscopy (EC-410CM; Fujinon, Saitama, Japan) at the Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, Japan, between March 1995 and April 2000. Clinical disease activity was assessed in each patient by the ulcerative colitis disease activity index (DAI) score covering four items, each scored from 0 to 3—namely, stool frequency, stool blood, endoscopic severity and overall well-being.²⁰ In accordance with the definition of Oren *et al*,²¹ DAI scores of ≤ 3 were judged to represent clinical remission. Only patients with an inactive mucosal appearance, obscure vascular patterns, granularity of the mucosa or erythema on routine high-resolution video-colonoscopy examination (EC-410HM; Fujinon) were included, whereas those with contact bleeding, spontaneous bleeding, erosions or ulceration were excluded. Moreover, patients who were on immunosuppressant treatment or had a higher degree of inflammation at the proximal colon were excluded. Ulcerative colitis was diagnosed in all patients on the basis of previous colonoscopic and histopathological examinations with unequivocal features of active ulcerative colitis including the rectum. Informed consent was obtained from all patients in accordance with the Helsinki Declaration.

High-resolution video-magnifying colonoscopy

Each patient was pretreated with an oral agent for bowel cleansing—ie, 2 l of polyethylene glycol. After examination of the entire bowel by conventional colonoscopy, mucus was

completely removed from the rectum by sufficient irrigation with water, and 20–30 ml of 0.1% methylene blue was sprayed over the mucosa. The colonoscope was removed, and the patient's posture was altered repeatedly between prone and supine for 5 min. A high-resolution video-magnifying colonoscope with a fixed focus (Fujinon EC410CM) was then inserted, and the pit pattern of the rectal mucosa and methylene blue staining were recorded. The patterns were classified into the following four magnifying colonoscopy (MCS) grades on the basis of the size, shape and arrangement of the pits (fig 1).

- Grade 1: pits small, round and regularly arranged (fig 1A).
- Grade 2: pits rather large, oval and somewhat irregular in arrangement (fig 1B).
- Grade 3: pits of various shapes and sizes and irregularly arranged (fig 1C).
- Grade 4: dispersed pits varying in morphology, associated with the presence of small erosions (fig 1D).

When the characteristics of more than one grade were present in the same patient, the higher grade was recorded.

When κ coefficients were calculated to examine the degree of agreement between readers on MCS grade, preliminary study confirmed that the intraobserver and interobserver coefficients for MCS grade were 0.89 and 0.79, respectively. There was no discordance of ≥ 2 MCS grades in either intraobserver or interobserver agreement.

Laboratory test and histological disease activity

Blood samples were obtained immediately before colonoscopy; white cell count (WBC), C reactive protein (CRP) and

Table 1 Patient characteristics and clinical profile by magnifying colonoscopy profile

MCS grade	Sex (M/F)	Age* (years)	Disease duration* (years)	Disease extent total/left-sided/proctitis
1, n=19	14/5	34.4 (20–61)	5.3 (0.6–13.2)	8/5/6
2, n=44	26/18	38.1 (18–82)	6.3 (3.4–26.7)	22/14/8
3, n=35	19/16	39.9 (22–69)	8.8 (0.3–22.2)	13/14/8
4, n=15	5/10	38.2 (18–68)	6.4 (1.2–15.2)	5/6/4

F, female; M, male; MCS, magnifying colonoscopy.

*Values are means (ranges).

Table 2 Haematological parameters by magnifying colonoscopy grade

MCS grade	WBC ($\times 10^3/\mu\text{l}$)	CRP (mg/dl)	ESR (mm/h)
1, n=19	5.80 (4.00–9.60)	0 (0–2.8)	5 (0–53)
2, n=44	5.35 (5.90–10.40)	0.1 (0–2.8)	4 (1–80)
3, n=35	6.50 (2.80–16.00)	0.1 (0–2.2)	6 (1–71)
4, n=15	6.70 (1.40–13.60)	0.1 (0–1.4)	9 (1–14)

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; MCS, magnifying colonoscopy; WBC, white cell count.
Values are medians (ranges).

erythrocyte sedimentation rate (ESR) were examined as laboratory test parameters of disease activity.

Under colonoscopic guidance, the biopsy specimens used for organ culture and microscopic examination were obtained by targeted biopsy of the rectal area where MCS grade was recorded to investigate the precise correlation among MCS grade, the degree of histological inflammation and mucosal IL8 activity. A pathologist who was blinded to the patient's clinical data and the results of pit patterns assessed histological disease activity by classifying haematoxylin-eosin preparations of specimens into five grades by Riley's method.²² The scores included grade 0, normal; grade 1, mild increase in chronic inflammatory cell infiltrate and no tissue destruction; grade 2, moderate increase in chronic inflammatory cell infiltrate and no tissue destruction; grade 3, marked increase in chronic inflammatory cell infiltrate and mild tissue destruction; and grade 4, marked increase in chronic inflammatory cell infiltrate and obvious tissue destruction. In a preliminary study, in a subgroup of 12 patients, we carried out detailed high-magnification chromoendoscopy and localised the spot with highest MCS grade. This spot was then biopsied in duplicate for assessment of histological grade. We found that the histological grades in the paired biopsies in 11 of the 12 patients (92%) were identical, whereas in the remaining patient the histological grades were discordant by only one grade. This result indicated that a single biopsy was a good representative of the state of mucosal inflammation in patients with quiescent ulcerative colitis, certainly when localised by MCS.

Organ culture and IL8 assay

Colonic biopsy tissues were cultured on a culture insert as described previously.²³ IL8 content in the culture supernatant was measured in duplicate by an ELISA (TFB, Tokyo, Japan) in accordance with the manufacturer's instructions.²⁴ The amount of IL8 secreted in the organ cultures was expressed relative to protein content in the biopsy tissue homogenate (pg/mg biopsy protein).

Follow-up

Patients were followed up at 4-week intervals until relapse or for a maximum of 12 months after the start of the study, whichever came first. DAI score was assessed at each visit. Following the definition of Oren *et al*,²¹ relapse was diagnosed if the score increased by ≥ 3 points compared with that at the time of magnifying colonoscopic examination.

Statistical analysis

Correlations of MCS grade with clinical profiles, laboratory test parameters, histological disease activity and mucosal chemokine activity were analysed by Spearman's rank correlation test. The Kruskal-Wallis test was used for comparisons of patients with and without relapse in regard to discrete variables such as disease extent. Prognostic factors affecting relapse were initially examined using a univariate proportional hazards model, after which multivariate analysis was carried out to adjust for potential confounders. Time-to-relapse curves after

the magnifying colonoscopic examination were estimated by the Kaplan-Meier method, and statistical significance was determined using the log rank test. Two-sided *p* values are reported, and significance was set at a value of $p \leq 0.05$.

RESULTS

Patients

A total of 113 patients comprising 64 men and 49 women with age at entry ranging from 18 to 82 years, fulfilled the inclusion criteria. A total of 48 patients had total colitis, 39 had left-sided colitis and 26 had proctitis. Mean duration of disease was 7.0 years (range 0.3–26.7 years). At the start of the study, 48 patients were receiving sulfasalazine alone (1.0–3.0 g/day), 14 were receiving 5-amino salicylic acid alone (1.0–2.25 g/day), 10 were receiving prednisolone alone (5–15 mg/day), 18 were being treated with prednisolone (2.5–20 mg/day) and sulfasalazine (1.0–4.0 g/day), and 12 with 5-amino salicylic acid (1.5–2.25 g/day) and 11 were not receiving any specific drugs. Change in treatment such as a decrease in the dosage of prednisolone, was permitted for any patient, at the discretion of the attending doctor who knew the MCS grade after the start of the study.

MCS grade

The duration of examination for magnifying endoscopy and pit scoring was generally <5 min/case. Of the 113 patients, 19 were MCS grade 1, 44 were grade 2, 35 were grade 3 and 15 were grade 4. No differences in grade were seen by sex, age, total duration of disease or disease extent (table 1). Moreover, there was no relationship between MCS grade and drug treatment (data not shown). The mucosa in the grade 1 and 2 cases had a greater dye affinity for methylene blue than in the grade 3 and 4 cases, suggesting that dye endoscopy using methylene blue allows estimation of the degree of repair of the colonic epithelium. No significant differences were found in WBC, CRP or ESR values by MCS grade (table 2).

Histopathology

When MCS grades were compared according to the histological grade, histological disease activity was found to increase with increasing MCS grade ($p = 0.001$; table 3). The severity of monocyte and neutrophil infiltration into the lamina propria also increased with MCS grade (data not shown).

Table 3 Histological activity according to Riley's histological grade by magnifying colonoscopy grade

MCS grade	Histological grade				
	0	1	2	3	4
1, n=19	2	9	7	1	0
2, n=44	1	16	22	5	0
3, n=35	0	8	19	8	0
4, n=15	0	2	7	4	2

MCS, magnifying colonoscopy.
 $p = 0.001$ (Spearman's rank test).

Table 4 Comparison of mucosal interleukin 8 activity with magnifying colonoscopy grades

MCS grade	Mucosal IL8 activity (pg/mg protein)
1, n=19	25 (5–86)
2, n=44	33 (2–165)
3, n=35	54 (9–277)
4, n=15	85 (1–197)

IL8, interleukin 8; MCS, magnifying colonoscopy
Values are median (range).
p<0.001 (Spearman's rank test).

MCS grade in patients with ulcerative colitis in remission thus reflected histological ulcerative colitis activity well, indicating that it provides greater accuracy in the determination of ulcerative colitis remission status than conventional colonoscopy.

IL8 activity

MCS grade showed a positive correlation with mucosal IL8 activity in organ cultures of colonoscopic biopsy specimens from patients with ulcerative colitis with quiescent disease (table 4), and thus reflected activity of chemokines such as IL8 in the rectal mucosa of patients with ulcerative colitis in remission. Mucosal IL8 activity also showed a positive correlation with the histological grade (p = 0.014).

Ulcerative colitis relapse rate

Follow-up for at least 12 months after the start of the study was possible in all patients. During the study, 33 (29.2%) patients relapsed, with a mean time to relapse of 6.8 months (range 1–12 months). When hazard ratios (HR), 95% confidence intervals (CI), and p values for clinical profile, MCS grade, haematological parameters, mucosal IL8 activity and histological grade were calculated, WBC (relative risk (RR) 1.14, 95% CI 1.00 to 1.29, p = 0.047), the HR of MCS grades (RR 2.31, 95% CI 1.56 to 3.41, p<0.001) and mucosal IL8 activity (RR 1.01, 95% CI 1.00 to 1.01, p = 0.004) were found to show a significant association with relapse. In

contrast, no influence on relapse was seen for clinical profile, ESR, CRP or histological grade (table 5). Multivariate analysis showed a significant relationship between MCS grade and relapse (RR 2.06, 95% CI 1.34 to 3.17, p = 0.001), but not between relapse and WBC or mucosal IL8 activity (table 6). In addition, when the relationship between MCS grade and relapse rate at 12 months after MCS was assessed by the Kaplan–Meier method, the relapse rate was found to increase with increasing grade, with rates of 0% (0/19) for grade 1, 21% (9/44) for grade 2, 43% (15/35) for grade 3 and 60% (9/15) for grade 4 (fig 2). On the other hand, the relapse rate showed no significant difference between those receiving prednisolone and other patients, with rates of 0% (0/4) and 0% (0/15) for grade 1, 36% (4/11) and 15% (5/33) for grade 2, 53% (9/17) and 33% (6/18) for grade 3 and 63% (5/8) and 57% (4/7) for grade 4, respectively. Moreover, relapse was significantly more frequent in the MCF grade 3 and 4 patients (24/50, 48.0%) than in those with grades 1 and 2 (9/63, 14.3%, p<0.001), and was also significantly more frequent in the MCF grade 3 and 4 patients (6/27, 54.2%) than in those with grades 1 and 2 (13/24, 22.2%, p = 0.02) when analysis was limited to patients with a reduction in therapeutic drugs such as prednisolone after the start of the study.

DISCUSSION

We performed magnifying colonoscopy using methylene blue spray in patients with ulcerative colitis in remission, and classified pit patterns in the rectal mucosa into four grades on the basis of the size, shape and arrangement of the pits. The term “pit” refers to the orifices of the colorectal crypts, and the “pit pattern” is the specific arrangement of the opening of the crypt. In patients with ulcerative colitis, pit pattern may be influenced by the process of destruction and regeneration of glandular ducts. Dye endoscopy with methylene blue has the advantage that the dye is absorbed by the colonic epithelial cells, making the pit pattern more distinct, and staining intensity reflects the absorption ability of the mucosal epithelium.²⁵ Kiesslich *et al*⁷ showed that chromoendoscopy using methylene blue permits more accurate diagnosis of the extent and severity of inflammatory activity in ulcerative colitis than conventional colonoscopy.

Table 5 Prognostic factors for relapse by a univariate proportional hazard model

	Non-relapse	Relapse	HR (95% CI)	p Value
n	80	33		
Sex (M:F)	64:49	14:19	1.96 (0.98 to 3.92)	0.06
Mean age (years)	38.4	37.2	1.00 (0.97 to 1.02)	0.70
Disease duration (years)	7.0	6.8	1.00 (0.99 to 1.00)	0.78
Disease extent				NS*
Proctitis	19	7	1	
Left-sided colitis	39	48	1.10 (0.43 to 2.80)	0.84
Total colitis	34	14	1.09 (0.44 to 2.71)	0.84
WBC ($\times 10^3/\mu\text{l}$)	6.10	7.13	1.14 (1.00 to 1.29)	0.047
CRP (mg/dl)	0.20	0.16	0.73 (0.25 to 2.17)	0.57
ESR (mm/h)	9	10	1.00 (0.98 to 1.03)	0.74
MCS grade			2.31 (1.56 to 3.41)	<0.001
Grade 1	19	0		
Grade 2	35	9		
Grade 3	20	15		
Grade 4	6	9		
Histological grade			1.49 (0.99 to 2.26)	0.058
0	3	0		
1	30	5		
2	33	22		
3	13	5		
4	1	1		
Mucosal IL8 activity (ng/mg protein)	46.9	74.2	1.01 (1.00 to 1.01)	0.004

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; F, female; IL, interleukin; M, male; MCS, magnifying colonoscopy; WBC, white cell count.

*Calculated by Kruskal–Wallis test for censored data (p=0.95).

Table 6 Prognostic factors for relapse by a multivariate proportional hazard model

	HR (95% CI)	p Value
WBC ($\times 10^3/\mu\text{l}$)	1.07 (0.94 to 1.20)	0.31
MCS grade	2.06 (1.534 to 3.17)	0.001
Mucosal IL8 activity (ng/mg protein)	1.00 (0.94 to 1.20)	0.24

MCS, magnifying colonoscopy; WBC, white cell count.

This method thus seemed to offer promise in evaluation of the degree of epithelial cell injury. Given that ulcerative colitis is a chronic inflammatory disease which mainly involves the colonic mucosal surface in continuous areas from the rectum, assessment of ulcerative colitis activity by observation of pit pattern was considered a rational means of judging the disease stage.

Various attempts have long been made to observe the magnified features of the gastrointestinal mucosa by stereomicroscopy of resected specimens. In 1980, Poulsen *et al*¹⁰ compared colonoscopic findings in patients with ulcerative colitis with stereomicroscopic findings in biopsy specimens and found a close correlation between the number of crypt openings and clinical disease activity. Recent advances in high-resolution video-magnifying colonoscopes have enabled observation of the surface microstructure of colorectal mucosa, with results approaching the diagnostic capability of the stereomicroscope.²⁶ Moreover, magnifying colonoscopy with chromoscopy helps to detect dysplasia and colitic cancer in patients with longstanding ulcerative colitis.^{7, 27} On the other hand, the diagnostic ability of the magnifying colonoscope in histological disease activity has been confirmed in patients with both inactive and active ulcerative colitis, and furthermore, use of the high-resolution video colonoscope facilitates the differentiation of quiescent from inflamed mucosa.^{7, 28–30} Moreover, it is not unusual for routine colonoscopy performed to assess the stage of ulcerative colitis to show quiescent colitis despite the histological persistence of inflammation,^{2, 3, 31} which later results in the relapse of colonic inflammation.⁴

Here, to determine the predictability of relapse in ulcerative colitis, we examined four grades of pit pattern in the rectal mucosa under a magnifying colonoscope in patients with ulcerative colitis in clinically and colonoscopically diagnosed remission. Results showed that the MCS grades used not only correlated well with histopathological activity but also reflected the mucosal chemokine activity of the rectal mucosa in these patients. In addition, whereas histopathological assessment by biopsy alone leads to diagnosis based on lesions at a single site, observation of magnified features allows diagnosis over an extensive area of mucosa.

Chemokines are deeply involved in the pathogenesis of ulcerative colitis. IL8, a member of the α -chemokine subfamily, attracts and activates primarily neutrophils, and increase in IL8 activity is in fact a well-known phenomenon in patients with ulcerative colitis.^{32, 33} Given the association of mucosal IL8 activity with the degree of mucosal inflammation in ulcerative colitis,^{13, 14} IL8 activity may be a useful factor in predicting the clinical course in patients who achieve remission. Yamamoto *et al*¹⁹ reported that mucosal IL8 levels could predict future exacerbations of ulcerative colitis. We examined the association of mucosal pit patterns as assessed by MCS with mucosal IL8 activity, and also evaluated whether this chemokine is able to predict disease relapse in patients with ulcerative colitis. Results showed that mucosal IL8 activity correlated positively with MCS grade, but that it is a less useful predictor of disease relapse than MCS grade.

In patients with ulcerative colitis in remission, stratification according to relapse risk seems useful in determining maintenance treatment, particularly for those identified at

high risk. Although several prospective studies have investigated the risk factors for relapse using various modalities and examinations,^{4, 19, 34–37} no reliable predictor has yet been identified. Here, we assessed the degree of inflammation in the mucosa of patients with inactive ulcerative colitis by MCS with chromoscopy and prospectively identified factors predictive of relapse. Multivariate analysis showed that MCS grade was a significant independent predictor of relapse for 12 months after colonoscopy. Particularly, early relapse within 6 months was frequent in grade 3 and 4 cases, with rates at this time of 0% for grade 1, 9.1% for grade 2, 17.1% for grade 3 and 26.7% for grade 4. These findings indicate the need for care in any reduction in therapeutic drugs such as prednisolone and 5-amino salicylic acid in patients with MCS grade 3 or 4 pits.

We classified pit patterns in the rectal mucosa into four MCS grades on the basis of size, shape and arrangement. When pit patterns were classified into two grades by combination—namely, MCS grade 1+2 and 3+4—this grading provided significant independent prediction of relapse for 12 months (RR 3.11, 95% CI 1.31 to 7.42, $p = 0.01$). However, when attention was restricted to patients with MCS grade 1 or 2, no relapse was seen within 12 months in the MCS grade 1 patients, although more than a few (21%) patients relapsed in the MCS grade 2 group. Moreover, the mode value of histological disease activity in the MCS grade 1 patients was in discord with that in the MCS grade 2 patients (histological grade 1 ν 2). On the other hand, when attention was focused on patients in the MCS grade 3 and 4 groups, more than half (60%) of the grade 4 patients relapsed within 12 months, whereas less than half (43%) of the grade 3 patients did so. We therefore consider our four MCS grades to provide adequate classification for the inflammation of the rectal mucosa and prediction of relapse in patients with ulcerative colitis in remission.

Although MCS grade positively correlated with histological grade and mucosal IL8 activity, the mucosal IL8 activity

Figure 2 Kaplan-Meier survival analysis showing the cumulative proportion of patients who had a relapse according to magnifying colonoscopy (MCS) grade group.

parameters were less accurate predictors of disease relapse, possibly because they are assessed in biopsy specimens derived from a specific and limited area. On the other hand, magnifying colonoscopy allows the observation of a more extended and representative area of colorectal mucosa and hence has greater accuracy by MCS grading.

In conclusion, the results of our study indicate that MCS grading based on observation of the colonic mucosa by MCS in patients with ulcerative colitis in remission reflects histological disease activity, and that MCS is a useful tool in predicting the relapse of ulcerative colitis.

Authors' affiliations

Y Nishio, T Ando, O Maeda, K Ishiguro, O Watanabe, N Ohmiya, Y Niwa, H Goto, Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, Japan
K Kusugami, Department of Food Science and Nutrition, Nagoya Women's University, Nagoya, Japan

Competing interests: None.

REFERENCES

- Ando T, Watanabe O, Furuta R, et al. Predictors of a response to cyclosporine or leukocyte removal therapy in patients with refractory ulcerative colitis. *Dig Endosc* 2005;17:153–8.
- Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. *QJM* 1961;30:393–407.
- Powell-Tuck J, Day DW, Buckell NA, et al. Correlation between defined sigmoidoscopic appearances and other measures of disease activity in ulcerative colitis. *Dig Dis Sci* 1982;27:533–7.
- Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991;32:174–8.
- Kudo S, Rubio CA, Teixeira CR, et al. Pit pattern in colorectal neoplasia: endoscopic magnifying view. *Endoscopy* 2001;33:367–73.
- Kato S, Fujii T, Koba I, et al. Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished? *Endoscopy* 2001;33:306–10.
- Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003;124:880–8.
- Hurlstone DP, Cross SS, Adam I, et al. Efficacy of high magnification chromoscopic colonoscopy for the diagnosis of neoplasia in flat and depressed lesions of the colorectum: a prospective analysis. *Gut* 2004;53:284–90.
- Hurlstone DP, Cross SS. Role of aberrant crypt foci detected using high-magnification-chromoscopic colonoscopy in human colorectal carcinogenesis. *J Gastroenterol Hepatol* 2005;20:173–81.
- Poulsen SS, Christensen KC, Petri M, et al. Stereomicroscopic examination of stained rectal biopsies in ulcerative colitis and Crohn's disease. *Scand J Gastroenterol* 1980;15:535–44.
- MacDermott RP. Alterations of the mucosal immune system in inflammatory bowel disease. *J Gastroenterol* 1996;31:907–16.
- Rogler G, Andus T. Cytokines in inflammatory bowel disease. *World J Surg* 1998;22:382–9.
- Ina K, Kusugami K, Yamaguchi T, et al. Mucosal interleukin-8 is involved in neutrophil migration and binding to extracellular matrix in inflammatory bowel disease. *Am J Gastroenterol* 1997;92:1342–6.
- Imada A, Ina K, Shimada M, et al. Coordinate upregulation of interleukin-8 and growth-related gene product- α is present in the colonic mucosa of inflammatory bowel disease. *Scand J Gastroenterol* 2001;36:854–64.
- Schreiber S, Nikolaus S, Hampe J, et al. Tumor necrosis factor α and interleukin 1 β in relapse of Crohn's disease. *Lancet* 1999;353:459–61.
- Arnott IDR, Drummond HE, Ghosh S. Gut mucosal secretion of interleukin 1 β and interleukin-8 predicts relapse in clinically inactive Crohn's disease. *Dig Dis Sci* 2001;46:402–9.
- Meresse B, Rutgeerts P, Malchow H, et al. Low ileal interleukin 10 concentrations are predictive of endoscopic recurrence in patients with Crohn's disease. *Gut* 2002;50:25–8.
- Yamamoto T, Umegae S, Kitagawa T, et al. Mucosal cytokine production during remission after resection for Crohn's disease and its relationship to future relapse. *Aliment Pharmacol Ther* 2004;19:671–8.
- Yamamoto T, Umegae S, Kitagawa T, et al. Systemic and local cytokine production in quiescent ulcerative colitis and its relationship to future relapse: a prospective, pilot study. *Inflamm Bowel Dis* 2005;11:589–96.
- Sandborn WJ, Tremaine WJ, Schroeder KW, et al. Cyclosporine enemas for treatment-resistant, mildly to moderately active, left-sided ulcerative colitis. *Am J Gastroenterol* 1993;88:640–5.
- Oren R, Arber N, Odes S, et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996;110:1416–21.
- Riley SA, Mani V, Goodman MJ, et al. Comparison of delayed release 5-aminosalicylic acid (mesalazine) and sulphasalazine in the treatment of mild to moderate ulcerative colitis relapse. *Gut* 1988;29:669–74.
- Kusugami K, Fukatsu A, Tanimoto M, et al. Elevation of interleukin-6 in inflammatory bowel disease is macrophage- and epithelial cell-dependent. *Dig Dis Sci* 1995;40:949–59.
- Ando T, Kusugami K, Ohsuga M, et al. Interleukin-8 activity correlates with histological severity in *Helicobacter pylori*-associated antral gastritis. *Am J Gastroenterol* 1996;91:1150–6.
- Tada M, Katoh S, Kohli Y, et al. On the dye spraying method in colonofiberscopy. *Endoscopy* 1977;8:70–4.
- Kudo S, Hirota S, Nakajima T, et al. Colorectal tumors and pit pattern. *J Clin Pathol* 1994;47:880–5.
- Sada M, Igarashi M, Yoshizawa S, et al. Dye spraying and magnifying endoscopy for dysplasia and cancer surveillance in ulcerative colitis. *Dis Colon Rectum* 2004;47:1816–23.
- Matsumoto T, Kuroki F, Mizuno M, et al. Application of magnifying chromoscopy for the assessment of severity in patients with mild to moderate ulcerative colitis. *Gastrointest Endosc* 1997;46:400–5.
- Fujiya M, Saitoh Y, Nomura M, et al. Minute findings by magnifying colonoscopy are useful for the evaluation of ulcerative colitis. *Gastrointest Endosc* 2002;56:535–42.
- Kunihiro M, Tanaka S, Sumii M, et al. Magnifying colonoscopic features of ulcerative colitis reflect histologic inflammation. *Inflamm Bowel Dis* 2004;10:737–44.
- Kleer CG, Appelman HD. Ulcerative colitis: patterns of involvement in colorectal biopsies and changes with time. *Am J Surg Pathol* 1998;22:983–9.
- Mahida YR, Ceska M, Effenberger F, et al. Enhanced synthesis of neutrophil-activating peptide-1/interleukin-8 in active ulcerative colitis. *Clin Sci* 1992;82:273–5.
- Mazzuchelli L, Hauzer C, Zraggen K, et al. Expression of interleukin-8 gene in inflammatory bowel disease is related to the histological grade of active inflammation. *Am J Pathol* 1994;144:997–1007.
- Ludwig D, Wiener S, Brüning A, et al. Mesenteric blood flow is related to disease activity and risk of relapse in ulcerative colitis: a prospective follow up study. *Gut* 1999;45:546–52.
- Tibble JA, Sigthorsson G, Bridger S, et al. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology* 2000;119:15–22.
- Bitton A, Peppercorn MA, Antonioli DA, et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. *Gastroenterology* 2001;120:13–20.
- Higaki S, Nohara H, Saitoh Y, et al. Increased rectal wall thickness may predict relapse in ulcerative colitis: a pilot follow-up study by ultrasonographic colonoscopy. *Endoscopy* 2002;34:212–19.

BNF for Children 2006, second annual edition

In a single resource:

- guidance on drug management of common childhood conditions
- hands-on information on prescribing, monitoring and administering medicines to children
- comprehensive guidance covering neonates to adolescents

For more information please go to bnf.org