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Fujiya, M; Saitoh, Y; Nomura, M; Maemoto, A; Fujiya, K; Watari, J; Ashida, T; Ayabe, T; Obara, T; Kohgo, Y

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Mikihiro Fujiya, MD, Yusuke Saitoh, MD, Masafumi Nomura, MD, Atsuo Maemoto, MD, Kaori Fujiya, MD, Jiro Watari, MD, Toshifumi Ashida, MD, Tokiyoshi Ayabe, MD, Takeshi Obara, MD and Yutaka Kohgo, MD

Third Department of Internal Medicine, Asahikawa Medical College, Asahikawa, Japan

Reprint requests and correspondence:

Yusuke Saitoh, M.D.,
Third Department of Internal Medicine,
Asahikawa Medical College,
2-1 Midorigaoka-Higashi, Asahikawa, 078-8510, Japan
Tel. +81-166-68-2462
Fax. +81-166-68-2469
E-mail. y52015@asahikawa-med.ac.jp

Running title;

The usefulness of minute findings by magnifying colonoscopy in Ulcerative colitis

ABSTRACT

Background: Colonoscopy has an important role in diagnosis of ulcerative colitis, but its findings are inadequate for the prediction of relapse without histologic examination. In this study, the use of magnifying colonoscopy was evaluated.

Methods: Between January 1994 and October 1998, 116 magnifying colonoscopy were conducted in 61 ulcerative colitis patients. We defined a simple classification of magnifying colonoscopic findings, with five categories as follows: regularly arranged crypt opening, villi-like appearance, minute defects of epithelia (MDE), small yellowish spots and coral reef-like appearance. The classification was compared with histologic findings, and 18 patients were prospectively analyzed to evaluate the usefulness of the classification in predicting relapsing periods.

Results: Magnifying colonoscpic classification correlated better than conventional colonoscopic grades with histologic findings (r_2 =0.807, 0.665 respectively). Of 18 patients prospectively studied, 7 of 9 with MDE relapsed within 6 months, and the cumulative non-relapsing rate was significantly lower in patients with MDE than in those without that (p=0.0059). Moreover, it was found to be a significant independent predictive factor in a multivariate setting by Cox proportional hazards model analysis (p=0.0203).

Conclusions: Our classification of magnifying colonoscopic findings is useful for the evaluation of disease activity and for the prediction of remission periods in patients with ulcerative colitis.

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation limited to the colon.[1-5] Patients with UC are usually treated with aminosalicylates, [6,7] glucocorticoid, [8, 9] immunosuppressive agents,[10, 11] or leukocyte apheresis[12] to achieve remission and to maintain a quiescent period. In order to evaluate the disease activity, the clinical criteria based on patients' symptoms have been commonly used[13] instead of the colonoscopic finding or pathological grading of biopsied specimens. It is considered that the clinical criteria are convenient and non-invasive and are appropriate to estimate patients' qualities of life. However, by using the clinical criteria alone, there is the drawback that 40% of patients who achieve remission relapse within one year. [14,15] This high relapse rate may be explained by the fact that remission-induction therapy was discontinued in UC-patients who had achieved clinical remission while 30-60% of patients who were in remission according to clinical criteria were actually still in active by histologic examinations. [16, 17] The clinical criteria are regarded as being insufficient for evaluating the remission; and so an alternative marker that reflects the remission period is needed to prevent the possibility of a short time in UC-patients.

For the evaluation of disease activity in UC, the pathological diagnosis of biopsied specimens has been considered to be the gold standard, because relapse periods can be predicted by the findings such as infiltration of leukocytes, surface erosion, and crypt abscess. [18] For this reason, biopsy has been recommended even though conducting a biopsy is not without disadvantage such as inconvenience and invasiveness, as well as expence and length of time for evaluation.

Alternatively, colonoscopy was thought to be useful for evaluating the disease activity because it is capable of observing mucosal changes directly. Up until now, many colonoscopic classifications have been proposed to accomplish this purpose,[16, 19-23] but it is still controversial whether colonoscopic grading correlates with histologic appearance.[16, 17, 19, 24] Recently, magnifying colonoscope has become available, especially for the diagnosis of colorectal tumors in addition to regular colonoscope. [25-27] However, concerning UC, only a few retrospective studies have been reported.[28-30]

In this study, we used magnifying colonoscopy for UC patients and made a new category based on several minute findings with simpler classifications than those proposed by others [28,30], and compared this with the histology. We then prospectively studied whether these minute findings may be helpful to predict the clinical relapsing periods in UC patients.

PATIENTS AND METHODS

Patients and colonoscope: Between January 1994 and October 1998, 116 colonoscopic procedures with magnifying colonoscope (Olympus CF-200Z, Olympus Corp., Tokyo, Japan) were performed in 61 consecutive UC patients. High-power view at the maximum 100 fold could be easily obtained at any time by manipulating the handle. Informed consents were obtained from all the enrolled patients.

Colonoscopic procedures: The entire colon was firstly evaluated by conventional colonoscopy using a 0.1% indigocarmine solution (chromoendoscopy) and then by magnifying colonoscopy at the most severe part of the rectum or sigmoid colon. Several

minutes were spent on each area with magnifying colonoscopy. Biopsy specimens were subsequently obtained from the corresponding sites.

Classification of histologic findings: Matts' criteria[24] were used: the specimens diagnosed as completely normal appearance, grade 1; some infiltration of the mucosa or lamina propria with either round cells or polymorphism, grade 2; much cellular infiltration of the mucosa, lamina propria, and submucosa, grade 3; presence of crypt abscesses, with much infiltration of all layers of the mucosa, grade 4; and ulceration, erosion, or necrosis of the mucosa, with cellular infiltration of some or all of its layers, grade 5. Grade 1 was defined as quiescent stage and grade 2 to 5 as active stage.

Classification of conventional colonoscopic findings: Matts' grades[24] were also used: the mucosa diagnosed as completely normal appearance, grade 1; mild granularity of the mucosa, with mild contact bleeding, grade 2; marked granularity and edema of the mucosa, contact bleeding, and spontaneous bleeding, grade 3; severe ulceration of mucosa with hemorrhage, grade 4.

Classification of magnifying colonoscopic findings: We made a new and simple classification system based on minute findings, in which the concept of previous reports was included. [28,30,31] The classification was comprised of five categories as follows: (1) regularly arranged crypt opening, that were round shaped and regularly arranged (Figure 1) which corresponds to visible crypt opening reported by Matsumoto et al. [30] ; (2) villi-like appearance, shaggy appearance like small intestinal villi without typical crypt openings (Figure 2) which appeared histologically during regeneration of the

colonic mucosa[31]; (3) minute defects of epithelia (MDE), minute or shallow depressions surrounded by edematous mucosa with irregular arrangements of crypt openings (Figure 3) which corresponds to microerosion reported by Tada et al[28]; (4) small yellowish spots (SYS), minute whitish or yellowish coats (Figure 4); (5) coral reef like appearance (Figure 5), coarse or nodular mucosa with ulceration. By conventional colonoscopy, both villi-like appearance and MDE were observed as the same granular mucosa and those two minute findings could not be discriminated.

Evaluation of colonoscopic and histologic findings: Three colonoscopists (F.M., S.Y. and N.M.) evaluated coloscopic findings in both retrospective and prospective studies. In order to unify the baseline of colonoscopic classification and obviate interobserver variability, the observers discussed and agree on conventional and magnifying colonoscopic findings beforehand using photographs of representative findings that corresponded to our magnifying colonoscopic classification. In the retrospective study, the observers recorded both conventional and magnifying colonoscopic findings during the examination and retrospectively reviewed all the pictures by the same three colonoscopists without pathological information. In the prospective study, conventional colonoscopic findings were classified, subsequently magnifying colonoscopic finding were evaluated during the examination, only knowing the patient had obtained clinical remission. Histologic findings were evaluated by a pathologist given no clinical information.

Prospective study: Eighteen consecutive patients whose clinical activity index (CAI) [32] was 4 or less (remission) were enrolled. There were 4 men and 14 women with a mean

age of 32.1 years (range: 12 ~ 65 years). All the patients were clinically relapse-remission type. Sixteen patients had pan-colitis and 2 had left-sided colitis. Glucocorticoid was administrated in all 18 patients to obtain remission. Leukocytapheresis were performed in 6 patients who were refractory to glucocorticoid to obtain remission. Patients were followed up once a month until the end point of the study (February 28, 1999). The clinical severity was diagnosed independently by clinicians other than the observers of colonoscopic findings. The clinicians were aware of all findings of conventional colonoscopy but not those of magnifying colonoscopy until the study was finished. During the follow-up periods, 5-aminosalicylic acid (5-ASA) or sulfasalazine (SASP) was administrated as a maintenance therapy. When CAI was calculated 5 or more by presenting frequent bloody diarrhea for one week or more and/or abdominal pain, patients were diagnosed as having clinical relapse. The following factors were evaluated: gender, duration of disease, remission-inducing therapy, extension of inflammatory change, conventional colonoscopic grades, magnifying colonoscopic findings, and histologic grades. Written consented was obtained from all patients and the study was approved by the IRB of Asahikawa Medical College.

Statistical analysis

Conventional colonoscopic grade or magnifying colonoscopic findings and histological grade were compared by Spearman rank correlation coefficient. [33] Survival curves were constructed using the Kaplan-Meyer method [34], and univariate survival distributions were compared with use of the Breslow-Gehan-Wilcoxon test. [35] A step-wise multivariate survival analysis by the Cox proportion hazard model [36] was

performed to determine whether the presence or absence of MDE was found to be an independent predictive factor. Bonferroni's method was utilized to correct significance levels for the multiple testing of data in univariate tests of significance. No correction was made in the analysis of predictive factors for relapse which was done in a multivariate setting by Cox proportional hazards model analysis. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Comparison of conventional colonoscopic grades to histologic grades

A total of 116 areas were evaluated by conventional colonoscopy and histologically (Table 1). By conventional colonoscopic grade (Matts' grading), 12 areas were evaluated as grade 1 and all these were diagnosed as histologic grade 1. In contrast, of 33 areas assessed as grade 3 or 4, one area was diagnosed as histologic grade 2, and the other 32 areas as histologic grade 3 or more. However, in the 71 areas assessed as grade 2 by conventional colonoscopy, histologic grades varied from mild to severe inflammation. Conventional colonoscopic grade was correlated with histologic grade (r_2=0.665).

Comparison of magnifying colonoscopic classification to histologic grades

A total of 116 areas were evaluated by additional magnifying colonoscopy. The classification of magnifying colonoscopic findings was compared with histologic grades (Table 2). All 14 areas of regularly arranged crypt openings by magnifying colonoscopy were categorized as grade 1 by histologic examination. Twenty-three of 31 areas

showing villi-like appearance on magnifying colonoscopy were categorized as grade 1, 7 as grade 2 and 1 as grade 3. Thus, thirty-seven (82.2 %) of 45 areas detected as regularly arranged crypt openings or villi-like appearance by magnifying colonoscopy corresponded with histologic grade 1.

In contrast, of total 16 areas of MDE by magnifying colonoscopy, 3 were categorized as grade 2, 8 as grade 3 and 5 as grade 4. Accordingly, all areas in which MDE, SYS or coral reef like appearances were observed by magnifying colonoscopy corresponded with histologic grade 2 or more (Table 2). Histologic grade were better correlated with magnifying colonoscopic findings (r_2 =0.807) than with conventional colonoscopy (r_2=0.665).

Comparison of magnifying colonoscopic classification to histologic in the 71 areas diagnosed as grade 2 mucosa by conventional colonoscopy

In those areas diagnosed as grade 2 by conventional colonoscopy, histologic grades varied from mild to severe inflammation. Magnifying colonoscopic classifications were compared with these grades and the results are shown in table 3. Of 71 areas diagnosed as grade 2 by conventional colonoscopy, 31 areas were categorized as regularly arranged crypt openings or villi-like appearance by magnifying colonoscopy, and 25 (80.6%) of 31 areas corresponded to histological grade 1. In contrast, all 40 areas that were categorized as MDE, SYS or coral reef like appearance by magnifying colonoscopy corresponded to histological grade 2 or more. Magnifying colonoscopic classification correlates well with histologic grades even in areas diagnosed as grade 2 by conventional colonoscopy.

Predictive factors for the non-relapsing periods in prospective study

During the study period, 16 (88.9%) of 18 patients complained of bloody diarrhea and relapses were confirmed by repeated colonoscopic examinations in those patients. Nine of those 16 patients had a relapse within 6 months, 4 within 12 months, and 3 had relapse within 24 months.

In order to elucidate what factors were associated with the non-relapsing periods in UC patients, cumulative non-relapsing rate was calculated using Kaplan-Meier method. By the univariate analysis, there was no significant difference between the cumulative non-relapsing rate and gender, remission-inducing therapy, extension of inflammatory change and conventional colonoscopic grade at clinical remission. On the other hand, in the patients with disease duration of 10 years or more and histologic grades at the initial examination, grade 2 or more, cumulative non-relapsing rate was significantly lower than those without these factors (Table 4) in single univariate tests of hypothesis; however, correction for multiple testing of data removes these findings of significance.

At the initial magnifying colonoscopy, MDE, villi-like appearance and regularly arranged crypt opening were observed in 9, 7 and 2 patients, respectively. Seven (78%) of 9 patients in which MDE was observed underwent relapse within 6 months and all the 9 patients eventually had relapse within 10 months. In contrast, only 2 (22%) of 9 patients without MDE (7 patients with villi-like appearance and 2 with regularly arranged crypt opening) relapsed within 6 months, 4 patients within 12 months and 2 patients did not relapse within the study period (36 months). The cumulative non-relapsing rate in the patients with MDE at the initial colonoscopy was significantly lower than in those without MDE ($p=0.0059$) (Figure 6).

Multivariate analysis using the Cox's proportional hazard model was performed in 6 factors mentioned above. The only significant predictive factor found in step-wise analysis was the absence of MDE on magnifying colonoscopy (hazard ratio: 0.24, 95%C.I.: 0.072-0.801).

DISCUSSION

The present study indicates that our classification of magnifying colonoscopy correlates well with histological findings and the sign of MDE is useful for predicting relapse within a short period of time.

It is known that the pathological findings such as infiltration of leukocytes, surface erosion, and crypt abscess are important for the evaluation of disease activity in UC. [15,17,18,24]. However, histologic examinations have disadvantages such as inconvenience, invasiveness and incur certain costs and time for diagnosis. Consequently, an alternative noninvasive method is warranted. It is thought that colonoscopy is an alternative and useful way for evaluating the disease activity because it is capable of observing mucosal changes such as erosions, ulcerations, and bleeding. However, it is still controversial whether or not colonoscopic grading correlates with histologic appearance.[16,17,19-23] In the present study, the normal mucosa assessed by conventional colonoscopy corresponded well with histologic grade 1, and grade 3 or more mucosa also corresponded with histologic grade 3 or more, suggesting that normal mucosa and apparently diseased lesions are easily recognized by conventional colonoscopy and an acceptable positive correlation between Matts' grades found in conventional colonoscopy versus histology. However, we also found that a grade 2 mucosa assessed by conventional colonoscopy varied histologically from quiescent to active stage (Table

2). Thus, conventional colonoscopy is insufficient to assess the minute mucosal changes that reflect the smoldering histologic inflammation. [16,19,24]

Recently, the magnifying colonoscope has become available especially for the diagnosis of colorectal tumors because images of the fine surface structures are easily obtained.[25,27] In addition, the magnifying colonoscopy was suggested to be also useful to predict the histologic activity in UC. [28-30] In our study, magnifying colonoscopic classification was successful in making distinctions even in the areas diagnosed as grade 2 mucosa which look the same by conventional colonoscopy but histologically varied from quiescent to severe active. Such a characteristic feature of our magnifying colonoscopic classification is beneficial for clinical use in addition to the advantages such as convenience, non-invasiveness and rapid evaluation of disease activity in UC-patients.

Another advantage of magnifying colonoscopy is the predictability of non-relapsing periods in UC patients. Our results showed that patients in whom MDE was observed during their clinical remission frequently relapsed within short periods, compared with those without MDE (i.e., patients with villi-like appearance). Seven (78%) of 9 patients with MDE relapsed within 6 months and the remaining 2 patients did so within 10 months. On the other hand, only 2 (22%) of 9 patients without MDE relapsed within 6 months. Moreover, multivariate analysis using Hazard proportional model revealed that the MDE was independently extracted as the most predictive factor among other factors such as 10 years or more disease duration, histologic grade and so on. Therefore, the magnifying colonoscopic finding of MDE is a useful predicting sign for relapse within 6 months in patients with clinically quiescent UC.

It is noteworthy that our results showed that 50% of patients who underwent clinical remission still had active inflamed mucosa of MDE, which is in accordance with previous reports that about 30-60% of patients in remission evaluated by their clinical symptoms were revealed to be still in an active stage by histologic examination.[16,17] Therefore, UC patients of remission-relapse type assessed clinically include some patients who were histologically continuous active type and these may frequently relapse within a short period. These latter UC patients in clinically remission stage are mostly histologically in an active stage that frequently relapses after a short period.

Prediction of remission periods may be useful for therapeutic decision making and may result in improvements in quality of life for UC-patients. If the relapse period is predictable, additional treatments such as steroid enema therapy or appropriate maintenance therapy can be conducted according to Ulcerative colitis practice guidelines[13].

Observers already had information on conventional colonoscopic findings when they evaluated the magnifying colonoscopic findings; within this study, therefore, a potential for bias dose exist. However, in normal clinical practice magnifying colonoscopy is regarded as just an extension of conventional colonoscopy and not a separate procedure. Accordingly, our investigation is considered to be a comparison between conventional colonoscopy and magnifying colonoscopy with conventional colonoscopy. Another potential sources of bias is caused by the small sample size of prospective study in a single institution. The inter-observer variability in detecting minute findings may not be clarified sufficiently in the study. A multicenter randomized study with large numbers is needed in order to elucidate the usefulness and applicability of our magnifying colonoscopic classification.

In conclusion, magnifying colonoscopy is useful for the evaluation of disease activity and may be useful for predicting relapses in patients with UC. In particular, our classification system of minute findings by magnifying colonoscopy is useful for the prediction of non-relapsing periods in UC patients without conducting biopsy.

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Figure legends

Figure 1

Regularly arranged crypt openings. A, Conventional colonoscopic findings; even mucosa with fine vascular networks is shown. B, Magnifying colonocopic findings with indigocarmine dye spray; regularly arranged round shaped crypts are demonstrated.

Figure 2

Villi-like appearance. A, Conventional colonoscopic findings; fine granular mucosa without ulceration or bleeding, which corresponded to Matts' grade 2, is shown. B, Magnifying colonoscopic findings with indigocarmine dye spray; shaggy appeared small intestinal villi like mucosa is shown without typical crypt openings.

Figure 3

Minute defects of epithelia. A, Conventional colonoscopic findings; fine granular mucosa without ulceration, which are observed similarly to villi-like appearance, is shown. B, Magnifying colonoscopic findings with indogocarmine dye spray; minute or shallow depressions surrounded by edematous mucosa are noted.

Figure 4

Small yellowish spots. A, Conventional colonoscopic findings with indigocarmine dye spray; a tiny white spot can be seen. B, Magnifying colonoscopic findings; minute whitish coats is clearly shown.

Figure 5

Coral reef-like appearance. A, Conventional colonoscopic findings; nodular mucosa with ulceration is shown. Magnifying colonoscopic findings with indogocarmine dye spray; coarse mucosa consisted of irregular shaped ulcerations and regenerative mucosa are noted.

Figure 6

Univariative analysis in Kaplan-Meier method was performed and cumulative non-relapsing rates in the UC-patients with or without MDE were shown. Seven (78%) of 9 patients in which MDE was observed underwent relapse within 6 months and all the 9 patients eventually had relapse within 10 months. The cumulative non-relapsing rate in the patients with MDE at the initial colonoscopy is significantly lower than in those without MDE ($p=0.0059$).

Table 4 The significance of each clinical factor in affecting relapse estimated by univariate Kaplan-Meier cumulative provability curves

factors		cases	relapse rates within 6 months	p-value
Gender	men	4	75.0 % (3/4)	0.0871
	wemen	14	42.9 % (6/14)	
Duration of disease				
	more than 10years	4	0% (0/4)	0.0276
	10 years or less	14	64.3 % (9/14)	
Remission induced therapy				
	glucocorticoid	12	41.7 % (5/12)	0.8488
	leukocytapheresis	6	66.7 % (4/6)	
Conventional colonoscopic grades				
	grade 2	14	42.9 % (6/14)	0.2892
	grade 3	4	75.0 % (3/4)	
Magnifying colonoscopic findings				
	abscent of MDEs	9	22.2 % (2/9)	0.0059
	present of MDEs	9	77.8 % (7/9)	
Histologic grades				
	grade 1	10	30.0 % (3/10)	0.0384
	grade 2-4	8	75.0 % (6/8)	
Extension of lesion				
	left sided colitis	2	0% (0/2)	0.0571
	total colitis	16	56.3% (9/16)	

The presence or absence of MDE's was found to be a significant independent predictive factor in a multivariate setting by Cox proportional hazards model analysis.