Introduction

Advances in treatment of ulcerative colitis (UC) have changed the treatment target [1,2]. Consensus guidelines for clinical practice and trial endpoints recommend achieving endoscopic mucosal healing, not just clinical remission [1,3]. Endoscopic mucosal healing is defined as resolution of visible mucosal inflammation and ulceration. Achievement of endoscopic mucosal healing is associated with clinical remission and lower rates of hospitalization and operations [4–6]. Several reports have shown that mucosa that had seemingly reached mucosal healing still had a slight histologically-defined inflammation and a possibility for relapse [7–9]. Therefore, an approach using assessment of mucosal healing is necessary [10]. Following endoscopic mucosal healing, histological remission becomes the next treatment target; a recent report showed that histological remission was a better predictor of corticosteroid use and hospitalization [11].

Several scoring systems for evaluation of severity of inflammation have been reported, with endoscopic assessment play-
Patient and methods

Patients

Colonoscopies were performed on patients with UC from January 2010 to December 2012 at our institute. Patients were included in this study if they had undergone a total colonoscopy with left-sided or total-colitis type UC, were in clinical remission, and had an endoscopic Mayo score of 0 or 1. Lack of clinical remission, rectal type UC, and a past history of colectomy were exclusion criteria.

Instrument

Magnifying colonoscopy (CF-H260AZI, Olympus, Tokyo, Japan) was used for the examinations. The endoscope unit used was an EVIS LUCERA ELITE system (Olympus). When insertion was difficult because of pain or stiffness, a PCF-H260ZI scope was used with CO₂ insufflation.

Procedure

Total colonoscopy was performed with white light and magnifying NBI to observe the mucosa of each segment of the colorectum. For the purpose of assessment, the colorectum was divided into six segments, defined as the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. A biopsy specimen was taken from each segment of the mucosa. After 1 year, a repeat colonoscopy was performed in the same manner as the original procedure.

We first defined the magnified NBI findings as three categories, as described below. The findings on white light and NBI were compared, with the white light images being divided into two groups: remitted mucosa with or without scars. We first assessed this to know if the standard classification of white light can predict NBI findings, which seemed to be just as mucosal healing and no other findings at a glance. Then, the pathological results from all of the biopsy specimens were compared, with the results of the magnified NBI findings to assess the relationship between imaging and pathological activity. The relationships between the initial and 1-year follow-up NBI findings were assessed to reveal the different prognoses for the NBI findings.

NBI findings

Those cases with a Mayo score of 0 and 1 showed some specific findings on magnifying NBI images. These NBI findings were newly divided into three types, according to their blood vessels. These types were honeycomb-like blood vessels (BV-H), where healthy hexagon-shaped vessels were visible; blood vessels shaped like bare branches (BV-BB), where only thin vessels were visible, and blood vessels shaped like vines (BV-V), where slightly thicker winding vessels were visible (Fig. 1). When the characteristics of more than one type were present in the same area, the higher grade was recorded.

Histological assessment

Mucosal biopsies were taken from each part of the colon. Biopsy specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin, and sectioned into 4-μm slices. Hematoxylin and eosin staining was used for histopathological examination. The pathologists, who belonged to the hospital pathology department, were blinded to the endoscopic findings. Definitions for histological findings followed those of the Japanese Ministry of Health, Labour, and Welfare. Existence of active inflammation was determined according to existence of one of three items: (1) diffuse infiltration of inflammatory cells; (2) erosion; and (3) a crypt abscess/cryptitis.

Statistical methods

Statistical analysis of the results of the pathological findings was performed using Fisher’s exact test. The upper and lower 95% confidence intervals (CI) were calculated based on a binomial distribution. A P value <0.05 was considered statistically significant. All statistical analyses were performed using R software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 185 UC patients underwent initial colonoscopy, with 52 patients fulfilling the inclusion criteria who underwent a second 1-year-follow-up colonoscopy and were enrolled in this study (Fig. 2). Patient characteristics are shown in Table 1. In this study, most patients were treated with SASA at the remission phase.

Biopsy specimens were taken from each segment of the mucosa, giving a total of 312 samples.

Inconsistency in findings of white light and NBI

First, we compared the findings from white light and NBI images (Fig. 3). More than 60% of mucosa with a normal appearance on white light showed BV-H on NBI. Two-thirds of mucosa with scars on white light showed BV-BB on NBI (Table 2).
NBI findings and histology

Results of histological findings from the examined lesions are shown in ▶Table 3. NBI BV-H (12/292 showing activity: 4%) and NBI BV-BB (8/299 showing activity: 3%) rarely showed activity on histology. To the contrary, a classification of NBI BV-V generally indicated pathological activity (27/33, 81%). There was a significant correlation between magnified NBI findings and histological findings (P<0.001).

▶Fig. 1 Classification of the NBI findings. BV-H, blood vessels with honeycomb-like appearance; BV-BB, blood vessels shaped like bare branches; BV-V, blood vessels shaped like vines.

▶Table 1 Patients characteristics

| Characteristic                  | Total colitis type | Left sided type |
|---------------------------------|--------------------|-----------------|
| Number of patients              | 33                 | 19              |
| Gender Male/Female              | 15/18              | 11/18           |
| Mean age ± SD                   | 50.3 ± 15.6        | 49.2 ± 14.8     |
| Mean duration of disease(years) ± SD | 9.7 ± 7.8          | 9.1 ± 7.4       |
| Mayo 0/1                        | 25/8               | 16/3            |
| Treatment                       |                    |                 |
| ▪ 5-ASA mesalazine              | 30                 | 14              |
| ▪ Salazosulfapyridine           | 2                  | 3               |
| ▪ Prednisolone                  | 0                  | 0               |
| ▪ Immunomodulator               | 1                  | 1               |
| ▪ Biologics                      | 0                  | 0               |
| ▪ No medication                 | 1                  | 2               |
Interval changes in the NBI findings

NBI findings for the first examination revealed 144 lesions with BV-H, 162 with BV-BB, and 6 with BV-V. The NBI findings for the second 1-year follow-up examination showed 148 lesions with BV-H, 137 with BV-BB, and 27 with BV-V (Table 4).

Of 144 lesions with NBI BV-H, two were histologically active the following year, while among 162 lesions with NBI BV-BB, 27 lesions were histologically active at 1-year follow-up. The odds ratio for NBI BV-BB showing active inflammation at 1-year follow-up was 14.2 (95% CI, 3.3–60.9) (Table 5). On the other hand, three BV-V lesions were spontaneously improved at the 1-year follow-up.

Clinical recurrence was observed in 10 cases, with treatment being intensified for these patients.

Discussion

This study showed effective results for investigations using NBI findings in the remission phase, and for predicting risk of recurrence of UC. First, we compared the white light images and magnified NBI images of the remission phase (Mayo 0 or 1) and found the results showed a discrepancy. Second, we focused on the shapes of capillary vessels with magnifying NBI and showed a good correlation between findings from NBI findings and histology. Third, the results revealed that cases showing NBI BV-BB had a higher risk of recurrence than those showing NBI BV-H; this indicated that the difference in NBI findings reflected a different prognosis.
In this study, the comparison between the white light images and magnified NBI images of UC remission showed a discrepancy. Vascular pattern, mucosal friability, and bleeding were included as evaluation items for the major previous endoscopic grading of UC, as they were recognized as important factors [8, 16]. Recently, another endoscopic score was proposed: the UC Endoscopic Index of Severity (UCEIS), which also included the above-mentioned factors [17]. The vascular pattern of “normal” on the white light images was defined as a normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins [17]. Our study results showed that some of the UC mucosa that had seemingly reached mucosal healing had different vascular patterns with magnification. This demonstrates the limits of the scoring system in evaluation of mucosal healing and subtle residual inflammation. Vascular patterns have been recognized as an important factor, and we think it is better to assess these patterns more carefully with magnification, when they are visible.

The results of our study showed that there was a correlation between the magnifying NBI findings and histological findings. As for the vasculature, mucosal angiogenesis plays an important role in neoplastic and non-neoplastic chronic inflammatory disorders [13, 18, 19]. Previous reports have documented an observed increase in vascular density in IBD, which directly correlated with increased IBD disease severity [18]. In our results, histologically inactive areas showed only thin vessels or sparsely visible vessels. Recently, endocytoscopy (Olympus, Tokyo) has been developed as a virtual histology method [20]. This enables real-time observation of cells and nuclei in vivo using 450 × ultra-magnification. Maeda et al assessed the capillaries in rectal mucosa with endocytoscopic NBI (EC-NBI) [21] and found that EC-NBI findings were correlated with histological inflammation and aided in differential diagnosis between active and inactive UC without biopsy. Unfortunately, this technique is still not widely available.

A notable finding in this study was that the different NBI vascular patterns had different risks of recurrence. Previously, Nishio et al reported on assessment of rectal mucosa with magnifying colonoscopy and reported that the grading scale had a good correlation with histological findings [22]. They also assessed prediction of the relapse of UC. To the contrary, rectal mucosa do not always reflect inflammation under the treatment intervention. Therefore, we assessed the whole length of the colonic mucosa in this study. Another high-definition colonoscopy system, the i-Scan (Pentax medical, Tokyo), also has the ability to enhance images [23, 24]. Iacucci et al observed whole segments of the colon and reported a good relationship between the i-Scan grading scale and histological activity [23]. Unfortunately, the report did not reveal information on prognosis. The findings for NBI-BB suggest a need for careful observation and treatment.

This study has several limitations, including the single center and small sample size, especially for NBI VB-B. Because patients in this study were mainly treated with 5-ASA alone, selection bias occurred. Long-term prognosis over more than 1 year was not analyzed. A further limitation is that the clinical endpoint was not compared with a definitive indicator such as total colectomy.

Conclusion

In conclusion, our analysis suggests that magnifying NBI observation is effective for assessment of UC follow-up. In cases with blood vessels shaped like bare branches, careful observation for relapse of UC is necessary.

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Competing interests

None
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