

# Magnifying image-enhanced endoscopy for collagenous colitis



## Authors

Masaaki Kobayashi<sup>1</sup>, Takahiro Hoshi<sup>1</sup>, Shin-ich Morita<sup>1</sup>, Tsutomu Kanefuji<sup>1</sup>, Takeshi Suda<sup>1</sup>, Go Hasegawa<sup>2</sup>, Shuji Terai<sup>3</sup>

## Institutions

- 1 Department of Gastroenterology and Hepatology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Niigata, Japan
- 2 Department of Pathology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Niigata, Japan
- 3 Division of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

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## Bibliography

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## Corresponding author

Masaaki Kobayashi, Department of Gastroenterology and Hepatology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, 4132 Urasa, Minami-Uonuma, Niigata 949-7302, Japan  
Fax: +81-25-777-2811  
[masakoba@med.niigata-u.ac.jp](mailto:masakoba@med.niigata-u.ac.jp)

## ABSTRACT

**Background and study aims** We report a case series of 5 patients with collagenous colitis (CC) presenting with chronic watery diarrhea, who were subjected to magnifying, chromoendoscopy and narrow band imaging (NBI). Magnifying chromoendoscopy revealed whitish-clouded, honeycomb-like appearance at orifices of the crypts. NBI with high magnification revealed irregular caliber variation of the subepithelial capillary network. Presence of these features corresponded with histological characteristics of CC indicated by thickening of the subepithelial collagen layer. We concluded that magnifying image-enhanced endoscopy is a reliable tool to diagnose CC.

## Introduction

Collagenous colitis (CC) is characterized by diffuse thickening (>10 µm) of the subepithelial collagen layer beneath the basement membrane and chronic inflammatory infiltration of the lamina propria [1]. CC has been known to cause chronic watery diarrhea, especially when patients are on several other medications, such as non-steroidal anti-inflammatory drugs (NSAIDs) [2] or proton pump inhibitors (PPI), especially lansoprazole (LPZ) [3]. Because conspicuous endoscopic abnormalities are usually absent [4], multiple biopsy sampling is considered as the gold standard for diagnosis of CC. Non-specific and subjective findings such as erythema patches, edema, or abnormal vascular pattern can be seen in up to 30% of CC patients [4, 5]. Interpretation of such findings appears to depend on endoscopist's experience [5]. Mucosal tears and linear ulcerations are identified objectively, but occasionally [2, 3, 5]. Although image-enhanced endoscopy (IEE) and magnifying endoscopy (ME) have emerged as the most popular tools for assessment of colorectal lesions, there have been few reports on IEE: nar-

row-band imaging (NBI) [6] and chromoendoscopy [7], and no report on ME for CC. We report here, specific features under IEE and ME, with an emphasis on the interpretation of the pathological findings, in a case series of CC.

## Patients and methods

Five consecutive patients at our hospital with biopsy-proven CC were selected for the case series, from September 2015 to December 2016. There were 4 men and 1 woman, ranging from 73 to 87 years of age, at the time of diagnosis. All patients presented with chronic watery diarrhea and were on LPZ to prevent aspirin-related gastroduodenal ulcers. The period between initiation of LPZ and onset of diarrhea varied from 2 to 9 months. All 5 patients were on aspirin. All patients gave written informed consent, and were examined under colonoscopy. Clinical data on the patients are summarized in ► **Table 1**.

Complete resolution of symptoms occurred in all patients within 28 days of discontinuing LPZ. In addition to the 5 patients with biopsy-proven CC, control subjects (n=12) who

► **Table 1** Clinical data for patients with collagenous colitis.

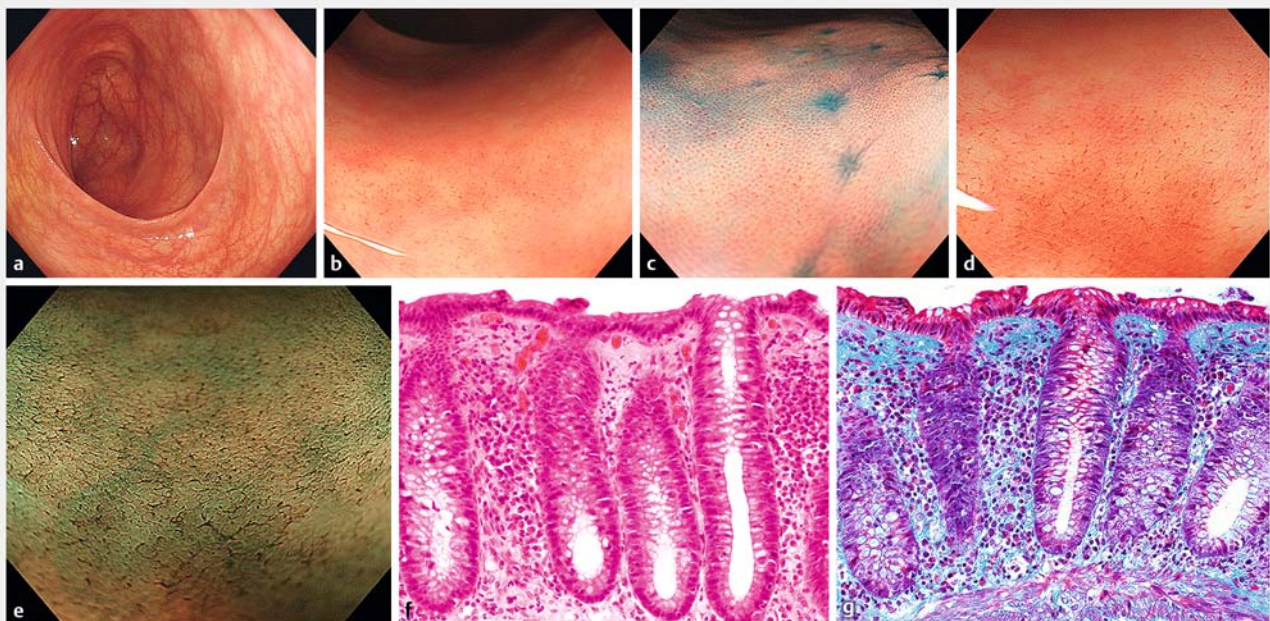
Case	Age	Sex	Comorbidity	Medication	Location
1	73	F	Cerebral infarction Hyperlipidemia	LPZ, aspirin Ethyl Icosapentate	AC-SC
2	84	M	Atrial fibrillation Hypertension	LPZ, aspirin Carvedilol	AC-SC
3	82	M	Myocardial infarction	LPZ, aspirin	TC-SC
4	87	M	ASO Hypertension Hyperlipidemia	LPZ, aspirin Cilostazol	AC-DC
5	74	M	Hypertension Cerebral hemorrhage Hyperlipidemia	LPZ, aspirin	AC-SC

LPZ, lansoprazole; AC, ascending colon; TC, transverse colon; DC, descending colon; SC, sigmoid colon; ASO, arteriosclerosis obliterans

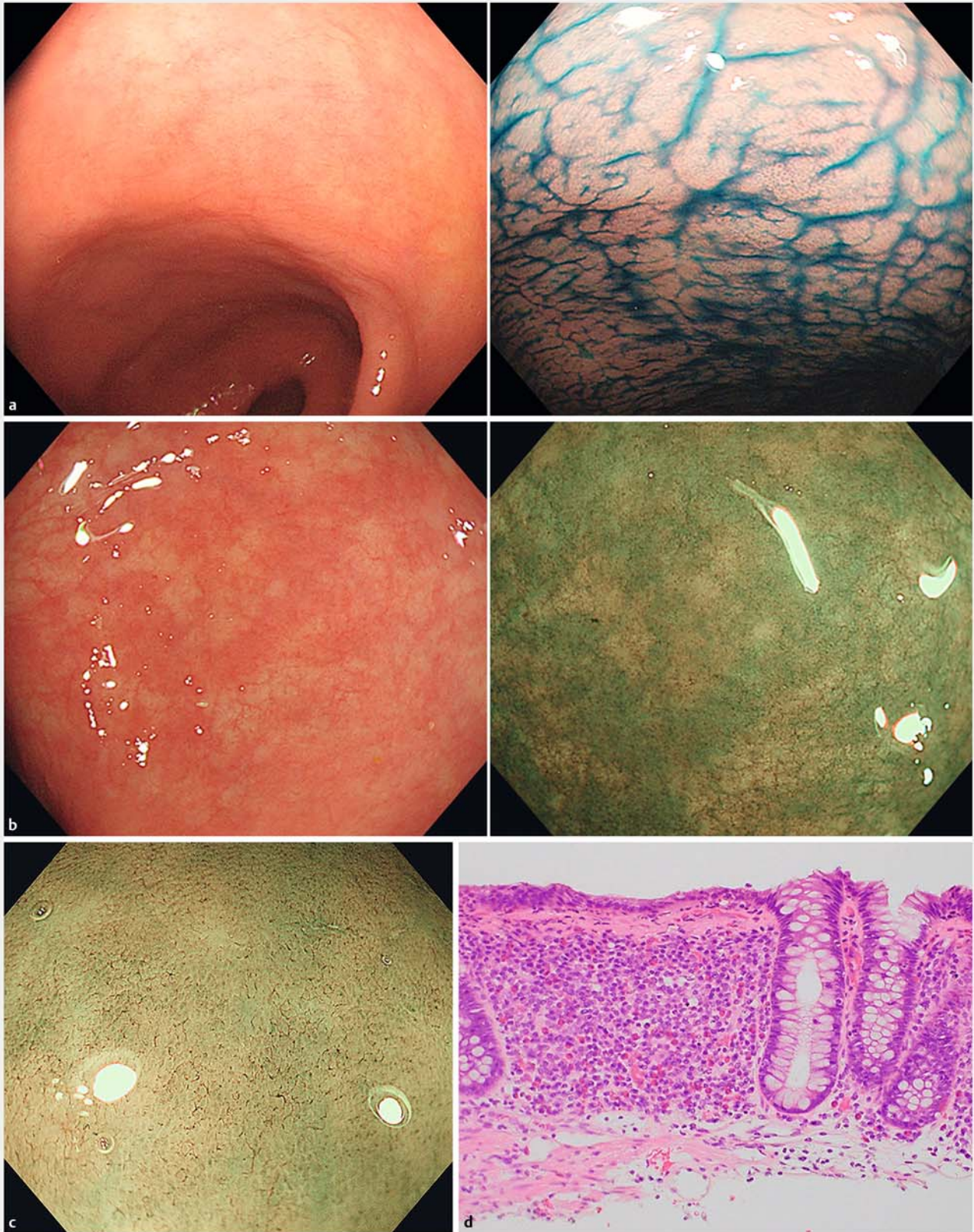
were on LPZ for treatment of reflux esophagitis or to prevent NSAIDs or aspirin related gastroduodenal ulcers, but did not complain of chronic watery diarrhea, were evaluated in this study. The control subjects underwent colonoscopy examination for colorectal cancer screening.

For all subjects, bowel preparation was done using 20 mL sodium picosulfate and 2 L polyethylene glycol solution. All colonoscopy examinations were carried out by highly experienced endoscopists (M. K., T. H., S. M.) using a magnifying videoendo-

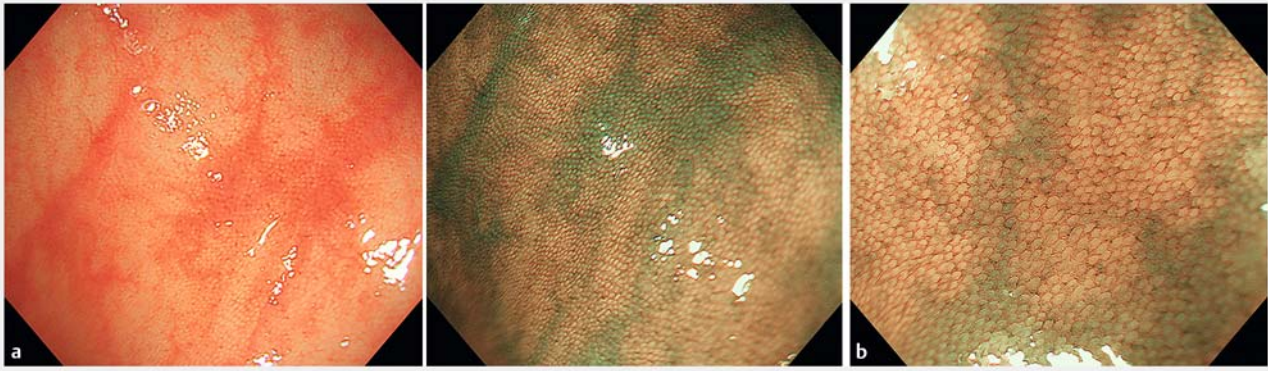
scope and an electronic endoscopic system (CF-HQ290ZI and LUCERA ELITE Spectrum; Olympus Corporation, Tokyo, Japan). To obtain the chromoendoscopic images, 0.5% indigo carmine was sprayed directly. Endoscopic features using white-light, NBI and indigo carmine spraying were observed under magnification. In addition to biopsies from the abnormal mucosal areas, one specimen was usually obtained from each part of the colon (i.e. ascending colon, transverse colon, descending colon, and sigmoid colon), after recording the endoscopic images. The



► **Fig. 1** a Collagenous colitis was detected in Case 1 who presented with chronic watery diarrhea and was on LPZ to prevent aspirin-related gastroduodenal ulcers. Conventional endoscopy did not reveal any findings in the transverse colon. b The crypt structure was regular on white-light magnifying endoscopy, but a whitish and clouded honeycomb-like frame was revealed by magnifying chromoendoscopy with indigo carmine staining. c Subepithelial capillaries were found to be dilated even on white-light magnifying endoscopy. Magnifying NBI revealed irregular dilatation and constriction of the honeycomb-like subepithelial capillary network. d Biopsy specimen revealed prominent subepithelial eosinophilic band-like deposits (20 μm) which contained entrapped capillaries and inflammatory cells (d, hematoxylin and eosin staining, HE; e, Masson's trichrome staining).



► **Fig. 2** **a** An uneven granular surface texture found in Case 2 with biopsy-proven collagenous colitis (white-light and indigo carmine spraying endoscopy). **b** Alteration of the vascular pattern, such as indistinct appearance of capillary network with a variable degree of erythema, was revealed by low-grade magnifying endoscopy (white-light and NBI). **c** The cloudiness at the intervening part of crypts corresponded to the indistinct appearance of the subepithelial capillary network on high-grade magnifying NBI. **d** Histological examination showed a diffuse thickening (20  $\mu$ m) of the subepithelial collagen layer beneath the basement membrane and chronic inflammatory infiltrate of the lamina propria (HE).



► **Fig. 3** **a** In the control group, the arrangement of the honeycomb-like capillary network was visualized clearly and appeared regular on low-grade magnifying white-light endoscopy and NBI in the ascending colon. **b** No evidence of cloudiness at the intervening part of crypts was present on high-grade magnifying NBI.

formalin-fixed, paraffin embedded biopsy specimens were sectioned and stained with hematoxylin and eosin (HE). Masson's trichrome staining for collagen fibers was done when CC was suspected on HE stains. Biopsy specimens were assessed by an experienced pathologist (G.H.). Histological criteria for CC were abnormally thickened subepithelial collagen layer  $>10\mu\text{m}$ , lamina propria infiltration (by lymphocytes, plasma cells, and mononuclear cells) and normal crypt architecture. Histological features and colonoscopy images were reviewed retrospectively to evaluate the presence of findings specific for CC.

## Results

Non-magnifying colonoscopy revealed no significant findings except in Case 2 and Case 5, which showed an uneven granular surface texture on chromoendoscopy. Mucosal tears or linear ulcerations were not observed in any of the five cases. IEE with ME can identify irregular dilatation and constriction of the honeycomb-like subepithelial capillary network. These features were further clearly visible on NBI with high magnification. Microsurface structure of the crypts was found to be regular, but as a whitish-clouded, honeycomb-like frame on magnifying NBI and chromoendoscopy. Cloudiness at the intervening part of crypts corresponded to the constriction of subepithelial capillary network on magnifying NBI. These features were observed in all patients, from the ascending to descending colon. Biopsy specimens revealed prominent subepithelial eosinophilic band-like deposits, which contained entrapped capillaries, red blood cells, and inflammatory cells. The thickness of collagen layer was similar ( $10\text{--}20\mu\text{m}$ ) in all 5 patients. Crypt distortion was not observed. In the control group, arrangement of the honeycomb-like capillary network was visualized clearly and regularly, under NBI with ME on all colonoscopy examinations. Eight control subjects were evaluated histologically on biopsy or mucosal resection for adenomas, and did not show any evidence of significant findings of CC. Three representative cases where the patients as well as the control group underwent colonoscopy

and pathological evaluation are shown in ► **Fig. 1**, ► **Fig. 2** and ► **Fig. 3**.

## Discussion

To identify characteristic findings indicative of CC, the evaluation focused on visualization of the honeycomb-like structure on IEE with ME. Furthermore, the morphology of honeycomb-like subepithelial capillary network was also evaluated by magnifying NBI, and the endoscopic findings corresponded with pathological findings. Subepithelial collagen deposits could be closely related to the appearance of cloudy intervening part of crypts and constriction of the subepithelial capillaries in this case series of CC.

From the initial descriptions of CC, normal or unremarkable colonoscopic and radiological findings have been a pathognomonic feature [4]. In recent years however, there have been several reports of endoscopic findings suggestive of CC [8]. Some of these reports using ordinary white-light endoscopy revealed that longitudinal ulcerations or scars have been associated with CC [2,3].

Chromoendoscopy has helped in recognizing even slight changes in the mucosal texture, such as an irregular nodular pattern or a mosaic pattern [7,9,10]. NBI may be helpful in diagnosing CC by detecting the slightest mucosal changes, including linear scratch marks, termed "cat scratch colon" [6]. These findings on non-magnifying endoscopy may be characteristic of CC with high specificity but low sensitivity, because it is difficult to identify pathological thickness of the subepithelial collagenous layer. Confocal laser endomicroscopy identified a well-defined "shell" around the crypts, corresponding to the increase in thickness of the subepithelial collagenous layer as evidenced on histology [11,12]. However, confocal laser microscopy incurs a high cost and has never been popular as a clinical tool yet. In recent times, IEE with ME have become popular assessment tools for colorectal lesions. Specific images using IEE with ME may be able to interpret pathological findings with high specificity and sensitivity.

There are certain limitations in this study. It was conducted at a single center, and images acquired via IEE and ME in a very small sample were reviewed retrospectively.

Multicenter, prospective, and real-time diagnostic studies with a larger sample size are necessary, to further ascertain the significance of honeycomb-like, irregular subepithelial capillary network and whitish-clouded microsurface structure under IEE with ME and their relationship with the histological CC findings.

### Competing interests

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None

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