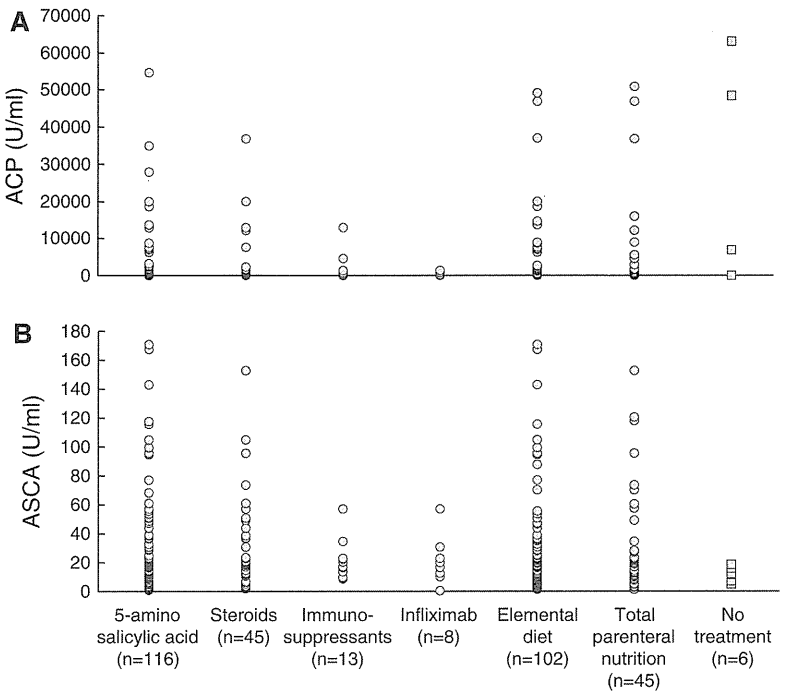

Fig. 6 Serum levels of antibodies to Crohn's disease peptide (ACP) (**a**) and anti-*Saccharomyces cerevisiae* antibodies (ASCA) (**b**) in patients with Crohn's disease, according to the current use of medications. Some of the patients were treated with more than one category of treatment

The detection of high ACP levels in patients with intestinal diseases, including infectious colitis and irritable bowel syndrome, remained a rare exception; only two cases with infectious colitis were found with remarkably high levels. The reason for this exceptional increase is unclear, but a careful follow-up of ACP levels and clinical features might be required for these patients. Another group of patients with autoimmune diseases, which have not previously been investigated, was also included as inflammatory controls. Because of pre-existing evidence of enhanced antibody responses to self-antigens in autoimmune diseases, we thought this would be a valuable control group when assessing whether ACP was specific for CD. The results showed that these patients carried no ACP, which confirmed the specificity of ACP for CD. Prospective studies are needed before translating this concept into clinical practice.

ASCA have been reported as screening tools for CD. ROC analysis showed that ACP provides higher sensitivity and specificity compared to ASCA for the screening of CD, indicating that ACP is a more useful test in our cohort of patients. It is a well-known fact that ASCA is a less useful test in the Asian population than the Caucasian population [29]. In fact, our results showed that only 47.4 % of our CD patients carried ASCA, which is in agreement with published studies in Japanese populations. It will be of interest to compare the diagnostic utility of ACP with other recently described markers for CD, such as anti-pancreas [12], anti-OmpC [13, 14], anti-I2 [15–17] or anti-flagellin antibodies [18, 19]. The combined use of ACP and these markers could result in a powerful combination that would improve their diagnostic utility. Furthermore, it will be of interest to investigate whether ACP can be used to screen for CD in patients from the general population who have undiagnosed gastrointestinal symptoms.

Among CD patients, we also investigated possible associations between ACP levels and clinical features. Stratification according to CDAI and laboratory parameters did not reveal any substantial differences in ACP levels, whereas ASCA levels showed significant correlation with CDAI and CRP. This may indicate that the antigen that relates to TCP-353, as a target of ACP, may always present to elicit strong immune responses in the intestine, irrespective of disease activity. It will be of interest to analyze the association between ACP and disease behavior, as well as with the need for surgery.

With regard to the disease location, CD patients with colonic, ileocolonic, and ileal disease have comparable levels of ACP, suggesting the wide distribution of TCP-353-related antigens throughout the intestine. This antigen may invade the intestinal mucosa, encounter immune cells and elicit unusual immune responses, resulting in the induction of higher levels of ACP. Furthermore, ACP has also been referred to as frequently positive in CD with only colonic involvement, but not UC, suggesting the hypothesis that increased ACP levels in CD is not just a secondary phenomenon induced by chronic inflammation of the bowel.

Interestingly, we found a negative correlation between ACP levels and disease duration in CD. The lower disease activity induced by the long-term medical treatment is unlikely because our results reveal that ACP levels were

not associated with the current use of drugs. Although the reason is unclear, one possible explanation is that TCP-353-related antigens may also be eliminated naturally during the course of the disease. Another explanation is that this antigen may not always elicit strong immune responses in the intestine even if it existed. A comparison of the ACP level and intestinal complications, such as structuring and internal penetrating disease behaviors, might be important. The association between the ACP levels and disease duration was relatively weak ($r = 0.157$). More information regarding the correlation between the ACP level at the time of diagnosis in an individual patient and the changes in the level over time would be useful.

The influence of medical treatment on ACP levels should be ruled out. A subgroup analysis among untreated and treated CD patients showed the current use of medications had no effects on ACP levels, although the number of patients in each group was too small. It would be interesting if ACP expression correlates with response to ongoing treatment, as it may be helpful in determining the effective treatment. Future studies sequentially assessing ACP levels in the same patient will be required to formally confirm this association.

At present, little is known about the underlying immunological mechanism that leads to the generation of ACP; it remains unclear whether expression of this marker antibody is a reflection of a specific mucosal immune-mediated response or only an epiphenomenon of intestinal insult. However, we have recently shown that TCP-353 peptide, a target of ACP, induces the release of pro-inflammatory cytokines, interleukin-1β, interleukin-6, and tumor necrosis factor-α, in blood mononuclear cells from CD but not UC patients [23]. This suggests that an aberrant immune response to TCP-353-related antigens contributes to the development of CD. At present, the putative target antigen remains unidentified, although the BLAST search shows partial homology to a variety of proteins from different organisms, such as some bacteria or food antigens [30–32]. Further experiments are currently underway to answer these possibilities.

Although it was a multicenter analysis, the limitation of this study is that our sample was comprised exclusively of Japanese subjects, and therefore our findings cannot be generalized to other Asian countries or other ethnic groups. Thus, an obvious next step is to perform the investigation in studies across multiple populations of patients and ethnic groups. Furthermore, the patients studied here have had established diagnoses for which they have received treatment. It seems likely, therefore, that the question as to the value of ACP for the diagnosis of CD is most likely to be answered in the context of a prospective study of patients from the time of clinical presentation.

In conclusion, this multicenter study showed that increased ACP, although not completely specific for CD, may have a future role in diagnosis as well as a pathogenic role. The assay described here could be used to address this question in the context of multiple populations of patients and ethnic groups, and more importantly, in prospective studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Evaluation of diagnostic criteria for Crohn's disease in Japan

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Abstract
Background In Japan, Crohn's disease (CD) is diagnosed according to a single, well-established set of diagnostic criteria. However, no nationwide attempt has been made to determine which specific criteria within these diagnostic criteria are used to make diagnoses.
Methods A questionnaire-based survey was conducted of patients given a definitive or suspected diagnosis of CD before January 2011 according to the Japanese Diagnostic Criteria for Crohn's Disease. The survey included 579 patients with a definitive diagnosis of CD and 59 patients with a suspected diagnosis of CD at 34 Japanese medical institutions.
Results A total of 87.4 % of definitive diagnoses of CD were based on the criterion in the definite category: major finding A "longitudinal ulcer (LU)" or B "cobblestone-like appearance (CSA)". A total of 30.4 % of definitive diagnoses were based on the criterion: major finding C "non-caseating epithelioid cell granuloma (NCEG)" with minor finding a "irregular-shaped and/or quasi-circular ulcers or aphthous ulcerations found extensively in the gastrointestinal tract" or b "characteristic perianal lesions". Finally, 7.1 % of definitive diagnoses were made according to the criterion: all minor findings a, b and c "characteristic gastric and/or duodenal lesions". Among suspected diagnoses of CD, 74.6 % were based on the criterion in the suspected category: one or two minor findings.
Conclusions The Japanese diagnostic criteria for Crohn's disease consist of combinations of specific morphological findings. Many of the diagnoses were based on the findings of LU or CSA.

Keywords Crohn's disease · Inflammatory bowel disease · Diagnostic criteria

Introduction

Crohn et al. [1] were the first to report subacute or chronic ileitis invading the terminal ileum as regional ileitis. This condition, Crohn's disease (CD), was subsequently established as a distinct pathological entity comprising lesions throughout the gastrointestinal tract, from the mouth to the anus. CD is a well-known type of refractory inflammatory bowel disease of unknown etiology, and the number of affected patients is growing in Japan [2]. CD causes both symptoms attributable to gastrointestinal lesions and complications throughout the body, appearing with many clinical manifestations, so accurate diagnosis of CD in the early stages is very important. No single gold standard for the diagnosis of CD is currently available. The diagnosis is therefore confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations [3].

In 1976, the Japanese Society of Gastroenterology (Nippon Shokakibyo Gakkai Zasshi 1976;73:1467–78) became the first Japanese organization to propose diagnostic criteria for CD. The criteria have been repeatedly revised to reflect the continually advancing understanding

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of CD. The Research Group of Intractable Inflammatory Bowel Disease granted by the Ministry of Health, Labour, and Welfare of Japan authored the latest version of the criteria [4] in 2011. As proposed, the current version of the CD diagnostic criteria contains five main sections: (1) disease concept; (2) primary features (including clinical symptoms, surgical findings, histopathological findings); (3) diagnostic criteria; (4) disease classification; and (5) severity classification. However, the diagnostic criteria for definitively diagnosing CD consist of morphological findings (i.e., radiographic, endoscopic, and pathological findings) only, and do not include symptomatology [5]. Differentiating those findings from morphological findings present in other disease is therefore very important.

We recently conducted a questionnaire-based nationwide survey to determine how diagnoses are made with the Japanese diagnostic criteria and to evaluate the suitability of these criteria.

Methods

A questionnaire on the diagnosis of CD was sent to each participating medical institution of the Research Group of Intractable Inflammatory Bowel Disease. These institutions were asked to base their responses on the 20 most recent consecutive cases of CD, as of January 2011, diagnosed according to the CD diagnostic criteria [4, 6] (Table 1). The survey also asked about suspected cases of CD identified during the period over which the 20 most recent cases were diagnosed. The respondents were asked to identify the sex, age, and symptoms of the patients as well as the particular criterion on which the diagnosis was based, the test methods used, and the time required to reach the diagnosis.

Results

The survey included 579 patients given a definitive diagnosis of CD and 59 patients given a suspected diagnosis of CD at the 34 responding medical institutions (Table 2).

Definite cases of CD

Mean age at the time of diagnosis for patients given a definitive diagnosis of CD was 27.8 ± 13.7 years. A mean interval of 3.1 ± 10.0 months passed between initial examination and definitive diagnosis. Abdominal pain was the most common clinical manifestation (414 patients, 71.5 %), followed by diarrhea (366 patients, 63.2 %) and weight loss (201 patients, 34.7 %). Ileocolonic type was the most common disease location (305 patients, 52.7 %), followed by ileal type (153 patients, 26.4 %) and colonic type (121 patients, 20.9 %) (Table 3).

The particular criteria used to make the diagnoses are listed in Table 4. A total of 87.4 % of the definitive diagnoses of CD were based on Definite 1 (D1): major finding A "longitudinal ulcer (LU)" or B "cobblestone-like appearance (CSA)". Moreover, 81.7 % of these diagnoses were based on major finding A "LU". A total of 30.4 % of the definitive diagnoses were based on Definite 2 (D2): major finding C "noncaseating epithelioid cell granuloma (NCEG)" with minor finding a "irregular-shaped and/or quasi-circular ulcers or aphthous ulcerations found extensively in the gastrointestinal tract" or b "characteristic perianal lesions". Finally, 7.1 % of the definitive diagnoses were made according to Definite 3 (D3): All minor findings a "irregular-shaped and/or quasi-circular ulcers or aphthous ulcerations found extensively in the gastrointestinal tract", b "characteristic perianal lesions", and c "characteristic gastric and/or duodenal lesions".

Endoscopy was the most common procedure used to make the finding on which the definitive diagnosis was based (512 patients). Many of the colon lesions leading to the diagnosis were identified with endoscopy, while many of the small bowel lesions were identified with radiography. The percentage of patients given a definitive diagnosis through biopsy, i.e., the detection rate of NCEG was 26.3 % (152 of 579 patients) (Table 5).

Suspected cases of CD

Mean age at the time of diagnosis of patients given a suspected diagnosis of CD was 36.3 ± 18.6 years. Abdominal pain was the most common clinical manifestation (41 patients, 69.5 %), followed by diarrhea (35 patients, 59.3 %). The most common disease location was colonic type (25 patients, 42.4 %) followed by ileal type (20 patients, 33.9 %) and ileocolonic type (13 patients, 22.0 %) (Table 6).

The particular criteria used to make suspected diagnoses are listed in Table 7. Of the suspected diagnoses of CD, 74.6 % were based on Suspected 4 (S4): One or two minor findings. Moreover, 16.9 % of suspected diagnoses were based on Suspected 2 (S2): major finding A "LU" or B "CSA", but cannot be differentiated from ischemic colitis or ulcerative colitis. Among patients given a suspected diagnosis of CD, the pathology could not be differentiated from ulcerative colitis (11 patients), Behçet's disease/simple ulcer (9 patients), intestinal tuberculosis (5 patients), ischemic colitis (2 patients), infectious enterocolitis (2 patients), sarcoidosis (1 patient), and collagenous colitis (1 patient).

Table 1 Proposed diagnostic criteria for Crohn's disease in Japan

(1) Major findings

A. Longitudinal ulcer [a]

B. Cobblestone-like appearance

C. Noncaseating epithelioid cell granuloma[b]

(2) Minor findings

a. Irregular-shaped and/or quasi-circular ulcers or aphthous ulcerations found extensively in the gastrointestinal tract [c]

b. Characteristic perianal lesions [d]

c. Characteristic gastric and/or duodenal lesions [e]

Definite

1. Major finding A or B [f]
2. Major finding C, with minor finding a or b
3. All minor findings a, b, and c

Suspected

1. Major finding C, with minor finding c
2. Major finding A or B, but cannot be differentiated from ischemic colitis or ulcerative colitis
3. Major finding C only [g]
4. One or two minor findings

[a] In the small intestine, the ulcer occurs more commonly on the mesentery side

[b] The rate of detection of this granuloma is improved by creating serial sections. It is advisable that a pathologist familiar with the gastrointestinal tract examine a specimen of it

[c] In typical cases, the ulcers are arranged longitudinally, but this does not occur in some cases. It is necessary that they persist for at least 3 months. With regard to this condition, it is necessary to exclude enteric tuberculosis, intestinal Behçet's disease, simple ulcers, nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers, and infectious enterocolitis

[d] These lesions consist of anal fissures, cavitating ulcers, anal fistulas, perianal abscesses, and edema-like anal skin tags. Preferably, colorectal surgeons familiar with Crohn's disease are consulted to examine such lesions, referring to the *Atlas of findings by visual observation of lesions in anus Crohn's disease*

[e] These lesions have a bamboo joint-like appearance, with notch-like depressions. Preferably, specialists familiar with Crohn's disease are consulted to examine such lesions

[f] In cases with only longitudinal ulcers, it is necessary to exclude ischemic intestinal lesions and ulcerative colitis. In cases with only a cobblestone-like appearance, it is necessary to exclude ischemic intestinal lesions

[g] It is necessary to exclude inflammatory diseases with granulomas such as intestinal tuberculosis

Discussion

The present survey represents the first nationwide attempt to determine which specific criteria in the Japanese diagnostic criteria for CD were used to make diagnoses. Physical examination, laboratory tests, and gastrointestinal investigations should be conducted when CD is suspected from the medical interview, and the definitive diagnosis of CD is made based on the Japanese diagnostic criteria of CD [4]. The Japanese diagnostic criteria of CD consist mainly of morphological findings from the gastrointestinal tract [6]. The criteria provide some supplemental information about these findings. LU and CSA, two of the criteria's three major findings, have long been considered characteristic of CD [3, 7–10]. The criteria define a LU as an ulcer $\geq$5 cm that runs longitudinally along the gastrointestinal tract and further state that LU encountered in ischemic and infectious enterocolitis rarely display a CSA. In CD, CSA is described as involving "dense protrusions of mucous membrane of uneven sizes, large or small, surrounded by LU and smaller ulcers". The criteria further state, "This appearance may be seen in ischemic colitis, but in ischemic colitis the protrusions are smaller and redness is more intense". NCEG [11–14] is an important histopathological finding, but also associated with intestinal tuberculosis. The criteria recommend creating serial sections and assigning assessment to a pathologist familiar with the gastrointestinal tract to improve diagnostic accuracy. Irregular-shaped and/or quasi-circular ulcers or aphthous ulcerations found extensively in the gastrointestinal

Table 2 Participated facilities in this study ($n = 34$)

Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka;
Akita Health Care Center, Japanese Red Cross Akita Hospital, Akita;
Department of Gastroenterology and Hematology, Hirosaki University Graduate School of Medicine, Aomori;
Department of Gastroenterology and Hepatology, Shimane University School of Medicine, Shimane;
Center for Gastroenterology and Hepatology, Ofune Chuo Hospital, Kanagawa;
Department of Gastroenterology, Osaka City Sumiyoshi Hospitsal, Osaka;
Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama;
Department of Gastroenterology, Tohoku University School of Medicine, Miyagi;
Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical College, Hokkaido;
Department of Gastroenterology, Kitasato University East Hospital, Kanagawa;
Department of Gastroenterology, Nagoya University Graduate School of Medicine, Aichi;
Department of Gastroenterology, Aichi Medical University School of Medicine, Aichi;
Department of Gastroenterology and Hepatology, Jikei University School of Medicine, Tokyo;
Department of Gastroenterology, Osaka General Hospital of West Japan Railway Company, Osaka;
Department of Gastroenterology, Nagoya City University Hospital, Aichi;
Department of Inflammatory Bowel Disease, Yokohama Municipal Citizen's Hostipal, Kanagawa;
Department of Internal Medicine, Social insurance Central General Hospital, Tokyo;
Department of Endoscopy Gastroenterology and Metabolism, Hiroshima University Hospital, Hiroshima;
Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto;
Department of Human and Environmental Sciences, Kagoshima University Graduate School of Medical and Dental Science, Kagoshima;
Department of Pediatrics, Gunma University Graduate School of Medicine, Gunma;
Center for Gastroenterology and Inflammatory Bowel Disease Research, Hamamatsu South Hospital, Shizuoka;
Third Department of Internal Medicine, Nara Medical University, Nara;
Department of Medicine, Shiga University of Medical Scinence, Shiga;
Department of Gastroenterology, Fukuoka University Chikushi Hospital, Fukuoka;
Division of Lower Gastroenterology, Hyogo College of Medicine, Hyogo;
Department of Internal Medicine, National Defense Medical College, Saitama;
Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Fukuoka;
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo;
IBD Center, Sapporo Kosei General Hospital, Hokkaido;
Department of Gastroenterology and Hepatology, Kansai Medical University Hirakata Hospital, Osaka;
Department of Pediatrics, Osaka Medical College, Osaka;
Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka;
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tract, one minor finding of the criteria, must persist for ≥3 months to be relevant. The listed characteristic perianal lesions are anal fissures, cavitating ulcers, anal fistulas, perianal abscesses, and edema-like anal skin tags. Perianal lesions in CD are an important feature that sometimes leads to the diagnosis, because of their high frequency and occasional appearance before abdominal features [15–18]. CD also commonly features upper gastrointestinal lesions [19–22]. Characteristic gastroduodenal lesions include a bamboo joint-like appearance and a notch-shaped appearance. Detailed testing is required to identify the findings of the diagnostic criteria. The diagnostic imaging and histopathological findings of this testing must be fully considered to properly differentiate CD from other diseases.

It should be noted that the present survey does not exhaustively represent CD diagnosis throughout Japan, because primarily IBD specialist institutions were surveyed. In the survey, 87.4 % of definitive diagnoses of CD were made based on D1. The vast majority of these definitive diagnoses were made based on the presence of LU and CSA are the first findings listed in the definite category of the criteria. As these findings are characteristic of CD, it follows that they would serve as the basis for many diagnoses. A total of 30.4 % of definitive diagnoses were based on D2. Finally, 7.1 % of definitive diagnoses were made according to D3. We can think of several reasons why D2 and D3 in the definite category did not contribute as substantially to the diagnoses. Even non-IBD specialists are capable of diagnosing CD based on full-blown, typical lesions such as LU and CSA. The expertise of an IBD specialist, however, is required to identify the three minor findings in the criteria list, and differentiating

Table 3 Clinical characteristics of a definitive diagnosis of CD ($n = 579$)

Male/female	459/120
Age (mean ± SD, years)	27.8 ± 13.7
Period from initial visit to diagnosis (mean ± SD, months)	3.1 ± 10.0
Clinical manifestations	
Abdominal pain	414
Diarrhea	366
Weight loss	201
Fever	189
Perianal disease	167
Intestinal obstruction	32
Intestinal perforation	14
Bleeding	19
Arthritis	19
Asymptomatic	14
Fistulas	10
Extent of lesions	
Ileal type	153
Colonic type	121
Ileocolonic type	305
Isolated upper disease	115

SD standard deviation

Table 4 Particular criteria used to make a definite diagnosis ($n = 579$)

Definite 1	
Major finding A or B	506/579 (87.4 %)
A	473/579 (81.7 %)
B	238/579 (41.1 %)
Definite 2	
Major finding C with minor finding a or b	176/579 (30.4 %)
C + a	148/579 (25.6 %)
C + b	71/579 (12.3 %)
Definite 3	
All minor findings a, b and c	41/579 (7.1 %)

Table 5 Morphological and pathological examinations to make a definitive diagnosis of CD

	Endoscopy ($n = 512$)	Radiography ($n = 346$)	Biopsy ($n = 152$)	Resected specimen ($n = 46$)
Upper gastrointestinal tract	115	5	10	0
Small intestine	161	311	46	38
Colon	416	67	116	18

Table 6 Clinical characteristics of a suspected diagnosis of CD ($n = 59$)

Male/female	37/22
Age (mean ± SD, years)	36.3 ± 18.6
Duration of suspected diagnosis of CD (mean ± SD, months)	22.2 ± 17.7
Clinical manifestations	
Abdominal pain	41
Diarrhea	35
Intestinal obstruction	8
Fever	7
Weight loss	5
Bleeding	5
Perianal disease	2
Fistulas	1
Asymptomatic	1
Extent of lesions	
Ileal type	20
Colonic type	25
Ileocolonic type	13
Isolated upper disease	1

SD standard deviation

Table 7 Particular criteria used to make a suspected diagnosis ($n = 59$)

Suspected 1	Major finding C with minor finding c	0/59 (0 %)
Suspected 2	Major finding A or B, but cannot be differentiated from ischemic colitis or ulcerative colitis	10/59 (16.9 %)
	A	9/59 (15.3 %)
	B	1/59 (1.7 %)
Suspected 3	Major finding C only	8/59 (13.6 %)
Suspected 4	One or two minor findings	44/59 (74.6 %)
	a	40/59 (67.8 %)
	b	2/59 (3.4 %)
	c	6/59 (10.2 %)

CD from other diseases can be difficult in patients presenting with these findings. General practitioners would sometimes be unable to diagnose CD based on perianal lesions, which should be examined by a proctologist familiar with CD. The somewhat low biopsy-based detection rate of NCEG (26.3 %) identified in the survey is likely another reason.

Several facilities and guidelines in the United States and Europe have proposed diagnostic criteria, many of which are composed of clinical symptoms and image-based, surgical, and histopathological findings [3, 23–30]. The European Crohn's and Colitis Organisation (ECCO) [3]

offers guidelines for managing CD. These guidelines state, "a single gold standard for the diagnosis of CD is not available. The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations".

As has been described, the Japanese diagnostic criteria for CD consist of several combinations of specifically defined morphological findings. The Japanese diagnostic criteria differ from the criteria used in the United States and Europe in that a definitive diagnosis of CD is made based on findings of LU and CSA, which are defined in detail, and in that aphthous lesions are defined for definitive diagnosis of CD. Patients benefit enormously when the disease can be diagnosed soon after onset based on aphthous lesions. CD is relatively easily diagnosed when classical morphological findings are present. CD, however, is difficult to differentiate from other diseases when only early findings or non-classical findings are present [31–33], and a substantial number of CD cases do not satisfy the diagnostic criteria. The suspected category in the Japanese diagnostic criteria was included for just such cases, which are definitively diagnosed only after repeated observations. CD with aphthous lesions alone is particularly difficult to identify. An early indicator of CD, aphthous lesions develop into LU and other classical findings in some patients [34–36]. However, no diagnosis can be made based on aphthous lesions alone, because these nonspecific findings also appear in infectious enterocolitis, intestinal Behçet's disease, and other related conditions. CD can be definitively diagnosed under the Japanese criteria by demonstrating NCEG with aphtha or by identifying all three minor findings. The fact that 67.8 % of suspected cases in the survey could not be differentiated from other diseases because of the presence of only irregular-shaped and/or quasi-circular ulcers or aphthous ulcerations found extensively in the gastrointestinal tract indicates just how difficult reaching a diagnosis can be.

In conclusion, in addition to short-term care, Crohn's disease requires a well-formulated, long-term treatment plan to be properly managed. Early, accurate identification of the disease and proper characterization of its manifestations are critical parts of such plans. Our survey indicates that the majority of CD diagnoses made in Japan are based on the classical finding of LU or CSA, representing an appropriate rationale. CD, however, remains underdiagnosed based on aphthous lesions and NCEG found in biopsy.

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Conflict of interest Toshiyuki Matsui received research grants from Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ajinomoto Pharmaceuticals Co., Ltd., Zeria Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Astellas Pharma Inc.; received lecture fees from Eisai Co., Ltd. Mamoru Watanabe received research grants from abbvie.co.jp., Astellas Pharma Inc., Asahi Kasei Kuraray Medical Co., Ltd, Ajinomoto Pharma Co., Ltd, Chugai Pharmaceutical Co., Ltd, DAIICHI SANKYO CO., LTD, Eisai Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Kyorin Pharmaceutical Co. Ltd, JIMRO Co.Ltd, Mitsubishi Tanabe Pharma Corporation, MSD K.K., Otsuka Pharma Co., Ltd, Takeda Pharmaceutical Co., Ltd, UCB Japan Co., Ltd, and Zeria Pharmaceutical Co., Ltd. Takashi Hisabe and Fumihito Hirai have no conflict of interest.

Appendix: Contributors in the development of the diagnostic criteria for Crohn's disease in Japan (the Research Group of Intractable Inflammatory Bowel Disease granted by the Ministry of Health, Labour and Welfare of Japan)

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ORIGINAL ARTICLE—ALIMENTARY TRACT

The ability of a novel blue laser imaging system for the diagnosis of invasion depth of colorectal neoplasms

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Abstract
Background Fujifilm has developed a novel endoscope system with two kinds of lasers that enables us to allow narrow-band light observation with blue laser imaging (BLI). The aim of this study was to evaluate BLI magnification in comparison with narrow-band imaging (NBI) magnification for the diagnosis of colorectal neoplasms.
Methods This was a multicenter open study. A total of 104 colorectal neoplasms were examined with BLI and NBI magnifications in Kyoto Prefectural University of Medicine and Fukuoka University Chikushi Hospital. Vascular and surface patterns of tumors under BLI magnification were compared with those under NBI magnification, using a published NBI classification. The main outcome was the correlation between the NBI classification diagnosed by BLI or NBI magnification and the histopathological analyses.
Results Sixty-two cases of adenoma, 34 cases of intramucosal cancer and shallowly invaded submucosal cancer, and eight cases of deeply invaded submucosal cancer were diagnosed. The diagnostic accuracy of BLI magnification in the NBI classification was 74.0 % (77/104), similar to that of NBI magnification (77.8 %). The consistency rate between BLI and NBI magnification in the NBI classification was 74.0 %. Concerning image evaluation, the interobserver variability of two expert endoscopists (N.Y. and T.H.) in BLI magnification was $\kappa = 0.863$. On the other hand, the intraobserver variability of the two endoscopists was $\kappa = 0.893$ (N.Y.) and 0.851 (T.H.).
Conclusions BLI magnification by laser source could predict histopathological diagnosis and invasion depth of colorectal neoplasms. The diagnostic effectiveness of this method was similar to that of NBI magnification.

Keywords BLI · Laser · NBI · Colorectal polyps · Image-enhanced endoscopy

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Introduction

Advancements in endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have facilitated the removal of large, early-stage colorectal cancers [1–3]. However, massively invading submucosal cancers sometimes have lymph node metastases [4]. Colonoscopy is considered an effective approach for the detection of colorectal neoplastic lesions. Chromoendoscopy, using Kudo and Tsuruta's pit pattern classification, is a powerful tool for the differential diagnosis of colorectal tumors including submucosal cancer [5–7]. However, the chromoendoscopy

procedure is relatively cumbersome and time consuming. Chromoendoscopy is one type of image-enhanced endoscopy (IEE) also called dye-based IEE; recently, another IEE method called equipment-based IEE has also been used for diagnosing gastrointestinal tumors [8]. This method is a change from conventional white light (WL) endoscopy without a dyeing solution, requiring only the push of a button. IEE procedures, including narrow-band imaging (NBI), flexible spectral imaging color enhancement (FICE), and autofluorescence imaging (AFI), have many advantages for the diagnosis of neoplastic tumors, evaluation of the invasion depth of cancerous lesions, and detection of neoplastic lesions. In the NBI system (Olympus Medical Co., Tokyo, Japan), optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are mechanically inserted between a xenon lamp and a red/green/blue (RGB) rotation filter [9–11]. NBI with or without magnification can enhance vascular patterns and pit-like structures, which were named "surface patterns" in a Japanese consensus symposium [12]. The FICE system (Fujifilm Co., Tokyo, Japan) can display color images with RGB components that have been assigned selected spectra in real time [13]. Similarly, FICE with or without magnification can enhance vascular and surface patterns [14, 15]. These current endoscope systems (NBI and FICE), as well as the conventional endoscope, use a xenon lamp as a light source. Recently, a new endoscope system with two kinds of semiconductor lasers as a light source was developed by the Fujifilm Corporation. This system allows for the capture of images from a narrow-band light observation, named blue laser imaging (BLI), as well as WL images. Thus, BLI is considered a novel IEE, useful for acquiring detailed mucosal surface information, such as vascular and surface patterns. This is the first study to show the function of BLI magnification by using a new endoscope system with a laser source for diagnosing neoplastic colorectal polyps. We assessed the potential of BLI magnification in predicting the histopathological diagnosis and invasion depth of colorectal neoplasms in comparison with NBI magnification.

Materials and methods

This study was a multicenter open study, conducted at the Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, and at the Department of Gastroenterology, Fukuoka University Chikushi Hospital, between August 2011 and March 2012. The inclusion criterion was the presence of neoplastic colorectal lesions that had been diagnosed using double-contrast barium enema or colonoscopy. We excluded non-neoplastic lesions in this study. All tumors were examined using both BLI and NBI and were histopathologically diagnosed using resected specimens obtained by EMR, ESD, or surgery. All patients provided written informed consent for undergoing colonoscopic examinations, including BLI and NBI. The study was approved by the ethics committee of Kyoto Prefectural University of Medicine and Fukuoka University Chikushi Hospital and carried out in accordance with the World Medical Association's Declaration of Helsinki. This study has been registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as study #UMIN000007304.

Patients took a 2-L meal of polyethylene glycol solution (Niflec; Ajinomoto Pharma Co., LTD, Tokyo, Japan) in the morning before the examination, to prepare their bowels. First, endoscopic images of the tumor were taken with either BLI or NBI by the two expert endoscopists (N.Y. and T.H.) at the two institutions. Then, endoscopic images of the same tumor were taken using the other modality (BLI or NBI) by the same experts on the next day. Two to three endoscopic images were taken for each tumor, consisting of one image of the whole tumor and the other images representing magnifications of the tumor. The experts selected magnified images to represent endoscopic views about the locus that could adequately depict tumor malignancy and invasion depth, considering both BLI or NBI images and WL images. Only BLI and NBI magnification images were used in this study; no WL images were obtained. All sets of images of a tumor obtained by either BLI or NBI magnification were collected from the two institutions. Information about the modality used (BLI or NBI) in the images was deleted to reduce bias (Figs. 1, 2). The endoscopic images were collected during the study period. Then, all sets of images of a tumor were numbered randomly. Each tumor was diagnosed by the two expert endoscopists, using a published NBI classification (Hiroshima classification) without the information of histopathological diagnosis [11]. The two endoscopists had experience in more than 50 cases each of BLI and NBI magnification before this study, and this reduced the influence of a learning curve on the analysis. If the classification of a tumor differs between N.Y. and T.H., the endoscopists consulted with each other to achieve a consensus.

Study outcomes

The correlation between the NBI classification, diagnosed by BLI or NBI magnification, and the histopathological diagnoses were analyzed. The accuracy of predicting histopathological diagnosis was calculated by analyzing the agreement between the two endoscopists' initial diagnostic accuracy and their consulted diagnostic accuracy. Moreover, the rate of classification consistency between the BLI

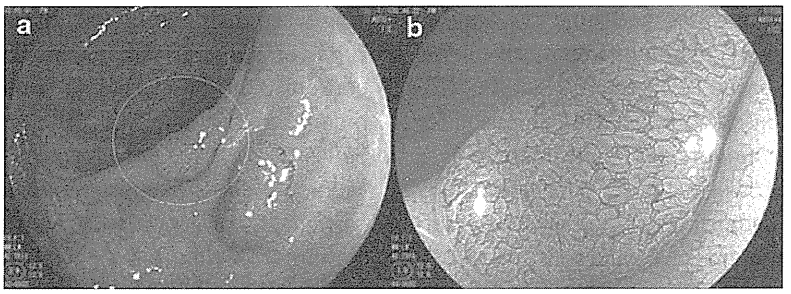

Fig. 1 BLI images. **a** BLI without magnification showing two colorectal polyps 6 mm in diameter. The *borderlines* of the polyps could be detected clearly. The polyp marked by a *white circle* was magnified. **b** BLI magnification: a meshed capillary pattern and an oval surface pattern were detected. The polyp was diagnosed as type B in the NBI classification

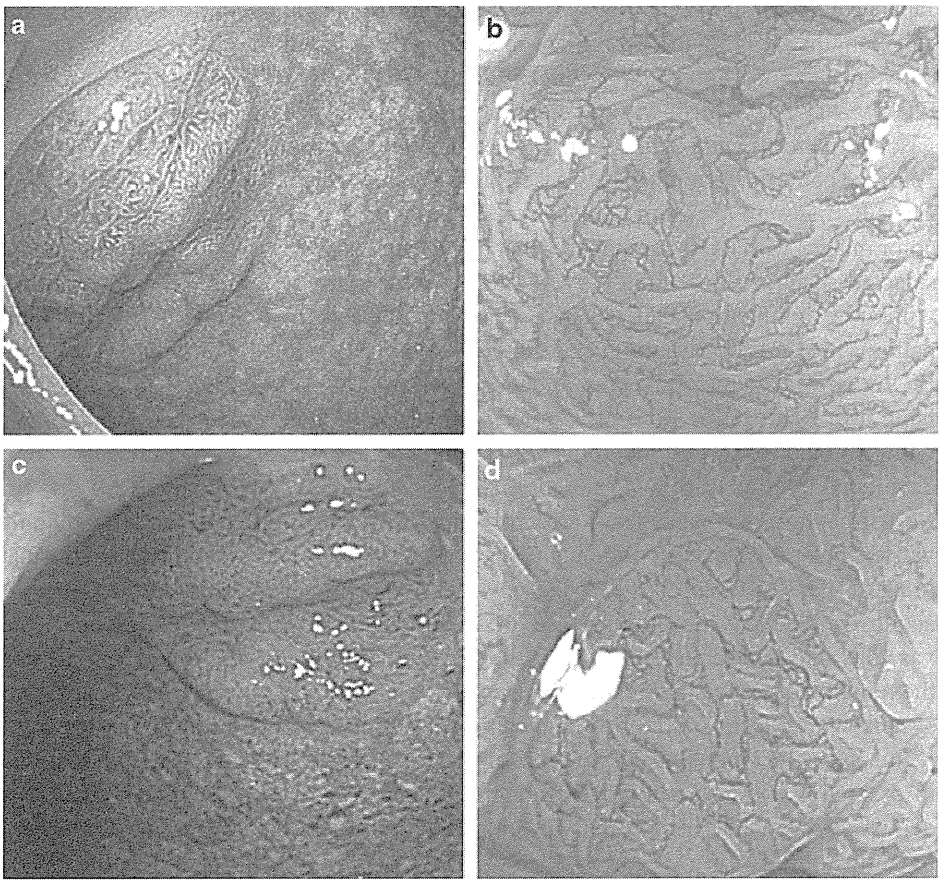

Fig. 2 BLI and NBI images of the same tumor. **a** The BLI-bright mode detected a type IIa polyp 35 mm in diameter. **b** BLI magnification images. A meshed capillary pattern and an oval surface pattern were detected. The polyp was diagnosed as type B in the NBI classification. **c** NBI detected a type IIa polyp 35 mm in diameter. **d** NBI magnification images. A meshed capillary pattern and an oval surface pattern were detected. The polyp was diagnosed as type B in the NBI classification

and NBI magnifications was evaluated. The image evaluation of BLI or NBI magnification with the NBI classification was validated by performing interobserver and intraobserver examinations according to a previous report [15]. Briefly, all sets of selected images were evaluated randomly by the two expert endoscopists (N.Y. and T.H.). The interobserver examination involved analyzing the agreement between the two endoscopists about the NBI classification of both BLI and NBI magnification images. On the other hand, the endoscopists also performed diagnosis with the NBI classification by using a set of BLI or NBI magnification images taken on 1 day, and then assessing the same set of images 1 week later. This comprised the intraobserver examination.

NBI classification

For performing the diagnosis using BLI or NBI magnification images, we adopted the NBI classification—the Hiroshima classification reported by Kanao et al [11]. Both surface patterns and vascular patterns were evaluated in each tumor using this classification. In the Hiroshima classification, type A indicates hyperplastic polyp (HP) and lesions in which microvessels are extremely opaque or not

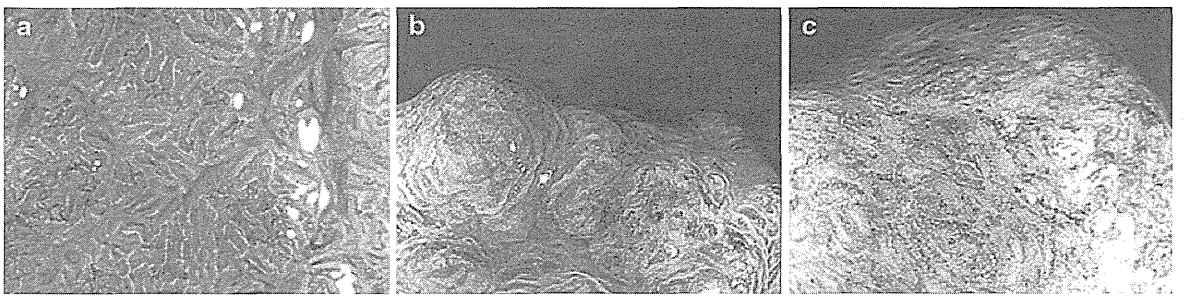

Fig. 3 BLI magnification. **a** Type C1 in the NBI classification (Hiroshima classification), **b** type C2, **c** type C3

observed. Type B includes lesions in which fine microvessels are observed around the surface pattern and a clear surface pattern can be observed through the nest of microvessels (Fig. 2b, d); it indicates adenoma (Ad). Type C is divided into three sub-types: C1, C2, and C3. In type C1, microvessels create an irregular network, the surface patterns observed through the microvessels are slightly nondistinct, and the vessel diameter or distribution is homogeneous (Fig. 3a). In type C2, microvessels create an irregular network, the surface patterns observed through the microvessels are irregular, and the vessel diameter or distribution is heterogeneous (Fig. 3b). Types C1 and C2 indicate intramucosal cancer (M) and shallowly invaded submucosal cancer (sSM). In type C3, the surface patterns are invisible through the microvessels, vessel diameters are large or irregular, and vessel distribution is heterogeneous or avascular areas are observed; it indicates deeply invaded submucosal cancer (dSM) (Fig. 3c). Thus, the classifications of histopathological diagnoses were as follows: type A, HP; type B, Ad; types C1 and C2, M-sSM; type C3, dSM. For larger lesions exhibiting a variety of types within a lesion, the most significant type was used to predict histopathological diagnosis.

Histopathological diagnosis

The specimens of the tumors were obtained by EMR, ESD, and surgical resection. Then, they were fixed with 10 % formalin and were evaluated histopathologically. Histopathological diagnosis was performed by two clinical pathologists (A.Y. and A.I.) according to the classification by the World Health Organization [16]. In this study, the

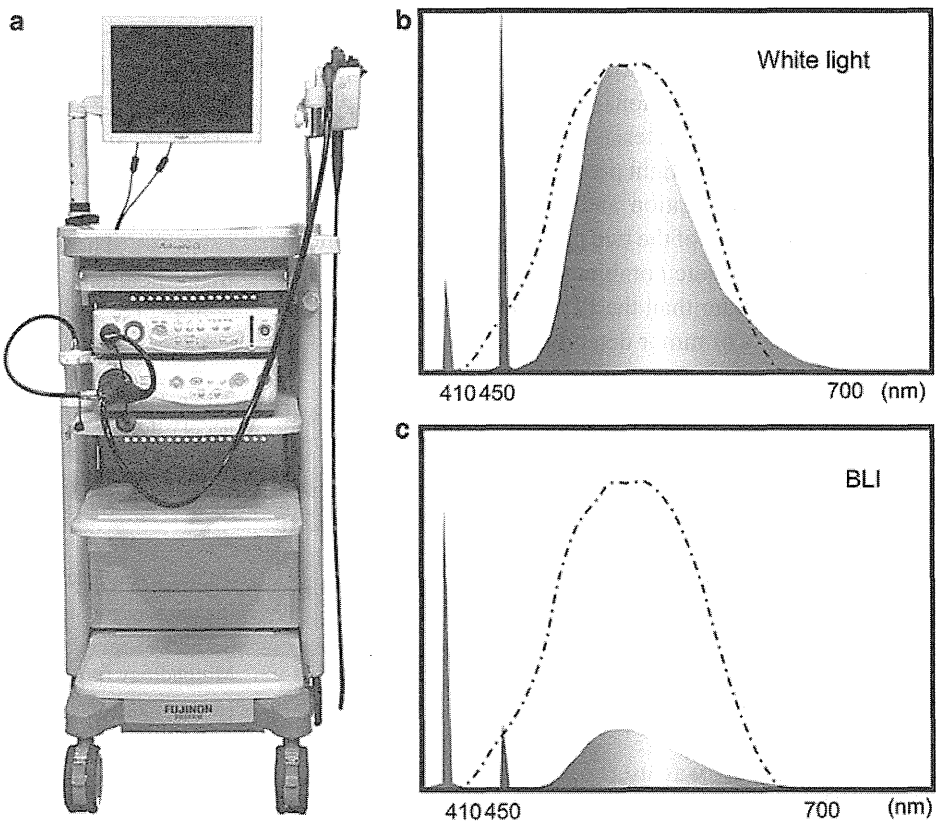

Fig. 4 The new endoscope system, LASEREO, and the principle of BLI and WL mode with a laser source. **a** Components of the LASEREO system. **b** The laser with a 450 nm wavelength makes phosphor irradiate an illumination similar to that of a xenon lamp. The combination of strong laser light with a 450 nm wavelength and fluorescent light provides an illumination that is almost equivalent to that of WL. **c** The BLI is made from the combination of strong laser light with a 410 nm wavelength and weak laser light with a 450 nm wavelength, and fluorescent light

dSM was defined as a tumor with a submucosal invasion length of 1000 μm or more. On the other hand, the sSM was defined as a tumor with a submucosal invasion length less than 1000 μm. Submucosal invasion length was calculated according to the Japanese classification of colorectal carcinoma proposed by the Japanese Society for Cancer of the Colon and Rectum [4, 17].

BLI magnification device

A new endoscope system, "LASEREO", developed by Fujifilm uses a semiconductor laser as light source. It has the narrow-band light observation function without a customized optical filter. The LASEREO system consists of the LL-4450 light source, the VP-4450HD processor, and a special scope series (Fig. 4a). The LL-4450 has two kinds of lasers whose wavelengths are 410 and 450 nm. The peak wavelength of both lasers varies in a certain range. The ranges of peak wavelength of both lasers are 410 ± 10 and 450 ± 10 nm. Additionally, both of bandwidths are less than about 2 nm, compared to the bandwidth of NBI (30 nm) [18]. The laser with a 450 nm wavelength makes phosphor irradiate an illumination similar to that of a xenon lamp (Fig. 4b). The combination of the strong light of the laser with a 450 nm wavelength and fluorescent light provides an illumination that is almost equivalent to that of WL. The laser with a 410 nm wavelength is for the "BLI", which functions as a narrow-band light. The BLI light is made from the combination of strong laser light with a 410 nm wavelength and weak laser light with a 450 nm wavelength, and fluorescent light (Fig. 4c). The BLI light is useful for acquiring mucosal surface information, such as surface blood vessel and surface structure patterns. More specific wavelengths and precisely regulated light power of lasers allow us to have detailed vessel information and clear surface patterns. By controlling the power of the two lasers, a "BLI-bright" mode is set by an appropriate combination of WL and BLI light. This mode is brighter than the BLI mode, and it is expected for the usefulness of tumor detection.

NBI magnification device

For NBI, examinations were performed using a colonoscope (PCF-Q240ZI, CF-H260AZI or CF-FH260AZI; Olympus Optical Co., Ltd., Tokyo, Japan) and a videoendoscope system (EVIS LUCERA SPECTRUM, Olympus Optical).

Statistical analysis

The Chi-square test was used for the comparison of diagnostic accuracy between BLI and NBI magnifications. The kappa value was calculated to assess the image evaluation by BLI and NBI magnifications. A p value of <0.05 was considered statistically significant.

Results

A total of 104 colorectal neoplasms were enrolled and analyzed in this study. The detailed characteristics of subjects and samples are given in Table 1. Among all tumors, there were 62 Ad, 34 M-sSM, and eight dSM diagnoses. The tumor morphologies diagnosed included 51 protruded tumors and 53 superficial tumors according to Japanese classification [17]. Regarding the sequence of BLI and NBI, the 76 cases in Kyoto Prefectural University of Medicine were observed using NBI first, followed by BLI. The 28 cases in Fukuoka University Chikushi Hospital were observed using BLI first, and NBI second. The two endoscopists' initial diagnostic accuracy according to our definition using BLI data before the consultation were 64.1 % (N.Y.) and 79.2 % (T.H.), respectively. On the other hand, those using NBI data first were 68.8 % (N.Y.) and 74.5 % (T.H.), respectively. Following this, the consulted diagnosis by the two endoscopists was performed. The relation between the NBI classification in BLI magnification and the histopathological diagnosis of colorectal neoplasms compared with that in NBI magnification is summarized in Table 2. Ad was observed in 83.3 % of type B lesions ($n = 60$). Ad, M-sSM, and dSM were observed in 31.4, 57.2, and 11.4 % of type C1 lesions ($n = 35$), respectively, and in 16.7, 66.6, and 16.7 %, of type C2 lesions ($n = 6$), respectively. Finally, dSM was observed in 100.0 % of type C3 lesions ($n = 3$). The consulted diagnostic accuracy of BLI magnification according to our definition was 74.0 %, similar to that of NBI magnification (77.8 %). The rate of consistency between BLI and NBI magnifications was 74.0 % (77/104) in the NBI classification. To assess the image evaluation accuracy by BLI

Table 1 Clinical characteristics of subjects and the 104 colorectal neoplastic polyps with BLI and NBI magnifications

Number of tumors	104
Median age (range) (years)	65.4 (45–80)
M/F	65/39
Tumor size (mean ± SD) (mm)	21.3 ± 17.2
Location (right-sided: left-sided: rectum)	42:27:35
Morphology (protruded or superficial)	51:53
Histopathological diagnosis	Ad: 62, M-sSM: 34, dSM: 8

SD standard deviation, *Ad* adenoma, *M* intramucosal cancer, *sSM* shallowly invaded submucosal cancer, *dSM* deeply invaded submucosal cancer

Table 2 Correlation between the Hiroshima classification by BLI or NBI magnification and the histopathological diagnosis

	Number	HP	Ad	M or sSM	dSM
BLI					
A	0				
B	60	0	50	10	0
C1	35	0	11	20	4
C2	6	0	1	4	1
C3	3	0	0	0	3
NBI					
A	0				
B	66	0	55	11	0
C1	29	0	7	19	3
C2	6	0	0	4	2
C3	3	0	0	0	3
Diagnostic accuracy					
BLI	50 + 20 + 4 + 3/104 = 77/104 = 74.0 %				
NBI	55 + 19 + 4 + 3/104 = 81/104 = 77.8 %				

HP hyperplastic polyp, *Ad* adenoma, *M* intramucosal cancer, *sSM* shallowly invaded submucosal cancer, *dSM* deeply invaded submucosal cancer

and NBI magnifications, we determined kappa values for interobserver variability by using readings from the two endoscopists. Under BLI magnification, the kappa value of the interobserver agreement between the endoscopists was 0.863. Using NBI magnification for the interobserver agreement, the kappa value was 0.777. Under BLI, the kappa values of the intraobserver agreement were 0.893 (N.Y.) and 0.851 (T.H.), respectively. Using NBI, the kappa values of the intraobserver agreement were 0.742 (N.Y.) and 0.737 (T.H.), respectively.

Discussion

In the current study, a novel endoscope system with a laser source, which was developed by the Fujifilm Corporation, was found useful for the diagnosis of invasion depth of colorectal tumors. BLI magnification could detect vascular and surface patterns clearly, and the NBI classification of colorectal tumors by BLI magnification correlated well with the histopathological diagnoses, similar to NBI magnification.

In the NBI classification (Hiroshima classification), all of the histopathological diagnoses of type B (100.0 %) by BLI magnification were Ad or M-sSM; therefore, these lesions were considered indications for EMR or ESD without chromoendoscopy. All type C3 lesions diagnosed by BLI were dSM, and these were considered indications for surgical resection. However, types C1 and C2 included various histopathological diagnoses such as Ad, M-SMs, and dSM. Similar data were obtained in the NBI magnification analysis in this study. For such lesions, chromoendoscopy with crystal violet should be performed for differential diagnosis; moreover, additional examinations, including endoscopic ultrasonography and barium enema, are indicated. In the report about Hiroshima classification of Kanao et al., most of the type B and C3 lesions were Ad and dSM, respectively; therefore, the method of treatment for these lesions could be endoscopic therapy or surgical resection only by NBI magnification [11]. On the other hand, dSM was detected in 11.1 % (5/45) of type C1 and 54.5 % (12/22) of type C2 lesions. According to these data, type C1 and C2 lesions should be subjected to further examinations, including chromoendoscopy. Our study suggests that BLI magnification could predict the histopathological diagnosis and invasion depth of colorectal neoplasms similar to NBI magnification, using the NBI classification, and could help decide the method of treatment for each colorectal neoplasm.

Confirming a diagnosis by using BLI and NBI magnification should be consistent among endoscopists. In our study, for the BLI magnification, the rate of the initial consistency of classification by the two endoscopists was 75.0 % (78/104). Additionally, image evaluation by BLI magnification was validated to be similar to that of NBI magnification. However, the procedures of BLI and NBI magnification are generally considered difficult for inexperienced endoscopists. In relation to this problem, a recent study reported the outcomes of a training program in performing NBI magnification. This study revealed that an hour-long training lecture could increase the differential diagnostic skills of inexperienced NBI magnification operators to expert levels [19]. Properly conducted short trainings in BLI magnification performed in our institution could potentially offer the same impact.

The consistency rate between BLI and NBI magnification in the NBI classification was high (74.0 %). In contrast, the rate of different diagnoses between BLI and NBI magnifications was 26.0 %. The reasons for these different diagnoses were analyzed. First, a different tumor locus was observed by BLI and NBI magnifications in most of the cases. Second, the surface and vascular patterns detected by BLI and NBI magnifications were different in some cases. Images of the same part of the tumor obtained by both BLI and NBI magnification were compared in detail (Fig. 5a–d). Different endoscopic images of vessels and surface patterns were detected in BLI magnification, compared to NBI magnification. We assumed that this was due to the differences of wavelength, bandwidth, and power of BLI light, compared to NBI light. Thus, the bandwidth of BLI and NBI were 2 and 30 nm, respectively [18]. Additionally, the wavelengths were 410 and 450 nm in BLI and 415 and 540 nm in NBI. However, the number

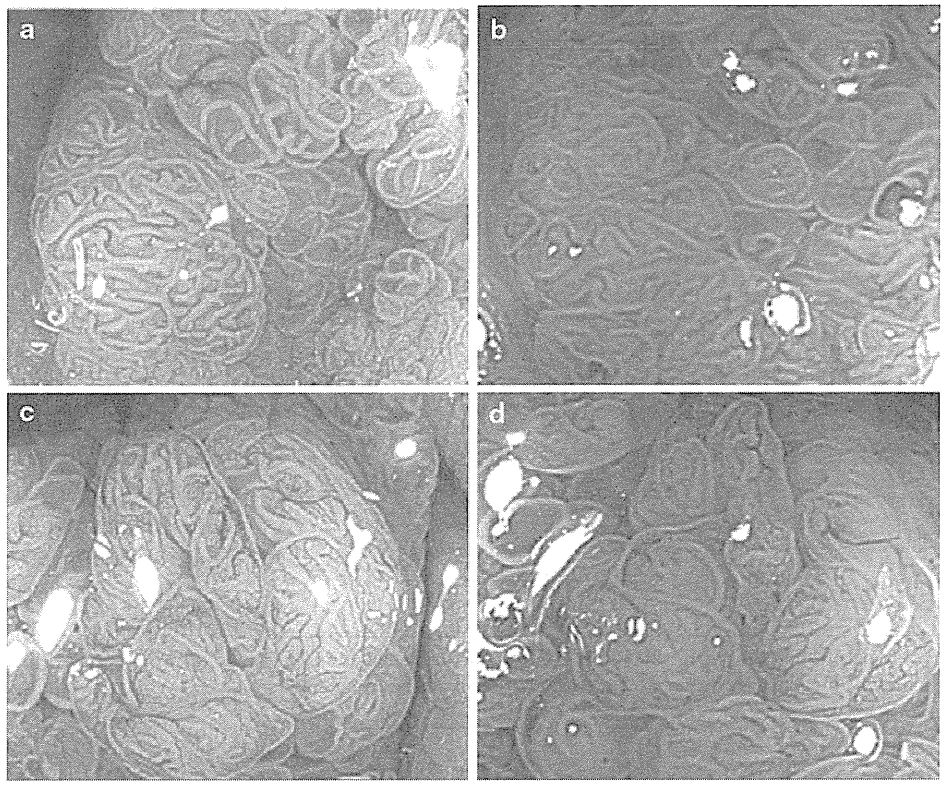

Fig. 5 Difference between the endoscopic images of BLI and NBI magnifications of the same portion of the same tumors. **a** Tumor A with BLI magnification. **b** Tumor A with NBI magnification. **c** Tumor B with BLI magnification. **d** Tumor B with NBI magnification

of cases was limited in our study, and further analysis of the difference between BLI and NBI should be performed.

In our previous report, FICE magnification findings corresponded well with histopathological diagnoses and the tumor classification by NBI magnification was concordant with that by FICE magnification [14, 15]. The details of FICE and NBI magnification were also compared. There were slight differences in surface pattern and vascular pattern visualization. The parts of microvessels were undetectable by FICE magnification because of their poor contrast. However, classification of tumors by FICE magnification was similar to NBI magnification without the findings of microvessels. However, in this study, we chose NBI as a competitor of BLI because we would diagnose the classification of the tumor using both surface pattern and vascular pattern.

The laser endoscope system reported here enabled us to perform FICE magnification. Thus, the BLI magnification images may be improved by the FICE function in the future. On the other hand, a laser source is electrically more economic than the currently used xenon lamp. Additionally, in this laser endoscope system there is a new mode called the BLI-bright mode, which is brighter than BLI mode. Thus, we intend to assess another clinical study on adenoma detection in the near future.

There were several limitations to this study. First, the subject samples were limited to neoplastic colorectal polyps and the lesions were not included continuously. Thus, selection bias for the participants would exist.

Second, the sequence of NBI and BLI was not randomized, though we diagnosed all cases using endoscopic figures of both NBI and BLI after the collection of all cases.

Third, the two expert endoscopists consulted each other to achieve a consensus when the diagnosis was different. However, the endoscopist might remember the histopathological diagnosis of the lesions in clinical practice even if the endoscopic figures were diagnosed randomly. Regarding NBI magnification, parts of the tumors were observed using a PCF-Q240ZI, which was not a high-definition colonoscope. Thus, the possibility of a disadvantage toward NBI might have existed.

In this study, we found that BLI magnification by laser source could predict histopathological diagnosis and invasion depth of colorectal neoplasms. The diagnostic effectiveness of this method was similar to that of NBI magnification.

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Conflict of interest The Fujifilm Co. contributed to the BLI system in this study for free. Besides this, none of the authors have any conflict of interest or financial support to declare.

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CLINICAL REVIEW

Diagnosis and management of intestinal Behçet's disease

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Abstract Behçet's disease (BD) is a chronic relapsing disease with multiple organ system involvement characterized clinically by oral and genital aphthae, cutaneous lesions, and ophthalmological, neurological, and/or gastrointestinal manifestations. Little clinical evidence is available regarding the management of patients with intestinal BD, despite recognition that the presence of intestinal lesions is a poor prognostic factor, causing perforation and massive bleeding. Many recent case reports have suggested that anti-tumor necrosis factor alpha (TNF)α monoclonal antibodies (mAbs) are effective in patients with intestinal BD. Adalimumab, a fully human anti-TNFα mAb, has been approved in Japan for the treatment of intestinal BD. Here, we review the pathogenesis, diagnosis and management of intestinal BD, including evidence of the efficacy of anti-TNFα mAbs.

Keywords Intestinal Behçet's disease · Anti-TNFα mAb · Trisomy 8 · Adalimumab

Abbreviations

ADA	Adalimumab
BD	Behçet's disease
CDAI	Crohn's disease activity index
CRP	C-reactive protein
5-ASA	5-Aminosalicylic acid
IFX	Infliximab
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MTX	Methotrexate
TNF	Tumor necrosis factor

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Introduction

Behçet's disease (BD) was first defined in 1937 by Hulusi Behçet [1], a Turkish dermatologist, as a triad of recurrent aphthous stomatitis, genital aphthae and relapsing uveitis. This disease is highly prevalent along the Silk Road, including Japan, Korea, the Middle East, and the Mediterranean region.

Although intestinal lesions associated with BD may cause serious complications, such as perforation, and decreasd quality of life, the diagnosis and management of intestinal BD lesions has not been standardized. Empirical therapies have been used anecdotally to treat intestinal BD. In Japan, adalimumab (ADA), an anti-tumor necrosis factor alpha (TNFα) monoclonal antibody (mAb), was approved for the treatment of intestinal BD in 2013. The introduction of anti-TNFα mAbs has altered treatment strategies and may improve the long-term prognosis of patients with intestinal BD. Here, we review current topics in intestinal BD, including its clinical characteristics, diagnosis, and management.

Diagnosis of intestinal Behçet's disease

BD is regarded as a chronic relapsing disease with multiple organ system involvement characterized clinically by oral

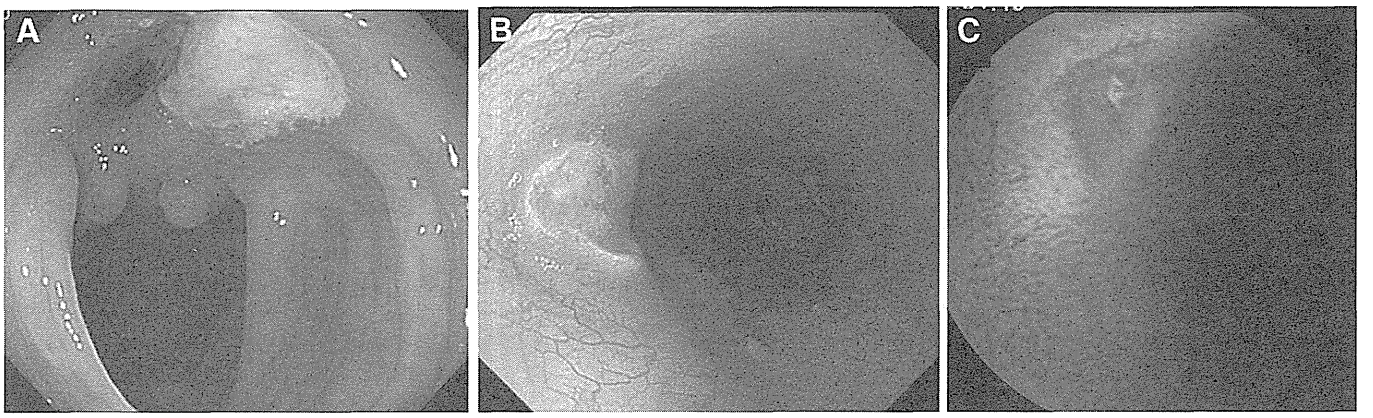

Fig. 1 Gastrointestinal lesions in BD. **a** A typical giant *oval-shaped* deep punched-out ulcer in the ileocecal area. **b** An atypical *oval-shaped* ulcer in the *middle* part of the esophagus in a patient with intestinal BD. **c** A discrete ulcer in the small intestine detected by capsule endoscopy in a MDS patient associated with trisomy 8

and genital aphthae, cutaneous lesions, and ophthalmological, neurological, and/or gastrointestinal manifestations [2, 3]. Several diagnostic criteria for BD have been proposed. The widely used International Study Group (ISG) for Behçet's disease criteria include recurrent oral ulcer, plus at least two of the following four factors—recurrent genital ulcers, eye lesions, skin lesions, and positive pathergy test [4]. The Japanese criteria proposed in 2004 are also widely used [5].

Approximately 3–16 % of patients with BD have gastrointestinal tract involvement [6]. A retrospective analysis of 2,313 patients with BD found that the male/female patient ratio was 1.03, with gastrointestinal involvement present in 1.4 % of both males and females [7]. A typical gastrointestinal lesion consists of a giant oval-shaped deep punched-out ulcer in the ileocecal area (Fig. 1a); however, involvement of the esophagus and small intestine has also been reported. The most common gastrointestinal symptoms are abdominal pain, diarrhea, and bleeding. Deep ulcers are responsible for the most common intestinal complications, such as severe bleeding and perforation. Therefore, intestinal lesions have been considered a factor associated with poor prognosis in BD patients, resulting in emergency abdominal surgery and bowel resection [8].

Confusion has arisen regarding the terminology used to describe this condition. Among the terms used are 'intestinal BD', 'entero-BD', and 'intestinal lesions associated with BD', with the various terms possibly due to a lack of standardized diagnostic criteria. In this review, we use the term 'intestinal BD' according to the diagnostic criteria reported by Kobayashi et al. [9]. Briefly, intestinal BD is diagnosed in patients meeting the Japanese diagnostic criteria of BD [5], by the presence of a typical oval-shaped large ulcer in the ileocecum. However, we have often encountered patients with these ulcers in the ileocecum who do not have typical BD manifestations. These patients, who cannot be diagnosed with intestinal BD by Japanese criteria, have been described as having 'simple ulcer syndrome' [10]. To date, similarities and differences in the pathogenesis, histopathology, and prognosis of Japanese patients with intestinal BD and simple ulcer syndrome have not been identified, although neutrophilic phlebitis may be involved in the pathogenesis of both [11]. The clinical manifestations of BD often show spatial and temporal diversity, making it difficult to differentiate between intestinal BD and simple ulcer syndrome in some patients. In addition, we often encounter patients with BD and atypical gastrointestinal lesions. Again, similarities and differences in the pathogenesis of these atypical lesions and typical oval-shaped ulcers have not been identified. A Korean group proposed novel diagnostic criteria for intestinal BD in Korean patients with ileocolonic ulcers [12]. They suggested that systemic BD patients with typical ileocecal ulcers should be diagnosed as having 'definite intestinal BD', patients with typical ileocecal ulcer and oral ulcers and patients with systemic BD and atypical ulcers should be diagnosed as having 'probable intestinal BD', and patients with typical ileocecal ulcers without any BD symptoms should be diagnosed with 'suspected intestinal BD'.

Although an oval-shaped ulcer at the ileocecum is considered typical of intestinal BD, esophageal lesions have also been reportedly associated with BD [13–17] (Fig. 1b). For example, one study reported that the incidence of esophageal involvement was relatively low (11 %) [18], and a retrospective analysis of 842 Korean patients diagnosed with BD found that 129 (15.3 %) experienced upper gastrointestinal symptoms, but esophageal involvement was found in only six (4.7 %) of these 129 patients [19]. Esophageal lesions may be helpful in the diagnosis of intestinal BD, but the necessity of upper gastrointestinal examination in asymptomatic BD patients has not been determined.