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Capsule Endoscopy for Differentiating Early Crohn's Disease from Behçet's Disease

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Abstract

Objective: Crohn's disease (CD) and Behçet's disease (BD) are two major causes of inflammatory lesions in the small bowel. For detecting such lesions, the most sensitive exam is small-bowel capsule endoscopy (CE), an imaging modality suitable for evaluating lesions of the small intestine, with a relatively low rate of capsule retention. However, few reports have employed CE to compare the small-bowel inflammation in early CD with that in early BD. Thus, the aim of our study was to obtain a systematic characterization of small-bowel lesions in early CD and BD by using CE.

Methods: This retrospective single-center study included 22 patients with early CD and 16 patients with early BD. The patients underwent small-bowel CE for detection and characterization of small-bowel lesions. After reviewing the CE findings in each patient, we assessed the small-bowel mucosal inflammation using the Lewis score, an inflammatory biomarker (C-reactive protein), and the disease activity index. The CE findings (number, distribution, and shape of lesions), Lewis score, disease activity index, and C-reactive protein levels were compared between the groups of CD and BD patients.

Results: Small-bowel lesions were observed in 90.9% of CD patients, and in 68.7% of BD patients. Regarding distribution, CD patients exhibited multiple concentrated ulcers, which were more severe distally, while BD patients mostly exhibited solitary ulcers. Regarding shape, linear and longitudinal ulcers were observed, respectively, in 68.2% and 50% of CD patients; however, no such ulcers were observed in BD patients. C-reactive protein levels and disease activity indices were poorly correlated with Lewis score for both diseases. Capsule retention during CE did not occur in any patient included in this study.

Conclusion: CE is a valuable tool to assess the mucosal inflammation of the small bowel in early CD and BD. Greater mucosal inflammation in the distal small bowel, and presence of linear and longitudinal ulcers may be the key findings for the differential diagnosis of small-bowel inflammation between early CD and BD.

Keywords: Crohn's disease; Behçet's disease; Small-bowel inflammation; Differential diagnosis; Capsule endoscopy; Linear ulcers; Longitudinal ulcers

Introduction

Behçet's disease (BD) is a systemic, chronic inflammatory-disease, whose major symptoms are recurrent oral aphthous ulcer, skin lesions, eye manifestations, and genital ulcerations [1]. Other clinical features include arthritis, epididymitis, vasculitis, gastrointestinal symptoms, and inflammation in the central nervous system. Involvement of the vascular, neural, and gastrointestinal systems is often noted. BD-associated lesions occur throughout the entire gastrointestinal tract, with ileocecal lesions as the most significant manifestation [2]. Although small-bowel lesions are observed relatively frequently, a detailed and systematic characterization of such lesions is not yet available.

In Crohn's disease (CD), lesions also occur throughout the entire intestinal tract, and are typically transmural, leading to stenosis, perforation, or fistula [3,4]. The clinical presentation of intestinal BD is similar to that of CD. Ileocecal lesion is the most frequent gastrointestinal manifestation in both CD and BD. Therefore, differentiation of CD from intestinal BD is challenging and relies on the characterization of small-intestine ulcers and aphthous lesions. However, few studies have compared the characteristics of small-intestine lesions in early stages of CD and BD.

For a long time, the anatomical evaluation of small-bowel lesions was difficult because there were no suitable examination approaches. With the recent progress of diagnostic tools such as capsule endoscopy (CE) or balloon endoscopy, it has become possible to distinguish the

features of such lesions in the small bowel [5-8]. It was previously assumed that CE would not be suitable in cases with stenotic complications. However, because of the properties of the patency capsule (i.e., the capsule for evaluating adequate patency of the small intestine), the rate of capsule retention in CE is significantly lower; thus, several studies involving confirmed CD patients have benchmarked CE against other small-bowel imaging-modalities. Most of these studies showed that CE is more sensitive with respect to the detection of subtle small-bowel inflammation, but reported insufficient specificity of CE findings, and thus the use of CE in diagnosing CD has not gained acceptance. Only few articles discuss CE findings in the context of early CD.

The present study aimed to apply CE in the systematic assessment of small-bowel lesions characteristic to early CD and early BD, the two major inflammatory diseases affecting the small intestine, and to identify markers of early CD by comparing the CD- and BD-specific findings.

Patients and Methods

We performed a retrospective single-center study regarding small-bowel inflammation in early CD and BD patients that were examined between October 2009 and December 2015 at the Hirosaki University Hospital. Institutional review board approval was obtained, and informed consent was provided by all patients.

Patients

A total of 38 consecutive biologic-naïve patients with known early CD or BD (disease duration under 2 years) who complained of gastrointestinal symptoms were enrolled in this study. They presented no evidence of obstructive symptoms, and did not receive any non-steroidal anti-inflammatory drugs for the 2 weeks prior to the CE examination.

CD was diagnosed according to the criteria provided by the Investigation and Research Committee for Intractable Inflammatory Bowel Disease, organized by the Japanese Ministry of Public Welfare, as previously described [9,10]. The patients' medical histories including abdominal symptoms, disease duration, current therapy, CD behavior, Crohn's disease activity index (CDAI), and C-reactive protein (CRP) were obtained.

BD was diagnosed based on the criteria provided by the 2003 Behçet's Disease Research Committee of Japan [11,12]. Patients diagnosed as having complete, incomplete, and "suspected" BD were included in this study. We evaluated demographic factors, gastrointestinal symptoms, disease subtype, as well as laboratory results including CRP, human leukocyte antigen (HLA) subtype, and clinical activity index using the Behçet's Syndrome Activity Score (BSAS) [13].

CE procedure

After performing a bowel patency test with an Agile™ Patency Capsule, the patients underwent a CE examination (PillCam SB, Given Imaging, Ltd, Yokneam, Israel). The preparation for the procedure included a fasting period of 12 hours, and a small-bowel preparation with administration of magnesium citrate. A belt with a data recorder was positioned at the anterior abdominal wall, and the patient was instructed to swallow the capsule. Completion of the examination was defined as the time when the capsule reached the colon. Capsule recordings were independently evaluated by 2 experienced observers. After evaluation of the images, he values of the total and partial Lewis score (LS) were calculated using a RAPID Reader v.6 workstation [14]. We also investigated all CE findings with respect to location, distribution, number, shape, and size. These findings were investigated separately for each of the three tertiles (divisions defined based on the capsule-passage time)of the small intestine: proximal, middle, and distal.

Statistical analysis

Collected data were presented as mean ± standard deviation (SD), and range. Statistical analysis was carried out using GraphPad Prism5 Software for Windows. Normal continuous variables were analyzed using Student's t-test, and non-normal continuous variables were analyzed using Mann-Whitney U test. Spearman's rank correlation coefficient was used to assess the correlation of LS, with CRP and clinical disease activity. Two-way ANOVA was used to compare the partial LS for CD and BD. Hypothesis testing was two-tailed, and values for which $p<0.05$ were considered statistically significant.

Results

Patients' characteristics

The demographic and clinical characteristics of the 38 patients are summarized in Table 1. Out of the 38 patients recruited during the study period, 22 were CD patients, and 16 were BD patients. In the group of CD patients, the mean age at diagnosis was 19.0 years (range: 11-52), the mean disease duration was 3.0 months (range: 1-13 months), and 5 patients (22.7%) were female. For CD patients, the incidence of various disease phenotypes was the following: 18 patients (81.8%) had an inflammatory phenotype, while 4 patients (18.2%) had stricturing subtypes. For the inflammatory phenotype CD patients, disease localization was the following: 16 patients had ileocolonic disease, and 2 patients had colonic disease.

In the group of BD patients, the mean age at diagnosis was 40.5 years (range: 17-76), the mean disease duration was 2.0 months (range: 1-20), and 5 patients (31.3%) were female. Furthermore, 4 patients were HLA-B51 positive, and 4 patients were HLA-A26 positive. According to the diagnostic criteria for BD, 1 patient (6.3%) had the complete type, 11 (68.7%) had the incomplete type, and 4 (25%) had the suspected type of disease (Table 2).

Characteristic	CD (n=22)	BD (n=16)
Age, median (range), years	23.9 ± 2.3	41.4 ± 3.5
Male gender, n (%)	17 (77.2)	11 (68.7)
Time between diagnosis and CE investigation, median (range), months	4.1 ± 0.63	6.9 ± 1.9
Disease location (CD)		
L1, n (%)	4 (18.2)	
L2, n (%)	2 (9.1)	
L3, n (%)	16 (72.7)	
L4, n (%)	1 (4.5)	
Disease behavior (CD)		

B1, n (%)	18 (81.8)	
B2, n (%)	4 (18.2)	
B3, n (%)	0 (0)	
p, n (%)	10 (45.5)	
Clinical subtype of BD		
complete, n (%)	1 (6.3)	
incomplete, n (%)	11 (68.7)	
suspected, n (%)	4 (25)	
positive HLA-B51, n (%)	4 (25)	
positive HLA-A26, n (%)	4 (25)	
Systemic symptoms and signs of BD		
recurrent oral ulcers, n (%)	15 (93.7)	
recurrent genital ulcers, n (%)	5 (31.5)	
ocular lesions, n (%)	2 (12.5)	
skin lesions, n (%)	11 (68.7)	
Symptoms and sign of intestinal involvement		
abdominal pain, n (%)	12 (54.5)	10 (62.5)
diarrhea, n (%)	16 (72.7)	9 (56.3)
blood in stool, n (%)	2 (9.1)	5 (31.3)
perianal pain, n (%)	5 (22.7)	0 (0)
Use of medication		
5-ASA	2 (9.1)	4 (25)
Immunomodulators (azathioprine or 6-MP)	0 (0)	1 (6.3)
Corticosteroids	0 (0)	3 (18.4)
elemental diet	2 (9.1)	
colchicine		5 (31.5)
C-reactive protein, mean ± SD, mg/dL	1.9 ± 0.46	1.3 ± 0.49
Clinical Activity Score		
CDAI, mean ± SD	219.5 ± 152.4	
BSAS, mean ± SD		16.1 ± 8.9
Total Lewis Score, mean ± SD	1388 ± 348.2	213.3 ± 28.5

Table 1: Demographic and clinical characteristics of the Crohn's disease (CD) and Behçet's disease (BD) patients included in this study. CD location refers to manifestations in the terminal ileum (L1), colon (L2), ileocolon (L3), or upper gastrointestinal (L4). CD behavior refers to nonstricturing and nonpenetrating (B1), stricturing (B2), penetrating (B3) with or without perianal disease (p). Only 2 out of 22 CD patients and 9 out of 16 BD patients underwent treatment with one or more medications. CE: capsule endoscopy; SD: standard deviation; HLA: human leukocyte antigen; 5-ASA: 5-aminosalicylic acid, 6-MP: 6-mercaptopurine; CDAI; Crohn's disease activity index; BSAS: Behçet's syndrome activity score.

		CD	BD
Exhibiting lesions, n (%)		22 (100.0)	16 (100.0)
Shape of ulcers, n (%)			
Erosions	Proximal	8 (36.3)	5 (31.3)
	Middle	3 (13.6)	4 (25.0)
	Distal	4 (18.1)	3 (18.7)
Aphthous ulcers	Proximal	1 (4.5)	2 (12.5)
	Middle	2 (9.1)	2 (12.5)
	Distal	2 (9.1)	4 (25.0)
Oval ulcers	Proximal	0 (0)	0 (0)
	Middle	0 (0)	3 (18.7)
	Distal	0 (0)	4 (25.0)
Linear ulcers	Proximal	6 (27.3)	0 (0)
	Middle	11 (50.0)	0 (0)
	Distal	15 (68.2)	0 (0)
Longitudinal ulcers	Proximal	4 (18.1)	0 (0)
	Middle	8 (36.3)	0 (0)
	Distal	11 (50.0)	0 (0)
Cobblestone appearance	Proximal	0 (0)	0 (0)
	Middle	2 (9.1)	0 (0)
	Distal	5 (22.7)	0 (0)
Total	Proximal	13 (59.1)	6 (37.5)
	Middle	15 (68.2)	4 (25.0)
	Distal	18 (81.8)	8 (50.0)
Distribution			
Solitary lesions	Proximal	7 (31.8)	5 (31.3)
	Middle	2 (9.1)	3 (18.7)
	Distal	1 (4.5)	8 (50.0)
Multiple lesions	Proximal	7 (31.8)	1 (6.3)
	Middle	14 (63.6)	1 (6.3)
	Distal	18 (81.8)	2 (12.5)

Table 2: Frequency of capsule endoscopy findings in the various tertiles (proximal, middle, and distal) of the small bowel in Crohn's disease (CD) and Behçet's disease (BD) patients included in this study. Tertiles were defined based on the capsule transition time: the total duration was divided in 3 equal periods, and the position of the capsule at the moment that indicated the transition between two periods was noted as the length-limit of each tertile.

Location and aspect of lesions

With respect to the 22 CD patients, small-bowel lesions were found in 20 cases (90.9%). Typical CE findings in the small bowel of CD patients are indicated in Figures 1A and 1B. Furthermore, for the CD group, the following results were found for the proximal, middle, and distal tertiles, respectively: lesions were found in 59.1%, 68.2%, and 81.8% of the patients; multiple ulcers were found in 31.8%, 63.6%, and 81.8% of the patients; solitary ulcers or erosions were found in 31.8%, 9.1%, and 4.5% of the patients; linear ulcers were found in 27.3%, 50%, and 68.2% of the patients; longitudinal ulcers were found in 18.1%, 36.3%, and 50.0% of the patients.

With respect to the 16 BD patients, small-bowel lesions were found in 11 cases (68.7%). Typical CE findings in the small bowel of BD patients are indicated in Figures 1C and 1D. Furthermore, for the BD group, the following results were found for the proximal, middle, and distal tertiles, respectively: lesions were found in 37.5%, 25.0%, and 50.0% of the patients; multiple ulcers were found in 6.3%, 6.3%, and 12.5% of the patients; solitary ulcers or erosions were found in 31.3%, 18.7%, and 50.0% of the patients; oval ulcers were found in 0%, 18.7%, and 25.0% of the patients; no patient exhibited linear or longitudinal ulcers.

Correlation of LS with CRP, CDAI, and BSAS

As shown in Table 1, the total LS for CD patients was significantly higher than that for BD patients (respectively: 1388 ± 348.2, 213.3 ± 28.5; p=0.0023). On the other hand, there were no statistically significant differences regarding levels of serum CRP between CD and BD patients (respectively: 1.9 ± 0.46, 1.3 ± 0.49; p=0.260). As shown in Figure 2, no statistically significant correlation was found between LS and CDAI for CD patients. Moreover, LS and CRP were not associated for CD patients. Furthermore, for BD patients, neither CRP nor BSAS showed correlation with LS.

As shown in Figure 3, the proximal, middle, and distal tertiles, respectively, exhibited mean LS values of: 292.5 ± 95.2, 497.4 ± 131.7, and 743.5 ± 153.1 in the CD patients; 39.4 ± 18.3, 59.1 ± 23.5, and 164.5 ± 36.7 in the BD patients.

Discussion

Our study demonstrated that CE assessment of mucosal inflammation in the small bowel is valuable in both BD and early CD, while clinical and serologic markers are not correlated with mucosal inflammation. Furthermore, CE revealed that linear ulcers represent a CD-specific finding, and can be used as a clinical indicator of early CD.

BD is a vasculitis involving multiple organs, characterized by recurrent oral and genital ulcerations, as well as ocular involvement [15]. In particular, gastrointestinal involvement of BD (also referred to as intestinal BD or entero-BD) mainly affects the ileum and cecum [16], with lesions observed most frequently in the small bowel [17]. The gastrointestinal symptoms of BD vary, with the most common being abdominal pain, which may be colicky, followed by nausea, vomiting, diarrhea with or without blood in the stool, and constipation. The association between these symptoms and small-intestine lesions remains unclear.

CE has recently been reported to allow the detection of small-intestine lesions in BD patients [18-20], with small-bowel erosions and aphthous ulcers identified in 10 out of 11 patients with gastrointestinal symptoms [18]. In our study, small erosions, aphthous ulcers, and small ulcers were identified in the small bowel of 11 out of 16 BD patients with abdominal symptoms but no typical ileocecal lesion. In addition, 6 out of 7 BD patients not receiving treatment exhibited findings in the small bowel. These results suggested that small-intestine lesions are associated with gastrointestinal symptoms in BD patients without typical ileocecal lesion. Our results thus support the use of CE as a valuable tool for the detection of BD-associated lesions of the small intestine.

The clinical presentation of intestinal BD is similar to that of CD, sharing also extraintestinal features such as oral lesions, uveitis, and arthritis [1,15]. Although longitudinal or striated ulcers are rare in intestinal BD, aphthous ulcer, erosion, and skip lesions are common in both CD and intestinal BD. Although the characterization of small-intestine lesions is key to differentiating intestinal BD from early-stage CD, few reports have compared the lesions specific to these diseases. In this study, we investigated and compared the frequency, distribution, form, and LS of small-intestine lesions detected by CE in BD and early CD patients.

In both BD and CD patients, lesions were distributed evenly throughout the small intestine (i.e., from the upper to the lower small intestine; Figure 4). However, in CD patients, the lesions occurred in clusters and formed segments and skips along the length of the small intestine. On the other hand, in BD patients, the lesions occurred sporadically, and formed patches that did not show any tendency to align along the length of the small intestine.

With respect to the form of the lesion, round-shaped and aphthous ulcers in the distal tertile of the small intestine were common for BD, but not for CD patients. Findings in the proximal tertile were mostly nonspecific, such as light erosion and redness.

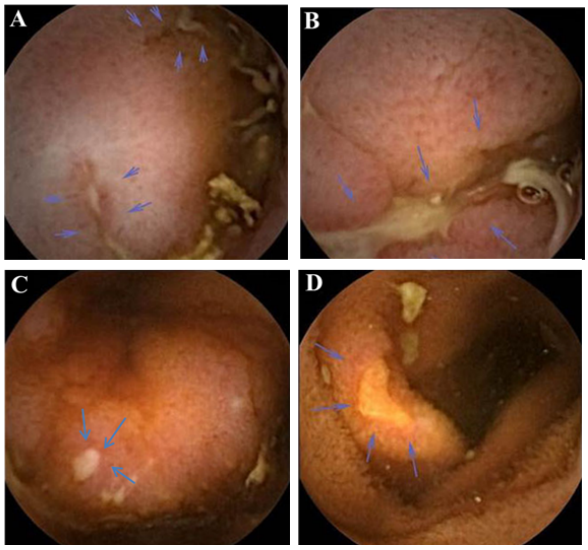

Figure 1. Assessing gastrointestinal lesions in Crohn's disease and Behçet's disease by capsule endoscopy, Typical lesions found in the patients included in our study: (A) linear ulcer; (B) longitudinal ulcer; (C) aphthous ulcer; (D) oval ulcer.

In CD patients, longitudinal ulcers and cobblestone appearance were common in the distal tertile of the small intestine, while linear ulcers were identified in both the distal and proximal tertiles. No

evidence of linear or longitudinal ulcers was found in BD patients, suggesting that linear and longitudinal ulcers are clinical indicators of CD, and can be used to differentiate BD from CD.

The LS was devised by Gralnek et al. for the purpose of evaluating the degree of inflammatory change in the small-bowel mucosa [14], and is useful in the objective assessment of mucosal healing [21]. Moreover, the LS showed significant positive correlation with the CD activity indicators such as CDAI, CRP, and fecal calprotectin [22,23]. In our study, the LS was significantly higher in the CD group, reflecting multiple aggregated lesions, extensive linear ulcers, longitudinal ulcers, and light mucosal damage in the small intestine. On the other hand, the low LS found in BD patients reflects focal and solitary lesions. In addition, the LS was higher in the distal than in the proximal tertile of the small intestine for CD patients, while no such differences were observed for BD patients. This suggests that the relationship between the LS of the distal and proximal tertiles is a characteristic finding that can be used to differentiate CD from BD.

However, we found no correlation between the LS and CDAI or CRP in the CD group. Previous reports indicated that the clinical and biological disease activity index was not a reliable predictor of CD-associated mucosal damage to the small bowel [24,25]; similarly, endoscopic findings in the small bowel were poorly associated with clinical symptoms, clinical activity index, and serum parameters [26-28]. The CD patients enrolled in our present study were diagnosed in the early stage of the disease (<2 years), and had relatively few large intestinal lesions. As a result, we did not find correlations between the LS and CDAI or CRP.

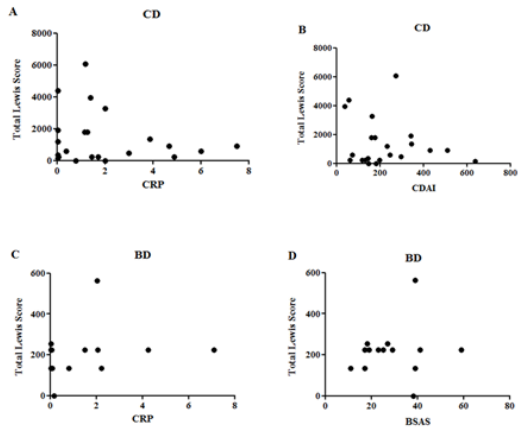

Figure 2: Correlation of the total Lewis score with c-reactive protein (CRP) levels, Crohn's disease activity index (CDAI), and Behçet's Syndrome Activity Score (BSAS) in Crohn's disease (CD) and Behçet's disease (BD) patients. The Spearman's rank correlation coefficient r and p-values were: r=-0.0481 and p=0.831 for CRP in CD patients (A); r=0.234 and p=0.381 for CDAI in CD patients (B); r=-0.192 and p=0.475 for CRP in BD patients (C); r=0.234 and p=0.381 for BSAS in BD patients (D).

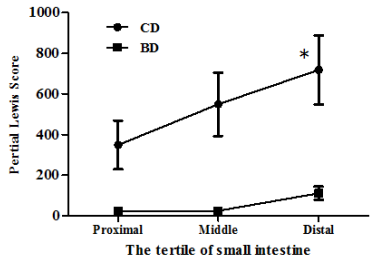

Figure 3: Partial Lewis scores for each tertile of the small intestine in Crohn's disease (CD) and Behçet's disease (BD) patients. Tertiles were defined based on the capsule transition time: the total duration was divided in 3 equal periods, and the position of the capsule at the moment that indicated the transition between two periods was noted as the length-limit of each tertile. The partial Lewis score for CD is significantly higher than that of BD in the distal tertile (two-way ANOVA, p=0.0008).

In the BD group, there were no correlations between the LS and BSAS or CRP. Moreover, even for relatively large ulcers with punched-out appearance, the LS peaked at 562, and the CRP levels were low, suggesting that it is difficult to predict the activity of the small-intestine inflammation based on clinical manifestations and serologic markers.

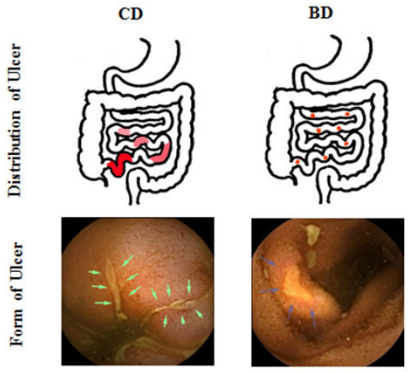

Figure 4: Disease-specific form and distribution of ulcers, based on capsule endoscopic findings in Crohn's disease (CD) and Behçet's disease (BD) patients.

For the early-stage CD patients included in our study, we found that CE was a useful tool for assessing inflammation in the small intestine. Considering that small-intestine lesions are the typical lesions managed by surgery in CD patients [29], and the typical lesions that cause bleeding or perforation in BD patients [30,31], accurate assessments of small-intestine lesions help to determine the most suitable therapeutic approach, and predict the response to medical treatments in the early stages of the disease, before life-threatening complications occur. However, because our study included few patients, further investigations involving a large number of patients are warranted.

Acknowledgement

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