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Detection Rates of Non-Cavitary Epithelioid Cell Granuloma by Gastrointestinal Biopsy in Patients with Treatment-Naïve Crohn's Disease

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Abstract
Introduction: Detecting non-cavitary epithelioid cell granuloma by gastrointestinal biopsy is important in the initial diagnosis of Crohn's disease (CD). In the present study, we aimed to determine the rate of granuloma detection by gastrointestinal biopsy according to the number of biopsies performed. ***Methods:*** The present study included patients newly diagnosed with CD at our hospital between April 2017 and March 2023. During endoscopic examinations, biopsy specimens were taken from affected lesions. Initially, one section per biopsy was examined to detect granuloma. In cases where no granulomas were detected, step sections were additionally prepared and examined. The rate of granuloma detection by gastrointestinal biopsy was retrospectively examined. ***Results:*** A total of 30 patients with a new diagnosis of CD were included in this study. In total, 284 gastrointestinal biopsies were performed in 29 cases. The rate of granuloma detection by gastrointestinal biopsy per case was 58.6% (17 out of 29 cases). The rate of granuloma detection by gastrointestinal biopsy per biopsy was 6.0% (17 out of 284 biopsies) on initial histological examination and 11.6% (33 out of 284 biopsies) following examination of step sections. The rate of granuloma detection was significantly improved by performing histological examination of step sections compared with initial examinations ($p < 0.05$). ***Conclusion:*** The rate of granuloma detection per biopsy was 11.6%, even after histological examination of step sections. These results indicate that performing multiple intestinal biopsies and assessing for the presence of granuloma using multiple section examinations are required in the initial diagnosis of CD.

Introduction

Crohn's disease (CD) is a chronic, progressive inflammatory bowel disease that may cause irreversible bowel injury or disfunction [1]. The diagnosis of CD at earlier stages of disease is important as early intervention and treatment can prevent disease progression and improve long-term prognosis [1–3].

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Table 1. Summary of the Japanese diagnostic criteria for CD [4]

Main findings
A. Longitudinal ulcer
B. Cobblestone appearance
C. Non-cavitary epithelioid cell granuloma
Secondary findings
a. Extensive irregular to round ulcers or aphthae in the GI tract
b. Characteristic anorectal lesions
c. Characteristic gastric and duodenal lesions
Confirmed diagnosis of CD
Pattern 1: patients with primary findings A or B. In cases with only one longitudinal ulcer, ischemic bowel disease, or ulcerative colitis should be excluded. In cases where only a cobblestone appearance is present, ischemic bowel lesions and type 4 colorectal cancer should be excluded
Pattern 2: the patient must have a primary finding of C and a secondary finding of a or b
Pattern 3: patients with all secondary findings (a, b, and c)

The diagnosis of CD is based on physical examination, endoscopic evaluation, imaging, and histological examination [4]. The diagnosis of CD is relatively straightforward in patients with advanced stages of disease as characteristic findings such as longitudinal ulcers and cobblestone appearances are frequently observed on endoscopic examination of the gastrointestinal (GI) tract; however, the diagnosis is often clinically challenging in cases without longitudinal ulcers or cobblestone appearances. In cases with earlier stages of CD which lack longitudinal ulcers or cobblestone appearances, histopathologic evidence of non-cavitary epithelioid cell granuloma is considered one of the most important findings for a definitive diagnosis of CD. The detection of non-cavitary epithelioid cell granuloma is also important for differentiating CD from other forms of enterocolitis including intestinal tuberculosis [5, 6]. Furthermore, a recent study reported a trend toward a more aggressive disease phenotype and poorer prognosis in granuloma-positive cases of CD [7]. Accordingly, the detection of granuloma at the time of initial diagnosis is important for the accurate prediction of prognosis.

In Japan, the diagnosis of CD is made according to the official Japanese diagnostic criteria for CD [4] (Table 1). A unique feature of these diagnostic criteria is that CD can be diagnosed according to the presence of granuloma on histological examination of GI biopsies in combination with other secondary findings, even in the absence of advanced lesions such as longitudinal ulcers or cobblestone appearances. A recent study reported that 176 (30.4%) out of the 579 cases of newly diagnosed CD in Japan were diagnosed based on the detection of non-cavitary epithelioid cell granuloma on histological examination of GI biopsies [8].

Although several previous studies have evaluated the rate of granuloma detection on histological examination of GI biopsies in CD according to the number of cases [9–14], few reports have examined the rate of granuloma detection per number of biopsies [5]. Further, the effects of using serial or step sections during histological examination of GI biopsy specimens on the rate of granuloma detection remain unknown.

The present study therefore evaluated the rate of granuloma detection on histological examination of GI biopsies in treatment-naïve CD and determined the effectiveness of histological examination of step sections of biopsy specimens when assessing the presence of granuloma. We also describe the characteristics of cases in which the detection of granuloma was essential for a diagnosis of CD.

Methods

Patients and Clinical Evaluations

This single-center retrospective cohort study comprised all consecutive patients newly diagnosed with CD at our hospital between April 2017 and March 2023. The diagnosis of CD was made based on physical examination, endoscopic findings, surgical findings, and histopathological findings according to the official Japanese diagnostic criteria for CD [4] (Table 1). During endoscopic examinations, biopsy specimens were taken from lesions including aphthae, erosions, ulcers, and areas of mucosa with cobblestone appearance. One biopsy specimen was obtained from each of these endoscopic findings. The models of biopsy forceps used in this study were Radial Jaw 4 (Boston Scientific Corporation, USA) for the upper GI and EndoJaw (Olympus Medical Systems Corp., JAPAN) for the lower GI, respectively. Initially, one section stained with hematoxylin and eosin (HE) per biopsy was examined to assess for the presence of non-cavitary epithelioid cell granuloma. A non-cavitary epithelioid cell granuloma was defined as a collection of epithelioid cells with or without accompanying multinucleated giant cells and without caseating necrosis or foreign material. In cases where granulomas were not detected, step sections (10 slides at 30 μm intervals) were additionally prepared and examined to assess for the presence of granuloma. All biopsies were reviewed by two experienced GI pathologists. This study was approved by the Institutional Ethics Committee (approval number: 2021-02-037). Informed consent was obtained from all patients.

Diagnosis of CD according to the Japanese Diagnostic Criteria for CD

The presence or absence of primary and secondary findings of CD according to the Japanese diagnostic criteria for CD was determined by retrospective analysis of medical records. The proportion of patients with each finding was then calculated. The proportions of patients with diagnostic patterns 1, 2, or 3 according to the Japanese diagnostic criteria for CD were also calculated. In diagnosis pattern 2, the detection of non-cavitary

epithelioid cell granuloma is essential for a diagnosis of CD. We therefore also investigated the clinical features of patients diagnosed with pattern 2 CD.

Rate of Non-Cavitary Epithelioid Cell Granuloma Detection

The positive rate of granuloma in the total number of CD cases was calculated. The comparison of the patient characteristics between the granuloma-positive cases and the granuloma-negative cases was performed. Furthermore, the frequency of granuloma detection in the total number of endoscopic biopsies was examined. Regarding the granuloma detection rate in the number of endoscopic biopsies, the improvement of the granuloma detection frequency after the step sectioning examination was evaluated.

Statistical Analyses

Statistical analyses were performed using JMP Pro 13.2.1 (SAS Institute Inc., Cary, NC, USA). Categorical variables were presented as numbers and percentages, and continuous variables were presented as median values and ranges. Data between the two groups were compared using the χ^2 test for categorical variables and the Mann-Whitney U test for numerical variables. p values <0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 30 patients with newly diagnosed CD were included in the present study. The baseline characteristics of included patients are summarized in Table 2. Study participants comprised 20 males (66.7%) and 10 females (33.3%). The median age at diagnosis was 24 years. All patients underwent both esophagogastroduodenoscopy (EGD) and ileocolonoscopy, with GI biopsies performed in 29 patients. Small bowel examinations were performed using several modalities on a case-by-case basis. Regarding disease location, 13.3%, 16.7%, and 70.0% of cases had ileitis, colitis, and ileocolitis, respectively. Regarding disease behavior, 83.4%, 13.3%, and 3.3% of cases had inflammatory type, structuring type, and penetrating type disease, respectively. Fifteen of the 30 cases (50%) had perianal disease. Two cases (6.7%) underwent intestinal resection for small bowel strictures and were diagnosed with CD based on histological examination of resected specimens.

Table 2. Patient characteristics (n = 30)

Gender, *n* (%)	
Male	20 (66.7)
Female	10 (33.3)
Age at diagnosis, years, median (range)	24 (12–54)
Modality to investigate GI tracts, *n* (%)	
EGD	30 (100)
Ileocolonoscopy	30 (100)
Small bowel capsule endoscopy	13 (43.3)
Small bowel enteroclysis	13 (43.3)
MR enterography or CT enterography	2 (6.7)
Disease location, *n* (%)	
Ileitis type	4 (13.3)
Colitis type	5 (16.7)
Ileocolitis type	21 (70.0)
Disease behavior, *n* (%)	
Inflammatory type	25 (83.4)
Stricturing type	4 (13.3)
Penetrating type	1 (3.3)
Perianal disease, *n* (%)	15 (50.0)
Intestinal resection at diagnosis, *n* (%)	2 (6.7)
Laboratory data at diagnosis	
Hemoglobin g/dL, median (range)	11.2 (7.8–14.5)
Albumin g/dL, median (range)	3.3 (2.0–4.4)
CRP mg/dL, median (range)	4.27 (0.03–11.53)

Frequency of Histological Findings and Diagnosis Pattern according to the Japanese Diagnosis Criteria for CD

The proportions of study participants with primary and secondary findings of CD according to the Japanese diagnosis criteria for CD are shown in Table 3. Regarding primary findings, longitudinal ulcers, cobblestone appearance, and non-cavitary epithelioid cell granuloma were present in 27 cases (90.0%), 12 cases (40.0%), and 19 cases (63.3%), respectively. In terms of secondary findings, extensive irregular to round ulcers or aphthae, characteristic anorectal lesions, and characteristic gastric and duodenal lesions were present in 16 cases (53.3%), 15 cases (50.0%), and 23 cases (76.7%), respectively. Twenty-seven of the 30 cases (90.0%) were diagnosed with CD according to diagnosis pattern 1, and 3 cases (10.0%) were diagnosed according to diagnosis pattern 2. Diagnosis pattern 3 was not observed in the present study.

Clinical Features of Patients with Diagnostic Pattern 2 CD

The present study comprised three cases diagnosed with CD according to diagnostic pattern 2 in which the detection of non-cavitary epithelioid granuloma is necessary for a definitive diagnosis of CD. The clinical features of each case were as follows.

Case 1

A 15-year-old male was diagnosed with ileocolonic CD (Fig. 1). EGD revealed small, round-shaped ulcers in the esophagus and mucosal redness and small erosions in the

stomach and duodenum. Ileocolonoscopy revealed multiple small ulcers in the ileum and edema and erosions in the rectum. Ten biopsy specimens were taken from the ileum and colon. Granuloma was detected in an ileal specimen only after histological examination of step sections. CD was diagnosed according to diagnostic pattern 2.

Case 2

A 19-year-old male was diagnosed with ileocolonic CD with perianal disease (Fig. 2). EGD revealed multiple aphthoid erosions in the stomach and duodenum. Ileocolonoscopy revealed multiple aphthoid erosions in the ileum, colon, and rectum. Eight GI biopsy specimens were taken from the ileum and colon. Granulomas were detected on histological examination of a biopsy specimen from the ascending colon only after examination of step sections. CD was diagnosed according to diagnostic pattern 2.

Case 3

A 15-year-old male was diagnosed with colonic CD (Fig. 3). Ileocolonoscopy revealed multiple erosions and irregular-shaped ulcers in the colon. Twelve biopsy specimens were taken from the colon. Granulomas were detected on histological examination of a biopsy specimen from the ascending colon. CD was diagnosed according to diagnostic pattern 2.

Rate of Non-Cavitary Epithelioid Cell Granuloma Detection per Case

The proportion of patients with non-cavitary epithelioid cell granuloma among patients newly diagnosed with CD was 63.3% (19 out of 30 cases; Table 3). Among these 19 cases, granuloma was detected on histological examination of biopsy specimens in 17 cases and of surgical specimens in 2 cases. There was no significant difference in the patient characteristics between granuloma-positive cases and granuloma-negative cases (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000533479).

Among all patients with a new diagnosis of CD, GI biopsies were performed in 29 cases. Accordingly, the rate of granuloma detection by GI biopsy per case was 58.6% (17 out of 29 cases). The anatomic locations and the endoscopic images where the granulomas were detected are shown in Table 4. The locations were scattered among the stomach, various parts of the large intestine, and the ileum, and no consistent trend was observed. Regarding endoscopic images, of the total 33 granulomas detected, 17 (51.5%) were detected from longitudinal ulcers, 12 (36.4%) from aphthae or erosions, and 4 (12.1%) from irregular- or round-shaped ulcers.

Table 3. Frequency of findings and proportion of diagnosis pattern based on the Japanese diagnosis criteria of CD

Findings adopted according to the Japanese diagnosis criteria of CD	*n* = 30
Main findings, *n* (%)	
A: Longitudinal ulcer	27 (90.0)
B: Cobblestone appearance	12 (40.0)
C: Non-cavitary epithelioid cell granuloma	19 (63.3)
Secondary findings, *n* (%)	
a: Extensive irregular to round ulcers or aphthae	16 (53.3)
b: Characteristic anorectal lesions	15 (50.0)
c: Characteristic gastric and duodenal lesions	23 (76.7)
Diagnosis pattern, *n* (%)	
Pattern 1: primary finding A or B	27 (90.0)
Pattern 2: primary finding C and a secondary finding of a or b	3 (10.0)
Pattern 3: all secondary findings (a, b, and c)	0 (0)

Rate of Non-Cavitary Epithelioid Cell Granuloma Detection per Biopsy Number

The rates of granuloma detection according to the number of biopsies taken are summarized in Table 5. EGD with biopsy was performed in 16 cases, with a total of 63 biopsies taken. The rate of granuloma detection on histological examination of upper GI tract biopsies was 0% on initial examination and 3.2% following examination of step sections. Ileocolonoscopy with biopsy was performed in 29 cases, with a total of 221 biopsies taken. The rate of granuloma detection on histological examination of lower GI tract biopsies was 7.7% on initial examination and 14.0% following examination of step sections. Regarding the lower GI tract, the rate of granuloma detection was significantly improved after histological examination of step sections (7.7 vs. 14.0%; $p < 0.05$). A total of 284 GI biopsies were taken in 29 cases. The total number of biopsy specimens found to contain granuloma on histological examination was 17 (6.0%) on initial examination and 33 (11.6%) following histological examination of step sections. The rate of granuloma detection was significantly improved following histological examination of step sections compared with the initial examination ($p < 0.05$).

Discussion

The present study evaluated the rate of non-cavitary epithelioid cell granuloma detection by histological examination of GI biopsies in patients with treatment-naïve CD.

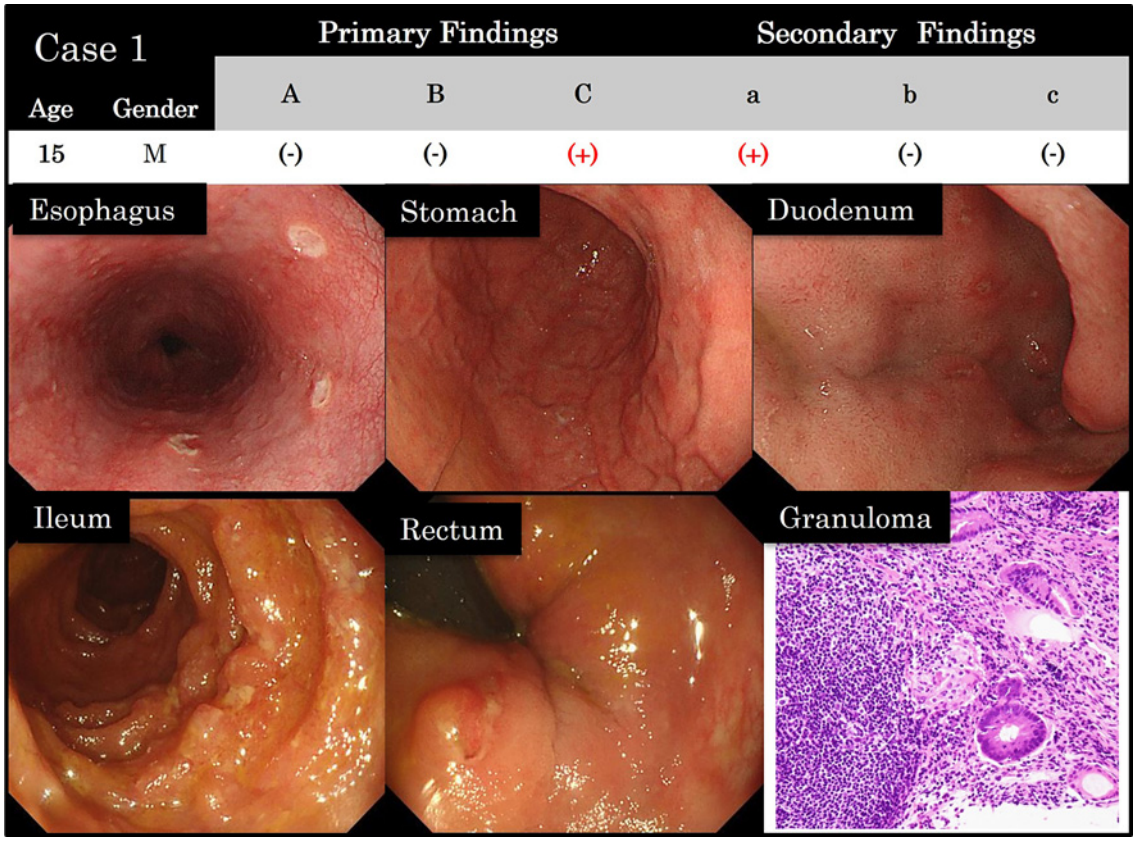

Fig. 1. Case 1 (15-year-old male with ileocolonic CD). EGD revealed round-shaped small ulcers in the esophagus and mucosal erythema and small erosions in the stomach and duodenum. Ileocolonoscopy revealed multiple small ulcers in the ileum and erosions in the rectum. Non-cavitary epithelioid granulomas were detected in an ileal biopsy specimen only after histological examination of step sections.

The findings of this study are noteworthy for the following two respects. First, this is a rare study that calculated the rate of granuloma detection according to the number of biopsies taken. Second, this is the first study to compare the rate of granuloma detection by conventional histological examination and examination of step sections of GI biopsies, with a significantly higher rate of granuloma detection following examination of step sections. Third, the analysis of endoscopic images of granuloma-detected sites showed a relatively high detection rate from aphthae and erosions, indicating their importance as biopsy target sites.

We used the official Japanese diagnostic criteria for CD. Using these diagnostic criteria, three diagnosis patterns can be used to make a definitive diagnosis of CD, as shown in Table 1. Hisabe et al. [8] studied the proportion of patients with each diagnostic pattern among Japanese patients with a new diagnosis of CD and found that 87.4% of patients were diagnosed according to pattern 1, 30.4% according to pattern 2, and 7.1% according to pattern 3. In our study, 90.0% of cases were diagnosed according to pattern 1. This finding corroborates the results of Hisabe et al. The proportion of patients with longitudinal ulcers was 81.7% in the study by Hisabe et al. and 90.0% in the present study. These results indicate that longitudinal ulcers may be the most frequent characteristic finding when diagnosing treatment-naïve CD.

On the other hand, the proportion of cases diagnosed according to pattern 2 were 30.4% in the study by Hisabe et al. and 10.0% in the present study. Notably, both longitudinal ulcers and cobblestone appearance were absent in cases diagnosed according to pattern 2, and the detection of a non-cavitary epithelioid cell granuloma was required for the diagnosis of CD. It is also worth noting that most cases diagnosed according to pattern 2 had early stages of disease. These

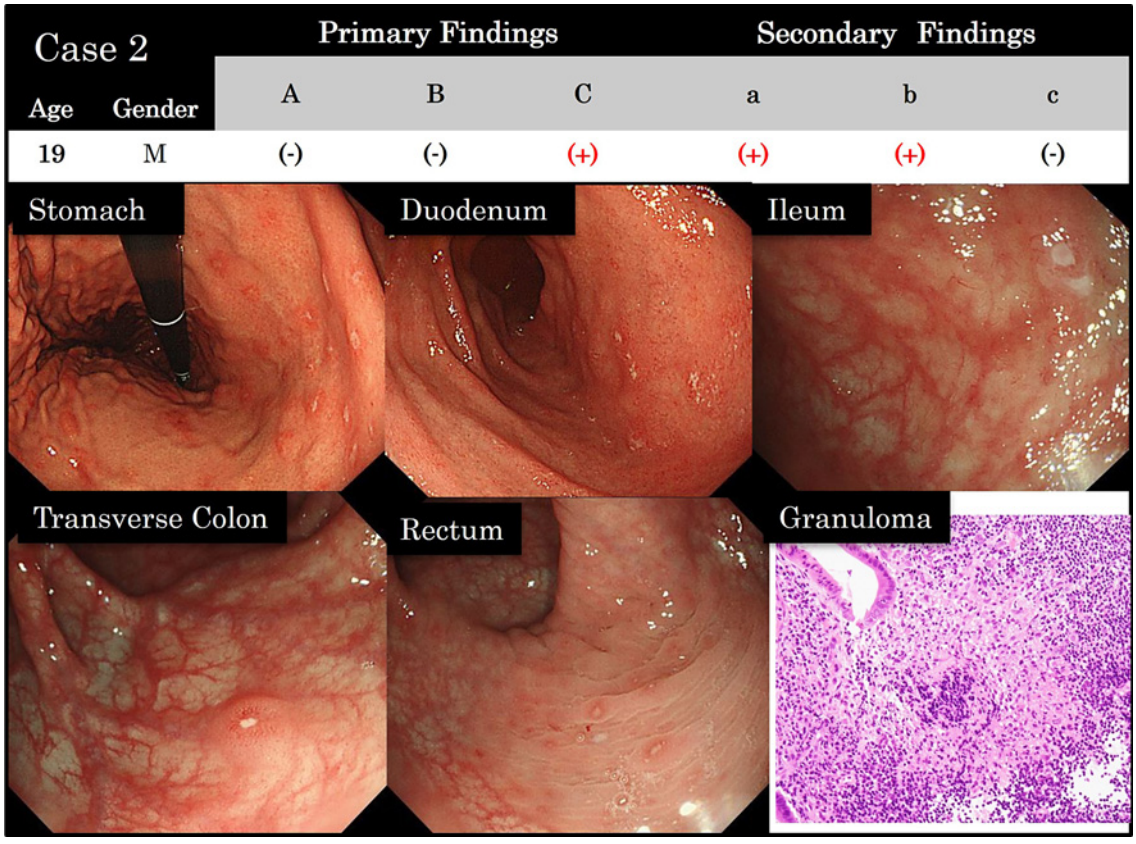

Fig. 2. Case 2 (19-year-old male with ileocolonic CD). EGD revealed multiple aphthoid erosions in the stomach and duodenum. Ileocolonoscopy revealed multiple aphthoid erosions in the ileum, colon, and rectum. Non-cavitary epithelioid granulomas were detected in an ascending colon biopsy specimen only after histological examination of step sections.

findings indicate the improvement of granuloma detection rates in GI biopsies is important to ensuring an accurate and definitive diagnosis of CD can be made at an early stage of disease. The findings of the present study also demonstrate the clinical characteristics of the 3 cases in which the detection of granuloma was essential for a diagnosis of CD. All 3 cases were considered to have early-stage disease, which predominantly consisted of aphthous erosions and small ulcers in the absence of longitudinal ulcers or cobblestone appearances. As CD is a chronic progressive disease, diagnosis at an early stage of disease stages is particularly important for improving the natural history and long-term prognosis of CD. In cases with early-stage CD with aphthous erosions and small ulcers, it is important to take multiple biopsies from the GI tract and perform histological examinations using multiple sections of biopsy specimens to ensure the detection of granuloma.

Several previous studies have evaluated the rate of granuloma detection on histological examination of GI biopsies from patients with CD. We summarized the main results of five studies in which the methods of biopsy and pathological examination were precisely described (Table 6) [5, 10, 11, 14, 15]. In these reports, the rate of granuloma detection following histological examination of GI biopsies ranged from 34% to 67%. Among these five studies, three studies reported that the rate of granuloma detection was 60% or greater [5, 10, 11]. It should be noted that multiple biopsies and histological examination of serial sections were intentionally performed in these three studies. A similar detection rate to these three reports was observed in the present study, highlighting the importance of multiple biopsies and additional histological examination of serial or step sections.

The number of GI biopsies that should be obtained for the detection of granuloma during the initial diagnosis of CD is currently unclear. A limited number of previous

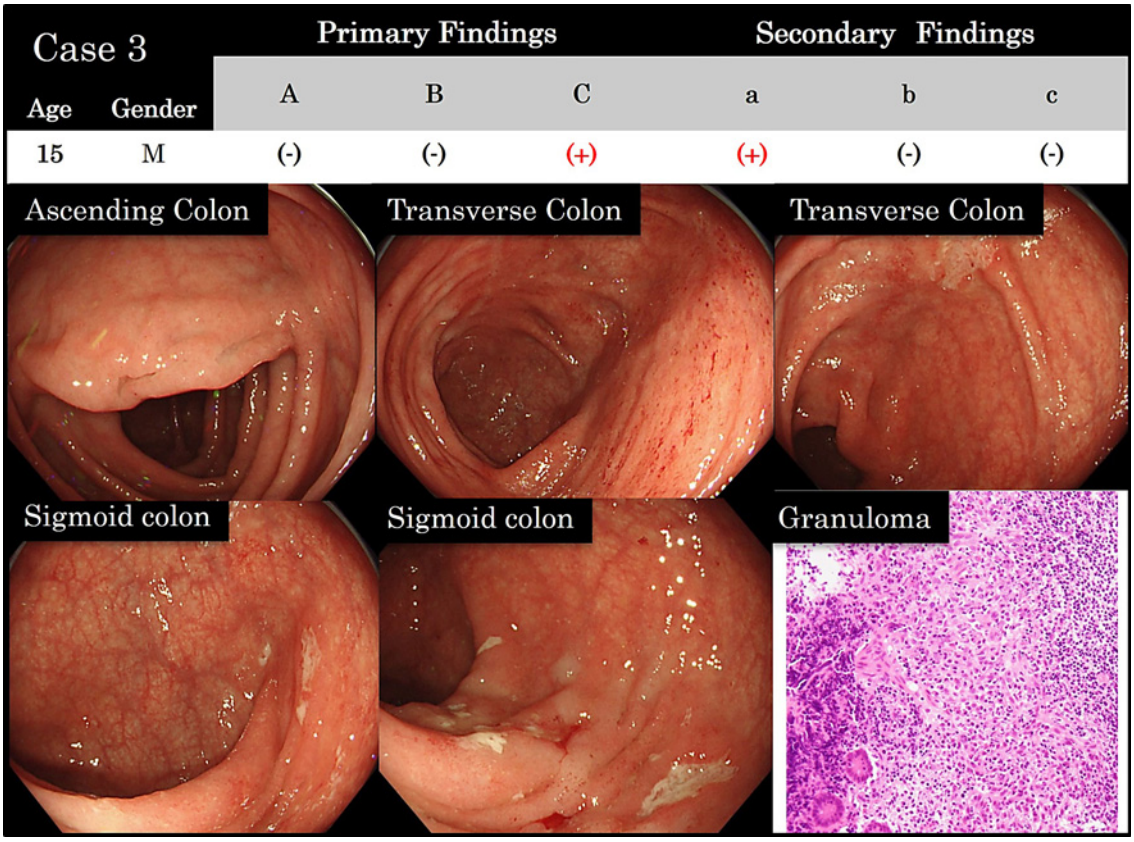

Fig. 3. Case 3 (15-year-old male with colonic CD). Ileocolonoscopy revealed multiple erosions and irregular-shaped ulcers in the colon. Non-cavitary epithelioid granulomas were detected in an ascending colon biopsy specimen.

Table 4. Locations and endoscopic images of the GI tract where granulomas were detected

	Aphthae or erosion	Irregular- or round-shaped ulcer	Longitudinal ulcer	Total *n*
Esophagus, *n*				
Stomach, *n*	1			1
Duodenum, *n*	1			1
Terminal ileum, *n*	5		4	9
Cecum, *n*		1		1
Ascending colon, *n*	2	2	5	9
Transverse colon, *n*		1	4	5
Descending colon, *n*	1		4	5
Sigmoid colon, *n*				
Rectum, *n*	2			2
Total *n*	12	4	17	33

studies have examined the rate of granuloma detection according to the number of biopsies taken. Ye et al. evaluated the rate of granuloma detection in 164 biopsies in a study of 52 patients with CD. In this study, an average of six biopsies were taken from each affected lesion of the lower GI tract, and histological examination of serial

Table 5. Rates of non-cavitary epithelioid cell granuloma detection according to number of biopsies taken

	Esophagogastroduodenoscopy (EGD)	Ileocolonoscopy (IC)	Total
Number of cases, *n*	16	29	29
Number of biopsies, *n*	63	221	284
Average number of biopsies per case, *n*	4	8	10
Detection rate of granuloma			
Before histological examination of step sections, *n* (%)	0 (0)	17 (7.7)	17 (6.0)
After histological examination of step sections, *n* (%)	2 (3.2)	31 (14.0)	33 (11.6)

Table 6. Summary of previous studies of granuloma detection on GI biopsies (detection rate according to number of cases)

Author	Year	Case, *n*	Biopsy and pathological examination methods	Granuloma detection rate, % (positive cases/ total cases)	Reference
Molanr et al.	2005	56	At least two biopsy specimens were obtained from each GI segment. Pathological examinations were performed without examination of serial or step sections	44.6 (25/56)	[15]
Rubio et al.	2007	64 (children) 41 (adults)	Biopsy specimens were obtained from ten different levels of the lower GI tract. Six sections from each biopsy specimen were examined	67.2 (43/46) 65.9 (27/41)	[10]
De Matos et al.	2008	184 (children)	At least two biopsy specimens were obtained from each GI site. Pathological examinations were performed using serial sections (16–20 sections for each paraffin block)	61.0 (112/184)	[11]
Ye et al.	2015	52	An average of six biopsies were obtained from each abnormal site in the lower GI tract. An average of six sections were examined for each specimen	67.3 (35/52)	[5]
Rothschild et al.	2017	289 (children)	At least two biopsy specimens were obtained from each GI segment. Pathological examinations were performed using serial sections	34 (99/289)	[14]
Present study		29	Biopsy specimens were obtained from each involved GI lesions. Only when no granulomas were detected, step sections (10 slides at 30 μm intervals) examination were added	58.6 (17/29)	

sections was performed to assess for the presence of granuloma, with a reported granuloma detection rate per biopsy of 39.6% (65 granulomas/164 biopsies). It should be emphasized that this report used a considerably more detailed series of examinations than conventionally used in clinical practice. The benefit of performing histological examinations using serial or step sections in detecting granuloma in GI biopsy specimens is also unclear. In the present study, we compared the rate of granuloma detection between the conventional histological examinations and examinations using step sections. In the present study, the rate of granuloma detection according to the number of biopsies taken was 0% from the upper GI tract and 7.7% from the lower GI tract before histological examination of step sections. However, the detection rates improved to 3.2% and 14.0% after histological

examination of step sections of biopsies from the upper and lower GI tracts, respectively. This finding indicates that the rate of granuloma detection was significantly improved after histological examination of step sections. The findings of Ye et al. report and the present study highlight the importance of performing multiple GI biopsies and pathological examinations of serial or step sections when assessing the presence of granuloma.

The endoscopic images where the granulomas were detected are another important issue. It should be noted that granulomas were frequently detected from longitudinal ulcers. Here, we also emphasize that granulomas were detected at a relatively high frequency from aphthae and erosions. The results suggest that intentional biopsy from aphthae and erosions is highly significant for the detection of granulomas, especially in the diagnosis of early CD that lacks ulcerative lesions.

The limitations of the present study include the small number of cases from a single center and the variability in the methods used to obtain GI biopsies given its retrospective study design. Prospective studies using uniform methods are required to determine the appropriate number of biopsies required and clarify the appropriate site of biopsy when assessing for the presence of granuloma.

In conclusion, the present study evaluated the rate of granuloma detection from histological examination of GI biopsies during the initial diagnosis of treatment-naïve CD. The rate of granuloma detection per case was approximately 60% in the present study. The rate of granuloma detection per number of biopsies performed was only 6.0% before histological examination of step sections; however, assessing for the presence of granuloma using histological examination of step sections significantly improved the detection rate to 11.6%. These results indicate that performing multiple GI biopsies and assessing for granuloma using histological examination of serial or step sections is necessary when making an initial diagnosis of CD.

Statement of Ethics

All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study design was observational. The study was approved by the Ethics Committee of the Institutional Review Board of Tohoku Medical and Pharmaceutical University School of Medicine. Approved IRB number is 2021-02-037. The study was performed in accordance with the ethics guidelines in Japan. For adult participants, written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. For underage participants, written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images. Patients who expressed unwillingness to participate in this study were excluded.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Katsuya Endo established the study design and was involved in designing the original study protocol, collecting data, and writing the manuscript. Yoko Kawakami, Yuki Yoshino, Shiho Kondo, Daisuke Fukushi, and Kazuhiro Murakami participated in data collection. Atsuko Takasu, Takayuki Kogure, Morihisa Hirota, and Kennichi Satoh contributed in discussing and critically reviewing the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to ethical reasons and the patients' personal information.

References

1 Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology. 2017 Feb;152(2):351–61.e5.

2 Bouguen G, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, Colombel JF, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015 Jun;13(6):1042–50.e2.

3 Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2021 Apr;160(5):1570–83.

4 Nakase H, Uchino M, Shinzaki S, Matsuura M, Matsuoka K, Kobayashi T, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol. 2021 Jun;56(6):489–526.

5 Ye Z, Lin Y, Cao Q, He Y, Xue L. Granulomas as the most useful histopathological feature in distinguishing between Crohn's disease and intestinal tuberculosis in endoscopic biopsy specimens. Medicine. 2015 Dec;94(49):e2157.

6 Qian Y, He W, Zheng CY, Xue JH, Fang JY, Chen XY, et al. Significance of granuloma and granulomatous lymphangitis in the differential diagnosis of Crohn's disease. J Dig Dis. 2020 Aug;21(8):454–61.

7 Hong SW, Yoon H, Shin CM, Park YS, Kim N, Lee DH, et al. Clinical significance of granulomas in Crohn's disease: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2020 Mar;35(3):364–73.

8 Hisabe T, Hirai F, Matsui T, Watanabe M. Evaluation of diagnostic criteria for Crohn's disease in Japan. J Gastroenterol. 2014 Jan; 49(1):93–9.
9 Heresbach D, Alexandre JL, Branger B, Bretagne JF, Cruchant E, Dabadie A, et al. Frequency and significance of granulomas in a cohort of incident cases of Crohn's disease. Gut. 2005 Feb;54(2):215–22.
10 Rubio CA, Orrego A, Nesi G, Finkel Y. Frequency of epithelioid granulomas in colonoscopic biopsy specimens from paediatric and adult patients with Crohn's colitis. J Clin Pathol. 2007 Nov;60(11):1268–72.
11 De Matos V, Russo PA, Cohen AB, Mamula P, Baldassano RN, Piccoli DA. Frequency and clinical correlations of granulomas in children with Crohn disease. J Pediatr Gastroenterol Nutr. 2008 Apr;46(4):392–8.
12 Turner K, Genta RM, Lujan G, Robiou C, Sonnenberg A. Significance of the epithelioid granuloma in biopsies of Crohn's colitis. Inflamm Bowel Dis. 2014 Dec;20(12): 2271–5.
13 So H, Ye BD, Park YS, Kim J, Kim JS, Moon W, et al. Gastric lesions in patients with Crohn's disease in Korea: a multicenter study. Intest Res. 2016 Jan;14(1):60–8.
14 Rothschild B, Rinawi F, Herman Y, Nir O, Shamir R, Assa A. Prognostic significance of granulomas in children with Crohn's disease. Scand J Gastroenterol. 2017 Jun;52(6–7):716–21.
15 Molnar T, Tiszlavicz L, Gyulai C, Nagy F, Lonovics J. Clinical significance of granuloma in Crohn's disease. World J Gastroenterol. 2005;11(20):3118–21.