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Diagnostic Process and Applied Criteria for Crohn's Disease in Patients Presenting with Perianal Lesions in Japan: A Retrospective Observational Multicenter Cohort Study

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Keywords
Colonoscopy · Crohn's disease · Diagnostic criteria · Non-caseating epithelioid cell granuloma · Perianal lesions

Abstract

Introduction: In Japan, the confirmed diagnosis of Crohn's disease (CD) is based on a single, historically established set of clinical criteria. However, for patients who present with a perianal lesion (PL), the diagnostic pattern actually applied is unclear. ***Methods:*** We conducted a retrospective observational multicenter study among patients who presented with a PL without synchronous abdominal symptoms and were subsequently diagnosed with confirmed or probable CD according to the Japanese diagnostic criteria from May 1996 to April 2024. In total, 100 patients with confirmed CD and 10 with probable CD were identified and enrolled. ***Results:*** Among the 100 patients with confirmed CD, 72% met the criterion for the category "confirmed 1: main finding *A* (longitudinal ulcer) or *B* (cobblestone appearance)." In the same cohort, 35% met the criterion for the category "confirmed 2: main finding *C* (non-caseating epithelioid cell granuloma [NCEG]) with secondary finding *a* (extensive irregular-to-round ulcers or aphthae in the gastrointestinal tract) or *b* (characteristic anorectal lesions)," including 24% without the main finding *A* or *B*. Finally, 4% met the criterion for the category "confirmed 3: all secondary findings *a*, *b*, and *c* (characteristic gastric and duodenal lesions)." All 10 patients with probable CD were diagnosed based on secondary finding *b* only or secondary findings *a* and *b*. ***Conclusion:*** In cases of suspected CD due to initial PLs, histological investigation of NCEG and precise total gastrointestinal inspection should be conducted to confirm the diagnosis.

Introduction

In 1976, the Japanese Society of Gastroenterology proposed the diagnostic criteria for Crohn's disease (CD). Since then, the diagnostic criteria have been repeatedly revised based on an increase in the number of patients with CD [1, 2]. The latest version of the criteria, which incorporated the improved diagnostic modalities for the small bowel (SB), was issued in April 2024 [3]. However, the criteria for CD remained largely unchanged.

Perianal lesions (PLs) are found in almost 50% of patients with newly diagnosed CD in Japan [4–6]. The prevalence of CD decreases with age, with individuals <40 years of age

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showing a higher prevalence than other age-groups [4–6]. In addition, approximately 70% of patients with CD-associated perianal fistulas (PFs) develop PFs before receiving a diagnosis of CD [7]. Therefore, PLs may be an initial presentation of CD in a healthy individual [8–10]. Due to these circumstances, the special guide for PLs in CD was revised [11]. However, PL remains one of the secondary findings of the diagnostic criteria even in the latest version [2, 3].

Recently, clinical practitioners have increasingly had opportunities to proceed with diagnosing CD following the initial presentation of PLs. However, the diagnostic criteria used in these cases remain unclear. Hisabe et al. [12] conducted a questionnaire-based nationwide survey to determine how gastroenterologists made a diagnosis using the Japanese diagnostic criteria and to evaluate the suitability of these criteria for the general population of patients with confirmed CD and probable CD. In the present retrospective study, we determined the characteristics associated with CD diagnosis in patients with PL and compared the findings with those of the nationwide study by Hisabe et al. [12].

Methods

A retrospective chart review of patients with a confirmed or probable diagnosis of CD presenting with perianal disease who visited Yokoyama Memorial Hospital (Nagoya, Japan), Saigusa Clinic of Coloproctology (Shizuoka, Japan), or Masuko Memorial Hospital (Nagoya, Japan) from May 1996 to April 2024 was conducted. This study was approved by the Institutional Review Board of Masuko Memorial Hospital (Approval No. Masuko MR6-2).

All patients who visited the aforementioned medical facilities with complaints such as pain, swelling, lumps, or discharge in the perianal region but did not have abdominal symptoms were included in this study. A total of 110 patients whose detailed findings of consecutive workups led to CD diagnosis were enrolled in this study, and data regarding their medical history and demographic characteristics were obtained. We collected the following data: sex; age at onset of PL; number of patients who had undergone anorectal exploration under anesthesia (EUA) before diagnosis; type of initial PL, including coexisting perineal lesions; specific clinical features of PLs leading to suspicion of latent CD; interval between the onset of PLs and the confirmed diagnosis; and interval between the onset of PLs and the first colonoscopy (CS) in patients with detailed findings of CS before the confirmed diagnosis.

To evaluate the proportion of patients with a confirmed or probable diagnostic criterion according to the current Japanese criteria [2, 3] (Table 1), the presence or absence of the main findings *A* (longitudinal ulcer [LU]), *B* (cobblestone appearance [CSA]), and *C* (non-caseating epithelioid cell granuloma [NCEG]); presence or absence of secondary findings *a* (extensive irregular-to-round ulcers or aphthae in the gastrointestinal tract), *b* (characteristic anorectal lesions), and *c* (characteristic gastric and duodenal lesions); and prediagnostic bowel resections were determined. The number of patients who met each criterion was counted and summarized. For patients with confirmed diagnoses, data regarding the site of the lesion of main finding LU or CSA and the modalities of bowel examination (multiple counting, if on the same day) by which each main finding was first detected were collected. The site of the lesion and the histological results of the major finding were also collected for NCEG. We defined LU and CSA in the gastrointestinal tract as "advanced lesions" and extensive irregular-to-round ulcers or aphthae as "early lesions" [13] based on the diagnostic criteria in Japan [1, 3] and Europe [14–17].

Finally, we compared the proportions of patients who had clinical manifestations and met the diagnostic criteria between this study and a previous study [12] using Fisher's exact test. Statistical analysis was performed using the EZR version 4.20 software [18], with a p value of <0.05 indicating a statistically significant difference.

Results

Study Subjects

Between May 1996 and April 2024, a total of 43,039 patients visited the aforementioned medical facilities with perianal complaints. However, many of these patients had multiple comorbidities unrelated to CD. Among them, 3,609 patients were identified as having PFs, including 3,513 (97.3%) patients with non-CD PF (10 of whom were classified as having probable CD) and 96 (2.7%) who were diagnosed with CD during the study period. In addition, 4 patients with CD initially presenting with other types of PLs were identified. Overall, 100 patients with confirmed CD diagnoses and 10 with probable CD diagnoses were included in this study.

Clinical Characteristics of Patients

The clinical characteristics of the patients are presented in Table 2. In the group of patients with confirmed CD, the median age at the onset of an initial PL was 20.5 years. The most common age-group at the time of presentation with Crohn's PL was 15–19 years, consisting of 35% of the patients (Fig. 1). Eighty-six patients (86%) had undergone EUA at least once before the diagnosis.

Table 1. Diagnostic criteria for CD [2, 3]

Main findings
A. LU (preferably on the mesenteric attachment when identified in the small intestine)
B. CSA
C. NCEG: serial sectioning of histological samples improves diagnostic yield. Diagnosis should be made by a pathologist familiar with the gastrointestinal tract
Secondary findings
a. Extensive, irregular-to-round ulcers or aphthae in the gastrointestinal tract: extensive gastrointestinal tract lesions indicate anatomical distribution over more than one organ, such as the upper gastrointestinal tract (esophagus, stomach, duodenum), small intestine, and large intestine. Lesions are typically, but not always, longitudinal. The lesions should be permanent for at least 3 months. Annular ulcers may be visible on Kerckring folds of the duodenum and small intestine on capsule endoscopy. It is necessary to exclude intestinal tuberculosis, intestinal Behçet's disease, simple ulcer, nonsteroidal anti-inflammatory drug-induced ulcer, and infectious enteritis
b. Characteristic anorectal lesions: e.g., anal fissure, cavitating ulcer, PF/abscess, and edematous skin tag. A diagnosis should be made based on the book "*All about perianal Crohn's disease*: *From diagnosis to treatment*" [11] or by a proctologist familiar with CD
c. Characteristic gastric and duodenal lesions: bamboo joint-like appearance, notch-like depression. Diagnosis should be made by a specialist familiar with CD
Confirmed diagnosis of CD
1. Patients with main findings *A* or *B*. If only LUs are identified, ischemic bowel disease and ulcerative colitis should be excluded. If a CSA is present alone, ischemic bowel lesions and type 4 colorectal cancer should be excluded
2. Patients with a main finding of *C* and a secondary finding of *a* or *b*
3. Patients with all secondary findings (*a*, *b*, and *c*)
Probable diagnosis of CD
1. Main finding *C* with secondary finding *c*
2. Main finding *A* or *B* but it cannot be differentiated from ischemic colitis or ulcerative colitis
3. Main finding *C* only: inflammatory diseases with granulomas such as intestinal tuberculosis should be excluded
4. One or two secondary findings

Perianal abscess/fistula was the most common (96%) type of PL, followed by fissure/ulcer (23%).

The major morphological features of PLs leading to suspicion of CD included complex PF with multiple primary and secondary orifices (17%), followed by NCEG detection in surgically resected PL specimens (14%). In contrast, the common clinical features during the clinical course cited as reasons for suspicion of CD were refractory fistula after surgical treatment (drainage/fistulotomy) (38%) and subsequent occurrence of bowel symptoms, such as abdominal pain or diarrhea (15%). All these features were confirmed during hospital visit or at the time of EUA. Four patients, including one who had undergone SB resection and three who had undergone small and large bowel resection, lacked records of tests performed prior to bowel resection for CD. Of the remaining 96 patients who did not undergo bowel resection, 95 who had detailed findings of the first CS could be ascertained before diagnosis, with a median interval of 6.9 months (range, 0.2–212.4) between PL onset and CS. The median interval between PL onset and confirmed diagnosis was 9.6 months (range, 0.2–511.6).

The group of patients with probable CD diagnosis showed similar characteristics to the confirmed diagnosis group. However, the interval between PL onset and the first CS was relatively short, with a median of 3.7 months (range 0.6–104.9). The median duration of the disease (the period from PL onset to April 30, 2024) was 110.2 months (1.6–322.6). All patients in this group had undergone EUA at least once during their clinical course.

First CS before Confirmed CD Diagnosis

The first CS detected the main finding *A* (LU) or *B* (CSA) in 52 (54.7%) of the 95 patients (Table 3). LU/CSA was detected in the ileum and colorectum of 14 (14.7%) and 43 (45.3%) patients, respectively, and 5 patients

Table 2. Clinical characteristics of patients

Characteristic	Confirmed (*N* = 100)		Probable (*N* = 10)	
Sex, *n* (%)				
Male	81	(81%)	8	(80%)
Female	19	(19%)	2	(20%)
Age at PL onset, median (range), years	20.5	(8–47)	24	(10–44)
Patients who underwent EUA before diagnosis, *n* (%)	86	(86%)	10	(100%)
Type of PL, *n* (%)				
Abscess/fistula (anovaginal fistula)	96 (3)	(96%)	10 (0)	(100%)
Fissure/ulcer	23	(23%)	2	(20%)
Edematous/ulcerated pile	6	(6%)	1	(10%)
Clinical features of PL leading to suspecting CD, *n* (%)				
Refractory fistula after surgical treatment	38	(38%)	5	(50%)
CD-like fissure/ulcer	20	(20%)	2	(20%)
Complex PF	17	(17%)	3	(30%)
Subsequent occurrence of bowel symptoms	15	(15%)	2	(20%)
NCEGs from resected PL specimen	14	(14%)	0	(0%)
Fistula not arising from the anal crypt	6	(6%)	2	(20%)
CD-like skin tag	6	(6%)	1	(10%)
Anal canal stenosis	3	(3%)	0	(0%)
Perineal lesion (pyoderma, anogenital granulomatosis)	3	(3%)	0	(0%)
Bowel resection with unavailable records of pre-surgery tests, *n* (%)	4	(4%)	0	(0%)
Interval between PL onset and the first CS, median (range)[a], months	6.9	(0.2–212.4)	3.7	(0.6–104.9)
Interval between PL onset and diagnosis, median (range), months	9.6	(0.2–511.6)	N/A	
Disease duration, median (range)[b], months	N/A		110.2	(1.6–322.6)
Extent of bowel lesions at confirmed diagnosis, *n* (%)				
Colorectal involvement (–)	25	(25%)	3	(30%)
Colorectal involvement (+)	75	(75%)	7	(70%)
Main finding *A/B* (+) with bowel examination	46	(46%)		
Main finding *A/B* (+) with colonic resection	3	(3%)		
Main finding *A/B* (–) but secondary finding *a* (+)	26	(26%)		
Phase of bowel lesion at confirmed diagnosis, *n* (%)				
No bowel lesions	4	(4%)		
Early (small ulcer, aphthoid ulcer, aphtha)	24	(24%)		
Advanced (LU/CSA)	72	(72%)		

CD, Crohn's disease; EUA, exploration under anesthesia; CS, colonoscopy; N/A, not applicable; NCEGs, non-caseating epithelioid cell granulomas; PLs, perianal lesions. [a]*n* = 95. [b]Disease duration represents the period from PL onset to April 30, 2024.

(5.3%) had LU/CSA in both the ileum and colorectum. Secondary finding *a* (extensive irregular-to-round ulcers or aphthae in the gastrointestinal tract) without LU/CSA was observed in 30 (31.6%) of the 95 patients. However, 13 (13.7%) had no bowel lesions on the first CS. In addition, 14 (93.3%) of the 15 patients who had undergone the first CS due to manifestation of bowel symptoms, such as abdominal pain or diarrhea, showed LU/CSA, and only 1 patient (6.7%) showed early lesions of secondary finding *a*.

Proportion of Confirmed CD by Criteria

In total, 72 (72%) patients with confirmed CD met the criterion for the category "confirmed 1 (C1): main finding *A* (LU) or *B* (CSA)" (Table 4). Among these 72 patients, 69 (95.8%) were diagnosed based on main finding *A*. Table 5 shows patient numbers per site of LU/CSA and morphological examinations, leading to a confirmed diagnosis. In the same cohort (C1 patients, *n* = 72), LU/CSA was detected on the first or subsequent CS in 54 (75.0%) patients, including 39 with LU/CSA in the colorectum, 9 with LU/CSA

Table 3. Numbers of patients who met each diagnostic criterion at the first CS (*N* = 95)

	Total		Ileum		Colorectum	
	n	(%)	*n*	(%)	*n*	(%)
Main finding *A* or *B*	52	(54.7%)	14	(14.7%)	43	(45.3%)
A	48	(50.5%)	14	(14.7%)	40	(42.1%)
B	5	(5.3%)	1	(1.1%)	4	(4.2%)
Secondary finding *a* without *A* or *B*	30	(31.6%)	14	(14.7%)	26	(27.4%)
No bowel lesions	13	(13.7%)	N/A		N/A	

N/A, not applicable.

in the SB, and 6 with LU/CSA in both. However, the total number of patients diagnosed with CD with only SB LU/CSA was 23 (31.9%) upon subsequent investigations, including 2 diagnoses via balloon endoscopy, 1 via SB videocapsule endoscopy, and 10 via SB X-ray series.

A total of 35 (35%) patients with confirmed CD diagnosis met the criterion for the category "confirmed 2" (C2), which required the presence of main finding *C* (NCEG) along with secondary findings *a* or *b* (characteristic anorectal lesions, i.e., PLs) (Table 4). This group included 24 (24%) patients who met only C2 and 11 (11%) patients who met both C1 and C2. In addition, 4 (4%) patients met criterion *C* + *b* alone but did not meet finding *A* or *B*. These 4 patients were diagnosed solely based on the presence of NCEGs in their PLs without any associated bowel lesions. Of the 35 confirmed cases, NCEGs were identified in 22 (62.9%) via endoscopic biopsies of the gastrointestinal tract and 14 (40.0%) via resected specimens obtained from fistulas or ulcerative/edematous skin tags. The detection rate of NCEGs was 29.7% in endoscopic biopsies and 53.8% in PL specimens, and the overall detection rate was 35% (Table 6). Finally, only 4 patients (4%) met the criterion for the category "confirmed 3 (C3): all secondary findings *a*, *b*, and *c* (characteristic gastric and duodenal lesions)" (Table 4).

Proportion of Probable CD by Criteria

All 10 patients with probable CD were classified as "probable 4," 7 (70%) of whom had minor findings *a* and *b* and 3 (30%) had only minor finding *b* (Table 7).

Comparison with a Previous Study

Compared with a previous study conducted by Hisabe et al. [12], a significantly lower proportion of patients in this study had abdominal symptoms and a significantly higher proportion had a PL (Table 8). The frequency of the patients who met the criterion of C1 (main finding *A* [LU] or *B* [CSA]) was significantly

Table 4. Numbers of patients diagnosed with confirmed CD, meeting each diagnostic criterion (*N* = 100)

Category and criterion	*n*	(%)
Confirmed 1		
Main finding *A* or *B*	72	(72%)
A	69	(69%)
B	10	(10%)
A + *B*	7	(7%)
Confirmed 2		
Main finding *C* with secondary finding *a* or *b*	35	(35%)
C + *a* or *b* (neither *A* nor *B*)	24	(24%)
C + *a* only	0	(0%)
C + *b* only	8	(8%)
C + *b* only (neither *A* nor *B*)	4	(4%)
C + *a* +*b*	27	(27%)
C + *a* + *b* (neither *A* nor *B*)	20	(20%)
Confirmed 3		
All secondary findings *a*, *b*, and *c*	4	(4%)

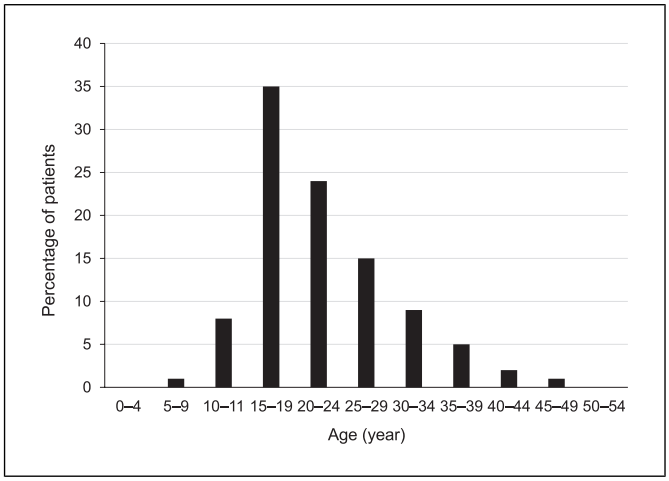

Fig. 1. Frequency distribution of patient ages at the time of presentation with Crohn's perianal lesions.

Table 5. Patient numbers by site of LU/CSA and morphological examinations, leading to confirmed diagnosis

	LU/CSA detection by morphological examinations					Resected bowel[a] (n = 4)	Overall (n = 72)
	CS (n = 54)	BE (n = 2)	SBVCE (n = 1)	SBX (n = 10)	proctoscopy during EUA (n = 1)		
UGI tract	N/A	0	0	0	N/A	N/A	0
SB only	9	2	1	10	N/A	1	23
CR only	39	0	0	0	1	3	43
SB + CR	6	0	0	0	0	0	6

BE, balloon enteroscopy; CR, colorectum; CS, colonoscopy; CSA, cobblestone appearance; EUA, exploration under anesthesia; LU, longitudinal ulcer; N/A, not applicable; SB, small bowel; SBVCE, small-bowel video-capsule endoscopy; SBX, small-bowel X-ray series; UGI, upper gastrointestinal. [a]Four patients whose records of morphological examinations prior to bowel resection were unavailable.

Table 6. Histological examinations for NCEGs before confirmed diagnosis

	Histological examinations					
	endoscopic biopsy		PL specimen		overall	
Patients with histological examinations	74	(100%)	26	(100%)	100[a]	(100%)
Granuloma detection	22	(29.7%)	14	(53.8%)	35	(35.0%)
UGI tract	1	(1.4%)	N/A	–	1	(1.0%)
SB	10	(13.5%)	N/A	–	10	(10.0%)
Colorectum	13	(17.6%)	N/A	–	13	(13.0%)
Perianal region	2[b]	(2.7%)	14[c]	(53.8%)	14	(14.0%)

N/A, not applicable; PL, perianal lesion; UGI, upper gastrointestinal. [a]Four patients, whose histological records of examinations prior to bowel resection were unavailable, were included as the denominator. [b]PF and anal canal ulcer (1 case each). [c]PF (12 cases), edematous skin tag (1 case), and pyoderma (1 case).

lower in this study than in the previous study (72.0% vs. 87.4%; $p < 0.001$). Although no significant difference was observed for C2 or C3, the frequency of the patients who met the criterion of C2 only (i.e., without main findings LU or CSA) was significantly higher in this study than in the previous study (24.0% vs. 5.5%; $p < 0.001$).

Discussion

In this study, the overall proportion of confirmed CD diagnosis among patients with PFs was 2.7%. This proportion was slightly lower than that reported in a previous Japanese study (3.5%), likely because our analysis included older data from a period when the prevalence of CD was lower [10]. The proportion of CD among patients presenting with an initial PL is significant given that the overall prevalence of CD in Japan is estimated to be only 0.05% [19]. Almost half of the patients who presented with Crohn's PL were under the age of 20 years, with the 15–19-year age-group being the most affected. Similarly, the iCREST study reported that Japanese patients diagnosed with CD accompanied by PLs, particularly PFs, were predominantly younger [4, 5]. The median interval between the onset of PLs and CD diagnosis was 9.6 months, consistent with the findings from a US study, which reported that most patients presenting with an initial PL were diagnosed with CD within 1 year of symptom onset [20].

Unlike lesions in the intestinal tract, even minor lesions in the sensitive perineal region can cause

Table 7. Numbers of patients diagnosed with probable CD, meeting each diagnostic criterion (N = 10)

Category	Criterion	*N*	(%)
Probable 1	Main finding *C* with secondary findings *c*	0	(0%)
Probable 2	*A*[a]	0	(0%)
	B[a]	0	(0%)
Probable 3	Main finding *C* only	0	(0%)
Probable 4	One or two secondary findings	10	(100%)
	a only	0	(0%)
	a + *b*	7	(70%)
	b only	3	(30%)
	b	10	(100%)
	c	0	(0%)

[a]Main finding *A* or *B* but it cannot be differentiated from ischemic colitis or ulcerative colitis.

Table 8. Comparison of study populations: present versus previous study

Author	Saigusa	Hisabe [12]	*p* value
Number of patients	100	579	–
Age, years	20.5 (median)	27.8 (mean)	–
Sex (M/F)	81/19	459/120	0.789
Clinical manifestations			
Abdominal symptoms	15 (15.0%)	414 (71.5%)	<0.001
PL	100 (100%)	167 (28.8%)	<0.001
Category			
C1 (main finding *A* or *B*)	72 (72.0%)	506 (87.4%)	<0.001
C2 (main finding *C* + secondary *a* or *b*)	35 (35.0%)	176 (30.4%)	0.352
C3 (all secondary findings *a*, *b*, and *c*)	4 (4.0%)	41 (7.1%)	0.382
C2 only	24 (24.0%)	32 (5.5%)	<0.001

C1, C2, and C3: confirmed 1, confirmed 2, and confirmed 3, respectively.

significant discomfort and may indicate latent CD in its early phase. Colorectal lesions are not always present when PLs are initially observed. However, during follow-up, 75% of patients with confirmed CD had some degree of colorectal involvement, most of which were early lesions, such as aphthoid ulcers, rather than LUs or CSA [9]. The frequency of patients presenting with a PL without bowel lesions has been reported to be 0.6%–5% [6, 21]. In this study, 4 patients (4%) with confirmed CD diagnosis did not show any bowel lesions. This finding suggests that a small proportion of patients with CD may present with a PL alone or that bowel lesions may appear a long period after the initial PL onset. In this study, some of the 10 patients with probable CD had a relatively shorter period between the onset of PLs and the end of the study period. If they were followed up without therapeutic intervention, they may have developed intestinal lesions in the future.

In patients with suspected CD, anorectal EUA performed by an experienced colorectal surgeon is considered the gold-standard diagnostic procedure. In this study, LUs were identified in 1 (1%) patient only via proctoscopy under anesthesia, whereas NCEGs were detected in PLs in 14 (14%) patients through EUA. During CS, LU or CSA were observed in the ileum alone in 9 (9%) patients. Additional diagnostic modalities, including balloon-assisted enteroscopy, SB video-capsule endoscopy, and SB X-ray, identified LU or CSA in the SB of other 13 (13%) patients. The results

revealed that 23% of patients with confirmed CD diagnosis had LU or CSA localized solely in the SB. Similarly, previous studies have reported that approximately 15% of patients with CD presenting with a PL exhibit CD lesions confined to the ileum [6, 20, 22]. Therefore, cannulation of the terminal ileum should be performed during initial CS to confirm the diagnosis. Furthermore, SB examinations can provide additional diagnostic value in cases with a negative conventional workup [23].

Compared with a previous study conducted by Hisabe et al. [12] among a general population of patients with confirmed CD, significantly fewer patients in this study had clinical manifestations other than PLs at the time of confirmed CD diagnosis. The frequency of patients who met the criterion of C1 (main finding LU or CSA) was significantly lower in this study than in the previous study. Conversely, the frequency of patients who met the criterion of C2 (main finding NCEG and with secondary finding *a* or *b*) was significantly higher in this study than in the previous study. Furthermore, given that a significant proportion of patients with confirmed CD exhibited neither bowel lesions nor abdominal symptoms, our study likely included a considerable number of patients in the early phase of CD. Among the 100 patients with confirmed CD, NCEGs were detected in resected PLs in 14 (53.8%) of 26 patients and in intestinal endoscopic biopsies in 22 (29.7%) of 74 patients during the follow-up period, leading to a confirmed diagnosis. The detection of NCEGs is particularly crucial in cases where LUs or CSA are absent as 24% of patients were diagnosed with confirmed CD solely based on the presence of NCEGs and PLs. Furthermore, NCEGs are reportedly identified more frequently in surgical specimens than in endoscopic biopsies [24]. Therefore, histological detection of main finding *C* (NCEG) in addition to direct inspection of the total gastrointestinal tract is crucial to make a confirmed diagnosis of CD for patients presenting with PL. However, no large-scale studies describing the detection of NCEG in patients with a PL have been performed.

Some PLs exhibit clinical or morphological features suggestive of latent CD, although they are not always indicative of early phase CD. According to Hughes' classification, PFs are categorized as either secondary or incidental lesions of perianal CD, rather than primary lesions [24]. Consequently, even for proctologists, distinguishing CD-related PF from non-CD PF can be challenging without histological examination or evidence of disease progression. Therefore, it remains challenging to include PLs alone as a main criterion in the Japanese diagnostic guidelines for CD.

This study had several limitations. First, as a retrospective study, it was not possible to capture precise initial complaints from all patients. Second, the patient cohort may have had a certain level of bias as the medical facilities involved specialize in coloproctology. Third, the sample size of 100 patients limited the generalizability of the findings to the broader population of Japanese patients with CD presenting with an initial PL. Therefore, comparisons between the proportions of patients meeting each diagnostic criterion in our study and those in Hisabe's study [12] should be made with caution, although the results appear reasonable. Finally, the number of confirmed CD diagnosis in this study may be underestimated. Some patients were not followed up for extended periods because of relocation or transfer to other hospitals, whereas others had only recently sought medical attention.

In conclusion, proactive gastrointestinal tract examination based on a high index of suspicion of CD, prompted by the detection of an initial PL, maintained a bowel LU/CSA detection frequency of 72%; however, NCEGs reached a detection rate as high as 35%. Therefore, in patients initially presenting with PL, histological examination of NCEG is crucial for a confirmed CD diagnosis in Japan.

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Statement of Ethics

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Masuko Memorial Hospital (Approval No. Masuko MR6-2). Because of the retrospective nature of the study, consent to patients was not required by the IRB.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Material preparation and data collection and analysis were performed by Naoto Saigusa, Naoki Hotta, and Jun-ichi Saigusa. The first draft of the manuscript was written by Naoto Saigusa. All authors contributed to the study conception and design, commented on revised versions of the manuscript, and read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing patients' information and Ethics Committee formalities but are available from the corresponding author upon reasonable request.

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