Incidence, clinical characteristics, long-term course, and comparison of progressive and non-progressive cases of aphthous-type Crohn's disease: a single-center cohort study

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Running head: Aphthous-type Crohn's disease

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ABSTRACT

Background/Aims: In Japan, aphthous-type Crohn's disease (type A CD) is thought to represent an early phase of Crohn's disease (CD), and diagnosis of type A CD is possible in the diagnostic criteria for CD in Japan. However, the details of type A CD are not well understood.

Methods: Subjects comprised 649 CD patients diagnosed between 1985 and 2011. The incidence of type A CD over time was clarified in two periods (1985-2004 and 2005-2011). The course of type A CD was also investigated, and cases that did and did not progress to typical CD were compared. **Results:** No significant difference was seen in the incidence of type A CD between the two periods (5.2% vs. 8.5%, p=0.125). Type A CD patients followed at our hospital progressed to typical CD at a rate of 59.3%. In comparing progressive and non-progressive cases, the frequency of large, densely distributed aphthous lesions in the small intestine was higher among progressive cases (p=0.018). **Conclusion:** Type A CD is an early phase of CD, and CD diagnostic criteria including early cases are valid in Japan.

Key Words: aphthous lesions; Crohn's disease; incidence; clinical characteristics; course

INTRODUCTION

Crohn's disease (CD) is a granulomatous inflammatory disease of unknown cause that occurs mainly in young people. Aphthous lesions are often seen in CD accompanying typical findings of longitudinal ulcers or cobblestone appearance, but a form of CD comprising aphthous lesions only also exists. We have named this type of CD as aphthous-type CD (type A CD), and it appears to represent an early phase of CD [1-7]. Several reports have described the progression of type A CD to typical CD [3-5,7], but details such as the incidence, clinical characteristics, course, and differences between cases that progress to typical CD and those that do not remain unclear. Type A CD is diagnosed in the stage of early lesions only, and a more detailed understanding is important for clarifying the natural history of CD. The aim of this study was to elucidate the incidence, clinical characteristics, and course of type A CD, as well as differences between progressive and non-progressive cases. The validity of the diagnostic criteria in Japan is also discussed.

METHODS

In the diagnostic criteria for CD in Japan (Table 1) [8], a definitive diagnosis of CD is possible even with aphthous lesions only if non-caseating epithelioid cell granuloma is seen histopathologically. Using the CD diagnostic criteria in Japan, type A CD was defined in the present investigation as disease meeting the criteria of major finding C (non-caseating epithelioid cell granuloma) of the diagnostic criteria plus secondary finding 2a (multiple small aphthous ulcerations with longitudinal arrangement) or 2b (multiple small aphthous ulcerations in both upper and lower digestive tract).

Subjects were 649 CD patients diagnosed between 1985 and 2011 in the department of gastroenterology at Fukuoka University Chikushi Hospital. The incidence of type A CD with respect to all CD diagnosed in the two time periods of 1985-2004 (first-term diagnosis group) and 2005-2011 (second-term diagnosis group) was determined with the aim of ascertaining the

incidence of type A CD over time. The reason why we have divided cases into these two periods was that 22 patients with type A CD from before 1985 until 2004 were summarized in a report by Hirai et al. [9].

In addition, clinical characteristics and course of type A CD, and characteristics of cases that progressed to typical CD (progressive group) and cases that had not progressed as of the end of the investigation (non-progressive group) were studied.

Furthermore, the course of cases of aphthous colitis without granuloma who did not meet the diagnostic criteria for CD was also analyzed separately.

X-ray and endoscopy methods

Aphthous lesions were defined as barium flecks <10 mm in diameter with or without surrounding radiolucency and as erythematous mucosal plaques with central depression on endoscopy. Aphthous lesions were defined as small if the barium flecks were <2 mm in

diameter and large if they were ≥2 mm. In cases when endoscopic examination only was done without X-ray examinations, endoscopic findings were applied to the above classifications. Aphthous lesions were defined as dense if there were ≥6 aphthous lesions within about 3 cm, and scattered if there were <6 lesions. With regard to severity, cases defined as having small or scattered lesions were placed in a mild group (Figs. 1-a, b), while those defined as having large and dense lesions were placed in a severe group (Figs. 2-a, b). The severity of colonic lesions in patients who have aphthous lesions only in the small intestine was classified as mild, and the severity of small intestinal lesions in patients who have aphthous lesions only in the colon was classified as mild in this study. All cases were classified into the two groups separately depending on lesions of the small and large intestine (Table 2). In both X-ray and endoscopic examinations, severity was evaluated at the site of maximum lesion severity. Progression to typical CD was defined as when the typical lesions of longitudinal lesions or cobblestone appearance were seen in either the small or large intestine.

Statistical analysis

An unpaired t-test was used in comparing mean values between groups, and the χ^2 test or Fisher's exact test was used for comparisons of incidence. The Kaplan-Meier method was used for the respective cumulative progression rates, and the Wilcoxon test was used for between-group comparisons.

RESULTS

Incidence of type A CD over time

Among all 649 subjects, 41 (6.3%) had type A CD. Among the 426 subjects in the first-term diagnosis group, 22 (5.2%) had type A CD. Among the 223 subjects in the second-term diagnosis group, 19 (8.5%) had type A CD. No significant differences were seen in the incidence of type A CD between the first- and second-term diagnosis groups (5.2% vs. 8.5%,

respectively; p=0.125) (Fig.3).

Clinical characteristics, course, and comparison of progressive and non-progressive cases of type A CD

A full-range X-ray or endoscopic search of the small and large intestines was performed at the time of diagnosis in 41 type A CD patients. Biopsies were taken at several sites and non-caseating epithelioid cell granuloma was detected in at least one location.

The male-female ratio in these 41 patients was 28:13, mean age at onset was 22.2±10.1 years, and mean age at diagnosis was 22.8±8.4 years. The mean clinical observation period was 96.9±89.2 months, and the mean observation period for imaging tests was 55.5±75.7 months. Initial blood test findings were hemoglobin (Hb) 13.0±1.55 g/dL, albumin (Alb) 4.0±0.38 g/dL, C-reactive protein (CRP) 1.9±3.4 mg/dL, and Crohn's disease activity index (CDAI) 111.5±65.5. Anal lesions were seen at the time of initial examination in 13 patients (48.1%).

Of the 41 patients, images of the course of gastrointestinal lesions could be observed for ≥24 months in 27 patients. Aphthous lesions in the small intestine were seen in 25 of 27 patients (92.6%). Aphthous lesions in the large intestine were seen in 23 patients (85.2%). Of these 27 patients, typical lesions appeared in the small or large intestine and the case progressed to typical CD in 16 patients (59.3%). The cumulative rate of progression to typical CD is shown in Figure 4. The mean image observation period until the appearance of typical lesions in progressive cases was 41.4±31.4 months. Progression to typical CD occurred in 9 of the 16 patients (56.3%) within 36 months, and in 14 patients (87.5%) within 60 months. Only 2 cases progressed to typical CD after a course of more than 60 months. The cumulative progression rate to typical CD was 85.1% at 230 months. Among the 16 patients that progressed to typical cases, typical lesions appeared in the small intestine and aphthous lesions disappeared or remained unchanged in the large intestine in 8 patients; in other words, the clinical entity in these patients changed to ileal CD (Figs. 5-a,b). Conversely, progression to typical lesions in

the large intestine only and a change in the clinical entity to colonic CD was seen in 4 patients (Figs. 6-a,b). A change to ileo-colic CD, in which typical lesions appeared first in the small intestine and then appeared later in the large intestine also, occurred in 4 patients.

Among 11 non-progressive cases, aphthous lesions were seen in the small intestine at the time of diagnosis in all 11 patients. These aphthous lesions disappeared and did not recur during observation in 5 patients, recurred in 1 patient, and did not show significant changes in 5 patients. Aphthous lesions were seen in the large intestine at the time of diagnosis in 10 of the 11 non-progressive cases. Aphthous lesions in the large intestine disappeared and did not recur later in 4 patients, recurred in 4 patients, and did not show significant changes in 2 patients. Non progressive cases needed fewer hospitalizations (0.4±0.9) than progressive cases needed (4.6±4.4). Non progressive cases underwent no surgery (0%) , in contrast, progressive cases underwent surgery much more frequently (31.3%) . No patients progressed to UC during the due course.

In a comparison of progressive and non-progressive groups, no significant differences were seen between the groups in the male-female ratio, age at onset, age at diagnosis, initial test findings (Hb, Alb, CRP), CDAI at initial examination, or incidence of anal lesions at the initial examination. With regard to the severity of aphthous lesions in the small intestine, the frequency of severe cases was significantly higher in progressive groups (9/16) than in non-progressive groups (1/11, $p=0.018$). No significant difference was seen between progressive and non-progressive groups in terms of the severity of aphthous lesions in the large intestine (Table 3). Among those patients who underwent both endoscopic and X-ray examinations, no cases showed differing severity of aphthous lesions between these investigations. There were no significant differences in initial or maintenance therapies in this study between the progressive and non-progressive groups (Table 4).

A search of aphthous colitis patients without granuloma revealed 5 such patients had been treated at our hospital to date in these 26 years. In these 5 patients, 2 or more examinations

were performed with an interval of at least 2 years, and biopsies were taken to confirm the persistent absence of granuloma and all 5 patients did not progress to typical CD.

DISCUSSION

The incidence of type A CD among all CD differs depending on the institution in Japan, but reports from leading specialty institutions indicates that the proportion is about 5-10% of all CD [4,5,7]. No reports appear to have described this incidence in other countries. In the present study, the incidence of type A CD was about the same as in previous studies. However, no previous investigations have reported rates of patients diagnosed with type A CD over time, as in this study.

The male-female ratio of the 41 type A CD patients in this study included more males, and mean age at the time of diagnosis was 22.8±8.4 years. This did not differ greatly from the characteristics of typical CD as reported in a national survey in Japan by Asakura et al. [10]. In

blood test findings, Hb and Alb values were maintained fairly well, while CRP appeared mildly elevated. CDAI was low. Anal lesions were seen in 48.1%, this frequency of anal lesions was comparable to the rate of anal lesions in typical CD reported in Japan by Yano et al. [11]. Typical lesions appeared during the course in 59.3% of cases, and while the observation period and numbers of patients differed, this was about the same as incidences reported elsewhere (44-80%) [4,5,7].

The mean time until typical lesions appeared was 41 months, and 14 patients (88%) progressed to typical CD within 60 months. Only 2 cases progressed to typical CD after a course of more than 5 years and, from the present results at least, cases in which progression was not seen at 5 years after diagnosis were presumed to be unlikely to progress subsequently. Therefore, the time needed to judge whether type A CD will progress to typical CD is thought to be about 5 years from diagnosis. The course during this period needs to be observed using modalities such as radiography or endoscopic examinations.

Type A CD was found to progress to typical CD at a regular rate. In our hospital, 5 patients with aphthous colitis and no granuloma have been treated to date, and all 5 patients did not progress to typical CD. This suggests that type A CD is an early phase of CD. In addition, the validity of the ability to diagnose type A CD using the diagnostic criteria for CD in Japan is thought to have been demonstrated.

In the 16 patients with progressive disease, the final disease type was ileal CD in 8 patients (50%), ileo-colic CD in 4 patients (25%), and colonic CD in 4 patients (25%). These proportions were similar to the proportions of CD type in Japan reported by Yano et al. [11]. Moreover, intestinal lesions at the time of progression from type A CD were similar to the lesions seen in morphologically typical CD. Thus, typical CD that has progressed through type A CD is not considered special in terms of either type frequency or morphology compared with CD reported to date.

Cases with no progression were also seen among the type A CD cases that were followed.

This was seen in about 40% of cases, but the relatively high remission maintenance is consistent with the natural history of CD [12, 13]. Previous analyses of the natural history of CD have indicated the existence of a group with a good course in CD. Veloso et al. [12] analyzed the course of 480 patients observed for an average of 7.2 years, and reported a remission rate of 40% in every year except for the year of diagnosis. Beaugerie et al. [13] investigated 1,188 cases and reported that the rate of non-disabling disease was 19.4% in the study population. That not all cases of CD reached the stage of disabling disease in these studies is consistent with the finding of non-progressive cases among type A CD patients in the present study.

The severity of aphthous lesions was analyzed, and the severity of aphthous lesions in the small intestine was suggested to contribute to subsequent progression. This is similar to the form of early postoperative recurrence [14]. Rutgeerts et al. [15] reported a trend for poorer prognosis with the appearance of aphthae with greater severity in the postoperative neoterminal

ileum. Patients in the present investigation had initial type A CD rather than being postoperative patients, but, interestingly, both this study and that by Rutgeerts et al. [15] found that the severity of small intestine lesions contributed to later progress.

No consensus has been reached regarding whether type A CD should be treated, and if so, what kind of treatment should be used. There were no significant differences in initial or maintenance therapies in this study between the progressive and non-progressive groups. So we concluded that any treatments have not affected significantly the course of type A CD. In the future, more detailed investigations are needed to identify patients who do not require treatment and to establish appropriate treatment regiments.

The limitations of the present study include the retrospective cohort study design, the difficulty of diagnosing type A CD beyond institutions that can coordinate with an expert pathologist, the potentially inadequate number of patients and observation period, and the fact that detailed radiographic examinations are possible only at special institutions. In addition,

while all 27 type A CD patients who could be followed underwent small bowel radiography and large bowel endoscopy, and not all patients underwent small bowel endoscopy or barium enema. However, the present study was highly meaningful in that the incidence of type A CD over time was found to be almost constant, clinical characteristics and course were clarified, and comparison of progressive and non-progressive cases was undertaken.

ACKNOWLEDGMENTS

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FIGURE LEGENDS

Figure 1. Mild group aphthous lesions in small bowel radiography. Dense, small aphthae are seen in the ileum (a). Mild group aphthous lesions in large bowel endoscopy. Scattered, small aphthae are seen in the large intestine (b).

Figure 2. Severe group aphthous lesions in small bowel radiography. Dense, large aphthae are seen in the ileum (a). Severe group aphthous lesions in large bowel endoscopy. Dense, large aphthae are seen in the large intestine (b).

Figure 3. Frequency of each disease type at each term of CD. No marked changes in the frequency of each disease type are seen in the two terms. Numbers in the graph indicate the frequency (percentage) of each disease type at each term.

Figure 4. Cumulative progression rate of aphthous type CD (n=27) using the Kaplan-Meier method. Mean observation period: 84 ± 80 months.

Figure 5. In the first small bowel radiography, dense and large aphthae are present in the ileum (a). In follow-up small bowel radiography, longitudinal ulcers together with convergence of mucous folds are seen at the same site (b).

Figure 6. In the first large bowel endoscopy, dense and large aphthae are present in the sigmoid colon (a). In follow-up endoscopy, longitudinal ulcers are seen at the same site (b).

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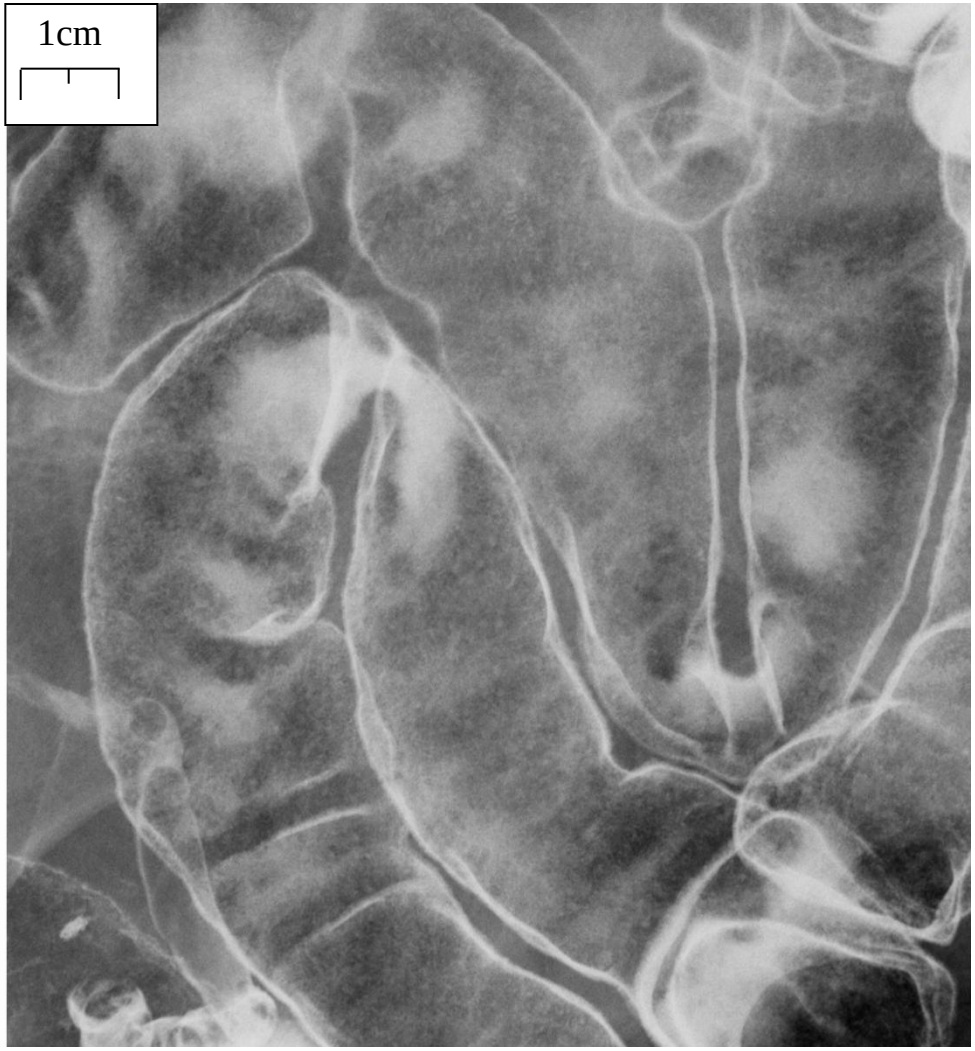
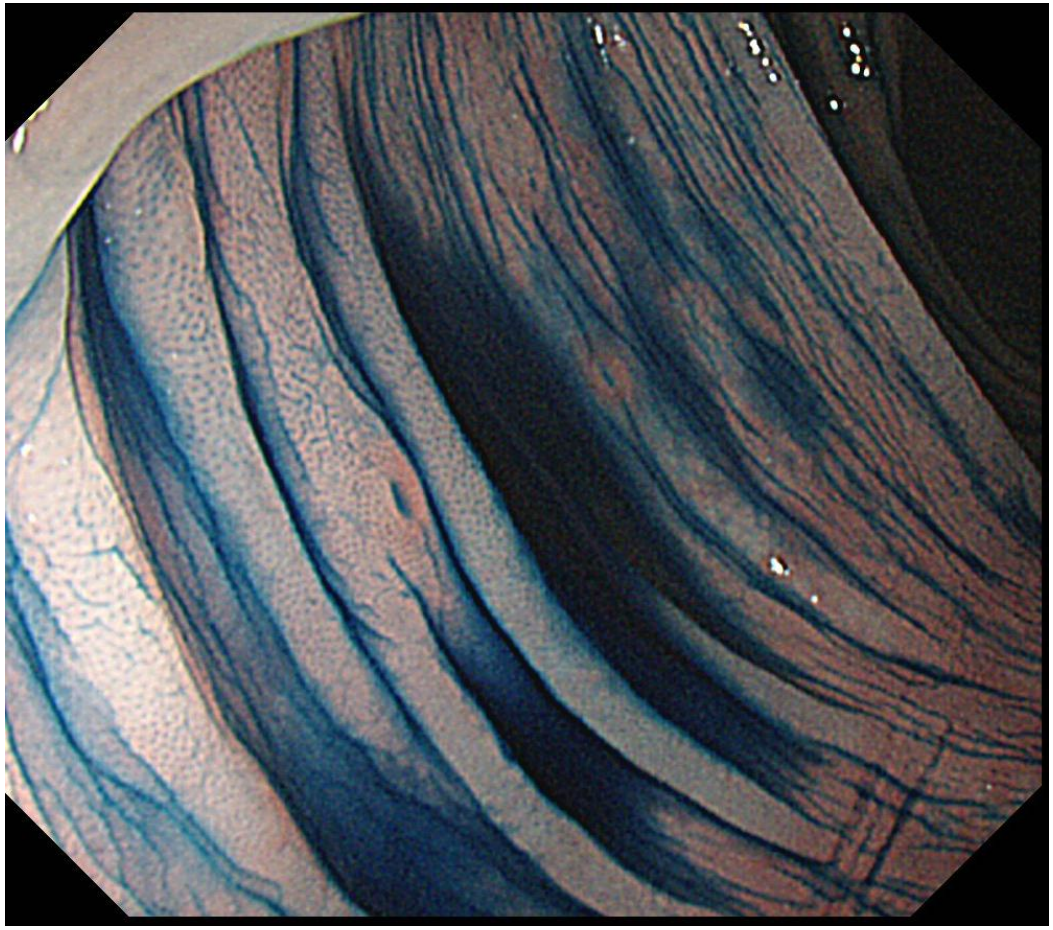


Fig. 1-a.



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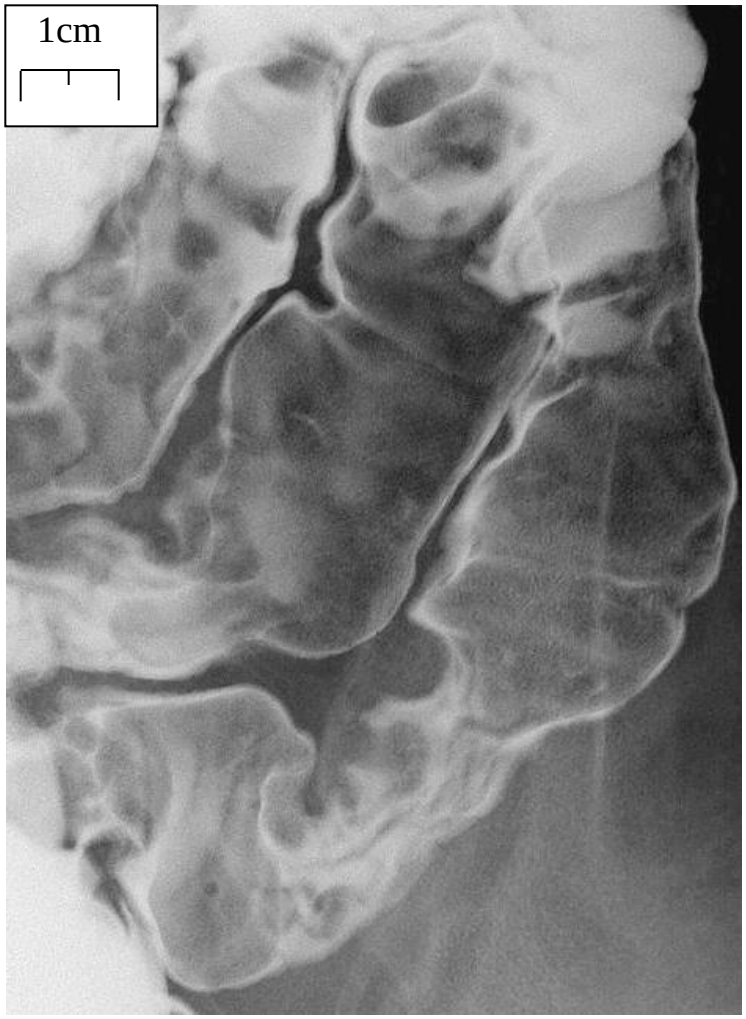

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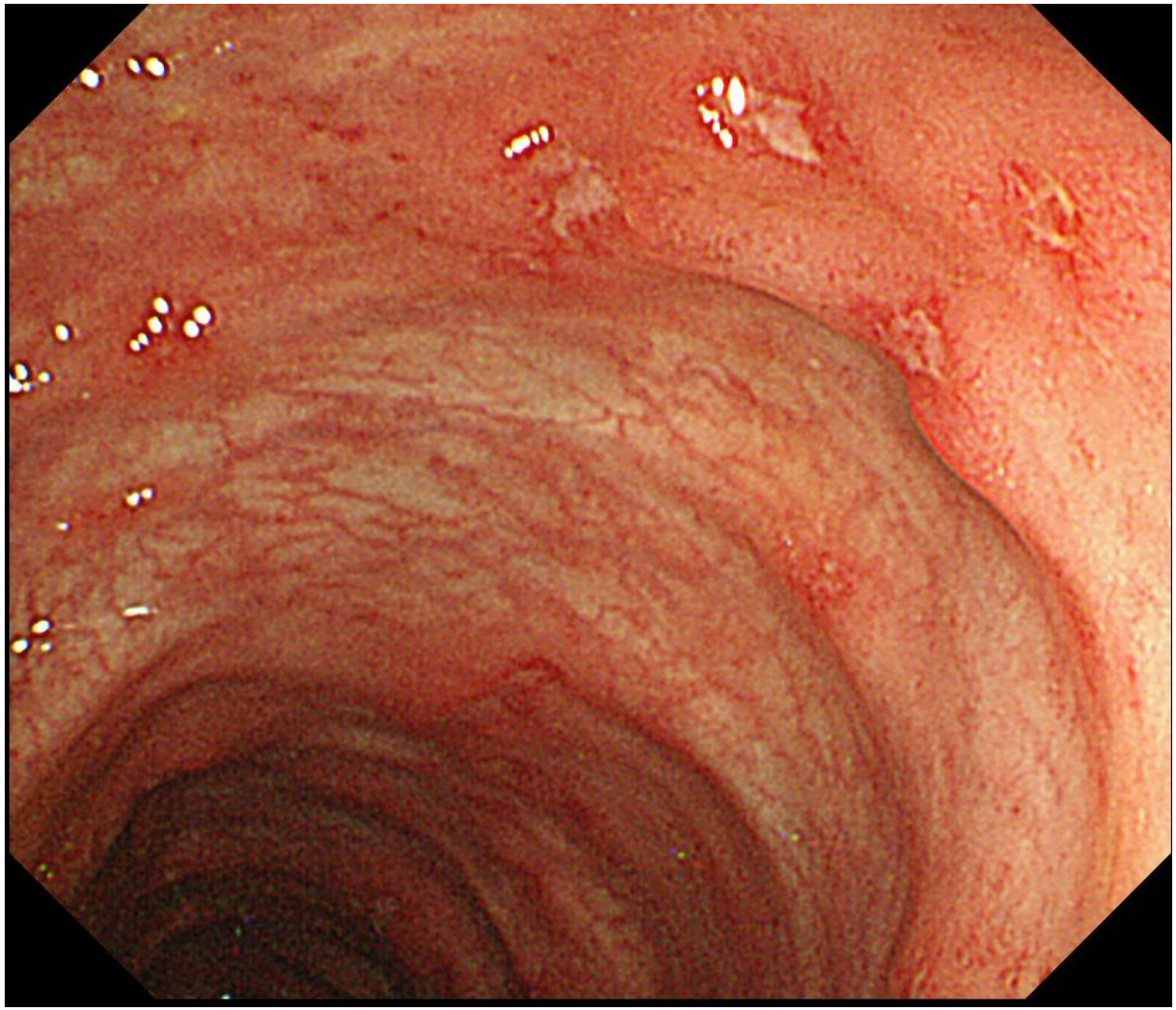

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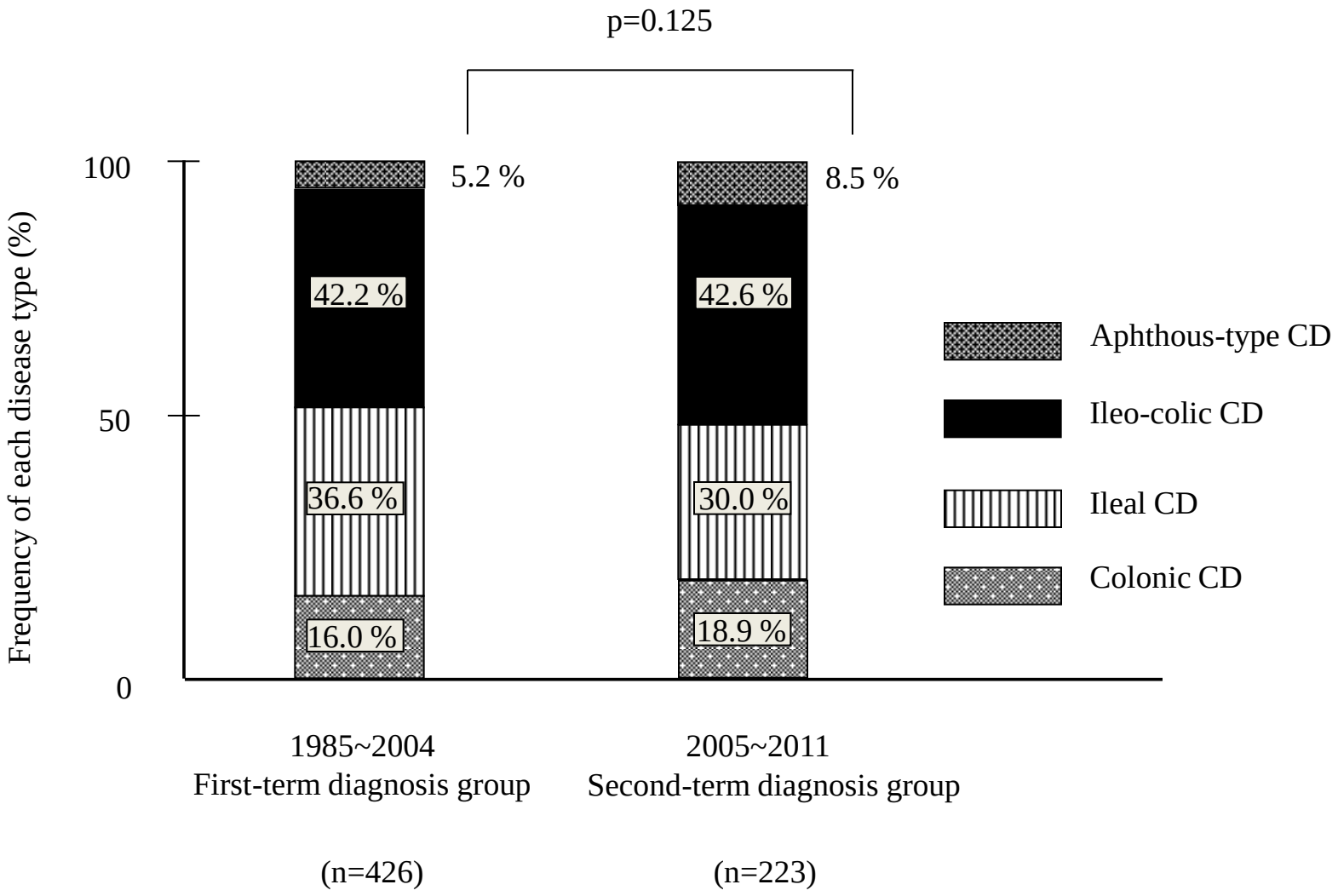
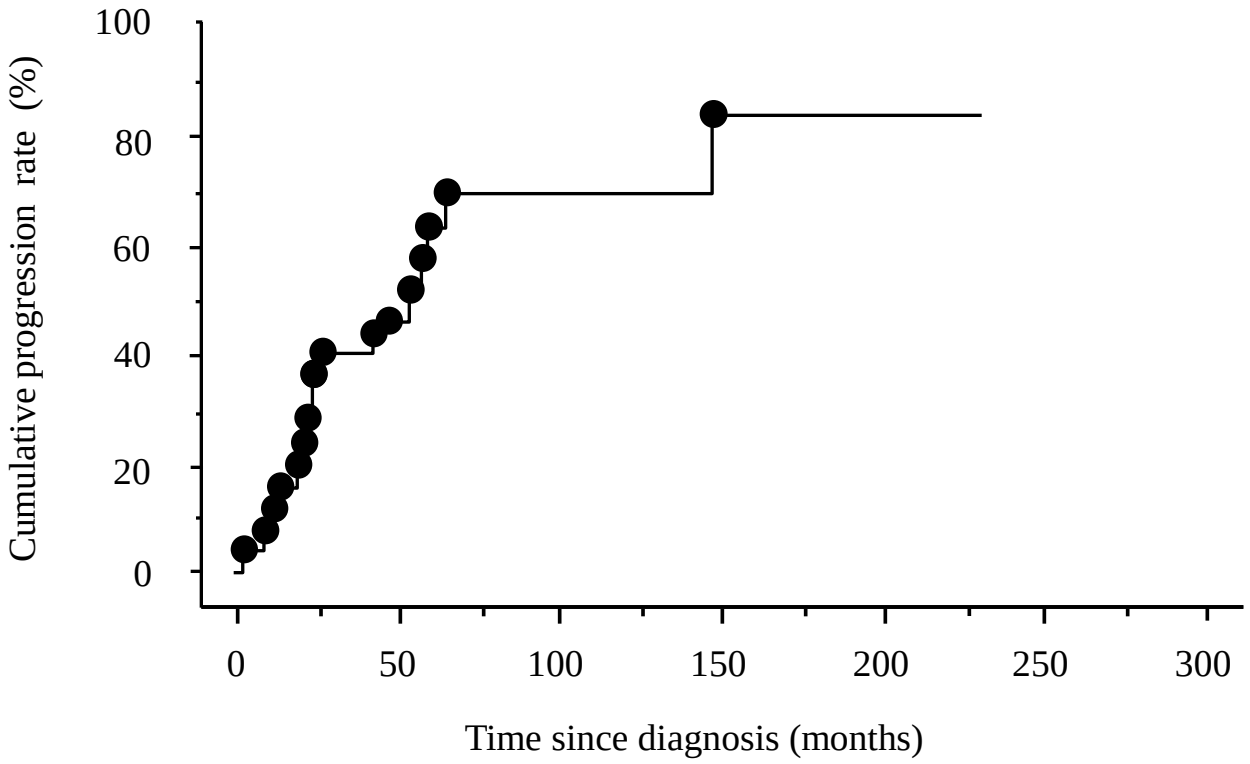

p=0.125
100
50
0
Frequency of each disease type (%)
5.2 %
8.5 %
42.2 %
42.6 %
36.6 %
30.0 %
16.0 %
18.9 %
Aphthous-type CD
Ileo-colic CD
Ileal CD
Colonic CD
1985~2004
First-term diagnosis group
2005~2011
Second-term diagnosis group
(n=426)
(n=223)

Fig. 3.


Cumulative progression rate (%)
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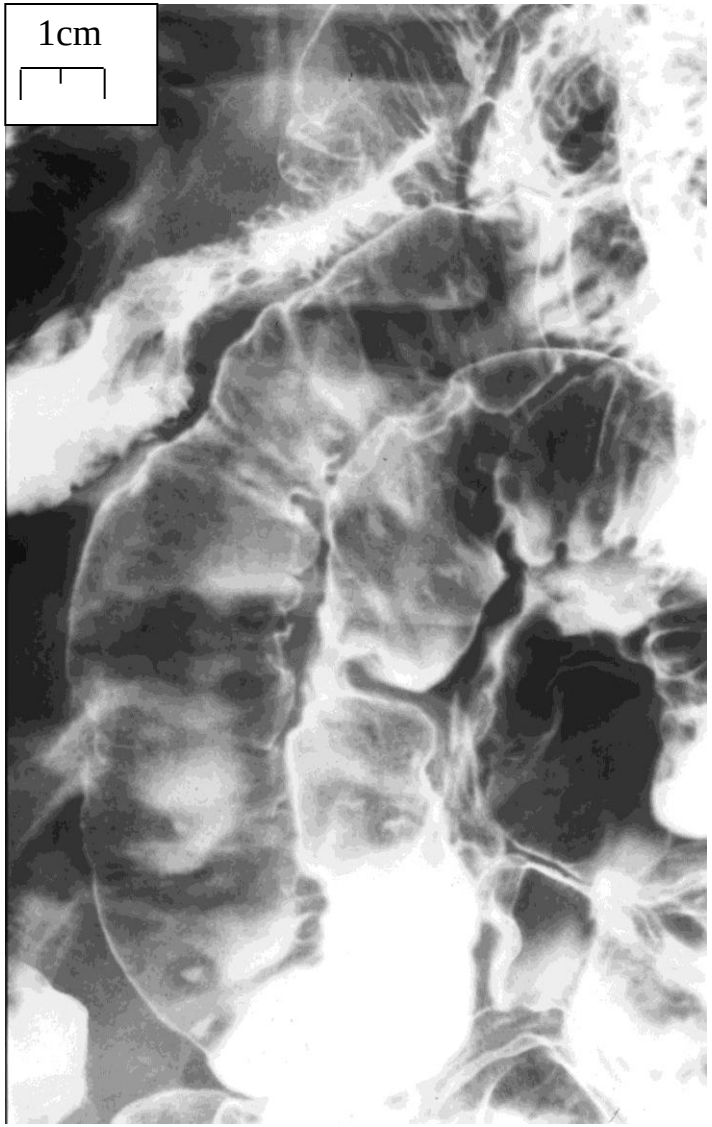
80
60
40
20
0
0
50
100
150
200
250
300
Time since diagnosis (months)

Fig. 4.



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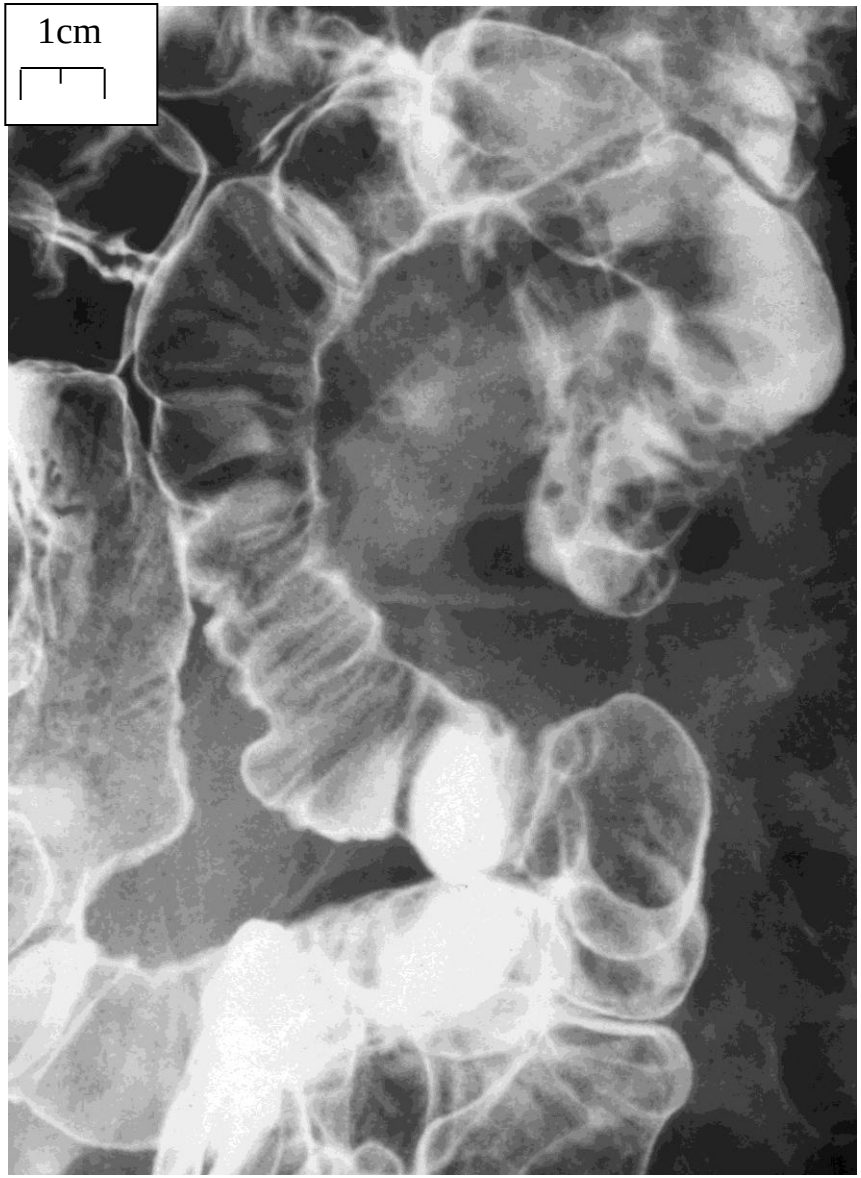

Fig. 5-b.

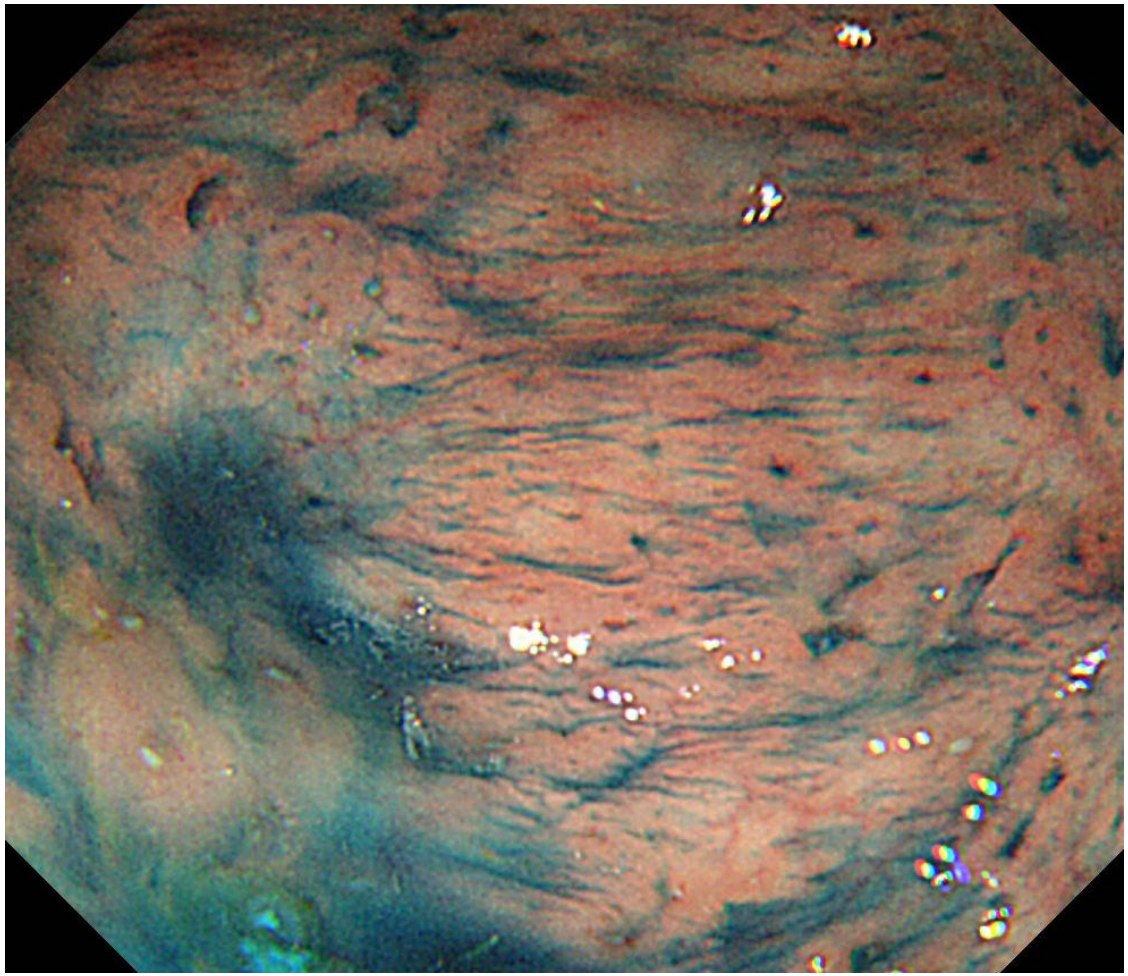

Fig. 6-a.

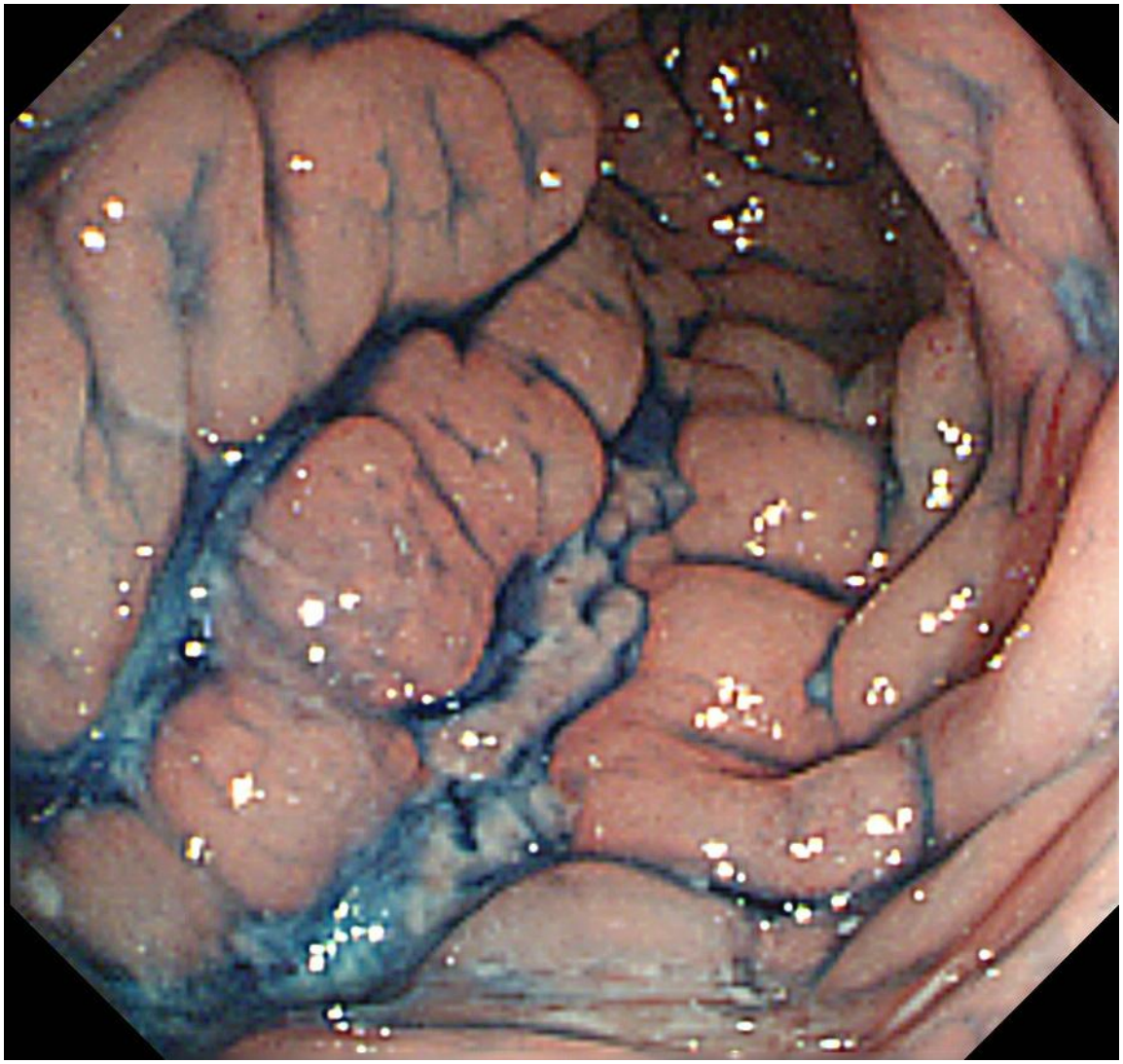

Fig. 6-b.

Table 1. Diagnostic criteria for Crohn's disease (1995)

1. Major findings

   A) Intestinal longitudinal ulcer
   B) Cobblestone appearance
   C) Noncaseating epithelioid cell granuloma

2. Secondary findings

   a) Multiple small aphthous ulcerations with longitudinal arrangement

   b) Multiple small aphthous ulcerations in both upper and lower digestive tract

3. Definite diagnosis:

   1) Presence of major finding A or B
   2) Presence of major finding C and one secondary finding

4. Suspected diagnosis:

   1) Presence of one secondary finding

   2) Presence of major finding C only

   3) Presence of major finding A or B without differential diagnosis from ischemic enterocolitis or ulcerative colitis

Table 2. Definitions for severity of aphthous lesions

	Scattered <6 lesions/3-cm segment	Dense ≥6 lesions/3-cm segment
Small <2 mm	mild	mild
Large ≥2 mm	mild	severe

Table 3. Comparison of initial findings in patients with type A CD who progressed and who did not progress

	Progressive group (n=16)	Nonprogressive group (n=11)	p
Male:female	13:3	8:3	0.66
Mean age at onset (years)	22.3±12.8	20.6±7.7	0.72
Mean age at diagnosis (years)	23.4±12.7	21.3±7.8	0.62
Test findings			
Hb, g/dL	13.2±1.5	13.1±1.6	0.97
Alb, g/dL	3.9±0.4	4.0±0.3	0.35
CRP, mg/dL	3.0±4.9	1.3±1.8	0.28
Activity			
CDAI	112.3±71.6	113.4±92.1	0.97
Aphthous lesions, severe /none or mild			
Small intestine	9/7	1/10	0.018
Large intestine	7/9	3/8	0.45
Perianal lesions	8/8	5/6	1

Table 4. Comparison of treatments before progression in patients with type A CD who progressed and who did not progress

	Progressive group (n=16)	Nonprogressive group (n=11)	p
Initial treatment			
Total Parenteral Nutrition	5/11	1/10	0.35
Elemental diet, ≥ 600 kcal/day	6/10	1/10	0.18
Prednisolone	3/13	2/9	1
Biologic	1/15	1/10	1
5-amino salicylid acid	4/12	6/5	0.22
Maintenance treatment			
Elemental diet, ≥ 600 kcal/day	4/12	4/7	0.68
Biologic	1/15	4/7	0.13
Immunomodulators	0/16	2/9	0.16
5-amino salicylid acid	7/9	6/5	0.70

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