Development, Disappearance, and Clinical Course of Melanosis Coli: Sex Differences in Progression of Severity

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Abstract

Background

Melanosis coli (MC) is an acquired colorectal disorder visualized as colonic mucosa pigmentation. Disease severity is confirmed based on MC depth, shape, and coloration, although the clinical course is not fully understood. This study sought to clarify characteristics of MC development and disappearance and to demonstrate its clinical course and severity. Contributors to progression of MC grade were also explored.

Methods

To investigate the patient and clinical features of developing and disappearing MC, this study reviewed colonoscopy cases at a single institution over a 10-year period. The clinical course of MC grade was evaluated to explore the predictive factors of progressive MC. Kaplan–Meier analysis was used to determine the probability of disease progression, and the log-rank test was used to calculate equality of the clinical course.

Results

Of all MC cases, 17 developing and 11 disappearing cases were detected. Anthranoid laxative use was a key factor: 29.4% of developing cases used this agent before initial diagnosis of MC, whereas 27.2% of disappearing cases discontinued anthranoids before detection of MC disappearance. Among 70 grade I cases, progression to grade II occurred in 16 cases during mean follow-up of 3.67 ± 2.1 years. Male sex was more frequent in progressive than stable cases, and probability of progression was higher for male versus female cases.

Conclusions

An association between anthranoid administration and MC presence was detected; a sex difference in the clinical course was confirmed; and mild MC was found to progress in severity over 5 years.

Background

Melanosis coli (MC) is a colorectal disorder that manifests as pigmentation on the colonic surface. The condition was first named by Virchow in 1857 [1]. Histologic findings of MC indicate that the coloration may be attributed to accumulation of lipofuscin [2], which is detected in other organs with aging and specific pathologic conditions, such as pathology of cardiomyocytes with aging [3], neurons with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [4], and retinal epithelial cells with Stargardt disease [5]. Macrophages containing apoptotic colonic epithelial cells

migrate and locate in the lamina propria, where they degrade to lipofuscin [6]. Accumulation of the yellow–brown pigment can be reversible. Lipofusucin on retinal cells was shown to be eliminated by treatment with omega-3 fatty acid [7]. However, the effects of this treatment on colonic mucosa and the mechanisms of lipofuscin metabolism in MC have not been clarified.

The cause of MC is thought to be excessive administration of laxatives, especially anthranoid-containing agents [8, 9]. Animal experiments [6, 10] and a few case reports and a case-control study supported this relation and indicated that MC is not a congenital condition [11]. However, due to the low prevalence of this disease, the clinical features of developing and disappearing MC have not been not elucidated. In addition, the clinical course of MC has rarely been studied. Only one study is available, which showed that most MC cases were stable over a 2-year period [12]. However, factors related to the clinical course of the MC degree or grade have not been investigated to date.

Several clinical studies have shown a relationship between MC and intestinal disease. The mutagenic potential of anthranoid laxatives has been reported in both in vitro and in vivo experiments [13, 14]. Although MC did not represent a higher incidence of colorectal cancer (CRC) compared with controls in human studies, clinical concern remains because MC is associated with a higher detection rate of colorectal adenoma [9, 15–17]. Most CRC follows the oncogenic pathway known as the *adenoma-carcinoma sequence*: after adenoma occurs, subsequent canceration occurs in the adenoma [18]. Thus, an increased incidence of adenoma in MC can lead to higher prevalence of CRC, and the long-term effect of MC on the intestine remains controversial. The association between MC severity and intestinal disorders in not fully understood. Research indicated that higher laxative doses result in a more severe grade of MC, defined by the number of apoptotic bodies in colonic mucosa [6]. Based on the finding that repeated anthranoid administration induced impaired intestinal peristalsis as the number of senna administrations increased [10], a tendency toward an increased severity of MC was noted in an animal model. Thus, clinically relevant involvement of the severity of MC in humans has also been implied. This study aimed to reveal features of developing and disappearing MC, to illustrate the clinical time course and severity of MC, and to detect patient and clinical factors associated with progression.

Methods

This retrospective cohort study was performed according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline [19]. The study enrolled patients undergoing colonoscopy between January 2011 and January 2021 in the endoscopy center at Kawasaki Medical School General Medical Center and Kawasaki Hospital, Okayama, Japan. The clinical course of MC cases was evaluated by consecutive findings obtained by follow-up of colorectal polyps and abdominal symptoms, as well as by examination at regular check-up. This clinical study was reviewed and approved by the Research Ethics Committee of Kawasaki Medical School and Hospital (IRB number 3056). Colonoscopy examinations were performed using CF-H260AI, CF-H260AZI, PCF-Q260 AZI, or CF-HQ291I (Olympus Medical Systems Corp., Tokyo, Japan). Each MC case was diagnosed by at least three experienced gastroenterologists (authors RK, NM, and MA) who are members of the Japan

Gastroenterological Endoscopy Society, and at least one board-certified trainer of the Japan Gastroenterological Endoscopy Society. The grades of MC were classified into three groups based on previous studies as grade I, II, or III [16, 17]. The preparation state of the colon was rated on a scale of 1 to 5 in accordance with a previous trial [20] as 1 (excellent), 2 (good), 3 (fair), 4 (poor), or 5 (inadequate). The MC cases with adequate preparation (1–3) and successful intubation to the cecum were defined as eligible for this study. These patient and clinical data were investigated by electronical medical records: sex, age, body mass index, social history, medications, indications for colonoscopy, and comorbidities. This survey includes two studies; an overview of the study flow is shown in Fig. 1.

Study 1: Analysis of developing and disappearing MC cases

Developing cases and disappearing cases of MC were confirmed when the patient was diagnosed as eligible for the study. Total colonoscopy findings without MC were demonstrated before the MC diagnosis in *developing cases* and after the MC diagnosis in *disappearing cases* (Fig. 2a, b). Endoscopic findings in each large intestine compartment—cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum—were confirmed in all eligible cases with and without MC. The minimal duration between MC diagnosis and MC disappearance was assessed. The patient and clinical characteristics of sex, age, body mass index, MC grade, and comorbidities were reviewed. Medications initiated before MC development in the developing cases or discontinued before MC disappearance in the disappearing cases were also explored in the medical records.

Study 2: Analysis of the clinical course of MC

Eligible patients with more than one diagnosis of MC were enrolled in Study 2. The clinical course of each patient was investigated for the MC grade. The case was defined as *stable* if the same grade was shown during the observation period, whereas *progression* described cases for which the MC grade deteriorated and *improvement* described cases for which the MC grade was reduced (Fig. 2c, d). The duration between first and last diagnosis of MC in the observation period was assessed. Clinical backgrounds at baseline were compared between stable and progression cases. The primary endpoint of this study was the rate of MC progression in terms of severity from grade I to grade II or grade III. Secondary endpoints were the characteristics of MC cases of progression compared with stable cases and the patient and clinical background of developing and disappearing MC cases.

Statistical analysis

Based on previous studies, the appropriate sample size for this study was determined to be at least 60 MC cases with data for the clinical course [12, 21]. The α and 1-β were set as 0.05 and 0.805, respectively. Continuous values including age and body mass index were described as the mean and standard deviation. Prevalence was described as the number and percentage. The unpaired *t* test (continuous data) and chi-square test (prevalence) were used to compare the stable and progression groups. Progression probabilities for the clinical course were estimated with Kaplan–Meier analysis. Equality of progressive functions between groups was evaluated by the log-rank test. The two-sided p value of $p <$

0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 27.0, IBM, Armonk, NY, USA).

Results

Study 1: Descriptive study for developing and disappearing MC

Among 9635 colonoscopy cases in this 10-year investigation, 17 developing cases and 11 disappearing cases of MC were detected. Endoscopic findings for developing and disappearing MC are shown in Fig. 2a, b. Demographic data, comorbidities, and medications for developing and disappearing cases are shown in Table 1 and Table 2, respectively. Sex analysis showed 58.8% of developing cases were male versus 18.1% of disappearing cases. Mean duration between last confirmation of MC absence and initial diagnosis of MC in developing cases was 24.8 months. Similarly, the mean duration between last diagnosis of MC and initial confirmation of MC absence in disappearing cases was 27.6 months. Of 17 participants, 5 (29.4%) were confirmed to have initiated an anthranoid laxative, and 4 (23.5%) started administration of mirabegron before development of MC. Of 11 participants, 3 (27.2%) discontinued anthranoids before disappearance of MC. Among disappearing cases, no participants discontinued mirabegron.

Table 1
Patient and clinical background and medication use for developing cases of melanosis coli

No.	Sex	Age	BMI	Grade	Duration (mo)	Initiated Medication	Comorbidities
1	F	80	22.8	I	33		Diabetes mellitus
2	M	80	22.9	I	12		
3	M	89	19.4	I	24	Mirabegron	Constipation
4	F	87	19.7	II	65	Anthranoids	Hemodialysis
5	F	36	21.6	I	52	Anthranoids	
6	F	50	25.7	I	21		
7	M	59	20.9	I	23		
8	M	65	36.	I	13	Mirabegron	Constipation
9	M	68	27.3	II	22	Anthranoids	Constipation
10	M	62	29.0	I	21	Anthranoids	Constipation, Parkinson disease
11	F	75	21.7	I	28		Constipation, diabetes mellitus
12	M	59	26.9	II	24		
13	M	38	33.6	I	12		
14	M	80	24.4	I	14	Anthranoids	Constipation
15	F	80	23.4	I	37	Mirabegron	Constipation, diabetes mellitus
16	F	75	20.9	II	10		Constipation
17	M	64	36.4	I	12	Mirabegron	Constipation

M: male, F: female, BMI: body mass index, duration: between last diagnosis of non-melanosis coli and diagnosis of melanosis coli.

Table 2
Patient and clinical background and medication use for disappearing cases of melanosis coli

No.	Sex	Age	BMI	Grade	Duration (mo)	Discontinued medication	Comorbidities
1	F	42	21.6	I	22	Anthranoids	
2	F	53	23.2	I	11		
3	M	74	28.1	I	9		Diabetes mellitus
4	F	77	23.4	II	29		Constipation, diabetes mellitus
5	M	82	15.5	I	35		
6	F	47	20.3	I	40		
7	F	86	20.0	I	56		Constipation, depression
8	F	67	18.9	II	42	Anthranoids	Constipation
9	F	80	25.2	I	13		
10	F	72	26.0	I	28		Constipation
11	F	87	14.2	I	19	Anthranoids	

M: male, F: female, BMI: body mass index, duration: between last diagnosis of melanosis coli and diagnosis of non-melanosis coli.

Study 2: Retrospective Cohort for Clinical Course of MC Grade

Of 216 eligible MC cases, 87 were enrolled for analysis of the clinical course. The mean follow-up was 44.1 ± 25.7 months. Endoscopic findings for the progression and improvement cases are shown in Fig. 2c, d. The stable cases were 12 grade II cases and 2 grade III cases during the observation period. For the improvement cases, 2 patients improved from grade II to grade I and 1 patient improved from grade III to grade I.

A total of 70 grade I cases were analyzed for the clinical course of MC. The severity of 16 grade I cases deteriorated to grade II during a period of 60 months (Fig. 3). No progression cases were found after 60 months from initial observation. As shown in Table 3, comparison of characteristics at baseline between stable and progressive cases revealed a higher ratio of male patients in the progression group (62.5% vs. 31.4%; $p = 0.04$). Comparative analysis of clinical course based on sex demonstrated significantly higher progression probability in male patients with MC (Fig. 4).

Table 3
Comparison between stable and progression cases of grade I melanosis coli

	Stable (n = 54)	Progression (n = 16)	*p*
Age, mean (SD)	69.6 (11.2)	69.2 (12.4)	0.90*
Sex, male (%)	17 (31.4)	10 (62.5)	0.04**
Body mass index, mean (SD)	22.7 (4.1)	23.7 (5.2)	0.25*
Smoking: Current smoker (%)†	3 (5.7)	3 (20.0)	0.12**
Alcohol: Regular drinker (%)‡	7 (13.7)	4 (25.0)	0.24**
Diabetes mellitus (%)	18 (33.3)	2 (12.5)	0.13**
Regular anthranoid use (%)	28 (51.8)	7 (43.7)	0.77**
Indication (%)			0.70**
Screening	14 (25.9)	1 (6.25)	
Positive fecal occult blood test	10 (18.5)	3 (18.75)	
Past colonic surgery	1 (1.8)	1 (6.25)	
Past EMR	8 (14.8)	3 (18.75)	
History of polyps	6 (11.1)	3 (18.75)	
Bleeding	4 (7.4)	1 (6.25)	
Anemia	2 (3.7)	0 (0)	
Constipation	1 (1.8)	0 (0)	
Other abdominal symptoms	6 (11.1)	2 (12.5)	
Surveillance	2 (3.7)	2 (12.5)	
Distribution of melanosis coli (%)			0.71**

*Unpaired *t* test was used to calculate the p value.

** Chi-square test was used to calculate the p value.

†Information on smoking was obtained for 53 stable cases (98%) and 15 progression cases (94%).

‡Information on alcohol consumption was obtained for 51 stable cases (94%) and 16 progression cases (100%).

	Stable (n = 54)	Progression (n = 16)	*p*
Right side	10 (18.5)	2 (12.5)	
Left side	1 (1.8)	0 (0)	
Whole colon	43 (79.6)	14 (87.5)	
*Unpaired *t* test was used to calculate the p value.			
** Chi-square test was used to calculate the p value.			
†Information on smoking was obtained for 53 stable cases (98%) and 15 progression cases (94%).			
‡Information on alcohol consumption was obtained for 51 stable cases (94%) and 16 progression cases (100%).			

Discussion

This retrospective cohort study is the first report of the long-term clinical course of MC. Over 5 years, 25% of grade I MC cases progressed, and no cases deteriorated in grade after 5-year follow-up. Male sex was confirmed as a predictive factor for progressive MC, and a sex difference in the clinical course was shown. Further, both developing and disappearing cases of MC were detected, which allowed elucidation of their clinical characteristics. These data suggest a minimum time for the development and disappearance of MC, as well as a relevant connection between anthranoid and mirabegron use and the pathogenesis of MC.

To the authors' best knowledge, only one clinical case report on the development of MC has been published [11]. In an animal experiment, MC developed several days after administration of anthranoids and disappeared soon after drug discontinuation [6]. Willems et al. documented a patient with MC development at 10-month follow-up after colonoscopy [11]. In the current analysis, the mean duration from the last diagnosis without MC to the time of initial diagnosis of MC was 24 months. Although detection of an accurate minimum time to MC development is challenging because of the lack of frequent follow-up, approximately 2 years seems sufficient for a non-MC colon to develop MC. In contrast, cases of MC disappearance were reported to be detected at 1-, 3,- and 10-year follow-up [11, 22, 23]. The present data show 27 months from the last diagnosis of MC to the initial diagnosis of MC absence, which also indicates that at least 2 years is sufficient period for MC to disappear.

As previously known, the sequence of initiation and discontinuation of anthranoids is associated with the development and disappearance of MC, respectively. This relationship was previously documented in several case reports and animal experiments [6]. A case showing MC development and subsequent disappearance in a single patient by initiating and discontinuing anthranoids indicated the strong connection of anthranoids to generation of MC [11]. However, MC cases without anthranoid administration have also been reported [8, 9]. Similarly, MC disappearance with anthranoid continuation

has been reported [23]. In fact, the current study revealed a number of MC development and disappearance cases without anthranoid administration and discontinuation, respectively. These findings suggest that various factors, including other agents than anthranoids, can be associated with pathogenesis of MC.

Of interest, this study revealed that several developing cases initiated mirabegron between the last confirmation of a nonpathologic state and the diagnosis of MC. Mirabegron is a selective β3-adrenergic receptor agonist used for patients with overactive bladder [24]. The relationship between MC and mirabegron has not been previously reported. Regarding constipation as adverse effect of mirabegron, which may be also associated with anthranoid use, one study reported that mirabegron users experienced constipation as frequently as placebo patients [25]. Other possible adverse effects seem unrelated to pathogenesis of MC. Additionally, the chemical structure of mirabegron and anthranoids does not share common features [26, 27]. The association between mirabegron and development of MC must be further investigated from wide range of viewpoints.

Only one study to date was available with regard to the clinical course of MC. Gökçe et al reported that only 15.4% of MC patients showed non-MC mucosa after 2-year follow-up observation, despite the fact that most patients discontinued use of laxatives and herbal preparations [12]. The current analysis also confirmed that most patients had stable disease, with 22.8% of grade I MC cases deteriorating in grade and very few cases of grade improvement. The low prevalence of improvement may be in part attributed to the possibility that MC can entirely disappear, rather than only alleviating its grade. In fact, severe-grade MC was reported to convert to non-MC mucosa without gradual improvement of its degree [22]. In the current survey as well, 2 cases demonstrated alteration from severe MC to normal mucosa. Interestingly, the clinical course of MC in humans was proven to differ from that in an animal model, which showed a high rate of immediate development and disappearance after anthranoid initiation and discontinuation, respectively [6]. The authors of the current study hypothesize that this divergence may be ascribed to several factors in humans, such as drugs other than anthranoids, lipofuscin metabolism, and immune status related to macrophage activity. Interventional prospective studies and close inspection of the molecular basis of MC are required to prove these hypotheses.

Of note, a sex difference in the clinical course of MC was first detected in this study, with a greater tendency to progression in male patients. Moreover, the study revealed a higher prevalence of male sex in developing cases and female sex in disappearing cases. Pigment metabolism may explain the sex disparity. Cytochrome P450 is thought to play crucial role in MC pathogenesis, which is proven to be located on colonic mucosa [28] and is associated with accumulation of lipofuscin. The decrease of cytochrome P450 also causes microsomal oxidative damage [29], which results in lipofuscin formation [30]. Actually, expression of the cytochrome P450-related gene was downregulated in MC [31]. The metabolism of lipofuscin pigment influenced by cytochrome P450 can vary between male and female individuals, which results in the different clinical course of MC according to sex. In fact, it was reported that clearance of nifedipine and verapamil, which are metabolized by cytochrome P450 as well, was

higher in female than male individuals [32, 33]. Although underlying mechanisms remain unclear, the sex difference in the clinical course of MC should be a consideration in management of patients with MC.

This study has several limitations. First, the retrospective cohort design may lead to information bias and inadequate data quality. Despite careful medical record review, it was not possible to perfectly reflect the medical history because anthranoid use may not have been documented. Some over-the-counter drugs and supplements can contain anthranoids, and these agents are not always reported in the drug history on medical interviews [34]. Although information accuracy regarding comorbidities, social habits, and medication use was influenced by reporting bias, measures were taken to elevate the quality of crucial information such as MC diagnosis by excluding cases with insufficient intubation and preparation for colonoscopy. In addition, the follow-up periods and frequencies were not unified among MC cases. However, because of the low prevalence of MC and no previous reports in this field, the retrospective cohort design was thought to be plausible as the initial step to investigate the clinical course of MC.

Second, with regard to selection bias, data were extracted from a limited region in Japan. However, these data suggest findings that are similar to those of other studies including MC cases [35]; therefore, the results of this survey may not be largely biased. Third, the findings regarding sex difference in the clinical course of MC were confirmed with inadequate statistical power because of small number of cases. Because the sex difference was not primary endpoint of this cohort, the power of the test was not appropriate. However, the results were statistically significant and highly suggestive to enhance an understanding of MC pathogenesis. Based on these results, validation of the relationship between sex and MC status in larger prospective studies is required.

In conclusion, this analysis of the development and disappearance of MC indicated that anthranoid use is related to the incidence of MC. Moreover, other unknown factors, such as agents other than anthranoid, can contribute to pathogenesis of MC. Of the mild MC cases (grade I), 25% experienced progression to a severe state in 5 years. Male patients showed a more detrimental clinical course than female patients in terms of severity. These results provide not only useful guideposts for clinical criteria but also valuable insight into pathogenesis of MC.

List Of Abbreviations

MC, Melanosis coli; CRC, colorectal cancer; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Declarations

Ethics approval and consent to participate: This study was reviewed and approved by the Research Ethics Committee of Kawasaki Medical School and Hospital (IRB No. 3056). The requirement of informed consent was waived because of the retrospective study design.

Consent for publication: The requirement of informed consent was waived because of the retrospective study design.

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Authors' contributions:

Conceptualization: Noriaki Manabe and Ken Haruma; Data curation: Ryo Katsumata, Noriaki Manabe, and Maki Ayaki; Formal analysis: Ryo Katsumata and Noriaki Manabe; Investigation: Ryo Katsumata, Noriaki Manabe, and Ken Haruma; Methodology: Ryo Katsumata, Noriaki Manabe, Minoru Fujita, Maki Ayaki, and Ken Haruma; Project administration: Noriaki Manabe; Resources: Ryo Katsumata, Noriaki Manabe, Minoru Fujita, Maki Ayaki, Mitsuhiko Suehiro, Tomoari Kamada, Yasumasa Monobe, Hirofumi Kawamoto, and Ken Haruma; Software: Ryo Katsumata, Noriaki Manabe, and Hirofumi Kawamoto; Supervision: Noriaki Manabe; Validation: Noriaki Manabe; Visualization: Ryo Katsumata and Noriaki Manabe; Writing – original draft: Ryo Katsumata; Writing – review & editing: Noriaki Manabe; Approval of the final manuscript: all authors.

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Figures

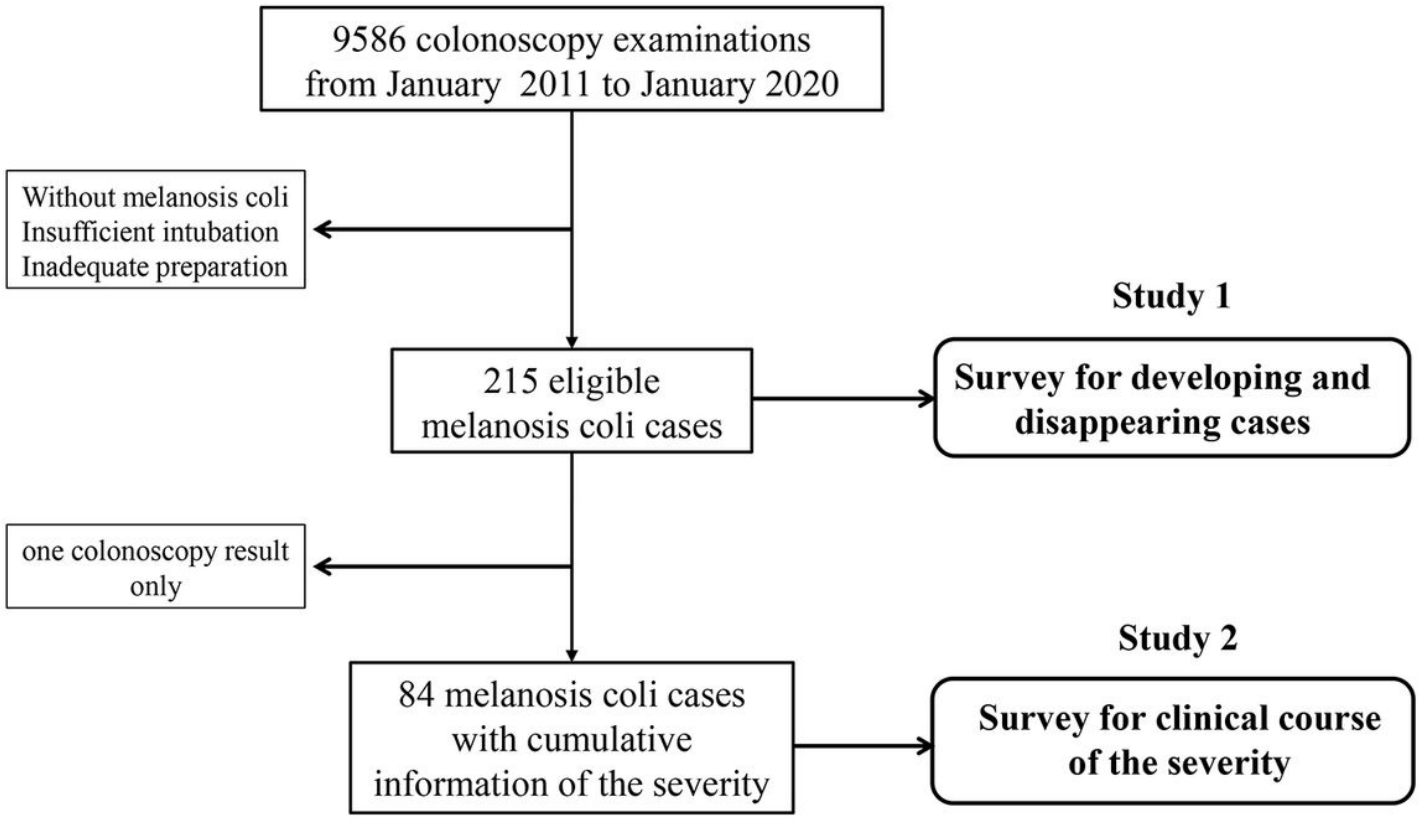

Figure 1

Overview of Study 1: a survey of cases for the development and disappearance of melanosis coli, and Study 2: a survey of cases for the clinical course and disease severity.

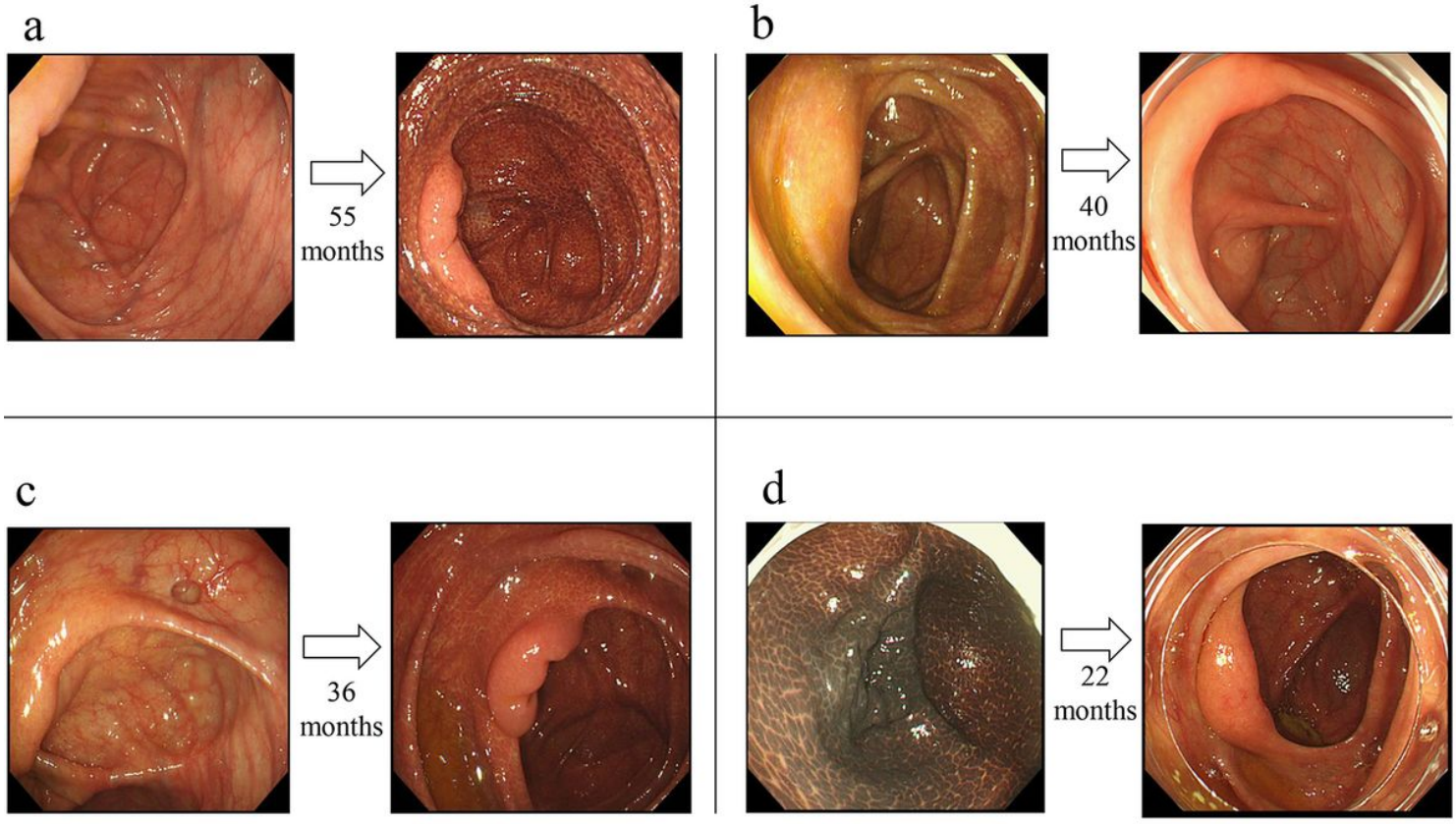

Figure 2

Development (a) and disappearance (b) of melanosis coli, and progression (c) and improvement (d) of grade of melanosis coli on colonoscopy.

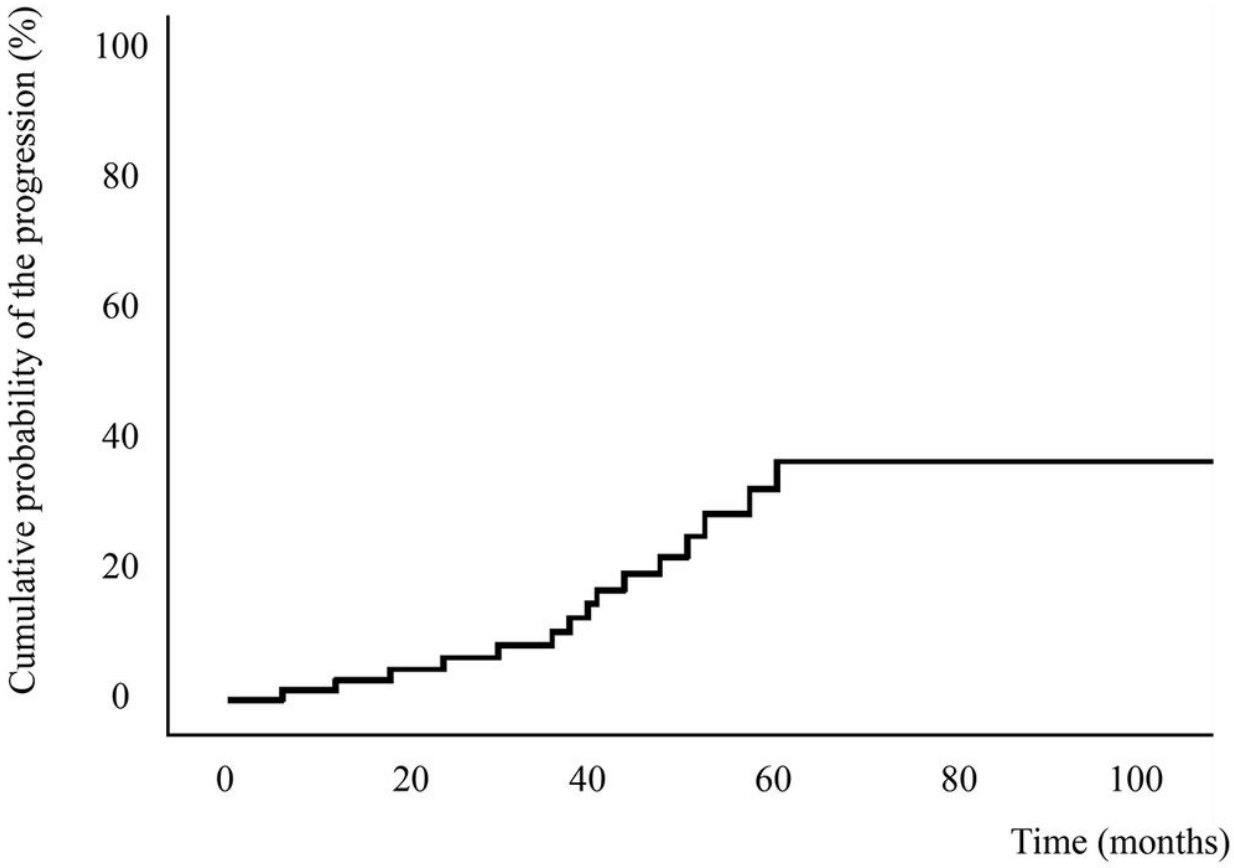

Figure 3

Cumulative probability of the grade progression of severity among cases of grade I melanosis coli.

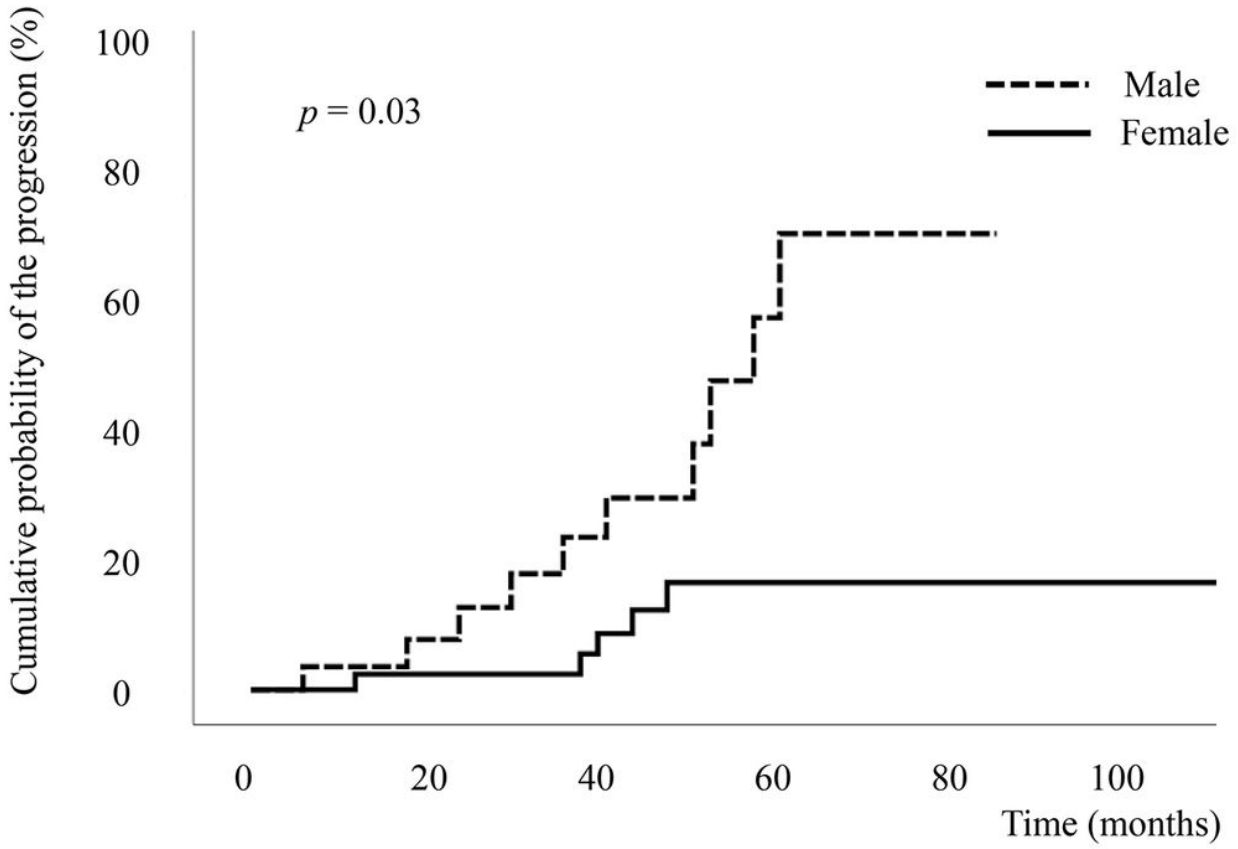

Figure 4

Sex difference in the cumulative probability of the grade progression of severity among cases of grade I melanosis coli.