

Severe grade of melanosis coli is associated with a higher detection rate of colorectal adenoma

Ryo Katsumata,¹ Noriaki Manabe,^{2,*} Yasumasa Monobe,³ Tomohiro Tanikawa,¹ Maki Ayaki,² Mitsuhiro Suehiro,¹ Minoru Fujita,² Tomoari Kamada,⁴ Ken Haruma,¹ and Hirofumi Kawamoto¹

¹Department of General Internal Medicine 2, ²Division of Endoscopy and Ultrasonography, ³Department of Pathology, and ⁴Department of Health Care Medicine, Kawasaki Medical School General Medical Center, 2-6-1 Nakasange, Kita-ku, Okayama 700-8505, Japan

(Received 13 February, 2022; Accepted 11 May, 2022; Released online in J-STAGE as advance publication 10 August, 2022)

The severity and distribution of melanosis coli differ among individuals, and the related factors remain unknown. Additionally, their clinical implications have not been sufficiently demonstrated. Thus, we aimed to detect clinical factors related to the severity and range of melanosis coli and elucidate the associations between the grade, location, and detection rate of colorectal neoplasms. Colonoscopy cases performed at our institution from January 2011 to February 2021 were included. Melanosis coli was classified into mild and severe grades. Clinical characteristics and neoplasm detection rates were compared between the mild and severe MC groups and between the right-sided and whole-colon melanosis coli groups. Overall, 236 MC (mild, $n = 143$; severe, $n = 93$) cases, of which 50 were right-sided, 5 were left-sided, and 181 were whole-colon melanosis coli cases, were enrolled. The proportion of anthranoid users was higher in the severe melanosis coli group than in the mild melanosis coli group. The adenoma detection rate was higher in the severe melanosis coli and whole-colon melanosis coli groups. The prevalence of neoplasms measuring 5–9 mm and >9 mm was higher in the severe melanosis coli group ($p < 0.01$ and $p = 0.04$). Severe melanosis coli due to anthranoid usage is associated with colorectal adenoma development.

Key Words: adenoma, anthraquinone, colorectal neoplasm, colonoscopy, laxative

Melanosis coli (MC) is characterized by a superficial discoloration of the colonic mucosa, which is attributed to the aggregation of lipofuscin in macrophages.^(1,2) MC is classified into three grades according to pigmentation pattern and color density.⁽³⁾ MC is largely detected on the entire colonic surface; however, several variations in the location of MC have also been reported, and factors related to the severity and location of the MC remain unknown.

Anthranoid laxatives are regarded as crucial triggers and retaining agents of MC. Animal experiments and a clinical survey indicated that the administration of anthranoids contributed to the development of MC.^(1,4,5) However, anthranoids were not administered in approximately half of the MC cases.^(5,6) Byers *et al.*⁽⁷⁾ suggested that apoptosis of colonic epithelial cells is essential, and anthranoids administration is not a risk factor for MC. The influence of administering anthranoids on the severity and distribution of MC is yet to be elucidated.

Several studies have demonstrated a relationship between MC and intestinal disorders. For example, in a worldwide meta-analysis study, colorectal adenoma and hyperplastic polyps were detected more frequently in patients with MC than in controls;⁽⁵⁾

in contrast, the risk of developing adenocarcinoma was similar in both or lower in patients with MC.⁽⁸⁾ The mechanism underlying the elevated risk of adenoma has been debated, and one crucial explanation is the “enhanced effect,” which implies that the contrast between the pigmented background and uncolored polyp improves visibility. Although the severity and expansion of MC appear to play an important role according to this theory, the effect of the severity and location of MC on the detection rate of colorectal neoplasms has not been adequately investigated.

Most colorectal cancers follow a pathological course known as the “adenoma-carcinoma sequence,” representing the consecutive progression from a small adenoma to a large adenocarcinoma following cancer initiation.⁽⁹⁾ The risk of malignant transformations of colorectal polyps has been reported to increase with an increase in their size.^(10,11) Therefore, the size of colorectal neoplasms has recently drawn attention. A study revealed that smaller lesions are observed more frequently in patients with MC than in controls, while the detection rate of larger lesions is similar between patients with MC and controls;⁽²⁾ however, the relationship between the size of colorectal polyps and the severity or distribution of MC has not been elucidated yet. Therefore, this study aimed to identify the factors associated with the severity or location of MC and elucidate the relationship between the severity and location as well as the detection rate of colorectal neoplasms.

Materials and Methods

Ethics. The Research Ethics Committee of Kawasaki Medical School and Hospital reviewed and approved this study (IRB no. 3056).

Patients. This retrospective study included patients who underwent colonoscopy between January 2011 and February 2021 in the endoscopy center at Kawasaki Medical School General Medical Center and Kawasaki Hospital in Okayama, Japan. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.⁽¹²⁾ The clinical backgrounds and comorbidities, such as age, sex, smoking, alcohol consumption, anthranoid use, aspirin use, diabetes mellitus, inflammatory bowel disease, Parkinson’s disease, and hypothyroidism, related to colorectal neoplasms or MC were investigated using electronic medical records.

*To whom correspondence should be addressed.
E-mail: n_manabe@med.kawasaki-m.ac.jp

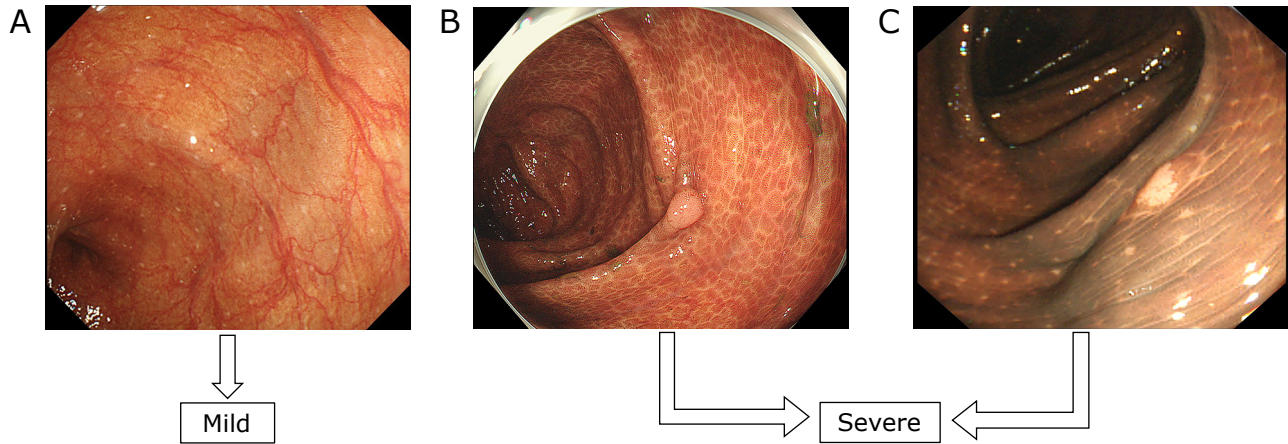


Fig. 1. Endoscopic findings of different grades and severities of melanosis coli. A: grade I (mild), B: grade II (severe), and C: grade III (severe).

Colonoscopy settings and evaluation. Colonoscopy was performed in all patients using CF-H260AI, CF-H260AZI, PCF-Q260AZI, or CF-HQ291I colonoscopes (Olympus Medical Systems Corp., Tokyo, Japan). The indications for colonoscopy in each case were reviewed. The severity of MC was defined using the previously reported classification of MC as follows: grade I, light-brown intestinal mucosa without an apparent boundary with normal mucosa; grade II, brown intestinal mucosa with a clear linear or non-continuous boundary with normal mucosa; and grade III, dark black intestinal mucosa with a linear or spotted boundary with normal mucosa.^(3,13) Based on this classification, MC was further categorized into two grades as follows: grade I as mild MC and grade II and III as severe MC (Fig. 1). The distribution of MC was classified into three categories as follows: right-sided (involving the cecum, ascending colon, and proximal transverse colon), left-sided (involving the distal transverse colon, descending colon, sigmoid colon, and rectum), and whole-colon MC. The quality of colon preparation was rated on a scale of 1 to 5 according to a previous study as follows: 1, excellent; 2, good; 3, fair; 4, poor; and 5, inadequate.⁽¹⁴⁾ The intubation rate was assessed based on the endoscopic findings as it was reported to be related to the adenoma detection rate.⁽¹⁵⁾ Cases were considered positive when at least one polyp lesion was diagnosed. The histological diagnosis of hyperplastic and inflammatory polyps and adenomas was confirmed using the Japan Narrow Band Imaging Expert Team (JNET) classification.⁽¹⁶⁾ The maximum polyp size in each patient was assessed based on endoscopic findings. The diagnosis of MC and colorectal neoplasms, as well as the severity and location of MC, were confirmed by at least three experienced members of the Japan Gastroenterological Endoscopy Society (JGES), including at least one board-certified JGES trainer. Adenocarcinoma was diagnosed by a pathologist based on the histological findings. We excluded cases wherein the preparation for colonoscopy was inadequate and/or clear images of each section of the large intestine (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum) were not obtained.

Endpoints. The primary endpoint was the detection rate of adenomas among patients with MC. In contrast, the secondary endpoints included the detection rate of hyperplastic/inflammatory polyps, incidence of adenocarcinoma, size of colorectal neoplasms, and prevalence of anthranoid use.

Statistical analyses. The sample size was set to be at least 203 MC cases at a significance level of 0.05 and a power of 0.803.⁽¹⁷⁾ Continuous variables are expressed as mean and SD, and categorical variables are presented as frequencies and percentages. Continuous and categorical variables were compared

between two groups (mild vs severe MC and right-sided vs whole-colon MC) using the unpaired *t* test and chi-square test, respectively. Two-sided *p* values of <0.05 were considered statistically significant. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for associations among grade, location, and detection rate of colorectal neoplasms. Statistical Package for the Social Sciences software for Macintosh (ver. 27.0; IBM Corp, Armonk, NY) was used for all statistical analyses.

Results

Demographics. In total, 236 patients with MC from 9,702 colonoscopy cases, including 143 grade I, 74 grade II, and 19 grade III cases, were enrolled. Overall, there were 50 right-sided, 5 left-sided, and 181 whole-colon MC cases. In addition, two cases of MC in the right colon and rectum were included in the whole-colon MC group. Since the incidence of inflammatory bowel disease (*n* = 1), Parkinson's disease (*n* = 2), and hypothyroidism (*n* = 4) was low and patients with Parkinson's disease and hypothyroidism have a higher potential of using anthranoid laxative because of secondary constipation, they were excluded from the analysis.

Comparison between mild and severe MC. The characteristics of each group are presented in Table 1. The prevalence of anthranoid use was higher in the severe MC group than in the mild MC group (60.2% vs 45.4%, *p* = 0.03), and the incidence of diabetes mellitus was higher in the mild MC group than in the severe MC group (27.9% vs 15.0%, *p* = 0.03). In the multivariate logistic regression analysis, after adjusting for sex, smoking status, drinking status, and diabetes mellitus, the OR of severe MC among anthranoid users (OR = 2.01; 95% CI, 1.07–3.74; *p* = 0.03) was higher than that among non-users. No significant differences were observed in the indications for colonoscopy, intubation rate, and preparation status between the two groups (Table 2). When the analysis was conducted based on the types of polyps, the adenoma detection rate was significantly higher in the severe MC group than in the mild MC group (67.7% vs 48.9%, *p* < 0.01). Similarly, severe MC showed a higher detection rate than mild MC for lesion sizes of 5–9 mm (27.9% vs 13.2%, *p* < 0.01) and ≥10 mm (24.7% vs 13.9%, *p* = 0.04) (Fig. 2).

Comparison between right-sided and whole-colon MC. Table 3 shows the clinical features of each group. No significant difference was observed between the groups. The indications, intubation rate, and preparation status were similar in both groups (Table 4). Regarding colorectal polyps, the adenoma detection rate was higher in the whole-colon MC group

Table 1. Comparison of demographic data and clinical backgrounds between mild and severe melanosis coli

Variables	Mild melanosis coli (n = 143)	Severe melanosis coli (n = 93)	p value
Age, mean (SD)	69.6 (13.3)	72.1 (11.8)	0.13 ^a
Sex, male (%)	53 (37.1)	37 (39.7)	0.68 ^b
BMI, mean (SD)	22.2 (4.3)	22.5 (4.1)	0.61 ^a
Smoking: current smokers, n (%)	11 (8.7)	10 (12.8)	0.35 ^b
Alcohol: regular drinker, n (%)	25 (19.2)	25 (31.2)	0.07 ^b
Diabetes mellitus, n (%)	40 (27.9)	14 (15.0)	0.03 ^b
Regular aspirin use, n (%)	7 (4.8)	2 (2.1)	0.49 ^b
Regular anthranoid use, n (%)	65 (45.4)	56 (60.2)	0.03 ^b

BMI, body mass index; n, number of cases. ^aUnpaired t test was performed. ^bChi-square test was performed.

Table 2. Comparison of colonoscopy settings among patients with mild and severe melanosis coli

Variables	Mild melanosis coli (n = 143)	Severe melanosis coli (n = 93)	p value
Indication, n (%)			0.48
Screening	38 (26.5)	18 (19.4)	
Positive fecal occult blood test	36 (25.1)	16 (17.2)	
Past colonic surgery	6 (4.1)	6 (6.5)	
Past EMR	12 (8.3)	10 (10.8)	
History of polyps	11 (7.6)	10 (10.8)	
Bleeding	8 (5.5)	6 (6.5)	
Anemia	3 (2.1)	2 (2.1)	
Constipation	5 (8.4)	8 (8.6)	
Other abdominal symptoms*	13 (9.1)	6 (6.4)	
Surveillance	10 (6.9)	11 (11.8)	
Others [#]	1 (0.6)	0 (0)	
Preparation, cases (%)			0.77
Excellent	122 (85.3)	80 (86.0)	
Good	9 (6.3)	5 (5.3)	
Fair	11 (7.7)	6 (6.5)	
Poor	1 (0.7)	2 (2.1)	
Intubation rate, n (%)	135 (94.4)	88 (94.6)	0.87

EMR, endoscopic mucosal resection; n, number of cases. Chi-square test was performed to calculate p values. *Other abdominal symptoms included abdominal pain, diarrhea, and distention nausea. [#]Others included follow-up for inflammatory bowel disease and volvulus.

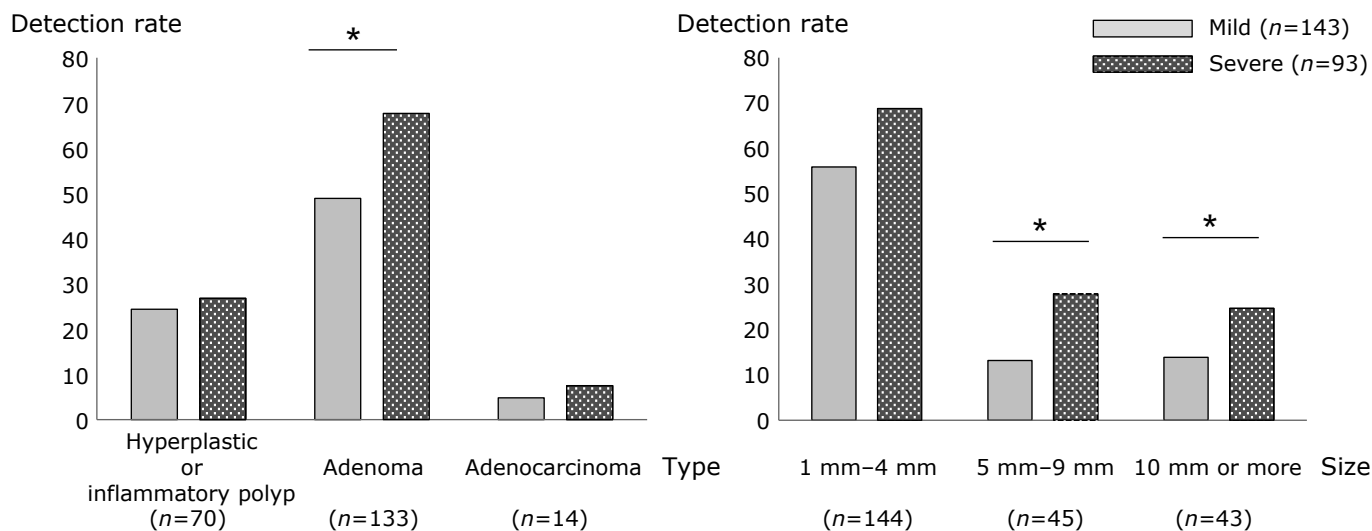
**Fig. 2.** Comparison of patients with mild and severe melanosis coli regarding the histological type and size of polyp lesions. *p<0.05.

Table 3. Comparison of demographic data and clinical backgrounds among patients with right-sided and whole-colon melanosis coli

Variables	Right-sided melanosis coli (n = 50)	Whole-colon melanosis coli (n = 181)	p value
Age, mean (SD)	68.4 (13.6)	71.1 (12.5)	0.27 ^a
Sex, male (%)	15 (30.0)	72 (39.7)	0.24 ^b
BMI, mean (SD)	23.1 (3.9)	22.0 (4.2)	0.11 ^a
Smoking: current smokers, n (%)	4 (10.5)	16 (9.8)	0.90 ^b
Alcohol: regular drinker, n (%)	12 (27.9)	38 (23.4)	0.55 ^b
Diabetes mellitus, n (%)	8 (16.0)	43 (23.7)	0.33 ^b
Regular aspirin use, n (%)	0 (0)	9 (4.9)	0.21 ^b
Regular anthranoid use, n (%)	21 (42)	98 (55.2)	0.15 ^b

BMI, body mass index. ^aUnpaired *t* test was performed. ^bChi-square test was performed.

Table 4. Comparison of colonoscopy settings among patients with right-sided and whole-colon melanosis coli

Variables	Right-sided melanosis coli (n = 50)	Whole-colon melanosis coli (n = 181)	p value
Indication, n (%)			0.47
Screening	13 (26)	41 (22.6)	
Positive fecal occult blood test	11 (22)	40 (22.1)	
Past colonic surgery	4 (8)	9 (4.9)	
Past EMR	3 (6)	18 (9.9)	
History of polyps	3 (6)	18 (9.9)	
Bleeding	1 (2)	12 (6.6)	
Anemia	2 (4)	3 (1.7)	
Constipation	4 (8)	9 (4.9)	
Other abdominal symptoms*	7 (14)	12 (6.6)	
Surveillance	2 (4)	18 (9.9)	
Others [#]	0 (0)	1 (0.6)	
Preparation, n (%)			0.31
Excellent	40 (85.6)	158 (87.2)	
Good	4 (6.1)	9 (4.9)	
Fair	6 (6.9)	11 (6.1)	
Poor	0 (1.3)	3 (1.6)	
Intubation rate, n (%)	48 (93.9)	168 (92.8)	0.21

EMR, endoscopic mucosal resection. Chi-square test was performed to calculate *p* values. *Other abdominal symptoms included abdominal pain, diarrhea, and distention/nausea. [#]Others included follow-up for inflammatory bowel disease and volvulus.

compared to the right-sided MC group (60.2% vs 42.0%, *p* = 0.02). Further, no difference was observed in the detection rate according to the lesion size (Fig. 3).

Risk factors of adenoma. In the multivariate logistic regression analysis, after adjusting for sex, smoking status, drinking status, diabetes mellitus, anthranoid use, indication rate, preparation quality, and MC distribution, the OR of adenoma detection in the severe MC group (OR = 2.38; 95% CI, 1.13–5.01; *p* = 0.02) was higher than that of the mild MC group. Conversely, after adjusting for sex, smoking status, alcohol consumption, diabetes mellitus, anthranoid use, indication rate, preparation quality, and MC severity, a higher risk of adenoma detection was not significantly observed in the whole-colon MC group (OR = 2.15; 95% CI, 0.92–5.01; *p* = 0.07) compared to the right-sided MC group.

Discussion

To the best of our knowledge, this is the first study demonstrating the relevance of severe-grade MC in detecting adenomas

and large colorectal neoplasms. Moreover, pancolonial MC was proven to be associated with a higher adenoma detection rate. To date, only two clinical studies have reported the degree- and distribution-based prevalence of MC. Similar to previous reports in China,^(3,13) our study revealed that the incidence of mild-grade and bilateral MC was higher than that of severe and one-sided MC among the study population. Similarly, we observed different detection rates of colorectal neoplasms of specific sizes according to the grade and distribution of MC.

The proportion of anthranoid users was higher in the severe MC group than in the mild MC group, consistent with the results of previous animal and human studies. In animal studies, anthranoid use induced melanosis in guinea pigs, and the number of pigmented macrophages in the colonic mucosa increased in a dose-dependent manner.⁽¹⁾ In clinical studies conducted in Germany, the prevalence of anthranoid laxative use was higher in patients with high-grade microscopic MC than in those with low-grade MC.⁽⁶⁾ Hence, the severity of MC may be related to the dose of anthranoids administered. Diabetes mellitus was also confirmed as relevant comorbidity, and its prevalence was

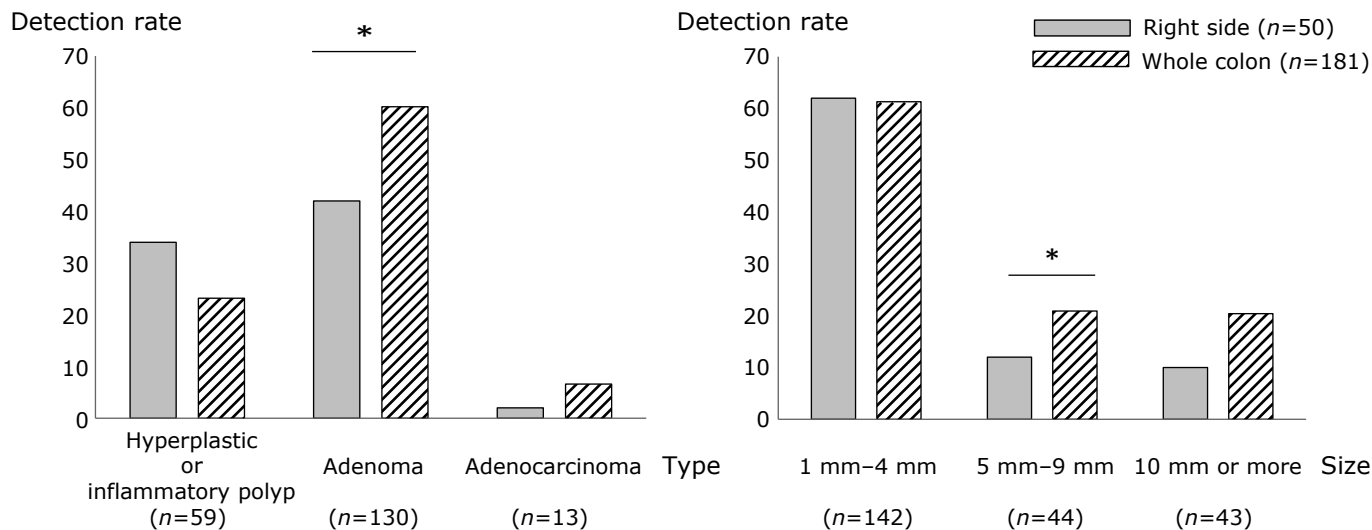


Fig. 3. Comparison of patients with right-sided and whole-colon melanosis coli regarding the histological type and size of polyp lesions. * $p < 0.05$.

different among patients with various grades of MC. Intriguingly, our data indicated a lower prevalence of diabetes mellitus, known to be associated with chronic constipation,^(18,19) which is strongly related to the pathogenesis of MC. However, insufficient diagnosis due to our study protocol might have affected the results, and further research with accurate clinical information is necessary.

Although the degree of MC was reported to be an insignificant factor for the detection rate of colorectal neoplasms in a previous study,⁽¹³⁾ our results suggested a higher adenoma detection rate and larger size of colorectal polyps in patients with severe-grade MC. As previously indicated, the contrast between colored mucosa and non-pigmented lesions facilitates polyp detection by endoscopy.⁽²⁰⁾ A darker mucosa in cases of MC leads to a more apparent contrast with the unpigmented polyps. A previous study reported an increased tumor detection rate using a new technique with improved visibility using a light-emitting diode (LED) light source.⁽²¹⁾ The color contrast and better visibility led to a higher detection rate of severe MC in our study.

Notably, we reported a higher detection rate of severe MC with a size >9 mm. As the detection rate of large polyps appears unrelated to the enhancement effect, other factors may have contributed to this result. Apart from the enhancement effect, the potential proliferation status may differ according to the MC grade. In a previous study, the expression of sonic-Hedgehog-related pathway proteins, which are associated with carcinogenesis, was observed to be enhanced in the mucosa of patients with MC.⁽²²⁾ The difference in the proliferation potential based on the severity of MC is yet to be confirmed. Therefore, histological and molecular studies should be performed in the future to elucidate this hypothesis.

Our analysis revealed that a broader distribution of MC was associated with a higher adenoma detection rate. A previous report demonstrated no relationship between the distribution of MC and adenoma detection rate.^(3,15) However, our result is plausible based on the enhancement effect, as the effect can reach the colonic mucosa more widely in the whole-colon MC. In addition, in a previous study, colorectal adenomas were detected in the entire colon,⁽²³⁾ further supporting our results.

Interestingly, the adenoma detection rate was higher in patients with severe and pancolonic MC, whereas that of hyperplastic polyps was not influenced by the degree or distribution of MC. However, both polyps were more frequently detected in patients with MC than in the controls.⁽⁵⁾ In addition to the inadequate

sample size, there are possible factors responsible for the study results. Regarding optimal enhancement, non-adenomatous polyps, such as inflammatory polyps, are pigmented, whereas adenomas are not pigmented on the mucosa of patients with MC.⁽³⁾ Owing to this difference, adenomas can show more significant contrast on the mucosa of patients with severe MC than that of those with non-adenomatous polyps, which can lead to their higher adenoma detection rate in patients with severe MC. In addition, different shapes of the polyps can contribute to their varying detection rates. The average height of adenomas is higher than that of hyperplastic polyps,⁽²⁴⁾ which leads to a more conspicuous appearance of adenomas on a colored background, resulting in a higher detection rate in patients with severe and broad MC. In addition to the appearance, molecular characteristics differ between hyperplastic polyps and adenomas.^(25,26) This disparity might also be associated with our results, and further investigations should be conducted to elucidate the detailed mechanisms.

This study has some limitations. First, this study was conducted retrospectively; thus, information bias could be present. Information regarding the administration of drugs and supplemental agents and comorbidities was obtained only from electronic medical records. Therefore, the prevalence of anthranoid use and diabetes mellitus could be inaccurate. Moreover, smoking and alcohol consumption status could not be assessed; however, owing to the rarity of MC, this retrospective study is insightful. Therefore, our results should be validated in future prospective studies. Second, we did not investigate the histological findings of MC and other polyps. To improve the quality of diagnosis, we confirmed the diagnosis of MC and histological types of colorectal lesions from experienced gastroendoscopists, including qualified examiners, who used the JNET classification that has been proven to accurately reflect pathological diagnosis.⁽²⁷⁾ When the diagnosis was inconsistent among investigators, we discussed the case with other board-certified trainers and concluded a diagnosis based on the consensus of more than three-quarters of the members. When a consensus was not obtained, we excluded those particular cases. Therefore, at least in clinical settings, our data are sufficiently robust. Third, several confounding factors were associated with the detection rate of colorectal neoplasms. We reviewed major potential variables related to the detection rate, such as risk factors for tumorous lesions (body mass index, smoking status, drinking status, and regular aspirin use).⁽²⁸⁻³³⁾ Additionally, the endoscopic setting was associated with the

detection rate of neoplasms. For instance, suppression of peristalsis by L-Menthol reportedly indicates a higher adenoma detection rate.^(34,35) We showed that endoscopic settings, such as intubation rate and preparation quality, were similar between the study groups.⁽¹⁵⁾ Furthermore, we performed a multivariate analysis to compensate for the influence of confounders.

In conclusion, a higher prevalence of anthranoid use was detected in patients with severe-grade MC, which was associated with a higher detection rate of colorectal neoplasms, including adenoma. In addition, severe MC was associated with a higher detection rate of colorectal adenomas. Accordingly, these clinically useful findings clarify the underlying mechanisms of MC.

Author Contributions

Conceptualization: NM and KH; Data curation: RK, NM, and

MA; Formal analysis: RK and NM; Investigations: RK, NM, and KH; Methodology: RK, NM, MA, and KH; Project administration: NM; Resources: RK, NM, YM, TT, MA, MS, MF, TK, KH, and HK; Software: RK, NM, and HK; Supervision: NM; Validation: NM; Visualization: RK and NM; Writing – original draft: RK; Writing – review and editing: NM; Approval of the final manuscript: all authors.

Acknowledgments

We would like to express our gratitude to the patient and to Editage (www.editage.com) for English language editing.

Conflict of Interest

No potential conflicts of interest were disclosed.

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