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Original Article

Clinical Significance of Depressed-Type Colorectal Neoplasms Based on Growth and Development

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A route of colorectal cancer development other than the adenoma-carcinoma sequence has recently become an issue due to the discovery of depressed-type early colorectal cancers. Moreover, the fact that some polyp-like cancers actually originate from depressed-type lesions has become obvious. Despite the protruding shapes of depressed-type early colorectal cancers, they probably have biological characteristics, which are different from those of the usual polyp lesions. We undertook this study to evaluate the clinical significance of depressed-type colorectal neoplasms. The authors recently experienced 87 cases of depressed-type colorectal neoplasms. Using Kudo's classification, we classified these 87 cases into three types based on their growth patterns, type IIc, type IIa + IIc, and type Is + IIc, and then analyzed these types on the basis of size, type, and submucosal invasion rate. The submucosal invasion rate of cancers of type IIa + IIc was significantly higher than that of type IIc ($p < 0.05$), and the rate for cancers of types IIa + IIc and Is + IIc together was significantly higher than that of type IIc ($p < 0.05$). However, no significant difference was found between the rates of types IIa + IIc and Is + IIc. In conclusion, the IIa + IIc and Is + IIc sub-types of depressed-type colorectal neoplasms, individually and together, have higher rates of submucosal invasion than type IIc lesions. Accordingly, type IIa + IIc and type Is + IIc must be differentiated from the usual polyps and should be managed cautiously, despite their protruding shapes.

Key Words: Depressed-type colorectal neoplasm, early colorectal cancer, de novo carcinoma, submucosally invasive cancer, growth and development.

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INTRODUCTION

Two theories are widely accepted to explain the growth and development of colorectal cancers, namely, the adenoma-carcinoma sequence theory and the de novo carcinoma theory, though which of these is the main route of colorectal cancer development remains the subject of controversy. Muto et al.[1] claimed that most colorectal cancers evolve through a polyp-cancer sequence, although most adenomatous polyps do not become cancers. They stated that the malignancy potential is related to size, villous component, and the grade of the epithelial atypia. However, they could not explain the discrepancy between the frequency of colorectal adenomas and colorectal carcinomas. In this regard, Spratt and Ackerman[2] had already suggested an alternative pathway in the early 1960s. They explained that lymph-node metastasis in colorectal cancers is not related to the size of the tumor and that metastasis occurred even from tumors which were not visible to the naked eye. They also suggested that we would fail to detect many types of curable cancers if we only tried to find intraluminal polypoid tumors.

One recent intriguing factor was the detection of depressed-type early colorectal cancers. Although this type of early cancer is still rarely detected, numbers are increasing. Moreover, it has become clear that some polyp-like cancers actually originate from depressed-type lesions. Despite the protruding shapes of these depressed-type lesions, they deserve careful attention because their biological behaviors probably differ from those of the usual polyp lesion. Accordingly, we designed this study to evaluate

the clinical significance of depressed-type early colorectal neoplasms.

MATERIALS AND METHODS

We experienced 87 cases of depressed-type colorectal neoplasms recently at Song Do Colorectal Hospital in Korea: 67 adenomas, 4 intramucosal cancers, and 16 submucosally invasive cancers. The submucosally invasive cancers included 10 well-differentiated and 6 moderately differentiated adenocarcinomas. According to Kudo's classification,[3] those 87 cases were classified into three types based on their growth patterns: type IIc, the depressed area was lower or nearly the same as the adjacent normal mucosa, though it might have shown a slight marginal elevation (Fig. 1); type IIa + IIc, the depressed area was slightly more elevated than the adjacent normal mucosa and the general shape was that of a flat-elevated-type lesion (Fig. 2); and type Is + IIc, the depressed area protruded and the general appearance was of a sessile-type lesion (Fig. 3). According to this classification, these were 56 type IIc neoplasms, 17 type IIa + IIc, and 14 type Is + IIc.

Those 87 cases were analyzed on a clinicopathological basis with an emphasis on size, type, and submucosal invasion rate. Statistical significance was determined according to the chi-square test and Fisher's exact test, and $p < 0.05$ was considered to be statistically significant.

RESULTS

The overall submucosal invasion rate was 18.4%. The rate of type IIc was 10.7%, and the rates of type IIa + IIc and type Is + IIc were 35.3% and 28.6%, respectively. The submucosal invasion rate for type IIa + IIc was significantly higher than that for type IIc (35.3% vs. 10.7%, $p < 0.05$), and the rate for types IIa + IIc and Is + IIc together was significantly higher than that for type IIc (32.3% vs. 10.7%, $p < 0.05$). There was no significant difference between the rates of type IIa + IIc and type Is + IIc (35.3% vs. 28.6%). None of the submucosal cancers were larger than 20 mm in diameter. The average size of type IIc neoplasms was 6 mm, and the sizes of type IIa + IIc and type Is + IIc neoplasms were 9 mm and 7 mm, respectively (Table 1).

DISCUSSION

The adenoma-carcinoma sequence is undoubtedly a reality, but the actual incidence of transformation of an adenoma to a carcinoma is not high. Moreover, it takes a long time for an adenoma to develop into a focal carcinoma and finally into an invasive carcinoma.[1] Then where do the large number of colorectal cancers come from? This has been an open question for a long time. A long time ago, some authors suggested a route of colorectal cancer development other than the adenoma-carcinoma sequence even though they had not identified its specific

Table 1. Submucosally Invasive Cancer Rate Based on Type and Size in Depressed-Type Colorectal Neoplasms

Type	Size (mm)			sm rate (%)
	≤ 10	11 - 20	Total	
IIc	50 (1)	6 (5)	56 (6)	10.7
IIa + IIc	10 (2)	7 (4)	17 (6)	35.3‡
Is + IIc	12 (2)	2 (2)	14 (4)	28.6‡
Total	72 (5)	15 (11)	87 (16)	18.4

*, †, 32.3

sm, submucosally invasive cancer; ( ), number of submucosally invasive cancers;
*Fisher's exact test $p < 0.05$; †chi-square test $p < 0.05$; ‡not significant.

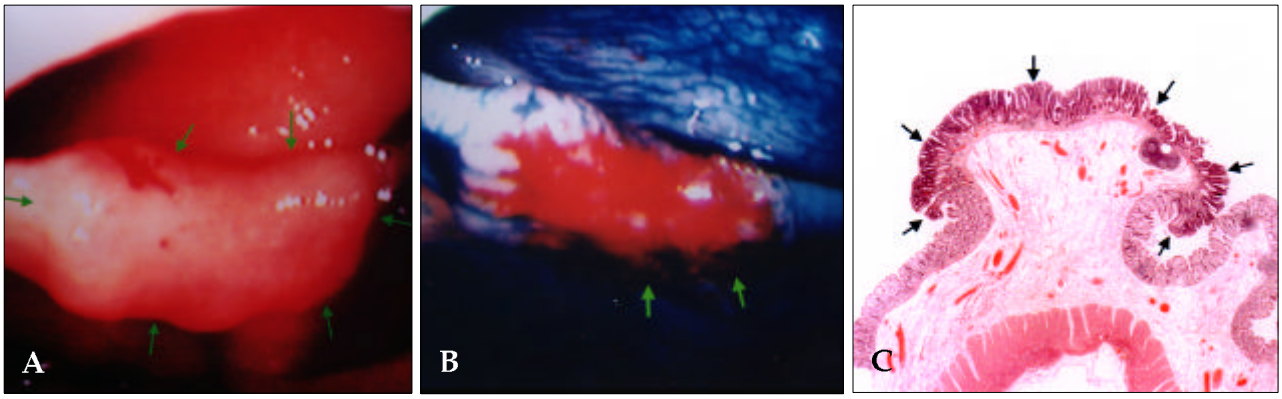

Fig. 1. (A) A 17-mm type IIc depressed early cancer in the transverse colon of a 52-year-old female patient (arrows). (B) A chromoscopic picture. A depressed area is clearly delineated, and arrows mark the lower margin of the lesion. The depressed lesion bled easily, even when sprayed with indigo carmine, and the entire depressed area was almost completely covered with blood. (C) A cut section of a resected specimen shows a well-differentiated adenocarcinoma confined to the mucosal layer (arrows) (H&E, ×

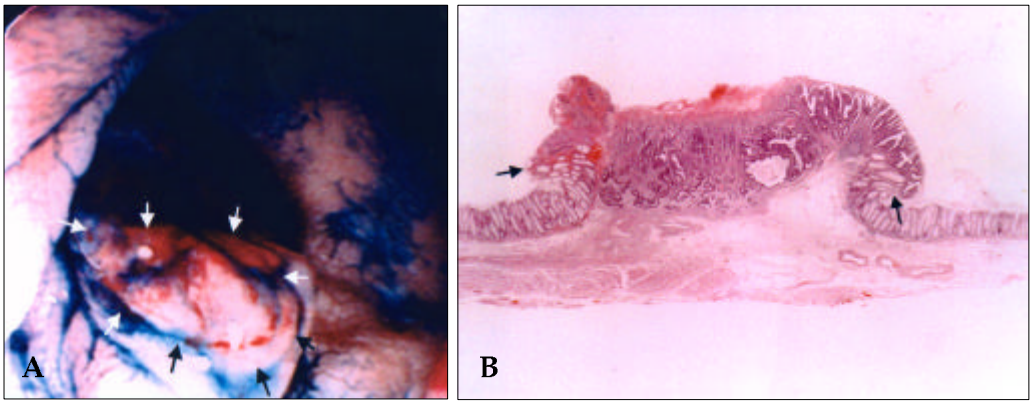

Fig. 2. (A) A 10-mm type IIa + IIc depressed-type early cancer in the lower rectum of a 55-year-old male patient. A depressed area is recognizable (arrows). (B) A cut section of a specimen of a trans-sphincteric excision shows a nonpolypoid growth of a submucosally invasive cancer. Notice that the growing cancerous lesion has pushed aside the normal mucosa (arrows) (H&E, × 2).

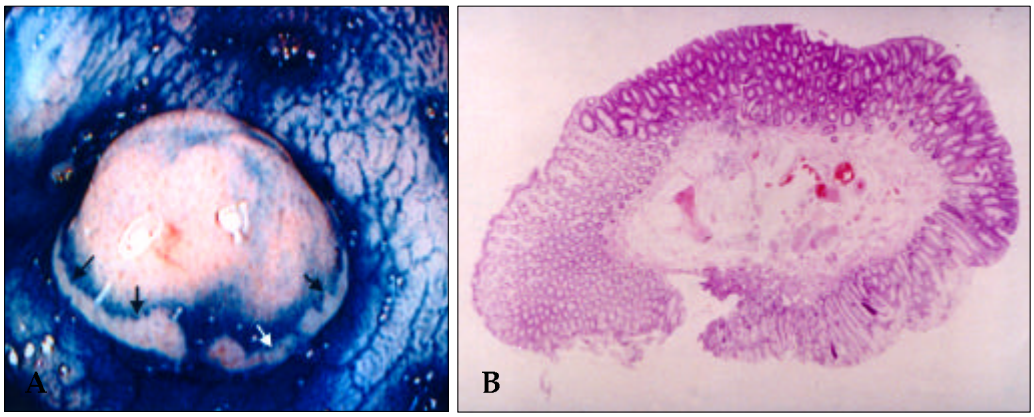

Fig. 3. (A) A 6-mm type Is + IIc lesion in the sigmoid colon of a 47-year-old female patient. A depressed area is clearly demarcated (arrows). (B) A cut section of an endoscopic mucosal resection specimen showing a tubular adenoma (H&E, × 4).

details.[2] Spjut et al.[4] suggested the existence of de novo cancers, stating that they had observed 4 small adenocarcinomas, which had no residual epithelial polyp and that probably originated directly from the colonic mucosa. Shimoda et al.[5] claimed that nonpolypoid early colorectal carcinomas progressed to advanced carcinomas easily and that de novo carcinomas comprised about 80% of all colorectal carcinomas. Meanwhile, the case for de novo carcinoma theory has been bolstered by the recent discovery of depressed-type early colorectal cancers. Although depressed early colorectal cancers have been detected mainly in Japan, they have also been discovered in Korea.[6,7] The existence of this type of cancer has provoked active controversy about colorectal cancer development.[8,9] The increasing number of depressed-type early colorectal cancers has made it obvious that some lesions, which used to be considered as normal polyp lesions, originated from depressed- type early cancers.[10,11] Moreover, some supporting evidence suggests, on a molecular basis, the existence of a pathway of colorectal carcinogenesis, which differ from the polyp-cancer sequence. Yugawa et al.[12] performed a comparative study upon ras p21 expression in flat- and polypoid- type colorectal tumors, and found that ras p21 was not expressed in flat lesions, but commonly expressed in polypoid-type neoplasms. Their study suggested that the genetic changes in flat-type cancers were different from those of polypoid-type cancers. Fujimori et al.[13] also studied a ras gene point mutation in small polypoid tumors and small flat tumors. They observed that the ras gene mutation occurred in 47% of the small polypoid tumors and in none of the small flat tumors, suggesting different genetic pathways of tumor progression for polypoid and flat colorectal carcinomas. Kojima et al.[14] later reported a similar result, namely, that the frequency of the Ki-ras point mutation in superficial type carcinomas was 14.3%, whereas in polypoid type carcinomas it was 50%. They also supported the idea that a different genetic pathway might exist in colorectal carcinogenesis. Furthermore, Okamoto et al.[15] reported more supporting evidence from a microsatellite instability study. They showed that 44% of the flat carcinomas in the proximal colon had at least one positive locus, whereas none of the polypoid carcinomas of the proximal colon showed microsatellite instability. They also suggested that the genetic pathway of flat carcinomas might differ from that in polypoid carcinomas. Another case suggested that a superficial depressed cancer is an earlier stage of an advanced colorectal cancer.[16] Nevertheless, the debate upon colorectal cancer development persists. Although uncertainty still surrounds de novo carcinomas, the possibility of their existence cannot be refuted. Superficial early colorectal cancer with submucosal invasion is still uncommon in general, and histopathologic interpretation can be crucial for determining the path of cancer development, giving the false impression of a de novo carcinoma. Moreover, if diagnosis is delayed, any adenomatous precursor lesion might be destroyed by a growing cancer, leading to a false diagnosis of a de novo carcinoma.[17] On the other hand, if de novo carcinomas do not exist, removal of adenomas in the context of population-based screening programs should lower the incidence of colorectal cancer, but it does not, thus implying the existence of some mechanism other than the adenoma-carcinoma sequence for the development of colorectal cancers.[18]

Due to the characteristic endoscopic features of depressed-type colorectal neoplasms, endoscopists can detect them during colonoscopy. These tumors have a clearly bordered depressed area, which becomes more distinguishable by spraying with a dye such as indigo carmine.[8,9] On many occasions, the lesion bleeds easily even on a light touch. By using magnifying colonoscopy, the endoscopist can confirm the existence of characteristic small round pits. In the case of malignancy, an irregularly shaped or nonstructural pit pattern can be a helpful diagnostic clue regarding the depth of invasion.[9]

Depressed-type colorectal neoplasms show different shapes according to their growth patterns, such as type IIc, type IIa + IIc, and type Is + IIc. It is important to identify these lesions, especially types IIa + IIc and Is + IIc, because type IIa + IIc and type Is + IIc lesions look very much like the usual polyp lesions; but, they have a biological behavior that differs from that of usual polyp

lesions. Kim et al.[19] studied the significance of depressed-type early colorectal cancers, and compared them with other types of early colorectal cancers. In their study, they confirmed that depressed-type early cancers have a significantly higher submucosal cancer rate than protruding lesions. Moreover, type IIa + IIc and type Is + IIc lesions invade the submucosa more frequently than type IIc, even when they are smaller than 10 mm, and progress to advanced cancers rapidly.[3,20] In our study, no submucosally invasive cancers were larger than 20 mm in diameter. This may suggest a characteristic biological behavior for the depressed-type of colon cancer. Although this is not a comparative study of depressed-type colorectal neoplasms and polypoid-type colorectal neoplasms, it seems that by the time a depressed-type colon cancer has become larger than 20 mm in size, it has already progressed into an advanced cancer. Kudo et al.[20] reported a 34% submucosal cancer rate for type IIa + IIc and type Is + IIc colorectal neoplasms, and a 21% rate for type IIc colorectal neoplasms. Their study also showed a significantly higher rate of submucosal invasion for type IIa + IIc and type Is + IIc cancers than for type IIc. Research on more cases of type IIa + IIc and type Is + IIc cancers will further clarify their characteristics and help provide an understanding of the growth and development of colorectal cancers.

In conclusion, the recognition of depressed-type colorectal neoplasms, especially type IIa + IIc and type Is + IIc neoplasms, is important. Type IIa + IIc and type Is + IIc, which used to be managed as normal polyp lesions, should be managed carefully. Because type IIa + IIc and type Is + IIc neoplasms have a higher rate of submucosal invasion than type IIc neoplasms, endoscopists should make efforts to differentiate them from the usual polyp lesions.

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