

Villous Tumors of the Large Intestine: Pathological Features and Mucin Phenotypic Expression

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Abstract: Although colorectal villous tumors are generally considered to be malignancies, questions remain about their pathogenesis. In this study, fifteen lesions of colorectal villous tumors from 15 patients were examined histopathologically and immunohistochemically to analyze pathological features, mucin phenotypes, and CD10 expression. The major anatomical sites of the colorectal villous tumors were the sigmoid colon and rectum. Macroscopically, villous tumors were generally broad-based, sessile lesions with a coarse, somewhat friable surface consisting of numerous fronds. Histologically, these leaf-like projections consisted of a narrow core of lamina propria covered by a sheet of neoplastic epithelial cells. Eight lesions (53.3%) of 15 villous tumors included carcinomatous components (extremely well- and well-differentiated adenocarcinoma in 6 and mucinous adenocarcinoma in 2). Based on their mucin expression profiles and CD10 expression, low-grade components in 15 villous tumors showed mixed gastric and intestinal phenotype. There was no significant difference in mixed gastric and intestinal phenotypic expression between low-grade and high-grade components. In all the adenocarcinoma components, the mucin expression pattern of intramucosal components was similar to that of invasive components. All the villous tumors were negative for CD10. In conclusion, our data suggested that colorectal villous tumors may be potentially or substantially malignant and that analysis of mucin expression profiles may be a potential ancillary tool for estimating the pathway of tumorigenesis of colorectal villous tumors. Our results also suggest that villous tumor of the large intestine may be a precursor of mucinous adenocarcinoma.

Key words: Villous tumors of the large intestine, Villous structure, Adenoma, Adenocarcinoma, Mucin phenotypic expression

Introduction

“Villous tumor” of the large intestine was first described clinically description by Quain in 1855.¹⁾ The World Health Organization (WHO) defines colorectal villous adenoma as an adenoma in which at least 80% of the tumor is composed of finger-like processes of lamina propria covered by epithelium that extends down to the muscularis mucosae.²⁾ However, the term “villous

adenoma” refers only to “benign” villous tumors. Villous neoplasias are very rare and most often occur within the sigmoid colon and rectum.^{3), 4), 5)} They have been reported to comprise 0.8-7.4% of all colorectal epithelial neoplasias.^{6), 7)}

The high incidence of malignant transformation in colorectal villous tumors has been well documented. The incidence of coexistence of invasive adenocarcinoma has been reported to be 15-28%.^{3), 4), 5)} Therefore, colorectal villous tumors show a wide spectrum of

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benign, borderline, and malignant lesions. Some villous tumors with cytological atypia graded as borderline show submucosal invasion or over the growth of submucosal tissue.⁶⁾ It is usually impossible to distinguish malignant villous tumors from benign ones not only based on macroscopic appearance but also by biopsy from the surface of the tumor. Accordingly, the term “villous tumor” is best used to describe colorectal epithelial neoplasia with a villous structure.

Recently, Yao *et al.*^{8), 9)} subclassified colorectal adenocarcinomas by immunohistochemical methods and revealed differences in clinicopathological features and tumor behavior among the phenotypic subtypes. Therefore, the purpose of our study was to clarify the correlations between pathological features, mucin phenotypes, and CD10 expression in colorectal villous tumors. We also aim to elucidate peculiar characteristics of these tumors.

Materials and Methods

Patients

We enrolled 15 patients of colorectal villous tumors from the surgically resected specimen files of 4808 patients diagnosed as having colorectal epithelial neoplasia (e.g., adenoma or adenocarcinoma) between March 1975 and July 2011 at our laboratory. Colorectal villous tumors were defined by the following 2 criteria proposed by Iwashita *et al.*⁶⁾ were used for the selection of colorectal villous tumors: (i) macroscopically, the tumor presents as a protuberant mass with a coarse, somewhat friable surface consisting of numerous fronds covering more than 90% of its surface area (Figure 1A) and (ii) microscopically, leaf-like projections lined by neoplastic epithelial cells comprise more than 90% of the luminal surface (Figure 1B).

Of the 15 lesions of villous tumors, 9 were surgically resected with regional lymph node dissection, and the remaining 6 lesions were locally resected. Patients with familial adenomatous polyposis or colitis-associated carcinoma were excluded from the study.

Macroscopic evaluation

All surgically resected specimens were fixed overnight in 20% neutral buffered formalin and examined macroscopically. Macroscopic types of colorectal villous tumor were classified into pure type and mixed granulonodular type (equivalent to non-pure type). Pure

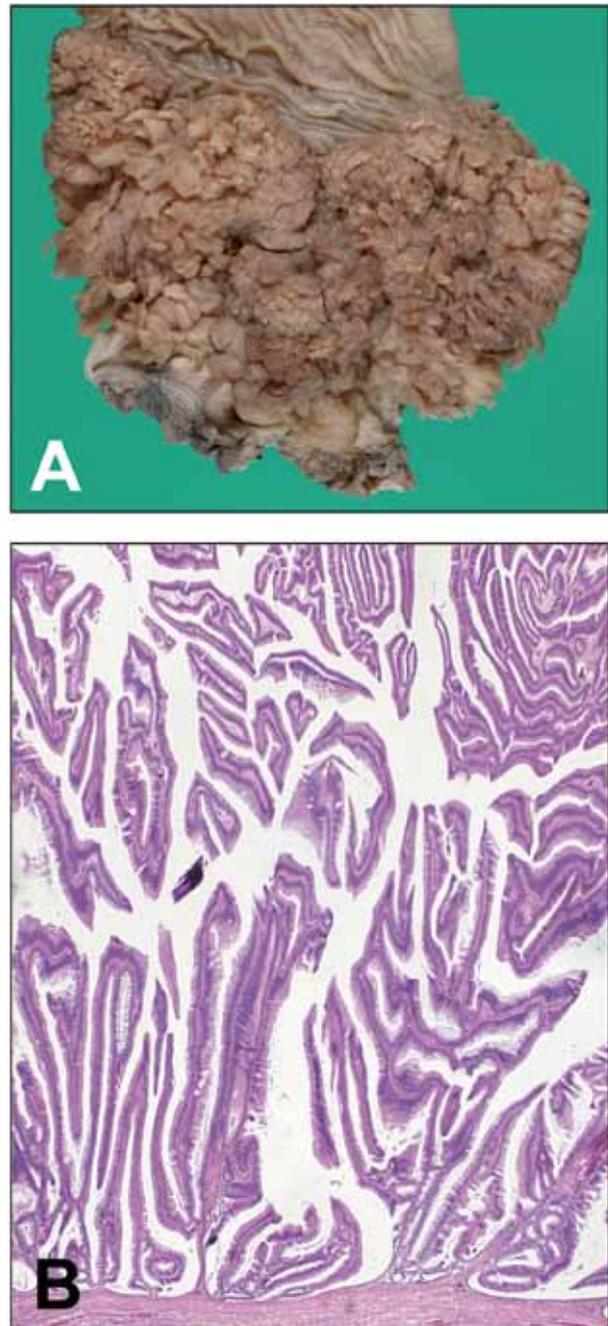


Fig 1. Macroscopic and histologic appearance of colorectal villous tumor (pure type). Pure-type villous tumor of the lower rectum presents as a protuberant mass with a coarse, somewhat friable surface consisting of numerous fronds covering more than 90% of its surface area. The tumor felt soft and velvety to the touch. Ulcer-associated tumor invasion was not found (A). Histologically, leaf-like projections consisted of a narrow core of lamina propria covered by a sheet of neoplastic epithelial cells (B).

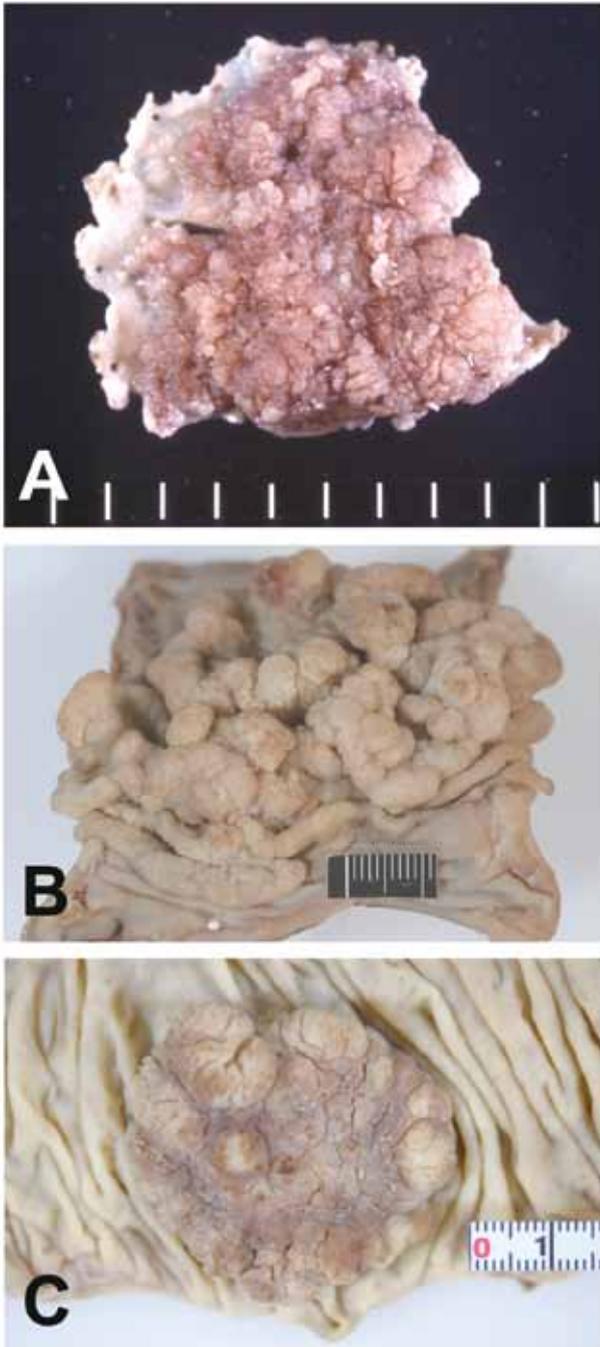


Fig 2. Macroscopic appearance of colorectal villous tumor (mixed granulonodular type/non-pure type). Mixed granulonodular type showing a fine granular appearance of the rectosigmoid. The surface of the tumor is also glaringly bright (A). Mixed granulonodular type with a mixture of gyrous and nodular patterns of the ascending colon (B). Mixed granulonodular type is recognized as a protuberant mass covered with a chapped surface of the ascending colon. Leaf-like projections were also not found on the surface of the tumor (C).

types were recognized as broad-based lesions with a shaggy surface as shown in Figure 1A, and mixed granulonodular types were recognized as conglomerated nodular lesions covered with small projections and/or a chapped surface (Figure 2). The maximum diameter of each colorectal lesion was measured with a ruler on macroscopic color photographs.

Histologic evaluation

The entire tumor tissue was sliced in serial fashion at approximately 5 mm in width, and tissue slices were routinely processed to paraffin blocks. The number of blocks prepared ranged from 3 to 28 (average, 9.8). All sections were cut at 3- μ m thickness and stained with hematoxylin and eosin (HE) for microscopic examination.

Histologic classification was based on the Japanese Classification of Colorectal Carcinoma.¹⁰⁾ Adenomas were subclassified into low grade (equivalent to adenomas with mild and moderate atypia), high grade (equivalent to adenomas with severe atypia), and a mixture of low and high grade, according to their degree of architectural and/or cytological atypia. Contrastingly, adenocarcinoma was subclassified into tubular adenocarcinoma, including a mixture of well- and moderately differentiated type, and mucinous adenocarcinoma, composed of neoplastic epithelial cells that produce a substantial amount of mucus outside the cells forming mucinodules. Representative examples of these adenomas and adenocarcinomas are shown in Figure 3. Furthermore, neoplastic epithelial cells were classified into clear cell and dark cell type, according to the criteria proposed by Yanagisawa *et al.*¹¹⁾ Villous tumors of the clear cell type were composed of tall columnar epithelial cells with clear cytoplasm (Figure 4A), whereas villous tumors of the dark cell type were composed of tall columnar epithelial cells with dark cytoplasm (Figure 4B).

Immunohistochemistry

For immunohistochemistry, 3- μ m-thick sections were mounted on silane-coated glass slides, deparaffinized, and heated in a microwave oven (700 W) for 10 min to expose antigens in 10 mM Na-citrate buffer (pH 6.0). Immunohistochemical staining was performed with the dextran polymer-peroxidase Envision System (Dako Japan, Tokyo, Japan) and metal-3,3'-diaminobenzidine (Pierce, Rockford, IL, USA). Finally, sections were

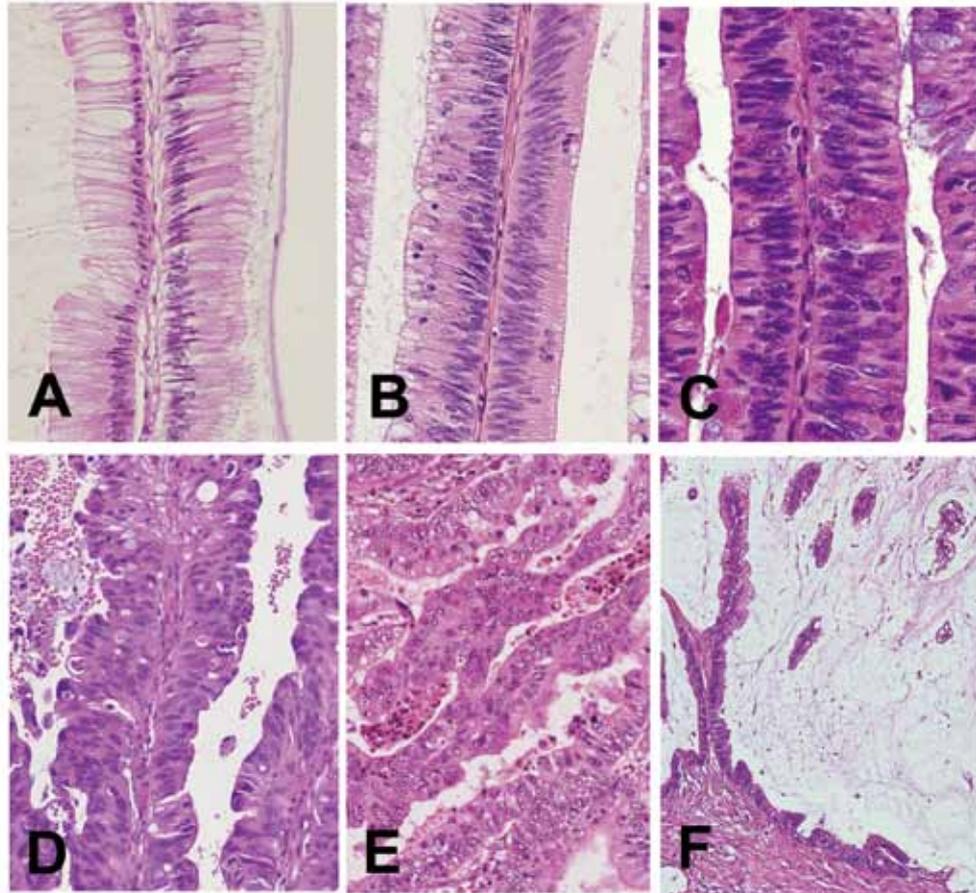


Fig 3. Histologic appearance of adenoma and adenocarcinoma in colorectal villous tumors. Adenomatous components are classified according to their degree of cytological atypia into low grade (equivalent to adenomas with mild to moderate atypia) (A, B) and high grade (equivalent to adenomas with severe atypia) (C). In mild atypia, nuclei are slightly enlarged, elongated, hyperchromatic, and crowded, but polarity is well preserved. In moderate atypia, nuclei are further enlarged, less elongated, and show focal loss of polarity. In severe atypia, nuclei are greatly enlarged, round or ovoid, and also show loss of polarity. In contrast, adenocarcinomas show various architectures: papillary (D), tubular (E), and muconodular (F).

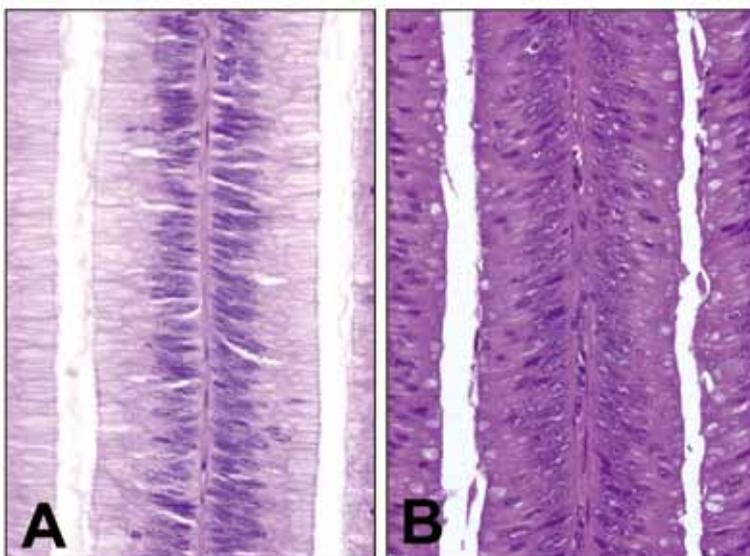


Fig 4. Histologic appearance of cell types in colorectal villous tumors. Adenoma of the clear cell type is composed of tall columnar epithelial cells with clear cytoplasm (A), whereas adenoma of the dark cell type is composed of tall columnar epithelial cells with dark cytoplasm (B).

counterstained with Mayer's hematoxylin.

Membrane staining for CD10 (56C6; Novocastra, Newcastle, UK) and cytoplasmic staining for MUC2 (Ccp58; Novocastra) and MUC5AC (CLH2; Novocastra) were judged as positive reactions when over 5% of tumor cells showed a positive reaction for each marker. Based on CD10 expression and mucin phenotypes (MUC2 and MUC5AC) determined by immunoreactivity, the villous tumors were further subclassified into five groups according to the criteria proposed by Yao *et al*^{8),9)}: small-intestinal type defined as CD10 (+), MUC2 (+/-), and MUC5AC (-); large-intestinal type as CD10 (-), MUC2 (+), and MUC5AC (-); gastric type as CD10 (-), MUC2 (-), and MUC5AC (+); mixed gastric and intestinal type as MUC5AC (+), CD10 (+/-), and MUC2 (+); and unclassified type as CD10 (-), MUC2 (-), and MUC5AC (-).

Statistics

Statistical analysis was performed with the Chi-squared test and Mann-Whitney *U*-test. A *P* value of <0.05 was regarded as significant.

Results

Clinicopathological data

The clinical and pathologic features of the patients

are summarized in Table 1. The patients with colorectal villous tumor accounted for 0.3% of the 4808 patients who underwent surgical resection of epithelial tumors of the large intestine. The mean age of the patients with colorectal villous tumor was 62.3±12.8 years (range, 35 to 81 years). The sex ratio in patients with colorectal villous tumor was male, 9 (60%) and female, 6 (40%). The chief complaints were hemorrhage in 11 patients (73.3%), tumor prolapse in 2 (13.3%), and abdominal pain in 2 (13.3%). The mean diameter of colorectal villous tumor was 49.9±21.3 mm (range, 23 to 100 mm).

Location of villous tumors

Among the 15 colorectal villous tumors, 1 (6.67%) was located in the cecum, 2 (13.3%) were in the proximal region of the ascending colon, 5 (33.3%) were in the sigmoid colon or rectosigmoid, and 7 (46.7%) were in the rectum (Table 1). The major anatomical sites of the colorectal villous tumor were the sigmoid colon, rectosigmoid, and lower rectum.

Macroscopic characteristics of villous tumors

Of the 15 colorectal villous tumors, 11 (73.3%) were recognized as broad-based, sessile lesions and 5 (26.7%) as semipedunculated lesions. The surfaces of the former were villous, indicating that they presented the typical image of a villous tumor. However, those of the

Table 1 Clinical features and histology of 15 cases of colorectal villous tumors

Age	Sex	Chief complaint	Location	Tumor size (mm)	Macroscopic type	Macroscopic feature	Ulceration	Grade	Cell-type	Associated carcinoma	Histologic type of carcinoma	Depth	Lymph node metastasis	
1	81	M	Bleeding	S	50	Broad-based	Villous	Absent	II to III	Dark	Present	Tubular	pT3	(-)
2	54	M	Bleeding	R	36	Semipedunculated	Villous	Absent	I to II	Clear	Absent			(-)
3	55	F	Abdominal pain	C	70	Broad-based	Villous	Absent	II to III	Dark	Present	Tubular	pT3	(-)
4	79	F	Bleeding	R	52	Broad-based	Villous	Absent	II to III	Dark	Present	Tubular	pTis	(-)
5	77	M	Bleeding	S	26	Semipedunculated	Villous	Absent	II to III	Dark	Absent			(-)
6	35	F	BMS	R	40	Broad-based	Granulonodular	Absent	II to III	Dark	Present	Tubular	pTis	NA
7	65	M	Bleeding	S	25	Broad-based	Villous	Absent	II to III	Dark	Absent			(-)
8	52	M	BMS	RS	35	Semipedunculated	Villous	Absent	II to III	Dark	Absent			NA
9	57	M	Prolapse	R	55	Broad-based	Villous	Absent	II to III	Dark	Absent			NA
10	64	F	Prolapse	R	62	Broad-based	Granulonodular	Absent	II to III	Dark	Absent			NA
11	72	F	Abdominal pain	A	75	Broad-based	Granulonodular	Absent	I to III	Dark	Present	Tubular	pT1	(-)
12	75	M	OBT	R	100	Broad-based	Villous	Absent	I to III	Dark	Present	Tubular	pTis	NA
13	53	F	OBT	A	40	Broad-based	Granulonodular	Absent	I to III	Dark	Present	Mucinous	pT3	(-)
14	62	M	BMS	R	60	Broad-based	Villous	Present	II to III	Dark	Present	Mucinous	pT3	(-)
15	53	M	OBT	RS	23	Semipedunculated	Villous	Absent	I to III	Dark	Absent			NA

M indicates male; F, female; BMS, bloody mucoid stool; OBT, positive for occult blood test; C, cecum; A, proximal region of ascending colon; S, sigmoid colon; RS, rectosigmoid; R, lower rectum; Grade, grade of cytologic atypia of neoplastic epithelial cells (I: mild atypia, II: moderate atypia, III: severe atypia); Cell-type, cell-type of neoplastic epithelial cells; Dark, dark cell type; Clear, clear cell type; Tubular, extremely well- and well-differentiated tubular adenocarcinoma; Mucinous, mucinous adenocarcinoma; Depth, depth of carcinoma invasion; pTis, intramucosal carcinoma; pT1, carcinoma with submucosal invasion; pT3, carcinoma invading through the muscularis propria into the subserosa, or into non-peritonealized perirectal tissues; NA, not assessed; and (-), no metastases.

latter were completely covered with small projections, indicating that their image was different from that of the typical one. An ulcer had formed in only 1 patient (6.67%), in which eruption of mucus was occurring.

Histopathologic characteristics of villous tumors

In all patients, intramucosal neoplastic areas had villous structures, parts of which were associated with the budding of small glands. Neoplastic epithelial cells that coated the villous projections were tall columnar epithelial cells, the cores of which were slender and arranged in an orderly manner at the basolateral surface. Of these neoplastic epithelial cells, dark cell type was dominant in 14 patients (93.3%), whereas clear cell type was dominant in only 1 patient (6.7%). Goblet cells were observed in all patients.

When the degree of cellular atypia of the neoplastic epithelial cells was divided into three grades, i.e., mild (grade I), moderate (grade II), and severe (grade III), the most severe grade of atypia was defined as cellular atypism of the tumor, and severe grade (Figure 3C) was observed in 14 patients (93.3%) and moderate grade (Figure 3B) in only 1 patient (6.7%). In 12 patients (80.0%), the border region between tumors with different degrees of cellular atypia was unclear and in the remaining 3 patients (20%) was relatively clear.

Incidence and histologic characteristics of associated invasive carcinoma in villous tumors

Of the 15 patients with colorectal villous tumor, 8 patients (53.3%) had developed complications of carcinoma. On the basis of depth of carcinoma invasion, 3 patients were categorized as pTis, 1 as pT1, and 4 as pT3. Histologic findings of associated carcinoma were adenocarcinoma in all. In regard to degree of tissue differentiation, 75.0% (6/8) was extremely well- to well-differentiated type (Figure 5A) and 25.0% (2/8) was mucinous adenocarcinoma (Figure 5B).

The 6 patients with well-differentiated adenocarcinoma included 3 patients with extremely well-differentiated type, which was histologically difficult to distinguish from adenomatous component, and 3 patients with a clear border region between the well-differentiated adenocarcinoma and the adenomatous component. The latter 2 patients with mucinous adenocarcinoma had adenocarcinoma that had invaded deep into the intestinal wall forming obvious muconodules. The carcinoma floating within the muconodules was well

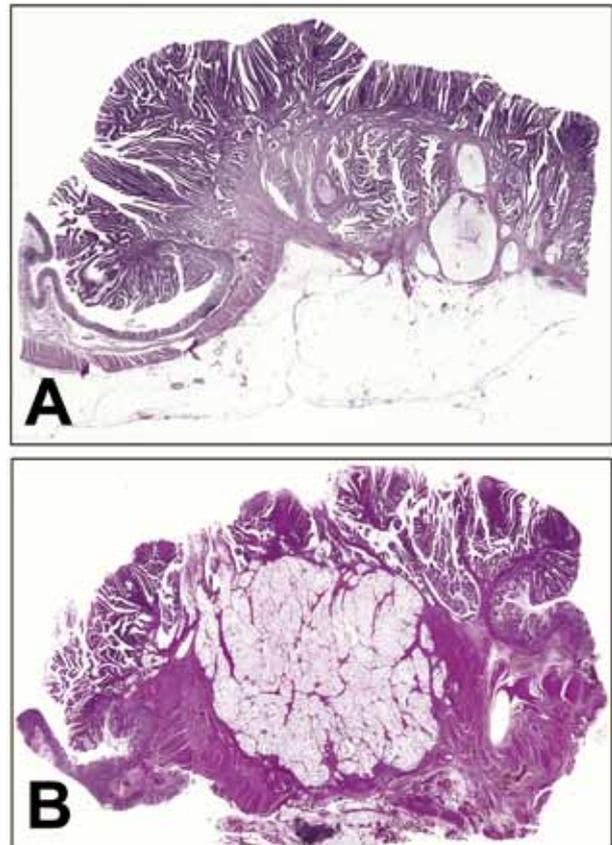


Fig 5. Whole-mount view of the cut section of colorectal villous tumors.

Extremely well- and well-differentiated adenocarcinoma has invaded through the muscularis propria into the subserosa. The invasive component of adenocarcinoma is nearly the same as the intramucosal component (A). Mucinous adenocarcinoma has invaded the deeper portion of the muscularis propria. Ulcerative change is also noted (B).

differentiated adenocarcinoma. Further, fibrosis in the area of stromal invasion by adenocarcinoma in general was not remarkable. In this study, no poorly differentiated adenocarcinoma was found (Table 1). In the 8 patients who underwent regional lymph node dissection, no lymph node metastasis of adenocarcinoma was observed.

Mucin expression profiles in villous tumors

Mucin expression profiles in colorectal villous tumors are summarized in Table 2 and shown in Figure 6. All 15 (100%) low-grade components of villous tumors showed markedly increased expression of MUC2 and MUC5AC, but all low-grade components were negative for CD10 expression. Thirteen of 15 (86.7%) high-grade components of villous tumors were positive for MUC2,

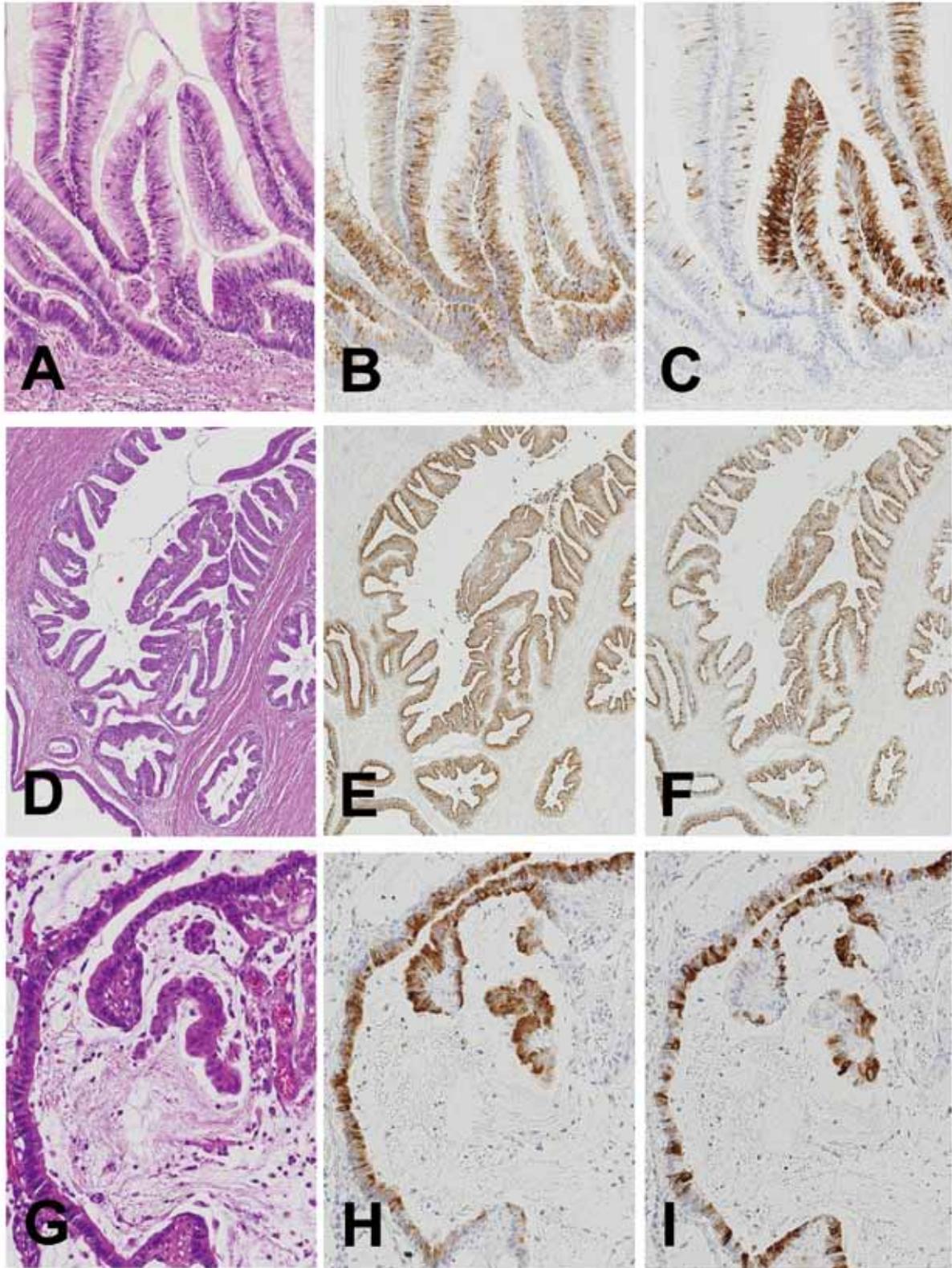


Fig 6. Mucin expression profiles in colorectal villous tumors. Histological appearance of intramucosal low-grade component (A), extremely well-differentiated adenocarcinoma component invading the muscularis propria (D), and mucinous adenocarcinoma invading the subserosa (G) of colorectal villous tumors. MUC2 and MUC5AC expressions show no difference between the intramucosal low-grade component (B, C) and the invasive component (E, F, H, I) of colorectal villous tumors. Both MUC2 (B, E, H) and MUC5AC (C, F, I) are expressed in epithelial neoplastic cells as a diffuse cytoplasmic staining.

Table 2 Mucin expression profiles in colorectal villous tumors

	Villous tumor (n=7)		Adenocarcinoma in villous tumor (n=8)			
	Low-grade components*	High-grade components**	Adenoma components		Associated adenocarcinoma components	
			Low-grade components*	High-grade components**	Extremely well- and well-differentiated type † (n=6)	Mucinous adenocarcinoma (n=2)
MUC2	7 (100%)	6 (85.7%)	8 (100%)	6 (75.0%)	5 (83.3%)	2 (100%)
MUC5AC	7 (100%)	6 (85.7%)	8 (100%)	7 (87.5%)	5 (83.3%)	2 (100%)
CD10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*: including villous adenoma with mild and moderate atypia, **: including villous adenoma with severe atypia, †: including papillary adenocarcinoma shown in Figure 3D.

and 13/15 (86.7%) high-grade components of villous tumors were positive for MUC5AC.

In associated adenocarcinoma components, 5/6 (83.3%) extremely well- and well-differentiated adenocarcinomas in villous tumors were positive for MUC2 and MUC5AC. Furthermore, 2/2 (100%) mucinous adenocarcinomas showed markedly increased expression of MUC2 and MUC5AC. In all the adenocarcinoma components, the mucin expression pattern of intramucosal components was similar to that of invasive components. All the villous tumors were negative for CD10.

Mucin phenotypic expression of villous tumors

Mucin phenotypic expression of villous tumors is summarized in Table 3. According to the mucin expression of neoplastic cells, 15 of 15 (100%) low-grade components of villous tumors were classified as mixed gastric and intestinal phenotype. The unclassified type (“null” type negative for CD10, MUC2, and MUC5AC expression) was characterized by a relatively higher grade of atypia and higher incidence of associated

adenocarcinoma when compared with the other types. There was no significant difference in mixed gastric and intestinal phenotypic expression between low-grade and high-grade components.

Discussion

The technical term “villous tumor” was first described by the English surgeon Quain in 1855.¹¹ In 1859, an atlas of macroscopic detailed drawings of subjects with villous tumors was published.¹² It is likely that the drawings had been recognized gradually by clinicians and pathologists as typical macroscopic images of villous tumor since then.

Since colonic villous tumors were reported one after another in Europe, colorectal tumors with similar pathology have been reported under various names such as villous adenoma,⁸ villous papilloma,⁹ villous polyp, papillary adenoma,¹⁰ and potassium-secreting tumor.¹³ It is speculated that variable names for villous tumors are caused by discordance in understanding

Table 3 Mucin phenotypic expression of colorectal villous tumors

	Villous tumor (n=7)		Adenocarcinoma in villous tumor (n=8)			
	Low-grade components*	High-grade components**	Adenoma components		Associated adenocarcinoma components	
			Low-grade components*	High-grade components**	Extremely well- and well-differentiated type † (n=6)	Mucinous adenocarcinoma (n=2)
Small-intestinal type	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Large-intestinal type	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gastric type	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mixed gastric and intestinal type	7 (100%)	6 (85.7%)	8 (100%)	7 (87.5%)	5 (83.3%)	2 (100%)
Unclassified type	0 (0%)	1 (14.3%)	0 (0%)	1 (12.5%)	1 (16.7%)	0 (0%)

*: including villous adenoma with mild and moderate atypia, **: including villous adenoma with severe atypia, †: including papillary adenocarcinoma shown in Figure 3D.

the biological classification of villous tumors as well as disagreement on how the technical terms reflecting the distinctive pathomorphology of villous tumors should be used.

Since the 1970s, in an attempt to resolve the confusion about these terms, the committee on classification of intestinal tumors of the WHO²⁾ and the Japanese Society for Cancer of the Colon and Rectum¹⁴⁾ have histologically subclassified benign epithelial tumors of the colon into tubular adenoma, tubulovillous adenoma, and villous adenoma, which have been recommended for use internationally as common technical terms. However, in Japan, the term “villous tumor” is used in clinical situations, the reason being that clinicians feel uncomfortable calling an adenoma-like tumor that invades deep into the intestinal wall simply “villous adenoma”. In other words, the technical term “villous adenoma” is insufficient for depicting the nature of villous tumors, and therefore the term “villous tumor” will be used hereafter. Villous tumors have malignant potential. Therefore, it is critical to understand the pathological features of the lesions when selecting treatment for colorectal villous tumors.

The 15 patients with villous tumor in this study were strictly selected on the basis of the definition by Iwashita *et al.*⁶⁾ The patients with villous tumor accounted for 0.3% of the 4808 patients who underwent surgical resection of epithelial tumor of the large intestine at our institution. Tanabe *et al.*¹⁵⁾ also reported that the rate of the patients with villous tumor was 0.2% (40/17657), indicating a rate as low as that at our institution. The location of 80% of the villous tumors was from the sigmoid colon to rectum, which was thought to be a favorite site of villous tumors.

The macroscopic morphology of villous tumors is roughly divided into two types, i.e., pure type, which has a villous appearance, and non-pure type, which has conglomerated nodular lesions. Among the 8 patients with complications of carcinoma (4 patients had advanced cancers), only 1 patient (12.5%) was accompanied by a cancerous ulcer, leading to difficulty in identifying sites of invasion before treatment, even if the villous tumor was advanced cancer.

With respect to the degree of atypia of intramucosal neoplasm, a variety of degrees from mild to severe were observed, and intramucosal neoplasms were considered to be adenomas. On the basis of histologic type of associated carcinoma, 6 patients had well-

differentiated adenocarcinomas and 2 patients had mucinous adenocarcinomas. Of the 6 patients with well-differentiated adenocarcinoma, in 3 patients, adenocarcinoma without a well-defined border between its lesion and the adenoma had invaded into the submucosal tissue and beyond. These were considered to be extremely well-differentiated adenocarcinoma, and it appeared extraordinarily difficult to confirm the diagnosis by preoperative biopsy. Therefore, it is almost impossible to assess the biological nature of villous tumors only through biopsy samples. When these features are recognized, clinicians and pathologists should together make an effort to exchange through informations for villous tumors among them.

We searched for mucin phenotype at the sites of intramucosal neoplasm and adenocarcinoma to estimate the histogenesis of tissue, with the result that both sites of intramucosal neoplasm and adenocarcinoma had mixed gastric and intestinal phenotypes regardless of the degree of atypism of cells and tissues. Previous studies have shown that increased expression of MUC2 and MUC5AC is also seen in colorectal mucinous adenocarcinomas.^{16), 17), 18)} In the present study, colorectal villous tumors had the same mucin expression profiles as those of mucinous adenocarcinomas. These results imply that colorectal villous tumors have the same pathway of tumorigenesis as that of mucinous adenocarcinomas.

In conclusion, our data suggested that colorectal villous tumors may be potentially or substantially malignant and that analysis of mucin expression profiles may be a potential ancillary tool for estimating the pathway of tumorigenesis of colorectal villous tumors. In addition, the results suggested that a villous tumor of the large intestine was a precursor of mucinous adenocarcinoma.

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