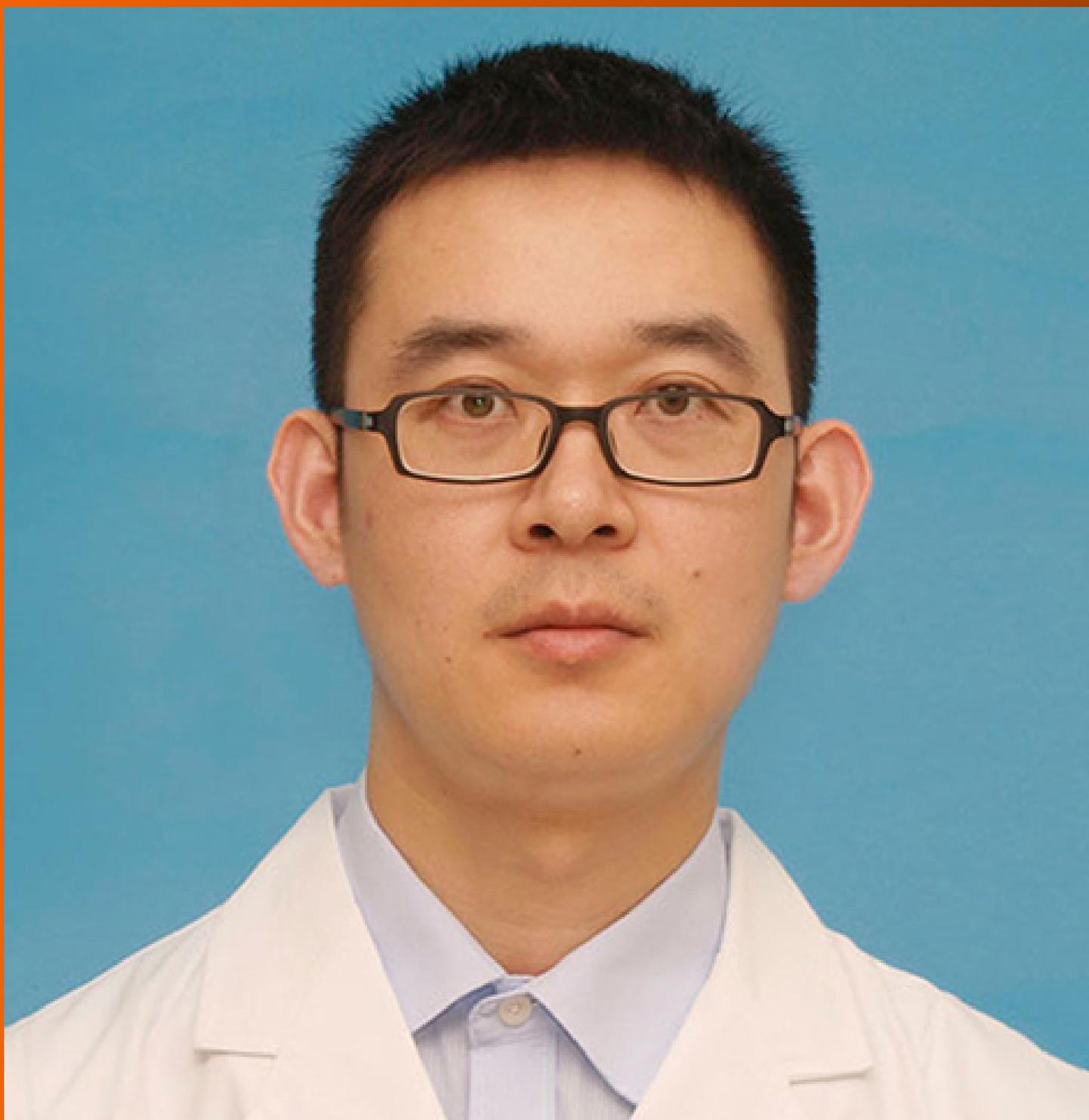


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**REVIEW**

- 1 Combining local regional therapy and systemic therapy: Expected changes in the treatment landscape of recurrent hepatocellular carcinoma  
*Liang J, Bai Y, Ha FS, Luo Y, Deng HT, Gao YT*
- 19 Roles of conventional and complementary therapies in recurrent hepatocellular carcinoma  
*Lai HC, Lin HJ, Jeng LB, Huang ST*
- 36 Traditional Chinese medicine for transformation of gastric precancerous lesions to gastric cancer: A critical review  
*Zhong YL, Wang PQ, Hao DL, Sui F, Zhang FB, Li B*
- 55 Challenges and exploration for immunotherapies targeting cold colorectal cancer  
*Li DD, Tang YL, Wang X*

**MINIREVIEWS**

- 69 Research progress of integrated traditional Chinese and Western medicine in the treatment of advanced gastric cancer  
*Ye HN, Liu XY, Qin BL*

**ORIGINAL ARTICLE****Basic Study**

- 76 Hsa\_circ\_0001658 accelerates the progression of colorectal cancer through miR-590-5p/METTL3 regulatory axis  
*Lu Y, Wang XM, Li ZS, Wu AJ, Cheng WX*

**Clinical and Translational Research**

- 90 Network pharmacology-based analysis of heat clearing and detoxifying drug JC724 on the treatment of colorectal cancer  
*Tang HZ, Yang ZP, Lu S, Wang B, Wang YY, Sun XB, Qu JX, Rao BQ*

**Case Control Study**

- 102 Diagnostic accuracy of the multi-target stool DNA test in detecting colorectal cancer: A hospital-based study  
*Gao HL, Lv LB, Zhao WF, Lu QW, Fan JQ*

**Retrospective Study**

- 112 Development and validation of a nomogram for predicting metachronous peritoneal metastasis in colorectal cancer: A retrospective study  
*Ban B, Shang A, Shi J*

- 128 Risk factors, prognostic predictors, and nomograms for pancreatic cancer patients with initially diagnosed synchronous liver metastasis  
*Cao BY, Tong F, Zhang LT, Kang YX, Wu CC, Wang QQ, Yang W, Wang J*
- 143 Short-term efficacy and influencing factors of conventional chemotherapy combined with irinotecan in patients with advanced gastric cancer  
*Wang JP, Du JL, Li YY*
- 155 Survival benefits and disparities in radiation therapy for elderly patients with pancreatic ductal adenocarcinoma  
*Cao BY, Wang QQ, Zhang LT, Wu CC, Tong F, Yang W, Wang J*

**META-ANALYSIS**

- 171 Rs3746444 T>C locus in miR-499 increases the susceptibility to hepatocellular carcinoma: A meta-analysis 14812 subjects  
*Jiang JK, Chen HS, Tang WF, Chen Y, Lin J*

**CASE REPORT**

- 186 Local recurrence after successful endoscopic submucosal dissection for rectal mucinous mucosal adenocarcinoma: A case report  
*Murakami Y, Tanabe H, Ono Y, Sugiyama Y, Kobayashi Y, Kunogi T, Sasaki T, Takahashi K, Ando K, Ueno N, Kashima S, Yuzawa S, Moriichi K, Mizukami Y, Fujiya M, Okumura T*
- 195 Intestinal natural killer/T-cell lymphoma presenting as a pancreatic head space-occupying lesion: A case report  
*Wang YN, Zhu YM, Lei XJ, Chen Y, Ni WM, Fu ZW, Pan WS*
- 205 Surgical treatments of recurrent small intestine metastatic melanoma manifesting with gastrointestinal hemorrhage and intussusception: A case report  
*Fan WJ, Cheng HH, Wei W*

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## Local recurrence after successful endoscopic submucosal dissection for rectal mucinous mucosal adenocarcinoma: A case report

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### Abstract

#### BACKGROUND

Mucinous adenocarcinoma of the colorectum is a rare histological subtype characterized by an abundant mucinous component. Mucinous tumors are frequently diagnosed at an advanced stage, which indicates an aggressive subtype. However, few case reports have been published, and little information is available concerning genetic alterations in mucinous adenocarcinoma.

#### CASE SUMMARY

A 76-year-old man underwent en bloc endoscopic submucosal dissection (ESD) for the management of a type 0-Is+IIa lesion. Histological examination revealed an intramucosal mucinous adenocarcinoma with signet-ring cell carcinoma and well-to-moderately differentiated tubular adenocarcinoma. Three years after the ESD, local recurrence was detected by an endoscopic examination, revealing a new 0-Is+IIa lesion with a phenotype similar to the previously resected lesion. Re-ESD was chosen for the management of the recurrent tumor, and the histological examination showed positive tumor infiltration at the vertical margin. Additional

surgical resection was performed for the curative treatment. Genetic analysis showed pathogenic alterations in *RNF43* and *TP53* in the adenoma and an additional *SMAD4* alteration in the carcinoma.

### CONCLUSION

This mucinous mucosal adenocarcinoma case was suggested to have an aggressive phenotype and a careful and close follow-up are required.

**Key Words:** Rectal cancer; Mucinous adenocarcinoma; Endoscopic submucosal dissection; TP53; Colitic cancer pathway; Case report

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**Core Tip:** Colorectal mucinous adenocarcinoma, as characterized by an abundant mucinous component, is a rare histological subtype frequently diagnosed at an advanced stage. Intramucosal mucinous adenocarcinoma was dissected by endoscopic submucosal dissection and local recurrence was detected three years after the treatment. Genetic analysis showed pathogenic alterations of *RNF43*, *TP53*, and *SMAD4*. This case of mucinous mucosal adenocarcinoma was suggested to have an aggressive phenotype based on the treatment course and advanced genotype identified by target sequencing. Careful and close follow-up should be performed, and additional surgery should be considered when managing patients with mucinous adenocarcinoma.

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## INTRODUCTION

The World Health Organization classifies colorectal cancers according to histology[1]. The most common type of colorectal cancer is adenocarcinoma, which is frequently heterogeneous and is composed of several histological variants: Mucinous adenocarcinoma, signet-ring cell carcinoma, neuroendocrine carcinoma, squamous cell carcinoma, medullary carcinoma, and undifferentiated carcinoma. The histological subtype presumably plays a role in tumor biology and patient prognosis. Approximately 10% of colorectal carcinomas are mucinous adenocarcinomas, which are characterized by an abundant mucinous component comprising more than 50% of the tumor volume[2]. The clinicopathological characteristics are reported include young age, proximal colon origin, and a larger tumor size[3,4]. Signet-ring cell carcinomas are observed in approximately 1% of colorectal carcinoma cases and are present as single cells with abundant cytoplasmic mucin. Mucinous adenocarcinomas with signet-ring cell carcinomas are distinctively different from adenocarcinoma in tumor biology, with an aggressive phenotype[5].

A multistep model of carcinogenesis has been proposed in colorectal cancer. Biallelic *APC* mutations are known to be an early event leading to adenoma, followed by activating mutations in *KRAS* in the advancing adenoma and *TP53* mutations during the transition to malignancy in common colorectal cancer[6]. Gene expression-based subtyping in colorectal cancers has been widely accepted as a relevant source of disease stratification in colorectal cancer. The genetic pathway of mucinous adenocarcinoma has also been investigated, suggesting a separate genetic pathway with high mutations in *K-RAS* and *TP53*[7]. However, these mutation frequencies differ among reports, indicating that colorectal mucinous adenocarcinomas have heterogeneous phenotypes[3,7,8]. Detailed examinations are required for genetic analysis of mucinous adenocarcinoma in the colorectum.

Although the overall survival of mucinous carcinoma patients was shown to be poorer than that of adenocarcinoma patients in some reviews, the prognosis and treatment options for mucinous adenocarcinoma remain controversial[3,9,10]. As mucinous adenocarcinomas are frequently diagnosed as advanced stages, so patients with mucinous carcinoma have poor prognosis. In contrast, only a few cases of intramucosal mucinous colorectal carcinoma have been reported thus far, and the prognosis of patients with early mucinous adenocarcinoma treated by endoscopic resection remains unclear[11,12].

We herein report a case of early mucinous rectal adenocarcinoma that was removed by endoscopic submucosal dissection (ESD), with recurrence observed after three years.

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## CASE PRESENTATION

---

### **Chief complaints**

A 76-year-old man with a history of hematochezia underwent colonoscopy at a hospital, and an elevated tumor was observed in the lower rectum. He was referred to our department.

### **History of present illness**

The patient had a history of hematochezia, with no abdominal symptoms.

### **History of past illness**

The patient had a history of appendectomy due to appendicitis and prostate cancer surgery.

### **Personal and family history**

The patient had no family history of malignant tumors.

### **Physical examination**

Physical examination was unremarkable, and his abdomen was soft, nontender, and nondistended with no palpable mass.

### **Laboratory examinations**

Routine laboratory examination showed normal blood counts with a white blood cell count of 5930/ $\mu\text{L}$ , red blood cell count of 4920/ $\mu\text{L}$ , and platelet count of 24.2/ $\mu\text{L}$ . Tumor markers were within the normal range; carcinoembryonic antigen was 3.2 ng/mL, and carbohydrate antigen 19-9 was < 2 U/mL.

### **Imaging examinations**

Colonoscopy revealed a 0-Is+IIa lesion with slight bleeding (Figure 1A), chromoendoscopy emphasized a laterally spreading flat lesion (IIa) at the base of the protrusion (Is) (Figure 1B), and magnified endoscopy with narrow-band imaging revealed an intense irregular microvascular pattern in the Is lesion and regular caliber vascular pattern in the IIa lesion (Figure 1C and D). Computed tomography (CT) did not show any lymph node metastasis or distant metastasis.

### **Next-generation sequencing**

We analyzed the genetic alterations of the lesions in a previous report[13]. In brief, genomic DNA was isolated from formalin-fixed paraffin embedded (FFPE) specimens using a GeneRead DNA FFPE kit (Qiagen, Hilden, Germany). The mutation profile was determined by target amplicon sequencing using a GeneStudio S5 system (Thermo Fisher Scientific, Carlsbad, CA). A colorectal cancer associated gene panel including *ARID1A*, *MUTYH*, *NRAS*, *CTNNB1*, *PIK3CA*, *FBXW7*, *APC*, *BRAF*, and *KRAS*[14,15] and a pancreatic ductal adenocarcinoma (PDA)-medium panel including *KRAS*, *TP53*, *SMAD4*, *CDKN2A*, *GNAS*, *BRAF*, *PIK3CA*, *RNF43*, *STK11*, and *HRAS* were designed using the Ampliseq Designer website (<https://www.ampliseq.com>). Variants were identified using the Variant Caller plugin (version 5.0.4.0). Genetic mutations of colorectal cancers reported in the Catalog of Somatic Mutations in Cancer (COSMIC) database (<https://cancer.sanger.ac.uk/cosmic/>) were identified.

A total of four pathogenic mutations were found when using the PDA-medium panel for genetic analysis (Table 1). *TP53* p. R273H and *RNF43* p. W159Afs\*8 were found in the adenoma, and *SMAD4* p. D351G, and *PIK3CA* p. T74N were additionally found in the adenocarcinoma (Figure 2). No mutations were detected in any other genes, including *KRAS*, *GRAS*, *BRAF*, *STK11*, and *HRAS*. The *TP53* mutation in the tumor cells was confirmed by p53 immunohistochemistry. Mutations were not found when using the colorectal cancer-associated gene panel, indicating no somatic mutations in *APC*. The protocol of the genetic analysis was approved by Asahikawa Medical University Research Ethics Committee, and written informed consent was obtained from the patient.

---

## FINAL DIAGNOSIS

---

The tumor was diagnosed as a mucosal (Tis) rectal adenocarcinoma.

Table 1 Genetic analysis of the colorectal tumor

Areas	Pathological diagnosis	Somatic mutations				Qubit (ng/ul)	Library yield (pM)	Mapped Reads	Mean Depth	Uniformity	Target base coverage at 100x (%)	Target base coverage at 500x (%)
		RNF43 p.W159Afs*8	TP53 p.R273H	SMAD4 p.D351G	PIC3CA p.T74N							
a	Mucinous and signet-cell adenocarcinoma	23.1%	21.5%	20.5%	0.0%	26.8	3736.6	384372	3040	98%	99%	98%
b	Tubular adenocarcinoma	77.3%	70.3%	72.1%	0.0%	55.0	2901.2	369702	2925	98%	99%	99%
c	Tubular adenocarcinoma	63.2%	56.8%	59.6%	0.0%	75.6	2025.8	411829	3280	97%	99%	99%
d	Adenoma	56.0%	38.9%	7.2%	8.0%	29.6	2832.3	421877	3376	99%	99%	99%
e	Adenoma	33.3%	19.1%	0.0%	0.0%	66.6	1614.0	620398	4949	98%	99%	99%
f	Normal epithelia	0.0%	0.0%	0.0%	0.0%	18.7	2280.3	645324	5114	98%	99%	99%

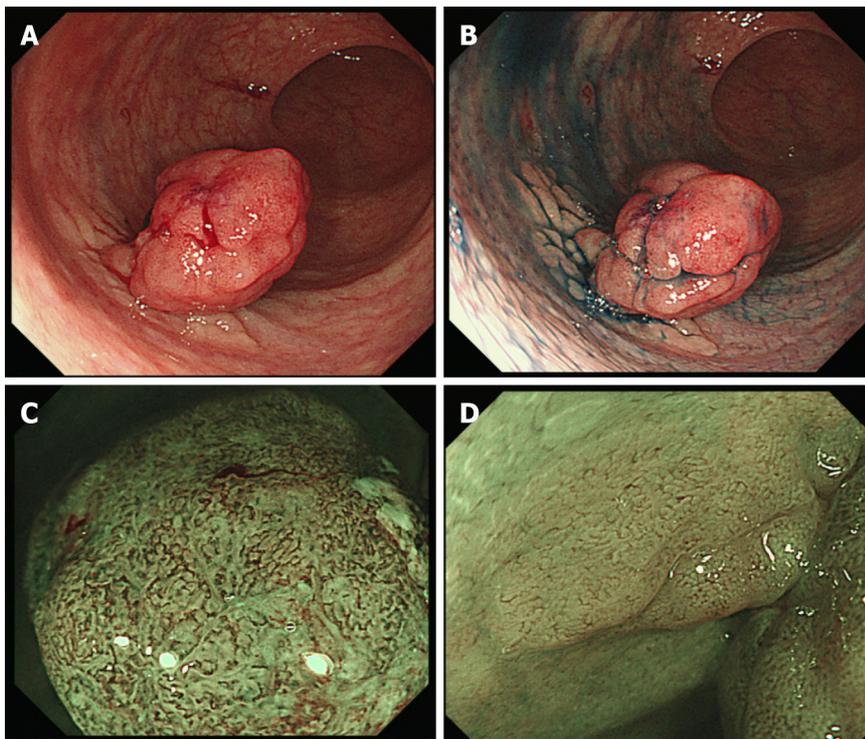
## TREATMENT

The tumor was removed by ESD. In the procedure, diluted hyaluronic acid solution was injected into the submucosa on the anal side of the tumor. Repeated local injections were needed while the submucosa was dissected just above the muscular layer toward the proximal side of the tumor. The en bloc resected tissue with the lateral normal epithelia measured 30 mm (Figure 3A).

A microscopic examination revealed an intramucosal mucinous adenocarcinoma with signet-ring cell carcinoma and well-to-moderately differentiated adenocarcinoma, with a negative margin in both the vertical and horizontal aspects (Figure 3B). A marked mucous lake was found in the center of the tumor, with signet-ring cells spreading in the mucin (Figure 3C). A basal spreading tumor 22 mm in diameter was composed of adenoma with mild to moderate dysplastic cells. The pathological diagnosis was Tis, ly0, v0, Stage 0.

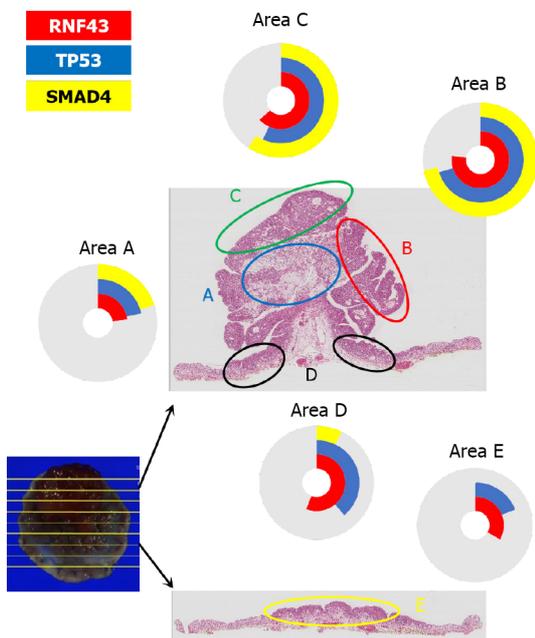
## OUTCOME AND FOLLOW-UP

Colonoscopy and CT were conducted every six months for one year, and the annual surveillance was conducted thereafter. An ESD scar was observed by the colonoscopy for two years (Supplementary Figure 1), and a 0-Is+IIa lesion was detected at the ESD scar three years later (Figure 4A). Chromoendoscopy emphasized a laterally spreading flat lesion (IIa) at the base of the protrusion (Is) (Figure 4B and C), and magnified endoscopy with crystal violet staining revealed an intense irregular microvascular pattern in the Is lesion and an invisible vascular pattern in the IIa lesion (Figure 3D and E). Three years after the ESD, CT showed no sign of lymph node metastasis. Re-ESD was chosen for the recurrent lesion, and a microscopic examination of the ESD specimens showed a submucosal invasive mucinous adenocarcinoma with well-to-moderately differentiated adenocarcinoma, and positive



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**Figure 1 Endoscopic findings of the rectal tumor.** A: A remarkable protrusion (I<sub>s</sub>) with slight bleeding is observed in the rectum; B: Chromoendoscopy enhances a flat elevated lesion (I<sub>la</sub>) which is located at the base of the protrusion lesion; C: Magnified endoscopy with narrow-band imaging reveals an intense irregular micro-vascular pattern indicating the existence of carcinoma in the I<sub>s</sub> lesion; D: Magnified endoscopy shows faint vascular pattern on the I<sub>la</sub> lesion.

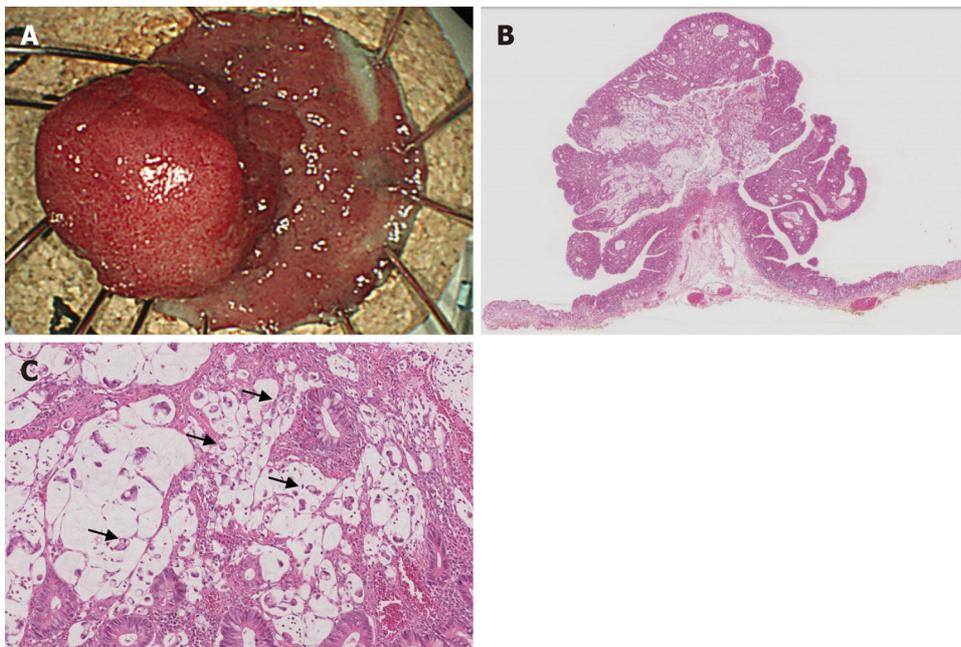


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**Figure 2 A comparison between the genetic mutations and the histopathological characteristics of the tumor.** Mucinous and signet-cell carcinoma (area A) and tubular adenocarcinoma (area B, C) shows the same mutational frequency in *RNF43*, *TP53*, and *SMAD4*. The adenoma (area D, E) shows a higher frequency for *RNF43* than for *TP53*.

vertical margins (Figure 3F). The mucinous adenocarcinoma had infiltrated the submucosal lesion under the I<sub>la</sub> lesion.

Based on these results, additional surgical resection was recommended, and Mile’s operation was performed (Supplementary Figure 2). The mucinous adenocarcinoma had infiltrated the muscle layer



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**Figure 3** A histopathological examination of the endoscopically resected specimen. A: A protruded polyp and flat elevation are removed by endoscopic submucosal dissection. The tumor margin is surrounded by normal epithelia, indicating R0 resection; B: Adenocarcinoma composed of mucinous and tubular carcinoma with an adenoma component; C: Signet ring cell carcinoma is observed in mucinous lake (arrows).

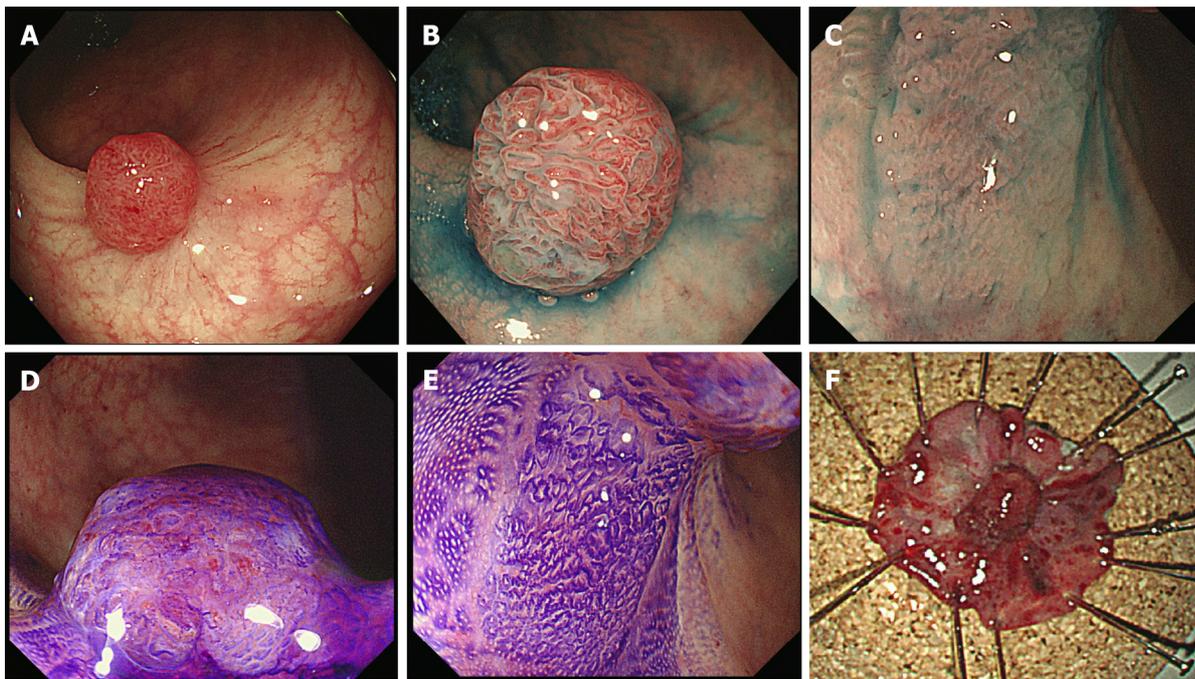
with lymphatic invasion, but there were no lymph node metastases. The eventual histological diagnosis was T2, N0, M0, Stage I. The postoperative course was normal, and the patient had no recurrence for one year.

## DISCUSSION

A mucosal mucinous adenocarcinoma with signet-ring cell carcinoma in the rectum was en bloc resected by ESD, but recurrence occurred at the scar three years later. Heterogenous histology, whereby the mucinous and tubular adenocarcinoma were developed from adenoma, was observed, and a genetic analysis revealed that a single mutated pathway was associated with these tumors. Thus, the mucinous adenocarcinoma was deemed to have originated from a laterally spreading adenoma with initial mutations in the *RNF43* and *TP53* cancer-suppressor genes.

Mucinous colorectal adenocarcinomas account for approximately 10% of colorectal carcinomas, and signet-ring cell carcinoma is rare (approximately 1%) in the incidence[16]. Signet-ring cell carcinoma has not been well evaluated due to its low incidence, and the most cases are found at an advanced stage [17]. Interestingly, as some signet-ring cell carcinomas are found in combination with adenoma, the origin of the carcinoma is speculated to originate from the adenoma[18,19]. Our case supports this theory, as the elevated lesion (Is) with an irregular vascular surface pattern developed from the IIa lesion with a regular vascular pattern. The endoscopic findings indicated the malignant histology of the tumors, with Is and IIa lesions from the carcinoma and adenoma, respectively. A histological feature of this tumor was its heterogeneity, comprising mucinous, tubular adenocarcinoma, and adenoma components.

Overall, a genetic approach is expected to clarify the tumor progression pathway. Adenoma-carcinoma sequences are proposed in common adenocarcinoma, in which sequential mutations in *APC*, *KRAS*, *TP53*, and *SMAD4* occur. However, a recent genetic examination of colorectal adenocarcinoma with a mucinous component indicated fewer *TP53* mutations than in classical adenocarcinoma[20]. In contrast, our genetic analyses of these mucinous adenocarcinomas with its adenoma component showed *TP53* p.R273H (c.818G>A, COSM10660), which is a frequent variant in common colorectal cancers. Mutations of *APC* and *KRAS*, which are frequently observed in colorectal cancers, are not observed in either adenocarcinoma or adenoma. *RNF43* W159Afs\*8 (c.474\_476delCTGinsA, which is not in the COSMIC database) was found in all areas of the tumor, and *SMAD4* D351G (c.1052A>G, COSM373800) was found in areas of the carcinoma. The mutation sequence in the progression from adenoma to adenocarcinoma was occurred from *RNF43* and *TP53*, followed by *SMAD4*. The process was similar to that observed in colitis-associated cancers, in which somatic mutation of *RNF43* is the driver genetic alteration linking chronic inflammation and cancer development in colitic cancers[21]. A lack of *APC*



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**Figure 4 Endoscopic findings of the recurrent tumor.** A: A protrusion tumor (Is) with redness is observed on the scar after endoscopic resection; B: Chromoendoscopy shows an elongated tubular surface tumor with a hypervascular pattern on the Is lesion; C: The flat elevated lesion (Ila) located at the base of Is tumor indicates dilated crypts; D: Crystal violet staining indicates irregular structured pits on the Is; E: Magnified endoscopy shows round crypts with a sessile pit pattern on the Ila lesion; F: Macroscopic view of the specimen resected by re-endoscopic submucosal dissection. The removed Is+Ila lesion is surrounded by normal mucosa.

mutations in mucinous cancer supports similarity to the colitic cancer pathway. Coincidentally, one of the characteristics of colitis-associated cancer is a high proportion of mucinous or signet-ring cell carcinomas. The histological nature corresponds to the genetic characteristics.

The mucinous colorectal adenocarcinoma-mucosal type, which was endoscopically resected in this case, was first reported in 2010[22]. To date, no other mucinous adenocarcinoma treated endoscopically has been reported in the English literature. The tumor in this case was extremely rare, as it was a limited intramucosal lesion and removed endoscopically. The presence of mucosal carcinoma with adenoma and genetic analyses of the lesions indicated the initiation of mucinous carcinogenesis. In this case, genetic mutational analysis confirmed that the mucinous adenocarcinomas derived from adenoma, and the involvement of the RNF43 pathway in mucinous carcinogenesis was proposed. In addition, the mucinous adenocarcinoma in the initial lesion was limited to the mucosal layer without a negative margin in the vertical or horizontal aspects, at the primary treatment. However, the mucinous adenocarcinoma recurred three years later. These findings suggested an aggressive genotype for the mucinous adenocarcinoma; thus, even mucosal tumors should receive close follow-up. The Japan Gastroenterological Endoscopy Society guidelines for ESD/EMR note that Tis carcinomas generally do not metastasize to lymph nodes or other organs[23]. Additional surgical resection should be considered for T1 carcinoma with malignant indicators, including a poorly differentiated phenotype (e.g., mucinous adenocarcinoma). The European Society of Gastrointestinal Endoscopy Guidelines recommend additional surgical intervention “in the cases with massive submucosal invasion, undifferentiated adenocarcinoma, positive or nonvaluable vertical margins, and/or lymphovascular infiltration by cancer cells” [24]. Mucosal (Tis) carcinoma with mucinous component is included in these criteria. The treatment strategy for mucosal (Tis) mucinous adenocarcinoma remains to be addressed.

One limitation associated with the present study warrants mentioning. The patient ultimately underwent Mile’s operation after undergoing ESD twice throughout the clinical course. Endoscopic ultrasound is useful for evaluating the depth of submucosal invasive lesions in rectal tumors before endoscopic resection[25]. The second ESD procedure might have been avoided if a more accurate pretreatment diagnosis concerning the depth of the local recurrence had been available.

## CONCLUSION

This case of mucinous mucosal adenocarcinoma was suggested to have an aggressive phenotype based on the treatment course and the advanced genotype detected by target sequencing. Careful and close

follow-up should be performed when managing patients with mucinous adenocarcinoma.

## FOOTNOTES

**Author contributions:** Murakami Y designed this case report and performed the whole study; Tanabe H helped to write the manuscript. Ono Y and Mizukami Y performed the genetic analyses. Sugiyama Y, Kobayashi Y, Takahashi K, Sasaki T, and Takahashi K were involved in the patient's diagnosis and endoscopic treatment. Ando K and Ueno N organized the patient's treatment in the hospital. Moriichi K and Kashima S processed the experimental data and performed the analysis. Yuzawa S performed the histological analysis. Fujiya M and Okumura T supervised the research.

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