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Case Report

Rectal Cancer With Distally Spreading Intramural Metastasis: A Case Report and Review of the Literature

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Introduction: Intramural metastasis (IM) is common in esophageal cancer, and it is an important factor in determining the resection area and tumor malignancy. However, IM is rare in rectal cancer; therefore, little is known about IM in rectal cancer, and the clinical significance remains unclear.

Case Presentation: We describe a case of rectal cancer with distally spreading IM. A 58-year-old man consulted a primary care physician, with a chief complaint of constipation; tests revealed a high carcinoembryonic antigen value. A colonoscopy revealed a type 2, advanced rectal tumor, which covered two-thirds of the circumference of the upper rectum. In addition, 3 protruding lesions were observed under the normal mucosa on the anal side of the primary tumor. A laparoscopic low anterior resection was performed. Pathologic findings showed that the primary tumor was a moderate-to-well-differentiated adenocarcinoma with a cribriform structure. The 3 lesions on the anal side found under normal mucosa were separate from the primary tumor, but morphologically similar to the primary adenocarcinoma; therefore, these were diagnosed as IMs. Based on a review of previous case reports, rectal carcinomas were often accompanied by vascular invasions and lymph-node metastases. Moreover, in rectal cancer, tumors with IMs often show vascular invasion. Therefore, we assumed that IM could be a marker of poor prognosis.

Conclusion: This study revealed that, in surgery, detection of a distally spreading IM is an important finding for determining the optimal surgical resection margin.

Key words: Intramural metastasis – Distal spread – Rectal cancer

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The most current statistics from the World Health Organization show that colorectal cancer is one of the most common types of cancer worldwide.[1] Curative resection remains the most effective therapy for colorectal cancer. In particular, for patients with rectal cancer, a total mesorectal excision (TME) is thought to be critical; it has provided the lowest reported rates of local recurrence and the best survival results.[2] Moreover, for rectal cancer, an abdominoperineal resection with a permanent colostomy is the most extensive and ideal surgery for curability. However, a permanent colostomy greatly affects the patient's quality of life (QOL). To preserve the anus, surgical techniques have been developed, known as "sphincter-preserving surgery," such as a low-anterior resection (LAR) or an intersphincteric resection. In removing cancers in the lower rectum, knowledge of the distal spread of tumor cells might be a critical factor for determining a safe, clear surgical margin. Many reports have described histologic findings of specimens on the anal side of rectal cancer, but distal spreading of the tumor is thought to be rare.

An intramural metastasis (IM) of gastrointestinal cancer is common in esophageal cancers, and it is important to consider in determining the resection area and tumor malignancy. However, in rectal cancer, IMs are considered rare; therefore, little is known about the clinical significance of IM in rectal cancer. Here, we describe a case of rectal cancer with a distally spreading IM. This case illustrates the difficulties involved in determining how far the resection margin should extend from the primary tumor.

Case Presentation

A 58-year-old Japanese man consulted a primary care physician with a chief complaint of constipation. The blood test revealed a high level of serum carcinoembryonic antigen (CEA; 13.6 ng/mL). An endoscopy revealed a type 2 advanced rectal cancer that occupied two-thirds of the rectum circumference (Fig. 1a). In addition, 3 "polyp-like" lesions, covered with normal mucosa, were observed on the anal side of the primary tumor. These lesions were suspected to be metastases in the rectal wall (Fig. 1b). A histologic examination of a biopsy specimen suggested that the rectal tumor was a moderately differentiated adenocarcinoma. Abdominal contrast-enhanced computed tomography (CT) images showed wall thickening in the upper rectum (Fig. 2a), swollen lymph nodes around the rectal tumor (Fig. 2b), and no distant metastasis. CT colonography showed that the primary tumor was located in the upper rectum (Fig. 2c).

A laparoscopic LAR was performed, with a proximal lymph node dissection, classified as D3 according to the Japanese Classification of Colorectal Carcinoma, 8th edition. During surgery, a rectal transection was performed for a curative resection on the anal side, to remove the "polyp-like" lesions, under the guidance of intraoperative endoscopy. Among the resected specimens, the main tumor in the upper rectum occupied two-thirds of the circumference and was classified as a type 2 advanced cancer (Fig. 3a). Three polyp-like lesions were observed on the anal side of the primary tumor (Fig. 3b). The tumor "polyp-like lesion" was present in the section plane of the rectum (Fig. 3b). A pathologic examination of the resected specimen suggested that the primary tumor was a moderate-to-well-differentiated adenocarcinoma, with a cribriform structure (Fig. 4a), and lymph node metastases of severe grade. The final diagnosis, according to the Japanese Classification of Colorectal Carcinoma, 8th edition, was, as follows; tub2>tub1, T3 (SS), ly1, v1, PN1a, N2 (17/20), PM0, DM0, RM0. In addition, the 3 "polyp-like" lesions on the anal side were found to have a morphology similar to that of the primary lesion, but clearly located apart from the primary lesion, and they were covered with normal mucosa, discontinuously. Therefore, these lesions were diagnosed as IMs (Fig. 4b and 4c). After the operation, the patient recovered without complications, and the patient was discharged. The postoperative CEA value decreased to undetectable levels.

Discussion

In 1895, Gerota[3] first described the pathologic rectal lymph flow, and in 1950, Blair *et al* classified the rectal lymph flow into three stream directions (upward, lateral, and downward), based on data from past studies.[4] Pathologic studies on rectal lymph flow revealed that the dominant flow directions around the rectum were upper and lateral; consequently, it would be difficult for lymphatic progression of rectal cancer to occur in a downward direction. In Japan, detailed pathologic studies have been carried out on rectal cancer surgical specimens to determine the distal spread of cancer in the rectum wall. For a radical resection of rectal cancer, the most extensive and ideal approach is an abdominoperineal resection with a

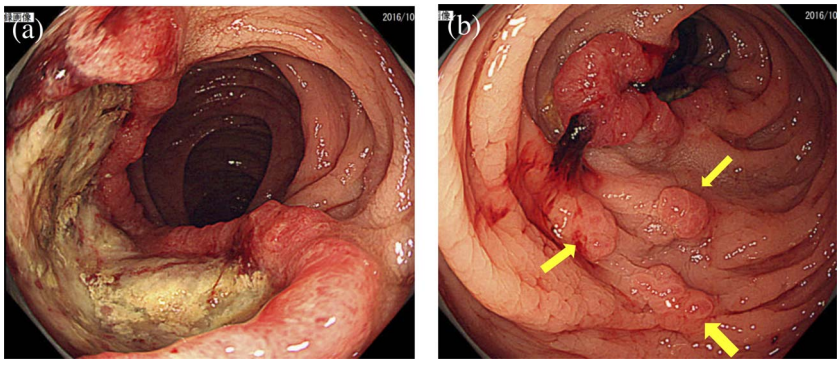

Fig. 1 Colonoscopy specimens. (a) Primary tumor extended two-thirds of the rectal circumference; it was a type 2 advanced cancer in the upper rectum (AV15 cm). The biopsy was classified as adenocarcinoma, tub1>tub2; (b) Three polyp-like lesions (*arrows*) were confirmed on the anal side of the main lesion.

permanent colostomy. However, a permanent colostomy greatly influences the patient's QOL. Recently, to preserve the anus, a remarkable technique was developed, known as sphincter-preserving surgery. When this technique is used for removing cancer in the lower rectum, knowledge of the distal spread of the tumor cells might be a critical factor in determining a safe, clear surgical margin. Shirouzu *et al*[5] comprehensively analyzed 610 resected specimens of rectal cancer and concluded that an anal resection margin of 1 cm was acceptable for most rectal cancers and that sphincter-preserving surgery was common.[6] According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines,[7] published in 2016, a 3-cm distal resection margin is necessary in removing rectosigmoid or rectal cancers with a distal edge above the peritoneal reflection, and a 2-cm distal resection margin is necessary in removing rectal cancers with a distal edge below the peritoneal reflection. However, some case reports have shown that IMs occurred 3 cm or more away from the primary tumor on the anal side.

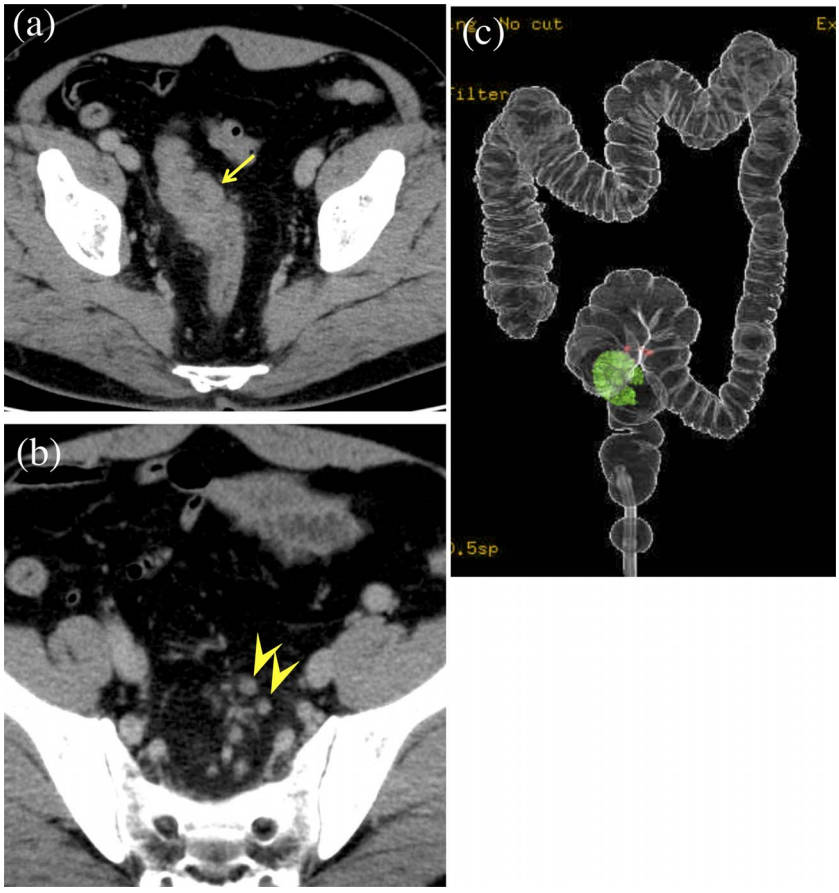

Fig. 2 Abdominal imaging of rectal cancer. (a) Contrast CT showed a wall hypertrophy (*arrow*) identified in the rectum. There were no findings of distant metastases. (b) Lymph node enlargement (*arrowhead*) detected around the lesion. (c) CT colonography shows the primary tumor (green) located in the rectosigmoid region.

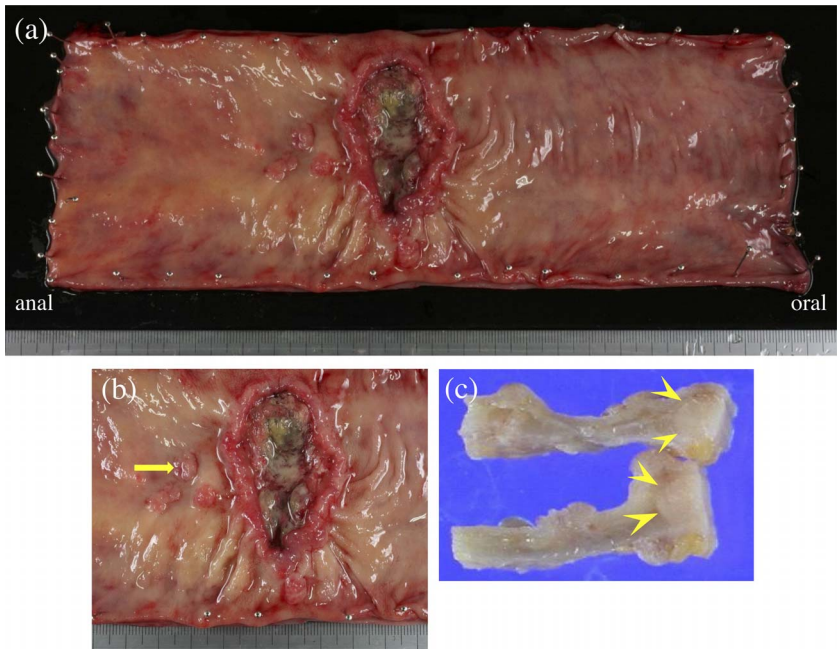

Fig. 3 Pathology of rectal cancer and intramural metastases. (a) Resected specimen. The main tumor, located in the upper rectum, occupied two-thirds of the rectal circumference, and was classified as a type 2 advanced cancer. (b) Three polyp-like lesions (*arrow*) were identified on the anal side of the primary tumor. (c) Sections of the surface of the polyp-like lesions. Tumor metastases are within the rectum wall (*arrowheads*).

Therefore, tumor remnants might occur when the JSCCR rules are applied in rectal cancers with distally spreading IMs.

We searched the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) through 2016 and the Japanese Ichushi database, maintained by the Japan Medical Abstracts Society (http://www.jamas.or.jp/), from 1983 through 2016 with the following search terms: "intramural metastasis" and "rectal cancer." We identified a total of 5 case studies[14–18] that described IM in rectal cancer (Table 1). Importantly, these IMs had formed on the anal side of the tumor in advanced cancer cases with severe lymph node metastasis. According to previous reports, in lymphovascular metastasis, massive lymphovascular invasion could obstruct the lymphovascular vessels and cause retrograde flow, which might, in turn, induce metastatic foci to seed

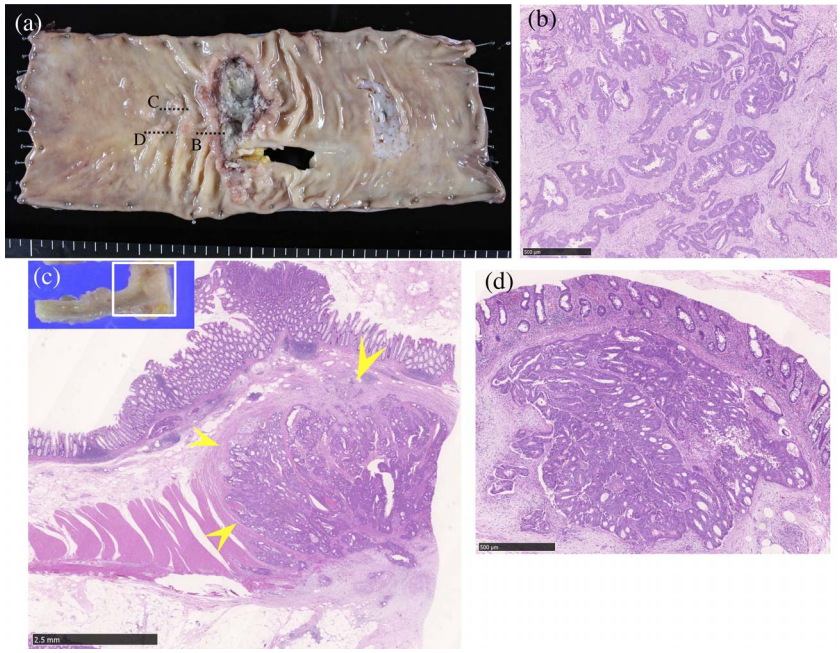

Fig. 4 Histologic analyses. (a) Resected specimen after formalin fixation. The dotted lines, labeled B, C, and D, indicate the regions shown in panels (b), (c), and (d), respectively. (b) The primary tumor is a moderate-to-well-differentiated adenocarcinoma with a cribriform structure. (c, d) Lesions on the anal side of the primary tumor were covered with normal mucosa, separate from the primary tumor, but with morphology similar to that of the primary adenocarcinoma. (c) Lesion in the muscle layer. (d) Lesion in the submucosal layer.

Table 1 Case studies of rectal cancer with intramural metastasis in the literature[a]

Author	Year	Sex	Tumor location	Histological type	T	Ly	V	N	M	Location	Distance (cm)	Recurrence site	Survival (month)
Mizutani	2003	f	Ra	tub2	T3	2	0	N1	M1 (Liver)	anal	7	Pelvic	21
Uchimoto	2007	m	RS	tub2	T3	3	2	N3	M1 (LYM)	anal	3.5	unknown	unknown
Takahashi	2008	f	Rb	SCC	T2	2	2	N1	M0	oral	7	–	19
Toda	2015	m	Rb	tub2	T1b	1	3	N0	M0	oral	2	–	48
Yamada	2017	f	Rb	tub2	T2	2	1	N3	M1 (LYM)	anal	1	–	4
Present study	2017	m	RS	tub2	T3	1	1	N2	M0	anal	3	Lung, Liver	12

[a]T, N, M = tumor size, nodal involvement, and metastasis, respectively, classified according to the Union for International Cancer Control. f = female; Ly, lymphatic invasion; LYM = lymph node; m = male; Ra = middle rectum; Rb = lower rectum; RS = upper rectum; SCC = squamous cell carcinoma; tub2 = moderately differentiated adenocarcinoma; V = venous invasion.

the perianal tissues.[7–9] From this viewpoint, it is possible that distally spreading IMs could occur, when a lymph flow reflux occurred due to a lymph duct obstruction upstream. Although we could not directly determine whether the lymph duct was obstructed in our resected specimens, we observed substantial lymph invasion; thus, it is possible that these distally spreading IMs were caused by metastasis via lymphatic vessels. In a case of early rectal cancer, described by Toda *et al*,[14] vascular invasion was more pronounced than lymph duct invasion, and numerous tumor emboli within blood, but not lymphatic, vessels were observed in regions surrounding the submucosal tumor. However, the early stages of rectal cancer might involve different pathologies. In our experience, these parts of the rectum are not typically investigated pathologically, unless there is an abnormality in the mucosa; however, when routine searches were conducted, several small IMs could be found in advanced rectal cancers.

Distally spreading IMs are a rare form of metastasis in rectal cancer. Only a few cases have been reported, and their clinical significance remains undefined and unclear.[14–18] On the other hand, IMs are often observed in esophageal cancer, and they are considered an independent prognostic factor. An IM in esophageal carcinoma was first reported by Watson[11] in 1933. In the Japanese Classification of Esophageal Cancer (11th edition), an IM is defined as a metastatic lesion in the esophageal, pharyngeal, or gastric wall, which is macroscopically (clearly) separate from the primary tumor. The frequency of IM was reported to be about 11% in esophageal squamous cell carcinoma.[12,13] The presence of IM in esophageal cancer indicates a poor prognosis, due to the high probability of lymph node metastasis and distant metastases. In the studies shown in Table 1, lymph node metastasis occurred in most cases, and postoperative adjuvant chemotherapy was performed. Lymph node metastasis and advanced vascular invasion were considered poor prognostic factors, although long-term outcomes were not reported. In 1 case report,[14] postoperative adjuvant chemotherapy was performed in Stage I, due to the high risk of malignancy associated with a tumor with IM.

It is important to identify distally spreading IMs in rectal cancer, when determining the optimal margin for a R0 resection, because some case reports identified IMs located 3 cm or more from the primary tumor on the anal side. In the present case, the distal resection margin was sufficient to avoid minimal residual cancer, because the preoperative examination identified the distally spreading IMs. Unfortunately, although a local recurrence due to minimal residual cancer was not detected, a distant metastasis recurrence was detected. Because the IMs were covered with a normal mucous membrane, visualizing malignancies would be expected to be difficult when collecting biopsies endoscopically. Previously, Uchimoto *et al*[16] reported that a preoperative endoscopic mucosal resection (EMR) of lesions suspected to be IMs was useful in determining the operative procedure. The general rule established by the JSCCR for the optimal surgical resection margin is important, but when findings lead to a suspicion of a distally spreading IM, we must eliminate the cancer completely with intraoperative endoscopy or perform a rapid pathologic diagnosis of the cut end.

Conclusion

This case study described an advanced rectal cancer with distally spreading IMs. Our pathologic analyses indicated a high-grade cancer with a poor prognosis, due to the high risk of vascular invasion and the severe grade of the lymph node metastases.

When an upstream lymphatic obstruction occurs due to severe lymphatic vessel invasion, reflux of the lymphatic flow can cause IMs to spread distally. Based on the small number of cases reported to date, it is difficult to make definitive treatment recommendations or predict outcomes. It is necessary to accumulate more data before definitive conclusions can be drawn.

Acknowledgments

The authors have no conflicts of interest to declare. This study was performed according to the ethical standards of the Declaration of Helsinki. The patient provided informed consent for the inclusion of data in this report.

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