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【 CASE REPORT 】

Single Rectal Neuroendocrine Tumor Associated with Multiple Endocrine Cell Micronests

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Abstract:
Although a few reports of neuroendocrine tumor (NET) in the stomach or appendix with surrounding micronests have been published, cases of rectal NET are rare. We herein report a unique case of a patient with single rectal NET treated endoscopically. A pathological examination revealed multiple endocrine cell micronests (ECMs) in the submucosal layer around the main NET lesion. Neither lymph node metastasis nor distant metastasis in computed tomography was observed six years after the treatment. Because case reports of multiple ECM are very rare, the significance of malignancy is unclear. It therefore appears to be necessary to accumulate similar cases.

Key words: rectal NET, ESMR-L, endocrine cell micronests

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Introduction

Neuroendocrine tumor (NET) of the gastrointestinal (GI) tract presents as a submucosal tumor (SMT). In Japan, rectal NET is the most common GI tract NET (1). While most rectal NET cases are single tumor lesions, some studies have reported multiple tumor lesions (2-5). The lesions described in these reports were less than 1 cm in diameter, although the exact size was not mentioned.

In the lung, nodular lesions of neuroendocrine cells at <0.5 cm in size are distinguished from carcinoid tumors as tumorlets; however, there is no universal regulation concerning the size of NETs in the GI tract. It is therefore difficult to judge whether or not micronests of neuroendocrine cells in GI tract are neoplasms, as the small nests cannot be pathologically recognized as neoplastic growth. In the stomach, such micronests are known as endocrine cell micronests (ECM). However, only a few reports of ECMs have been reported in the colorectum (2, 3, 5, 6), and their significance has not been clarified.

We herein report a case of single rectal NET associated with ECMs revealed by pathological exploration that was treated with endoscopic submucosal resection with band ligation (ESMR-L).

Case Peport

A 53-year-old man with no remarkable medical history of major illness and family history was referred to our hospital for endoscopic treatment of SMT in the rectum. Colonoscopy revealed a yellowish-white rectal SMT approximately 4 mm in diameter.

The lesion did not show any irregularity of the vessels, irregularity of the surface pattern, or depression (Fig. 1). Endoscopic ultrasonography (EUS) (20 MHz, UM-DP20-25R;

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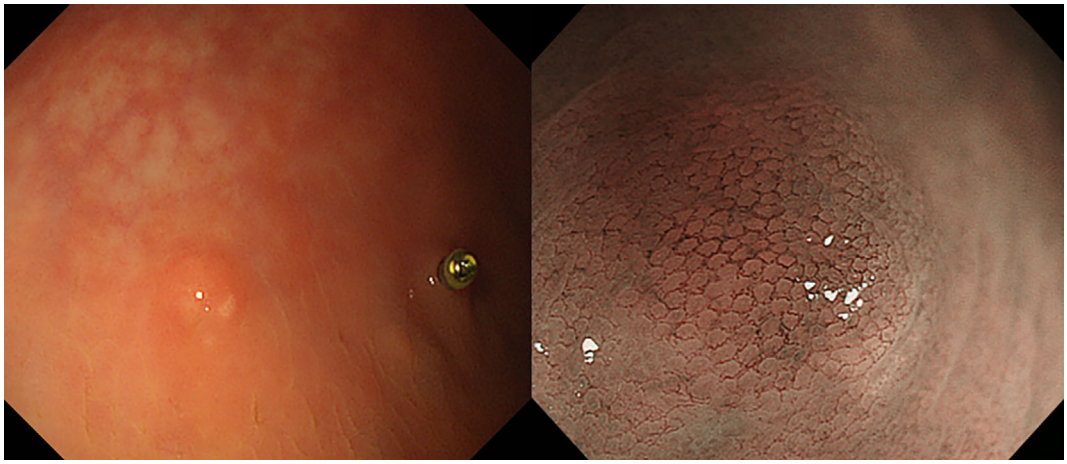

Figure 1. **Colonoscopy. Endoscopic findings of the tumor. The tumor size was approximately 4 mm in diameter. No other tumors were observed. Narrow-band imaging showed no irregularity of the micro-surface or vessel patterns.**

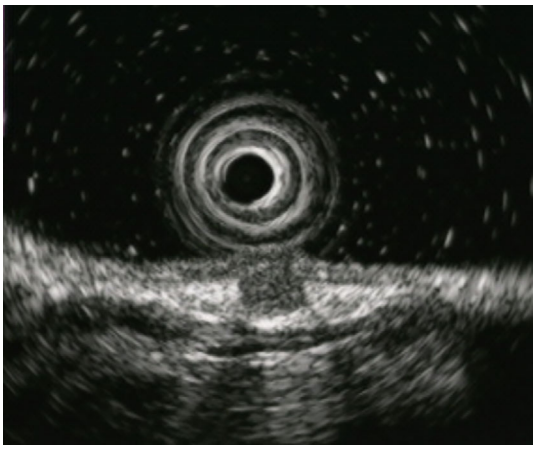

Figure 2. **Endoscopic ultrasonography. Using endoscopic ultrasonography (EUS), the submucosal tumor is depicted as a round hypoechoic mass with a clear border located at the third layer of the rectal wall. EUS showed no other hypoechoic lesions suggestive of multiple endocrine cell micronests.**

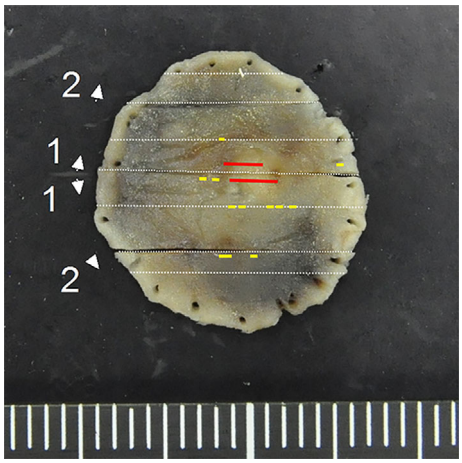

Figure 3. **Resected specimen after endoscopic submucosal resection with a ligating device. The red lines show the NET and the yellowish lines the endocrine cell micronests.**

Olympus, Tokyo, Japan) revealed a hypoechoic monotonous tumor located in the third layer that extended from the second or shallow third layer of the rectal wall. Rectal leiomyoma was considered as a differential diagnosis when the lesion was visualized using EUS as a hypoechoic tumor extending from the second layer. However, the lesion did not seem to be leiomyoma considering the endoscopic findings of a small, yellowish-white submucosal raised lesion, which suggested a rectal NET.

Enhanced computed tomography showed no evidence of hepatic metastases or intraperitoneal lymph node enlargement. Colorectal malignant lymphoma has various endoscopic findings, as a result, it thus has no characteristic features. However, malignant lymphoma was quite unlikely to be the diagnosis in this case because there was no intraperitoneal lymph node enlargement. No other hypoechoic areas were seen around the tumor (Fig. 2), nor were any signs indicative of carcinoid syndrome observed.

His blood tests showed no particular abnormalities, and tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) were also within normal limits. We therefore diagnosed the tumor as rectal NET based on endoscopic and ultrasonographic findings.

Because of the tumor size, we planned to perform endoscopic treatment as a total biopsy. *En bloc* ESMR-L was performed without any adverse events. Endoscopically, no apparent residual tumor was seen. Macroscopically, the tumor was resected with a sufficient margin, and we detected no tumors other than the main tumor (Fig. 3). Microscopically, a solid mass measuring 2 mm in diameter was found in the submucosa, composed of oval-to-round cells. NETs and micronests were not found to have proliferated in the nerves (Fig. 4).

Immunohistochemistry showed positive results for endocrine markers (synaptophysin and chromogranin A, Fig. 5).

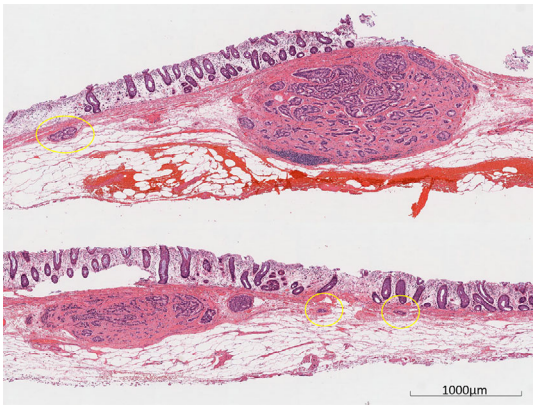

Figure 4. Microscopic image. A solid mass was seen in the submucosal layer. Multiple tiny cellular clusters (circles) were present in the muscularis mucosa or the submucosa around or apart from the main tumor (×100).

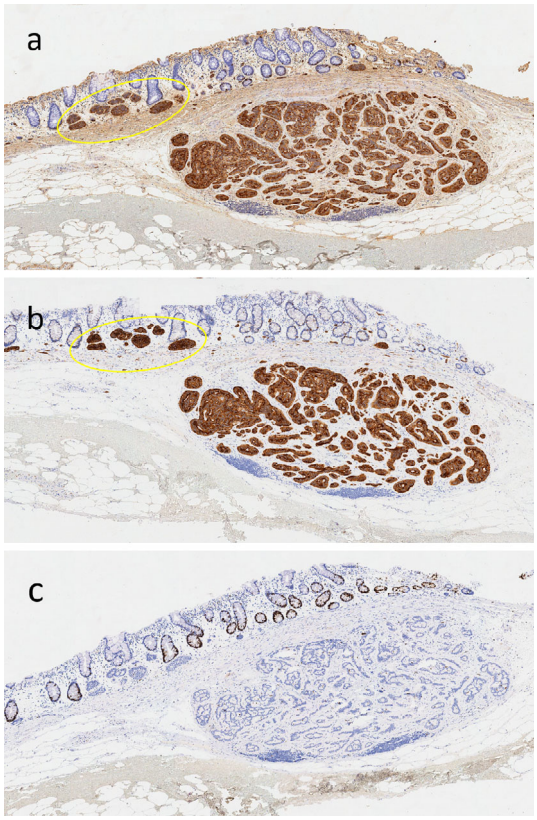

Figure 5. Immunohistochemical images. The main tumor mass and multiple endocrine cell micronests (ECMs) (circles) were positive for neuroendocrine markers by immunohistochemistry. ECMs were present in the lamina propria (×100). a: Chromogranin A, b: Synaptophysin, c: MIB-1.

Mitoses were not detected, and the MIB-1 labeling index of the tumor cells was 1.5%. Lymphovascular invasion was not detected with CD34- and D2-40-immunostained sections in the main lesion or surrounding micronests. The diagnosis of NET (Grade 1) was thus confirmed.

Micronests, which were multiple tiny cellular clusters approximately 90-250 μm in diameter and positive for synaptophysin and chromogranin A staining, were present in the lamina propria of the mucosa or submucosa near the tumor. Some of these ECMs appeared to be round and were considered endocrine cell hyperplasia. The possibility of residual ECMs near the resection site was of concern. Because the malignancy potential of ECMs is unknown, we suggested the following therapeutic options: perform additional surgical resection or monitor the situation via close follow-up. The patient ultimately refused surgery and wished to undergo close follow-up. To date, no recurrence has been observed after six years of follow-up.

Discussion

We described a case of rectal NET (Grade 1) associated with ECMs that was treated with ESMR-L. No evidence of recurrence was observed in long-term follow-up.

In the Japanese population, rectal NET is the most frequently reported GI tract NET (1). To date, only a few reports of multiple rectal NETs associated with multiple ECMs have been published (2, 3, 5, 6). ECMs may be regarded as the initial phase or intermediate stage of development of a carcinoid tumor (3). Five cases of rectal NET with ECMs have been reported (Table). All reported cases, except ours, had multiple rectal NETs. No preoperative diagnosis of ECM was made, and ECMs were only able to be identified by a postoperative pathological diagnosis.

In the case of gastric carcioids, neoplasias mainly develop from enterochromaffin-like cells in the corpus mucosa. The most common type of gastric carcinoid develops in atrophic gastritis type A and is accompanied by multiple ECMs. Hypergastrinemia induces the proliferation of enterochromaffin-like cells, which ultimately results in the development of carcinoid tumors in atrophic gastritis type A (7). Maruyama et al. (3) described the origin of ECM around a rectal NET. They reported three types of endocrine cell proliferations: i) micro-carcinoid, ii) endocrine cell microproliferation, and iii) transitional form of endocrine cell proliferation. However, whether extraglandular endocrine cells are derived from the neuroectoderm along the nerve fibers or whether they descend from endodermal stem cells is unclear. Wong et al. (8) showed that ECMs occurring in patients with inflammatory bowel disease (IBD) arose in areas of active disease, with evidence of both chronic and active inflammation in the region of the ECMs, suggesting that IBD-induced mucosal damage is causally related to the development of ECMs. However, ECMs were also present in areas of intact crypts and in the muscularis mucosae, but the causal association between IBD and NET/ECMs is unclear. Incidentally, our case was not diagnosed as IBD.

The clinical significance of ECMs is unclear. As cases of rectal NET with ECMs are very rare, the need for treatment of these structures is unclear. However, ECMs may be regarded as the initial phase or intermediate stage of the development of a carcinoid tumor (3). Furthermore, ECMs might be a sign indicating the presence of multiple carcinoid

Table. **Previous Reports of Rectal Neuroendocrine Tumor with Endocrine Cell Micronests.**

References (year)	Age	Sex	Number of NETs	Maximum tumor size (mm)	Differentiated grade	Lesion site	Location of micronests	ECM			MIB-1 index (%)	LNM	Therapy
								Synaptophysin	CGA	Grimelius			
3) (1988)	52	M	5	10	ND	Rectum and sigmoid colon	Mucosal layer	NT	NT	+	ND	-	Surgery
6) (2007)	69	M	30	<10	ND	Rectum	Mucosal and submucosal layers	NT	NT	NT	ND	-	Surgery
2) (2012)	51	M	35	8	Grade 1	Rectum	Lamina propria, muscularis mucosa, and/or submucosa	NT	+	+	0-0.6 (0-6/1,000)	+	EMR + Surgery
2) (2012)	58	M	31	7	Grade 2	Rectum	Lamina propria, muscularis mucosa, and/or submucosa	NT	+	+	0-1.9 (0-19/1,000)	+	Surgery
5) (2018)	57	M	12	5	Grade 1	Lower rectum	Submucosal layer	+	+	N3	<1	+	Surgery
Present case (2019)	53	M	1	2	Grade 1	Lower rectum	Submucosal layer	+	+	NT	1.5 (5/340) ECM: 0.3 (2/711)	-	ESMR-L

NET: neuroendocrine tumor, ECM: endocrine cell micronests, LNM: lymph node metastasis, CGA: chromogranin A, M: male, ND: not described, NT: not tested, EMR: endoscopic mucosal resection, ESMR-L: endoscopic submucosal resection with ligation

tumors and lymph node metastasis, considering the findings of previous reports (2, 5). However, Wong et al. (8) suggested that ECMs do not seem to develop into NETs, and the identification of ECMs on surveillance biopsies may not require any further clinical work-up or invasive procedures, such as endoscopic mucosal resection, which is usually performed for NET. The MIB-1 indices of the NET and ECM in the present case were 1.5% (5/340) and 0.3% (2/711), respectively. In some previous reports, the MIB-1 index for NET with ECMs was about 1%; the MIB-1 index of the ECMs was not described. These index values suggested that the NET and ECM proliferative capacity was not very high. During six years of long-term follow-up, there was no recurrence of NET in the rectum. As reported by Wong et al. (8), ECMs may not be the initial lesion of NET in the rectum. However, many points remain unclear, so further studies are required to confirm the distinct role of the ECMs.

In the present case, we reviewed the EUS images retrospectively, but ECMs could not be detected. Previous reports also failed to detect ECMs preoperatively. These results suggest that accurately diagnosing ECMs may be difficult when using EUS/intraductal ultrasound. Therefore, the appropriate diagnosis of ECMs is still a controversial issue. If multiple biopsies are performed to identify ECMs before treatment, it may be possible to detect the structures, but the precise biopsy regions and the ideal number of samples have not been clarified.

To our knowledge, this is the first report of a single rectal NET associated with ECMs. Because the relationship between ECMs and the prognosis is unknown, careful follow-up is necessary in order to catch local and distant recurrence. Such cases, while rare, should be recognized to exist.

Conclusion

Because case reports of rectal NET with ECM are very rare, the significance of malignancy is unclear. It seems necessary to accumulate similar cases.

The authors state that they have no Conflict of Interest (COI).

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