Rectal Neuroendocrine Tumor with Synchronous Pancreatic Metastasis: A Case Report

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Introduction: Gastrointestinal neuroendocrine tumors (GI-NETs) often show hematogenous metastasis, with the liver being the most common metastatic site; however, metastasis to the pancreas is rare. Case presentation: We report a rare case of rectal NETs with pancreatic metastases in a 75-year-old man who presented with a chief complaint of constipation. Imaging and endoscopic findings revealed a rectal submucosal tumor, a pancreatic hypovascular mass, and multiple liver masses. The rectal lesion and pancreatic lesions were diagnosed as neuroendocrine tumors using biopsy and endoscopic ultrasound fine-needle aspiration, respectively. Synchronous rectal NET and pancreatic NET (P-NET) with liver metastasis of either of these two were preoperatively diagnosed. A two-stage surgery was performed, comprising abdominoperineal resection and distal pancreatectomy. Pre-operative imaging findings showed a solitary mass in the pancreas, although the resected specimen contained multiple lesions. Immunohistochemical staining of the resected rectal and pancreatic lesions showed that both were synaptophysin positive and chromogranin A (CgA) negative. Generally, rectal NET cells are positive for synaptophysin and negative for CgA, while the majority of P-NETs are positive for both. The final diagnosis was rectal NETs with pancreatic and liver metastases. Till date, there have been no reports on the outcomes in patients with pancreatic metastasis of GI-NETs. Conclusions: More case reports on metastatic NETs are needed to arrive at a consensus for a standardized treatment regimen.

Key words: pancreatic metastasis, gastrointestinal neuroendocrine tumor, rectal neuroendocrine tumor, chromogranin A

INTRODUCTION

Gastrointestinal neuroendocrine tumors (GI-NETs) often show hematogenous metastasis, with the liver being the most common and pancreas being a rare metastatic site [1–4]. There are few reports on pancreatic metastasis of GI-NETs; thus, the clinical course and the indication for resection in such cases are unknown. Here we report a rare case of rectal NETs with pancreatic metastases.

CASE REPORT

A 75-year-old man visited our hospital with the chief complaint of constipation. His past medical history included hypertension, while his family history was observed to be unremarkable. Lower gastrointestinal endoscopy showed a submucosal tumor with bleeding-related mucosal erosion (delle) located approximately 25-mm from the anal verge. Abdominal computed tomography (CT) showed a 30-mm mass in the left rectal wall. T2-weighted magnetic resonance imaging (MRI) showed a high-intensity mass in the rectum (Fig. 1). The rectal mass was diagnosed as a NET on biopsy. Moreover, abdominal dynamic CT showed a 17-mm solitary hypovascular mass with an irregular border in the pancreatic body. The pancreatic parenchyma of the pancreatic tail was atrophic with dilatation of the main pancreatic duct. A thrombus-like structure was also present in the region from the splenic vein to the superior mesenteric vein (Fig. 2). Endoscopic retrograde cholangiopancreatography (ERCP) showed interruption of the main pancreatic duct in the pancreatic body. Endoscopic ultrasound (EUS) showed a 35-mm irregular low-echoic mass containing a high-echoic area (Fig. 3). EUS fine-needle aspiration confirmed the presence of a NET. Biochemical examination showed no elevation of serum insulin, glucagon, and gastrin levels, while serum calcium levels were within the normal range. Gadoxetic acid-enhanced MRI showed multiple intrahepatic masses with low intensity in the hepatobiliary phase (Fig. 4). The tumors of rectum, pancreas, and liver did not show fluorodeoxyglucose (FDG) accumulation on positron emission tomography-CT (PET-CT).

We preoperatively diagnosed synchronous tumors of rectal NET and pancreatic NETs (P-NETs), with liver metastasis in either of them. For reducing invasiveness during surgery, we performed a two-stage operation. Distal pancreatectomy with portal vein resection was performed for the pancreatic lesion, and partial

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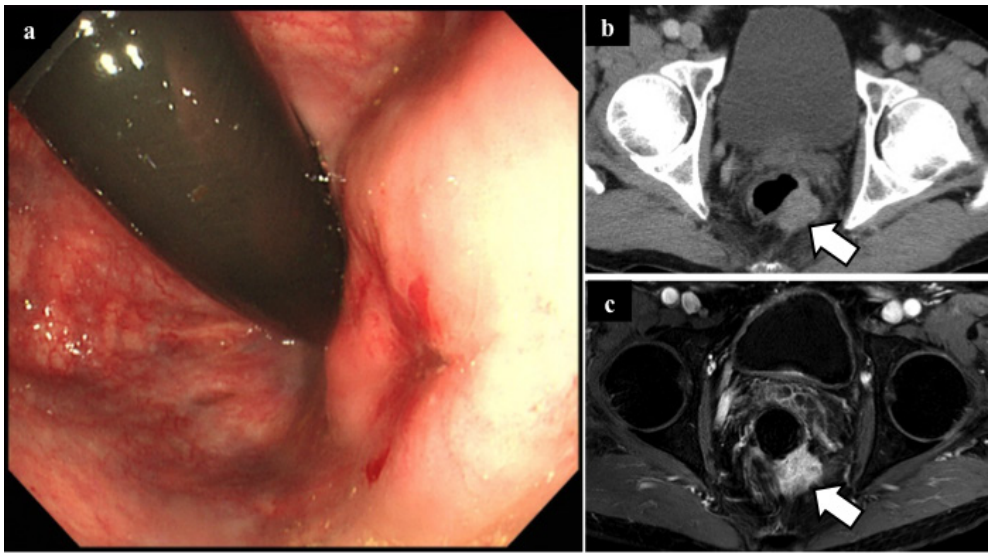

Fig. 1 Lower gastrointestinal endoscopy, abdominal computed tomography (CT), and magnetic resonance imaging (MRI) of the rectum.
Lower gastrointestinal endoscopy (a) showed a submucosal tumor with delle located 25 mm from the anal verge. Abdominal CT (b) and T2-weighted MRI (c) showed a mass (white arrow) in the left rectal wall.

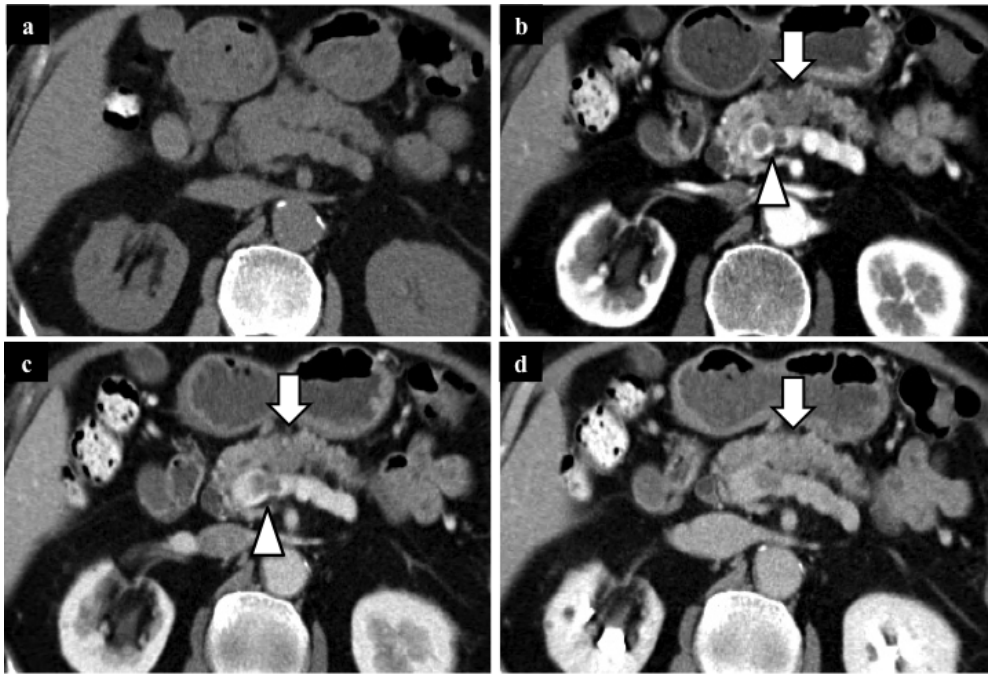

Fig. 2 Abdominal dynamic computed tomography of the pancreas.
a: plane, b: artery phase, c: portal venous phase, d: late phase
The tumor of the pancreatic body was gradually contrasted (white arrow), and a tumor thrombus-like structure was also present in the region from the splenic vein to the superior mesenteric vein (arrowhead).

resection of segment V was performed for biopsy of the hepatic lesion. Two months after pancreatectomy, abdominoperineal resection (APR) of the rectal lesion was performed.

The resected rectum showed a submucosal tumor measuring 20 x 20 mm with ulceration (Fig. 5). Microscopically, the multiple fibrotic tumor nests were distributed between the mucosa and subserosa. The tumor nodules consisted of tumor cells with trabecular, nodular, and glandular structure. Tumor cells possessed round nuclei and eosinophilic cytoplasm. Invasion to the large vessels was also identified. Immunohistochemically, tumor cells were positive for synaptophysin and CD56 but negative for chromogranin A (Fig. 6). The Ki67 labeling index was 11.3% and the mitotic index value was 0/10 high-power fields (HPFs). The rectal tumor was diagnosed as a NET G2. The simultaneously resected liver showed a metastatic nodule of NET with synaptophysin-positive and chromogranin A-negative characteristics.

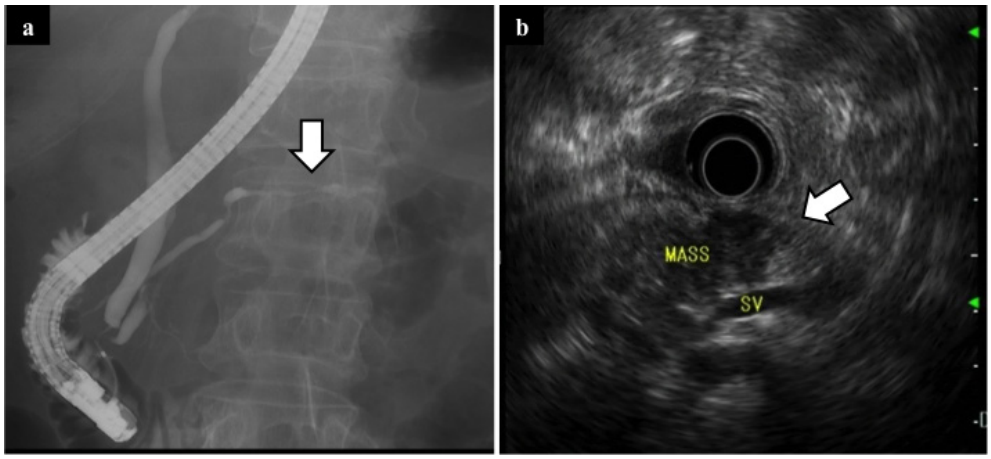

Fig. 3 Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound(EUS) of the pancreas.
ERCP (a) showed interruption of the main pancreatic duct in the pancreatic body (white arrow). EUS (b) showed a 35-mm irregular low-echoic mass containing a high-echoic area (white arrow).

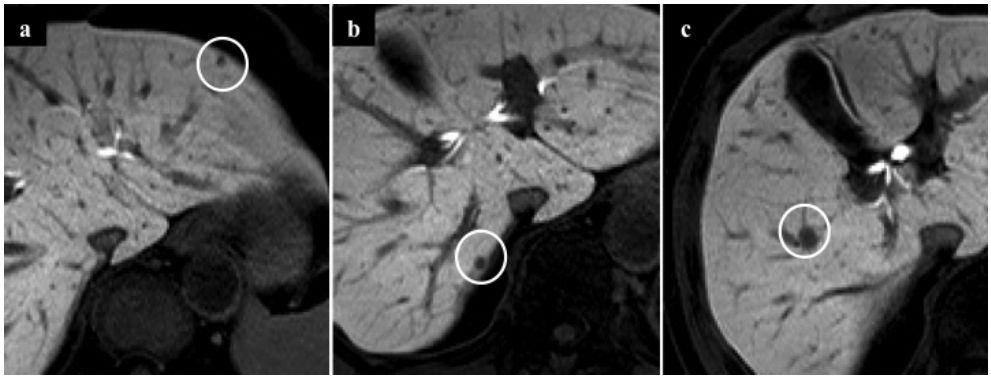

Fig. 4 Gadoxetic acid-enhanced magnetic resonance imaging (MRI) of the liver.
Gadoxetic acid-enhanced MRI showed multiple intrahepatic masses with low intensity in the hepatobiliary phase (a, b, c: white circle).

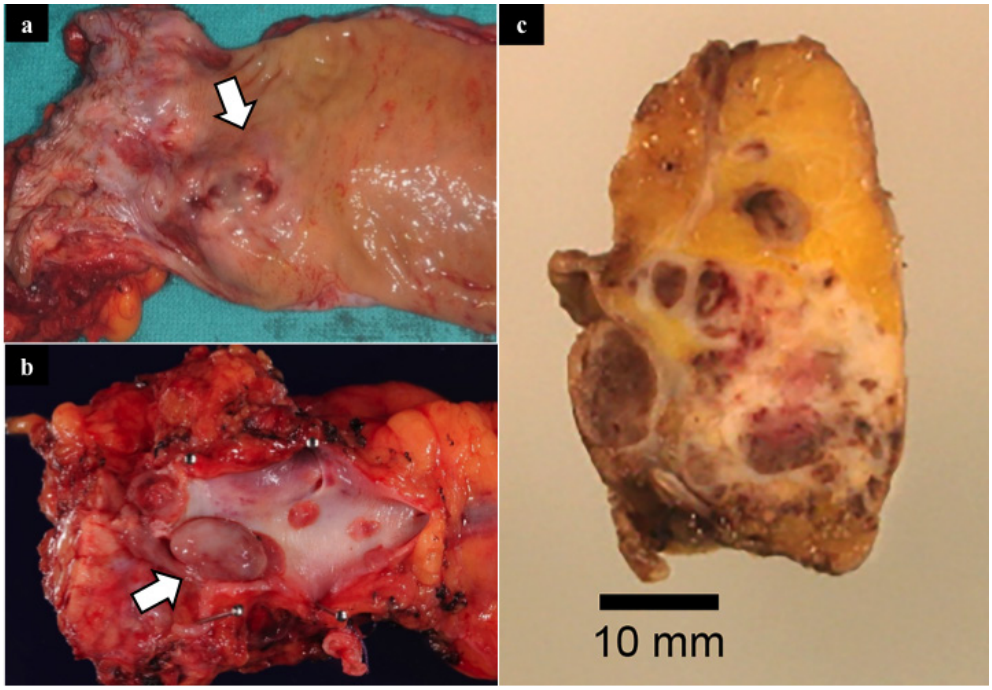

Fig. 5 Surgical specimens.
The rectal lesion (a) was a submucosal tumor with delle. The pancreatic tumor extended into the splenic vein (white arrow) (b). The resected pancreatic body and tail showed variably-sized, multiple nodular lesions with a brownish-colored cut surface (c).

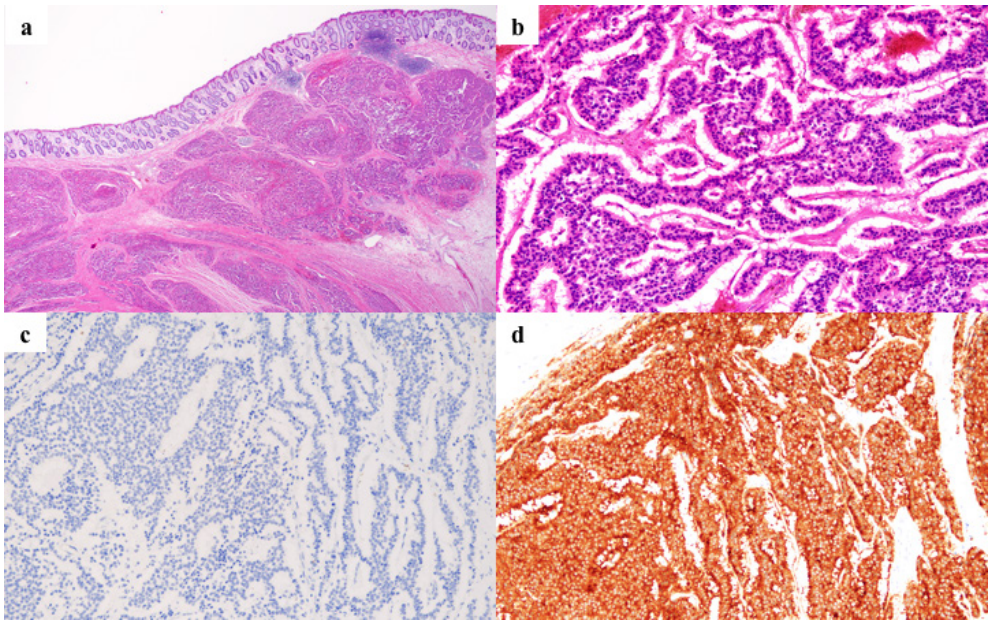

Fig. 6 Pathological findings in the rectum.
The multiple fibrotic tumor nests were distributed between the mucosa and subserosa (hematoxylin and eosin staining; magnification, x2) (a). The tumor cells possessed round nuclei and eosinophilic cytoplasm. (hematoxylin and eosin staining; magnification, x200) (b). The tumor cells were positive for synaptophysin (c), but negative for chromogranin A (d).

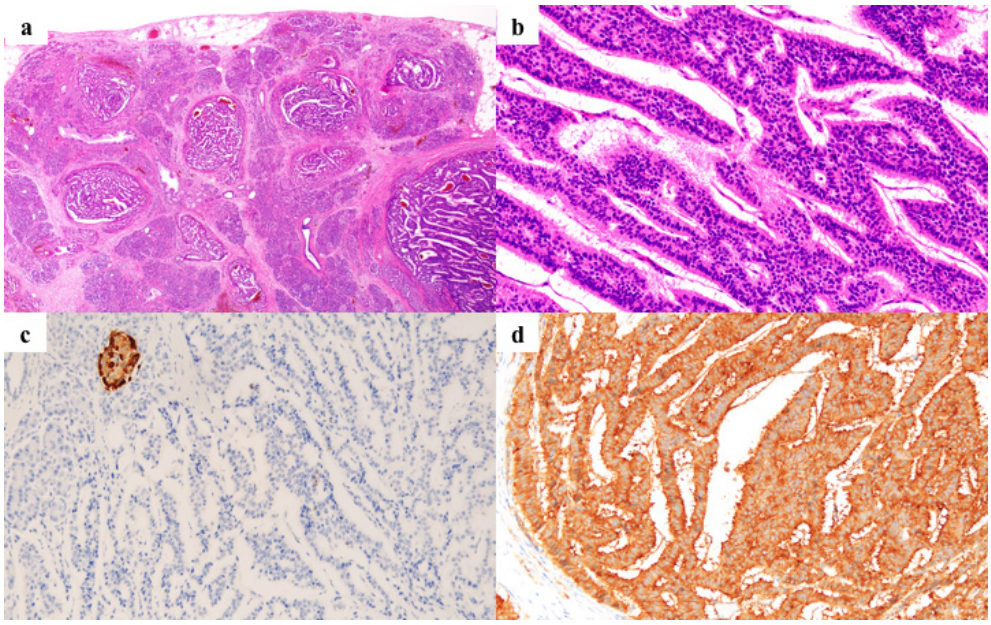

Fig. 7 Pathological findings in the pancreas.
The tumor cells had oval nuclei in a tubercular arrangement similarly to the rectal lesion (hematoxylin and eosin staining; magnification, (a): x2, (b): x200). The tumor cells were positive for synaptophysin (c), but negative for chromogranin A (d).

The resected pancreatic body and tail showed variably-sized, multiple nodular lesions with a brownish-colored cut surface. The maximum diameter of the tumor nodule was approximately 10 mm. It was apparent that the tumor had invaded into the splenic vein (Fig. 5). Microscopically, the tumor nodules were mainly located in the interlobular regions. Neither hyperplastic changes nor neoplastic changes were apparent in the islet cells. The tumor consisted of tumor cells similar to the rectal tumor. Vascular invasion, including the aforementioned splenic vein invasion, was frequently present. Immunohistochemically, tumor cells were positive for synaptophysin and CD56 but negative for chromogranin A (Fig. 7). The Ki67 labeling index was 12.3% and the mitotic index value was 0/10 HPFs. The pancreatic tumor was diagnosed as a NET G2.

In addition, this case was believed to not be a multiple endocrine neoplasia (MEN) because of the lack of familial history, lack of adrenal tumors, no elevation of serum insulin levels, glucagon, and gastrin levels, and a normal range of serum calcium.

From the following observations, we diagnosed the

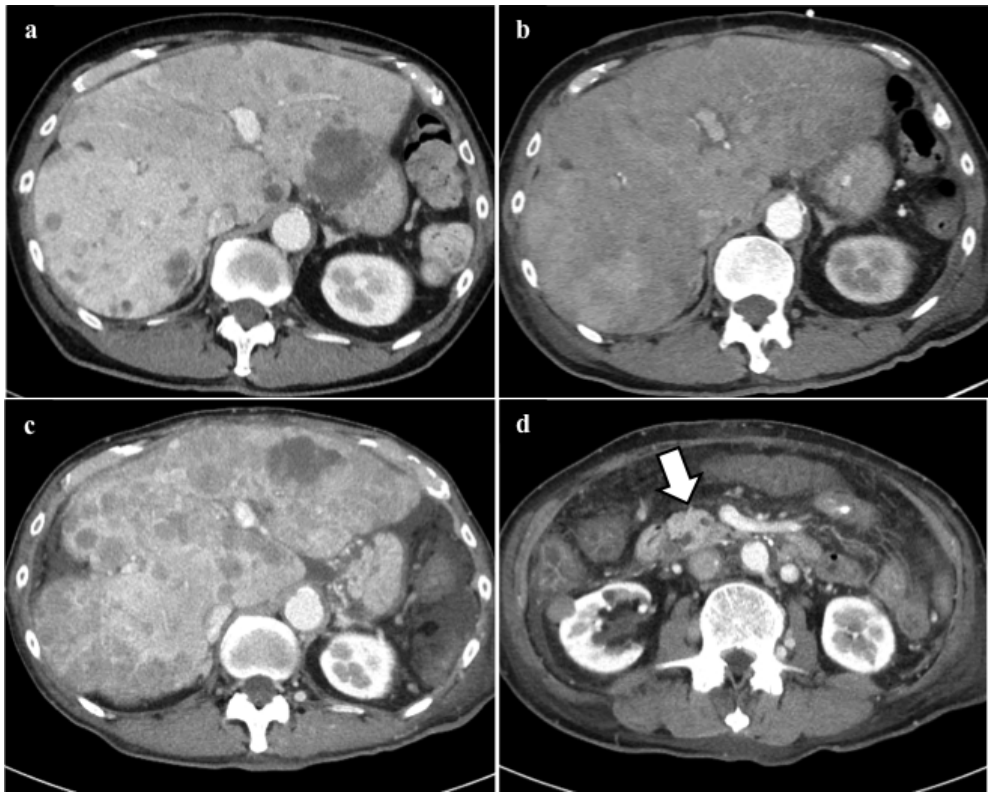

Fig. 8 Temporal change in liver metastases visualized on abdominal computed tomography (CT).
Multiple liver metastases were observed at 15 months postoperatively (a). Liver metastases were controlled after transarterial chemoembolization. A lesion on the lateral segment became unclear. (b). At 21 months postoperatively, the liver metastases spread (c), but no masses were detected in the remnant pancreas (white arrow) (d).

primary rectal NET with pancreatic and liver metastases; 1) The tumors of the rectum, pancreas, and liver showed similar histological features, 2) Tumor cells were positive for synaptophysin but negative for chromogranin A, and 3) The pancreatic tumor showed multiple nodular lesions mainly located in the interlobular regions but the existing islet cells were preserved and there was no evidence of MEN syndrome.

Four weeks after resection of rectal mass, everolimus administration was initiated. A CT performed 6 months postoperatively showed spread of the liver metastases. Therefore, a sequential administration of sunitinib, streptozocin and octreotide was initiated, but discontinued due to side effects. The liver metastatic lesions appeared stable on abdominal CT during chemotherapy. Transarterial chemoembolization (TACE) was performed for liver metastatic lesions. After the second TACE, peritoneal dissemination, pleural effusion and ascites were detected on CT, with no recurrence in the remnant pancreas (Fig. 8). The patient's general condition also gradually worsened; thus, it was impossible to continue the treatment, and he died 23 months after APR.

DISCUSSION

We encountered a rare case of a rectal NET with pancreatic and liver metastases. Pancreatic metastasis from a rectal NET is rare. According to the autopsy data on the prevalence of metastatic pancreatic tumors, 3%–12% of malignant pancreatic tumors are metastatic [1–4]. In addition, among 690 autopsy cases with malignant tumors, 103 cases had metastatic pancreatic tumors. Of those cases, only five had pancreatic metastases of a NET, with the primary being the stomach in two cases, and the extrahepatic bile duct, gallbladder, and ureter in one case each [5]. To the best of our knowledge, there are few case reports of a rectal NET with pancreatic metastasis.

The four possible metastatic routes to the pancreas are as follows: (1) continuous involvement from an adjacent organ, (2) entry into the pancreatic parenchyma through lymphatic metastasis to the surrounding lymph nodes, (3) carcinomatous peritonitis, and (4) hematogenous metastasis. In the present case, the rectal NET seemed to have spread to the pancreas by hematogenous metastasis. Even though both liver and pancreatic metastases are hematogenous, the tumor cells metastasize to the liver through the portal vein system and to the pancreas through the systemic circulation. GI-NETs including rectal NETs generally metastasize to the liver, and lung-NETs, which spread through the systemic circulation, metastasize to multiple organs such as the liver, nervous system, and bones [6]. This difference in metastatic routes through the portal vein system or the systemic circulation may lead to the high frequency of liver metastases and the rarity of pancreatic metastases.

Preoperative diagnostic imaging showed lesions in the rectum, pancreas and liver. The diagnosis was limited to one of the following three possibilities: (1) pancreatic and liver metastases of a rectal NET, (2) synchronous tumors of rectal NET and P-NETs with

liver metastasis of either NET, and (3) rectal and liver metastases of P-NETs. In the present case, the preoperative diagnosis was synchronous rectal NET and P-NET; and we thus conducted a resection of the pancreatic lesion as a P-NET. We believed that the rectal lesion involved low risk of large bowel obstruction due to tumor growth. However, pancreatectomy with increased invasiveness was probably necessary because the portal vein was occluded due to the growth of a portal vein tumor thrombus. Thus, we decided to perform a two-stage operation involving distal pancreatectomy followed by APR. Based on the number of tumors and immunohistochemical staining results, the final diagnosis was metastatic pancreatic lesions of a rectal NET. The preoperative imaging findings of the pancreatic lesion revealed a solitary mass, but the actual resected specimen contained multiple lesions.

Immunohistochemical staining showed that both the rectal and pancreatic lesions were synaptophysin positive and CgA negative. Most tumor cells of rectal NETs are usually positive for synaptophysin and negative for CgA [7, 8], whereas most P-NETs are positive for both synaptophysin and CgA [9]. Chromogranin positivity is generally correlated with the extent of granularity on electron microscopy. CgA is a major component of the secretory granules and has been used as a tumor marker for NETs. GI-NETs can be classified as midgut-type lesions with an enterochromaffin cells phenotype (EC-cell NETs) or as hindgut-type lesions with an L-cell phenotype (L-cell NETs). Rectal NETs are L-cell NETs that are usually negative for CgA [8,10]. In general, both G1 and G2 NETs often stain positive for CgA. Well-differentiated G1 and G2 NETs tend to exhibit diffuse and intense expression of CgA and synaptophysin, whereas poorly-differentiated neuroendocrine carcinomas show significantly reduced CgA expression while maintaining intense staining for synaptophysin [11].

We conducted a FDG-PET-CT for evaluating the tumor expansion. The tumors of the rectum, pancreas, and liver did not show FDG accumulation. PET-CTs have low sensitivities for NETs owing to their low proliferation potentials [12, 13]. Somatostatin receptor scintigraphy (SRS) is highly sensitive and clinically useful for NETs [14, 15]. However, in the present case, we did not perform SRS because it was not covered by the Japanese health insurance at the time.

To our knowledge, there have been no reports on the outcomes of patients with pancreatic metastasis of GI-NETs undergoing pancreatectomy for pancreatic metastasis. The pancreatectomy was performed because we preoperatively diagnosed the initial pancreatic lesion as a P-NET. In cases of P-NET with metastasis, the resection of the primary lesion seems to be advantageous for the improvement of prognosis and symptoms such as bowel obstruction, colic pain, and bleeding [16–20]. Systemic therapies including chemotherapy, somatostatin analog, and molecular targeted therapies are provided for metastatic GI-NETs [21]. In addition to these systemic therapies, local treatment options such as TACE and resection are indicated for localized liver metastases [22, 23]. The metastatic lesions were left only in the liver after rectal and pancreatic resections, and we performed TACE for their treatment. While we increased the liver metastasis treatment options, by performing a pancreatectomy, we were not able to ensure the long-term survival of our patient.

CONCLUSION

Herein, we report a rare case of rectal NET with pancreatic metastases. Pancreatic metastasis from a rectal NET is rare and more case reports are required for arriving at a consensus for a standardized treatment regimen.

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