INTERNAL MEDICINE

□ CASE REPORT □

Rectal Neuroendocrine Tumor G1 with a Solitary Hepatic Metastatic Lesion

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Abstract

Rectal neuroendocrine tumor (NET) is a relatively rare tumor. NET is classified as G1, G2, or G3 according to the degree of mitosis or Ki-67 proliferation index, which reflect the malignant potential of the tumor, such as metastasis. Advanced cases with metastasis are indicated for chemotherapy treatment. However, the efficacy of chemotherapy is limited. Therefore, resection is considered, even in metastatic cases, if complete resection is possible. We herein report a case of small rectal NET discovered with hepatic metastasis classified as G1. The patient showed good progress with no recurrence after undergoing hepatectomy and endoscopic resection of rectal NET.

Key words: rectal neuroendocrine tumor, liver metastasis, Ki-67 index, endoscopic resection

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Introduction

Neuroendocrine tumor (NET) is a relatively rare tumor with predominant neuroendocrine differentiation and it is found in most organs of the body (1). Most NETs are located in the gastrointestinal tract, pancreas, and bronchopulmonary system (2). Well-differentiated NETs were originally classified as carcinoid tumors and are frequently found in the rectum (3). However, given that NETs show a diverse malignant grade in the histological findings, the World Health Organization (WHO) advocated their classification as a histopathological hallmark, and the name "carcinoid" disappeared (4). A new histopathological classification system proposed by the WHO at 2010 now classifies NETs based on the Ki-67 proliferation index or the mitotic count, which reflect the proliferative capacity of the tumor, and facilitates predicting the prognosis (3-5).

A large tumor size, invasion into the muscularis propria, central depression or ulceration, vascular invasion, high mitotic count, and a high Ki-67 proliferation index have been proposed as risk factors of NET metastasis (6, 7). Regarding the treatment of gastrointestinal NET, surgical resection is recommended for patients without these risk factors (8-10), and endoscopic resection is widely performed for rectal NET if the size of the tumor is less than 10 mm and the depth of invasion is less than submucosal (11). In rectal NETs, the incidence of lymph node metastasis is very high for tumors greater than 10 mm in size, and radical surgery is therefore recommended (12). In contrast, systemic chemotherapy has poor efficacy for metastatic gastrointestinal NETs (13-15). Therefore, surgical resection for hepatic metastasis of gastrointestinal NETs is recommended if complete resection is possible (16-18).

We herein report a case of rectal NET graded as G1 discovered by sporadic metastasis in the liver. In this case, a metastatic lesion was found in the liver despite the small size of the primary rectal lesion and the lack of any risk factors for metastasis. The patient showed good progress following partial hepatectomy and endoscopic resection of the rectal lesion.

Case Report

A 59-year-old Japanese man was admitted to our hospital with a liver tumor. His family had no history of hepatic dis-

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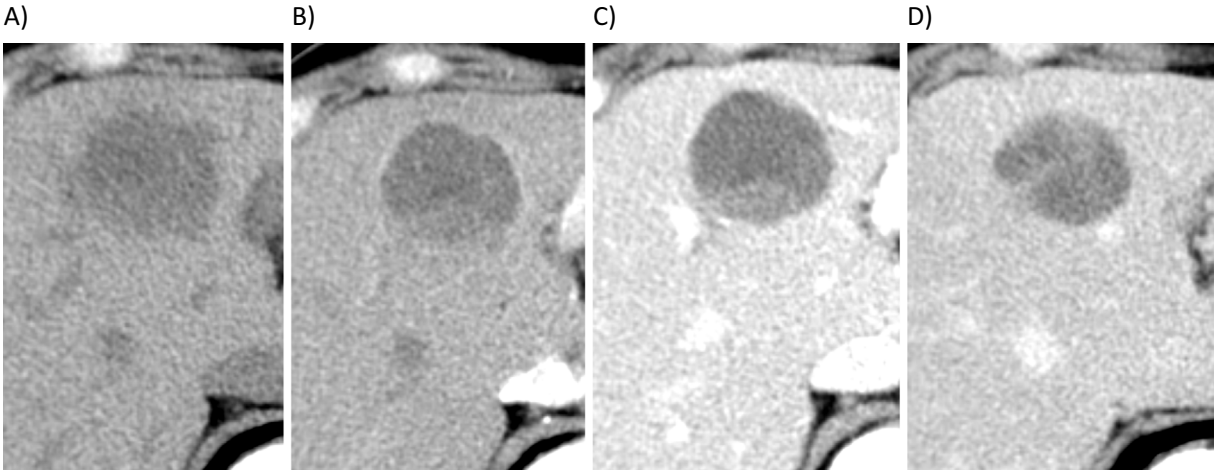

Figure 1. **A: plain phase. A tumor about 40 mm in diameter was found in S4/8 of the liver, most of which showed low intensity, but the dorsal area and periphery of the mass showed high intensity. B: Artery phase. The peritumoral area was slightly enhanced. C: Portal phase. The peritumoral area and dorsal area of the tumor were slightly enhanced. D: Equilibrium phase. The intratumoral septum was identified.**

ease. On the initial visit, his conjunctivas were not jaundiced, and the heart and respiratory sounds were normal. He did not show any symptoms related to functional carcinoids, such as flushing, asthma-like attack, or diarrhea. The liver, spleen, and tumor were not palpable. Laboratory tests showed almost normal liver biochemistry (aspartate aminotransferase, 36 IU/L; alanine aminotransferase, 29 IU/L). Hepatitis B surface antigen and hepatitis B envelope antibody were positive, while hepatitis B envelope antigen and hepatitis C virus antibody were negative. The serum hepatitis B virus (HBV) DNA level was elevated to 5.0 log copies/mL. The serum serotonin and urine hydroxyindoleacetic acid levels were within the respective normal ranges. Regarding the tumor markers, serum carbohydrate 12-5, carcinoembryonic antigen, carbohydrate antigen 19-9, and protein induced by vitamin K absence or antagonist-II levels were within the respective normal ranges. The serum alpha-fetoprotein (AFP) levels were slightly elevated, to 6.8 ng/mL, although within the normal upper limit (normal range: 0-10.0 ng/mL). The AFP-L3 fraction was negative, likely due to a chronic HBV infection.

Abdominal computed tomography (CT) showed a tumor about 40 mm in diameter in S4/8 of the liver. Most of the mass showed a low-density area, but the dorsal area and periphery of the mass showed high density. These high-density areas showed mild enhancement in arterial phase contrast-enhanced CT (Fig. 1). Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced magnetic resonance imaging, angiography, and endoscopic retrograde cholangiopancreatography in addition to abdominal CT were also performed for the evaluation of the liver tumor. The periphery of the liver tumor showed slight vascularity and slight high intensity in T2-weighted images. We noted no abnormal findings in the biliary tract except for exclusion due to the tumor. Esophagogastroduodenoscopy revealed no neoplastic lesions. In contrast, total colonoscopy revealed a small submucosal tumor at the rectum. The tumor measured 8 mm in diameter without central depression (Fig. 2A). Biopsy showed that this submucosal tumor was a well-differentiated NET (Fig. 2B). Endoscopic ultrasonography (EUS) using a miniature probe (20 MHz) with the water-filling method indicated a homogeneous hypoechoic mass, originating from the mucosa and submucosa that infiltrated within the upper two thirds of the submucosa at maximum (Fig. 2C). The depth of mural invasion was estimated to be limited to the submucosa. Capsule endoscopy for screening of the small intestinal lesion did not show any tumors in the small intestine. Fluorodeoxyglucose-positron emission tomography (FDG-PET) did not show any abnormal uptake (data not shown).

Therefore, we suspected that the liver tumor was a primary hepatic tumor, such as atypical hepatocellular carcinoma. The patient underwent partial hepatectomy, and the tumor was found to be composed of uniform cells, arranged in cords and with a ribbon-like pattern on microscopy. The tumor also contained a central region of necrosis, probably due to ischemia (Fig. 3A and B). The mitotic count was low, and the Ki-67 proliferation index was less than 2% (Fig. 3C). Immunohistologically, the tumor cells were positive for chromogranin, synaptophysin, and CD56 (data not shown). These findings indicated that the liver tumor was NET, graded as G1. We therefore suspected that the liver tumor might have metastasized from the rectal NET.

Given that the rectal tumor had a maximum diameter of 8 mm, no invasion of the muscularis propria, and no depression or ulceration in the lesion, the tumor was a candidate for endoscopic complete resection. Surgical resection with lymph node dissection was also considered, but no definite lymph node metastasis was found on CT or EUS examination (data not shown). We performed endoscopic submucosal

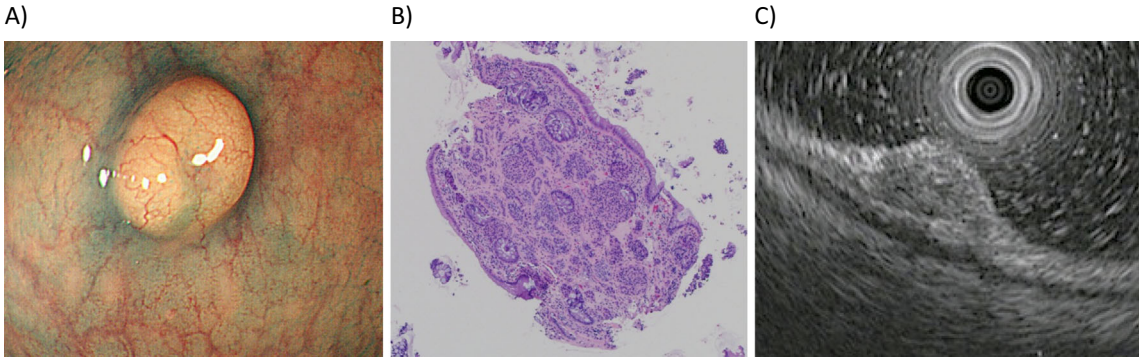

Figure 2. **The colonoscopy and pathological findings. A: A yellow-colored submucosal tumor 8 mm in diameter at the rectum was found. B: Biopsy showed peripheral ribbon-like tumor cells (Hematoxylin and Eosin staining, ×4). C: Endoscopic ultrasonography revealed a homogeneous hypoechoic mass located within the submucosal layer.**

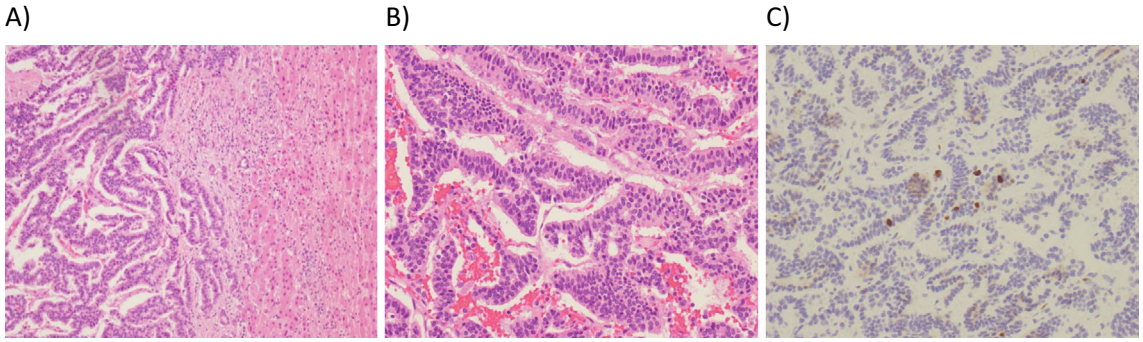

Figure 3. **The pathological findings of partial hepatectomy. A: The tumor was composed of uniform cells, arranged in cords and with a ribbon-like pattern [Hematoxylin and Eosin (H&E) staining, ×40]. B: H&E staining, ×200. C: The immunohistochemical findings of Ki-67 staining.**

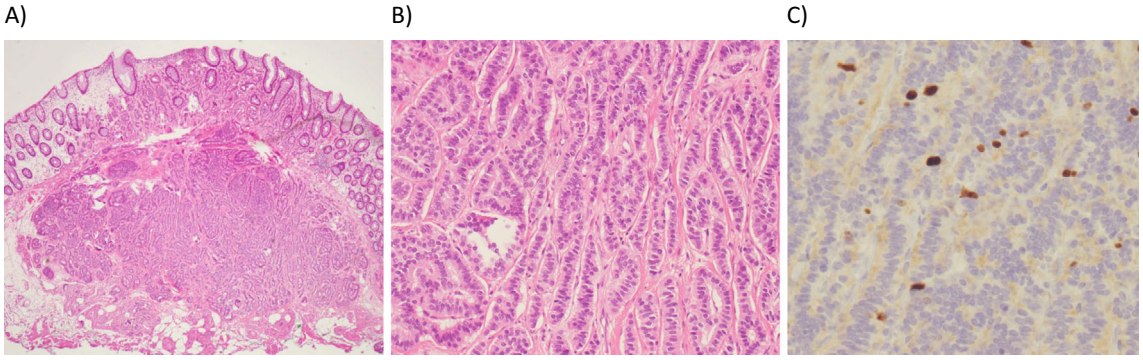

Figure 4. **The pathological findings of endoscopic submucosal resection with a ligation device (ESMR-L). A: Complete resection of the tumor in the submucosal layer. B: The tumor was composed of uniform cells, arranged in cords and with a ribbon-like pattern (Hematoxylin and Eosin staining, ×200). C: The immunohistochemical findings of Ki-67 staining.**

resection with a ligation device (ESMR-L). If any invasion to the muscularis propria or vessels was found in the specimen, we considered additional surgical resection. The histopathological findings of the resected specimen showed an 8-mm submucosal tumor with no vascular invasion, and complete resection with negative both lateral and vertical margins was confirmed. Immunohistchemical staining of a deeper section with anti-D2-40 and CD31 antibodies revealed no invasion into the vessels. Central depression was also not found in the specimen (Fig. 4A). The depth of invasion was mainly submucosal, but partly lamina propria mucosae. As with the hepatic lesion, the mitotic count was low, and the Ki-67 proliferation index was less than 2% in the resected specimen (Fig. 4B and C). Immunohistologically,

the tumor cells were also positive for chromogranin, synaptophysin, and CD56 (data not shown). These findings indicated that the rectal submucosal tumor was NET, graded as G1. The patient was followed up as an outpatient for two years with evaluation by CT and endoscopic examination every three months, and no recurrence of NET has been found.

Discussion

Rectal NET is a relatively rare tumor with an incidence rate of 0.14-0.76/100,000 cases (19, 20). Lymph node and liver metastasis are frequently found in patients with NET, and bone or lung metastases have also been reported (6). Resection is the gold standard for treatment of rectal NET. Therefore, the presence of metastasis is an important issue in the treatment decision for rectal NET. Metastasis in the present patient was discovered based on a solitary hepatic tumor. He was an HBV carrier, and his serum AFP level was slightly elevated, which made it difficult to distinguish the tumor from the primary hepatic tumor and to decide on an appropriate treatment strategy. Partial hepatectomy confirmed that the hepatic tumor was NET G1. The possibility of metastasis from the liver to the submucosal layer of the rectum was unlikely. At first, the rectal NET was not thought to be the primary lesion of hepatic metastasis because of the size and shape. However, a total gastrointestinal examination showed that only the rectal NET was the primary lesion, suggesting that the rectal NET had metastasized to the liver.

However, the tumor of the rectum found in this case was small, with no depression or ulceration. Furthermore, a histological examination showed no definite invasion into the muscularis propria or vessels, a low mitotic count, and low Ki-67 proliferation index. Thus, none of the previously reported risk factors for NET metastasis were present in this case (6, 7). There have been a few reports of rectal NET with liver metastasis even in the absence of the above risk factors, especially after the proposal of the new WHO classification system. Larger studies adopting the new WHO classification are needed. In this case, hepatic metastasis was found despite the primary rectal NET being graded as G1. Therefore, the possibility of metastasis should be considered in all cases of rectal NET.

However, it may be necessary to consider the possibility of a hepatic tumor as the primary hepatic NET. The characteristics of the hepatic tumor in this case, such as its solitary nature and enhanced capsule, was relatively compatible with those found in primary hepatic NET (21). However, primary hepatic NET is an extremely rare tumor (19, 22). Although synchronous multiple occurring NETs have been reported within the same organ, such as the small intestine or stomach (19, 23, 24), there have been no reports of synchronous multiple NETs occurring in other organs. Therefore, in the present case, we suspected that the primary rectal NET had metastasized to the liver and progressed at the metastatic site. Most previous reports did not examine the whole gastrointestinal tract. Therefore, they could not exclude the possibility that primary small intestinal NET could not be diagnosed. In the present case, we examined all of the gastrointestinal tract, including the small bowel, and found no other primary lesions except that in the rectum. Bellutti et al. reported that small intestinal NETs were discovered by double balloon endoscopy in 33% of cases with primary unknown metastatic NETs (25). Small intestinal lesions should be examined by capsule endoscopy or double balloon endoscopy to determine the primary lesions of hepatic NETs. However, capsule endoscopy might overlook small submucosal lesions because small intestinal neoplastic lesions have been reported to be overlooked by capsule endoscopy in approximately 20% of cases (26). Double balloon endoscopy might be considered for the diagnosis of small intestinal NETs.

With regard to the treatment options, surgical resection for liver metastases of NET G1/2 has been reported to show a good survival rate of 60-80% at 5 years (27). In this case, we diagnosed the hepatic tumor as metastasis of NET after liver resection. Therefore, we focused on treatment for the primary rectal NET. Endoscopic resection is recommended for rectal NET, which is estimated as 10 mm in diameter and confined to the submucosal layer (7). For endoscopic resection, ESMR-L and endoscopic submucosal dissection have been reported to provide overall high complete resection rates (28, 29). In this case, we were able to resect the rectal NET completely by ESMR-L. As this case had liver metastasis, surgical resection was considered. If the histopathological findings of endoscopic resected specimen had shown any invasion into the muscularis propria or vessels, an additional surgery would have been planned. Consequently, the rectal tumor and liver metastatic tumor were both resected completely, and we found no residual lesions on imaging studies after resection. Systemic chemotherapy did not show efficacy for metastatic gastrointestinal NETs (13-15), and only octreotide LAR showed prolongation of time to tumor progression in a randomized controlled trial for midgut NETs (30). However, adjuvant chemotherapy is not recommended in the guidelines (9, 10, 27), and a recent study showed a low incidence of recurrence after endoscopic resection for rectal NETs, even in cases of incomplete resection (31). Therefore, our patient has been followed up carefully without chemotherapy. Further observation over a long period is required in this case.

In conclusion, the findings in the present case suggested that rectal NET without any risk factors for metastasis can spread to the liver. If the primary and metastatic lesions are both completely resectable, then the outcome may be favorable in patients with NETs.

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

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