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【 CASE REPORT 】

Intratumoral Hemorrhage of Liver Metastasis from a Rectal Neuroendocrine Tumor

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Abstract:
A 56-year-old healthy woman was referred to our hospital for abdominal pain. Contrast-enhanced computed tomography (CT) showed a 14-cm-diameter liver tumor with intratumoral hemorrhage. We performed emergent transcatheter arterial embolization. She was referred to hepatic surgeon (M.M.) for resection. Preoperative colonoscopy showed an elevated lesion measuring 2 cm in diameter that was pathologically diagnosed as a rectal neuroendocrine tumor (NET). We performed low anterior resection of the rectum, followed by extended right hepatectomy for all hepatic lesions. Intratumoral hematoma was observed in the largest hepatic lesion (size: 150 mm×100 mm). Microscopy also indicated NET G2. We pathologically diagnosed a liver tumor from a rectal NET that bled spontaneously.

Key words: intratumoral hemorrhage, liver metastasis, neuroendocrine tumor

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Introduction

Spontaneous hemorrhage of a malignant liver tumor represents a life-threating event, and hepatocellular carcinoma (HCC) is the most common cause of spontaneous hemorrhage of liver tumors (1-3). While there have been a few reports on spontaneous hemorrhage of liver metastasis accompanied by hemoperitoneum (3, 4), reports of intratumoral hemorrhage of metastatic liver lesions are rare. We herein report the first case of intratumoral hemorrhage of liver metastasis from a rectal neuroendocrine tumor (NET).

Case Report

A 56-year-old healthy woman was referred to our hospital for abdominal and lower back pain and a liver tumor that was detected on emergent computed tomography (CT). The sudden onset pain was dull, and had worsened in the 2 days before her admission. The patient was pale, her arterial blood pressure was 112/72 mmHg, and her heart rate of 135 beats per minute. A physical examination revealed a tender, palpable abdominal mass in the right upper abdominal quadrant. The laboratory data on admission are shown in Table. The patient's white blood count, and total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyltransferase and C-reactive protein levels were elevated. Her platelet count, prothrombin time, and albumin, sodium and chloride levels were decreased. All of the other values were normal. The patient's tumor maker levels (α-fetoprotein and des-γ-carboxy-prothrombin) were within the normal limits and the patient was negative for hepatitis B surface antigen and hepatitis C antibodies (Table). Ultrasonography of the liver showed a well-defined, large hepatic tumor with heterogenous and predominantly high echoic lesion and echo-free space with posterior echo enhancement, and suspected intratumoral hemorrhage (Fig. 1a). Plain CT showed a liver tumor of 14 cm in diameter on the right lobe with heterogeneous attenuation without ascites (Fig. 1b); contrast-enhanced

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Table. **Laboratory Data on Admission.**

Variable	Results	Normal range	Variable	Results	Normal range
<Hematology>			γ-GTP	68 IU/L	9-32
WBC	225 $\times 10^2$/mm^3	33-86	Total protein	7.0 g/dL	6.6-8.1
RBC	435 $\times 10^4$/mm^3	386-492	Albumin	4.0 g/dL	4.1-5.1
Hemoglobin	12.1 g/dL	11.6-14.8	BUN	18 mg/dL	8-20
Platelet	12.0 $\times 10^4$/mm^3	15.8-34.8	Creatinine	0.8 mg/dL	0.5-0.8
<Coagulation>			Sodium	134 mEq/L	138-145
PT	70 %	80-120	Potassium	3.8 mEq/L	3.6-4.8
PT-INR	1.2	0.9-1.1	Chloride	100 mEq/L	101-108
APTT	39.4 s	25-40	Blood glucose	107 mg/dL	73-109
<Biochemistry>			CRP	26 mg/dL	<0.14
T. bil.	3.7 mg/dL	0.4-1.5	<Immunology>		
D. bil.	0.8 mg/dL	<0.2	AFP	2.6 ng/mL	<13.4
AST	182 IU/L	13-30	DCP	32 mAU/mL	<40
ALT	64 IU/L	7-23	<Viral maker>		
LDH	2,818 IU/L	124-222	Hepatitis B surface antigen	Negative	
ALP	204 IU/L	106-322	Hepatitis C antibody	Negative	

WBC: white blood cell, RBC: red blood cell, PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, T. bil.: total bilirubin, D. bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyltransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, AFP: α-fetoprotein, DCP: Des-γ-carboxy-prothrombin

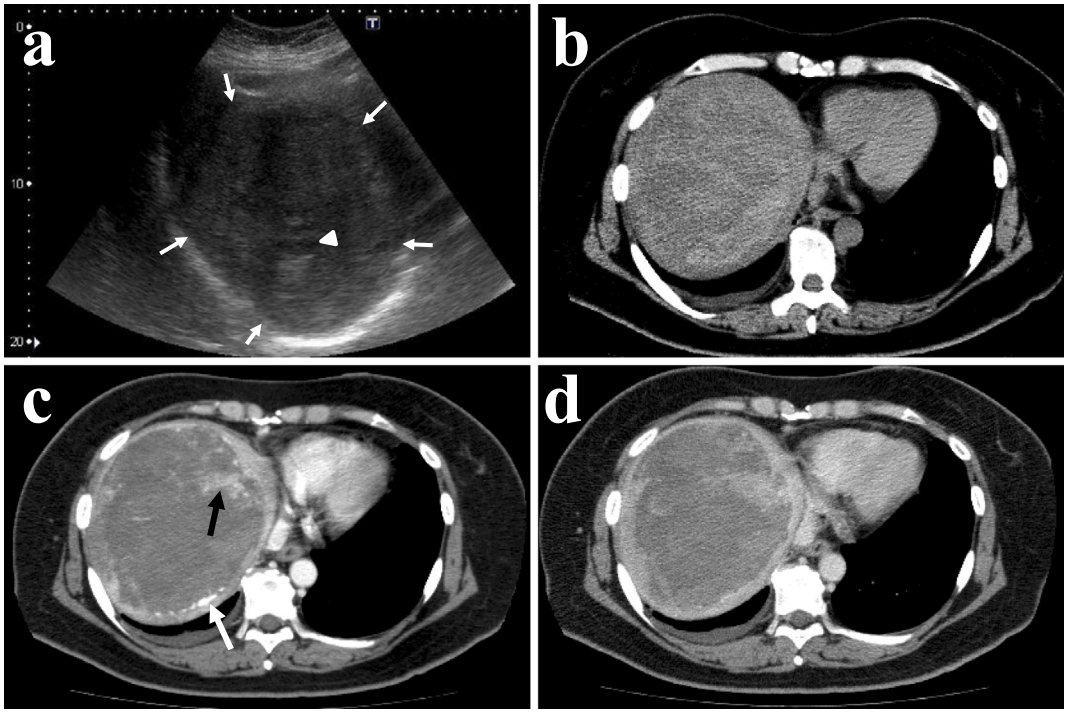

Figure 1. **Ultrasonography of the liver showed a well-defined, large hepatic tumor with heterogenous and predominantly high echoic lesion (white arrowheads), which was suspected to represent hemorrhagic debris. At the centro-dorsal area in the tumor, a small echo-free space with posterior echo enhancement (white triangle) indicating fluid collection in the tumor (a). Plain computed tomography (CT) showed a liver tumor of 14 cm in diameter on the right lobe with heterogeneous attenuation without ascites (b); Contrast-enhanced CT showed high attenuation areas on the left and anterior side of the tumor (black arrowhead) and enlarged arteries on the posterior side of the tumor (white arrowhead) (c). The high attenuation areas gradually spread into the tumor (d), suggesting intratumoral hemorrhage.**

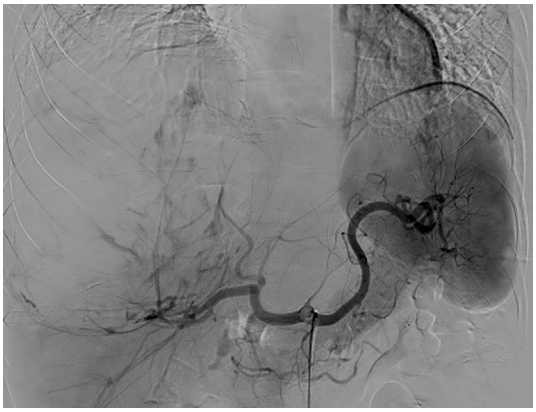

Figure 2. **Angiography of the celiac artery showed multiple faint tumor stains and extravasation on the medial and cranial sides in the tumor. Transcatheter hepatic artery embolization (TAE) was performed with ethanol, lipiodol, and gelatin particles from the middle hepatic artery and right anterior hepatic arteries.**

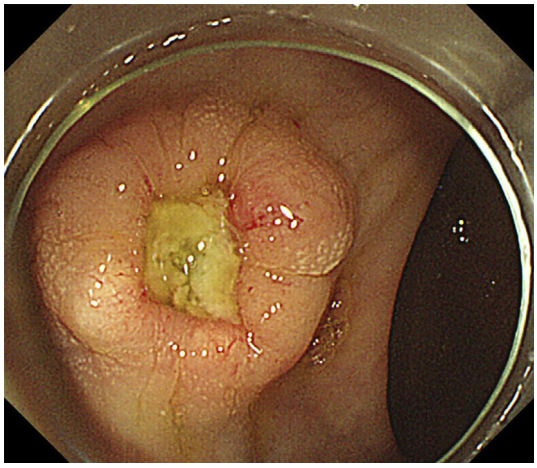

Figure 3. **Colonoscopy showed an elevated lesion of 2 cm in diameter with central necrosis resembling a submucosal tumor in the lower rectum.**

CT showed high-attenuation areas on the left anterior side of the tumor and enlarged arteries on the posterior side of the tumor (Fig. 1c). The high attenuation areas gradually spread into the tumor (Fig. 1d), suggesting intratumoral hemorrhage. We made a tentative diagnosis of intratumoral hemorrhage associated with HCC and emergent angiography was performed. Angiography of the celiac artery showed multiple faint tumor stains and extravasation at the medial and cranial sides of the tumor (Fig. 2). Transcatheter hepatic artery embolization (TAE) with ethanol, lipiodol, and gelatin particles was performed from the middle and right anterior hepatic arteries. The patient's abdominal pain gradually subsided, and she was discharged 9 days after TAE. We referred her to hepatic surgeon (M.M.) for resection. Preoperative colonoscopy showed an elevated lesion measuring 2 cm in diameter resembling a submucosal tumor with central necrosis in the lower rectum (Fig. 3). A tumor biopsy was performed, and pathological examination indicated a rectal NET. Thus, we strongly suspected that the liver tumor with intratumoral hemorrhage was metastasis from the NET. A preoperative CT scan showed that the liver was the only site of distant metastasis. Thus, surgical treatment for the primary rectal lesion followed by liver resection was scheduled. Right portal vein embolization (5) and low anterior resection of the rectum with lymph node dissection were carried out. A pathological examination showed a small alveolar, ribbon-like trabecular structure; the mitotic index was 4 per 10 high-power fields. Immunohistochemical staining was negative for chromogranin A, positive for synaptophysin, and the Ki-67 index was 15%, suggesting NET G2 (Fig. 4). Subsequently, extended right hepatectomy was performed to resect all of the hepatic lesions. Macroscopic examination of the liver specimen revealed 7 lesions, the total weight of the specimen was 1,432 g and hematoma was observed in the largest tumor (size: 150 mm×100 mm) due to intratumoral hemorrhage. A microscopic examination showed that the findings were consistent with the rectal tumor. Immunohistochemical staining was weakly positive for chromogranin A and positive for synaptophysin and somatostatin receptor type 2a; the Ki-67 index was 20%, indicating NET G2 (Fig. 5). We pathologically diagnosed the bleeding liver tumor as metastasis from rectal NET. Recurrence of multiple lung metastases and liver metastases of NET were observed on follow-up enhanced CT and magnetic resonance imaging (MRI) at one year after surgery. The patient is currently receiving octreotide long-acting release therapy.

Discussion

The major etiology of spontaneous hemorrhage of liver tumor is HCC (1), which is the most common type of primary liver tumor. Spontaneous hemorrhage can lead to intratumoral or subcapsular or intraperitoneal hemorrhage with or without signs of hypovolemic shock. Spontaneous hemorrhage of HCC occurs in 3-15% of HCC patients, and is reported to result in a high in-hospital mortality rate of 25-75% (6). While liver adenoma is also frequently encountered in liver tumors with spontaneous bleeding, bleeding from other types of liver tumors is extremely rare (7). Among these hemangioma and biliary cysts are the most frequently encountered entities (7). Thus, spontaneous hemorrhage of liver metastasis is highly unusual; fewer than 50 cases have been reported to date (7). One possible explanation is that liver metastases tend to be more fibrotic, less vascular, and invasive, and to penetrate the liver capsule less frequently than HCC (4). Although a case of spontaneous intraperitoneal hemorrhage of liver metastasis of small cell neuroendocrine carcinoma (NEC) of the maxillary sinus has been previously reported (8), there are no previous reports of spontaneous intratumoral hemorrhage of liver metastasis of rectal NET. To the best of our knowledge, this is the first reported case of intratumoral hemorrhage of liver metastasis.

The locations of the primary tumors in the reported cases

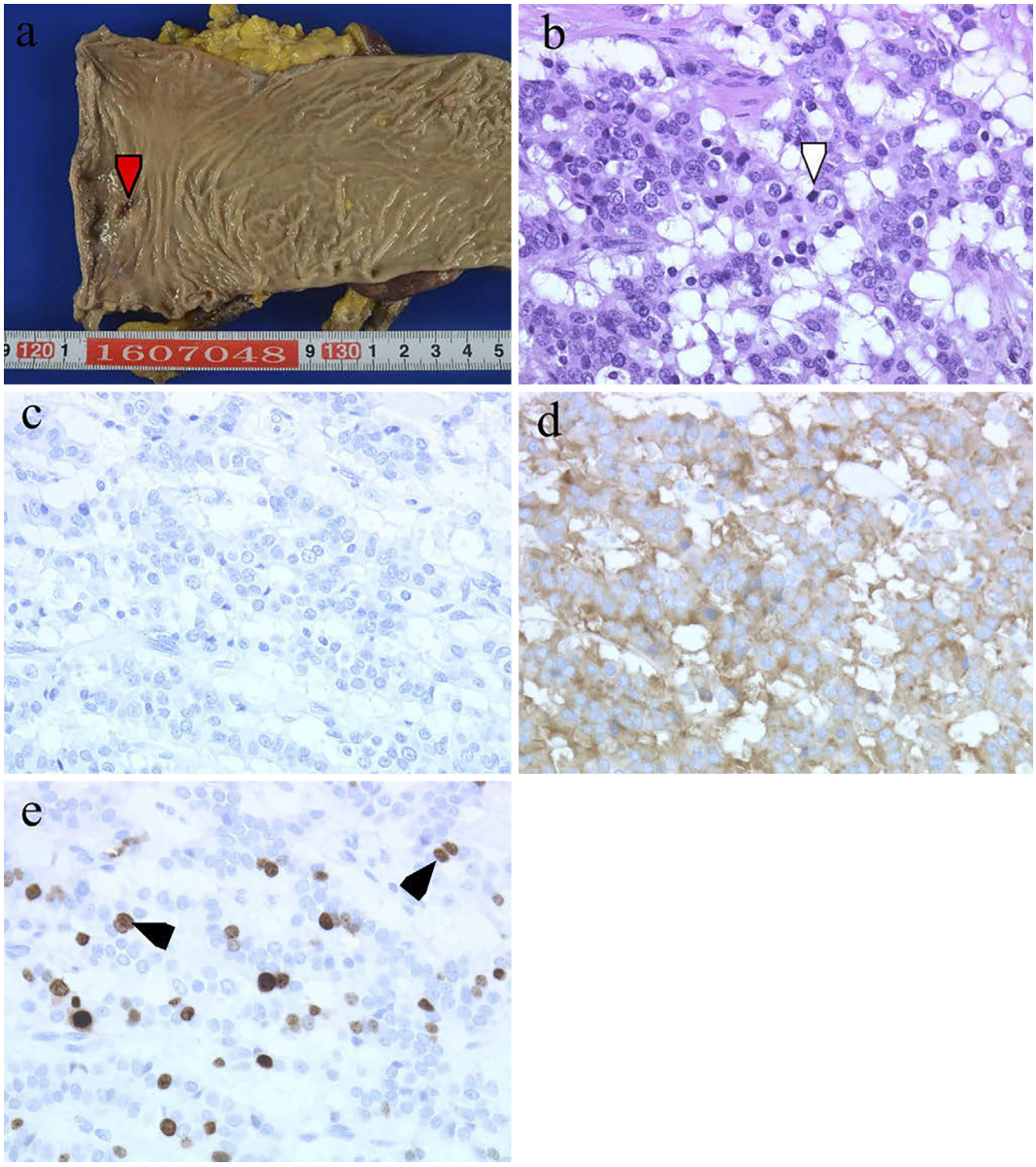

Figure 4. **Macroscopic findings (a). A rectal neuroendocrine tumor (NET) of 20 mm×20 mm in size was found (red arrowhead). On histological examination, small alveolar, ribbon-like, trabecular structures were observed, and one mitotic cell was found (white arrowhead); the mitotic index was determined to be 4 per 10 high-power fields (b). Immunohistochemical staining was negative for chromogranin A (c), positive for synaptophysin (d), and the Ki-67 index, which was calculated as the percentage of positively stained nuclei (black arrowheads) in several areas of the section that were considered to be pathologically representative of the tumor characteristics, was 15% (e), suggesting neuroendocrine tumor-grade 2 (NET-G2).**

of hemorrhage from liver metastases are as follows: skin melanoma (n=6) (9-13), colon (n=4) (9, 14, 15), lung (n=4) (13, 16-18), choriocarcinoma (n=3) (19), ovary (n=2) (26), breast (n=1) (9), angiosarcoma (unknown origin, n=1) (23), nasopharynx (n=1) (27), maxillary sinus (n=1) (8), embryonal cell carcinoma (n=1) (28), testicle (n=1) (29), epidermoid carcinoma (unknown origin, n=1) (30), plasmacytoma (n=1) (31), kidney (n=1) (32), lymphoma (n=1) (33), esophagus (n=1) (34), and tongue (n=1) (23). Liver metastases were reported to have been found in 85% of pancreatic cancer patients with metastatic disease, 78% of colon cancer patients, 71% of rectal cancer patients, 52% of esophageal cancer patients, 39% of gastric cancer patients and 30% of breast cancer patients (35). Further studies are needed to confirm which of the primary cancers are associated with easy bleeding in patients with liver metastasis.

Neuroendocrine neoplasms (NENs), which originate from various tissues, are neoplasms that show a wide spectrum of biological behaviors, ranging from benign to malignant (36). They are composed of either a well-developed neuroendocrine phenotype or poorly differentiated cells but still have recognizable and prominent neuroendocrine features. They

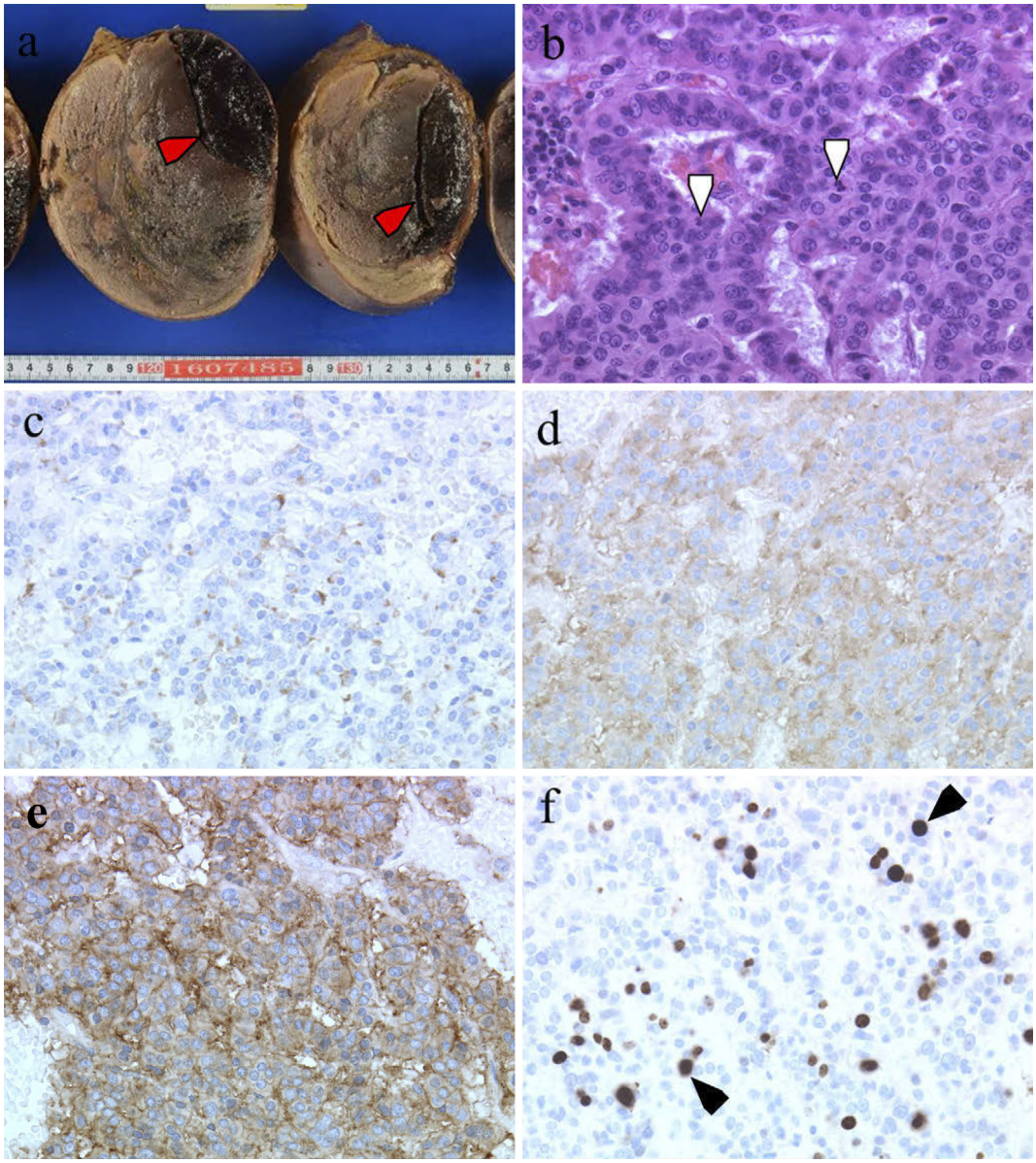

Figure 5. **In the macroscopic examination of the liver specimen, the total weight of the specimen was 1,432 g and hematoma was observed in the largest tumor lesion (size: 150 mm×100 mm). Red arrowheads indicate signs of intratumoral hematoma (a). The tumor cells were cubic with round nuclei and eosinophilic cytoplasm in a small alveolar, ribbon-like, trabecular arrangement and two mitotic cells were found (white arrowhead); thus, the mitotic index was 5 per 10 high-power fields (b). Immunohistochemical staining was weakly positive for chromogranin A (c), positive for synaptophysin (d), positive for somatostatin receptor type 2a (SSTR2a) (e), and the Ki 67 index, which was calculated as the percentage of positively stained nuclei (black arrowhead), was 20% (f), indicating a neuroendocrine tumor-grade 2 (NET-G2).**

share common histochemical features, including the expression of chromogranin A and synaptophysin, which are essential for a pathological diagnosis. The proliferation potential should be evaluated according to the mitotic index and staining for Ki-67, a proliferation marker. The World Health Organization 2010 classifications include four categories of NEN: NET G1, NET G2, NEC, and mixed adenoneuroendocrine carcinomas (37). Some studies have reported that the World Health Organization 2010 grading classification may be useful for predicting the survival of NEN patients (38, 39). However, NENs remain to be fully studied because they are rare and heterogeneous.

The aim of treatment for a malignant liver tumor with spontaneous hemorrhage is to control the bleeding quickly and effectively in order to prevent the aggravation of the patient's general condition. Emergent surgery, such as hepatic resection, suture ligation of the active bleeding source, or ligation of the hepatic artery were the standard treatments until 1990s (1, 7, 14). However, according to the advancement of techniques in interventional radiology, the first

choice of treatment is now TAE. TAE is now widely used for the treatment of HCC with spontaneous hemorrhage (40) because it is an effective and minimally invasive procedure. Thus, it should also be chosen for patients with liver metastases with spontaneous hemorrhage. In our case, because the diagnosis of liver metastasis with spontaneous hemorrhage is rarely made preoperatively due to its uncommon event (41), we first made a tentative diagnosis of HCC with intratumoral hemorrhage and performed TAE treatment, which immediately achieved hemostasis.

Most patients with liver metastasis have advanced-stage disease, and liver metastasis with spontaneous hemorrhage is usually a terminal event. Thus, patients typically live for less than 6 months and most live for less than 6 weeks (14). However, in our case, we observed multiple lung and multiple liver metastases of NET on enhanced CT and MRI at one year after surgical treatment, indicating better survival in comparison to previous reports (14). One important reason for this difference is that most NETs are more indolent and thought to present better prognosis than other epithelial malignancies (36).

According to the European Society for Medical Oncology clinical practice guidelines, cytoreductive surgery should be considered for NET when metastatic disease is localized or if >70% of the tumor load is thought to be resectable, as it may reduce the endocrine and local symptoms and might help to improve systemic treatment (42). Based on the fact that all lesions, including the primary rectal lesion and multiple liver lesions, were thought to be resectable, we first performed preoperative right portal vein embolization and low anterior resection of the rectum along with lymph node dissection. We then performed partial hepatic resection to resect all hepatic lesions. We thought that aggressive surgical treatment of liver metastases of a rectal NET would improve the patient's survival.

In conclusion, we presented the first case of intratumoral hemorrhage of liver metastasis from a rectal NET. TAE was an effective treatment for controlling the bleeding from liver metastasis. When encountering liver tumors with spontaneous bleeding, it is important to consider the possibility of bleeding from liver metastasis of NET.

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

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