Scientific Research Publishing

Case Reports in Clinical Medicine, 2020, 9, 275-281
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Radical Operation and Everolimus Therapy for Rectal Neuroendocrine Tumor with Liver Metastases: A Case Report with Review of the Literature

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How to cite this paper: Xu, J.Q., Cui, Y.J., Huang, X.F., Meng, Y.B., Xin, J. and Cheng, Y. (2020) Radical Operation and Everolimus Therapy for Rectal Neuroendocrine Tumor with Liver Metastases: A Case Report with Review of the Literature. *Case Reports in Clinical Medicine*, **9**, 275-281.
https://doi.org/10.4236/crcm.2020.99039

Received: July 9, 2020
Accepted: September 14, 2020
Published: September 17, 2020

Abstract

Neuroendocrine tumors (NETs) are often misdiagnosed because they can involve any part of the body and have non-specific symptoms. Here, we report a case of a 39-year-old man with rectal neuroendocrine tumor (RNET) and hepatic metastases treated with a combination of radical surgery and Everolimus therapy. The patient complained of abdominal distension, pain, and constipation of one month duration. Enhanced CT scan of the abdomen, colonoscopy and Biopsy findings confirmed the diagnosis of rectal neuroendocrine tumor. As the anatomical structures were clear and the masses seemed to be resectable, we decided to initiate treatment with radical operation and Everolimus therapy. The patient has responded well to the treatment with no evidence of recurrence after 4 years of follow-up. This case is interesting because of the rarity of this neoplasm and its initial misdiagnosis as a giant hepatic carcinoma (hepatoma). It also demonstrates that a combination of curative surgical resection and Everolimus is a good option in a patient with large colorectal neuroendocrine tumors and massive hepatic metastases.

Keywords

Rectal Neuroendocrine Tumor, Liver Metastases, Everolimus, Radical Operation

1. Introduction

Neuroendocrine tumors (NETs) originate from neuroendocrine cells, which are present throughout the body. Thus, NETs can involve any part of the body;

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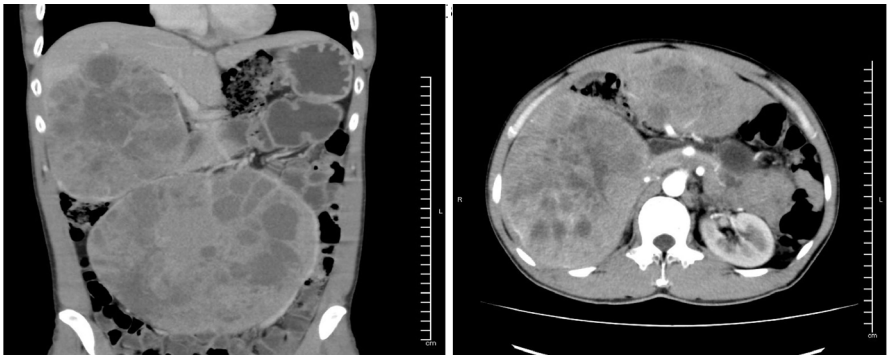
however, the most common sites are the digestive organs such as the stomach, intestines, and pancreas [1]. NETs occurring in the liver are typically metastatic; primary hepatic NETs are very rare. Thus, when a NET is found in the liver, it is imperative that tests for extrahepatic tumors be undertaken [2]. The incidence of hepatic NETs has increased 5-fold over the past 30 years [3]. The precise etiology of NETs is not clear. These tumors are sporadic and show no sex-related differences [4]. A few NETs are associated with genetic conditions, such as multiple endocrine neoplasia. Because the clinical manifestations of NETs are non-specific, it is difficult to obtain an early diagnosis [5], and misdiagnoses are not uncommon. As NETs can produce a variety of hormones, they may cause symptoms related to hormone secretion. For example, an insulin-producing NET would cause hypoglycemia and is often misdiagnosed as a nervous system disease. A gastrinoma stimulates gastric secretions and may be misdiagnosed as a peptic ulcer. Thus, an accurate diagnosis of a NET is often delayed, and the opportunity for prompt treatment is often lost. Here, we report a case of RNET with hepatic metastasis in a 39-year-old man, who was successfully treated with radical resection and Everolimus therapy as an adjuvant therapy.

2. Case Presentation

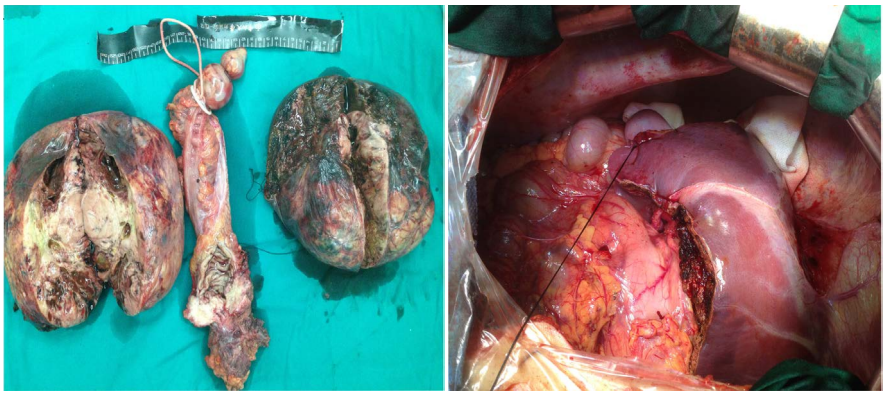
A 39-year-old man presented to our hospital in January 2016, with a 1-month history of abdominal distention, abdominal pain, and constipation. A computed tomography (CT) scan at a local hospital had revealed multiple large neoplasms in the right and left hepatic lobes, and the patient had been diagnosed with liver cancer. On March 23, 2016, a CT scan performed in the cancer center affiliated to Sun Yat-sen University revealed a significant thickening of the lower rectal wall, which was suggestive of a rectal tumor. The large tumors in the right hepatic lobe and the pelvis were considered to be metastases, as shown in **Figure 1**. On March 24, 2016, abdominal ultrasonography revealed two hepatic lesions with diameters of 19.0 cm and 7.3 cm; both lesions were elliptic, showed mixed echogenicity, and had clear borders and diminished blood supply. On March 25, 2016, a colonoscopy performed at the same hospital showed a cauliflower-shaped rectal neoplasm, situated 2 cm - 8 cm from the anus and measuring approximately 5 cm × 6 cm. Histopathological evaluation of a biopsy specimen showed fibrous tissue within funicular segments and cell nests distributed in heterocysts, as shown in **Figure 2**, which is consistent with a malignant tumor. Immunohistochemical analysis revealed the following: CK (+), Syn (+), CD56 (+), NSE (+), CK20 (+), CgA (−), CDX-2 (−), and Ki67 index, 2% (+). The histopathological and immunohistochemical results were consistent with a diagnosis of NET (G1), as shown in **Figure 3**.

The patient had no complaints of discomfort, headache, or sweating, and had no other clinical findings like paroxysmal hypertension, spontaneous hypoglycemia, or Whipple triad. He had no history of hepatitis. A physical examination showed that the abdominal wall was raised by a huge, palpable, hard mass measuring approximately 15 cm × 20 cm. The boundaries of the mass were not clear,



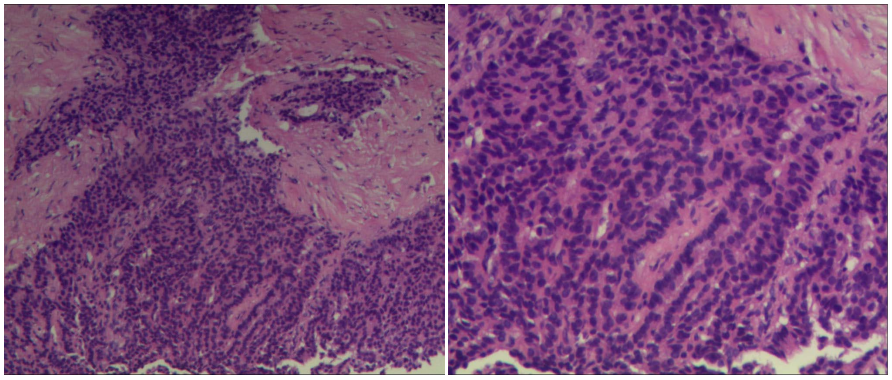
(A) (B)

Figure 1. Multidetector computed tomography images. Multiple, well-circumscribed, heterogeneous, and hypodense liver masses are seen. The largest of these is located in the left lobe and measures 203 mm × 92 mm × 232 mm. The background liver tissue is not cirrhotic.



(A) (B)

Figure 2. Surgical specimens. (A) The left mass was located in the right hepatic lobe; the middle one was located in the rectum; and the right mass was located in the left hepatic lobe. Several grey irregular necrotic areas are seen on the left and right sides of the neoplasms. (B) The cut edge of the liver appears clean and smooth.



(A) (B)

Figure 3. Histopathological examination. (A) Tumor cells with red staining within the cytoplasm are cylindrically arranged around a glass-like substance. The nucleus is darkly stained (high-power field, ×100). (B) The tumor cells are arranged in funicular patterns and nests (high-power field, ×200).

and no tenderness was present. Routine laboratory tests, including liver function tests, were normal. Blood tests for tumor markers revealed the following: alpha-fetoprotein, 11.04 ng/mL (normal, <7 ng/mL); carbohydrate antigen (CA) 19-9, 42.5 U/mL (normal, <34 U/mL); neuron-specific enolase (NSE), 19.25 μg/L (normal, <17 μg/L); CA-724, negative; and carcinoembryonic antigen, negative.

3. Treatment

The diagnosis of a rectal NET (RNET) with liver metastases was established. No extrahepatic metastases were found. Resection of the hepatic metastases and radical resection of the rectal tumor were performed under general anesthesia. With the patient in a supine position, the abdomen was thoroughly disinfected, and a midline incision was made from the xiphoid process to the pubic symphysis (~35 cm long) and into the abdomen. No abnormal ascites was noted. A large tumor was seen in the left lobe of the liver. It had originated from the lower margin of the S3 vertebra and had grown into the pelvis. It measured approximately 21 cm × 21 cm × 10 cm and was encapsulated. Dilated, tortuous veins were visible on the tumor surface. No adhesions to the greater omentum were present. Another tumor was seen in the right hepatic lobe. It measured approximately 15 cm × 15 cm × 10 cm and was similar to the left lobe tumor. A hard tumor, measuring approximately 5 cm× 5 cm × 4 cm, could be palpated in the left and posterior walls of the rectum and in the pelvic floor. The tumor was not fixed and could be moved. No ulcers or scars were found in the stomach or duodenum. The pancreas was soft and without any masses. No splenomegaly was noted. There were no abnormalities in the colon and small intestines. No metastatic nodules were found in the mesentery. Combined with the preoperative imaging and puncture biopsy results, the operative findings confirmed a RNET with liver metastases.

The left hepatic tumor was carefully resected, taking care to keep the tumor capsule intact. The right hepatic triangle and coronal ligament were successively dissociated from the right half of the liver. The hepatic portal vessels, right hepatic artery, and right portal vein were ligated to block the blood flow to the right side of the liver. The liver capsule was then incised along the ischemic plane by using an electrocautery knife, and the liver parenchyma was resected using an ultrasonic knife. The right half of the liver was gradually removed, and the cut edge was sutured with 4-0 Prolene continuous sutures, after which hemostasis was achieved.

We also found a neoplasm that was located approximately 4 cm from the anus and measured approximately 4 cm × 5 cm. The tumor did not break through the serous membrane, and its boundaries were well-defined. The tumor was resected, and no tumor cells were detected on histopathological examination of both the liver and the rectal incisions. The tumor invaded the muscularis propria but did not break through the serous membrane. As the reference of UICC Tumor Node Metastases classification of RNET, 8th edition (**Table 1**). Post-operative tumor stage was T2N0M1a.

Table 1. UICC tumor node metastases classification of RNET, 8th edition.

TX	Primary tumor status cannot be assessed
T0	No evidence of primary tumor
T1a	Invades lamina propria or submucosa and size <1 cm
T1b	Invades lamina propria or submucosa and size 1 - 2 cm
T2	Invades lamina propria or submucosa and size >2 cm
	Or invades muscularis propria
T3	Invades the subserosal tissue without invading serosa
T4	Invades peritoneum or other organs
NX	Regional lymph-node status not evaluable
N0	No regional lymph-node metastasis
N1	Regional lymph-node metastases
MX	Metastatic status not evaluable
M0	No distant metastasis
M1	Distant metastases
M1a	Hepatic metastasis only
M1b	Extrahepatic metastasis only
M1c	Hepatic and extrahepatic metastases

Post-operatively, the patient was administered Everolimus 10 mg/d but developed hypoalbuminemia and reactive pleural effusion on the day after the operation; both complications improved with nutritional support. The patient was discharged from the hospital after 13 days and has been followed up for 51 months now, with no signs of tumor recurrence.

4. Discussion

NETs are rare tumors, accounting for only 1% - 2% of all gastrointestinal tumors [5]. But, RNET account for approximately one third of all digestive neuroendocrine neoplasms (NEN) [6]. However, their effective incidence may be Underestimated. Most RNETs are non-functional and are not associated with carcinoid syndrome. They have non-specific symptoms such as pain, anemia, and bloody defecation. Another primary tumor or liver metastasis can also cause similar symptoms via a mass effect. Therefore, the diagnosis of RNET is difficult. Part of the RNETs is detected by accident under colonoscopy. Diagnostic tests must establish a qualitative diagnosis as well as accurately locate the lesion. Biopsy and histopathological evaluations are commonly used methods. Chromogranin A and NSE are common serological indexes for NETs. Tumor localization is a key factor for surgical therapy of colorectal NETs, and imaging methods such as ultrasonography, multidetector CT, magnetic resonance imaging, and endoscopic biopsy, are used for this purpose [7].

Tumor stage is an important prognostic factor of RNET [8]. Numerous studies are now exploring the risk factors for tumor metastasis and spread. In localized tumors, the main factors associated with prognosis are the invasion of the muscularis layer or tumor size, infiltration depth and lymphatic vessel invasion [8]. RNET is classified according to the 8th edition of UICC Tumor Nodes Metastases classification (**Table 1**) [9].

The risk of metastatic disease of NETs increases with tumour size—2% when <1 cm, 10% - 15% 1 - 2 cm, 60% - 80% ≥ 2 cm—with no involvement of the

muscularis propria. NETs are often localized—75% - 85%—and rarely have distant metastasis at diagnosis—2% - 8% [10].

The liver is the main site of metastasis. Surgical resection is the treatment of choice provided that the following conditions are met: well-differentiated (G1 or G2) tumor, no lymph node metastases, no diffuse liver metastases, no peritoneal metastases, and no right cardiac insufficiency. The 5-year survival rate of patients after resection of liver metastases is 47% - 76%, but the recurrence rate can reach 76%, with most cases of recurrence occurring within 2 years [11]. Neuroendocrine carcinomas (NECs) tend to have lower overall survival when compared with NETs and surgical or endoscopic tumor removal has a major impact on overall survival, regardless the histological characteristics [12].

There are two approved drugs to be applied in this setting, lanreotide, and everolimus [8] [9].

Molecular targeting drugs such as Sunitinib and Everolimus have good efficacy and tolerability in patients with advanced and metastatic colorectal NETs. Everolimus is an antitumor drug that inhibits the mammalian target of rapamycin (mTOR) pathway, which is involved in cell proliferation and angiogenesis [13] [14] [15]. Everolimus can induce amenorrhea, which is a rare adverse effect of this drug; the underlying mechanism is not clear. There is no high-quality evidence-based research showing a benefit of adjuvant therapy (with long-acting somatostatin, molecular-targeting drugs, or chemotherapy) in patients with colorectal NETs who have undergone R0 resection. Thus, routine adjuvant therapy after radical resection of NET (G1 - G2) is not recommended [14].

5. Conclusion

Our patient had a good postoperative course with no signs of tumor recurrence followed-up for 51 months. Radical resection of both the primary and the metstatic tumors and adjuvant therapy with Everolimus is an effective treatment in patients with well-differentiated gastrointestinal NETs and liver metastasis showing no extrahepatic metastasis as seen in this case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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