CASE REPORT

Living-related liver transplantation for multiple liver metastases from rectal carcinoid tumor: A case report

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Abstract

A 42-year-old woman was admitted to our hospital because of multiple liver tumors detected by ultrasonography. Colonoscopy revealed submucosal tumor in the rectum, which was considered the primary lesion. Endoscopic mucosal resection followed by histopathological examination revealed that the tumor was carcinoid. The resected margin of the tumor was positive for malignant cells. Two courses to transcatheter arterial chemotherapy for liver metastasis were ineffective. Accordingly, the rectal tumor and metastatic lymph nodes were surgically resected. One month after the operation, she received liver transplantation (left lateral segment and caudate lobe) from her son. No recurrent lesion has been observed at two years after the liver transplantation. Liver transplantation should be considered as a treatment option even in advanced case of carcinoid metastasis to the liver. We also discuss the literature on liver transplantation for metastatic carcinoid tumor.

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INTRODUCTION

Carcinoid tumors are slow-growing neuroendocrine tumors, and often metastasize to the liver. There is no established treatment for liver metastases and the prognosis is poor[1, 2]. Liver transplantation for metastatic neuroendocrine tumor has already been reported worldwide[3-16], but the procedure is rarely performed in Japan[17]. We report here a case of living-related liver transplantation for liver metastases of rectal carcinoid tumor.

CASE REPORT

A 42-year-old woman was admitted to our hospital because of multiple liver tumors detected by ultrasonography. The medical history included bronchial asthma. There was no history of blood transfusion. Physical examination revealed a hard and swollen liver in the upper abdomen. Laboratory tests showed erythrocyte count of $367 \times 10^4/mm^3$ (normal: $400\text{-}500 \times 10^4/mm^3$), hemoglobin 10.5 g/dL (11.8-15.1 g/dL), leukocyte count 8200/mm^3 (4000-9600/mm^3), platelet count $25.9 \times 10^4/mm^3$ ($16.0\text{-}35.0 \times 10^4/mm^3$), serum albumin 4.2 g/dL (3.9-5.0 g/dL), total bilirubin (T-Bil) 1.0 mg/dL (0.3-1.2 mg/dL), aspartate aminotransferase (AST) 30 IU/L(13-33 IU/L), alanine aminotransferase (ALT) 39 IU/L (6-27 IU/L), alkaline phosphatase (ALP) 311 IU/L (115-359 IU/L), γ-glutamyl transpeptidase (γ -GTP) 137 IU/L (10-47 IU/L), blood urea nitrogen (BUN) 20.0 mg/dL (8.0-20.0 mg/dL), and creatine (Cr) 0.9 mg/dL (0.6-1.0 mg/dL). Hepatitis B surface and hepatitis C virus antibody were negative. Serotonin and 5-HIAA in serum were within the normal range. Carcinoembryonic antigen, CA19-9, alfa-fetoprotein and protein induced by vitamin K antagonist (PIVKA)-II were normal but neuron-specific enolase (NSE) was elevated 46.1 ng/mL (0-10.0 ng/mL).

Abdominal ultrasonography (US) revealed multiple hyperechoic masses in both lobes of the liver (Figure 1A). Abdominal computed tomography (CT) also revealed multiple liver tumors enhanced mildly (Figure 1B). Abdominal angiography showed hepatomegaly and multiple liver tumors supplied by the hepatic artery. Colonoscopy showed
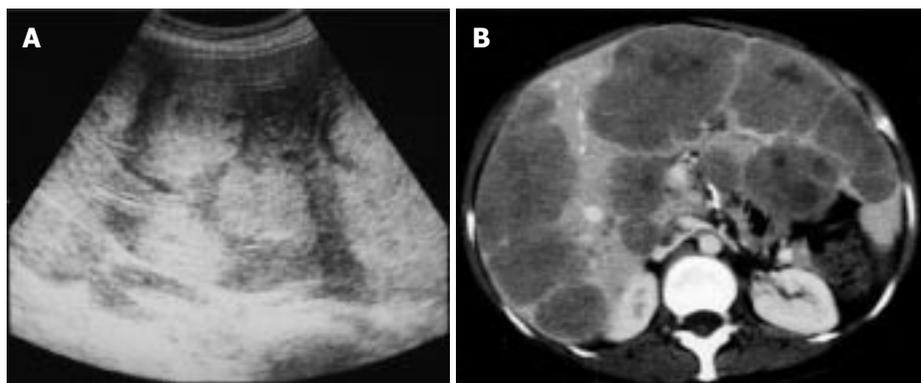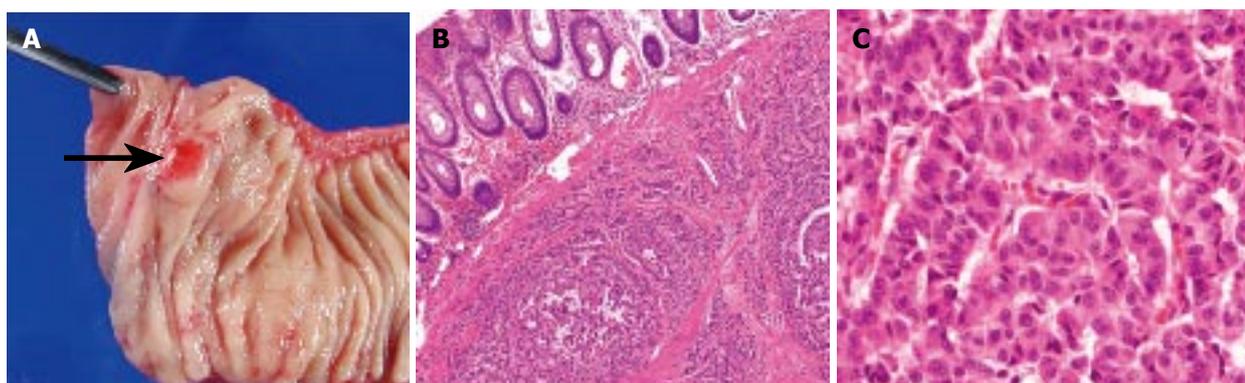
Figure 1 A: Ultrasonography showed multiple hyperechoic masses in the liver; **B**: Dynamic computed tomography showed multiple liver tumors. The surfaces of these tumors showed mild enhancement.

Figure 2 A: Macroscopic findings of the resected rectum. Arrow shows the primary lesion; **B**: The tumor cells showed tubular and alveolar formation, and their nuclei were slightly swelling (**C**). (**B**, **C**: H&E, original magnification, **B**: x 40, **C**: x 400).
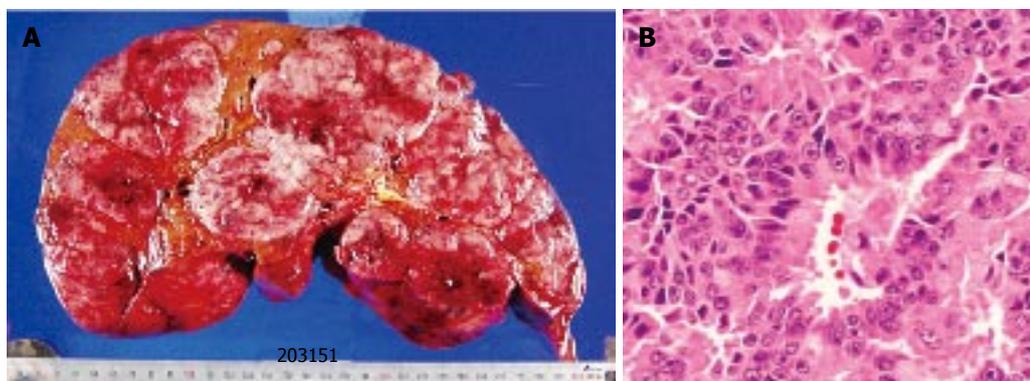
Figure 3 A: The cut surface of the resected specimen showed multiple tumors; **B**: Histopathological findings of the liver tumor were similar to those of the rectal tumor (H&E, original magnification, x 400).

submucosal tumor in the rectum. This tumor appeared as a low echoic mass by endoscopic ultrasonography (EUS). Then we performed endoscopic mucosal resection (EMR) for the submucosal tumor of the rectum, which was histopathologically diagnosed as carcinoid tumor. The resected margin of the tumor was positive for malignant cells. Transcatheter arterial chemotherapy for liver metastasis was applied twice (first: 5-fluorouracil [5-FU] + epirubicin [EPI] + mitomycin C [MMC], second: 5-FU + methotrexate [MTX]), but was ineffective because the liver tumors did not decrease in size and even grow 2 mo after the TACE. Accordingly, the rectal tumor and metastatic lymph nodes were resected surgically. Macroscopically, the rectal tumor was an elevated lesion with a central depression, measuring 58 mm in a diameter (Figure 2A). Histopathological examination showed atypical cells forming

tubular and alveolar structures, with slightly swollen nuclei (Figures 2B and 2C). Lymph node metastases and blood vessel invasions were detected. Immunohistochemical examination revealed that most tumor cells were stained with chromogranin A, NSE and synaptophysin. The Ki-67 index was 6.1, but p53 protein was negative.

One month after the operation, there were no recurrence except for the liver. She received a liver transplantation (left lateral segment and caudate lobe) from her son. Standard liver volume (SLV) was 1 014.4 g, graft volume (GV) was 450 g, GV/ SLV ratio was 44.4% and graft-to-recipient weight ratio (GR-WR) was 0.98. The volume of the resected liver was 4750 g, and multiple nodules of white and brown colors occupied the whole liver (Figure 3A). The histopathological findings of the liver tumor (Figure 3B) were similar to those of the primary lesion.

Table 1 Literature review of liver transplantation for metastatic neuroendocrine tumors

Reference	Number of patients	Median follow-up (m)	Survival rate (%)			Disease-free survival rate (%)	
			1-yr	3-yr	5-yr	1-yr	5-yr
Rosenau et al (2002)[3]	19	38	89	89	80	56	21
Coppa et al (2001)[4]	9	39	100	100	70	100	53
Lehnert et al (1998)[5]	103	-	68	54	47	60	24
Le Treut et al (1997)[6]	31	25	59	47	36	45	17
Florman et al (2004)[7]	11	30	73	48	36	-	-
Cahlin et al (2003)[8]	10	28	80	80	-	-	-
Olausson et al (2002)[9]	9	22	89	89	-	-	-
Ringe et al (2001)[10]	5	18	80	80	-	-	-
Pascher et al (2000)[11]	4	42	100	75	50	-	-
Frilling et al (1998)[12]	4	54	50	50	50	-	-
Lang H et al (1997)[13]	12	49.5	83	83	83	-	-
Dousset et al (1996)[14]	9	29	33	33	33	-	-
Anthuber et al (1996)[15]	4	11	25	0	0	-	-
Routley et al (1995)[16]	11	-	82	-	57	-	-
Japan (2005)[17]	6	-	66.7	66.7	-	-	-

No invasion of the portal vein, hepatic vein, and bile duct was noted.

Her clinical course has been good and no recurrence has been demonstrated two years since the liver transplantation.

DISCUSSION

Neuroendocrine tumors have generally been classified by the site of origin. Furthermore, a new histopathological classification was reported by WHO[18]. The WHO classification has been considered by the size of the tumor, the depth of the tumor invasion, angiogenesis, lymphatic invasion, cellular atypia, necrosis, mitoses, Ki-67 index and p53 protein. Based on this classification, neuroendocrine tumors are divided into three types, well-differentiated endocrine tumor (carcinoid), well-differentiated endocrine carcinoma (malignant carcinoid), and poorly-differentiated endocrine carcinoma (small cell carcinoma)[18]. Although the standard therapy for liver metastasis of neuroendocrine origin is surgical resection[19], the prognosis of neuroendocrine tumor with liver metastasis is usually poor[1, 2]. When curative hepatic resection is difficult, transcatheter arterial chemo-embolization (TACE) and intra-arterial chemotherapy are performed and have been reported to be effective[20-23]. Our patient received two courses of intra-arterial chemotherapy but no satisfactory response was observed. Somatostatin analogue and interferon have been used for the treatment of carcinoid tumors[24-27]. These therapies are excellent for improvement of symptoms but the tumor response rate is usually low[24-27].

Liver transplantation has been widely performed in patients with end-stage liver disease and metastatic liver cancers from neuroendocrine tumors[3-6]. The 5-year survival rate of transplant recipients for neuroendocrine tumors metastases to the liver ranges from 0 to 83% (median, 50%) (Table 1). The main cause of death is recurrence of the carcinoid tumors. In Japan, the accumulative living related liver transplantations between 1996 and 2002

are more than 2000. Among these, transplantation was performed in only 6 cases of metastatic neuroendocrine tumors (0.2 %) and the 3-year survival rate is 66.7%[17]. Strictly speaking, the 5-year survival rate of liver transplantation for metastatic carcinoid tumor is 69% but is poor in noncarcinoid neuroendocrine tumors (4-year survival rate, 8%)[6]. Thus, histopathological discrimination is very important to predict the prognosis of neuroendocrine tumors. Our patient had a typical carcinoid tumor which is compatible with well-differentiated neuroendocrine carcinoma, with metastases in the liver and was considered to show good prognosis after transplantation. However, the case was advanced stage with lymph node metastasis, lymphatic and vascular invasion and extensive liver metastasis, and thus was considered a high recurrent risk requiring careful follow-up. Unexpectedly good prognosis of this case could be related to the radical resection of the tumor including primary and metastatic lesion and not classified in poor prognosis such as non-pancreatic primary lesion (rectum) and noncarcinoid apudoma[6]. The prognosis was markedly improved by transplantation and she remains well 2 years and 9 mo after surgery without local recurrence and metastasis. Although much longer follow-up period would provide more meaningful information to elucidate the prognosis of such unusual case, liver transplantation could be life-saving procedure for patients with metastatic neuroendocrine tumor resistant to alternative treatments.

Pelosi *et al*[28] reported that Ki-67 index is a significant predictor of prognosis and survival of patients with pancreatic neuroendocrine tumors. Furthermore, Moyana *et al*[29] reported that MIB-1 and p53 were associated with metastasis of the gastrointestinal carcinoid tumors. Rosenau *et al*[3] pathologically investigated patients who received a liver transplantation for metastatic neuroendocrine tumors. They reported that the survival rate of patients with high Ki-67 index (> 5%) or overexpression of the E-cadherin was low, and suggested that Ki-67 index and E-cadherin expression could be potentially useful prognostic markers after liver transplantation[3]. Our pa-

tient showed moderately positive Ki-67 index (6.1%, rate for carcinoid is around 2-3%) and should be followed as high recurrence risk case.

The Japanese medical insurance system covers liver transplantation for liver cirrhosis and hepatocellular carcinoma (HCC) based on Milan criteria[30]. However, the system does not cover metastatic liver cancer. Liver transplantation is a kind of special treatment for the end-stage liver disease and is also expensive. So, not all the patient in the end-stage liver disease has been covered by medical insurance in Japan. In our patient, distant and lymph node metastases were completely resected, and metastatic neuroendocrine tumors in the liver were removed through hepatectomy and liver transplantation even though the metastasis was far advanced within the liver though localized in the liver. We propose that metastatic neuroendocrine tumors of the liver should be classified as similar to HCC although cases beyond Milan criteria[30], like our case, could be also included in such classification because of its biological low malignant character.

In conclusion, we reported a female patient who underwent successful living liver transplantation for advanced liver metastases of rectal carcinoid tumor. She has been well for the last two postoperative years and remains alive without any recurrence in spite of positivity of poor prognostic parameters. Other parameters, such as oncogene, suppressor gene and cyclin shown in hepatocellular carcinoma[31], apart from those of histopathology and immunohistochemistry, are needed to help in clinical decision making with respect to the indications of transplantation.

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